A Stochastic Gompertz Model with Jumps for an Intermittent Treatment in Cancer Growth

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Abstract. To analyze the effect of a therapeutic program that provides intermittent suppression of cancer cells, we suppose that the Gompertz stochastic diffusion process is influenced by jumps that occur according to a probability distribution, producing instantaneous changes of the system state. In this context a jump represents an application of the therapy that leads the cancer mass to a return state randomly chosen. In particular, constant and exponential intermittence distribution are considered for different choices of the return state. We perform several numerical analyses to understand the behavior of the process for different choices of intermittence and return point distributions.

1 Introduction

Growing attention is devoted to the analysis of growth models because they play an important role in many fields such as economy, biology, medicine, ecology. These models are described generally via a deterministic differential equation in which it introduces the effect of random oscillations for modeling environmental fluctuations that are not captured by deterministic models. The curves that best describe the phenomenon of growth are of exponential type characterized by the presence of a carring capacity that represents the limit of the size of the population. Among all the exponential growths, the Gompertz curve plays an important role because in several contexts it seems to fit experimental data in a reasonable precise way ([5], [8]). In particular, various stochastic models based on this curve have been proposed recently to analyze the evolution of a tumor mass subject to anti-proliferative or pro-apoptotic therapies that alter the growth rates of cells ([1], [4]).

In this paper, we consider a diffusion process $\{X(t), t > 0\}$ based on the Gompertz model to construct the corresponding process with jumps $X_J(t)$ in order to analyze the effect of a therapeutic program that provides intermittent suppression of cancer cells. The process $X_J(t)$ consists of recurring cycles whose

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duration is described by a random variable, interjump interval, that represents the time elapsing between successive jumps or applications of the therapy.

The paper is organized as follows. In Section 2 we introduce the model. To analyze the evolution of $X_J(t)$ we study its transition probability density function (pdf), the average state of the system, representing the mean size of the tumor, and the number of therapy applications to be carried out in time intervals of fixed amplitude. In Section 3, we focus our attention on two probability distributions for the interjump intervals and for each of these we consider three distributions for the random variable describing the return point, because we want to take into account that the therapy would not be precise. Finally, in Section 4, various simulations are performed in order to understand the behavior of the process for different choices of intermittence and return point distributions.

2 The Model

Let $\{X(t),\, t > 0\}$ be the Gompertz stochastic process, it is described by the following stochastic differential equation

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

where $\alpha, \beta \geq 0$ denote growth and decay rates respectively, $\sigma > 0$ is the amplitude of the random fluctuations and $W(t)$ is a standard Wiener process. The time homogeneous process $X(t)$ is defined in $I = (0, \infty)$ and it is characterized by a lognormal pdf:

$$f(x,t|y) = \frac{1}{x\,\sqrt{2\,\pi\,V^2(t)}}\, \exp\left\{\frac{[\ln x - M(t|\ln y)]^2}{2\,V^2(t)}\right\}, \tag{1}$$

where

$$M(t|y) = e^{-\beta(t)} \log y + \frac{\sigma^2/2 - \alpha}{\beta}\big(1 - e^{-\beta\, t}\big), \qquad V^2(t) = \frac{\sigma^2}{2\beta}\big(1 - e^{-2\beta\, t}\big).$$

Morever, the moments of $X(t)$ are

$$\mu^{(n)}(t|y) = \exp\left\{n\, M(t|\ln y)] + \frac{n^2}{2}\, V^2(t)\right\}. \tag{2}$$

In order to analyze the effect of a therapeutic program that provides intermittent suppression of cancer cells, (cf. [3], [7]), we suppose that $X(t)$ is influenced by jumps that occur according to a probability distribution, producing instantaneous changes of the system state. More precisely, we define the resulting process with jumps $X_J(t)$ as follows (cf. [6]). Starting from $X_J(0) = X(0) = x_0$, $X_J(t)$ evolves as $X(t)$ as long as a jump occurs leading the process in a state $\rho > 0$ randomly chosen according to the probability density $\phi(x)$; from here, after a variable time interval, coinciding with the duration of the therapeutic application, $X_J(t)$ evolves with the same dynamics of $X(t)$ as long as another

