Resampling Techniques and their Application

-Class 12-

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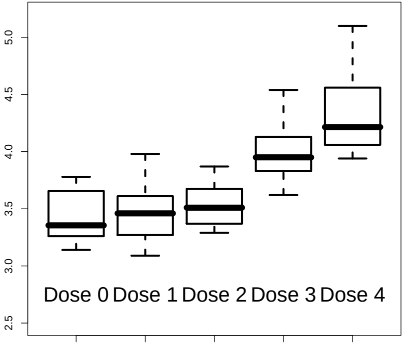
Example: Liver Weights of Wistar Rats

- Toxicity trial: 40 rats were randomized into 5 dose groups (Dose 0 - Dose 4)
- After treatment: relative liver weight of each animal
- Question: Which dose(s) differ from control? Trend?




```
x1 = c(3.78, 3.40, 3.29, 3.14, 3.55, 3.76, 3.23, 3.31)
x2 = c(3.46, 3.98, 3.09, 3.49, 3.31, 3.73, 3.23)
x3 = c(3.71, 3.36, 3.38, 3.64, 3.41, 3.29, 3.61, 3.87)
x4 = c(3.86, 3.80, 4.14, 3.62, 3.95, 4.12, 4.54)
x5 = c(4.19, 4.16, 3.94, 4.26, 4.86, 3.96, 4.24, 5.10)
```

Statistical Model: Independent Samples

- Statistical Model
  - $X_{ik} \sim N(\mu_i, \sigma_i^2)$
  - $i = 1, \ldots, a$; $k = 1, \ldots, n_i$; $N = \sum_{i=1}^{a} n_i$
  - $i = 1$: Control group
  - $\boldsymbol{\mu} = (\mu_1, \ldots, \mu_a)'$ (Expectations)
- Aim: Multiple comparisons

$$H_0^{(\ell)} : \mathbf{c}_\ell' \boldsymbol{\mu} = 0, \; \ell = 1, \ldots, q$$

- **Multiple hypotheses**

General Contrasts

- In general

$$H_0 : \mathbf{C}\boldsymbol{\mu} = \mathbf{0} \;\; \text{vs.} \;\; H_1 : \mathbf{C}\boldsymbol{\mu} \neq \mathbf{0}$$

- It is on us to define the alternative H_1
- The contrast matrix $\mathbf{C}$ is nothing but the pattern of the alternative H_1
- In general, $\mathbf{C}$ is a $q \times a$ matrix. Each row vector is a contrast.

$$\boldsymbol{C} = \begin{pmatrix} \mathbf{c}_1' \\ \vdots \\ \mathbf{c}_q' \end{pmatrix} = \begin{array}{c} \begin{array}{cccc} \mu_1 & \mu_2 & \cdots & \mu_a \end{array} \\ \begin{pmatrix} c_{11} & c_{12} & \cdots & c_{1a} \\ c_{21} & c_{22} & \cdots & c_{2a} \\ \vdots & \vdots & \vdots & \vdots \\ c_{q1} & c_{q2} & \cdots & c_{qa} \end{pmatrix} \end{array} ; \sum_{i=1}^{a} c_{\ell i} = 0, \; \ell = 1, \ldots, q$$

General Contrasts

- Example 1: Many-to-one comparisons (Dunnett):

$$H_1 : \left\{ \begin{array}{c} \mu_1 \neq \mu_2 \\ \mu_1 \neq \mu_3 \\ \vdots \\ \mu_1 \neq \mu_a \end{array} \right. \Leftrightarrow \boldsymbol{C} = \begin{pmatrix} -1 & 1 & 0 & \cdots & 0 \\ -1 & 0 & 1 & \cdots & 0 \\ \vdots & \vdots & \vdots & \vdots & \vdots \\ -1 & 0 & \cdots & \cdots & -1 \end{pmatrix}$$

General Contrasts (II)

