Bounded-noise-induced transitions in a tumor-immune system interplay

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By studying a recent biophysical model of tumor growth in the presence of the immune system, here we propose that the phenomenon of evasion of tumors from immune control at a temporal mesoscale might, in some cases, be due to random fluctuations in the levels of the immune system. Bounded noises are considered, but the Gaussian approach is also used for analytical reference. After showing that in the case of bounded noises there may be multiple attractors in the space of probability densities, we numerically show that the velocity of convergence toward asymptotic density is very slow and that a transitory analysis is needed. Then, by simulations using the sine-Wiener and the Tsallis noises, we show that if the level of the noise is sufficiently large then there may be the onset of noise-induced transitions in the transitory density evaluated at realistic times. Namely, the transitions are from unimodal density centered at low values of tumor burden to bimodal densities that have a second maximum centered at higher values. However, those transitions depend on the distribution of the noise.

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I. INTRODUCTION

The complex and nonlinear interplay of the immune system (IS) with non-self-entities [1] offers an ideal area of research for the statistical physics of nonequilibrium systems [2] and, indeed, has long been a source of great interest for physicists [3]. In particular, the interaction of IS with tumors is a classical challenge in the field of biophysics [3–10].

Molecular biology has shown that tumor cells (TCs) are characterized by a vast number of genetic events leading to the appearance of specific antigens, which trigger actions by the IS [11]. These experimental observations have provided a theoretical basis to the old empirical hypothesis of immune surveillance, i.e., that the IS may act to control or eliminate tumors [12]. Only in recent years, has a sufficient amount of experimental and epidemiologic evidence been accumulated in favor of this hypothesis and it has been demonstrated that the IS can suppress tumors [13].

An important point to stress is that the structure of the tumor-immune system (T-IS) interactions is also *time varying* at two different scales, fast and slow, which may be a cause of evasion of the tumor from immune control [9,13,14]. The fast scale is related to the very initial phases of growth when immune system cells dynamically learn to recognize and target TCs [15], which might allow many neoplasms to escape from the immune control [16].

At the slow scale, remarkably, the TCs are characterized by a considerable evolutionary ability to enhance their survival in a hostile environment [9,13,17]. Indeed, if the IS is not able to eliminate a neoplasm, a suboptimal control is possible by establishing a dynamic equilibrium, such that the tumor may only survive in a small steady state [8]. However, over a long period of time [13] the neoplasm may develop multiple strategies to circumvent the action of the IS [11,13], which may allow it to recommence growing to its carrying capacity [9].

In [9] those behavioral strategies interrelated with phenotype changes were described by means of models similar to the Lotka-Volterra models with slowly varying parameters representing adaptively changing interaction strengths [18]. The objective of this work is the investigation of the phenomenon of evasion of TCs from immune control at a temporal mesoscale.

Of course in the very short term if either the tumor is lowly immunogenic or the level of IS is *per se* low (e.g., because of an immunodeficiency [1]) it is obvious that the transformed cells can easily and in short times evade control. Over the long temporal range not only those slow evolutionary processes but also the IS degradation due to natural senescence [14] can explain long-term evasions. However, middle-term evasions are presumably representative of the vast majority of cases of immune surveillance failure.

An important factor that has been extensively investigated [4,5,19,20,22] is the influence of the fluctuations in the proliferation rates of a tumor. Those fluctuations, however, play a dual role since they can also trigger the elimination of the neoplasm.

Given the complexity and multistability of the T-IS interplay, we think that a natural approach is to investigate the role of statistical fluctuations of immune levels that might trigger noise-induced transitions. Moreover, from a modeling point of view, the extreme intricacy of the interactions between tumor cells and immune effectors [2,21] further justifies the inclusion of noise on a deterministic model of T-IS interplay in order to take into account a plethora of relevant phenomena such as the variable strength of the neoantigens in stimulating the immune response, the expression or absence of expression of molecules needed for T cell activation, the dynamics of Treg cells that generate a state of tolerance to cancer antigens, and many others [1,16].

