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Dynamical Behaviors of Stochastic Tumor-Immune Model

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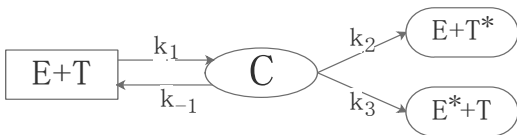Examples and numerical simulations

- At present, cancer is considered to be one of the most complicated diseases to be treated clinically and one of the most dreadful killers in the world today.

- "According to the World Health Organization (WHO), the number of new cancer cases is expected to increase by 70 percent over the next two decades (World Health Organization, 2015)." (Mahasa etc. 2016)

- Keeping in mind its devastating nature, a great deal of human and economic resources are devoted to the research on cancer biology and subsequent development of proper therapeutic measures.

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- Surgery, radiation therapy, and chemotherapy are the three traditional therapy procedures that are practised for treatment of cancer.

- All these procedures are characterized by a relatively low efficacy and high toxicity for the patient.

- Compared with traditional treatment methods, emerging immunotherapy has great development prospects.

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Mathematical models of tumour-immune system and their dynamical behaviors, help us to understand better how host immune cells and cancerous cells evolve and interact.

- Adam-Bellomo 1997

- Araujo-McElwain 2004

- Kuznetsov etc. 1994

- Galach 2003, Yafia 2006, 2007, Rihan etc. 2014

- A. S. Perelson, G. Weisbuch, 1997

- R. Bürger, N. H. Barton, 2000

- M. A. Nowak, R. M. May, 2000

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Kuznetsov-Taylor Model, 1994

E: the local concentrations of effector cells (ECs); T: tumor cells (TCs); C: effector cell-tumor cell conjugates; E^*: inactivated effector cells; T^*: "lethally hit" TC cells, which are destined to perish, and also called "programmed to die".

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$$\begin{cases} \mathrm{d}E & = (s + F(C,T) - d_1 E - k_1 ET + (k_{-1} + k_2)C)\,\mathrm{d}t, \\ \mathrm{d}T & = (aT(1 - bT_{tot}) - k_1 ET + (k_{-1} + k_3)C)\,\mathrm{d}t, \\ \mathrm{d}C & = (k_1 ET - (k_{-1} + k_2 + k_3)C)\,\mathrm{d}t, \\ \mathrm{d}E^* & = (k_3 C - d_2 E^*)\,\mathrm{d}t, \\ \mathrm{d}T^* & = (k_2 C - d_3 T^*)\,\mathrm{d}t. \end{cases}$$

Kuznetsov 1992, Kuznetsov etc. 1994 revealed

$$F(C,T) = \frac{fC}{g+T}, \qquad \frac{\mathrm{d}C}{\mathrm{d}t} \approx 0,$$

namely,

$$C \approx KET, \qquad K = \frac{k_1}{k_2 + k_3 + k_{-1}}.$$

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- Kuznetsov-Makalkin-Taylor-Perelson, 1994
  proposed a simplified tumour-immune model

$$
\left\{
\begin{array}{rcl}
\mathrm{d}x(t) & = & \left(\sigma + \dfrac{\rho x(t)y(t)}{\eta + y(t)} - \mu x(t)y(t) - \delta x(t)\right)\mathrm{d}t, \\
\mathrm{d}y(t) & = & \left(\alpha y(t) - \beta y^2(t) - x(t)y(t)\right)\mathrm{d}t,
\end{array}
\right.
\tag{1}
$$

where x represents non-dimensional local concentration of EC,
y represents non-dimensional local concentration of TC.

Local and global bifurcations for parameters were calculated,
and the possible connection between two different mechanisms
of the tumor: tumor dormancy and sneaking through was illus-
trated.

