Resistance to antitumor chemotherapy due to bounded-noise-induced transitions

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(Received 20 July 2010; revised manuscript received 20 October 2010; published 2 December 2010)

Tumor angiogenesis is a landmark of solid tumor development, but it is also directly relevant to chemotherapy. Indeed, the density and quality of neovessels may influence the effectiveness of therapies based on blood-born agents. In this paper, first we define a deterministic model of antiproliferative chemotherapy in which the drug efficacy is a unimodal function of vessel density, and then we show that under constant continuous infusion therapy the tumor-vessel system may be multistable. However, the actual drug concentration profiles are affected by bounded even if possibly large fluctuations. Through numerical simulations, we show that the tumor volume may undergo transitions to the higher equilibrium value induced by the bounded noise. In case of periodically delivered boli-based chemotherapy, we model the fluctuations due to time variability of both the drug clearance rate and the distribution volume, as well as those due to irregularities in drug delivery. We observed noise-induced transitions also in case of periodic delivering. By applying a time dense scheduling with constant average delivered drug (metronomic scheduling), we observed an easier suppression of the transitions. Finally, we propose to interpret the above phenomena as an unexpected non-genetic kind of resistance to chemotherapy.

DOI: 10.1103/PhysRevE.82.061901 PACS number(s): 87.19.xj, 87.18.Tt, 87.50.yt

I. INTRODUCTION

Clonal resistance (CR), i.e., the emergence through fast mutations of drug-insensitive cells in a tumor under chemotherapy, was up to the recent past, and to some extent it is still at present, the main paradigm used to explain the high rate of relapses during chemotherapeutic treatments of tumors [1].

However, in the last ten years, a number of investigations [2] revealed that a significant fraction of cases of resistance to therapy is actually linked to phenomena that may, broadly speaking, be defined as physical resistance (PR) to drugs [3]. This means that resistance cannot only be imputed to a sort of Darwinian evolution of the cancerous population through the birth of new clones but also to the dynamics of the molecules of the drugs in the tumor. A nonexhaustive list of such physical phenomena is the following: (i) limited ability of the drug to penetrate into the tumor tissue because of ineffective vascularization [4] and poor or nonlinear diffusivity [5]; (ii) binding of drug molecules to the surface of tumor cells or to the extracellular matrix [6]; (iii) scarce effectiveness of cytotoxic drugs due to the existence of large regions of hypoxia and to the consequent prevalence of quiescent cells in the tumor cell population [7]; and (iv) collapse of blood vessels [8].

We recently proposed [9] a deterministic population-based model to describe the cytotoxic chemotherapy of vascularized solid tumors that may have multiple stable equilibria under constant continuous drug infusion, unlike other models of tumor growth. That model describes the modulation of the average drug concentration in the tumor tissue by means of a nonmonotone and unimodal function of the density of tumor vessels that multiplies the blood drug concentration. The variability of the drug concentration in the tumor tissue is due to two facts: (i) for small vessel density there is a minor drug perfusion and (ii) for large vessel density the drug penetration may be reduced since the tumor vessels in such condition are mostly dysfunctional with respect to the physiological ones [10]. The multistability is the consequence of the interplay between these physical vessel-related phenomena and the population dynamics of the tumor cells.

We have shown in a deterministic framework that the gradual onset of mild forms of clonal resistance, with a consequent decrease in the effectiveness of the drug, may induce jump phenomena. Here we suggest the possible existence of a third path for the insurgence of the resistance, different from CR and having some relationships with PR, due to the interaction between the multistability of the tumor and the unavoidable fluctuations of the blood concentration of the delivered drug, through the well-known mechanism of noise-induced transitions [12]. This non-genetic kind of resistance thus comes from the complex interplay among the pharmakocinetics of the agent, the physiological condition of the patient, the physical barriers caused by the abnormal nature of tumor blood vessels, and the interaction between tumor and endothelial cell populations.

However, in contrast with the classical theory of noise-induced transition, we shall not assume that the noise affecting the drug concentration is Gaussian. In [13,14] we stressed that possible biological inconsistencies might derive from the use of Gaussian noise, and here we shall then consider only bounded noises, whose theoretical study has recently attracted a number of physicists [14–16].

Concerning the origin of those fluctuations, we shall consider two separate and different settings, corresponding to two different ways of delivering the antitumor chemothera-

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pies. In the first, we shall consider a continuous infusion of drug during which, because of temporal changes of the pharmacokinetics parameters and/or imperfect delivering, the agent concentration in blood is not constant and affected by stochastic fluctuations. In the second case, we consider a therapy periodically delivered by means of boli. Here we may have two different irregularities: the first is inherent to intrasubject temporal variability of pharmacokinetics parameters, among them the clearance rate constant(s) of the drug. The other source of fluctuations is linked with irregularities of the time of delivering. Note that in case of boli-based therapy there is the copresence of both stochastic fluctuations and periodic deterministic fluctuations due to the periodicity of the administration of the agent.

II. GROWTH AND THERAPY OF A VASCULARIZED SOLID TUMOR

The vascularization of a tumor is a milestone of tumoral development *in vivo*. Solid tumors in their first phase of growth, indeed, are small aggregates of proliferating cells that receive oxygen and nutrients only through diffusion from external blood vessels. In order to grow beyond $1-2$ mm^3, the formation of new blood vessels inside the tumor mass is required. Poorly nourished tumor cells start producing a series of molecular factors that stimulate and also control (via inhibition) the formation of an internal vascular network [17]. This process, called neoangiogenesis, is sustained by a variety of mechanisms [17], such as the cooption of existing vessels and the formation of new vessels from the pre-existing ones. As far as the tumor-driven control of the vessel growth is concerned, endogenous antiangiogenic factors have been both evidenced experimentally [19] and studied theoretically [18,19].

To describe the interplay between the tumor and its vasculature, we further generalize a family of models previously proposed in [9] that includes as particular cases the models in [18,20–22] (for different approaches to the modeling of untreated vascularized tumors or of tumors undergoing antiangiogenic therapies, see [23]). We assume that (i) the carrying capacity $K(t)$ of the tumor vasculature is simply proportional to the amount of vessels and that (ii) the specific growth and apoptosis rates of the tumor and the specific proliferation rate of vessels depend on the ratio ρ between the carrying capacity and the tumor size. Following Hahnfeldt *et al.* [18], the growth of the neovasculature is antagonized by endogenous factors that depends on the tumor volume. Since the ratio $\rho=K/V$ may be interpreted as proportional to the tumor vessel density, assumption (ii) agrees with the model proposed by Agur *et al.* [24]. As a consequence, we can write in absence of therapy

$$V' = P\left(\frac{K}{V}\right)V - \delta\left(\frac{K}{V}\right)V, \tag{1}$$

$$K' = K\left[\beta\left(\frac{K}{V}\right) - \psi(V) - \mu\right], \tag{2}$$

where $P(u)$ is the (specific) proliferation rate of the tumor with $P(0)=0$, $P'(u)>0$, and $P(+\infty)<\infty$; $\delta(u)$ is the apoptosis rate with $\delta'(u)<0$ and $\delta(+\infty)=0$; $\beta(u)$ is the proliferation rate of the vessels with $\beta(0)\leq+\infty$, $\beta'(u)<0$, and $\beta(+\infty)=0$; $\psi(V)$ represents the vessels loss due to the possible accumulation into the tumor of endogenous inhibitory factors secreted by the tumor cells, and μ represents the natural loss of vessels. We prescribe $P(1)=\delta(1)$ so that at the equilibrium $K_e/V_e=1$.

