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Longtime behavior of a class of stochastic tumor-immune systems

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ABSTRACT

This paper focuses on a class of stochastic systems describing tumor-immune dynamics. The underlying systems are given by stochastic differential equations. Our study concentrates on longtime behavior. A sharp threshold-type condition is obtained, which characterizes the dynamic systems, and pinpoints sufficient and nearly necessary conditions for persistence and extinction. Examples and numerical results are provided to illustrate our findings.

1. Introduction

Because of the pressing need for understanding cancer biology and the development of proper therapeutic treatments, much effort has been devoted to modeling and analyzing mathematical models of tumor-immune systems and their dynamical behaviors; see e.g., [1–6]. One of the earliest mathematical models for nonlinear dynamics of immunogenic tumors was [2] that simulates the interaction of the cytotoxic T lymphocyte with immunogenic tumor cells and considers the inactivation of effector cells as well as the penetration of effector cells into tumor cells. The dynamics are described by a system of differential equations as follow:

$$\begin{cases} \dfrac{dX(t)}{dt} = & \sigma + \dfrac{\rho X(t)Y(t)}{\eta + Y(t)} - \mu X(t)Y(t) - \delta X(t), \\ \dfrac{dY(t)}{dt} = & Y(t)\left(\alpha - \beta Y(t) - X(t)\right), \end{cases} \tag{1.1}$$

where $X(t)$, $Y(t)$ represent dimensionless local concentration of effector cells (ECs) and tumor cells (TCs), respectively, σ is the baseline EC "source rate", δ is the EC "death rate" or the culling rate of ECs, and α is the intrinsic growth rate of TCs; see [2] for more discussion on the system setup and motivations from a biological point of view.

As is widely recognized now, it is important to take the impact of random noises into consideration. When the stochastic variation of the environment mainly affects δ (the culling rate of ECs) and α (the intrinsic growth rate of TCs) in that $\delta dt \to \delta dt + \sigma_1 dW_1(t)$, and $\alpha dt \to \alpha dt + \sigma_2 dW_2(t)$, system (1.1) becomes

$$\begin{cases} dX(t) = & \left(\sigma + \dfrac{\rho X(t)Y(t)}{\eta + Y(t)} - \mu X(t)Y(t) - \delta X(t)\right) dt \\ & +\sigma_1 X(t) dW_1(t), \\ dY(t) = & Y(t)\left(\alpha - \beta Y(t) - X(t)\right) dt + \sigma_2 Y(t) dW_2(t), \end{cases} \tag{1.2}$$

where $W_1(t)$, $W_2(t)$ are two independent standard Brownian motions, and σ_1, σ_2 are the intensities of the noises.

Eq. (1.2) is often referred to as the stochastic Kuznetsov–Taylor tumor-immune model [2,4,5]. In the past few years, much attention and effort were devoted to studying stochastic models for cancer cells. For example, the stochastic stability for a stochastic virus-tumor-immune model was studied in [7]. Oana, Dumitru, and Riccardo in [5] considered the stochastic stability of the stochastic Kuznetsov–Taylor model near the equilibria. The tumor growth model describing the interaction and competition between the TCs based on the Michaelis–Menten enzyme kinetics was analyzed and the threshold conditions for extinction, weak persistence, and stochastic persistence of TCs were obtained in [8]. Most recently, the asymptotic behaviors including the stochastic ultimately boundedness in moment, the limit distribution, as well as the ergodicity have been investigated in [4].

In this paper, our main aim is to characterize the longtime behavior of the stochastic tumor-immune model (1.2). The novelty and main contributions of this work are follows.

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- Inspired by the works [9,10] (see also [11–13]), a threshold $\lambda := \alpha - \frac{\sigma_2^2}{2} - \frac{\sigma}{\delta}$ is introduced by taking a dynamical system point of view. This enables us to characterize the longtime behavior of tumor-immune systems without proposing complex conditions on the coefficients. Such methodology and idea can be also used to determine systematically the thresholds characterizing the longtime behavior of many biological models.
- We obtain a sharp result on the threshold given by a quantity λ without assuming additional conditions on the coefficients of the system and cover untreated cases in [4]. In particular, we prove that if $\lambda < 0$ then $Y(t)$ tends to 0 with exponential rate while if $\lambda > 0$, the existence and uniqueness of invariant measure concentrated on $\{(x, y) \in \mathbb{R}^2 : x, y > 0\}$ is guaranteed. The proofs of our results are obtained by using stochastic analysis (stochastic Lyapunov analysis, comparison principle for SDEs, etc.), theory of stochastic processes (recurrence and transient properties of non-degenerate diffusion processes), and certain occupation measures. Combining these tools enables us to reveal the features of stochastic system (1.2).
- Numerical experiments are conducted to illustrate our findings. In addition, some interesting examples are given to show that small noise can be used to stabilize the deterministic systems. We demonstrate that the stochastic systems can escape from unstable points and converge (or jump) to stable points although the deterministic system may be stuck at these unstable points.

In term of biological interpretation, the results obtained in this paper enable us to understand the dynamics of the tumor cell and impacts of the noises on the dynamics of the system, which also give us insights on how to eliminate tumor cells and to improve the treatment of cancer. By looking at the threshold $\lambda = \alpha - \frac{\sigma_2^2}{2} - \frac{\sigma}{\delta}$, one can see from our results that in order to control the tumor, we can reduce λ aiming to make it negative. Reducing the intrinsic growth rate α of tumor cells or decreasing the culling rate δ of effector cells or increasing effector cells source rate σ are some solutions. Surprisingly, the system changes only the intensity of fluctuation of the dynamics of tumor cell by injecting noise perturbations to the dynamics of effector cells, but does not affect the persistence and extinction of the tumor cells since λ does not depend on the intensity σ_1.

The rest of this paper is organized as follows. Section 2 states our main results, whose proofs are postponed to Section 4, in which the threshold is determined from a dynamical system point of view, which can generalize to many other models. Section 3 is devoted to discussions and simulations. Finally, Section 5 concludes the paper.

