TOWARDS A STOCHASTIC TWO-COMPARTMENT MODEL IN TUMOR GROWTH

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ABSTRACT. A stochastic model of tumor growth incorporating several key elements of the growth processes is presented. Generalizing a previous work by the authors, two one-dimensional diffusion processes representing populations of proliferating and quiescent cells are obtained. Their forms turn out by their relation with total tumor population analysed in [1]. The proposed model is able to incorporate the effects of the mutual interactions between the two subpopulations. It is also used to simulate the effects of two kinds of time-dependent therapies: non-specific cycle and specific cycle drugs. Moreover, the first-exit-time problem is analyzed to study cancer evolution in the presence of a time-dependent therapy.

1 Introduction and background Tumor is one of the main causes of death in our society so, in the last twenty years a lot of attempts have been made to describe the tumor kinetic.

Cancer cells population consists of a combination of proliferating, quiescent and dead cells that determine tumor growth based on surrounding environmental conditions (cf. [5]). Furthermore, since experimental data show the existence of more or less intense random fluctuations in tumor growth, in a previous work (see [1]) the authors provided a stochastic generalization of the Gompertz law in order to model monoclonal tumor growth. So tumor size is described by means of a one-dimensional diffusion process X(t) and the first exit time problem (FET) for X(t) from a region D has been analysed. In particular, D is restricted by two absorbing boundaries representing healing threshold and the carrying capacity.

A first natural generalization consists of including all the essential biological phenomena of a cellular population. To this aim, following Kozusko and Bajzer (cf. [7]), we split tumor population in two subpopulations: proliferating and quiescent cells. In this direction, in [7], the authors proposed a deterministic model to describe tumor dynamics, assuming that the transition rates between proliferating and quiescent populations depend on the total population size. By imposing that the total population is governed by the Gompertz law, Kozusko and Bajzer resolved analytically the model and obtained the dynamics of proliferating and quiescent populations as functions of the whole population size. Following this approach, we describe proliferating and quiescent populations via two new diffusion processes, generally time-non-homogeneous, connected to the process X(t). The FET problem for such processes through suitable boundaries is considered. The followed approach permits to analyse the effect of different therapies on tumor cells.

In Section 2 we will review the main characteristics of the model proposed in [1] in which the effect of a therapy is seen as a moderation term of the growth rate of the tumor cells. In Section 3 we generalize the deterministic model by Kozusko and Bajzer by obtaining two diffusion processes P(t) and Q(t) representing the populations of proliferating and quiescent cells, respectively. Finally, in Section 4 the effect of a therapy on X(t) is investigated

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to simulate the corresponding modification of the processes P(t) and Q(t). The cases of non-specific cycle and specific cycle drugs are considered.

2 Generalizing Gompertz growth In [1] the diffusion process X(t) representing tumor size in the case of a monoclonal tumor is obtained by generalizing Gompertz growth

(1)
$$\dot{x}(t) = \alpha x - \beta x \log x$$

with the initial condition $x(0) = x_0$. More precisely, to make the "random environment" assumption, we considered the discrete version of Eq. (1), i.e.:

(2)
$$x_{(n+1)\tau} - x_{n\tau} = (\alpha \tau - \beta \tau \log x_{n\tau}) x_{n\tau}$$

and we interpreted $\alpha \tau$, i.e. the intrinsic relative change in the population size during the time interval $[n\tau, (n+1)\tau)$ n = 0, 1, ..., as the mean of a sequence of random variables (r.v.'s) independent and identically distributed $Z_0, Z_{\tau}, ..., Z_{n\tau}, ...$ characterized by the following probability distribution:

(3)
$$Pr(Z_{n\tau} = \sigma\sqrt{\tau}) = \frac{1}{2} + \frac{\alpha\sqrt{\tau}}{2\sigma}, \qquad Pr(Z_{n\tau} = -\sigma\sqrt{\tau}) = \frac{1}{2} - \frac{\alpha\sqrt{\tau}}{2\sigma},$$

where $\sigma > 0$ is an arbitrary constant representing the width of the environmental fluctuations. So we obtained a time-homogeneous diffusion process X(t) characterized by drift and infinitesimal variance

(4)
$$A_1(x) = \alpha x - \beta x \ln x , \qquad A_2(x) = \sigma^2 x^2$$

and defined on the interval $I \equiv (0, +\infty)$. The boundaries 0 and $+\infty$ of the process (4) are natural non attracting.

