Computational Statistics and Data Analysis 56 (2012) 1723–1736

Contents lists available at SciVerse ScienceDirect

Computational Statistics and Data Analysis

journal homepage: www.elsevier.com/locate/csda

Inference on a stochastic two-compartment model in tumor growth

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ARTICLE INFO

Article history:
Received 31 March 2011
Received in revised form 15 October 2011
Accepted 16 October 2011
Available online 20 October 2011

Keywords:
Gompertz diffusion processes
Proliferative and quiescent cells
ML estimation
Regression

ABSTRACT

A continuous-time model that incorporates several key elements in tumor dynamics is analyzed. More precisely, the form of proliferating and quiescent cell lines comes out from their relations with the whole tumor mass, giving rise to a two-dimensional diffusion process, generally time non-homogeneous. This model is able to include the effects of the mutual interactions between the two subpopulations. Estimation of the rates of the two subpopulations based on some characteristics of the involved diffusion processes is discussed when longitudinal data are available. To this aim, two procedures are presented. Some simulation results are developed in order to show the validity of these procedures as well as to compare them. An application to real data is finally presented.

1. Introduction

Tumor growth has received in the past three decades an increasing interest in medical and more generally in scientific fields. From a mathematical point of view, arrangements of growth models able to describe more and more fine aspects of tumor growth have occurred. Between the proposed models, very popular are these ones based on ordinary differential equations (de Pillis et al., 2009; Parfitt and Fyhrie, 1997; Sachs et al., 2001). Moreover, the model that seems better to fit experimental data is the Gompertz model, since it is able to include an incoming lack of nutrients for cancer cells (Castorina and Zappalà, 2006; de Vladar et al., 2003; de Vladar and Gonzalez, 2004). Further, the response of tumor to an antiangiogenetic treatment is still a challenging issue, so the introduction of more and more realistic terms representing the effect of a therapy in tumor growth is a fundamental problem in such fields. Really, it is reasonable to suppose that a therapy is able to modify the growth rates of the tumor population. On the other hand, it is known that tumor presents different behaviors, so it appears natural to suppose that an antiangiogenetic treatment acts in different ways on the subpopulations. More precisely, in the prevascular phase in the absence of tumor host interactions, the tumor mass shows three layers: necrotic core (laying in the center of tumor), quiescent (non-proliferating) cells and proliferating cells (Cameron et al., 1997, 2001; Feizabadi et al., 2008; Freyer and Sutherland, 1986; Kozusko and Bajzer, 2003; Kozusko and Bourdeau, 2007). Quiescent population is characterized by a null-growth rate, but interactions with proliferative cells are possible, i.e. transition rates between the two populations are possible.

In Albano and Giorno (2006), the authors introduced a stochastic model based on the Gompertz deterministic growth to describe the dynamics of a tumor population obtaining a diffusion process characterized by lognormal transition density. In the second instance, the drift of the process was modified introducing an exogenous term representing the effect of an antiangiogenetic therapy. More precisely, they assumed that the therapy is able to modify the growth rate of the tumor.

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doi:10.1016/j.csda.2011.10.016

Afterward, in Albano and Giorno (2008) dynamics of the proliferative and quiescent subpopulations was studied by means of two diffusions. This approach permitted to include in the model the effect of two classical therapy protocols: specific-cycle acting only on the proliferative cells and non-specific-cycle drugs able to destroy both the proliferative and the quiescent populations.

In this paper, we focus on the inference of the parameters of the model. A first step in this sense was made in Albano et al. (2011) where a methodology to fit the effect of a therapy on the whole population was proposed. More precisely, we propose two methodologies to estimate the rates of the proliferative and quiescent populations.

In Section 2 the deterministic models for the involved tumor populations are briefly introduced. In particular we derive some useful relations between the two subpopulations, proliferative and quiescent. Moreover an explicit expression is derived for the net-transition rate function. In Section 3 a stochastic generalization of the model is presented, discussing the main characteristics of the diffusion processes representing the tumor populations. In Section 4 estimation of the rates of the two subpopulations is discussed when longitudinal data are available. To this end, two estimation methods are considered: the first one consisting in maximum likelihood method and the second one based on linear regression. Finally, in Section 5, some simulation results and an application to real data are presented in order to show and compare the validity of the procedures presented.

2. The deterministic model

Let us denote by t_0 the initial time, i.e. the time of diagnosis of the disease, and let $y(t)$ be the tumor size at time t ($t \geq t_0 \geq 0$). Generally, $y(t_0) = 1$; anyway, we can consider the tumor size normalized with respect the initial one, i.e. $x(t) = y(t)/y(t_0)$. Let us assume that dynamics of the population $x(t)$ is described by the following deterministic Gompertz-type equation:

$$\dot{x}(t) = [\alpha - \beta \log x(t)]x(t), \qquad x(t_0) = 1 \quad (t \geq t_0), \tag{1}$$

where α and β are positive constants representing the birth rate and the death rate of the tumor population, respectively; their measurement units are $[time]^{-1}$. The solution of (1) is

$$x(t) = \exp\left\{\frac{\alpha}{\beta}\left[1 - e^{-\beta(t-t_0)}\right]\right\} \tag{2}$$

characterizing a Gompertz curve. For simplicity, in the following we will assume $t_0 = 0$.

We point out that Eq. (1) describes an undiversified tumor-mass, i.e. it is assumed that tumor cells are all characterized by the same proliferation rate. A natural generalization of the model (2) consists to incorporate the main biological phenomena of a cellular population. In every cellular population we recognize three separate compartments in base of their proliferating capability: (i) the compartment A constituted by proliferating cells, in phase G1 (GAP 1); (ii) the compartment B constituted by quiescent cells, in phase G0 (out cellular cycle); (iii) the compartment C which contains cells in necrosis or diversified. By extending a previous model by Gyllenberg and Webb (see Gyllenberg and Webb (1989)), Kozusko and Bajzer (2003) 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. Many authors have showed the usefulness of the Gompertz law determined by (1) in this sense. For example, Helmlinger et al. (1997) remark that this law is able to model the evolution in vitro of multicellular tumor spheroids and apply it to demonstrate that solids stress inhibits their growth. Recently, D'Onofrio et al. (2011) have presented a new extension of Gompertz law for tumor growth compatible with the two-compartment model. For this model, denoting by $p(t)$ and $q(t)$ the sizes of proliferating and quiescent populations on the time t, we have:

$$x(t) = p(t) + q(t). \tag{3}$$

Following Kozusko and Bajzer (2003) and Kozusko and Bourdeau (2007) we assume that the proliferating and quiescent populations dynamics are described from the scheme of Fig. 1. More precisely, the parameters $\mu_p \geq 0$ and $\mu_q \geq 0$ represent the death rates for the proliferating and quiescent cells, respectively and $\eta > 0$ denotes the birth rate of the proliferating population. Further, the functions $r_0(x) \geq 0$ and $r_1(x) \geq 0$ are the transition rates between the two populations and they are assumed to be functions of the total number of cells. In particular, $r_0(x)$ characterizes the transitions from proliferative subpopulation into quiescent one and $r_1(x)$ specifies the rate from the quiescent compartment into the proliferative one. The scheme of Fig. 1 leads to the following relations:

$$\dot{p}(t) = [\eta - \mu_p - r_0(x)]p(t) + r_1(x)q(t) \tag{4}$$

and

$$\dot{q}(t) = r_0(x)p(t) - [r_1(x) + \mu_q]q(t). \tag{5}$$

From (3), by using (4) and (5), one obtains:

$$\dot{x}(t) = \dot{p}(t) + \dot{q}(t) = \left[\eta - \mu_p\right]p(t) - \mu_q\, q(t)$$

