Communications in Information and Systems
Volume 22, Number 2, 169–186, 2022

Gaussian and non-Gaussian colored noise induced escape in a tumor-immune model

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We investigate the mean first passage time of a tumor-immune model with Gaussian colored noise by the two analytic approximation methods of singular perturbation analysis and small correlation time approximation. For the first time, it is shown that the singular perturbation analysis is accurate in the sense of retaining linear term of the small correlation time parameter, while the small correlation time approximation keeps all the even higher-order terms of the same small parameter, but it neglects the linear leading order term. This contrast suggests that the singular perturbation method has a better accuracy than the small correlation approximation method when the correlation time parameter is small. As a further application of the singular perturbation method, the mean first passage time in the case of non-Gaussian noise is also deduced and discussed. It is shown that as the strength of immunization or the non-Gaussian deviation parameter increases, the mean first passage time decreases, and thus both enhancing immunization and applying heavy-tailed random perturbation can accelerate the extinction of tumor cells.

AMS 2000 subject classifications: Primary 37H10, 60H10; secondary 62P10.
Keywords and phrases: Tumor-immune model, mean first passage time, singular perturbation analysis, small correlation approximation, non-Gaussian noise.

1. Introduction

Noise-induced escape has been one of the classical topics in the field of stochastic nonlinear dynamics since Kramers' rate theory for chemical reaction [1],[2]. It has attracted wide interest ranging from stable and metastable systems[3],[4] to excitable system [5],[6] and nonlinear maps with bifurcating attractors [7] etc. Mean first passage time (MFPT), usually defined as the inverse escape rate, actually acts as the internal time scale that underlies the basic escape or the rare random transition event[8],[9],[10],[11].

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The MFPT plays a critical role investigating many noise-induced unintuitive effects such as resonant activation [12], stochastic resonance [13] and stochastic synchronization [14].

Many Fokker-Planck equation based methods including Laplace transform [8], population over flux method [3], threshold integration method [15] etc. have been developed for calculating the MFPT in nonlinear systems driven by Gaussian white noise. For nonlinear systems driven by Gaussian colored noise, the singular perturbation method [16, 17, 18] and the small correlation time approximation [21] are the two most frequently-used techniques. The former is designed for treating the Gaussian colored noise as an Ornstein-Uhlenbeck process, while the latter essentially transforms the Gaussian colored noise into an effective Gaussian white noise based on the stochastic Liouville equation and Novikov formula [19, 20, 21, 22, 23, 24]. Noting that the both techniques can be used for calculating the MFPT when the Gaussian colored noise of small correlation time is additive, but their accuracy has never been compared. Based on this consideration, with the both techniques applied to a tumor-immune model with weak Gaussian colored noise, a systematic comparison on their accuracy is carried out, and it is found when the correlation time is small, the singular perturbation method is more accurate than the small correlation time approximation method.

The anomalous diffusion of long-range spatial correlation or long-time memory is ubiquitous in biological transport processes [25, 26, 27]. Some biological experiments including the sensory system of crayfish and rat shin have offered strong indication that the noise source in this biological system may be non-Gaussian [28, 29, 30, 31, 32, 33, 34]. Thus, the non-Gaussian noise of heavy-tailed distribution [32, 33, 34] should be more appropriate for depicting the fluctuations in the tumor growth system. In order to deduce the mean first passage time in physically more realistic fluctuating environment, we further apply the more accurate method, namely the singular perturbation analysis to the tumor-immune model driven by non-Gaussian noise. In tumor-immune systems, the MFPT depicts the mean time for the tumor cells to escape from a higher stable concentration state to extinction under random perturbation, and it could provide a theoretical evidence for the medical therapy and radiotherapy cycles to certain extent [35], so the investigation on the MFPT in the general non-Gaussian colored noise case should be significant in theoretical treatment options with the cancer.

The paper is organized into four parts. In Section 2, we employ the singular perturbation method to derive the MFPT formula of the tumor-immune model. In Section 3, we derive the MFPT by means of the small correlation approximation. Comparison and discussion about the accuracy of the two methods are also given in the part. In Section 4, the singular perturbation method is applied to the tumor-immune system with non-Gaussian noise, and the theoretical results are checked and discussed. Finally, conclusion is drawn in Section 5.

