The effects of environmental disturbances on tumor growth

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Abstract

In this study, the analytic expressions of the steady probability distribution of tumor cells were established based on the steady state solution to the corresponding Fokker-Planck equation. Then, the effects of two uncorrelated white noises on tumor cell growth were investigated. It was found that the predation rate plays the main role in determining whether or not the noise is favorable for tumor growth.

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I. INTRODUCTION

As tumors seriously threaten human health, extensive attention has been paid to this issue by researchers in various fields[1–27]. It is known that tumor cell growth is a complex process, and is governed by environmental fluctuations such as the people’s spiritual status, as well as other diseases from which they suffer. Recently, researchers from the field of nonlinear physics have introduced noise into the model of tumor cell growth, where noise refers to the various disturbances involved in tumor growth. For example, Ai and coworkers[2, 3, 5] studied the effects of correlated Gaussian white noise in a logistic growth model. This model is often as a basic model for cell growth, particularly tumor cell growth[28, 29], to describe such growth under ideal conditions without fluctuation. Ai and coworkers found that noise during tumor cell growth can induce phase transition, and that intensive environmental fluctuations may even cause the extinction of tumor cells. Furthermore, Zhong and coworkers[7, 26] investigated the random resonance of tumor growth with noise. It was found that the steady distribution probability of tumor growth changed from a uni-peak state to a bi-peak state when the intensity of multiplicative noise increased. An appropriate intensity of multiplicative noise can destroy the mechanism of tumor growth. In contrast, superfluous noise can be beneficial for their growth. Mei and coworkers[9] investigated the tumor cell growth model in the presence of correlated noises and found that the correlation intensity $\lambda$ and correlation time $T$ play opposite roles in the static properties and the state transition of the system. An increase in $\lambda$ can produce a smaller mean value of the cell population and slow down the state transition. However, an increase in $T$ can produce a larger mean value of the cell population and enhance the state transition.

The abovementioned results demonstrate that tumor growth models with noise are closer to the real situation, although most models exhibit some differences from the real process of tumor growth. In such studies, researchers have attempted to obtain deeper insights into the intrinsic mechanisms of tumor growth and provide new ideas for tumor treatment.

The noises introduced into the tumor growth model are generally a single noise, correlated multiplicative noise[3, 5], etc. It has been shown that different types and numbers of noise may be operating in the context of tumor growth[2, 3, 5, 8, 10, 26], and the corresponding tumor growth behaviors have also been observed to be different. The random fluctuations
introduced in our study are different from those in previous studies. In this paper, the effects of two uncorrelated Gaussian white noises on tumor growth will be studied. These are the effect of additive noise on the birth rate of tumor cells and that of multiplicative noise on the predation rate of anticancer cells. It is shown that the effect of noise on the tumor growth is mainly determined by the predation rate of anticancer cells. With changes in the parameters, the steady distribution probability of tumor growth changes between a single steady state and bi-stable state.

II. THE DETERMINISTIC MODEL OF TUMOR CELL GROWTH

Lefever and Garay[30] studied tumor growth under immune surveillance against cancer using the enzyme dynamics model. The model is as follows:

\[
\text{Normal Cells} \rightarrow X,
\]

\[
X \rightarrow 2X,
\]

\[
X + E_0 \rightarrow E \rightarrow E_0 + P,
\]

\[
P \rightarrow ,
\]

Here, \(X, P, E_0,\) and \(E\) are cancer cells, dead cancer cells, immune cells, and the compounds of cancer cells and immune cells, respectively. This model reveals that normal cells can transform into cancer cells, and then the cancer cells reproduce, decline, and ultimately die out.

Based on the model by Lefever and Garay, we investigate the Logistic model of Verhulst, and only consider the growth of tumor cells and anticancer cells. We assume that tumor cells satisfy the following equation[31,32]:

\[
\frac{dX}{dt} = r_B X \left(1 - \frac{X}{k_B}\right) - P(X),
\]

where \(X\) is the relative number of tumor cells, \(r_B\) is the birth rate of the tumor cells, and \(k_B\) is carrying capacity. \(P(X)\) represents predation generated by anticancer cells. We take the \(P(X)\) expression suggested by Ludwing[31]. In his work \(P(X)\) is expressed by
\(BX^2/(A^2 + X^2)\), where \(A\) is a positive constant and \(B\) represents the predation rate of the anticancer cells.

