Stochastic model for tumor growth with immunization

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We analyze a stochastic model for tumor cell growth with both multiplicative and additive colored noises as well as nonzero cross correlations in between. Whereas the death rate within the logistic model is altered by a deterministic term characterizing immunization, the birth rate is assumed to be stochastically changed due to biological motivated growth processes leading to a multiplicative internal noise. Moreover, the system is subjected to an external additive noise which mimics the influence of the environment of the tumor. The stationary probability distribution P_s is derived depending on the finite correlation time, the immunization rate, and the strength of the cross correlation. P_s offers a maximum which becomes more pronounced for increasing immunization rate. The mean-first-passage time is also calculated in order to find out under which conditions the tumor can suffer extinction. Its characteristics are again controlled by the degree of immunization and the strength of the cross correlation. The behavior observed can be interpreted in terms of a biological model of tumor evolution.

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I. INTRODUCTION

A fundamental aspect of all biological systems is the understanding of emergence of cooperative behavior. The competitive interaction among different growth and death processes and the inclusion of external mechanism are widely believed to influence the global properties of such systems [1]. The analysis of tumor growth is one of the examples where those features had been attracted attention over several decades. Mathematical modeling of the growth of a certain tumor cell population is based on a heuristic approach where the logistic growth and the Gompertz law are the most popular deterministic models [2]. Otherwise, a population of proliferating cells is a stochastic dynamical system far from equilibrium [3]. Proteins and other molecules are produced and degraded permanently. Cells grow, divide, and inherit their properties simultaneously to the next generation. To gain some more insight into the generic behavior of phenomena such as tumor cell growth, it is desirable to take into account both internal and external stochastic noises as well as spatial correlations. Therefore, a more refined model was presented in [4]; however, we argue that the solutions for the stationary probability distribution (SPD) and the mean-first-passage time (MFPT) are not calculated correctly. The details and the corrections are given in our paper in Secs. IV and V. A similar model had been considered likewise in [5]. However, the stationary distribution function presented in that paper is also not correct as pointed out in [6] and replied in [7] (see also our results discussed below). The role of pure multiplicative noise may induce stochastic resonance, which appears in an antitumor system [8]. In that work the deterministic forces are modified as it will be also discussed in the present paper. The mean-first-passage time of a tumor cell growth is altered by cross correlations of the noise (compare [9], too). Essential for tumor modeling is the inclusion of therapy elements as proposed in [10]. In our model we analyze a special immunization term which enhances the death rate of the tumor cells. The influence of spatiotemporal triggering infiltrating tumor growth is studied in [11].

Much effort had been devoted to model the dynamics of competing population through a nonlinear set of stochastic rate equations [12–14]. Prey-predator systems are likewise related to that kind of models, where recently also fluctuations and correlations have been discussed [15,16] as well as instabilities with respect to spatial distributions [17].

Generally, our approach can be grouped into the permanent interest in statistical modeling of growth models, where evolution equations of Langevin- or Fokker-Planck-type play an important role [18]. In particular, the focus is concentrated on correlated colored noises [19] as multiplicative [20] and additive noises [21]. A similar approach is also applied for the Bernoulli-Malthus-Verhulst model [22]. In the context of population dynamics different aspects have been studied such as time delay effects [23], a general classification scheme for phenomenological universality in growth problems [24], extinction in birth-death systems [25], the complex population dynamics as competition between multiple-time-scale phenomena [26] and the dissipative branching in population dynamics [27].

The goal of our paper is inspired with regard to a modification of models in such a manner that both immunization and correlated noise will be included. Especially, we want to demonstrate that a finite correlation time and a nonzero immunization rate have a significant impact on the different steady states realized within the model. Additionally we analyze the interplay between an internal noise leading to a stochastic birth rate and an external noise. Furthermore, the mean-first-passage time is calculated which enables us to analyze under which conditions, depending on the correlation time and the immunization rate, the tumor population can suffer extinction.

Our paper is organized as follows. In Sec. II we offer a more biological motivation for our model by presenting experimental data concerning tumor growth. Especially, we discuss the relation of some experimental observations in

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terms of the deterministic logistic growth equation. Furthermore, we present some brief information about the interaction between tumor cells and the immune system from the perspective of immunology. Then we introduce an immunization term, the influence of which will be analyzed in the paper. The form of such an additional term is motivated. It leads to a significantly modified death rate. Section III is dedicated to the mathematical formulation of the tumor model in terms of a Langevin equation with different multiplicative and additive noises and their cross-correlation functions. The meaning of those quantities is considered in detail. Based on the corresponding Fokker-Planck equation (FPE) the SPD of the tumor cell population is studied in Sec. IV. The MFPT and its relevance are analyzed in Sec. V. In addition, we discuss a possible relation of our results to real tumor growth. The paper is finished by the conclusion in Sec. VI.

II. BIOLOGICAL MOTIVATION

Before developing a stochastic model for tumor growth let us start with some remarks on tumor biology. In the absence of an immune reaction, tumor evolution is thought to follow a limited growth law that can be approximated by a logistic function [28–30]. In [28] experimental data had been presented which support the validity of this hypothesis. In that system based on mouse models the immune system of the mice were deactivated. Our experimental observation obtained from tumor cell cultivation *in vitro* [31] leads to the same conclusions. To this aim four different cell lines [SH-SY5Y (neuroblastoma), HEK 293 (derived by human embryonic kidney transformed by sheared adenovirus type 5), Hela (cervical carcinoma), and Jurkat (T-cell leukemia)] were cultivated in a nutrient solution and the growth curves were measured utilizing a method of automated cell counting based on fluorescence. Acting for the whole experiment, data referring to the tumor cell line Hela are depicted in Fig. 1. In addition the logistic function of the form

$$N(t) = \frac{N_0 e^{\hat{a}\tau}}{1 + N_0 \frac{\hat{b}}{\hat{a}}(e^{\hat{a}\tau} - 1)} \tag{1}$$

is supplemented to this plot as solid line. This function obeys the differential equation

$$\frac{d}{d\tau}N(\tau) = \hat{a}N(\tau) - \hat{b}N^2(\tau) = \hat{f}(N), \tag{2}$$

where $N(\tau)$ denotes the cell number per volume. The parameters $\hat{a}$ and $\hat{b}$ are the growth and the death rates, respectively. As one can see from this figure Eq. (1) approximates the experimental data in a reasonable manner where, in particular, the data points in the vicinity of the saturation $\hat{a}/\hat{b}$ are fitted quite well by this function. The quantity $\hat{a}/\hat{b}$ is termed carrying capacity which is a measure for the greatest possible number to which the tumor cells can be extended. The carrying capacity is determined by the resources of the system in which the tumor will be embedded. Based on these findings, a logistic function seems to be appropriate for modeling tumor growth without taking into account the interplay with the immune system.

