Resampling Techniques and their Application

-Class 11-

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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?


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

$$H_0^{(1j)} : \mu_1 = \mu_j, \; j = 2, \ldots, a$$

- **Multiple hypotheses**

Multiple Hypotheses

- Individual hypothesis

$$H_0^{(1j)} : \mu_1 = \mu_j,\ j = 2, \ldots, a$$

- **Family of hypotheses**

$$\boldsymbol{\Omega} = \left\{ H_0^{(12)}, H_0^{(13)}, \ldots, H_0^{(1a)} \right\}$$

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

$$H_0 : \bigcap_{j=2}^{a} \left\{ H_0^{(1j)} : \mu_1 = \mu_j \right\} \Leftrightarrow H_0 : \mu_1 = \ldots = \mu_a$$

- Reject H_0, if any $H_0^{(1j)}$ is rejected

Point Estimators

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

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

- Variance of a contrast

$$\sigma^2_{(1j)} = Var(\overline{X}_{1\cdot} - \overline{X}_{j\cdot}) = \sigma^2 \left(\frac{1}{n_1} + \frac{1}{n_j} \right)$$

$$\widehat{\sigma}^2_{(1j)} = s^2 \left(\frac{1}{n_1} + \frac{1}{n_j} \right)$$

```
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)
s2<- sum((n-1)*si2[,2])/(N-a)

s1j<-sapply(2:5,function(j)s2*
(1/n[1] + 1/n[j]))
```

Multiple Comparisons

- For $H_0^{(1j)} : \mu_1 = \mu_j$

$$T_{(1j)} = \frac{\overline{X}_{1\cdot} - \overline{X}_{j\cdot}}{s \cdot \sqrt{\frac{1}{n_1} + \frac{1}{n_j}}}, \; j = 2, \ldots, a$$

```
diff <-sapply(2:5,
function(j)(Xbar[1]-Xbar[j]))
T1j<-diff/sqrt(s1j)
```

- More than one test is performed
- Reject H_0, if any $T_{(1j)}$ exceeds a critical value

$$T_0 = \max\{|T_{12}|, \ldots, |T_{1a}|\} \geq z_{1-\alpha}(max)$$

```
T0<-max(abs(T1j))
```

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

Bonferroni Correction

- Each $T_{(1j)} \sim t_{N-a}$ (under H_0)
- p-values: $pv_{(12)}, \ldots, pv_{(1a)}$
- Let $t = t_{1-\alpha/2}(N-a)$ quantile from t_{N-a} distribution
- If we rejected H_0 if if $T_0 \geq t$, would this test control α? (equivalently $\min\{pv_{1j} < \alpha\}$)
- No, because $P(|T_{1j}| \geq t) = \alpha$
- Hence $P(|T_0| \geq t) \geq \alpha$:

$$P(T_0 \geq t) = \underbrace{P\left(\bigcup_{j=2}^{a}\{|T_{1j}| \geq t\}\right)}_{\text{any } |T_{1j}| \text{ exceeds t}} \leq \sum_{j=2}^{a} \underbrace{P(|T_{1j}| \geq t)}_{=\alpha} = (a-1)\alpha$$

- Bonferroni correction: Divide α (significance level) by $(a-1)$ (number of tests)
- Or use **adjusted** p-values: Multiply each individual p-value by $(a-1)$ and compare with α

Multiple Contrast Test Procedures (MCTP)

- Quality of the method?
- Are the test statistics $T_{(1j)}$ and $T_{(1j')}$ independent?
- Covariance of $(\overline{X}_{1\cdot} - \overline{X}_{j\cdot})$ and $(\overline{X}_{1\cdot} - \overline{X}_{j'\cdot})$:

$$\begin{aligned} Cov(\overline{X}_{1\cdot} - \overline{X}_{j\cdot}, \overline{X}_{1\cdot} - \overline{X}_{j'\cdot}) &= Cov(\overline{X}_{1\cdot}, \overline{X}_{1\cdot}) - Cov(\overline{X}_{1\cdot}, \overline{X}_{j'\cdot}) - Cov(\overline{X}_{j\cdot}, \overline{X}_{1\cdot}) + Cov(\overline{X}_{j\cdot}, \overline{X}_{j'\cdot}) \\ &= Cov(\overline{X}_{1\cdot}, \overline{X}_{1\cdot}) = Var(\overline{X}_{1\cdot}) = \sigma^2 \frac{1}{n_1} \end{aligned}$$

- Covariance matrix of $\widehat{\boldsymbol{\delta}} = (\widehat{\delta}_{(12)}, \ldots, \widehat{\delta}_{(1a)})'$, $\widehat{\delta}_{(1j)} = \overline{X}_{1\cdot} - \overline{X}_{j\cdot}$

$$\boldsymbol{\Gamma} = Cov(\widehat{\boldsymbol{\delta}}) = \begin{pmatrix} \sigma^2_{(12)} & \sigma^2 \frac{1}{n_1} & \cdots & \sigma^2 \frac{1}{n_1} \\ \sigma^2 \frac{1}{n_1} & \sigma^2_{(13)} & \cdots & \sigma^2 \frac{1}{n_1} \\ \vdots & \vdots & \vdots & \vdots \\ \sigma^2 \frac{1}{n_1} & \sigma^2 \frac{1}{n_1} & \cdots & \sigma^2_{(1a)} \end{pmatrix} = diag(\sigma^2_{(1j)}) + \sigma^2 / n_1 (\mathbf{J} - \mathbf{I})$$

