Comment on "Correlated noise in a logistic growth model"

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We argue that the results published by Ai *et al.* [Phys. Rev. E **67**, 022903 (2003)] on "correlated noise in logistic growth" are not correct. Their conclusion that, for larger values of the correlation parameter λ, the cell population is peaked at $x=0$, which denotes a high extinction rate, is also incorrect. We find the reverse behavior to their results, that increasing λ promotes the stable growth of tumor cells. In particular, their results for the steady-state probability, as a function of cell number, at different correlation strengths, presented in Figs. 1 and 2 of their paper show different behavior than one would expect from the simple mathematical expression for the steady-state probability. Additionally, their interpretation that at small values of cell number the steady-state probability increases as the correlation parameter is increased is also questionable. Another striking feature in their Figs. 1 and 3 is that, for the same values of the parameters λ and α, their simulation produces two different curves, both qualitatively and quantitatively.

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In a recent paper [1], Ai *et al.* investigated the steady-state properties of tumor cell growth and studied the effects of correlated noise. In their study they started with the logistic differential equation, which reads as

$$\frac{dx}{dt} = ax - bx^2, \tag{1}$$

where x is the tumor cell mass, a the growth rate, and b the cell decay rate. Considering the effects due to external factors such as radiotherapy, temperature, and drugs, etc, they introduced Gaussian white noise (both additive and multiplicative) and as a result they obtained the following equation:

$$\frac{dx}{dt} = ax - bx^2 + x\epsilon(t) - \Gamma(t), \tag{2}$$

where $\epsilon(t)$ and $\Gamma(t)$ are Gaussian white noise terms with the following properties:

$$\langle \epsilon(t)\rangle = \langle \Gamma(t)\rangle = 0, \tag{3}$$

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

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

$$\langle \epsilon(t)\Gamma(t')\rangle = 2\lambda\sqrt{D\alpha}\,\delta(t-t'), \tag{6}$$

where α and D are the intensity of the additive and multiplicative noise terms, respectively, and λ denotes the strength of correlation between $\epsilon(t)$ and $\Gamma(t)$ with $0 \le \lambda < 1$. According to the Langevin equation (2), one can derive the Fokker-Plank equation [2] for positive values of x:

$$\frac{\partial p(x,t)}{\partial t} = -\frac{\partial}{\partial x}[A(x)p(x,t)] + \frac{\partial^2}{\partial x^2}[B(x)p(x,t)], \tag{7}$$

where $p(x,t)$ is the probability distribution function, and $A(x)$ and $B(x)$ are respectively defined as

$$A(x) = ax - bx^2 + Dx - \lambda\sqrt{D\alpha}, \tag{8}$$

$$B(x) = Dx^2 - 2\lambda\sqrt{D\alpha}\,x + \alpha. \tag{9}$$

According to the reflecting boundary condition, the steady-state probability distribution function (SPDF) of Eq. (7) is [3]

$$p_{st}(x) = \frac{N}{B(x)}\exp\left(\int^x \frac{A(x')dx'}{B(x')}\right), \tag{10}$$

where N is the normalization constant. According to [3], one can obtain the final expression for the SPDF using the forms of $A(x)$ and $B(x)$,

$$p_{st}(x) = NB(x)^{C-1/2}\exp\left[f(x) + \frac{E}{F}\arctan\left(\frac{G(x)}{F}\right)\right] \quad \text{for } (0 \le \lambda < 1) \tag{11}$$

where

$$C = \frac{a - 2\lambda\sqrt{\alpha/D}b}{2D}, \quad f(x) = -\frac{b}{D}x,$$

$$E = b\frac{\alpha}{D} + \left(a - 2\lambda\sqrt{\frac{\alpha}{D}}b\right)\lambda\sqrt{\frac{\alpha}{D}}.$$

It is to be noted here that the expression for E in Ref. [1] appears to have an error. Finally,

$$F = \sqrt{D\alpha(1-\lambda^2)}, \quad G(x) = Dx - \lambda\sqrt{\alpha D}.$$

In Figs. 1 and 2, we present the results of our model for the steady-state probability distribution $p_{st}(x)$ as a function of x at different values of the correlation parameter λ. It is evident from the figures that, as the correlation strength increases, the probability for the smaller x values decreases and then rises sharply, crossing the curves of lower λ values before reaching the peak at $x \in [7.0, 8.15]$. This implies that