2. Derivation of the MFPT by singular perturbation analysis

Increasing experimental evidences show that the severity of cancer depends on the population/concentration of the tumor cells in body, which ranges from a biochemically cancer-free state to a serious illness state. Thus how fast the transition events between the extinct and active states occur directly reflects the sensitivity of the tumor evoluting mechanism, especially it could quantitatively characterize the treatment efficiency when the therapy is introduced. This naturally proposes a necessity to explore the event timing of the tumor concentration at certain state transiting to the other state, which relates the fundamental biological events with the physical problem of the mean first passage time. Before exploring that, let us give a brief introduction to the tumor-immune model [36, 37, 38]

$$\frac{dx}{dt} = rx(1 - \frac{x}{K}) - \frac{\beta x^2}{1 + x^2} + \eta(t), \tag{1}$$

where x is the concentration of the tumor cells at time t, r denotes the growth rate, K represents the saturated concentration, and $\frac{\beta x^2}{1+x^2}$ characterizes the immunization effect. Obviously, β describes an upper limit for the immunological saturation when the concentration of tumor cells tends to infinite, and immunization effect will vanish when the tumor cells disappear. In Eq. (1), $\eta(t)$ is the Gaussian colored noise of small correlation time $\epsilon^2(\epsilon \ll 1)$ obeying

$$\langle \eta(t) \rangle = 0, \langle \eta(t)\eta(t') \rangle = \sigma^2/\epsilon^2 exp(-|t - t'|/\epsilon^2), \tag{2}$$

For applying the technique of singular perturbation technique [16, 17, 18], let us rewrite the Gaussian colored noise as $\eta(t) = \epsilon^{-1}\sigma z(t)$ so that Eq. (1) has the form

$$\begin{cases} \frac{dx}{dt} = f(x) + \frac{\sigma}{\epsilon} z \\ \frac{dz}{dt} = -\frac{z}{\epsilon^2} + \frac{\sqrt{2}}{\epsilon}\xi(t). \end{cases} \tag{3}$$

Here $f(x) = -U'(x) = rx(1 - \frac{x}{K}) - \frac{\beta x^2}{1+x^2}$ with $U(x)$ being potential function (Fig.1) and $\xi(t)$ is the standard Gaussian white noise of zero mean and

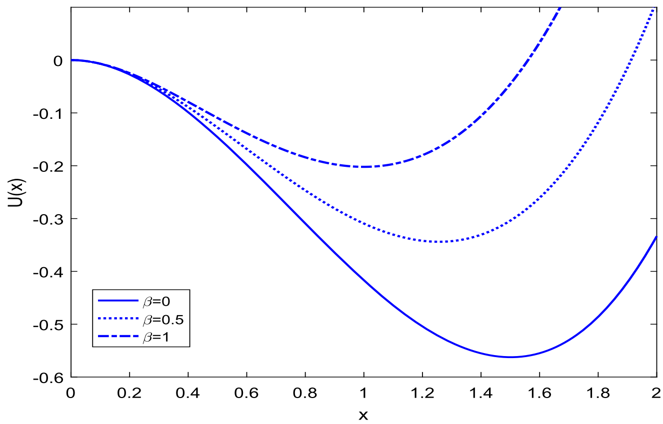


Figure 1: The schema of the effective potential when $r = 1.5$,$K = 1.5$ are fixed: $\beta = 0$ with the stable equilibrium point $x_s = 1.5$ (solid line), $\beta = 0.5$ with $x_s \approx 1.26$ (dotted line) and $\beta = 1$ with $x_s = 1$(dashed-dotted line). The other barrier at the unstable equilibrium point all lies at $x_u = 0$.

unit variance. Now let us calculate the MFPT from the potential well at x_s to the potential barrier at the unstable state at $x_u = 0$ with the singular perturbation method. Let $P(x, z, t)$ be the solution to the Fokker-Planck equation (FPE)

$$P_t = -[\partial_x(f(x) + \frac{\sigma}{\epsilon}z) - \frac{1}{\epsilon^2}\partial_z z]P + \frac{1}{\epsilon^2}\partial_z^2 P, \tag{4}$$

with the initial condition $P(x, z, 0) = \delta(x - x_u)\mu(z)$ and a half-range absorbing boundary condition at $x = x_u$. Here $\mu(z)$ denotes the initial probability density function of the O-U process $z(t)$ and it has the form $\mu(z) = exp(-z^2/2)/\sqrt{2\pi}$. Then the MFPT can be defined as

$$\langle T\rangle = \int_{x_u}^{+\infty}\int_{-\infty}^{+\infty}\int_0^{+\infty} P(x, z, t)dtdzdx. \tag{5}$$

