A stochastic model for tumor growth with immunization

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Abstract

We analyze a stochastic model for tumor cell growth with both multiplicative and additive colored noise as well as a non-zero 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 is again controlled by the degree of immunization and the strength of the cross-correlation. The behavior observed can be interpreted in terms of the three state model of a tumor population.

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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]. In this context much effort has been devoted to model the dynamics of competing population through a nonlinear set of rate equations such as proposed by Lotka and Volterra [2, 3] or a broad variety of their variants as a stochastic model for ecosystems [4], coexistence versus extinction [5] or special clustering in Lotka-Volterra model [6]. Prey-predator systems are likewise related to that kind of models, where recently also fluctuations and correlations are discussed [7, 9] as well as instabilities with respect to spatial distributions [8]. The heuristic approach is based upon deterministic evolution equations. Otherwise, a population of proliferating cells is a stochastic dynamical system far from equilibrium [10]. 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.

In the present paper we are interested in tumor growth which had been attracted attention over several decades. Mathematical modeling of the growth of a certain population is based on different equations where the logistic growth and the Gompertz law are the most popular deterministic models [11]. A more refined model was presented in [12], however we argue that the solutions for the stationary probability distribution and the mean-first-passage time are not calculated correctly. The details and the corrections are given in our paper in Sec.III and IV. Nevertheless, the model in [12] includes already both additive and multiplicative noise terms considered likewise in [13]. However, the stationary distribution function presented in that paper is also not correct as pointed out in [14] and replied in [15], see also our results discussed below. The role of pure multiplicative noise may induce stochastic resonance, which appears in an anti-tumor system [16]. 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, see already [17]. Essentially for tumor modeling is also the inclusion of therapy elements as proposed in [18]. In our
model we analyze a special immunization term which enhances the death rate. Another model \cite{19} is devoted to the spatiotemporal triggering infiltrating tumor growth.

Our approach can be grouped into the permanent interest in a statistical modeling of growth model, where evolution equations of Langevin or Fokker-Planck-type play an decisive role \cite{20}. In particular, the focus is concentrated on correlated colored noises \cite{21} in the form of multiplicative noise \cite{22} and additive noise \cite{23}. A similar approach is also applied in \cite{24} for the Bernoulli-Malthus-Verhulst model. In the context of population dynamics different aspects has been studied such as time delay effects \cite{25}, a general classification scheme for phenomenological universality in growth problems \cite{26}, extinction in birth-death-systems \cite{27}, the complex population dynamics as competition between multiple-time-scale phenomena \cite{28} and the dissipative branching in population dynamics \cite{29}.

The goal of our paper is inspired with the view to alter the models in such a manner that both immunization and correlated noise are included. Especially, we want to demonstrate that a finite correlation time and a nonzero immunization rate have an 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 define the Langevin equation with different multiplicative noises and their cross-correlation functions, the meaning of that is considered in detail. Then we introduce an immunization term the influence of which will be analyzed in the paper. Such an additional term leads to a significantly modified death rate. Based on the related Fokker-Planck equation the stationary probability distribution (SPD) is studied in Sec. III. The expression for the mean-first-passage time (MFPT) and its meaning is explained in Sec. IV. Further we discuss the relation of our results to real tumor growth. In Sec. V we finish with some conclusions.

II. THE TUMOR MODEL

In order to develop a statistical tumor growth model, we consider the general type of Langevin equation, that reads

\[
\frac{dx}{dt} = f(x) + g_1(x)e_1(t) + g_2(x)e_2(t),
\]  

(1)
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-correlation. These statistical properties are given by \( \langle \epsilon_1(t) \rangle = 0; \ \langle \epsilon_2(t) \rangle = 0 \) and the corresponding correlation functions

\[
C(t - t') = \begin{pmatrix}
\langle \epsilon_1(t) \epsilon_1(t') \rangle & \langle \epsilon_1(t) \epsilon_2(t') \rangle \\
\langle \epsilon_2(t) \epsilon_1(t') \rangle & \langle \epsilon_2(t) \epsilon_2(t') \rangle
\end{pmatrix} = \begin{pmatrix}
\frac{M}{\tau_1} \exp\left( -\frac{|t-t'|}{\tau_1} \right) & \frac{M \alpha}{\tau_3} \exp\left( -\frac{|t-t'|}{\tau_3} \right) \\
\frac{M \alpha}{\tau_3} \exp\left( -\frac{|t-t'|}{\tau_3} \right) & \frac{\alpha}{\tau_2} \exp\left( -\frac{|t-t'|}{\tau_2} \right)
\end{pmatrix}
\]