As an example of possible expressions of the net proliferation rate $F(u)=P(u)-\delta(u)$ we may consider the generalized logistic: $F(u)=\alpha(1-u^{-\nu})$, $\nu>0$. The function $\beta(u)$ may include power laws $\beta(u)=bu^{-w}$, $w>0$, functions such as $\beta(u)=\beta_M/(1+ku^n)$, $n\geq1$, i.e., Hill functions in the variable u^{-1}, and combinations of the above two expressions: $\beta(u)=\beta_1u^{-w}+\beta_2/(1+ku^n)$. The power law with $w=1$ yields $K\beta(K/V)=bV$, as proposed by Hahnfeldt *et al.* [18]. Concerning the function ψ, we recall that $\psi(V)=dV^{2/3}$ has been assumed in [18].

The model predicts, as it is easy to show, that the system has a unique equilibrium point, which is globally attractive.

The antiproliferative or the cytotoxic efficacy of a blood-born agent on the tumor cells will depend on its actual concentration at the cell site, and thus it will be influenced by the geometry of the vascular network and by the extent of blood flow. The efficacy of a drug will be higher if vessels are close each other and sufficiently regular to permit a fast blood flow; it will be lower if vessels are distanced or irregular and tortuous so to hamper the flow. To represent simply these phenomena, we assume, as in [9], that the drug action to be included in Eq. (1) is dependent on the vessel density, i.e., in our model on the ratio $\rho=K/V$. If $\vartheta(t)$ is the concentration of the agent in blood, we assume that its effectiveness is modulated by an unimodal function $\gamma(\rho)$ with $\gamma(0)=0$, and γ increasing for ρ small and decreasing for large ρ after having reached a unique absolute maximum.

As far as the measure units are concerned, we shall assume that volumes are measured in cubic millimeters, the time is measured in days and that the concentration of the agent in blood is appropriately nondimensionalized. In order to make simpler the notation, we shall uniquely denote the temporal units.

III. ANTIPROLIFERATIVE DRUGS

In case of delivering of an antiproliferative agent, Eq. (1) has to be modified by including in it a multiplicative factor $0<Z<1$ that expresses the drug-induced reduction of the proliferation:

$$V' = Z\left(\frac{K}{V};\vartheta(t)\right)P\left(\frac{K}{V}\right)V - \delta\left(\frac{K}{V}\right)V, \tag{3}$$

where $Z(\rho;\vartheta)$ is a decreasing function with respect to the variable ϑ and such that in absence of therapy the normal proliferation is unaffected, i.e., $Z(\rho;0)=1$. According to the above assumption, the dependence of Z on ρ and ϑ will be expressed through the product $\gamma(\rho(t))\vartheta(t)$, and an example might be a function like:

$$Z(\rho(t);\vartheta(t)) = \frac{H_{50}}{H_{50}+\gamma(\rho(t))\vartheta(t)}.$$

In the case of constant continuous infusion (for example, realized for drugs with small clearance rate constant by a frequent delivery at small doses so that the blood drug concentration can be considered constant with good approximation) it is $\vartheta(t)=C$, and by setting $V'=0$, equilibrium values for the ratio ρ are determined by the equation

$$A(\rho) = J(\rho;C), \tag{4}$$

where $A(\rho)=P(\rho)/\delta(\rho)$ and $J(\rho;C)=1/Z(\rho;C)$. Note that $A(\rho)$ is an increasing function of ρ, whereas $J(\rho;C)$ is an unimodal function of ρ. It is easy to verify that Eq. (4) for $C>0$ has $n\geq 1$ solutions: $1<\rho_1(C)<\rho_2(C)<\cdots<\rho_n(C)$. Provided that $\beta(\rho_i(C))-\mu>0$, the equation $K'=0$ has the unique positive solution:

$$V_i(C) = \psi^{-1}\{\beta[\rho_i(C)] - \mu\}.$$

Of course, this suggests that if it exists C^* such that $\beta(\rho_1(C^*))-\mu=0$, then for $C>C^*$ there is tumor eradication. However, since μ is usually small, the eradication would be only possible for very large values of C. If $C<C^*$, then there are $m\leq n$ co-existing equilibria $E_i=(V_i,K_i)$. It is easy to show that the condition $A'(\rho_i)>\partial_\rho J(\rho_i;C)$ guarantees the local stability of E_i, which, on the contrary is unstable if $A'(\rho_i)<J'(\rho_i)$.

IV. CYTOTOXIC DRUGS

In case of cytotoxic drugs, Eq. (1) will be modified by adding the logarithmic-kill term $\gamma(\rho)\vartheta(t)V(t)$ but also Eq. (2) has to be modified since often cytotoxic agents also disrupt the vessels (see [11] and references therein), leading to the following model (proposed in [9]):

$$V' = V\left[F\left(\frac{K}{V}\right) - \gamma\left(\frac{K}{V}\right)\vartheta(t)\right], \tag{5}$$

$$K' = K\left[\beta\left(\frac{K}{V}\right) - \psi(V) - \mu - \chi\vartheta(t)\right], \tag{6}$$

where: $F(\rho)=P(\rho)-\delta(\rho)$ and $\chi\geq 0$.

In case of constant continuous infusion $\vartheta(t)=C$, we have [9] $n\geq 1$ equilibrium vessel densities $\rho_i(C)$, whose corresponding equilibrium volumes $V_i(C)$ are given by

$$V_i(C) = \psi^{-1}\{\beta[\rho_i(C)] - \mu - \chi C\},$$

provided, of course, that $M(C;\chi)=\beta(\rho_i(C))-\mu-\chi C>0$. Thus, also here there is a threshold drug level C^*, defined by $M(C;\chi)=0$, and such that $C>C^*$ implies tumor eradication. We note that the main difference with the tumor response to antiproliferative agents is that now, if $\chi>0$, the eradication is more easy to be reached, whereas if $\chi=0$ also in this case the eradication is difficult or impossible. The vessel-disrupting action of a chemotherapic agent so appears very important for the cure.

V. HYSTERESIS BIFURCATION

Let us assume that an antiproliferative drug is delivered through a constant continuous infusion therapy, $\vartheta(t)=C$, and let us set C as bifurcation parameter. Since

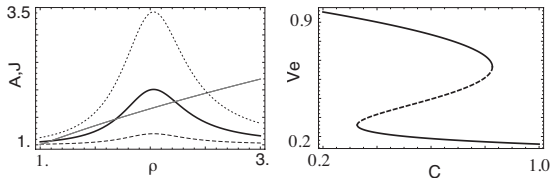

FIG. 1. Chemotherapy with an antiproliferating agent: occurrence of hysteresis bifurcation. Left panel: changing number of equilibria when varying C. In gray it is plotted $A(\rho)$, $J(\rho;C)$ is plotted in black. Dotted curve: $C=1.2$, one equilibrium point; thick curve: $C=0.5$, three equilibria; dashed curve: $C=0.1$, again a single equilibrium point. Right panel: bifurcation diagram, V_e (normalized) versus C. Dashed: unstable equilibria; solid: locally stable equilibria.