2. Main results

Let $(\Omega, \mathcal{F}, \{\mathcal{F}_t\}_{t\geq 0}, \mathbb{P})$ be a complete filtered probability space. $\mathbb{P}_{x,y}$ and $\mathbb{E}_{x,y}$ denote the probability and expectation corresponding to the initial condition $X(0) = x$, $Y(0) = y$, respectively. Moreover, throughout the paper, we denote $\mathbb{R}^2_+ := \{(x, y) \in \mathbb{R}^2 : x \geq 0, y \geq 0\}$, $\mathbb{R}^{2,\circ}_+ := \{(x, y) \in \mathbb{R}^2 : x > 0, y > 0\}$, and $\mathbb{R}^{2,*}_+ := \{(x, y) \in \mathbb{R}^2 : x \geq 0, y > 0\}$, respectively. We begin with the following theorem on the existence and uniqueness of the solution of (1.2) and a complete characterization of its positivity.

Theorem 2.1. *For any initial data $(x, y) \in \mathbb{R}^2_+$, there exists a global solution $(X(t), Y(t))$ to (1.2) such that $\mathbb{P}_{x,y}\{(X(t), Y(t)) \in \mathbb{R}^2_+,\ \forall t \geq 0\} = 1$. Moreover, $\mathbb{P}_{x,0}\{Y(t) = 0,\ \forall t \geq 0\} = 1$ for all $x \geq 0$, and $\mathbb{P}_{x,y}\{(X(t), Y(t)) \in \mathbb{R}^{2,\circ}_+,\ \forall t > 0\} = 1$, for any $(x, y) \in \mathbb{R}^{2,*}_+$. In addition, the solution process $(X(t), Y(t))$ is a Feller-strong Markov process with transition probability denoted by $P(t, x, y, \cdot)$.*

Moment boundedness of the solution We proceed to investigate the moment boundedness of the nonnegative solutions. It also implies the compactness properties of the solution in finite time. Namely, for any initial values in a compact set, the solution still remains in a compact set with large probability in finite time.

Proposition 2.1. *For any $q > 0$ sufficiently small, there exist $C_q > 0$ and $D_q > 0$ such that*

$$\mathbb{E}_{x,y}\left(X^{1+q}(t) + Y^2(t)\right) \leq \frac{(1 + x^{1+q} + y^2)}{e^{D_q t}} + \frac{C_q}{D_q}, \quad \forall t \geq 0. \tag{2.1}$$

Moreover, for any $H, \varepsilon, T > 0$, there exists an $M_{H,\varepsilon,T} > 0$ such that

$$\mathbb{P}_{x,y}\left\{\sup_{t\in[0,T]} \{X(t) + Y(t)\} \leq M_{H,\varepsilon,T}\right\} \geq 1 - \varepsilon, \quad \forall (x, y) \in [0, H]^2. \tag{2.2}$$

The proof of the first assertion above can be found in [4, Section 3], whereas the second one follows from (2.1) (see e.g., [12, Lemma 2.1]).

Threshold of permanence and extinction. Consider the first equation of (1.2) on the boundary (i.e., the case when $Y(t) \equiv 0$), it becomes

$$d\widetilde{X}(t) = \left(\sigma - \delta\widetilde{X}(t)\right) dt + \sigma_1\widetilde{X}(t)dW_1(t). \tag{2.3}$$

In [4], we have that $\widetilde{X}(t)$ has a unique invariant measure $\boldsymbol{\nu}_0$ on $[0, \infty)$ and $\boldsymbol{\nu}_0((0, \infty)) = 1$. Thus, $\boldsymbol{\nu}_0 \times \boldsymbol{\delta}$ is the unique invariant measure on the boundary $[0, \infty) \times \{0\}$ of $(X(t), Y(t))$, where $\boldsymbol{\delta}$ is the Dirac measure at 0. In fact, by solving the Fokker–Planck equation, the unique invariant measure $\boldsymbol{\nu}_0$ has density f^* given by

$$f^*(x) = \frac{b^a}{\Gamma(a)} x^{-(a+1)} e^{-\frac{b}{x}},\ x > 0, \tag{2.4}$$

where $a = \dfrac{2\delta + \sigma_1^2}{\sigma_1^2}$, $b = \dfrac{2\sigma}{\sigma_1^2}$ and $\Gamma(\cdot)$ is Gamma function. Inspired by the works [9,10], our idea is to determine whether $Y(t)$ converges to 0 or not by considering the Lyapunov exponent $\limsup_{t\to\infty} \dfrac{\ln Y(t)}{t}$ when $Y(t)$ is small. Using Itô's formula, we get

$$\begin{aligned}\frac{\ln Y(t)}{t} = \frac{\ln y}{t} + \frac{\sigma_2 W_2(t)}{t} + \left(\alpha - \frac{\sigma_2^2}{2}\right) \\ - \frac{1}{t}\int_0^t \Big(\beta Y(u) + X(u)\Big) du.\end{aligned} \tag{2.5}$$

Intuitively, $\limsup_{t\to\infty} \frac{\ln Y(t)}{t} < 0$ implies $\lim_{t\to\infty} Y(t) = 0$ and when $Y(t)$ is small then $X(t)$ is close to $\widetilde{X}(t)$ and therefore, when t is sufficiently large we have

$$\frac{1}{t}\int_0^t \Big(\beta Y(u) + X(u)\Big) du \approx \frac{1}{t}\int_0^t \widetilde{X}(u)du.$$

By the ergodic theorem [14, Theorem 3.16, p.46] for $\widetilde{X}(t)$, and (2.5), we obtain that the Lyapunov exponent of $Y(t)$ is approximated by

$$\alpha - \frac{\sigma_2^2}{2} - \int_0^\infty x f^*(x)dx = \alpha - \frac{\sigma_2^2}{2} - \frac{\sigma}{\delta}. \tag{2.6}$$

Therefore, we define

$$\lambda := \alpha - \frac{\sigma_2^2}{2} - \frac{\sigma}{\delta}. \tag{2.7}$$

Roughly, if $\lambda > 0$, whenever $Y(t)$ is small enough, $\limsup_{t\to\infty} \frac{\ln Y(t)}{t} \approx \lambda > 0$ and it leads to $Y(t)$ cannot be very small for a long

