Applied Mathematical Sciences, Vol. 10, 2016, no. 31, 1525 - 1535
HIKARI Ltd, www.m-hikari.com
http://dx.doi.org/10.12988/ams.2016.6257

Steady State Analysis for the Effect of Tumor Microenvironmental Factors on Tumor Growth Dynamics Driven by Correlated Noises

Mohd Rizam Abu Bakar[a] and Ibrahim Mu'awiyya Idris[a,b,*]

[a]Department of Mathematics, Universiti Putra Malaysia

[b]Department of Mathematics
Umaru Musa Yar'adua University Katsina, Nigeria

Abstract

The steady state analysis for the effect of non-immunogenic tumor microenvironmental factors modeled by correlated additive and multiplicative noises with zero correlation time is investigated. The underlying transition probability for the stochastic model equation satisfies the Markovian Fokker-Planck equation, and the steady state distribution $\rho_{st}(x)$ for the tumor growth system is derived. Based on the numerical computation, we find that the effect of non-immunogenic microenvironmental factors within the tumor site with strength θ have a diffusive effect on the steady state distribution $\rho_{st}(x)$, and the tumor response to the surrounding non-immunogenic microenvironmental factors effects with strength D inhibits growth on both the steady state distribution $\rho_{st}(x)$ and the mean $\langle x \rangle_{st}$ of the tumor population. The result also indicates that the stronger the correlation strength ϕ, the more the tumor responded to the surrounding non-immunogenic microenvironmental factors effect.

Mathematics Subject Classification: 92C05

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

1 Introduction

Complex systems subject to external random effects are the features of many biological, physical, chemical and engineering systems. Theoretical description of these systems requires a link between deterministic equations and stochastic process. In application, the theoretical model equation is the Langevin stochastic equation and the corresponding Fokker Planck equation for the time evolution of probability density, and such theoretical descriptions have been used in different context to study the behavior of noise driven systems [1–3], where the driven noises are either Gaussian white or colored noises and in the form of additive or multiplicative. Research in [4] first discovered that physical systems driven by simultaneous noises with common origin leads to correlated effects, and the study of complex systems driven by correlated noises have been given much attention especially in bistable system [5–7], in mode laser system [8, 9], in gene selection and genetic transcription regulatory models [10–12] and in all these systems, interesting properties and system behaviors were discovered at the influence of noise correlated effects. In the study of tumor cell growth, mathematical model equations that closely captures the general features of tumor growth are considered in literature, and logistic equation is the most widely used deterministic model for theoretical study [13]. Moreover, real tumor growth model should be subject to influences from internal and external random environmental factors such as effects from external therapeutic control [14–16], and from internal tumor microenvironmental processes [17–19].

Tumor microenvironment comprise of immunogenic and non-immunogenic biological processes within the tumor site, such as the $CD4^+$ and $CD8^+$ T immune cells, macrophages, fibroblast cells, extracellular-matrix proteins, inflammatory cells and nutrients. Moreover, clinical and experimental investigations revealed that tumor microenvironmental factors have strong influence on tumor evolution and progression [20–23], and the study of interaction between tumor and its microenvironment will give insight into the dynamical complexities associated to tumor growth. In addition, the random nature of the tumor microenvironmental factors induces stochastic effect on the tumor growth system. In this paper, we model the non-immunogenic microenvironmental factors fluctuations within the tumor site by positive additive noise $\eta(t)$, and the tumor response generates a multiplicative noise $\xi(t)$ on the tumor growth system, and the noises are correlated having the same origin. The 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 theoretical model equation is written in the form of Langevin stochastic equation

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

where the over dot in Eq. (1) represent derivative with respect to time and the function $f(x)$ is the deterministic evolution equation for tumor growth, which in this case corresponds to the logistic equation

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

where a and b are the growth and decay constants respectively. In addition, the stochastic terms $\xi(t)$ and $\eta(t)$ in Eq. (1) are the multiplicative and additive white Gaussian noises respectively with the following statistical properties:

