Spatiotemporal fluctuation-induced transition in a tumor model with immune surveillance

Wei-Rong Zhong, Yuan-Zhi Shao,* and Zhen-Hui He
State Key Laboratory of Optoelectronic Materials and Technologies, Department of Physics, Sun Yat-sen University, Guangzhou 510275, People's Republic of China
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We report on a simple model of spatially extended antitumor system with a fluctuation in growth rate, which can undergo a nonequilibrium phase transition. Three states as excited, subexcited and nonexcited states of a tumor are defined to describe its growth. The multiplicative noise is found to have opposite effects: The positive effect on a nonexcited tumor and the negative effect on an excited tumor.

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In the past decades, many studies have focused on biodynamics [1–5], especially noise biodynamics [6–10]. 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 foundations in recent years [11,12]. 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 [1,13,14].

Chemotherapy and immunotherapy remain far from good understanding, although they as a potential practical partnership have attracted much attention of scientists for at least one decade [15,16]. Focusing on the different responses of tumor cells to chemotherapy and immunotherapy, more recently Lake and Robinson suggested an interesting and significant case for combining chemotherapy and immunotherapy in tumor treatments [15].

In this paper, chemotherapy and immunotherapy are joined by a spatially extended antitumor model with three elements, which are (1) a spatiotemporal fluctuation of growth rate induced by chemotherapy, (2) a model for an immune response, and (3) a spatially extended form. On the basis of the analyses of the stochastic differential equation and relevant Fokker-Planck equation, we will show that the spatiotemporal fluctuation can lead to a transition of the growth of a tumor through both theoretical analyses and numerical computations. Although noise-induced phase transition is a well-known phenomenon, double-faced effects 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 effects depend on the initial state of tumor. Our results are clearly inconsistent with the zero-dimensional reports that suggest the fluctuation of growth rate always puts a tumor at a disadvantage [11,12].

The tumor-growth under immune surveillance can be described by means of insect outbreak model [1,17–19], which in nondimensional units is given by

$$\frac{du}{dt} = ru\left(1 - \frac{u}{K}\right) - \frac{\beta u^2}{1+u^2}, \tag{1}$$

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. $\beta u^2/(1+u^2)$, defined as an immune form, 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 [10,11]. If we wish to consider the spatiotemporal component 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 noise, 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 σ^2 is the noise level and i,j are lattice sites. The equivalent stochastic differential equation of Eq. (1) will be [19,20],

$$\frac{du_i}{dt} = r_0 u_i\left(1 - \frac{u_i}{K}\right) - \frac{\beta u_i^2}{1+u_i^2} + u_i\left(1 - \frac{u_i}{K}\right)\xi_i(t) - \frac{D}{2d}\sum_{j\in n(i)}(u_i - u_j), \tag{2}$$

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

The above equations are general and cover different kinds of tumor growth and diffusion phenomena, especially nonequilibrium growth. We would like to seek 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 [20,21]. If set $f(u_i) = r_0 u_i(1-u_i/K) - \beta u_i^2/(1+u_i^2)$ and $g(u_i) = u_i(1-u_i/K)$, one will obtain the corresponding 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

*Corresponding author; Electronic address: stssyz@mail.sysu.edu.cn

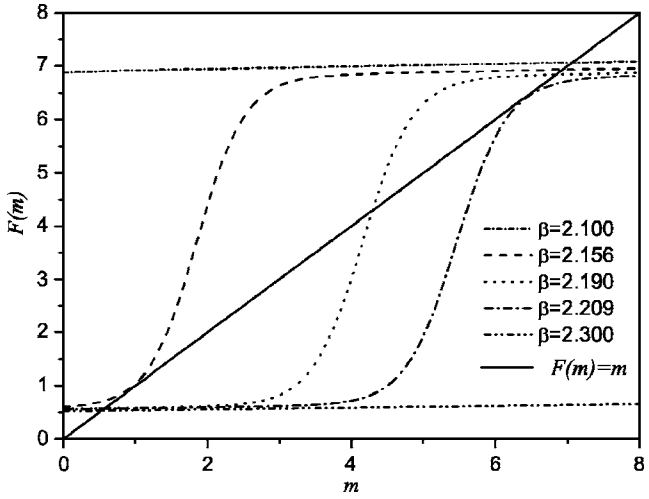

FIG. 1. The solution, m, of the self-consistency equation is the intersection point between $F(m)=m$ and $F(m)=y(m)$ for noise level $\sigma^2=8.0\times10^{-3}$.

