Population Growth and Control in Stochastic Models of Cancer Development

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Abstract

We study the joint effect of thermal bath fluctuations and an external noise tuning activity of cytotoxic cells on the triggered immune response in a growing cancerous tissue. The immune response is assumed to be primarily mediated by effector cells that develop a cytotoxic activity against the abnormal tissue. The kinetics of such a reaction is represented by an enzymatic-like Michaelis-Menten two step process. Effective free-energy surface for the process is further parameterised by the fluctuating energy barrier between the states of high and low concentration of cancerous cells. By analysing the far from equilibrium escape problem across the fluctuating potential barrier, we determine conditions of the most efficient decay kinetics of the cancer cell-population in the presence of dichotomously fluctuating concentration of cytotoxic cells.

Key words: models of population growth, noise-driven activation

PACS: 05.40.Ca, 02.50.Ey, 87.10.+e

1 Introduction

Mathematical models of population growth based on nonlinear ordinary differential equations have been widely studied (see e.g. [1,2]), since despite their simplicity they can often capture the essence of complex biological interactions and explain characteristics of proliferation phenomena. However, biological

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Preprint submitted to Elsevier Science 10 December 2013
processes are not purely deterministic: systems existing in nature are subject to different types of natural noises. Generally, one can divide them into two types: (i)-internal noises (thermodynamic fluctuations) that display system parameters variability at the thermodynamic equilibrium, and (ii)-external (mostly conformational) noises, due solely to the effect of time-variability of the environment. In consequence, the information about dynamics of complex biological systems with underlying conformational transitions may be relevantly addressed by use of the mesoscopic approach in which the time-evolution of a collective coordinate is governed by stochastic differential equations [3]. In such an approach, system kinetics is described in terms of an analogue to the Kramers scenario with the Brownian particle wandering over an effective free energy potential. In many cases, the potential experienced by the Brownian particle (or, correspondingly by a collective coordinate of the system) cannot be regarded as static but as affected by some random fluctuations with characteristic time scale that is comparable with one of the time scales governing the passage over the potential barrier separating basins of stationary states [4,5,6,7,8,9]. Some examples include the escape of O$_2$ or CO ligand molecule from the myoglobin after dissociation, the ion channel kinetics in the lipid cell membrane or protein folding [6]. Another illustration of a coupling between the external noise and and a collective variable is an effect of cell-mediated immune surveillance against the cancer [10]. Most of tumoral cells bear antigens which are recognised as strange by the immune system. A response against these antigens may be mediated either by immune cells such as T-lymphocytes or other cells, not directly related to the immune system (like macrophages or natural killer cells). The process of damage to tumour proceeds via infiltration of the latter by the specialised cells which subsequently develop a cytotoxic activity against the cancer cell-population. The series of cytotoxic reactions between the cytotoxic cells and the tumour tissue may be considered to be well approximated [10] by a saturating, enzymatic-like process whose time evolution equations are similar to the standard Michaelis-Menten kinetics. The variability of kinetic parameters defining this process naturally affects the extinction of the tumour [10,11].

In this paper we investigate an extension of the above-mentioned problem: We discuss properties of a two state cancer-growth model subject to independent Markovian dichotomous noise (affecting the immunological response) and to an additive thermal noise (equilibrium fluctuations around stationary states representing low and high concentrations of cancer cells). As a model of the cancer cells dynamics, we have considered an overdamped Brownian particle moving in a two-well quasi-potential between reflecting and absorbing boundaries, in the presence of noise that modulates the height of the barrier dividing two stable states of the population. Transitions from one state to the other (here: from a fixed-size tumour to a cancer-free state or vice versa) are induced by additive thermal noise. In models of this kind, it is of particular interest
how fast the system escapes the potential well, surmounting the fluctuating
potential barrier. In the case of the cancer growth model, we are especially
interested in the rate at which the system escapes the fixed-size tumour state,
that leads to the extinction of the tumour. The mean escape time from the
meta-stable state across the fluctuating barrier may exhibit non-monotonic
dependence on the characteristic time scale of these fluctuations, as has been
exemplified in other studies [4,5,7,8,12,13,14,15]. Here, the phenomenon is dis-
cussed for the model system in which existence of the dichotomous Markovian
noise in one of the parameters may change relative stability of meta-stable
states and therefore reverse the direction of the kinetic process.
The following section presents briefly a generic model system that has been
used for the analysis of cancer growth kinetics. Subsequent paragraphs are
devoted to the presentation of the deterministic model and analysis of its
stochastic counterpart.