(2)

Here, the elements of the correlation matrix \( C_{ij}(t-t') \) are assumed to be symmetric \( C_{ij} = C_{ji} \). The quantities \( M \) and \( \alpha \) are the noise intensities and \( \tau_1 \) and \( \tau_2 \) are the correlation times of the autocorrelation functions \( C_{11} \) and \( C_{22} \). The parameters \( \lambda \) and \( \tau_3 \) characterize the strength of the cross-correlation function between \( \epsilon_1(t) \) and \( \epsilon_2(t) \) and the cross-correlation time, respectively. In our model we consider a modified logistic growth model with

\[
f(x) = ax - b(x)x^2, \quad b(x) = b_0 + \phi(x) \equiv b_0 + \frac{\beta}{1 + x^2}.
\]

(3)

Here, the parameter \( a \) is the deterministic growth rate and \( b_0 \) denotes the decay rate proportional to the inverses carrying capacity, respectively. This death rate is altered by inclusion of a tumor-immunization interaction represented by the function \( \phi(x) \) \[1\], where the parameter \( \beta \) designates the strength of the immunization. Under immunization the effective death rate \( b(x) \) is enhanced where the decay of the rate depends on the immunization strength \( \beta \). The behavior of the effective death rate is depicted in Fig.\[1\] 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, modeled by the deterministic function \( \phi(x) \), the effective birth rate should be influenced by the stochastic force \( \epsilon_1(t) \). This leads to the assumption

\[
g_1(x) = -x.
\]

(4)

Furthermore, the effect of additive noise represented by \( \epsilon_2(t) \) is incorporated into the system by

\[
g_2(x) = 1.
\]

(5)

Notice that all parameters are dimensionless, so that the prefactors in the last equations could be set as unity. With regard to the discussions in Sec.IV let us introduce an effective potential \( V(x) \) according to the deterministic force \( f(x) \), that reads

\[
V(x) = - \int f(x) \, d(x).
\]

(6)
FIG. 1: Plot of the death rate $b$ as a function of the cell number $x$ when $b_0 = 1$ is fixed: $\beta$ takes 0 (solid line), 0.2 (dotted line), 0.5 (dashdotted line) and 1 (dashed line).

Evaluating (6) yields the following expression for $V(x)$:

$$V(x) = \frac{1}{3} b_0 x^3 - \frac{1}{2} a x^2 + \beta (x - \arctan x).$$

(7)

The potential $V(x)$ is presented in Fig. 2. 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 of them are real in the parameter range considered. The remaining stationary points take complex values and will not be discussed furthermore. Thus, we have derived a potential with a minimum at $x_1 = x_s > 0$ and a maximum at $x_2 = 0$.

III. FOKKER-PLANCK-EQUATION

A. Derivation of the stationary probability distribution (SPD)

As a next step the Langevin Equation (1) is transformed into an equivalent Fokker-Planck equation (FPE) [12, 20, 23, 30]. To that aim let us consider $x(t)$ as a random variable whose
FIG. 2: Plot of the effective potential $V$ as a function of the cell number $x$ where $a = 1$, $b_0 = 1$ and $\beta = 1$.

probability density function $\rho(w, t)$ is a delta-function

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

From here one can find the stochastic Liouville equation [30] for the probability distribution function

$$P(w, t) = \langle \rho(w, t) \rangle. \quad (8)$$

Here, $P(w, t)$ 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. [1] - (5), one obtains the FPE in the form

$$\frac{\partial P(w, t)}{\partial t} = -\frac{\partial}{\partial w} [A(w)P(w, t)] + \frac{\partial^2}{\partial w^2} [B(w)P(w, t)]. \quad (9)$$

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

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

$$B(w) = \frac{M}{1 + a\tau_1} w^2 - \frac{2\lambda \sqrt{M \alpha}}{1 + a\tau_3} w + \frac{\alpha}{1 + a\tau_2}. \quad (10)$$
Notice there is a relation between the functions $A(w), B(w)$ and $f(w)$ of the form

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

(11)

The stationary probability distribution (SPD) of the system can be obtained from Eqs. (9)-(11) and can be written as

