International Journal of Pure and Applied Mathematics
Volume 103 No. 3 2015, 467-476
ISSN: 1311-8080 (printed version); ISSN: 1314-3395 (on-line version)
url: http://www.ijpam.eu
doi: http://dx.doi.org/10.12732/ijpam.v103i3.8

EFFECT OF INTERNAL MICRO ENVIRONMENTAL FLUCTUATIONS ON TUMOR GROWTH DYNAMICS

Ibrahim Mu'awiyya Idris[1 §], Mohd Rizam Abu Bakar[2]
[1,2]Department of Mathematics
University Putra Malaysia
MALAYSIA

Abstract: The effect of internal micro environmental fluctuations on tumor growth dynamics modeled by additive white Gaussian noise is investigated. The logistic growth law is considered as the deterministic evolution equation for tumor growth and the steady-state probability distribution is derived within the context of Fokker-Planck equation. We study the influence of micro environmental fluctuations on the steady state dynamics of tumor growth and found out that, the micro environmental fluctuations modeled by additive white Gaussian noise enhances tumor growth at an uncertain threshold.

AMS Subject Classification: 60
Key Words: Langevin equation, Fokker-Planck equation, tumor growth dynamics

1. Introduction

Nonlinear stochastic systems have been studied and applied to many fields of knowledge such as in biology, chemistry, engineering and physics. Theoretical description of these systems provide a link between the deterministic equations and stochastic process, hence stochastic differential equations. The phenomenological model equation is the Langevin dynamical equation and the corresponding Fokker-Planck equation for the time evolution of probability den-

Received: April 25, 2015

© 2015 Academic Publications, Ltd.
url: www.acadpubl.eu

§Correspondence author

sity of the stochastic system under study. Such theoretical descriptions have been used in different context to study the behavior of noise driven systems [1, 2, 3, 4, 5], where the noise are either white or colored and in the form of additive, multiplicative or both as in the case with correlated effects.

In the study of tumor cell growth, mathematical model equations that closely captures the general characteristics of tumor growth and which give an insight into the process are considered in literature. Such equations includes among others the logistic and Gompertz sigmoidal equations which are popularly used in the study of cell growth particularly tumor growth [6, 7], in addition an experimental data were shown to fit the logistic model in [8]. Stochastic differential equations are used as a tool for the study of complex systems affected by noise including the cross correlated noises, and mostly the quantities of interest are the stationary and non-stationary solutions of the Fokker-Planck equation depending on the process under study. Noise effect on tumor growth especially the cross-correlated noises have been widely studied [6, 7, 8, 9], and many complex properties of tumor growth process such as tumor extinction, response to therapy among others were reported at the influence of noise. The effect of noise especially correlated effects are the subject of many communications such as in bistable systems [10, 11, 12], in laser systems [1, 14], in genetic networks [15, 13], and in all these, many properties and system behaviors were studied and discovered. In a related communication, the direct effect of multiplicative colored noise on bacteria growth system was investigated using logistic growth model as a deterministic growth mechanism [16].

In this research, the effect of non-immunogenic micro environmental fluctuations on tumor growth dynamics modeled by additive white Gaussian noise is investigated. The noise is assumed to be external to the system variable, moreover the micro environmental fluctuations here refer to the tumor microscopic habitat that includes the surrounding non-immunogenic microscopic processes such as the genetic instability, signal transduction in cellular activity, cell mutations, fibroblast cells, extracellular matrix and some other metabolic processes that interact with the tumor constantly. The non-immunogenic tumor micro environmental processes could have a pro-malignancy effect, anti-malignancy effect or some times neutral to tumorigenesis [19]. Stochastic approach to the study of micro environmental influence on tumor growth dynamics has not been reported to our knowledge. The paper is organized as follows, Section 2 present the model description, Section 3 present the steady-state analysis based on the Fokker-Planck equation, Section 4 present the numerical results and discussions and Section 5 concludes the paper.