2 Generic Model System

We adhere to the model of an overdamped Brownian particle moving in a
potential field between absorbing and reflecting boundaries in the presence of
noise which modulates the barrier height. The evolution of a state variable
$x(t)$ is described in terms of the Langevin equation

$$
\frac{dx}{dt} = -\frac{dV(x)}{dx} + \sigma \xi(t) + g(x) \eta(t) = -\frac{dV^\pm(x)}{dx} + \sigma \xi(t).
$$

Here $\xi(t)$ is a Gaussian process with zero mean and correlation

$$
< \xi(t) \xi(t') > = \delta(t - t')
$$

i.e. the Gaussian white noise of intensity $\sigma = \sqrt{2k_BT}$ arising from the heat
bath of temperature $T$), whereas $\eta(t)$ stands for a Markovian dichotomous
noise switching between two levels $\{\Delta^+, \Delta^-\}$ with mean frequency $\gamma$ and cor-
relation time $1/2\gamma$. This means that its autocorrelation function is

$$
\langle (\eta(t) - \langle \eta \rangle) (\eta(t') - \langle \eta \rangle) \rangle = \frac{(\Delta^+ - \Delta^-)^2}{4} e^{-2\gamma|t-t'|}.
$$

Both noises are assumed to be statistically independent, i.e. $< \xi(t) \eta(s) >= 0$.

Eq. (1) can be considered as describing an overdamped motion of the state
variable, subject to an effective force

$$
-\frac{dV^\pm(x)}{dx} = -\frac{dV(x)}{dx} + \Delta^\pm g(x).
$$
Based on eq. (1), one can write a set of the Fokker-Planck equations which describe the evolution of probability density of finding the state variable in a “position” \( x \) at time \( t \):

\[
\partial_t p(x, \Delta^\pm, t) = \partial_x \left[ \frac{dV^\pm(x)}{dx} + \frac{1}{2} \sigma^2 \partial_x \right] p(x, \Delta^\pm, t) \\
- \gamma p(x, \Delta^\pm, t) + \gamma p(x, \Delta^\mp, t) 
\]

(2)

In the above equations time has dimension of \([\text{length}]^2/\text{energy}\) due to a friction constant that has been “absorbed” in a time variable. With the initial condition

\[
p(V^\pm, x_s, t)|_{t=0} = \frac{1}{2} \delta(x - x_s),
\]

(3)

the equations for the mean-first-passage time (MFPT) read:

\[
\begin{align*}
-\frac{1}{2} & = -\gamma \tau^+(x) + \gamma \tau^-(x) - \frac{dV^+(x)}{dx} \frac{d\tau^+(x)}{dx} + \frac{\sigma^2}{2} \frac{d^2\tau^+(x)}{dx^2} \\
-\frac{1}{2} & = \gamma \tau^+(x) - \gamma \tau^-(x) - \frac{dV^-(x)}{dx} \frac{d\tau^-(x)}{dx} + \frac{\sigma^2}{2} \frac{d^2\tau^-(x)}{dx^2}
\end{align*}
\]

(4)

where \( \tau^+(x) \) and \( \tau^-(x) \) denote MFPT for \( V^+(x) \) and \( V^-(x) \), respectively.

The overall MFPT for the system

\[
MFPT(x) = MFPT^+(x) + MFPT^-(x) = \tau^+(x) + \tau^-(x)
\]

(5)

can be obtained after solving eq.(4) with appropriate boundary conditions. Here we assume a motion between a reflecting boundary \( a \) and an absorbing boundary \( b \):

\[
\begin{align*}
\left. \frac{d\tau^+(x)}{dx} \right|_{x=a} & = 0 \\
\left. \frac{d\tau^-(x)}{dx} \right|_{x=a} & = 0 \\
\tau^+(x)|_{x=b} & = 0 \\
\tau^-(x)|_{x=b} & = 0
\end{align*}
\]

(6)

