Research Article

Dynamic Analysis of a Tumor-Immune System under Allee Effect

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In this paper, we develop a definite tumor-immune model considering Allee effect. The deterministic model is studied qualitatively by mathematical analysis method, including the positivity, boundness, and local stability of the solution. In addition, we explore the effect of random factors on the transition of the tumor-immune system from a stable coexistence equilibrium point to a stable tumor-free equilibrium point. Based on the method of stochastic averaging, we obtain the expressions of the steady-state probability density and the mean first-passage time. And we find that the Allee effect has the greatest impact on the number of cells in the system when the Allee threshold value is within a certain range; the intensity of random factors could affect the likelihood of the system crossing from the coexistence equilibrium to the tumor-free equilibrium.

1. Introduction

With the continuous improvement of living standards, individuals pay more attention to their own health. As one of the most harmful diseases to human health and life, malignant tumor has aroused wide concern in the world. At the same time, it has also become a research hotspot in academia. Thompson [1] discussed strategies to target YAP/TAZ activity in cancer and suggested that YAP and TAZ are important drivers of solid tumor growth, metastasis, and resistance to therapy. Du et al. [2] represented a first-time report of NSCLC-intrinsic PD-1 expression and a potential mechanism by which PD-1 blockade may promote cancer growth. Studies on ascorbic acid, which chemosensitize colorectal cancer cells and synergistically inhibit tumor growth, were presented in [3]. Chaoul et al. [4] found that the lack of MHC class II molecules was beneficial to the infiltration of T-cells into tumors, thus enhancing the control of tumor growth. Vilalobos et al. [5] demonstrated the anticancer effect of SOCS1 in prostate cancer and identified its potential inhibitory mechanism. Volz et al. [6] studied a new family of potent TLR9 agonists, EnanDIM, and it can inhibit tumor growth.

Although there are some achievements on finding factors which can effectively inhibit or control tumor growth. What we should not ignore is that the human body itself has a mechanism that can resist tumor cells—the immune system. It can not only protect the body from various internal and external factors against the normal immune system but also defend the body from tumor interference so that the normal operation of the body tissues. This function of the immune system has urged mathematicians and biologists exert to the research on its dynamic properties. Adriana et al. [7] discussed the regulation of angiogenesis by innate immune cells in the tumor microenvironment, specific features, and roles of major players. Key steps for visualizing the complex interaction between malignant tumors and the immune system were proposed and discussed in [8]. Jin et al. [9] summarized the current understanding of autophagy and its regulation in cancer. Medzhitov and Janeway [10] introduced the role of innate immune mechanism in the development of organisms and illustrated that it is the first line of defense of human immunity. The dynamics between tumor and immune cells in microenvironment can be referred to [11–14]. Khajanchi [15]

described how tumor cells evolve and survive after encounter with the immune system. Terry et al. [16] presented new insights on the role of EMT in tumor-immune escape.

At present, the research on tumor-immune system has obtained above results, and Katrin et al. [17] showed that tumors have the Allee effect. According to the study of literature [18], the Allee effect is a correlation between any component of individual fitness and the number or density of the same individual. Since the Allee effect has been shown to change the optimal control decisions and control costs and estimate the potential risks in ecology, Katrin et al. [17] believed that it was also crucial for tumor growth control. However, so far, it has been neglected in tumor growth and persistence. Therefore, under the excitation of the above research, we attempt to add the Allee effect on the basis of Pillis [19] model, study its dynamic behavior, and explore the influence of Allee effect on tumor cells.

The remainder of the paper is organized as follows. In Section 2, we develop a definite tumor-immune model with the Allee effect and analyze the property of the deterministic model, including the positivity, boundness, and local stability. Section 3 is devoted to discuss the tumor-immune model with the Allee effect, which is disturbed by white noise. We carry out numerical simulations in Section 4. In Section 5, we take a discussion and draw a conclusion.

2. The Deterministic Tumor-Immune Model with Allee Effect

2.1. Establishment of Deterministic Model. In 2003, Pillis and Radunskaya [20, 21] proposed a mathematical model to describe the relationship between the tumor and immune system:

$$\begin{cases} \frac{dE}{dt} = s + \frac{\rho ET}{\alpha + T} - \beta_1 ET - d_1 E, \\ \frac{dN}{dt} = r_1 N(1 - b_1 N) - \beta_2 NT, \\ \frac{dT}{dt} = r_2 T(1 - b_2 T) - \beta_3 ET - \beta_4 NT. \end{cases} \quad (1)$$

Yet, for the tumor itself, it has its own optimal density in the process of growth and reproduction, whether it is too dense or too thin will have an inhibitory effect on its growth.

