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Inferring the effect of therapies on tumor growth by using diffusion processes

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HIGHLIGHTS

- The effects of therapies in experimental studies of cancer growth is modeled.
- Known methodologies require that known diffusion processes fit the control group.
- A new methodology is presented by considering a hypothetical control group.
- For particular process for the hypothetical group the methodology is developed.
- The methodology is validated with real data.

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ABSTRACT

Modeling the effect of therapies in cancer animal models remains a challenge. This point may be addressed by considering a diffusion process that models the tumor growth and a modified process that includes, in its infinitesimal mean, a time function modeling the effect of the therapy. In the case of a Gompertz diffusion process, where a control group and one or more treated groups are examined, a methodology to estimate this function has been proposed by Albano et al. (2011). This method has been applied to infer the effect of cisplatin and doxorubicin+cyclophosphamide on breast cancer xenografts. Although this methodology can be extended to other diffusion processes, it has an important restriction: it is necessary that a known diffusion process adequately fits the control group. Here, we propose the use of a stochastic process for a hypothetical control group, in such a way that both the control and the treated groups can be modeled by modified processes of the former. Thus, the comparison between models would allow estimating the real effect of the therapy. The new methodology has been validated by inferring the effects in breast cancer models, and we have checked the robustness of the procedure against the choice of stochastic model for the hypothetical control group. Finally, we have also applied the methodology to infer the effect of a therapeutic peptide and ovariectomy on the growth of a breast cancer xenograft, and its efficiency in modeling the effect of different treatments in the absence of control group data is shown.

1. Introduction

Mathematical modeling of tumor growth has undergone great development in the last decades. Several models have been implemented to follow tumor growth evolution and better understanding tumor behavior. These approaches are very promising for the development of more successful treatment strategies. Among the proposed models, those based on ordinary differential equations for the deterministic case (see, for instance, de Pillis et al., 2009; Parfitt and Fyhrie, 1997; Sachs et al., 2001) have been particularly widespread.

The deterministic models more commonly used in the study of tumor growth have been the Malthusian (associated with the exponential curve) and those related to sigmoidal curves as the logistic or Gompertz. However, it should be stressed that quite often discrepancies exist between clinical data and theoretical deterministic models (see Figs. 1, 12(a), 14 and 15). Two sources of variability are to be considered in the growth of human tumors in animals: inter-individual variability, mainly due to the intrinsic heterogeneity of the tumoral tissues engrafted into mice, and environmental stochasticity, which results from random fluctuations in the environment (differences in the graft implantation site, physiological differences among mice, etc.). Deterministic

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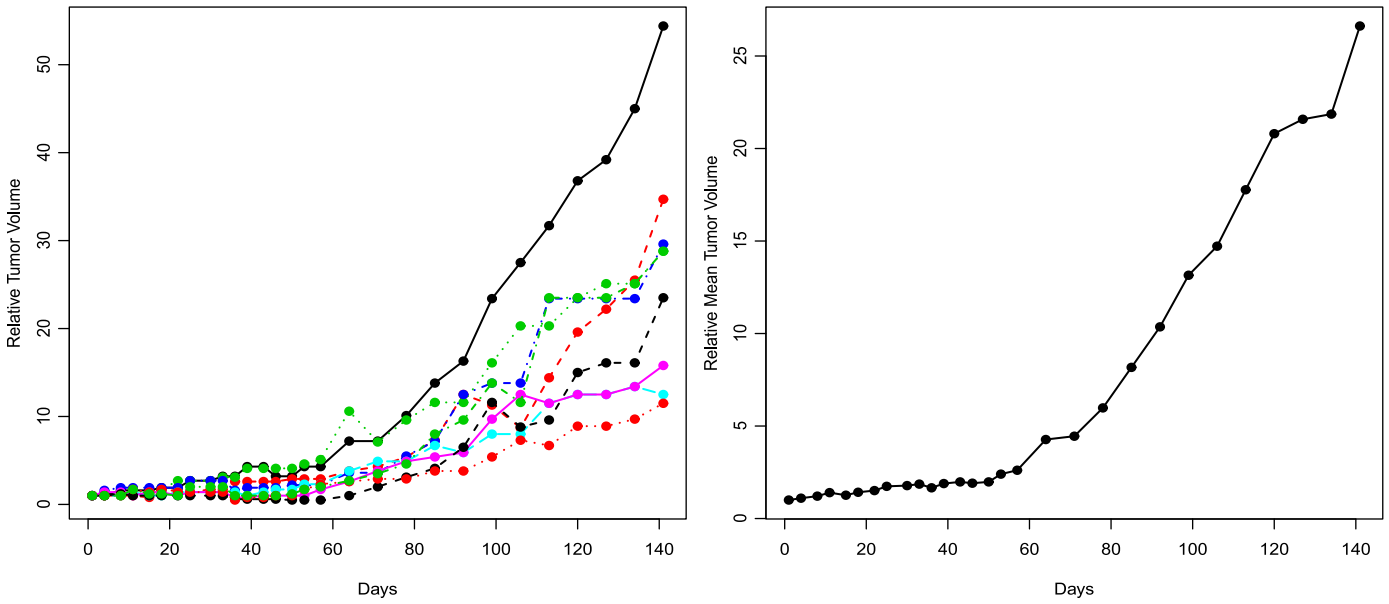