According to a vast literature on the subject, the most interesting aspect of the escape over such a fluctuating potential is the non-monotonic behaviour of
the MFPT as a function of the driving noise [4,8,12,13,14]. In particular, we expect that for the frequency of potential switching \( \gamma \) tending to zero (i.e. in the limit of a long correlation time of the dichotomous noise \( \eta(t) \)) the overall MFPT will be a mean value of MFPTs for both configurations,

\[
\lim_{\gamma \to 0} \text{MFPT}(V^+, V^-, \gamma) = \frac{1}{2} \left[ \text{MFPT}(V^+) + \text{MFPT}(V^-) \right],
\]

whereas for \( \gamma \) tending to infinity (in the limit of a short correlation time) the system will “experience” a mean barrier:

\[
\lim_{\gamma \to \infty} \text{MFPT}(V^+, V^-, \gamma) = \text{MFPT} \left( \frac{V^+}{2} + \frac{V^-}{2} \right),
\]

with the MFPT\((V^+)\) and MFPT\((V^-)\) obtained from formula

\[
\text{MFPT}(x) = \frac{2}{\sigma^2} \int_{-b}^{b} dy \exp \left( \frac{2V_x(y)}{\sigma^2} \right) \int_{-a}^{a} dz \exp \left( -\frac{2V_x(z)}{\sigma^2} \right)
\]

for \( V = V^\pm \), separately.

Although the solution of (4) is usually unique, a closed, “ready to use” analytical formula for \( \tau \) can be obtained only for the simplest cases of the potentials. More complex cases require either use of approximation schemes [7], perturbative approach [8] or direct numerical evaluation methods [9].

### 3 Population Model of Cancer Growth

We use the predator-prey model ([3], [11]) to describe the cancer cells population growth in presence of cytotoxic cells. The population dynamics can be described as follows: First, the cytotoxic cells bind to the tumour cells at a rate proportional to the kinetic constant \( k_1 \); second, the cancer cells which have been bound are killed and the complex dissociates at a rate proportional to \( k_2 \). The process can be described schematically:

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

Here \( X \) represents the population of tumour cells. Similarly, \( Y, Z \) and \( P \) represent active cytotoxic cells, bound cells and dead tumour cells, respectively. In a given (small) volume element, there is an upper limit \( N \) to the number of cells which may be present, given that each cell has a typical diameter equal to \( a \). From now on, we will use normalised cellular densities: \( x = \frac{X}{N} \) instead
of \( X \), etc). Following the original presentation [11], we assume that (i) cancer cells undergo replication at a rate proportional to the time constant \( \lambda \); (ii) as a result of cellular replication in limited volume, a diffusive propagation of cancer cells is possible, with transport coefficient \( \lambda a^2 \); (iii) dead cancer cells undergo elimination at a rate proportional to a certain constant \( k_3 \); (iv) local cytotoxic cell population remains constant, i.e. \( Y + Z = \text{const} \); (v) free cytotoxic cells can move with a “diffusion” coefficient \( D \). The spatio-temporal evolution of the tumour due to the above processes can be then described by the set of balance equations:

\[
\begin{align*}
\frac{\partial x}{\partial t} &= \lambda [1 - (x + p)] x - k_1 E y x + \lambda a^2 (1 - p) \nabla^2 x + \lambda a^2 x \nabla^2 p \\
\frac{\partial y}{\partial t} &= -k_1 y x + k_2 z + D \nabla^2 y \\
\frac{\partial z}{\partial t} &= k_1 y x - k_2 z \\
\frac{\partial p}{\partial t} &= k_2 E z - k_3 p
\end{align*}
\]

(11)

where

\[ y + z = E = \text{const}. \]

(12)

In the limit when the effector cells diffuse much faster than the cancer cells propagate by cellular replication and in which the dead cells are rapidly eliminated, the spatial distribution of \( Y \) and \( Z \) cells equilibrates rapidly with respect to the local density of living tumour cells and the above scheme of kinetics can be recasted in the form of the scalar problem [10,11]:

\[
\frac{\partial x}{\partial t} = (1 - \theta x) x - \beta \frac{x}{x + 1} + \nabla^2 x,
\]