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In the tumor tissue, the growth rate and cytotoxic parameters are influenced by many environmental factors, e.g., the supply of nutrients, chemical agents, temperature, etc. Due to the complexity, it is unavoidable that in the course of time the parameters of the system undergo random variations which give them a stochastic character, refer to

- N.S. Goel, N. Richter-Dyn, 1975
- R.P. Garay, R. Lefever, 1978
- A. Mantovani, P. Allavena, A. Sica, 2004
- R.L. Elliott, G.C. Blobe, 2005

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Considering the impact of the stochastic volatility of environment, we assume that environmental fluctuations mainly affect the culling rate of ECs δ and the intrinsic growth rate of TCs α

$$-\delta \mathrm{d}t \rightarrow -\delta \mathrm{d}t + \sigma_1 \mathrm{d}B_1(t), \quad \alpha \mathrm{d}t \rightarrow \alpha \mathrm{d}t + \sigma_2 \mathrm{d}B_2(t).$$

Thus, the stochastic tumor-immune model is described by

$$\begin{cases} \mathrm{d}x(t) = \Big(\sigma + \dfrac{\rho x(t)y(t)}{\eta + y(t)} - \mu x(t)y(t) - \delta x(t)\Big)dt + \sigma_1 x(t)\mathrm{d}B_1(t), \\ \mathrm{d}y(t) = y(t)\Big(\alpha - \beta y(t) - x(t)\Big)dt + \sigma_2 y(t)\mathrm{d}B_2(t). \end{cases}$$
$$(2)$$

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- Lyapunov exponent method and Fokker– Planck method are used to investigate the stability of the stochastic models by numerical simulations.

  - Mukhopadhyay-Bhattacharyya, 2009
    analyzed the stochastic stability for a stochastic virus-tumor-immune model.
  - Oana-Dumitru-Riccardo, 2013
    studied the stochastic stability of the stochastic Kuznetsov–Taylor model near their equilibriums.

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- L, Song, Xia, Yuan, 2019
  obtained the criteria to the asymptotic behavior of (1) including the
  stochastic ultimately boundedness in moment, the limit distribution
  as well as the ergodicity.

- Tuong, Nguyen and Yin, 2020
  obtained the sufficient and nearly necessary threshold-type condition
  for the permanence and extinction of TCs, which extends our result
  to a better version.

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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.

- Continuous-time finite-state Markov chain is widely used to characterize this kind of environmental noise in different mathematical models,

- The dynamics of the stochastic differential equations (SDEs) modulated by Markov chain are full of uncertainty.

- The theory of SDEs with Markovian switching is systematically introduced in Mao-Yuan 2006, Yin-Zhu 2009.

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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

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

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 are positive constants.

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Assume that the Markov chain is irreducible and $\pi = (\pi_1, \pi_2, \cdots, \pi_{m_0})$ is the stationary distribution. Define

$$
\begin{aligned}
\mathbb{R}_+ &:= \{x \in \mathbb{R} : x \geq 0\}, \\
\mathbb{R}_+^0 &:= \{x \in \mathbb{R} : x > 0\}, \\
\mathbb{R}_+^2 &:= \{(x,y) \in \mathbb{R}^2 : x \geq 0, \ y \geq 0\}, \\
\mathbb{R}_+^{2,0} &:= \{(x,y) \in \mathbb{R}^2 : x > 0, \ y > 0\}, \\
\mathbb{R}_+^{2,*} &:= \{(x,y) \in \mathbb{R}^2 : x \geq 0, \ y > 0\}.
\end{aligned}
$$

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Theorem

The following assertions hold.

(i) *For any initial value $(x_0, y_0, r_0) \in \mathbb{R}^{2,*}_+ \times \mathbb{S}$, model (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 $\mathbb{P}(t, x, y, r, \cdot)$.*

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

$$\limsup_{t \to \infty} \mathbb{E}[(1 + x(t) + cy(t))^{1+p}] \leq K(p, c). \qquad (4)$$

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Consider the first equation of (3) on the boundary $y(t) = 0$, that is

$$\mathrm{d}\tilde{x}(t) = \big(\sigma(r(t)) - \delta(r(t))\tilde{x}(t)\big)\mathrm{d}t + \kappa_1(r(t))\tilde{x}(t)\mathrm{d}B_1(t). \qquad (5)$$

The solution pair $(\tilde{x}(t), r(t))$ of (5) has a unique invariant measure ν on $[0, \infty) \times \mathbb{S}$ and $\nu((0, \infty) \times \mathbb{S}) = 1$.

$\nu \times \delta_0$ can be regarded as the invariant measure of $(x(t), y(t), r(t))$ on the boundary of $\mathbb{R}_+^2 \times \mathbb{S}$.