2. Model Description

The phenomenological model equation is the Langevin dynamical equation

$$\frac{d}{dt}x(t) = f(x) + g(x)\eta(t). \tag{1}$$

Here $x(t)$ is the stochastic variable representing the state of the system which is assumed to evolve into space at a point in time ($x(t) \geq 0$), and $g(x) = 1$ so that $\eta(t)$ is an additive noise. Thus, $f(x)$ is linked to the deterministic logistic growth model

$$f(x) = -\frac{dU}{dx} = ax - bx^2, \tag{2}$$

and $U(x)$ is the potential with respect to $f(x)$

$$U(x) = -\frac{ax^2}{2} + \frac{bx^3}{3}, \tag{3}$$

where a is the growth parameter and b the decay parameter and in addition, the function $f(x)$ approaches an asymptote on the long run (infinity index) due to the presence of the quadratic term in eq (2). In the stochastic term of eq (1), $\eta(t)$ will mimic the non-immunogenic micro environmental effect modeled by the additive white Gaussian noise with the following statistical properties:

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

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

where θ is the strength of the additive noise. In addition, since eq (1) is only perturbed by an additive noise, then no further stochastic interpretation is required for solution. We define the following relation on the diffusion part of eq (1)

$$G(x)\beta(t) = \eta(t). \tag{6}$$

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

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

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

where the two time correlation of $G(x)\beta(t)$ in eq (6) be equivalent to the two time correlations of $\eta(t)$ in eq (1)

$$G(x)^2 \langle \beta(t)\beta(t') \rangle = \langle \eta(t)\eta(t') \rangle, \tag{9}$$

$$G(x) = \sqrt{\theta}. \tag{10}$$

3. Steady State Analysis

The Fokker-Planck equation for the time evolution of probability density of the stochastic variable $x(t)$ is given by

$$\frac{\partial \rho(x,t)}{\partial t} = -\frac{\partial}{\partial x}A(x)\rho(x,t) + \frac{\partial^2}{\partial x^2}B(x)\rho(x,t), \tag{11}$$

where $\rho(x,t)$ is the probability density function, $A(x)$ and $B(x)$ are the drift and diffusion terms respectively

$$A(x) = ax - bx^2, \tag{12}$$

$$B(x) = G(x)^2 = \theta, \tag{13}$$

$$\frac{\partial \rho(x,t)}{\partial t} = -\frac{\partial}{\partial x}\{(ax - bx^2)\rho(x,t) - \theta\frac{\partial}{\partial x}\rho(x,t)\}. \tag{14}$$

Eq (14) can be written in the form of conservation equation for probability

$$\frac{\partial \rho(x,t)}{\partial t} + \frac{\partial J}{\partial x} = 0. \tag{15}$$

where J in eq (15) is known as the probability current which in other words represent the flow of probability. At stationarity, the rate of change of probability $\rho(x,t)$ with time is constant

$$\frac{\partial \rho(x,t)}{\partial t} = 0. \tag{16}$$

Therefore we have a stationary current $J_{\mathsf{st}}(x)$ which is time independent and is given by

$$J_{\mathsf{st}}(x) = (ax - bx^2)\rho_{\mathsf{st}}(x) + \theta\frac{\partial}{\partial x}\rho_{\mathsf{st}}(x), \tag{17}$$

from eq (17) and using reflecting boundary condition, we have the following stationary distribution for the system [17, 18]

$$\rho_{\mathsf{st}}(x) = N\exp\left\{-\frac{1}{\theta}\int(ax - bx^2)dx\right\}, \tag{18}$$