As we do not intend to investigate the constant \(A\), it was concealed in the model for the convenience of discussion. The transformation parameters can be given by

\[
x = \frac{X}{A}, r = Ar_B, q = \frac{K_B}{A}, \tau = \frac{t}{A}, \beta = B,
\]

(2)

and by substituting this into Eq. (1), we obtain:

\[
\frac{dx}{d\tau} = rx \left( 1 - \frac{x}{q} \right) - \frac{\beta x^2}{1 + x^2},
\]

(3)

where \(r\) is the tumor cell growth rate and \(\beta\) is the predation rate of anticancer cells. By letting \(\frac{dx}{d\tau} = 0\), we can obtain the steady states of the system from the Eq. (3). Clearly, one of the solutions is \(x = 0\), while the other solutions satisfy:

\[
r \left( 1 - \frac{x}{q} \right) = \frac{\beta x}{1 + x^2}.
\]

(4)

When \(r\) varies and keeps \(\beta\) and \(q\) constant, the number of solutions (namely equilibria) changes between one and three\(^{32}\). The range with three solutions changes with the values of \(\beta\) and \(q\). This also occurs for a variable \(\beta\) (or \(q\)) and fixed \(r\) and \(q\) (or \(\beta\)).

Based on Eq. (3) (let \(f(x) = \frac{dx}{d\tau}\)), we can draw the curves of \(f(x) - x\) as shown in Fig. 1. For a curve with \(r = 1.0\) and \(\beta = 2.0\), \(x = 0\) and \(x = x_2\) are unstable states, since \(\partial f/\partial x > 0\) at \(x = 0, x_2\). However, \(x_1\) and \(x_3\) are stable steady states since \(\partial f/\partial x < 0\) at these two points.

FIG. 1: The equilibria of \(f(x)\) vary with a decreases in \(r\) and increases in \(\beta\) for \(q = 10.0\) (arbitrary units).

In Fig. 1, when \(r\) decreases or \(\beta\) increases, the solutions \(x_2\) and \(x_3\) will disappear and only the stable state \(x_1\) on the left side can be observed (e.g. the curve for \(r = 1.0, \beta = 3.0\)). In contrast, when \(r\) increases or \(\beta\) decreases, only the stable state \(x_3\) on the right side can be observed (as shown in Fig. 2). Clearly, \(x_1\) is the refuge equilibrium, while \(x_3\) is the outbreak equilibrium. From a tumor control point of view, we need to keep the number of tumor cells in the refuge state rather than allowing it to reach an outbreak situation.
FIG. 2: The equilibria of $f(x)$ vary with an increases in $r$ and decreases in $\beta$ for $q = 10.0$ (arbitrary units).

When considering the noise, the range of three equilibria is also related to the noises. Similarly, the equilibrium state changes between 1 and 3 by varying the parameters. Therefore, it is necessary to investigate them by using the steady probability distribution function (SPDF).

III. TUMOR CELL GROWTH MODEL WITH NOISE

Equation (3) only describes the tumor growth behavior under ideal conditions, without fluctuation. When considering a real situation, external environmental disturbances such as the individual’s state of health, body temperature, and other disease may affect tumor growth. In addition, artificial behavior like chemotherapy may also have an effect. Because of these external disturbances, the growth rate of tumor cells and the predation rate of anticancer cells may vary greatly. In our work, the effects of additive noise on the birth rate of tumor cell and multiplicative noise on the predation rate of anticancer cells are further considered. Hence the tumor growth equation considering external disturbances can be rewritten as:

$$\frac{dx}{d\tau} = rx \left( 1 - \frac{x}{q} \right) - \frac{(\beta + \xi(t))x^2}{1 + x^2} + \Gamma(t),$$

where $\xi(t)$ and $\Gamma(t)$ are Gaussian white noises. They have the following properties:

$$< \xi(t)\xi(t') > = 2\sigma \delta(t - t'), \quad < \Gamma(t)\Gamma(t') > = 2D \delta(t - t'),$$

where $\sigma$ and $D$ are the strength of the noises $\xi(t)$ and $\Gamma(t)$, respectively. From this, we can derive the corresponding Fokker-Planck equation for the evolution of SPDF based on Eq. (5) and Eq. (6). The equation is as follows [11]:

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

where $P(x,t)$ is the probability of the relative numbers of tumor cells, and:

$$A(x) = rx \left( 1 - \frac{x}{q} \right) - \frac{\beta x^2}{1 + x^2} + \sigma \frac{2x^3}{(1 + x^2)^3}, \quad (8)$$
\[ B(x) = \sigma \left[ \frac{x^2}{1 + x^2} \right]^2 + D. \]  

(9)

IV. STEADY STATE ANALYSIS OF THE MODEL

Usually, what we are concerned with is the steady state. For Eq. (7), when \( \frac{\partial P(x,t)}{\partial t} = 0 \), we can obtain the SPDF of the tumor cells [11]:

\[ P_{st}(x) = \frac{N}{B(x)} \exp \left[ \int^{x} \frac{A(x)}{B(x)} \, dx \right], \]  

(10)

or

\[ P_{st}(x) = \frac{N}{B(x)} \exp[M(x)], \]  

(11)

where \( N \) is the normalization constant,

\[ M(x) = \int^{x} \frac{A(x)}{B(x)} \, dx. \]  

(12)

When considering Eqs. (8), (9), and (12) together, we can obtain:

\[ M(x) = ax + bx^2 + cx^3 + d \ln |E(x)| + l \ln \left( \frac{U(x)}{V(x)} \right) + \ln \sqrt{\frac{E(x)}{1 + x^2}} \]  

\[ + m \arctan H(x) + n (\arctan K(x) + \arctan L(x)), \]  

(13)

where

\[ a = -\frac{2r\sigma + q\beta(D + \sigma)}{q(D + \sigma)^2}, \]  

(14)

\[ b = \frac{r}{2(D + \sigma)}, \]  

(15)

\[ c = \frac{r}{3q(D + \sigma)}, \]  

(16)

\[ d = \frac{r\sigma}{2(D + \sigma)^2}, \]  

(17)

\[ l = \frac{r\sigma}{(3D + \sigma + 2\sqrt{D(D + \sigma)}) + q\beta(D + \sigma)(\sigma - D + \sqrt{D(D + \sigma)})}, \]  

(18)

\[ m = \frac{r\sqrt{\sigma(\sigma - D)}}{\sqrt{2\sqrt{D(D + \sigma)} - 2D}}. \]  

(19)
\[ n = \frac{r\sigma (3D - \sigma + 2\sqrt{D(D + \sigma)}) + q\beta(D + \sigma)(D - \sigma + \sqrt{D(D + \sigma)})}{2q(D + \sigma)^2 \sqrt{2\sqrt{D(D + \sigma)} + 2D}}, \]  

(20)

\[ E(x) = D + 2Dx^2 + (D + \sigma)x^4, \]  

(21)

\[ U(x) = \sqrt{D} + \sqrt{2\sqrt{D(D + \sigma)} - 2Dx + (D + \sigma)x^2}, \]  

(22)

\[ V(x) = \sqrt{D} - \sqrt{2\sqrt{D(D + \sigma)} - 2Dx + (D + \sigma)x^2}, \]  

(23)

\[ H(x) = \frac{(D + \sigma)x^2 + D}{\sqrt{D\sigma}}, \]  

(24)

\[ K(x) = \frac{2\sqrt{D + \sigma}x + \sqrt{2\sqrt{D(D + \sigma)} - 2D}}{\sqrt{2\sqrt{D(D + \sigma)} + 2D}}, \]  

(25)

\[ L(x) = \frac{2\sqrt{D + \sigma}x - \sqrt{2\sqrt{D(D + \sigma)} - 2D}}{\sqrt{2\sqrt{D(D + \sigma)} + 2D}}. \]  

(26)

Equation (11) is the main result in this study. Based on this equation, we can plot the figures and obtain the curves for \( P_{st}(x) \), \( r \), \( D \), \( \beta \), and \( \sigma \). In this way, we can determine the mechanisms of tumor growth model.

