Lecture Notes 18
Multiple Testing and Confidence Intervals

Suppose we need to test many null hypotheses

$$\mathcal{H} = \{H_{0,1}, \ldots, H_{0,N}\}$$

where $N$ could be very large. We cannot simply test each hypotheses at level $\alpha$ because, if $N$ is large, we are sure to make lots of type I errors just by chance. To see this, imagine flipping $N$ coins. Suppose that the probability of heads on each coin is $\alpha$. The probability of at least one head is

$$1 - (1 - \alpha)^N = 1 - e^{N\log(1-\alpha)} \approx 1 - e^{-N\alpha}$$

which is close to 1 when $N$ is large. We are certain to make at least one type I error when doing many tests even though we control each test to have type I error $\alpha$. We need to do some sort of multiplicity adjustment.

**Familywise Error Control.** Suppose we get a $p$-value $p_j$ for each null hypothesis. Let $I = \{i : H_{0,i} \text{ is true} \} \subset \mathcal{H}$. If we reject $H_{0,i}$ for any $i \in I$ then we have made an error. Let $R = \{j : \text{we reject } H_{0,j} \} \subset \mathcal{H}$ be the set of hypotheses we reject. We say that we have controlled the familywise error rate at level $\alpha$ if

$$\mathbb{P}(R \cap I \neq \emptyset) \leq \alpha.$$

The easiest way to control the familywise error rate is the *Bonferroni method*. The idea is to reject $H_{0,i}$ if and only if $p_i < \alpha/N$. Then

$$\mathbb{P}(\text{making a false rejection}) = \mathbb{P}\left(p_i < \frac{\alpha}{N} \text{ for some } i \in I\right) \leq \sum_{i \in I} \mathbb{P}(p_i < \frac{\alpha}{N}) = \sum_{i \in I} \frac{\alpha}{N} \text{ since } p_i \sim \text{Unif}(0,1) \text{ for } i \in I = \frac{\alpha |I|}{N} \leq \alpha.$$

So we have overall control of the type I error. However, it can have low power.

**The Normal Case.** Suppose that we have $N$ sample means $\overline{Y}_1, \ldots, \overline{Y}_N$ each based on $n$ Normal observations with variance 1. So $\overline{Y}_j \sim N(\mu_j, \sigma^2/n)$. To test $H_{0,j} : \mu_j = 0$ we can use the test statistic $T_j = \sqrt{n} \overline{Y}_j / \sigma$. The p-value is

$$p_j = 2\Phi(-|T_j|).$$
If we did uncorrected testing we reject when \( p_j < \alpha \), which means, \( |T_j| > z_{\alpha/2} \). A well known inequality for the tail probability of a Gaussian is

\[
\frac{\phi(x)}{x + 1/x} \leq 1 - \Phi(x) \leq \frac{\phi(x)}{x}.
\]

From this it can be shown that\(^1\)

\[ z_{\alpha} \approx \sqrt{2 \log(1/\alpha)}. \]

So we reject when

\[ |T_j| > \sigma \sqrt{2 \log(2/\alpha)}/n. \]

Under the Bonferroni correction we reject when \( p_j < \alpha/N \) which corresponds to

\[ |T_j| > \sigma \sqrt{2 \log(2N/\alpha)}/n. \]

Hence, the familywise rejection threshold grows like \( \sqrt{\log N} \).

**False Discovery Control.** The Bonferroni adjustment is very strict. A weaker type of control is based on the *false discovery rate*. Suppose we reject a set of hypotheses \( R \). Define the *false discovery proportion*

\[ \text{FDP} = \frac{|R \cap I|}{|R|} \]

where the ratio is defined to be 0 in case both the numerator and denominator are 0. Our goal is to find a method for choosing \( R \) such that

\[ \text{FDR} = \mathbb{E}(\text{FDP}) \leq \alpha. \]

The *Benjamini-Hochberg method* works as follows:

1. Find the ordered p-values \( P_{(1)} < \cdots < P_{(N)} \).
2. Let \( j = \max\{i : P_{(i)} < i\alpha/N\} \). Let \( T = P_{(j)} \).
3. Let \( R = \{i : P_i \leq T\} \).

Let us see why this controls the FDR. Consider, in general, rejecting all hypothesis for which \( P_i < t \). Let \( W_i = 1 \) if \( H_{0,i} \) is true and \( W_i = 0 \) otherwise. Let \( \hat{G} \) be the empirical distribution of the p-values and let \( G(t) = \mathbb{E}(\hat{G}(t)) \). In this case,

\[ \text{FDP} = \frac{\sum_{i=1}^{N} W_i I(P_i < t)}{\sum_{i=1}^{N} I(P_i < t)} = \frac{1}{N} \sum_{i=1}^{N} W_i I(P_i < t) \frac{1}{N} \sum_{i=1}^{N} I(P_i < t). \]

\(^1\)In fact, it can be shown that

\[ z_{\alpha} = \sqrt{2 \log(1/\alpha)} - r \]

where \( 0 \leq r \leq 1.5 \).
Hence,

\[
\mathbb{E}(\text{FDP}) \approx \frac{\mathbb{E}(\frac{1}{N} \sum_{i=1}^{N} W_i I(P_i < t))}{\frac{1}{N} \mathbb{E}(\sum_{i=1}^{N} I(P_i < t))} = \frac{\frac{1}{N} \sum_{i=1}^{N} W_i \mathbb{E}(I(P_i < t))}{\frac{1}{N} \sum_{i=1}^{N} \mathbb{E}(I(P_i < t))} = \frac{t|I|}{G(t)} < \frac{t}{G(t)} \approx \frac{t}{G(t)}.
\]

Let \( t = P_{(i)} \) for some \( i \); then \( \tilde{G}(t) = i/N \). Thus, \( \text{FDR} \leq P_{(i)} N/i \). Setting this equal to \( \alpha \) we get \( P_{(i)} < i \alpha/N \) is the Benjamini-Hochberg rule.

FDR control typically has higher power than familywise control. But they are controlling different things. You have to decide, based on the context, which is appropriate.

**Example 1** Figure 1 shows an example where \( Y_j \sim N(\mu_j, 1) \) for \( j = 1, \ldots, 1,000 \). In this example, \( \mu_j = 3 \) for \( 1 \leq j \leq 50 \) and \( \mu_j = 0 \) for \( j > 50 \). The figure shows the test statistics, the p-values, the sorted log p-values with the Bonferroni threshold and the sorted log p-values with the FDR threshold (using \( \alpha = 0.05 \)). Bonferroni rejects 7 hypotheses while FDR rejects 22.

**Multiple Confidence Intervals.** A similar problem occurs with confidence intervals. If we construct a confidence interval \( C \) for one parameter \( \theta \) then \( \mathbb{P}(\theta \in C) \geq 1 - \alpha \). But if we construct confidence intervals \( C_1, \ldots, C_N \) for \( N \) parameters \( \theta_1, \ldots, \theta_N \) then we want to ensure that

\[
\mathbb{P}(\theta_j \in C_j, \text{ for all } j = 1, \ldots, N) \geq 1 - \alpha.
\]

To do this, we construct each confidence interval \( C_j \) at level \( 1 - \alpha/N \). Then

\[
\mathbb{P}(\theta_j \notin C_j \text{ for some } j) \leq \sum_j \mathbb{P}(\theta_j \notin C_j) \leq \sum_j \frac{\alpha}{N} = \alpha.
\]
Figure 1: Top left: 1,000 test statistics. Top right: the p-values. Bottom left: sorted log p-values and Bonferroni threshold. Bottom right: sorted log p-values and FDR threshold.