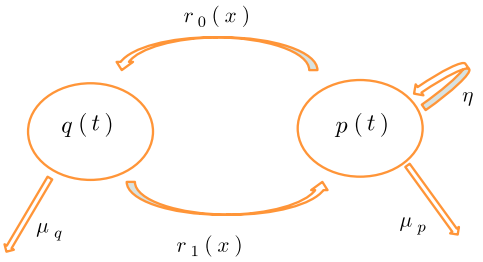

Fig. 1. Two-compartment model of cell population growth.

and from (3) it follows:

$$\dot{x}(t) = \left[\eta - \mu_p + \mu_q\right] p(t) - \mu_q\, x(t). \tag{6}$$

From (6), making use of definition (1), one has:

$$p(t) = \frac{x(t)}{\eta_- \mu_p + \mu_q}\left[\alpha - \beta\, \log x(t) + \mu_q\right]$$

that, recalling (2), can be written as

$$p(t) = \rho(t) x(t) \tag{7}$$

where

$$\rho(t) = \frac{\mu_q + \alpha e^{-\beta t}}{\eta - \mu_p + \mu_q} \tag{8}$$

denotes the fraction of the tumor mass that defines the proliferating subpopulation.

Note that (8) has to be a positive function. This leads to the following assumptions on the rates of the model:

$$\eta > \mu_p - \mu_q.$$

Further, from (3) or, equivalently, from (5), one has:

$$q(t) = \left[1 - \rho(t)\right] x(t) \tag{9}$$

that describes the size of the quiescent subpopulation in terms of the total tumor population size.

Let us observe that the transition rates $r_0(x)$ and $r_1(x)$ can be easily obtained as functions of the parameters η, μ_p and μ_q as shown in Kozusko and Bajzer (2003).

We point out that here the total cancer population is viewed as a little net (cf. Fig. 1) with two nodes representing the proliferating and quiescent subpopulations. It is interesting to analyze the net transition rate function defined as follows:

$$\Phi(x, t) = r_0(x) p(t) - r_1(x) q(t). \tag{10}$$

Note that if $\Phi(x, t)$ is positive then the net transition rate is from the proliferating compartment into the quiescent compartment; while, negative values of $\Phi(x, t)$ mean a flow from quiescent subpopulation into proliferating subpopulation.

To evaluate the net transition rate we note that from definition (4), making use of (10), it follows:

$$\dot{p}(t) = [\eta - \mu_p] p(t) - \Phi(x, t),$$

so, from (10), recalling (7), after some simple calculations one can obtain:

$$\begin{aligned}\Phi(x, t) &= \left[\eta - \mu_p\right] p(t) - \dot{p}(t) \\ &= \frac{x(t)}{\eta - \mu_p + \mu_q}\left\{\left(\mu_q + \alpha\, e^{-\beta t}\right)\left(\eta - \mu_p - \alpha\, e^{-\beta t}\right) + \alpha\beta\, e^{-\beta t}\right\}.\end{aligned} \tag{11}$$

Eq. (11) indicates that the net transition rate is linear with respect to the whole population size.

3. Generalizing the deterministic model

In order to overcome frequent discrepancies observed between clinical data and theoretical predictions, due to more or less intense environmental fluctuations, we introduce the stochastic process $\{X(t), t \geq t_0 \geq 0\}$:

$$dX(t) = [\alpha X(t) - \beta X(t)\ \ln X(t)]\, dt + \sigma X(t)\, dW(t), \tag{12}$$

where σ is a positive constant representing the width of random fluctuations and $W(t)$ is a standard Brownian motion. The model (12) is obtained from (1) by introducing the stochastic term $\sigma X(t)\, dW(t)$. The process $\{X(t), t \geq t_0 \geq 0\}$ is a diffusion defined in $I = (0, +\infty)$, characterized by drift and infinitesimal variance:

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

respectively. We point out that the effect of a antiangiogenetic therapy was modeled in Albano and Giorno (2006) via the introduction of a time-dependent function $C(t)$ in the drift term, giving rise to the following time non-homogeneous process:

$$dX^C(t) = \left\{[\alpha - C(t)]X^C(t) - \beta\, X^C(t)\ \ln X^C(t)\right\} dt + \sigma X^C(t)\, dW(t). \tag{13}$$

Let $f_X(x, t|y, \tau)$ be the transition probability density function (pdf) of $X(t)$:

$$f_X(x, t|y, \tau) = \frac{\partial}{\partial x} Pr[X(t) < x|X(\tau) = y] \quad (x, y \in I, t > \tau > t_0).$$

It is solution of the Kolmogorov equation

$$\frac{\partial f_X(x, t|y, \tau)}{\partial \tau} + [\alpha\, y - \beta\, y\ \ln y]\, \frac{\partial f_X(x, t|y, \tau)}{\partial y} + \frac{\sigma^2}{2} y^2 \frac{\partial^2 f_X(x, t|y, \tau)}{\partial y^2} = 0, \tag{14}$$

satisfying the initial delta condition:

$$\lim_{\tau \to t} f_X(x, t|y, \tau) = \delta(x - y).$$

In order to find the solution of the Eq. (14) we consider the transformation:

$$\begin{aligned} &\tilde{x} = e^{\beta t}\left[\log x + \frac{1/\beta}{\sigma^2/2 - \alpha}\right], \qquad \tilde{y} = e^{\beta \tau}\left[\log y + \frac{1/\beta}{\sigma^2/2 - \alpha}\right], \\ &\tilde{t} = \frac{e^{2\beta t}}{2\beta}, \qquad \tilde{\tau} = \frac{e^{2\beta \tau}}{2\beta}. \end{aligned} \tag{15}$$

It reduces the diffusion equation (14) to the analogous one of the Wiener process $\tilde{X}(t)$ with drift and infinitesimal variance

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

respectively. Denoting by $\tilde{f}$ the transition pdf of $\tilde{X}(t)$, we have

$$\tilde{f}(\tilde{x}, \tilde{t}|\tilde{y}, \tilde{\tau}) = x\, e^{-\beta t} f_X(x, t|y, \tau). \tag{16}$$

Since $\tilde{f}$ is Gaussian with mean $\tilde{y}$ and variance $\sigma^2\ (\tilde{t} - \tilde{\tau})$, making use of (15) and of (16), one has:

$$f_X(x, t|y, \tau) = \frac{1}{x\sqrt{2\pi\sigma^2(t|\tau)}} \exp\left\{-\frac{[\log x - M(t|\log y, \tau)]^2}{2\sigma^2(t|\tau)}\right\}, \tag{17}$$

that is, $[X(t)|X(\tau) = y]$ has a lognormal distribution $\Lambda[M(t|\log y, \tau); \sigma^2(t|\tau)]$, with

$$M(t|y, \tau) = e^{-\beta(t-\tau)} y + \left(\alpha - \frac{\sigma^2}{2}\right) \frac{1 - e^{-\beta\,(t-\tau)}}{\beta}$$

and

$$\sigma^2(t|\tau) = \frac{\sigma^2}{2\beta}\left[1 - e^{-2\beta\,(t-\tau)}\right].$$

Furthermore, the n-th moment ($n = 1, 2, \ldots$) of the process $X(t)$ is:

$$\mathbb{E}[X^n(t)|y, \tau] = \exp\left\{n\left[M(t|\log y, \tau) + \frac{n}{2}\sigma^2(t|\tau)\right]\right\}. \tag{18}$$

