Monitoring noise-resonant effects in cancer growth influenced by external fluctuations and periodic treatment

Alessandro Fiasconaro\textsuperscript{123} a, Anna Ochab–Marcinek\textsuperscript{24}, Bernardo Spagnolo\textsuperscript{3}, and Ewa Gudowska–Nowak\textsuperscript{12}

\textsuperscript{1} Mark Kac Complex Systems Research Center, Jagellonian University, Reymonta 4, 30-059 Kraków, Poland.
\textsuperscript{2} Marian Smoluchowski Institute of Physics, Jagellonian University, Reymonta 4, 30-059 Kraków, Poland.
\textsuperscript{3} Dipartimento di Fisica e Tecnologie Relative and CNISM, Group of Interdisciplinary Physics, Università di Palermo, Viale delle Scienze, I-90128 Palermo, Italy.
\textsuperscript{4} Institut für Physik, Universität Augsburg, Universitätsstraße 1, 86135 Augsburg, Germany.

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Abstract. In the paper we investigate a mathematical model describing the growth of tumor in the presence of immune response of a host organism. The dynamics of tumor and immune cells is based on the generic Michaelis-Menten kinetics depicting interaction and competition between the tumor and the immune system. The appropriate phenomenological equation modeling cell-mediated immune surveillance against cancer is of the predator-prey form and exhibits bistability within a given choice of the immune response-related parameters. Under the influence of weak external fluctuations, the model may be analyzed in terms of a stochastic differential equation bearing the form of an overdamped Langevin-like dynamics in the external quasi-potential represented by a double well. We analyze properties of the system within the range of parameters for which the potential wells are of the same depth and when the additional perturbation, modeling a periodic treatment, is insufficient to overcome the barrier height and to cause cancer extinction. In this case the presence of a small amount of noise can positively enhance the treatment, driving the system to a state of tumor extinction. On the other hand, however, the same noise can give rise to return effects up to a stochastic resonance behavior. This observation provides a quantitative analysis of mechanisms responsible for optimization of periodic tumor therapy in the presence of spontaneous external noise. Studying the behavior of the extinction time as a function of the treatment frequency, we have also found the typical resonant activation effect: For a certain frequency of the treatment, there exists a minimum extinction time.

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1 Introduction

Although cancer is a leading cause of death in the world, it is still little known about the mechanisms of its growth and destruction. Surgery, chemo- and radio-therapies play key roles in treatment, but in many cases they do not represent a cure. Even when patients experience tumor regression, later relapse can occur. The need to address more successful treatment strategies is clear. Currently, efforts are made to investigate, among others, the methods of adoptive cellular immunotherapy \cite{1,2}. These methods of tumor treatment are based on the use of the injection of cultured immune cells, which have anti-tumor reactivity, into the tumor-bearing host. Therefore, a detailed theoretical study on the mechanisms of interaction between tumor tissue and immune system is necessary for planning efficient strategies of treatment \cite{3,4,5,6,7,8,9,10,11,12,13,14,15,16,17,18,19,20,21,22,23,24}. The immune response against the antigens generated by certain tumors, may be mediated by so called effector cells such as T-lymphocytes, macrophages or natural killer cells. The process of damage to tumor proceeds via infiltration of the latter by the specialized cells which subsequently develop a cytotoxic activity against the cancer cell-population. The series of cytotoxic reactions between the immune cells and the tumor tissue may be considered to be well approximated \cite{34,56,78} by a saturating, enzymatic-like process whose time evolution equations are similar to the standard Michaelis-Menten kinetics: The development of tumor tissue and its reaction to immune response can be described in terms of a predator-prey model \cite{37,89,101,11,12,13,14,15,16,17,18,19,23,24}. The population of tumor cells plays the role of "preys", and immune cells act as "predators". The activity of the predator in a certain territory, or, in this case, the activity of immune cells in tissue, resemble the mode of action of enzymes or catalysts in a chemical reaction, where the enzymes transform substrates in a continuous manner without destroying themselves. The constant immune cell population is assumed to act in a similar way, binding the tumor cells and releasing them unable to replicate.