$$\frac{d\rho_i}{dC} = \frac{\partial_C J(\rho_i;C)}{A'(\rho_i) - \partial_\rho J(\rho_i;C)},$$

it holds that if i is *odd* then $\rho_i'(C)>0$, else if i is *even* then $\rho_i'(C)<0$. With standard methods [25] it is easy to show that this implies that if the number m, $m\leq n$, of coexisting equilibria is such that $m\geq 3$ then there is at least a hysteresis bifurcation, as shown in Fig. 1. In Fig. 1, $m=3$ and there are two bifurcations at $C=C_1$ (with a "jump" to a larger tumor size) at $C=C_2$ (with a jump to a smaller size). With reference to Fig. 1, it is $C_1\approx 0.327$ and $C_2\approx 0.827$. For the simulation of Fig. 1, we chose in model (2) and (3) $P(\rho)=\alpha\sqrt{\rho}/(a+\sqrt{\rho})$, $\delta(\rho)=\alpha\rho^{-0.5}/(a+1)$, $Z(\rho,C)=1/(1+\gamma(\rho)C)$, $\gamma(\rho)=\rho/\{1+[(\rho-\rho_m)/R]^2\}$, $\beta(\rho)=b/\rho$, $\psi(V)=dV^{2/3}$, and $\alpha=Ln(2)/1.5$, $a=1$, $\rho_m=2$, $R=0.35$, $b=4.64$, $d=0.01$, and $\mu=0$.

Similar bifurcating behavior is possible also in the case of delivering of a cytotoxic drug [9].

VI. BOUNDED NOISE-INDUCED TRANSITIONS: CONSTANT CONTINUOUS INFUSION THERAPIES

The hysteresis bifurcations, as that in Fig. 1, are characterized by the existence of two values of the bifurcation parameter such that infinitesimal changes in the parameter imply that the behavior of the solutions has a sudden change. This means that near those two points "the behavior of the system is extremely sensitive to any kind of perturbations… As a result the treatment.. requires that the fluctuations be explicitly incorporated into" the model [12,26].

These observations led Horsthemke and Lefever to define the theory of noise-induced transitions (NITs) [12] that study the phase transitions that are induced by zero-mean noises in nonequilibrium systems. Those transitions depend on characteristics of the noise, such as its variance, and have the effect of changing the nature of the stationary probability density functions of state variables, for example, from unimodal to bimodal or vice versa. Note that NITs are also called phenomenic stochastic bifurcations [27]. The NIT theory is of the utmost interest in biomedicine, since "in-vivo the environmental situations are… extremely complex and thus likely to present important fluctuations" [28]. For applications in the field of oncology see [28,29].

The properties of our models strongly suggest that also in the therapy of solid vascularized tumors such noise-induced transitions may occur because of the unavoidable presence of stochastic fluctuations in some parameters. The most remarkable point is that such transitions would correspond to sudden tumor relapses during therapy that are not due to genetic causes or to physical resistance.

Although these transitions may be caused by any of the parameters appearing in the equation modeling the dynamics of $V(t)$, here we are mainly interested on the fluctuations of the chemotherapy, since, in case of constant infusion therapy, $\vartheta(t)=C$ is an idealization. Thus, in order to give a more realistic description, we set

$$\vartheta(t) = C_m + \nu(t),$$

where $\nu(t)$ is a "noise" and C_m is the average value of the drug profile.

A classical approach consists in assuming that $\nu(t)$ is a Gaussian white noise, however this is, in our case, an inappropriate solution for two reasons. The first is linked to the functional form of our models, since the white noise might be used for the model of cytotoxic treatment, where the dependence of model [5,6] on $\vartheta(t)$ is linear, whereas it would have no sense in the case of model [2,3]. In fact it is well-known that when the dependence on a fluctuating parameter is nonlinear, this kind of noise cannot be used [12]. The second reason is more general, since, as stressed in [13] in analyzing a different kind of Gaussian noise-induced transition, the use of Gaussian noise leads to biological inconsistencies. Let us consider indeed model [5,6], and let us allow that $\nu(t)$ be a Gaussian noise.

Since the noise is unbounded, there will be a non-null probability that $\vartheta(t)<0$ in any arbitrary time interval Δt. In other words, there will be a non-null probability that a cytotoxic chemotherapy adds neoplastic cells to its target tumor, which is a nonsense. As a consequence, the Gaussian noise cannot be applied to investigate the effects of fluctuations in the concentration of a chemotherapic drug.

For these reasons, we shall assume that $\nu(t)$ is a bounded noise, i.e., that it exists a $B>0$ such that $|\nu(t)|<B<+\infty$, with $C_m-B>0$.

Although the literature devoted to the study of bounded noises is far more limited than that concerning the Gaussian noise, in recent years a number of interesting works have been published [15,16,30]. In particular, there is an increasing body of literature [14,15] (and references therein) focusing on the noises $\nu(t)$ that are defined by the following family of Langevin equations:

$$\nu'(t) = \tau^{-1}[-f(\nu) + \sqrt{2D}\zeta(t)]. \tag{7}$$

Equation (7) describes the velocity of a nonlinearly overdamped particle subject to a random force, where $\zeta(t)$ is a Gaussian noise with zero mean and unitary variance and $f(\nu)$ is a function that is continuous in $(-1,1)$, antisymmetric $f(-\nu)=-f(\nu)$, and such that $f(-B^+)=-\infty$, $f(B^-)=+\infty$. Of particular interest is the family of noises obtained choosing for $f(t)$ the form [15]

$$f_q(\nu) = \frac{\nu}{1-\dfrac{\tau(1-q)}{D}\dfrac{\nu^2}{2}}, \quad q<1. \tag{8}$$

Such non-Gaussian noises, which we shall call Tsallis noises, have zero mean and the following bounds:

$$-B<\nu(t)<B, \quad B=\sqrt{\frac{2D}{\tau(1-q)}}. \tag{9}$$

The stationary density of ν is

$$P_{TS}(\nu) = A(q,B)\left(1-\frac{\nu^2}{B^2}\right)_+^{1/(1-q)},$$

where $A(q,B)$ is a normalization constant. Note that the density at $\pm B$ is null. Finally, the autocorrelation is approximately given by [15]

$$\frac{\langle \nu(t)\nu(t+s)\rangle}{\langle \nu^2(t)\rangle} \approx \exp\left(-\frac{|s|}{\tau_{\rm corr}}\right),$$

where

$$\tau_{\rm corr} = \frac{2\tau}{5-3q}.$$

Another interesting class of noise is the so-called sine-Wiener noise [16,30], i.e., the process

$$\nu(t) = B\,\sin\left(\sqrt{\frac{2}{\tau_s}}w(t)\right), \tag{10}$$

where $w(t)$ is a Wiener process. The stationary density for this process is [30]

$$P_{SW}(\nu) = \frac{S}{\pi\sqrt{B^2-\nu^2}},$$

implying that $P_{SW}(\pm B)=+\infty$ and $\tau_{\rm corr}=\tau_s$.

Because of the structure of their stationary densities, the Tsallis and the sine-Wiener noises are somewhat complementary. A real noise may lie in between them, so we shall adopt in our simulations the assumption that the noise ν is generated by Eqs. (7) and (8) or by Eq. (10), and we shall use as main bifurcation value the bound B.

