Spatiotemporal Fluctuation Induced Transition in a Tumor Model with Immune Surveillance

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We report on a simple model of spatial extend anti-tumor system with a fluctuation in growth rate, which can undergo a nonequilibrium phase transition. Three states as excited, sub-excited and non-excited states of a tumor are defined to describe its growth. The multiplicative noise is found to be double-face: The positive effect on a non-excited tumor and the negative effect on an excited tumor.

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In the past decades, many studies have focused on biodynamics [1-4], specially noise biodynamics [5-9]. More than ever, cancer research is now an interdisciplinary effort which requires a basic knowledge of commonly used terms, facts, issues, and concepts. Phase transition of tumor growth induced by noises is one of the most novel foundations in recent years [10, 11]. However, in all these studies the systems are zero-dimension and insufficient to describe the real progress in the field of tumor growth, furthermore at present the space has become a fundamental variable to study [1, 12, 13].

Chemotherapy and Immunotherapy remain far from good understanding, although they as a potential practical partnership have attracted numerous attentions of scientists for at least one decade [14, 15]. Due to the different responses of tumor cells to chemotherapy and immunotherapy, more recently Lake and Robinson suggested that there is an interesting and significative case for combining chemotherapy and immunotherapy in tumor treatment [14].

In this paper, chemotherapy and immunotherapy are joined by a spatial extend anti-tumor model with three elements, which are (1) a spatiotemporal fluctuation of growth rate induced by chemotherapy, (2) an immune form, and (3) a spatial extend form. Based on the

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analysis on its unique stochastic differential equation and relevant Fokker-Planck equation, we will show that the spatiotemporal fluctuation can lead to a transition of tumor-growth state through both theoretical analysis and numerical calculation. Although noise-induced phase transition is a well known phenomenon, double-faces effect of a noise on a tumor system have not been reported. Here we will show how this transition affects the tumor-growth and how the effect depends on the initial state of tumor. Our results are inconsistent with the zero-dimensional reports that suggest the fluctuation of growth rate always puts the tumor at a disadvantage [10, 11].

The tumor-growth under immune surveillance can be described by means of insect outbreak model [1, 16, 17], which in non-dimensional units is given by

\[
\frac{du}{dt} = ru(1 - \frac{u}{K}) - \frac{\beta u^2}{1 + u^2}
\]

where \(u\) is the population of tumor cells; \(r\) is their linear per capita birth rate and \(K\) is the carrying capacity of the environment, respectively. \(\beta u^2/(1 + u^2)\) quantifies the abilities of immune cells to recognize and attack tumor cells. In general, chemotherapy can lead to a fluctuation of tumor growth, simply a fluctuation of tumor growth rate \(r\). If considering the space of tumor-growth, the growth rate \(r\) in Eq.(1) should be rewritten as \(r_0 + \xi_i(t)\), where \(\xi_i(t)\) is the Gaussian noises, white in time and space, with zero mean and autocorrelation defined by \(\langle \xi_i(t) \rangle = 0, \langle \xi_i(t)\xi_j(t') \rangle = 2\sigma^2\delta_{i,j}\delta(t - t')\), in which \(\sigma^2\) is the noise level and \(i, j\) are lattice sites. The equivalent stochastic differential equation of Eq.(1) will be,

\[
\frac{du_i}{dt} = r_0u_i(1 - \frac{u_i}{K}) - \frac{\beta u_i^2}{1 + u_i^2} + u_i(1 - \frac{u_i}{K})\xi_i(t) - \frac{D}{2d} \sum_{j\in n(i)}(u_i - u_j)
\]

here \(n(i)\) is the set of the 2\(d\) nearest neighbors of site \(i\), \(d\) and \(D\) are the spatial dimension and the diffusion coefficient, respectively.

Equations of this kind are general and cover different tumor growth and diffusion phenomena, especially nonequilibrium growth. We would like to track down the existence of nonequilibrium phase transition induced by multiplicative noise, in systems described by these equations. Such a phase transition is characterized by the appearance of multiple steady state probability distributions \(p_{st}(\{u_i\})\), which has been applied successfully in numerous stochastic problems [18, 19]. If set \(f(u_i) = r_0u_i(1 - u_i/K) - \beta u_i^2/(1 + u_i^2)\), and
\[ g(u_i) = u_i(1 - u_i/K), \] one will obtain the equivalent Fokker-Planck equation of Eq.(2),

\[
\frac{\partial p\{\{u_i\}, t\}}{\partial t} = -\frac{\partial [A(u_i)p(\{u_i\}, t)]}{\partial u_i} + \frac{\partial^2 [B(u_i)p(\{u_i\}, t)]}{\partial u_i^2} \tag{3}
\]

in which

\[
A(u_i) = f(u_i) + \sigma^2 g(u_i)g'(u_i) + \frac{D}{2d} \sum_{j \in n(i)} (u_i - u_j)
\]

\[
B(u_i) = \sigma^2 g^2(u_i) \tag{4}
\]