(13)

where

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

In our paper, we will consider the spatially homogeneous form of eq. (13). As presented here, the model has a long history of analytical studies ([11], [16]). In a slightly modified form it turned out to be also of practical use in biophysical modelling of radiation-induced damage production and processing [17,18,19]. In particular, the kinetic scheme eq. (10) has been adapted for the purpose of studying kinetics of double-strand breaks rejoining and formation of simple chromosome exchange aberrations [17] after DNA exposure to ionising radiation. Similar kinetics has been proposed in analysis of saturable repair models [18,19] devoted to study evolution of radio-biological damage.
In the latter, the saturable repair modelled by a Michaelis-Menten kinetics describes processing of damage by enzyme systems that can be overloaded. In the forthcoming section, we will analyse some versions of the model eq.(13) taking into account time variability of parameters as an effect of the environmental noise. Below, following [11], we briefly remind its deterministic properties.

Equation (13) can be considered as describing an overdamped motion of the state variable moving in a quasi-“free energy potential”:

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

(14)

where \( V(x) \) has at most three extrema (stationary points of the system):

\[ x_1 = 0, \]

(15)

\[ x_2 = \frac{1 - \theta + \sqrt{(1 + \theta)^2 - 4\beta\theta}}{2\theta} \]

(16)

and

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

(17)

Stability analysis reveals a strong dependence on \( \theta \):

(i) For \( \theta > 1 \) and \( \beta > 1 \), \( x_1 \) is the only minimum of \( V(x) \). For \( \theta > 1 \) and \( 0 < \beta < 1 \), \( x_1 \) becomes maximum and \( x_2 \) is a new minimum.

(ii) For \( \theta < 1 \), outside the region with \( 0 < \beta < \frac{(1+\theta)^2}{4\theta} \), the properties of the system are identical to (i). Inside the region, \( V(x) \) has two minima: \( x_1 \), \( x_2 \) and one maximum at \( x_3 \). For certain values of parameters, namely for

\[ \theta < 1, \quad 0 < \beta < \frac{(1+\theta)^2}{4\theta}, \]

(18)

the system is bistable. In a forthcoming section, we will consider this system subject to the joint effect of independent noises: to a multiplicative dichotomous noise in \( \beta \) with exponential time-correlation and to a white additive noise representing thermal fluctuations.

\[ ^1 \text{Depending on } \theta, \text{ there exists a unique value of } \beta = \beta_0, \text{ at which both states } x_1 \text{ and } x_3 \text{ are equally stable. Further stochastic analysis of the model is performed for } \theta = 0.1, \text{ and consequently } \beta_0 \approx 2.669 \]
Fig. 1. Cancer growth kinetics has been studied for four indicated cases. MFPT was computed for intervals \([a, b]\), where \(a\) and \(b\) are reflecting and absorbing boundaries, respectively. Arrows point directions of a transition.

4 Stochastic Model of Cancer Growth

We investigate the system described by the equation

\[
\frac{dx}{dt} = (1 - \theta x)x - (\beta + \Delta \pm) \frac{x}{x + 1} + \sigma \xi(t),
\]

where \(\Delta \pm\) is a two-state, Markovian noise and \(\xi(t)\) is the Gaussian noise of intensity \(\sigma\). In this form the model includes the influence of the heat bath (modelled by a memoryless Gaussian noise) and the fluctuations in the immunological response of the organism (here assumed to be represented by a symmetric dichotomous noise in parameter \(\beta\)). Correspondingly, the process of population growth and decay can be described as a motion of a fictitious particle in a potential switching between two conformational states (cf. Fig. 1).

\[
V^\pm(x) = -\frac{x^2}{2} + \frac{\theta x^3}{3} + (\beta \pm \Delta)(x - \ln(x + 1)).
\]

For negligible additive noise and small concentration of cancerous cells, this model resembles standard Verhulst equation with a perturbing multiplicative dichotomous noise and as such has been shown [3] to exhibit a com-
Fig. 2. Linear approximation of the original potential. The line connects minima of the potential $V(x, \Delta = 0)$ with the maximum of $V(x, \Delta \pm)$. Dotted lines: $V(x, \Delta \pm)$, solid lines: the approximated potential.