Based on this, we study the relationship between tumor cells, normal cells, and immune cells under the background of the Allee effect. The mathematical model is as follows:

$$\begin{cases} \frac{dE}{dt} = s + \frac{\rho ET}{\alpha + T} - \beta_1 ET - d_1 E, \\ \frac{dN}{dt} = r_1 N(1 - b_1 N) - \beta_2 NT, \\ \frac{dT}{dt} = r_2 T(1 - b_2 T)(T - m) - \beta_3 ET - \beta_4 NT, \end{cases} \quad (2)$$

where E represents the number of immune cells, T is the amount of tumor cells, N can be thought of the quantity of normal cells, s and d_1 represent the resource constant and mortality of effector immune cells, respectively, and m is Allee threshold and satisfies the condition of $m \cdot b_2 < 1$. Since the presence of tumor cells would activate effector immune cells, this term is expressed as $(\rho ET/\alpha + T)$ by Michaelis–Menten expression. Competition between effector immune cells and tumor cells would lead to the death of two types of cells, which are expressed as $-\beta_1 ET$ and $-\beta_3 ET$. The maximum growth rate and environmental carrying capacity of normal cells are represented by r_1 and b_1^{-1} , respectively. Similarly, the tumor cells are expressed by r_2 and b_2^{-1} . β_2 and β_4 stand for the cell death rate caused by the competition between normal cells and tumor cells, respectively.

In this study, we assume that the tumor is homogeneous. And according to the physical meaning of each variable, the initial conditions of model (2) are

$$\begin{aligned} E(0) &= E_0 > 0, \\ N(0) &= N_0 > 0, \\ T(0) &= T_0 > 0. \end{aligned} \quad (3)$$

2.2. Positiveness and Boundedness of Solutions

Theorem 1. For any t greater than 0, the solution of system (2) is positive and bounded under the initial conditions (3), when $d_1 > \rho$.

Proof. (1) Positiveness: integrating both sides of formula (2), we have the following relations:

$$\begin{cases} E(t) = E_0 \exp \left[\int_0^t \frac{\rho T(\xi)}{\alpha + T(\xi)} - \beta_1 T(\xi) - d_1 d\xi \right] + s \int_0^t \exp \left[\int_0^t \frac{\rho T(\xi)}{\alpha + T(\xi)} - \beta_1 T(\xi) - d_1 d\xi \right] d\theta, \\ N(t) = N_0 \exp \left[\int_0^t r_1 (1 - b_1 N(\xi)) - \beta_2 T(\xi) d\xi \right], \\ T(t) = T_0 \exp \left[\int_0^t r_2 (1 - b_2 T(\xi))(T(\xi) - m) - \beta_3 E(\xi) - \beta_4 N(\xi) d\xi \right]. \end{cases} \quad (4)$$

The initial condition is $E(0) > 0, N(0) > 0, T(0) > 0$. When $t > 0$, it can be obtained from the above equation:

$$\begin{aligned} E(t) &> 0, \\ N(t) &> 0, \\ T(t) &> 0. \end{aligned} \quad (5)$$

$$\begin{aligned} \dot{V} = & s + \frac{\rho ET}{\alpha + T} - \beta_1 ET - d_1 E + r_1 N(1 - b_1 N) - \beta_2 NT + r_2 T(1 - b_2 T)(T - m) - \beta_3 ET - \beta_4 NT \leq s \\ & + \frac{r_1}{4b_1} + R + \eta - \min\{\beta_1, \beta_2, \beta_3, \beta_4\}V. \end{aligned} \quad (6)$$

Then, the above equation can be written as follows:

$$\frac{dV}{dt} + \tau V \leq \varphi, \quad (7)$$

where $\tau = \min\{\beta_1, \beta_2, \beta_3, \beta_4\}$ and $\varphi = s + (r_1/4b_1) + R + \eta$, where R is the maximum value obtained by $r_2 T(1 - b_2 T)(T - m)$ within the range of $T(t) > 0$ and η is a positive number selected which is greater than the difference between $E + N + T$ and $(E + N)T$. We then have

$$0 < V(E, N, T) < \frac{\varphi}{\tau} (1 - \exp(-\tau t)) + V(E_0, N_0, T_0) \exp(-\tau t). \quad (8)$$