In eq (18), N is the normalization constant which is choosing so that the following relation is satisfied

$$\int_{-\infty}^{\infty}\rho_{\mathsf{st}}(x)dx = 1. \tag{19}$$

From eq (18) we've

$$\rho_{\mathsf{st}}(x) = N \exp\left\{-\frac{b}{3\theta}\left(x - \frac{a}{4b}\right)^2\right\}. \tag{20}$$

where

$$N = \sqrt{\frac{b}{3\pi\theta}}.$$

Using eq (20), the mean and other properties of the tumor growth $x(t)$ under the influence of internal micro environmental fluctuations can be obtained on average

$$\langle x \rangle = \int_0^{\infty} x \rho_{\mathsf{st}}(x) dx. \tag{21}$$

4. Results and Discussion

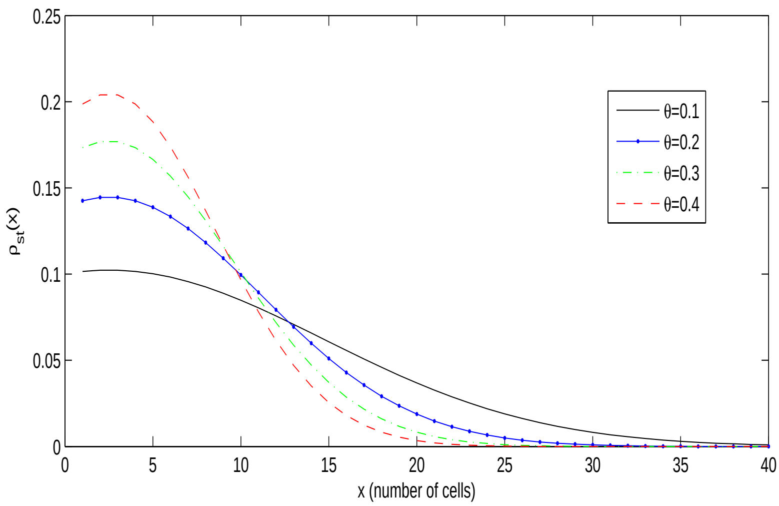

Figure 1: Plot of $\rho_{\mathsf{st}}(x,t)$ (probability density) against x (cell number) for different values of environmental noise θ. $a = 1$, $b = 0.1$ (units are arbitrary).

Figures 1 and 2 shows the effect of the strength of the micro environmental fluctuations $\eta(t)$ on the steady state distribution $\rho_{\mathsf{st}}(x)$ of the tumor cell population. In Figure 1, varying θ over some values or in particular increasing the

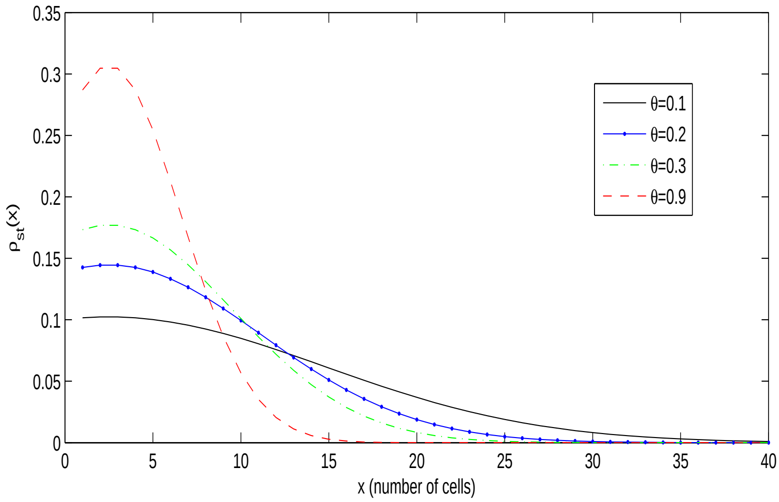

Figure 2: Plot of $\rho_{\text{st}}(x, t)$ (probability density) against x (cell number) for different values of environmental noise θ. $a = 1$, $b = 0.1$ (units are arbitrary).