Complex scenario of noise-induced transitions observable in a pattern of the stationary probability density. Here, we will address kinetic properties of this model by studying the mean first passage time (4) between high and low population states in the system. In order to compute $MFPT$, as a working example we use an approximation of the potential by a linear slope with a reflecting barrier placed at $x_1 = a = 0$ and an absorbing barrier at $x_2 = b = [1 - \theta + \sqrt{(1 + \theta)^2 - 4\beta\theta}](2\theta)^{-1}$. In a linear setup, it is frequently possible to formulate analytical solutions to the problem [5,12]. Moreover, as expected based on former analysis [15], due to the smoothing of the kinetics by irregular diffusive motions, the solutions for the piecewise linear potential are not qualitatively different from those for smooth differentiable potentials. In such a case a fully analytic expression for the $MFPT$ can be obtained, even though the algebra involved in such an evaluation requires use of symbolic computer softwares (here: Maple 7 procedure dsolve/numeric/BVP).

Based on the original potential, we build its linear approximation in the following way: In general, inclusion of a noise term in the parameter $\beta$ influences positions of stationary states of the potential $V(x, \Delta \pm)$ and affects their relative stability. However, if the effective change in the barrier height is very small compared to its total height, the location of extrema can be considered constant (cf. Fig.(2)). Our analysis demonstrates that even in such cases of weak perturbation of the barrier height, presence of noise has dramatic consequences on the overall kinetics of cancer and its extinction.

In order to keep constant the positions $x_1$, $x_2$ and $x_3$ of the extrema when changing the barrier height $V(x, \Delta \pm)$, we approximate them with positions of
the extrema of the potential $V(x, \Delta = 0)$. Thus, $x_1 = 0$, $x_2 = \frac{1-\theta+\sqrt{(1+\theta)^2-4\theta}}{2\theta}$ and $x_3 = \frac{1-\theta-\sqrt{(1+\theta)^2-4\theta}}{2\theta}$. Next, we connect points $[x_1, V(x_1, \Delta = 0)]$, $[x_2, V(x_2, \Delta^+)]$ and $[x_3, V(x_3, \Delta = 0)]$ or, respectively, $[x_1, V(x_1, \Delta = 0)]$, $[x_2, V(x_2, \Delta^-)]$ and $[x_3, V(x_3, \Delta = 0)]$ with straight lines, as has been depicted in Fig.2.

By defining 

$$A_\Delta := \sqrt{1 + \theta^2 + 2\theta (1 - 2(\beta + \Delta))}$$ (21)

and 

$$A_0 := A_{\Delta=0} = \sqrt{1 + \theta^2 + 2\theta (1 - 2\beta)},$$ (22)

the height of the barrier seen by the particle located close to the $x_3$ can be expressed as

$$V(x_3(\Delta), \Delta) - V(x_2(\Delta), \Delta) = -\frac{A_\Delta(9\theta^2 - 12\theta + 3 + A_\Delta^2)}{12\theta^3} +$$

$$+ (\beta + \Delta) \left( \frac{-A_\Delta}{\theta} - \ln \left( \frac{\theta + 1 - A_\Delta}{\theta + 1 + A_\Delta} \right) \right)$$ (23)

Similarly, the height of the barrier calculated from the bottom of the left-side minimum $x_1 = 0$ is

$$V(x_3(\Delta), \Delta) = \frac{(\theta - 1 + A_\Delta)^2(4\theta - 1 + A_\Delta)}{24\theta^3} +$$

$$+ (\beta + \Delta) \left( \frac{-\theta + 1 - A_\Delta}{2\theta} - \ln \left( \frac{\theta + 1 - A_\Delta}{2\theta} \right) \right)$$ (24)

Piecewise linear approximation of the potential results in:

$$V(x_3(0), \Delta) - V(x_2(0), \Delta) = -\frac{A_0(-12\theta + 9\theta^2 + A_0^2 + 3)}{12\theta^3} +$$

$$+ \beta \left( \frac{-A_0}{\theta} - \ln \left( \frac{\theta + 1 - A_0}{\theta + 1 + A_0} \right) \right) + \Delta \left( \frac{-\theta + 1 - A_0}{2\theta} - \ln \left( \frac{\theta + 1 - A_0}{2\theta} \right) \right)$$ (25)

and

$$V(x_3(0), \Delta) = -\frac{(\theta - 1 + A_0)^2(4\theta - 1 + A_0)}{24\theta^3} +$$
Fig. 3. Relative MFPTs as a function of the rate of the barrier fluctuations $\gamma$ computed for various values of $\Delta$, for an approximated linear potential. Parameters of the generic model has been set to $\beta = 2.669 = \beta_0$, $\sigma = 0.5$ and $\theta = 0.1$.

