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False discovery rate control for non-positively regression dependent test statistics

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Abstract

In this paper we present a modification of the Benjamini and Hochberg false discovery rate controlling procedure for testing non-positive dependent test statistics. The new testing procedure makes use of the same series of linearly increasing critical values. Yet, in the new procedure the set of p-values is divided into subsets of positively dependent p-values, and each subset of p-values is separately sorted and compared to the series of critical values. In the first part of the paper we introduce the new testing methodology, discuss the technical issues needed to apply the new approach, and apply it to data from a genetic experiment.

In the second part of the paper we discuss pairwise comparisons. We introduce FDR controlling procedures for testing pairwise comparisons. We apply these procedures to an example extensively studied in the statistical literature, and to test pairwise comparisons in gene expression data. We also use the new testing procedure to prove that the Simes procedure can, in some cases, be used to test all pairwise comparisons.

The control over the FDR has proven to be a successful alternative to control over the family wise error rate in the analysis of large data sets; the Benjamini and Hochberg procedure has also made the application of the Simes procedure to test the complete null hypothesis unnecessary. Our main message in this paper is that a more conservative approach may be needed for testing non-positively dependent test statistics: apply the Simes procedure to test the complete null hypothesis; if the complete null hypothesis is rejected apply the new testing approach to determine which of the null hypotheses are false. It will probably yield less discoveries, however it ensures control over the FDR.

Keywords: False discovery rate; Pairwise comparisons; Dependent test statistics

1. Introduction

The Benjamini and Hochberg (1995) false discover rate controlling procedure (BH procedure) is known to control the FDR for positively dependent test statistics (Benjamini and Yekutieli, 2001). In this paper we present a modification of the BH procedure for controlling the FDR for non-positive dependent test statistics. The new testing procedure makes use of the series of linearly increasing critical values used in the BH procedure—$\{iq/m\}_{i=1}^{m}$. But while in the BH procedure the entire set of p-values is sorted and compared to the series of critical values, in the new procedure the set of p-values is divided into subsets of positively dependent p-values, and each subset of p-values is separately sorted and compared to the series of critical values.

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The idea of applying the BH procedure to separate subsets was first used in Benjamini and Yekutieli (2005) for testing m, non-positively dependent, two-sided test statistics. The authors suggested to separately apply the BH procedure at level $q/2$ to the two corresponding sets of m positively dependent one-sided test statistics null hypotheses, and showed that the FDR is controlled at level q on all $2m$ one-sided hypotheses. In this paper we will generalize this idea to more than two, not necessarily disjoint, subsets of positively dependent test statistics.

Throughout the paper the vector of p-values are co-monotone transformations of the corresponding test statistics (e.g. one-sided p-values), hence posses equivalent positive dependency properties. For the sake of brevity, we will alternately discuss p-values or test statistics. $\vec{P} = \{P_1, \ldots, P_m\}$ is the vector of p-values corresponding to the tested hypotheses; $P_{(1)} \leqslant \cdots \leqslant P_{(m)}$ are the sorted p-values; m_0 is the number of true null hypotheses ($0 \leqslant m_0 \leqslant m$) and the distribution of each true null hypotheses p-value is stochastically larger than U[0, 1]; we will denote the complete null hypothesis—H_c^0 ($m_0 = m$).

The series of linearly increasing critical values was originally employed (Simes, 1986; Seeger, 1968) to test whether any of the null hypotheses are false:

Definition 1.1. Level α Simes test: if $\exists\ P_{(i)} \leqslant \alpha \cdot i/m$ then reject H_c^0.

It was shown that for independent test statistics (Simes, 1979) and later for positively dependent test statistics (Sarkar and Chang, 1997; Sarkar, 1998) that under H_c^0 the probability that the Simes procedure rejects H_c^0 is less than or equal to α. If, however, H_c^0 is not true ($m_0 < m$) the series of critical values cannot be used to determine which hypotheses are false null hypotheses, while controlling the probability of making at least on type I error at level α.

In their seminal paper, Benjamini and Hochberg (1995) introduced a new measure for type I error in multiple testing—the FDR—employed the series of critical values to test the individual null hypotheses, and showed that the resulting procedure controls the FDR at level $q \cdot m_0/m$ for independently distributed test statistics.

Definition 1.2. The level q BH procedure:

1. Let $k = \max\{i : P_{(i)} \leqslant iq/m\}$.
2. If $\exists k > 0$ then reject the null hypotheses associated with $\vec{R}_{\mathrm{BH}} = \{P_{(i)} : i = 1 \cdots k\}$; otherwise do not reject any of the null hypotheses.

Benjamini and Yekutieli (2001) proved that if the vector of test statistics, $\vec{T}$, is positive regression dependent on the subset of true null hypotheses test statistics $\vec{T}_0$ then the FDR of the level q BH procedure is less than or equal to $q \cdot m_0/m$.

Definition 1.3. $\vec{T}$ is positive regression dependent on $\vec{T}_0$: for any increasing set D, and for each $T_i \in \vec{T}_0$, $\Pr(\vec{T} \in D | T_i = t)$ is non-decreasing in t.

Benjamini and Yekutieli (2001) also presented a general-dependency FDR controlling procedure: applying the BH procedure at level $q/(\sum_{i=1}^{m} 1/i)$ offers FDR control at level q for all joint test statistic distributions. The shortcoming of this testing procedure is that it is considerably less powerful than the BH procedure.

In Section 2 we will define the new testing approach, address the problem of constructing positively dependent sub-vectors, and apply the new testing procedure to data from a genetic experiment. Section 3 is dedicated to the problem of testing pairwise comparisons. We will present FDR controlling procedures for testing pairwise comparisons. Apply these testing procedures to an example extensively studied in the statistical literature, and to test the pairwise comparisons in the expression level of 7129 genes. Following Yekutieli (2001), we also use the FDR controlling property of the new testing procedure to prove that the Simes procedure can be used to test all pairwise comparisons. In Section 4 we discuss the suggested use of the new testing approach.

2. The separate subsets BH (ssBH) procedure

To apply the ssBH procedure the vector of m p-values, $\vec{P}$, is divided into S sub-vectors, $\vec{P}^s$, for $s = 1 \cdots S$; let m^s denote the number of test statistics in $\vec{P}^s$ and let $\vec{P}_0^s$ denote the p-values corresponding to the true null hypotheses in $\vec{P}^s$.