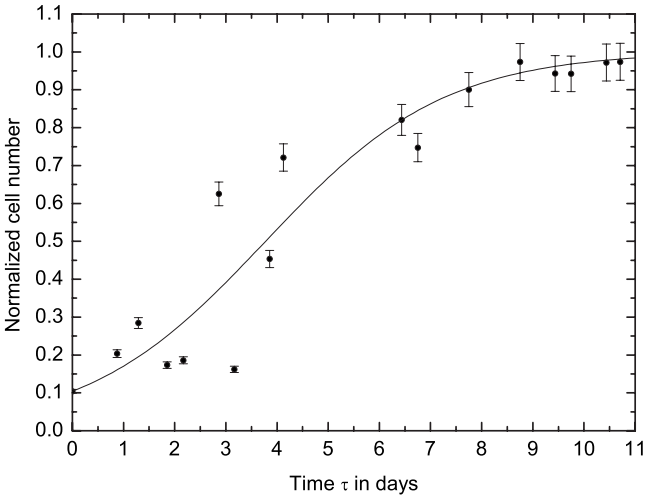

FIG. 1. Growth curve of a tumor cell population (Hela) cultivated *in vitro*, cell number in units of the carrying capacity $\hat{a}/\hat{b}$. The experimental data represent the mean of two experiments. The error bars show a deviation of 5% for every data point. The volume of the nutrient solution is 100 μl. The parameter values are $N_0 = 2.5 \times 10^5$ cells/ml, $\hat{a} = 0.57$ day^{-1}, and $\hat{b} = 4.2 \times 10^{-6}$ ml/cells day.

Since we are interested in tumor-immune interactions let us proceed with the concept of "immunoediting" which has been established in the last years [32,33]. This dynamic process consists of three phases: elimination, equilibration, and escape. The elimination phase is identical to immunosurveillance in the classical sense where both the innate and the adaptive immune systems collaborate to eradicate the tumor cells. This phase includes the recognition of the nascent transformed cells by components of the innate immune system, such as natural killer (NK) cells, natural killer T (NKT) cells, and $\gamma\delta$ T cells. These cell types are able to produce interferon γ (IFN-γ) which is an important immunologic regulator [34] and plays a significant role in cancer elimination [35] as well as in the concept of immunoediting as a whole [36]. The released IFN-γ promotes both the innate [activation of macrophages and presentation of antigens by dendritic cells (DCs)] and the adaptive immune responses (generation of antigen-specific B and T lymphocytes). Finally, the lymphocytes (CD8-positive T cells) migrate to the tumor site, recognize the tumor cells, and initiate a powerful immune reaction that ends up in the destruction of the tumor tissue. Whenever not all of the tumor cells are destroyed during the elimination phase, a transition into the equilibrium phase will occur. The effector cells of the immune system further attack the tumor and exert a selective pressure on the cancer cells. In this manner only the susceptible cancer cell variants will be eliminated by the immune system, whereas tumor cell clones that are nonimmunogenic will survive leading to a sculpting of the immunogenic phenotype of the tumor. This immunoediting may contains genetic alterations due to defective intracellular control mechanisms as well as selective or complete loss of Human Leukocyte Antigen (HLA) class I molecules (that present antigens to CD8-

positve T cells) or the activation of the nonclassical HLA-G molecule (which is thought to weaken the immune response through several pathways) on the surface of the tumor cells [37]. One can attribute a random nature to these processes, which justifies the inclusion of stochastic forces as it will be discussed in Sec. III. The evolution of resistant tumor cell variants that are able to evade the control of the immune system will eventually lead to tumor progression. In that case the tumor can pass into the escape phase. Let us remark that the equilibrium phase is not stable in a strict mathematical sense. Sooner or later the equilibrium phase can cross over to one of the other phases. Once the system is entered into the escape phase the tumor cells can evade the immune system by avoiding, suppressing, or resisting an immune reaction.

In general the tumor-immune interaction consists of deterministic parts (the classical immune response, a program that is executed when cells are recognized as nonself ones) supplemented by stochastic elements such as genetic mutations, alterations of the surface of tumor cells, e.g., including classical HLA class I and nonclassical HLA G. Thus a mathematical model should contain a deterministic function as well as random forces that complementarily describe the influence of the immune system on tumor growth. Here, we introduce the deterministic part while the stochastic components are considered in the following section. Since we are interested in the generic behavior of the immunization, let us assume that the deterministic operation of the immune system can be described by means of an additional term in the evolution equation, which has been already discussed in relation to an insect outbreak model [1,38]. Below we adopt this term in the deterministic part of the evolution equation. A similar approach has already been applied to a tumor model [8]. The modified logistic growth now reads

$$\frac{dN}{d\tau} = \hat{f}(N) - \psi(N), \quad \psi(N) = \frac{cN^2}{d^2 + N^2} \tag{3}$$

with the two model parameters c and d. The function $\psi(N)$ in Eq. (3) provides a finite value for large N. This saturation implies that the immune response is limited and, moreover, depends explicitly on the tumor cell number. Both hallmarks are sensible with regard to real tumor growth. We are thoroughly aware of the strong simplification delineated in the text above. Although the tumor-immune interaction is certainly much more complicated in detail, we think that Eq. (3), combined with the stochastic elements introduced in Sec. III, is able to describe some generic properties of real processes.

III. TUMOR MODEL

In this section we proceed in completing the model by introducing the stochastic noise terms. For simplicity let us also introduce a dimensionless formulation. To that aim we consider the general type of Langevin equation that reads

$$\frac{dx}{dt} = f(x) + g_1(x)\epsilon_1(t) + g_2(x)\epsilon_2(t), \tag{4}$$

where $x(t)$ denotes the number of tumor cells at time t; $f(x)$, $g_1(x)$, and $g_2(x)$ are deterministic functions; and $\epsilon_1(t)$ and $\epsilon_2(t)$ are colored noises with zero mean and colored cross correlations. These statistical properties are given by $\langle \epsilon_1(t) \rangle = 0$, $\langle \epsilon_2(t) \rangle = 0$, and the corresponding correlation functions

$$C(t-t') = \begin{pmatrix} \langle \epsilon_1(t)\epsilon_1(t') \rangle & \langle \epsilon_1(t)\epsilon_2(t') \rangle \\ \langle \epsilon_2(t)\epsilon_1(t') \rangle & \langle \epsilon_2(t)\epsilon_2(t') \rangle \end{pmatrix} = \begin{pmatrix} \frac{M}{\tau_1}\exp\left(-\frac{|t-t'|}{\tau_1}\right) & \frac{\lambda\sqrt{M\alpha}}{\tau_3}\exp\left(-\frac{|t-t'|}{\tau_3}\right) \\ \frac{\lambda\sqrt{M\alpha}}{\tau_3}\exp\left(-\frac{|t-t'|}{\tau_3}\right) & \frac{\alpha}{\tau_2}\exp\left(-\frac{|t-t'|}{\tau_2}\right) \end{pmatrix}. \tag{5}$$