For simplicity of notation, we drop the subscript \( i \). The stationary solution to Eq.(3) is given to be

\[
p_{st}(u) = Z \exp\left[ \frac{2}{\sigma^2} \int_0^u dv f(v) - \frac{\sigma^2}{2} g(v)g'(v) - D[v - E(v)]/g^2(v) \right] \tag{5}
\]

where \( Z \) is a normalization constant, and

\[
E(v) = \langle v_i|v_j \rangle = \int v_j p_{st}(v_j|v_i)dv_j, \tag{6}
\]

represents the steady state conditional average of \( v_j \) at neighboring sites \( j \in n(i) \), given the value \( v_i \) at site \( i \).

Using the Weiss mean field approximation [20, 21], neglecting the fluctuation in the neighboring sites, i.e., \( E(v) = \langle u \rangle \), independent of \( v \), and imposing the self-consistent requirement \( m = \langle u \rangle \), we obtain

\[
m = \frac{\int_0^{+\infty} up_{st}(u, m)du}{\int_0^{+\infty} p_{st}(u, m)du} = F(m) \tag{7}
\]
FIG. 1: $m$ as a function of $\sigma^2$ given by Eq.(7). The points correspond to the intersection of curves in Fig.1. The critical immune coefficients are $\beta_{c1} = 2.156$ and $\beta_{c2} = 2.209$, respectively, which divide the state of a tumor into three levels: excited (E), sub-excited (S) and non-excited (N).

The solution, $m$, of the self-consistency equation is the intersection point between $F(m) = m$ and $F(m)$ for noise level $\sigma^2 = 8.0 \times 10^3$.

The numerical solution of this last equation for parameter values $r_0 = 1.0$, $D = 0.01$, 
FIG. 2: Stationary probability distributions of average population of tumor cells for different noise intensities and immune coefficients. The parameters are (a) $\beta = 2.12, \sigma^2 = 0.01$, (b) $\beta = 2.30, \sigma^2 = 0.01$, (c) $\beta = 2.12, \sigma^2 = 0.40$, (d) $\beta = 2.30, \sigma^2 = 0.40$. and $\sigma^2 = 8.0 \times 10^{-3}$ is shown in Figs. 1 and 2. The solution, $m$, as a function of immune coefficient, $\beta$, is obtained by the intersection point between $F(m) = m$ and $F(m) = y(m)$ (here $y(m)$ represents the function in the middle position of Eq. (7)). Obviously, the average populations of tumor cells exhibit monostable state for low and high values of $\beta$, but unstable state for intermediate value of $\beta$. The critical points are $\beta_{c1} = 2.156$ and $\beta_{c2} = 2.209$, which divide the states of tumor into three levels: excited state (E), sub-excited state (S), and non-excited state (N). Here E and N correspond to stable states but S represents an un-stable state, which has two or three possible values. This result means the state of tumor is determined by the immune coefficient for low value of noise intensity.

When the noise level $\sigma^2$ increases, what will happen? To answer this question, we consider E and N, respectively, shown in Fig. 3, the stationary probability distributions $p_{st}(u)$ change from monostable state to bistable state with increasing noise intensity and more quantitative results are given by Fig. 4. For a tumor with excited state, shown in Fig. 4, when noise level increase, its growth can be hold back to a sub-excited state. Conversely, for the non-excited
tumor, noise can lead the tumor to sub-excited state or even cancerization. This theoretical results are confirmed by corresponding simulations of a one-dimensional system, shown in Fig.5, obtained through a numerical integration of the set of stochastic differential equations (2) [22, 23]. In the simulation, we consider three sizes but not find one-dimensional finite size effect. It is an important future work to analyze multi-dimensional phase transition of tumor system in such a homogeneous circumstance.

In conclusion, we have found strong evidence for the existence of a noise-induced different nonequilibrium phase transitions of tumor growth, in which whether the noise advantage the tumor depends on the initial state of tumor. When the tumor is excited, noise induces a decay. On the contrary, if the tumor is inactive, the noise can stimulate its growth. Provided that the noise results from the treatment as chemotherapy, our results suggest that estimating the state of a tumor is a crucial work just before treatment begins.

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FIG. 4: One dimensional simulation for the relationship between $m$ and $\sigma^2$. The parameters are same as for Fig.4

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