\[
+ (\beta + \Delta) \left( \frac{-\theta + 1 - A_0}{2\theta} - \ln \left( \frac{\theta + 1 - A_0}{2\theta} \right) \right). \tag{26}
\]

For the purpose of analysis, the MFPT has been computed for 4 chosen cases (cf. Figure 1): (i) transition from large to small population when the small population state is a global minimum; (ii) transition from large to small population when the large population state is a global minimum; (iii) transition from small to large population when the small population state is a global minimum. (iv) transition from small to large population when the large population state is a global minimum.

Figure 3 displays the graphs of MFPT as a function of the barrier fluctuation rate $\gamma$ and the noise intensity $\Delta$. The results are presented in the form of a ratio $T_p/T_l$ of forward/backward mean first transition times calculated as a fraction of a corresponding ratio of transition times estimated for static ($\Delta = 0$) barriers.

The results indicate that the escape kinetics (from right to left and vice versa) depends on the slope of the approximated linear potential (cf. eqs.(23-26) and exhibits characteristic features of the noise-induced enhancement of the activation process. Moreover, for the critical (deterministic) value of parameter
Fig. 4. Relative escape time as a function of the rate of the barrier fluctuations $\gamma$ estimated for various duration of the integration time $t_I$ as compared with the down-hill relaxation time $t_r$ for a static barrier.

$\beta = \beta_0$, fluctuations of the barrier may facilitate the forward/backward transfer and within given intervals of frequencies either the growth or diminishment of cancer population can be expected. For either of the transitions (from small- to large- and from large- to small concentrations of cancerous cells), depending on the frequency of the barrier fluctuations $\gamma$, there exists an optimal value of the barrier fluctuation rate, for which the mean first passage time is minimal $[4,5,8,14,15])$. The analysis reveals that the intensity of the effect depends on the strength of the barrier noise (the minimum/maximum of the relative $T_p/T_l$ deepens/lowers for larger $\Delta$). Also, the resonant frequency of the $MFPT$ minimum $\gamma_{\text{min}}$ increases monotonically with the intensity $\sigma$ of the additive white Gaussian noise as displayed in Figure 6.

Numerically estimated $MFPT$ values have been compared with their asymptotes for $\gamma \to \infty, \gamma \to 0$ evaluated directly from formulas (8), where

$$MFPT(x) = \frac{x - b}{A} + \frac{\sigma^2}{2A^2} \left[ \exp \frac{2A}{\sigma^2}(b - a) - \exp \frac{2A}{\sigma^2}(x - a) \right]$$ \hspace{1cm} (27)$$

and

$$A = \frac{V(a) - V^\pm(b)}{a - b}$$ \hspace{1cm} (28)$$
for $MFPT(V^\pm)$, or

$$A = \frac{V(a) - V(b)}{a - b}$$  \hspace{1cm} (29)$$

for $MFPT(V^+ + V^-)$, where $a = x_1$ and $b = x_2$. The results display full agreement with numerical evaluation.

Finally, we have used a recently proposed [8] approximated method for studying activation over a fluctuating barrier that involves considering separately the slow and fast components of barrier fluctuations and applies for any value of the correlation time $\tau = 1/\gamma$. By decomposing the barrier noise into two independent terms

$$\eta(t) = \eta_s(t) + \eta_f(t)$$  \hspace{1cm} (30)$$

the escape problem may be considered as a three-dimensional Markovian process described by a joint probability distribution $P(x, \eta_s, \eta_f, t)$ which evolves accordingly to the Fokker-Planck equation with two separate operators responsible for the time evolution of slow and fast variables. In particular, by definition, $\eta_s(t)$ remains constant while the trajectory climbs the barrier and its dynamics can be analysed by the kinetic approach [8,12]. On the contrary, $\eta_f$ vanishes for the barrier correlation times slightly greater than the relaxation time from the top of the barrier to the bottom of the well, so that the probability distribution $P(x, \eta_s, \eta_f, t)$ can be deconvoluted to the
form $p(x, \eta_f, t; \eta_s)q(\eta_s, t)$ and in consequence, the rate theory formalism can be safely applied. The equilibration process in a fast $\eta_f(t)$ variable leads then to an effective Fokker-Planck equation (with a new form of the quasi-potential [8,13]) from which the appropriate effective MFPT($\eta_s$) can be calculated. For dichotomous switching the procedure captures ideology of the kinetic rate estimated as an inverse of