Here, the elements of the correlation matrix $C_{ij}(t-t')$ are assumed to be symmetric $C_{ij}=C_{ji}$. The quantities M and α are the noise intensities and τ_1 and τ_2 are the correlation times of the autocorrelation functions C_{11} and C_{22}. The parameters λ and τ_3 characterize the strength of the cross-correlation function between $\epsilon_1(t)$ and $\epsilon_2(t)$ and the cross-correlation time, respectively. Notice that the parameters M and α occur in the corresponding autocorrelation function as well as in the cross-correlation function. The deterministic part $f(x)$ is given by a modified logistic growth model according to Sec. II as follows:

$$f(x) = ax - b(x)x^2, \quad b(x) = b_0 + \phi(x) \equiv b_0 + \frac{\beta}{1+x^2}, \tag{6}$$

where the quantities in Eq. (3) are rescaled according to

$$x = \frac{N}{d}, \quad a = \hat{a}\delta, \quad b_0 = bd\delta, \quad \beta = \frac{c}{d}\delta, \quad t = \frac{\tau}{\delta}.$$

In Eq. (6) the parameter a is the deterministic growth rate and b_0 denotes the decay rate proportional to the inverse carrying capacities, respectively. The parameter δ is an arbitrary time constant. The death rate is altered by including the tumor-immunization interaction represented by the function $\phi(x)$ according to Eq. (3), where the parameter β designates the strength of the immunization. Due to the immunization the effective death rate $b(x)$ is enhanced and depends on the immunization strength β. The behavior of the effective death rate is depicted in Fig. 2. The decay rate b tends to a fixed value for an increasing population as discussed before.

The tumor cell evolution is further coupled to internal and external noises denoted by $\epsilon_1(t)$ and $\epsilon_2(t)$, respectively. Whereas the death rate is systematically enhanced by immunization due to the deterministic function $\phi(x)$ in Eq. (6), the effective birth rate should be influenced by the multiplicative noise $\epsilon_1(t)$. This leads to the assumption

$$g_1(x) = -x. \tag{7}$$

Furthermore, the system is subjected to an additive noise represented by $\epsilon_2(t)$. As the consequence we choose

$$g_2(x) = 1. \tag{8}$$

Notice that all parameters are dimensionless, so that the prefactors in the last equations could be set as unity. Now let us impute to the noise terms a meaning within the biological or physical context, respectively. External noise is thought to be originated from the extracellular matrix embedding the tumor, e.g., comprising the production of cytokines such as IFN-γ in the microenvironment of the tumor cells. From a

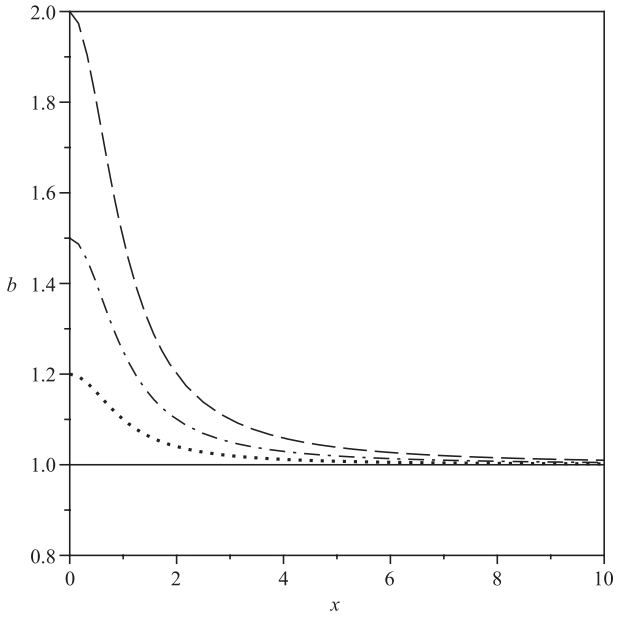

FIG. 2. Death rate b as a function of the cell number x when $b_0=1$ is fixed: β takes 0 (solid line), 0.2 (dotted line), 0.5 (dashed-dotted line), and 1 (dashed line).

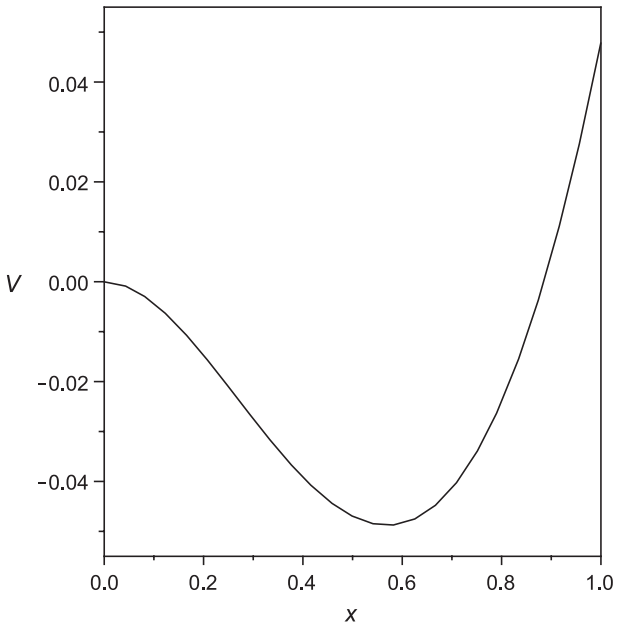

FIG. 3. The effective potential V as a function of the cell number x where $a=1$, $b_0=1$, and $\beta=1$.

more physical point of view, external noise should also be caused by thermal fluctuations. In contrast the internal noise is supposed to be generated directly within the tumor system as a kind of self-organization, for instance, by gene mutations resulting in a multitude of genetically different tumor cells within the same system. These processes are based on internal mechanisms inside the tumor without contact to its environment. In our model we identify the multiplicative noise as internal noise, whereas the additive noise is equated with the external noise. Although the origins of both stochastic processes are different, one should argue that there exists an interrelation among both ones. For example the assumed coupling between internal and external noises can be imagined as follows with regard to [39]. The normal tissue adjacent to the malignant one produces antigrowth signals in order to avoid an uncontrolled growth. The tumor may respond by insensitivity with respect to these signals by alteration or down regulation of the corresponding receptors. Furthermore, some tumor cells are able to develop self-sufficiency in generating growth signals. Another correlation concerns the nutrient supply. With a growing tumor tissue the competition is intensified regarding the nutrients between normal tissue and the nascent transformed cells. The tumor can sustain and induce angiogenesis via an "angiogenic switch" from vascular quiescence in order to progress to a larger size. Another characteristic of tumor growth is the acquisition of a diversity of strategies to evade apoptotic signals that are emitted on one hand by the tumor environment and on the other hand generated within the tumor cells. We attribute a random nature to the mechanisms of the tumor evolution because the details of the growth and decay processes differ from patient to patient. Therefore, tumor growth and the interplay with the environment can be regarded as stochastic processes as discussed above.