We stress that in this problem the methods of noise-induced transitions theory have to be somewhat adapted. Indeed, recent studies have shown that the classical approach based on Gaussian perturbations in biology has a limited range of applications (see [24] and references therein), and that suitable bounded noises should be used [25].

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Another major point is that the classical theory of noise-induced transitions [4] is an asymptotic theory since it refers to the study of the qualitative changes in stationary probability densities: $P_{st}(x)=\lim_{t\to\infty} P(x,t)$, where x stands, in biological applications of this theory, for some biological property such as the size of a cellular population, as in our case, or the viral load or the average activity, etc. Here, of course, we shall assume that x denotes the tumor size. However, living beings have a finite lifespan. Thus, the lifespan of the host organisms must set a natural limit to the investigations, which makes the velocity of convergence to $P_{st}(x)$ an essential parameter. If this velocity is low and the attractor is practically reached in times that are greater than the average lifespan of the organisms in study, one has to investigate the possible qualitative changes in $P(x,t)$ during its transitory, namely, at some given realistic times. Moreover, also in other fields of applied physics the necessity of transitory analyses has been stressed [26].

Very interestingly, in [5] the problem of the influence of the fluctuations of the immune system strength had been faced, with the interesting result that by increasing the variance of the noise, the corresponding effect is the (partial) rejection of the neoplasm. However, in the model [5] the effect of the immune system is increasing for whatever size of tumor, whereas there is evidence that for large sizes of the tumor there is a decrease in the effect of the immune system [8]. Thus, the important results of [5] may be considered as referring to the class of largely immunogenic tumors.

To take into account the decreased cytotoxic effectiveness of immune effectors, we study here a phenomenological model that was proposed in [20,22] by adapting previously existing prey-predator models [23]. Here, we shall give a precise biological interpretation of the model and of its limits. We shall then focus on the response of this biological system to stochastic bounded perturbation in the immune levels, differently from [20,22], where the influence of Gaussian stochastic changes in the proliferation rate was investigated. Here, we also shortly investigate our model in the Gaussian settings, in order to set a reference framework and to make appropriate comparisons. Another key difference between our analyses is that in [20] the stochastic model was framed in the Stratonovich theory, whereas here we use Ito calculus, which is more apt for modeling tumor-immune system interplay [4,5].

II. MODELING TUMOUR-IMMUNE SYSTEM INTERPLAY

In [20,22] a qualitative model of T-IS interactions was proposed, which was obtained by a simple analogy with some prey-predator models [23]. Although the model was based on an ecological analogy between predation and killing of tumor cells by immune effectors, the results that one may obtain are biologically sound. For this reason before starting our analysis we shall briefly examine it for its biological soundness and deficiencies.

In dimensional form the model can be written as follows:

$$X' = (p_0 - \delta_0)X - jX^2 - m_0X - \frac{\beta_0 X^2}{1+\left(\frac{X}{c}\right)^2}, \tag{1}$$

where $X(t)$ is the size of the neoplasm at time t, p_0X is the baseline proliferation rate and δ_0X is the baseline apoptotic rate (i.e., they are, respectively, the proliferation and apoptotic rates for small tumors where competition effects are very small), jX^2 accounts for intercellular competition (e.g., for nutrients), and $\phi(X)X := \beta_0X^2/[1+(X/c)^2]$ is the rate of lysis of TCs by the IS. We call β the baseline IS strength.

Note that here we added to the original model [20,22] a new term $-m_0X$ that takes into account the interplay of TCs with innate immune defense [1]. This also allows us to identify $\phi(X)X$ as the contribution due to specific immune defenses.

