STATS300A - Lecture 19

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Contents

1 Announcements

A practice exam will be posted online today. It is designed to take 3 hours like the final exam.

2 Set up

Recall that we have been studying multiple testing. Thus we have data $X \sim \mathbb{P} \in \mathcal{P}$ where $\mathbb{P}$ is unknown. For each $i = 1, \dots, n$, we have a null hypothesis $H_{0,i} \subseteq \mathcal{P}$ and a p-value $p_i(X) \in [0,1]$ such, under $H_{0,i}$

$$\mathbb{P}(p_i(X) \le t) \le t,$$

for all $t \in [0,1]$. Our objects of study are decision procedures $\Phi : [0,1]^n \to \{0,1\}^n$ where the input of Φ is our n p-values $p = (p_1, \dots, p_n)$ and

$$\Phi_i(p) = \begin{cases} 1 & \text{if we reject } H_{0,i} \text{ based on the p-values } p, \\ 0 & \text{if we accept } H_{0,i} \text{ based on the p-values } p. \end{cases}$$

For a given decision procedure Φ we define two random varaibles V and R, where

$$\begin{aligned} V &= \#\text{ of false discoveries} \\ &= \#\text{ of nulls } H_{0,i} \text{ which are true and are rejected by } \Phi \\ &= \sum_{i:H_{0,i}} \Phi_i, \end{aligned}$$

where the subscript $i\!:\!H_{0,i}$ means that we sum over all indices i such that the null $H_{0,i}$ is true. Likewise we have,

$$\begin{aligned} R &= \#\text{ of rejections} \\ &= \#\text{ of } i \text{ with } \Phi_i = 1, \\ &= \sum_{i=1}^{n} \Phi_i. \end{aligned}$$

We then defined two quantities which we wanted to control

$$FWER = \mathbb{P}(V \geq 1) \quad \text{and} \quad FDR = \mathbb{E}\left[\frac{V}{\max\{R,1\}}\right]$$

Last time we looked at the Bonferroni and Holm's procedure which both control $FWER$ but are quite conservative. Today we will see some less conservative methods that allow us to reject more nulls while still gaurding against making too many false rejections.

3 Controling $FWER$

3.1 Closed testing

We will first introduce some notation. For $I \subseteq \{1,\dots,n\}$, define $H_{0,I} = \bigcap_{i\in I} H_{0,i}$.

Example 1. Suppose we have $X \sim \mathcal{N}(\mu, I_3)$ where $\mu \in \mathbb{R}^3$ is unknown and $I_3 \in \mathbb{R}^{3\times 3}$ is the identity matrix. Suppose we have nulls $H_{0,i} : \mu_i = 0$ for $i = 1,2,3$. Then $H_{0,\{1,2\}} : \mu_1 = \mu_2 = 0$ and $H_{0,\{1,2,3\}} : \mu_1 = \mu_2 = \mu_3 = 0$.

Definition 1. Suppose that for each $I \subseteq \{1,\dots,n\}$, we have a level α-test ϕ_I. The *closed testing procedure* is a procedure that simulateneously tests $H_{0,I}$ for all $I \subseteq \{1,\dots,n\}$. Under the closed testing procedure we reject $H_{0,I}$ if and only if $\phi_J = 1$ for all $J \subseteq \{1,\dots,n\}$ such that $I \subseteq J$.

That is, when using the closed testing procedure, we reject $H_{0,I}$ if and only if ϕ_J rejects for all J that are supersets of I.

Example 2. Suppose that we have three hypotheses $H_{0,i}$, $i = 1,2,3$. The results of the test ϕ_I might take this form:

$$\phi_{\{1,2,3\}} = 1$$

$$\phi_{\{1,2\}} = 0 \qquad \phi_{\{2,3\}} = 1 \qquad \phi_{\{1,3\}} = 1$$

$$\phi_{\{1\}} = 1 \qquad \phi_{\{2\}} = 1 \qquad \phi_{\{3\}} = 1$$

Since $\phi_{\{1,2\}} = 0$, the closed testing procedure does not reject $H_{0,1}$ or $H_{0,2}$. For every J that contains 3 we have $\phi_J = 1$ and so $H_{0,3}$ is rejected. The tests in red correspond to nulls that are rejected under the closed testing procedure. The other three nulls are not rejected.

Note that the closed testing procedure is consistent in the sense that if $I \subseteq I'$ and we reject $H_{0,I}$, then we also reject $H_{0,I'}$ which is a subset of $H_{0,I}$. As presented here, closed testing requires an exponential number of tests ϕ_I. We will see some examples were we can exploit the structure of our tests and perform fewer tests.

