Applied Mathematical Sciences, Vol. 10, 2016, no. 10, 451 - 460
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http://dx.doi.org/10.12988/ams.2016.512731

Effect of Tumor Microenvironmental Factors on the Steady State of Tumor Growth with Non-zero Correlation Time

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Abstract

The effect of non-immunogenic tumor microenvironmental factors on the steady state tumor growth dynamics modeled by multiplicative colored noise is investigated. Using the Novikov theorem and Fox approach, an approximate Fokker-Planck equation for the non-Markovian stochastic model is obtained and analytic expression for the steady state distribution $P_{st}(x)$ is derived. We find that the strength of the tumor response to the microenvironmental factors effect θ reduces the value of the steady state distribution $P_{st}(x)$ of tumor growth at weak correlation time τ which is an inhibitive effect, and at strong correlation time the inhibitive effect is suppressed and instead the value of the steady state distribution is increased which corresponds to growth enhancement. The result indicated that the growth effect exerted by the non-immunogenic tumor microenvironmental factors on tumor growth depend on the correlation time strength τ of the tumor response.

Mathematics Subject Classification: 92C05

Keywords: Langevin equation, Fokker-Planck equation, colored noise, tumor growth dynamics

1 Introduction

Study of systems driven by noise have been of growing interest in the last three decades, and stochastic approach is proving to be a reliable approach with its application cutting across many fields such as in biology, physics and chemistry. A more realistic approach to modeling biological systems driven by noise especially from external source formulated as Langevin equation is that involved colored effect, where the correlation at different times are not proportional to the delta function $\delta(t-t')$ [1,2]. Systems driven by colored noise are non-Markovian, the underlying transition probability and does not satisfy the Fokker-Planck equation which is derived under the Markovian assumption. However, to the leading order in the correlation time, an approximate approach to the Markovian Fokker-Planck equation can be found [3,4]. The study of complex biological and physical systems driven by colored noise have been given much attention in the recent decades [5–9]. Moreover, Transitions in a logistic growth model induced by noise coupling and noise color shows some interesting behavior [10]. Recently, an investigation revealed that noise color enhances stochastic resonance in an anti-tumor model [11], and also the influence of colored correlated noises on the steady state probability distribution and the mean of tumor cell number are analyzed and discussed [12]. The effect of multiplicative colored noise on the steady state probability distribution of bacterium growth system was investigated [13] and the result shows that, the strength of the multiplicative colored noise influences the bacterium number and even bacterium extinction.

In this research, we are interested in studying the tumor response to the effects of non-immunogenic microenvironmental factors within the tumor site. Tumor growth is an open biological system that interact constantly with its internal surrounding microenvironment and also respond to the external environmental factors such as the effects from therapy [14–16]. Moreover, the non-immunogenic tumor microenvironmental factors includes extracellular matrix protein, fibroblast cells and nutrients, and the tumor interaction with these factors influences tumor growth [17–19]. In the study of tumor cell growth, the logistic growth equation is the most popular deterministic model equation, this is due to the fact that the logistic equation describes the general features of tumor growth [20]. In this paper, we model the tumor response to the microenvironmental factors effects using multiplicative colored noise and the logistic growth equation as the deterministic evolution equation. In addition, the tumor microenvironmental factors considered in this research are non-immunogenic but their natural biological functions within the tumor site influences tumor growth. This paper is organized as follows, Section 2 present the model formulation, Section 3 present the steady-state analysis based on the

approximate Fokker-Planck equation, Section 4 present the numerical results and discussions and Section 5 concludes the paper.