The effect of a therapy is introduced in the deterministic equation (1) by assuming that it consists in the elimination of a portion C(t) of the tumor cells. More precisely, C(t) represents the regression rate of the tumor due to the therapy. By proceeding as for the process X(t), we obtained a diffusion process $X_C(t)$, generally time-non-homogeneous, characterized by infinitesimal moments:

(5)
$$A_1^C(x,t) = [\alpha - C(t)]x - \beta x \ln x , \qquad A_2^C(x) = \sigma^2 x^2$$

and defined in $(0, +\infty)$. We are interested on the evolution of the process $X_C(t)$ inside the region delimited by a lower boundary S_1 , representing the "recovery level", and an upper boundary S_2 , representing the carrying capacity, already present in the deterministic model. So our problem becomes a FET problem for a time-non-homogeneous process. Figure 1 shows an hypothetical sample path of the considered process.

Generally, FET problems for time-non-homogeneous processes are mathematically not accessible; however, as shown in [1], $X_C(t)$ can be transformed in a time-homogeneous Ornstein-Uhlenbeck (OU) process Y(t) with infinitesimal moments

(6)
$$B_1(z) = \left(\alpha - \sigma^2/2\right) - \beta z, \qquad B_2(z) = \sigma^2$$

via the transformation

(7)
$$z = \ln x + d(t), \quad z_0 = \ln x_0 + d(t_0),$$

with

(8) $d(t) = \varphi(t) \exp(-\beta t),$



Figure 1: A realization of the process $X_C(t)$ in the region (S_1, S_2) .

where

(9)
$$\varphi(t) = \int^t C(\tau) \exp(\beta \tau) \ d\tau.$$

In this way, the FET problem for $X_C(t)$ from (S_1, S_2) is equivalent to the FET problem of Y(t) from $(\bar{S}_1(t), \bar{S}_2(t))$, where

(10)
$$\bar{S}_1(t) = \ln S_1 + d(t), \quad \bar{S}_2(t) = \ln S_2 + d(t).$$

We explicitly observe that the only hypothesis related to the function C(t) is that it is C^1 -class. Moreover, we point out that the process X(t), i.e. resulting in the absence of therapy, is obtained from $X_C(t)$ by setting C(t) = 0 in (5). In this case the transformed boundaries for the OU process Y(t) are

(11)
$$\bar{S}_1 = \ln S_1 \qquad \bar{S}_2 = \ln S_2$$

Assuming $Y(0) = y_0 \in (\bar{S}_1(0), \bar{S}_2(0))$, we define the r.v.'s:

$$\begin{aligned} T^{-} &= \inf_{t \ge 0} \{ t : Y(t) < \bar{S}_1(t); Y(\theta) < \bar{S}_2(\theta), \forall \ \theta \in (0, t) \}, \quad Y(0) = y_0, \\ T^{+} &= \inf_{t \ge 0} \{ t : Y(t) > \bar{S}_2(t); Y(\theta) > \bar{S}_1(\theta), \forall \ \theta \in (0, t) \}, \quad Y(0) = y_0, \\ T &= \inf \{ T^{-}, \ T^{+} \}, \qquad Y(0) = y_0 \end{aligned}$$

and the respective probability density functions (pdf's)

(12)

$$\gamma^{-}(t|y_{0}) = \frac{\partial}{\partial t} P(T^{-} < t);$$

$$\gamma^{+}(t|y_{0}) = \frac{\partial}{\partial t} P(T^{+} < t);$$

$$\gamma(t|y_{0}) = \frac{\partial}{\partial t} P(T < t).$$

The FET problem for the OU process Y(t) and for a width class of boundaries can be solved by using the numerical procedure introduced by Buonocore *et al.* in [2]. In [1] the authors considered also the effects of a logarithmic therapy:

$$C(t) = C_0 \log(e + \xi t).$$

However, we observe that the results obtained in [1] are limited to consider an un-diversified tumor mass, i.e. it is assumed that the tumor cells are all characterized by a same proliferation rate.

3 Proliferating and quiescent populations A first and natural generalization of the model proposed in [1] is to consider a model that incorporates all the essential biological phenomena of a cellular population. To this aim, in every cellular population we recognize three separate compartments in base of their proliferating capability:

- the compartment A constituted by proliferating cells, in phase G1 (GAP 1);
- the compartment B constituted by quiescent cells, in phase G0 (out cellular cycle);
- the compartment C which contains cells in necrosis or diversified.

