Multiple Comparisons

Omnibus test

Omnibus or global test: is explained variance statistically larger than unexplained variance?

- What does it tell us?
 - population Means/Medians are different
- How?
 - Don't know.

Getting the specifics

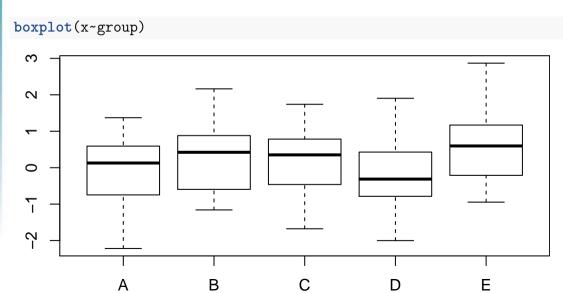
- Multiple comparisons
 - which population means are different?
 - more generally which medians, means, trimmed means are different?
- Omnibus test is usually not required first
- Possible for omnibus test to not find anything, while multiple comparisons procedure finds significant results!

A five group example

```
set.seed(554)
x <- rnorm(100); group <- factor( rep( LETTERS[1:5], each=20 ) )
tapply(x, group, mean)

## A B C D E
## -0.09851133 0.24606290 0.22823887 -0.24223872 0.59744611</pre>
```

A five group example, pg 2



Test each pair?

```
t.test( x[ group=='A' ], x[ group=='B' ])
## Welch Two Sample t-test
##
## data: x[group == "A"] and x[group == "B"]
## t = -1.0839, df = 37.85, p-value = 0.2853
## alternative hypothesis: true difference in means is not equal to 0
## 95 percent confidence interval:
## -0.9882436 0.2990951
```

How many pairs?

k groups	$m=\frac{k(k-1)}{2}$	pairs
3	3	
4	6	
5	10	
6	15	
7	21	
:	÷	

Examine All Pairs

```
## B 0.28380983 NA NA NA NA ## C 0.30931125 0.9556525 NA NA NA ## D 0.65401777 0.1299588 0.1443946 NA ## E 0.03195149 0.2744607 0.2510068 0.01005151
```

- $\mu_A \neq \mu_E$ and $\mu_D \neq \mu_E \Rightarrow 2$ Type I errors
- Multiple tests ⇒ increased risk of errors

Error Rates

- Individual: α_I
 - prob. Type I error for single comparison
- Experimentwise Error Rate: α_E
 - ullet also called Familywise Error Rate (FWER or FW $_{lpha}$)
 - prob. at least one Type I error for m comparisons
 - strongly controlling FWER can lower the power of a test

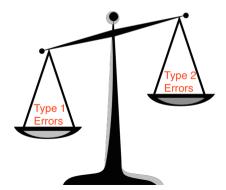
Goal: control FWER (α_E)

No procedure works well in all scenarios

- Considerations
 - Normal distributions?
 - Equal variances?
 - Same shaped distributions?
 - All pairs or a few contrasts or pairs?
 - Confidence intervals needed or just hypothesis tests?

A side note

- Genomics and other fields make 100's or 1000's comparisions
- False Discovery Rate $\approx \frac{\# false\ positives}{\# positives}$



Going beyond pairs

- mean of groups 1 and 2 different than mean of groups 3 and 4?
- textbook
 - Ott Section 9.2
 - don't worry about orthogonal contrasts
 - Example 9.3
 - F-test is same as t-test here, because $F = t^2$
- onewayComp() code
 - handles arbitrary linear contrasts
 - uses Welch type corrections for unequal variances
- formulas for t-tests of contrasts at end of slides

Bonferroni Correction

- Bonferroni Inequality: $\alpha_E \leq m\alpha_I$
- To make α_E small, reduce α_I
- To get $\alpha_E \leq \alpha$, set $\alpha_I = \alpha/m$.

Bonferroni Example - compare P to reduced α

5 groups, 10 comparisons, $\alpha_I = .05/10 = .005$

```
## B 0.28380983 NA NA NA NA ## C 0.30931125 0.9556525 NA NA NA ## D 0.65401777 0.1299588 0.1443946 NA ## E 0.03195149 0.2744607 0.2510068 0.01005151
```

For $\alpha_E = .05$ we reject each individual HT if p < .005

Bonferroni Example - adjust P and compare to α_E

```
## A B C D
## B 1.0000000 NA NA NA
## C 1.0000000 1 NA NA
## D 1.0000000 1 1 NA NA
## E 0.3195149 1 1 0.1005151
```

For $lpha_{\it E}=$.05 we reject each individual HT if $p_{\it adi}=10p<$.05

Bonferroni Pros and Cons

Pros

- any number of simultaneous hypothesis tests or confidence intervals
- any procedures allowed

Cons

- overly conservative / reduced power too many Type II errors
- avoid, if possible, unless the number of comparisons is small