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Lemma

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. By the similar techniques as (4),

$$\mathbb{E}[(\tilde{x}(t))^{1+\tilde{p}}] \leq K, \qquad \forall\ t \geq 0. \tag{6}$$

The desired assertion comes from the uniform integration of $\int_0^t \tilde{x}(s)\mathrm{d}s/t$ and the ergodicity of $\tilde{x}(t)$.

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Utilizing the generalized Itô formula, we obtain that

$$
\begin{aligned}
\frac{\ln y(t)}{t} =& \frac{1}{t} \int_0^t \Big(\alpha(r(s)) - \frac{1}{2}\kappa_2^2(r(s)) - \beta(r(s))y(s) - x(s) \Big) \mathrm{d}s \\
&+ \frac{\ln y_0}{t} + \frac{1}{t} \int_0^t \kappa_2(r(s)) \mathrm{d}B_2(s).
\end{aligned}
\tag{7}
$$

If $y(t)$ is small, $x(t) \approx \tilde{x}(t)$. Therefore, for sufficiently large t we have

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

Then the Lyapunov exponent of $y(t)$ can be approximated by

$$
\lambda := \sum_{i=1}^{m_0} \pi_i \Big(\alpha_i - \frac{1}{2}\kappa_2^2(i) - \frac{\sigma_i}{\delta_i} \Big).
$$

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Lemma

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

$$\mathbb{P}_{x_0, y_0, r_0}\left\{ \lim_{t \to \infty} \frac{\ln y(t)}{t} = \lambda \right\} \geq 1 - \varepsilon,$$

for all $(x_0, y_0, r_0) \in [0, H] \times (0, \gamma_1] \times \mathbb{S}$.

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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.,

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

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Prove it by contradiction. Lemma implies that $(x(t), y(t), r(t))$ is transient on $\mathbb{R}^{2,0}_+ \times \mathbb{S}$. Hence, $(x(t), y(t), r(t))$ 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 $\mathbb{R}^2_+ \times \mathbb{S}$. Fix $(x_0, y_0, r_0) \in \mathbb{R}^{2,*}_+ \times \mathbb{S}$. Then the sequence of the occupation measures

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

is tight on $\mathbb{R}^2_+ \times \mathbb{S}$. $\nu \times \delta_0$ is the uniquely weak limit of $\Pi^t_{x_0,y_0,r_0}(\cdot)$.

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Then for any $\varepsilon > 0$, $\gamma_1 > 0$, there exists a $T_0 > 0$ such that for any $\hat{T} > T_0$,

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

Define a stopping time $\hat{\tau} := \inf\{t \geq 0 : y(t) \leq \gamma_1\}$. Therefore,

$$\mathbb{P}\{\hat{\tau} \leq \hat{T}\} > 1 - \varepsilon.$$

Applying the strong Markov property and Lemma, we have

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

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Theorem

Assume $\lambda > 0$. Then $(x(t), y(t), r(t))$ has a unique invariant measure ν^* on $\mathbb{R}_+^{2,0} \times \mathbb{S}$. Moreover, for any $(x_0, y_0, i_0) \in \mathbb{R}_+^{2,*} \times \mathbb{S}$,

$$\lim_{t \to \infty} \|P(t, x_0, y_0, i_0, \cdot) - \nu^*(\cdot)\|_{TV} = 0. \qquad (8)$$

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Prove it by contradiction. Assume that there is no invariant measure of $(x(t), y(t), r(t))$ on $\mathbb{R}_+^{2,0} \times \mathbb{S}$. Then $(x(t), y(t), r(t))$ 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 $\mathbb{R}_+^2 \times \mathbb{S}$. $\{\Pi_{x_0,y_0,i_0}^t, t \geq 1\}$ is tight. Π_{x_0,y_0,i_0}^t converges weakly to $\nu \times \delta_0$ as $t \to \infty$. Then

$$\lim_{t \to \infty} \mathbb{E}_{x_0,y_0,i_0} \frac{1}{t} \int_0^t y(s)\mathrm{d}s = 0,$$

$$\lim_{t \to \infty} \mathbb{E}_{x_0,y_0,i_0} \frac{1}{t} \int_0^t x(s)\mathrm{d}s = \sum_{i=1}^{m_0} \frac{\pi_i \sigma_i}{\delta_i}.$$

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This together with the Jensen inequlity implies

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

As a consequence, this constraction reveals that there must exist an invariant measure ν^* of $(x(t), y(t), r(t))$ on $\mathbb{R}_+^{2,0} \times \mathbb{S}$. One notices that the diffusion coefficient is nongenerate in any compact set of $\mathbb{R}_+^{2,0} \times \mathbb{S}$. Then, for any $t_0 > 0$, the skeleton process $\{(x(nt_0), y(nt_0), r(nt_0)), \ n \in \mathbb{N}\}$ is irreducible and aperiodic. Thus by the similar argument as [Hening-Nguyen, 2018], we obtain the desired assertions.

