Spatiotemporal noise triggering infiltrative tumor growth with immunosurveillance

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Abstract – A spatiotemporal noise is assumed to reflect the environmental fluctuation in a spatially extended tumor system. We introduce firstly the structure factor to reveal the invasive tumor growth quantitatively. The homogenous environment can lead to an expansive growth of the tumor cells, while the inhomogenous environment underlies an infiltrative growth. The different responses of the above two cases are separated by a characteristic critical intensity of the spatiotemporal noise. Theoretical and numerical results present a close annotation to the clinical images.

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Introduction. – Expansive and infiltrative growths are two major forms of tumor invasion. In general, the former corresponds to benign tumors and the latter is regarded as one of the principal features of malignant tumors [1]. Figure 1 observed by ourselves shows two typical clinical computerized tomographic (CT) pictures of these two growth forms, for example, brain glioma (A region) and meningoma (B region). Apparently, brain meningoma presents an expansive growth pattern with a clear-cut envelope, while brain glioma typically yields another diffusive, infiltrative growth pattern. Tumor cells can sometime produce a mutation from a benign to a malignant state in a special condition. How does a tumor exhibit a malignant infiltrative growth pattern? To answer this question, some scientists reported their molecular biological annotations, e.g., the influences of the extracellular matrix, genic heterogenesis, the podoplanin and the integrins on the invasive tumor growth [2–6]. In these annotations a common point is that the changing microenvironment of tumor cells affects them crucially. From the physical point of view, the environmental fluctuation has a main effect on the growth and invasion of tumor cells.

In previous mathematical models, which focus on the tumor growth-diffusion described by deterministic reaction-diffusion equations, have yielded many valuable results [7–12]. Likewise, new insights into tumor growth, for example, the studies of noise effects on the tumors, have gained many interesting findings [13–15]. Recently, more and more researches confirm that immune responses to tumors are substantially valid in tumor therapy [16,17]. These studies, however, have not given a sufficient consideration to the environmental fluctuation under immune reaction-diffusion equations, have yielded many valuable results [7–12]. Likewise, new insights into tumor growth, for example, the studies of noise effects on the tumors, have gained many interesting findings [13–15]. Recently, more and more researches confirm that immune responses to tumors are substantially valid in tumor therapy [16,17]. These studies, however, have not given a sufficient consideration to the environmental fluctuation under immune

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Fig. 1: Clinical CT images of brain glioma (A) and meningoma (B). The squares guide to the regions of tumors. A and B are the infiltrative and the expansive growth, respectively.
surveillance against tumor, and furthermore, how to analyze the growth pattern of tumor invasion and metastasis is less clear.

In this letter, we model the growth pattern of an invasive tumor system with the inhomogeneous microenvironment by numerically approaching two-dimensional spatiotemporal stochastic differential equations. We gain a new insight into the molecular mechanism of the invasive tumor growth as well as quantify the growth form by introducing firstly a structure factor to evaluate the order degree of the spatiotemporal structure (ODSS) of the invasive tumor growth. We also figure out the characteristic critical intensity of the spatiotemporal fluctuation to discriminate the expansive tumor invasion from the infiltrative one.

**Model and equation.** – Considering the growth of tumor cells subject to an immunosurveillance against cancer modeled by the enzyme dynamic process [18,19], we assume that the two variable species diffusion dynamic equations can be expressed as below:

\[
\frac{\partial u_i}{\partial t} = ru_i \left(1 - \frac{u_i}{K}\right) - \frac{\beta u_i^2}{1 + u_i^2} + D_u (1 - \varepsilon v_i) \nabla^2 u_i, \\
\frac{\partial v_i}{\partial t} = \frac{\beta u_i^2}{1 + u_i^2} - \theta v_i + D_v u_i \nabla^2 v_i,
\]

