Noise-induced first-order transition in anti-tumor immunotherapy

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We studied the single-variable dynamics model of the tumor growth. A first-order phase transition induced by an additive noise is shown to reproduce the main features of tumor growth under immune surveillance. The critical average cells population has a power-law function relationship with the immune coefficient.

PACS numbers: 87.10.+e 05.40.-a 02.50.Ey 05.70.Fh

During the past two decades, due to the increasing abilities of scientists to manipulate molecule, studies of tumor immunology and immunotherapy have entered the mainstream of current studies in immunology and cancer research [1-3]. Simultaneously, with the development of mathematics and computation science, more and more attempts confirm that simple math can model a world of complexity [4]. Mathematics is then respected to bring about astonishment into oncology. Generally, dynamics differential equations are used to describe the growth and diffusion phenomenon of biology including tumors [5, 6]. However, there are some deficiencies for deterministic differential equation in depicting the instability and complexity of biology. Recently, to fill these deficiencies, stochastic noise was introduced into the dynamics equation [7, 8].

Phase transitions, especially noise-induced phase transitions, had been reported in various areas including oncology, mathematical biology and biological physics [7-12]. In Ref.[8] and [11], it was reported that multiplicative noise induces a transition in tumor growth. Regretfully, two references above have yet not specified the role of additive noise as well as what kind of the phase transition it is. Here we explore what to our knowledge is the first dynamical analysis of the noise-induced first-order transition in an anti-tumor immunotherapy model.

Lefever and Garay [13] studied the tumor growth under immune surveillance against cancer using enzyme dynamics model. The model is

\[ \text{Normal Cells} \xrightarrow{\gamma} X, \]
\[ X \xrightarrow{\lambda} 2X, \]
\[ X + E_0 \xrightarrow{k_1} E \xrightarrow{k_3} E_0 + P, \]
\[ P \xrightarrow{\delta} X, \]

in which \(X, P, E_0\) and \(E\) are respectively cancer cells, dead cancer cells, immune cells and the compound of cancer cells and immune cells, \(\gamma, \lambda, k_1, k_2, k_3\) are velocity coefficients. This model reveals that normal cells may transform into cancer cells, and then the cancer cells reproduce, decline and die out ultimately. Qi and Du had ever derived its equivalent single-variable deterministic dynamics equation [11]. Obviously, a fluctuation of tumor cells population is inevitable, which results from the change of the environment as well as the intrinsic instability of a tumor. Therefore, it is more reasonable to consider the stochastic differential equation. Model (1) is then described by the Langenvequation

\[ \frac{dX}{dt} = r_0 X (1 - \frac{X}{K}) - \frac{\beta X}{1 + X} + \xi(t) \] (2)

where \(X\) is the cancer cells population, \(r_0, K\) and \(\beta\) are the linear per capita birth rate, the carrying capacity of the environment and the anti-tumor ability of immune cells respectively. \(\xi(t)\) is the Gaussian white noise, \(\langle \xi(t)\xi(t') \rangle = A \delta(t - t')\). \(A\) is the intensity of noise. Since \(X\) is non-negative, according to the absorption boundary condition, then \(X(t)\) can be done. We define an order parameter, \(\langle X \rangle\), i.e., the average tumor cells population, whose form is given by

\[ \langle X \rangle = \frac{\int_{\tau_0}^{\tau} X(t)dt}{\tau - \tau_0} \] (3)

where \(\tau_0\) is the initial time as \(X(t)\) reach a stable-state distribution. \(\tau - \tau_0\) is the stable-state periodicity. The “dynamic” four-order cumulant ratio \(U_X\) is

\[ U_X = 1 - \frac{\langle X^4 \rangle}{3\langle X^2 \rangle^2} \] (4)

which is useful for determining the location of a phase transition [14].

In a discussion of additive noise in tumor growth, Ai et al [8] reported that additive noise leads tumor cells far from extinction. They presented the fixedness of peak position of the stable-state distribution probability induced by the additive noise, which denotes no transition induced by any additive noise. Here we suggested it is because the potential function they concerned is an unstable state structure. However, the equivalent potential function of Eq.(2) is a bi-stable state one. Fig.1. shows that the order parameter \(\langle X \rangle\) is fixed under a weak noise. As the intensity of the noise reaches an enough strength, the order parameter undergoes a sharp transition from non-zero to zero. This will lead to a deep minimum of the four-order cumulant ratio \(U_X\) at the transition point. It is obviously a first-order transition like that reported in
thermodynamics. This implies that noise could lead the tumor to extinction. The critical point of the transition is dependent upon the immune coefficient $\beta$.

In the absence of noise, $\langle X \rangle$ changes continuously with $\beta$ as $K < 1$, i.e., there is a second-order transition induced by parameter $\beta$ in the growth of a tumor (see Ref.[11]). In the presence of noise, however, the variety of $\langle X \rangle$ with immune coefficient, $\beta$, shown in Fig.2, is of a first-order transition under an additive noise action. This is perhaps because of the noise-induced discontinuous transition of the potential function from an uni-stable state to a bi-stable one. The surface in Fig.2 includes two divisions: the non-zero division of $\langle X \rangle$, here refers to an invalid immunity; and the zero division as a valid immunity. The critical average tumor cells population, $\langle X \rangle_c$, means there exists a critical nucleus in a tumor growth, which is the minimal volume or population for a tumor to grow and outspread.

The relationship between critical average tumor cells population, $\langle X \rangle_c$, and immune coefficient, $\beta$, is plotted more precisely in Fig.3, which represents $\langle X \rangle_c$ as a power-law function of $\beta$, which has a form with characteristic critical exponents.

$$\langle X \rangle_c = N(1 - \frac{\beta}{\beta_c})^\alpha$$

(5)

in which $N = 0.33 \pm 0.01$, $\beta_c = 1.95 \pm 0.01$ and $\alpha = 0.77 \pm 0.03$.

In summary, additive noise will induce a first-order transition in the growth of a tumor under immune surveillance. In other words, additive noise can cause the decay of a tumor. There may be a critical nucleus in a tumor growth, which is dependent on the immune coefficient as a power-law function.

This work was partially supported by the National Natural Science Foundation (Grant No. 60471023) and the Natural Science Foundation of Guangdong Province (Grant No. 031554), P. R. China.

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\[ \langle X \rangle_c = 0.33 \left(1 - \frac{\beta}{1.95} \right)^{0.77} \]