The network of tumor-immune system interactions is subjected to random fluctuations. The growth rate of tumor tissue is affected by many environmental factors, e.g. the degree of vascularization of tissues, the supply of oxygen, the supply of nutrients, the immunological state of the host, chemical agents,
temperature, radiations, etc. As a result of this complexity, it is unavoidable that in the course of time the parameters of the system undergo random variations which give them a stochastic character [7,14,18,23].

In our previous works the effect of noise in the cancer dynamics has been studied both analytically and numerically finding in its evolution the well known phenomena of resonant activation (RA) [25] and the noise enhanced stability (NES) [2,10,11,12,26].

The aim of this study is to explore the dependence between the intensity of external fluctuations and the transition time from the state of a stable tumor to the state of its extinction under the influence of a moderate periodic treatment. Low intensity of therapy presents the advantage of minimizing side effects of treatment. The latter, if occasionally combined with spontaneous environmental fluctuations, can also cause the reoccurrence of cancer bearing a similarity to a stochastic resonance (SR) effect. Accordingly, our studies aim to understand the constraints of stochastically attacked by immune cytotoxic cells is based on a reaction scheme [6,7,13,14,15,16,17,18,19,23] representative of the catalytic Michaelis-Menten scenario:

\[
X \xrightarrow{\lambda} 2X \\
X + Y \xrightarrow{k_1} Z \xrightarrow{k_2} Y + P.
\]  

(1)

Here cancer cells X are assumed to proliferate spontaneously at a rate \(\lambda\) whereas their local interactions with cytotoxic cells \(Y\) are modeled by a simplified kinetics with \(k_1\) standing for the rate of binding of immune cells to the complex \(Z\) which subsequently dissociates at a rate \(k_2\). The dissociation results in a product \(P\) representing dead or non-replicating tumor cells. In the limit case, when the production of \(X\)-type cells inhibited by a hyperbolic activation is the simplest process under consideration, and by assuming a conserved number of immune cells \(Y + Z = E = \text{const}\), the resulting kinetics can be recast in the form of the first order differential equation. This can be interpreted as an overdamped equation of motion in a pseudo-potential \(U(x)\) (see [13,14,15] for the details)

\[
\frac{dx}{dt} = -\frac{dU(x)}{dx}
\]  

(2)

where

\[
U(x) = -\frac{x^3}{2} + \theta x^3 + \beta x - \beta \ln(x + 1),
\]  

(3)

\(x\) stands for the normalized molecular density of cancerous cells with respect to the maximum tissue capacity and the following scaling relations for the kinetic parameters have been used

\[
x = \frac{k_1 x}{k_2}, \quad \theta = \frac{k_2}{k_1}, \quad \beta = \frac{k_1 E}{\lambda}, \quad t = \lambda t.
\]  

(4)

Typical experimental values of the parameters are [7,15,16]: \(k_1 = 0.1 - 18 \text{day}^{-1}\), \(k_2 = 0.2 - 18 \text{day}^{-1}\), \(\lambda = 0.2 - 1.5 \text{day}^{-1}\). In the above deterministic model, weak fluctuations, that is temperature variations or changes in local concentrations of biochemical agents, can be incorporated by including additional source of stochastic fluxes represented by an additive noise \(\xi(t)\)

\[
\frac{dx}{dt} = -\frac{dU(x)}{dx} + \xi(t)
\]  

(5)

which is assumed to be uncorrelated and Gaussian distributed with zero mean: \(\langle \xi(t)\xi(t') \rangle = D\delta(t - t')\), and \(\langle \xi(t) \rangle = 0\), with the constraint \(x \geq 0\). In the above formulation the parameter \(D^{1/2}\) stands for the intensity of the fluctuations. The resulting stochastic differential equation Eq. (5) is Langevin-type. Alternatively, the dynamics of the system described by the Langevin equation may be characterized by determining the probability density \(p(x,t)\) of \(x\) which carries information about the instantaneous state of the system and fulfills the Feynman-Planck equation

\[
\frac{\partial}{\partial t} p(x,t) = \frac{\partial}{\partial x} \left[ D \frac{\partial U(x)}{\partial x} p(x,t) \right] + D \frac{\partial^2 p(x,t)}{\partial x^2}.
\]  

