Stochastic properties of tumor growth with coupling between non-Gaussian and Gaussian noise terms*

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Dynamical behavior of tumor-growth model with coupling between non-Gaussian and Gaussian noise terms is investigated. The departure from the Gaussian noise can not only reduce the probability of tumor cells in the active state, induce the minimum of the average tumor-cell population to move toward a smaller non-Gaussian noise, but also decrease the mean first-passage time. The increase of white-noise intensity can increase the tumor-cell population and shorten the mean first-passage time, while the coupling strength between noise terms has opposite effects, and the noise correlation time has a very small effect.

Keywords: tumor growth, stochastic property, non-Gaussian noise, Gaussian noise

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1. Introduction

Since tumor growth is a complex process that is dependent ultimately on tumor cells proliferating and spreading in host tissues, chemotherapy remains a traditional form of therapy for most advanced cancers. Shortly after Ehrlich proposed the idea that the immune system scans and eradicates the nascent transformed cells before they are manifested clinically,[1] experiments verified that tumor could be repressed by the immune system, and immune surveillance was postulated.[2] In recent years, a sufficient amount of experimental and epidemiologic evidences have been accumulated in favor of this hypothesis and demonstrated that the immune system can suppress tumors.[3,4]

Recently, the investigations into tumor-cell growth have attracted intensive attentions due to its potential applications in various fields,[5−18] including noise-induced phase transition,[11] control of tumor growth,[12] the mean first passage time of the tumor-cell growth system driven by colour Gaussian noise,[13] the stochastic resonance phenomenon induced by the multiplicative periodic signal in a cancer growth system with cross-correlated noises and time delay,[14] the effect of time delay on tumor growth,[15,16] and the bounded-noise-induced transitions in the transitory tumor-cell density.[17] It has been revealed that an enhancement of the immune response increases the pressure on the tumor surface, and therefore limits its development. A large number of experimental data from various mouse models of cancer, together with convincing, correlative clinical data from human patients have provided clear evidences that the immune system may maintain cancers in a dormant state.[18] In most of previous analyses, the fluctuations in biological systems were assumed to be Gaussian noise,[5−20] and the stationary properties of non-Gaussian noise were often considered in a single-mode laser system.[21] However, the non-Gaussian noise can be interpreted to be more related to biological systems[22] and natural phenomena.[23] Some recent experimental results for one kind of crayfish and rat skin offer strong indications that there could be non-Gaussian noise sources in these sensory systems.[24,25] Moreover, the stochastic resonance in a FitzHugh–Nagumo neural system subjecting to multiplicative non-Gaussian noise has been studied.[26] However, for different patients, there appear different tumor growth and decay processes. Thus, the dynamical behavior of tumor-growth model

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with coupling between non-Gaussian and Gaussian white-noise terms requires to be discussed.

In this paper, a tumor-growth model with coupling between non-Gaussian and Gaussian white-noise terms is investigated. In Section 2, a general form of the Fokker–Planck equation with coupling between non-Gaussian and Gaussian white-noise terms is obtained. In Section 3, the tumor-growth model is presented. An approximate Fokker–Planck equation is derived in the absence of the coupling between multiplicative non-Gaussian noise and additive Gaussian white-noise terms by means of the method of path integral. In Section 4, the effects of non-Gaussian noise on the average population of tumor cells and the mean first-passage time (MFPT) are analyzed. In Section 5, the numerical simulations are performed to check the validity of the theoretical results. Finally, we present a brief discussion and the main conclusions.

2. General form of Fokker–Planck equation

For a stochastic system that contains non-Gaussian noise with non-Markovianicity, the path-integral approach can be applied to obtain a consistent Markovian approximation.

A general stochastic system can be described by the following differential equation:

$$\frac{\mathrm{d}x}{\mathrm{d}t} = f(x) + g_1(x)\,\xi(t) + g_2(x)\,\eta(t), \tag{1}$$

where $f(x)$ is the deterministic part, $g_1(x)$ and $g_2(x)$ are coefficients of non-Gaussian noise $\xi(t)$ and and Gaussian noise $\eta(t)$, respectively. The $\eta(t)$ is the additive Gaussian white noise, and $\xi(t)$ has a non-Gaussian distribution

$$\frac{\mathrm{d}\xi(t)}{\mathrm{d}t} = -\frac{1}{\tau}\frac{\mathrm{d}}{\mathrm{d}\xi}V_q(\xi) + \frac{1}{\tau}\Gamma(t), \tag{2}$$

and

$$V_q(\xi) = \frac{D}{\tau(q-1)}\ln\left[1 + \frac{\tau}{D}(q-1)\frac{\xi^2}{2}\right]. \tag{3}$$

