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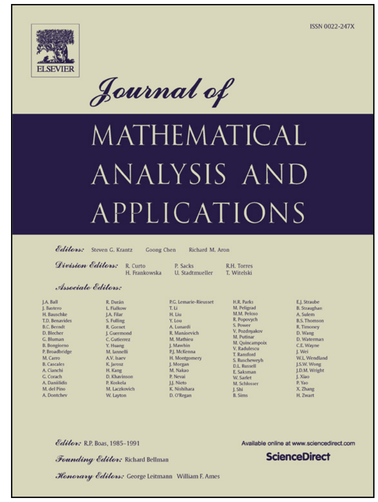

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The Threshold of Stochastic Tumor-Immune Model with Regime Switching

Xing Chen* Xiaoyue Li† Yuting Ma‡ Chenggui Yuan§

Abstract

In response to the pressing needs for comprehending the cancer biology, this paper focuses on dynamical behaviors of a class of stochastic tumor-immune models in random environment modulated by Markov chains. A sufficient and nearly necessary threshold-type criterion is investigated, which shows the long-time behavior of the system can be classified by a real-value parameter λ. Precisely, if $\lambda < 0$, tumor cells die out. If $\lambda > 0$, the system exists a unique invariant probability measure, and the transition probability of the solution process converges to this invariant measure. Moreover, we also estimate the expectations with respect to the invariant measure under some conditions. Two numerical examples are provided to illustrate our results.

Keywords. Markov chain; Stochastic tumor-immune systems; Invariant measure; Ergodicity; Permanence; Extinction.

1 Introduction

Providing an analytical framework to gain insight into the evolution and interaction mechanism of immunity and tumor, mathematical models of tumor-immune systems are theoretically and practically important in cancer treatment. Thus to describe reality accurately, more and more tumor-immune models have been studied, see, e.g., [2, 6, 10, 14, 16, 17, 25]. In particular, Kuznetsov et al. [10] proposed a classic tumor-immune model

$$\begin{cases} \mathrm{d}x(t) = & \left(\sigma + \dfrac{\rho x(t)y(t)}{\eta + y(t)} - \mu x(t)y(t) - \delta x(t)\right)\mathrm{d}t, \\ \mathrm{d}y(t) = & \big(\alpha y(t) - \beta y^2(t) - x(t)y(t)\big)\mathrm{d}t, \end{cases} \tag{1.1}$$

*School of Mathematics and Statistics, Northeast Normal University, Changchun, Jilin, 130024, China.

†School of Mathematics and Statistics, Northeast Normal University, Changchun, Jilin, 130024, China. Research of this author was supported by the National Natural Science Foundation of China (No. 11971096), the National Key R&D Program of China (2020YFA0714102), the Natural Science Foundation of Jilin Province (No. YDZJ202101ZYTS154), the Education Department of Jilin Province (No. JJKH20211272KJ), and the Fundamental Research Funds for the Central Universities.

‡School of Mathematics and Statistics, Northeast Normal University, Changchun, Jilin, 130024, China.

§Department of Mathematics, Swansea University, Bay Campus, SA1 8EN, UK.

where $x(t)$ and $y(t)$ denote dimensionless local concentration of effector cells (ECs) and tumor cells (TCs), respectively, σ represents the source rate of the baseline ECs, ρ and η are the parameters of the rate at which ECs accumulate due to the presence of the tumor, μ describes the elimination rates of ECs due to binding of ECs to TCs, δ denotes the elimination rates of ECs due to destruction and migration, α is the intrinsic growth rate of TCs, and α/β is the maximal carrying capacity of biological environment of TCs; see [10] for more details on the system setup. This model simulates the interaction of the cytotoxic T lymphocyte with immunogenic TCs, the inactivation of ECs as well as the penetration of ECs into TCs.

As a matter of fact, the tumor-immune reactions are often subject to environmental random perturbations, such as the supply of nutrients, temperature, radiation, and so on. Since the elimination rate of ECs and the intrinsic growth rate of TCs are essentially influenced by protein which is sensitive to white noises, namely,

$$\delta \mathrm{d}t \to \delta \mathrm{d}t + \kappa_1 \mathrm{d}B_1(t),\ \alpha \mathrm{d}t \to \alpha \mathrm{d}t + \kappa_2 \mathrm{d}B_2(t),$$

model (1.1) becomes

$$\begin{cases} \mathrm{d}x(t) = & \Big(\sigma + \dfrac{\rho x(t)y(t)}{\eta + y(t)} - \mu x(t)y(t) - \delta x(t)\Big)\mathrm{d}t + \kappa_1 x(t)\mathrm{d}B_1(t), \\ \mathrm{d}y(t) = & \big(\alpha y(t) - \beta y^2(t) - x(t)y(t)\big)\mathrm{d}t + \kappa_2 y(t)\mathrm{d}B_2(t), \end{cases} \tag{1.2}$$

where $B_1(\cdot)$, $B_2(\cdot)$ are two independent Brownian motions, κ_1, κ_2 are the intensity of noise. The stochastic stability around the equilibrium points of (1.2) is investigated in [20]. Li et al. [12] obtained the criteria to the asymptotic behavior of (1.2) including the stochastic ultimately boundedness in moment, the limit distribution as well as the ergodicity. Recently, Tuong, Nguyen and Yin [24] obtained the sufficient and nearly necessary threshold-type condition for the extinction and permanence of TCs, which extends the result of [12] to a better version.

Additionally, due to the sudden change of temperature, virus and other physical factors in biochemical reactions, the tumor-immune model may experience abrupt changes in their parameters [1]. Continuous-time finite-state Markov chain is widely used to characterize this kind of environmental noise in different mathematical models, for instance, [4, 11, 13, 22, 23, 29, 30] and references therein. Among them, Takeuchi et al. [22] revealed the complicated dynamics of the stochastic predator-prey model modulated by Markov chain. Moreover, the theory of stochastic differential equations with Markovian switching is systematically introduced in [18, 26]. Therefore, to describe the interaction of ECs and TCs more precisely in random environmental, it is reasonable to consider the stochastic tumor-immune system with Markovian switching

$$\begin{cases} \mathrm{d}x(t) = & \Big(\sigma(r(t)) + \dfrac{\rho(r(t))x(t)y(t)}{\eta(r(t)) + y(t)} - \mu(r(t))x(t)y(t) - \delta(r(t))x(t)\Big)\mathrm{d}t \\ & +\kappa_1(r(t))x(t)\mathrm{d}B_1(t), \\ \mathrm{d}y(t) = & \big(\alpha(r(t))y(t) - \beta(r(t))y^2(t) - x(t)y(t)\big)\mathrm{d}t + \kappa_2(r(t))y(t)\mathrm{d}B_2(t), \end{cases} \tag{1.3}$$

with an initial value $x(0) = x_0 \geq 0, y(0) = y_0 > 0, r(0) = r_0 \in \mathbb{S}$ ($\mathbb{S} = (1, 2, \cdots m_0)$), where $r(t)$ is a Markov chain, all parameters $\sigma(i)$, $\rho(i)$, $\eta(i)$, $\mu(i)$, $\delta(i)$, $\alpha(i)$, $\beta(i)$, $\kappa_1(i)$, $\kappa_2(i)$ are positive constants ($i \in \mathbb{S}$), and $B_1(\cdot)$, $B_2(\cdot)$, $r(\cdot)$ are mutually independent, which is defined on the probability space. To our best knowledge, there is no work on the dynamical behaviors of (1.3).

In this paper, our aim is to investigate the extinction and permanence of (1.3) which are two important properties in the study of tumor-immune systems. The main contributions of this work are as follows.

- Inspired by [5, 24], by analyzing the dynamics of the first equation of (1.3) on the boundary, we obtain a threshold $\lambda = \sum_{i=1}^{m_0} \pi_i\big(\alpha_i - \kappa_2^2(i)/2 - \sigma_i/\delta_i\big)$. Therefore we can characterize the dynamical behavior of (1.3) by λ without other coefficient restrictions.
- Utilizing the stochastic Lyapunov analysis, the stochastic comparison theorem, the strong ergodicity theorem and the occupation measure theory, we obtain a key criteria on the threshold λ. Precisely, we prove that if $\lambda < 0$, $y(t)$ will tend to 0 with exponential rate, while if $\lambda > 0$, the system will have a unique invariant measure which has support on $\{(x, y, i) \in \mathbb{R}^2 \times \mathbb{S} : x, y > 0\}$. The moment estimate with respect to this invariant measure is also obtained under some relaxed condition.
- Two numerical examples are given to illustrate the main result. The simulations exhibit that as the subsystems have different dynamics, the long-time behaviors of (1.3) depends on the stationary distribution of corresponding Markov chain.

The rest of the paper is arranged as follows. Section 2 obtains the threshold of extinction and permanence λ. Section 3 discusses the extinction of (1.3). Section 4 investigates the permanence of (1.3), and obtains the moment estimations with respect to the invariant measure under some conditions. Section 5 presents two numerical examples to illustrate our results. Section 6 concludes this paper.

2 Threshold of extinction and permanence

Throughout this paper, unless otherwise specified, let $(\Omega, \mathcal{F}, \{\mathcal{F}_t\}_{t\geq 0}, \mathbb{P})$ be a complete probability space with a filtration $\{\mathcal{F}_t\}_{t\geq 0}$ satisfying the usual condition (that is, it is right continuous and $\mathcal{F}_0$ contains all $\mathbb{P}$-null sets). Let $r(t)$, $t \geq 0$, be a right continuous Markov chain on the probability space taking values in a finite state space $\mathbb{S} = \{1, 2, \cdots, m_0\}$ with generator $\Gamma = (\gamma_{ij})_{m_0\times m_0}$ given by

$$\mathbb{P}\{r(t+\Delta) = j | r(t) = i\} = \begin{cases} \gamma_{ij}\Delta + o(\Delta), & i \neq j, \\ 1 + \gamma_{ij}\Delta + o(\Delta), & i = j, \end{cases}$$

where $\Delta \downarrow 0$, $o(\Delta)$ means $\lim_{\Delta\to 0} o(\Delta)/\Delta = 0$. Here $\gamma_{ij} \geq 0$ is the transition rate from i to j if $i \neq j$ while $\gamma_{ii} = -\sum_{i\neq j} \gamma_{ij}$. Here we assume that the Markov chain is irreducible (i.e. the linear equation $\pi\Gamma = 0$ and $\sum_{i=1}^{m_0} \pi_i = 1$ has a unique solution $\pi = (\pi_1, \pi_2, \cdots, \pi_{m_0})$ satisfying $\pi_i \geq 0$ for each $i \in \mathbb{S}$. Such a solution is termed as a stationary distribution). We also denote $\mathbb{R}_+ := \{x \in \mathbb{R} : x \geq 0\}$, $\mathbb{R}_+^o := \{x \in \mathbb{R} : x > 0\}$, $\mathbb{R}_+^2 := \{(x, y) \in \mathbb{R}^2 : x \geq 0,\ y \geq 0\}$, $\mathbb{R}_+^{2,o} := \{(x, y) \in \mathbb{R}^2 : x > 0,\ y > 0\}$, and $\mathbb{R}_+^{2,*} := \{(x, y) \in \mathbb{R}^2 : x \geq 0,\ y > 0\}$. For any constant sequence $\{c_i\}_{1\leq i\leq m_0}$, define $\hat{c} = \min_{1\leq i\leq m_0} c_i$ and $\check{c} = \max_{1\leq i\leq m_0} c_i$. For any $a, b \in \mathbb{R}$, $a \vee b := \max\{a, b\}$, $a \wedge b := \min\{a, b\}$ and $[a]^+ = a \vee 0$. For simplicity, we let $c(i) = c_i$. K is a generic positive constant whose value changes at different appearances. We begin with the nature of the solution of (1.3).

Theorem 2.1. *The following assertions hold.*

(*i*) *For any initial value* $(x_0, y_0, r_0) \in \mathbb{R}_+^{2,*} \times \mathbb{S}$, *model* (1.3) *has a unique global positive solution* $(x(t), y(t), r(t))$ *for all* $t \geq 0$ *with probability one. In addition, the solution process* $(x(t), y(t), r(t))$ *is a strong Feller and Markov process with transition probability denoted by* $P(t, x_0, y_0, r_0, \cdot)$.