Kozusko and Bajzer in [7], by extending a previous model by Gyllenberg and Webb (cf. [6]), proposed a dynamic model for the populations of proliferating and quiescent cells in which the transition rates of the two populations are functions of the total tumor population. Furthermore, the form of the two subpopulations emerges from the assumption that the total population is governed by the Gompertz equation. Under such assumption they analytically solved the model of Gillenberg-Webb, by getting the expressions for the proliferating and quiescent populations as functions of the total tumor population. In particular, called p(t) and q(t) the size of proliferating and quiescent populations respectively, in [7], the authors showed that

$$p(t) = \rho(t) \, x(t)$$

$$q(t) = \omega(t) x(t)$$

with

(13)

(14)
$$\rho(t) = \frac{\mu_q + \alpha e^{-\beta t}}{\eta - \mu_p + \mu_q} \quad \text{and} \quad \omega(t) = \frac{\eta - \mu_p - \alpha e^{-\beta t}}{\eta - \mu_p + \mu_q}.$$

Clearly x(t) = p(t) + q(t) describes the total population and, in the deterministic case, it follows the Gompertz law. The parameters $\mu_p \ge 0$ and $\mu_q \ge 0$ represent the death rates of the populations p(t) and q(t) respectively; $\eta > 0$ is the birth rate of the proliferating cells p(t). Like before, the parameters α and β represent the growth rates of the total population x(t). Moreover, in order to get p(t) and $q(t) \ge 0$, it has to be $\eta - \mu_p > \alpha$.

By the stochastic generalization of the Gompertz equation or rather of the population x(t) discussed in [1] and briefly summarized in Section 2, it is natural to generalize the model by Kozusko and Bajzer so to obtain the following stochastic relations:

(15)
$$P(t) = \rho(t) X(t)$$
$$Q(t) = \omega(t) X(t),$$

where X(t) is characterized by infinitesimal moments (4) (in the absence of therapy), so its transition pdf is:

(16)
$$f_X(x,t|x_0,t_0) = \frac{1}{x\sqrt{2\pi V(t-t_0)}} \exp\left\{-\frac{\left[\ln x - M(t|x_0,t_0)\right]^2}{2V(t-t_0)}\right\}$$

with

$$M(t|x_0, t_0) = \frac{\alpha - \sigma^2/2}{\beta} \left(1 - e^{-\beta (t - t_0)} \right) + \ln x_0 e^{-\beta (t - t_0)},$$
$$V(t) = \frac{\sigma^2}{2\beta} \left(1 - e^{-2\beta t} \right).$$

Since $\rho(t)$ and $\omega(t)$ are strictly monotone and non negative functions, from relations (15), it follows that P(t) and Q(t) are diffusion processes defined in the interval $(0, +\infty)$. We point out that by expressing the relations between the quiescent and proliferating subpopulations and the total population, we can study in a separate way the processes P(t)and Q(t) even if they are strictly connected. Indeed, the covariance of the two populations is:

$$\operatorname{cov}[P(t), Q(t)] = \operatorname{cov}[\rho(t)X(t), \omega(t)X(t)] = \rho(t)\omega(t)\operatorname{var} X(t)$$

and, since it results

$$E[X(t)] = \exp\left\{M(t \mid x_0, t_0) + \frac{V(t - t_0)}{2}\right\},\$$
$$var[X(t)] = \exp\left\{2[M(t \mid x_0, t_0) + V(t - t_0)]\right\} - \exp\left\{2M(t \mid x_0, t_0) + V(t - t_0)\right\},\$$

one has:

$$\operatorname{cov}[P(t), Q(t)] = \rho(t)\omega(t) \exp\left\{2[M(t \mid x_0, t_0) + V(t - t_0)]\right\} (e^{V(t - t_0)} - 1).$$

The transition pdf's of the processes P(t) and Q(t) describing the proliferating and quiescent populations are linked to (16) by the following relations:

$$f_P(x,t|x_0,t_0) = \frac{1}{\rho(t)} f_X\left(\frac{x}{\rho(t)},t \mid \frac{x_0}{\rho(t_0)},t_0\right)$$