Despite its simplicity, this model is able to reproduce some of the basic properties of the interactions between tumor cells and the immune system, in primis multistability [20,22]. In our opinion, this model is interesting since the specific rate of lysing of tumor cells by the immune effectors $\phi(X)$ is nonmonotone, which correlates with the fact that small tumors might produce an insufficient amount of antigens, whereas large tumors decrease the ability of the IS to react [8,16], because of the production of immunosuppressors and because of a general compromising of the host bone marrow in the presence of advanced tumors.

On the other hand, if $m_0 < p_0 - \delta_0$ the model is slightly pessimistic since it implies that the effectiveness of specific immune defense toward TCs is limited: the possibility of tumor suppression is precluded since for small tumors Eq. (1) reads $x' = (p_0 - \delta_0 - m_0)x > 0$. Of course, since immune surveillance for small tumors is excluded, there cannot be, in the absence of therapies, a tumor eradication induced by the immune system unless the innate defenses are so strong that $m_0 > p_0 - \delta_0$. This is a limit of the model that must be stressed, with the validity of the model being limited to tumors whose immunogenic activity, for low levels of X, is intermediate or low.

As in many models of tumor growth, in this model there is no direct representation of the myriad of complex dynamical biomolecular mechanisms that underlie the processes leading to proliferation, programmed cell death, senescence, and—of course—interaction with the IS. Thus, virtually all parameters appearing in Eq. (1) may be considered variables and affected by a major or minor extent of noise. Here, we shall focus on noisy variations of the baseline IS interaction rate β_1.

If $m_0 > p_0 - \delta_0$ it is convenient to adimensionalize by assuming as the time unit $\tau_u = (p_0 - \delta_0 - m_0)^{-1}$ and as the tumor size unit $X_u = c$, which yields

$$x' = x - \frac{x^2}{K} - \frac{\beta x^2}{1+x^2}, \tag{2}$$

where $K = cj\tau_u$ and $\beta = \beta_0 c \tau_u^{-1}$. The deterministic behavior of the solutions of Eq. (2) is simple: there exist β^* and $\beta^{**} > \beta^*$ such that if $0 < \beta < \beta^*$ there is a unique and globally attractive macroscopic equilibrium that is near the carrying capacity K, if $\beta > \beta^{**}$ there is a small globally attractive equilibrium, and whereas if $\beta^* < \beta < \beta^{**}$ there also is a central unstable equilibrium and two equilibria: one is microscopic and the other is macroscopic. As a consequence at $\beta = \beta^*$ and at $\beta = \beta^{**}$ there is a hysteresis bifurcation.

Let the baseline strength of IS, β, be subjected to stochastic varying of the IS by adding a white noise,

$$\beta(t) = \beta + \sigma\xi(t),$$

where $\xi(t)$ is a white noise of unitary intensity; we obtain the following Langevin-Ito stochastic differential equation (SDE):

$$x' = x - \frac{x^2}{K} - \frac{\beta x^2}{1+x^2} - \xi(t)\sigma\frac{x^2}{1+x^2}. \tag{3}$$

We recall here that given a SDE $x' = f(x) + \sigma g(x)\xi(t)$ the probability density $P(x,t)$ is given by solving the Fokker-Planck equation that may have a unique stationary solution of the form

$$P_{st}(x) = M\ \exp\left(-2\ \ln[g(x)] + \frac{2}{\sigma^2}\int_x \frac{f(z)}{g^2(z)}\right),$$

which, if it exists, is globally attractive, i.e., for all initial condition $P(x,0) = \rho_0(x)$ it is

$$\lim_{t\to+\infty} P(x,t;\rho_0(x)) = P_{st}(x). \tag{4}$$

Thus to Eq. (3) is associated the following stationary probability density for x:

$$P_{st}(x) = M\ \exp\left(-\frac{2}{\sigma^2}U_{eff}(x)\right), \tag{5}$$

where the stationary potential $U_{eff}(x)$ is

$$U_{eff}(x) = \frac{x^3}{3K} + x\left(\frac{2}{K} + \beta\right) - \frac{K\beta + 1}{Kx} - \sigma^2\ \ln(x^2+1) - \frac{x^2}{2} + \frac{1}{2x^2} - 2(1-\sigma^2)\ln(x). \tag{6}$$

In the next section we shall numerically assess how σ^2 influences the probability potential $U_{eff}(x)$.