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

$$B(u_i) = \sigma^2 g^2(u_i). \tag{4}$$

For simplicity of notation, we drop the subscript i. The stationary solution to Eq. (3) is given to be [20],

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

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 [22,23], 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

$$m = \frac{\int_0^{+\infty} up_{st}(u,m)du}{\int_0^{+\infty} p_{st}(u,m)du} = F(m). \tag{7}$$

For future transaction we set in all the analyses and simulations $r_0=1.0$ and $K=10.0$, respectively. The numerical solution of this last equation for parameter values $D=0.01$ and $\sigma^2=8.0\times10^{-3}$ is shown in Figs. 1 and 2. The solution, m, as a function of immune coefficient, β, 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 a

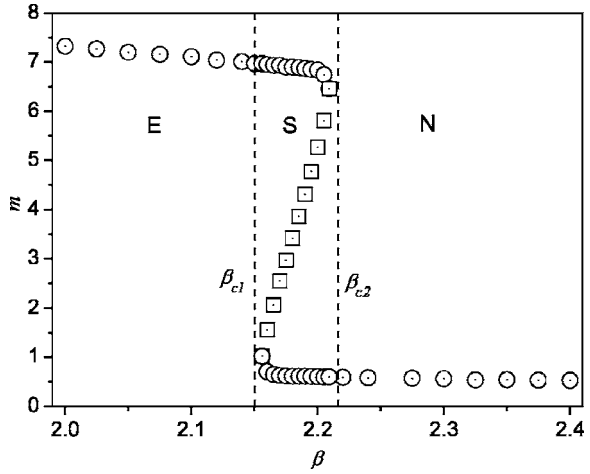

FIG. 2. m as a function of σ^2 given by Eq. (7). The points correspond to the intersection of curves in Fig. 1. The critical immune coefficients are $\beta_{c1}=2.156$ and $\beta_{c2}=2.209$, respectively, which divide the state of a tumor into three levels: excited (E), subexcited and (S), nonexcited (N).

monostable state for low and high values of β, but unstable state for intermediate value of β. The critical points are $\beta_{c1}=2.156$ and $\beta_{c2}=2.209$, which divide the states of the tumors into three levels: excited state (E), subexcited state (S), and nonexcited state (N). Here E and N correspond to stable states but S represents an unstable state, which has two or three possible values. From the biological point of view, we noted that N, S, and E correspond to the early, rapid and saturated stage of the development of a tumor, respectively. Such distribution is based on the curve of a tumor growth. In the case of weak noise level, the above results mean that the state of a tumor is determined by the immune coefficient.

When the noise level, σ^2, increases, what will happen? To answer this question, we consider E and N, respectively. As shown in Fig. 3, the stationary probability distributions $p_{st}(u)$ change from a monostable state to a bistable state with increasing noise intensity, and more quantitative results are