Fig. 1. BC52EDWp20 tumor growth for a control group.

models neglect such sources of variability, connatural to any growth process and not always quantifiable or simply unknown.

In order to take such environmental fluctuations into account, as well as the variation between individuals, the notion of growth in random environments has been formulated (see Ricciardi, 1979 and references therein) so that the tumor growth can be described by means of stochastic differential equations (see Rosenkranz, 1985, for the case the reproduction rate of a population depends on the actual population size, Lisei and Julitz, 2008 and references therein). These models include a noise term in the ordinary differential equation associated to the corresponding deterministic model, and their solutions are stochastic processes (called diffusion processes) that can be treated with the stochastic methods of diffusion equations (Lande et al., 2003 popularized these methods for biologists).

In this context, the Gompertz curve has been widely used to model the growth of tumors (see Castorina and Zappalà, 2006; de Vladar and Gonzalez, 2004 for deterministic models) and several authors have dealt with stochastic models based on this curve (Ferrante et al., 2000; O'Rourke and Behera, 2009).

In the field on oncology, preclinical evaluation of new treatments in relevant animal models is crucial to determine the efficacy of novel therapeutic agents. Human tumors can be grafted subcutaneously in immunodeficient mice and their growth can be easily followed by measuring the tumor volume. These xenografts constitute valuable tools to assess new antitumor agents or new therapeutic combinations. A good interpretation of data coming from these in vivo experiments is challenging, and modeling the effect of therapies in tumor growth in mice could help pharmacologists to adapt protocols and better understand the time-frame in which treatments are efficient. One way of addressing this modeling is considering a diffusion process that models tumor growth in such a way that the data about the growth of tumors in each mouse is considered as a single observation (sample path) of the process. Thus, the study of tumor growth under the effect of a given treatment can be dealt with as a modification of the process fitted to the control group. This modification is performed by including the effect of therapy as a time function affecting its trend.

To this end, several models have been analyzed by using the Gompertz curve. For instance, Albano and Giorno (2006) have proposed a stochastic model in order to simulate the effects of a time-dependent therapy in the case of a parathyroid tumor. In addition, they have also studied the first exit time problem for the process limited by two absorbing boundaries representing healing threshold and patient death. Ferrante et al. (2005) have considered the problem of parameter estimation and extinction probability for a Gompertzian stochastic process that includes a time function to describe the interaction between drugs and bacterial populations. Lo (2007) has generalized the model introduced by Albano and Giorno (2006) in order to include both cell fission and mortality rates.

It must be pointed out that, for the above-mentioned models, the functional form of the therapy effect (that is, the time function included) is assumed as known and it is not calculated from data. Nevertheless, it seems reasonable to assume that in the first stages of a new medical treatment, the time function is unknown and, in experimental studies, it cannot be instantly deduced from a treatment protocol. In general, developing mathematical models capable of functionalizing the effect of a therapy and, specifically, methodologies for the inference of this function in preclinical settings, may result in valuable tools to get a fast and accurate determination of the protocol for administering new drugs. Such tools may save time and mice in the experimental procedures by avoiding complex preliminary pharmacokinetic studies.

Albano et al. (2011) have proposed a methodology for the estimation of a time function for a Gompertz diffusion process in experiments including a control group and one or more treated groups. Such a methodology has been applied to infer the effect of cisplatin and doxorubicin+cyclophosphamide on breast cancer xenografts. In that case, it was assumed that tumor growth in the absence of treatment (that is, the control group) showed a Gompertz-type behavior pattern associated with a deterministic model defined by the ordinary differential equation

$$\frac{dx(t)}{dt} = \alpha x(t) - \beta x(t) \log x(t) \tag{1}$$

where α and β are positive constants representing growth and death rates. Thus, the Gompertz diffusion process under consideration in their study is defined by the stochastic differential equation

$$dX(t) = (\alpha X(t) - \beta X(t) \log X(t))\, dt + \sigma X(t)\, dW(t) \tag{2}$$