- Example 2: Trend (Williams)

$$H_1 : \begin{cases} \mu_1 \neq \mu_a \\ \mu_1 \neq \mu_{a-1} = \mu_a \\ \vdots \\ \mu_1 \neq \mu_2 = \ldots = \mu_a \end{cases} \Leftrightarrow \boldsymbol{C} = \begin{pmatrix} -1 & 0 & 0 & \cdots & 1 \\ -1 & 0 & 0 & \frac{n_{a-1}}{n_{a-1}+n_a} & \frac{n_a}{n_{a-1}+n_a} \\ \vdots & \vdots & \vdots & \vdots & \vdots \\ -1 & \frac{n_2}{n_2+\ldots+n_a} & \cdots & \cdots & \frac{n_a}{n_2+\ldots+n_a} \end{pmatrix}$$

General Contrasts (III)

- Example 3: All-pairs (Tukey):

$$H_1 : \begin{cases} \mu_1 \neq \mu_2 \\ \mu_1 \neq \mu_3 \\ \vdots \\ \mu_1 \neq \mu_a \\ \mu_2 \neq \mu_3 \\ \vdots \\ \mu_{a-1} \neq \mu_a \end{cases} \Leftrightarrow \boldsymbol{C} = \begin{pmatrix} -1 & 1 & 0 & \cdots & 0 \\ -1 & 0 & 1 & 0 & 0 \\ \vdots & \vdots & \vdots & \vdots & \vdots \\ 0 & 0 & \cdots & -1 & 1 \end{pmatrix}$$

- And many more
- See *contrMat* function in *multcomp* package

Multiple Hypotheses

- Individual hypothesis

$$H_0^{(\ell)} : \mathbf{c}'_\ell \boldsymbol{\mu} = 0, \;\; \ell = 1, \ldots, q$$

- **Family of hypotheses**

$$\boldsymbol{\Omega} = \left\{ H_0^{(1)}, H_0^{(2)}, \ldots, H_0^{(q)} \right\}$$

- We relate all inference with respect to $\boldsymbol{\Omega}$
- Global null hypothesis

$$H_0 : \mathbf{C}\boldsymbol{\mu} = \mathbf{0}$$

- Reject H_0, if any $H_0^{(\ell)}$ is rejected

Multiple Contrast Tests

- Estimators
  - $\overline{\mathbf{X}}_{\cdot} = (\overline{X}_{1\cdot}, \dots, \overline{X}_{a\cdot})'$ (vector of means)
- Variance of contrasts in means

$$
\begin{aligned}
\mathbf{S} &= Cov(\overline{\mathbf{X}}_{\cdot}) = diag\left(\frac{\sigma_1^2}{n_1}, \dots, \frac{\sigma_a^2}{n_a}\right) \\
\Gamma &= Cov(\boldsymbol{C}\overline{\mathbf{X}}_{\cdot}) = \boldsymbol{C}\mathbf{S}\boldsymbol{C}' = \boldsymbol{C} diag\left(\frac{\sigma_1^2}{n_1}, \dots, \frac{\sigma_a^2}{n_a}\right)\boldsymbol{C}' \\
\sigma_\ell^2 &= Var(\boldsymbol{c}_\ell'\overline{\mathbf{X}}_{\cdot}) = \sum_{i=1}^{a} \sigma_i^2 \frac{c_{\ell i}^2}{n_i} = \mathbf{c}_\ell' \boldsymbol{S} \mathbf{c}_\ell
\end{aligned}
$$

Point Estimators

- Estimators
  - Means: $\overline{\mathbf{X}}_{\cdot} = (\overline{X}_{1\cdot}, \ldots, \overline{X}_{a\cdot})'$
  - Variance estimators

$$s_i^2 = \frac{1}{n_i - 1} \sum_{k=1}^{n_i} (X_{ik} - \overline{X}_{i\cdot})^2$$

