Optimal Designs for Contingent Response Models

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Summary. We study D- and c-optimal designs for the contingent response models of Li, Durham, and Flournoy (1995). In the contingent response model there are two types of failure. We call one failure type *toxicity* and the other *disease failure*. No toxicity and no disease failure is a *success* or *cure*. We assume disease failures are *contingent* on toxicity in that they can only be observed in the absence of toxicity. We also assume the probability of toxicity increases with the dose, and the probability of disease failure given no toxicity decreases with dose. Interest is in finding c-optimal designs for estimating the dose that maximizes the cure probability.

Key words: Dose response, D-optimal, c-optimal, continuation ratio model, phase II clinical trials, stress tests, ternary responses.

1 Introduction

We study D- and c-optimal designs for the contingent response models of Li, Durham, and Flournoy (1995). In the contingent response model there are two types of failure. We call one failure type *toxicity* and the other *disease failure*. No toxicity and no disease failure is a *success* or *cure*. We assume disease failures are *contingent* on toxicity in that they can only be observed in the absence of toxicity. We also assume the probability of toxicity increases with the dose, and the probability of disease failure given no toxicity decreases with dose. Interest is in finding c-optimal designs for estimating the dose that maximizes the cure probability. We call this dose *the optimal dose* and denote it by ν.

Examples of data well fit by a contingent response model arise in many areas of study, with phase II clinical trials being an obvious one. In many phase II trials, a toxicity failure is fatal or so severe as to stop the trial. Then efficacy results are obtained only in the absence of toxicity failures. Hayes, Edie, and Durham describe testing the compressive strength of fibers. A fiber may fail after it is stressed under tension to a predetermined level.

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Only if the fiber does not break under initial tension is a recoil test initiated. If the initial stress level is sufficiently high (but not high enough to lead to a failure), the fiber may then fail due to compressive stresses generated as the stored strain energy is recovered. The goal is to find the stress level that maximizes the probability of a recoil success without tensile failure. Other examples are described in Fan and Chaloner (2003).

In Section 2, we define the contingent response model, give examples, and show the continuation ratio model Agresti (1990) to be a special case. In Section 3, we define Fisher's information matrix for a location-scale family of contingent response models. A location-scale family of optimal designs is constructed, in the spirit of Ford, Torsney, and Wu (1992) by defining a single design called the *canonical optimal design* for the family. Then all other designs in the family are generated by transforming the canonical optimal design in a prescribed way. In Section 4, we establish a general location-scale family of D-optimal designs, and we find some D-optimal designs for the canonical positive/negative extreme value models which is defined in Section 2. In Section 5, we established a location-scale family of c-optimal designs for the positive/negative extreme value model, and find c-optimal designs for some canonical models. Tables of optimal designs can be obtained from the author. Complete proofs of the Lemma and Theorems 1-4 can be found in Rabie (under preparation).

2 The Contingent Response Model

Let

$$Y_{1j} = \begin{cases} 1 & \text{if the } j\text{th subject has a toxic response} \\ 0 & \text{else} \end{cases}$$

$$Y_{2j} = \begin{cases} 1 & \text{if the } j\text{th subject has disease failure} \\ 0 & \text{else} \end{cases}$$

for $j = 1, \ldots, N$. Only three outcomes are possible, namely, $\{Y_{1j} = 0, Y_{2j} = 0, \}, \{Y_{1j} = 0, Y_{2j} = 1\}$, and $\{Y_{1j} = 1\}$. We consider a location-scale family of parametric models: $P\{Y_{1j} = 1 \mid x\} = F(\alpha_1 + \beta_1 x) = F_x$; and $P\{Y_{2j} = 0 \mid Y_{1j} = 0, x\} = G(\alpha_2 + \beta_2 x) = G_x$ with $\bar{F}_x = 1 - F_x$ and $\bar{G}_x = 1 - G_x$; x is log dose. Note the probability of success is

$$H_x = P\{Y_{1j} = 0, Y_{2j} = 0 \mid x\} = \bar{F}_x G_x; \tag{1}$$

the probability of toxicity is F_x; and the probability of disease failure is $P(Y_{1j} = 0, Y_{2j} = 1) = \bar{F}_x \bar{G}_x$.

The optimal dose is the maximum of H_x which in some cases may be found by setting the derivative of (1) equal to zero, that is,