STATS300A - Lecture 18

Dominik Rothenhaeusler
Scribed by Michael Howes

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Contents

1 Announcements

- The final exam is at 3:30pm December 8^{th} Wednesday.
- The exam is an online timed assignment.
- The exam is three hours long and has the same rules as the midterm.
- Approximately 1/3 of the exam will be on the first half of the course and approximately 2/3 of the exam will be on the second half.

2 Multiple testing

Historically people haved worked in a setting where first they will fix a question, then collect data and then perform inference. Today people are more likely to collect a lot of data, then ask data dependent questions and then do inference. This can be viewed as asking many many questions about the data and requires different techniques.

2.1 Setting

As before we have data $X \sim \mathbb{P} \in \mathcal{P}$ where we observe X but we do not know $\mathbb{P}$. We are given n null hypotheses $H_{0,i}$ for $i = 1, \dots, n$. Rather than thinking of each null as a partition of our parameter space we will work directly with $\mathcal{P}$. That is $\mathcal{P} = H_{0,i} \cup H_{1,i}$ where $H_{1,i} = H_{0,i}^c$.

For each null hypothesis we have a p-value p_i such that under $H_{0,i}$,

$$\mathbb{P}(p_i \le t) \le t.$$

That is, under the null $H_{0,i}$, the p-value p_i stochastically dominante the uniform distribution. For simplicity we will in fact assume that p_i is uniformly distributed under $H_{0,i}$ so that $\mathbb{P}(p_i \le t) = t$ under $H_{0,i}$.

2.2 Motivation

What is the problem that multiple testing is meant to solve? Suppose that we have $X_i \sim \mathcal{N}(\theta_i, 1)$ $i = 1, \ldots, n$ where $n = 10,000$ and X_i are independent. Suppose we want to test $H_{0,i} : \theta_i = 0$ against $H_{0,i} : \theta_i < 0$. We can define our p-values as

$$p_i = \psi(X_i),$$

where ψ is the CDF of a standard Gaussian distribution. The test $\phi_i = \mathbf{1}_{p_i \le \alpha}$ is thus the UMP level-α test for $H_{0,i}$. If $\alpha = 0.05$ and $\theta_i = 0$ for all i, then we would expect approximately $n \times \alpha = 500$ false discoveries.

2.3 Different goals

There are different quantities we can work with in multiple testing. For example:

(a) We can test the *global null*. That is we wish to test the null $H_0 = \bigcap_{i=1}^n H_{0,i}$ where every null is true. In this setting we wish to find a function $\Phi_G : [0,1]^n \to \{0,1\}$ where Φ_G is a function of our p-values $p = (p_1, \ldots, p_n)$ and $\Phi_G(p) = 1$ means that for the given p-values p we reject the global null and $\Phi_G(p) = 0$ means we do not reject the global null. In this setting we wish to control the *global type I error* of Φ_G which is

$$\text{Global type I error}(\Phi_G) = \begin{cases} \mathbb{P}(\Phi_G = 1) & \text{if } H_0 \text{ is true,} \\ 0 & \text{if } H_0 \text{ is false.} \end{cases}$$

(b) We can also work with the *family wise error rate (FWER)*. This is the probability of making one or more false discoveries. In this case we want a function $\Phi : [0,1]^n \to \{0,1\}^n$ where each component Φ_i is a function of our p-values and $\Phi_i(p) = 1$ means we reject the null $H_{0,i}$ and $\Phi_i(p) = 0$ means we do not reject the null $H_{0,i}$. In this setting we can define a random variable V which counts the i's such that $\Phi_i(p) = 1$ and $H_{0,i}$ is true. Thus V is the number of false discoveries. We then define

$$FWER = FWER(\Phi) := \mathbb{P}(V > 1).$$

We wish to find powerful procedures Φ such that $FWER \le \alpha$.

(c) We can also work with the *false discover rate (FDR)*. Let R be the total number of rejections and define

$$FDR = FDR(\Phi) := \mathbb{E}\left[\frac{V}{\max\{R, 1\}}\right].$$

Again we are interested in powerful procedures Φ such that $FDR \le \alpha$.

2.4 Comparing error rates

Given a procedure $\Phi : [0,1]^n \to \{0,1\}$ for $H_{0,i}$, $i = 1, \ldots, n$, we can define a global procedure for $H_0 = \bigcap_{i=1}^n H_{0,i}$ by

$$\Phi_G(p) = \max\{\Phi_1(p), \ldots, \Phi_n(p)\}.$$

Thus Φ_G rejects the global null H_0 if and only if for some i, Φ_i rejects the null $H_{0,i}$. This procedure is natural in settings were we expect the false nulls to be sparse. For this choice of Φ_G, we have the following comparison between the different quantities we want to control:

$$\text{Global null type I error}(\Phi_G) \leq FDR(\Phi) \leq FWER(\Phi).$$

Proof. If the global null H_0 is false, then Global null type I error$(\Phi_G) = 0$ so we automatically have Global null type I error$(\Phi_G) \leq FDR$. If H_0 is true, then all of nulls $H_{0,i}$ are true and so every rejection is a false rejection. This implies that $V = R$ and so

$$FDR = \mathbb{P}(V > 0) = \mathbb{P}(\Phi_G = 1) = \text{Global null type I error}(\Phi_G).$$

For the second inequality we have $V \leq R$ and so

$$\frac{V}{\max\{R,1\}} \leq \frac{V}{\max\{V,1\}} = \mathbf{1}_{V>0}.$$

Thus

$$FDR = \mathbb{E}\left[\frac{V}{\max\{R,1\}}\right] \leq \mathbb{E}[\mathbf{1}_{V>0}] = \mathbb{P}(V>0) = FWER. \qquad \square$$

The different error criteria have different uses.

