RESEARCH ARTICLE

THE DOUBLE-EDGE EFFECT OF TUMOR MICROENVIRONMENT ON TUMOR GROWTH

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ARTICLE INFO	ABSTRACT
	The resonance effect likely exhibited by some non-immunogenic micro-environmental factors and its influence on tumor growth system modeled by correlated additive and multiplicative white noises is investigated. An analytic expression for the steady state distribution of the tumor growth system is obtained via the Fokker-Planck equation. Numerical results revealed that the resonance effect likely exhibited by some surrounding non-immunogenic micro-environmental factors within the tumor site may be one of the factors responsible for the double-edge effect of tumor micro-environment of either promoting or antagonizing tumor growth

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Introduction

Tumor growth from the theoretical view point is an open biological process in which the growth pattern exhibited is non-linear, and interaction between the tumor cells and the surrounding tumor micro-environmental factors induce random effect on tumor growth that cannot be understood from the clinical, experimental and deterministic mathematical investigations. It is therefore absolutely indispensable in the theoretical study of tumor growth system to consider impacts from the surrounding tumor micro-environmental factors, and of which stochastic methods provide a powerful tool for theoretical study. Tumor microenvironment is an embodiment of noisy (random) immunogenic and non-immunogenic biological micro-processes that interact with the tumor cells constantly, and the interaction induce a random effect on the tumor growth system. Such biological processes includes among others the tumor-infiltrating lymphocytes $CD4^+$ and $CD8^+$ T cells, macrophages, fibroblast cells, extracellular matrix proteins ECM and nutrients, Ai et.al (2003); Yu and Fu (2006);Strell et.al (2012); Xuejing et.al (2010). Meanwhile, clinical and experimental investigations revealed that tumor micro-environmental factors within the tumor site have strong influence on tumor initiation, progression and therapy, Witz (2008, 2009); Han et.al (2007); Whiteside (2008); Zhang and Ai (2010); Zhang and Cao (2010). Therefore, the study of interactions between the tumor cells and its surrounding micro-environmental processes will give additional insight into the dynamical complexities likely exhibited by the tumor growth process, Ibrahim and Rizam (2016); Behera and O'Rourke (2008); Thomas and Trimper (2009); Wang et.al (2011). Furthermore, the random nature of tumor micro-environmental factors within the tumor site induce stochastic effects on the tumor growth system, and as well the micro-environmental factors within the tumor site may possess resonance effect due to vibration of some surrounding biological micro-processes such as the signal transduction in cellular activities, Li et.al (2011); Yang et.al (2014). In this article, effects due to tumor interaction with the noisy non-immunogenic tumor micro-environmental factors with resonance effect are considered, and since their biological functions within the tumor site are not mainly for immune purpose, we therefore model the non-immunogenic micro-environmental factors fluctuations within the tumor site by positive additive white Gaussian noise with coupling deterministic impulse function mimicking the resonance effect likely exhibited by some surrounding micro-environmental factors. This means that the noisy non-immunogenic tumor micro-environmental factors effect should have a periodic element, and for simplicity, we consider the cosinoidal form $A \cos \omega(t)$, Li et.al (2011).

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Moreover, A is the amplitude of the periodic impulse signal and ω is the frequency. In our case, we assumed that the frequency of the coupled impulse signal is negligible, i.e., $\omega \rightarrow 0$, hence there is enough time for the system to reach the steady state. Therefore, since the tumor micro-environmental factors are non-immunogenic, then the tumor response is a random process which consequence generates a multiplicative noise on the tumor growth system. Thus, the additive and multiplicative noises are correlated having originated from the same source, Fulinski and Telejko (1991).