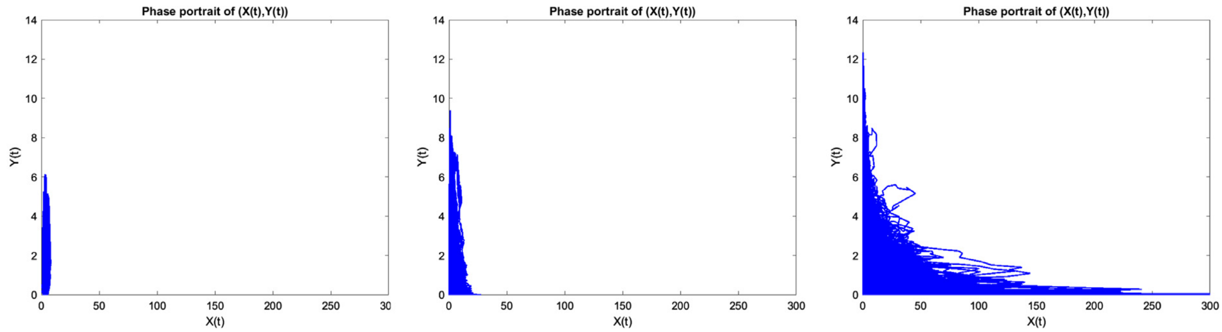

Fig. 1. Phase portraits of $(X(t), Y(t))$ when $\sigma_1 = 0.2$, $\sigma_1 = 1$, $\sigma_1 = 6$, respectively.

time. Conversely, when $\lambda < 0$, if the solution starts from a initial point (x, y), where y is sufficiently small, then $\limsup_{t\to\infty} \frac{\ln Y(t)}{t} \approx \lambda < 0$ and which implies $Y(t) \to 0$. However, the detailed proofs are very technical and complex and need to be carefully done.

Characterization of the longtime behavior. The following theorem presents our main results, in which we prove that the threshold λ defined above enables us to characterize the permanence and extinction of the longtime behavior of stochastic nonlinear tumor-immune system (1.2). There is only the critical case $\lambda = 0$ left. If one equips the space of parameters in (1.2) with the Lebesgue measure, then the set $\{\lambda = 0\}$ has Lebesgue measure 0. In real applications, this case happens rarely. Thus, our results can be applied to many applications because they cover most of the possible cases of λ.

Theorem 2.2. *The longtime behavior of the system is characterized by the threshold λ defined by (2.7).*

1. *If $\lambda > 0$, the system is permanent in the sense that there exists an invariant measure $\boldsymbol{\nu}^*$ of $(X(t), Y(t))$ on $\mathbb{R}^{2,\circ}_+$. Moreover, the transition probability converges to the invariant measure in total variation, i.e.,*

$$\lim_{t\to\infty} \|P(t, x, y, \cdot) - \boldsymbol{\nu}^*(\cdot)\|_{TV} = 0,\ \forall (x, y) \in \mathbb{R}^{2,*}_+. \tag{2.8}$$

2. *If $\lambda < 0$, then regardless of the initial values in $\mathbb{R}^2_+$, the tumor cells go extinct exponentially fast (with the rate λ) almost surely, i.e.,*

$$\mathbb{P}_{x,y}\left\{\lim_{t\to\infty} \frac{\ln Y(t)}{t} = \lambda < 0\right\} = 1. \tag{2.9}$$

3. Discussion and numerical examples

3.1. Discussion

We start this section by comparing our results with existing results in literature. In [4], the authors characterized the longtime behavior of the system (1.2) as the follows.

Theorem 3.1. *(see [4]) If $\alpha - \frac{\sigma_2^2}{2} < 0$, one has*

$$\limsup_{t\to\infty} \frac{\ln Y(t)}{t} \le (\alpha - \frac{\sigma_2^2}{2}) a.s \tag{3.1}$$

On the other hand, if $\delta > h^2$, where $h := \max\{0, \sqrt{\rho} - \sqrt{\mu\eta}\}$ and

$$\alpha - \frac{\sigma_2^2}{2} - \frac{\sigma}{\delta - h^2} > 0, \tag{3.2}$$

the solution $(X(t), Y(t))$ has a unique invariant measure concentrated on $\mathbb{R}^{2,\circ}_+$.

Compared with the results above, it is readily seen that our results in Theorem 2.2 are sharper. We are able to determine the extinction and persistence of tumor cells using the sign of the threshold $\lambda := \alpha - \frac{\sigma_2^2}{2} - \frac{\sigma}{\delta}$. Moreover, we also characterize the longtime behavior of the system without assuming any additional conditions on the parameters. In addition, the rate of convergence of the extinction case is obtained.

3.2. Perturbation in immune dynamics makes no impact on longtime behavior of tumor cells

It is clear from the formula for λ that the large the σ_2, the smaller the λ. Thus σ_2 can be helpful to reduce the tumor cells. On the other hand, σ_1, the intensity of the perturbing noise term in the dynamics of the effector cells has no impact on the longtime behavior of the tumor cells. This is somewhat surprising, but it is confirmed by the threshold $\lambda := \alpha - \frac{\sigma_2^2}{2} - \frac{\sigma}{\delta}$, which is independent of σ_1. As a consequence, to control the tumor cells, one can focus on controlling the parameter α, σ, σ_2, and δ. However, the variance of the dynamics still depends on σ_1. Although the changes in σ_1 do not affect the extinction and persistence of the system, they change the intensities of the fluctuation of the dynamics. As a result, this fact makes diagnosis and prediction more difficult.

Figs. 1, 2, and 3 display computational results for demonstration. In which, we consider system (1.2) with the parameters $\sigma = 1, \rho = 1, \eta = 1, \delta = 1, \mu = 1, \alpha = 4, \beta = 1, \sigma_2 = 1$, and three values of $\sigma_1 \in \{0.2, 1, 6\}$.

3.3. Small noises stabilize the deterministic system: Numerical examples

In this section, we discuss chaotic phenomena of the nonlinear tumor-immune system. We show that noise can stabilize the deterministic system. In the deterministic case, the system can be stuck in unstable points and may not converge to the stable points. However, by adding a small noise to the deterministic systems, the trajectory can escape from the unstable points, and concentrates near a stable point or jumps between the stable points. We refer the reader to [15–17] for further references.

Numerical examples will be given to illustrate this interesting phenomena. Consider the deterministic system (1.1) with the parameters $\sigma = 10, \rho = 4.4, \eta = 2.7, \delta = 3, \mu = .05, \alpha = 52, \beta = 1$. There are three equilibrium points, two stable points (blue ones) and one unstable points (the red point); see Fig. 4.