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

$$\langle \xi(t)\xi(t') \rangle = 2D\delta(t - t'), \tag{4}$$

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

$$\langle \xi(t)\eta(t') \rangle = 2\phi\sqrt{D\theta}\delta(t - t'), \tag{6}$$

where D and θ are the multiplicative and additive noise strengths respectively, ϕ is the strength of the correlation between multiplicative noise and additive noise under the condition that ϕ lie between the interval $[0 \leq \phi < 1]$, and the state variable x for the tumor growth system is strictly $x \geq 0$ since it represent growth. However, Eq. (1) can be written in an equivalent Stratonovich form via the following transformation

$$\dot{x}(t) = f(x) + G(x)\beta(t). \tag{7}$$

Here $\beta(t)$ is a Gaussian white noise with statistical properties

$$\langle \beta(t) \rangle = 0, \tag{8}$$

$$\langle \beta(t)\beta(t') \rangle = 2\delta(t - t'), \tag{9}$$

where the two time correlation of $G(x)\beta(t)$ in Eq. (7) be equivalent to the two time correlations of $x\xi(t) + \eta(t)$ in Eq. (1), such that the relation below is established [24]

$$G(x)\beta(t) = x\xi(t) + \eta(t). \tag{10}$$

From Eq's. (3)-(6) we've

$$G(x) = \sqrt{Dx^2 + 2\phi\sqrt{D\theta}x + \theta}. \tag{11}$$

3 Steady state analysis

The corresponding Fokker-Planck equation for the time evolution of probability density $\rho(x,t)$ in Eq. (1), and interpreted in the sense of Stratonovich is given by

$$\partial_t \rho(x,t) = -\partial_x A(x)\rho(x,t) + \partial_{xx} B(x)\rho(x,t), \tag{12}$$

where $\rho(x,t)$ is the probability density function for the realization of $\xi(t)$ and $\eta(t)$, the modified drift term reads

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

thus, $A(x)$ and $B(x)$ in Eq. (12) are the drift and diffusion terms respectively and are given as

$$A(x) = ax - bx^2 + Dx + \phi\sqrt{D\theta}, \tag{14}$$

$$B(x) = Dx^2 + 2\phi\sqrt{D\theta}x + \theta. \tag{15}$$

In addition, Eq. (12) can be written in terms of the conservation equation for probability current

$$\partial_t \rho(x,t) + \partial_x J(x) = 0, \tag{16}$$

$$J(x) = (ax - bx^2 + Dx + \phi\sqrt{D\theta})\rho_{st}(x,t) - (Dx^2 + 2\phi\sqrt{D\theta}x + \theta)\partial_x \rho_{st}(x,t), \tag{17}$$

where $J(x)$ in Eq. (17) is the probability current density for the system. At steady state, it is required that the rate of change of probability $\rho(x,t)$ with time is constant, i.e, $\partial_t \rho(x,t) = 0$, thus, we have a stationary current independent of the state variable x given by

$$(ax - bx^2 + Dx + \phi\sqrt{D\theta})\rho_{st}(x) - (Dx^2 + 2\phi\sqrt{D\theta}x + \theta)\partial_x \rho_{st}(x) = 0. \tag{18}$$

The steady-state distribution $\rho_{st}(x)$ is obtained by solving Eq. (18) with reflecting boundary condition, [25, 26].

$$\rho_{st}(x) = NB(x)^{-\frac{1}{2}} \exp\left[\int^x \frac{A(x')}{B(x')}dx'\right], \tag{19}$$

where N is a constant which is choosing to normalize $\rho_{st}(x)$ such that

$$\int_{-\infty}^{\infty} \rho_{st}(x)dx = 1, \tag{20}$$

$$N = \left[\int_{-\infty}^{\infty} B(x)^{-\frac{1}{2}} \exp\left[\int^{x} \frac{A(x')}{B(x')} dx'\right] dx\right]^{-1}. \tag{21}$$