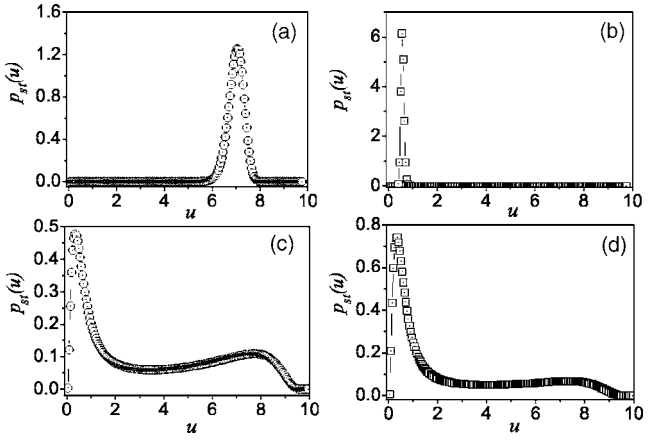

FIG. 3. Stationary probability distributions of average population of tumor cells for different noise intensities and immune coefficients. The parameters are (a) $\beta=2.12$, $\sigma^2=0.01$, (b) $\beta=2.30$, $\sigma^2=0.01$, (c) $\beta=2.12$, $\sigma^2=0.40$, (d) $\beta=2.30$, $\sigma^2=0.40$.

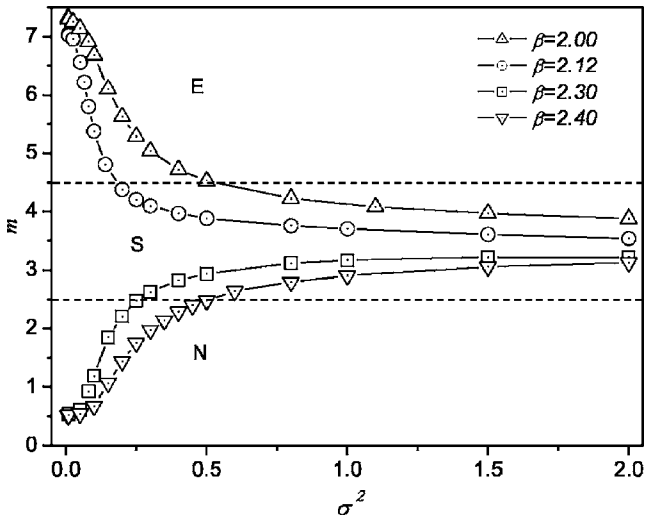

FIG. 4. m as a function of σ^2 given by Eq. (7). The points are obtained by a method which is the same as for Figs. 1 and 2.

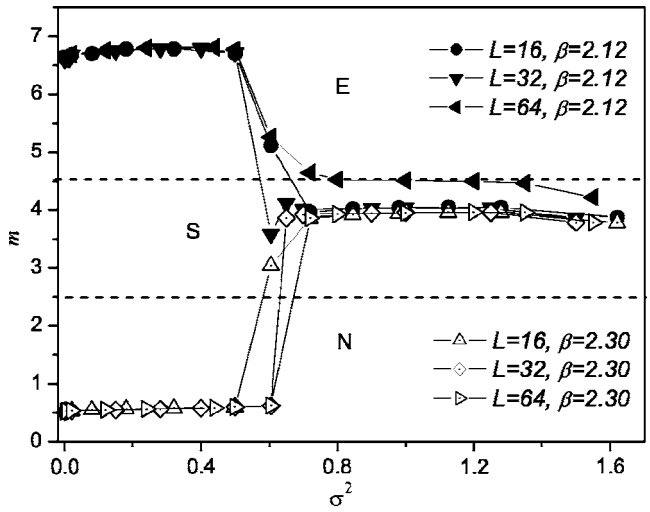

FIG. 5. One-dimensional simulation for the relationship between m and σ^2. L is the lattice size. The parameters are the same as for Fig. 4.

given by Fig. 4. For a tumor with excited state, Fig. 4 displays that the growth of a tumor can be held back to a subexcited state with increasing the noise level. Conversely, for a nonexcited tumor, the noise can lead the tumor to the subexcited state. Note that the nonexcited state can have a phase transition to the subexcited state, but not to the excited state, which might depend on not only the noise but also other factors. These theoretical results are confirmed by corresponding simulations of a one-dimensional system, which is indicated schematically in Fig. 5. Our computational results are strictly obtained through a numerical integration of the set of stochastic differential equations (2) [24,25]. In the simulations, we consider three sizes, 16, 32, and 64 lattices, but do not find the one-dimensional finite size effect. It is an important future work to analyze multidimensional phase transition of a tumor system in such a homogeneous circumstance.

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

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