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We proceed to analyze the property of ν^*. Define

$$f(y, i) = \rho_i y / (\eta_i + y) - \mu_i y, \ y > 0, i \in \mathbb{S}.$$

The monotonicity analysis of f implies

$$f(y, i) \leq h_i^2 \quad \text{for any } y > 0. \tag{9}$$

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

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

The comparison theorem shows that, $x(t) \leq \psi(t)$ a.s. for all $t \geq 0$.

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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

$$
y(t) \leq \varphi(t) \text{ a.s. for all } t \geq 0.
$$

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Assume $\lambda > 0$. Then

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

$$\leq \frac{1}{\hat{\sigma}}\sum_{i=1}^{m_0} \pi_i\Big[\frac{\check{\mu}}{\hat{\beta}}\Big(\alpha_i - \frac{1}{2}\kappa_2^2(i)\Big) + \delta_i + \frac{1}{2}\kappa_1^2(i)\Big].$$

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Assume $\lambda > 0$ and $\min\limits_{i \in \mathbb{S}}\{a_i\} > 0$. Then

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

$$\leq \frac{1}{\hat{\beta}} \sum_{i=1}^{m_0} \pi_i\Big(\alpha_i - \frac{1}{2}\kappa_2^2(i)\Big).$$

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We select the data in [Kuznetsov-Makalkin-Taylor-Perelson,1994] and [Siu-Vitetta-May-Uhr,1986]. We firstly discuss the tumor-immune model in environment 1

$$\begin{cases} \mathrm{d}x(t) = & \Big(\sigma + \dfrac{\rho_1 x(t)y(t)}{\eta + y(t)} - \mu x(t)y(t) - \delta x(t)\Big)\mathrm{d}t \\ & \quad + \kappa_1(1)x(t)\mathrm{d}B_1(t), \\ \mathrm{d}y(t) = & \big(\alpha y(t) - \beta y^2(t) - x(t)y(t)\big)\mathrm{d}t + \kappa_2(1)y(t)\mathrm{d}B_2(t), \end{cases}$$
(10)

where $\kappa_1(1) = 0.2$, $\kappa_2(1) = 0.25$, and $x(0) = 5$, $y(0) = 50$.

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Using the non-dimensionalization method in [Kuznetsov-Makalkin-Taylor-Perelson,1994] yields coefficients in the model (10) as follows

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

Then we compute

$$
\alpha - \kappa_2^2(1)/2 - \sigma/\delta = 1.2892 > 0.
$$

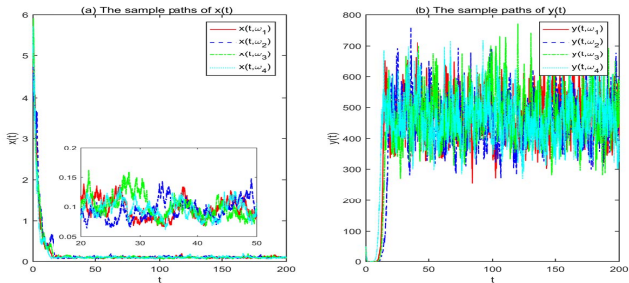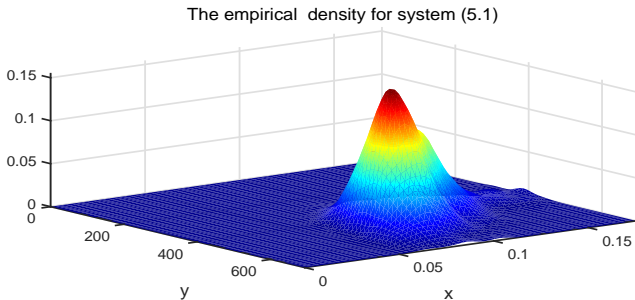ECs and TCs in (10) are permanent and have a unique invariant measure.