Model Description

The theoretical model equation for the tumor growth system subject to non-immunogenic tumor micro-environmental factors with micro-environmental resonance effect is given by

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

where in Eq. (1), $f(x)$ is the logistic growth model, $\zeta(t)$ is the positive additive noise term representing the surrounding noisy non-immunogenic microenvironmental factors effect within the tumor site coupled with additional deterministic impulse function mimicking the micro-environmental resonance effect, and $\eta(t)$ is the multiplicative noise term representing tumor response to the surrounding non-immunogenic tumor micro-environmental factors and micro-environmental resonance effects respectively with the following statistical properties, in addition to the fact that both the stochastic forces $\eta(t)$ and $\zeta(t)$ are zero-mean processes, thus

$$\langle \eta(t)\eta(t') \rangle = 2\alpha \cos A \delta(t - t'), \tag{2}$$

$$\langle \zeta(t)\zeta(t') \rangle = 2\theta \cos A \delta(t - t'). \tag{3}$$

The additive and multiplicative noises in Eq. (2) and Eq. (3) above are correlated with white cross-correlation

$$\langle \zeta(t)\eta(t') \rangle = \langle \eta(t)\zeta(t') \rangle = 2\lambda\sqrt{\alpha\theta} \cos A \delta(t - t') \tag{4}$$

where α and θ are the strengths of multiplicative and additive noises respectively, and λ is the strength of the correlation between the multiplicative noise and additive noise under the condition that λ lies within the interval of absolutely zero correlation to perfect correlation $0 \leq \lambda < 1$. Therefore, since one of the stochastic terms in the tumor model as given in Eq. (1) is multiplicative, i.e., $x\eta$(t), then a chosen stochastic interpretation is required for solution, and hence we define the following transformation to Stratonovich interpretation

$$\dot{x}(t) = f(x) + G(x)\Gamma(t), \tag{5}$$

such that

$$G(x)\Gamma(t) = A \cos x \eta(t) + A \cos \zeta(t), \tag{6}$$

where $\Gamma(t)$ is a Gaussian white noise and A is the amplitude of the associated deterministic periodic force, further, $\Gamma(t)$ has the following statistical properties

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

$$\langle \Gamma(t)\Gamma(t') \rangle = 2\delta(t - t'). \tag{8}$$

Let the two time correlation of $G(x)\Gamma(t)$ in Eq. (5) be equivalent to the two time correlation of the stochastic terms $A \cos x \eta(t) + A \cos \zeta(t)$ in Eq. (6). To achieve this, we drop the component of deterministic force and square both sides of Eq. (1) and take the ensemble average, thus

$$\langle \left(G(x)\Gamma(t)\right)^2 \rangle = \langle (x\eta(t) + \zeta(t))^2 \rangle, \tag{9}$$

$$G(x)^2\langle \Gamma(t)\Gamma(t') \rangle = x^2\langle \eta(t)\eta(t') \rangle + x\langle \eta(t)\zeta(t') \rangle + x\langle \zeta(t)\eta(t') \rangle + \langle \zeta(t)\zeta(t') \rangle, \tag{10}$$

substituting Eq's. (2), (3), (4) and (8) into Eq. (10) and bringing back the component of the deterministic force, we have

$$2G(x)^2\delta(t - t') = 2\alpha A \cos x^2 \delta(t - t') + 4\lambda\sqrt{\alpha\theta}A \cos x \delta(t - t') + 2A \cos \theta \delta(t - t'). \tag{11}$$

Finally, an explicit expression for the diffusion term is obtained as

$$G(x) = \sqrt{\alpha A \cos x^2 + 2\lambda\sqrt{\alpha\theta}A \cos x + A \cos \theta} \tag{12}$$

3 Steady State Distribution with Resonance Effect

The underlying transition probability $\rho(x, t | x_0, t_0)$ for the realizations of the stochastic forces $\eta(t)$ and $\zeta(t)$ in Eq. (1) satisfies the Fokker Planck equation interpreted in the sense of Stratonovich. Therefore, the drift and diffusion terms $A(x)$ and $B(x)$ for the tumor growth system are respectively given by

$$A(x) = G(x) \frac{d}{dx} G(x), \tag{13}$$

$$= ax - bx^2 + \alpha x - \alpha A \sin Ax - \lambda \sqrt{\alpha \theta} \sin A, \tag{14}$$

$$B(x) = \alpha A \cos x^2 + 2\lambda \sqrt{\alpha \theta} A \cos x + A \cos \theta. \tag{15}$$

