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One-sided multiple comparisons for treatment means with a control mean

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ABSTRACT

We study comparisons of several treatments with a common control when it is believed *a priori* that the treatment means, μ_i, are at least as large as the control mean, μ_0. In this setting, which is called a tree ordering, we study multiple comparisons that determine whether $\mu_i > \mu_0$ or $\mu_i = \mu_0$ for each treatment. The classical procedure by Dunnett (1955) and the step-down and step-up techniques by Dunnett and Tamhane (1991, 1992) are well known. The results in Marcus and Talpaz (1992) provide multiple comparisons based on the maximum likelihood estimates restricted by the tree ordering. We also study two-stage procedures that consist of the likelihood ratio test of homogeneity with the alternative constrained by the tree ordering followed by two-sample t comparisons with possibly different critical values for the two-sample comparisons. Marcus et al. (1976) discuss the use of closed tests in such situations and propose using a closed version of the restricted likelihood ratio test. We describe step-down versions of the Marcus–Talpaz, the two-stage, and the likelihood ratio procedures, as well as a closed version of the Marcus–Talpaz multiple comparison procedure. Using Monte Carlo techniques, we study the familywise errors and powers of these procedures and make some recommendations concerning techniques that perform well for all tree ordered mean vectors.

1. Introduction

We consider situations in which one compares several treatment means with a common control mean when it is believed that the treatment means are at least as large as the control mean (if it is believed that the treatment means are no larger than the control mean, then the procedures discussed here can be used after multiplying all of the observations by -1). A survey of some applicable methods is included in Dunnett (1997). To be specific, we consider multiple comparisons that determine whether $\mu_i = \mu_0$ or $\mu_i > \mu_0$ when it is believed that the means satisfy a tree ordering, which is defined by $\mu_0 \leq \mu_i$ for $1 \leq i \leq k$. If a researcher knows a priori that the means satisfy a simple ordering, for example, $\mu_0 \leq \mu_1 \leq \cdots \leq \mu_k$, then multiple comparisons that use this stronger ordering information will tend to be more powerful than those based on the tree ordering (see Nashimoto and Wright, 2005a,b, 2007, and their references). Section 4 contains a limited comparison of methods for tree-ordered means with those for simply ordered means.

For normal distributions, maximum likelihood estimates (MLEs) of means that are known to satisfy the tree ordering are discussed in Robertson et al. (1988, p. 19), and the likelihood ratio tests (LRTs) of homogeneity with the alternative constrained by the tree ordering on the means are discussed in Bartholomew (1961) and Robertson et al. (1988, Chapter 2). We denote these by TMLEs and TLRTs. Because the critical values for the TLRTs can be tedious to compute, several other

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procedures have been considered. Tang and Lin (1997) develop an approximate TLRT and give a thorough discussion of other competitors to the TLRT. Cohen and Sackrowitz (2002) study estimates and tests in this situation that have desirable monotonicity properties.

We consider the following procedures, which can be used for multiple comparisons in this setting: the classical one by Dunnett (1955), the step-down one in Dunnett and Tamhane (1991), which is a special case of the closed test of Marcus et al. (1976), the step-up one in Dunnett and Tamhane (1992), and the two in Marcus and Talpaz (1992) and Chakraborti and Hettmansperger (1996). Because a two-stage procedure, which is the LRT of global homogeneity with the alternative constrained by the simple ordering followed by pairwise comparisons, worked well when the means are known to be nondecreasing (see Nashimoto and Wright, 2005b), we propose an analogous procedure for the tree ordering. We also consider step-down versions of the Marcus–Talpaz test, the two-stage procedure and the TLRT, as well as closed versions of the Marcus–Talpaz test and the TLRT.

With $\boldsymbol{\mu} = (\mu_0, \mu_1, \ldots, \boldsymbol{\mu}_k)'$, the familywise error rate of a procedure C, denoted by $FWE(\boldsymbol{\mu}, C)$, is the probability that C makes at least one type I error in the pairwise comparisons, that is, it declares $\mu_i > \mu_0$ when $\mu_i \le \mu_0$ for some $1 \le i \le k$. To make recommendations concerning the use of these multiple comparisons, we investigate their FWE and power functions. Because the power function of the TLRT is complicated for even a moderate number of treatments (Singh et al., 1993, see), we use Monte Carlo techniques. For each $1 \le i \le k$, in our study, we consider the ith power, that is, the probability that μ_i is declared larger than μ_0.

