Survival-Adjusted Isotonic Trend Tests

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1. INTRODUCTION

An isotonic regression approach for common trend tests is proposed in this paper. This approach enables trend tests to be applied under the monotonicity constraint of the dose response, and substantially increases the statistical power of the tests while controlling the probability of a Type I error.

Consider an animal carcinogenicity experiment with g groups of increasing dose levels $0 = d_1 < d_2 < \cdots < d_g$. Suppose n animals are initially placed on experiment, and n_i animals are assigned randomly to group i. The animals are followed over time for the development of the tumor of interest. We assume that all animals come from the same population and are born tumor-free on day zero of the experiment. All animals are examined for the existence of the tumor at death, but cause-of-death information is not collected. The objective of this study is to test for trend in the proportions of animals with the tumor at death in the presence of competing risks which are causes of death other than the tumor of interest.

Suppose that the set of values $\boldsymbol{p} = (p_1, p_2, \cdots, p_g)$ consists of the binomial parameters indicating the actual probabilities of a positive response for each dose level. Under the monotonicity constraint of the dose-response relationship (i.e., $p_1 \leq p_2 \leq \cdots \leq p_g$), our objective is to test the following hypotheses:
$H_0 : \ p_1 = p_2 = \cdots = p_g \equiv p_0$ versus $H_1 : \ p_1 \leq p_2 \leq \cdots \leq p_g$ with at least one strict inequality.

2. ISOTONIC MODIFICATION OF THE CA-TYPE TREND TESTS

Bailer and Portier (1988) made an adjustment of the Cochran-Armitage (CA) test to correct for treatment lethality unrelated to the tumor of interest. Their test is called the Poly-3 test, and an improved version of it was given by Bieler and Williams (1988). We propose an isotonic modification of the CA-type (CA and Poly-3) trend tests in this paper. An

amalgamation process based on the pool-adjacent-violators algorithm (PAVA), first published by Ayer et al. (1955), is adopted here. The bootstrap method is applied in finding the empirical distributions of the test statistics and the corresponding critical values in the isotonic versions of the CA-type tests.

3. ORDER-RESTRICTED LIKELIHOOD RATIO TEST WITH A SURVIVAL ADJUSTMENT

A likelihood ratio test (LRT) can also be used to test for trend in the proportions, and an isotonic LRT is given by Robertson et al. (1988). In this paper, we develop a survival-adjusted LRT and its isotonic counterpart. A monotonic MLE of $\boldsymbol{p}$ is needed for conducting the isotonic LRT. Under the constraint that the event incidence rates are isotonic, the PAVA is used for computing $\hat{\boldsymbol{p}}^* = \{\hat{p}_i^* : i = 1, 2, \cdots, g\}$, the set of monotonic MLEs of p_i's.

The presence of treatment-induced mortality unrelated to the tumor of interest may mislead tests that only focus on the crude lifetime tumor incidence rates. To address this issue in the LRT, we adopt the weighting scheme given in Bieler and Williams (1988) and propose a survival-adjusted LRT.

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RESUME

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