To transform the time-dependent problem into the time-independent one, a new function [16, 17, 18]

$$G(x, z) = \int_0^{+\infty} P(x, z, t)dt, \tag{6}$$

which gives the mean time staying at points (x, z) before reaching the half-range absorbing boundary[16], is introduced to transform Eq. (5) into

$$\langle T \rangle = \int_{x_u}^{+\infty} \int_{-\infty}^{+\infty} G(x,z) dz dx. \tag{7}$$

Integrating the both sides of Eq. (4) with respect to t from zero to infinity and noting the fact that all the population escape from the potential at enough time, a time-independent equation is obtained as

$$\frac{1}{\epsilon^2}\partial_z^2 G - \left[\partial_x (f(x) + \frac{\sigma}{\epsilon} z) - \frac{1}{\epsilon^2}\partial_z z\right] G = -\delta(x - x_s)\mu(z). \tag{8}$$

Following the singular perturbation frame [16, 17, 18], Eq. (8) can be rewritten as

$$\left[\frac{1}{\epsilon^2} L_0 + \frac{1}{\epsilon} L_1 + L_2\right] G(x,z) = -\delta(x - x_s)\mu(z), \tag{9}$$

with $\mu(z) = \frac{1}{\sqrt{2\pi}} exp(-\frac{z^2}{2})$, $L_0 = \partial_z^2 + \partial_z z$, $L_1 = -\sigma\partial_x z$ and $L_2 = -\partial_x f(x)$. Due to the smallness of ϵ, we can make the ansatz

$$G(x,z) = G_0(x,z) + \epsilon G_1(x,z) + \epsilon^2 G_2(x,z) + \cdots . \tag{10}$$

Substitution of Eq. (10) into Eq. (9) and comparison of the coefficients of $\epsilon' s$ power yield a set of recurrent equations

$$L_0 G_0 = 0, \tag{11(a)}$$

$$L_0 G_1 + L_1 G_0 = 0, \tag{11(b)}$$

$$L_2 G_0 + L_0 G_2 + L_1 G_1 = -\delta(x - x_s)\mu(z), \tag{11(c)}$$

$$L_0 G_3 + L_1 G_2 + L_2 G_1 = 0. \tag{11(d)}$$

The embedded equations can be iteratively solved by means of Hermite functions [39] $\rho_n(z) = e^{-z^2/2}/\sqrt{2\pi} He_n(z)$ with $He_n(z) = (-1)^n e^{z^2/2} \times \frac{d^n}{dz^n} e^{-z^2/2}$ being Hermite polynomial, which satisfies $\partial_z \rho_n(z) = -\rho_{n+1}(z)$, $z\rho_n(z) = \rho_{n+1}(z) + \rho_{n-1}(z)$ and

$$L_0 \rho_n(z) = -n\rho_n(z), n = 0, 1, 2, \cdots \tag{12}$$

From Eq.(11(a)), it is easy to see that $G_0(x,z)$ belongs to the kernel subspace and thus there should exist

$$G_0(x,z) = r_0(x)\rho_0(z), \tag{13}$$

with $r_0(x)$ to be determined. Substitution of Eq. (13) into Eq.(11(b)) obtains

$$L_0G_1 = \sigma\rho_1(z)\partial_x r_0(x), \tag{14}$$

which implies that $G_1(x,z)$ belongs to the subspace spanned by $\rho_0(z)$ and $\rho_1(z)$, so there should hold true

$$G_1(x,z) = r_1(x)\rho_0(z) - \sigma\rho_1(z)\partial_x r_0(x). \tag{15}$$

Continuing this procedure leads to

$$\begin{aligned} L_0G_2 = {} & \rho_0(z)[\partial_x f(x)r_0(x) - \sigma^2\partial_x^2 r_0(x)] + \sigma\rho_1(z)\partial_x r_1(x) \\ & - \sigma^2\rho_2(z)\partial_x^2 r_0(x) - \delta(x-x_s)\mu(z). \end{aligned} \tag{16}$$

Since the operator L_0 is not reversible in the subspace spanned by $\rho_0(z)$, the condition of integrability for Eq. (16) implies that the coefficient for $\rho_0(z)$ must vanish, that is to say,

$$\partial_x f(x)r_0(x) - \sigma^2\partial_x^2 r_0(x) = \delta(x-x_s). \tag{17}$$

