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Optimal designs for tumor regrowth models

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ABSTRACT

Most growth curves can only be used to model the tumor growth under no intervention. To model the growth curves for treated tumor, both the growth delay due to the treatment and the regrowth of the tumor after the treatment need to be taken into account. In this paper, we consider two tumor regrowth models and determine the locally *D*- and *c*-optimal designs for these models. We then show that the locally *D*- and *c*-optimal designs are minimally supported. We also consider two equally spaced designs as alternative designs and evaluate their efficiencies.

1. Introduction

Statistical modeling of tumor growth has a long history in biology and biostatistics. It is well known that the growth of an unperturbed tumor can be fitted well by the Gompertz curve (Kidwell et al., 1960; Laird, 1964; Rygaard and Spang-Thomsen, 1997)

$$g(t) = \alpha \exp\{-\beta e^{-kt}\}, \tag{1}$$

where $g(t)$ is the tumor volume at time t and α is the asymptotic maximum tumor volume. Gompertz function is monotonic and the maximum growth rate $k\alpha/e$ is achieved at the point of reflection $t = \log(\beta)/k$. However, modeling the growth curves for treated tumors is a more challenging problem in mathematical biology and biostatistics. After the tumor is treated by a therapy such as radiation or chemotherapy, it may shrink soon after the treatment and then grow again. In this situation, it is evident that monotonic functions such as Gompertz function cannot be used to characterize such non-monotonic growth curve.

Demidenko (2004) developed a regrowth curve theory by combining two existing theories: traditional growth curve theory and survival curve theory. In this theory, traditional growth curve is used to describe the further growth of surviving cells and the survival curve is used to model the proportion of the cells killed by the treatment. Double-exponential regrowth curve is one such regrowth curve that describes the dynamics of post-irradiated tumors based on the two-compartment model. In a subsequent work, Demidenko (2006) proposed another model, viz., LINEXP model, to describe the growth delay and regrowth for treated tumor.

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Proper choices of experimental designs can help to improve the efficiency of the experiment as well as the quality of statistical inference. The theory of optimal experimental designs is an important tool for the experimenters to find the best design to meet the experimental objectives. Let $\mathcal{H}$ denote the set of probability distributions on the Borel sets of $\chi=[t_{min},t_{max}]$; then any $\xi\in\mathcal{H}$ is called an approximate or continuous design (Kiefer, 1974). Let θ be the vector of k unknown model parameters and $M(\xi,\theta)$ be the Fisher information matrix induced by the approximate design measure ξ. Each objective of the experiment is usually expressed as a concave criterion function of the Fisher information matrix and the optimal design is then determined by maximizing this criterion function. When the objective is to estimate the model parameters, two commonly adopted criteria are D-optimality and c-optimality. The D-optimality criterion function is defined as the logarithm of $|M(\xi,\theta)|$, the determinant of the Fisher information matrix, if $M(\xi,\theta)$ is non-singular and $-\infty$ if $M(\xi,\theta)$ is singular (Silvey, 1980). The D-optimal design minimizes the volume of the confidence ellipsoid for θ. A c-optimal design maximizes $\{c^TM^-(\xi,\theta)c\}^{-1}$, where the maximum is taken over the set of all designs for which the linear combination $c^T\theta$ is estimable. For some other criteria and related results, interested readers may refer to Fedorov (1972), Silvey (1980), Atkinson and Donev (1992), and Pukelsheim (1993).

For nonlinear models, the information matrix depends on the unknown parameters θ. It therefore becomes quite a complicated problem to determine optimal designs for nonlinear models. A simple and natural approach is to adopt a best guess for the parameters, say $\theta^{(0)}$, and then to consider designs which maximize the criterion function of $M(\xi,\theta)$ evaluated at $\theta=\theta^{(0)}$. The resulting design is called locally optimal design (Chernoff, 1953). Locally D- and c-optimal designs for nonlinear models have been studied extensively by many authors; see Ford et al. (1992), Sitter and Wu (1993), Hedayat et al. (1997), Han and Chaloner (2003), Dette et al. (2006), and Li and Majumdar (2008, 2009). Besides the local optimality approach, there are some other alternative approaches, including the Bayesian approach (Chaloner and Larntz, 1989) and standardized maximin approach (Dette, 1997). In this paper, we consider the problem of determining locally D- and c-optimal designs for two tumor regrowth models. We first review two tumor regrowth models of interest in Section 2. In Section 3, we present some preliminary results and then apply them to determine the locally D- and c-optimal designs for the two tumor regrowth models in Sections 4 and 5. Finally, the D-optimal designs for the regrowth models are used as benchmarks for evaluating the merits of two alternative designs with equally spaced support points.

2. Tumor regrowth models

2.1. Double-exponential regrowth model

Demidenko (2004) developed a double-exponential regrowth model to describe the dynamics of post-irradiated tumors based on the two-compartment model. In this setup, tumor cells are categorized into two compartments: proliferating, P, and quiescent, Q. Under three hypotheses (i) proliferating cells divide with constant rate, ν, (ii) quiescent cells die with a constant rate, ϕ, and (iii) a portion of proliferating cells become quiescent with rate τ, the tumor growth is characterized by the system of differential equations

$$\frac{dP}{dt}=\nu P,\quad \frac{dQ}{dt}=\tau P-\phi Q.$$

The total number of tumor cells at time t is the sum $N(t)=P(t)+Q(t)$ with a closed-form expression given by $N(t)=N_0[\beta e^{\nu t}+(1-\beta)e^{-\phi t}]$, where $0<\beta<1$, and N_0 is the total number of tumor cells at the starting time $t=0$. Assuming the tumor volume to be proportional to the total number of cells, the natural logarithm of the tumor volume is characterized by

$$g_1(t)=\alpha+\ln[\beta e^{\nu t}+(1-\beta)e^{-\phi t}], \tag{2}$$

where α is the logarithm of the initial tumor volume.

2.2. LINEXP regrowth model

In a follow-up work, Demidenko (2006) proposed a LINEXP model to describe the whole range of tumor growth delay and regrowth data. Under LINEXP model, the natural logarithm of the tumor volume is

$$g_2(t)=\alpha+\gamma t+\beta(e^{-\delta t}-1), \tag{3}$$

where α is the baseline logarithm of the tumor volume, γ is the final growth rate, and δ is the rate at which killed cells get washed out. The LINEXP model can be applied to model both monotonic growth and non-monotonic regrowth. Note that if $\gamma>\delta\beta$, the mean function is monotonic; otherwise, the mean function is non-monotonic. Consequently, this model can be used to fit the data from the untreated tumor growth and treated tumor regrowth simultaneously.