- Testing the global null is for "detecting."
- Controlling the FWER or FDR is for "locating."

Multiple testing is an active area of research and if you are interested, you should consider attending the International seminar on selective inference.

3 Multiple testing proceedures

We will now consider a number of methods that can be used when doing multiple testing.

3.1 Bonferroni correction

Define $\Phi_i = \mathbf{1}_{p_i \leq \frac{\alpha}{n}}$. We will show that this proceedure control FWER at α. That is, $FWER \leq \alpha$. Note that

$$\begin{aligned}
\mathbb{P}(V > 0) &= \mathbb{P}(\Phi_i = 1 \text{ for some } i \text{ such that } H_{0,i} \text{ is true}) \\
&\leq \sum_{i, H_{0,i} \text{ is true}} \mathbb{P}(\Phi_i = 1) \\
&= \sum_{i, H_{0,i} \text{ is true}} \mathbb{P}(p_i \leq \alpha/n) \\
&= \frac{n_0}{n}\alpha \\
&\leq \alpha,
\end{aligned}$$

where $n_0 \leq n$ is the number of true nulls. Note that we did not put any independence assumptions on our p-values. The optimality of Bonferroni depends on the correlation between our p-values. Suppose that p_i are all independent and uniform and consider a test of the form $\Phi_i(p) = \mathbf{1}_{p_i \leq t}$ for some value of t that does not depend on i. Suppose that the global null is true. Under this assumption, we have

$$\begin{aligned} FWER &= 1 - \mathbb{P}(V = 0) \\ &= 1 - \mathbb{P}(p_i > t, \text{ for all } i) \\ &= 1 - (1-t)^n. \end{aligned}$$

If we wish to have $FWER = \alpha$ we get $t = 1 - (1-\alpha)^{1/n} \approx \alpha/n$. So that Bonferroni is approximately optimal for small α, large n and independent p-values. If instead the p-values have positive dependence, then Bonferroni is sub-optimal. Suppose in an extreme case that $p_1 = \ldots = p_n$. Then

$$FWER = 1 - \mathbb{P}(V = 0) = 1 - \mathbb{P}(p_1 > t) = t.$$

So the optimal choice of t is α which is much larger than α/n. In the case of negative dependence, it can be shown that Bonferroni is optimal.

3.2 Holm's procedure

How can we improve Bonferroni? Note that after we reject $H_{0,i}$ we have two possibilities. Either we have made a false discovery or we have made a true discovery and the remaining hypotheses become a multiple testing problem with $n-1$ null hypotheses. Thus after making on rejection we can "relax" the rejection criteria. More formally, we first order the p values

$$p_{(1)} \leq p_{(2)} \leq \ldots \leq p_{(n)},$$

and relabel the corresponding null hypotheses $H_{0,(1)}, H_{0,(2)}, \ldots, H_{0,(n)}$. Let

$$j = \min \left\{ i : p_{(i+1)} > \frac{\alpha}{n-i}, i = 0, 1, \ldots, n-1, \right\}.$$

We then reject the nulls $H_{0,(1)}, \ldots, H_{0,(j)}$. Thus $p_{(i)} \leq \frac{\alpha}{n-i+1}$ for rejected $H_{0,(i)}$.

Proposition 1. *Holm's procedure controls FWER at level α.*

Proof. Let i_0 be the first index i for which $H_{0,(i)}$ is true. The quantity i_0 is a random variable since it depends on the ordering of the random variables p_i. Let n_0 be the number of true nulls, we thus have $i_0 \leq n - n_0 + 1$ and so $n_0 \leq n - i_0 + 1$ and $\frac{\alpha}{n_0} \geq \frac{\alpha}{n-i_0+1}$. Now note that

$$\begin{aligned} FWER &= \mathbb{P}(V > 0) \\ &= \mathbb{P}\left(p_{(1)} \leq \frac{\alpha}{n}, p_{(2)} \leq \frac{\alpha}{n-1}, \ldots, p_{(i_0)} \leq \frac{\alpha}{n - i_0 + 1} \right) \\ &\leq \mathbb{P}\left(p_{(i_0)} \leq \frac{\alpha}{n - i_0 + 1} \right) \\ &\leq \mathbb{P}\left(p_{(i_0)} \leq \frac{\alpha}{n_0} \right) \\ &= \mathbb{P}\left(p_i \leq \frac{\alpha}{n_0}, \text{ for some } i \text{ such that } H_{0,i} \text{ is true} \right) \\ &\leq \sum_{i, H_{0,i} \text{ is true}} \mathbb{P}\left(p_i \leq \frac{\alpha}{n_0} \right) \\ &= n_0 \cdot \frac{\alpha}{n_0} \\ &= \alpha. \end{aligned}$$

□

3.3 Hochberg's procedure

As before order the p-value and null hypotheses so that $p_{(1)} \leq p_{(2)} \leq \ldots \leq p_{(n)}$ and $p_{(i)}$ corresponds to $H_{0,(i)}$. Define

$$j = \max\left\{i : p_{(i)} \leq \frac{\alpha}{n-i+1}, i = 1, \ldots, n\right\},$$

where we define $\max \emptyset = 0$. We the reject $H_{0,(1)}, \ldots H_{0,(j)}$. If the p-values are independent, then this procedure also has level α FWER control. This procedure is more powerful that Holm's procedure in the sense that it rejects more often.