(6)

The estimation of the fluctuation in cancer dynamics can be obtained by analyzing the cancer growth trajectories. An example of paper showing the time series for different patients is reported in [30], where we observe fluctuations in agreement with the range here investigated.
The potential profile Eq. (3) exhibits three equilibrium states of the system (see Fig. 1):

\[
x_1 = 0, \quad x_2 = \frac{1 - \theta + \sqrt{(1 + \theta)^2 - 4\beta\theta}}{2\theta}, \quad x_3 = \frac{1 - \theta - \sqrt{(1 + \theta)^2 - 4\beta\theta}}{2\theta}.
\]

The essential feature captured by the model is, for a constant parameter \( \theta \), the \( \beta \)-dependent bi-stability (7910111213 14151819) of stationary (long-time) solutions. In a certain range of values of the above parameters the model possesses two stable states: the state of extinction, where no tumor cells are present, and the state of stable tumor, where its density does not increase but stays at a certain constant level. The bistable behavior of the system can also be examined by examining the stationary (time-independent) solution \( p_{eq} = const \times e^{-U(x)/D} \) to Eq. (6) which, for small value of the noise intensity \( D^{1/2} \), is sharply peaked around the minima of the potential \( U(x) \).

In the present work we are interested in situations where the stationarity of the system is broken due to coupling to an external driving representing a controllable therapy. Here, the influence of therapeutic factors is studied by considering a periodic treatment (chemo- or radiation- therapy) whose action, at the level of the kinetic equation can be modelled by a contribution:

\[
d(t) = -A[1 - \Theta(\cos(2\pi\nu t))],
\]

to the RHS of Eq. (5) This term results in a periodic decrease of \( X \) cell concentration. The \( \Theta \)-symbol stands here for the Heaviside function reflecting the on-off switch of the cyclical treatment performed with the intensity \( A \) and frequency \( \nu \). Accordingly, the \( d(t) \) term leads to a modulation of the pseudo-potential whose time-dependent part is given by:

\[
U_d(x, t) = Ax[1 - \Theta(\cos(2\pi\nu t))].
\]

The overall kinetic equation describing the evolution of the cancer cells population is then of the form

\[
\frac{dx}{dt} = -\frac{d(U(x) + U_d(x,t))}{dx} + \xi(t)
\]

\[
= x(1 - \theta x) - \frac{\beta x}{x+1} - A[1 - \Theta(\cos(2\pi\nu t))] + \xi(t)
\]

For the purpose of these studies, we consider the situation in which both wells of \( U(x) \) are of equal depth, using the parameters \( \theta = 0.25 \), and \( \beta = 1.48 \) (See Fig. 1). Since the cell number \( X \) cannot be negative, we investigate numerically the properties of the system corresponding to the Langevin equation (12) under the constraint \( x \geq 0 \). In the absence of noise, the existence of the potential barrier prevents the trajectories (solutions to Eq. (12)) from switching between potential wells, which correspond to well defined cancer states. If noise is present but there is no periodic forcing \( (A = 0) \), a spontaneous tumor extinction or occurrence become possible: solutions to the Langevin equation will cross the potential barrier at random times whose expectation value is given by an inverse of Kramers rate, i.e. \( \tau \propto e^{\Delta U(x)/D} \) where \( \Delta U(x) \) stands for the height of the barrier. Under the action of periodic forcing \( -d(U_d(x, t))/dx \), representing action of irradiation or chemical therapy, the overall potential profile changes and the barrier will still be crossed at random times but with a preference for the instants of minimal barrier height. In particular, if the noise intensity is large enough compared to the barrier height \( \Delta U \), transitions between the wells become likely to occur twice per period. This phenomenon, addressed in literature (2021) as a stochastic resonance (SR), is a generic phenomenon manifested in nonlinear systems where a weak signal can be amplified and optimized by the presence of noise. Obviously, if discussed in the context of periodic therapy administration, the SR effect (multiple synchronized re-crossings of the barrier) should be avoided as leading to possible recurrence and regrowth of tumor.