(*ii*) *For any* $p > 0$ *sufficient small and* $c > 0$ *sufficient large, there exists a positive constant* $K(p, c)$ *such that*

$$\limsup_{t\to\infty} \mathbb{E}[(1 + x(t) + cy(t))^{1+p}] \leq K(p, c). \tag{2.1}$$

Proof. We can prove the first assertion in the similar way as [24, Theorem 2.1] and the second assertion by the similar techniques as [12, Theorem 3.2]. Since the proof is standard, we omit it to avoid duplications. □

Now let us turn to find the threshold λ which is the key to characterize the long-time behavior of (1.3). Consider the first equation of (1.3) on the boundary $y(t) = 0$, that is

$$\mathrm{d}\tilde{x}(t) = \big(\sigma(r(t)) - \delta(r(t))\tilde{x}(t)\big)\mathrm{d}t + \kappa_1(r(t))\tilde{x}(t)\mathrm{d}B_1(t). \tag{2.2}$$

In [28], we obtain that the global positive solution $(\tilde{x}(t), r(t))$ of (2.2) has a unique invariant measure ν on $[0, \infty) \times \mathbb{S}$ and $\nu((0, \infty) \times \mathbb{S}) = 1$. In the same way as (2.1) was proved, we obtain $\limsup_{t\to\infty} \mathbb{E}[(\tilde{x}(t))^{1+\tilde{p}}] \leq K$ for sufficient small $\tilde{p} > 0$. This together with the continuity of $\mathbb{E}[(\tilde{x}(t))^{1+\tilde{p}}]$ implies

$$\mathbb{E}[(\tilde{x}(t))^{1+\tilde{p}}] \leq K, \qquad \forall\ t \geq 0. \tag{2.3}$$

Thus, by embedding $[0, \infty) \times \mathbb{S}$ into $[0, \infty) \times \{0\} \times \mathbb{S}$, $\nu \times \delta_0$ can be regarded as the invariant measure of $(x(t), y(t), r(t))$ on the boundary of $\mathbb{R}_+^2$, where δ_0 denotes the Dirac measure at 0 in $\mathbb{R}_+$. We further obtain the property of the invariant measure ν.

Lemma 2.1. *The invariant measure* ν *of the process* $(\tilde{x}(t), r(t))$ *has the property*

$$\sum_{i=1}^{m_0} \int_0^\infty x\nu(\mathrm{d}x, i) = \sum_{i=1}^{m_0} \frac{\pi_i\sigma_i}{\delta_i}.$$

Proof. For any initial value $(\tilde{x}(0), r(0)) \in \mathbb{R}_+^o \times \mathbb{S}$, it follows from (2.2) that

$$\tilde{x}(t) - \tilde{x}(0) = \int_0^t \sigma(r(s))\mathrm{d}s - \int_0^t \delta(r(s))\tilde{x}(s)\mathrm{d}s + \int_0^t \kappa_1(r(t))\tilde{x}(s)\mathrm{d}B_1(s).$$

Taking expectation on both sides of the above equation yields

$$\mathbb{E}[\tilde{x}(t)] - \tilde{x}(0) = \mathbb{E}\int_0^t \big(\sigma(r(s)) - \delta(r(s))\tilde{x}(s)\big)\mathrm{d}s.$$

Utilizing the Hölder inequality, one observes from (2.3), that $\mathbb{E}[\tilde{x}(t)] \le K$, $\forall t \ge 0$. This together with the positivity of $\tilde{x}(t)$ implies that $-K \le \mathbb{E}\int_0^t \big(\sigma(r(s)) - \delta(r(s))\tilde{x}(s)\big)\mathrm{d}s \le K,\ t > 0$. Since $\hat{\delta} \le \delta(i) \le \check{\delta}$ for $i \in \mathbb{S}$ and K represents different values at different appearances, we have that for any $t > 0$,

$$-K \le \mathbb{E}\int_0^t \Big(\frac{\sigma(r(s))}{\delta(r(s))} - \tilde{x}(s)\Big)\mathrm{d}s \le K.$$

Thus dividing t on both sides of the above equation and taking the limit of t, we derive that

$$\lim_{t\to\infty} \frac{1}{t}\mathbb{E}\int_0^t \Big(\frac{\sigma(r(s))}{\delta(r(s))} - \tilde{x}(s)\Big)\mathrm{d}s = 0. \tag{2.4}$$

By the Hölder inequality, Fubini's theorem and (2.3), we derive that for any $t > 0$,

$$\mathbb{E}\Big[\frac{1}{t}\int_0^t \tilde{x}(s)\mathrm{d}s\Big]^{1+\tilde{p}} \le \mathbb{E}\Big[\frac{1}{t}\int_0^t \tilde{x}^{1+\tilde{p}}(s)\mathrm{d}s\Big] = \frac{1}{t}\int_0^t \mathbb{E}\Big(\tilde{x}^{1+\tilde{p}}(s)\Big)\mathrm{d}s < \infty,$$

which implies that $\int_0^t \tilde{x}(s)\mathrm{d}s/t$ is uniformly integrable [21, p.190, Lemma 3]. Using [21, p.188, Theorem 4] and the ergodicity of $\tilde{x}(t)$ implies that

$$\lim_{t\to\infty}\frac{1}{t}\mathbb{E}\int_0^t \tilde{x}(s)\mathrm{d}s = \mathbb{E}\Big[\lim_{t\to\infty}\frac{1}{t}\int_0^t \tilde{x}(s)\mathrm{d}s\Big] = \sum_{i=1}^{m_0}\int_0^\infty x\nu(\mathrm{d}x, i). \tag{2.5}$$

We notice that $\Big|\int_0^t(\sigma(r(s))/\delta(r(s)))\mathrm{d}s/t\Big| \le \check{\sigma}/\hat{\delta},\ t > 0$. Therefore using the dominated convergence theorem and the ergodicity of Markov chain, we obtain that

$$\lim_{t\to\infty}\frac{1}{t}\mathbb{E}\int_0^t \frac{\sigma(r(s))}{\delta(r(s))}\mathrm{d}s = \mathbb{E}\Big[\lim_{t\to\infty}\frac{1}{t}\int_0^t \frac{\sigma(r(s))}{\delta(r(s))}\mathrm{d}s\Big] = \sum_{i=1}^{m_0}\frac{\pi_i\sigma_i}{\delta_i}. \tag{2.6}$$

Combining (2.4), (2.5) and (2.6), we obtain the desired assertion. $\square$

Inspired by [24], we estimate the Lyapunov exponent $\limsup_{t\to\infty}\ln y(t)/t$ given that $y(t)$ is small. Utilizing the generalized Itô formula, we obtain that

$$\begin{aligned}\frac{\ln y(t)}{t} =& \frac{\ln y_0}{t} + \frac{1}{t}\int_0^t \Big(\alpha(r(s)) - \frac{1}{2}\kappa_2^2(r(s)) - \beta(r(s))y(s) - x(s)\Big)\mathrm{d}s \\ &+ \frac{1}{t}\int_0^t \kappa_2(r(s))\mathrm{d}B_2(s).\end{aligned} \tag{2.7}$$

From (1.3), we know that if $y(t)$ is small, $x(t)$ is close to $\tilde{x}(t)$. Therefore, for sufficiently large t we have

$$\frac{1}{t}\int_0^t (\beta(r(s))y(s) + x(s))\mathrm{d}s \approx \frac{1}{t}\int_0^t \tilde{x}(s)\mathrm{d}s.$$

Using the strong law of large numbers [18, Theorem 1.6], the ergodicity of $\tilde{x}(t)$ and the Markov chain, we obtain that the Lyapunov exponent of $y(t)$ can be approximated by

$$\lambda := \sum_{i=1}^{m_0} \Big[\pi_i\Big(\alpha_i - \frac{1}{2}\kappa_2^2(i)\Big) - \int_0^\infty x\nu(\mathrm{d}x, i)\Big].$$

In view of Lemma 2.1, we have $\lambda = \sum_{i=1}^{m_0} \pi_i\big(\alpha_i - \kappa_2^2(i)/2 - \sigma_i/\delta_i\big)$. Intuitively, one can see that if $\lambda < 0$, $y(t)$ decays to zero exponentially, while $y(t)$ does not tend to zero if $\lambda > 0$ which means the disease will be permanent. In fact, we shall prove that the sign of the threshold λ determines the extinction and permanence of (1.3) in the following sections.

3 Extinction: The case $\lambda < 0$

This section focuses on the case $\lambda < 0$. In this case, we obtain the extinction of TCs with exponential rate.

Theorem 3.1. *Assume $\lambda < 0$. Then for any $(x_0, y_0, r_0) \in \mathbb{R}_+^{2,*} \times \mathbb{S}$, $(x(t), y(t),\ r(t))$ has a unique invariant measure $\nu \times \delta_0$ on $\mathbb{R}_+^2 \times \mathbb{S}$, and TCs go extinct exponential fast almost surely, i.e.,*

$$\mathbb{P}_{x_0,y_0,r_0}\Big\{\lim_{t\to\infty} \frac{\ln y(t)}{t} = \lambda\Big\} = 1.$$

In order to prove this theorem we prepare a lemma which shows that when $\lambda < 0$, there exists a field such that TCs go extinct exponential fast in probability if the process $(x(t), y(t), r(t))$ starts from it.

Lemma 3.1. *Assume $\lambda < 0$. Then for any $\varepsilon > 0$ and $H > 0$, there exists a positive constant γ_1 such that*

$$\mathbb{P}_{x_0,y_0,r_0}\Big\{\lim_{t\to\infty} \frac{\ln y(t)}{t} = \lambda\Big\} \geq 1 - \varepsilon, \quad \textit{for all} \ \ (x_0, y_0, r_0) \in [0, H] \times (0, \gamma_1] \times \mathbb{S}. \tag{3.1}$$

Proof. Since the proof is rather technical we divide it into two steps.

Step 1. The main aim of this step is to prove that $y(t)$ is bounded for $t \in [0, \infty)$ with the sufficiently large probability. Based on the priori estimate of $y(\cdot)$ we give one comparison equation for the lower bound of $x(t)$. We prove that $y(t)$ is upper bounded in some finite interval $[0, T]$, and then by using the comparison theorem and constructing an appropriate stopping time we extend this result to the whole interval $[0, +\infty)$.