Therefore, the explicit expression for $\rho_{st}(x)$ is given by

$$\rho_{st}(x) = NB(x)^{-\frac{1}{2}} \exp\left[-U(x)/D\right], \tag{22}$$

where $U(x)$ is an effective potential given as

$$\begin{aligned} U(x) = bx - Q_1 \ln\left|\frac{(Dx + \phi\sqrt{D\theta})^2}{D\theta(1-\phi^2)} + 1\right| \\ + \frac{Q_2}{\sqrt{D\theta(1-\phi^2)}} \arctan\left(\frac{Dx + \phi\sqrt{D\theta}}{\sqrt{D\theta(1-\phi^2)}}\right), \end{aligned} \tag{23}$$

$$Q_1 = \frac{(a+D)}{2} + \phi b\sqrt{\frac{\theta}{D}}, \tag{24}$$

$$Q_2 = \left(a + 2\phi b\sqrt{\frac{\theta}{D}}\right)\phi\sqrt{D\theta} - b\theta. \tag{25}$$

For quantitative analysis of the steady state properties of tumor response to the surrounding non-immunogenic microenvironmental factors effects, we compute the mean $\langle x\rangle_{st}$ of the tumor population define as

$$\langle x\rangle_{st} = \int_0^x x\rho_{st}(x)dx. \tag{26}$$

4 Results and Discussion

We make the numerical simulation for the steady state distribution $\rho_{st}(x)$ and the mean $\langle x\rangle_{st}$ of the tumor population in Eq's. (22) and (26), and analyze the effect of non-immunogenic tumor microenvironmental factors on tumor growth dynamics. Figure 1 show the effect of the non-immunogenic tumor microenvironmental factors modeled by additive noise $\eta(t)$ with strength θ on the steady state distribution $\rho_{st}(x)$, it is observed that the value of the steady state distribution $\rho_{st}(x)$ is decreases with increasing θ and the position of the extrema is unaffected. This indicates that the non-immunogenic microenvironmental factors within the tumor site have a diffusive effect on tumor growth dynamics. Figure 2 depict the response of tumor to the non-immunogenic microenvironmental factors effects modeled by multiplicative noise $\xi(t)$ with strength D, it is observed that increasing the strength of the tumor response D affects the position of the extrema of the steady state distribution $\rho_{st}(x)$, and since x represent tumor population, then the position of the extrema shifts from

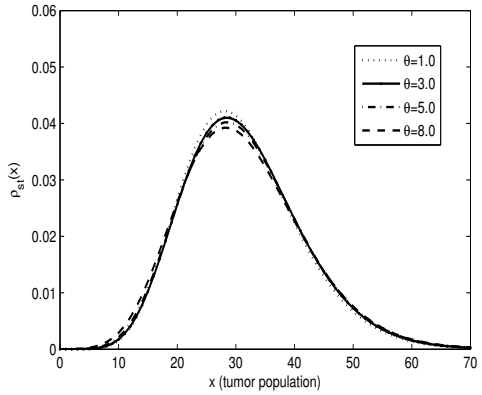


Figure 1: Plot of the steady state distribution $\rho_{st}(x)$ against the tumor population x at varying tumor microenvironmental factors strength θ. Other parameter values remain fixed at $D = 0.3$, $\phi = 0.6$, $a = 1.0$, $b = 0.1$ (units are arbitrary).

large tumor population to small tumor population. This indicates that the non-immunogenic microenvironmental factors within the tumor site may inhibits tumor growth but not sufficient enough to cause extinction, in addition, this property indicates that the multiplicative noise induce a drift effect on the tumor growth system as first reported in [14]. Figure 3 depict the effect of correlation strength ϕ on the steady state distribution $\rho_{st}(x)$ and by contrasting between Figures 3(a) and 3(b), it is observed that the stronger the strength θ of the surrounding non-immunogenic microenvironmental factors effect the more effective the cross-correlation ϕ. In other words, this indicates that the surrounding non-immunogenic microenvironmental factors effects on tumor growth dynamics is directly proportional to the cross-correlation strength ϕ between noises. Furthermore, in order to quantitatively analyze the effect of the non-immunogenic tumor microenvironmental factors on tumor growth dynamics, we use the mean of the tumor population $\langle x \rangle_{st}$ in Eq. (26). Figure 4 shows the effect of the tumor response with strength D on the mean of the tumor population $\langle x \rangle_{st}$, it is observed that increasing the strength D of tumor response to the non-immunogenic microenvironmental factors effects, the mean $\langle x \rangle_{st}$ of the tumor population decreases which is an inhibitive effect.