In the derivation of Eq. (17), the fact $\mu(z) = \rho_0(z)$ has been used. Eq. (17) can be solved by Green function method. Integration of the both sides of Eq. (17) with respect to x from x to x_s when x belongs to (x_u, x_s) arrives at

$$r_0(x) = \frac{1}{\sigma^2}\int_x^{x_u} exp[\int_z^{+\infty}\frac{f(x')}{\sigma^2}dx']dz \cdot exp[-\int_x^{+\infty}\frac{f(x')}{\sigma^2}dx']. \tag{18}$$

Then integration of Eq. (17) with respect to x from x to x_s when $x \in (x_s, +\infty)$ gives

$$r_0(x) = d_2 exp[-\int_x^{+\infty}\frac{f(x')}{\sigma^2}dx']. \tag{19}$$

Combining Eq. (18) with Eq. (19) and using the consistence at x_s, we solve out d_2 as

$$d_2 = \frac{1}{\sigma^2}\int_{x_s}^{x_u} exp[\int_z^{+\infty}\frac{f(x')}{\sigma^2}dx']dz, \tag{20}$$

and thus we finally obtain

$$r_0(x) = \begin{cases} \frac{1}{\sigma^2}\int_x^{x_u} exp[\int_z^{+\infty}\frac{f(x')}{\sigma^2}dx']dz \cdot exp[-\int_x^{+\infty}\frac{f(x')}{\sigma^2}dx'], x \in [x_u, x_s] \\ \frac{1}{\sigma^2}\int_{x_s}^{x_u} exp[\int_z^{+\infty}\frac{f(x')}{\sigma^2}dx']dz \cdot exp[-\int_x^{+\infty}\frac{f(x')}{\sigma^2}dx'], x \in (x_s, +\infty) \end{cases} \tag{21}$$

with constant A to be determined. With Eq. (17) in mind, from Eq. (16) there deduces

$$G_2(x,z) = r_2(x)\rho_0(z) - \sigma\rho_1(z)\partial_x r_1(x) + \frac{1}{2}\sigma^2\rho_2(z)\partial_x^2 r_0(x), \tag{22}$$

and then substituting Eq. (22) into Eq.(11(d)) obtains

$$\begin{aligned} L_0 G_3 = {} & \rho_0\left[\partial_x f(x) r_1 - \sigma^2\partial_x^2 r_1(x)\right] \\ & + \rho_1\left[\sigma\partial_x r_2(x) - \sigma\partial_x^2 f(x) r_0(x) + \frac{1}{2}\sigma^3\partial_x^3 r_0(x)\right] \\ & - \sigma^2\rho_2\partial_x^2 r_1(x) + \frac{1}{2}\rho_3\sigma^3\partial_x^3 r_0(x). \end{aligned} \tag{23}$$

Again, annihilating the coefficient of ρ_0 gives

$$\partial_x f(x) r_1 - \sigma^2\partial_x^2 r_1(x) = 0 \tag{24}$$

whose solution can be found by direct integration as

$$r_1(x) = Bexp\left(\int_{+\infty}^{x}\frac{f(x')}{\sigma^2}dx'\right). \tag{25}$$

The constant B in Eq. (25) can be determined by the half-range absorbing boundary condition $G(x_u, z)$ for $z > -\frac{\epsilon}{\sigma}f(x_u)$. According to the singular perturbation theory [16-18], the half-range absorbing boundary condition can be transformed into

$$r(x_u) = \epsilon\sigma\alpha r'(x_u) \tag{26}$$

with $\epsilon\sigma\alpha$ the Milne extrapolation length and $\alpha \equiv -\zeta(1/2) \approx 1.46$ determined by the Riemann Zeta function. Considering $r(\theta) = r_0(\theta) + \epsilon r_1(\theta) + \cdots$, there holds true $B = \frac{\alpha}{\epsilon}exp[-\int_{+\infty}^{x_u}\frac{f(x')}{\sigma^2}dx']$, and thus we have

$$r_1(x) = \frac{\alpha}{\epsilon}exp\left[\int_{x_u}^{x}\frac{f(x')}{\sigma^2}dx'\right]. \tag{27}$$

Combining Eqs. (18) and (19) with Eqs. (13) and (15) and using the consistence at x_s, then from Eq. (7) one can approximate the MFPT as

(28)
$$\langle T\rangle = \int_{x_u}^{x_s}\int_{+\infty}^{z}\frac{1}{\sigma^2}exp\left[-\int_x^{+\infty}\frac{f(x')}{\sigma^2}dx'\right]dx\cdot exp\left[\int_z^{+\infty}\frac{f(x')}{\sigma^2}dx'\right]dz$$
$$+\epsilon\frac{\alpha}{\sigma}\int_{x_u}^{+\infty} exp\left[\int_{x_u}^{x}\frac{f(x')}{\sigma^2}dx'\right]dx,$$

which is exact within the range of keeping the linear terms of ϵ.

