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Estimating a non-homogeneous Gompertz process with jumps as model of tumor dynamics

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HIGHLIGHTS

- A non-homogeneous Gompertz process with jumps is built as model of tumor dynamics.
- In real applications the instants of therapeutical application can be known or not.
- The estimation of the model is developed in both cases.
- A strategy for obtaining optimal instants of therapeutical application is developed.

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ABSTRACT

A non-homogeneous stochastic model based on a Gompertz-type diffusion process with jumps is proposed to describe the evolution of a solid tumor subject to an intermittent therapeutic program. Each therapeutic application, represented by a jump in the process, instantly reduces the tumor size to a fixed value and, simultaneously, increases the growth rate of the model to represent the toxicity of the therapy. This effect is described by introducing a time-dependent function in the drift of the process. The resulting model is a combination of several non-homogeneous diffusion processes characterized by different drifts, whose transition probability density function and main characteristics are studied. The study of the model is performed by distinguishing whether the therapeutic instances are fixed in advance or guided by a strategy based on the mean of the first-passage-time through a control threshold. Simulation studies are carried out for different choices of the parameters and time-dependent functions involved.

1. Introduction

Due to increasing interest, in the last decades various mathematical models of cancer dynamics have been proposed to analyze the evolution of the illness, when a therapy is administered. Moreover, in order to take into account some discrepancies between clinical data and theoretical predictions that can be ascribed to more or less intense environment fluctuations, the notion of growth in random environment has been formulated (cf., for instance, Lo, 2007, 2010 and references therein). Attention is often placed on the definition of particular time-dependent functions that change the natural growth rates of the cancer by modeling anti-proliferative and pro-apoptotic effects. However, another aspect of

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interest is the interaction between proliferating and quiescent cells (cf. Kozusko and Bourdeau, 2007), which has also been studied to analyze the relevant differences between non-specific cycle drugs (that can damage tumor cells in any phase of the cellular cycle) and specific cycle drugs (that act on tumor cells only in a fixed phase of the cellular cycle; cf., Albano and Giorno, 2008, Albano et al., 2012). The problem of model estimation has also been taken into account, first by considering the estimation of the natural growth parameters and then by designing ad hoc procedures to estimate the time-dependent functions used to describe the effects of therapies (cf. Albano et al., 2011, 2015 and Ferrante et al., 2000).

Recently, following Hirata et al. (2010) and Tanaka et al. (2010), in Giorno and Spina (2013) a stochastic model was proposed to analyze the effect of a therapeutic program that provides intermittent suppression of cancer cells. In Spina et al. (2014) we assumed that each application of the therapeutic program leads the cancer mass to a return state ρ, producing a deleterious effect on the organism by increasing the growth rate of the cancer cells at a constant rate. The result was a diffusion process with jumps. Note that, although in different contexts, in the last years such processes have been extensively studied (cf., Abundo, 2004, 2013a,b for instance). Specifically, following the widespread assumption that the Gompertz law is adapted to describe the growth of a solid tumor (cf., for instance, Cameron, 1997, Haustein and Schumacher, 2012, Migita et al., 2008 and Norton, 1988), we assumed that starting from $\rho > 0$ at the initial time, the process evolves according to the Gompertz law with positive parameters $\alpha_0 = \alpha$ and β, which represent, respectively, the growth and death rates of the tumor cells in the absence of therapies. After a fixed time, a therapy is applied, the effect of which is to reduce tumor size to ρ on the one hand and to increase growth rate at a constant rate on the other. In this way process $X(t)$, which describes tumor size at time t, consists of independent cycles, each of which is described by a stochastic diffusion process $X_k(t)$, $k = 1, 2, \ldots$, with different time-independent growth rates. The effectiveness of the therapeutic program is considerably influenced by the choice of the instants at which the therapy is applied. For this reason, Spina et al. (2014) proposed a strategy to select the inter-jump intervals in such a way that the first-passage-time of $X(t)$ through a constant control boundary is as large as possible and cancer size remains under this control threshold during the treatment. An estimation of parameters based on the maximum likelihood method was also provided.

In the present paper we modify the model discussed in Spina et al. (2014), assuming that, after the kth therapeutic application, the process evolves with a time-dependent growth parameter given by $\alpha_k(t) = \alpha + h_k(t)$, being $h_k(t)$ a function that includes time dependence. In this way, the single processes $X_k(t)$, as well as $X(t)$, become time non-homogeneous, and we can focus on the estimation of the model.

The paper is organized as follows. Section 2 introduces the stochastic model and provides the main characteristics of the related stochastic process. In Section 3 we assume that the instants of therapeutic applications are fixed before the beginning of the experimental phase. This being the case, only the estimation of the parameters and functions $h_k(t)$ is addressed. In Section 4 we suppose that the time instants are unknown, and propose, in the first place, a strategy for determining optimal time instants of therapeutic application based on the first-passage-time of the process through a control threshold. Since determining each time instant requires having knowledge of the process until the previous application cycle, a recursive procedure for estimating the model is proposed. Some simulation studies illustrate the procedures of estimation in both scenarios for different choices of the involved parameters and time-dependent functions $h_k(t)$.

2. The model

Let $X(t)$ be the stochastic process describing the growth of a tumor mass. We assume that each application of the therapy resets the cancer mass to a state ρ, and that it produces a deleterious effect on the organism by increasing the growth rate of the cancer cells. Let $\tau_0 = 0$ be the initial time, and τ_k the instants of therapeutic application for $k = 1, 2, \ldots, N$ and $\tau_{N+1} = \infty$. We suppose that the return state ρ is equal to the initial tumor mass, i.e. the tumor size recorded at the time of diagnosis. Therefore, one has:

$$X(t) = \sum_{k=0}^{N} X_k(t) 1_{[\tau_k, \tau_{k+1})}(t), \tag{1}$$

where $X_0(t)$ represents the evolution of the tumor in the absence of therapies, whereas $X_k(t)$ describes the dynamics of the tumor between the kth and the $(k+1)$th therapeutic application. We assume that $X_k(t)$ is a stochastic Gompertz process whose sample paths are the solution of

$$\begin{aligned} &dX_k(t) = [\alpha + h_k(t) - \beta \ln X_k(t)] X_k(t) dt + \sigma X_k(t) dW(t), \quad \tau_k < t < \tau_{k+1}, \\ &X_k(\tau_k) = \rho, \quad k = 0, 1, 2, \ldots, N. \end{aligned} \tag{2}$$

In Eq. (2), α and β are the growth and death rates in the absence of therapy, $\sigma > 0$ measures the width of environment fluctuations and $W(t)$ is a standard Brownian motion. Functions $h_k(t)$ represent the harmful effect of the kth therapeutic application. As a matter of fact, after each jump the tumor growth rate increases, becoming larger as therapies become more aggressive. This perspective represents the effect of targeted drugs with a certain degree of toxicity for the patient. Unlike in the past (cf. Spina et al., 2014), we now consider that after a therapeutic application the growth parameter changes according to a time-dependent function. Specifically, we assume that $h_0(t) = 0$ and that for $k = 1, 2, \ldots, N$ the functions $h_k(t) \geq 0$ are continuous and increasing with k.