2 Model Formulation

The phenomenological model equation used is the Langevin dynamical equation below:

$$\dot{x}(t) = f(x) + g(x)\zeta, \tag{1}$$

where $g(x) = x$, and the function $f(x)$ is the deterministic logistic equation given as

$$f(x) = ax - bx^2, \qquad a > 0,\, b > 0 \tag{2}$$

To account for the contribution of the second term in Eq. (1), we consider the following equation

$$\dot{\zeta}(t) = -\frac{1}{\tau}\zeta + \Gamma(t), \tag{3}$$

where $\Gamma(t)$ is a Gaussian white noise with properties:

$$\langle \Gamma(t) \rangle = 0, \tag{4}$$

$$\langle \Gamma(t)\Gamma(t') \rangle = 2\theta\delta(t - t'). \tag{5}$$

Eq. (3) has a formal solution given by

$$\zeta(t) = \zeta(0)\exp(-t/\tau) + \int_0^t \exp[-(t - t')/\tau]\Gamma(t')dt' \tag{6}$$

for which the mean and the correlation function are given as

$$\langle \zeta(t) \rangle = 0 \tag{7}$$

$$\langle \zeta(t)\zeta(t') \rangle = \frac{2\theta}{\tau}\exp\left[-\frac{|t - t'|}{\tau}\right] \tag{8}$$

where in Eq. (8), as $\tau \to 0$, we recover the white noise case in Eq. (5).

3 Steady State Analysis

The stochastic Liouville equation corresponding to Eq. (1) for the time evolution of probability density is given by

$$\partial_t \rho(x, t) = -\partial_x\{f(x)\rho(x, t) + g(x)\zeta(t)\}\rho(x, t), \tag{9}$$

where $g(x) = x$ and $\rho(x,t)$ is the probability distribution for the possible realization of $\zeta(t)$. By averaging Eq. (9) we have a non-stochastic form with an averaged probability distribution $P(x,t)$, and this fact is known as the Van Kampen lemma [21]

$$P(x,t) = \langle \rho(x,t) \rangle, \tag{10}$$

where

$$\rho(x,t) = \delta(x(t) - x). \tag{11}$$

The general equation satisfying the probability distribution $P(x,t)$ is given by

$$\partial_t P(x,t) = -\partial_x f(x) P(x,t) - \partial_x g(x) \langle \zeta(t) \delta(x(t) - x) \rangle. \tag{12}$$

For the average in Eq. (12), we follow the approach given in [3,4,22] to derive an approximate Fokker-Planck equation for the tumor growth system in the steady state regime.

$$\partial_t P(x,t) = -\partial_x f(x) P(x,t) + \frac{\theta}{M} \partial_x g(x) \partial_x g(x) P(x,t), \tag{13}$$

where

$$M = 1 - \tau \left[f'(x_s) - \frac{g'(x_s)}{g(x_s)} f(x_s) \right]. \tag{14}$$

In Eq. (14), x_s is the steady state value for the process $x(t)$ and τ is the correlation time. In addition, Eq. (13) is valid under the condition that $M > 0$, and interpreted in the sense of Stratonovich we,ve

$$\partial_t P(x,t) = -\partial_x A(x) P(x,t) + \partial_{xx} B(x) P(x,t), \tag{15}$$

where $A(x)$ and $B(x)$ are the noise-induced drift and diffusion terms respectively

$$A(x) = ax - bx^2 + \frac{\theta x}{1 + a\tau}, \tag{16}$$

$$B(x) = \frac{\theta x^2}{1 + a\tau}. \tag{17}$$

Re-writing Eq. (15) in-terms of conservation equation for probability as

$$\partial_t P(x,t) + \partial_x J(x) = 0, \tag{18}$$

where $J(x)$ is the probability current density for the system, and at steady state it is required that $\partial_t P(x,t) = 0$, and we have the steady state current.

$$J_{st} = A(x) P_{st}(x) - B(x) \partial_x P_{st}(x). \tag{19}$$

Integrating Eq. (19) with reflecting boundary condition, the steady state distribution $P_{st}(x)$ for the system is obtained, [23, 24]