In view of the discussions in Sec. IV let us introduce an effective potential $V(x)$ related to the deterministic force $f(x)$ in Eq. (6) that reads

$$V(x) = -\int f(x)d(x).$$

The evaluation of the last equation yields the following expression for the potential $V(x)$:

$$V(x) = \frac{1}{3}b_0x^3 - \frac{1}{2}ax^2 + \beta(x - \arctan x). \tag{9}$$

The potential $V(x)$ is presented in Fig. 3. The stationary points can be determined by setting $f(x)=-\frac{d}{dx}V(x)=0$. From here we discriminate between four extrema, from which only two ones are real in the parameter range considered. The remaining stationary points take complex values and will not be discussed furthermore. Thus we get a potential with a minimum at $x_1=x_s>0$ and a maximum at $x_2=0$.

IV. FOKKER-PLANCK EQUATION

A. Derivation of the SPD

As a next step the Langevin equation (4) is transformed into an equivalent FPE [4,18,21,40]. To that aim let us consider $x(t)$ as a random variable whose probability density function $\rho(w,t)$ is given by

$$\rho(w,t) = \delta[x(t) - w].$$

From here one can find the stochastic Liouville equation [40] for the probability distribution function

$$P(w,t) = \langle \rho(w,t) \rangle, \tag{10}$$

where $P(w,t)$ is the density of the probability distribution function that the process $x(t)$ takes the value w at time t.

From this relation combined with Eqs. (4)–(8), one obtains the FPE in the form

$$\frac{\partial P(w,t)}{\partial t} = -\frac{\partial}{\partial w}[A(w)P(w,t)] + \frac{\partial^2}{\partial w^2}[B(w)P(w,t)]. \tag{11}$$

The explicit expressions for $A(w)$ and $B(w)$ are

$$A(w) = \left(a + \frac{M}{1-f'(w_s)\tau_1}\right)w - \left(b_0 + \beta\frac{1}{1+w^2}\right)w^2 - \frac{\lambda\sqrt{M\alpha}}{1-f'(w_s)\tau_3},$$

$$B(w) = \frac{M}{1-f'(w_s)\tau_1}w^2 - 2\frac{\lambda\sqrt{M\alpha}}{1-f'(w_s)\tau_3}w + \frac{\alpha}{1-f'(w_s)\tau_2}, \tag{12}$$

where $f'(w_s)$ denotes the derivation of $f(w)$ defined in Eq. (6) at the stationary point $w_s>0$ of the potential $V(w)$, introduced in Eq. (9). To be precise the value is

$$f'(w_s) = a - 2\left(b_0 + \frac{\beta}{(1+w_s^2)^2}\right)w_s. \tag{13}$$

Notice that the values of the process $x(t)$ are substituted by w now. Since w_s is a minimum and due to the definition in Eq. (9) the expression $1-f'(w_s)\tau_k>0$ $(k=1,2,3)$ is always fulfilled. The functions $A(w),B(w)$ are related to $f(w)$ by

$$A(w) = f(w) + \frac{1}{2}\frac{d}{dw}B(w). \tag{14}$$

The SPD of the system can be obtained from Eqs. (11)–(14). According to [18] we write

$$P_s(w) = \frac{\mathcal{N}}{\sqrt{B(w)}}\exp\left[\int^w \frac{f(w')}{B(w')}dw'\right], \tag{15}$$

where $\mathcal{N}$ is the normalization constant determined by

$$\int_0^\infty P_s(w)dw = 1. \tag{16}$$

Depending on the cross-correlation strength λ one has to distinguish between different cases. The solution of the SPD for $0\le\lambda<\frac{1-f'(w_s)\tau_3}{\sqrt{[1-f'(w_s)\tau_1][1-f'(w_s)\tau_2]}}$ reads

$$P_s(w) = \frac{N}{\sqrt{B(w)}}\exp\left[-\frac{\tilde{U}(w)}{M}\right], \tag{17}$$

where we have introduced a generalized potential according to

$$\tilde{U}(w) = \tilde{h}(w) - \tilde{E}\ln[B(w)] - \frac{\tilde{F}_1-\tilde{F}_2}{\sqrt{\tilde{M}\tilde{\alpha}-\tilde{\lambda}^2}}\arctan\left[\frac{\tilde{M}w-\tilde{\lambda}}{\sqrt{\tilde{M}\tilde{\alpha}-\tilde{\lambda}^2}}\right]. \tag{18}$$

Here, the following abbreviations are utilized:

$$\tilde{M} = \frac{M}{1-f'(w_s)\tau_1}, \quad \tilde{\alpha} = \frac{\alpha}{1-f'(w_s)\tau_2}, \quad \tilde{\lambda} = \frac{\lambda\sqrt{M\alpha}}{1-f'(w_s)\tau_3}. \tag{19}$$

The nonuniversal exponent $\tilde{E}$ reads

$$\tilde{E} = \left(\frac{a}{2} - b_0\frac{\tilde{\lambda}}{\tilde{M}}\right)[1-f'(w_s)\tau_1] - \frac{\beta M\tilde{\lambda}}{K} \tag{20}$$

with

$$K = (\tilde{M}-\tilde{\alpha})^2 + 4\tilde{\lambda}^2. \tag{21}$$

Further we use

$$\tilde{F}_1 = \left[a\tilde{\lambda} + b_0\left(\tilde{\alpha} - 2\frac{\tilde{\lambda}^2}{\tilde{M}}\right)\right][1-f'(w_s)\tau_1],$$

$$\tilde{F}_2 = \frac{\beta M}{K}(\tilde{\alpha}^2 + 2\tilde{\lambda}^2 - \tilde{M}\tilde{\alpha}),$$

$$\tilde{h}(w) = \tilde{y}(w) + \frac{\beta M}{K}\{(\tilde{M}-\tilde{\alpha})\arctan[w] - \tilde{\lambda}\ln[1+w^2]\},$$

$$\tilde{y}(w) = b_0[1-f'(w_s)\tau_1]w. \tag{22}$$

Let us remark that by setting $\tau_1=\tau_2=0$ and $\beta=0$ one obtains the correct solution for the SPD in [4] [Eqs. (19)–(22)]. For simplicity we assume that all correlation times take the same values, that is, $\tau_1=\tau_2=\tau_3=\tau$ resulting in new expressions for the generalized potential denoted now as $U(w)$. In case of the condition $0\le\lambda<1$ we get

$$P_s(w) = \frac{N}{\sqrt{B(w)}}\exp\left[-\frac{U(w)}{M}\right], \tag{23}$$

where the function $B(w)$ changes according to Eq. (12) to

$$B(w) = \frac{M}{1-f'(w_s)\tau}w^2 - \frac{2\lambda\sqrt{M\alpha}}{1-f'(w_s)\tau}w + \frac{\alpha}{1-f'(w_s)\tau}. \tag{24}$$

