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Subject–treatment interactions in crossover trials: performance evaluation of subgrouping methods

Subir Ghosh[a,*], Heather R. Crosby[b]

[a] *Department of Statistics, University of California, Riverside, CA 92521-0138, USA*
[b] *Amylin Pharmaceuticals, San Diego,USA*

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Abstract

Ghosh and Fairchild (J. Statist. Plann. Inference 88 (2000) 301; In: Sen and Rao (Eds.), Handbook of Statistics 18: Bioenvironmental and Public Health Statistics, North-Holland, Amsterdam, 2000, p. 547.) proposed a model for drawing inference on the subject–treatment interactions in a two-period crossover trial and presented a method of subgrouping subjects in a group. In this paper we present another method of subgrouping for the same purpose of drawing inference on the subject–treatment interactions. This new method is based on a threshold level, a critical adjacent factor (CAF), and a majority rule. We then compare these two methods of subgrouping. Three performance measures are used for our comparison. The first measure is the probability of identifying the correct number of subgroups. The second measure is the probability that a subject is correctly placed in a subgroup under the condition that the number of subgroups has been correctly identified. The third measure is defined for subjects ordered from lowest to highest differences in their responses for two treatments. For the subjects placed into a subgroup by a method, the third measure determines the number of distinct subgroups beyond a single subgroup that these subjects really belong to. Extensive simulations are used for calculating the estimated numerical values of the performance measures and then for comparing the methods of subgrouping.

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Keywords: Clinical trials; Critical adjacent factor; Crossover design; Gap values; Simulations; Subgrouping; Subject–treatment interactions

* Corresponding author.
E-mail address: ghosh@ucrac1.ucr.edu (S. Ghosh).

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1. Introduction

In a crossover trial for comparing two treatments A and B in two periods, n subjects in Group 1 receive treatment A first and then crossover to treatment B after a specified period of time but n subjects in Group 2 receive treatment B first and then treatment A (see Grizzle, 1965, 1974; Chinchilli and Esinhart, 1996; Ekbohm and Melander, 1989). The data collected from such a trial is analyzed for drawing conclusions on the significant difference between two treatments and then one treatment is recommended over the other for curing a disease. Note that the number of subjects could be different in two groups. In the standard 2×2 crossover trial, it is customary to refer Group 1 as sequence AB and Group 2 as sequence BA.

It is known that two subjects may respond differently to the same treatment (see Ekbohm and Melander, 1989). Therefore the response difference for two treatments does not remain the same for all subjects, see Ghosh and Fairchild (2000a, b). Treatment A may be better than treatment B for some subjects with certain health conditions. Treatment B may be better than treatment A for some other subjects with different health conditions. Treatments A and B may be equivalent for the remaining subjects with different health conditions from all other subjects. In other words, subjects may interact with treatments. The study of such subject–treatment interactions is important not only for treating disease but also for protecting subjects from various side effects. Ghosh and Fairchild (2000a, b) presented the model below for estimating the subject–treatment interactions and testing their significance:

$$Y_{iju(k)} = \mu + \gamma_k + \delta_{u(k)} + \xi_{ju(k)} + \tau_{i(k)} + (\tau\delta)_{iu(k)} + \varepsilon_{iju(k)},$$

where μ is the general mean, γ_k is the effect of the kth group, $\delta_{u(k)}$ is the effect of the uth subgroup within the kth group, $(\tau\delta)_{iu(k)}$ is the effect of the interaction between the ith treatment and the uth subgroup with the kth group and $\varepsilon_{iju(k)}$ is the error term. The parameters μ, γ_k, $\delta_{u(k)}$, $\tau_{i(k)}$ and $(\tau\delta)_{iu(k)}$ are fixed unknown constants. The random variables $\xi_{ju(k)}$'s are independently identically distributed (i.i.d.) with mean 0 and variance σ^2_ξ, $\varepsilon_{iju(k)}$'s are i.i.d. with mean 0 and variance σ^2_ε; $\xi_{iju(k)}$'s and $\varepsilon_{iju(k)}$'s are independent and the variances σ^2_ξ and σ^2_ε are unknown positive constants. We have

$$E(Y_{iju(k)}) = \mu + \gamma_k + \delta_{u(k)} + \tau_{i(k)} + (\tau\delta)_{iu(k)}.$$

It can be checked that

$$\begin{aligned} &E(Y_{Aj'u'(k)} - Y_{Bj'u'(k)} - Y_{Aju(k)} + Y_{Bju(k)}) \\ &\quad = (\tau\delta)_{Au'(k)} - (\tau\delta)_{Bu'(k)} - (\tau\delta)_{Au(k)} + (\tau\delta)_{Bu(k)}. \end{aligned}$$

The linear function $Y_{Aj'u'(k)} - Y_{Bj'u'(k)} - Y_{Aju(k)} + Y_{Bju(k)}$ represents the gap value $D_{(j')} - D_{(j)}$ defined in Section 2 with $D_{(j)} = Y_{Aju(k)} - Y_{Bju(k)}$. Note that the expected value of this linear function is zero for two subjects in the same subgroup. The expected value represents a subgroup–treatment interaction contrast for two subjects in different subgroups.

Testing the significance of subject–treatment interactions requires the replications of subjects. Ghosh and Fairchild (2000a, b) gave a method of subrouping of subjects within a group considering the similarity of their response differences for treatments. The idea