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Algorithms for finding locally and Bayesian optimal designs for binary dose–response models with control mortality

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Abstract

Algorithms for finding optimal designs for three-parameter binary dose–response models that incorporate control mortality are described. Locally and Bayesian optimal designs for models with a range of link functions are considered. Design criteria looked at include D-optimal, D_A-optimal and V-optimal designs, together with D_s-optimal designs where the control mortality parameter is regarded as a nuisance parameter. The range of prior distributions for the Bayesian optimal designs includes uniform, trivariate normal and a combination of a bivariate normal prior for the parameters of the underlying dose–response with an independent uniform prior for the control mortality parameter.

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1. Introduction

An extensive literature exists on experimental designs for binary data. Morgan (1992, Chapter 8) provides an overview. Much of this is concerned with dose–response experiments in which the probability of response, π, is dependent on the applied dose, d, of a stimulus. Ford et al. (1992), and Sitter and Wu (1993), investigated locally D-optimal designs for binary dose–response experiments in which the probability of response, π, to dose d of a

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stimulus is of the form

$$\pi(x;\boldsymbol{\theta}) = F(\beta(x-\mu)) = F(z), \tag{1}$$

where $\boldsymbol{\theta}^{\mathrm{T}} = (\mu, \beta)$ is a vector of unknown parameters, $F()$ is a cumulative distribution function, $z = \beta(x-\mu)$, and x is some transformation of d. The inverse function $F^{-1}()$ is termed the *link function*. In practice, model (1) is often inadequate, because some individuals exhibit a response for reasons unrelated to the stimulus. Because the most common application of the binary models considered here is in bioassay, where response is often death, this response unrelated to stimulus is termed *control mortality* or alternatively *natural mortality*. Morgan (1992, Section 3.2) discusses models of control mortality, and gives examples, e.g. bioassays of insecticides, where a proportion of insects may die naturally, or as a result of the experimental handling procedures. The data from two of these examples are used later in this article to illustrate practical applications of the algorithms described. Morgan (1992, p. 105) comments that control (natural) mortality is frequently present and that it needs to be included in the models used. The simplest extension of (1) (Morgan, 1992, p. 94) to incorporate control mortality is

$$\pi(x;\boldsymbol{\theta}) = \lambda + (1-\lambda)F(z), \tag{2}$$

where $\boldsymbol{\theta}^{\mathrm{T}} = (\mu, \beta, \lambda)$ or $\boldsymbol{\theta}^{\mathrm{T}} = (\alpha, \beta, \lambda)$ is now the vector of unknown parameters. This model which originated in/with Abbott (1925), is a mixture model in which the parameter λ is the probability that an individual succumbs to control mortality. The present paper considers algorithms for finding locally optimal and Bayesian optimal designs for $\boldsymbol{\theta}$ in this extended model. For a given value of λ, optimal designs can be characterized in terms of $F(z_i)$, $\pi(x_i)$ or z_i.

Optimal designs minimize some function of the Fisher information matrix, termed the *criterion function*. For nonlinear models, such as (1) and (2), the information matrix depends on the unknown parameters $\boldsymbol{\theta}$. As a result, the criterion function cannot be optimized directly. Two approaches have been widely used to get round this problem. *Locally optimal designs* arise when the unknown parameters in the criterion function are replaced by the experimenter's "best guess" of the true values. *Bayesian optimal designs* instead require the uncertainty about the parameters to be expressed as a prior distribution, with the optimal design chosen to minimize the expectation of the criterion function over the prior distribution. Chaloner and Verdinelli (1995) provide an extensive review of Bayesian design. Chaloner and Larntz (1989) discuss locally and Bayesian optimal designs for the logit link function. Smith and Ridout (1998) extended this to other link functions and a wider range of distributions.

The paper is organised as follows. Sections 2–4 describe, respectively, link functions, prior distributions and design criteria. Sections 5 and 6 describe algorithms for finding locally and Bayesian optimal designs, respectively. Section 7 gives examples. An appendix describes a program used to find optimal designs for binary data with control mortality.

2. Link functions

Table 1 shows the link functions considered. These are the same as those considered by Ford et al. (1992) and Smith and Ridout (1998).