The potential takes the form

$$U(w) = h(w) - E\ln[B(w)] - \frac{F[1-f'(w_s)\tau]}{\sqrt{M\alpha(1-\lambda^2)}}\arctan\left[\frac{Mw-\lambda\sqrt{M\alpha}}{\sqrt{M\alpha(1-\lambda^2)}}\right] \tag{25}$$

with

$$E = \frac{a[1-f'(w_s)\tau]}{2} - \left(b_0 + \frac{\beta M^2}{Q}\right)\lambda\sqrt{\frac{\alpha}{M}}[1-f'(w_s)\tau],$$

$$Q = M^2 + \alpha^2 + 2M\alpha(2\lambda^2-1),$$

$$F = a\lambda\sqrt{M\alpha} - b_0\alpha(2\lambda^2-1) - \frac{\beta M\alpha[\alpha + M(2\lambda^2-1)]}{Q},$$

$$h(w) = \frac{\beta M[1 - f'(w_s)\tau]}{Q}\{(M - \alpha)\arctan[w] - \lambda\sqrt{M\alpha}\,\ln[1 + w^2]\} + y(w),$$

$$y(w) = b_0[1 - f'(w_s)\tau]w. \tag{26}$$

Setting $\beta=0$ and $\tau=0$ one gets the correct result for the SPD instead of the erroneous one presented in [5]. Our results are in agreement with those obtained in [6]. The case of $\lambda=1$ has to be considered separately. The corresponding solution is

$$P_s(w) = \frac{N}{\sqrt{B(w)}}\exp\left[-\frac{U^*(w)}{M}\right] \tag{27}$$

and the generalized potential reads

$$U^*(w) = h^*(w) - E^*\,\ln[B(w)] - \frac{F^*[1 - f'(w_s)\tau]}{\sqrt{M\alpha} - Mw}. \tag{28}$$

The nonuniversal exponent is written in the form

$$E^* = \frac{a[1 - f'(w_s)\tau]}{2} - \left(b_0 + \frac{\beta M^2}{Q}\right)\sqrt{\frac{\alpha}{M}}[1 - f'(w_s)\tau] \tag{29}$$

with

$$Q^* = (M + \alpha)^2,$$

$$F^* = a\sqrt{M\alpha} - b_0\alpha - \frac{\beta M\alpha(\alpha + M)}{Q^*},$$

$$h^*(w) = \frac{\beta M[1 - f'(w_s)\tau]}{Q^*}\{(M - \alpha)\arctan[w] - \sqrt{M\alpha}\,\ln[1 + w^2]\} + y(w). \tag{30}$$

The function $y(w)$ remains unchanged and is given by Eq. (26). In the following sections we only analyze the results for $0 \le \lambda < 1$ given by Eqs. (23)–(26).

B. Properties of the SPD

In this section we discuss the behavior of the SPD calculated analytically in the previous section. In Fig. 4 the SPD is represented as function of the tumor cell population w under different immunization rates β. The SPD reveals a maximum indicating the most probable cell population. The maximum becomes more pronounced the higher the immunization rate β is. The maximum is shifted to smaller tumor population with increasing rate β. The SPD is influenced significantly by the cross correlation characterized by the parameter λ. The maximum is strongly enhanced by an increasing cross-correlation strength as shown in Fig. 5. The correlation time τ of the noises affects the SPD, too. The result is shown in Fig. 6. There appears already a maximum which is more articulated when the correlation time is enhanced.

C. Biological interpretation

In this section let us discuss the results from a more biological point of view. The importance of an efficient immunization against tumor evolution is illustrated in Fig. 4. This efficacy depends on the competence of the immune system to detect the malignant cancer cells and thus to initiate a powerful immune response. The tumor elimination is the more probable and consequently the escape of the tumor from the control of the immune system is the more improbable, the higher the immune coefficient β is. A further discussion of this point is shifted to Sec. V C.

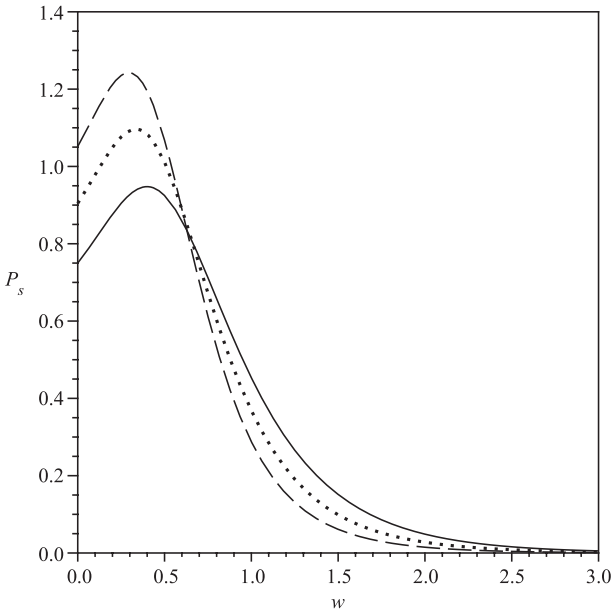

FIG. 4. The SPD P_s as a function of the cell population w for fixed $a=0.5$, $b_0=1.0$, $\alpha=0.3$, $M=0.7$, $\tau=0.5$, and $\lambda=0.5$. The immunization β varies from 0.0 (solid line), 0.5 (dotted line), and 1.0 (dashed line).