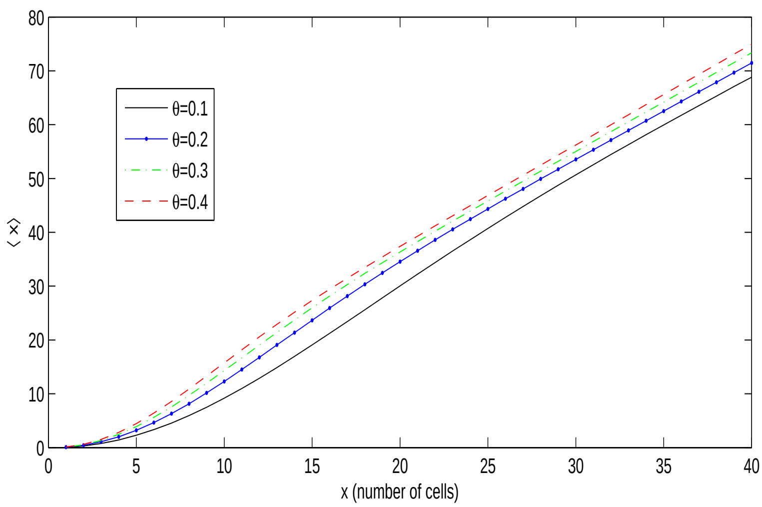

Figure 3: Plot of $\langle x \rangle$ (average mean value) against x (cell number) for different values of environmental noise θ. $a = 1$, $b = 0.1$ (units are arbitrary).

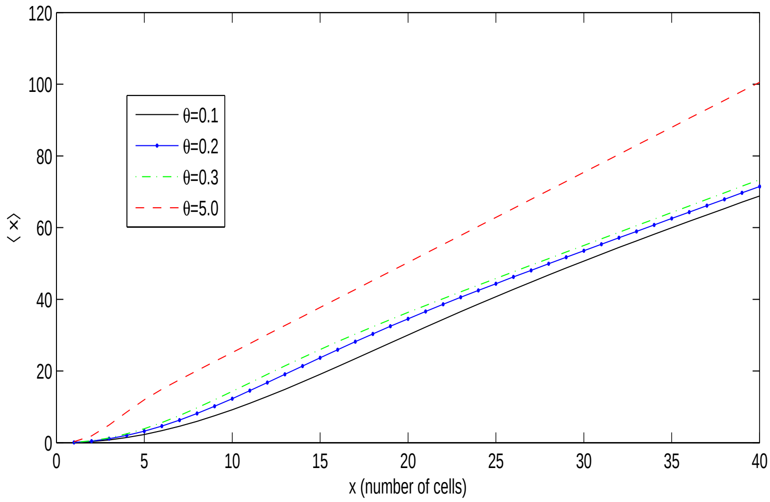

Figure 4: Plot of $\langle x\rangle$ (average mean value) against x (cell number) for different values of environmental noise θ. $a = 1$, $b = 0.1$ (units are arbitrary).

θ values results to enhancing growth and more apparently in Figure 2 given θ some high value the growth is seen to be enhanced accordingly. Figures 3-4 depicts the mean average $\langle x\rangle$ of tumor cells against the tumor cells number, where Figure 3 shows the effect of the micro environmental fluctuations $\eta(t)$ on the mean average and it is observed that the average mean $\langle x\rangle$ increases at increasing θ values while in Figure 4, severe effect ($\theta = 5.0$) of the micro environment is observed to promote the average mean of the tumor cell in a more apparent way. However from the results obtained we noticed that the severe effects of non-immunogenic micro environmental fluctuations $\eta(t)$ modeled by additive Gaussian noise promote and enhance tumor growth. The micro environmental fluctuations adjust to the fact that within the system there are some environmental processes such as the signal transduction in cellular activity, genetic instability, fibroblast, nutrients etc which can affect the tumor growth by providing some pro or anti malignancy effect. For example, fibroblast cells secretions can contribute to tumor growth through deposition of extracellular matrix proteins which in turn can provide a high chance of growth and invasion for tumors.