The parameter D denotes the strength of the multiplicative Gaussian noise, q denotes the departure from the Gaussian noise, and $\Gamma(t)$ is the Gaussian noise. In the limit $q \to 1$, the process $\xi(t)$ coincides with the Gaussian colored noise with a noise correlation time τ. That is, it is an Ornstein–Uhlenbeck process with correlation function given by $\langle \xi(t)\,\xi(t')\rangle = (D/\tau)\,\mathrm{e}^{-|t-t'|/\tau}$. If $q \neq 1$, the $\xi(t)$ is a non-Gaussian process. The statistical properties of $\Gamma(t)$ and $\eta(t)$ are characterized by their first and second moments

$$\begin{aligned}
&\langle \Gamma(t)\rangle = \langle \eta(t)\rangle = 0,\\
&\langle \Gamma(t)\,\Gamma(t')\rangle = 2D\delta(t-t'),\\
&\langle \eta(t)\,\eta(t')\rangle = 2Q\delta(t-t'),\\
&\langle \Gamma_1(t)\,\eta(t')\rangle = \langle \Gamma_1(t')\,\eta(t)\rangle = 2\lambda\sqrt{DQ}\,\delta(t-t'),
\end{aligned} \tag{4}$$

where Q is the intensity of the Gaussian noise $\eta(t)$, λ is the coupling between the two noise terms, and $-1 \leq \lambda \leq 1$.

The stationary probability distribution of Eq. (2) can be given by[27–29]

$$P_q^{\mathrm{st}}(\xi) = \frac{1}{Z_q}\left[1 + \frac{\tau}{D}(q-1)\frac{\xi^2}{2}\right]^{-1/(q-1)}, \tag{5}$$

where Z_q is a normalization constant. This distribution can be normalized for $q < 3$ and the moments of ξ are given by $\langle\xi\rangle = 0$ and $\langle\xi^2\rangle = 2\mathrm{D}/\tau\,(5-3\mathrm{q})$, the second moment is finite only for $\mathrm{q} < 5/3$.

Using the path-integral approach,[27–29] we have

$$\begin{aligned}
\frac{1}{\tau}\frac{\mathrm{d}}{\mathrm{d}\xi}V_q(\xi) &= \frac{\xi}{\tau}\left[1 + \frac{\tau}{D}(q-1)\frac{\xi^2}{2}\right]^{-1}\\
&\approx \frac{\xi}{\tau}\left[1 + \frac{\tau}{D}(q-1)\frac{\langle\xi^2\rangle}{2}\right]^{-1} = \frac{\xi}{\tau_{\mathrm{eff}}},
\end{aligned} \tag{6}$$

with

$$\tau_{\mathrm{eff}} = \frac{2(2-q)}{5-3q}\tau. \tag{7}$$

In principle, the approximation applied in Eqs. (6) and (7) is valid for $|q-1| \ll 1$. Thus, equation (2) can be reduced to a re-normalized Ornstein–Uhlenbeck process with an effective noise correlation time τ_{eff} and an effective multiplicative noise intensity $D_{\mathrm{eff}} = (2(2-q)/(5-3q))^2 D$. Apparently, $\tau_{\mathrm{eff}} \to \tau$ and $D_{\mathrm{eff}} \to D$ when $q \to 1$. Therefore, the non-Gaussian noise ξ in Eq. (2) can be rewritten as

$$\frac{\mathrm{d}\xi}{\mathrm{d}t} = -\frac{1}{\tau_{\mathrm{eff}}}\xi + \frac{1}{\tau_{\mathrm{eff}}}\Gamma_1(t), \tag{8}$$

with

$$\begin{aligned}
&\langle \Gamma_1(t)\,\Gamma_1(t')\rangle = 2D_{\mathrm{eff}}\delta(t-t'),\\
&\langle \Gamma_1(t)\,\eta(t')\rangle = \langle \Gamma_1(t')\,\eta(t)\rangle = 2\lambda\sqrt{D_{\mathrm{eff}}Q}\,\delta(t-t').
\end{aligned} \tag{9}$$