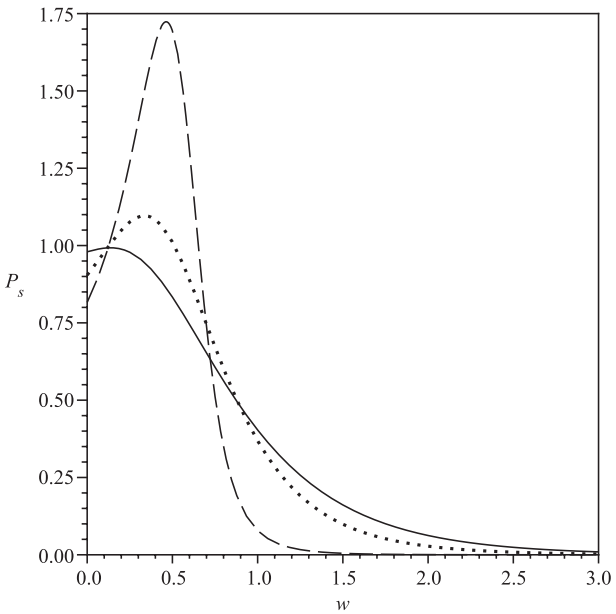

FIG. 5. The SPD P_s as a function of the cell population w for fixed $a=0.5$, $b_0=1.0$, $\alpha=0.3$, $M=0.7$, $\tau=0.5$, and $\beta=0.5$. The strength of the cross correlation λ takes 0.1 (solid line), 0.5 (dotted line), and 0.9 (dashed line).

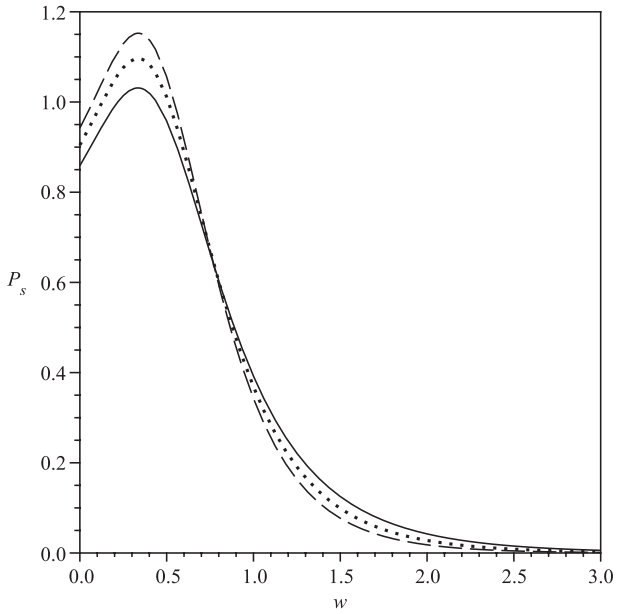

FIG. 6. The SPD P_s as a function of the cell number w when a=0.5, b_0=1.0, λ=0.5, M=0.7, α=0.3, and β=0.5 are fixed: τ takes 0.0 (solid line), 0.5 (dotted line), and 1.0 (dashed line).

Instead of that let us analyze here the influence of the internal noise ϵ_1 and the external noise ϵ_2, introduced in Eq. (4). Especially, we are interested in the interplay among each other. A measure for such a correlation is the strength of the cross correlation denoted by λ, compare Eq. (5), as well as the correlation time τ. The behavior of the SPD depending on the strength of the cross correlation is shown in Fig. 5. An increasing λ is equated with an increasing ability of the tumor to compensate the external interferences via internal reactions, e.g., by alteration of the surface structure of the tumor cells. Thus, in case of strong correlations the tumor has an improved ability to evade the attacks of the immune system. In order to explain the dependence of our results on the correlation time, let us remind that τ is the correlation time of the cross correlation as well as the correlation time of the autocorrelation functions of the additive (external) and the multiplicative (internal) noises, respectively. Here we have assumed that the correlation time for both kinds of noises is relevant on the same time scale τ. Taking this into account the appearance of a finite correlation time leads to a higher probability of a certain tumor size but does not change the most likely tumor size as presented in Fig. 6. This behavior implies that longer correlations among the stochastic processes will not lead to a tumor extinction. Instead of that the tumor persists in the body.

V. MFPT

A. Derivation of the MFPT

In cancer biology it is of interest whether a tumor that reached a certain size can suffer extinction by external or internal interference, i.e., is it possible that the influences of the noises and the immune system, introduced before, cause extinction of the tumor. A further concern is the transition time between these two states: the injurious tumor size and the tumor-free state, respectively, not knowing whether the possible transition is lasting. This problem is not far from reality because a prediction whether the tumor-free state is long living is not possible generally. In order to describe these transient properties of the system, we study the mean-first-passage time that is given by the following expression [41,42]:

$$T_{w_1w_2} = \int_{w_1}^{w_2} \frac{dw}{B(w)P_s(w)} \int_{w}^{\infty} P_s(v)dv. \tag{31}$$

The MFPT describes the transition time from an initial point w_1 to an end point w_2 which are chosen as the stationary points of the effective potential (9). More specifically, we set $w_1=x_s$ and $w_2=0$, i.e., the MFPT is calculated in such a way the system will reach the tumor-free state. There is a finite probability that the system evolves back to the tumor state $w>0$ or, alternatively, it remains with a finite probability in the tumor-free state. A comparable problem had been discussed in [43]. In the following we use an approximation scheme that is valid for small M and α in comparison with the height $[U(w_2)-U(w_1)]$ [18,44]. This concept has been already applied for a similar situation in [9]. Notice that the problem is comparable to the calculation of the inverse Kramers escape rate [43]. In that case we can derive an analytical expression for Eq. (31), namely,

$$T_{w_1w_2} = \frac{2\pi}{\sqrt{|V''(0)V''(w_1)|}} \exp\left[\frac{1}{M}[U(0) - U(w_1)]\right], \tag{32}$$

where the double prime denotes the second derivation with respect to w. Inserting Eqs. (9), (25), and (26) into Eq. (32) leads to the final expression

$$T_{w_1w_2} = \frac{2\pi}{aR} \exp\left\{\frac{1}{M}\left[E \ln\left[\frac{B(w_1)}{B(0)}\right] - h(w_1) + \frac{F[1+V''(w_1)\tau]}{\sqrt{M\alpha(1-\lambda^2)}}\left(\arctan\frac{\lambda\sqrt{M\alpha}}{\sqrt{M\alpha(1-\lambda^2)}} - \arctan\frac{\lambda\sqrt{M\alpha} - Mw_1}{\sqrt{M\alpha(1-\lambda^2)}}\right)\right]\right\}, \tag{33}$$

with the abbreviations

$$R = \sqrt{\frac{V''(w_1)}{a}},$$

$$B(w_1) = \frac{M}{1+V''(w_1)\tau} w_1^2 - \frac{2\lambda\sqrt{M\alpha}}{1+V''(w_1)\tau} w_1 + \frac{\alpha}{1+V''(w_1)\tau},$$

$$B(0) = \frac{\alpha}{1+V''(w_1)\tau},$$

$$h(w_1) = \frac{\beta M[1+V''(w_1)\tau]}{Q}\{(M-\alpha)\arctan[w_1] - \lambda\sqrt{M\alpha}\ln[1+w_1^2]\} + y(w_1),$$