(17)

$$f_Q(x,t|x_0,t_0) = \frac{1}{\omega(t)} f_X\left(\frac{x}{\omega(t)},t \mid \frac{x_0}{\omega(t_0)},t_0\right),$$

therefore, we have

(18)
$$f_P(x,t|x_0,t_0) = \frac{1}{x\sqrt{2\pi V(t-t_0)}} \exp\left\{-\frac{\left[\ln x - \ln \rho(t) - M(t \mid \frac{x_0}{\rho(t_0)},t_0)\right]^2}{2V(t-t_0)}\right\}$$

(19)
$$f_Q(x,t|x_0,t_0) = \frac{1}{x\sqrt{2\pi V(t-t_0)}} \exp\left\{-\frac{\left[\ln x - \ln \omega(t) - M(t \mid \frac{x_0}{\omega(t_0)},t_0)\right]^2}{2V(t-t_0)}\right\}.$$

From (18) and (19) we obtain the infinitesimal moments of the processes P(t) and Q(t). Indeed, called $A_i^P(x,t)$ and $A_i^Q(x,t)$ the infinitesimal moments of P(t) and Q(t) respectively, we have:

(20)
$$A_{i}^{L}(x,t) = \lim_{\Delta t \downarrow 0} \frac{1}{\Delta t} \int_{0}^{\infty} (z-x)^{i} f_{L}(z,t+\Delta t \mid x,t) dz$$
$$i = 1,2; \qquad L = P, Q.$$

After some calculations we get:

(21)
$$A_1^P(x,t) = \left[\alpha + \frac{\rho'(t)}{\rho(t)} + \beta \ln \rho(t)\right] x - \beta x \ln x \qquad A_2^P(x,t) = \sigma^2 x^2$$

and

(22)
$$A_1^Q(x,t) = \left[\alpha + \frac{\omega'(t)}{\omega(t)} + \beta \ln \omega(t)\right] x - \beta x \ln x \qquad A_2^Q(x,t) = \sigma^2 x^2$$

so the processes P(t) and Q(t) are time-non-homogeneous. We can obtain the infinitesimal moments (21) and (22) in a more immediate way by relations (15), as shown in the following:

Remark 1 The processes P(t) and Q(t) satisfy the following stochastic differential equations:

(23)
$$dP(t) = \left[\frac{\rho'(t)}{\rho(t)} + \alpha - \beta \log\left(P(t)/\rho(t)\right)\right] P(t) dt + \sigma P(t) dW(t)$$

(24)
$$dQ(t) = \left[\frac{\omega'(t)}{\omega(t)} + \alpha - \beta \log\left(Q(t)/\omega(t)\right)\right] Q(t) dt + \sigma Q(t) dW(t)$$

Proof. From (15) we have:

(25)
$$dP(t) = d[\rho(t) X(t)] = \rho'(t) X(t) dt + \rho(t) dX(t) = \rho'(t) X(t) dt + \rho(t) [\alpha X(t) - \beta X(t) \log (X(t))] dt + \sigma X(t) dW(t)$$

and substituting in the second member $X(t) = P(t)/\rho(t)$, we obtain (23). In analogous way we obtain (24).

In Figure 2 four hypothetical sample paths of the processes P(t) and Q(t) are shown for different choices of the parameter σ representing the width of the random fluctuations on the population X(t).

An interesting remark is the following:

Remark 2 The infinitesimal moments (21) and (22) can be write as in (5), indeed

$$A_1^P(x,t) = [\alpha - G(t)] x - \beta x \ln x,$$

$$A_1^Q(x,t) = [\alpha - H(t)] x - \beta x \ln x,$$

where

(26)
$$G(t) = -\frac{\rho'(t)}{\rho(t)} - \beta \ln \rho(t) \qquad e \qquad H(t) = -\frac{\omega'(t)}{\omega(t)} - \beta \ln \omega(t)$$

Remark 2 allows us to analyse mathematically the processes P(t) and Q(t). Indeed, we can see P(t) and Q(t) as particular cases of $X_C(t)$, so that it is possible to find a transformation which leads P(t) and Q(t) in an OU process, as shown in the following proposition:

Proposition 1 The processes P(t) and Q(t) are transformable in an OU process characterized by infinitesimal moments (6).

Proof. We note that, from Remark 2, the process P(t) can be formally write as a process $X_G(t)$ describing the whole tumor population in the presence of a therapy G(t) given in (26). So, as shown in Section 2, P(t) can be transformed into an OU process with infinitesimal moments (6) through the transformation (7) where d(t) and $\varphi(t)$ are given in (8) and (9) respectively, so

$$d(t) = -\ln \rho(t).$$

Analogously, Q(t) is transformed in OU process (6) by using (7) with

(28)
$$d(t) = -\ln \omega(t).$$



Figure 2: Trajectories of P(t) (red curve) and Q(t) (blue curve) for different choices of the parameter σ . From left to right and from top to bottom we choose $\sigma = 0, 0.1, 0.5, 1$).