When $t \rightarrow \infty$, $0 < V < (\varphi/\tau)$. This shows that, under initial conditions (3), the solution of system (2) is bounded. $\square$

(2) Boundedness: considering a function $V = E(t) + N(t) + T(t)$ when $d_1 > \rho$, according to equation (2), we can obtain that

2.3. *Classification of Equilibrium Points.* According to equation (2), we get the following three kinds of equilibrium points:

- (1) Tumor-free equilibrium point: $P_0 = ((s/d_1), (1/b_1), 0)$.
- (2) Coexisting equilibrium point: $P_1 = (((sa + sT^*)/((\beta T^* + d_1)(\alpha + T^*) - \rho T^*)), (r_1 - \beta_2 T^*/r_1 b_1), T^*)$, where T^* satisfies the equation

$$f(T^*) = T^4 + BT^3 + CT^2 + DT + E = 0, \quad (9)$$

and the coefficients of equation (9) are

$$\begin{aligned} B = & \alpha - m - \frac{1}{b_2} + \frac{d_1 - \rho}{\beta_1} + \frac{\beta_2 \beta_4}{r_1 r_2 b_1 b_2}, \\ C = & -m\alpha + \frac{\alpha d_1 + m\rho - md_1}{\beta_1} + \frac{m - \alpha}{b_2} + \frac{\rho - r_2 d_1}{r_2 b_2 \beta_1} + \frac{\beta_1 \beta_4 (r_1 - \alpha \beta_2) + \beta_2 \beta_4 (\rho - d_1)}{r_1 r_2 b_1 b_2 \beta_1}, \\ D = & \frac{\alpha d_1 r_1 r_2 m b_1 + r_1 b_1 \beta_3 s \alpha + r_1 \alpha d_1 \beta_4}{r_1 r_2 b_1 b_2 \beta_1}. \end{aligned} \quad (10)$$

- (3) Abnormal equilibrium point: $p_2 = ((s/d_1), 0, 0)$, $P_3 = ((s\alpha + sT^*/(T^* + d_1)(\alpha + T^*) - \rho T^*), 0, T^*)$, where T^* is determined by the equation

$$f(T^*) = A_1 T^4 + B_1 T^3 + C_1 T^2 + D_1 T + E_1 = 0, \quad (11)$$

and the coefficients of above equation are

$$\begin{aligned} A_1 = & r_2 b_2 \beta_1, \\ B_1 = & r_2 b_2 \alpha \beta_1 + r_2 b_2 d_1 - \rho r_2 b_2 - \beta_1 r_2 - m r_2 b_2 \beta_1, \\ C_1 = & r_2 b_2 \alpha d_1 - r_2 \alpha \beta_1 - r_2 d_1 + r_2 \rho - m r_2 b_2 d_1 + m \rho r_2 b_2 + m \beta_1 r_2 - m r_2 b_2 \alpha \beta_1, \\ D_1 = & m r_2 \alpha \beta_1 + m r_2 d_1 - m r_2 \rho - \alpha r_2 d_1 - \alpha m d_1 r_2 b_2 + \beta_3 s, \\ E_1 = & \alpha s \beta_3 + \alpha m r_2 d_1. \end{aligned} \quad (12)$$

2.4. Stability of Equilibrium Points. In this section, we analyze the local stability of the equilibrium points. The calculation shows that the number of normal cells at the abnormal equilibrium point is zero, which is not consistent with the practical significance of biology, so we only discuss

the local asymptotic stability of tumor-free equilibrium point and coexistence equilibrium point.