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

(12)

where $N$ is the normalization constant that is determined by

$$\int_0^\infty P_s(w) dw = 1.$$

(13)

Depending on the cross-correlation strength $\lambda$ one has to distinguish between different cases. The solution of the SPD for $0 \leq \lambda < \frac{1+\alpha\tau_3}{\sqrt{(1+\alpha\tau_1)(1+\alpha\tau_2)}}$ is

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

(14)

where we have introduced a generalized potential according to

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

(15)

Here, the following abbreviations are utilized:

$$\bar{M} = \frac{M}{1 + a\tau_1}, \quad \bar{\alpha} = \frac{\alpha}{1 + a\tau_2}, \quad \bar{\lambda} = \frac{\lambda\sqrt{M\alpha}}{1 + a\tau_3}.$$

(16)

The non-universal exponent $\bar{E}$ reads

$$\bar{E} = \frac{a(1 + a\tau_1)}{2} - b_0\lambda \sqrt{\frac{\alpha}{M}} \frac{(1 + a\tau_1)^2}{1 + a\tau_3} - \frac{\beta M \lambda \sqrt{M\alpha}}{K(1 + a\tau_3)}$$

(17)

with

$$K = \left( \frac{M}{1 + a\tau_1} - \frac{\alpha}{1 + a\tau_2} \right)^2 + \frac{4\lambda^2 M\alpha}{(1 + a\tau_3)^2}.$$

(18)

Further we use

$$\bar{F}_1 = a\lambda \sqrt{M\alpha} \frac{1 + a\tau_1}{1 + a\tau_3} + b_0\alpha(1 + a\tau_1) \left( \frac{1}{1 + a\tau_2} - 2\lambda^2 \frac{1 + a\tau_1}{(1 + a\tau_3)^2} \right),$$

$$\bar{F}_2 = \frac{\beta M \alpha}{K} \left( \frac{\alpha}{(1 + a\tau_2)^2} - \frac{M}{(1 + a\tau_1)(1 + a\tau_2)} + \frac{2\lambda^2 M\alpha}{(1 + a\tau_3)^2} \right),$$

$$\bar{h}(w) = \frac{\beta M}{K} \left( \left( \frac{M}{1 + a\tau_1} - \frac{\alpha}{1 + a\tau_2} \right) \arctan w - \frac{\lambda\sqrt{M\alpha}}{1 + a\tau_3} \ln \left[ 1 + w^2 \right] \right) + \bar{g}(w),$$

$$\bar{g}(w) = b_0(1 + a\tau_1) w.$$

(19)
Let us remark, that by setting \( \tau_1 = \tau_2 = 0 \) and \( \beta = 0 \) one obtains the corrected solution for the SPD in \([12]\) (equations (19)-(22)). In the present paper 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 \( 0 \leq \lambda < 1 \) we get

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

where \( B(w) \) according to Eq. (10) changes to

\[
B(w) = \frac{M}{1 + a\tau} w^2 - \frac{2\lambda \sqrt{M\alpha}}{1 + a\tau} w + \frac{\alpha}{1 + a\tau}.
\]

The potential takes the form

\[
U(w) = h(w) - E \ln \left[ B(w) \right] - \frac{F(1 + a\tau)}{\sqrt{M\alpha(1 - \lambda^2)}} \arctan \left[ \frac{M w - \lambda \sqrt{M\alpha}}{\sqrt{M\alpha(1 - \lambda^2)}} \right]
\]

with

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

\[
Q = M^2 + \alpha^2 + 2M\alpha(2\lambda^2 - 1)
\]

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

\[
h(w) = \frac{\beta M(1 + a\tau)}{Q} \left( (M - \alpha) \arctan w - \lambda \sqrt{M\alpha} \ln \left[ 1 + w^2 \right] \right) + y(w)
\]

\[
y(w) = b_0(1 + a\tau) w.
\]

We want to point out that setting \( \beta = 0 \) and \( \tau = 0 \) gives the right results for the SPD that is not correct in \([13]\). These solutions are in agreement with those mentioned in \([14]\). The second case of \( \lambda = 1 \) has to be considered separately. The corresponding solution is

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

and the generalized potential reads

\[
U^*(w) = h^*(w) - E^* \ln \left[ B(w) \right] - \frac{F^*(1 + a\tau)}{\sqrt{M\alpha - M w}}.
\]