For deriving an explicit expression, we apply the steepest descent method [8] to approximate the infinite integral in Eq. (28) to get

$$\int_{+\infty}^{z} exp[-\int_x^{+\infty}\frac{f(x')}{\sigma^2}dx']dx \approx \int_{-\infty}^{+\infty} exp[-\frac{U(x)}{\sigma^2}]dx$$
$$\approx \sqrt{\frac{2\pi}{|f'(x_s)|}}\sigma\cdot exp[-\frac{U(x_s)}{\sigma^2}],$$

and then an approximation of the MFPT is obtained as

$$\langle T\rangle = \frac{1}{\sigma}\sqrt{\frac{2\pi}{|f'(x_s)|}}\int_{x_u}^{x_s} exp\left[\int_x^{x_s}\frac{f(x')}{\sigma^2}dx'\right]dx$$
$$+\epsilon\alpha\sqrt{\frac{2\pi}{|f'(x_s)|}}exp\left[\int_{x_u}^{x_s}\frac{f(x')}{\sigma^2}dx'\right]. \tag{29}$$

3. Derivation of the MFPT by small correlation time approximation

Let $P(x,t) = \langle\delta(x(t)-x)\rangle$be the probability density function of the stochastic process (1), then the corresponding stochastic Liouville equation [8, 19, 20] reads

$$\frac{\partial P(x,t)}{\partial t} = -\frac{\partial}{\partial x}f(x)P(x,t) - \frac{\partial}{\partial x}\langle\delta(x(t)-x)\rangle. \tag{30}$$

As $x(t)$ and $\eta(t)$ are both functions of t, we take functional differential from the formal solution to the system (1) to yield

$$\frac{\delta x(t)}{\delta\eta(t')} = 1 + \int_{t'}^{t} f'(x(s))\frac{\delta x(s)}{\delta\eta(t')}ds, t\geq t' \tag{31}$$

and thus it is easy to find that $\frac{\delta x(t)}{\delta\eta(t')} = H(t-t')exp(\int_{t'}^{t} f'(x(s))ds)$. Here $H(\cdot)$ is the Heaviside unit step function. Meanwhile, with the fact $f(y)\frac{\partial}{\partial x}\delta(y-x) = \frac{\partial}{\partial x}(f(x)\delta(y-x))$ for any function $f(y)$ [20, 24] in mind, we have

(32)
$$\begin{aligned}\frac{\delta(\delta(x(t)-x))}{\delta\eta(t')} &= \frac{\partial(x(t)-x)}{\partial x(t)}\frac{\delta x(t)}{\delta\eta(t')} \\ &= -\frac{\partial(x(t)-x)}{\partial x}\frac{\delta x(t)}{\delta\eta(t')} = -\frac{\partial}{\partial x}\frac{\delta x(t)}{\delta\eta(t')}|_{x(t)=x}\delta(\delta(x(t)-x)),\end{aligned}$$

and then following the Novikov formula [19-20], there holds

(33)
$$\begin{aligned}\langle\eta(t)\delta(x(t)-x)\rangle &= \int_0^t dt'\langle\eta(t)\eta(t')\rangle\left\langle\frac{\delta[\delta(x(t)-x)]}{\delta\eta(t')}\right\rangle \\ &= -\frac{\partial}{\partial x}\int_0^t dt'\langle\eta(t)\eta(t')\rangle\left\langle exp\left[\int_{t'}^t f'(x(s))ds\right]\delta(x(t)-x)\right\rangle \\ &= -\sigma^2/\epsilon^2\frac{\partial}{\partial x}\int_0^t dt' exp[-|t-t'|/\epsilon^2] \\ &\quad\times\left\langle exp\left[\int_{t'}^t f'(x(s))ds\right]\delta(x(t)-x)\right\rangle \\ &= -\sigma^2\int_0^{1/\epsilon^2} d\theta exp(-\theta) \\ &\quad\times\left\langle\delta(x(t)-x)exp\left[\int_{t-\epsilon^2\theta}^t f'(x(s))ds\right]\right\rangle \\ &\approx -\sigma^2\int_0^{1/\epsilon^2} d\theta exp(\theta(\epsilon^2 f'(x_s)-1))\frac{\partial}{\partial x}\langle\delta(x(t)-x_s)\rangle \\ &\approx -\frac{\sigma^2}{1-\epsilon^2 f'(x_s)}\frac{\partial}{\partial x}P(x,t),\end{aligned}$$

with $\theta \triangleq (t-t')/\epsilon^2$. We emphasize that the Fox method [21] which holds true in the case of $\epsilon \ll 1$ is adopted to get the above approximations. Noting $f'(x_s) = -U''(x_s)$ and inserting Eq. (31) into Eq. (30) give an approximate Fokker-Planck equation