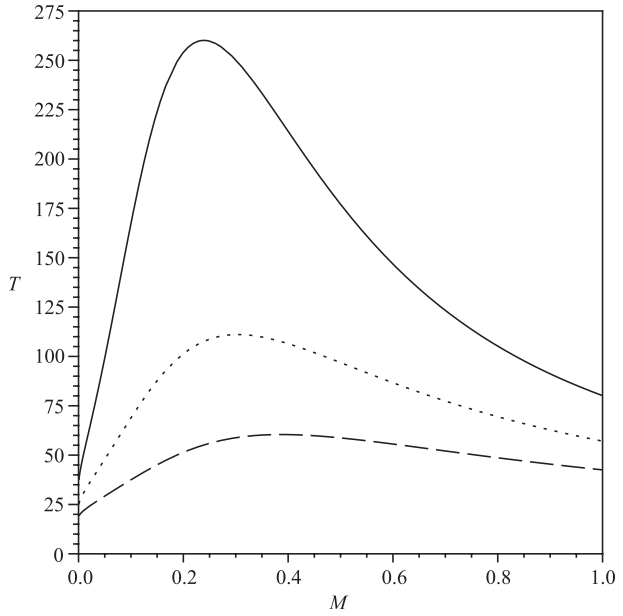

FIG. 7. MFPT as a function of M when for fixed values $a=1.0$, $b_0=1.0$, $\tau=0.5$, $\alpha=0.1$, and $\lambda=0.8$. The immunization strength β varies from 0.3 (solid line), 0.5 (dotted line), and 0.7 (dashed line).

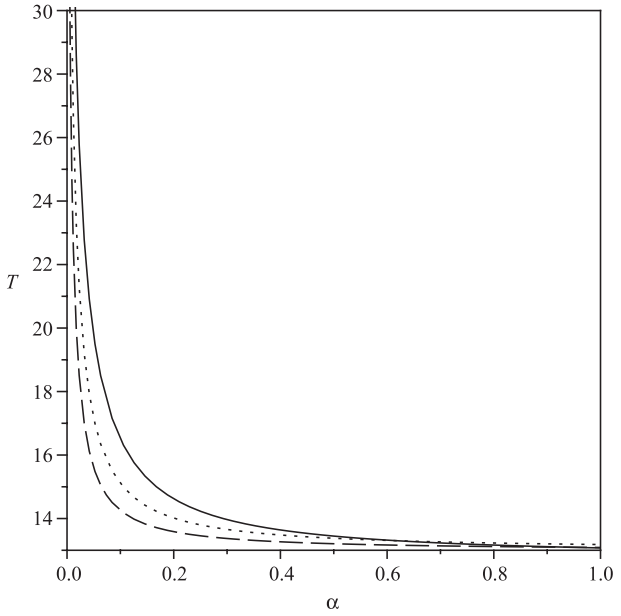

FIG. 8. The MFPT as a function of α when $a=0.5$, $b_0=1.0$, $\tau=0.5$, $M=0.8$, and $\lambda=0.5$ are fixed. The parameter β takes 0.1 (solid line), 0.5 (dotted line), and 0.9 (dashed line).

$$y(w_1) = b_0 w_1 [1 + V''(w_1)\tau],$$

$$V''(w_1) = 2\left(b_0 + \frac{\beta}{(1+w_1^2)^2}\right) w_1 - a. \tag{34}$$

Both constants, E and F, are still the same as those in Eq. (26). Notice that applying our solutions obtained by Eqs. (18)–(22) into Eq. (32); therefore substituting $U(0)$ and $U(w_1)$ by $\tilde{U}(0)$ and $\tilde{U}(w_1)$, respectively; and setting $\tau_1=\tau_2=0$ and $\beta=0$ yield the correction of the expression in [4] [see Eq. (27) there].

B. Properties of the MFPT

In this section we discuss the behavior of MFPT within our model. In Fig. 7 the MFPT is presented as a function of the parameter M introduced in Eq. (5). This parameter M is a measure for both the autocorrelation function of the multiplicative (internal) noise and the cross-correlation function between internal and external noises. As a feature there occurs a maximum indicating a long-lived cell population. The maximum is more pronounced the lower the immunization rate is and, simultaneously, it is shifted toward smaller values of M. Increasing the rate β the MFTP is smaller and an extinction of the tumor population is more probable.

In Fig. 8 the MFPT is shown depending on the parameter α according to Eq. (5). Here α characterizes the strength of the autocorrelation of the additive noise as well as the strength of cross correlation. The increase in α leads to a decrease in the MFPT. This decay is very strong in case of a high immunization rate. The direct influence of the immunization strength β on the MFPT is offered in Fig. 9. There appears already a maximum which is shifted to higher values of β when the correlation time τ is reduced. A similar behavior of the MFPT as function of β is also observed in dependence on the parameter λ. A very instructive behavior can be observed in Fig. 10 where the MFPT is depicted as function of the immunization coupling β with variation in the global noise strength M. The maximum becomes more pronounced if the noise strength increases. A nearly linear behavior of the MFPT as function of the correlation time τ is observed in Fig. 11. The increase in the MFTP is weaker the stronger the immunization rate β is.

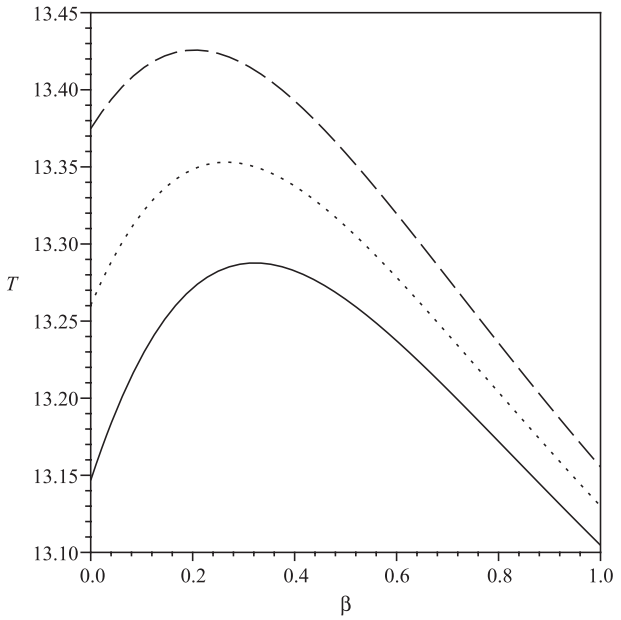

FIG. 9. The MFPT as a function of β for fixed values for $a=0.5$, $b_0=1.0$, $\alpha=0.6$, $M=0.8$, and $\lambda=0.5$. The correlation time τ varies from 0.1 (solid line), 0.5 (dotted line), and 0.9 (dashed line).