The Jacobian matrix J of system (2) at the equilibrium point is as follows:

$$\begin{bmatrix} \frac{\rho T}{\alpha + T} - \beta_1 T - d_1 & 0 & \frac{\alpha \rho E}{(\alpha + T)^2} - \beta_1 E \\ 0 & -2r_1 b_1 N + r_1 - \beta_2 T & -\beta_2 N \\ -\beta_3 T & -\beta_4 T & [-3r_2 b_2 T^2 + (2mb_2 r_2 + 2r_2)T - mr_2 - \beta_3 E - \beta_4 N] \end{bmatrix}. \quad (13)$$

2.4.1. Stability of Tumor-Free Equilibrium Point P_0 . The eigenvalues of Jacobian matrix at P_0 are

$$\begin{aligned} \lambda_1 &= -d_1 < 0, \\ \lambda_2 &= -r_1 < 0, \\ \lambda_3 &= -mr_2 - \frac{s\beta_3}{d_1} - \frac{\beta_4}{b_1}. \end{aligned} \quad (14)$$

And by calculation, the equilibrium solution P_0 is locally asymptotically stable if and only if $-(s\beta_3/r_2 d_1) -$

$(\beta_4/r_2 b_1) < m < (1/b_2)$, while P_0 is the saddle point with index two when $m < -(s\beta_3/r_2 d_1) - (\beta_4/r_2 b_1)$.

2.4.2. Stability of Coexistence Equilibrium Point P_1 . When the equilibrium point is P_1 , the characteristic equation of matrix (13) at this point is

$$|J - \lambda E| = \lambda^3 + (r_1 - C_2 - A_2 + \beta_4 N^* - \beta_2 T^*)\lambda^2 + D_2 \lambda + E_2 = 0, \quad (15)$$

where T^* satisfies equation (9), and

$$\begin{aligned} A_2 &= \frac{\rho T^*}{\alpha + T^*} - \beta_1 T^* - d_1, \\ B_2 &= \left[\frac{\alpha \rho}{(\alpha + T^*)^2} - \beta_1 \right] \left[\frac{s\alpha + sT^*}{(\beta T^* + d_1)(\alpha + T^*) - \rho T^*} \right], \\ C_2 &= -3r_2 b_2 T^* + (2mr_2 b_2 + 2r_2)T^* - mr_2 - \frac{s\beta_3(\alpha + T^*)}{(\beta T^* + d_1)(\alpha + T^*) - \rho T^*}, \\ D_2 &= (A_2 - r_1)(C_2 - \beta_4 N^*) - r_1 A_2 + (A_2 \beta_2 + B_2 \beta_3 + C_2 \beta_2)T^* - 2\beta_2 \beta_4 N^* T^*, \\ E_2 &= r_1 A_2 C_2 - B_2 \beta_2 \beta_3 T^* - A_2 C_2 \beta_2 T^* - A_2 \beta_4 r_1 N^* + B_2 r_1 \beta_3 T^* + 2A_2 \beta_2 \beta_4 N^* T^*, \\ N^* &= \frac{r_1 - \beta_2 T^*}{r_1 b_1}. \end{aligned} \quad (16)$$

According to Routh–Hurwitz criterion, we know that

$$a_0 = 1,$$

$$\begin{aligned} a_1 &= r_1 + mr_2 + d_1 + (3 - 2m)r_2 b_2 + \left(\beta_1 - 2r_2 - \frac{\rho}{\alpha + T^*} \right) T^* + \frac{r_1 - \beta_2 T^*}{r_1 b_1} \beta_4 + \left[\beta_3 - \frac{\alpha \rho T^*}{(\alpha + T^*)^2} + \beta_1 T^* \right] \left[\frac{s\alpha + sT^*}{(\beta T^* + d_1)(\alpha + T^*) - \rho T^*} \right], \\ a_2 &= (A_2 - r_1) \left(C_2 - \frac{r_1 - \beta_2 T^*}{r_1 b_1} \beta_4 \right) - r_1 A_2 + (A_2 \beta_2 + \beta_3 B_2 + C_2 \beta_2) T^* - 2\beta_2 \beta_4 T^* \frac{r_1 - \beta_2 T^*}{r_1 b_1}, \\ a_3 &= (r_1 - \beta_2 T^*) A_2 C_2 + (r_1 - \beta_2) B_2 \beta_3 T^* + (2\beta_2 T^* - r_1) \frac{r_1 - \beta_2 T^*}{r_1 b_1} A_2 \beta_4. \end{aligned} \quad (17)$$

The determinant of Hurwitz can be calculated according to the above expressions:

$$\begin{aligned}\Delta_1 &= a_1, \\ \Delta_2 &= \begin{vmatrix} a_1 & a_0 \\ a_3 & a_2 \end{vmatrix}, \\ \Delta_3 &= \begin{vmatrix} a_1 & a_1 & 0 \\ a_3 & a_2 & a_1 \\ 0 & 0 & a_3 \end{vmatrix}.\end{aligned}\quad (18)$$

Thus, when $\Delta_1 > 0$, $\Delta_2 > 0$, and $\Delta_3 > 0$ are satisfied at the same time, coexistence balance P_1 is locally asymptotically stable.