Procedures for Cl's

Simu	ıltaneous	Distributions	
Confidence Intervals		Normal	Not Normal
wo or	٨॥	Tukey-Kramer	Bonferroni
		or Games-	corrected
	pail wise	Howell	bootstrapped CI's
	Few pairs	t-intervals with	or other more
	or	Bonferroni	advanced
	contrasts	correction	procedures

CI's for All Pairs and Normal

Simu	ltaneous	Distri	butions
Confidence Intervals		Normal	Not Normal
mog or	٨Ⅱ	Tukey-Kramer	Bonferroni
		or Games-	corrected
	pail wise	Howell	bootstrapped CI's
	Few pairs	t-intervals with	or other more
	or	Bonferroni	advanced
	contrasts	correction	procedures

Tukey-Kramer

$$\overline{x}_i - \overline{x}_j \pm q_{\mathsf{crit}} s_p \sqrt{\frac{\frac{1}{n_i} + \frac{1}{n_j}}{2}}$$

 q_{crit} is the upper-tail critical value of the Studentized range distribution (qtukey() in R).

$$s_p = \sqrt{MSE}, df = N - k$$

exact control of FWER if samples balanced and population variances equal.

Games-Howell

$$\overline{x}_i - \overline{x}_j \pm q_{\mathsf{crit}} \sqrt{\frac{\frac{s_i^2}{n_i} + \frac{s_j^2}{n_j}}{2}}$$

 q_{crit} is the upper-tail critical value of the Studentized range distribution (qtukey() in R).

"Welch" corrected degrees of freedom:
$$v_i=rac{s_i^2}{n_i}, v_j=rac{s_j^2}{n_j}, df=rac{(v_i+v_j)^2}{rac{v_i^2}{n_j-1}+rac{v_j^2}{n_j-1}}$$

approximate control of FWER

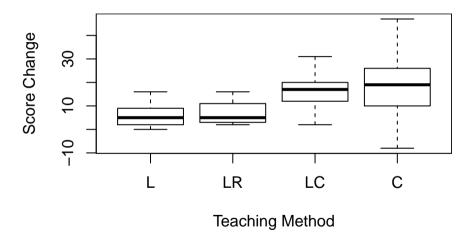
Tukey-Kramer vs. Games-Howell

- Tukey-Kramer
 - approximately balanced (equal) sample sizes
 - and approximately equal variances
- Games-Howell
 - unbalanced sample sizes
 - and/or unequal variances
 - don't transform, use this instead

Reading Example

- data from Ott, problem 7.22, page 393
- compare improvement in reading score for 4 teaching methods:
 - (L) Lecture only
 - (LR) Lecture and Remedial textbook
 - (LC) Lecture and Computer assistance
 - (C) Computer Assistance only

Reading Example (2)



Note: variances are different!

Reading Example (3)

Ignoring the equal variances for a moment . . .

TukeyHSD(aov(scoreInc~group, data=d))\$group

```
## LR-L 1.385714 -11.7198702 14.49130 0.99159633

## LC-L 10.100000 -2.1190235 22.31902 0.13399125

## C-L 11.766667 -0.4523568 23.98569 0.06243555

## LC-LR 8.714286 -4.6877469 22.11632 0.30906387

## C-LR 10.380952 -3.0210802 23.78299 0.17477900

## C-LC 1.666667 -10.8697869 14.20312 0.98361676
```

Reading Example (4)

Tukey-Kramer with onewayComp()

```
source('./onewayComp.R') # included in weekly download
onewayComp(scoreInc~group, data=d, var.equal=T)$comp[,c(1,2,3,6)]
```

```
## LR-L 1.385714 -11.7198702 14.49130 0.99159633

## LC-L 10.100000 -2.1190235 22.31902 0.13399125

## C-L 11.766667 -0.4523568 23.98569 0.06243555

## LC-LR 8.714286 -4.6877469 22.11632 0.30906387

## C-LR 10.380952 -3.0210802 23.78299 0.17477900

## C-LC 1.666667 -10.8697869 14.20312 0.98361676
```

No significant differences (all the intervals contain 0)

Reading Example (5)

Unequal variances so use Games-Howell:

```
onewayComp(scoreInc~group, data=d, var.equal=F)$comp[,c(1,2,3,6)]
```

```
## LR-L 1.385714 -6.2096361 8.981065 0.94875286

## LC-L 10.100000 0.6763831 19.523617 0.01776619

## C-L 11.766667 -5.3317545 28.865088 0.16624444

## LC-LR 8.714286 -1.3500848 18.778656 0.07550173

## C-LR 10.380952 -6.9040031 27.665908 0.27902060

## C-LC 1.666667 -16.0794366 19.412770 0.99231005
```

LC reading improvement is 0.7 to 19.5 greater than L reading improvement!