$$\text{MFPT}(\eta_s) = \frac{k^+ + k^- + 4\gamma}{2[k^+k^- + (k^+ + k^-)\gamma]}, \quad (31)$$

where kinetic rates $k^+$, $k^-$ describe escape kinetics in two different configurations of the barrier. Note, that although the above formula resembles a typical kinetic scenario [12] which is known not to produce the resonant activation effect, the evaluation of the MFPT($\eta_s$) takes into account fast kinetics of the dynamics hidden in the form of kinetic constants evaluated from the effective Fokker-Planck equation. Crucial for the approach is the determination of the value of the integration interval $t_t$ which is describing climbing stage of the process. Its duration for the unperturbed potential equals the relaxation time $t_r$ from the top to the bottom of the well. Obviously, fluctuations of the potential break that equality [12,8]. However, since we are not discussing the relationship between the process of climbing up and relaxing down the fluctuating barrier, but rather need a time-estimate for the following escape event, as a first approximation for $t_t$ the MFPT from the top of the barrier to the bottom of the well has been used.

To test the method, we have presented in Figures 4 and 5 the exact analytical results for the triangular barrier (cf. Figure 2) along with the approximation
based on the approach described above. The agreement with the original results is quite good and depends only slightly on the time of integration $t$ of the slow $\eta(t)$ component, as discussed elsewhere [8]. Nevertheless, we expect that such a comparison will be less positive for kinetics over a relatively low barriers (data not shown).

5 Conclusions

We have considered a standard problem of an escape over a fluctuating potential barrier for a system describing efficiency of the immunological response against cancer. The basic component of the model is the mode of action of immunologically active cells that behave as catalysts in a chemical reaction. Analytical results for the model have been obtained after approximating a smooth double well potential by a piecewise-linear one. Although the method presented in this paper allows to estimate only the shortest possible time of transition (by placing an absorbing boundary condition at the top of the barrier), the results demonstrate fine sensitivity of the process to the correlation time of the barrier noise. In particular, by controlling the frequency of barrier fluctuations (or equivalently, the correlation time of changes in the effector cells response), the process of tissue growth can be reversed. Further analysis should tackle the problem of obvious nonlinearity of the process and the interplay of the noise with the stability criteria for the double-well system. The formalism of a partial noise-averaging method [8] may provide a way to analyse this case.

It seems worthy mentioning that despite its simplicity, the model eq.(11) can be considered as a generic one for kinetic description of many processes that use allosteric transition and phosphorylation of proteins in their metabolic pathways [17,18]. However, to ensure modelling of relevant interactions and to determine proper estimates of the kinetic parameters, an additional computer analysis of rate constants is required, which in turn has to rely on experimental observations. In particular, local stability analysis of such models leads to conditions on rate parameters and steady state concentrations that need to be compared with experimental data. If the binding kinetics was controllable in such cases by an external (stochastic or deterministic) time-dependent field, the analysis similar to presented in this paper could be used for prediction of a most effective action of the catalyst leading to an expected shortest reaction time. In modelling tumor treatment or experiments on cell killing by external agents based on ordinary differential equations, a very common assumption is that treatment modifies the growth, so that the Verhulst- or Gompertz-type growth rate has to be accompanied by an extra term supressing the proliferating population [19]. The inhibition and deceleration of the tumor growth can often be assumed to follow a saturable repair model [2,17,18,19] of
the Michaelis-Menten kinetics. Therefore, consequences of the above analysis may appear realistic in those situations where, given a full identification of the parameters, the cellular populations would exhibit extinction controlled by external, time dependent fields like time-dependent administration of cytotoxic agents or therapeutic radiation.

Acknowledgements

We would like to express our gratitude to Dr. Jan Iwaniszewski for helpful and inspiring discussions.

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