At this point it is natural to extend the FET analysis of the process describing the total tumor population to the two subpopulations P(t) and Q(t). From Proposition 1 we have that the FET problem for P(t) [Q(t)] through an arbitrary real interval (S_1^P, S_2^P) $[(S_1^Q, S_2^Q)]$ is equivalent to the FET problem for the OU process Y(t) characterized by infinitesimal moments (6) through the interval $(\bar{S}_1^P, \bar{S}_2^P)$ $[(\bar{S}_1^Q, \bar{S}_2^Q)]$, where, for i = 1, 2, we have set

$$\bar{S}_i^P(t) = \ln\left(\frac{S_i^P(t)}{\rho(t)}\right) \qquad \left[\bar{S}_i^Q(t) = \ln\left(\frac{S_i^Q(t)}{\omega(t)}\right)\right].$$

As made in [1], we choose two boundaries S_1 and S_2 for the total tumor population; this infers two boundaries on the populations P(t) and Q(t). Indeed from (13), called $S_1^P(t)$ and $S_2^P(t)$ the boundaries for the process P(t), they are connected to S_1 and S_2 introduced for the process X(t) by the relation:

(29)
$$S_i^P(t) = \rho(t) S_i \qquad i = 1, 2.$$

In the same way, called $S_1^Q(t)$ and $S_2^Q(t)$ the boundaries for Q(t), we have:

(30)
$$S_i^Q(t) = \omega(t) S_i \qquad i = 1, 2.$$

The following proposition shows the relation between the FET problem of the process P(t) [Q(t)] and the already analysed FET problem for X(t).

Proposition 2 The first-exit-time problem for P(t) [Q(t)] from the region $(S_1^P(t), S_2^P(t))$ $[(S_1^Q(t), S_2^Q(t))]$ is equivalent to the FET problem for X(t) from (S_1, S_2) where $S_1 = S_1^P(t) + S_1^Q(t)$ and $S_2 = S_2^P(t) + S_2^Q(t)$, with $S_i^P(t), S_i^Q(t)$ (i = 1, 2) defined in (29) and (30).

Proof. We obtain the thesis for the process P(t). An analogous argument can be used for Q(t). By Proposition 1 the FET problem for P(t) through $(S_1^P(t), S_2^P(t))$ is equivalent to the FET problem for the OU process (6) through the interval $(\bar{S}_1^P(t), \bar{S}_2^P(t))$ with

(31)
$$\bar{S}_{i}^{P}(t) = \ln\left(\frac{S_{i}^{P}(t)}{\rho(t)}\right) = \ln S_{i} \quad (i = 1, 2),$$

where use of (27) has been made. So, the analysis of the FET problem for P(t) through $S_i^P(t)$ (i = 1, 2) given in (29) corresponds to consider the FET problem for the process Y(t) through \bar{S}_1 and \bar{S}_2 defined in (10). Since this last one is equivalent to the FET problem from (S_1, S_2) for X(t), we obtain the thesis.

4 The effect of a therapy On the basis of connection between cytotoxic activity and cell cycle, antitumoral drugs are classified in two classes:

- Non-specific cycle drugs: they can damage tumor cells in any phase of the cellular cycle;
- Specific-cycle drugs: they can damage tumor cells only in a fixed phase of the cell cycle.

Our approach, consisting to "split" the total tumor population in the two subpopulations P(t) and Q(t), allows us to introduce in our model the effect of the aforementioned drugs, as we will see in this section.

4.1 Non-specific cycle drugs We said that the effect of non-specific cycle drugs is unconnected to the presence of cells in cycle, so this drugs type damages both the proliferating population and quiescent population. Our aim is to analyse how the effect of a therapy C(t) applied at the whole population X(t) is transferred on the populations P(t) and Q(t).