The aim of our study is therefore to investigate the role of weak random contributions to deterministic dynamics of the tumor growth model in the case when the intensity (amplitude) of cyclical treatment is subthreshold, i.e. not sufficient to induce cancer extinction. A modeled action of irradiation/chemical treatment is studied based on the one-dimensional kinetic equation (12), expressing growth of neoplastic cells population restricted to a saturation level and subject to the immunological surveillance mechanism of a host. Neither a particular histological type of tumor, nor other factors determining cancer response to fractionated treatment (like redistribution of cells in various phases of cell cycle (22)) are specified. Within this simplified description, our main purpose is to analyze the effectiveness of a treatment intended to cause the extinction of a tumor which is already present in a tissue and whose size is described by the density of cancer cell population \( x_3 \).

![Fig. 2. Deterministic (D = 0) and stochastic (D > 0) trajectories of cancer evolution with the same parameters of Fig. 1. For D = 0, the trajectory is localized in the cancer state at the minimum of the well. In contrast, a low level of noise is instead able to induce the extinction acts (D = 0.011). For increasing intensities of noise, the reappearance of cancer is detected (D = 0.016). In turn, for noise intensity close to the value D = 0.035 a stochastic resonance effect becomes visible.](image)
3 Results

The extinction and the reappearance of the tumor cells are studied by the statistics of both the first extinction time (FET) and the first return time (FRT). We define FET as the time needed by a trajectory \( x(t) \) starting from the stable state \( x(0) = x_3 \), to reach the value \( x = 0 \) for the first time. Similarly, the FRT is the time needed by a trajectory \( x(t) \) to return to the initial state \( x_3 \) for the first time, after having reached the value \( x = 0 \). To avoid the unphysical situation of trajectories crossing the state \( x = 0 \), we place there a reflecting boundary when analyzing the FRT, while an absorbing boundary is present in the analysis of FET. Numerical evaluation of typical trajectories \( x(t) \) established for the "dose"-intensity of a treatment \( A = 0.03 \) is depicted in Fig. 2 Without addition of noise \( (D = 0) \) the concentration of cancer cells remains close to the \( x_3 \) level and the \( x(t) \) trajectories are localized within the right potential well (cf. Fig 1). In turn, a small amount of noise added to the system can give rise to cancer extinction whose occurrence is displayed for \( D = 0.011 \).

The realistic values of the noise intensity used in this work, or the corresponding standard deviation \( \sigma = \sqrt{D} \in [0.005, 0.32] \), can be estimated using the scaling of the Eq. 4 and the experimental values of parameters (see the previous Section), obtaining \( \sigma_{\text{real}} \approx \lambda \sqrt{D} \in [0.014, 0.47] \) in day, or, in percentage of the maximum tumor cell density, \( \sigma_{\text{real}} \in [1.4\%, 47\%] \).

The statistics of such occurrences observed on the ensemble of \( N = 5 \times 10^4 \) realizations \( x(t) \) is shown in Fig. 3 for different noise intensities. At values of \( D \) of order of 0.011 separate peaks in histograms of FETs are visible, suggesting that the extinction events (passages from \( x_3 \) to \( x = 0 \) state) are possible only during the "treatment-on" session, beginning at \( t = T/4 \) up to \( t = 3T/4 \), and repeated recursively in a period \( T = 1/\nu = 1,000 \) (in unit of 1/\( \lambda \)). According to the experimental data mentioned in the previous Section, the period of treatment used in our simulations lies in the range (using \( T_{\text{real}} = T/\lambda \) [days]), \( T_{\text{Real}} \in [666, 5000] \) days. In literature cancer recurrence has been observed from 9 up to 17 months after a chemical treatment time of at least 10 months [29], so the low values of that range seem to be the most realistic.