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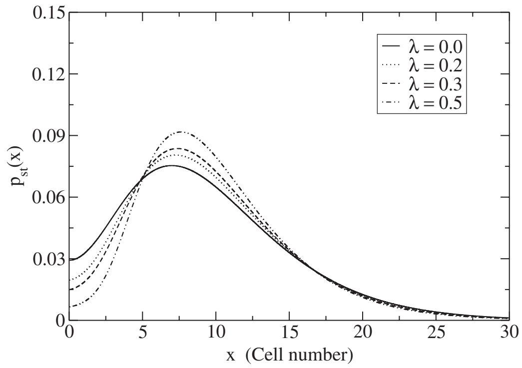

FIG. 1. Plot of $p_{st}(x)$ as a function of x for low values of correlation parameter λ. $D=0.3$, $\alpha=3.0$, $a=1.0$, $b=0.1$, and $\lambda=0.0,0.2,0.3,0.5$. All the parameter values are in arbitrary units.

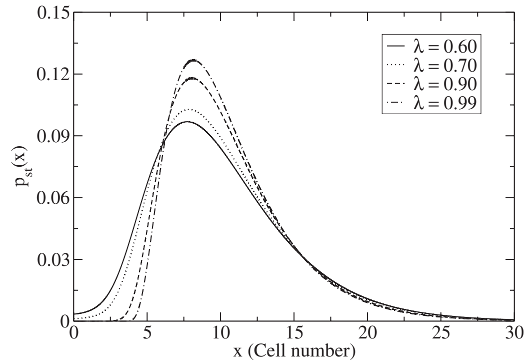

FIG. 2. Plot of $p_{st}(x)$ as a function of x for low values of correlation parameter λ. $D=0.3$, $\alpha=3.0$, $a=1.0$, $b=0.1$, and $\lambda=0.6,0.7,0.9,0.99$. All the parameter values are in arbitrary units.

higher values of λ promote cell growth instead of leading to the extinction of cells. The close correlation between the two noises reflects the adaptability of a tumor to the treatments and does not cause extinction of the tumor cells. Our results indicate that a treated tumor, after adaptation, grows better than an untreated tumor. These results possibly reflect an inappropriate therapeutic treatment strategy which does not lead to tumor cell death but instead contributes to their malignant growth.

Note also that the extrema $p_{st}(x)$ satisfy the equation

$$A(x) - \frac{dB(x)}{dx} = 0. \tag{12}$$

This can be written more explicitly using Eqs. (8) and (9) as

$$bx^2 + (D-a)x - \lambda\sqrt{D\alpha} = 0, \tag{13}$$

which is the same as Eq. (14) of Ref. [1]. The two solutions of this quadratic equation are

$$\frac{a - D \pm \sqrt{(a-D)^2 + 4\lambda b\sqrt{D\alpha}}}{2b}. \tag{14}$$

Analysis of Eq. (14) shows that the peaks cannot move toward zero with increasing λ. It is clear that, with all the parameters (a, b, D, α, and λ) as given in Figs. 1 and 2, one root is positive and the other is negative. The positive root will always increase with λ, contrary to the statement reported in Ref. [1]. Therefore, the peak positions in Figs. 1 and 2 of Ref. [1] cannot move toward zero—they should move away from zero. The present Figs. 1 and 2 confirm this behavior. We consider the physical solution which gives the position values of x (as x, the cell number, cannot be negative).

It is clear from studying Eq. (14) that, as λ increases, the peaks of the distribution function shift toward the more positive values of x (see Fig. 2), and the magnitude of $p_{st}(x)$ increases, which confirms the stable growth of the tumor cells.

In conclusion, we have studied the effect of environmental fluctuations on tumor cell growth and its steady-state properties. We have found that the discrepancy between our results and those of Ai *et al.* arises due to a sign issue concerning the correlation between additive and multiplicative noise. This corresponds to a change of sign of the correlation between additive and multiplicative noise, which leads to a better biological interpretation of Eq. (2). In fact, it may be shown in Eq. (2) that the additive and multiplicative noise have opposite effects (when one is positive and the other is negative). This interpretation indicates that a positive λ indicates a negative feedback between noise terms. On the contrary, a negative λ, or alternatively a change in sign of either of the two noise terms in Eq. (2), is correct, to simulate positive feedback of two effects in the tumor treatment.

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