From (18) it is immediate to obtain the conditional mean and the conditional variance of the process $X(t)$:

$$\mathbb{E}[X(t)|y, \tau] = \exp\left\{\left[M(t|\log y, \tau) + \frac{1}{2}\sigma^2(t|\tau)\right]\right\}$$

and

$$\mathrm{Var}[X(t)|y,\tau] = \exp\Big\{2\,M(t|\log y,\tau) + \sigma^2(t|\tau)\Big\}\Big[\exp\{\sigma^2(t|\tau)\} - 1\Big]. \tag{19}$$

By the stochastic Gompertz-type equation (12) it is natural to generalize the models (7) and (9) of the previous section so to obtain the following stochastic relations:

$$P(t) = \rho(t)X(t) \tag{20}$$

and

$$Q(t) = \big[1 - \rho(t)\big]X(t). \tag{21}$$

We point out that in (20) and (21) the function $\rho(t)$ is deterministic and specified in (8). So we are assuming that a noise affects the whole tumor population $X(t)$ and we are studying the consequences of this noise on the proliferating and quiescent cells. This assumption seems reasonable since the most common diagnostic instruments are usually able to detect the whole tumor volume $X(t)$.

From (20) and (21), by Ito's formula it is easy to obtain the stochastic differential equations governing the processes $P(t)$ and $Q(t)$:

$$dP(t) = \left[\frac{\rho'(t)}{\rho(t)} + \alpha - \beta\log\frac{P(t)}{\rho(t)}\right]P(t)\,dt + \sigma P(t)dW(t) \tag{22}$$

and

$$dQ(t) = \left[-\frac{\rho'(t)}{1-\rho(t)} + \alpha - \beta\log\frac{Q(t)}{1-\rho(t)}\right]Q(t)\,dt + \sigma Q(t)dW(t), \tag{23}$$

resulting that $P(t)$ and $Q(t)$ are diffusion processes defined in the interval $(0,\infty)$.

Moreover from (22) and (23) the infinitesimal moments of $P(t)$ and $Q(t)$ can be written, respectively, as follows:

$$A_1^P(x,t) = [\alpha - G(t)]\,x - \beta x\log x, \qquad A_2^P(x) = \sigma^2x^2 \tag{24}$$

and

$$A_1^Q(x,t) = [\alpha - H(t)]\,x - \beta x\log x, \qquad A_2^Q(x) = \sigma^2x^2, \tag{25}$$

where

$$G(t) = -\frac{\rho'(t)}{\rho(t)} - \beta\log\rho(t) \qquad \text{and} \qquad H(t) = \frac{\rho'(t)}{1-\rho(t)} - \beta\log[1-\rho(t)]. \tag{26}$$

An interesting remark is the following: (24) and (25) suggest that the processes $P(t)$ and $Q(t)$ have the same form of the process $X^C(t)$ in (13) with $C(t) = G(t)$ in the case of $P(t)$ and $C(t) = H(t)$ for $Q(t)$.

Finally, from (17), (20) and (21) by making the corresponding change of variables, we obtain the transition pdfs of the processes $P(t)$ and $Q(t)$:

$$f^P(x,t|y,\tau) = \frac{1}{x\sqrt{2\pi\sigma^2(t|\tau)}}\exp\left\{-\frac{\left[\log x - \log\rho(t) - M\left(t|\log\frac{y}{\rho(\tau)},\tau\right)\right]^2}{2\sigma^2(t|\tau)}\right\} \tag{27}$$

and

$$f^Q(x,t|y,\tau) = \frac{1}{x\sqrt{2\pi\sigma^2(t|\tau)}}\exp\left\{-\frac{\left[\log x - \log\omega(t) - M\left(t|\log\frac{y}{\omega(\tau)},\tau\right)\right]^2}{2\sigma^2(t|\tau)}\right\},$$

where $\omega(t) = 1 - \rho(t)$.

We point out that by expressing the relations between the quiescent and proliferating subpopulations and the whole population, we can study in a separate way the process $P(t)$ and $Q(t)$ even if they are strictly connected. Indeed, the conditional covariance of the two subpopulations is

$$\begin{aligned}\mathrm{Cov}[P(t),Q(t)|y,\tau] &= \mathrm{Cov}[\rho(t)X(t),[1-\rho(t)]X(t)|y,\tau]\\ &= \rho(t)[1-\rho(t)]\,\mathrm{Var}\,[X(t)|y,\tau]\end{aligned}$$

where $\mathrm{Var}\,[X(t)\mid y,\tau]$ is given in (19).

4. Inference

In this section we will estimate the parameters of the processes $P(t)$ and $Q(t)$. We point out that the parameters characterizing the whole population, α, β and σ can be estimate by maximum likelihood (ML) method (see Albano et al., 2011) so only the estimations of μ_p, μ_q and η are needed. In the following we provide two alternative methods for the estimation of μ_q and $\eta - \mu_p$, i.e. the growth net rate of the population $P(t)$: ML method for the processes $P(t)$ and $Q(t)$ and the second one based on the estimation of $G(t)$ and $H(t)$ defined in (26) and on a linear relation derived by (8).

4.1. Maximum likelihood estimation of the parameters of $P(t)$

In the following we will focus on the process $P(t)$. An analogous procedure can be developed for $Q(t)$. Let us consider a discrete sampling of $P(t)$, based on d sample paths, for times t_{ij}, $(i = 1, \ldots, d, j = 1, \ldots, n_i)$ with $t_{i1} = t_1, i = 1, \ldots, d$ and denote these values as $\left\{x_{ij}^P\right\}_{i=1,\ldots,d;j=1,\ldots,n_i}$. For simplicity we will consider $t_{ij} - t_{i,j-1} = h$.

From (27), denoting $n = \sum_{i=1}^{d} n_i$ and $\mathbf{x}^P$ the vector containing the x_{ij}^P values, and considering a lognormal initial distribution $P(t_1) \sim \Lambda_1(\mu_1, \sigma_1^2)$, the log-likelihood function is

$$\begin{aligned}\log L_{\mathbf{x}^P}(\mu_1, \sigma_1^2, \eta, \mu_p, \mu_q) = &-\frac{n}{2}\log(2\pi) - \frac{d}{2}\log\sigma_1^2 - \frac{n-d}{2}\log\sigma^2(h|0) - \sum_{i=1}^{d}\log x_{i1}^P - \sum_{i=1}^{d}\sum_{j=1}^{n_i}\log x_{ij}^P \\ &- \frac{1}{2\sigma_1^2}\sum_{i=1}^{d}\left[\log(x_{i1}^P - \mu_1)\right]^2 - \frac{1}{2\sigma^2(h|0)}\sum_{i=1}^{d}\sum_{j=1}^{n_i}\Big[(\log x_{ij}^P - M(h|\log x_{i,j-1}^P, 0)) \\ &- \log B_{ij}^{(2)} + e^{-\beta h}\log B_{ij}^{(1)} + (1 - e^{-\beta h})\log(\eta - \mu_p + \mu_q)\Big]^2,\end{aligned}$$

where

$$B_{ij}^{(1)} = \mu_q + \alpha e^{-\beta t_{i,j-1}}, \qquad B_{ij}^{(2)} = \mu_q + \alpha e^{-\beta(t_{i,j-1}+h)}.$$