Although the Gaussian noise approach allows the above interesting analytical results, it has an inherent pitfall. Indeed, in an infinitesimal interval $(t, t+dt)$ the IS contribution to the change in the tumor size x is

$$\text{Prob}\left(-\frac{\beta x^2}{1+x^2}dt - W(t)\sqrt{dt}\sigma\frac{x^2}{1+x^2} > 0\right) > 0,$$

which means that the killer cells of the immune system instead of killing the TCs may generate them. The key point is that a Gaussian perturbation of a positive parameter π is a good approximation if its standard deviation is far smaller than the average value of π, because in this case the probability of negativity of the now randomly varying π is very small and can be tolerated.

Unfortunately, in biological systems the parameters are subjected to such large fluctuations that they are considered small even if their standard deviations are on the order of 10%, thus making the use of Gaussian noises quite questionable. In order to graphically represent this point, we simulated (Euler method with $N = 10^3$ points) the model in the range $0 < t < 1$ with $\beta = 1.8$, $\sigma = 0.18$, and $K = 10$. In Fig. 1 we plotted the corresponding $\beta dt + \sigma W(t)\sqrt{dt}$: a very large percentage ($\approx 37.9\%$) of the simulated killing rate of TCs by the IS is negative.

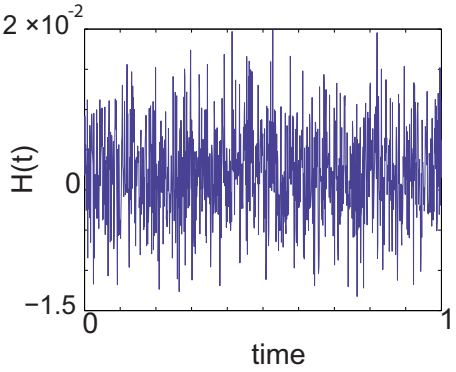

FIG. 1. (Color online) Plot of the time series of a (approximate) realization of the infinitesimal stochastic coefficient $H(t) = \beta dt + \sigma W(t)\sqrt{dt}$ for $\beta = 1.8$, $\sigma = 0.18$, and $dt = 10^{-3}$. In a large fraction of the simulation time the coefficient is negative.

As a consequence, it is more appropriate to perform an analysis based on the introduction of bounded noises $\nu(t)$, with $|\nu(t)| \le B < \beta$ [so that $\beta + \nu(t) > 0$], leading to the equation

$$x' = x - \frac{x^2}{K} - [\beta + \nu(t)]\frac{x^2}{1+x^2}. \tag{7}$$

Let us consider a β such that the deterministic model has three equilibria and a B such that $\beta^* < \beta - B$ and $\beta + B < \beta^{**}$. This implies that, in the unperturbed case, there are three equilibria at $\beta - B$ and three at $\beta + B$. Let us call these equilibria a_L, b_L, and c_L for the lower bound and a_U, b_U, and c_U for the upper bound. Of course it is $a_U < a_L$, $b_U > b_L$, and $c_U < c_L$. From the differential inequalities

$$x - \frac{x^2}{K} - (\beta + B)\frac{x^2}{1+x^2} \le x' \le x - \frac{x^2}{K} - (\beta - B)\frac{x^2}{1+x^2}, \tag{8}$$

it follows that if $x(0) < b_2$ then for large times $x(t) \in (a_1, a_2)$, whereas if $x(0) \in (b_1, +\infty)$ then for large times $x(t) \in (c_1, c_2)$, so that in principle $\varrho(x)$ is non-null only in $(a_1, a_2) \cup (c_1, c_2)$.