V. RESULTS AND DISCUSSION

A. The relationships between \( r \), \( \beta \), and \( x \) under SPDF extremum condition

In order to discuss the effects of the fluctuation on the steady probability distribution (SPD) of tumor growth, it is necessary to discuss the relationships between \( r \), \( \beta \), and \( x \). The condition to obtain the extremum of SPDF is:

\[ A(x) - B'(x) = 0, \]  

(27)

By considering Eqs. (8), (9), and (27) together, we can obtain:

\[ r \left(1 - \frac{x}{q}\right) - \frac{\beta x}{1 + x^2} - \sigma \frac{2x^2}{(1 + x^2)^3} = 0. \]  

(28)
Based on Eq. (28), we can draw the curves of $r - x$ and $\beta - x$ in Fig. 3 and 4, respectively. As shown in Fig. 3, when $0.1 \leq \sigma \leq 1.0$, one value of $r$ ($0.9 \leq r \leq 1.3$) corresponds to three values of $x$ with a fixed $\beta$ and $q$. That is, the SPDF of tumor growth will exhibit two peaks (corresponding to the three solutions, namely the two stable steady states in the section 2) if $r$ is in that range. For different values of $\sigma$ (or $\beta$), the curves almost overlap with each other, except in the position around $x = 1$. This demonstrates that only when $x$ is around 1 can we observe the difference of $r$ for different values of $\sigma$ (or $\beta$).

FIG. 3: Plot of the SPDF extrema as a function of $x$ for different $\sigma$ values, using $\beta = 2.25$ and $q = 10.0$ (arbitrary units).

FIG. 4: Plot of the predation rate $\beta$ of anticancer cells as a function of $x$ for different values of $r$ and $\sigma$ with $q = 10.0$ under the SPDF extremum condition (arbitrary units).

Similarly, adopting $r = 1.0$ in Fig. 4, one value of $\beta$ ($1.7 \leq \beta \leq 2.5$) corresponds to three values of $x$. The range of the two peaks is different with different $r$ values.

As Eq. (28) is irrelevant to $D$, the ranges of the two peaks is mainly determined by $r$ and $\beta$. In addition to the aforementioned ranges, for smaller or larger values of $r$ (or $\beta$), each curve has only one peak (mono-stability). This corresponds to the situation shown in the section 2, but there are four parameters here ($r$, $\beta$, $q$ and $\sigma$).

It is clear that the SPD of tumor growth switches between bi-stability and mono-stability when the parameter $r$ changes. As shown in Fig. 5, the positions of the peaks vary with the different $r$ values. For a small $r$ value, there is only one peak on the left side, which represents a small quantity of tumor cells in healthy people or the annihilation of tumor cells. With the increase of $r$ value, two peaks can be observed. With a further increase in the $r$ value, the peak number is again reduced to one and its position shifts to the right side, indicating the steady growth of the tumor cells. Comparing the growth behaviors under different $r$ values, it can be concluded that a large value of $r$ is favorable for tumor
cell growth.

FIG. 5: Plot of $P_{st}(x)$ against $x$ for different $r$ values, using $\beta = 2.3, q = 10.0, D = 0.5, \text{ and } \sigma = 0.5$ (arbitrary units).

FIG. 6: Plot of $P_{st}(x)$ against $x$ for different $\beta$ values, using $q = 10.0, r = 1.0, D = 0.5, \text{ and } \sigma = 0.5$ (arbitrary units).

Fig. 6 shows the effects of the $\beta$ value on the tumor growth. With the increase of the $\beta$ value, the number of peaks on the curve changes from one to two, and finally back to one. It is clear that a large predation rate is unfavorable for tumor growth.

B. The effects of fluctuations on tumor growth rate

Figure 7 shows the effects of $D$ on tumor growth for a small $\beta$ value (e.g. $\beta = 1.7$). When the value of $D$ increases, the peak intensity of the probability density decreases, which demonstrates that an increase in $D$ is unfavorable for tumor growth.

In the case of a large $\beta$ value (e.g. $\beta = 2.6$), the peak position shifts to the left side, as shown in Fig. 8. When the $D$ value increases, the SPD of tumor cells moves to the more positive $x$ direction. When healthy people receive chemotherapy, normal tissue cells and anticancer cells may be killed rather than tumor cells. Therefore, in such a case, chemotherapy is favorable for tumor growth (although there is usually a small quantity of tumor cells in
healthy people, they can be controlled by the immunity of the human body).