Due to $\lambda < 0$ and the positivity of all parameters, we choose a $\gamma_0 > 0$ sufficiently small such that

$$\bar{\lambda} := \sum_{i=1}^{m_0} \pi_i\Big(\alpha_i - \frac{1}{2}\kappa_2^2(i) - \frac{\sigma_i}{\gamma_0\mu_i + \delta_i}\Big) < 0, \quad \hat{\delta} - \frac{\check{\rho}\gamma_0}{\hat{\eta}} > 0. \tag{3.2}$$

Assume $\bar{x}(t)$ is the solution of equation

$$\mathrm{d}\bar{x}(t) = \big(\sigma(r(t)) - (\gamma_0\mu(r(t)) + \delta(r(t)))\bar{x}(t)\big)\mathrm{d}t + \kappa_1(r(t))\bar{x}(t)\mathrm{d}B_1(t),$$

where the initial value $(\bar{x}(0), r(0)) = (x_0, r_0) \in \mathbb{R}^o_+ \times \mathbb{S}$. Since $\gamma_0\mu_i + \delta_i > 0$ for all $i \in \mathbb{S}$, by the similar analysis as $(\tilde{x}(t), r(t))$, we know that $(\bar{x}(t), r(t))$ has a unique invariant measure $\bar{\nu}$ on $\mathbb{R}^0_+ \times \mathbb{S}$ and $\sum_{i=1}^{m_0} \int_0^\infty x \mathrm{d}\bar{\nu}(x, i) = \sum_{i=1}^{m_0} \pi_i\sigma_i/(\gamma_0\mu_i + \delta_i)$. The strong ergodicity of $(\bar{x}(t), r(t))$ derives

$$\lim_{t\to\infty} \frac{1}{t} \int_0^t \bar{x}(s)\mathrm{d}s = \sum_{i=1}^{m_0} \frac{\pi_i\sigma_i}{\gamma_0\mu_i + \delta_i} \quad \text{a.s.}$$

This implies that for any $\varepsilon > 0$, there exists a $T_1 = T_1(\varepsilon) > 0$ such that $\mathbb{P}(\Omega_1) \geq 1 - \varepsilon/4$, where

$$\Omega_1 = \Big\{\omega \in \Omega : \frac{1}{t} \int_0^t \bar{x}(s)\mathrm{d}s \geq \sum_{i=1}^{m_0} \frac{\pi_i\sigma_i}{\gamma_0\mu_i + \delta_i} - \frac{|\bar{\lambda}|}{4}, \quad \text{for all } t \geq T_1\Big\}. \tag{3.3}$$

The strong ergodicity of Markov chain gives

$$\lim_{t\to\infty} \frac{1}{t} \int_0^t \Big(\alpha(r(s)) - \frac{1}{2}\kappa_2^2(r(s))\Big)\mathrm{d}s = \sum_{i=1}^{m_0} \pi_i\Big(\alpha_i - \frac{1}{2}\kappa_2^2(i)\Big) \quad \text{a.s.}$$

As a consequence, there exists a $T_2 = T_2(\varepsilon) > 0$ such that $\mathbb{P}(\Omega_2) \geq 1 - \varepsilon/4$, where

$$\Omega_2 = \Big\{\omega \in \Omega : \frac{1}{t} \int_0^t \Big(\alpha(r(s)) - \frac{1}{2}\kappa_2^2(r(s))\Big)\mathrm{d}s \leq \sum_{i=1}^{m_0} \pi_i\Big(\alpha_i - \frac{1}{2}\kappa_2^2(i)\Big) + \frac{|\bar{\lambda}|}{4}, \text{ for all } t \geq T_2\Big\}. \tag{3.4}$$

Utilizing the strong law of large numbers [18, Theorem 1.6], we have

$$\lim_{t\to\infty} \frac{|\int_0^t \kappa_2(r(s))\mathrm{d}B_2(s)|}{t} = 0 \quad \text{a.s.} \tag{3.5}$$

Hence, there exists a $T_3(\varepsilon) > 0$ such that $\mathbb{P}(\Omega_3) \geq 1 - \varepsilon/4$, where

$$\Omega_3 = \Big\{\omega \in \Omega : \frac{|\int_0^t \kappa_2(r(s))\mathrm{d}B_2(s)|}{t} \leq \frac{|\bar{\lambda}|}{4}, \quad \text{for all } t \geq T_3\Big\}. \tag{3.6}$$

Let $T = \max\{T_1, T_2, T_3\}$. We choose $M > \check{\alpha}T$ sufficiently large such that $\mathbb{P}(\Omega_4) \geq 1 - \varepsilon/4$, where

$$\Omega_4 = \Big\{\omega \in \Omega : \Big|\int_0^t \kappa_2(r(s))\mathrm{d}B_2(s)\Big| \leq M - \check{\alpha}T, \quad \text{for all } t \in [0, T]\Big\}. \tag{3.7}$$

Let $\gamma_1 \in (0, \gamma_0 \exp\{-M\})$. From (2.7) and (3.7), we obtain that for any $y_0 \leq \gamma_1$ and $\omega \in \Omega_4$

$$y(t) \leq y_0 \exp\Big\{\check{\alpha}t + \int_0^t \kappa_2(r(s))\mathrm{d}B_2(s)\Big\} \leq \gamma_1 e^M < \gamma_0, \quad \text{for any } t \in [0, T]. \tag{3.8}$$

Define the stopping time $\tilde{\tau} := \inf\{t \geq 0 : y(t) \geq \gamma_0\}$. Then for any $\omega \in \Omega_4$, we have $\tilde{\tau}(\omega) > T$. Rewriting the first equation of (1.3) yields

$$\begin{aligned}\mathrm{d}x(t) = &\Big[\sigma(r(t)) + \Big(\frac{\rho(r(t))y(t)}{\eta(r(t)) + y(t)} + \mu(r(t))(\gamma_0 - y(t))\Big)x(t) \\ &- (\delta(r(t)) + \gamma_0\mu(r(t)))x(t)\Big]\mathrm{d}t + \kappa_1(r(t))x(t)\mathrm{d}B_1(t).\end{aligned}$$

Applying the stochastic comparison theorem, one obtains $\bar{x}(t) \le x(t)$ a.s. for $t \in (0, \tilde{\tau})$. Then this together with the generalized Itô formula implies that for $t \in (0, \tilde{\tau})$

$$y(t) \le y_0 \exp\Big\{ \int_0^t \Big(\alpha(r(s)) - \frac{1}{2}\kappa_2^2(r(s))\Big)\mathrm{d}s - \int_0^t \bar{x}(s)\mathrm{d}s + \int_0^t \kappa_2(r(s))\mathrm{d}B_2(s)\Big\}. \tag{3.9}$$

Inserting (3.3)-(3.6) into (3.9) yields that for $\omega \in \cap_{j=1}^4 \Omega_j$ and $y_0 \le \gamma_1$

$$\begin{aligned} y(t) &\le y_0 \exp\Big\{ \sum_{i=1}^{m_0} \pi_i \Big(\alpha_i - \frac{1}{2}\kappa_2^2(i) - \frac{\pi_i \sigma_i}{\gamma_0 \mu_i + \delta_i}\Big)t + \frac{3|\bar{\lambda}|}{4}t\Big\} \\ &\le y_0 \exp\Big\{\frac{\bar{\lambda}t}{4}\Big\} \le \gamma_1 < \gamma_0, \quad t \in [T, \tilde{\tau}). \end{aligned} \tag{3.10}$$

Then $\tilde{\tau} = \infty$ for any $\omega \in \cap_{j=1}^4 \Omega_j$ and $y_0 \le \gamma_1$. In fact, if it does not hold, there exists a set $\Omega_5 \subset \cap_{j=1}^4 \Omega_j$ with $\mathbb{P}(\Omega_5) > 0$ such that for any $\omega \in \Omega_5$, we have $\tilde{\tau} < \infty$. Noticing $T < \tilde{\tau}$ for $\omega \in \cap_{j=1}^4 \Omega_j$ and using the almost sure continuity of $y(t)$ as well as (3.10), we have $\lim_{t\to\tilde{\tau}} y(t) = y(\tilde{\tau}) < \gamma_0$, for $\omega \in \Omega_5$. This is a contradiction with the definition of $\tilde{\tau}$. Thus we have $\tilde{\tau} = \infty$ for any $\omega \in \cap_{j=1}^4 \Omega_j$ and $y_0 \le \gamma_1$, which implies $y(t) \le y_0 \exp\{\bar{\lambda}t/4\}$, for any $t \ge T$. Therefore, this together with (3.8) implies that for any $\omega \in \cap_{j=1}^4 \Omega_j$ and $y_0 \le \gamma_1$,

$$y(t) \le \gamma_0 \ (t \ge 0), \quad \text{and} \quad \lim_{t\to\infty} y(t) = 0. \tag{3.11}$$

Step 2. The main aim of this step is to obtain the desired assertion. Based on the upper boundedness of $y(t)$ we give the comparison equation for the upper bound of $x(t)$, which facilitates the tightness analysis of the occupation measures $\tilde{\Pi}^t(\cdot)$ with respect to $(x(\cdot), y(\cdot), r(\cdot))$. By the weak convergence of $\tilde{\Pi}^t(\cdot)$ we derive the unique invariant measure $\nu \times \delta_0$ of $(x(\cdot), y(\cdot), r(\cdot))$. Finally, the desired assertion follows from the properties of $\tilde{\Pi}^t(\cdot)$ and ν.

Consider

$$\begin{cases} \mathrm{d}\hat{x}(t) = \Big(\sigma(r(t)) - \Big(\hat{\delta} - \frac{\check{\rho}\gamma_0}{\hat{\eta}}\Big)\hat{x}(t)\Big)\mathrm{d}t + \kappa_1(r(t))\hat{x}(t)\mathrm{d}B_1(t), \\ \hat{x}(0) = x_0 > 0, \quad r(0) = r_0 \in \mathbb{S}. \end{cases}$$

For $\omega \in \cap_{j=1}^4 \Omega_j$ and $y_0 \le \gamma_1$, using the first inequality of (3.11) and the stochastic comparison theorem, we obtain $x(t) \le \hat{x}(t)$ for $t \ge 0$ a.s. Owing to (3.2), by the similar analysis as $(\tilde{x}(t), r(t))$, we obtain that $(\hat{x}(t), r(t))$ has a unique invariant measure $\hat{\nu}$ and satifies $\limsup_{t\to\infty} \mathbb{E}[\hat{x}^{1+\hat{p}}(t)] \le K$, for a sufficiently small $\hat{p} > 0$. Therefore the ergodicity of $(\hat{x}(t), r(t))$ gives that for almost all $\omega \in \cap_{j=1}^4 \Omega_j$

$$\limsup_{t\to\infty} \frac{1}{t}\int_0^t x^{1+\hat{p}}(s)\mathrm{d}s \le \lim_{t\to\infty} \frac{1}{t}\int_0^t \hat{x}^{1+\hat{p}}(s)\mathrm{d}s = \sum_{i=1}^{m_0} \int_0^\infty x^{1+\hat{p}}\hat{\nu}(\mathrm{d}x, i) < \infty. \tag{3.12}$$

Now we define the family of random occupation measures

$$\tilde{\Pi}^t(\cdot) := \frac{1}{t}\int_0^t \mathbf{1}_{\{(x(s),y(s),r(s))\in\cdot\}}\mathrm{d}s, \ t > 0.$$

In view of (3.11) and (3.12), one observes that $\{\tilde{\Pi}^t(\cdot;\omega), t > 0, \omega \in \cap_{j=1}^4 \Omega_j\}$ is tight, see [23]. [5, Lemma 5.7] reveals that with probability 1, any weak limit of $\tilde{\Pi}^t$ is an invariant probability measure of the process $(x(t), y(t), r(t))$, which has the support on $[0,\infty) \times \{0\} \times \mathbb{S}$. Obviously, $\nu \times \delta_0$ is the unique invariant measure of $(x(t), y(t), r(t))$ supported on $[0,\infty) \times \{0\} \times \mathbb{S}$. Thus $\tilde{\Pi}^t(\cdot)$ weakly converges to $\nu \times \delta_0$, for almost all $\omega \in \cap_{j=1}^4 \Omega_j$. Using the weak convergence, (3.5), (3.12) and Lemma 2.1, we observe that for any $\omega \in \cap_{j=1}^4 \Omega_j$, $(x_0, y_0, r_0) \in [0, H] \times (0, \gamma_1] \times \mathbb{S}$,

$$\begin{aligned}
\lim_{t\to\infty} \frac{\ln y(t)}{t} &= \lim_{t\to\infty} \frac{1}{t} \int_0^t \Big(\alpha(r(s)) - \frac{1}{2}\kappa_2^2(r(s)) - \beta(r(s))y(s) - x(s)\Big)\mathrm{d}s \\
&\quad + \lim_{t\to\infty} \frac{\int_0^t \kappa_2(r(s))\mathrm{d}B_2(s)}{t} \\
&= \lim_{t\to\infty} \int_{\mathbb{R}_+^2 \times \mathbb{S}} \Big(\alpha(r) - \frac{1}{2}\kappa_2^2(r) - \beta(r)y - x\Big)\tilde{\Pi}^t(\mathrm{d}x, \mathrm{d}y, \mathrm{d}r) \\
&= \sum_{i=1}^{m_0} \int_{\mathbb{R}_+^2} \Big(\alpha_i - \frac{1}{2}\kappa_2^2(i) - \beta_i y - x\Big)\nu(\mathrm{d}x, i) \times \delta_0(\mathrm{d}y) \\
&= \sum_{i=1}^{m_0} \pi_i(\alpha_i - \frac{1}{2}\kappa_2^2(i) - \frac{\sigma_i}{\delta_i}) = \lambda < 0.
\end{aligned}$$

Thus, the required assertion follows from $\mathbb{P}(\cap_{j=1}^4 \Omega_j) > 1 - \varepsilon$. □

Next we begin to prove Theorem 3.1.

