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On the effect of a therapy able to modify both the growth rates in a Gompertz stochastic model

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In memory of Prof. Luigi M. Ricciardi, great scientist, beloved "maestro" and dear friend

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ABSTRACT

A Gompertz-type diffusion process characterized by the presence of exogenous factors in the drift term is considered. Such a process is able to describe the dynamics of populations in which both the intrinsic rates are modified by means of time-dependent terms. In order to quantify the effect of such terms the evaluation of the relative entropy is made. The first passage time problem through suitable boundaries is studied. Moreover, some simulation results are shown in order to capture the dependence of the involved functions on the parameters. Finally, an application to tumor growth is presented and simulation results are shown.

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1. Introduction

Predictive modeling is a key field in various contexts such as economy, biology, medicine, ecology, computer science. Growth curves often contain a final phase in which the growth rate decreases and finally reaches zero, so that an asymptotic size is reached. In such cases, Gompertz curve seems to be able to model a lot of phenomena. It was proposed as e.g. bacterial growth [16] and to analyze the monthly average Money & Quasi Money's growth data from People's Bank [12]. In [1], a stochastic model based on the deterministic Gompertz curve was used to describe the growth of a solid tumor treated with a time-dependent therapy able to modify the birth rate of the tumor cells. Moreover, in [3] the estimation of the involved parameters was performed and a strategy based on two or more control groups was proposed to estimate the function representing the effect of the therapy. An application to infer the net effect of cisplatin and doxorubicin + cyclophosphamide in actual murine models was presented. Thereafter other models were proposed to include more and more features of the tumor growth. For example, in [2] a model based on a two-dimensional process was proposed to consider the differentiation between proliferating cells (in phase G1) and quiescent ones (out of the cellular cycle). The study was focused on the analysis of the influence of specific (able to damage tumor cells only in a fixed phase of the cell cycle) and non specific cycle drugs (able to damage tumor cells in any phase of the cellular cycle). Furthermore, in [4] the estimation of the parameters describing the proliferating cells was proposed comparing two different methods: the first one based on the maximum likelihood method and the second one based on linear regression.

In the present paper, we generalize the model in [1] assuming that the effect of the therapy also modifies the death rate of the tumor cells. Indeed, anti-angiogenetic drugs can have both anti-proliferative and pro-apoptotic action as, for example, the anti-oestrogen tamoxifen in the breast cancer (see [7,8]).

We analyze the relative entropy (Kullback Leibler divergence) as a non symmetric measure of the distance between the distributions of the processes in the presence of suitable protocol treatments. Finally, we focus on the first passage time (FPT) problem of the process through an upper boundary that in the context of cancer growth can be interpreted as the maximum tumor volume carried by the host.

The paper is organized as follows. In Section 2 we introduce the model and we analyze its transition probability density function (pdf), the related moments and its asymptotic behavior. The relative entropy is analyzed to study the effect of different therapies on the distribution of the involved process. In Section 3 a numerical approach is considered to evaluate the FPT pdf and, for suitable choices of the boundary, some closed form results for the FPT problem are considered. Finally, in Section 4 a computational study on the effect of therapies is performed comparing different models by means of the relative entropy and the FPT's.

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2. The model

A Gompertz-type diffusion in which the growth rates are time-dependent can be used to modeling systems in which the natural growth parameters are modified by exogenous factors. Let $\{X(t), t \geqslant t_0 \geqslant 0\}$ be a diffusion stochastic process characterized by drift and infinitesimal variance:

$$A_1(x,t) = h(t)x - g(t)x\ln x, \quad A_2(x) = \sigma^2 x^2, \tag{2.1}$$

respectively. In (2.1) $h(t)$ and $g(t)$ are positive functions of the time representing the growth and the death rates modified by an exogenous term, respectively. Moreover, σ is a positive constant representing the width of random fluctuations. The process $X(t)$ is defined in $I = (0, +\infty)$ and its sample-paths are described by the following stochastic differential equation:

$$dX(t) = [h(t)X(t) - g(t)X(t)\ln X(t)]dt + \sigma X(t)dW(t),$$

where $W(t)$ is a standard Brownian motion.

Let $F(x,t|y,\tau) = Pr[X(t) < x | X(\tau) = y]$ be the transition distribution function and let $f(x,t|y,\tau)$ be the transition pdf of $X(t)$, i.e.:

$$f(x,t|y,\tau) = \frac{\partial}{\partial x}F(x,t|y,\tau) \quad (x,y \in I, t_0 < \tau < t).$$

It is solution of the Fokker–Planck equation:

$$\frac{\partial f(x,t|y,\tau)}{\partial t} = -\frac{\partial}{\partial x}\{[h(t)x - g(t)x\ln x]f(x,t|y,\tau)\} + \frac{\partial^2}{\partial x^2}\left[\frac{\sigma^2}{2}x^2 f(x,t|y,\tau)\right] \tag{2.2}$$

and of the Kolmogorov equation:

$$\frac{\partial f(x,t|y,\tau)}{\partial \tau} + [h(\tau)y - g(\tau)y\ln y]\frac{\partial f(x,t|y,\tau)}{\partial y} + \frac{\sigma^2}{2}y^2\frac{\partial^2 f(x,t|y,\tau)}{\partial y^2} = 0 \tag{2.3}$$

and it satisfies the initial delta condition:

$$\lim_{t\to\tau} f(x,t|y,\tau) = \lim_{\tau\to t} f(x,t|y,\tau) = \delta(x-y), \tag{2.4}$$

where $\delta(z)$ is the Dirac-delta function in z.