It can thus be concluded that $\beta$ plays a very important role in tumor growth, especially if $\beta$ is very small or very large, while $\sigma$ is less important for the tumor growth. In a real situation, the magnitude of the predation rate can determine the body’s anticancer ability.

For a moderate $\beta$ value, for example $\beta = 2.26$, there are two peaks for all the $D$ values, as shown in Fig. 8: Plot of $P_{st}(x)$ against $x$ for different $D$ and $\sigma$ values, using $\beta = 2.6, q = 10.0, and r = 1.0$ (arbitrary units).

FIG. 8: Plot of $P_{st}(x)$ against $x$ for different $D$ and $\sigma$ values, using $\beta = 2.6, q = 10.0, and r = 1.0$ (arbitrary units).

shown in Fig. 9 and 10. For a fixed $\beta$, the SPDF curve becomes flatter with an increase in $D$. The noise interferes with the tumor growth as well as the predation rate of anticancer cells. For example, by using chemotherapy, tumor cells may be extinguished. At the same time, normal tissue cells and anticancer cells may also be damaged. Here, whether or not the increase of $D$ is favorable for tumor growth is determined by $\sigma$. For a small value of $\sigma$, as shown in Fig. 9 ($\sigma = 0.1$), the intensity of the right peak decreases with an increase in $D$, which means that it is unfavorable for tumor growth. In contrast, for a large value of $\sigma$, as shown in Fig. 10 ($\sigma = 0.8$), even though the intensities of two peaks decrease at the same time, the SPD of tumor cells moves to the more positive direction of $x$. That is, when $\sigma$ is larger, interference with the anticancer cells is dominant. Thus, the increase of $D$ in the case of a larger $\sigma$ when $\beta$ is a middle value is favorable for tumor growth.

For a different value of $r$, for example, $r = 1.2$, the results indicate that the laws acting on

FIG. 9: Plot of $P_{st}(x)$ against $x$ for different $D$ values, using $\beta = 2.26, q = 10.0, r = 1.0, and \sigma = 0.1$ (arbitrary units).

FIG. 10: Plot of $P_{st}(x)$ against $x$ for different $D$ values, using $\beta = 2.26, q = 10.0, r = 1.0, and \sigma = 0.8$ (arbitrary units).

$P_{st}(x)$ and $D$ are same as that of $r = 1.0$. However, the range of the two peaks is different.
If the curves for \( r = 1.0 \) shift to the more positive direction of \( \beta \), they can nearly overlap with the curves for \( r = 1.2 \). For example, Fig. 11 is almost same to Fig. 9, except that the relevant \( \beta \) value (2.72) is higher by around 0.46 larger than that for \( r = 1.0 \) (\( \beta = 2.26 \)). This means that the laws of tumor growth are similar even with a different tumor growth rate.

FIG. 11: Plot of \( P_{st}(x) \) against \( x \) for different \( D \) values, using \( \beta = 2.72, q = 10.0, r = 1.2, \) and \( \sigma = 0.1 \) (arbitrary units).

C. The effects of fluctuations on predation rate

Different values of \( r, \beta, D, \) and \( \sigma \) are adopted in this study. The corresponding results show that the effects of fluctuations on \( \beta \) are similar to those on \( r \). For a small value of \( \beta \), an increase in \( \sigma \) is unfavorable for tumor growth. For a large value of \( \beta \), on the other hand, an increase in \( \sigma \) is favorable for tumor growth. This effect is independent of \( D \). However, for a moderate value of \( \beta \), whether or not the noise is favorable for tumor growth is determined by \( D \). For a small value of \( D \), interference with \( \beta \) is dominant; this is favorable for tumor growth. In contrast, large values of \( D \) are unfavorable for tumor growth. If \( r \) is changed, the laws are same as those mentioned above, but the corresponding \( \beta \) will be different. This is also similar to the effects of the fluctuation of \( r \).