Proof of Theorem 3.1. Lemma 3.1 implies that $(x(t), y(t), r(t))$ is transient on $\mathbb{R}_+^{2,o} \times \mathbb{S}$. Hence by Theorem 2.1, $(x(t), y(t), r(t))$ has no invariant measure on $\mathbb{R}_+^{2,*} \times \mathbb{S}$. Then $\nu \times \delta_0$ is the unique invariant measure of $(x(t), y(t), r(t))$ on $\mathbb{R}_+^2 \times \mathbb{S}$. The second assertion of Theorem 2.1 implies that the process $(x(t), y(t), r(t))$ is tight. Fix $(x_0, y_0, r_0) \in \mathbb{R}_+^{2,*} \times \mathbb{S}$. Then the sequence of the occupation measures

$$\Pi_{x_0,y_0,r_0}^t(\cdot) = \frac{1}{t} \int_0^t \mathbb{P}_{x_0,y_0,r_0}\{(x(s), y(s), r(s)) \in \cdot\}\mathrm{d}s$$

is tight on $\mathbb{R}_+^2 \times \mathbb{S}$. Since any weak limit of $\Pi_{x_0,y_0,r_0}^t(\cdot)$ is an invariant measure of $(x(t), y(t), r(t))$, $\nu \times \delta_0$ is the unique weak limit of $\Pi_{x_0,y_0,r_0}^t(\cdot)$. Owing to $\nu((0,\infty) \times \mathbb{S}) = 1$, for any $\varepsilon > 0$, one may choose H sufficient large such that $\nu((0, H) \times \mathbb{S}) > 1 - \varepsilon/2$. By virtue of Lemma 3.1, for this ε and H, there is a $\gamma_1 > 0$ such that (3.1) holds. The property of the weak convergence of $\Pi_{x_0,y_0,r_0}^t(\cdot)$ implies that there exists a $\hat{T} > 0$ such that

$$\Pi_{x_0,y_0,r_0}^{\hat{T}}((0, H) \times (0, \gamma_1) \times \mathbb{S}) > 1 - \varepsilon.$$

Recalling the definition of $\Pi_{x_0,y_0,r_0}^t(\cdot)$ we derive

$$\frac{1}{\hat{T}} \int_0^{\hat{T}} \mathbb{P}_{x_0,y_0,r_0}\{x(t) \le H, y(t) \le \gamma_1\}\mathrm{d}t > 1 - \varepsilon.$$

As a result, we yield $\mathbb{P}_{x_0,y_0,r_0}\{\hat{\tau} \le \hat{T}\} > 1-\varepsilon$, where $\hat{\tau} := \inf\{t \ge 0 : \ x(t) \le H, \ y(t) \le \gamma_1\}$ is a stopping time. Applying the strong Markov property and Lemma 3.1, we have

$$\mathbb{P}_{x_0,y_0,r_0}\Big\{\lim_{t\to\infty}\frac{\ln y(t)}{t} = \lambda\Big\} > 1-2\varepsilon.$$

Since ε is arbitrary, the desired assertion is proved. □

4 Permanence: The case $\lambda > 0$

Focusing on the case $\lambda > 0$, this section demonstartes the permanence of the process $(x(t), y(t), r(t))$ in the sense of the existence of the invariant measure, and further obtains the estimate of the expectation with respect to the invariant measure under some conditions.

Theorem 4.1. *Assume $\lambda > 0$. Then $(x(t), y(t), r(t))$ has a unique invariant measure ν^* on $\mathbb{R}_+^{2,o} \times \mathbb{S}$. Moreover, for any $(x_0, y_0, i_0) \in \mathbb{R}_+^{2,*} \times \mathbb{S}$, the transition probability of the process $(x(t), y(t), r(t))$ converges to the invariant measure ν^* under total variation sense, namely,*

$$\lim_{t\to\infty} \|P(t, x_0, y_0, i_0, \cdot) - \nu^*(\cdot)\|_{TV} = 0. \tag{4.1}$$

Proof. We prove it by contradiction. Assume that there is no invariant measure of $(x(t), y(t), r(t))$ on $\mathbb{R}_+^{2,o} \times \mathbb{S}$. Then by virtue of Theorem 2.1, $(x(t), y(t), r(t))$ also has no invariant measure on $\mathbb{R}_+^{2,*} \times \mathbb{S}$. This implies that $\nu \times \delta_0$ is the unique invariant measure of $(x(t), y(t), r(t))$ on $\mathbb{R}_+^2 \times \mathbb{S}$. For every initial value $(x_0, y_0, i_0) \in \mathbb{R}_+^{2,o} \times \mathbb{S}$, $t > 0$, define the occupation measure

$$\Pi^t_{x_0,y_0,i_0}(\cdot) := \frac{1}{t}\mathbb{E}_{x_0,y_0,i_0}\int_0^t \mathbf{1}_{\{(x(s),y(s),r(s))\in\cdot\}}\mathrm{d}s.$$

Due to Theorem 2.1, $\{\Pi^t_{x_0,y_0,i_0}, t \ge 1\}$ is a tight family of probability measures on $\mathbb{R}_+^2 \times \mathbb{S}$. By virtue of [3, Proposition 8.4], any weak limit of $\Pi^t_{x_0,y_0,i_0}$ is an invariant measure of $(x(t), y(t), r(t))$. Therefore $\Pi^t_{x_0,y_0,i_0}$ converges weakly to $\nu \times \delta_0$ as $t \to \infty$. By the stochastic comparison theorem and Lemma 2.1, we have

$$\lim_{t\to\infty}\mathbb{E}_{x_0,y_0,i_0}\frac{1}{t}\int_0^t y(s)\mathrm{d}s = \sum_{i=1}^{m_0}\int_{\mathbb{R}_+^2} y\nu(\mathrm{d}x, i) \times \delta_0(\mathrm{d}y) = 0,$$
$$\lim_{t\to\infty}\mathbb{E}_{x_0,y_0,i_0}\frac{1}{t}\int_0^t x(s)\mathrm{d}s = \sum_{i=1}^{m_0}\int_{\mathbb{R}_+^2} x\nu(\mathrm{d}x, i) \times \delta_0(\mathrm{d}y) = \sum_{i=1}^{m_0}\frac{\pi_i\sigma_i}{\delta_i}.$$

On the other hand, taking expectations on both sides of (2.7) gives

$$\begin{aligned}\mathbb{E}_{x_0,y_0,i_0}\frac{\ln y(t)}{t} = \frac{\ln y_0}{t} &+ \frac{1}{t}\mathbb{E}_{x_0,y_0,i_0}\int_0^t\Big(\alpha(r(s)) - \frac{1}{2}\kappa_2^2(r(s))\Big)\mathrm{d}s \\ &- \frac{1}{t}\mathbb{E}_{x_0,y_0,i_0}\int_0^t \beta(r(s))y(s)\mathrm{d}s - \frac{1}{t}\mathbb{E}_{x_0,y_0,i_0}\int_0^t x(s)\mathrm{d}s.\end{aligned}$$

Since every term on the right side of the above equality converges as $t \to \infty$, we have

$$\lim_{t\to\infty}\mathbb{E}_{x_0,y_0,i_0}\frac{\ln y(t)}{t} = \sum_{i=1}^{m_0}\pi_i\Big(\alpha_i - \frac{1}{2}\kappa_2^2(i) - \frac{\sigma_i}{\delta_i}\Big) = \lambda > 0. \tag{4.2}$$

By Theorem 2.1 and the Hölder inequality we know that $\mathbb{E}_{x_0,y_0,i_0}y(t)$ is unformly bounded for $t \geq 0$. This leads to $\lim_{t\to\infty}\mathbb{E}_{x_0,y_0,i_0}y(t)/t = 0$. Using (4.2) and the Jensen inequality, we obtains that

$$0 < \lim_{t\to\infty}\frac{\mathbb{E}_{x_0,y_0,i_0}\ln y(t)}{t} \leq \lim_{t\to\infty}\frac{\mathbb{E}_{x_0,y_0,i_0}y(t)}{t} = 0.$$

As a consequence, this constraction reveals that there must exist an invariant measure ν^* of $(x(t), y(t), r(t))$ on $\mathbb{R}_+^{2,o} \times \mathbb{S}$. One notices that the diffusion coefficient is nondegenerate in any compact set of $\mathbb{R}_+^{2,o} \times \mathbb{S}$ which implies that the skeleton process $\{(x(nt_0), y(nt_0), r(nt_0)),\ n \in \mathbb{N}\}$ is irreducible and aperiodic. Thus, by virtue of [19, Theorem 6.1], it follows that the transition probability $P(t, x_0, y_0, i_0, \cdot)$ of the process $(x(t), y(t), r(t))$ converges to the invariant measure $\nu^*(\cdot)$ in total variation mean. The proof is completed. □

We proceed to describe the bounds of expectation with respect to the invariant measure ν^*. For each $i \in \mathbb{S}$, by [12, p.2203, line 21], we have that

$$\frac{\rho_i y}{\eta_i + y} - \mu_i y \leq h_i^2 =: h^2(i), \quad \forall\ y > 0, \tag{4.3}$$

where $h_i = (\sqrt{\rho_i} - \sqrt{\mu_i\eta_i}) \vee 0$. Then by the positivity of $y(t)$ one observes from (1.3) that

$$\mathrm{d}x(t) \leq \big(\sigma(r(t)) + h^2(r(t))x(t) - \delta(r(t))x(t)\big)\,\mathrm{d}t + \kappa_1(r(t))x(t)\mathrm{d}B_1(t).$$

We introduce an auxiliary process $\psi(t)$ with respect to $x(t)$ described by

$$\begin{cases} \mathrm{d}\psi(t) = \big(\sigma(r(t)) - \big(\delta(r(t)) - h^2(r(t))\big)\psi(t)\big)\mathrm{d}t + \kappa_1(r(t))\psi(t)\mathrm{d}B_1(t), \\ \psi(0) = x_0 > 0,\ r(0) = r_0 \in \mathbb{S}. \end{cases}$$

Owing to the stochastic comparison theorem we can see that $x(t) \leq \psi(t)$ a.s. for all $t \geq 0$. If $a_i := \delta_i - h_i^2 > 0$, for all $i \in \mathbb{S}$, by the similar analysis to $(\tilde{x}(t), r(t))$, we know that $\mathbb{E}[\psi^{1+q}(t)]$ is uniformly bounded for $q > 0$ sufficiently small and $t \geq 0$. Furthermore, $(\psi(t), r(t))$ has a unique invariant measure $\check{\nu}$ with

$$\sum_{i=1}^{m_0}\int_0^\infty x\check{\nu}(\mathrm{d}x, i) = \sum_{i=1}^{m_0}\frac{\pi_i\sigma_i}{a_i}. \tag{4.4}$$

To proceed, we further introduce an auxiliary process $\varphi(t)$ with respect to $y(t)$, that is

$$\begin{cases} \mathrm{d}\varphi(t) = \varphi(t)\big(\alpha(r(t)) - \beta(r(t))\varphi(t)\big)\mathrm{d}t + \kappa_2(r(t))\varphi(t)\mathrm{d}B_2(t), \\ \varphi(0) = y_0 > 0, \quad r(0) = r_0 \in \mathbb{S}. \end{cases}$$

By the stochastic comparison theorem, we have $y(t) \leq \varphi(t)$ a.s. for all $t \geq 0$. Due to the direction of inequalities, it is difficult to obtain the lower bound of the expectation with respect to the invariant measure ν^* directly. Alternatively, to take advantage of the ergodicity we analyze the upper bound of $1/x(t)$ in time average.