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Figure: Sample paths of $x(t)$, $y(t)$ for (10).

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The empirical density for system (5.1)

Figure: The empirical density of (10) using 1000 sample points and time $t = 200$.

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We then discuss the tumor-immune model in environment 2

$$
\begin{cases}
\mathrm{d}x(t) = & \Big(\sigma + \dfrac{\rho_2 x(t)y(t)}{\eta + y(t)} - \mu x(t)y(t) - \delta x(t)\Big)\mathrm{d}t \\
& + \kappa_1(2)x(t)\mathrm{d}B_1(t), \\
\mathrm{d}y(t) = & \big(\alpha y(t) - \beta y^2(t) - x(t)y(t)\big)\mathrm{d}t + \kappa_2(2)y(t)\mathrm{d}B_2(t).
\end{cases}
\tag{11}
$$

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

$$
\alpha - \kappa_2^2(2)/2 - \sigma/\delta = -0.6795 < 0.
$$

TCs become extinct while the measures of ECs converge to the unique invariant one corresponding to the inverse gamma distribution $IG(5.67875, 1.47625)$.
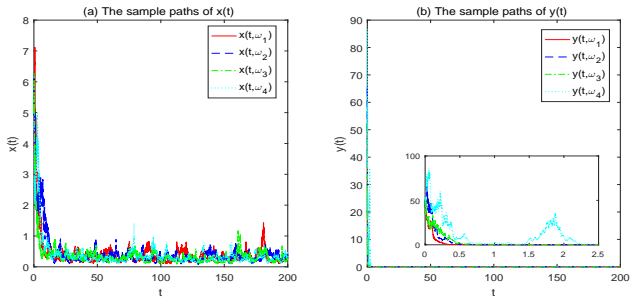
Background and motivation
Global positive solution
Extinction: The case $\lambda < 0$
Permanence: The case $\lambda > 0$
Examples and numerical simulations

Figure: Sample paths of $x(t)$, $y(t)$ for (11).

Background and motivation
Global positive solution
Extinction: The case $\lambda < 0$
Permanence: The case $\lambda > 0$
Examples and numerical simulations
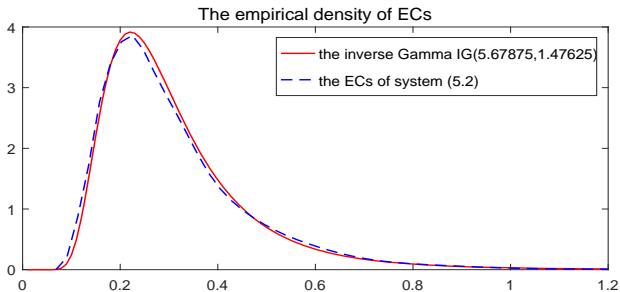
Figure: The empirical density of ECs of (11) using 1000 sample points and time $t = 200$.

Background and motivation
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Examples and numerical simulations

Due to the random environmental change, tumor-immune system switches between two habitat (10) and (11).

Case 1 Let the generator of Markov chain $r(t)$

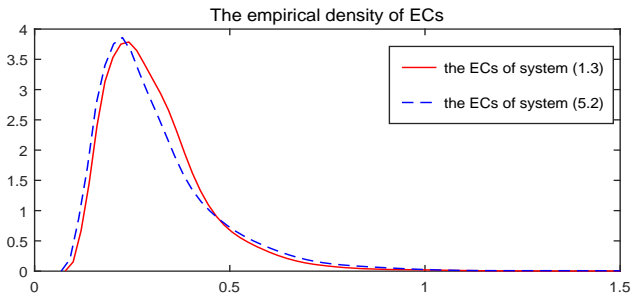$$\Gamma = \begin{pmatrix} -3 & 3 \\ 1 & -1 \end{pmatrix}.$$

Then its stationary distribution is $\pi = (\pi_1, \pi_2) = \left(\frac{1}{4}, \frac{3}{4}\right)$. Compute

$$\lambda = -0.1873 < 0.$$

Thus, TCs become extinct while the measures of ECs $x(t)$ converges to the unique invariant one.