Where, Eq. (14) is the noise-induced drift and Eq. (15) is the diffusion. Thus, the probability current density (probability flux) for the tumor growth system is given by

$$J(x) = \left(ax - bx^2 + \alpha x - \alpha A \sin Ax - \lambda \sqrt{\alpha \theta} \sin A\right)\rho(x,t) - \left(\alpha A \cos x^2 + 2\lambda \sqrt{\alpha \theta} A \cos x + A \cos \theta\right)\frac{\partial \rho(x,t)}{\partial x}. \tag{16}$$

Therefore, at steady state the rate of change of probability density with time is constant, and therefore the probability current density is constant independent of the state variable x, and integrating ones we have

$$\left(ax - bx^2 + \alpha x - \alpha A \sin Ax - \lambda \sqrt{\alpha \theta} \sin A\right)\rho_{st}(x) + \left(\alpha A \cos x^2 + 2\lambda \sqrt{\alpha \theta} A \cos x + A \cos \theta\right)\frac{\partial \rho_{st}(x)}{\partial x} = 0. \tag{17}$$

The steady state distribution for the tumor growth system is obtained by solving Eq. (17) with reflecting boundary condition, Gardiner (1985); Risken(1996). Hence, the steady state distribution for the tumor growth system is given as

$$\rho_{st}(x) = NB(x)^{-\frac{1}{2}} exp\left[-\frac{U(x)}{\alpha \cos A}\right], \tag{18}$$

where $B(x)$ is the diffusion coefficient and $U(x)$ is an effective potential given by

$$U(x) = bx + L_1 \ln\left|\left(\frac{\alpha x + \lambda \sqrt{\alpha \theta}}{\sqrt{\alpha \theta (1-\lambda^2)}}\right)^2 + 1\right| - L_2 \tan^{-1}\left(\frac{\alpha x + \lambda \sqrt{\alpha \theta}}{\sqrt{\alpha \theta (1-\lambda^2)}}\right), \tag{20}$$

and L_1 and L_2 in Eq. (20) are respectively given by

$$L_1 = \frac{\alpha(1-\sin A) + a + 2\lambda b \sqrt{\frac{\theta}{\alpha}}}{2}, \tag{21}$$

$$L_2 = \frac{\left[\alpha(1-\sin A) + a + 2\lambda b \sqrt{\frac{\theta}{\alpha}}\right]\lambda\sqrt{\frac{\theta}{\alpha}} - \lambda\sqrt{\alpha \theta} \sin A - \frac{b}{\alpha}\theta}{\sqrt{\frac{\theta(1-\lambda^2)}{\alpha}}}. \tag{22}$$

Moreover, A is the amplitude of the deterministic periodic impulse function and N is the normalization constant.

Numerical Results and Discussion

We make the numerical simulation of Eq. (18), and Figure1 depict the effect of the surrounding micro-environmental resonance on the steady state distribution $\rho_{st}(x)$, it is observed that the amplitude of the micro-environmental resonance affects the extrema of the steady state distribution $\rho_{st}(x)$ directly but in a rather alternating manner with increasing amplitude strength A. This behavior indicates that the resonance effect which is as a result of the surrounding non-immunogenic micro-environmental factors vibrating with the same natural frequency as the frequency of some micro-processes within the tumor microenvironment(such as the signal transduction in cellular activity and molecular signaling pathways) may affect tumor growth systematically.