- $\mathbf{J}$: matrix of $1's$, $\mathbf{I}$ identity matrix

Multiple Contrast Test Procedures (MCTP)

- Correlation of $(\overline{X}_{1\cdot} - \overline{X}_{j\cdot})$ and $(\overline{X}_{1\cdot} - \overline{X}_{j'\cdot})$:
- Collect all test statistics in a vector $\boldsymbol{T}$
- $\boldsymbol{T} = (T_1, \ldots, T_q)' \sim T(\mathbf{0}, N - a, \boldsymbol{R})$ (under H_0)
- Computation of $\boldsymbol{R}$ = Correlation matrix:

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

- $diag(\boldsymbol{\Gamma})$: diagonal matrix obtained from diagonal elements of $\boldsymbol{\Gamma}$

- $\boldsymbol{R}$ is always known

Multiple Contrast Test Procedures (MCTP)

- Test decisions
  - Reject $H_0^{(ij)}: \mu_1 = \mu_j$ if $|T_{(1j)}| \geq t_{1-\alpha}(\boldsymbol{R})$

$$CI_{(12)} = (\overline{X}_{1\cdot} - \overline{X}_{j\cdot}) \pm t_{1-\alpha}(\boldsymbol{R}) s \cdot \sqrt{\frac{1}{n_1} + \frac{1}{n_j}}$$

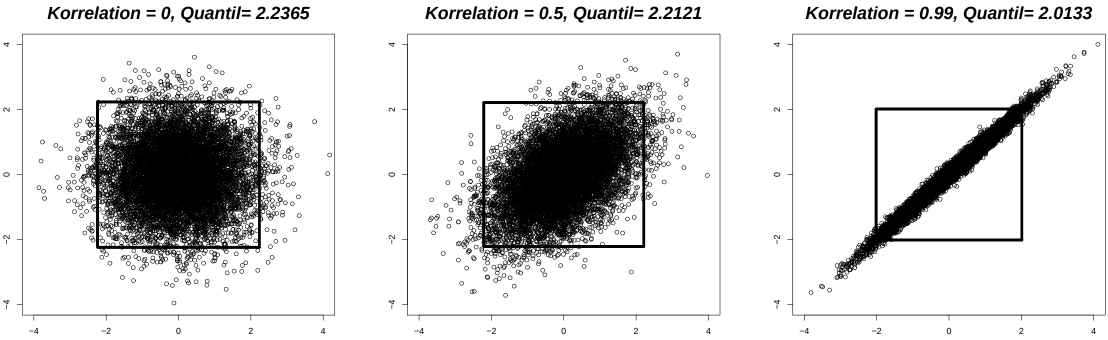
  - Reject H_0 if $T_0 \geq t_{1-\alpha}(\boldsymbol{R})$
  - $t_{1-\alpha}(\boldsymbol{R})$: $(1-\alpha)$-quantile of the multivariate $T(\mathbf{0}, N-a, \boldsymbol{R})$ distribution
  - Or, compute adjusted p-values using the $T(\mathbf{0}, N-a, \boldsymbol{R})$ distribution

```
library(multcomp)
Gamma= matrix(0,ncol=4,nrow=4)
for(i in 1:4){
for(j in 1:4){
if(i==j){Gamma[i,j]=s2*(1/n[1]+1/n[j+1])}
if(i!=j){Gamma[i,j]=s2*(1/n[1])}}}

R<-cov2cor(Gamma)
tmax=qmvt(0.95,tail="both",corr=R,
df=N-5)$quantile
T0>=tmax
$

pv<-sapply(1:4,function(j)
1-pmvt(-abs(T1j[j]),abs(T1j[j]),df=N-a,
delta=rep(0,4),corr=R)[1])
```

Quantiles



- Equicoordinate quantiles of different bivariate $T(\mathbf{0}, N-a, \boldsymbol{R})$ distributions
- cuboid with quadratic area
- Computation with R-Package „mvtnorm"

Example: Evaluation with multcomp

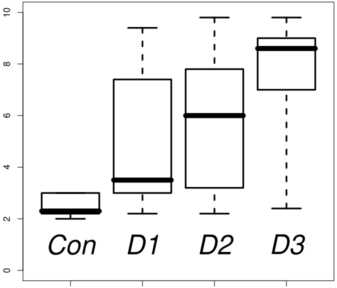
```
> library(multcomp)
# set up a one-way ANOVA
amod <- aov(X ~ grp, data = Dat)

# set up Dunnett comparisons for factor ‘Group’
erg <- glht(amod, linfct = mcp(grp = "Dunnett"))
summary(erg)
Linear Hypotheses:
           Estimate Std. Error t value Pr(>|t|)
2 - 1 == 0   0.0375     0.1562   0.240  0.99770
3 - 1 == 0   0.1013     0.1509   0.671  0.90708
4 - 1 == 0   0.5718     0.1562   3.661  0.00331 **
5 - 1 == 0   0.9062     0.1509   6.005  < 0.001 ***

plot(erg)
```

Example: Reaction Times

- Reaction times [sec] of mice
  - 1 control group and three dose groups
  - 10 animals per group



- Impact of the dose?

