Resampling Techniques and their Application

-Class 13-

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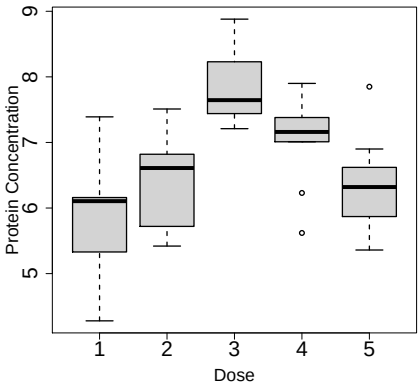
Example: Yeast Study

- $n = 10$ medical yeast samples
- Each sample grown on different growth mediums (increasing fertility)
- Response: protein concentration



ID	M1	M2	M3	M4	M5
1	6.16	6.04	7.21	7.23	6.22
2	4.28	5.42	7.44	6.23	6.03
3	5.26	5.72	7.40	7.02	5.87
4	6.11	6.65	7.44	7.09	6.62
5	6.15	6.67	7.79	5.62	5.80
6	5.33	7.50	8.23	7.38	6.42
7	5.47	6.82	7.94	7.01	6.57
8	6.10	6.57	8.73	7.90	6.90
9	7.39	5.44	7.50	7.32	5.36
10	7.07	7.51	8.88	7.70	7.85

Statistical Model

- Statistical Model
  - $\mathbf{X}_k = (X_{1k}, \ldots, X_{dk})' \sim \mathbf{F}$
  - $E(\mathbf{X}_k) = \boldsymbol{\mu} = (\mu_1, \ldots, \mu_d)'$
  - Covariance matrix $\boldsymbol{V} = Cov(\mathbf{X}_1)$
  - No normal distribution
- Hypotheses $H_0 : \mu_1 = \ldots = \mu_d$

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

- $\boldsymbol{C}$: Contrast matrix

Point Estimators

- Means and covariance matrix
  - $\overline{\mathbf{X}}_{\cdot} = (\overline{X}_{1\cdot}, \ldots, \overline{X}_{d\cdot})'$: Means
  - Empirical covariance matrix

$$\widehat{\boldsymbol{V}} = \frac{1}{n-1} \sum_{k=1}^{n} (\overline{\mathbf{X}}_k - \overline{\mathbf{X}}_{\cdot})(\overline{\mathbf{X}}_k - \overline{\mathbf{X}}_{\cdot})'$$

```
x=matrix(c(6.16, 6.04, 7.21, 7.23, 6.22,
4.28, 5.42, 7.44, 6.23, 6.03,
5.26, 5.72, 7.40, 7.02, 5.87,
6.11, 6.65, 7.44, 7.09, 6.62,
6.15, 6.67, 7.79, 5.62, 5.80,
5.33, 7.50, 8.23, 7.38, 6.42,
5.47, 6.82, 7.94, 7.01, 6.57,
6.10, 6.57, 8.73, 7.90, 6.90,
7.39, 5.44, 7.50, 7.32, 5.36,
7.07, 7.51, 8.88, 7.70, 7.85),ncol=5,byrow=T)
```

```
Xbar=colMeans(x)
```

```
Vhat=var(x)
```

Test Statistics

- Multiple contrast test procedures (last classes)
- In addition today: global testing procedures
- Idea: If $H_0 : \mu_1 = \mu_2 = \ldots = \mu_a$ holds, then each $\mu_\ell = \frac{1}{d}\sum_{j=1}^{d} \mu_j$
- So, contrast of interest is the *GrandMean* contrast

$$\mathbf{C} = \begin{pmatrix} \frac{d-1}{d} & -\frac{1}{d} & \cdots & -\frac{1}{d} \\ -\frac{1}{d} & \frac{d-1}{d} & \cdots & -\frac{1}{d} \\ \vdots & \vdots & \vdots & \vdots \\ -\frac{1}{d} & -\frac{1}{d} & \cdots & \frac{d-1}{d} \end{pmatrix} = \mathbf{I} - \frac{1}{d}\mathbf{J}$$

- $\mathbf{I} = diag(d)$ and $\mathbf{J}$: $d \times d$ matrix of 1's
- Note that $\mathbf{c}_\ell' \boldsymbol{\mu} = \mu_\ell - \frac{1}{d}\sum_{j=1}^{d} \mu_j$
- $\boldsymbol{C}$ is also known as centering matrix

Test Statistics: Wald-Type

- Wald-Type Statistics
  - $W = n(\boldsymbol{C}\overline{\boldsymbol{X}}_{\cdot})' \left[\boldsymbol{C}\widehat{\boldsymbol{V}}\boldsymbol{C}'\right]^{+} \boldsymbol{C}\overline{\boldsymbol{X}}_{\cdot}$
  - $[\mathbf{A}]^{+}$: generalized inverse of a matrix
  - Under H_0, WTS has a $\chi^2_{rank(\boldsymbol{C})}$ distribution
  - When do we reject the hypothesis?

```
library(multcomp)
library(MASS)
C=contrMat(n=rep(10,5),"GrandMean")
CX=C%*%Xbar
CVhat = C%*%Vhat%*%t(C)
W=n*t(CX)%*%ginv(CVhat)%*%CX
pvalue= 1-pchisq(W, d-1)
```