The maximum temporal window explored is \( t_{\text{max}} = 10T \). The distinction between the two intervals ("on" and "off" treatment response) becomes blurred at higher noise intensities as visible in Fig. 3. Moreover, by increasing the noise, the extinction events occur earlier at times the maximum of the probability \( P(t) \) shifts towards shorter first exit times. This means that the "energy supply" pumped into the system by the noise contributes positively to the response of the tumor cell population towards extinction even in the no-treatment intervals (cf. Fig. 3 left-bottom panel, \( D = 0.035 \)). To elucidate the role of the spontaneous fluctuations around the deterministic trajectories, we have analyzed the statistics of cancer recurrence as addressed in Fig. 4. Cancer regrowth events occur first during the no-treatment time-interval for low level of noise intensity \( (D = 0.011) \) and, by increasing the noise-intensity, may be also detected during the "treatment-on" intervals. This apparent competition effect between the extinction and recurrence events will be addressed further by analyzing the ratio between the mean first exit time (MFET) and the mean return time (MFRT).

![Fig. 3. Probability distribution of extinction times. At very low level of the noise intensity, extinction events are significantly probable only during the treatment periods whereas no extinction is detected in the "treatment-off" periods. By increasing noise intensities the extinction events occur also in the no-treatment intervals. Consequently, differences between the response during "treatment-on" and "treatment-off" intervals decrease significantly.](image-url)
The deterministic character of the trajectories is mirrored in very high values of the MFRT and MFET, respectively. By increasing noise intensity, both MFET and MFRT decay sharply and MFET tends to become proportional to MFRT at a value of $D \approx 0.1$. A moderate noise intensity makes the transitions between the wells more likely to occur and thus shortens the average extinction time of cancer. On the other hand, at higher noise intensities, duration of returning trajectories is (roughly) twice longer than duration of exiting ones. This behavior is consistent with the results as predicted by inspection of $P(t)$ histograms: clearly, at sufficiently high noise intensities distributions of first exit and first return times become similar with some asymmetry in shape related to the asymmetry of the potential and to the constraints of motion imposed by the boundary condition. Consequently, the ratio $\text{MFET} / \text{MFRT}$ is slightly higher than one half, as indicated in Fig. 6. The two averages have been made using the actual number of trajectories having reached the related boundary ($x_1$ for the exit case, $x_1$ and then $x_3$ for the return one), excluding the trapped trajectories from the related calculations. The behavior of the MFET and MFRT response, which is different for low noise intensities, but similar for high noise intensities (where the two means have the same trend and their values tend to become proportional), accounts for the non-monotonic behavior of the MFET/MFRT ratio as observed in Fig. 6. In fact, for the chosen set of parameters, the minimum of MFET/MFRT is observed for $D_{\text{opt}} \approx 0.013$ which is the optimum noise-intensity value giving the best compromise between noise induced extinction of the cancer cells and their reappearance.

Fig. 5 reports also the behavior of both the Kramers mean exit time and mean return time calculated in the case of the fixed potential, the expressions are the following: i) $\tau_{\text{Exit}} = 2\pi e^{2h/D} / \sqrt{\sigma_{\text{Exit}}^2} \sqrt{U''(x_1)U''(x_2)}$; ii) $\tau_{\text{Ret}} = \tau_{\text{Exit}} + \tau_f$ with $\tau_f = 2\pi e^{2h/D} / \sqrt{U''(x_1)U''(x_2)}$, where $h$ is the height of the barrier in absence of treatment. The ratio $\tau_{\text{Exit}} / \tau_{\text{Ret}}$ shows only a constant reference value because of the equal depth of the potential. Finally, in Fig. 7 the behavior of the standard deviation of the FET and FRT distributions is reported, showing also a well visible minimum in the ratio $\sigma_{\text{Exit}} / \sigma_{\text{Ret}}$ at $D \approx 0.015$, close to the noise intensity at which the minimum of the ratio MFET/MFRT has been observed. This means that also the relative precision of the exit/return times evaluations shows an optimal value in the same noise surroundings than the corresponding ratio of the means. Moreover, the MFET has been analyzed as a function of the frequency of the treatment, founding the resonant activation phenomenon (25) (see Fig. 8) in a certain range of the noise intensity (see also (27,28)). Note that...
the numerical simulations, as discussed in this work, have been performed with the frequency of treatment $\nu = 10^{-3}$, corresponding to the minimum of the MFET detectable in the $(D, \nu)$ space (Fig. 5).