More interestingly, the fact that two initial distributions of $x(0)$ lead to two different and mutually exclusive asymptotic behaviors means that the asymptotical probability distribution, if it exists, depends on the initial conditions, i.e., there are multiple equilibria in the space $\mathfrak{I}$ of the probability measures. If the equilibrium does not exist, there are however multiple attracting sets in $\mathfrak{I}$. This behavior is markedly different from the case of Gaussian noise where, as represented in Eq. (4), there is a unique and globally attractive stationary density.

Since we are interested only in the natural history behavior of the T-IS interplay, in the absence of human intervention, we are mainly interested in random small or moderate initial values $x(0)$. Thus, here we are not interested in the general assessment of the influence of B on the samples $x(t)$ for large times, but in the subcase where the initial condition is suitably small. More formally we are interested in the assessment of the qualitative changes in the conditional

probability density, conditional to $x(0) \in A=(0,a^*)$, where a^* is a suitable small value, for example, 1% of the carrying capacity. Finally, we briefly mention that in the case where the innate system is sufficiently reactive to have $m_0 > p_0 - \delta_0$, from

$$x' < -[m_0 - (p_0 - \delta_0)]x, \tag{9}$$

it follows that $P_{st}(x)=\delta(x)$, independent of the type of bounded noise.

III. MODELS OF BOUNDED NOISE

Since the noise-induced transitions are dependent on the kind of density of noise adopted [27], we shall assume two kind of bounded noise. The first bounded noise we consider is the so-called sine-Wiener noise [28] given by

$$\nu(t) = B \sin\left(\sqrt{\frac{2}{\tau}}W(t)\right),$$

where $W(t)$ is a white noise. The sine-Wiener noise, as it is easy to verify, is such that $\langle \nu(t) \rangle = 0$, $\langle \nu^2(t) \rangle = B^2/2$, and

$$\langle \nu(t)\nu(t+z) \rangle = \frac{B^2}{2}\exp\left(-\frac{z}{\tau}\right)\left[1 - \exp\left(-4\frac{t}{\tau}\right)\right],$$

where $z \geq 0$. A different approach consists of using noises $\nu(t)$, which we shall call Tsallis noises [29], and which are derived by the following Langevin equation [29,30]:

$$\nu'(t) = \tau^{-1}\left(-\frac{\nu}{1 - \frac{\tau(1-q)}{D}\frac{\nu^2}{2}} + \sqrt{2D}\zeta(t)\right), \tag{10}$$

where $0 < q < 1$ and $\zeta(t)$ is a Gaussian noise with zero mean and unitary intensity. Thus, $\nu(t)$ is a non-Gaussian noise with zero average and the following bounds:

$$-B < \nu(t) < B, \quad B = \sqrt{\frac{2D}{\tau(1-q)}}. \tag{11}$$

The stationary density of ν is

$$P_{st}(\nu) = A_q\left[\left(1 - \frac{\nu^2}{B^2}\right)_+\right]^{1/(1-q)},$$

where A_q is a normalization constant and $(z)_+ = \max(z,0)$. Finally, the autocorrelation of $\nu(t)$ is approximately given by [30]

$$\frac{\langle \nu(t)\nu(t+s) \rangle}{\langle \nu^2(t) \rangle} \approx \exp\left(-|s|\frac{5-3q}{2\tau}\right).$$

IV. NUMERICAL SIMULATIONS

In this section we shall assess the role of noise by means of simulations for various values of B, which will be our bifurcation parameter. Regarding the order of greatness of the parameters, since at $x=1$ the killing rate is maximal and equal to $\beta/2$, we may assume that $K > 10$. Thus, we shall use $K=10$ as a test value. For β we note that there is a critical value $\beta_c = 2(1-1/K)$ such that the microscopic equilibrium is at $x=1$, i.e., in correspondence to the maximum of $\phi(x)$. Finally, it is important to stress that for chimeric mice $\tau_u \approx 5.56$ days [32]. We shall use these values as reference values.