Applying the functional analysis, the Fokker–Planck equation corresponding to Eqs. (1), (8), and (9) can be written as

$$\begin{aligned}\frac{\partial P(x,t)}{\partial t} &= -\frac{\partial}{\partial x}f(x)P(x,t)\\ &+\frac{D_{\rm eff}}{1-\tau_{\rm eff}\left(f'(x_{\rm s})-(g_1'(x_{\rm s})/g_1(x_{\rm s}))f(x_{\rm s})\right)}\frac{\partial}{\partial x}g_1(x)\frac{\partial}{\partial x}g_1(x)P(x,t)\\ &+\lambda\sqrt{D_{\rm eff}Q}\frac{\partial}{\partial x}g_1(x)\frac{\partial}{\partial x}g_2(x)P(x,t)+\lambda\sqrt{D_{\rm eff}Q}\frac{\partial}{\partial x}g_2(x)\frac{\partial}{\partial x}g_1(x)P(x,t)\\ &+Q\frac{\partial}{\partial x}g_2(x)\frac{\partial}{\partial x}g_2(x)P(x,t),\end{aligned} \tag{10}$$

where $x_{\rm s}$ is the steady-state value of the potential. The detailed derivation of Eq. (10) is presented in Ref. [30].

3. Theoretical analysis of tumor-growth model

An enzyme dynamical model of tumor growth in immune system[31] is given by

$$\begin{aligned}&\text{Normal Cells} \xrightarrow{\gamma} X,\\ &X\xrightarrow{\lambda}2X,\\ &X+E_0\xrightarrow{k_1}E\xrightarrow{k_2}E_0+P,\\ &P\xrightarrow{k_3}\ ,\end{aligned} \tag{11}$$

where γ, λ, k_1, k_2, and k_3 are velocity coefficients, X denotes cancer cells, P denotes dead cancer cells, E_0 denotes immune cells, and E denotes the compounds of cancer cells and immune cells. An equivalent single-variable deterministic differential equation can be obtained by simplifying this model.[32,33] Then, we have

$$\frac{{\rm d}x}{{\rm d}t}=rx\left(1-\frac{x}{k}\right)-\frac{\beta x^2}{1+x^2}, \tag{12}$$

where x is the population of tumor cells, r is the linear birth rate per capita, k is the carrying capacity of the environment, $\beta x^2/(1+x^2)$ is an immune form and means the ability of immune cells to recognize and attack tumor cells, and β is the immune coefficient.

It is clear that equation (12) describes a deterministic model. However, there are some kinds of random fluctuations appearing in Eq. (12) when the tumor system is driven by multiplicative and additive noise terms. In the biological or physical context, multiplicative noise can be identified as internal noise which influences the effective birth rate of tumor cells. The internal noise is based on mechanisms inside the tumor without contact with its environment. It is assumed to be generated directly by a self-organization manner within the tumor system. For example, a great deal of genetically different tumor cells within the same system can be generated by gene mutations. The additive noise can be equated as external noise which is caused by its environment. It is supposed to originate from the thermal fluctuations and the extracellular matrix embedding the tumor which comprises the production of cytokines in the microenvironment of the tumor cells. Though the origins of the internal and external noises are different, there may exist coupling between both stochastic processes.[5] For example, adjacent to the malignant tissue, the normal one produces antigrowth signal to avoid an uncontrolled growth. The tumor may evade these signals by altering or down regulating the corresponding receptor, and even develop self sufficiency in generating growth signals. Meanwhile, the competition between normal tissue and nascent transformed cells, who obtain the nutrients, will be intensified when the tumor tissue is in the growing process. For additive (external) noise, the use of Gaussian noise is reasonable in physical, biological, and other systems. While for multiplicative (internal) noise in biological systems, there are some experimental evidences indicating that the noise sources could be non-Gaussian.[24,25] Though the interaction in tumor-immune system is certainly much more complicated in detail, equation (12) combined with random noise terms could be able to describe some genetic properties of real processes.

Thus for an asymmetric double well driven by the multiplicative non-Gaussian and additive Gaussian white noise terms, one has

$$\frac{{\rm d}x}{{\rm d}t}=rx\left(1-\frac{x}{k}\right)-\frac{\beta x^2}{1+x^2}-x\xi(t)+\eta(t), \tag{13}$$

where $\xi(t)$ is a multiplicative non-Gaussian noise, and $\eta(t)$ is an additive Gaussian white noise. The noise terms are given by Eqs. (2)–(4). Applying the approximate method of deriving Eq. (6) and the functional analysis with the steady-state value $x_{\rm s}$ which is obtained by the method of recursion, the Fokker–Planck equation corresponding to Eq. (13) can be obtained

from Eq. (10) as

$$\frac{\partial P(x,t)}{\partial t} = -\frac{\partial}{\partial x}[A(x)P(x,t)] + \frac{\partial^2}{\partial x^2}[B(x)P(x,t)], \quad (14)$$

with

$$\begin{aligned} A(x) &= f(x) + \frac{D_{\rm eff}}{T_1}x - \lambda\sqrt{D_{\rm eff}Q}, \\ B(x) &= \frac{D_{\rm eff}}{T_1}x^2 - 2\lambda\sqrt{D_{\rm eff}Q}x + Q, \\ f(x) &= rx\left(1-\frac{x}{k}\right) - \frac{\beta x^2}{1+x^2}, \\ T_1 &= 1 - \tau_{\rm eff}f'(x_{\rm s}). \end{aligned} \quad (15)$$