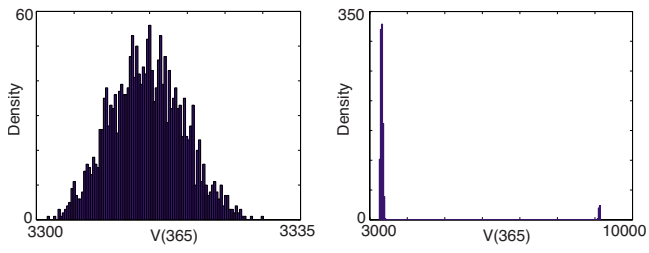

FIG. 2. (Color online) Constant continuous infusion chemotherapy with an antiproliferative agent whose blood profile is affected by Tsallis noise. Plot of the conditional probability density function of the random variable $V(365)$ (mm^3). Parameters: $C_m=0.36$, $\tau_{\rm corr}=0.5$ day, and $q=0.0$. Left panel: for $B=0.01$ the PDF is unimodal; right panel: for $B=0.06$ the PDF is bimodal.

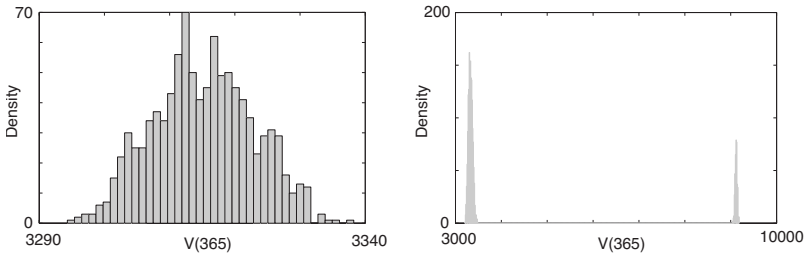

FIG. 3. Constant continuous infusion chemotherapy with an antiproliferative agent whose blood profile is affected by sine-Wiener noise. Plot of the conditional probability density function of the random variable $V(365)$ (mm^3). Parameters: $C_m=0.36$ and $\tau_{corr}=0.5$ day. Left panel: for $B=0.01$ the PDF is unimodal; right panel: for $B=0.06$ the PDF is bimodal.

VII. NUMERICAL SIMULATIONS OF CONSTANT INFUSION THERAPY

In this section we shall study numerically the qualitative changes of the conditional probability density function (PDF) of the tumor volume at time t_{ref}, namely the density Q defined by

$$Q(V,t_{ref};V_0,K_0)dV = \text{Prob}\{V < V(t_{ref}) < V + dV | (V,K)(0) = (V_0,K_0)\}.$$

With a slight abuse of notation we shall call such qualitative changes noise-induced transitions at time t_{ref}.

In all simulations (if not explicitly noted) we set $V(0)=3900$ and $K(0)=8000$, i.e., we chose an initial value belonging to the basin of attraction of the smaller equilibrium point of system (2) and (3) when $\vartheta(t)=C=0.36$, i.e., $V_e \approx 3315$. As reference time t_{ref}, we set $t_{ref}=365$ day.

A. Proliferation inhibiting agents

We start our numerical investigation by analyzing the tumor behavior in response to the delivering of an antiproliferative drug, whose blood concentration profile stochastically fluctuates around the average value C_m.

We performed our simulations by using the functions and parameters reported in Sec. V. In a first set of simulations we set $C_m=0.36$ and $\tau_{corr}=0.5$ day. In case of Tsallis noise with $q=0$, we observed a noise-induced transition at $B=B^* \approx 0.04$. For $B=0.01$ the PDF of tumor volume is unimodal (left panel of Fig. 2), whereas for $B=0.06$ the PDF is bimodal (right panel of Fig. 2). Similar patterns were observed with sine-Wiener noise (see Fig. 3).

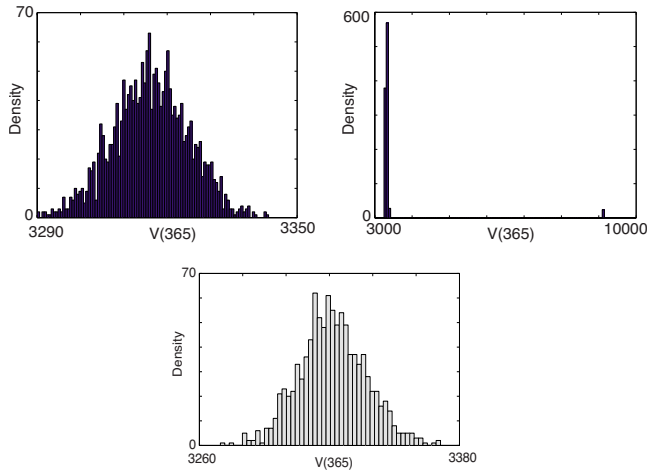

FIG. 4. (Color online) Effect of changing τ_{corr} of the noise affecting a constant continuous infusion therapy with an antiproliferative agent. $C_m=0.36$, noise amplitude $B=0.04$. Left panel: Tsallis noise with $q=0$ and $\tau_{corr}=0.1$ day: the PDF is unimodal, as it is for $\tau_{corr}=0.2$ day. Central panel: Tsallis noise with $q=0$ and $\tau_{corr}=1$ day: Right panel: sine-Wiener noise with $\tau_{corr}=0.07$ day: for larger values the PDF is bimodal. Tumor volumes in mm^3.

Our simulations evidenced that in case of Tsallis noise the effect of decreasing τ_{corr} is to reduce the extent of the NIT by increasing the B value needed for this phenomenon to happen, whereas by increasing τ_{corr} the onset of NIT is facilitated and there is a greater probability of escape from the low equilibrium. This is illustrated in Fig. 4, where we show that for $B=0.04$ and for $\tau_{corr}=0.1$ days there is no bimodality in the PDF (left upper panel), whereas the right upper panel of the same picture shows the bimodal PDF for $\tau_{corr}=1$ day. As far as the sine-Wiener noise is considered, the lower panel of Fig. 4 shows that in such a case to reverse the bimodality one has to use a quite smaller value of the correlation time.

Concerning the role of the initial conditions, we simulated a continuous therapy ($C_m=0.36$) affected by fluctuations modeled with a Tsallis noise with $q=0$, $\tau_{corr}=0.5$ day and $B=0.06$, setting $(V(0),K(0))=(390,800)$. Unlike the case with $(V(0),K(0))=(3900,8000)$, no transitions at one year were observed.

We also performed some simulations to asses the influence of the parameter q. The simulations suggest that the peak at the larger tumor volumes is decreasing with q, whereas the peak at the smaller volumes is increasing, and the transition can disappear (see Fig. 5).

Finally, to compare the above results with the effect of a deterministic pattern of disturbances, we performed some simulations by assuming a periodic oscillating therapy: $\vartheta(t)=C_m+B\sin(2\pi t/T_p)$. For values of $B=0.04$ and $C_m=0.36$, for which there is bimodality in the stochastic setting for τ_{corr} of the order of fractions of *days*, in the deterministic

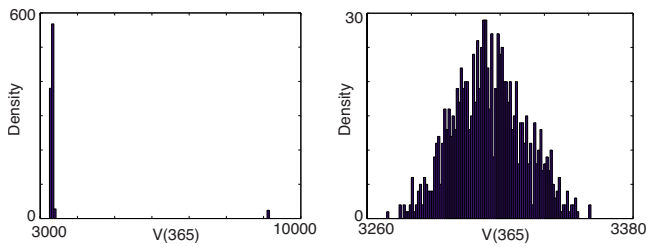

FIG. 5. (Color online) Effect of changing q in the Tsallis noise affecting a constant continuous infusion therapy with an antiproliferative agent. $C_m=0.36$, noise amplitude $B=0.04$ and $\tau_{corr}=1$ day. Left panel: $q=0$; right panel $q=0.8$. Tumor volumes in mm^3.