4 Conclusions

In this paper we investigate a mathematical model describing the growth of tumor in the presence of the immune response of a host organism. The model is supplemented with periodic treatment and external fluctuations in the tumor growth rate. The formulation of the model is based on a reaction scheme [6, 7, 13, 14, 15, 16, 17, 18, 19], representative of the catalytic Michaelis-Menten scenario.

The resulting phenomenological equation modelling cell-mediated immune surveillance against cancer exhibits bistability. The two stationary points correspond to the state of a stable tumor and the state of its extinction. The influence of therapeutic factors is introduced in the form of an on-off switch of the cyclic treatment, performed with a certain intensity and frequency, which (when switched on) acts in favor of a decrease of the tumor cell concentration. Under the influence of weak fluctuations, the model is analyzed in terms of a stochastic differential equation. It has the form of an overdamped Langevin-like dynamics in the external quasi-potential represented by a double well. We analyze properties of the system within the range of parameters for which the potential wells are of the same depth and when the periodic treatment alone (without external noise) is insufficient to overcome the barrier height and to cause cancer extinction.

The aim of our study was to explore the dependence between the intensity of fluctuations and the transition time from the stable tumor to the extinction state. We performed a series of numerical simulations of the stochastic trajectories of the system and analyzed the distributions of their duration times. Without addition of noise, the concentration of cancer cells remains close to the stable tumor state: the treatment is insufficient to cause the extinction. A small amount of noise added to the system can give rise to cancer extinction in the time intervals when the treatment is switched on. At higher noise intensities, the extinction occurs even in the “treatment-off” intervals. However, the presence of noise also causes the tumor recurrence. Cancer regrowth events occur during the no-treatment time interval for low noise intensity and, at higher noise intensity, may also be detected during the “treatment-on” intervals. At low noise intensities, the return probability can be even more than one order of magnitude lower than the extinction probability, but at sufficiently high noise the times to cross the barrier in both forward and back direction are approximately equal.

We found that there exists an optimal noise intensity $D_{opt}$ for which the ratio MFET/MFRT of the mean first extinction time to the mean first return time is the smallest. Since the duration of particular realizations of extinction and recurrence processes vary in the presence of noise, we also studied the width of FET and FRT distributions. Interestingly enough, the ratio of the corresponding standard deviations $\sigma_{E}/\sigma_{R}$ also has a minimum at a certain noise intensity $D_{σ opt}$, which is close to $D_{opt}$. Not far from the same value we also find a maximum for the ‘extinction without return’ probability as a function of the noise intensity. Our study shows that the presence of noise gives the possibility of tumor extinction even at a weak radiation or chemical treatment. Treatment strategies which take into account the noise contribution can reduce the radiation (or chemotherapeutic) dose. On the other hand, the presence of noise implies also the possibility of a recurrence. We show, however, that it is possible to observe an optimal noise value in the competition between the extinction and return events.

Fig. 7. Standard deviation derived from the probability densities of first exit and first return times. Similarly to the situation observed for the means, the ratio $\sigma_{E}/\sigma_{R}$ attains a minimum within the range of investigated noise intensities, very close to the MFET/MFRT minimum at $D_{opt}$ (See Fig. 6).

Fig. 8. Resonant Activation Effect due to the competitive presence of noise and the periodic treatment. The plot shows the mean escape time as a function of the noise intensity $D$ and the frequency of the treatment $\nu$. The parameters are the same than those of Fig. 4.

Fig. 9. The MFET and FRT as a function of frequency $\nu$ for different noise intensities $D$. The parameters are the same than those of Fig. 4.
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