Lemma 4.1. *The solution of* (1.3) *has the property that*

$$\liminf_{t\to\infty}\frac{1}{t}\int_0^t\frac{1}{x(s)}\mathrm{d}s \geq \frac{1}{\check{\sigma}}\Big[\sum_{i=1}^{m_0}\pi_i\Big(\delta_i+\frac{1}{2}\kappa_1^2(i)-h_i^2\Big)\Big]^+ \quad a.s., \tag{4.5}$$

and if $\sum_{i=1}^{m_0}\pi_i\big(\alpha_i-\kappa_2^2(i)/2\big)>0$ *then*

$$\limsup_{t\to\infty}\frac{1}{t}\int_0^t\frac{1}{x(s)}\mathrm{d}s \leq \frac{1}{\hat{\sigma}}\sum_{i=1}^{m_0}\pi_i\Big[\frac{\check{\mu}}{\hat{\beta}}\Big(\alpha_i-\frac{1}{2}\kappa_2^2(i)\Big)+\delta_i+\frac{1}{2}\kappa_1^2(i)\Big] \quad a.s. \tag{4.6}$$

Proof. We begin with the proof of (4.5). For convenience, define $\iota_i=\delta_i+\kappa_1^2(i)/2-h_i^2, i\in\mathbb{S}$. If $\sum_{i=1}^{m_0}\pi_i\iota_i\leq 0$, (4.5) follows directly from the positivity of $x(t)$. Then we only consider the case $\sum_{i=1}^{m_0}\pi_i\iota_i>0$. By the generalized Itô formula, we compute

$$\begin{aligned}\ln x(t) = & \ln x_0+\int_0^t\Big(\frac{\sigma(r(s))}{x(s)}+\frac{\rho(r(s))y(s)}{\eta(r(s))+y(s)}-\mu(r(s))y(s)-\delta(r(s))-\frac{1}{2}\kappa_1^2(r(s))\Big)\mathrm{d}s\\ &+\int_0^t\kappa_1(r(s))\mathrm{d}B_1(s).\end{aligned} \tag{4.7}$$

This together with (4.3) implies

$$\ln x(t) \leq F_1(t)+\check{\sigma}\int_0^t\frac{1}{x(s)}\mathrm{d}s, \tag{4.8}$$

where $F_1(t)=\ln x_0-\int_0^t\big(\delta(r(s))+\kappa_1^2(r(s))/2-h^2(r(s))\big)\mathrm{d}s+\int_0^t\kappa_1(r(s))\mathrm{d}B_1(s)$. Using the strong law of large numbers [18, Theorem 1.6] and the ergodicity of Markov chain, we obtain

$$\begin{aligned}\lim_{t\to\infty}\frac{F_1(t)}{t} &= \lim_{t\to\infty}\frac{\ln x_0-\int_0^t\big(\delta(r(s))+\frac{1}{2}\kappa_1^2(r(s))-h^2(r(s))\big)\mathrm{d}s+\int_0^t\kappa_1(r(s))\mathrm{d}B_1(s)}{t}\\ &= -\sum_{i=1}^{m_0}\pi_i\iota_i \qquad \text{a.s.}\end{aligned}$$

Thus, there exists a set $\Omega_6\in\mathcal{F}$ with $\mathbb{P}(\Omega_6)=1$ such that for any fixed $0<\varepsilon<\sum_{i=1}^{m_0}\pi_i\iota_i/2$ and $\omega\in\Omega_6$, there exists a constant $T_4=T_4(\varepsilon,\omega)>0$ such that

$$\frac{F_1(t)}{t}\leq-\sum_{i=1}^{m_0}\pi_i\iota_i+\varepsilon, \quad t\geq T_4.$$

Inserting this into (4.8) implies that

$$\ln x(t)\leq\Big(-\sum_{i=1}^{m_0}\pi_i\iota_i+\varepsilon\Big)t+\check{\sigma}\int_0^t\frac{1}{x(s)}\mathrm{d}s, \quad t\geq T_4.$$

Let $g_1(t):=\int_0^t 1/x(s)\mathrm{d}s$. We compute

$$e^{\check{\sigma}g_1(t)}\frac{\mathrm{d}g_1(t)}{\mathrm{d}t}\geq e^{(\sum_{i=1}^{m_0}\pi_i\iota_i-\varepsilon)t}, \quad t\geq T_4.$$

Integrating the above inequality from T_4 to t derives

$$\frac{1}{\check{\sigma}}\Big(e^{\check{\sigma}g_1(t)}-e^{\check{\sigma}g_1(T_4)}\Big)\geq\frac{e^{(\sum_{i=1}^{m_0}\pi_i\iota_i-\varepsilon)t}-e^{(\sum_{i=1}^{m_0}\pi_i\iota_i-\varepsilon)T_4}}{\sum_{i=1}^{m_0}\pi_i\iota_i-\varepsilon}.$$

Rearranging the above inequality, we obtain that

$$g_1(t) \geq \frac{1}{\check{\sigma}} \ln \left\{ e^{\check{\sigma} g_1(T_4)} + \frac{\check{\sigma}\Big(e^{(\sum_{i=1}^{m_0} \pi_i \iota_i - \varepsilon)t} - e^{(\sum_{i=1}^{m_0} \pi_i \iota_i - \varepsilon)T_4}\Big)}{\sum_{i=1}^{m_0} \pi_i \iota_i - \varepsilon} \right\}, \quad t \geq T_4.$$

By the definition of $g_1(t)$, dividing t on both sides and letting $t \to \infty$, we have

$$\liminf_{t\to\infty} \frac{1}{t} \int_0^t \frac{1}{x(s)} \mathrm{d}s \geq \frac{1}{\check{\sigma}} \liminf_{t\to\infty} \frac{1}{t} \ln \left\{ e^{\check{\sigma} g_1(T_4)} + \frac{\check{\sigma}\Big(e^{(\sum_{i=1}^{m_0} \pi_i \iota_i - \varepsilon)t} - e^{(\sum_{i=1}^{m_0} \pi_i \iota_i - \varepsilon)T_4}\Big)}{\sum_{i=1}^{m_0} \pi_i \iota_i - \varepsilon} \right\}.$$

Using L'Hospital's rule twice gives

$$\liminf_{t\to\infty} \frac{1}{t} \int_0^t \frac{1}{x(s)} \mathrm{d}s \geq \frac{1}{\check{\sigma}} \sum_{i=1}^{m_0} \pi_i \iota_i - \frac{\varepsilon}{\check{\sigma}}.$$

The desired assertion (4.5) follows from the arbitrariness of ε. On the other hand, utilizing the fact $y(t) \leq \varphi(t)$ a.s. one derives from (4.7) that for all $t \geq 0$,

$$\ln x(t) \geq F_2(t) + \hat{\sigma} \int_0^t \frac{1}{x(s)} \mathrm{d}s,$$

where $F_2(t) = \ln x_0 - \check{\mu} \int_0^t \varphi(s)\mathrm{d}s - \int_0^t \big(\delta(r(s)) + \kappa_1^2(r(s))/2\big)\mathrm{d}s + \int_0^t \kappa_1(r(s))\mathrm{d}B_1(s)$. By virtue of $\sum_{i=1}^{m_0} \pi_i\big(\alpha_i - \kappa_2^2(i)/2\big) > 0$ and [11, Theorem 5.1] it follows that

$$\liminf_{t\to\infty} \frac{F_2(t)}{t} \geq -\sum_{i=1}^{m_0} \pi_i \Big(\frac{\check{\mu}}{\hat{\beta}}\Big(\alpha_i - \frac{1}{2}\kappa_2^2(i)\Big) + \delta_i + \frac{1}{2}\kappa_1^2(i)\Big) \qquad \text{a.s.}$$

By the similar technique as (4.5), we obtain

$$\limsup_{t\to\infty} \frac{1}{t} \int_0^t \frac{1}{x(s)} \mathrm{d}s \leq \frac{1}{\hat{\sigma}} \sum_{i=1}^{m_0} \pi_i \Big[\frac{\check{\mu}}{\hat{\beta}}\Big(\alpha_i - \frac{1}{2}\kappa_2^2(i)\Big) + \delta_i + \frac{1}{2}\kappa_1^2(i)\Big] \qquad \text{a.s.}$$

Thus the desired assertion (4.6) holds. □

Obviously, if $\lambda > 0$, $\sum_{i=1}^{m_0} \pi_i\big(\alpha_i - \kappa_2^2(i)/2\big) > 0$ holds. Therefore combining Theorem 4.1 with Lemma 4.1, using the ergodicity of $(x(t), y(t), r(t))$, we yield the upper bound and lower bound of the expectation of $1/x$ with respect to the invariant measure ν^*.

Theorem 4.2. *Assume* $\lambda > 0$. *Then*

$$\frac{1}{\check{\sigma}}\Big[\sum_{i=1}^{m_0} \pi_i\Big(\delta_i + \frac{1}{2}\kappa_1^2(i) - h_i^2\Big)\Big]^+ \leq \sum_{i=1}^{m_0} \int_{\mathbb{R}_+^2} \frac{1}{x} \nu^*(\mathrm{d}x, dy, i),$$

$$\sum_{i=1}^{m_0} \int_{\mathbb{R}_+^2} \frac{1}{x} \nu^*(\mathrm{d}x, dy, i) \leq \frac{1}{\hat{\sigma}} \sum_{i=1}^{m_0} \pi_i \Big[\frac{\check{\mu}}{\hat{\beta}}\Big(\alpha_i - \frac{1}{2}\kappa_2^2(i)\Big) + \delta_i + \frac{1}{2}\kappa_1^2(i)\Big].$$

To end this section we give the upper and lower bounds of the expectation of y with respect to the invariant measure ν^*.

Theorem 4.3. *Assume* $\lambda > 0$ *and* $\min_{i\in\mathbb{S}}\{a_i\} > 0$. *Then*

$$\frac{1}{\check{\beta}}\Big[\sum_{i=1}^{m_0}\pi_i\Big(\alpha_i - \frac{1}{2}\kappa_2^2(i) - \frac{\sigma_i}{a_i}\Big)\Big]^+ \leq \sum_{i=1}^{m_0}\int_{\mathbb{R}_+^2} y\nu^*(\mathrm{d}x, dy, i) \leq \frac{1}{\hat{\beta}}\sum_{i=1}^{m_0}\pi_i\Big(\alpha_i - \frac{1}{2}\kappa_2^2(i)\Big).$$

Proof. By (2.7), we obtain that

$$\ln y(t) \leq F_3(t) - \hat{\beta}\int_0^t y(s)\mathrm{d}s,$$

where $F_3(t) = \ln y_0 + \int_0^t \big(\alpha(r(s)) - \kappa_2^2(r(s))/2\big)\mathrm{d}s + \int_0^t \kappa_2(r(s))\mathrm{d}B_2(s)$. Then in the similar way as Lemma 4.1 was proved, we obtain that

$$\limsup_{t\to\infty}\frac{1}{t}\int_0^t y(s)\mathrm{d}s \leq \frac{1}{\hat{\beta}}\sum_{i=1}^{m_0}\pi_i\Big(\alpha_i - \frac{1}{2}\kappa_2^2(i)\Big) \quad \text{a.s.} \tag{4.9}$$

On the other hand, it follows from (2.7) and the fact that $x(t) \leq \psi(t)$ a.s. that for all $t \geq 0$

$$\ln y(t) \geq F_3(t) - \int_0^t \psi(s)\mathrm{d}s - \check{\beta}\int_0^t y(s)\mathrm{d}s \quad \text{a.s.}$$

Since $\min_{i\in\mathbb{S}} a_i > 0$, it follows from the ergodicity of $(\psi(t), r(t))$ and (4.4) that

$$\lim_{t\to\infty}\frac{1}{t}\Big(F_3(t) - \int_0^t \psi(s)\mathrm{d}s\Big) = \sum_{i=1}^{m_0}\pi_i\Big(\alpha_i - \frac{1}{2}\kappa_2^2(i) - \frac{\sigma_i}{a_i}\Big) \quad \text{a.s.}$$

Using the similar techniques as Lemma 4.1 was proved yields

$$\liminf_{t\to\infty}\frac{1}{t}\int_0^t y(s)\mathrm{d}s \geq \frac{1}{\check{\beta}}\Big[\sum_{i=1}^{m_0}\pi_i\Big(\alpha_i - \frac{1}{2}\kappa_2^2(i) - \frac{\sigma_i}{a_i}\Big)\Big]^+ \quad \text{a.s.} \tag{4.10}$$

Since $\lambda > 0$, we obtain the desired assertion by (4.9), (4.10), Theorem 4.1 and the strong ergodicity theorem. □

5 Discussion and numerical simulations

To start this section, we compare our results with the existing results in literature. Compared with those in [24], our results indicate that the dynamical behaviors of (1.3) are associated with not only random perturbation as [24] but also the regime switching. To be precise, assuming $\mathbb{S} = \{1, 2\}$, we explain the impacts of regime switching by two possibility of all subsystems:

- Subsystems have the same dynamical behaviors. For instance, for subsystems $\alpha_i - \kappa_2^2(i)/2 - \sigma_i/\delta_i < 0$, $\forall i \in \mathbb{S}$, then for model (1.3), $\lambda < 0$. This implies that for all subsystems, TCs become extinct. Then TCs in (1.3) still become extinct, which implies that regime switching do not change the dynamical behaviors.

