kyotil Package Vignette

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1 p.adj.perm: resampling-based approach to assessing statistical significance (Sue Li)

Suppose that we are interested in testing m hypotheses, $H_1, \cdots, H_m$. Corresponding P-values are denoted by $p_1, \cdots, p_m$. Two commonly used criteria for error correction are familywise error rates (FWER) and false discovery rates (FDR). The analytical approaches are conservative for correlated data. The Monte Carlo approach (Westfall and Young, 1993) retains the correlations between the p-values, and can therefore provide a more accurate control of FWER and FDR. The correctness of the Monte Carlo approach depends on the *subset pivotality* assumption (Westfall and Troendle, 2008), i.e. the distributions of $\max_{i \in I} T_i | H_I$ and $\max_{i \in I} T_i | H_{\{1,\ldots,m\}}$ are identical, for all $I \subset \{1, \ldots, m\}$.

1.1 Familywise error rates

FWER is the probability of rejecting at least one true hypothesis:

$$FWER = \Pr(\text{rejecting at least one } H_j, j = j_1, \cdots, j_t | H_{j_1}, \cdots, H_{j_t}, \text{are true}).$$

A simultaneous test is controlled with the FWER at α level if FWER$\leq \alpha$.

Bonferroni correction procedure
Simply reject hypothesis H_j if the p-value $p_j \leq \alpha/m$.

Holm's step-down procedure
Let $p_{(1)} \leq p_{(2)} \leq \cdots \leq p_{(m)}$ be the ordered p-values and $H_{(1)}, \cdots, H_{(m)}$ be the corresponding hypotheses.

- Reject $H_{(1)}$ if $p_{(1)} \leq \alpha/m$.
- If $H_{(1)}$ is rejected, we reject $H_{(2)}$ if $p_{(2)} \leq \alpha/(m-1)$.
- If $H_{(1)}$ and $H_{(2)}$ are rejected, we use $\alpha/(m-2)$ for $H_{(3)}$.
- $\cdots$

Monte Carlo resampling methods

- Resample the data B times such that all null hypotheses are satisfied (e.g. permute the case-control status for the case-control data; or permute the survival time and censor indicator together for the survival data; or permute the markers)
- For each permuted data ($b = 1, \cdots, B$), repeat the analyses and obtain the p-values denoted as $p_1^b, \ldots, p_m^b$ for the corresponding hypotheses $H_{(1)}, \cdots, H_{(m)}$

There are two ways to do the adjustment. The step-down adjustment is more complex but less conservative.
The single-step adjusted p-values

$$\begin{aligned} p_{(j)}^{FWER} &= Pr\left(\min_{1\le k\le m} P_k \le p_{(j)} | \text{null H}_{(j)}, 1 \le k \le m\right) \\ &= \sum_b I\left(\min_{1\le k\le m} p_k^b \le p_{(j)}\right)/m \end{aligned}$$

The step-down adjusted p-values

1. Calculate

$$\begin{aligned} q_j &= \Pr\left(\min_{j\le k\le m} P_k \le p_{(j)} | \text{null H}_{(j)}, j \le k \le m\right) \\ &= \sum_b I\left(\min_{j\le k\le m} p_k^b \le p_{(j)}\right)/m \end{aligned}$$

2. Enforce monotonicity using successive maximization

$$\begin{aligned} p_{(1)}^{FWER} &= q_1 \\ p_{(2)}^{FWER} &= \max\left(q_2, p_{(1)}^{FWER}\right) \\ &\cdots \\ p_{(m)}^{FWER} &= \max\left(q_{m-1}, p_{(m-1)}^{FWER}\right). \end{aligned}$$

1.2 False discovery rate

Frequency distribution for the hypotheses

	Not rejected	rejected	Total
True hypotheses	W_0	R_0	m_0
False hypotheses	W_1	R_1	m_1
Total	W	R	m

FDR is defined in Benjamini and Hochberg (1995) as

$$p_j^{FDR} = \min\left\{q\text{: } H_j \text{ is rejected at } FDR \le q\right\}.$$

Benjamini and Hochberg procedure

- $p_{(m)}^{FDR} = p_{(m)}$
- $p_{(j)}^{FDR} = \min\left\{\min\left(\frac{m}{j}p_{(j)}, 1\right), p_{(j+1)}^{FDR}\right\},\ j = 1, \cdots, m-1$

Monte Carlo resampling approach

R_0 is a non-increasing function of R for any given the critical value. This, by Jensen's inequality on R the following equality holds

$$E\left\{\frac{R_0}{R}\right\} \leq \frac{E\{R_0\}}{E\{R\}}$$

So if $\frac{E\{R_0\}}{E\{R\}}$ is less or equal to q, then FDR is less or equal to q. Thus, we estimate

$$E\left(R\left(p\right)\right) \cong R\left(p\right) = \sum_{j=1}^{m} I\left(p_j \leq p\right)$$

$$E\left(R_0\left(p\right)\right) = \sum_{b}\sum_{j=1}^{m} I\left(p_j^b \leq p\right)/B$$

and

$$FDR\left(p\right) \leq \min\left(\frac{E\left(R_0\right)}{R}, 1\right).$$

The FDR adjusted p-values can be estimated in the following two steps:

1. For each p-value $p_{(j)}$, calculate $\mathrm{FDR}\big(p_{(j)}\big)$
2. $p_{(m)}^{FDR} = FDR(p_{(m)})$, and $p_{(j)}^{FDR} = \min\left\{FDR\left(p_{(j)}\right),\ p_{(j+1)}^{FDR}\right\},\ j = 1, \cdots, m-1$.

References

Benjamini, Y. and Hochberg, Y. (1995), "Controlling the false discovery rate: a practical and powerful approach to multiple testing," *Journal of the Royal Statistical Society. Series B (Methodological)*, 57, 289–300.

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Westfall, P.H. and Young, S.S. (1993), *Resampling-based multiple testing: Examples and methods for p-value adjustment*, vol. 279, John Wiley & Sons.