5. Conclusion

We have studied the effect of micro environmental fluctuations $\eta(t)$ on tumor growth dynamics at steady state. Micro environmental fluctuations which in this case are non-immunogenic are modeled by an additive Gaussian white noise which are incorporated into the deterministic evolution equation. Our numerical results based on Figures 1-4 shows that, the micro environmental fluctuations modeled by additive white Gaussian noise enhances tumor growth, and also the internal micro environment not only enhances growth but are also capable of instigating tumor growth at an uncertain threshold. Tumor growth is an adaptive process on its micro environment, it takes advantage of many surrounding metabolic processes towards growth, aggression and invasion of the host. In view of this, the study of the influence and interaction of tumors with its surrounding micro environment is imperative towards understanding cancer initiations and proliferation, and stochastic methods can be employed as a tool for theoretical study.

Acknowledgements

This research was supported by the Department of Mathematics, University Putra Malaysia.

References

[1] Jia Ya, Cao Li and Wu Da-jin. Effect of a Dye Laser With Correlation Between Additive and Multiplicative Noise: Transient Properties. American Physical Society. Vol.51, No.4, (1995), pp 3196-3202.

[2] Bao-Quan Ai, Xian-Ju Wang, Guo-Tao Liu, and Liang-Gang Liu. Noise in an Insect Outbreak Model. Chinese Journal of Physics, Vol.41, No.4 (2003), pp 1-8.

[3] Matthew J. Berryman, Sabrina L. Spencer, Andrew Allison, and Derek Abbott: Fluctuations and noise in cancer development, Ann Arbor, MI 48109, USA (2004).

[4] XM Liu, HZ Xie, LG Liu, ZB Li. Effect of multiplicative and additive noise on genetic transcriptional regulatory mechanism. Physica A 388 (2009), pp 392-398.

[5] Zhu Ping. Dynamical Properties of a Bistable System Driven by Cross-Correlated Additive and Multiplicative Colored Noises. Chinese Journal of Physics, Vol.44, No.2, (2006), pp 117-126.

[6] 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), 022903.

[7] A. Behera and S. F. C. ORourke. Effect of Correlated Noise in a Gompertz Tumor Growth Model. Brazilian Journal of Physics, Vol.38, No.2, (2008), pp 272-278.

[8] Thomas Bose and Steffen Trimper. Stochastic Model for Tumor Growth With Immunization. Physical Review E 79, (2009), 051903.

[9] Can-Jun Wang, Qun Wei and Dong-Cheng Mei. Associated relaxation time and the correlation function for a tumor cell growth system subject to color noises. Physics Letters A, Vol.372, Issue 13, (2008), pp 2176-2182.

[10] Andrzej Fulinski and Tomasz Telejko. On the effect of interference of additive and multiplicative noises. Physics Letters A, Vol.152, Issue 1-2 (1991), pp 11-14.

[11] Xiaoyan Zhang, Wei Xu, Bingchang Zhou. Mean first-passage time in a bistable system driven by multiplicative and additive colored noises with colored cross-correlation. Commun Nonlinear. Sci Numer Simulat 14 (2009), pp 42204225.

[12] 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, Vol.59, No.4 (1999), pp 3880-3883.

[13] Zhang Li and Cao Li. Effect of Correlated Noises in a Genetic Model. Chin. Phys. Lett. Vol.27, No.6 (2010) 060504.

[14] Han Li-Bo, 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. Commun. Theor. Phys. Vol.42, No.1 (2004), pp 5963.

[15] 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 388 (2009), pp 392-398.

[16] Hong-Yan Liao, Bao-Quan Ai, and Lian Hu. Effects of Multiplicative Colored Noise on Bacteria Growth. Brazilian Journal of Physics, Vol.37, No.3B, (2007), pp 1125-1128.

[17] C.W. Gardiner. Handbook of Stochastic Methods for Physics, Chemistry and the Natural Sciences. Second Edition, Springer-Verlag, Berlin, (1985).

[18] H. Risken. The Fokker Planck Equation Method of Solution and Application. Springer-Verlag, Berlin, (1996).

[19] Isaac P. Witz. The Tumor Microenvironment: The Making of a Paradigm. Journal of Cancer Microenvironment, Vol.2, Supplement 1, (2009), pp 9-17.