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Experimental designs for drug combination studies

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ABSTRACT

The interest in drug combinations is growing rapidly due to the opportunities they create to increase the therapeutic effect and to reduce the frequency or magnitude of undesirable side effects when single drugs fail to deliver satisfactory results. Considerable effort in studying benefits of the joint action of drugs has been matched by the development of relevant statistical methods and tools for statistical analysis of the data obtained in such studies that allow important statistical assumptions to be taken into account, i.e. the appropriate statistical model and the distribution of the response of interest (e.g. Gaussian, Binomial, Poisson). However, much less attention has been given to the choice of suitable experimental designs for such studies, while only high quality data can ensure that the objectives of the studies will be fulfilled. Methods for construction of such experimental designs which are economical and make most efficient use of the available resources are proposed. It is shown how this can be performed when the distribution of the response is one of those belonging to the exponential family of distributions, and provide specific examples for the most common cases. In addition simple but flexible experimental designs, called ray–contour designs, are proposed. These designs are particularly useful when the use of low or high doses is undesirable and hence a standard statistical analysis of the data is not possible. Useful features of these designs are illustrated with an application in cancer study.

1. Introduction

Combinations of drugs have been known to be highly successful in treating different diseases for many years. They provide additional opportunities over single drug therapies to achieve sufficient therapeutic effect at a lower and potentially safer dose. Extensive discussions of the scientific background of such studies, include Greco et al. (1995), Tallarida (2000) and Chou (2006). Frequently experimental designs in drug combination studies are required to collect data for the response of interest at different combinations (*rays*) of doses of the studied drugs. These *ray designs* (Mantel, 1958; Tallarida, 2000) are easy to implement in practice. The results obtained using them are also easy to interpret as each drug combination can be treated as a new drug. Therefore the study of each ray can be done in a similar way to that used for single drugs, with the dose been split between the drugs according to the definition of the combination. However, all existing work related to the choice of dose levels for the rays is based on the assumption of a Gaussian distribution of the response. We consider the case when the distribution can be any distribution belonging to the exponential family of distributions, and provide examples for the most common cases, i.e. Gaussian, inverse Gaussian, Binomial, Poisson and Gamma, as response variables with such distributions are often used and software for analyzing the data is already available. Thus, the design problem becomes one for generalized nonlinear models. We construct our designs using the ideas of the optimum design theory. While the method for constructing designs for generalized linear models has been established (see for example Chapter 22, Atkinson et al., 2007), that is not the case when optimum designs for generalized nonlinear models are needed.

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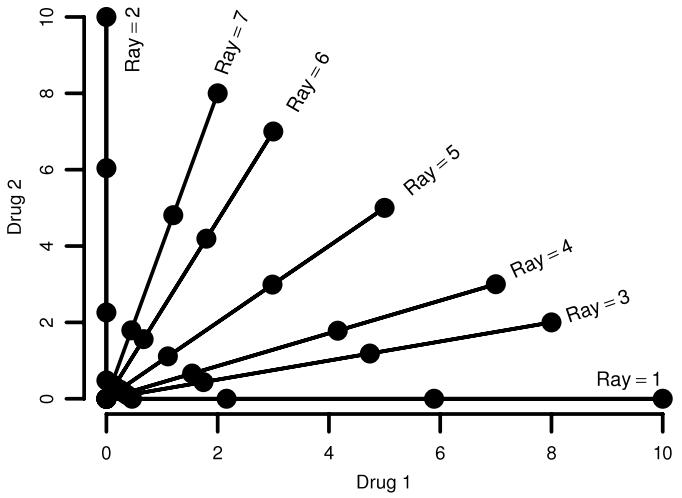

Fig. 1. Pseudo-Bayesian D- and G-optimum ray design for Gamma distributed errors.

In the next section we summarize common models used in the analysis of data collected in bioassay and present a way of assessing the joined action of drugs. We also describe useful statistical properties of the results that depend on the choice of the experimental design. We discuss how economical but efficient ray designs can be constructed using information obtained in previous studies of the individual drugs in Section 3. Designs constructed this way can be useful for many experimental situations and are particularly useful for preclinical studies.

In Section 4 we propose the use of a new class of *ray–contour designs* that permit a variety of combination studies to be designed in such a way that low or high doses can be avoided and the statistical analysis can be simplified as they aim at collecting enough data to estimate whether there is synergistic or antagonistic effect only at chosen inhibition levels (i.e. percentages of maximum possible effects). For example, ray–contour designs are particularly useful in combination studies where large doses should be avoided due to ethical considerations, e.g. in animal studies and in early studies in men when the use of higher doses may not be desirable because of a concern for their safety. A similar suggestion and a discussion of the possible benefits of using such experimental designs is given in Gennings (1995). However, a simple situation is only considered. We illustrate some benefits of using ray–contour designs with an example based on the results of a recent pilot study carried out at the Paterson Institute for Cancer Research, Manchester, UK. We also compare the ray–contour designs with the very popular and simple *diagonal* designs of Chou and Talalay (1984).

All discussions in the paper are limited to cases where the combination of two drugs is required. However, the presented methodology can be extended to situations when combinations of more drugs are studied. Computer programs, written using the computer package R (freely available at http://www.R-project.org), implementing the algorithms constructing the designs described in this paper will be made available with its publication.

2. Statistical analysis of combination studies

The statistical analysis of the data involves the estimation of a model relating the response of interest, Y_{ij}, and the doses of the first drug, d_{ij1}, and the second drug, d_{ij2}, where i, $i = 1, \ldots, t$, denotes the drug combination (ray) and j, $j = 1, \ldots, c$, denotes the dose level at which the response is measured. An example of a ray design discussed in relation to Example 2 later in the paper is shown in Fig. 1.

When a ray design has been used, it is convenient to obtain individual models in terms of the total dose $x_{ij} = d_{ij1} + d_{ij2}$ for all rays. We consider the case when the response has a probability distribution belonging to the exponential family of distributions (McCullagh and Nelder, 1989) which includes all distributions which are likely to be needed in practice, e.g. Gaussian, inverse Gaussian, Binomial, Poisson and Gamma. We consider models with nonlinear predictor

$$\eta(x_{ij}, \theta) = \gamma + \frac{\delta - \gamma}{\left(1 + 10^{(x_{ij} - \alpha_i)\beta_i}\right)^{\lambda_i}}, \tag{1}$$

where $\theta = (\alpha_i\ \beta_i\ \gamma\ \delta\ \lambda_i),\ i = 1, \ldots, t$, is a vector of all model parameters. We denote $r_i = d_{ij1}/d_{ij2},\ d_{ij2} \neq 0$, the ratios of the drugs in the combinations and $p_i = d_{ij2}/(d_{ij1} + d_{ij2})$, $d_{ij1} + d_{ij2} \neq 0$, the corresponding proportions of the second drug. They both are the same for the doses of each of the rays.

The link function between the nonlinear predictor and the expectation of the response μ_{ij} is given by a function $g(\cdot)$ such that $g(\mu_{ij}) = \eta(x_{ij}, \theta)$. In all results we have used the canonical link function (McCullagh and Nelder, 1989). As