Table 1: The significance and value of the parameters

Parameter	Real value/unit	Biological significance
n	0.18 /day	the intrinsic growth rate of TCs
b	2.0×10^{-9} /day	the reciprocal of environmental capacity of TCs
s	1.3×10^4 cells/day	the normal rate of inflow into the tumor site for ECs
d	0.0412 /day	the elimination rate of ECs due to destruction and migration
g	2.019×10^7 cells	the coefficient of response functional to TCs of ECs
q	0.06749 /day	the coefficient of response functional to TCs of ECs
r_1	2.422×10^{-10} /day×cells	the elimination rate of ECs due to binding of ECs to TCs
r_2	1.101×10^{-7} day×cells	the elimination rate of TCs due to binding of ECs to TCs
E_0	10^6 cells	the order of magnitude scales for ECs
T_0	10^6 cells	the order of magnitude scales for TCs

- Subsystems have different dynamical behaviors. For example, $\alpha_1 - \kappa_2^2(1)/2 - \sigma_1/\delta_1 > 0$, $\alpha_2 - \kappa_2^2(2)/2 - \sigma_2/\delta_2 < 0$, in other words, TCs in (5.1) are permanent while TCs in (5.3) become extinct. In this case, if $\lambda < 0$, then the TCs in (1.3) become extinct; if $\lambda > 0$, then the TCs in (1.3) are permanent. Due to the representation of λ, the dynamical behaviors of (1.3) in this case essentially depend on the stationary distribution of Markov chain.

In the following, two examples with $\mathbb{S} = \{1, 2\}$ and $\mathbb{S} = \{1, 2, 3\}$ are provided to illustrate the above conclusions, where the data is mainly selected from [10] and [12].

Example 5.1. In this example, we firstly discuss the tumor-immune model in environment 1

$$\begin{cases} \mathrm{d}x(t) = & \Big(\sigma + \dfrac{\rho_1 x(t)y(t)}{\eta + y(t)} - \mu x(t)y(t) - \delta x(t)\Big)\mathrm{d}t + \kappa_1(1)x(t)\mathrm{d}B_1(t), \\ \mathrm{d}y(t) = & \big(\alpha y(t) - \beta y^2(t) - x(t)y(t)\big)\mathrm{d}t + \kappa_2(1)y(t)\mathrm{d}B_2(t), \end{cases} \tag{5.1}$$

where $\kappa_1(1) = 0.2,\ \kappa_2(1) = 0.25$, and $x(0) = 5,\ y(0) = 50$. Table 1 shows the parameters of the dimensional system in [10]. Using the nondimensionalization method [10, p.304], we obtain the nondimensional parameters for (5.1) from the data in Table 1

$$\begin{array}{lll} \sigma = \frac{s}{r_2 E_0 T_0} = 0.1181, & \rho_1 = \frac{q}{r_2 T_0} = 0.613, & \mu = \frac{r_1}{r_2} = 0.00311, \\ \delta = \frac{d}{r_2 T_0} = 0.3743, & \alpha = \frac{n}{r_2 T_0} = 1.636, & \eta = \frac{g}{T_0} = 20.19, \\ \quad \text{and} & \beta = \frac{nb}{r_2} = 3.272 \times 10^{-3}. & \end{array} \tag{5.2}$$

Then we compute $\alpha - \kappa_2^2(1)/2 - \sigma/\delta = 1.2892 > 0$. By [24], ECs and TCs in (5.1) are permanent and have a unique invariant measure. Figure 1 plots the sample paths of $x(t)$, $y(t)$ for (5.1). Figure 2 predicts the empirical density functions for (5.1) using 1000 sample points and time $t = 200$.

We then discuss the tumor-immune model in environment 2

$$\begin{cases} \mathrm{d}x(t) = & \Big(\sigma + \dfrac{\rho_2 x(t)y(t)}{\eta + y(t)} - \mu x(t)y(t) - \delta x(t)\Big)\mathrm{d}t + \kappa_1(2)x(t)\mathrm{d}B_1(t), \\ \mathrm{d}y(t) = & \big(\alpha y(t) - \beta y^2(t) - x(t)y(t)\big)\mathrm{d}t + \kappa_2(2)y(t)\mathrm{d}B_2(t). \end{cases} \tag{5.3}$$

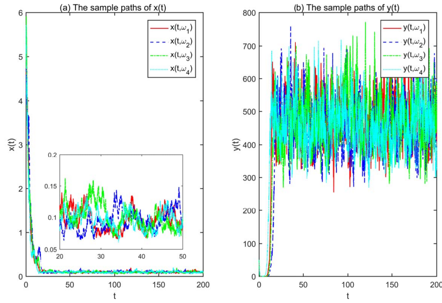

Figure 1: Sample paths of (5.1).

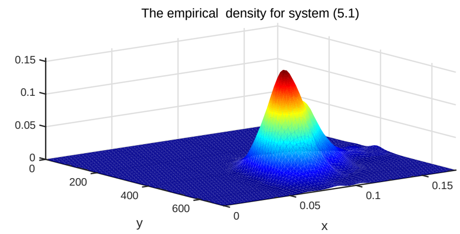

Figure 2: The empirical density of (5.1).

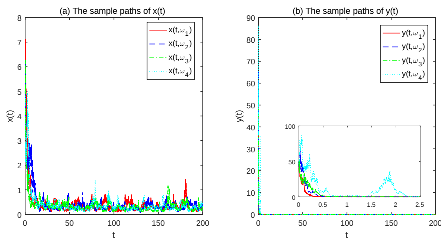

Figure 3: Sample paths of (5.3).

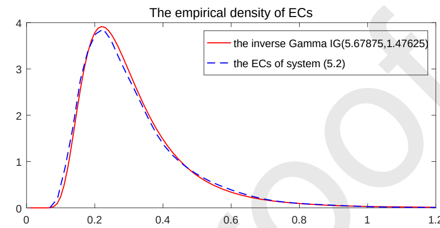

Figure 4: The empirical density of ECs of (5.3).

The binding rate of EC to TC will be increased when the immune response of EC to TC is strong. Let $\rho_2 = 0.712$, $\kappa_1(2) = 0.4$, $\kappa_2(2) = 2$, and $x(0) = 5,\ y(0) = 50$. Compute $\alpha - \kappa_2^2(2)/2 - \sigma/\delta = -0.6795 < 0$. By [24], TCs become extinct while the measures of ECs converge to the unique invariant one corresponding to the inverse gamma distribution $IG(5.67875, 1.47625)$. Figure 3 plots the sample paths of $x(t)$, $y(t)$ for (5.3). Figure 3 predicts the empirical density functions of the ECs of (5.3) using 1000 sample points and time $t = 200$.

Due to the random environmental change, tumor-immune system switches between two habitat (5.1) and (5.3). Thus we regard model (1.3) as the results of Markovian switching between (5.1) and (5.3) with the initial data $x_0 = 5$, $y_0 = 50$, $r_0 = 1$, where the Markov chain $r(t)$ takes values in $\mathbb{S} = \{1, 2\}$. To proceed, we discuss model (1.3) by two cases.

Case 5.1.1. Let the generator of Markov chain $r(t)$

$$\Gamma = \begin{pmatrix} -3 & 3 \\ 1 & -1 \end{pmatrix}.$$

Then its stationary distribution is $\pi = (\pi_1, \pi_2) = \left(\frac{1}{4}, \frac{3}{4}\right)$. Compute $\lambda = \sum_{i=1}^{2} \pi_i\big(\alpha - \kappa_2^2(i)/2 - \sigma/\delta\big) = -0.1873 < 0$. Theorem 3.1 reveals that TCs become extinct while the measures of ECs $x(t)$ converges to the unique invariant one. Moreover, Lemma 2.1 tells us that $\sum_{i=1}^{2} \int_0^\infty x\nu(\mathrm{d}x, i) = \sum_{i=1}^{2} \pi_i \sigma/\delta = 0.3155$.

Figure 5 plots the sample paths of $r(t)$, $x(t)$ and $y(t)$ for (1.3). Figure 6 predicts the empirical density functions of the ECs of (1.3) using 1000 sample points and time $t = 200$.

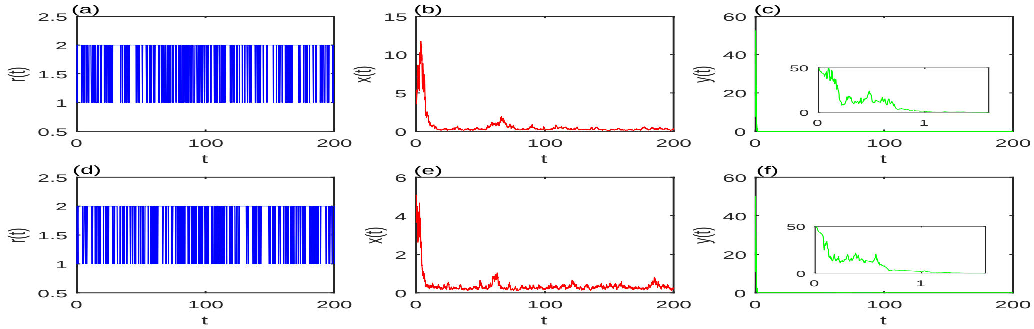

Figure 5: Case 5.1.1. For (1.3) figure (a), (b) and (c) plot a sample path of $r(t)$, $x(t)$ and $y(t)$, respectively; figure (d), (e) and (f) plot another sample path of $r(t)$, $x(t)$ and $y(t)$, respectively.

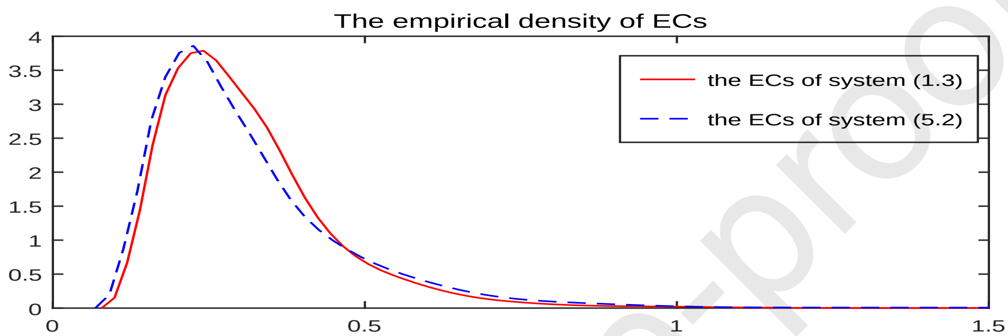

Figure 6: Case 5.1.1. The empirical density functions of ECs $x(t)$: solid line for (1.3); dashed line for (5.3).

Case 5.1.2. Consider the generator of Markov chain $r(t)$

$$\Gamma = \begin{pmatrix} -1 & 1 \\ 2 & -2 \end{pmatrix}.$$

Then the unique stationary distribution is $\pi = (\pi_1, \pi_2) = \left(\frac{2}{3}, \frac{1}{3}\right)$. Compute $\lambda = \sum_{i=1}^{2} \pi_i\big(\alpha - \kappa_2^2(i)/2 - \sigma/\delta\big) = 0.633 > 0$. From Theorem 4.1, we know that (1.3) owns a unique invariant measure ν^* on $\mathbb{R}_+^{2,o} \times \mathbb{S}$ which implies TCs and ECs are permanent. Figure 7 plots the sample paths of $r(t)$, $x(t)$ and $y(t)$ for (1.3) which verifies the permanence of TCs and ECs. To further describe the invariant probability measure ν^*, Figure 8 depicts the empirical marginal density function for (1.3) using 1000 sample points and $t = 200$. Obviously, the invariant measure ν^* of (1.3) is different completely from that of (5.1).