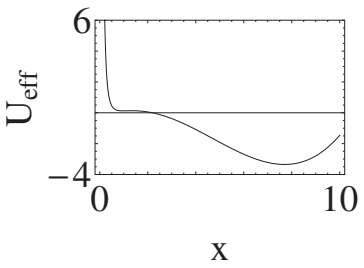

FIG. 2. Plot of $U_{eff}(x)$ for $\sigma=0.01$, $\beta=1.8$, and $K=10$.

For the autocorrelation time τ_c, we may assume that many variations of the immune strength are on the order of some days since they may reflect various phenomena related to the behavior of the patient and external additional pathologies such as infections or temporary immunodepressions [1], so that we used $\tau_c=0.2$ (slightly more than 1 day) and $\tau_c=1$.

In the previous section we analytically obtained the steady-state probability density corresponding to white-noise perturbations, and we referred to the important fact that it is globally attractive. In Fig. 2 the potential $U_{eff}(x)$ for $\beta=1.8$ and $\sigma=0.1$ is shown. Since $\sigma^{-2}=100$ and $U_{eff}(x)$ at the two minima is ≈ 0 and ≈ -3 it follows that the asymptotic distribution is very near to a Dirac's delta centered at x_M. The other peak is negligible even in case of large σ, as shown in Fig. 3, which refers to $\sigma=1.8/1.96$. To have equal values at the two minima of the potential one has to increase up to approximately $\sqrt{2.2}$.

As a consequence, this might lead one to infer that the statistical fluctuation affecting the immune system *does* make the tumor evade from immune control in all cases. However, from the biophysical point of view, this answer is neither complete nor satisfactory since it is an asymptotic result, which implies that it is fundamental to assess the velocity of convergence. The density of x at $t=1000$ for $\sigma=0.1$ is shown in Fig. 4 and we can see that the steady distribution has been fully reached. However, in dimensional time it corresponds to 5560 days ≈ 15.21 years (yr), which is an interval of time far longer than the average life of chimeric mice, which ranges from approximately 2 to 3 yr [31], and—of course—it is also longer than the characteristic times of the evolutionary escape of the tumor from IS.

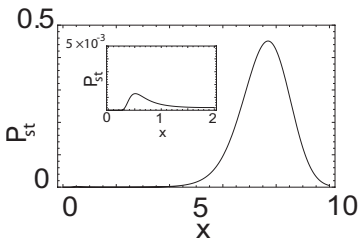

FIG. 3. Gaussian noise. Plot of $P_{st}(x)$ for $\sigma=1.8/1.96$, $\beta=1.8$, and $K=10$. In the inset a zoom is shown, for $0 < x < 2$, of the left part of the plot.

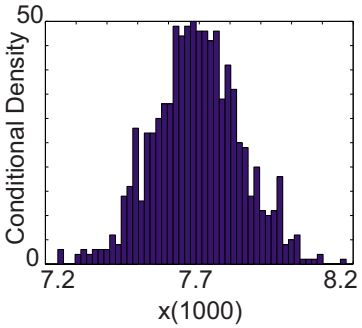

FIG. 4. (Color online) Probability density of x at $t=1000$ (≈ 15.2 yr) induced by a Gaussian perturbation of $\beta=1.8$ with $\sigma=0.15$. Initially $x(0) \in (0,0.1)$.

In other words, the velocity of convergence is low, so that we have to assess transient values of $P(x,t)$ for some realistic values of t. We performed some simulations to assess these densities, under the hypothesis of bounded noise of sine-Wiener and of Tsallis types, conditional to initial values uniformly distributed in a small range, which we assumed equal to (0,0.1). Namely, we estimated $P(x,T)$ for $T=3$, 6, 12 months.

