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Optimal response and covariate-adaptive biased-coin designs for clinical trials with continuous multivariate or longitudinal responses

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HIGHLIGHTS

- First paper for clinical trials with normally distributed longitudinal responses that balances efficiency and randomness.
- Design is both covariate and response adaptive.
- Extensions introduced to optimum design theory for multivariate responses.

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ABSTRACT

Adaptive randomization of the sequential construction of optimum experimental designs is used to derive biased-coin designs for longitudinal clinical trials with continuous responses. The designs, coming from a very general rule, target pre-specified allocation proportions for the ranked treatment effects. Many of the properties of the designs are similar to those of well-understood designs for univariate responses. A numerical study illustrates this similarity in a comparison of four designs for longitudinal trials. Designs for multivariate responses can likewise be found, requiring only the appropriate information matrix. Some new results in the theory of optimum experimental design for multivariate responses are presented.

1. Introduction

Response-adaptive designs are becoming increasingly popular in phase III clinical trials with sequential entrance of patients. The ethical objective is to use the accumulating data to skew the allocation in favour of the better treatments, so ensuring that as few patients as possible receive bad treatments. The advantages of response-adaptive designs are extolled by Zelen and Wei (1995), Hu and Rosenberger (2003) and Rosenberger and Hu (2004). Gallo et al. (2006) provide a perspective from the pharmaceutical industry.

Our procedure is based on the adaptive randomization of treatment allocations from the sequential construction of optimum experimental designs. As a consequence, we require optimum designs for multivariate continuous responses that

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provide balance over the prognostic factors that may be included in the estimation of treatment effects. Unfortunately, the majority of the adaptive designs that have been developed are for a single binary response per patient in the absence of covariates. Examples include the play-the-winner (PW) design (Zelen, 1969), the randomized play-the-winner (RPW) design (Wei and Durham, 1978), the success driven design (Durham et al., 1998) and the drop-the-loser (DL) rule (Ivanova, 2003). Related designs for continuous responses, using non-parametric methods to discretize the problem, include Rosenberger (1993) and Bandyopadhyay and Biswas (2004).

These designs work well in skewing the allocation in favour of the better treatment, although they are not derived from any optimality criterion. One form of optimality, for binary responses, consists of minimizing an aspect of behaviour, such as the total expected number of failures, for a given variance of the estimated treatment difference. Such designs include those of Rosenberger et al. (2001) and Biswas and Mandal (2007) for binary responses. Zhang and Rosenberger (2006, 2007) and Biswas et al. (2007) find optimum designs for continuous responses.

Several of these procedures have been extended to design in the presence of covariates, giving rise to Covariate Adjusted Response Adaptive (CARA) designs. For the randomized play-the-winner rule, Bandyopadhyay and Biswas (1999) combined polytomous covariates with binary responses and Bandyopadhyay and Biswas (2001) incorporated covariates in their design for continuous responses. Zhang et al. (2007) studied asymptotic properties of CARA designs under widely satisfied conditions. Optimum biased-coin designs for covariate balance, without response adaptivity, were introduced by Atkinson (1982). This form of optimality was extended to response-adaptive designs for univariate responses by Atkinson and Biswas (2005a,b). Rosenberger and Sverdlov (2008) discuss the arguments that have been advanced in the clinical trials literature for and against treatment allocation rules that provide some balance over covariates, as do Shao et al. (2010).

There is an appreciable literature on the analysis of data from clinical trials when the responses are observed at a series of monitoring times, for example Everitt and Pickles (2004, Chapters 5–7). Molenberghs et al. (2004) describe data from three clinical trials of anti-depressants in which the responses can be treated as continuous. Galbraith and Marschner (2002) provide guidelines for designing non-adaptive longitudinal clinical trials.

By comparison there is very limited literature on the design of adaptive longitudinal trials. Biswas and Dewanji (2004b) describe a trial of pulsed electro-magnetic field therapy in which each patient was monitored for about 16 weeks. The original responses in this trial had a complicated multivariate structure, which was ignored in the design. Instead a binary variable 'recurrence' was used. Biswas and Dewanji developed an urn design for longitudinal binary responses, which is a modification and simple extension of the RPW design where the covariates were ignored. See also Biswas and Dewanji (2004a,c). Sutradhar et al. (2005) used a similar urn model based design and allowed for the possibility of time-dependent covariates. Subsequently, Sutradhar and Jowaheer (2006) extended this approach for longitudinal count data. Biswas et al. (2012) provided an optimum response-adaptive design for longitudinal binary responses. Atkinson and Biswas (2014, Chapter 5) provide an account of work on response-adaptive designs for longitudinal responses. Further, Huang et al. (2013) proposed a general framework for longitudinal covariate-adjusted response-adaptive randomization procedures, and studied the related asymptotic properties.

In contrast, we obtain optimum biased-coin designs for multivariate and longitudinal responses by the extension of methods for univariate responses. The optimum designs in both cases are functions of the information matrix for the observations. The model for multivariate data is introduced in Section 2.1. In the rest of Section 2 we explore the consequences of a general formulation for randomized response-adaptive designs for univariate or multivariate responses. These designs use optimum design theory to provide covariate balance in a general adaptive rule that skews allocation to the better treatments, whilst maintaining a controllable degree of randomness. We stress that these results are extremely general; to apply the rules we merely need to be able to provide the information matrix of the observations. Loss and bias, used to compare the designs, are presented in Section 3 with the information matrix for longitudinal designs explicitly presented in Section 4.

Four specific allocation rules are described in Section 5. These include the extension of the rule of Atkinson and Biswas (2005a), which achieves adaptivity through use of the link function of Bandyopadhyay and Biswas (2001), and our new rule. We take the particular form of this rule which targets specified proportional allocations to the ranked treatments: in our numerical example with two treatments, our target is that 80% of patients should be allocated to the unknown better treatment. This procedure overcomes the instability in early allocations with the link-function based rule that can lead to imbalance if the trial is stopped early. In our application we apply the results to the particular information pattern and covariance structure arising with longitudinal responses developed in Section 4. The numerical results are in Section 7.

Two main contributions of our paper are the provision of our general rule and its application to longitudinal trials. In the form we use here, the design ceases to be response-adaptive once the correct ordering of the treatments has been established. We can then extend standard results of the effect of randomization on inference (Burman, 1996; Atkinson, 2002) to multivariate designs. For longitudinal designs with correlated observations we define an effective number of observations that permits calculation of the loss from randomization. This important quantity indicates the average number of patients on whom information is lost due to a particular randomization rule. Simulations in Section 7 confirm the accuracy of this definition.

The methods of optimum experimental design are central to our construction of allocation rules. In Appendix A.1 we develop new results on multivariate D_A-optimality that allow us to estimate linear combinations of the treatment effects, such as differences, in the presence of the parameters associated with the prognostic factors over which we are

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