Then, the steady-state probability distribution function $P_{\rm st}(x)$ of this tumor model can be derived if the coupling $\lambda \neq 0$, and we have

$$P_{\rm st}(x) = N\exp(-U_{\rm eff}/Q), \quad (16)$$

where N is a normalization constant ensuring $\int_0^\infty P_{\rm st}(x){\rm d}x = 1$. The modified potential $U_{\rm eff}$ is given by

$$\begin{aligned} U_{\rm eff} &= M_1 \arctan\frac{D_1x/T_1 - \lambda\sqrt{D_1}}{\sqrt{D_1/T_1 - \lambda^2 D_1}} \\ &\quad + M_2\arctan x + M_3\ln\left(1+x^2\right) \\ &\quad + M_4\ln\left(D_1Qx^2/T_1 - 2Q\lambda\sqrt{D_1} + Q\right) \\ &\quad + \frac{rT_1}{kD_1Q}x, \end{aligned} \quad (17)$$

where

$$\begin{aligned} M_1 &= -\frac{1}{\sqrt{D_1/T_1 - \lambda^2 D_1}} \\ &\quad \times\left[\frac{kr\lambda\sqrt{D_1}/T_1 + r/T_1 - 2r\lambda^2}{kD_1/{T_1}^2} \right. \\ &\quad \left. + \frac{\beta\left(D_1/T_1 - 2\lambda^2 D_1 - 1\right)}{\left(D_1/T_1 - 1\right)^2 + 4\lambda^2 D_1}\right], \\ M_2 &= \frac{\beta\left(D_1/T_1 - 1\right)}{\left(D_1/T_1 - 1\right)^2 + 4\lambda^2 D_1}, \\ M_3 &= -\frac{\beta\lambda\sqrt{D_1}}{\left(D_1/T_1 - 1\right)^2 + 4\lambda^2 D_1}, \\ M_4 &= \frac{\beta\lambda\sqrt{D_1}}{\left(D_1/T_1 - 1\right)^2 + 4\lambda^2 D_1} + \frac{r\lambda}{kD_1{}^{3/2}/T_1} \\ &\quad - \frac{r}{2D_1/T_1} + \frac{Q}{2}, \\ D_1 &= D_{\rm eff}/Q. \end{aligned} \quad (18)$$

In molecular biology, the interaction of immune system with tumors is a classical challenge.[34] This will infer that the statistical fluctuation affecting the immune system does make the tumor cells evade from immune control. Some experimental evidences are presented for 16 types of tumors, and the growth of tumor cell surface diffusion may be the main responsible mechanism in vivo.[35]

As a consequence, the process of tumor population growth can be simulated by a motion of a fictitious particle in a potential $U_{\rm eff}(x)$, as shown in Fig. 1(a). The modified potential is an asymmetrical bistable potential well. The positions of the potential minima, x_1 and x_2, are regarded as the inactive and the active states of tumor cells, respectively. The position of the potential maximum x_u is regarded as an unstable state. The steady-state probability distribution of Eq. (16) is plotted as lines in Fig. 1(b). From Fig. 1(b), it can be seen that there is a double-peak structure in the curve of $P_{\rm st}(x)$. The left peak is much higher than the right peak. That is, the tumor cell lies mostly in the inactive state instead of in the active state. The right peak decreases as the value of q increases. This means that the tumor-cell population can decrease when increasing the departure q from Gaussian noise. In order to check the validity of the approximate method employed in the derivation, it is necessary to perform numerical simulation. The numerical results (denoted by symbols) based on Eq. (2) is also plotted in Fig. 1(b). The height of the peaks of the theoretical analysis is lower than that of the simulations.