In addition, it is observed from Figure2 that keeping the amplitude parameter low at $A = 1.0$, then varying the tumor response parameter α cause the extrema of the steady state distribution $\rho_{st}(x)$ to shift from large tumor population to small tumor population. Figure3 depict the same result as in Figure2 but with increased value A, i.e., $A = 5.0$, it is observed that the pattern alternate, instead the extrema of the steady state distribution $\rho_{st}(x)$ shift from small tumor population to large tumor population systematically. Moreover, Figure4 also depict the same result with relatively higher value of A, i.e., $A = 8.0$, it is observed that similar pattern for the effect of tumor response parameter α on the steady state distribution $\rho_{st}(x)$ as in Figure2 is recovered. This shows that the associated micro environmental resonance may be one of the factors responsible for the double-edge effect

exhibited by tumor micro-environmental factors, because some tumor micro-environmental factors play opposing roles in tumor progression by either enhancing growth or alternatively antagonizing growth, Witz (2008).
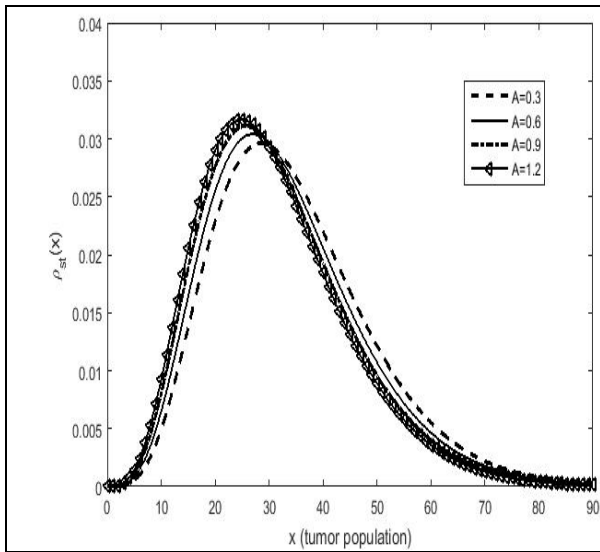

Figure 1. Plot of the steady state distribution $\rho_{st}(x)$ against the tumor population x at varying amplitude strength$A = 0.3, 0.6, 0.9, 1.2$ (units are arbitrary)
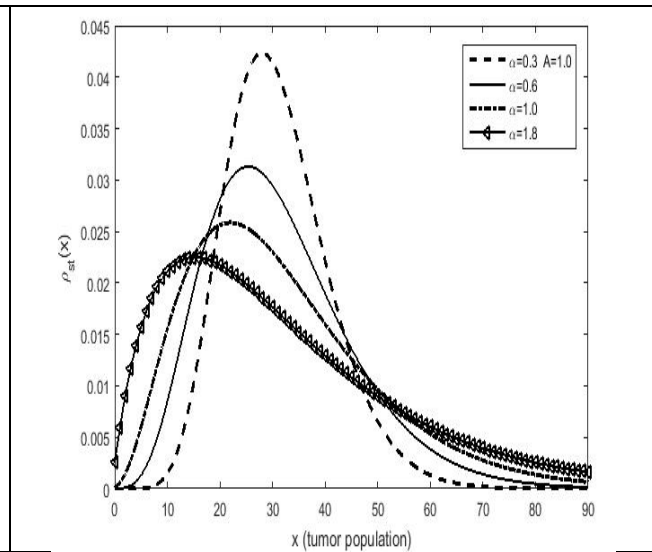
Figure 2. Plot of the steady state distribution $\rho_{st}(x)$ against the tumor population x at varying tumor response α, $A = 1.0$, other parameter values remain fixed at $a = 1.0, b = 0.1, \theta = 0.5$ and $\lambda = 0.6$ (units are arbitrary)
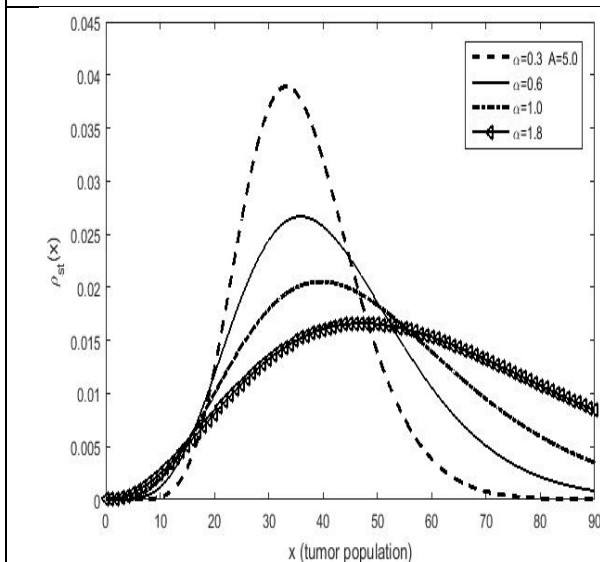
Figure3: Plot of the steady state distribution $\rho_{st}(x)$ against the tumor population x at varying tumor response α, $A = 5.0$, other parameter values remain fixed at $a = 1.0, b = 0.1, \theta = 0.5$ and $\lambda = 0.6$ (units are arbitrary)