The parameters to estimate are μ_1, σ_1, related to the initial distribution, and μ_p, μ_q and η connected to the two-compartment model. We consider α, β and σ^2 as fixed values; this means that the inference on $P(t)$ is provided after the estimation of $X(t)$. The ML estimations of μ_1 and σ_1^2 are

$$\widehat{\mu}_1 = \frac{1}{d}\sum_{i=1}^{d}\log x_{i1}^P, \qquad \widehat{\sigma}_1^2 = \frac{1}{d}\sum_{i=1}^{d}(\log x_{i1}^P - \widehat{\mu}_1)^2.$$

Moreover, the likelihood equations for η and μ_p are equal, so it is possible to estimate μ_q and $\eta - \mu_p$. Concretely the following system of equations can be obtained:

$$\sum_{i=1}^{d}\sum_{j=2}^{n_i}\left[\log x_{ij}^P - \log B_{ij}^{(2)} - M(h|\log x_{i,j-1}^P, 0) + e^{-\beta h}\log B_{ij}^{(1)} + (1 - e^{-\beta h})\log(\eta - \mu_p + \mu_q)\right] = 0 \tag{28}$$

and

$$\sum_{i=1}^{d}\sum_{j=2}^{n_i}\left[\log x_{ij}^P - \log B_{ij}^{(2)} - M(h|\log x_{i,j-1}^P, 0) + e^{-\beta h}\log B_{ij}^{(1)} + (1 - e^{-\beta h})\log(\eta - \mu_p + \mu_q)\right]C_{ij} = 0 \tag{29}$$

with $C_{ij} = \frac{1}{B_{ij}^{(2)}} - \frac{e^{-\beta h}}{B_{ij}^{(1)}}$. We denote by

$$X_1^P = \sum_{i=1}^{d}\sum_{j=2}^{n_i}\log x_{ij}^P, \qquad X_2^P = \sum_{i=1}^{d}\sum_{j=2}^{n_i}\log x_{i,j-1}^P,$$

$$X_{1,*}^P = \sum_{i=1}^{d}\sum_{j=2}^{n_i}\log x_{ij}^P C_{ij}, \qquad X_{2,*}^P = \sum_{i=1}^{d}\sum_{j=2}^{n_i}\log x_{i,j-1}^P C_{ij},$$

$$B_k = \sum_{i=1}^{d}\sum_{j=2}^{n_i}\log B_{ij}^{(k)}, \qquad B_{k,*} = \sum_{i=1}^{d}\sum_{j=2}^{n_i}\log B_{ij}^{(k)} C_{ij} \quad (k = 1, 2),$$

$$C = \sum_{i=1}^{d}\sum_{j=2}^{n_i}C_{ij}, \qquad Z = \left(\alpha - \frac{\sigma^2}{2}\right)\frac{1 - e^{-\beta h}}{\beta}.$$

After some algebra, from Eqs. (28) and (29), we obtain

$$X_1^P - e^{-\beta h}X_2 - (n-d)Z + (n-d)(1-e^{-\beta h})\log(\eta - \mu_p + \mu_q) = B_2 - e^{-\beta h}B_1 \tag{30}$$

and

$$X_{1,*}^P - e^{-\beta h}X_{2,*} - C\,Z + C(1-e^{-\beta h})\log(\eta - \mu_p + \mu_q) = B_{2,*} - e^{-\beta h}B_{1,*}. \tag{31}$$

From (30) we have

$$\log(\eta - \mu_p + \mu_q) = \frac{B_2 - e^{-\eta h}B_1 + (n-d)Z - X_1^P + e^{-\beta h}X_2^P}{(n-d)\left(1-e^{-\beta h}\right)} \tag{32}$$

and substituting in (31) we conclude

$$(n-d)\left[B_{2,*} - X_{1,*}^P + e^{-\beta h}\left(X_{2,*}^P - B_{1,*}\right)\right] + C\left[X_1^P - B_2 + e^{-\beta h}(B_1 - X_2^P)\right] = 0. \tag{33}$$

The last equation does not have an explicit solution with respect to μ_q, so the estimation of μ_q can be obtained by numerical methods. Once the estimation of μ_q is obtained, $\eta - \mu_p$ can be estimated through (32).

4.2. A method based on linear regression for estimating the parameters of $P(t)$

As already point out in Section 3.1 the process $P(t)$ has the form of the process $X^C(t)$ defined in (12) when $C(t) \equiv G(t)$ defined in (13). So the function $G(t)$ can be estimated using the technique suggested in Albano et al. (2011).

This technique is based on the following relation between the mean of the process in the absence of therapy, i.e. $X(t)$, and that of the process in the presence of a therapy, i.e. $X^C(t)$:

$$\frac{E\left[X^C(t)\right]}{E\left[X(t)\right]} = \exp\left(-e^{-\beta t}\int_{t_0}^{t} C(\theta)e^{\beta\theta}\,d\theta\right)$$

from which

$$C(t) = -e^{-\beta t}\,\frac{d}{dt}\left\{e^{\beta t}\log\left(\frac{E\left[X^C(t)\right]}{E\left[X(t)\right]}\right)\right\}.$$

This last expression suggests a method to find an approximation of the function $C(t)$ based on the following procedure:

- From observed data of the process $X(t)$, estimate the parameters α, β and σ^2, by using the maximum likelihood method. From this first step we obtain the ML estimators $\widehat{\alpha}$, $\widehat{\beta}$ and $\widehat{\sigma}^2$.
- Denoting by x_i and x_i^C the mean tumor size at time t_i in the control group, modeling by $X(t)$, and in the treated group, modeling by $X^C(t)$, respectively, obtain the function $m(t)$ by the interpolation of values

$$m_i = e^{\widehat{\beta}t_i}\log\left(\frac{x_i^C}{x_i}\right).$$

- Finally, consider the following function as an approximation of $C(t)$:

$$\widehat{C}(t) = -m'(t)e^{-\widehat{\beta}t}.$$

Then, from (26), we consider the ordinary differential equation

$$\frac{\rho'(t)}{\rho(t)} + \beta\log\rho(t) = -G(t)$$

with the initial condition

$$\rho(t_0) = P(t_0)/X(t_0)$$

whose solution is

$$\rho(t) = \exp\left(e^{-\beta(t-t_0)}\left[\log\rho(t_0) - \int_{t_0}^{t} G(s)e^{\beta(s-t_0)}\,ds\right]\right). \tag{34}$$

Moreover from (8) we obtain:

$$\rho(t)(\eta - \mu_p + \mu_q) - \mu_q = \alpha\,e^{-\beta t},$$

showing a straight line relation between the values of $\rho(t)$ and $\alpha\,e^{-\beta t}$. So, we consider a linear regression between these two variables:

$$Y = a + bX + \epsilon \tag{35}$$

where $a = -\mu_q$ and $b = \eta - \mu_p + \mu_q$, being $\alpha\,e^{-\beta t_i}$ $(i = 1, \ldots, n)$ the values of the dependent variable Y and $\rho(t_i)$ the corresponding values of the independent variable X. Obviously, $\widehat{\mu_q} = -\widehat{a}$ and $\widehat{\eta - \mu_p} = \widehat{b} + \widehat{a}$.

