Report on Independent Hypothesis Weighting

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1. Introduction

Numerous techniques have been devised for the analysis of high-throughput data to accurately quantify biological features, including genes and proteins. To ensure the reliability of discoveries, the false discovery rate (FDR) has become the dominant approach for setting thresholds. The methods for controlling FDR primarily rely on p-values, among which the Benjamini-Hochberg (BH) procedure (Benjamini and Hochberg 1995) and Storey's q-value(Storey 2002) are popular.

However, Ignatiadis, Klaus, Zaugg, and Huber suggest that FDR methods based solely on p-values exhibit suboptimal power when the individual tests vary in their statistical properties. (Ignatiadis et al. 2016). When these methods focus exclusively on p-values, they overlook potentially relevant covariates. For example, in RNA-seq differential expression analysis, one such covariate could be the normalized mean counts of genes. Intuitively, genes with higher counts are likely to have greater power in detection compared to those with lower counts, and it would be optimal to include this relationship in the analysis.

To address this limitation, a novel approach known as independent hypothesis weighting (IHW) has been introduced. IHW improves the power of multiple hypothesis testing while controlling the FDR rate. The key innovation of IHW is that it recognizes that not all tests have the same power or the same prior probability of being true. It allows for the assignment of different weights to different hypotheses based on covariates that are predictive of the test's power or its probability of being a true discovery. These covariates can be anything from the biological characteristics of the genes being tested to the technical aspects of the measurements. More explorations will be done in the following sections on this method.

2. Methodology and Simulation

There have been existing attempts to increase power by using covariates and this sections starts off by introducing some known methods.

2.1 Weighted and Group weighted BH procedure

The weighted BH method has m hypotheses $H_1, H_2, ..., H_m$ and m weights $w_1, w_2, ..., w_m \geq 0$ that satisfy $\frac{1}{m}\sum_{i=1}^{m} w_i = 1$. After the weights are obtained, the BH procedure is applied on the modified p-values: $\frac{p_i}{w_i}$. In this scenario, selecting the weights before observing the p-values is essential, relying on prior knowledge or information indicating the likelihood of some hypotheses being true over others. This requirement presents a significant challenge, one that IHW seeks to address, and it utilizes the grouped weighted BH procedure (GBH). In this method, there are G groups where each X_i takes the same value within each group. GBH first estimates the proportion of null hypotheses by $\hat{\pi}_0(g)$, then weights the hypotheses proportionally to $\frac{1-\hat{\pi}_0(g)}{\hat{\pi}_0(g)}$, and finally apply the BH procedure. However, the asymptotic theories in this method doesn't function well when the number of hypotheses $\frac{m}{G}$ is finite (Ignatiadis and Huber 2021). To resolve this issue, cross-weighting is used, where the idea is analogous to cross-fitting in regression settings, and this gives rise to the naive version of IHW.

2.2 Naive IHW and two-groups model

This version, also abbreviated as IHW-GBH since it is based off GBH, first divides the hypothesis tests into G groups based on the values of covariate $X = (X_1, X_2, \dots, X_m)$, with m_g number of hypotheses in the g-th group. It is also assumed that we have access to the p-values $P = (P_1, P_2, \dots, P_m)$, which is independent of X under the null. With this setup, $\sum_{g=1}^{G} m_g = m$. Then the weighted BH procedure is applied with each possible weight vector $w = (w_1, w_2, \dots, w_G)$, while the optimal w^* is the vector that lead to the most rejections. This method extends the BH procedure, making it pertinent to discuss the associated maximization problem. This problem stems from the two groups model (Efron 2008), which is a Bayesian framework that explains the BH procedure. Formally, assume that H_i takes values 0 or 1, and $\pi_0 = \mathbb{P}(H_i = 0)$. The distributions are as follows:

$$\begin{aligned} H_i &\sim \text{ Bernoulli } (1 - \pi_0) \\ P_i \mid H_i = 0 &\sim U[0, 1] \\ P_i \mid H_i = 1 &\sim F_1 \end{aligned}$$

The marginal distribution for p-value P_i is then

$$P_i \sim F(t) = \pi_0 t + (1 - \pi_0) F_1(t)$$

With this, the Bayesian FDR becomes:

$$\text{Fdr}(t) = \mathbb{P}\left[H_i = 0 \mid P_i \leq t\right] = \frac{\pi_0 t}{F(t)}$$

A natural empirical estimator for the CDF would be the ECDF, and it can be written in terms of $R(t)$, which denotes the total number of rejections:

$$R(t) = m\widehat{F}(t) = \sum_{i=1}^{m} \mathbf{1}_{\{P_i \leq t\}}$$

Hence if $\widehat{\pi_0}$ is an estimator of π_0,

$$\widehat{\text{Fdr}}(t) = \frac{\widehat{\pi_0} t}{\widehat{F}(t)} = \frac{\widehat{\pi_0} m t}{R(t)}$$

If a conservative estimate is made: $\widehat{\pi_0} = 1$, then

$$\widehat{\text{Fdr}}(t) = \frac{mt}{R(t)} \tag{1}$$

With this, the optimization problem is:

$$\text{maximize } R(t), \text{ s.t. } \widehat{\text{Fdr}}(t) \leq \alpha, t \in [0, 1]$$