Wald-Type Test: Properties

Advantages

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-
-

Disadvantages

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-

ANOVA-Type Statistic

- $\widehat{\boldsymbol{V}}$ causes issues in the WTS, let us remove it

$$\begin{aligned} A_1 &= n(\boldsymbol{C}\overline{\mathbf{X}}_{\cdot})' \left[\boldsymbol{C}\boldsymbol{C}'\right]^{+} \boldsymbol{C}\overline{\mathbf{X}}_{\cdot} \\ &= n\overline{\mathbf{X}}_{\cdot}' \boldsymbol{C}' \left[\boldsymbol{C}\boldsymbol{C}'\right]^{+} \boldsymbol{C}\overline{\mathbf{X}}_{\cdot} \\ &= n\overline{\mathbf{X}}_{\cdot}' \boldsymbol{T}\overline{\mathbf{X}}_{\cdot}. \end{aligned}$$

- The final test is given by

$$\begin{aligned} A &= n\overline{\mathbf{X}}_{\cdot}' \boldsymbol{T}\overline{\mathbf{X}}_{\cdot} / \mathit{Trace}(\boldsymbol{T}\widehat{\boldsymbol{V}}), \\ f &= \frac{\mathit{Trace}(\boldsymbol{T}\widehat{\boldsymbol{V}})^2}{\mathit{Trace}(\boldsymbol{T}\widehat{\boldsymbol{V}}\boldsymbol{T}\widehat{\boldsymbol{V}})} \end{aligned}$$

- Under H_0, ATS has a $F(f, \infty)$ distribution
- When do we reject the hypothesis?

```
TT <- t(C)%*%ginv(C%*%t(C))%*%C
TrTV <-sum(c(diag(TT%*%Vhat)))
A <- n*t(Xbar)%*%TT%*%Xbar/TrTV

TVTV<-TT%*%Vhat%*%TT%*%Vhat
TrTVTV <-sum(c(diag(TVTV)))
f <- TrTV^2/TrTVTV

pvalue <- 1-pf(A,f,10^10)

#10^10=infty, arbitrary high nr#
```

ANOVA-Type Test: Properties

Advantages

-
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-
-

Disadvantages

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R Package MANOVA.RM

- R-package *MANOVA.RM*

```
data=data.frame(x=c(x),ID=rep(1:10,5),
dose=sort(rep(1:5,10)))
library(MANOVA.RM)

fit<-RM(x~dose, subject="ID", data=data)

summary(fit)
```

MCTP: Motivation

- Is the global hypothesis always the question?
- Revise the example
- Hypotheses
  - Contrast matrix $\boldsymbol{C} = \begin{pmatrix} \boldsymbol{c}_1' \\ \vdots \\ \boldsymbol{c}_q' \end{pmatrix} = \begin{pmatrix} c_{11} & \dots & c_{1d} \\ \vdots & \dots & \vdots \\ c_{1q} & \dots & c_{qd} \end{pmatrix}$, $(\boldsymbol{C}\mathbf{1} = \mathbf{0})$
  - $H_0^\ell : \boldsymbol{c}_\ell' \boldsymbol{\mu} = 0$ simultaneously
  - $H_0 : \boldsymbol{C}\boldsymbol{\mu} = \mathbf{0}$

Why MCTP and SCI?

- ANOVA based evaluation: Three steps
  1. $H_0 : \mu_1 = \mu_2 = \cdots = \mu_d$ (overall hypothesis)

     (Using WTS or ATS)

  2. Multiple Comparisons after rejecting the global hypothesis
     - $H_0^{(1,2)} : \mu_1 = \mu_2$
     - $H_0^{(1,3)} : \mu_1 = \mu_3$
     - $\ldots$

  3. Confidence intervals for the effects
     - Regulatory authorities require confidence intervals (ICH E9)
- Problems
  - Overall result and multiple comparisons may be incompatible

Why MCTP and SCI?