5 Conclusion

We make the steady state analysis for the effect of non-immunogenic microenvironmental factors on tumor growth dynamics. Moreover, the non-immunogenic microenvironmental factors within the tumor site are random

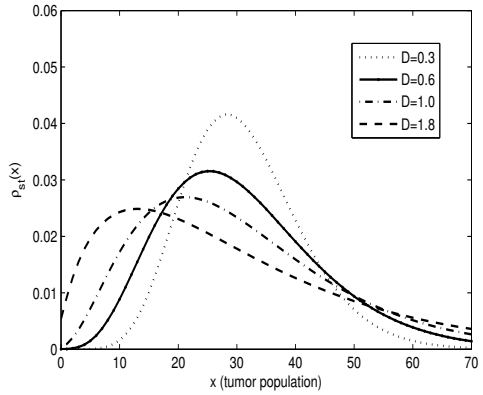
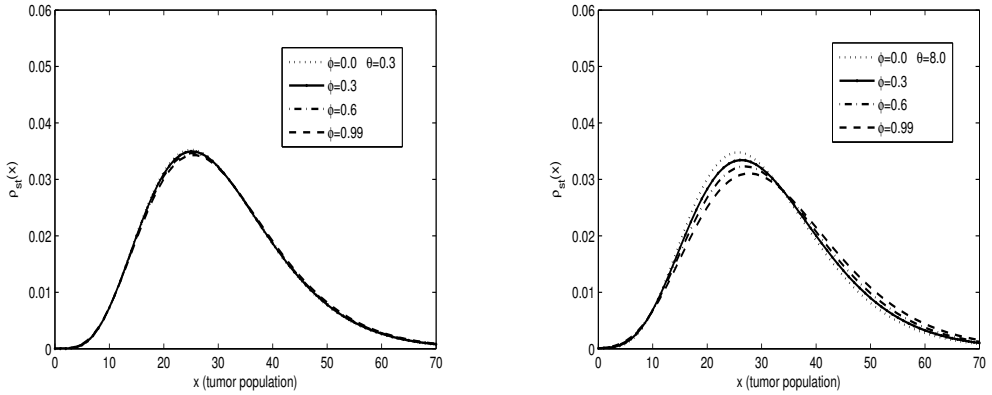


Figure 2: Plot of the steady state distribution $\rho_{st}(x)$ against the tumor population x at varying tumor response strength D. Other parameter values remain fixed at $\theta = 0.3$, $\phi = 0.6$, $a = 1.0$, $b = 0.1$ (units are arbitrary).



(a) (b)

Figure 3: (a) Plot of the steady state distribution $\rho_{st}(x)$ against the tumor population x at varying cross-correlation strength ϕ. $D = 0.5$, $\theta = 0.3$, $a = 1.0$, $b = 0.1$ (b) Plot of the steady state distribution $\rho_{st}(x)$ against the tumor population x at varying cross-correlation strength ϕ. Other parameter values remain fixed at $D = 0.5$, $\theta = 3.0$, $a = 1.0$, $b = 0.1$. (units are arbitrary).

processes with external influence on the tumor and are therefore modeled as additive noise $\eta(t)$ with strength θ, and the corresponding tumor response to the non-immunogenic microenvironmental factors effect generates a multiplicative noise $\xi(t)$ on the tumor growth system with strength D, and the two driven noises are correlated. We find that the non-immunogenic microenvironmental factors within the tumor site θ have a diffusive effect on the tumor growth system, and the stronger the correlation strength ϕ the more the

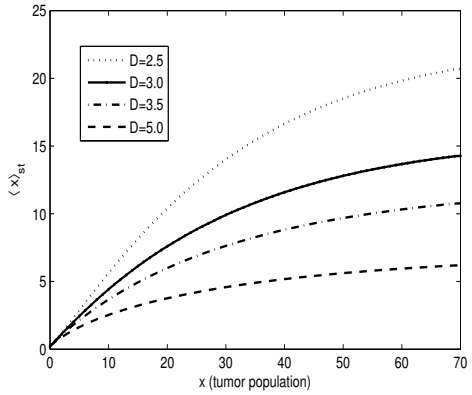


Figure 4: Plot of the stationary mean $\langle x \rangle_{st}$ against the tumor population x at varying tumor response strength D. Other parameter values remain fixed at $\theta = 6.0$, $\phi = 0.6$, $a = 1.0$, $b = 0.1$ (units are arbitrary).