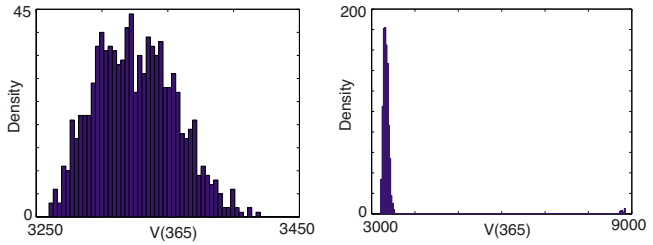

FIG. 6. (Color online) Constant continuous infusion chemotherapy with a cytotoxic agent, whose blood profile is affected by Tsallis noise. Plot of the conditional probability density function of the random variable $V(365)$ (mm^3). Parameters: $C_m=0.15$, $\tau_{corr}=0.5$ day, and $q=0.0$. Left panel: for $B=0.02$ the PDF is unimodal; right panel: for $B=0.036$ the PDF is bimodal.

case we obtained switches to the larger equilibrium only for huge values of the periods T_p, namely, for $T_p \approx 11$ month.

B. Cytotoxic agents

Here we report simulations of a chemotherapy based on a cytotoxic agent delivered in constant continuous infusion to a tumor having the following dynamic features [see model (5) and (6)]: $F(\rho)=[\ln(2)/1.5](1-\rho^{-0.5})$, $\beta(\rho)=4.64/\rho$, $\mu=0$, $\gamma(\rho)=1/\{1+[(\rho-2)/0.35]^2\}$ (slightly different from the one that was used for antiproliferative agents), and $\Psi(V)=0.01\ V^{2/3}$. With these values, there are two hysteresis bifurcations at $C_a \approx 0.133\,76$ and at $C_b \approx 0.2866$.

In the simulations we assumed an average drug profile $C_m=0.15$, whose associated equilibrium points are $E_1=(3323,6924)$, $U=(4053,7398)$ and $E_3=(8794,9577)$. Also here we used as initial condition $(V_0,K_0)=(3900,8000)$, which belongs to the basing of attraction of E_1.

In case of Tsallis noise with $q=0$ and $\tau_{corr}=0.5$ day, we observed a noise-induced transition for B slightly greater than 0.02. Indeed, for $B=0.02$ the PDF is unimodal (see Fig. 6), whereas at $B=0.036$ the PDF is bimodal. Similar patterns are observed in case of sine-Wiener noise (see Fig. 7).

Also in this case our simulations showed that the effect of decreasing τ_{corr} is to reduce the occurrence of NITs by increasing the B value needed for this phenomenon to happen, whereas by increasing τ_{corr} the onset of NIT is facilitated. This is illustrated in Fig. 8, where we show the case of therapy with $C_m=0.15$ and Tsallis noise with $B=0.05$, $q=0$, and $\tau_{corr}=0.5$ day (left panel) and $\tau_{corr}=1$ day (right panel). Similar results were obtained in case of sine-Wiener noise (not shown).

VIII. BOLI-BASED THERAPIES

Although continuous infusion therapies are increasingly important from the biomedical point of view, and although they allow interesting analytical inferences, the majority of therapies are scheduled by means of periodic delivery of boli of an antitumor agent. Thus, in the hypothesis that the agent has monoexponential pharmacokinetics, we have that the drug concentration profile is ruled by the following impulsive differential equation:

$$\vartheta' = -a\vartheta, \tag{11}$$

$$\vartheta(nT^+) = \vartheta(nT^-) + S, \quad n=0,1,2,\ldots, \tag{12}$$

where S is the ratio between the delivered dose and the distribution volume W of the agent, T is the constant interval between two consecutive boli, and a is the clearance rate constant (also called elimination rate [31]).

We start our analysis by examining the major stochastic factors that could perturb system (11) and (12). Although the delivered doses might, in principle, not be constant, nowadays their dosing is quite accurate. For this reason we shall disregard this source of fluctuations, and instead, we shall focus on three phenomena of relevance in clinical oncology: (i) stochastic fluctuations in the clearance of the drug [32] that are due to changes that affect the physiologic mechanisms of drug elimination by the body. The reasons underlying this kind of noises are due to manifold factors of disparate endogenous and exogenous nature, including, for example, the meals that may be considered among the major perturbations [33]; (ii) the scheduling itself of the drug is source of irregularities since the times of delivering may be subject to unpredictable delays and anticipations [34]; and (iii) stochastic fluctuations of the distribution volume.

A. Stochastic fluctuations in the clearance rate

Equations (11) and (12) are here modified by considering a stochastic time-varying clearance rate

$$a(t) = a_m + \nu_a(t),$$

where $\nu_a(t)$ is a bounded noise defined by the stochastic Eq. (7) such that $a_m+\nu_a(t)>0$. Moreover, we suppose that the pair (a_m,T) is such that, in absence of noise, the tumor size asymptotically oscillates around a low value, i.e., in the deterministic setting there is no jump to large tumor size. Note that, given the structure of the pharmacokinetic equations, the noise here is "filtered."

We started by simulating a cytotoxic therapy characterized by $a_m=1/7$ day^{-1}, $T=6$ day, and in the deterministic case by $C_m=0.18$ so that the delivered bolus is $S=Ta_mC_m=0.154$. The initial conditions of the tumor were $V(0)=3900$ and $K(0)=8000$. In case of Tsallis noise with $q=0$ and $\tau_{corr}=0.5$ day, we observed the onset of NIT at B

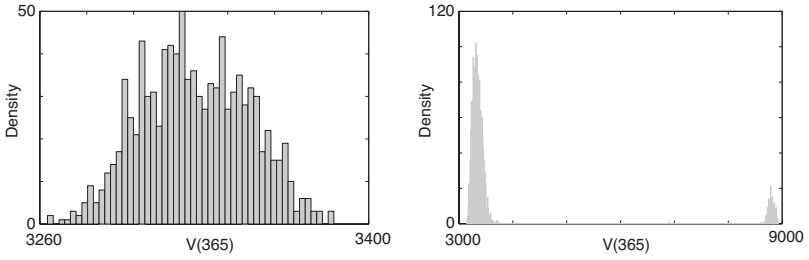

FIG. 7. Constant continuous infusion chemotherapy with a cytotoxic agent whose blood profile is affected by sine-Wiener noise. Plot of the conditional probability density function of the random variable $V(365)$ (mm^3). Parameters: $\tau_{corr}=0.5$ day, $C_m=0.15>C_1$. As in the Tsallis noise case, for $B=0.02$ (left panel) the PDF is unimodal. For $B=0.036$ the PDF is bimodal.

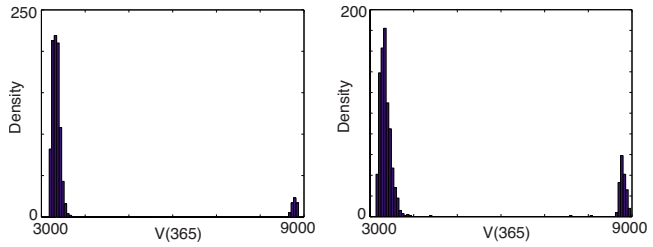

FIG. 8. (Color online) Effect of changing τ_{corr} days of the Tsallis noise affecting a constant continuous infusion therapy with a cytotoxic agent. $C_m=0.15$, noise amplitude $B=0.05$, and $q=0$. Left panel: $\tau_{\text{corr}}=0.5$ day; right panel: $\tau_{\text{corr}}=1$ day. Tumor volumes in mm^3.