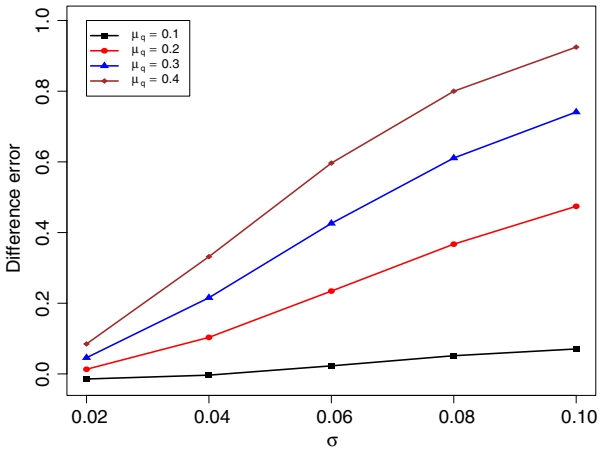

Fig. 2. Example 1. Difference between ML and regression errors. We choose $\eta - \mu_p = 0.5$.

So the suggested procedure to estimate μ_q and $\eta - \mu_p$ is the following:

- estimate the parameters α, β and σ of the process $X(t)$ by using ML method;
- estimate $G(t)$ defined in (26) by using the fitting procedure of Albano et al. (2011);
- estimate the parameters $a = -\mu_q$ and $b = \eta - \mu_p + \mu_q$ in the linear regression (35) by ordinary least squares.

5. Numerical results

In this section we compare the two proposed methods to estimate the parameters of the process $P(t)$. In particular, we consider two examples: the first one consisting of a study based on the simulation of the paths of the process $X(t)$; in the second one real data are considered. In both the cases the estimation of the parameters in the process $X(t)$, i.e. α, β and σ, is performed a priori via ML method. Then the estimation of the parameters in $P(t)$, i.e. μ_q and $\eta - \mu_p$, is obtained by applying the two proposed procedures. The comparison is finally made by considering the sum of the relative absolute errors of estimation for each parameter, that is

$$E = \frac{|\widehat{\mu_q} - \mu_q|}{\mu_q} + \frac{|\widehat{\eta - \mu_p} - (\eta - \mu_p)|}{\eta - \mu_p}.$$

5.1. Example 1: simulation study

The paths of the process $X(t)$ are simulated by fixing the values of α and β, whereas several values for σ are chosen. The corresponding values in $P(t)$ are obtained by using the relation (20) and by considering a range of values for η, μ_p and μ_q.

In particular, we choose $\alpha = 0.3$, $\beta = 0.1$ and $\sigma = 0.02\,j$ ($j = 1, \ldots, 5$), whereas the process $P(t)$ is obtained from (20) choosing in (8) $\eta = 0.8 + 0.1\,j$ and $\mu_q = \mu_p = 0.1 + 0.1\,j$ ($j = 0, \ldots, 3$). For the process $X(t)$, 100 sample paths, with 501 values each one, are simulated taking $t_0 = 0$, $t_i - t_{i-1} = 0.1$, $i = 1, \ldots, 500$, and choosing an initial lognormal distribution $\Lambda_1(1; 0.2)$. For each choice of the parameters α, β and σ the ML estimation is obtained. Then, by considering these values as fixed, the estimation for the parameters of $P(t)$, that is, μ_q and $\eta - \mu_p$, is realized by applying the two proposed procedures.

In Table 1 several values of $\eta - \mu_p$ and μ_q are considered and the estimation of the parameters carried out by the two procedures as well as the related errors are shown.

In Table 1, the value of $\eta - \mu_p$ is fixed. Moreover, in order to analyze the effect of the variability on the results, various values of σ are chosen.

The numerical results seem to show that the regression-based method works better than the ML estimation. Only for $\mu_q = 0.1$, and $\sigma = 0.02$ or $\sigma = 0.04$, that is when the paths are characterized by a small variability, we can observe a little improvement in the ML estimation, but this trend is not general. Indeed, the regression method allows to obtain estimations closer to the real values of the parameters as we can see from the last two columns of the tables where the errors above defined are listed. Moreover, the ML errors increases as μ_q increases, whereas the regression error exhibits a slow decrease as μ_q increases.

In Fig. 2 the difference between the error in the ML procedure and that one in the regression-based method as a function of σ is plotted for different values of μ_q. In all the curves we choose $\eta - \mu_p = 0.5$. A similar trend can be observed for different values of $\eta - \mu_p$. Moreover as σ increases the difference between the errors gets bigger and bigger, so it seems that the performance of the regression-based method improves when the variability in the paths of the processes $P(t)$ and $X(t)$ increases. Now we consider the case in which σ is fixed. More precisely in Table 2 we choose $\sigma = 0.02$ (small variability) whereas in Table 3 it is $\sigma = 0.1$ (large variability). As before, also in these cases the regression method provides

Table 1
Example 1. Estimated values and errors for some combinations of the parameters.

True value			ML estimation		Regr. estimation		Errors	
$\eta - \mu_p$	μ_q	σ	$\widehat{\mu_q}$	$\widehat{\eta - \mu_p}$	$\widehat{\mu_q}$	$\widehat{\eta - \mu_p}$	ML error	Reg. error
0.4	0.1	0.02	0.09899	0.39848	0.09818	0.39606	0.01380	0.02803
		0.04	0.09481	0.38839	0.09448	0.38837	0.08084	0.08417
		0.06	0.08810	0.37161	0.08901	0.37714	0.18995	0.16694
		0.08	0.07971	0.35074	0.08190	0.36271	0.32603	0.27417
		0.1	0.07048	0.32835	0.07331	0.34550	0.47427	0.40306
	0.2	0.02	0.19566	0.39355	0.19702	0.39606	0.03780	0.02469
		0.04	0.18032	0.36861	0.19106	0.38837	0.17684	0.07376
		0.06	0.15803	0.33204	0.18225	0.37714	0.37972	0.14587
		0.08	0.13320	0.29134	0.17082	0.36271	0.60561	0.23907
		0.1	0.10903	0.25204	0.15708	0.34550	0.82469	0.35083
	0.3	0.02	0.28877	0.38726	0.29587	0.39606	0.06927	0.02358
		0.04	0.25432	0.34677	0.28763	0.38837	0.28530	0.07029
		0.06	0.20996	0.29453	0.27548	0.37714	0.56378	0.13885
		0.08	0.16633	0.24336	0.25975	0.36271	0.83715	0.22737
		0.1	0.12843	0.19928	0.24084	0.34550	1.07365	0.33342
	0.4	0.02	0.37732	0.37963	0.39472	0.39606	0.10761	0.02302
		0.04	0.31632	0.32387	0.38420	0.38837	0.39950	0.06855
		0.06	0.24705	0.26072	0.36871	0.37714	0.73054	0.13533
		0.08	0.18629	0.20569	0.34867	0.36271	1.02002	0.22152
		0.1	0.13807	0.16249	0.32460	0.34550	1.24857	0.32472
0.5	0.1	0.02	0.09899	0.49798	0.09818	0.49491	0.01405	0.02837
		0.04	0.09481	0.48503	0.09448	0.48494	0.08176	0.08521
		0.06	0.08810	0.46356	0.08901	0.47037	0.19187	0.16904
		0.08	0.07971	0.43683	0.08190	0.45163	0.32922	0.27768
		0.1	0.07048	0.40812	0.07331	0.42926	0.47891	0.40828
	0.2	0.02	0.19566	0.49175	0.19702	0.49491	0.03818	0.02503
		0.04	0.18032	0.46010	0.19106	0.48494	0.17817	0.07480
		0.06	0.15803	0.41372	0.18225	0.47037	0.38238	0.14798
		0.08	0.13320	0.36210	0.17082	0.45163	0.60977	0.24258
		0.1	0.10903	0.31222	0.15708	0.42926	0.83035	0.35606
	0.3	0.02	0.28877	0.48384	0.29587	0.49491	0.06974	0.02391
		0.04	0.25432	0.43264	0.28763	0.48494	0.28694	0.07133
		0.06	0.20996	0.36660	0.27548	0.47037	0.56691	0.14095
		0.08	0.16633	0.30188	0.25975	0.45163	0.84178	0.23088
		0.1	0.12843	0.24610	0.24084	0.42926	1.07966	0.33865
	0.4	0.02	0.37732	0.47425	0.39472	0.49491	0.10819	0.02336
		0.04	0.31632	0.40390	0.38420	0.48494	0.40139	0.06959
		0.06	0.24705	0.32419	0.36871	0.47037	0.73396	0.13744
		0.08	0.18629	0.25469	0.34867	0.45163	1.02487	0.22503
		0.1	0.13807	0.20006	0.32460	0.42926	1.25467	0.32994
0.6	0.1	0.02	0.09899	0.59748	0.09818	0.59376	0.01422	0.02859
		0.04	0.09481	0.58167	0.09448	0.58151	0.08237	0.08590
		0.06	0.08810	0.55550	0.08901	0.56361	0.19315	0.17045
		0.08	0.07971	0.52292	0.08190	0.54056	0.33135	0.28002
		0.1	0.07048	0.48789	0.07331	0.51302	0.48200	0.41176
	0.2	0.02	0.19566	0.58995	0.19702	0.59376	0.03842	0.02525
		0.04	0.18032	0.55159	0.19106	0.58151	0.17906	0.07549
		0.06	0.15803	0.49540	0.18225	0.56361	0.38416	0.14938
		0.08	0.13320	0.43286	0.17082	0.54056	0.61254	0.24492
		0.1	0.10903	0.37240	0.15708	0.51302	0.83413	0.35954
	0.3	0.02	0.28877	0.58041	0.29587	0.59376	0.07006	0.02413
		0.04	0.25432	0.51851	0.28763	0.58151	0.28804	0.07202
		0.06	0.20996	0.43867	0.27548	0.56361	0.56899	0.14236
		0.08	0.16633	0.36041	0.25975	0.54056	0.84486	0.23322
		0.1	0.12843	0.29292	0.24084	0.51302	1.08366	0.34213
	0.4	0.02	0.37732	0.56886	0.39472	0.59376	0.10857	0.02358
		0.04	0.31632	0.48392	0.38420	0.58151	0.40264	0.07029
		0.06	0.24705	0.38766	0.36871	0.56361	0.73623	0.13885
		0.08	0.18629	0.30369	0.34867	0.54056	1.02811	0.22737
		0.1	0.13807	0.23763	0.32460	0.51302	1.25874	0.33342