In the case of sine-Wiener noise with $\tau=1$ and $B=0.2$ we obtained that at $T=3$ months there is no or very scarce probability of escape, with extreme values equal to $x=2$ [Fig. 5(a)], whereas at $T=6$ months the probability of escape is significant with some tumors reaching values near to the carrying capacity [Fig. 5(b)]. Finally, for $T=1$ yr and again $B=0.2$ the probability of escape and macroscopic growth is very large and the density is bimodal, whereas at $B=0.04$ we obtained a unimodal density. Thus, the increase in B caused a transition, i.e., a qualitative change in $P(x,T)$ (Fig. 6).

For $\tau=0.2$ (i.e., approximately 1 day) and $B=0.2$ at $T=6$ months there is a small but non-null probability of escape, whereas at $T=1$ yr there is transition to bimodality with a considerable probability of tumor explosion, as shown in Fig. 7 where the densities corresponding to $B=0.04$ and 0.2 are compared. A time series of an immunoevasion with $\tau=0.2$ and $B=0.3$ is shown in Fig. 8.

In the case of Tsallis noise with $\tau=1$ and $B=0.2$ we obtained transitions to bimodality at 1 yr both for $q=0.5$ (see Fig. 9) and for $q=0.1$. No transitions were observed at 3 or 6 months, where the density is unimodal centered at the lower values of x. By decreasing τ to 0.2, at 1 yr we obtained the result that for $q=0.1$ there is a very small (one case on 1000)

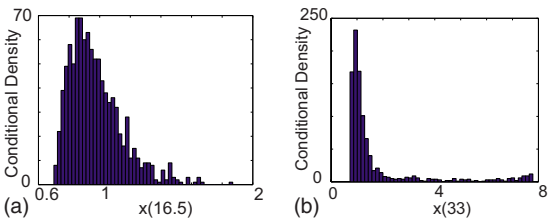

FIG. 5. (Color online) Simulation of the effects that a bounded noise of the sine-Wiener type with $\tau=1$ and $B=0.2$ acts on the conditional probability density $P(x,t)$ at finite times T with $x(0) \in (0,0.1)$. (a) $T=3$ months; (b) $T=6$ months.

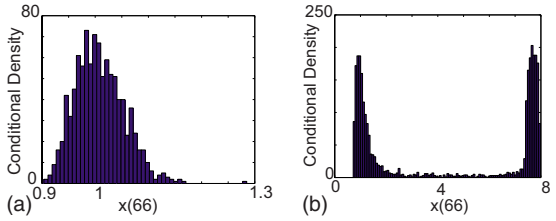

FIG. 6. (Color online) Transitions induced to $P(x,T)$ with $T=66=1$ yr by a sine-Wiener noise with $\tau=1$ and $x(0) \in (0,0.1)$. (a) At $B=0.04$ the density is unimodal. (b) At $B=0.2$ the density is bimodal.

probability of $x(66)$ reaching the large values, whereas for $q=0.5$ there is macroscopic increase in 11 cases out of 1000. By increasing B to 0.4 we have transitions at 1 yr for $q=0.5$, which is similar to Fig. 9.

Finally, we stress that, of course, other fluctuations that are faster or far slower may be present, with the latter being due, for example, to the state of psychological depression. Our simulations, confirming the biological intuition, suggest that the first type of fluctuations is filtered out or has small effects, whereas the second type easily induces immunoevasion.

V. CONCLUDING REMARKS

We have developed an analysis of the immunoevasion process in tumors based on the effects of multiplicative bounded noises modeling the random fluctuations of the levels of the immune system. Our results seem to show that these perturbations may contribute to triggering the tumor escape, but—generally speaking—not so easily.

Although our analysis was mainly numerical, we have analytically shown that in the model under investigation in the case of bounded noise (and independently from the specific choice of it) with small (but not necessarily infinitesimal) amplitude there is no global convergence toward a unique stationary density, which is, conversely, what happens if the noise is Gaussian.