(34) $$P_t(x,t) = -\frac{\partial}{\partial x}f(x)P(x,t) + \frac{\sigma^2}{1-f'(x_s)\epsilon^2}\frac{\partial^2}{\partial x^2}P(x,t),$$

from which the MFPT for the system Eq. (1) can be directly acquired [8] as (35)

$$\langle T\rangle = \int_{x_u}^{+\infty} dx \int_{-\infty}^{x} \frac{(1-f'(x_s)\epsilon^2)dz}{\sigma^2} \frac{exp((1-f'(x_s)\epsilon^2)\int_{+\infty}^{z}\frac{f(x')}{\sigma^2}dx')}{exp((1-f'(x_s)\epsilon^2)\int_{+\infty}^{x}\frac{f(x')}{\sigma^2}dx')}.$$

Again, using the steepest decent method, we finally obtain

$$\langle T\rangle \approx 2\pi|f'(x_s)f'(x_u)|^{-1/2}exp((1-f'(x_s)\epsilon^2)\int_{x_u}^{x_s}\frac{f(x')}{\sigma^2}dx'). \quad (36)$$

By means of Taylor series expansion, it can be seen that Eq. (36) consists of all the even-order terms of the small parameter ϵ.

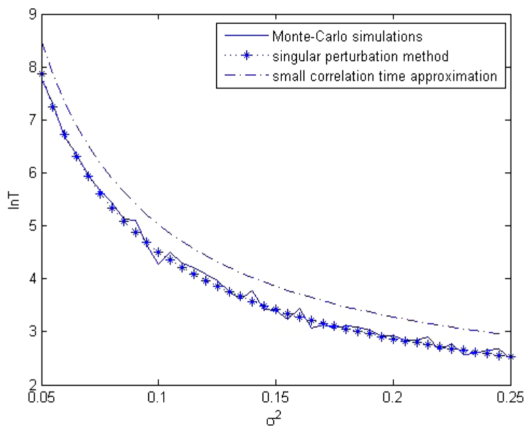


Figure 2: The MFPT of the tumor-immune system as a function of the noise intensity with $r = 1.5$, $K = 1.5$, $\beta = 0.5$, $\epsilon = 0.1$.

With Eq. (29) compared with Eq. (36), it is easy to see that although the small correlation time approximation can keep all the even higher-order terms of the small correlation time parameter, it neglects all the linear odd-order terms which include the first-order term; by contrast, the method of singular perturbation analysis is generally accurate in the sense of keeping the linear terms of the same small parameter. Since the first-order term is the leading-order one in the case of small correlation time, we are convincing that the singular perturbation method has better accuracy than the small correlation time approximation method. In fact, this theoretical analysis can be verified by Monte-Carlo simulation. In Figs. 2-4, we exhibit the theoretical results based on Eq. (29) and Eq. (36) as well as the simulated

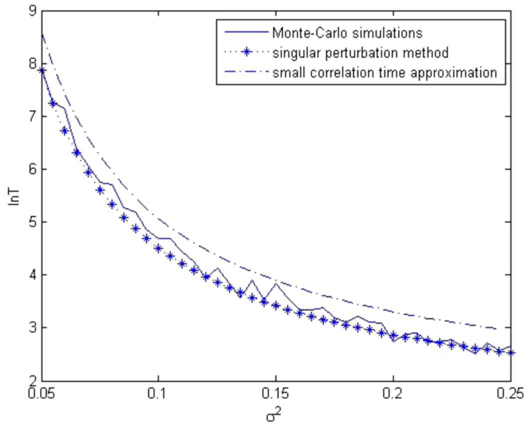


Figure 3: The MFPT of the tumor-immune system as a function of the noise intensity with $r = 1.5$, $K = 1.5$, $\beta = 0.5$, $\epsilon = 0.15$.

curves from 10^4 samples, and it is clear that in the weak noise level, the MFPT derived from the singular perturbation method has a better agreement with the simulated result than that derived from the small correlation time approximation method.