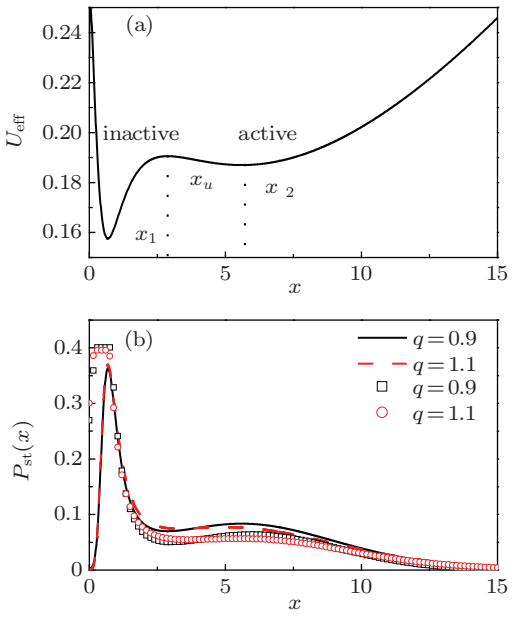


Fig. 1. (colour online) (a) An asymmetric double-well structure, and (b) the stationary probability distribution $P_{\rm st}(x)$ as functions of x when $r=1$, $k=10$, $\beta=2$, $Q=0.02$, $D=0.1$, $\tau=0.3$, and $\lambda=0.2$.

Though noticeable deviations can be observed, the result shows a good agreement between the theoretical analysis and the numerical simulations.

In Fig. 1, the two minima of x_1 and x_2 in the potential $U_{\rm eff}(x)$ correspond to two peaks in the steady-state probability distribution $P_{\rm st}(x)$. The deeper the minimum potential is, the higher of the peak in the distribution is.

4. Effects of non-Gaussian noise

In order to investigate the effects of non-Gaussian noise in the system, the stationary mean value $\langle x\rangle$ of the tumor cell population x, and the mean first passage time T are introduced.

The stationary mean value of the tumor-cell population x is given by

$$\langle x\rangle = \int_0^\infty x P_{\rm st}\,(x)\,{\rm d}x, \tag{19}$$

where $\langle x\rangle$ refers to the average population of tumor cells. Decreasing x means the decaying of tumor cells. The average population $\langle x\rangle$ as a function of the non-Gaussian noise strength D is plotted in Fig. 2 when the departure from the Gaussian noise q, the white-noise intensity Q, the noise correlation time τ, and the coupling strength λ are varied. It is found that there is a valley in $\langle x\rangle$ when the noise intensity D increases. When q, Q, τ, and λ are varied, either the position or the shape of the valley is changed. That is, only with suitable non-Gaussian and Gaussian white noise, the minimum of average tumor cell population exists. It is different from the monotonic characteristics of average tumor cell population without non-Gaussian noise.[15,16] The existence of the stable average tumor cell population is helpful in controlling the growth of tumor cells.

The average population $\langle x\rangle$ is plotted as a function of the noise strength D in Fig. 2(a) when the departure q from Gaussian noise is varied. Though the depth of the valley in $\langle x\rangle$ is almost constant, the position of the valley moves toward a smaller value of D, and the valley becomes sharper and deeper when q increases. The $\langle x\rangle$ is plotted as a function of D in Fig. 2(b) when the white noise intensity Q is varied. The depth of the valley in $\langle x\rangle$ reduces, while the position of the valley moves toward a larger value