Now, consider stochastic system (1.2), which can be thought of as (1.1) perturbed by white noises. Let $\sigma_1 = .15, \sigma_2 = .03$, and keep the other parameters unchanged as in the deterministic system.

The stochastic system spends very little time around the unstable point and stays in a domain near one stable point, and

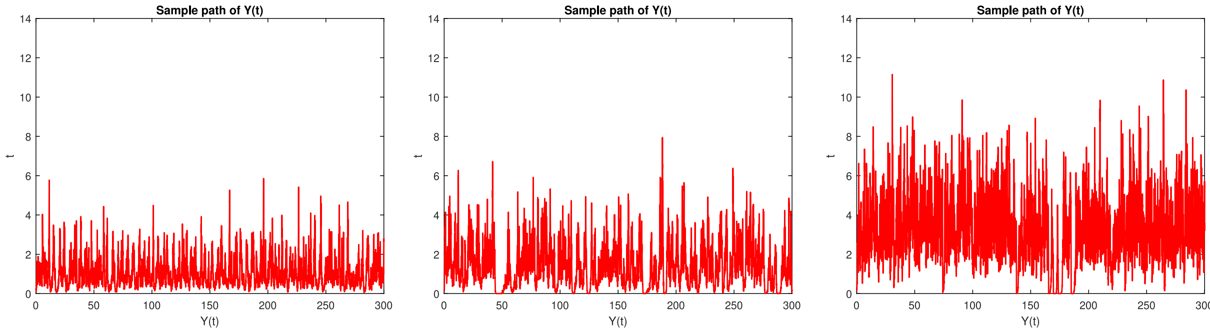

Fig. 2. Sample paths of $Y(t)$ when $\sigma_1 = 0.2$, $\sigma_1 = 1$, $\sigma_1 = 6$, respectively.

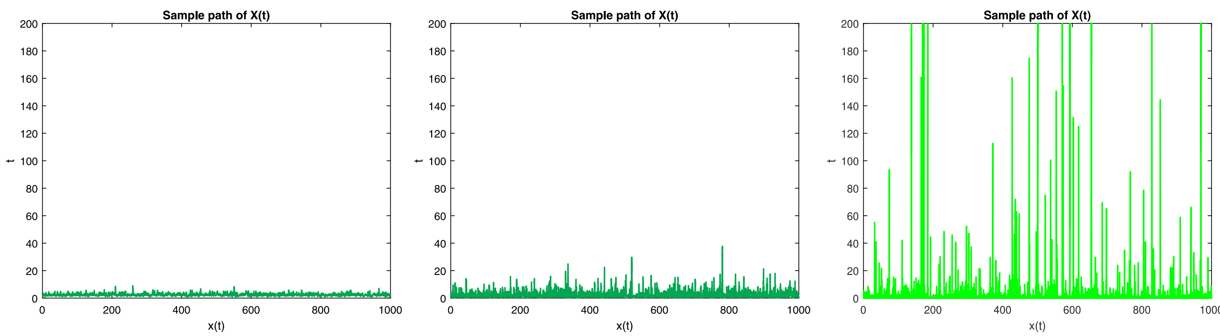

Fig. 3. Sample paths of $X(t)$ when $\sigma_1 = 0.2$, $\sigma_1 = 1$, $\sigma_1 = 6$, respectively.

then jumps quickly to a domain near the other stable point, and continues the movements going back and forth between the stable equilibria. The sample paths of $X(t), Y(t)$ are shown in Fig. 5 and the density of the occupation measure on the interval $[0, 5 \times 10^4]$, which approximates the density of the invariant measure is shown in Fig. 6. It can be seen that the invariant measure puts most of the mass near the two stable points of the corresponding deterministic system.

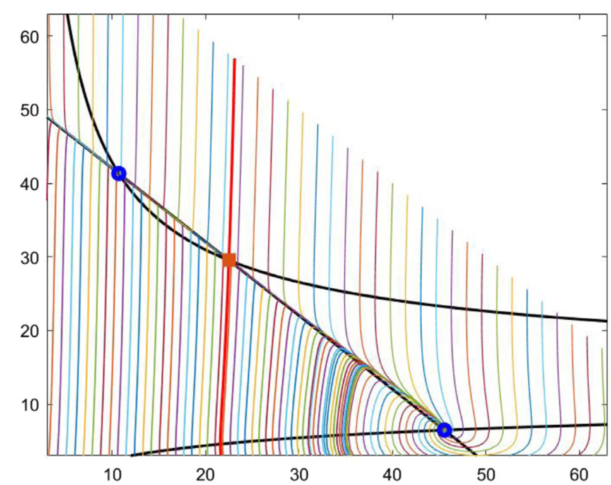

Fig. 4. Vector field of system (1.1). The red point is the unstable equilibrium point while the two blue points are the stable points. The red curve through the red point is its stable manifold, which splits the space into two domains each of which contains a stable equilibrium point. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

4. Proof of main results

4.1. Proof of Theorem 2.1

The existence and uniqueness of the solution of (1.2) and the positivity of $X(t), Y(t)$ with positive initial values, $\mathbb{P}_{x,y}((X(t), Y(t)) \in \mathbb{R}^{2,\circ}_+) = 1 \ \forall (x, y) \in \mathbb{R}^{2,\circ}_+$ can be found in [4, Theorem 2.1] (see also [18]). Moreover, it is also easy to obtain that $\mathbb{P}_{x,0}\big\{X(t) > 0 : t > 0\big\} = 1$ if $x > 0$ and that $\mathbb{P}_{x,0}\big\{Y(t) = 0 : t > 0\big\} = 1$.

Furthermore, it follows from [19, Theorem 2.9.3] and [20, Section 2.5] that the solution of (1.2) is a Feller and (homogeneous) strong Markov process if the coefficients are globally Lipschitz. Therefore, we obtain from the local Lipschitz property of coefficients of (1.2) and a truncation argument that $(X(t), Y(t))$ is a Feller and (homogeneous) strong Markov process. The details of this argument and this result can be found in [21, Theorem 5.1].