We now consider the settings for Dunnett's (1955) two-sided and one-sided procedures. For these procedures, the collection of means is $\Omega = \{\boldsymbol{\mu} : -\infty < \mu_i < \infty \text{ for } i = 0, 1, \ldots, k\}$ and the one-sided procedure tests $H_{0,D} : \mu_0 \ge \mu_i$ for all $i = 1, 2, \ldots, k$ versus $H_{1,D} = \Omega - H_{0,D}$. If one believes that the means are tree ordered, then restricting Ω and these hypotheses accordingly yields

$$\Omega_T = \{\boldsymbol{\mu} : -\infty < \mu_0 \le \mu_i < \infty \text{ for all } i = 1, 2, \ldots, k\}, \qquad H_0 : \mu_0 = \mu_1 = \cdots = \mu_k \quad \text{and} \quad H_1 = \Omega_T - H_0. \quad (1)$$

It is not surprising that some of the tests of these more restrictive hypotheses are more powerful than Dunnett's (1955) test at some points in H_1. However, Dunnett's (1955) procedure has some advantages, particularly, if the means are not tree ordered.

1. Dunnett's procedure strictly controls FWE, i.e., $FWE(\boldsymbol{\mu}, D) \le \alpha$ for all $\boldsymbol{\mu}$. However, some of the other procedures only control FWE for tree-ordered means, i.e., $FWE(\boldsymbol{\mu}, C) \le \alpha$ for all tree-ordered $\boldsymbol{\mu}$, but there exists a $\boldsymbol{\mu}$ that is not tree ordered for which $FWE(\mu, C) > \alpha$. This point will be discussed further in Section 2 when the procedures are considered.
2. Even for unbalanced designs, adjusted p-values and critical values for Dunnett's procedure can be obtained from statistical software, see Section 2.1, and powers can be obtained from the non-central, multivariate t-distribution. However, for these other procedures, Monte Carlo techniques must be used.

Both Dunnett's and the Marcus–Talpaz procedures yield simultaneous one-sided confidence bounds, and Dunnett's procedure provides simultaneous confidence intervals.

To close this section, we mention some other work on tree orderings. Cheung and Holland (1991) extend Dunnett's procedure to make simultaneous comparisons in r groups, each consisting of k treatments and a control, and Peng et al. (2000) extend the latter to a two-way factorial design. Lee et al. (2006) develop lower confidence bounds for $\mu_{(k)} - \mu_0$, with $\mu_{(k)}$ the largest treatment mean.

2. Procedures

Let $X_{i,j} = \mu_i + \varepsilon_{i,j}$ for $i = 0, 1, \ldots, k$ and $j = 1, 2, \ldots, n_i$ with $\varepsilon_{i,j} \sim$ iid $N(0, \sigma^2)$ and H_0 and H_1 be defined as in (1). The sample size vector, total sample size, sample mean vector, and an independent variance estimator are denoted by

$$\boldsymbol{n} = (n_0, n_1, \ldots, n_k)'; \qquad N = \sum_{i=0}^{k} n_i; \qquad \bar{\mathbf{X}} = (\bar{X}_0, \bar{X}_1, \ldots, \bar{X}_k)'; \quad \text{and} \quad S^2 \text{ with } \nu S^2/\sigma^2 \sim \chi^2_\nu.$$

For the usual pooled variance estimator, $\nu = N - k - 1$. If the treatment sample sizes are equal, (i.e., $n_1 = n_2 = \cdots = n_k$), then we say the design is partially balanced and denote the common treatment sample size by n.

2.1. Dunnett-type procedures

For Dunnett's (1955) procedure, denoted by D, let

$$T_i = (\bar{X}_i - \bar{X}_0)/\left(S\sqrt{1/n_i + 1/n_0}\right) \quad \text{and} \quad U_i = \{\bar{X}_i - \bar{X}_0 - (\mu_i - \mu_0)\}/\left(S\sqrt{1/n_i + 1/n_0}\right), \quad (2)$$

for $1 \le i \le k$. Let $d(\alpha, k, \mathbf{n}, \nu)$ satisfy $P(\max_{1\le i\le k} U_i > d(\alpha, k, \mathbf{n}, \nu)) = \alpha$. Then D declares $\mu_i > \mu_0$ if $T_i > d(\alpha, k, \mathbf{n}, \nu)$, and D rejects H_0 if $\max_{1\le i\le k} T_i > d(\alpha, k, \mathbf{n}, \nu)$. Clearly, $FWE(\boldsymbol{\mu}, D) \le \alpha$ for all $\boldsymbol{\mu}$. For a partially balanced design and $1 \le i \ne j < k$, U_i and U_j have correlation $\rho = 1/(r + 1)$, where $r = n_0/n$, and the critical value, denoted by $d_b(\alpha, k, \rho, \nu)$, can be obtained from the tables in Bechoffer and Dunnett (1988) or Dunnett (1964). For unbalanced designs, the algorithm in Dunnett (1989) is available in PROBMC in SAS (SAS Institute Inc, 2009) and in MULTCOMP in R (R Development Core Team, 2010).