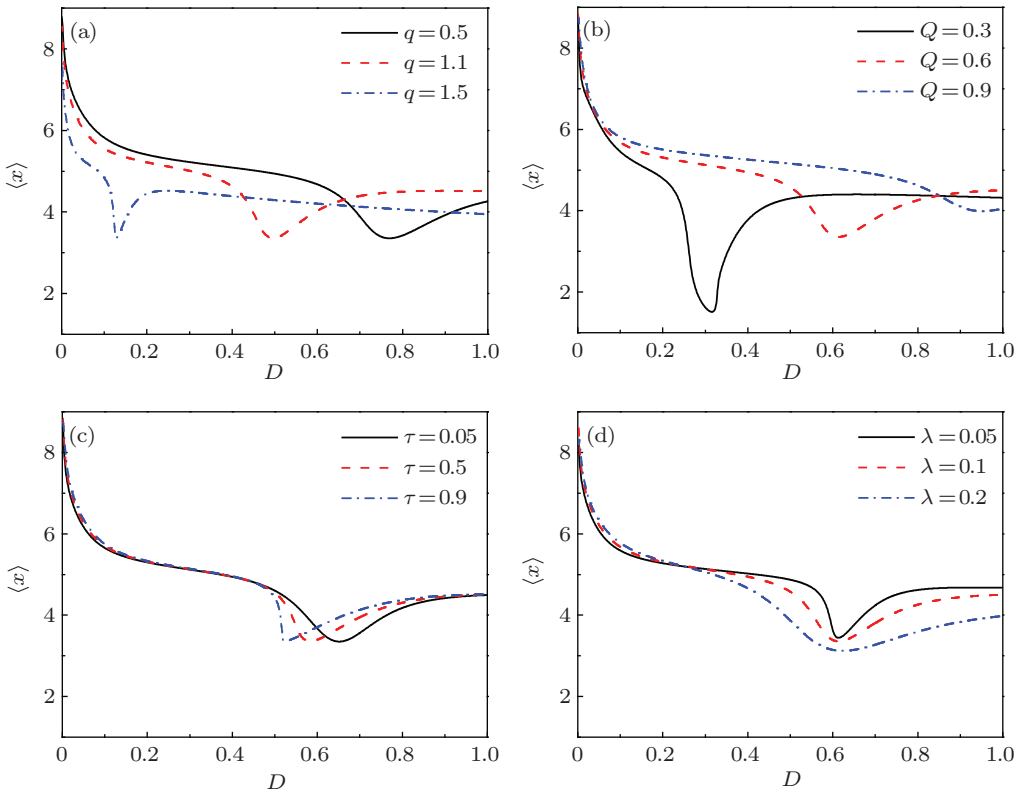


Fig. 2. (colour online) Average population of tumor cells $\langle x\rangle$ is plotted as a function of D for different values of q, Q, τ, and λ with $r = 1$, $k = 10$, and $\beta = 2$. (a) The q is varied when $Q = 0.6$, $\tau = 0.3$, and $\lambda = 0.1$. (b) The Q is varied when $q = 0.9$, $\tau = 0.3$, and $\lambda = 0.1$. (c) The τ is varied when $q = 0.9$, $Q = 0.6$, and $\lambda = 0.1$. (d) The λ is varied when $q = 0.9$, $Q = 0.6$, and $\tau = 0.3$.

of D, and the width of the valley is also broadened as Q increases. The $\langle x\rangle$ is plotted as a function of D in Fig. 2(c) when the noise correlation time τ is varied. The depth of the valley in $\langle x\rangle$ is almost constant, while the position of the valley moved toward a smaller value of D, and the valley becomes sharper when τ increases. The $\langle x\rangle$ is plotted as a function of D in Fig. 2(d) when the coupling λ between noise terms is varied. The depth of the valley in $\langle x\rangle$ increases, while the position of the valley is almost constant, and the width of the valley is also broadened when λ increases. From Fig. 2, it can be seen that the deepest valley can be obtained by decreasing Q and increasing λ.

Tumor growth is a stochastic process that is influenced by environment. The resonant activation phenomenon occurs at certain intensity of the multiplicative non-Gaussian noise. Thus, a minimum of average tumor cell population occurs. This is a suitable opportunity of treatment.

In cancer biology, it is of interest whether a tumor that reaches some certain size can suffer extinction by external or internal interference, namely, whether it is possible that the influences of the noises and the immune system can induce the extinction of the tumor. The transition between active states and inactive states is further discussed by investigating the MFPT. The expression of the MFPT for a particle transiting from the initial state x_1 to the final state x_2 is given by[28,36−39]

$$T\left(x_1 \to x_2\right) = \int_{x_1}^{x_2} \frac{\mathrm{d}x}{B\left(x\right) P_{\mathrm{st}}\left(x\right)} \times \int_{-\infty}^{x} P_{\mathrm{st}}\left(y\right) \mathrm{d}y. \tag{20}$$

The mean first-passage time T as a function of D is plotted in Fig. 3 when q, Q, τ, and λ are varied. There are two peaks and a valley between two peaks in the MFPT.

The mean first-passage time $\ln T$ is plotted as a function of D in Fig. 3(a) when q is varied. From Fig. 3(a), it can be seen that the depth of the valley and the height of the peaks are almost constant, while the locations of the valley and peaks are shifted to a smaller value of D as q increases. The MFPT $\ln T$ is plotted as a function of D in Fig. 3(b) when Q is varied. From Fig. 3(b), it is clear that the depth of the valley and the height of the peaks decreases while the positions of the valley and peaks are shifted to a larger value of D as Q increases. The highest peak is obtained when $Q = 0.3$, $q = 0.9$, $\tau = 0.3$, and $\lambda = 0.1$. The highest peak decreases quickly when Q increases. The MFPT $\ln T$ is plotted as a function of D in Fig. 3(c) when τ is varied. From Fig. 3(c), it is clear that the depth of the valley and the height of the peaks are almost constant while the positions of the highest peak are shifted to a smaller value of D as τ increases. The highest peak becomes narrower and higher, and the position of the lower peak is slightly shifted to a larger value of D when τ increases. The MFPT $\ln T$ is plotted as a function of D in Fig. 3(d) when λ is varied. From Fig. 3(d), it is seen that the height of the left peak decreases and that of the right peak increases when λ increases. Meanwhile, the depth of the valley increases with the increase in λ. The positions of the valley and the right peak move toward a smaller value of D when λ increases, while the position of the left peak moves toward a larger value of D when λ increases. From Fig. 3, it is seen that the positions of two peaks and the valley mainly depend on the departure q from Gaussian noise and the white-noise intensity Q, while the heights of two peaks and the valley depend mainly on the Gaussian noise intensity Q and the coupling strength of two noises λ. The influence of noise correlation time τ on the the curves of MFPT is quite weak. It is worth pointing out that the emergence of the highest peak in MFPT allows more time for oncotherapy.