(*continued on next page*)

Table 1 (*continued*)

True value			ML estimation		Regr. estimation		Errors	
$\eta - \mu_p$	μ_q	σ	$\widehat{\mu_q}$	$\widehat{\eta - \mu_p}$	$\widehat{\mu_q}$	$\widehat{\eta - \mu_p}$	ML error	Reg. error
0.7	0.1	0.02	0.09899	0.69697	0.09818	0.69260	0.01434	0.02875
		0.04	0.09481	0.67832	0.09448	0.67808	0.08280	0.08640
		0.06	0.08810	0.64744	0.08901	0.65684	0.19407	0.17145
		0.08	0.07971	0.60901	0.08190	0.62948	0.33287	0.28169
		0.1	0.07048	0.56765	0.07331	0.59679	0.48421	0.41425
	0.2	0.02	0.19566	0.68816	0.19702	0.69260	0.03860	0.02541
		0.04	0.18032	0.64308	0.19106	0.67808	0.17969	0.07599
		0.06	0.15803	0.57708	0.18225	0.65684	0.38542	0.15038
		0.08	0.13320	0.50362	0.17082	0.62948	0.61452	0.24659
		0.1	0.10903	0.43258	0.15708	0.59679	0.83682	0.36202
	0.3	0.02	0.28877	0.67699	0.29587	0.69260	0.07029	0.02429
		0.04	0.25432	0.60439	0.28763	0.67808	0.28882	0.07252
		0.06	0.20996	0.51074	0.27548	0.65684	0.57048	0.14336
		0.08	0.16633	0.41894	0.25975	0.62948	0.84707	0.23489
		0.1	0.12843	0.33974	0.24084	0.59679	1.08653	0.34462
	0.4	0.02	0.37732	0.66348	0.39472	0.69260	0.10885	0.02374
		0.04	0.31632	0.56395	0.38420	0.67808	0.40354	0.07078
		0.06	0.24705	0.45114	0.36871	0.65684	0.73786	0.13985
		0.08	0.18629	0.35269	0.34867	0.62948	1.03042	0.22904
		0.1	0.13807	0.27520	0.32460	0.59679	1.26164	0.33591
0.8	0.1	0.02	0.09899	0.79647	0.09818	0.79145	0.01443	0.02887
		0.04	0.09481	0.77496	0.09448	0.77465	0.08313	0.08677
		0.06	0.08810	0.73939	0.08901	0.75007	0.19475	0.17220
		0.08	0.07971	0.69510	0.08190	0.71840	0.33401	0.28295
		0.1	0.07048	0.64742	0.07331	0.68055	0.48587	0.41612
	0.2	0.02	0.19566	0.78636	0.19702	0.79145	0.03873	0.02553
		0.04	0.18032	0.73457	0.19106	0.77465	0.18016	0.07636
		0.06	0.15803	0.65875	0.18225	0.75007	0.38637	0.15114
		0.08	0.13320	0.57438	0.17082	0.71840	0.61600	0.24785
		0.1	0.10903	0.49276	0.15708	0.68055	0.83885	0.36389
	0.3	0.02	0.28877	0.77356	0.29587	0.79145	0.07046	0.02441
		0.04	0.25432	0.69026	0.28763	0.77465	0.28941	0.07289
		0.06	0.20996	0.58281	0.27548	0.75007	0.57160	0.14411
		0.08	0.16633	0.47747	0.25975	0.71840	0.84872	0.23615
		0.1	0.12843	0.38656	0.24084	0.68055	1.08867	0.34648
	0.4	0.02	0.37732	0.75810	0.39472	0.79145	0.10905	0.02386
		0.04	0.31632	0.64397	0.38420	0.77465	0.40422	0.07116
		0.06	0.24705	0.51461	0.36871	0.75007	0.73908	0.14060
		0.08	0.18629	0.40168	0.34867	0.71840	1.03215	0.23030
		0.1	0.13807	0.31277	0.32460	0.68055	1.26382	0.33778
0.9	0.1	0.02	0.09899	0.89597	0.09818	0.89030	0.01450	0.02896
		0.04	0.09481	0.87160	0.09448	0.87123	0.08338	0.08706
		0.06	0.08810	0.83133	0.08901	0.84331	0.19529	0.17279
		0.08	0.07971	0.78119	0.08190	0.80733	0.33489	0.28392
		0.1	0.07048	0.72719	0.07331	0.76431	0.48716	0.41757
	0.2	0.02	0.19566	0.88456	0.19702	0.89030	0.03884	0.02562
		0.04	0.18032	0.82606	0.19106	0.87123	0.18053	0.07665
		0.06	0.15803	0.74043	0.18225	0.84331	0.38711	0.15172
		0.08	0.13320	0.64514	0.17082	0.80733	0.61716	0.24882
		0.1	0.10903	0.55294	0.15708	0.76431	0.84042	0.36534
	0.3	0.02	0.28877	0.87014	0.29587	0.89030	0.07060	0.02451
		0.04	0.25432	0.77613	0.28763	0.87123	0.28987	0.07318
		0.06	0.20996	0.65488	0.27548	0.84331	0.57246	0.14470
		0.08	0.16633	0.53600	0.25975	0.80733	0.85001	0.23712
		0.1	0.12843	0.43337	0.24084	0.76431	1.09034	0.34793
	0.4	0.02	0.37732	0.85272	0.39472	0.89030	0.10921	0.02395
		0.04	0.31632	0.72400	0.38420	0.87123	0.40474	0.07144
		0.06	0.24705	0.57808	0.36871	0.84331	0.74003	0.14119
		0.08	0.18629	0.45068	0.34867	0.80733	1.03350	0.23127
		0.1	0.13807	0.35034	0.32460	0.76431	1.26552	0.33923
1	0.1	0.02	0.09899	0.99547	0.09818	0.98915	0.01455	0.02904
		0.04	0.09481	0.96824	0.09448	0.96780	0.08358	0.08729
		0.06	0.08810	0.92327	0.08901	0.93654	0.19571	0.17326
		0.08	0.07971	0.86728	0.08190	0.89625	0.3356	0.28470
		0.1	0.07048	0.80696	0.07331	0.84808	0.48819	0.41873