By equation (9), we know that coexistence equilibrium expression T^* is the root of quartic equation, namely, there are at most four coexistence equilibrium points. Considering the meaningful number of equilibrium and its stability is related to parameter selection, and in order to make the results more intuitive, we carry out numerical simulation according to effective range of variables. As a result, the number and stability of the coexistence equilibrium point are shown in Figure 1. In this numerical simulation, the horizontal axis is ρ value from 0 to 2, while the vertical axis is m value from -2 to 1 .

In order to reveal the role of the Allee effect in the system, we only change the value of m . By referring to [20, 21], we make $\rho = 0.01$; then, the time history diagrams of three cells in different m are as follows.

Observing Figure 2, we know when $m \in (-\infty, -1.2) \cup (-0.5, 1)$, the number of the three types of cells do not change significantly. When m belongs to $(-1.2, -0.5)$, the cell change trend is the most significant. This indicates that when the Allee threshold of tumor cells is within the range of -1.2 to -0.5 , the Allee effect has the greatest influence on the number of cells in the system, and this also proves that the Allee effect has an impact on the tumor-immune system.

3. Stochastic Tumor-Immune Model with Allee Effect

3.1. Establishment of Stochastic Model. Considering that the growth of tumor cells can be affected by various uncertainties, such as vibration and temperature, and these can be simulated with noise, therefore, based on the deterministic model (2), we propose the following stochastic model:

$$\begin{cases} \dot{E}_1 = s + \frac{\rho E_1 T_1}{\alpha + T_1} - \beta_1 E_1 T_1 - d_1 E, \\ \dot{N}_1 = r_1 N_1 (1 - b_1 N_1) - \beta_2 N_1 T_1 + N_1 W_1(t), \\ \dot{T}_1 = r_2 T_1 (1 - b_2 T_1) (T_1 - m) - \beta_3 E_1 T_1 + \beta_4 N_1 T_1 \\ \quad + T_1 W_2(t). \end{cases}\quad (19)$$

Among them, $E_1(t)$, $N_1(t)$, and $T_1(t)$ are three random processes, which represent the number of immune cells, normal cells, and tumor cells, respectively. $W_i(t)$ is the independent Gaussian white noise with zero mean intensity D_i ($i = 1, 2$), which acts on the natural growth rate of normal cells ρ and the nature growth rate of tumor r_2 , and we assume that both damping and excitation are small. The specific meanings of other parameters are the same as those in model (2).

3.2. The Stochastic Averaging Method. In order to facilitate the application of the stochastic average method, we first simplified model (19), setting

$$f = -r_2 m, g = r_1 b, G_3 = -\gamma_1 b_1 N_1,$$

$$G_1(E_1, N_1, T_1) = \frac{s}{E_1} + \frac{\rho T_1}{a + T_1} - \beta_1 T_1, \quad (20)$$

$$G_2 = rT(1 - b_2 T_1 + b_2 m) - \beta E.$$

Then, model (19) can be written as follows:

$$\begin{cases} \dot{E}_1 = E_1 [-d_1 + G_1(E_1, N_1, T_1)], \\ \dot{N}_1 = N_1 [r_1 - \beta_2 T_1 + G_3(E_1, N_1, T_1)] + N_1 W_1(t), \\ \dot{T}_1 = T_1 [-\beta_4 N_1 + f + G_2(E_1, N_1, T_1)] + T_1 W_2(t). \end{cases}\quad (21)$$