jump occurs, representing a new application of the therapy, which leads $X_J(t)$ in ρ, and so on. The process $X_J(t)$ consists of recurring cycles $\mathcal{I}_1$, $\mathcal{I}_2$ ... whose durations are described by the independent and identically distributed random variables $I_1,\ I_2, \ldots$ with pdf $\psi(\cdot)$. Moreover, we denote by $\Theta_1, \Theta_2, \ldots$ the times in which the jumps occur. The variables I_k and Θ_k are related, indeed it results: $\Theta_1 = I_1$ and for $k > 1$ one has $\Theta_k = I_1 + I_2 + \ldots I_k$. Furthermore, for $0 < \tau < t$, $\xi_t(\tau)d\tau \sim P(\tau < \Theta_i < \tau + d\tau)$ represents the probability that a jump occurs in the infinitesimal interval $(\tau, \tau + d\tau)$. The transition density of $X_J(t)$ can be expressed in terms of the transition pdf of $X(t)$ via the following relations:

$$f_J(x,t|y) = R_t(0)\, f(x,t|y) + \int_0^t \xi_t(\tau)\, R_t(\tau) \left(\int_0^\infty \phi(z)\, f(x, t-\tau|z)\, dz \right) d\tau, \tag{3}$$

where $R_t(\tau) = 1 - P(\tau < I_k < t) = 1 - \int_\tau^t \psi(s)\, ds$ and $f(x,t|y)$ is given in (1). The first term represents the case in which there aren't jumps between 0 and t. The second term analyses the case in which at the time $0 < \tau < t$ the last jump occurs and then the process starts at ρ and evolves according to $X(t)$ to reach the state x in the time interval of width $t - \tau$.

The moments of $X_J(t)$, $\mu_J^{(n)}(t|y,\tau)$, follow from (3):

$$\mu_J^{(n)}(t|y) = R_t(0)\mu^{(n)}(t|y) + \int_0^t \xi_t(\tau)\, R_t(\tau) \left(\int_0^\infty \phi(z)\, \mu^{(n)}(t-\tau|z)\, dz \right) d\tau \tag{4}$$

with $\mu^{(n)}(t|y)$ given in (2). Moreover, we consider the stochastic process $N(t)$ representing the number of therapeutic treatments to be applied until a fixed time t.

In the following we analyze some therapeutic protocols assuming that different pdf's characterize the interjump intervals I_k.

3 Analysis of Some Intermittent Therapeutic Treatments

In the present section we consider two kinds of intermittent therapeutic treatments defined in terms of the pdf's characterizing the random variables I_k. In particular, we assume that the function ψ is a degenerate pdf (constant intermittence) and an exponential pdf (exponential intermittence). Furthermore, for the specified ψ we assume three pdf's for the random variable ρ: degenerate, uniform and bounded bi-exponential. In the first case we suppose that the therapy is so precise that the process jumps exactly in the chosen point; otherwise the therapy would lead the cancer mass in a its neighborhood of a certain amplitude without any preferences, in the first case; with the other choice the situation is similar, but ρ is the favorite point.

3.1 Constant Intermittence Therapeutic Treatment

We assume that intermittent therapeutic treatments are at fixed time intervals of duration $1/\zeta$, $(\zeta > 0)$ so that I_k can be described by a degenerate pdf

$\psi(t) = \delta\left(t - \frac{1}{\zeta}\right)$, where $\delta(\cdot)$ is the Dirac delta-function. In this case the time instant $\Theta_k = k/\zeta$, almost surely (a.s.). Let N_t the number of treatments to be applied until the time t, one has that

$$N_t = \sum_{k=1}^{\infty} H\left(t - \frac{k}{\zeta}\right),$$

where $H(x) = \int_{-\infty}^{x} \delta(u)\, du$ denotes the Heaviside unit step function. Note that in this case $\xi_t(\tau) = \delta\left(\tau - \frac{N_t}{\zeta}\right)$ and $R_t(\tau) = H\left(1/\zeta - t\right) + H\left(\tau - 1/\zeta\right)$ so that

$$\mu_J^{(n)}(t|y) = \begin{cases} \mu^{(n)}(t|y), & t < 1/\zeta \\ \int_0^{\infty} \phi(z)\mu^{(n)}\left(t - \frac{N_t}{\zeta}|z\right) dz, & t > 1/\zeta. \end{cases} \tag{5}$$

Hence, $\mu_J^{(n)}(t|y) \equiv \mu^{(n)}(t|y)$ for $t < 1/\zeta$.

