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Effect of tumor microenvironmental factors on tumor growth dynamics modeled by correlated colored noises with colored cross-correlation

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HIGHLIGHTS

- Effect of non-immunogenic microenvironmental factors on tumor growth is investigated.
- The steady state distribution for the tumor growth system is derived.
- The non-immunogenic microenvironmental factors effects inhibits tumor growth.
- The strength of the correlation time τ exerts growth effect on the tumor growth system.

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ABSTRACT

The effect of non-immunogenic tumor microenvironmental factors on tumor growth dynamics modeled by correlated additive and multiplicative colored noises is investigated. Using the Novikov theorem, Fox approach and Ansatz of Hanggi, an approximate Fokker–Planck equation for the system is obtained and analytic expression for the steady state distribution $P_{st}(x)$ is derived. Based on the numerical results, we find that fluctuations of microenvironmental factors within the tumor site with parameter θ have a diffusive effect on the tumor growth dynamics, and the tumor response to the microenvironmental factors with parameter α inhibits growth at weak correlation time τ. Moreover, at increasing correlation time τ the inhibitive effect of tumor response α is suppressed and instead a systematic growth promotion is noticed. The result also reveals that the strength of the correlation time τ has a strong influence on the growth effects exerted by the non-immunogenic component of tumor microenvironment on tumor growth.

1. Introduction

The dynamical study of complex systems subject to random environmental influences have been of interest in the recent decades, and stochastic method have been a reliable approach with application in biology, physics, chemistry and economics among others. Moreover, many complex biological and chemical diffusion cannot be realistically modeled in the normal Brownian diffusion paradigm, where the auto-correlation function $\langle x(t)x(t')\rangle$ which is approximated by the mean square value of a system displacement is not proportional to time but is given by the power law $\langle x^2(t)\rangle \propto Dt^{\Theta}$, where D is some constant measuring the rate of diffusion and $x(t)$ represents state of a system with respect to time. The parameter $\Theta \neq 0$ is a

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critical parameter that gives rise to sub-diffusion for $0 < \Theta < 1$, normal Brownian diffusion for $\Theta = 1$ and super-diffusion for $\Theta > 1$. The case for the sub-diffusion and super-diffusion defines the so-called anomalous diffusion with long memory, and the fractional Gaussian noise is a random process with long memory effect [1]. Anomalous diffusion is mostly seen in situations where the diffusion involves a real diffusing particle in a crowded environment with many obstacles [2]. However, for situation where the diffusion does not involve a real diffusing particle, but instead an evolution of a macroscopic open system subject to influence from random microenvironmental factors within the immediate neighborhood of the system, the normal Brownian diffusion paradigm is sufficient for theoretical study, and the Ornstein Uhlenbeck noise is a random process with memory effect [3].

In literature, stochastic method have been successfully applied in the study of complex systems affected by noise such as in bistable system [4–6], in mode laser system [7,8], in genotype selection model and genetic transcription regulation [9,10] and in tumor growth [11–13]. Moreover, many interesting phenomena such as the noise induced transport, noise induced phase transition have been discovered at the influence of noise [14,15], and the phenomenological model equation is written in the form of Langevin equation and the corresponding Fokker Planck equation for the time evolution of probability density. For realistic study of physical systems, the correlation time of the noise no matter how small it may be should be non-zero, and noise with non-zero correlation time are termed as colored or non-white, and in literature consideration of colored noise in stochastic models has been the subject of many research [16–19]. Stochastic model driven by colored noise is non-Markovian with associated correlation time, and the underlying transition probability does not satisfy the Fokker–Planck equation derived under the Markovian assumption. However, to the leading order of the correlation time, an approximate Fokker–Planck equation can be obtained [20,21].

Tumor growth is an open biological system of growth that responds to internal and external environmental influences such as the effect from the surrounding microenvironmental factors and as well as effect from external therapeutic control. The effect of external therapeutic control such as radiotherapy, chemotherapy and drugs on tumor growth dynamics has been studied [22,23], where the therapeutic control restrains the tumor cell number giving rise to negative additive noise and the tumor response to the therapeutic effect gives rise to multiplicative internal noise. Furthermore, a more refined and advanced stochastic model for tumor growth that takes into account tumor–immune interaction has been reported [24], in the model, the internal noise that gives rise to multiplicative noise is assumed to be generated by the internal mechanisms inside the tumor without contact to the external surrounding microenvironment which gives rise to additive noise, moreover the internal multiplicative noise and external additive noise have different origin but are argued to be interrelated.

It has been reported that tumor microenvironment plays a critical role in tumor initiation, pro-malignancy and anti-malignancy activities [25–28]. An experimental study also revealed that tumor developing in-vivo has most of its cell proliferation concentrated at the tumor surface, which further indicates that tumor surface diffusion is the main mechanism responsible for growth in tumors [29]. In this paper, we are interested in studying the response of tumor to the surrounding microenvironmental factors effect within the tumor site using stochastic method, the study will help towards more understanding of the dynamical complexities associated with tumor growth. Moreover, the tumor microenvironmental factors considered in this research are non-immunogenic but their natural biological functions within the tumor site are capable of supporting or undermining tumor growth, and such non-immunogenic microenvironmental factors include extracellular matrix proteins, fibroblast cells, signal transduction in cellular activities, inflammatory cells and nutrients. The fluctuations of the tumor microenvironmental factors within the tumor site are the source of the external noise and are modeled as positive additive colored noise, and the response of the tumor to the microenvironmental factors effect generates an internal multiplicative colored noise and the two noises are correlated having the same origin [30]. The paper is organized as follows, Section 2 presents the theoretical model formulation in the form of Langevin stochastic equation using the logistic equation as the deterministic growth model, Section 3 presents the steady state analysis using an approximate Fokker–Planck equation, Section 4 presents the numerical results and discussion and Section 5 concludes the paper.

2. Model formulation

The phenomenological model equation is the Langevin stochastic equation

$$\dot{x}(t) = f(x) + g_1(x)\eta(t) + g_2(x)\zeta(t), \tag{1}$$

where $g_1(x) = x$, $g_2(x) = 1$ and the function $f(x)$ is the logistic growth equation which is given by

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

The over dot in Eq. (1) represents derivative with respect to time and since the state of the system with respect to time $x(t)$ depends on the stochastic forces $\eta(t)$ and $\zeta(t)$, then $x(t)$ automatically inherits the properties of these stochastic forces. Moreover, $\eta(t)$ and $\zeta(t)$ are the multiplicative and additive colored noises respectively with the following statistical properties:

$$\langle \eta(t) \rangle = 0 = \langle \zeta(t) \rangle, \tag{3}$$

$$\langle \eta(t)\eta(t') \rangle = \frac{2\alpha}{\tau_1} \exp\left[-\frac{|t-t'|}{\tau_1} \right], \tag{4}$$