The non-universal exponent is written in the form

\[
E^* = \frac{a(1 + a\tau)}{2} - \left( b_0 + \frac{\beta M^2}{Q} \right) \sqrt{\frac{\alpha}{M}} (1 + a\tau)
\]
with
\[
Q^* = (M + \alpha)^2 \\
F^* = a\sqrt{M\alpha} - b_0\alpha - \frac{\beta M\alpha(\alpha + M)}{Q^*} \\
h^*(w) = \frac{\beta M(1 + a\tau)}{Q^*} \left( (M - \alpha) \arctan w - \sqrt{M\alpha} \ln \left[ 1 + w^2 \right] \right) + y(w).
\]

The function \( y(w) \) remains unchanged and is given by Eq. (23). In the following sections we only consider the first case and analyze the results for \( 0 \leq \lambda < 1 \), i.e. our further computations refer to the solutions given by Eqs. (20) - (23).

### B. Properties of the SPD

In this section we discuss the behavior of the stationary probability distribution (SPD) calculated analytically in the previous subsection. In Fig. 3 the SPD is represented as function of the tumor cell population \( w \) under different immunization rates \( \beta \). The SPD reveals a maximum indicating the most probable cell population. The maximum becomes the more pronounced the higher the immunization rate \( \beta \) is. The maximum is shifted to smaller tumor population with increasing rate \( \beta \). The SPD is influenced significantly by the cross-correlation characterized by the parameter \( \lambda \). The maximum is strongly enhanced by an increasing cross-correlation strength as shown in Fig. 4. The SPD is also influenced by the correlation time \( \tau \) of the noises. The result is shown in Fig. 5. There appears already a maximum which is more articulated when the correlation time is enhanced.

### C. Biological interpretation

The importance of an efficient immunization against tumor evolution is illustrated in Fig. 3. This efficacy depends on the competence of the immune system to detect the malignant cancer cells, and thus to initiate a powerful immune response. In [31, 32] the 'Three E’s of cancer immunoediting' are described, i.e. the tumor-immune interaction can result into three different phases: elimination, equilibrium and escape, whereas sooner or later the equilibrium phase offers a cross-over to the other phases. Adopting this concept to the behavior of the SPD the tumor elimination phase is the more probable and the escape phase
FIG. 3: Plot of 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 $\beta$ varies from 0.0 (solid line), 0.5 (dotted line), 1.0 (dashed line).

is the more improbable the higher the immune coefficient $\beta$ is, for further remarks compare also subsection IV.C.

Now, we want to relate the internal noise $\epsilon_1$ and the external noise $\epsilon_2$, introduced in Eq. (1), to real processes that occur in the tumor and its environment including the hallmarks of cancer [33], and moreover to point out to the connections among each other. External noise is thought to be originated in the extracellular matrix embedding the tumor or it is a consequences of drug delivery from outside of the host. Additionally, external noise can be caused by thermal fluctuations. In contrast the internal noise is 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. The process is based upon internal mechanisms inside the tumor without contact to its environment. Although the origins of both stochastic processes are different one should argue that there exists an interrelation among both ones. A measure for such a correlation is the strength
FIG. 4: Plot of 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 $\lambda$ takes 0.1 (solid line), 0.5 (dotted line), 0.9 (dashed line).

of the cross-correlation denoted by $\lambda$ in Eq. 2 as well as the correlation time $\tau$. The expected coupling between external and internal noises can be understood as follows. The normal tissue adjacent to the malignant one produces anti-growth signals in order to avoid an uncontrolled growth. The tumor may respond with 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 the one hand by the tumor environment and on the other hand generated within the tumor cells.

Therefore, the behavior of the SPD depending on the strength of the cross-correlation is
clearly shown in Fig. 4. An increasing $\lambda$ is equated with an increasing ability of the tumor to compensate the external interferences via internal reactions described above. Thus, in case of strong correlations the tumor has an improved ability to reach the escape phase.

In order to explain the dependence of our results on the correlation time let us remind that $\tau$ is the correlation time of the cross-correlation as well as the correlation time of the auto-correlation functions of the additive (external) and multiplicative (internal) noise, respectively. Here we have assumed that the correlation time for both kind of noises is relevant on the same time scale $\tau$. 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 likeliest tumor size as presented in Fig. 5.

Notice that we attribute a random nature to the mechanisms of the tumor evolution because the details of the growth and decay processes differs from patient to patient. Therefore, tumor growth and the interplay with the environment can be regarded as a stochastic
process and is interpreted by introducing external and internal noises.