4. Effect of non-Gaussian noise on the MFPT

Let us turn to the tumor-immune model with non-Gaussian noise

$$\frac{dx}{dt} = rx\left(1 - \frac{x}{K}\right) - \frac{\beta x^2}{1 + x^2} + u(t), \tag{37}$$

where the non-Gaussian noise [24],[32, 33] $u(t)$ is described by a nonlinear Ornstein-Uhlenbeck process

$$\frac{du(t)}{dt} = -\frac{1}{\tau_0} dV_p(u)/du + \frac{1}{\tau_0}\zeta(t), \tag{38}$$

with $V_p(u) = D/(\tau_0(p-1))ln(1 + \tau_0/D(p-1)u^2/2)$. $\zeta(t)$ is Gaussian white noise with noise intensity D, the deviation parameter p characterizes the non-Gaussianity, and τ_0 is correlation time. For $p > 1$, $u(t)$ denotes the heavy-tailed non-Gaussian noise and corresponds to the bounded noise for $p < 1$.

In order to apply the singular perturbation method to derive the MFPT of the system Eq. (37), let us follow the path integral technique [32, 33].

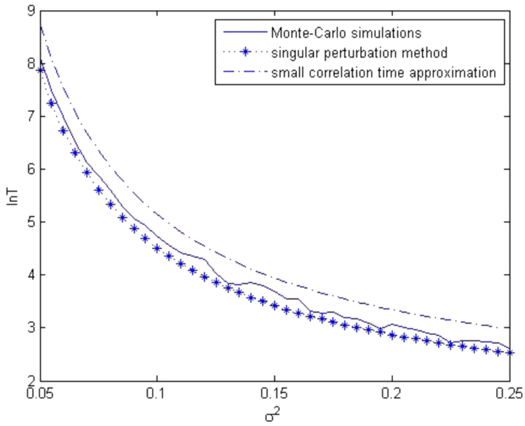


Figure 4: The MFPT of the tumor-immune system as a function of the noise intensity with $r = 1.5$, $K = 1.5$, $\beta = 0.5$, $\epsilon = 0.2$.

When $|p-1| \ll 1$, the above non-Gaussian colored noise can be effectively approximated to the Gaussian colored one

$$\frac{du(t)}{dt} = -\frac{1}{\tau_1}u(t) + \frac{1}{\tau_1}\xi(t),$$

where $\frac{1}{\tau_0}dv_p(u)/du \approx \frac{u}{\tau_1}$, $\tau_1 = \frac{2(2-p)}{5-3p}\tau_0$ and Gaussian white noise $\xi(t)$ satisfies $\langle\xi(t)\rangle = 0$, $\langle\xi(t)\xi(t')\rangle = 2D_1\delta(t-t')$ with $D_1 = (2(2-p)/(5-3p))^2 D$. To make sense of τ_1, we can see that here p should belong to $(0, 5/3)$. With $\sqrt{\tau_1}$ being the small perturbation parameter and repeating the procedure in Section 2, we derive the MFPT in the non-Gaussian noise case

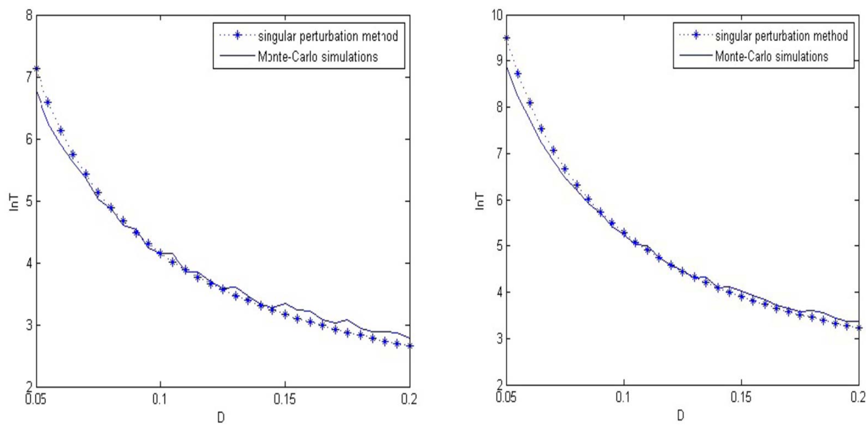
(39)