$\approx 0.1a_m$. The bimodal PDF of the random variable $V(365)$ for $B=0.2a_m$ is shown in the right upper panel of Fig. 9, whereas in the left upper panel it is shown the unimodal PDF for $B=0.08a_m$. In case of sine-Wiener noise, the density is bimodal also for $B=0.11a_m$ (not shown).

In a second simulation, we changed the scheduling passing to a more time dense (metronomic [36]) scheduling, without decreasing the total quantity of delivered drug. Namely, we halved both the period, $T=3$, and the dose of the bolus, $S=0.077$. The effect obtained is the almost total suppression of the bimodality in the PDF at $B=0.2a_m$, as illustrated in the lower panel of Fig. 9. Suppression of the bimodality was also observed in case of Sine-Wiener noise where at $B=0.2a_m$ the density turned to be unimodal.

This result suggests that metronomic scheduling might have not only the beneficial effects of reducing the side-effects as well as of being more effective in reducing the tumor mass, but they also might reduce the possibility of relapse, here suggested, due to the nonlinear interplay between tumor and vessels.

B. Stochastic fluctuations in the delivery times

Here we shall assume that the clearance rate and the delivered dose are constant, whereas the time of delivering is slightly irregular, so that the initial conditions prescribed by Eq. (12) become

$$\vartheta(T_n^+) = \vartheta(T_n^-) + S, \tag{13}$$

$$T_n = nT_m + \nu_n, \quad n = 0,1,2,\ldots, \tag{14}$$

where ν_n is a discrete-time stochastic process such that $\langle \nu_n \rangle = 0$ and $T_m + \nu_n > 0$. Thus, $\langle T_n \rangle = nT_m$.

In our simulations of a citotoxic therapy we have supposed that $\{\nu_n\}$ are independent random variables uniformly distributed in the interval $[-A, A]$. The simulations showed that noise-induced transitions occur for $A \geq 0.33$ day.

C. Stochastic fluctuations in the distribution volume

In this case we shall consider that the clearance rate, the delivered dose and the delivery times are not affected by fluctuations, whereas the distribution volume $W(t)$ is stochastically changing according a law of the type:

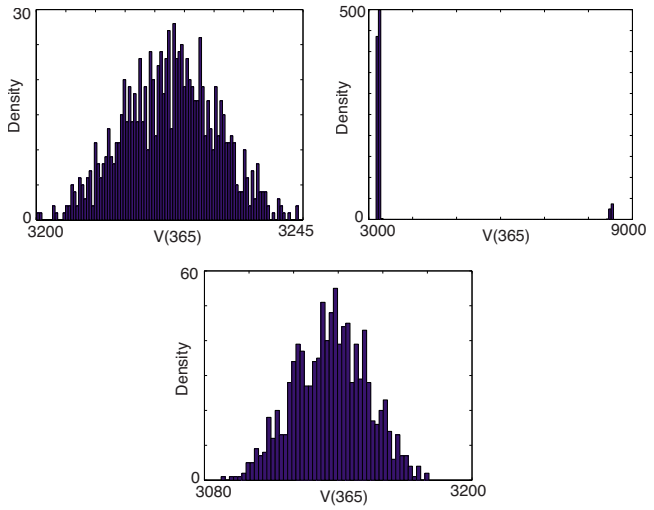

FIG. 9. (Color online) Stochastically varying clearance rate $a(t)=a_m+\nu(t)$ of a cytotoxic agent. Parameters: $T=6$, $a_m=1/7$, and $S=0.154$. $\nu(t)$ is a Tsallis noise with $q=0$ and $\tau_{\text{corr}}=0.5$ day. Upper left panel: plot of the PDF at one year for $B=0.08a_m$. Upper right panel: plot of the bimodal PDF for $B=0.2a_m$. Lower panel: suppression of the bimodality for $B=0.2a_m$ by metronomic scheduling with $T=3$ and $S=0.077$. Tumor volumes in mm^3.

$$W(t) = W_m[1 + \nu(t)],$$

where $\nu(t)$ is a bounded noise such that $\nu(t) > -1$. As a consequence, the initial conditions prescribed in Eq. (12) become:

$$\vartheta((nT)^+) = \vartheta((nT)^-) + \frac{S}{1 + \nu(nT)}. \tag{15}$$

Our simulations of the cytotoxic therapy, which—as suggested by the nature of the phenomenon under study—assumed large autocorrelation times ($\tau_{\text{corr}} \approx 30$ day), suggest that both considering $\nu(t)$ being a sine-Wiener noise (see Fig. 10) or a Tsallis noise (results not shown) a noise-induced tumor regrowth is possible.

IX. ALTERNATE CONTINUOUS INFUSION THERAPIES

In this section, we shall briefly analyze a class of therapies that is intermediate between the constant continuous infusion therapy analyzed in Sec. VII and the boli-based therapies studied in Sec. VIII. We refer to periodic therapies in which intervals of constant infusion alternate with intervals where no therapy is delivered. Indicating with T as the period of the therapy and with u as the fraction of the period when the constant infusion is delivered, we may set

$$\vartheta(t) = C_*\{1 - \text{Heaviside}[\text{mod}(t,T) - uT]\}. \tag{16}$$

Note that $\langle \vartheta(t) \rangle = uC_*$.

Our simulations show that also under this kind of drug scheduling noise-induced transitions may onset. For example, setting $T=7$, $u=2/7$ (i.e., 2 day of therapy followed by 5 day of rest), $C_*=0.675$ and $\tau_{\text{corr}}=0.5$, we observed that in case of Tsallis noise with $q=0$ and $B=0.1$ there is an

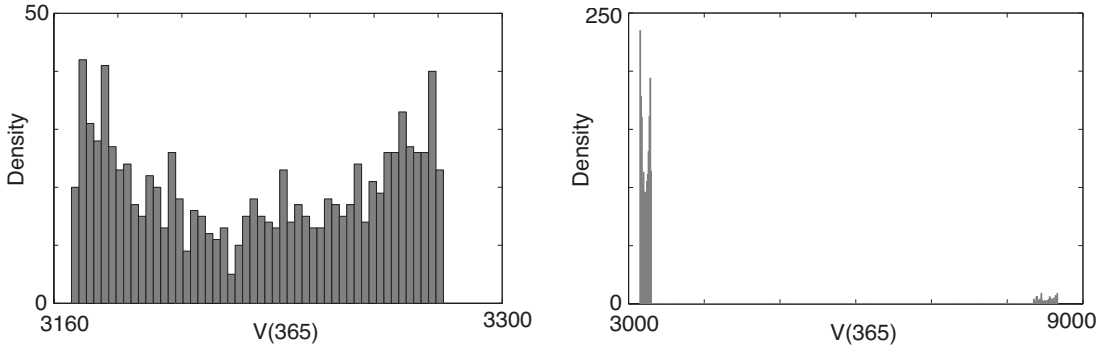

FIG. 10. Therapy with a cytotoxic agent delivered at times $T_n=nT$, where $T=6$ day, with distribution volume affected by sine-Wiener noise with $\tau_{\text{corr}}=30$ day. Parameter of the $\vartheta(t)$: $C_m=0.18$, $a=1/7$, and $S=TaC_m$. Initial conditions $V(0)=3900$ and $K(0)=8000$. For $B=0.07$ the distribution is unimodal although horn-shaped (left panel), whereas the bimodality is present for $B=0.09$ (right panel). Tumor volumes in mm^3.

unimodal PDF of tumor volume located at small tumor size, whereas for $B=0.1575$ the density is bimodal and the peak at the large tumor size is bigger than the other maximum (left panel of Fig. 11). Also by using a sine-Wiener noise with $B=0.09$ (and the same autocorrelation time), the PDF is bimodal, with large prevalence of the second maximum (right panel of Fig. 11).