The corresponding estimator in IHW-GBH is of the form

$$\widehat{\mathrm{Fdr}}(t, \mathbf{w}) = \frac{mt}{R(t, \mathbf{w})} = \frac{\sum_{g=1}^{G} m_g w_g t}{R(t, \mathbf{w})}$$

where $R(t, \mathbf{w}) = \sum_{i=1}^{m} \mathbf{1}_{\{P_i \leq w_g t\}}$ is the number of rejections in bin g. Now the optimization problem is:

$$\text{maximize}\, R(t, \mathbf{w}), \text{ s.t. } \widehat{\mathrm{Fdr}}(t, \mathbf{w}) \leq \alpha$$

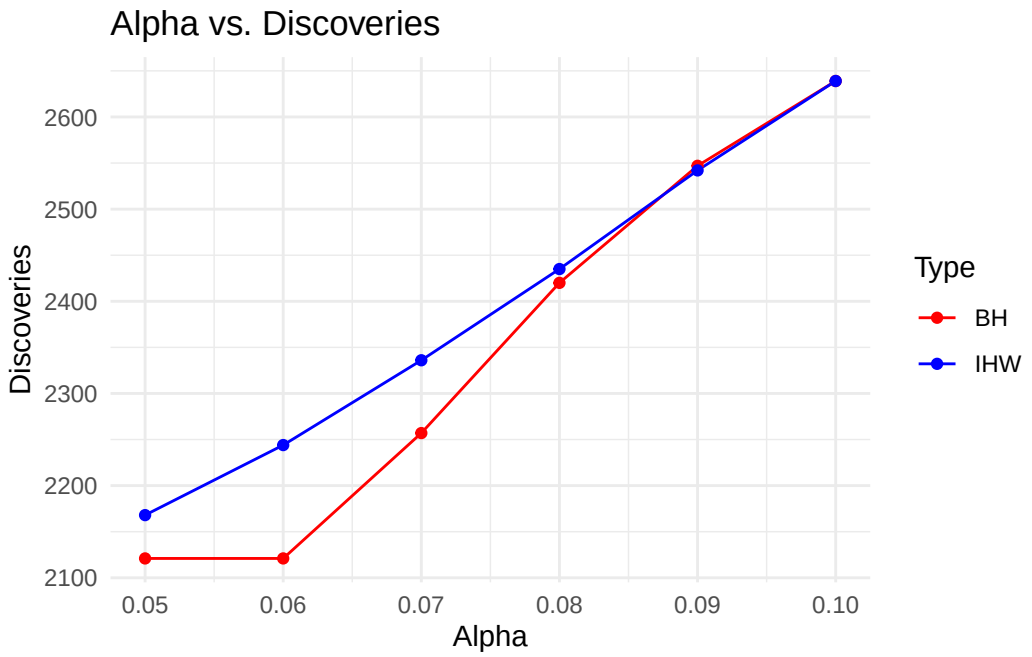
However, with this approach, there are also some disadvantages including potential loss of Type I error, complications in solving the maximization problem, and its inability to scale when large number of tests are present. That is why modifications are made, leading to the IHW method.

2.3 IHW

In the first modification, the ECDF $\hat{F}_g$ of the p-values in group g is replaced by the least concave majorant version called the Grenander estimator $\tilde{F}_g$. With this the maximization problem can be efficiently solved. The second modification involves randomly splitting the hypotheses into K folds, where K is usually taken to be 5. Then the maximization problem with the previous modification is applied to the remaining folds, leading to a weight $\widetilde{w} = (\widetilde{w}_1, \ldots, \widetilde{w}_G)$. The independence criterion between the hypotheses would guarantee the p-value P_i to be independent of the assigned weight w_i when the null hypothesis is true. The third modification ensures that the weights learned with $K - 1$ folds can be generalized to the held-out fold by adding a regularization parameter λ. The specific constraints are customized to whether the covariates are ordered or not.

2.4 Simulation

Wanting to see how this packages work exactly, I used one of the datasets suggested by the paper using RNA-seq data with read counts for genes as a covariate (Bottomly et al. 2011). It is worth noting that in the original dataset provided in the paper by Bottomly, the column of read counts is only binary, providing information of whether the counts are considered low or not based on a threshold after a log transformation. Without knowing the specific transformation applied, it is hard to achieve the original column, hence I self-generated a column of count reads using the negative binomial distribution. After trying some combinations, I chose the dispersion parameter to be 0.2 while the mean read counts is 10,000. The plot generated is as follows. There is a discrepancy between this plot and that generated in the paper possibly because the difference in the read counts, however, it can still be observed that the number of discoveries of IHW is no fewer than that of BH.



2.5 Discussions

One challenge that this method faces is that it largely depends on selecting an appropriate covariate that influences the power of each hypothesis test but is independent of the p-values under the null hypothesis. Identifying such a covariate is challenging and crucial; an unsuitable choice can diminish IHW's benefits or even degrade performance compared to traditional correction methods. This is a reason of why the plot above doesn't show great improvements. Another possible limitation is when there are datasets with high heterogeneity, where the covariate's relationship to test power varies significantly. In such cases, IHW's ability to accurately weight hypotheses could be compromised, potentially leading to less effective multiple testing correction.

3. Extensions

References

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