We further compute

$$\begin{aligned}
&\breve{\sigma} = \hat{\sigma} = \sigma = 0.1181, \qquad \breve{\beta} = \hat{\beta} = \beta = 3.272 \times 10^{-3}, \qquad \breve{\mu} = \mu = 0.00311,\\
&h_1^2 = [(\sqrt{\rho_1} - \sqrt{\mu\eta}) \vee 0]^2 = 0.2834, \qquad h_2^2 = [(\sqrt{\rho_2} - \sqrt{\mu\eta}) \vee 0]^2 = 0.3519,\\
&a_1 = \delta - h_1^2 = 0.0909 > 0, \qquad a_2 = \delta - h_2^2 = 0.0224 > 0,
\end{aligned}$$

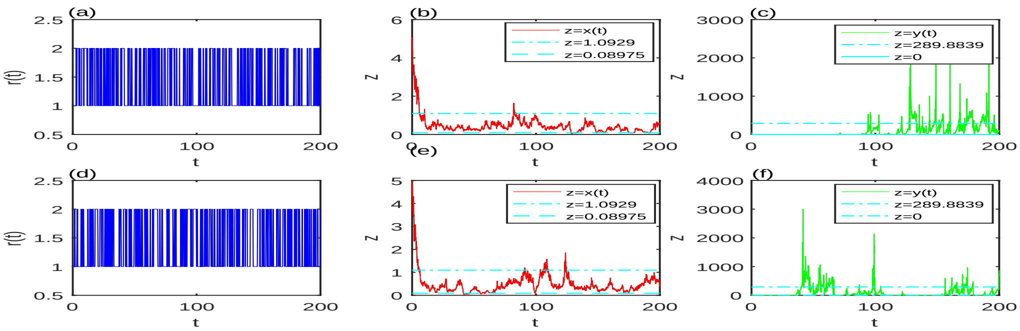

Figure 7: Case 5.1.2. For (1.3) solid lines in figure (a), (b) and (c) plot a sample path of $r(t)$, $x(t)$ and $y(t)$, respectively; solid lines in figure (d), (e) and (f) plot another sample path of $r(t)$, $x(t)$ and $y(t)$, respectively. Other lines are reference lines.

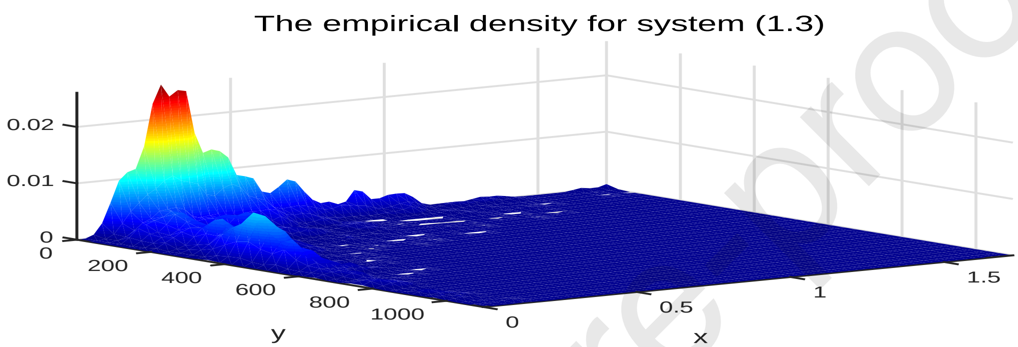

Figure 8: Case 5.1.2. The empirical density of the stochastic tumor-immune model (1.3).

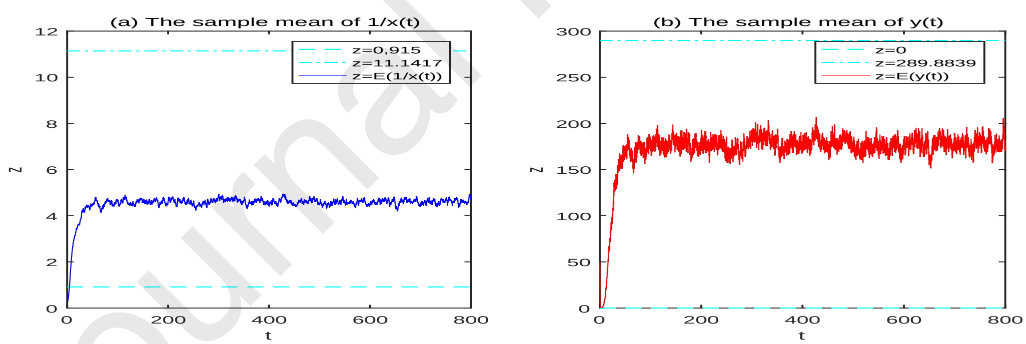

Figure 9: Case 5.1.2. For (1.3) solid lines in figure (a) and figure (b) depicts the sample mean of $1/x(t)$ and $y(t)$, respectively; the other lines are reference lines.

$$\frac{1}{\check{\sigma}}\Big[\sum_{i=1}^{2}\pi_i\Big(\delta+\frac{1}{2}\kappa_1^2(i)-h_i^2\Big)\Big]^+=0.915,$$

$$\frac{1}{\hat{\sigma}}\sum_{i=1}^{2}\pi_i\Big[\frac{\check{\mu}}{\hat{\beta}}\Big(\alpha-\frac{1}{2}\kappa_2^2(i)\Big)+\delta+\frac{1}{2}\kappa_1^2(i)\Big]=11.1417,$$

$$\frac{1}{\breve{\beta}}\Big[\sum_{i=1}^{2}\pi_i\Big(\alpha-\frac{1}{2}\kappa_2^2(i)-\frac{\sigma}{a_i}\Big)\Big]^+=0,\quad \frac{1}{\hat{\beta}}\sum_{i=1}^{2}\pi_i\Big(\alpha-\frac{1}{2}\kappa_2^2(i)\Big)=289.8839.$$

Using Theorem 4.2 and Theorem 4.3 yields the upper and lower bounds of the expectations of TCs and ECs with respect to the invariant probability measures ν^*

$$0.915\le\sum_{i\in\mathbb{S}}\int_0^\infty\frac{1}{x}\nu^*(\mathrm{d}x,dy,i)\le 11.1417,\quad 0\le\sum_{i\in\mathbb{S}}\int_0^\infty y\nu^*(\mathrm{d}x,dy,i)\le 289.8839.$$

Figure 9 predicts the expectation of $1/x(t)$ and $y(t)$ with respect to the invariant measure ν^* by the sample mean of $1/x(t)$ and $y(t)$ for 1000 sample points and $t\in[0,200]$. The ergodic theorem tells us that the paths of $1/x(t)$ and $y(t)$ in (1.3) are almost surely between the corresponding reference lines of Figure 9 in time average.

Example 5.2. Let $r(t)$ take values in $\mathbb{S}=\{1,2,3\}$. Model (1.3) is regarded as the result of Markovian switching between (5.1), (5.3) and

$$\begin{cases}\mathrm{d}x(t) &= \Big(\sigma+\dfrac{\rho_3 x(t)y(t)}{\eta+y(t)}-\mu x(t)y(t)-\delta x(t)\Big)\mathrm{d}t+\kappa_1(3)x(t)\mathrm{d}B_1(t),\\ \mathrm{d}y(t) &= \big(\alpha y(t)-\beta y^2(t)-x(t)y(t)\big)\mathrm{d}t+\kappa_2(3)y(t)\mathrm{d}B_2(t),\end{cases}\tag{5.4}$$

where $\rho_3=1.131$, $\kappa_1(3)=0.2$, $\kappa_2(3)=2$, and $x(0)=5$, $y(0)=50$. Compute $\alpha-\kappa_2^2(3)/2-\sigma/\delta=-0.6795<0$. Then one observes that for (5.4), TCs become extinct while the measures of ECs converge to the unique invariant one corresponding to the inverse gamma distribution $IG(19.715,5.905)$.

Figure 10 plots the sample paths of $x(t)$, $y(t)$ for (5.4). Figure 11 predicts the empirical density

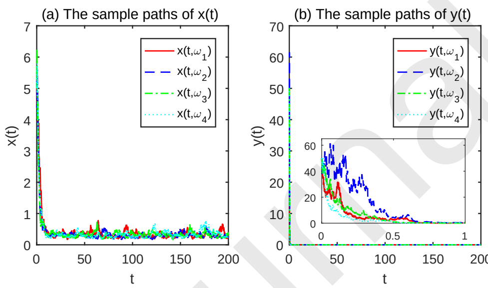

Figure 10: Sample paths of (5.4).

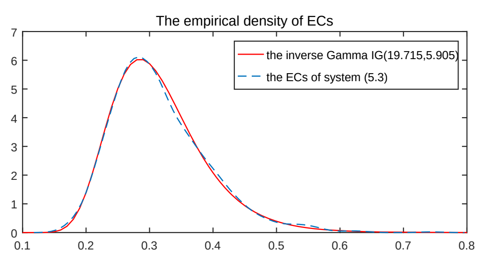

Figure 11: The empirical density of ECs of (5.4).

function of the ECs of (5.4) using 1000 sample points and time $t=200$. Next, we discuss model (1.3) by two cases.

Case 5.2.1. Let the generator of Markov chain $r(t)$

$$\Gamma=\begin{pmatrix}-5 & 2 & 3\\ 1 & -1 & 0\\ 3 & 0 & -3\end{pmatrix}.$$

Then the unique stationary distribution is $\pi = (\pi_1, \pi_2, \pi_3) = \left(\frac{1}{4}, \frac{1}{2}, \frac{1}{4}\right)$. Compute $\lambda = \sum_{i=1}^{3} \pi_i\big(\alpha - \kappa_2^2(i)/2 - \sigma/\delta\big) = -0.1873 < 0$. Using Theorem 3.1 yields that TCs are exponentially decreasing, see Figure 12 for the sample paths of $r(t)$, $x(t)$ and $y(t)$. Meanwhile, Theorem 3.1 reveals that the measures of ECs $x(t)$ converge to the unique invariant measure ν. Figure 13 plots the empirical density functions of the ECs of (5.3), (5.4) and (1.3), respectively, for 1000 sample points and $t = 200$. Obviously, the invariant measure ν of ECs of (1.3) is different completely from those of (5.3) and (5.4).

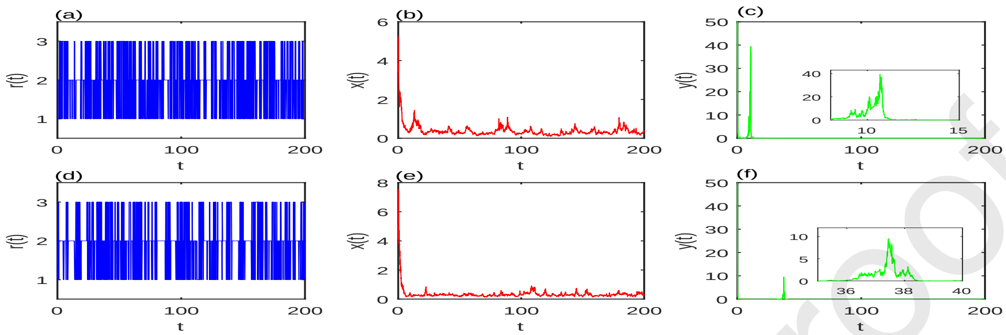

Figure 12: Case 5.2.1. For (1.3) figure (a), (b) and (c) plot a sample path of $r(t)$, $x(t)$ and $y(t)$, respectively; figure (d), (e) and (f) plot another sample path of $r(t)$, $x(t)$ and $y(t)$, respectively.