Table 1 (*continued*)

True value			ML estimation		Regr. estimation		Errors	
$\eta - \mu_p$	μ_q	σ	$\widehat{\mu_q}$	$\widehat{\eta - \mu_p}$	$\widehat{\mu_q}$	$\widehat{\eta - \mu_p}$	ML error	Reg. error
	0.2	0.02	0.19566	0.98276	0.19702	0.98915	0.03892	0.02569
		0.04	0.18032	0.91755	0.19106	0.96780	0.18083	0.07688
		0.06	0.15803	0.82211	0.18225	0.93654	0.38771	0.15219
		0.08	0.13320	0.71589	0.17082	0.89625	0.61808	0.24960
		0.1	0.10903	0.61312	0.15708	0.84808	0.84168	0.36650
	0.3	0.02	0.28877	0.96672	0.29587	0.98915	0.07070	0.02458
		0.04	0.25432	0.86200	0.28763	0.96780	0.29023	0.07341
		0.06	0.20996	0.72695	0.27548	0.93654	0.57316	0.14517
		0.08	0.16633	0.59452	0.25975	0.89625	0.85103	0.23790
		0.1	0.12843	0.48019	0.24084	0.84808	1.09168	0.34909
	0.4	0.02	0.37732	0.94734	0.39472	0.98915	0.10934	0.02402
		0.04	0.31632	0.80402	0.38420	0.96780	0.40516	0.07168
		0.06	0.24705	0.64155	0.36871	0.93654	0.74079	0.14166
		0.08	0.18629	0.49968	0.34867	0.89625	1.03458	0.23205
		0.1	0.13807	0.38792	0.3246	0.84808	1.26688	0.34039

Table 2
Example 1. Estimated values and errors for some combinations of the parameters. $\sigma = 0.02$.

True value		ML estimation		Regr. estimation		Errors	
$\eta - \mu_p$	μ_q	$\widehat{\mu_q}$	$\widehat{\eta - \mu_p}$	$\widehat{\mu_q}$	$\widehat{\eta - \mu_p}$	ML error	Reg. error
0.4	0.1	0.09899	0.39848	0.09818	0.39606	0.01380	0.02803
	0.2	0.19566	0.39355	0.19702	0.39606	0.03780	0.02469
	0.3	0.28877	0.38726	0.29587	0.39606	0.06927	0.02358
	0.4	0.37732	0.37963	0.39472	0.39606	0.10761	0.02302
0.5	0.1	0.09899	0.49798	0.09818	0.49491	0.01405	0.02837
	0.2	0.19566	0.49175	0.19702	0.49491	0.03818	0.02503
	0.3	0.28877	0.48384	0.29587	0.49491	0.06974	0.02391
	0.4	0.37732	0.47425	0.39472	0.49491	0.10819	0.02336
0.6	0.1	0.09899	0.59748	0.09818	0.59376	0.01422	0.02859
	0.2	0.19566	0.58995	0.19702	0.59376	0.03842	0.02525
	0.3	0.28877	0.58041	0.29587	0.59376	0.07006	0.02413
	0.4	0.37732	0.56886	0.39472	0.59376	0.10857	0.02358
0.7	0.1	0.09899	0.69697	0.09818	0.69260	0.01434	0.02875
	0.2	0.19566	0.68816	0.19702	0.69260	0.03860	0.02541
	0.3	0.28877	0.67699	0.29587	0.69260	0.07029	0.02429
	0.4	0.37732	0.66348	0.39472	0.69260	0.10885	0.02374
0.8	0.1	0.09899	0.79647	0.09818	0.79145	0.01443	0.02887
	0.2	0.19566	0.78636	0.19702	0.79145	0.03873	0.02553
	0.3	0.28877	0.77356	0.29587	0.79145	0.07046	0.02441
	0.4	0.37732	0.75810	0.39472	0.79145	0.10905	0.02386
0.9	0.1	0.09899	0.89597	0.09818	0.89030	0.01450	0.02896
	0.2	0.19566	0.88456	0.19702	0.89030	0.03884	0.02562
	0.3	0.28877	0.87014	0.29587	0.89030	0.07060	0.02451
	0.4	0.37732	0.85272	0.39472	0.89030	0.10921	0.02395
1	0.1	0.09899	0.99547	0.09818	0.98915	0.01455	0.02904
	0.2	0.19566	0.98276	0.19702	0.98915	0.03892	0.02569
	0.3	0.28877	0.96672	0.29587	0.98915	0.07070	0.02458
	0.4	0.37732	0.94734	0.39472	0.98915	0.10934	0.02402

better estimations than the ML procedure. Moreover the errors of both the procedures show a similar trend for the different choices of $\eta - \mu_p$. Further, for fixed values of $\eta - \mu_p$, the ML error increases as μ_q increases whereas the regression error holds essentially constant, showing a negligible decrease. This is more evident in Fig. 3 in which the ML and the regression errors are plotted as functions of μ_q in the cases $\sigma = 0.04$ (on the left) and $\sigma = 0.08$ (on the right).

Indeed, as shown in Table 2, for the regression method, the estimations of $\eta - \mu_p$ are the same for each value of μ_q whereas those for μ_q show a little variation. Same conclusions can be drawn from Table 3 although in it the errors are bigger.

5.2. Example 2: application to real data

In this subsection we focus on an experimental study in breast cancer xenografts illustrated from the authors in a recent paper (see Albano et al., 2011). It was observed the growth of *BC297MONp5* from an experimental group of mice. The

Table 3
Example 1. Estimated values and errors for some combinations of the parameters. $\sigma = 0.1$.