It remains to show that $\mathbb{P}_{0,y}\{X(t) > 0 : t > 0\} = 1$ for all $y \geq 0$. Let $\varepsilon > 0$ be sufficiently small such that

$$\sigma + \frac{\rho \tilde{x}\tilde{y}}{\eta + \tilde{y}} - \mu \tilde{x}\tilde{y} - \delta \tilde{x} \geq \frac{\sigma}{2}, \tag{4.1}$$

for any $(\tilde{x}, \tilde{y}) \in \mathbb{R}^2$ satisfying $\tilde{x} + |\tilde{y} - y| < \varepsilon$. Let

$$\tilde{\tau}_1 = \inf\{t > 0 : X(t) + |Y(t) - y| \geq \varepsilon\}.$$

By the continuity of $(X(t), Y(t))$, $\mathbb{P}_{0,y}\{\tilde{\tau}_1 > 0\} = 1$. Using the variation of constants formula (see [19, Chapter 3]), we can write $X(t)$ in the form

$$\begin{aligned} X(t) = \Phi(t)\bigg[\int_0^t \Phi^{-1}(u)\bigg(\sigma + \frac{\rho X(u)Y(u)}{\eta + Y(u)} \\ -\mu X(u)Y(u) - \delta X(u)\bigg)\,du\bigg] \text{ for } t \in [0, \tilde{\tau}_1), \end{aligned} \tag{4.2}$$

where $\Phi(t) = \exp\left(-\frac{\sigma_1^2 t}{2} + \sigma_1 W_1(t)\right)$. It follows from (4.1) that

$$\sigma + \frac{\rho X(u)Y(u)}{\eta + Y(u)} - \mu X(u)Y(u) - \delta X(u) > 0 \text{ if } u \in (0, \tilde{\tau}_1].$$

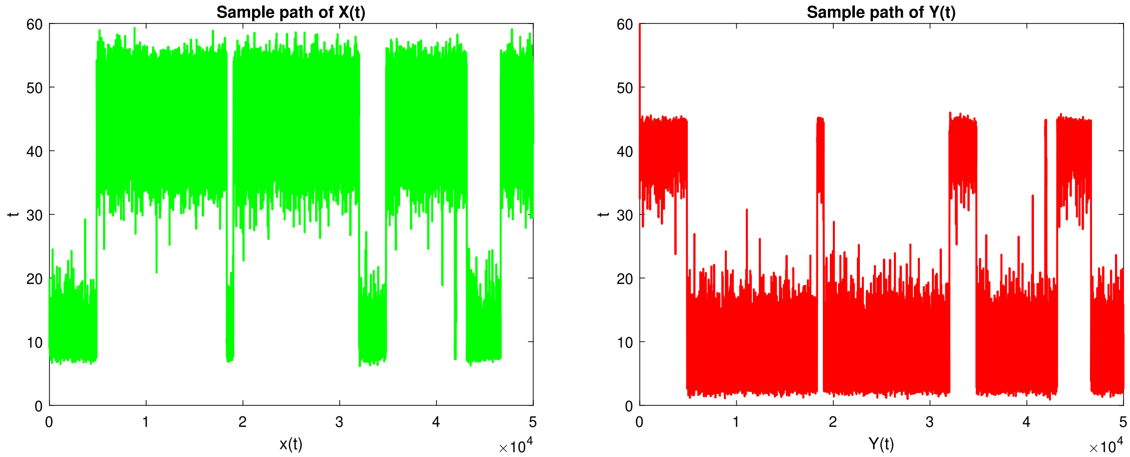

Fig. 5. Sample paths of $X(t), Y(t)$ of stochastic system (1.2).

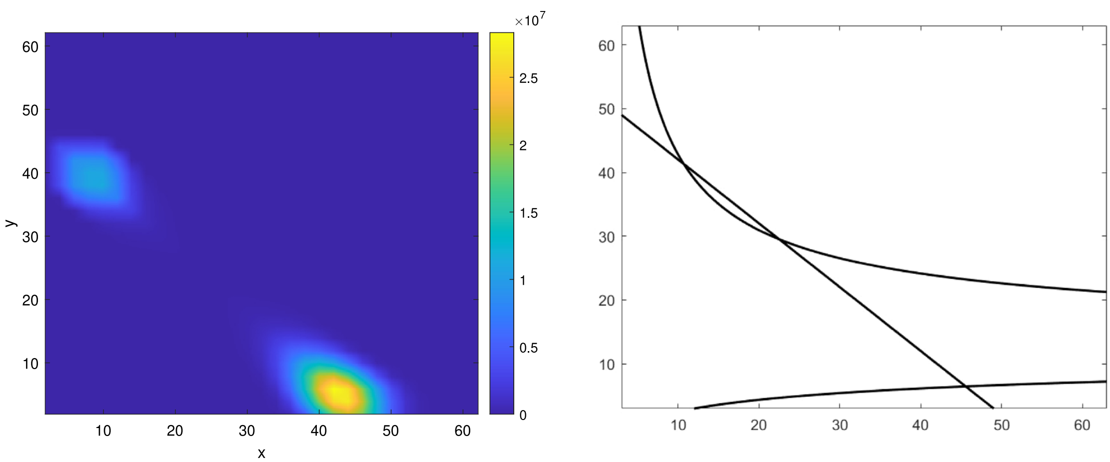

Fig. 6. Left figure: 2-dimensional density of the invariant measure of the solution of (1.2). Right figure: Nullclines of the corresponding deterministic system.

This and (4.2) imply that

$$\mathbb{P}_{0,y}\{X(t) > 0, t \in (0, \tilde{\tau}_1]\} = 1,$$

which combined with the fact $\mathbb{P}_{x,y}((X(t), Y(t)) \in \mathbb{R}_+^{2,\circ}) = 1\ \forall (x, y) \in \mathbb{R}_+^{2,\circ}$ and the strong Markov property of $(X(t), Y(t))$ yields that

$$\mathbb{P}_{0,y}\{X(t) > 0, t \in (0, \infty)\} = 1.$$

The theorem is therefore proved.