X. CONCLUDING REMARKS

In this work, we have presented an analysis of the possible onset of resistance to chemotherapy in vascularized tumors induced by the effects of bounded noises. The noises model stochastic fluctuations in the time course of the concentration of the agents in blood. Their interplay with the intrinsic multistability of the system may generate noise-induced transitions. The multistability in our model origins from the drug effectiveness that is dependent on the vessel density.

The assumption of boundedness for the noise, in contrast with the use of Gaussian noises, allows a more faithful modelization of real biological phenomena and allows us to avoid artifact results deriving from the temporary negativity of parameters. Moreover, in nonlinear systems of the form $X'=f(X;p)$, where p is a parameter, in the vast majority of cases the velocity $f(X;p)$ of the state variables depends nonlinearly on the parameters, and this fact precludes the possibility of modeling the fluctuations of p by means of Gaussian white noise, whereas such fluctuations are perfectly modelizable by means of bounded noises.

We started our work by defining a mathematical model of antimitotic therapy in solid tumors, where the effectiveness γ of the delivered agent is unimodally dependent on a variable, ρ, summarizing the average vessel density, and where the growth rate of the tumor is nonlinearly dependent on the drug concentration in blood. We concisely studied the system and showed that it may exhibit multistability and hysteresis bifurcations, similarly to what we had previously found in a model of cytotoxic chemotherapy [9]. The assumption of unimodality for the function γ was based on the biological background illustrated in the Introduction. We stress, however, that multistability may also be retained in case of increasing and saturating $\gamma(\rho)$.

These bifurcations, novel in the context of nonimmunogenic tumors, suggested the possible onset of noise-induced

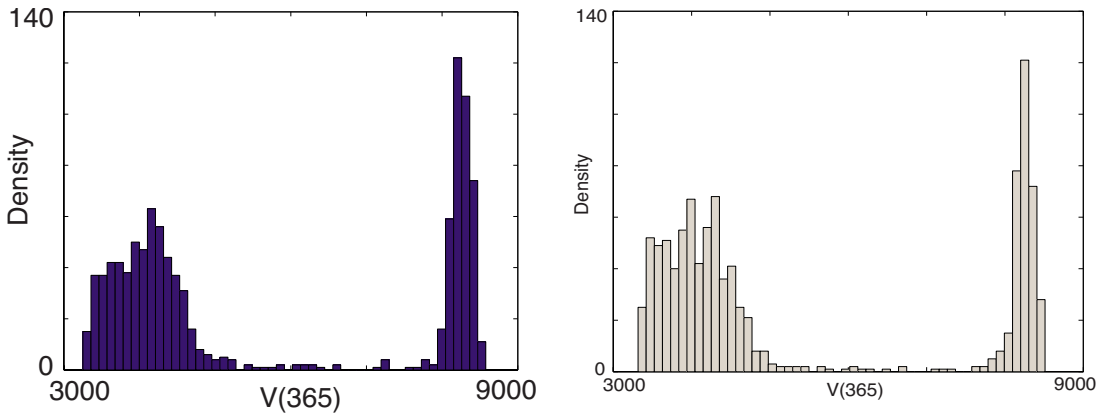

FIG. 11. (Color online) Therapy with a cytotoxic agent delivered by following an alternate constant infusion or rest scheduling, as described by Eq. (16) with $T=7$ day, $u=2/7$, and $C_*=0.675$. Effect of Tsallis and sine-Wiener noises are shown. In both cases: $\tau_{\text{corr}}=0.5$ day. Left panel: NIT induced by a Tsallis noise with $q=0$ and $B=0.1575$; right panel: sine-Wiener noise with $B=0.09$. Initial conditions: $V(0)=3900$ and $K(0)=8000$. Tumor volumes in mm^3.

transitions that might represent a nongenetic and nondiffusion-related path for resistance to chemotherapy in the class of tumors under study. We numerically approached the study of the onset of such resistance by means of a series of targeted numerical simulations.

Our simulations suggest the possibility of dangerous transitions in case of therapies potentially able of leading to a stable disease, in a variety of biologically meaningful scenarios, which may be divided in two classes: (i) delivery-related fluctuations (continuous infusion therapy and bolus-based therapy irregularly delivered) and (ii) stochasticity of pharmacokinetics (fluctuations in the clearance rate constant or in the distribution volume).

As far as the control of the effects of fluctuations in the drug clearance rate is concerned, in order to reduce the possibility of relapse (i.e., of noise-induced transitions) our simulations suggest a possible beneficial option in the so called metronomic scheduling of the therapeutical agent. Moreover, our simulations of the case of irregular intake of the therapy show that a rigorous adherence to the prescribed scheduling can avoid therapeutic failures. More difficult appears the control of other fluctuation sources such as the distribution volume of the drug, which should probably require a feedback adaptation of the delivered dose.

Finally, the proposed model might be extended to include dose saturation effects by multiplying $\gamma(\rho)$, e.g., in Eq. (5), by a saturating function of $\vartheta(t)$. However, let us consider a sharp saturation at $\vartheta=\vartheta_{cr}$. If $\langle\vartheta(t)\rangle$ is such that $\langle\vartheta(t)\rangle+B<\vartheta_{cr}$, then $\vartheta(t)$ is fully in the linear zone and the presence or absence of noise-induced transition is not influenced by the saturation. On the contrary, if $\langle\vartheta\rangle+B>\vartheta_{cr}$ and $\langle\vartheta\rangle-B<\vartheta_{cr}$ then the onset of a noise-induced transition will be "helped" by the saturation, because the largest positive fluctuations of ϑ are now less effective in reducing the tumor volume.

Summarizing, we may say that the possible multistability of the chemotherapy in solid tumors, suggested by our model, calls for a more effort in monitoring the drug delivery, also in view of therapy optimization. We also stress that we have selected only some of the major causes of fluctuations during therapy. Among the chronobiological phenomena that we have not considered, a prominent role is played by the circadian oscillations [35]. Indeed, we shall devote a follow up work to the influence of those rhythms on the effectiveness of chemotherapy, where we shall also investigate for the possible emergence of stochastic resonances [37], as a result of the interaction between circadian oscillations and the above illustrated stochasticity of therapies.

ACKNOWLEDGMENTS

The work of A.d'O. was conducted within the framework of the EU Integrated Project Advancing Clinico-Genomic Trials on CancerACGT. This work was also partially supported by MIUR Italy, Grant No. PRIN 2008RSZPYY. We wish to thank two anonymous referees, whose suggestions helped us in significantly improve this work.