The feature mentioned above differs from the unimodal distribution of MFPT in a modified logistic growth model.[5,9] Due to the influence of stochastic process, bimodal distribution occurs as a function of the multiplicative non-Gaussian noise, which indicates suitable opportunities in early treatment and terminal cure. Since the fluctuation of immune system is small and the influence of environment fluctuation is a result of a long cycle, the average tumor cell population and the mean first-passage time is weakly dependent on the correlation time and coupling strength. The influence of non-Gaussian noise increases with increasing values of the departure from Gaussian noise in inactive state, and then the immune system plays a greater role in the therapy. Thus, the average tumor cell population and the mean first-passage time are small, but the time of therapy is slightly longer.

In this paper, non-Gaussian and Gaussian noises are chosen to describe the random fluctuations of the levels of the immune system instead of bounded noise model.[17] These perturbations can limit the tumor cell in a controllable inactive state and restrain the diffusion of the tumor cell.

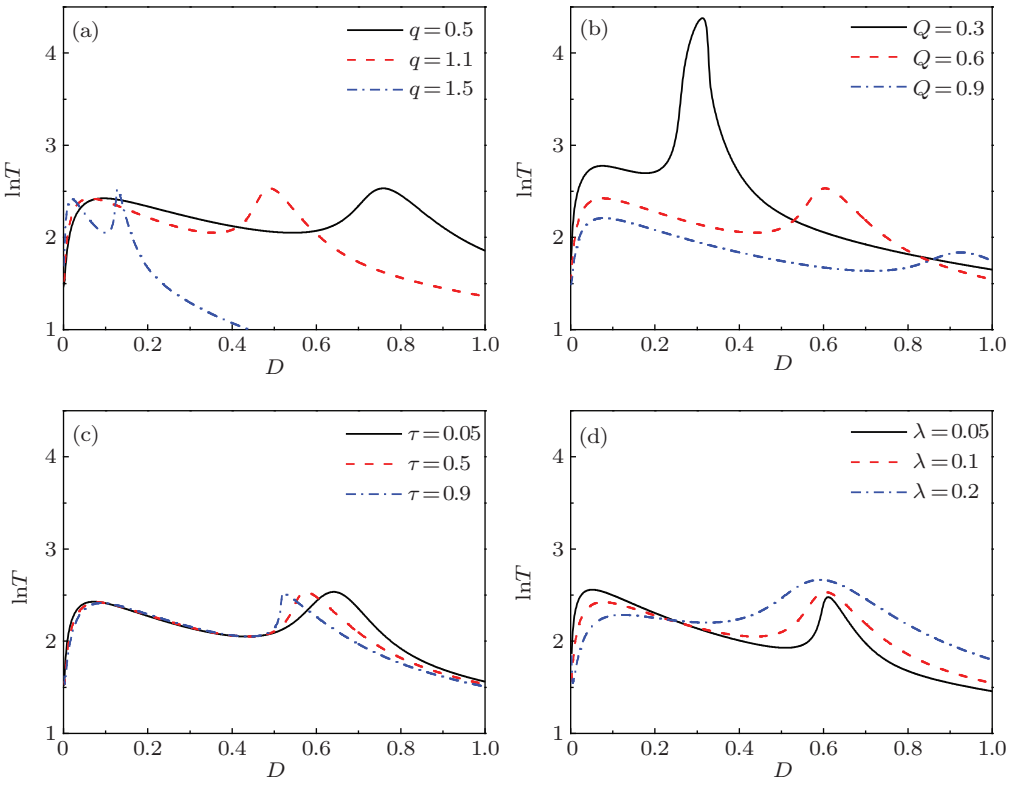


Fig. 3. (colour online) Mean first-passage time $\ln T$ is plotted as a function of D for different values of q, Q, τ, and λ with $r = 1$, $k = 10$, and $\beta = 2$. (a) The q is varied when $Q = 0.6$, $\tau = 0.3$, and $\lambda = 0.1$. (b) The Q is varied when $q = 0.9$, $\tau = 0.3$, and $\lambda = 0.1$. (c) The τ is varied when $q = 0.9$, $Q = 0.6$, and $\lambda = 0.1$. (d) The λ is varied when $q = 0.9$, $Q = 0.6$, and $\tau = 0.3$.