Case a): Degenerate ρ. We suppose that $\phi(z) = \delta(z - \rho)$, is a degenerate distribution in ρ. In this case from (5) one has:

$$\mu_J^{(n)}(t|y) = \mu^{(n)}\left(t - \frac{N_t}{\zeta}|\rho\right), \qquad t > 1/\zeta.$$

Case b): Uniform ρ. We consider $\phi(z) = \frac{1}{2l}$ for $z \in [\rho - l,\, \rho + l]$. In this case (5) becomes:

$$\mu_J^{(n)}(t|y) = \frac{1}{2l} \int_{\rho-l}^{\rho+l} \mu^{(n)}\left(t - \frac{N_t}{\zeta}|z\right) dz, \qquad t > 1/\zeta.$$

In particular one has:

$$\mu_J^{(n)}(t|y) = \frac{1}{2l} \exp\left\{\frac{n^2}{2}\sigma^2(1 - e^{-2\beta(t-k/\zeta)}) - n\frac{\sigma^2/2 - \alpha}{\beta}(1 - e^{-\beta(t-k/\zeta)})\right\}$$
$$\times \frac{1}{n(e^{-\beta(t-k/\zeta)} + 1)} \left[(\rho + l)^{ne^{-\beta(t-k/\zeta)}+1} - (\rho - l)^{ne^{-\beta(t-k/\zeta)}+1}\right], \quad t > 1/\zeta$$

where

$$c_{1,2} = \frac{1}{\sqrt{2V^2(t - k/\zeta)}} \Big\{ e^{-\beta(t-k/\zeta)} \ln(\rho \mp l) - \Big[\ln x + \frac{\sigma^2/2 - \alpha}{\beta}\big(1 - e^{-\beta(t-k/\zeta)}\big)\Big]$$
$$- \sigma^2\big(e^{\beta(t-k/\zeta)} - e^{-\beta(t-k/\zeta)}\big)\Big\}$$

and $Erf(x) = \frac{2}{\sqrt{\pi}} \int_0^x e^{-s^2} ds$ is the error function.

Case c): Bounded bi-exponential ρ. We assume that $\phi(z) = \frac{1}{2(1-e^{\lambda l})} e^{-\lambda|z-\rho|}$ for $z \in (\rho - l,\, \rho + l)$ so that from (5) it results:

$$\mu_J^{(n)}(t|y) = \frac{1}{2(1 - e^{\lambda l})} \int_{\rho-l}^{\rho+l} e^{-\lambda|z-\rho|} \mu^{(n)}\left(t - \frac{N(t)}{\zeta}|z\right) dz, \qquad t > 1/\zeta.$$

3.2 Exponential Intermittence Therapeutic Treatment

In this subsection we assume that I_k is described by an exponential pdf with mean $1/\zeta$, i.e. $\phi(x) = \zeta e^{-\zeta x}$ for $x > 0$. In this case $R_t(\tau) = e^{-\zeta(t-\tau)}$, $\xi_t(\tau) = \zeta$, consequently, from (3) and (4) one has:

$$f_J(x,t|y) = e^{-\zeta t} f(x,t|y) + \zeta \int_0^t d\tau e^{-\zeta(t-\tau)} \int_0^\infty f(x,t-\tau|z)\phi(z)dz \qquad (6)$$

and

$$\mu_J^{(n)}(t|y) = e^{-\zeta t}\mu^{(n)}(t|y) + \zeta \int_0^t d\tau e^{-\zeta(t-\tau)} \int_0^\infty \mu^{(n)}(t-\tau|z)\phi(z)dz. \qquad (7)$$

The number of treatments to be applied until the time t is a Poisson process of parameter ζ.
Case a): Degenerate ρ. If $\phi(z) = \delta(z-\rho)$ from (7) the moments of $X_J(t)$ follow:

$$\mu_J^{(n)}(t|y) = e^{-\zeta t}\mu^{(n)}(t|y) + \zeta \int_0^t e^{-\zeta(t-\tau)}\mu^{(n)}(t-\tau|\rho)d\tau.$$

If $\rho = 1$, $\alpha = \sigma^2/2$, from (6) and (7) we have the following closed forms:

$$f_J(x,t|y) = e^{-\zeta t} f(x,t|y) + \frac{\zeta}{2x}\left[C_1(\log x) - C_2(\log x, t)\right],$$

and

$$\mu_J^{(n)}(t|y) = e^{-\zeta t}\mu^{(n)}(t|y)$$

$$-\frac{\zeta}{2\beta}\left(\frac{4\beta}{n^2\sigma^2}\right)^{\frac{\zeta}{2\beta}} e^{\frac{n^2\sigma^2}{4\beta}}\left[\Gamma\left(\frac{\zeta}{2\beta}, \frac{n^2\sigma^2}{4\beta}\right) - \Gamma\left(\frac{\zeta}{2\beta}, \frac{n^2\sigma^2}{4\beta}e^{-2\beta t}\right)\right]$$