[1] D. Tüerk and G. Szakács, Curr. Opin. Drug Discovery Dev. **12**, 246 (2009); M. Kimmel and A. Swierniak, Lect. Notes Math. **1872**, 185 (2006).
[2] J. K. Tunggal, D. S. M. Cowan, H. Shaikh, and I. F. Tannock, Clin. Cancer Res. **5**, 1583 (1999); D. S. M. Cowan and I. F. Tannock, Int. J. Cancer **91**, 120 (2001); R. K. Jain, Annu. Rev. Biomed. Eng. **1**, 241 (1999).
[3] R. K. Jain, J. Controlled Release **74**, 7 (2001); N. S. Wijeratne and K. A. Hoo, Cell Prolif **40**, 283 (2007).
[4] P. Carmeliet and R. K. Jain, Nature (London) **407**, 249 (2000).
[5] A. R. Tzafriri, A. D. Levin, and E. R. Edelman, Cell Prolif **42**, 348 (2009).
[6] P. A. Netti, D. A. Berk, M. A. Swartz, A. J. Grodzinsky, and R. K. Jain, Cancer Res. **60**, 2497 (2000).
[7] J. P. Cosse, M. Ronvaux, N. Ninane, M. J. Raes, and C. Michiels, Neoplasia **11**, 976 (2009).
[8] R. P. Araujo and D. L. S. McElwain, J. Theor. Biol. **228**, 335 (2004).
[9] A. d'Onofrio and A. Gandolfi, J. Theor. Biol. **264**, 253 (2010).
[10] J. W. Baish, Y. Gazit, D. A. Berk, M. Nozue, L. T. Baxter, and R. K. Jain, Microvasc. Res. **51**, 327 (1996).
[11] R. S. Kerbel and B. A. Kamen, Nat. Rev. Cancer **4**, 423 (2004).
[12] W. Horstemke and H. Lefever, *Noise-Induced Transitions in Physics, Chemistry, and Biology* (Springer, Heidelberg, 2007).
[13] A. d'Onofrio, in *Aspects of Mathematical Modeling*, edited by E. Venturino and R. H. Hoskins (Birkhauser, Zurich, 2006); Appl. Math. Lett. **21**, 662 (2008).
[14] A. d'Onofrio, Phys. Rev. E **81**, 021923 (2010).
[15] M. A. Fuentes, R. Toral, and H. S. Wio, Physica A **295**, 114 (2001); M. A. Fuentes, H. S. Wio, and R. Toral, *ibid.* **303**, 91 (2002); J. A. Revelli, A. D. Sanchez, and H. S. Wio, Physica D **168–169**, 165 (2002); H. S. Wio and R. Toral, *ibid.* **193**, 161 (2004).
[16] R. B. Bobryk and A. Chrzeszczyk, Physica A **358**, 263 (2005).
[17] J. Folkman, Adv. Cancer Res. **43**, 175 (1985); G. D. Yancopoulos, S. Davis, N. W. Gale, J. S. Rudge, S. J. Wiegand, and J. Holash, Nature (London) **407**, 242 (2000).
[18] P. Hahnfeldt, D. Panigrahy, J. Folkman, and L. Hlatky, Cancer Res. **59**, 4770 (1999); R. K. Sachs, L. R. Hlatky, and P. Hahnfeldt, Math. Comput. Modell. **33**, 1297 (2001).
[19] M. S. O'Reilly *et al.*, Cell **79**, 315 (1994); M. S. O'Reilly *et al.*, *ibid.* **88**, 277 (1997); S. Ramanujan *et al.*, Cancer Res. **60**, 1442 (2000); J. Folkman, Annu. Rev. Med. **57**, 1 (2006).
[20] A. d'Onofrio and A. Gandolfi, Math. Biosci. **191**, 159 (2004).
[21] A. d'Onofrio and A. Gandolfi, Appl. Math. Comput. **181**, 1155 (2006); A. d'Onofrio, A. Gandolfi, and A. Rocca, Cell Prolif **42**, 317 (2009).
[22] A. d'Onofrio and A. Gandolfi, IMA J. Math. Appl. Med. Biol. **26**, 63 (2008).
[23] B. Capogrosso Sansone, M. Scalerandi, and C. A. Condat, Phys. Rev. Lett. **87**, 128102 (2001); M. Scalerandi, B. Capo-

grosso Sansone, and C. A. Condat, Phys. Rev. E **65**, 011902 (2001); M. Scalerandi and B. Capogrosso Sansone, Phys. Rev. Lett. **89**, 218101 (2002); M. Scalerandi and F. Peggion, Phys. Rev. E **66**, 031903 (2002); L. Arakelyan, V. Vainstein, and Z. Agur, Angiogenesis **5**, 203 (2002); B. R. Stoll *et al.*, Blood **102**, 2555 (2003); D. Tee and J. DiStefano III, J. Cancer Res. Clin. Oncol. **130**, 15 (2004); M. Kohandel *et al.*, Phys. Med. Biol. **52**, 3665 (2007); M. A. J. Chaplain, in *A Survey of Models for Tumor-Immune System Dynamics*, edited by J. A. Adam and N. Bellomo (Birkhauser, Boston, 1997); A. R. A. Anderson and M. A. J. Chaplain, Bull. Math. Biol. **60**, 857 (1998); E. De Angelis and L. Preziosi, Math. Models Meth. Appl. Sci. **10**, 379 (2000); T. L. Jackson, J. Math. Biol. **44**, 201 (2002); C. J. W. Breward, H. M. Byrne, and C. E. Lewis, Bull. Math. Biol. **65**, 609 (2003); U. Forys, Y. Kheifetz, and Y. Kogan, Math. Biosci. Eng. **2**, 511 (2005); P. G. Kevrekidis, N. Whitaker, D. J. Good, and G. J. Herring, Phys. Rev. E **73**, 061926 (2006).

[24] Z. Agur, L. Arakelyan, P. Daugulis, and Y. Ginosar, Discrete Contin. Dyn. Syst., Ser. B **4**, 29 (2004).

[25] J. K. Hale and H. Kocak, *Dynamics and Bifurcations* (Springer, Heidelberg, 1991).

[26] W. Horstemke and R. Lefever, Phys. Lett. **64A**, 19 (1977).

[27] L. Arnold, *Random Dynamical Systems* (Springer, Heidelberg, 1997).

[28] R. Lefever and H. Horsthemke, Bull. Math. Biol. **41**, 469 (1979).

[29] A. d'Onofrio and I. P. M. Tomlinson, J. Theor. Biol. **244**, 367 (2007).

[30] G. Q. Cai and C. Wu, Probab. Eng. Mech. **19**, 197 (2004); G. Q. Cai and Y. K. Lin, Phys. Rev. E **54**, 299 (1996).

[31] A. Rescigno, Pharm. Res. **35**, 363 (1997).

[32] P. Lansky, V. Lanska, and M. Weiss, J. Controlled Release **100**, 267 (2004); S. Ditlevsen and A. de Gaetano, Bull. Math. Biol. **67**, 547 (2005).

[33] C. Csajka and D. Verotta, J. Pharmacokin. Pharmacodyn. **33**, 227 (2006).

[34] J. Li and F. Nekka, J. Pharmacokin. Pharmacodyn. **34**, 115 (2007).

[35] B.-B. C. Youan, J. Controlled Release **98**, 337 (2004).

[36] T. Browder, C. E. Butterfiled, B. M. Kraling, B. Shi, B. Marshall, M. S. O'Reilly, and J. Folkman, Cancer Res. **60**, 1878 (2000); P. Hahnfeldt, J. Folkman, and L. Hlatky, J. Theor. Biol. **220**, 545 (2003).

[37] L. Gammaitoni, P. Haenggi, P. Jung, and F. Marchesoni, Rev. Mod. Phys. **70**, 223 (1998).