IV. MEAN-FIRST-PASSAGE TIME (MFPT)

A. Derivation of the MFPT

In cancer treatment it is of interest whether a tumor that reached a certain size can suffers extinction by external or internal interferences, i.e. is it possible that the influences of the noises and the immune system introduced in the previous sections can cause extinction of the tumor. A further concern is the transition time between these two states: the lethal tumor size and the tumor free state, respectively. In order to describe these transient properties of the system we apply the mean-first-passage time that is given by the following expression

\[ T_{w_1w_2} = \int_{w_1}^{w_2} \frac{dw}{B(w)P_s(w)} \int_{w}^{\infty} P_s(v)dv, \]  

(28)

i.e. the transition from an initial point \( w_1 \) to an end point \( w_2 \) is considered. We choose the stationary points of the effective potential (7), more specifically \( w_1 = x_s \) and \( w_2 = 0 \), i.e. the MFPT of the system reaching the tumor free state is studied. Now we make use of an approximation scheme that is valid for small \( M \) and \( \alpha \) in comparison with the potential barrier height \( [U(w_2) - U(w_1)] \) [20, 36], what has already been applied to tumor models, e.g. [17]. We derive an analytical expression for (28), namely

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

(29)

where the double-prime denote the second derivation with respect to \( w \). Inserting Eq. (7) and Eqs. (22)-(23) into the Eq. (29) leads to the final expression

\[ T_{w_1w_2} = \frac{2\pi}{aR} \exp \left\{ \frac{1}{M} \left[ E \ln \frac{B(w_1)}{B(0)} - h(w_1) \right. \right. \]

\[ + \frac{F(1 + a\tau)}{\sqrt{M\alpha(1 - \lambda^2)}} \left( \arctan \frac{\lambda\sqrt{M\alpha}}{\sqrt{M\alpha(1 - \lambda^2)}} - \arctan \frac{\lambda\sqrt{M\alpha - Mw_1}}{\sqrt{M\alpha(1 - \lambda^2)}} \right) \right\}, \]  

(30)
where

\[ R = \sqrt{\frac{2w_1}{a} \left( b_0 + \frac{\beta}{(1 + w_1)^2} \right) - 1} \]

\[ B(w_1) = \frac{M}{1 + a\tau} w_1^2 - \frac{2\lambda\sqrt{M\alpha}}{1 + a\tau} w_1 + \frac{\alpha}{1 + a\tau}, \quad B(0) = \frac{\alpha}{1 + a\tau} \]

\[ h(w_1) = \frac{\beta M(1 + a\tau)}{Q} \left( (M - \alpha) \arctan w_1 - \lambda\sqrt{M\alpha} \ln \left[ 1 + w_1^2 \right] \right) + y(w_1) \]

\[ y(w_1) = b_0 w_1 (1 + a\tau). \]  \hspace{1cm} (31)

Both constants, \( E \) and \( F \), are still the same as those in Eq. (23). Notice, that applying our solutions obtained by Eqs. (15) - (19) into Eq. (29), 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 \( \beta = 0 \) yields the correction of the expression in Eq. (27) in [12].

### B. Properties of the MFPT

In this subsection we discuss the properties of our system and the behavior of the MFPT. In Fig. 6 we present the MFPT as function of the parameter \( M \) introduced in Eq. (2). This parameter \( M \) is a measure for both the auto- and the cross-correlation function between internal and external noise. As a feature there occurs a maximum indicating a long living cell population. The maximum is the more pronounced the lower the immunization rate is and it is shifted towards higher values of \( M \). Increasing the rate \( \beta \) the MFTP is smaller and an extinction of the tumor population is more probable. In Fig. 7 the MFPT is represented depending on the parameter \( \alpha \) according to Eq. (2). Here \( \alpha \) characterizes the strength of the auto-correlation of the additive noise as well as the strength of cross-correlation. The increase of \( \alpha \) leads to a decrease of the MFPT. This decay is very strong in case of a high immunization rate as expected. The direct influence of the immunization strength \( \beta \) on the MFPT is shown in Fig. 8. There appears already a maximum which is shifted to higher values of \( \beta \) when the correlation time \( \tau \) is reduced. A similar behavior of the MFPT as function of \( \beta \) is also observed in dependence on the parameter \( \lambda \). A very instructive behavior can be observed in Fig. 9 where the MFPT is depicted as function of the immunization coupling \( \beta \) with variation of 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 \( \tau \) is observed in Fig. 10. The increase of the MFTP is weaker for a stronger
FIG. 6: Plot of the 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 $\beta$ varies from 0.3 (solid line), 0.5 (dotted line), 0.7 (dashed line).

immunization rate $\beta$.