Background and motivation
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Examples and numerical simulations
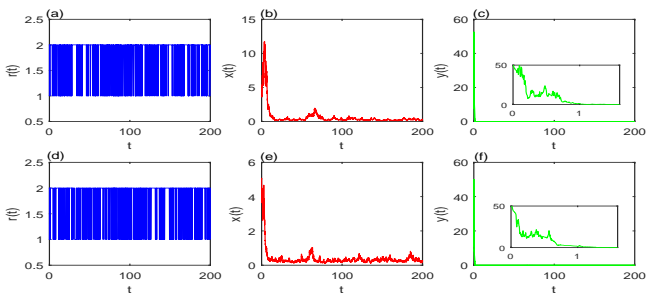
Figure: Case 1. For (3) figure (a), (b) and (c) plot a sample path of $r(t)$, $x(t)$ and $y(t)$, respectively; figure (d), (e) and (f) plot another sample path of $r(t)$, $x(t)$ and $y(t)$, respectively.

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The empirical density of ECs

- the ECs of system (1.3)
- - the ECs of system (5.2)

Figure: Case 1. The empirical density functions of ECs $x(t)$: solid line for (3); dashed line for (11), using 1000 sample points and time $t = 200$.

Background and motivation
Global positive solution
Extinction: The case $\lambda < 0$
Permanence: The case $\lambda > 0$
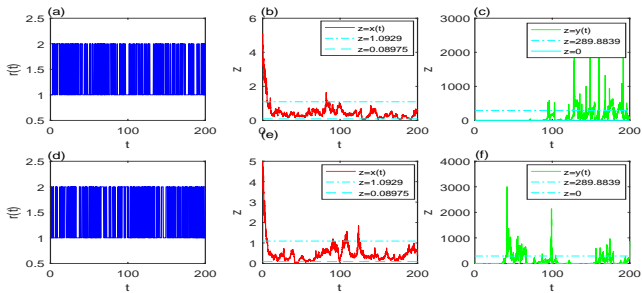**Examples and numerical simulations**

<u>Case 2.</u> 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

$$\lambda = \sum_{i=1}^{2} \pi_i \left(\alpha - \kappa_2^2(i)/2 - \sigma/\delta\right) = 0.633 > 0.$$

(3) owns a unique invariant measure ν^* on $\mathbb{R}_+^{2,0} \times \mathbb{S}$ which implies
TCs and ECs are permanent.

Background and motivation
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Figure: Case 2. For (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.

Background and motivation
Global positive solution
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Permanence: The case $\lambda > 0$
Examples and numerical simulations

The empirical density for system (1.3)
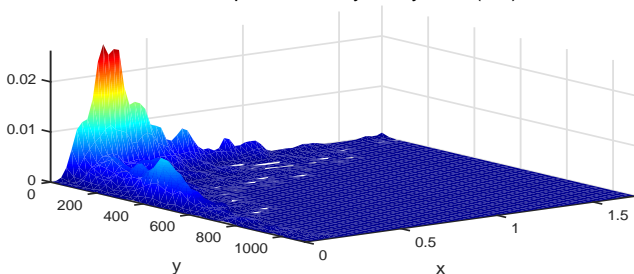
Figure: Case 2. The empirical density of the stochastic tumor-immune model (3).

Background and motivation
Global positive solution
Extinction: The case $\lambda < 0$
Permanence: The case $\lambda > 0$
Examples and numerical simulations
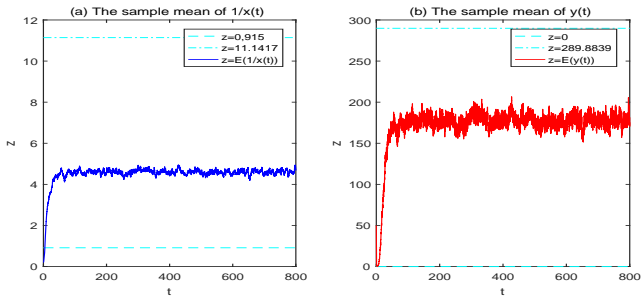
Figure: Case 2. For (3) solid lines in figure (a) and figure (b) depicts the sample mean of $1/x(t)$ and $y(t)$, respectively; the other lines are reference lines.

Thank You for your attention and concern!!!