- Variance of a contrast

$$\begin{aligned}
\widehat{\mathbf{S}} &= diag\left(\frac{s_1^2}{n_1}, \ldots, \frac{s_a^2}{n_a}\right) \\
\widehat{\Gamma} &= \boldsymbol{C}\widehat{\mathbf{S}}\boldsymbol{C}' = \boldsymbol{C} diag\left(\frac{s_1^2}{n_1}, \ldots, \frac{s_a^2}{n_a}\right) \boldsymbol{C}' \\
\widehat{\sigma}_\ell^2 &= \mathbf{c}_\ell' \widehat{\mathbf{S}} \mathbf{c}_\ell
\end{aligned}$$

```
library(multcomp)
C <-contrMat(rep(1,5),"Dunnett")
X<-c(x1,x2,x3,x4,x5)
n<-c(8,7,8,7,8)
N<-sum(n)
grp<-factor(c(rep(1:5,n)))
a<-5
Dat<-data.frame(X=X,grp=grp)
Xbar<-aggregate(X~grp,data=Dat,mean)[,2]
si2 <-aggregate(X~grp,data=Dat,var)[,2]

Shat <- diag(si2/n)
Gammahat<-C%*%Shat%*%t(C)
```

Multiple Comparisons

- For $H_0^{(\ell)} : \mathbf{c}'_\ell \boldsymbol{\mu} = 0$

$$T_\ell = \frac{\mathbf{c}'_\ell \overline{\mathbf{X}}_.}{\sqrt{\widehat{\sigma}^2_\ell}}, \ell = 1, \ldots, q$$

- Distribution of T_ℓ can be approximated by a t-distribution with

$$\nu_\ell = \frac{\widehat{\sigma}^4_\ell}{\sum_{i=1}^a \frac{c^4_{\ell i}}{n_i^2(n_i-1)} s_i^4}$$

- Reject H_0, if any $T_{(\ell)}$ exceeds a critical value

$$T_0 = \max\{|T_1|, \ldots, |T_q|\} \geq z_{1-\alpha}(max)$$

- **Needed: Distribution of the maximum value T_0 to compute $z_{1-\alpha}(max)$**

```
diff <-C%*%Xbar
Tl<-diff/sqrt(c(diag(Gammahat)))

nul = sapply(1:nrow(C),function(arg){
c(t(C[arg,])%*%Shat%*%C[arg,])^2/
sum(C[arg,]^4*si2^2/(n^2*(n-1)))})

T0<-max(abs(Tl))
```

Multiple Contrast Test Procedures (MCTP)

- Are the test statistics $T_{(\ell)}$ and $T_{(\ell')}$ independent?

- Covariance of $\boldsymbol{c}_\ell' \overline{\mathbf{X}}_\cdot$ and $\boldsymbol{c}_m' \overline{\mathbf{X}}_\cdot$:

Multiple Contrast Test Procedures (MCTP)

- Collect all test statistics in a vector $\boldsymbol{T} = (T_1, \ldots, T_q)'$
- The distribution of $\boldsymbol{T}$ can be approximated by a multivariate $T(\mathbf{0}, \nu, \boldsymbol{R})$ distribution, $\nu = \min\{\nu_1, \ldots, \nu_q\}$
- Computation of c orrelation matrix$\boldsymbol{R}$:

$$\begin{aligned} \mathbf{R} &= (r)_{\ell,m} = \frac{\gamma_{\ell,m}}{\sqrt{\gamma_{\ell,\ell}\gamma_{m,m}}}, \ \mathbf{\Gamma} = (\gamma)_{\ell,m} \\ &= diag(\mathbf{\Gamma})^{-1/2}\mathbf{\Gamma} diag(\mathbf{\Gamma})^{-1/2} \end{aligned}$$

- $diag(\mathbf{\Gamma})$: diagonal matrix obtained from diagonal elements of $\mathbf{\Gamma}$
- $\boldsymbol{R}$ is unknown under heteroscedasticity
- $\widehat{\mathbf{R}} = diag(\widehat{\mathbf{\Gamma}})^{-1/2}\mathbf{\Gamma} diag(\widehat{\mathbf{\Gamma}})^{-1/2}$

Multiple Contrast Test Procedures (MCTP)

- Test decisions
  - Reject $H_0^{(\ell)}: \mathbf{c}_\ell' \mu = 0$ if $|T_\ell| \geq t_{1-\alpha}(\widehat{\boldsymbol{R}})$

$$\boldsymbol{c}_\ell' \overline{\mathbf{X}}_\cdot \pm t_{1-\alpha}(\widehat{\boldsymbol{R}})\widehat{\sigma}_\ell,\ \ell = 1, \ldots, q$$