Figure 4: Plot of the steady state distribution $\rho_{st}(x)$ against the tumor population x at varying tumor response α, $A = 8.0$, other parameter values remain fixed at $a = 1.0, b = 0.1, \theta = 0.5$ and $\lambda = 0.6$ (units are arbitrary)
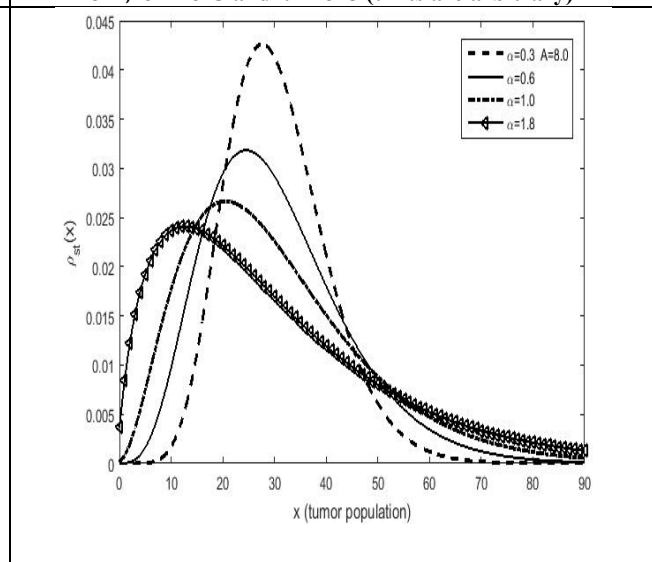
Summary and Conclusion

In this paper, tumor response to the resonance effect likely exhibited by some surrounding non-immunogenic micro-environmental factors which is due to their vibrations with the same natural frequency as the vibrations of some surrounding biological micro-processes within the tumor site. Moreover, the resonance effect likely exhibited by some surrounding non-immunogenic tumor micro-environmental factors within the immediate neighborhood of tumor cells is modeled by additive noise $\eta(t)$ with strength θ coupled with deterministic impulse function $A \cos \omega (t) \omega \to 0$, and the tumor cells respond by generating a multiplicative noise $\zeta(t)$ with strength α, and the driven noises are correlated with white cross-correlation λ. The steady state distribution $\rho_{st}(x)$ for the tumor growth system is obtained via the Fokker-Planck equation, and numerical result show that the resonance effect likely exhibited by some surrounding non-immunogenic micro-environmental factors within the tumor site may be one of the factor responsible for the double-edge effect of tumor microenvironment. Since a highly heterogeneous tumor has the potential to adapt to any microenvironment, therefore, understanding how interactions between the growing tumor and its immediate microenvironment will unravel many complex mechanisms of tumor development.

Acknowledgement

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