4.2. Proof of Theorem 2.2

Proof for the case $\lambda > 0$. We assume by contradiction that there is no invariant measure on $\mathbb{R}_+^{2,\circ}$, which also means that there is no invariant measure on $\mathbb{R}_+^{2,*}$ because the solutions starting in $\mathbb{R}_+^{2,*}$ will enter and remain in $\mathbb{R}_+^{2,\circ}$. As a result, $\boldsymbol{\nu}_0 \times \boldsymbol{\delta}$ is the unique invariant probability measure of the process $\{X(t), Y(t)\}$ on $\mathbb{R}_+^2$. For each initial value $(x, y) \in \mathbb{R}_+^{2,\circ}$, consider the occupation measure

$$\Pi_t^{x,y} := \frac{1}{t}\mathbb{E}_{x,y}\int_0^t \mathbf{1}_{\{(X(u),Y(u))\in\cdot\}}du.$$

Because of (2.1), $\{\Pi_t^{x,y}, t \geq 1\}$ is a tight family of probability measures on $\mathbb{R}_+^2$. Applying [10, Lemma 3.4], the tightness implies that any weak limit of $\Pi_t^{x,y}$ is an invariant probability measure of the process $\{X(t), Y(t)\}$. Since $\boldsymbol{\nu}_0 \times \boldsymbol{\delta}$ is the unique invariant probability measure, we have that $\Pi_t^{x,y}$ converges weakly to $\boldsymbol{\nu}_0 \times \boldsymbol{\delta}$ as $t \to \infty$. Due to the uniform integrability in (2.1), [10, Lemma 3.4] again implies that

$$\lim_{t\to\infty}\frac{1}{t}\mathbb{E}_{x,y}\int_0^t Y(u)du = \int_{\mathbb{R}_+^2} y\boldsymbol{\nu}_0(dx)\boldsymbol{\delta}(dy) = 0, \tag{4.3}$$

and

$$\lim_{t\to\infty}\frac{1}{t}\mathbb{E}_{x,y}\int_0^t X(u)du = \int_{\mathbb{R}_+^2} x\boldsymbol{\nu}_0(dx)\boldsymbol{\delta}(dy) = \frac{\sigma}{\delta}. \tag{4.4}$$

On the other hand,

$$\mathbb{E}_{x,y}\frac{\ln Y(t)}{t} = \mathbb{E}_{x,y}\frac{\ln y}{t} + \alpha - \frac{\sigma_2^2}{2} - \frac{1}{t}\mathbb{E}_{x,y}\left(\beta\int_0^t Y(u)du + \int_0^t X(u)du\right) + \mathbb{E}_{x,y}\frac{\sigma_2 W_2(t)}{t}.$$

(Note that $\mathbb{E}_{x,y}\frac{\ln Y(t)}{t}$ exists because all the expectations on the right-hand side exist. In particular $\mathbb{E}\frac{\sigma_2 W_2(t)}{t}$ exists and equals 0). As a result, we have

$$\lim_{t\to\infty}\mathbb{E}_{x,y}\frac{\ln Y(t)}{t} = \alpha - \frac{\sigma_2^2}{2} - \lim_{t\to\infty}\mathbb{E}_{x,y}\frac{1}{t}\left(\beta\int_0^t Y(u)du + \int_0^t X(u)du\right) = \lambda > 0.$$

This contradicts the fact that

$$\lim_{t\to\infty}\mathbb{E}_{x,y}\frac{\ln Y(t)}{t} \leq \lim_{t\to\infty}\mathbb{E}_{x,y}\frac{Y(t)}{t} = 0,$$

because $\ln y \le y$ while (2.1) implies $\lim_{t\to\infty} \mathbb{E}_{x,y}\frac{Y(t)}{t} = 0$. As a result, there exists an invariant measure $\boldsymbol{\nu}^*$ on $\mathbb{R}^{2,\circ}_+$. Moreover, (2.8) follows easily from a well-known property of non-degenerate diffusions. □

Proof for the case $\lambda < 0$. Suppose $\lambda := \alpha - \frac{\sigma_2^2}{2} - \frac{\sigma}{\delta} < 0$. Let $\gamma_0 > 0$ be sufficiently small that

$$\widetilde{\lambda} := \alpha - \frac{\sigma_2^2}{2} - \frac{\sigma}{\mu\gamma_0 + \delta} < 0. \tag{4.5}$$

Now, let $\overline{\mathcal{X}}(t)$ be the solution to

$$d\overline{\mathcal{X}}(t) = \left[\sigma - (\mu\gamma_0 + \delta)\,\overline{\mathcal{X}}(t)\right]dt + \sigma_1\overline{\mathcal{X}}(t)dW_1(t). \tag{4.6}$$

Similar to $\widetilde{X}(t)$, we can obtain that $\overline{\mathcal{X}}(t)$ has a unique invariant measure $\boldsymbol{\nu}_{\gamma_0}$ on $(0,\infty)$ and

$$\int_{(0,\infty)} x\boldsymbol{\nu}_{\gamma_0}(dx) = \frac{\sigma}{\mu\gamma_0+\delta}.$$

By the ergodic theorem, we have

$$\lim_{t\to\infty}\frac{1}{t}\int_0^t \overline{\mathcal{X}}_0(u)du = \frac{\sigma}{\mu\gamma_0+\delta} \text{ a.s.,} \tag{4.7}$$

where $\overline{\mathcal{X}}_0(t)$ is the solution to (4.6) with $\overline{\mathcal{X}}(0) = 0$. (Note that $\overline{\mathcal{X}}_0(t) > 0$ for any $t > 0$).

Lemma 4.1. *Let γ_0 satisfy (4.5). For any $\varepsilon > 0$ and $H > 0$, there exists a $\gamma_1 > 0$ such that for all $(x,y) \in [0,H]\times(0,\gamma_1]$, we have*

$$\mathbb{P}_{x,y}\left\{\lim_{t\to\infty}\frac{\ln Y(t)}{t} = \lambda < 0\right\} \ge 1-\varepsilon. \tag{4.8}$$

Proof. In view of (4.5) and (4.7), for any $\varepsilon > 0$, there exists a $T_1 = T_1(\varepsilon) > 0$ such that $\mathbb{P}(\Omega_1) \ge 1 - \frac{\varepsilon}{4}$, where

$$\Omega_1 = \left\{\omega\in\Omega : \frac{1}{t}\int_0^t \overline{\mathcal{X}}_0(u)du \ge \frac{\sigma}{\mu\gamma_0+\delta} - \frac{|\widetilde{\lambda}|}{4} \quad \text{for all } t \ge T_1\right\}. \tag{4.9}$$