The above equation (21) is converted into the following $It\hat{o}$ stochastic differential equation by $It\hat{o}$ formula:

$$\begin{cases} dE_1 = E_1 [-d_1 + G_1(E_1, N_1, T_1)]dt, \\ dN_1 = N_1 \left[r_1 - \beta_2 T_1 + G_3(E_1, N_1, T_1) + \frac{1}{2} D_1 \right] dt \\ \quad + \sqrt{D_1} N_1 dB_1(t), \\ dT_1 = T_1 \left[f - \beta_4 N_1 + G_2(E_1, N_1, T_1) + \frac{1}{2} D_2 \right] dt \\ \quad + \sqrt{D_2} T_1 dB_2(t), \end{cases}\quad (22)$$

where $B_1(t)$ and $B_2(t)$ are independent Wiener process and $(1/2)D_1 E_1 dt$ and $(1/2)D_2 T_1 dt$ are the Wong-Zakai amendments. Defining a random process,

$$R(N_1, T_1) = \beta_2 T_1 - \beta_4 N_1 + f - r_1 + f \ln \frac{\beta_4 N_1}{f} - r_1 \ln \frac{\beta_2 T_1}{r_1}. \quad (23)$$

Among them, $R((f/\beta_4), (r_1/\beta_2)) = 0$. β_2 , β_4 , and r_1 are positive, $m < 0$. Then, the $It\hat{o}$ stochastic differential equation of random process $R(t)$ is

FIGURE 1: The number of coexistence equilibrium points and their stability.

FIGURE 2: Continued.

FIGURE 2: Time history diagram of different m ($\rho = 0.01$). (a) $m = 0.5$. (b) $m = 0.1$. (c) $m = 0.0$. (d) $m = -0.5$. (e) $m = -0.7$. (f) $m = -0.8$. (g) $m = -1.0$. (h) $m = -1.2$. (i) $m = -1.5$.

$$dR = \left[(f - \beta_4 N_1)G_3 + (\beta_2 T_1 - r_1)G_2 - \frac{1}{2}\beta_4 N_1 D_1 + \frac{1}{2}\beta_2 T_1 D_2 \right] dt + \sqrt{D_1}(f - \beta_4 N_1)dB_1 + \sqrt{D_2}(\beta_2 T_1 - r_1)dB_2. \quad (24)$$

$$dR = m(R)dt + \sigma(R)dB(t). \quad (25)$$

Using the random average principle of Stratonovich-Khasminskii, the average $It\hat{o}$ stochastic differential equation of $R(t)$ is

Whence,

$$m(R) = \langle (f - \beta_4 N_1)G_3 + (\beta_2 T_1 - r_1)G_2 \rangle_t + \frac{1}{2}\beta_2 D_2 \langle T_1 \rangle_t - \frac{1}{2}\beta_4 D_1 \langle N_1 \rangle_t, \quad (26)$$

$$\sigma^2(R) = D_1 \langle (f - \beta_4 N_1)^2 \rangle_t + D_2 \langle (\beta_2 T_1 - r_1)^2 \rangle_t, \quad (27)$$

and according to the formula,

$$\langle \cdot \rangle_t = \frac{1}{T(R)} \oint [\cdot] dt. \quad (28)$$

We have the following expressions:

$$\langle N_1 \rangle_t = \frac{f}{\beta_4}, \quad (29)$$

$$\langle T_1 \rangle_t = \frac{r_1}{\beta_2},$$

$$r_1 \langle (f - \beta_4 N_1)^2 \rangle_t = f \langle (r_1 - \beta_2 T_1)^2 \rangle_t = \frac{g(R)}{T(R)}, \quad (30)$$

where

$$g(R) = r_1 \oint \frac{f - \beta_4 N_1}{T_1} dT_1. \quad (31)$$

Then, with the help of equations (26)–(30), the drift coefficient and diffusion coefficient can be simplified as follows:

$$m(R) = \frac{1}{2}r_1 D_2 - \frac{1}{2}f D_1 - b_1 \frac{g(R)}{T(R)}, \quad (32)$$

$$\sigma^2(R) = \frac{f D_1 - r_1 D_2}{r_1 f} \frac{g(R)}{T(R)}.$$

3.2.1. Stationary Probability Density. Base on equation (23), we obtain that

$$\ln \frac{\beta_4 N_1}{f} \approx 1 + \frac{\beta_4 N_1 - f}{f} - \frac{1}{2} \left(\frac{\beta_4 N_1 - f}{f} \right)^2, \quad (33)$$

$$\ln \frac{\beta_2 T_1}{r_1} \approx 1 + \frac{\beta_2 T_1 - r_1}{r_1} - \frac{1}{2} \left(\frac{\beta_2 T_1 - r_1}{r_1} \right)^2. \quad (34)$$