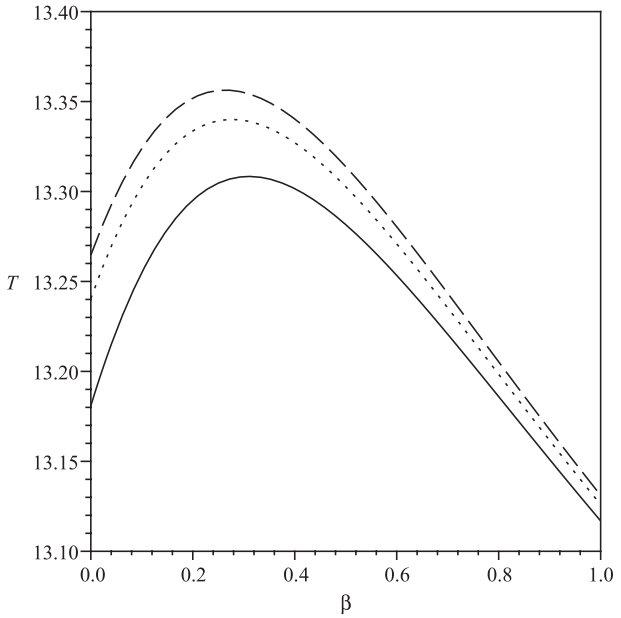

FIG. 10. The MFPT as a function of β when $a=0.5$, $b_0=1.0$, $\alpha=0.6$, $\lambda=0.5$, and $\tau=0.5$ are fixed. The noise strength M is 0.1 (solid line), 0.5 (dotted line), and 0.9 (dashed line).

C. Biological aspects

In this section the behavior of the MFPT is discussed with regard to biological aspects. Let us stress that a decrease in the MFPT is tantamount to an increase in the probability of the transition to the tumor-free state. At first, we consider the influence of the multiplicative noise on the MFPT and its relation to the immune system. Figure 7 indicates the existence of an appropriate M leading to a maximal MFPT. The increasing part of the curve reveals that the stronger the internal stochastic noises are correlated the more probable the tumor states are long lived, possibly due to genetic alterations. But after reaching the maximum the decay of the curve suggests that this mechanism is limited. As soon as the optimal value of the strength of the multiplicative noise is exceeded, the MFPT decreases and consequently the ability of the self-organized growth seems to be reduced. The improvement of the effectiveness of the immune system leads to a reduction in the MFPT. Second, the influence of the external (additive) noise offers the following behavior. All supposed external interferences arising from this noise source, for example, the release of antigrowth signals in the microenvironment of the tumor, seem to impair the living conditions of the tumor. Therefore, increasing the additive noise strength α leads to a decline of the MFPT and enhances the probability of the extinction of the cancer.

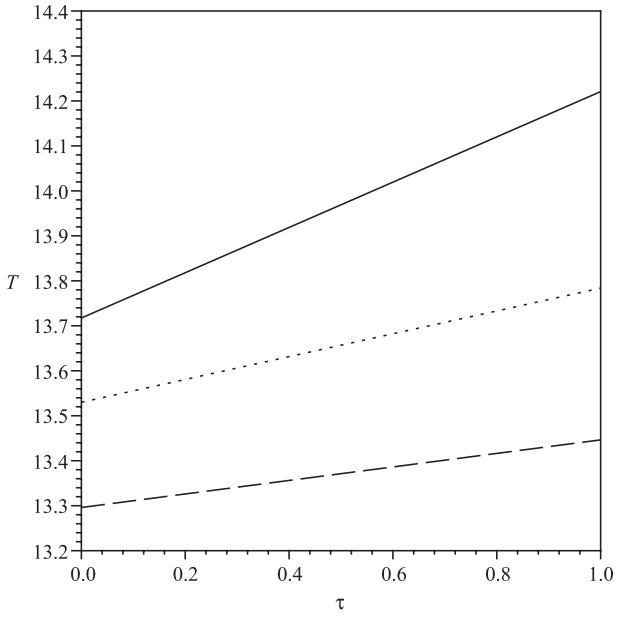

FIG. 11. The MFPT as a function of τ when $a=0.5$, $b_0=1.0$, $\alpha=0.3$, $M=0.8$, and $\lambda=0.5$ are fixed: β takes 0.1 (solid line), 0.5 (dotted line), and 0.9 (dashed line).

In order to interpret the behavior of the MFPT as a function of the immunization strength β depicted in Figs. 9 and 10, let us refer to the concept of immunoediting discussed in Sec. II. Although the three phases of immunoediting are not directly visible in Figs. 9 and 10 the principle of this concept becomes apparent. A certain nonzero immunization strength β favors long-lived tumor states and eventually makes a transition to the tumor-free state less probable. This observation can be related to the sculpting of the immunogenic phenotype of the tumor cells by the interaction with the immune system in such a manner that less susceptible tumor cell variants will survive. A similar effect can be observed by changing the strength of the multiplicative noise M and the strength of the cross correlation τ. An increase in both parameters M and τ leads to a retardation of the transition to the tumor-free state. Likewise the correlation time τ affects the MFPT. An increase in τ is related to a slowing down of the transition between the different tumor states. The longer the correlation time τ, the more probable the long-living tumor populations. Consequently, a rising value of τ simplifies the opportunity of the tumor to evade the immune system.

VI. CONCLUSIONS

In this work we have proposed and analyzed a more refined model describing tumor cell growth. Starting from a logistic model we have modified the model in several directions. The decay term is supplemented by a deterministic nonlinear immunization term which enhances the death rate of the tumor. Furthermore, the birth rate is assumed to be stochastically distributed leading to a multiplicative noise. The occurrence of such a noise term is motivated by the underlying biological situation. Additionally, the system is subjected to an additive external noise which is originated from the external conditions as the environment of the tumor. Both kinds of colored noises are correlated, i.e., there are autocorrelation functions and a cross-correlation function with different strengths. The resulting equation has the form of a Langevin equation which can be transformed into a Fokker-Planck equation. Using standard methods we find the steady-state solutions which are discussed depending on the strength of the cross correlation, the finite correlation time, and the degree of immunization. The behavior of the station-

ary probability distribution is analyzed taking into account biological aspects. In particular, the stationary probability distribution offers a maximum indicating the appearance of very probable states. This maximum becomes more pronounced the higher the immunization rate is, for instance. As a further quantity of interest we have studied the mean-first-passage time which indicates when the tumor suffers extinction. The MFPT is likewise calculated analytically and analyzed under consideration of biological aspects. The MFPT is influenced in a significant manner by the immunization strength and the cross correlation as well as the finite correlation time of the underlying colored noises. The observed behavior is related to the principle of immunoediting.

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