where \( u_i \) and \( v_i \) are the densities of tumor cells and dead cells at site \( i \), respectively; \( r \) is the linear per capita birth rate of tumor cells, and \( K \) is the carrying capacity of the environment. The term \( \frac{\beta u_i^2}{1 + u_i^2} \), defined as an immune form, quantifies the abilities of immune cells to identify and attack tumor cells. \( D_u \) and \( D_v \) are the invasion coefficients of \( u_i \) and \( v_i \), respectively. \( \varepsilon \) and \( \theta \) are the velocity coefficients. From the second term of the first equation in (1), immune attacks are only valid to the lively tumor cells. Generally, the environmental fluctuation and tumor heterogeneity may lead to a spatiotemporal fluctuation of tumor growth rate \( r \) [20], which indicates that the growth rate fluctuates not only in time (evolution fluctuation) but also in space (inhomogenization). Therefore the spatiotemporal fluctuation is a main feature of the tumor system, and the growth rate \( r \) in eq. (1) should be rewritten as \( r_0 + \xi(t) \), where \( \xi(t) \) is the Gaussian noise, white in time and space, with zero mean and autocorrelation defined by \( \langle \xi(t) \rangle = 0, \langle \xi_i(t) \xi_j(t') \rangle = 2\sigma \delta_{ij} \delta(t - t') \), in which \( \sigma \) is the noise level and \( i, j \) are the lattice sites. Assuming that the dead cells can be depolymerized by the environmental tissues rapidly, we write the equivalent single variable stochastic differential equation of (1) as [18,19],

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

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

The above equations are general and cover different kinds of tumor growth and invasion phenomena, especially nonequilibrium growth. We explore 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 [21,22].

If set \( f(u_i) = r_0 u_i \left(1 - u_i/K\right) - \beta u_i^2/(1 + u_i^2) \) and \( g(u_i) = u_i(1 - u_i/K) \), one may obtain the corresponding Fokker-Planck equation of eq. (2),

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

in which

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

\[
B(u_i) = \sigma^2 g''(u_i).
\]

In ref. [20], we have detailed the method of the calculation. For simplicity of notation, here we drop the subscript \( i \). The stationary solution to the Fokker-Planck equation of eq. (2) is given to be,

\[
p_{st}(u) = Z \exp \left[ \frac{1}{\sigma} \int_0^u dv \int_0^v \frac{f(v) - \sigma g(v)g'(v) - D[v - E(v)]}{g^2(v)} \right],
\]

where \( Z \) is a normalization constant,

\[
f(v) = r_0 v(1 - v/K) - \beta v^2/(1 + v^2),
\]

\[
g(v) = \sigma v(1 - v/K)
\]

and

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

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

The maxima of \( p_{st}(u) \) are obtained from \( f(u) - \sigma g(u)g'(u) - D[v - E(v)] = 0 \). For the low value of \( \sigma \), the stationary probability distributions (SPD) takes on a monostable state as shown in fig. 2. With increasing noise intensity, the SPD changes from a monostable state to a bistable state. Note that the spatiotemporal noise can change the potential of the tumor growth and diffusion. This kind of bistable state easily leads the system to two separate phases in space [19,20], which agrees with the following numerical simulations.

**Result and analysis.** – We performed the numerical computations of eq. (1) using the two-dimensional (2D) cellular automaton method [23,24]. We set \( r_0 = 1.0 \),
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Fig. 2: Stationary probability distributions of the average population of tumor cells for different noise intensities $\sigma = 0.01$ (a), 0.40 (b). The parameters are $r_0 = 1.0$, $\beta = 2.12$, $K = 10.0$, and $D = 0.5$.

Fig. 3: Evolution patterns of tumor invasion using cellular automatons of eq. (2) with periodic boundary at times 0, 900, and 2700. The top three pictures are for the noise level $\sigma = 0.15$ and the bottom three pictures are corresponding to the noise level $\sigma = 0.60$. They have the same initial condition. The system size is 128.

$\beta = 2.2$, $K = 10.0$, and $D = 0.8$ respectively, and configure the initial condition as a 2D Gaussian distribution function with the maximum in the center of the lattice. To be closer to the clinical observation, we carried out 2D computations systematically at various spatiotemporal noise levels. Figure 3 displays six typical evolution patterns for the duration of 0, 900, and 2700 in the case of a low and high value of noise intensity $\sigma$, respectively. The bright pixel renders tumors and the dark one represents the normal tissue, respectively. The tumor invasion exhibits an expansive growth form for a low value of $\sigma$, while it undergoes an infiltrative growth form for a high value of $\sigma$. The tumors with the expansive growth feature grow and expand with time until they reach a definite size with a clear boundary. The tumor cells with infiltrative growth will, however, keep spreading rapidly all the time. Finally, they will overgrow through the whole lattice.

