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Efficient experimental designs for sigmoidal growth models

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Abstract

For the Weibull- and Richards-regression model robust designs are determined by maximizing a minimum of D- or D_1-efficiencies, taken over a certain range of the non-linear parameters. It is demonstrated that the derived designs yield a satisfactory solution of the optimal design problem for this type of model in the sense that these designs are efficient and robust with respect to misspecification of the unknown parameters. Moreover, the designs can also be used for testing the postulated form of the regression model against a simplified sub-model.

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1. Introduction

Sigmoidal growth curves are widespread tools for analyzing data from processes arising in various fields. Numerous mathematical functions have been proposed for modelling sigmoidal curves. Typical applications include subject areas such as biology (see Landaw and DiStefano, 1984), chemistry, pharmacokinetics (see Liebig, 1988; Krug and Liebig, 1988), toxicology (Becka and Urfer, 1996; Becka et al., 1993) or microbiology (see Coleman and Marks, 1998). An appropriate choice of the experimental conditions can improve the quality of statistical inference substantially. Although optimal designs for non-linear regression models have been discussed by many authors, much less attention has been paid to the problem of designing experiments for sigmoidal regression models.

In non-linear models the Fisher information matrix of the maximum likelihood estimator depends on the unknown parameters and for this reason optimal designs, which maximize some function of the Fisher information matrix, are difficult to implement in practice. Many authors concentrate on locally optimal designs, where it is assumed that a preliminary guess for the unknown parameters is available (see Chernoff, 1953; Silvey, 1980). Most locally optimal designs for non-linear regression models have been criticized for two reasons. First these designs are not necessarily robust with respect to a misspecification of the non-linear parameters in the model. Secondly they advice the experimenter to take observations only at a few different points. The number of these points usually coincides with

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the number of parameters in the regression model and as a consequence these designs are not applicable for testing the goodness-of-fit of the assumed model.

Several proposals have been made to obtain robust designs with respect to misspecification of the parameters (see Pronzato and Walter, 1985; Chaloner and Verdinelli, 1995; Müller, 1995; Dette, 1997; Imhof, 2001; Dette and Biedermann, 2003), but less literature is available to address the possibility of model checking in the construction of optimal designs. In linear models some suggestions can be found in Stigler (1971) or Studden (1982) in the context of a polynomial regression model, who suggested to embed the postulated model in an extended model (usually a polynomial of larger degree) and to construct an optimal design for testing the postulated against the extended model. Discrimination designs for polynomial regression models in a more general context have been discussed in Dette (1990, 1995), but not much literature seems to be available in the context of non-linear models. Atkinson and Fedorov (1975) proposed the *T*-optimality criterion, which adapts Stigler's idea to the non-linear setup. However, their criterion is local and therefore not necessarily robust with respect to a misspecification of the unknown parameters. Recently, Dette et al. (2005) considered the Michaelis–Menten model and constructed robust and efficient designs, which can on the one hand be used for testing this model against an extension (called EMAX model) and are on the other hand robust with respect to misspecification of the non-linear parameters.

It is the purpose of the present paper to demonstrate that this approach is more broadly applicable and useful for the construction of efficient and robust designs in non-linear models for several objects. For this we consider two commonly used sigmoidal regression models and its corresponding extension. The first model under consideration is the exponential regression model

$$\eta(t,\theta) = a - b\mathrm{e}^{-\lambda t} \tag{1.1}$$

(with $\theta=(a,b,\lambda)$), which is called von Bertalanffy growth curve or Mitscherlichs growth law. Numerous authors studied optimal designs for this model from various points of view (see Dette and Neugebauer, 1997; Han and Chaloner, 2004 for example). Most of these optimal designs are 3-point designs and can for this reason not be used for testing the goodness-of-fit of the postulated model. For this purpose we consider the Weibull regression model

$$\eta(t,\theta) = a - b\mathrm{e}^{-\lambda t^h} \tag{1.2}$$

(here $\theta = (a,b,\lambda,h)$), which is an extension of model (1.1). The Weibull model is also widely used for describing sigmoidal growth (see e.g. Ratkowsky, 1983; Zeide, 1993; Vanclay and Skovsgaard, 1997 among many others). Our goal is to construct an optimal experimental design for models (1.1) and (1.2) which fulfills at least three requirements.

(1) The design should allow to test the hypothesis

$$\mathrm{H}_0\colon\ h=1 \quad \text{vs} \quad \mathrm{H}_1\colon\ h\neq 1 \tag{1.3}$$

in the extended model (1.2).

(2) The design should be efficient for the estimation of the parameters in the regression models (1.1) and (1.2).

(3) The design should be robust with respect to misspecification of the non-linear parameters in the regression models.

The second pair of sigmoidal growth models, where a similar question is considered, is given by the logistic regression model

$$\eta(t,\theta) = \frac{a}{1+b\mathrm{e}^{-\lambda t}} \tag{1.4}$$

(with $\theta = (a,b,\lambda)$), and the Richards-regression model

$$\eta(t,\theta) = \frac{a}{(1+b\mathrm{e}^{-\lambda t})^h} \tag{1.5}$$

(here $\theta = (a,b,\lambda,h)$). Models (1.2) and (1.5) are serious competitors to models (1.1) and (1.4), respectively, and therefore it is desirable to incorporate in the construction of an experimental design the flexibility to test hypothesis (1.3) in the regression models (1.2) or (1.5).