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STAT 210A
Lecture #27
11/29/2016

1 Multiple Testing

A *multiple testing problem* is one where we test >1 hypotheses using same data set.

Example 1.1. $X_i \stackrel{\text{iid}}{\sim} N(\mu_i, 1)$, $i = 1, \ldots, n$
$H_{0,i} : \mu_i = 0$, $H_{1,i} : \mu_i \neq 0$

Common setup:

- Measuring crop yields / patient outcomes under different treatments
- Gene expression of n genes in cancer vs controls / FMRI meas. in n voxels

Example 1.2. $p_i \in [0,1]$, $i = 1, \ldots, n$ ($i \in \mathcal{I}$)
$H_{0,i} : p_i \sim U[0,1]$ [or p_i stoch. larger than $U[0,1]$]
$H_{1,i} : p_i$ "smaller"
Genome-wide association study (GWAS), for SNP i

	healthy	diseased
wild-type	·	·
mutant	·	·

Observe $X \sim P \in \mathcal{P}$, return set of rejected hypotheses.
[Ex. 1] Suppose $n = 100$, $\mu_i = 0$, $\forall i = 1, \ldots, n$,
$\mathbb{E}[\text{\# Rejections}] = n\alpha = 5$ ($\alpha = 0.05$)
$\mathbb{P}[\text{at least one false rejection}] \approx 1$
Classic proposal: control *familywise error rate* (FWER)

$$FWER = \sup_{P \in \mathcal{P}} \mathbb{P}_P[\text{any true } H_{0,i} \text{ rejected}] \tag{1.1}$$

1.1 Bonferroni / Šídák Correction

First rule (Bonferroni): Reject $H_{0,i}$ if $p_i \leq \frac{\alpha}{n}$

$$\mathbb{P}[\text{any false rejection}]] = \mathbb{P}\left[\cup_{i \in \mathcal{H}_0} H_{0,i} \text{ reject}\right] \tag{1.2}$$

$$\leq \sum_{i \in \mathcal{H}_0} \mathbb{P}\left[H_{0,i} \text{ rejected}\right] \leq |\mathcal{H}_0| \frac{\alpha}{n} \leq \alpha \tag{1.3}$$

where $\mathcal{H}_0 : \{i : H_{0,i} \text{ true}\}$.
More liberal (Ŝidák): If p_i independent, can use the rule: Reject $H_{0,i}$ if $p_i \leq \tilde{\alpha}_n$ where $\tilde{\alpha}_n = 1 - (1-\alpha)^{1/n} \approx \frac{\alpha}{n}$. Improvement in power over Bonferroni: $\tilde{\alpha}_n > \frac{\alpha}{n}$

1.2 Correlated Statistics

Often test stats are dependent

Example 1.3 (Pairwise comparisons)**.** $X_i \overset{\text{ind.}}{\sim} N(\mu_i, 1) = \mu_i + \varepsilon_i$.
$H_{0,ij} : \mu_1 = \mu_j$, $H_{1,ij} : \mu_i \neq \mu_j$
$\binom{n}{2}$ hypotheses.
$X_i - X_j = \mu_i - \mu_j + (\varepsilon_i - \varepsilon_j) \sim N(\mu_i - \mu_2, 2)$
Could use Bonferroni: Reject if $\frac{|X_i - X_j|}{\sqrt{2}} > z_{\frac{\alpha}{2\binom{n}{2}}}$
More powerful: Reject $H_{0,ij}$ if $|X_i - X_j| > r_\alpha$ where

$$\mathbb{P}\left[\max_{i,j} |\varepsilon_i - \varepsilon_j| > r_\alpha\right] = \alpha \tag{1.4}$$

This is less conservative than the Bonferroni correction: apply the union bound to get

$$\mathbb{P}\left[\max_{i,j} |\varepsilon_i - \varepsilon_j| > z_{\frac{\alpha}{2\binom{n}{2}}}\sqrt{2}\right] \leq \binom{n}{2} \mathbb{P}\left[|\varepsilon_i - \varepsilon_j| > z_{\frac{\alpha}{2\binom{n}{2}}}\sqrt{2}\right] \tag{1.5}$$

$$= \binom{n}{2} \frac{\alpha}{\binom{n}{2}} = \alpha \tag{1.6}$$

This is called *Tukey's Honestly Significant Difference* procedure

Example 1.4. Comparing all linear combos, $X_i \sim \text{ind.} N(\mu_i, 1)$.
$H_{0,\nu} : \nu'\mu = 0, \nu \in \mathbb{R}^n$
Reject when $\frac{|X'\nu|}{\|v\|} > \chi_n(\alpha)$.
This is because

$$\mathbb{P}[\text{any false rej.}] = \mathbb{P}\left[\frac{|X'\nu}{\|\nu\|} > \chi_n(\alpha), \text{ any } \nu \text{ s.t. } \nu'\mu = 0\right] \tag{1.7}$$

$$\leq \mathbb{P}\left[\max_{\|\nu\|=1} |\varepsilon'\nu| > \chi_n(\alpha)\right] \tag{1.8}$$

$$= \mathbb{P}\left[\|\varepsilon\| > \chi_n(\alpha)\right] = \alpha \tag{1.9}$$

called *Scheffé's S-method*

$$\chi_n(\alpha) \approx \sqrt{n} \gg z_{\frac{alpham}{2\binom{n}{2}}}\sqrt{2} \tag{1.10}$$

$$\approx \sqrt{2 \cdot 2 \log \binom{n}{2}} \approx 2\sqrt{2 \log n} \tag{1.11}$$

More generally $X_i \sim N(\mu_i, \sigma^2)$ where σ^2 is unknown, $\hat{\sigma}^2 \sim \sigma^2 \chi^2_d \perp X$.
Test $H_{0,\nu} : \mu'\nu = 0, \forall \nu \in \Xi \subset \mathbb{R}^n$.
Reject $H_{0,\nu} A$ if $\frac{|X_i'\nu|}{\hat{\sigma}\|\nu\|} \geq c_\alpha$

$$\mathbb{P}\left[\sup_{\nu \in \Xi} \frac{|\varepsilon_i'\nu|}{\hat{\sigma}\|\nu\|} > c\right] = \tag{1.12}$$

2 Simultaneous Intervals

Construct CI for ...