Example: Data

```
> library(nparcomp)
>  data(reaction)
> reaction
Group Time
0  2.4
...
0  3.0
1  2.8
...
1  7.4
2  9.8
...
2  3.4
3  7.0
...
3  7.8
```

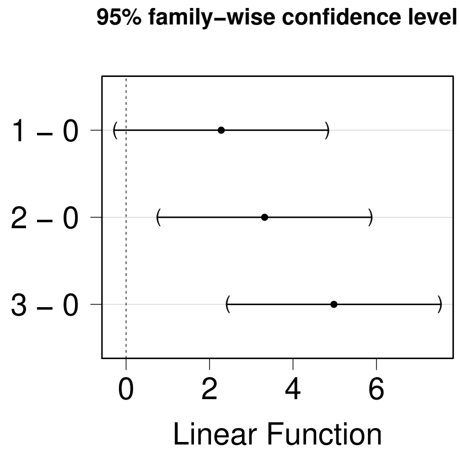
Example: Evaluation

```
> library(multcomp)
# set up a one-way ANOVA
amod <- aov(Time ~ Group, data = reaction)

# set up Dunnett comparisons for factor 'Group'
> erg <- glht(amod, linfct = mcp(Group = "Dunnett"))
> summary(erg)
Linear Hypotheses:
Estimate Std. Error t value Pr(>|t|)
1 - 0 == 0    2.280      1.038   2.196  0.08767 .
2 - 0 == 0    3.320      1.038   3.198  0.00799 **
3 - 0 == 0    4.980      1.038   4.798  < 0.001 ***
```

Example: Evaluation

```
> plot(erg)
```



General Contrasts

- Before, we studied many to one comparisons
- We can generalize the testing problem to general contrasts

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

- 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.

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

General Contrasts

- Example 1: Many-to-one comparisons:

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

General Contrasts (II)

- Example 2: Trend

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

General Contrasts (III)

- Example 3: All-pairs:

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

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

Multiple Contrast Tests

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

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

Multiple Contrast Tests

- Pooled variance estimator

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

- Variance estimators

$$\begin{aligned}
\widehat{\mathbf{S}} &= s^2 diag\left(\frac{1}{n_1}, \ldots, \frac{1}{n_a}\right) \\
\widehat{\boldsymbol{\Gamma}} &= s^2 \boldsymbol{C}\left(\frac{1}{n_1}, \ldots, \frac{1}{n_a}\right)\boldsymbol{C}' \\
\widehat{\sigma}_\ell^2 &= s^2 \sum_{i=1}^{a} \frac{c_{\ell i}^2}{n_i} = s^2 \mathbf{c}_\ell' \mathbf{c}_\ell
\end{aligned}$$

Parametric MCTP

- Multiple Comparisons
  - For $H_0 : \boldsymbol{c}_\ell' \boldsymbol{\mu} = 0$:

$$T_\ell = \frac{\boldsymbol{c}_\ell' \overline{\mathbf{X}}_\cdot}{s\sqrt{\mathbf{c}_\ell' \mathbf{c}_\ell}}, \ell = 1, \ldots, q$$

  - $T_\ell \sim t_{N-a}$ (under H_0)
  - Collect all test statistics in a vector $\mathbf{T} = (T_1, \ldots, T_q)'$

General MCTP

- Joint distribution of $\boldsymbol{T}$
- $\boldsymbol{T} = (T_1, \ldots, T_q)' \sim T(\mathbf{0}, N - a, \boldsymbol{R})$ (under H_0)
- Computation of $\boldsymbol{R}$:

$$\boldsymbol{R} = diag(\boldsymbol{\Gamma})^{-1/2} \boldsymbol{\Gamma} diag(\boldsymbol{\Gamma})^{-1/2}$$

- $diag(\boldsymbol{\Gamma})$: diagonal matrix obtained from diagonal elements of $\boldsymbol{\Gamma}$
- **Only depends on sample sizes and *C***
- In R: *cov2cor(.)* (since σ^2 cancels, use $\boldsymbol{\Gamma}$ without it)

Parametric MCTP

- Note that each component is studentized with the same χ^2-variable
- Test decisions
  - Reject $H_0 : \boldsymbol{c}_\ell' \boldsymbol{\mu} = 0$ if $|T_\ell| \geq t_{1-\alpha}(\boldsymbol{R})$

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

  - Reject $H_0 : \boldsymbol{C}\boldsymbol{\mu} = \mathbf{0}$ if $T_0 = max(|T_1|, \ldots, |T_q|) \geq t_{1-\alpha}(\boldsymbol{R})$
  - $t_{1-\alpha}(\boldsymbol{R})$: $(1-\alpha)$-quantile of the multivariate $T(\mathbf{0}, N-a, \boldsymbol{R})$ distribution