tumor response to the non-immunogenic microenvironmental factors effects. Furthermore, both the steady state distribution $\rho_{st}(x)$ and the mean $\langle x \rangle_{st}$ of the tumor population decreases from large tumor population to small tumor population at increasing D, which indicates that the tumor response to the non-immunogenic tumor microenvironmental factors effects within the tumor site may inhibit tumor growth.

Acknowledgements. The authors acknowledge support from the Department of Mathematics Universiti Putra Malaysia, and one of the Authors (Ibrahim Muawiyya Idris) acknowledge financial support from Umaru Musa Yaradua University katsina Nigeria, under the TETFUND staff training programme.

References

[1] Xue-Mei Liu, Hui-Zhang Xie, Liang-Gang Liu and Zhi-Bing Li, Effect of multiplicative and additive noise on genetic transcriptional regulatory mechanism, *Physica A: Statistical Mechanics and its Applications*, **388** (2009), no. 4, 392-398. http://dx.doi.org/10.1016/j.physa.2008.10.030

[2] Can-Jun Wang, Qun Wei and Dong-Cheng Mei, Associated relaxation time and the correlation function for a tumor cell growth system subjected to color noises, *Physics Letters A*, **372** (2008), no. 13, 2176-2182. http://dx.doi.org/10.1016/j.physleta.2007.11.040

[3] Lin-Jing Yang, Feng Lv and Dong-Cheng Mei, Effects of periodic force on the stability of the metastable state in logistic system, *Physica A: Statistical Mechanics and its Applications*, **432** (2015), 331-336. http://dx.doi.org/10.1016/j.physa.2015.03.056

[4] Andrzej Fuliski and Tomasz Telejko, On the effect of interference of additive and multiplicative noises, *Physics Letters A*, **152** (1991), no. 1, 11-14. http://dx.doi.org/10.1016/0375-9601(91)90619-j

[5] Xiaoyan Zhang, Wei Xu and Bingchang Zhou, Mean first-passage time in a bistable system driven by multiplicative and additive colored noises with colored cross-correlation, *Communications in Nonlinear Science and Numerical Simulation*, **14** (2009), no. 12, 4220-4225. http://dx.doi.org/10.1016/j.cnsns.2009.02.029

[6] Dongcheng Mei, Guangzhong Xie, Li Cao and Dajin Wu, Mean first-passage time of a bistable kinetic model driven by cross-correlated noises, *Physical Review E*, **59** (1999), no. 4, 3880-3883. http://dx.doi.org/10.1103/physreve.59.3880

[7] Ping Zhu, Dynamical Properties of a Bistable System Driven by Cross-Correlated Additive and Multiplicative Colored Noises, *Chinese Journal of Physics*, **44** (2006), 117.

[8] Jia Ya, Cao Li and Wu Da-jin, Effects of a dye laser with correlations between additive and multiplicative noise: Transient properties, *Physical Review A*, **51** (1995), no. 4, 3196-3202. http://dx.doi.org/10.1103/physreva.51.3196

[9] Li-Bo Han, Cao Li, Wu Da-Jin and Wang Jun, Intensity Correlation Function of a Single-Mode Laser Driven by Two Colored Noises with Colored Cross-Correlation, *Communications in Theoretical Physics*, **42** (2004), no. 1, 59-63. http://dx.doi.org/10.1088/0253-6102/42/1/59

[10] Li Zhang and Cao Li, Effect of Correlated Noises in a Genetic Model, *Chinese Physics Letters*, **27** (2010), no. 6, 060504. http://dx.doi.org/10.1088/0256-307x/27/6/060504

[11] X-M. Zhang and B-Q. Ai, Genotype selection model with two time-correlated white noises, *The European Physical Journal B*, **73** (2010), no. 3, 433-437. http://dx.doi.org/10.1140/epjb/e2010-00015-8