In order to analyze these patterns quantitatively, we defined the structure factor (SF) (which is obtained by circularly averaging the normalized form factor $S(k_x,k_y,t)$) [21,22]

$$S(k,t) = \langle u(k,t) u(-k,t) \rangle,$$

where $u(k,t)$ is the spatial Fourier transform of the autocorrelation density of the cells $u_i(k,t)$; $k$ is the magnitude of the wave vector $k$, and $t$ the time. Usually, a sharp peak in $S(k,t)$ discloses the existence of an order spatiotemporal structure. Figure 4 shows that, in the case of a low noise level, the peak of the SF increases with the time, i.e., the ODSS rises during the tumor invasion. Conversely, a descendant trend is observed for the high noise level. Judging by the SF of the clinical images shown in fig. 5, we find that the expansive growth produces a sharp peak while the infiltrative growth exhibits a low peak of SF. Here all clinical images have been processed using the same gray scale criterion, and the SF of the clinical images is also worked out through eq. (8). This suggests that the tumor with expansive growth is characteristic of a conservative system in physics, which is less influenced by the environmental fluctuations due to the rounded envelope and clear boundary. Besides the brain glioma and meningoma mentioned above, we studied

Fig. 4: Graphs of the structure factor $S(k,t)$ for $\sigma = 0.15$ (a) and 0.60 (b) at various times $t$. The times of panel (a) are 30, 240, 1200, and 3000, respectively. The times of panel (b) are 60, 300, 1200, and 3000, respectively.
also giant-cell tumor and bone osteogenic sarcoma, which produce also the same evidence of figs. 1 and 5. Therefore it is probably a universal phenomenon that expansive growth corresponds to benign tumors, while infiltrative growth to malignant tumors.

The sharpness of the spatiotemporal structure can be also quantified by considering the height of the SF over its half-peak width, which is denoted by $P(t)$. This quantity, as shown in fig. 6(a), varies at first and then tends to a stable value. Different trends are observed for different noise levels, namely, ascending trend for low noise level and descending one for the high counterpart. Calculating the variance $\Delta P$ between initial and stable values of $P(t)$, we show in fig. 6(b) that $\Delta P$ has a linear relationship with the square of noise levels. If $\Delta P$ is negative, it means a decrease of the ODSS of the tumor growth pattern during the tumor invasion. Conversely, if $\Delta P$ is positive, it means an increase. The critical noise level, at which $\Delta P$ equals zero, classifies the tumor invasion into two growth types, i.e., expansive growth in weak spatiotemporal fluctuations and infiltrative growth in strong spatiotemporal fluctuations.

We have to take into account an additional point when comparing theoretical and simulated patterns with clinical images. The infiltrative growth patterns of our model fill the whole plane and the denser inner proliferative region is located in the center of the patterns. In clinical images, however, the denser region looks like a loop with a dark center for infiltrative growth. This little contrast probably contributes to the dead cells that have been assumed to be decompounded immediately in our model. Nevertheless, the invasive growth forms and the structure factors of our simulations are in principle consistent with the clinical data.

**Conclusion.** – In summary, the clinical images show that the growth form of the benign tumor cells is quite different from the malignant one. The former takes on an expansive growth, while the latter an infiltrative growth. We have firstly introduced a spatiotemporal noise into the tumor system to model its environmental fluctuations and formulated the structure factor to quantitatively characterize the evolution patterns of tumor invasion. We suggest the benign tumors with expansive growth be regarded as a conservative system with weak fluctuation and high spatiotemporal order, and the malignant tumors as a nonconservative system with a strong fluctuation and low spatiotemporal order. The change in the order of the spatiotemporal structure of a tumor has a linear relationship with the square of the noise level. There exists a critical noise level to distinguish the expansive growth form from the infiltrative counterpart.

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