$$P_{st}(x) = NB(x)^{-\frac{1}{2}} \exp[-U(x)/\theta], \tag{20}$$

where N is the normalization factor and $U(x)$ is given by

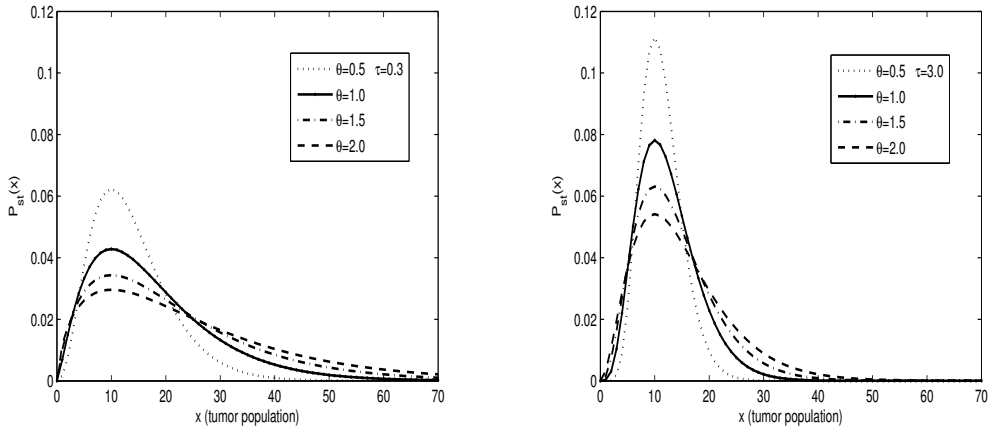
$$U(x) = b(1 + a\tau)x - [a(1 + a\tau) + \theta] \ln(x). \tag{21}$$

The stationary mean for the tumor population is determined from

$$\langle x \rangle_{st} = \frac{\int_0^\infty x P_{st}(x) dx}{\int_0^\infty P_{st}(x) dx}. \tag{22}$$

4 Results and Discussion

Figure 1(a) shows the behavior of the steady state distribution $P_{st}(x)$ against the tumor population with intervening parameters τ and θ. Keeping the correlation time strength weak and constant at $\tau = 0.3$, it is observed that increasing the strength of the tumor response to the non-immunogenic microenvironmental factors effects θ result to decreasing the value of the steady state distribution $P_{st}(x)$, this indicates that the strength of non-immunogenic microenvironmental factors effects within the tumor site inhibits tumor growth at weak correlation time τ. Figure 1(b) shows the same result as in Figure 1(a) but with increased correlation time $\tau = 3.0$, and a sharp increase in the value of the steady state distribution $P_{st}(x)$ is noticed, this indicates that increasing τ suppresses the inhibitive effect of θ and tumor growth is enhanced. This is evident in Figure 2 where the effect of the correlation time τ on the steady state distribution $P_{st}(x)$ is depicted at constant θ, it is observed that increasing the correlation time τ increases the value of the steady state distribution $P_{st}(x)$ which corresponds to growth enhancement. In other words, the above discussion shows that the ability of the non-immunogenic tumor microenvironmental factors to enhance tumor growth depends on the strength of the correlation time τ. Furthermore, Figure 3(a) depict the quantitative effect of tumor response θ on the stationary mean $\langle x \rangle_{st}$ of the tumor population, and it is seen that the stationary mean $\langle x \rangle_{st}$ of the tumor population decreases with increasing tumor response θ. This indicates that increasing θ decreases the tumor population on average. While Figure 3(b) shows the effect of correlation time strength τ on the stationary mean at constant θ, it is observed that increasing τ increases the stationary mean $\langle x \rangle_{st}$ of the tumor population which in turn corresponds to enhancing the tumor population.



(a) (b)

Figure 1: (a) Plot of the stationary distribution $P_{st}(x)$ against the tumor population x at different microenvironmental noise strength θ. Other parameter values remain fixed $\tau = 0.3$, $a = 1.0$, $b = 0.1$ (b) Plot of the stationary distribution $P_{st}(x)$ against the tumor population x at different micro environmental noise strength θ. Other parameter values remain fixed $\tau = 3.0$, $a = 1.0$, $b = 0.1$ (units are arbitrary).