[12] Xiao-miao Zhang, Bao-quan Ai and Jian-wen Xiong, Genetic transcriptional regulatory model driven by the time-correlated noises, *Brazilian Journal of Physics*, **40** (2010), no. 3, 295-300. http://dx.doi.org/10.1590/s0103-97332010000300006

[13] Miljenko Marušič, Željko Bajzer, Stanimir Vuk-Pavlovic and James P. Freyer, Tumor growth in vivo and as multicellular spheroids compared by mathematical models, *Bulletin of Mathematical Biology*, **56** (1994), no. 4, 617-631. http://dx.doi.org/10.1007/bf02460714

[14] Bao-Quan Ai, Xian-Ju Wang, Guo-Tao Liu and Liang-Gang Liu, Correlated noise in a logistic growth model, *Physical Review E*, **67** (2003), no. 2, 022903. http://dx.doi.org/10.1103/physreve.67.022903

[15] Anita Behera and S. F. C. O'Rourke, The effect of Correlated Noise in a Gompertz Tumor Growth Model, *Brazilian Journal of Physics*, **38** (2008), no. 2, 272-278. http://dx.doi.org/10.1590/s0103-97332008000200011

[16] D. C. Mei, C. W. Xie and L. Zhang, The stationary properties and the state transition of the tumor cell growth mode, *The European Physical Journal B-Condensed Matter and Complex Systems*, **41** (2004), no. 1, 107-112. http://dx.doi.org/10.1140/epjb/e2004-00300-1

[17] Thomas Bose and Steffen Trimper, Stochastic model for tumor growth with immunization, *Physical Review E*, **79** (2009), 051903. http://dx.doi.org/10.1103/physreve.79.051903

[18] T. Yang, Q. L. Han, C. H. Zeng, H. Wang, Z. Q. Liu, C. Zhang and D. Tian, Transition and resonance induced by colored noises in tumor model under immune surveillance, *Indian Journal of Physics*, **88** (2014), no. 11, 1211-1219. http://dx.doi.org/10.1007/s12648-014-0521-7

[19] Ibrahim Muawiyya Idris and Mohd Rizam Abu Bakar, Effect of Tumor Microenvironmental Factors on the Steady State of Tumor Growth with Non-zero Correlation Time, *Applied Mathematical Sciences*, **10** (2016), no. 10, 451-460. http://dx.doi.org/10.12988/ams.2016.512731

[20] Isaac P. Witz, The tumor microenvironment: the making of a paradigm, *Cancer Microenvironment*, **2** (2009), no. 1, 9-17. http://dx.doi.org/10.1007/s12307-009-0025-8

[21] Isaac P. Witz, Yin-Yang Activities and Vicious Cycles in the Tumor Microenvironment, *Cancer Research*, **68** (2008), no. 1, 9-13. http://dx.doi.org/10.1158/0008-5472.can-07-2917

[22] Xuejing Zhang, Daotai Nie and Subhas Chakrabarty, Growth factors in tumor microenvironment, *Frontiers in Bioscience: a Journal and Virtual Library*, **15** (2010), 151-165.

[23] Carina Strell, Helene Rundqvist and Arne Östman, Fibroblasts-a key host cell type in tumor initiation, progression, and metastasis, *Upsala Journal of Medical Sciences*, **117** (2012), no. 2, 187-195. http://dx.doi.org/10.3109/03009734.2012.654859

[24] Da-Jin Wu, Cao Li and Ke Sheng-Zhi, Bistable kinetic model driven by correlated noises: Steady-state analysis, *Physical Review E*, **50** (1994), no. 4, 2496-2502. http://dx.doi.org/10.1103/physreve.50.2496

[25] C.W. Gardiner, *Handbook of Stochastic Methods for Physics, Chemistry and the Natural Sciences*, second ed., Springer-Verlag, Berlin, 1985.

[26] H. Risken, *The Fokker-Planck Equation Method of Solution and Applications*, Springer-Verlag, Berlin, 1996. http://dx.doi.org/10.1007/978-3-642-61544-3

Received: February 28, 2016; Published: April 26, 2016