Another point of some interest that we stressed in our model, but that is of general relevance in the biophysics of diseases, is that the velocity of convergence toward a (unique or non unique) steady-state density is a key parameter. Indeed, if this velocity is slow, the related inferences are biologically unsound since they refer to time spans that are

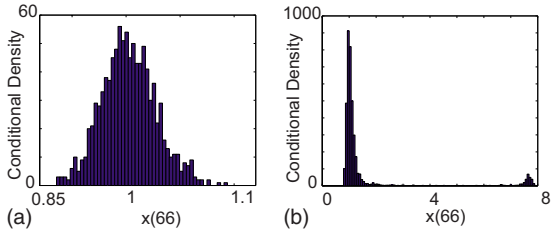

FIG. 7. (Color online) Transitions induced to $P(x,T)$ with $T=66=1$ yr by a sine-Wiener noise with $\tau=0.2$ and $x(0) \in (0,0.1)$. (a) At $B=0.04$ the density is unimodal. (b) At $B=0.2$ the density is bimodal.

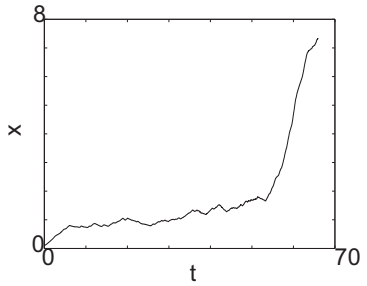

FIG. 8. Simulation of a tumor immunoevasion induced by a sine-Wiener noise. Parameters: $B=0.3$ and $\tau=0.2$.

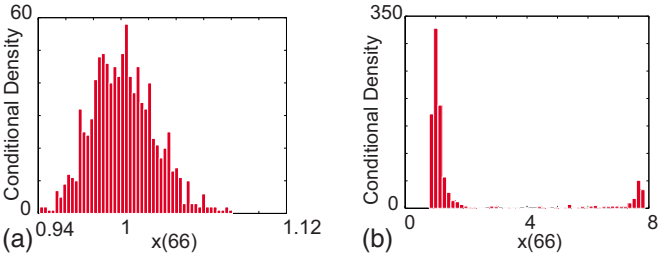

FIG. 9. (Color online) Transitions induced to $P(x,T)$ with $T=66=1$ yr by a Tsallis noise with $\tau=1$ and $q=0.5$. $x(0) \in (0,0.1)$. (a) At $B=0.04$ the density is unimodal. (b) At $B=0.2$ the density is bimodal.

greater than the average lifespan of the host organism. This is critical in our case since if when using the Gaussian model and the analysis of the dependence of the effective potential U_{eff}, then the asymptotic result is up to quite large values of σ the density of the tumor size is centered at large values. Conversely, we showed that limiting the analysis at finite significant times, the transition to large values is not reached if the oscillation B of the noise is too small or, for the Tsallis noise, if the autocorrelation time τ_{corr} is small. Note that transition depends somewhat on the noise model adopted.

A limitation of this work is that scalar models in oncology are too oversimplified, which is particularly true in the field of immuno-oncology, due to the strong heterogeneity of the involved cellular populations [2,21] as well as to the evolutionary nature of the tumor-immune system interaction [9]. One should at least consider a minimal model where the dynamics of immune cells is explicitly included, which we will study in further research on more biologically realistic finite-dimensional [7,32] and infinite-dimensional [10] models. However, we believe that the results of this work should not be changed in their essential features.

We stress here that many of the results that we obtained are neither strictly related to the specific functional form of the growth or death rates nor are they related to that of the specific killing rate function $\phi(x)$. What is really important is the shape of the involved functions.

Finally, although some inferences of biological interest are presented here, and although we offered sufficiently sound biological justifications to our modeling choices, we must honestly stress that our stochastic model is speculative and it needs experimental confirmations. The aim of this work is to trigger such investigations.

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