Proposition 1. *If ϕ_I is level α for all $I \subseteq \{1,\dots,n\}$, then the closed testing procedure controls the $FWER$ of testing $H_{0,I}, I \subseteq \{1,\dots,n\}$ at α.*

Proof. Let I_0 be the set of all $i \in \{1, \dots, n\}$ such that $H_{0,i}$ is true. If the closed testing procedure falsely rejects $H_{0,I}$ for some $I \subseteq \{1, \dots, n\}$, then we must have $I \subseteq I_0$ and thus $\phi_{I_0} = \alpha$. Thus

$$FWER \le \mathbb{P}(\phi_{I_0} = 1) \le \alpha. \qquad \square$$

Remark 1. One might ask why this method is important.

- Firstly, suppose that ϕ_I is a Bonferroni test of $H_{0,i}, i \in I$. That is $\phi_I = 1$ if and only if $p_i \le \frac{\alpha}{|I|}$ for some $i \in I$. Then if we apply the closed testing procedure to ϕ_I, we get Holm's testing procedure which is more powerful than Bonferroni.
- Pharmaceutical methods are often based on closed testing procedure since they offer a lot of flexibility.

3.2 Nested hypotheses

Definition 2. We will say that the hypotheses $H_{0,i}$ for $i = 1, \dots, n$ are *nested* if for all i, $H_{0,i} \subseteq H_{0,i+1}$.

For example, we may have $H_{0,1} : \mu_1 = \mu_2 = \mu_3 = 0$, $H_{0,2} : \mu_1 = \mu_2 = 0$, $H_{0,3} : \mu_1 = 0$. Note that if $H_{0,i}$ are nested and $I \subseteq \{1, \dots, n\}$, then $H_{0,I} = H_{0,i_0}$ where $i_0 = \min(I)$. Thus the closed testing procedure becomes

$$\text{reject } H_{0,i} \iff \phi_1 = \phi_2 = \ldots = \phi_i = 1.$$

Thus for nested hypotheses, the closed testing procedure controls $FWER$ at level α and we only need a linear number of tests.

3.3 Online $FWER$ control

Suppose we have a sequence of p-values $p_1, p_2, \dots,$ that we recieve sequentially. This may be the setting for clinical trials or online experiments. At each step i we want to decide whether to reject $H_{0,i}$ based on $p_1, p_2, \dots, p_i$.

Proposition 2. *For a fixed level α, let $\Phi_i = \mathbf{1}_{p_i \le \alpha_i}$ where $\alpha_i = \frac{\alpha}{i^2} \cdot \frac{6}{\pi^2}$. Then the procedure Φ controls $FWER$ at level α.*

Proof. Note that $\sum_{i=1}^{\infty} \frac{1}{i^2} = \frac{\pi^2}{6}$. Thus

$$\begin{aligned} FWER &= \mathbb{P}(V \geq 1) \\ &\leq \mathbb{E}[V] \\ &= \mathbb{E}\left[\sum_{i:H_{0,i}} \Phi_i\right] \\ &= \mathbb{E}\left[\sum_{i:H_{0,i}} \mathbf{1}_{p_i \leq \alpha_i}\right] \\ &= \sum_{i:H_{0,i}} \mathbb{P}(p_i \leq \alpha_i) \\ &\leq \sum_{i:H_{0,i}} \alpha_i \\ &\leq \sum_{i=1}^{\infty} \alpha_i \\ &= \frac{6\alpha}{\pi^2} \sum_{i=1}^{\infty} \frac{1}{i^2} \\ &= \alpha. \end{aligned}$$

□

Note that we could have taken any choice of α_i as long as $\sum_{i=1}^{\infty} \alpha_i = \alpha$. If we assume that the p-values are independent we can get a stronger test,

Proposition 3. *For a fixed level α, let $\Phi_i = \mathbf{1}_{p_i \leq \alpha_i}$ where $\alpha_i = 1 - (1-\alpha)^{\gamma_i}$ where $\sum_{i=1}^{\infty} \gamma_i = 1$. If the p-values p_i are independent, then Φ control $FWER$ at level α. Furthermore, under the global null $\cap_{i=1}^{\infty} H_{0,i}$, the procedure Φ has $FWER$ exactly α.*

Note that the previous procedure does not have $FWER$ exactly α under the global null. Thus this second online procedure is more powerful but it requires an independence assumption.

Proof. Note that

$$\begin{aligned} \mathbb{P}(V = 0) &= \mathbb{P}(p_i \geq \alpha_i, \text{ for all } i : H_{0,i}) \\ &= \prod_{i:H_{0,i}} \mathbb{P}(p_i \geq \alpha_i) \\ &= \prod_{i:H_{0,i}} (1 - \alpha_i) \\ &= \prod_{i:H_{0,i}} (1-\alpha)^{\gamma_i} \\ &= (1-\alpha)^{\sum_{i:H_{0,i}} \gamma_i} \\ &\geq (1-\alpha)^{\sum_{i=1}^{\infty} \gamma_i} \\ &= 1 - \alpha, \end{aligned}$$

and we have equality under the global null. Thus

$$FWER = 1 - \mathbb{P}(V = 0) \leq 1 - (1-\alpha) = \alpha,$$

and again we have equality under the global null. □

4 FDR control

We will now briefly talk about FDR control. This will be discussed in more detail in 300C with Professor Candes. Recall that

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

We observed last lecture that

$$FDR \leq FWER,$$

thus controlling FDR instead of $FWER$ allows for more powerful procedures.