Substitute (33) and (34) into (23); then, it can be written as follows:

$$r_1(\beta_4 N_1 - f)^2 + f(\beta_2 T_1 - r_1)^2 \approx 2r_1 f R. \quad (35)$$

Due to equations,

$$\begin{aligned} \langle (\beta_4 N_2 - f)^2 \rangle_t &\approx f R, \\ \langle (r_1 - \beta_2 T_1)^2 \rangle_t &\approx r_1 R, \end{aligned} \quad (36)$$

thus, we obtain that

$$\begin{aligned} m(R) &\approx \frac{1}{2} r_1 D_2 - \frac{1}{2} f D_1 - b_1 r_1 f R, \\ \sigma^2(R) &\approx (f D_1 - r_1 D_2) R. \end{aligned} \quad (37)$$

When $R \rightarrow 4.3782$, the boundary is nonsingular; when $R \rightarrow \infty$, it is the second kind of singular boundary. The diffusion index $a = 1$, the drift index $\beta = 1$, $m(+\infty) < 0$. Therefore, the nontrivial stationary probability density exists. And its steady-state probability density function $p(r)$ satisfies the following FPK equation:

$$\frac{d}{dr} [m(r)p(r)] - \frac{1}{2} \frac{d^2}{dr^2} [\sigma^2(r)p(r)] = 0. \quad (38)$$

Whence,

$$\begin{aligned} m(r) &= m(R)|_{R=r}, \\ \sigma^2(r) &= \sigma^2(R)|_{R=r}. \end{aligned} \quad (39)$$

Solving the FPK equation, we then have

$$p(r) = C \frac{T(r)}{g(r)} \exp \left[\int_0^r \frac{r_1 f (r_1 D_2 - f D_1) T(x) - 2r_1 b_1 f g(x)}{(f D_1 - r_1 D_2) g(x)} dx \right], \quad (40)$$

where C is a normalization constant, and

$$\begin{aligned} C &= \frac{C_1 r_1 f}{f D_1 - r_1 D_2}, \\ \frac{dg(r)}{dr} &= r_1 \oint \frac{\beta_4 N_1}{T_1 (\beta_4 N_1 - f)} dT_1. \end{aligned} \quad (41)$$

Hence, equation (40) can be simplified as follows:

$$\begin{aligned} p(r) &= CT(r) \exp(vr), \\ v &= \frac{-2r_1 b_1 f}{f D_1 - r_1 D_2}. \end{aligned} \quad (42)$$

Suppose $R = r$, the conditional probability density of random process N_1 is $p(N_1/r)$; then, the joint probability density of R and N_1 can be expressed as follows:

$$p(r_1, N_1) = \frac{p(r)}{|N_1 (r_1 - \beta_2 T_1)| T(r)}. \quad (43)$$

As a result, we obtain the stationary probability density of N_1 and T_1 :

$$p(N_1, T_1) = \frac{C}{N_1 T_1} \exp(vr). \quad (44)$$

Thus, we get the steady-state probability densities of N_1 and T_1 , respectively. They are

$$\begin{aligned} p(N_1) &= \int_0^\infty p(N_1, T_1) dT_1 = \int_0^\infty \frac{C}{N_1 T_1} \exp(vr) dT_1, \\ p(T_1) &= \int_0^\infty p(N_1, T_1) dN_1 = \int_0^\infty \frac{C}{N_1 T_1} \exp(vr) dN_1. \end{aligned} \quad (45)$$

3.2.2. Mean First-Passage Time. When people are suffering from tumor, we hope that the number of tumor cells go to zero. However, according to the calculation in the above section, we know that the steady-state probability density of tumor cells is present, which indicates that tumor cells will not be extinct under natural state, but the effects of random factors may change this. Therefore, it is practical to study the average first-passage time β from the coexistence equilibrium point to the tumor-free equilibrium point, and the Pontryagin equation is satisfied that

$$1 + m(x_0) \left| \frac{d\beta}{dx_0} + \frac{1}{2} \sigma^2(x_0) \frac{d^2\beta}{dx_0^2} \right| = 0, \quad (46)$$

where

$$\begin{aligned} m(x_0) &= m(R)|_{R=x_0}, \\ \sigma^2(x_0) &= \sigma^2(R)|_{R=x_0}. \end{aligned} \quad (47)$$