2.1. Transition probability distribution

In order to find the solution of the Eqs. (2.2) and (2.3) with the initial condition (2.4), we consider the transformation (cf. [13]):

$$\begin{aligned} &\tilde{x} = k(t)\ln x + d(t), \quad \tilde{y} = k(\tau)\ln y + d(\tau), \\ &\tilde{t} = \phi(t), \quad \tilde{\tau} = \phi(\tau), \\ &\tilde{f}(\tilde{x},\tilde{t}|\tilde{y},\tilde{\tau}) = \frac{x}{k(t)}f(x,t|y,\tau), \end{aligned} \tag{2.5}$$

with

$$\begin{aligned} k(t) &= \exp\left\{\int_{t_0}^t g(\theta)d\theta\right\}, \\ d(t) &= \int_{t_0}^t \left[\frac{\sigma^2}{2} - h(\theta)\right]k(\theta)d\theta, \\ \phi(t) &= \int_{t_0}^t k^2(\theta)d\theta. \end{aligned} \tag{2.6}$$

Such transformation reduces the Eqs. (2.2) and (2.3) to the analogous equations for a Wiener process $\widetilde{X}(t)$ with drift and infinitesimal variance

$$B_1 = 0, \quad B_2 = \sigma^2,$$

respectively. The transition pdf of $\widetilde{X}(t)$ is Gaussian with mean $\tilde{y}$ and variance $\sigma^2(\tilde{t} - \tilde{\tau})$ so, making use of (2.5), one has:

$$f(x,t|y,\tau) = \frac{1}{x\sqrt{2\pi V^2(t|\tau)}}\exp\left\{-\frac{[\ln x - M(t|\ln y,\tau)]^2}{2V^2(t|\tau)}\right\} \quad (x,y > 0; t_0 < \tau < t), \tag{2.7}$$

where

$$\begin{aligned} M(t|y,\tau) &= \frac{k(\tau)}{k(t)}y + \frac{1}{k(t)}\int_\tau^t \left[h(\theta) - \frac{\sigma^2}{2}\right]k(\theta)d\theta \\ &= \frac{k(\tau)}{k(t)}y - \frac{1}{k(t)}[d(t) - d(\tau)] \end{aligned} \tag{2.8}$$

and

$$V^2(t|\tau) = \frac{\sigma^2}{k^2(t)}\int_\tau^t k^2(\theta)d\theta = \frac{\sigma^2}{k^2(t)}[\phi(t) - \phi(\tau)] \tag{2.9}$$

with $k(t), \phi(t)$ and $d(t)$ defined in (2.6). The conditional cumulative transition distribution is given by

$$\begin{aligned} F(x,t|y,\tau) &= \int_0^x f(z,t|y,\tau)dz \\ &= \frac{1}{2}\left\{1 + \mathrm{Erf}\left[\frac{\ln x - M(t|\ln y,\tau)}{\sqrt{2V^2(t|\tau)}}\right]\right\}, \end{aligned} \tag{2.10}$$

where $\mathrm{Erf}(z) = \frac{2}{\sqrt{\pi}}\int_0^z e^{-\xi^2}d\xi$ is the error function.

2.2. Some statistical indexes

From (2.7) it is easy to obtain the conditional nth moment $(n = 1, 2, \ldots)$ of $X(t)$:

$$E[X^n(t)|X(\tau) = y] = \exp\left\{nM(t|\ln y,\tau) + \frac{n^2}{2}V^2(t|\tau)\right\};$$

so, the conditional mean, the conditional variance and the variation coefficient are

$$\begin{aligned} &E[X(t)|X(\tau) = y] = \exp\left\{M(t|\ln y,\tau) + \frac{1}{2}V^2(t|\tau)\right\}, \\ &Var[X(t)|X(\tau) = y] = \exp\left\{2M(t|\ln y,\tau) + V^2(t|\tau)\right\}\left[\exp\{V^2(t|\tau)\} - 1\right], \\ &CV[X(t)|X(\tau) = y] = \frac{\sqrt{Var[X(t)|y,\tau]}}{E[X(t)|y,\tau]} = \left[\exp\{V^2(t|\tau)\} - 1\right]^{1/2}, \end{aligned}$$

respectively. Moreover, one has:

$$\begin{aligned} &\text{median} = \exp\{M(t|\ln y,\tau)\}, \\ &\text{mode} = \exp\{M(t|\ln y,\tau) - V^2(t|\tau)\}, \\ &\text{skewness} = \left(\exp\{V^2(t|\tau)\} + 2\right)\sqrt{\exp\{V^2(t|\tau)\} - 1}, \\ &\text{kurtosis} = \exp\{4V^2(t|\tau)\} + 2\exp\{2V^2(t|\tau)\} + 3\exp\{3V^2(t|\tau)\} - 3. \end{aligned} \tag{2.11}$$

2.3. Asymptotic behavior

In many contexts it is interesting to analyze the behavior of the system for large times. This behavior can be studied via the steady state pdf of the process. In particular, if the following limits exist

$$\lim_{t\to\infty} M(t|\ln y,\tau) = m, \quad \lim_{t\to\infty} V^2(t|\tau) = s^2, \tag{2.12}$$

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