C. Biological aspects

In this subsection the behavior of the MFPT is discussed with regard to biological aspects. Let us stress that a decrease of the MFPT is tantamount to an increase of 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, where the noise is originated from all the distinct processes described in subsection III.C. Here, we assume that the multiplicative noise is mainly determined by the gene mutations. Fig. 6 indicates that there exists an appropriate $M$ leading to a high MFPT. Improving the effectiveness of the immune system leads to a reduction of the MFPT. Moreover, the tumor system requires more gene mutations in order to maximize the MFPT. More genetic alterations induce a deterioration of the ability of the immune system to identify tumor cells. But this mechanism is limited
FIG. 7: Plot of the MFPT as a function of $\alpha$ when $a = 0.5$, $b_0 = 1.0$, $\tau = 0.5$, $M = 0.8$ and $\lambda = 0.5$ are fixed. The parameter $\beta$ takes 0.1 (solid line), 0.5 (dotted line), 0.9 (dashed line).

as it is visible by the descent of the curves in Fig. 8. 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-organization is reduced.

The influence of the external (additive) noise offers the expected behavior. All interferences impair the living conditions of the tumor. Therefore, a growing parameter $\alpha$ leads to a decline of the MFPT and enhances the probability of the extinction of the cancer.

Following the explanation made for the interpretation of Figs. 8 and 9 let us introduce the principle of immunoediting presented in [31, 32]. On the one hand the immune system is able to cause extinction of the tumor, otherwise it can facilitate tumor progression by sculpting the immunogenic phenotype of tumors. During this process immune-resistant variants of the tumor cells are able to survive and even more proliferate in order to develop a tumor tissue that can sustain further immune attacks. This behavior is displayed in Figs. 8 and 9. The increasing part of the curve is thought to be connected with the process of tumor sculpting which may end up in the tumor escape phase. The decreasing part of the MFPT is identified
FIG. 8: Plot of the MFPT as a function of $\beta$ for fixed values for $a = 0.5$, $b_0 = 1.0$, $\alpha = 0.6$, $M = 0.8$ and $\lambda = 0.5$. The correlation time $\tau$ varies from 0.1 (solid line), 0.5 (dotted line), 0.9 (dashed line).

with immunosurveillance that leads to tumor elimination. This process is the more likely the bigger the immunization strength is. The effect of the strength of the multiplicative noise $M$ and the strength of the cross-correlation $\tau$ are similar. Due to the fact that the increase of both parameters $M$ and $\tau$ and the biological mechanisms beyond promotes the tumor growth, one should expect a retardation of the transition to the elimination phase as shown in Figs. 8 and 9.

The correlation-time $\tau$ also effects the MFPT. An increase of $\tau$ leads to a slowing down of the transition between the different states of the tumor. The longer the correlation time $\tau$ is the more probable are long living tumor populations. Consequently, a rising value of $\tau$ simplifies the opportunity of the tumor to evade the immune system.

V. 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.
FIG. 9: Plot of the MFPT as a function of $\beta$ 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), 0.9 (dashed line).

The decay term is supplemented by a deterministic non-linear immunization term which enhances the death rate of the tumor. Furthermore, the birth rate as 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 by the external conditions as the environment of the tumor. Both kinds of colored noises are correlated, i.e. there are autocorrelation and a cross-correlation functions with different strength. 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 stationary probability distribution is analyzed taking into account biological aspects above all the three different states of the tumor: elimination, equilibration and escape phase. In particular, the SPD offers a maximum indicating the appearance of very probable states. This maximum becomes for instance the more pronounced the higher
FIG. 10: Plot of the MFPT as a function of $\tau$ when $a = 0.5$, $b_0 = 1.0$, $\alpha = 0.3$, $M = 0.8$ and $\lambda = 0.5$ are fixed: $\beta$ takes 0.1 (solid line), 0.5 (dotted line), 0.9 (dashed line).

the immunization rate is. 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 and the cross-correlation as well as the finite correlation time of the underlying colored noises. The observed behavior can be understood in terms of the above mentioned three phases of a tumor population.

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