True value		ML estimation		Regr. estimation		Errors	
$\eta - \mu_p$	μ_q	$\widehat{\mu_q}$	$\widehat{\eta - \mu_p}$	$\widehat{\mu_q}$	$\widehat{\eta - \mu_p}$	ML error	Reg. error
0.4	0.1	0.07048	0.32835	0.07331	0.34550	0.47427	0.40306
	0.2	0.10903	0.25204	0.15708	0.34550	0.82469	0.35083
	0.3	0.12843	0.19928	0.24084	0.34550	1.07365	0.33342
	0.4	0.13807	0.16249	0.32460	0.34550	1.24857	0.32472
0.5	0.1	0.07048	0.40812	0.07331	0.42926	0.47891	0.40828
	0.2	0.10903	0.31222	0.15708	0.42926	0.83035	0.35606
	0.3	0.12843	0.24610	0.24084	0.42926	1.07966	0.33865
	0.4	0.13807	0.20006	0.32460	0.42926	1.25467	0.32994
0.6	0.1	0.07048	0.48789	0.07331	0.51302	0.48200	0.41176
	0.2	0.10903	0.37240	0.15708	0.51302	0.83413	0.35954
	0.3	0.12843	0.29292	0.24084	0.51302	1.08366	0.34213
	0.4	0.13807	0.23763	0.32460	0.51302	1.25874	0.33342
0.7	0.1	0.07048	0.56765	0.07331	0.59679	0.48421	0.41425
	0.2	0.10903	0.43258	0.15708	0.59679	0.83682	0.36202
	0.3	0.12843	0.33974	0.24084	0.59679	1.08653	0.34462
	0.4	0.13807	0.27520	0.32460	0.59679	1.26164	0.33591
0.8	0.1	0.07048	0.64742	0.07331	0.68055	0.48587	0.41612
	0.2	0.10903	0.49276	0.15708	0.68055	0.83885	0.36389
	0.3	0.12843	0.38656	0.24084	0.68055	1.08867	0.34648
	0.4	0.13807	0.31277	0.32460	0.68055	1.26382	0.33778
0.9	0.1	0.07048	0.72719	0.07331	0.76431	0.48716	0.41757
	0.2	0.10903	0.55294	0.15708	0.76431	0.84042	0.36534
	0.3	0.12843	0.43337	0.24084	0.76431	1.09034	0.34793
	0.4	0.13807	0.35034	0.32460	0.76431	1.26552	0.33923
1	0.1	0.07048	0.80696	0.07331	0.84808	0.48819	0.41873
	0.2	0.10903	0.61312	0.15708	0.84808	0.84168	0.36650
	0.3	0.12843	0.48019	0.24084	0.84808	1.09168	0.34909
	0.4	0.13807	0.38792	0.3246	0.84808	1.26688	0.34039

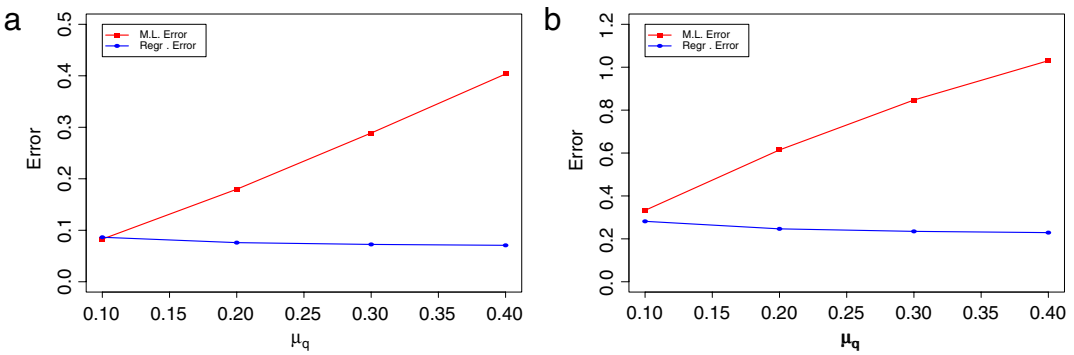

Fig. 3. Example 1. ML and regression errors for the cases $\sigma = 0.04$ (a) and $\sigma = 0.08$. In both cases, $\eta - \mu_p = 0.7$.

estimations of the parameters, measured in $[days]^{-1}$, in the process $X(t)$ were (see Albano et al., 2011)

$$\widehat{\alpha} = 0.112784, \qquad \widehat{\beta} = 0.0184158, \qquad \widehat{\sigma^2} = 0.010992.$$

As regards the process $P(t)$, we choose $\eta = 0.7$ and $\mu_p = \mu_q = 0.1$. Further, three values for σ are considered: 0.01, 0.05 and 0.1, i.e. the estimated value of σ in the above mentioned study. Table 4 summarizes the results. When $\sigma = 0.01$ (that is, the trajectories have a small variability), both procedures provide good estimations, although the error in the regression-based procedure is smallest. Nevertheless, the situation is quite different for the other values of σ. Indeed, when $\sigma = 0.05$ the estimations obtained from the regression method are clearly better than those ones obtained from the ML procedure (the difference between the errors is substantial). Finally, when $\sigma = 0.1$ the ML method provides an estimation of μ_q that is less than zero, that is an inadmissible value of μ_q.

In Fig. 4 the likelihood equation (33) is plotted as function of μ_q choosing $\sigma = 0.05$ (on the left) and $\sigma = 0.1$ (on the right). Note that the difference between the ML estimate and the real value of μ_q increases as σ increases.

Table 4
Example 2. Estimated values and errors. $\eta = 0.7$, $\mu_p = \mu_q = 0.1$.

	ML estimation		Regr. estimation		Errors	
σ	$\widehat{\mu_q}$	$\widehat{\eta - \mu_p}$	$\widehat{\mu_q}$	$\widehat{\eta - \mu_p}$	ML error	Reg. error
0.01	0.094810	0.573896	0.103629	0.601960	0.095404	0.039556
0.05	0.035460	0.307715	0.098126	0.586658	1.132540	0.040970
0.1	−0.013472	0.127034	0.071567	0.511487	1.923000	0.431842

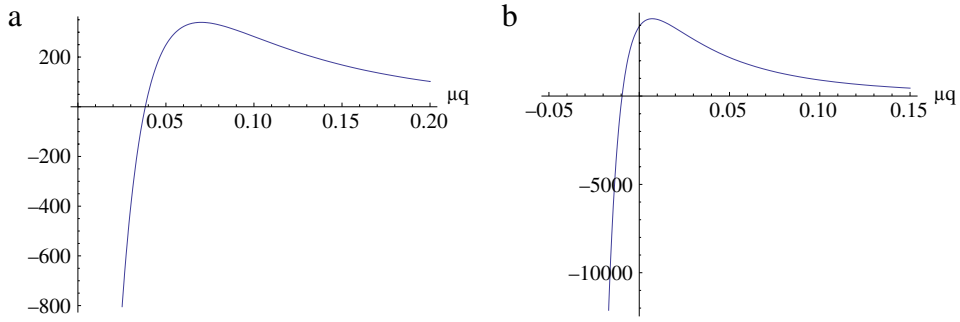

Fig. 4. Example 2. Likelihood equation (33) for μ_q for $\sigma = 0.05$ (a) and $\sigma = 0.1$ (b).

6. Concluding remarks

In this work a two-compartment model to describe tumor dynamics is discussed. More precisely, the tumor population is split in a proliferating and a quiescent compartment, the first one characterized by a non-negative birth rate and the second one characterized by a zero birth rate. The transitions between the two compartment are regulated by two positive rates, generally depending on the whole tumor size. The estimation of involved rates in the proliferative and quiescent populations is performed using two different procedures: the first one consisting in ML method and the second one based on the linear regression. A simulation study and an application to real data permit to argue that the regression-based method works better with respect the ML method.

We point out that this work opens the way to a further generalization in the estimation of the growth rates in tumor dynamics so to better understand how a therapy protocol acts on different compartments in a tumor population. Indeed, a therapy protocol leads to a change of the growth rates in the tumor population $X(t)$ and consequently in the proliferating and quiescent populations. So a procedure to estimate the involved rates permits to compare different protocols through the analysis of experimental data obtained from in vitro studies.

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