Remark 2. Some people prefer to work directly with $FDP = \frac{V}{\max\{R,1\}}$. Instead of controlling $FDR = \mathbb{E}[FDP]$, these people wish to control $\mathbb{P}(FDP \geq c)$.

Definition 3 (Benjamini-Hochberg procedure)**.** Fix $q \in [0,1]$. First order our p-values $p_{(1)} \leq p_{(2)} \leq \ldots \leq p_{(n)}$ and sort the corresponding nulls $H_{0,(1)}, H_{0,(2)}, \ldots, H_{0,(n)}$. Let i_0 be the largest i such that

$$p_{(i)} \leq \frac{i}{n}q.$$

The *Benjamini-Hochberg procedure* (BH) rejects all nulls $H_{0,(i)}$ for $i = 1, \ldots, i_0$.

In partice $q = 0.1$ is a popular threshold.

Proposition 4. *If the p-values are independent, then the Benjamini-Hochberg procedure controls FDR at level q.*

Proof. Let Φ be the decision procedure from BH. For each $i, k = 1, \ldots, n$, define an event $C_k^{(i)}$ as follows

$$C_k^{(i)} = \left\{\sum_{j=1}^{n} \Phi_j(p_1(X), \ldots, p_{i-1}(X), 0, p_{i+1}(X), \ldots, p_n(X)) = k\right\}.$$

Thus $C_k^{(i)}$ is the event when BH would reject exactly k hypotheses if we fixed $p_i = 0$. Note that since our p-values are independent, p_i is independent of $C_k^{(i)}$ for all i and k.

Without loss of generality, we can reorder $H_{0,i}$ so that

$$H_{0,1}, \ldots, H_{0,n_0} \text{ are true,}$$

and

$$H_{0,n_0+1}, \ldots, H_{0,n} \text{ are false.}$$

Thus $V = \sum_{i=1}^{n_0} \Phi_i$ and if $R \neq 0$, then $\frac{1}{R} = \sum_{k=1}^{n} \frac{1}{k}\mathbf{1}_{R=k}$. Thus

$$\begin{aligned}
FDR &= \sum_{k=1}^{n} \frac{1}{k}\mathbb{E}[\mathbf{1}_{R=k}V] \\
&= \sum_{k=1}^{n}\sum_{i=1}^{n_0} \frac{1}{k}\mathbb{E}[\mathbf{1}_{R=k}\Phi_i] \\
&= \sum_{k=1}^{n}\sum_{i=1}^{n_0} \frac{1}{k}\mathbb{P}(R = k \text{ and } \Phi_i = 1) \\
&= \sum_{k=1}^{n}\sum_{i=1}^{n_0} \frac{1}{k}\mathbb{P}\left(R = k \text{ and } p_i \leq \frac{k}{n}q\right).
\end{aligned}$$

Note that
$$\left\{R = k \text{ and } p_i \leq \frac{k}{n}q\right\} = C_k^{(i)} \cap \left\{p_i \leq \frac{k}{n}q\right\}.$$
This is because requiring that $R = k$ and $p_i \leq \frac{k}{n}q$ is equivalent to $p_i \leq \frac{k}{n}q$ and requiring that $R = k$ if $p_i = 0$. Thus we have
$$\begin{aligned}
FDR &= \sum_{k=1}^{n}\sum_{i=1}^{n_0}\frac{1}{k}\mathbb{P}\left(C_k^{(i)} \cap \left\{p_i \leq \frac{k}{n}q\right\}\right) \\
&= \sum_{k=1}^{n}\sum_{i=1}^{n_0}\frac{1}{k}\mathbb{P}\left(C_k^{(i)}\right)\mathbb{P}\left(p_i \leq \frac{k}{n}q\right) \\
&= \sum_{k=1}^{n}\sum_{i=1}^{n_0}\frac{q}{n}\mathbb{P}\left(C_k^{(i)}\right) \\
&= \frac{q}{n}\sum_{i=1}^{n_0}\sum_{k=1}^{n}\mathbb{P}\left(C_k^{(i)}\right).
\end{aligned}$$
For each i, if $p_i = 0$, then $R \geq 1$. Thus, for each i, our sample space is the disjoint union of $C_k^{(i)}$ for $k = 1, \ldots, n$. Thus
$$\begin{aligned}
FDR &= \frac{q}{n}\sum_{i=1}^{n_0}\sum_{k=1}^{n}\mathbb{P}\left(C_k^{(i)}\right) \\
&= \frac{q}{n}\sum_{i=1}^{n_0}1 \\
&= \frac{qn_0}{n} \\
&\leq q
\end{aligned}$$
$\square$