Likewise, we have from the strong law of large numbers for martingales that

$$\lim_{t\to\infty}\frac{W_2(t)}{t} = 0 \text{ a.s.} \tag{4.10}$$

As a consequence, there is a $T_2(\varepsilon) > 0$ such that $\mathbb{P}(\Omega_2) \ge 1 - \frac{\varepsilon}{4}$, where

$$\Omega_2 = \left\{\omega\in\Omega : \frac{|\sigma_2 W_2(t)|}{t} \le \frac{|\widetilde{\lambda}|}{4} \quad \text{for all } t \ge T_2\right\}. \tag{4.11}$$

Let $T = \max\{T_1, T_2\}$. In addition, we can choose $M > \alpha T$ sufficiently large so that

$$\begin{aligned}\mathbb{P}(\Omega_3) \ge 1 - \frac{\varepsilon}{4},\ &\text{where } \Omega_3 = \{\omega\in\Omega : |\sigma_2 W_2(t)| \\ &\le M - \alpha T,\ \text{ for all } t\in[0,T]\}.\end{aligned} \tag{4.12}$$

Let $\gamma_1 \in \left(0, \gamma_0 e^{-M}\right)$. Combining the second equation of (1.2) and (4.12) implies that

$$\begin{aligned} Y(t) =& Y(0)\exp\left\{\left(\alpha - \frac{\sigma_2^2}{2}\right)t - \int_0^t (\beta Y(u) + X(u))\,du + \sigma_2 W_2(t)\right\} \\ \le& Y(0)\exp\left\{\left(\alpha - \frac{\sigma_2^2}{2}\right)t + \sigma_2 W_2(t)\right\} \\ \le& \gamma_1 e^M < \gamma_0 \text{ for any } t\in[0,T],\ \text{ if } Y(0)\le\gamma_1, \omega\in\Omega_3. \end{aligned} \tag{4.13}$$

Now, we define the stopping time

$$\widetilde{\tau} := \inf\{t \ge 0 : Y(t) \ge \gamma_0\}. \tag{4.14}$$

As a consequence, for $\omega\in\Omega_3$ we have $\widetilde{\tau} > T$. Note that we can write

$$\begin{aligned} dX(t) &= \left[\sigma + X(t)\left(\frac{\rho X(t)Y(t)}{\eta + Y(t)} - \mu Y(t) + \mu\gamma_0\right)\right. \\ &\quad \left. - (\delta + \mu\gamma_0)\,X(t)\right]dt + \sigma_1 X(t)dW_1(t). \end{aligned} \tag{4.15}$$

Applying a comparison argument to (4.6) and (4.15), we have $X(t) \ge \overline{\mathcal{X}}_0(t)$ for $t \le \widetilde{\tau}$ given that $X(0) > 0$. Thus, from the first equation of (4.13), if $t \le \widetilde{\tau}$,

$$\begin{aligned} Y(t) =& Y(0)\exp\left\{\left(\alpha - \frac{\sigma_2^2}{2}\right)t - \int_0^t (\beta Y(u) + X(u))\,du + \sigma_2 W_2(t)\right\} \\ \le& Y(0)\exp\left\{\left(\alpha - \frac{\sigma_2^2}{2}\right)t - \int_0^t \left(\overline{\mathcal{X}}(u)\right)du + \sigma_2 W_2(t)\right\}. \end{aligned} \tag{4.16}$$

Combining (4.9), (4.11), and (4.13), for $\omega \in \bigcap_{j=1}^3 \Omega_j$ and $Y(0) = y \le \gamma_1$, we have $\widetilde{\tau} > T$ and

$$\begin{aligned} Y(t) \le& Y(0)\exp\left\{\left(\alpha - \frac{\sigma_2^2}{2}\right)t - \int_0^t \left(\overline{\mathcal{X}}(u)\right)du + \sigma_2 W_2(t)\right\} \\ =& Y(0)\exp\left\{\left(\alpha - \frac{\sigma_2^2}{2}\right)t - \frac{\sigma t}{\mu\gamma_0+\delta} + \frac{|\widetilde{\lambda}|t}{4} + \frac{|\widetilde{\lambda}|t}{4}\right\} \\ <& Y(0)\exp\left(\frac{\widetilde{\lambda}t}{2}\right) \le \gamma_1 < \gamma_0,\ t\in[T,\widetilde{\tau}). \end{aligned} \tag{4.17}$$

Therefore, we must have $\widetilde{\tau} = \infty$ for almost all $\omega \in \bigcap_{j=1}^3 \Omega_j$, $Y(0) \le \gamma_1$. [We obtain this claim by contradiction argument as follows. If the claim is false then we have a set $\Omega_4 \in \bigcap_{j=1}^3 \Omega_j$ with $\mathbb{P}(\Omega_4) > 0$ and $\widetilde{\tau} < \infty$ for any $\omega \in \Omega_4$. Note that we already proved that $T < \widetilde{\tau}$ for $\omega \in \bigcap_{j=1}^3 \Omega_j$. Moreover, in view of (4.17), we have $Y(t) \le \gamma_1 < \gamma_0$ for any $t \in [T, \widetilde{\tau})$. Since $Y(t)$ is continuous almost surely, for almost all $\omega\in\Omega_4$ we have $\lim_{t\to\widetilde{\tau}} Y(t) = Y(\widetilde{\tau}) \le \gamma_1 < \gamma_0$ which is a contradiction]. Because $\widetilde{\tau} = \infty$, one has

$$Y(t) \le Y(0)\exp\left\{\frac{\widetilde{\lambda}t}{2}\right\},\ \text{ for any } t \ge T, \omega \in \bigcap_{j=1}^3 \Omega_j, Y(0) = y \le \gamma_1.$$

This clearly implies that $\lim_{t\to\infty} Y(t) = 0$ for almost $\omega \in \bigcap_{j=1}^3 \Omega_j$.