  - Reject H_0 if $T_0 \geq t_{1-\alpha}(\widehat{\boldsymbol{R}})$
  - $t_{1-\alpha}(\widehat{\boldsymbol{R}})$: $(1-\alpha)$-quantile of the multivariate $T(\mathbf{0}, \nu, \widehat{\boldsymbol{R}})$ distribution
  - Or, compute adjusted p-values using the $T(\mathbf{0}, \nu, \widehat{\boldsymbol{R}})$ distribution

```
library(multcomp)

nu=round(min(nul))
Rhat<-cov2cor(Gammahat)
set.seed(1)
tmax=qmvt(0.95,tail="both",corr=Rhat,
df=nu)$quantile
T0>=tmax
$

pv<-sapply(1:4,function(j)
1-pmvt(-abs(Tl[j]),abs(Tl[j]),df=nu,
delta=rep(0,4),corr=Rhat)[1])
```

Properties

- Method is a multiple t-test
- In case of small samples, method might be liberal or conservative
- Resampling methods to improve the approximation /method
- Goal: Approximate the distribution of the maximum

Resampling Methods

1. Fix the data in $\mathbf{X} = (X_{11}, \dots, X_{an_a})'$
2. Generate resampling variables $\mathbf{X}^* = (X^*_{11}, \dots, X^*_{an_a})'$
3. Reassign: $X^*_{11}, \dots, X^*_{1n_1}$ are group 1, etc.
4. Compute $\overline{X}^*_{i\cdot}$ and $s_i^{2,*}$ (means and variances)
5. Compute means $\overline{\mathbf{X}}^*_{\cdot}$ and variance estimator $\widehat{\sigma}^{2,*}_{\ell}$ with the resampling variables
6. Compute the vector of test statistics

$$T^*_\ell = \frac{\boldsymbol{c}'_\ell(\overline{\mathbf{X}}^*_{\cdot} - E(\overline{\mathbf{X}}^*_{\cdot}|\mathbf{X}))}{\widehat{\sigma}^*_\ell}$$

7. Compute $T^*_0 = \max\{|T^*_1|, \dots, |T^*_q|\}$ and safe in A_1
8. Repeat the above n_{boot} times and estimate the $(1-\alpha)$ quantile from $A^*_1, \dots, A^*_{n_{boot}}$
8. Reject H_0, if the p-value

$$\frac{1}{n_{boot}} \sum_{s=1}^{n_{boot}} \mathcal{I}(A^*_s \geq T_0) < \alpha$$

A Parametric Bootstrap Approach

- Many different ways of generating $\mathbf{X}^*$ are possible
- One possibility: Parametric Bootstrap
- Generate

$$X_{i1}^*, \ldots, X_{in_i}^* \sim N(0, s_i^2), \; i = 1, \ldots, a$$

- Compute $\overline{X}_{i\cdot}^*$ and $s_i^{2,*}$ (means and variances)
- Vector of test statistics

$$T_\ell^* = \frac{\boldsymbol{c}_\ell'(\overline{\mathbf{X}}_\cdot^*)}{\widehat{\sigma}_\ell^*}$$

- Compute $T_0^* = \max\{|T_1^*|, \ldots, |T_q^*|\}$ and safe in A_1
- Repeat the above n_{boot} times and estimate the p-value

```
A1<-c()
nboot <- 10000

s2vec<-rep(si2,n)
for(h in 1:nboot){
XB <- rnorm(N,0,sqrt(s2vec))
DatB<-data.frame(XB=XB,grp=grp)
XbarB<-aggregate(XB~grp,data=DatB,mean)[,2]
si2B <-aggregate(XB~grp,data=DatB,var)[,2]
ShatB <- diag(si2B/n)
GammahatB<-C%*%ShatB%*%t(C)
diffB <-C%*%XbarB
T1B<-diffB/sqrt(c(diag(GammahatB)))
A1[h]<-max(abs(T1B))}

mean(A1>=T0) #pvalue
#Simulation: Use matrix techniques
```