VI. SUMMARY

We investigated the effects of the environmental disturbances on tumor cell growth. By solving the corresponding Fokker-Planck equation, we obtained analytic expressions of the steady state probability distribution of tumor cells. It was found that the effects of noise on the tumor growth are mainly determined by the predation rate \( \beta \): (1) For a small value of \( \beta \), the effects of the disturbance on tumor growth and anticancer cells are unfavorable for tumor growth; (2) A large value of \( \beta \) is favorable for tumor growth. (3) For a moderate
value of $\beta$, the effect is determined by the fluctuation in the relative strength of the two noises: (a) If the fluctuation strength of the predation rate $\sigma$ is small, the increase of the tumor growth rate fluctuation intensity $D$ is unfavorable for tumor growth; in contrast, it is favorable for tumor growth if $\sigma$ is large; (b) if $D$ is small, increasing $\sigma$ is favorable for the tumor growth; in contrast, decreasing $\sigma$ is unfavorable for tumor growth. Although further work is still necessary, it is believed that the present results can give some useful insights for the clinical treatment of tumors.

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\( r = 0.8, \beta = 2.0 \)
\( r = 1.0, \beta = 2.0 \)
\( r = 1.0, \beta = 2.1 \)
\( r = 1.0, \beta = 3.0 \)
\( r = 0.4, \beta = 2.0 \)
The diagram illustrates the function $f(x)$ for different values of $r$ and $\beta$.

- For $r=1.0, \beta=1.90$, the curve reaches a peak at $x_1$.
- For $r=1.0, \beta=1.85$, the curve peaks at $x_2$.
- For $r=1.0, \beta=1.60$, the curve reaches a peak at $x_3$.
- For $r=1.1, \beta=1.90$, the curve shows a different shape compared to the others.

The $x$-axis represents $x$, and the $y$-axis represents $f(x)$. The values on the axes range from $-1.5$ to $1.5$.
$x$ (relative number of tumor cells)

$r$ (tumor cells growth rate)

- $\sigma = 0.1$
- $\sigma = 0.5$
- $\sigma = 1.0$
\[ \beta = \frac{1}{2} \left( \frac{x}{r + \sigma^2} \right) \]

\[ x \text{ (relative number of tumor cells)} \]

\[ r = 1.0, \sigma = 0.1 \]
\[ r = 1.0, \sigma = 1.0 \]
\[ r = 1.2, \sigma = 0.1 \]
\[ r = 1.2, \sigma = 1.0 \]
The graph shows the relationship between the relative number of tumor cells ($x$) and the probability of survival ($P_{st}(x)$) for different values of $r$. The curves are labeled with $r = 0.8$, $r = 1.0$, $r = 1.1$, and $r = 1.3$. The x-axis represents the relative number of tumor cells, ranging from 0 to 10, while the y-axis represents the probability of survival, ranging from 0.00 to 0.50.
\[ P_{st}(x) \]

\[ \beta = 2.80 \]
\[ \beta = 2.50 \]
\[ \beta = 2.26 \]
\[ \beta = 2.00 \]
\[ \beta = 1.60 \]

\( x \) (relative number of tumor cells)
\( P_{st}(x) \)

\( x \) (relative number of tumor cells)

\( \sigma = 0.1, D = 0.1 \)

\( \sigma = 0.1, D = 0.5 \)

\( \sigma = 1.0, D = 0.1 \)

\( \sigma = 1.0, D = 0.5 \)

\( \sigma = 1.0, D = 1.0 \)
The diagram illustrates the distribution of tumor cells with different parameters. The y-axis represents $P_{st}(x)$, which is the probability density function of tumor cells, and the x-axis represents the relative number of tumor cells.

Curves are labeled with different combinations of $\sigma$ and $D$ values:
- $\sigma = 0.1, D = 0.1$
- $\sigma = 1.0, D = 0.1$
- $\sigma = 0.1, D = 0.5$
- $\sigma = 1.0, D = 0.5$
- $\sigma = 1.0, D = 1.0$

The curves show how the distribution changes with different parameters, indicating the probability density for different relative numbers of tumor cells.
$P_{st}(x)$

$x$ (relative number of tumor cells)

$D = 0.1$

$D = 0.5$

$D = 1.0$
$P_{st}(x)$

- $D = 0.1$
- $D = 0.5$
- $D = 1.0$

$x$ (relative number of tumor cells)