$$\langle T\rangle = \int_{x_u}^{x_s}\int_{+\infty}^{z}\frac{1}{D_1}exp\left(-\int_x^{+\infty}\frac{f(x')}{D_1}dx'\right)dx exp\left(\int_z^{+\infty}\frac{f(x')}{D_1}dx'\right)dz + \alpha\sqrt{\frac{\tau_1}{D_1}}\int_{x_u}^{+\infty}exp\left(\int_{x_u}^{x}\frac{f(x')}{D_1}dx'\right)dx,$$

which is exact within the range of keeping the linear terms of $\sqrt{\tau_1}$. Similar to Eq. (29), Eq. (39) also can be approximated as

$$\langle T\rangle = \sqrt{\frac{2\pi}{|f'(x_s)|D_1}}\int_{x_u}^{x_s} exp\left(\int_x^{x_s}\frac{f(x')}{D_1}dx'\right)dx + \alpha\sqrt{\frac{\pi\tau_1}{|f'(x_s)|}}exp\left(\int_{x_u}^{x_s}\frac{f(x')}{D_1}dx'\right), \tag{40}$$

which holds true in the range of $|p-1| \ll 1$ and$\tau_1 \ll 1$, as shown in Fig. 5.



(a) (b)

Figure 5: The MFPT of the tumor cell growth system driven by non-Gaussian noise as a function of the noise intensity with $\tau_0 = 0.1$ (a) $p = 1.2$;(b) $p = 0.9$.

Now let us check the effect of the deviation parameter p and the immunological coefficient β on the MFPT of the tumor-immune system. From Figs. 2-5, the MFPT of the tumor-immune system declines with the increase of the noise intensity, and this means the growth of tumor can be inhibited by adding external perturbation. Noting that the MFPT decreases as the deviation parameter increases, which equivalently implies that the MFPT decreases as the non-Gaussian noise turns from the bounded-noise case ($p < 1$) to the heavy-tailed case ($p > 1$), so we can infer that the heavy-tailed perturbation might be more effective in the potential treatment on cancer. Besides, Fig. 6 shows that increase in the strength of immunization also leads to a decline of MFPT, and thus our result further confirms that

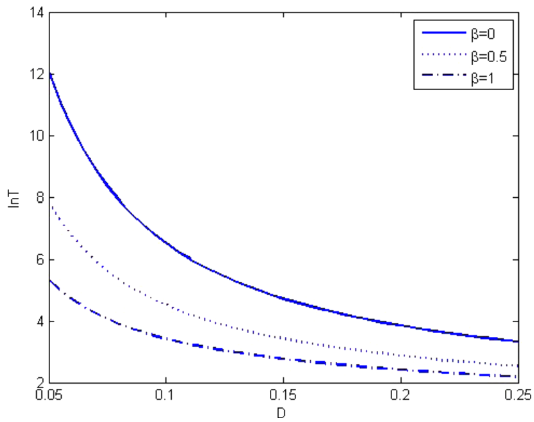


Figure 6: The MFPT of the tumor-immune system driven by Gaussian colored noise as a function of the noise intensity with different strengths of immunization where $r = 1.5$, $K = 1.5$,$\epsilon = 0.2$.

in given perturbation, the improvement of the effectiveness of the immune system can accelerate the extinction of the cancer [37].

5. Conclusion

We have explored the MFPT in tumor-immune model with Gaussian/non-Gaussian colored noise. At first, the singular perturbation method and the small correlation time approximation method have been applied to the tumor-immune model with the weak Gaussian colored noise for analytically calculating the MFPT. It is found that the small correlation time approximation neglects all the linear odd-order terms of the small correlation time parameter, although it can keep all the even higher-order terms. By contrast, the method of singular perturbation analysis is accurate in the sense of keeping the linear terms of the same small parameter. With the analytical results compared with that obtained from Monte-Carlo simulation, the same conclusion holds true, namely, the result derived from the singular perturbation method has a better agreement with the simulated result than that derived from the small correlation time approximation method in the weak noise level. And then, we apply the singular perturbation method to the system with non-Gaussian colored noise. It is shown that the increase in the strength of immunization is helpful for accelerating the extinction of the tumor cells. Moreover, since the increase of the non-Gaussian deviation parameter can lead to a reduction of the MFPT, the heavy-tailed non-Gaussian perturbation has more benefit for tumor treatment.

Acknowledgments

The work was financially supported by Chinese National Natural Science Foundation with Grant Nos. 11372233, 11972270, 12101473 and the Basic Research Program of Natural Science in Shaanxi Province with Grant Nos. 2021JQ-764 and 2021JQ-766.

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Received October 31, 2021