5. Numerical simulations

In order to check the validity of the approximately theoretical analysis, it is necessary to perform numerical simulation. The numerical data of time series of Eq. (13) are collected using second-order Runge–Kutta algorithm with a time step of $\delta t = 0.015$. To reduce the variance of the result, typical 3000 ensembles of time series, each containing over 10^6 periods, are averaged. The detailed description of the numerical simulation is presented in Ref. [30].

The numerical results of the average population $\langle x \rangle$ and the MFPT are plotted in Fig. 4. The average population $\langle x \rangle$ is plotted in Fig. 4(a) as a function of the noise strength D when the departure from Gaussian noise q is varied. From Fig. 4(a), it is seen that the depth of the valley in $\langle x \rangle$ is almost constant, while the position of the valley moves toward a smaller value of D when q increases. Figure 4(b) shows the MFPT $\ln T$ as a function of D when q is varied. It is shown that there are two peaks in the curve, and the peaks move to a smaller value of D when q increases. It is clear that the numerical simulation data shown in Fig. 4 are satisfactorily acceptable compared with the analytic results shown in Figs. 2(a) and 3(a), in spite

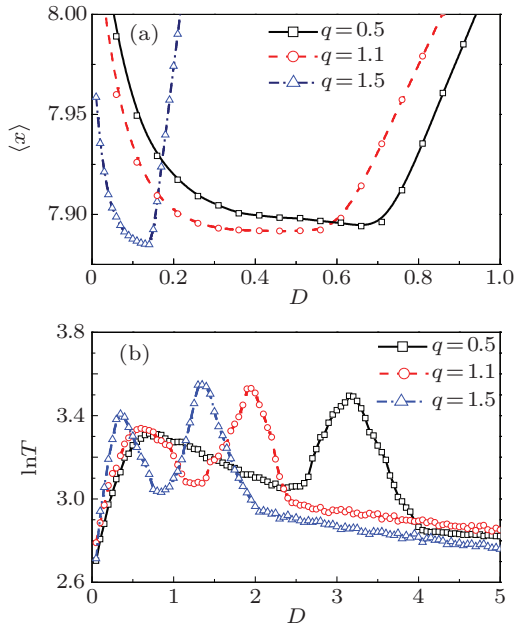


Fig. 4. (colour online) Numerical simulation results of the average population of tumor cells $\langle x \rangle$ and the mean first-passage time $\ln T$ as functions of D for different values of q with $r = 1$, $k = 10$, $\beta = 2$, $Q = 0.6$, and $\tau = 0.3$. (a) Average population of tumor cells $\langle x \rangle$ for $q = 0.5$, 1.1, 1.5. (b) Mean first-passage time $\ln T$ for $q = 0.5, 1.1, 1.5$.

of noticeable deviations. The approximation methods seem to work well for $0.5 < q < 1.5$.

6. Conclusions

In summery, the tumor-growth model with coupling between non-Gaussian and Gaussian noise terms is studied. The numerical results of the steady-state probability distribution verifies that the approximation method used in the derivation of the Fokker–Planck equation is valid. The average population of tumor cells $\langle x \rangle$ and the mean first-passage time are analyzed. It is found that there is always a valley in the curve of the average tumor-cell population, but the depth and position of the valley mainly depend on the departure from the Gaussian noise q and the white-noise intensity Q. These results suggest that it is possible to control the tumor cell in an inactive state when proper values of q, λ, and Q are chosen. It is also shown that the double-peak structure appears in the curves of MFPT, and the height of peak changes with Q, τ, and λ. It is found that the positions of two peaks mainly depend on q and Q, and the heights of two peaks mainly depend on Q and λ. The noise correlation time τ has little effect on $\langle x \rangle$ and MFPT. These results demonstrate that more time of therapy can be obtained when the departure from the Gaussian noise q and the white noise intensity Q are relatively small.

In tumor-cell growth, the parameter q of the departure from the Gaussian noise may be controlled by varying the immunity of the patient if the patient can keep a relatively good health and a hopeful mood. The coupling λ between two noise terms may be varied by changing the nutrient supply for the normal tissue and the tumor. The intensity Q of the additive noise can be changed if the temperature and environment of the tumor cell are varied. In general, the methods of controlling the parameters q, λ, and Q need to be further developed.

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