To this aim, we assumed that the effect of a therapy applied to the tumor population X(t) mathematically corresponds to the parametric perturbation

(32)
$$\alpha \to \alpha - C(t),$$

where C(t) represents the regression rate of the tumor due to the therapy. So, called $P_C(t)$ and $Q_C(t)$ the proliferating and quiescent population size in the presence of a non-specific-therapy C(t), introducing the parametric perturbation (32) in (15), we obtain:

$$P_C(t) = \tilde{\rho}(t) X_C(t)$$

(33)

$$Q_C(t) = \tilde{\omega}(t) X_C(t),$$

where $X_C(t)$ is defined in (5) and the functions $\tilde{\rho}(\cdot)$ and $\tilde{\omega}(\cdot)$ are obtained from $\rho(\cdot)$ and $\omega(\cdot)$ defined in (14) substituting α with the parameter $\alpha - C(t)$, that is

$$\tilde{\rho}(t) = \frac{\mu_q + [\alpha - C(t)] e^{-\beta t}}{\eta - \mu_p + \mu_q}$$
$$\tilde{\omega}(t) = \frac{\eta - \mu_p - [\alpha - C(t)] e^{-\beta t}}{\eta - \mu_p + \mu_q}$$

Proposition 3 The processes $P_C(t)$ and $Q_C(t)$ satisfy the following stochastic differential equations:

$$dP_C(t) = \left[\alpha - C(t) + \frac{\tilde{\rho}'(t)}{\tilde{\rho}(t)} - \beta \log\left(P_C(t)/\tilde{\rho}(t)\right)\right] P_C(t) dt + \sigma P_C(t) dW(t)$$

(34)

$$dQ_C(t) = \left[\alpha - C(t) + \frac{\tilde{\omega}'(t)}{\tilde{\omega}(t)} - \beta \log\left(Q_C(t)/\tilde{\omega}(t)\right)\right]Q(t)\,dt + \sigma Q(t)\,dW(t)$$

Proof. The thesis follows from (33), proceeding as in Remark 1.

So, by Proposition 3 the process $P_C(t)$ $[Q_C(t)]$ is characterized by infinitesimal moments:

$$A_1^{P_C}(x,t) = \left[\alpha - C(t) + \frac{\tilde{\rho}'(t)}{\tilde{\rho}(t)} - \beta \log\left(\frac{x}{\tilde{\rho}(t)}\right)\right] x \qquad A_2^{P_C}(x,t) = \sigma^2 x^2$$

(35)

$$\left[A_1^{Q_C}(x,t) = \left[\alpha - C(t) + \frac{\tilde{\omega}'(t)}{\tilde{\omega}(t)} - \beta \log\left(\frac{x}{\tilde{\omega}(t)}\right)\right] x \qquad A_2^{Q_C}(x,t) = \sigma^2 x^2\right].$$

In the following proposition, we present an analogous result to Proposition 2.

Proposition 4 The FET problem for the process $P_C(t)$ [$Q_C(t)$] through the interval ($S_1^{P_C}(t), S_2^{P_C}(t)$) [$(S_1^{Q_C}(t), S_2^{Q_C}(t))$] with

$$S_i^{P_C}(t) = \tilde{\rho}(t) S_i \qquad [S_i^{Q_C}(t) = \tilde{\omega}(t) S_i]$$

for i = 1, 2, is equivalent to the FET problem for the process $X_C(t)$ through the boundaries S_1 and S_2 .

Proof. It is similar to Proposition 2.

4.2 Specific cycle drugs To analyse the effect of a specific cycle drugs we note that the perturbation (32) corresponds to the following parametric perturbation in the populations P(t) and Q(t):

(36)
$$\begin{aligned} \mu_p \to \tilde{\mu}_p(t) &:= \mu_p - C(t) \mathrm{e}^{-\beta t} \\ \mu_q \to \tilde{\mu}_q(t) &:= \mu_q - C(t) \mathrm{e}^{-\beta t}, \end{aligned}$$

indeed we can write $\tilde{\rho}(t)$ in the following form:

$$\tilde{\rho}(t) = \frac{\tilde{\mu}_q + \alpha e^{-\beta t}}{\eta - \tilde{\mu}_p + \tilde{\mu}_q}.$$