From the above studies, we know that x_l is nonsingular and x_s is natural. According to the constant variation method, β can be written as follows:

$$\beta(x_0) = 2 \int_{x_0}^{x_s} \psi^{-1}(\mu) \left[\int_{x_l}^{\mu} \frac{1}{\sigma^2(v)} \psi(v) + C_1 \right] d\mu, \quad (48)$$

where C_1 is the integral constant, and

$$\psi(v) = \exp \left[\int \frac{2m(v)}{\sigma^2(v)} dv \right]. \quad (49)$$

4. Numerical Simulation

Refer to the experimental data of article [20–29] (Table 1) and the analysis of stability of equilibria in the previous section, and we obtain that system (19) of the tumor-free equilibrium is stable, and the corresponding critical state is denoted by x_s . Calculate based on Table 1 and reference to the Figure 1, we know the result of coexisting equilibrium belongs to the red area when the m value is -0.8 , -0.9 , and -1.0 . Namely, system (19) has only one stable coexistence equilibrium, and the corresponding critical state is denoted by x_l . As a result, x_l is nonsingular, x_s is natural, and the expression of the first-passage time from x_l to x_s satisfies equation (46). In order to investigate the effect of the Allee

TABLE 1: The definitions and corresponding value of variables in models (2) and (19).

Parameter	Definition	Value	Source
s	Constant source of effector cells	0.33	[21, 23]
ρ	Maximum effector cells recruitment rate by tumor cells	0.01	[20, 21]
α	Steepness coefficient of the effector cells recruitment	0.3	[20, 22]
β_1	Effector cells inactivation rate by tumor cells	1.0	[23, 24]
d_1	Death rate of effector cells	0.2	[20, 29]
r_1	Normal cells' growth rate	1.0	[20, 25]
r_2	Tumor growth rate	1.5	[26, 27]
b_2	Reciprocal of tumor carrying capacity	1.0	[20, 28]
b_1	Reciprocal of normal cells' carrying capacity	1.0	[20, 28]
β_2	Fractional normal cells killed by tumor cells	1.0	[23, 24]
β_3	Fractional tumor cells killed by effector cells	0.5	[23, 24]
β_4	Inactivation rate of tumor cells owing competition with normal cells	1.0	[20, 23]
m	Threshold value of Allee effect	$m < 1$

FIGURE 3: Mean first-passage time varies with D_1 . (a) $m = -1.0$. (b) $m = -0.9$. (c) $m = -0.8$. FIGURE 4: Mean first-passage time varies with D_2 . (a) $m = -1.0$. (b) $m = -0.9$. (c) $m = -0.8$.

threshold and noise intensity on the first-passage time, we numerically simulate the above results and obtain Figures 3 and 4.

As can be seen from Figures 3 and 4, the time of first passage is limited only when the random intensity is within a certain range. This indicates that the existence of random

factors does not cause the first-passage to occur, and only when the random intensity is within a certain range will the system cross from the coexistence equilibrium to the tumor-free equilibrium.

5. Conclusions

In this paper, we analyze the property of the deterministic tumor-immune model under the Allee effect, including the positivity and boundness. The results show that, in the condition of $d_1 > \rho$, the solution of system (2) is positive and bounded. At the same time, we know that the Allee effect affects the growth and reproduction of cells in the tumor-immune system according to Figure 2. And the influence is most significant when the Allee threshold of tumor cells is in the range of -1.2 to -0.5 .

And in the meantime, we are devoted to explore the effect of random factors on the transition of the tumor-immune system from the stable coexistence equilibrium to the stable tumor-free equilibrium. Based on the method of stochastic averaging, we obtain the expressions of the steady-state probability density and the mean first-passage time. Through the numerical simulation about the expression of first-passage time, we know that the existence of random factors will not make the first-passage must happen, in other words, the random strength only within a certain range; the system will pass from the stable coexistence equilibrium point to the tumor-free equilibrium point. Our conclusions provide a possible method to change the number of tumor cells, which is expected to be helpful for the treatment of tumors.

Data Availability

The data used to support the findings of this study are included within the article.

Conflicts of Interest

The authors declare that there are no conflicts of interest regarding the publication of this paper.

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