Moreover, since $Y(t) \le \gamma_0$ for any $t \ge 0$ for almost $\omega \in \bigcap_{j=1}^3 \Omega_j$, a comparison argument ([19, Theorem 6.1.1]) implies that $X(t) \le \hat{X}(t)$, where

$$d\hat{X}(t) = \left[\sigma - \left(-\frac{\rho\gamma_0}{\eta} + \delta\right)\hat{X}(t)\right]dt + \sigma_1\hat{X}(t)dW_1(t). \tag{4.18}$$

Similar to (4.6), if γ_0 is sufficiently small that $\left(-\frac{\rho\gamma_0}{\eta} + \delta\right) > 0$, the solution to (4.18) has a unique invariant measure $\hat{\boldsymbol{\nu}}$ and we have from the ergodicity of $\hat{X}(t)$ that for some small $\hat{p} > 0$

$$\begin{aligned} &\limsup_{t\to\infty}\frac{1}{t}\int_0^t X^{1+\hat{p}}(u)du \le \lim_{t\to\infty}\frac{1}{t}\int_0^t \hat{X}^{1+\hat{p}}(u)du \\ &= \int x^{1+\hat{p}}\hat{\boldsymbol{\nu}}(dx) < \infty \text{ for almost all } \omega \text{ in } \bigcap_{j=1}^3 \Omega_j. \end{aligned} \tag{4.19}$$

Due to (4.19) and $\lim_{t\to\infty} Y(t) = 0$, the family of random occupation measure

$$\widetilde{\Pi}^t(\cdot) := \frac{1}{t}\int_0^t \boldsymbol{1}_{\{(X(u),Y(u))\in\cdot\}}du$$

is tight for almost all $\omega \in \bigcap_{j=1}^3 \Omega_j$. From [10, Lemma 5.6], with probability 1, any weak-limit of $\widetilde{\Pi}^t(\cdot)$ as $t\to\infty$ (if it exists) is an invariant probability measure of the process $(X(t), Y(t))$, which has support on $[0,\infty)\times\{0\}$. It is easily seen that $\boldsymbol{\nu}_0\times\boldsymbol{\delta}$ is the unique invariant probability measure on $[0,\infty)\times\{0\}$. As a result, $\widetilde{\Pi}^t(\cdot)$ converges weakly to $\boldsymbol{\nu}_0\times\boldsymbol{\delta}$ for almost every $\omega\in\cap_{j=1}^3\Omega_j$ as t tends to ∞. By the weak convergence, as well as the uniform integrability in (4.19), we have

$$\begin{aligned}\lim_{t\to\infty}\frac{\ln Y(t)}{t} &= \lim_{t\to\infty}\frac{1}{t}\left(\alpha t - \frac{\sigma_2^2 t}{2} - \beta\int_0^t Y(u)du\right.\\ &\quad \left. - \int_0^t X(u)du\right) + \lim_{t\to\infty}\frac{\sigma_2 W_2(t)}{t}\\ &= \lim_{t\to\infty}\int_{\mathbb{R}^2_+}(\alpha - \frac{\sigma_2^2}{2} - \beta y - x)\widetilde{\Pi}^t(dx,dy) = \lambda < 0,\end{aligned}$$

for almost every $\omega\in\cap_{j=1}^3\Omega_j$, $(x,y)\in[0,H]\times(0,\gamma_1]$. The proof is complete by noting that $\mathbb{P}(\cap_{j=1}^3\Omega_j) > 1-\varepsilon$. □

Now we complete the proof of Theorem 2.2, part 2. In view of Lemma 4.1, the process $(X(t), Y(t))$ is transient in $\mathbb{R}^{2,\circ}_+$. Thus, the process has no invariant probability measure in $\mathbb{R}^{2,\circ}_+$, and $\boldsymbol{\nu}_0\times\boldsymbol{\delta}$ is the unique invariant probability measure of $(X(t), Y(t))$ in $\mathbb{R}^2_+$. Thanks to (2.1), the process $(X(t), Y(t))$ is tight. Consequently the occupation measure

$$\Pi^t_{x,y}(\cdot) = \frac{1}{t}\int_0^t \mathbb{P}_{x,y}\left\{(X(u), Y(u))\in\cdot\right\}du$$

is tight in $\mathbb{R}^2_+$. Since any weak-limit of $\Pi^t_{x,y}$ as $t\to\infty$ must be an invariant probability measure of $(X(t), Y(t))$, we have that $\Pi^t_{x,y}$ converges weakly to $\boldsymbol{\nu}_0\times\boldsymbol{\delta}$ as $t\to\infty$. As a result, for any $\gamma_1 > 0$, there exists a $\hat{T} > 0$ such that

$$\Pi^{\hat{T}}_{x,y}((0,\infty)\times(0,\gamma_1)) > 1-\varepsilon,$$

or equivalently, $\frac{1}{\hat{T}}\int_0^{\hat{T}}\mathbb{P}_{x,y}\{Y(t)\le\gamma_1\}dt > (1-\varepsilon)$. As a result,

$$\mathbb{P}_{x,y}\{\hat{\tau}\le\hat{T}\} > 1-\varepsilon, \quad \text{where } \hat{\tau} = \inf\{t\ge 0 : Y(t)\le\gamma_1\}.$$

Using the strong Markov property and Lemma 4.1, we have that

$$\mathbb{P}_{x,y}\left\{\lim_{t\to\infty}\frac{\ln Y(t)}{t} = \lambda < 0\right\} \ge 1-2\varepsilon,$$

for any $(x,y)\in\mathbb{R}^{2,*}_+$. Since $\varepsilon > 0$ is arbitrary, (2.9) must follow (by letting $\varepsilon\to 0$). This completes the proof of Theorem 2.2. □

5. Concluding remarks

This paper is devoted to studying longtime behavior of a class of tumor-immune systems. Under broad conditions, we obtain sufficient and nearly necessary conditions for persistence and extinction of the stochastic systems. Note that at the beginning, we assumed the two Brownian motions to be independent. In fact, we can treat the case $W_1(t) = W_2(t) = W(t)$, resulting in degenerate case in the two-dimensional system. The techniques can also be adopted to treat correlated Brownian motions.

The model in this paper is spatially homogeneous in the sense that the density of the effector cells or tumor cells does not depend on the space variable, just depend on the time variable. Taking the spatial inhomogeneity into consideration will make the model more versatile but also pose many challenges; see [22–24]. The problems can be studied using a stochastic partial differential equation frameworks, which will present a much different perspective compared with systems given by stochastic differential equations (SDEs), or ordinary differential equations (ODEs), or partial differential equations (PDEs).

Further research can also be devoted to study diffusion systems that are also subject to an additional random switching process. Consideration of systems involving delays and more complex stochastic functional differential equations is another worthwhile direction.

CRediT authorship contribution statement

T.D. Tuong: Formulation, Analysis, Examples of the paper. **N.N. Nguyen:** Formulation, Analysis, Examples of the paper. **G. Yin:** Formulation, Analysis, Examples of the paper.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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