The previous observation allows to introduce in the model the effect of the phase-specific drugs, i.e. able to act on cells in a fixed phase of the cell cycle. So cells in phase G_0 are left out from the action of the drug. Mathematically, this one corresponds to a parametric perturbation in the only parameter μ_p . So the resulting processes $P_C(t)$ and $Q_C(t)$ are characterized by infinitesimal moments (35) where

$$\tilde{\rho}(t) = \frac{\mu_q + \alpha \mathrm{e}^{-\beta t}}{\eta - \mu_p + C(t)\mathrm{e}^{-\beta t} + \mu_q}$$

and

$$\tilde{\omega}(t) = 1 - \tilde{\rho}(t).$$

5 Numerical results To provide a numerical analysis of the results shown in the previous sections, we shall choose the parameters α and β as in [1] so to extend the results obtained in it to the populations P(t) and Q(t). To this aim we choose $\alpha = 6.46 \ years^{-1}$ and $\beta = 0.314 \ years^{-1}$ corresponding to a parathyroid tumor with mean age of 19.6 $\ years^{-1}$. Moreover we take $\mu_p = 0.2 \ years^{-1}$, $\mu_q = 0.2 \ years^{-1}$, $\eta = 1 \ years^{-1}$ and $\sigma = 1 \ years^{-1}$ and $P(0) = \rho(0) x(0)$ almost surely, with $x_0 = 1.074 \cdot 10^8$ corresponding to a total tumor weight equal to 0.1 g, i.e. the smallest weight of tumor likely to be detectable (see [9]). We introduce in the population P(t) the two boundaries

$$S_1^P = 1$$
 and $S_2^P = 5 \cdot 10^8$

By using the numerical algorithm proposed in [2], we can evaluate numerically the pdf's $\gamma^$ and γ^+ of the r.v.'s T^- and T^+ representing the first exit times of P(t) through S_1^P and S_2^P respectively. In Figures 3 and 4 approximations of γ^- and γ^+ (curve on the left) and the corresponding probabilities (curve on the right) are plotted. We can observe that the probability to reach the boundary S_1 before crossing S_2 is near to zero in the absence of therapy. In the following we want to analyse numerically the FET problem for P(t) in the presence of a therapy of constant intensity C_0 .



Figure 3: FET pdf through the boundary $S_1^P = 1$ (curve on the left) and the corresponding probability (curve on the right) for the process P(t).

In the case of a non-specific cycle drugs, by choosing $C(t) = C_0 = 1$ years⁻¹, which corresponds to a therapy able to reduce nearly of the 15 per cent the growth rate of the total tumor cells, we obtain the approximation of γ^- and γ^+ , with the corresponding probabilities plotted in Figure 5 and 6 respectively. Finally, in the case of specific cycle drugs, choosing $C_0 = 1$ years⁻¹ we obtain γ^- and γ^+ (with the corresponding probabilities) as in Figures 7 and 8. By comparing Figures 6 and 8, we can observe that non-specific cycle drugs are more effective when we consider a wide interval of administration of the drug. This result is in agreement with clinical results since the proliferating population tends to become small as we can see in Figure 2.



Figure 4: FET pdf through the boundary $S_2^P = 5 \cdot 10^8$ (curve on the left) and the corresponding probability (curve on the right) for the process P(t).



Figure 5: FET pdf through the boundary $S_1^P = 1$ (curve on the left) and the corresponding probability (curve on the right) for the process P(t) in the presence of a non-specific cycle drugs with fixed intensity $C_0 = 1 \ years^{-1}$.

Concluding remarks The aim of this paper has been to provide some quantitative information on the role of proliferation and quiescence in tumor growth where the whole tumor



Figure 6: FET pdf through the boundary $S_2^P = 5 \cdot 10^8$ (curve on the left) and the corresponding probability (curve on the right) for the process P(t) in the presence of a non-specific cycle drugs with fixed intensity $C_0 = 1$ years⁻¹.



Figure 7: FET pdf through the boundary $S_1^P = 1$ (curve on the left) and the corresponding probability (curve on the right) for the process P(t) in the presence of a specific cycle drugs with fixed intensity $C_0 = 1$ years⁻¹.



Figure 8: FET pdf through the boundary $S_2^P = 5 \cdot 10^8$ (curve on the left) and the corresponding probability (curve on the right) for the process P(t) in the presence of a specific cycle drugs with fixed intensity $C_0 = 1 \ years^{-1}$.

population is modeled by means of a generalized Gompertz law. The proposed model allows to include the effect of a non-specific cycle drug and specific cycle drug applied on the total tumor cell population. The followed analysis on the proposed model highlights that, in agreement with clinical results, non-specific cycle drugs are more effective if applied on a wide interval. Our study opens the way to future endeavors focusing on a systematic computational analysis of the role of various types of therapies applied on the proliferating and quiescent populations.

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