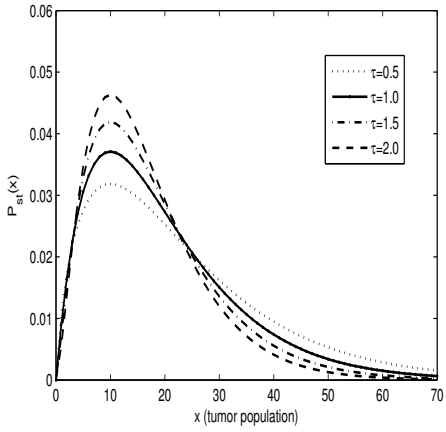
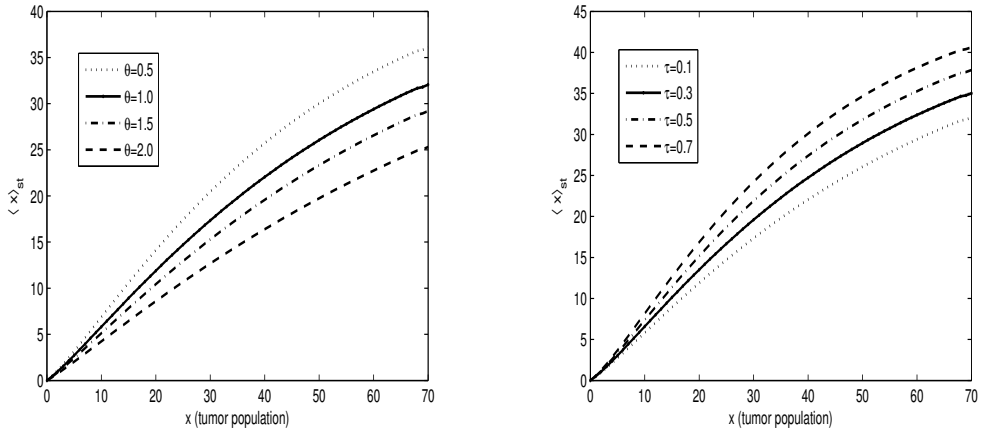


Figure 2: Plot of the stationary distribution $\rho_{st}(x)$ against the tumor population x at different correlation time τ. Other parameter values remain fixed $\theta = 2.0$, $a = 1.0$, $b = 0.1$ (units are arbitrary).

5 Conclusion

We make the steady state analysis of tumor response to the effects of non-immunogenic tumor microenvironmental factors modeled by multiplicative col-



(a) (b)

Figure 3: (a) Plot of the stationary mean $\langle x\rangle_{st}$ against the tumor population x at different different microenvironmental strength θ. Other parameter values remain fixed $\tau = 0.1$, $a = 1.0$, $b = 0.1$. (b) Plot of the stationary mean $\langle x\rangle_{st}$ against the tumor population x at different correlation time strength τ. Other parameter values remain fixed $\theta = 5.0$ $a = 1.0$, $b = 0.1$ (units are arbitrary).

ored noise. The numerical simulation for the steady state distribution $P_{st}(x)$ and the stationary mean $\langle x\rangle_{st}$ of the tumor population are obtained. Our result shows that the strength of the tumor response θ to the surrounding microenvironmental factors effects inhibits tumor growth at weak correlation time τ as evident in Figure 1, and at strong correlation time τ a systematic growth enhancement is noticed as seen in Figures 2 and evident in Figure 3. Biologically this means that tumor is an adaptive process that utilizes the surrounding non-immunogenic tumor microenvironmental factors towards growth and invasion, and the stronger the correlation time τ for the tumor response to the microenvironmental factors effects, the more the chances of growth, and also the weaker the correlation time τ, the less the chances of growth. The result indicated that the growth effect exerted by some non-immunogenic tumor microenvironmental factors depend on the strength of the correlation time τ of the tumor response.

Acknowledgments. The authors acknowledge support from the Department of Mathematics, University Putra Malaysia, and one of the authors (Ibrahim Muawiyya Idris) acknowledge financial support from Umaru Musa Yaradua University, Katsina, Nigeria.

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Received: December 29, 2015; Published: February 9, 2016