- Better: Start with multiple comparisons ($\rightarrow$ multiple contrast test)
  - Control the multiple level α in the strong sense

$$P(\text{reject at least one true } H_0^i)$$

- How?
  - Adapt the concept of MCTP from Bretz, Genz and Hothorn (2001)
  - Idea: For each partial hypothesis one t-Test
  - Compare the t-values with one critical value (Gabriel, 1969)

Multiple Contrast Tests

- Estimators
  - $\overline{\mathbf{X}}_{\cdot} = (\overline{X}_{1\cdot}, \ldots, \overline{X}_{a\cdot})'$ (vector of means)
  - $\widehat{\boldsymbol{V}}$: empirical covariance matrix
- Variance of a contrast

$$\sigma_\ell^2 = Var(\boldsymbol{c}_\ell' \overline{\mathbf{X}}_{\cdot}) = \boldsymbol{c}_\ell' \boldsymbol{V} \boldsymbol{c}_\ell, \quad \widehat{\sigma}_\ell^2 = \boldsymbol{c}_\ell' \widehat{\boldsymbol{V}} \boldsymbol{c}_\ell$$

- $\widehat{\sigma}_\ell^2 = \boldsymbol{c}_\ell' \widehat{\boldsymbol{V}} \boldsymbol{c}_\ell$

Parametric MCTP

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

$$T_\ell = \sqrt{n} \frac{\boldsymbol{c}_\ell' (\overline{\mathbf{X}}_\cdot - \boldsymbol{\mu})}{\widehat{\sigma}_\ell}, \ell = 1, \ldots, q$$

  - $T_\ell \sim t_{n-1}$ (under H_0)
  - More than one test is performed, hence the type-1 error rate will increase
  - Need to be adjusted

Parametric MCTP

- Quality of the method?
- Are the test statistics T_ℓ and T_m independent?
- Covariance of $\boldsymbol{c}_\ell' \overline{\mathbf{X}}_{\cdot}$ and $\boldsymbol{c}_m' \overline{\mathbf{X}}_{\cdot}$:

Parametric MCTP

- Collect all test statistics in a vector $\boldsymbol{T}$
- $\boldsymbol{T} = (T_1, \ldots, T_q)' \sim T(\mathbf{0}, n-1, \boldsymbol{R})$
- $\boldsymbol{R} =$
- Empirical correlation $\widehat{\boldsymbol{R}} =$

Parametric MCTP

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

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

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

MCTP: Properties

Advantages

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Disadvantages

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MCTP vs ANOVA

- ANOVA
  - Quadratic test procedure for global hypothesis $H_0 : \boldsymbol{C\mu} = \mathbf{0}$
  - Derivation based on multivariate normality, but transformation in $\mathbb{R}$ via quadratic forms
  - No information for particular dose levels available
- MCTP
  - Linear test statistics
  - Test decisions via using multivariate critical values
  - Informations and SCI for particular dose levels available

Generalisations?

- Are there any drawbacks of the model assumptions?
- Of the method?
- What to do in case of small sample sizes?
- Resampling strategies?

Resampling Strategies

- Goal: Estimate the quantiles from a distribution of a maximum of correlated t-statistics
- How?
- next slide

Nonparametric Bootstrap

- Fix the data $\mathbf{X} = (\mathbf{X}_1, \ldots, \mathbf{X}_n)$
  - Draw n vectors $\mathbf{X}_k^*$ with replacement from $\mathbf{X}$
  - Compute their means: $\overline{\mathbf{X}}_\cdot^*$
  - Compute their empirical covariance matrix: $\widehat{\boldsymbol{V}}^*$
  - Compute $\boldsymbol{T}^* = (T_1^*, \ldots, T_q^*)'$; $T_\ell^* = \sqrt{n}\frac{\boldsymbol{c}_\ell'(\overline{\mathbf{X}}_\cdot^* - \overline{\mathbf{X}}_\cdot)}{\sqrt{\boldsymbol{c}_\ell' \widehat{\boldsymbol{V}}^* \boldsymbol{c}_\ell}}$
  - Compute $T_0 = \max\{|T_1^*|, \ldots, |T_q^*|\}$ and safe in $T_{0,s}^*$
  - Repeat the above a large number of times $(M = 10,000)$
- Estimate $t_{1-\alpha}(\boldsymbol{R})$ by the $(1-\alpha)$-quantile of

$$|T_{0,1}^*|, \ldots, |T_{0,M}^*|$$

Parametric Bootstrap

- Fix the data $\mathbf{X} = (\mathbf{X}_1, \ldots, \mathbf{X}_n)$
  - Draw n vectors $\mathbf{X}_k^*$ from $N(\mathbf{0}, \widehat{\boldsymbol{V}})$
  - Compute their means: $\overline{\mathbf{X}}_\cdot^*$
  - Compute their empirical covariance matrix: $\widehat{\boldsymbol{V}}^*$
  - Compute $\boldsymbol{T}^* = (T_1^*, \ldots, T_q^*)'$; $T_\ell^* = \sqrt{n}\frac{\boldsymbol{c}_\ell'(\overline{\mathbf{X}}_\cdot^*)}{\sqrt{\boldsymbol{c}_\ell'\widehat{\boldsymbol{V}}^*\boldsymbol{c}_\ell}}$
  - Compute $T_0 = \max\{|T_1^*|, \ldots, |T_q^*|\}$ and safe in $T_{0,s}^*$
  - Repeat the above a large number of times $(M = 10,000)$
- Estimate $t_{1-\alpha}(\boldsymbol{R})$ by the $(1-\alpha)$-quantile of

$$|T_{0,1}^*|, \ldots, |T_{0,M}^*|$$