with

$$C_1(w) = \frac{2^{1+\zeta/(2\beta)}}{\sigma\zeta}\sqrt{\frac{\beta}{\pi}}\,\Gamma\left(\frac{\zeta}{2\beta}+1\right)\exp\left\{-\frac{\beta w^2}{2\sigma^2}\right\}D_{-\zeta/\beta}\left(\frac{w\sqrt{2\beta}}{\sigma}\right),$$

$$C_2(w,t) = \frac{1}{\sigma\sqrt{\beta\pi}}\sum_{k=0}^{+\infty}(-1)^k\binom{-\frac{\zeta}{2\beta}-1}{k}\left[\exp\left\{-\frac{\beta w^2}{\sigma^2}\right\}\Psi\left(1,\frac{1}{2}-k;\frac{\beta w^2}{\sigma^2}\right)\right.$$

$$\left.-\left(1-e^{-2\beta t}\right)^{k+1/2}\exp\left\{-\frac{\beta w^2}{\sigma^2\left(1-e^{-2\beta t}\right)}\right\}\Psi\left(1,\frac{1}{2}-k;-\frac{\beta w^2}{\sigma^2\left(1-e^{-2\beta t}\right)}\right)\right],$$

where $\Gamma(\nu)$ is the Gamma function, $\Gamma(a,\nu)$ is the Incomplete Gamma function, $D_{-\nu}(x)$ is the Parabolic Cylinder function (cf. [2], p. 1028, n. 9.240) and $\Psi(a,b;x)$ is the Kummer's function of the second kind (cf. [2], p. 1023, n. 9.210.2).
Case b): Uniform ρ. For $\phi(z) = \frac{1}{2l}$ for $z \in [\rho - l,\ \rho + l]$ (7) one has:

$$\mu_J^{(n)}(t|y) = e^{-\zeta t}\mu^{(n)}(t|y) + \frac{\zeta}{2l}\int_0^t d\tau e^{-\zeta(t-\tau)}\int_{\rho-l}^{\rho+l}\mu^{(n)}(t-\tau|z)\phi(z)dz.$$

Case c): Bounded bi-exponential ρ. When $\phi(z) = \frac{1}{2(1-e^{\lambda l})} e^{-\lambda|z-\rho|}$ for $z \in (\rho - l, \rho + l)$ making use of (7) we obtain:

$$\mu_J^{(n)}(t|y) = e^{-\zeta t}\mu^{(n)}(t|y) + \frac{\lambda\zeta}{2(1-e^{\lambda l})}\int_0^t d\tau e^{-\zeta(t-\tau)}\int_{\rho-l}^{\rho+l} e^{-\lambda|z-\rho|}\mu^{(n)}(t-\tau|z)\phi(z)dz.$$

4 Numerical Results

The aim of this section is to analyze the effects of the proposed intermittent treatments by comparing the means of the process $X_J(t)$ in the corresponding of the two therapeutic protocols for the three different return distributions. We assume that the growth rates of $X(t)$ are $\alpha = 1$, $\beta = 0.5$, furthermore $\sigma = 1$, $y = 0.1$, $\rho = 0.5$ and $\zeta = 0.1$.

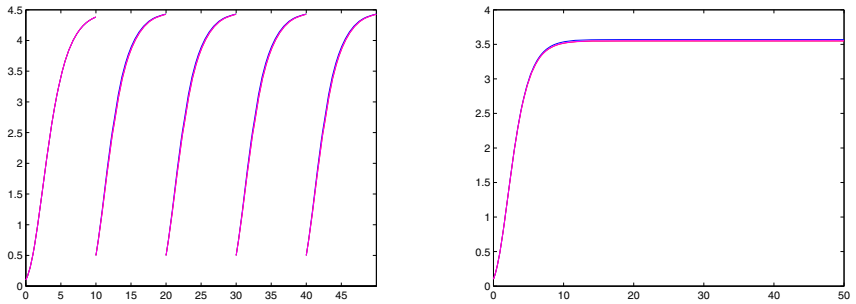

Fig. 1. The means of $X_J(t)$ are shown with $\alpha = 1$, $\beta = 0.5$, $\sigma = 1$, $y = 0.1$ and $\rho = 0.5$, $\zeta = 0.1$ for constant (on the left) and exponential (on the right) intermittences and for different return pdf: degenerate (blue curve), uniform (red curve) and bi-exponential (magenta curve) for $l = 0.4$ and $\lambda = 1$.