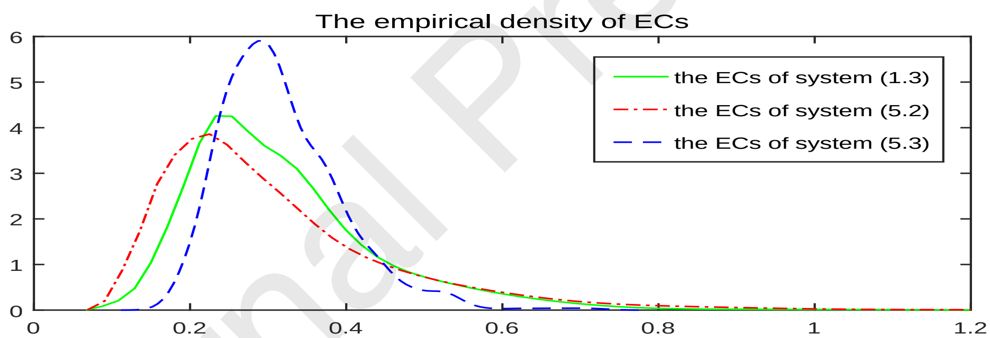

Figure 13: Case 5.2.1. For (1.3) the empirical density function of ECs $x(t)$: The dashed line for (5.3); the dashed-dotted line for (5.4); the solid line for (1.3).

Case 5.2.2. Let the generator of Markov chain $r(t)$

$$\Gamma = \begin{pmatrix} -2 & 1 & 1 \\ 3 & -4 & 1 \\ 1 & 1 & -2 \end{pmatrix}.$$

Then the unique stationary distribution is $\pi = (\pi_1, \pi_2, \pi_3) = \left(\frac{7}{15}, \frac{1}{5}, \frac{1}{3}\right)$. Compute $\lambda = \sum_{i=1}^{2} \pi_i\big(\alpha - \kappa_2^2(i)/2 - \sigma/\delta\big) = 0.2392 > 0$. From Theorem 4.1, we know that (1.3) owns a unique invariant

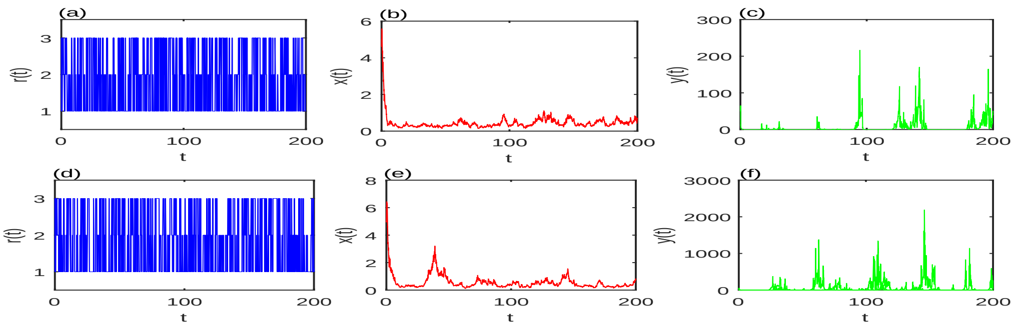

Figure 14: Case 5.2.2. For (1.3) figure (a), (b) and (c) plot a sample path of $r(t)$, $x(t)$ and $y(t)$, respectively; figure (d), (e) and (f) plot another sample path of $r(t)$, $x(t)$ and $y(t)$, respectively.

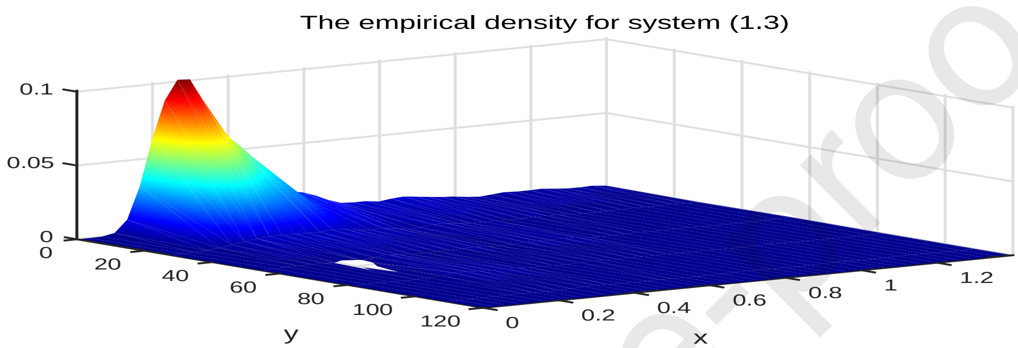

Figure 15: Case 5.2.2. The empirical density of the stochastic tumor-immune model (1.3).

measure ν^* on $\mathbb{R}_+^{2,o} \times \mathbb{S}$. Thus TCs and ECs in (1.3) are permanent, see Figure 14 for the sample paths of $r(t)$, $x(t)$ and $y(t)$. To describe the invariant measures of (1.3), Figure 15 plots the empirical density function for (1.3) using 1000 sample points and time $t = 200$.

6 Conclusions

This paper studies the long-time dynamical behaviors of the tumor-immune system in a stochastic environment. It is revealed how the interaction of different types of environmental noise impact the dynamical behaviors of ECs and TCs. Firstly, by the analysis of the dynamic of (1.3) on the boundary, the threshold λ is preestimated. Next, by constructing several appropriate comparison equations, making use of the properties of the corresponding diffusion processes and occupation measures, we obtain that if $\lambda < 0$, the TCs will die out, while if $\lambda > 0$, the system (1.3) is permanent in the sense of the existence of the invariant probability measure supported on $\mathbb{R}_+^{2,o} \times \mathbb{S}$. Moreover, as (1.3) is permanent, the lower bound and the upper bound of the expectation with respect to the invariant measure are obtained. Finally, our results are illustrated by two numerical examples. Overall, the fact is revealed that both the intensity of the white noise of TCs and the stationary distribution of Markov chain play the critical roles in the elimination of TCs. It is worth noting that the dynamical behaviors of the overall system may be different completely from those of subsystems, which depends on the stationary distribution of the Markov chain closely.

Remark 6.1. *Through our study, the threshold λ is the key to determine the extinction or permanence of TCs. Obviously, the value λ does not depend on the parameters ρ_i, η_i, μ_i and β_i. We notice that ρ_i and η_i are the parameters of the rate at which ECs accumulate due to the presence of TCs, μ_i describes the elimination rates of ECs due to binding of ECs to TCs, $\beta_i (i \in \mathbb{S})$ is the parameter of the maximal carrying capacity of biological environment of TCs. It is reasonable that they do not affect the determination of the extinction of TCs. But when the system* (1.3) *is permanent, as we proved in Theorem 4.2 and 4.3, they do affect the lower bound and the upper bound of the expectation of $1/x$ and y with respect to the underlying invariant measure ν^*.*

References

[1] Y. Deng, M. Liu, Analysis of a stochastic tumor-immune model with regime switching and impulsive perturbations, Appl. Math. Model. 78 (2020) 482-504.

[2] L. Derbel, Analysis of a new model for tumor-immune system competition including long-time scale effects, Math. Models Methods Appl. Sci. 14(11) (2004) 1657-1681.

[3] S.N. Evans, A. Hening, S.J. Schreiber, Protected polymorphisms and evolutionary stability of patch-selection strategies in stochastic environments, J. Math. Biol. 71(2) (2015) 325-359.

[4] D. Greenhalgh, Y. Liang, X. Mao, Modelling the effect of telegraph noise in the SIRS epidemic model using Markovian switching, Phys. A 462 (2016) 684-704.

[5] A. Hening, D.H. Nguyen, Coexistence and extinction for stochastic Kolmogorov systems, Ann. Appl. Probab. 28(3) (2018) 1893-1942.

[6] K. Khan, Some mathematical models and survival curves for growth and decay of tumour, Punjab Univ. J. Math. (Lahore) 35 (2002) 15-41.

[7] R. Khasminskii, Stochastic Stability of Differential Equations, 2nd ed., Springer, Heidelberg, 2012.

[8] R. Khasminskii, C. Zhu, G. Yin, Stability of regime-switching diffusions, Stochastic Process. Appl. 117(8) (2007) 1037-1051.

[9] H. Kushner, Approximation and Weak Convergence Methods for Random Processes, with Applications to Stochastic Systems Theory, Vol.6, MIT Press, 1984.

[10] V.A. Kuznetsov, I.A. Makalkin, M.A. Taylor, A.S. Perelson, Nonlinear dynamics of immunogenic tumors: Parameter estimation and global bifurcation analysis, Bull. Math. Biol. 56(2) (1994) 295-321.

[11] X. Li, A. Gray, D. Jiang, X. Mao, Sufficient and necessary conditions of stochastic permanence and extinction for stochastic logistic populations under regime switching, J. Math. Anal. Appl. 376(1) (2011) 11-28.

[12] X. Li, G. Song, Y. Xia, C. Yuan, Dynamical behaviors of the tumor-immune system in a stochastic environment, SIAM J. Appl. Math. 79(6) (2019) 2193-2217.

[13] X. Li, G. Yin, Logistic models with regime switching: permanence and ergodicity, J. Math. Anal. Appl. 441(2) (2016) 593-611.

[14] X. Liu, Q. Li, J. Pan, A deterministic and stochastic model for the system dynamics of tumor-immune responses to chemotherapy, Phys. A 500 (2018) 162-176.

[15] Q. Luo, X. Mao, Stochastic population dynamics under regime switching, J. Math. Anal. Appl. 334(1) (2007) 69-84.

[16] K.J. Mahasa, R. Ouifki, A. Eladdadi, L.G. De Pillis, Mathematical model of tumor-immune surveillance, J. Theoret. Biol. 404 (2016) 312-330.

[17] D.G. Mallet, L.G. De Pillis, A cellular automata model of tumor-immune system interactions, J. Theoret. Biol. 239(3) (2006) 334-350.

[18] X. Mao, C. Yuan, Stochastic Differential Equations with Markovian Switching, Imperial College Press, London, 2006.

[19] S.P. Meyn, R.L. Tweedie, Stability of markovian processes II: continuous-time processes and sampled chains, Adv. Appl. Probab. 25(3) (1993) 487-517.

[20] C. Oana, O. Dumitru, C. Riccardo, Review of stochastic stability and analysis tumor-immune systems, Curr. Bioinform. 8(4) (2013) 390-400.

[21] A. Shiryaev, Probability, 2nd ed, Springer-Verlag, New York, 1996.

[22] Y. Takeuchi, N.H. Du, N.T. Hieu, K. Sato, Evolution of predator-prey systems described by a Lotka-Volterra equation under random environment, J. Math. Anal. Appl. 323(2) (2006) 938-957.

[23] T. Tuong, N.N. Nguyen, Characterization of long-term behavior of stochastic NP ecological model under regime switching, Commun. Nonlinear Sci. Numer. Simul. 93 (2021) 105497, 10 pp.

[24] T. Tuong, N.N. Nguyen, G. Yin, Longtime behavior of a class of stochastic tumor-immune systems, Systems Control Lett. 146 (2020) 104806, 8 pp.

[25] M. Villasana, A. Radunskaya, A delay differential equation model for tumor growth, J. Math. Biol. 47(3) (2003) 270-294.

[26] G. Yin, C. Zhu, Hybrid Switching Diffusions: Properties and Applications, Springer, New York, 2009.

[27] X. Zhang, D. Jiang, A. Alsaedi, T. Hayat, Stationary distribution of stochastic SIS epidemic model with vaccination under regime switching, Appl. Math. Lett. 59 (2016) 87-93.

[28] Y. Zhu, K. Wang, Y. Ren, Dynamics of a mean-reverting stochastic volatility equation with regime switching, Commun. Nonlinear Sci. Numer. Simul. 83 (2020) 105110, 8 pp.

[29] C. Zhu, G. Yin, Asymptotic properties of hybrid diffusion systems, SIAM J. Control Optim. 46(4) (2007) 1155-1179.

[30] C. Zhu, G. Yin, On strong Feller, recurrence, and weak stabilization of regime-switching diffusions, SIAM J. Control Optim. 48(3) (2009) 2003-2031.