In Fig. 1 the means of $X_J(t)$ are shown when a constant treatment (on the left) and exponential protocol (on the right) is applied. For both therapeutic treatments the three different return distributions are compared: degenerate pdf (blue curve), uniform pdf (red curve) with $l = 0.4$ and bi-exponential pdf (magenta curve) for $l = 0.4$ and $\lambda = 1$. Note that, although the red and magenta curves are below the blue curve, they are comparable, so we can study the only degenerate case without loss of generality.

Figures 2 and 3 show the mean of $X_J(t)$ for the constant (blue full curve) and exponential (dashed curve) intermittences in the corresponding of degenerate distribution of the return point. In particular, in Fig. 2 we choose $1/\zeta = 10$ (on the left) and $1/\zeta = 5$ (on the right), whereas in Fig. 3 $1/\zeta = 4$ (on the left) and $1/\zeta = 3$ (on the right). The green line represents the carrying capacity of the deterministic Gompertz growth: $k = \exp\{\alpha/\beta\}$, the magenta line is $k/2$

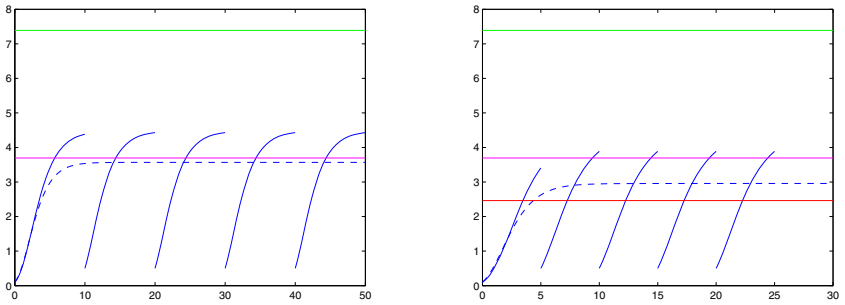

Fig. 2. The means of $X_J(t)$ are shown with $\alpha = 1$, $\beta = 0.5$, $\sigma = 1$, $y = 0.1$ and $\rho = 0.5$ for a constant (blue full curve) and exponential (dashed curve) intermittences with $1/\zeta = 10$ (on the left) and $1/\zeta = 5$ (on the right) for degenerate return point. The green, magenta and red lines are $k, k/2$ and $k/3$, respectively.

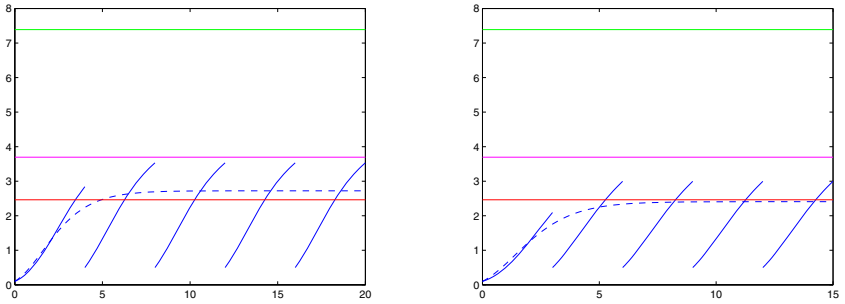

Fig. 3. As in Fig. 2 with $1/\zeta = 4$ (on the left) and $1/\zeta = 3$ (on the right). The green, magenta and red lines are $k, k/2$ and $k/3$, respectively.

and the red one is $k/3$. In all cases we note that the mean of the process for the exponential distribution is less than the mean for the constant case. In particular, for $1/\zeta = 10$ (on the left of Fig. 2), only for the exponential treatment the mean size is kept under the level $k/2$. Its understandable because in the exponential case the probability of occurrence of more than one jump before of the time 10 is non-zero, while in the constant case it is equal to zero. The mean of the jump process decreases by reducing the mean of the interjump intervals, however the better results are obtained for the exponential intermittences (dashed curves). In particular for $1/\zeta = 3$ (on the right of Fig. 3) the exponential treatment reduces the mean of the tumor size below $k/3$.

Conclusions

To analyze the effect of a intermittent treatment in tumor growth we have considered a return process based on the Gompertz diffusion process. We have assumed that the time elapsing between successive applications of the therapy is constant or exponentially distributed; for both cases we have considered that the effect of the therapy leads the cancer mass to a fixed value or, more generally, to a random variable of assigned pdf. The performed simulations have showed that the mean of the considered process is not influenced by the distribution of the return point. So, the return point can be considered as fixed. In this case we have analyzed the effectiveness of the two treatments by comparing the mean of the jump process for different mean durations of interjump intervals. Based on the considered model and on the chosen parameters, we can conclude that the exponential protocol produces better effects than the constant one.

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