CI's for few pairs or contrasts

Simultaneous Confidence Intervals		Distributions	
		Normal	Not Normal
Compare Type Pairwise Few pairs or	ΔΙΙ	Tukey-Kramer	Bonferroni
		or Games-	corrected
	Howell	bootstrapped CI's	
	Few pairs	t-intervals with	or other more
	or	Bonferroni	advanced
	contrasts	correction	procedures

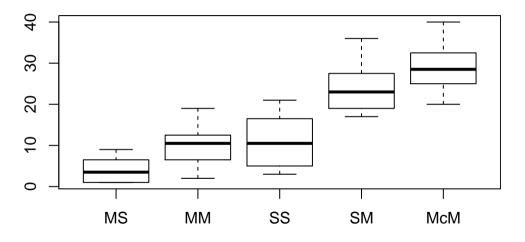
Bonferroni Correction for Cl's

- 4 comparisons
- want familywise error rate $\alpha_E = 0.05$
- familywise confidence level $1 \alpha_E = 0.95$
- individual comparison error rate $\alpha_I = 0.05/4 = 0.0125$
- individual comparison confidence level $1 \alpha_I = 0.9875$

Morphine Tolerance Example

- Record pain sensitivity after rats developed morphine tolerance
- 5 treatment groups: MS, MM, SS, SM, McM
- from David Howell's book: Statistical Methods for Psychology Chapter 12 (included with download)
- original study: www.eou.edu/psych/re/morphinetolerance.doc

Morphine Tolerance Example (2)



• Normality and equal variances seem OK

Morphine Tolerance Example (3)

- Particular comparisons of interest
 - average of MS, MM, SS vs average of SM, McM
 - MM vs McM
 - MS vs SS
 - MM vs SS
- build a contrast matrix with weights (next slide)

Morphine Tolerance Example (4)

- contrast matrix
 - each contrast is a row
 - weights in each row add to zero
 - absolute value of weights in each row adds to 2 (standard contrasts)

Morphine Tolerance Example (5)

- Approach 1: use glht() from package 'multcomp'.
- Bonferroni with 4 comparisons, want familywise 0.95, so individual 0.9875.

```
require(multcomp) # install package if necessary
# setup oneway ANOVA
amod <- aov(pain ~ treat, data = morph)
comp.glht <- glht( amod, linfct = mcp( treat = K) )</pre>
```

Output on next slide.

Morphine Tolerance Example (6)

```
confint( comp.glht )
## 95% family-wise confidence level
##
## Linear Hypotheses:
##
                  Estimate lwr
                                  upr
## ave2 -ave3 == 0 18.1667 13.4668 22.8665
##
   McM - MM == 0 19.0000 11.7190 26.2810
## SS - MS == 0 7.0000 -0.2810 14.2810
## MM - SS == 0 -1.0000 -8.2810 6.2810
```

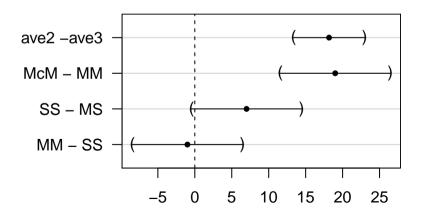
- multcomp family of confidence intervals use a "Tukey" like procedure
- requires approximately balanced and equal variances

Morphine Tolerance Example (7)

Can do the Bonferroni correction manually:

```
confint( comp.glht, calpha=univariate_calpha(), level = 1-.05/4 )
## 98.75% confidence level
##
## Linear Hypotheses:
##
                  Estimate lwr
                                  upr
## ave2 -ave3 == 0 18.1667 13.3587 22.9746
##
   McM - MM == 0 19.0000 11.5516 26.4484
## SS - MS == 0 7.0000 -0.4484 14.4484
   MM - SS == 0 -1.0000 -8.4484 6.4484
##
```

Morphine Tolerance Example (8)



Morphine Tolerance Example (9)

```
## ave2 -ave3 18.16667 13.3587469 22.974586 9.9502931 3.862945e-11
## McM - MM 19.00000 11.5516028 26.448397 6.7175144 3.548925e-07
## SS - MS 7.00000 -0.4483972 14.448397 2.4748737 7.327455e-02
## MM - SS -1.00000 -8.4483972 6.448397 -0.3535534 1.000000e+00
```

Morphine Tolerance Example (10)

- With 95% confidence
 - Average population mean for SM and McM is 13.4 to 23.0 higher than average population mean of MS, MM, and SS
 - population mean for McM is 11.6 to 26.4 larger than population mean for MM

CI's for Non-normal Distributions

Simultaneous		Distributions	
Confidence Intervals		Normal	Not Normal
96	All	Tukey-Kramer	Bonferroni
Compare Type	pairwise	or Games-	corrected
		Howell	bootstrapped Cl's
	Few pairs	t-intervals with	or other more
	or	Bonferroni	advanced
	contrasts	correction	procedures

Bootstrap with onewayComp

If distributions deviate significantly from normal, then set nboot > 0.

```
## ave2 -ave3 18.16667 13.1171931 23.201579 9.9502931 0.0000
## McM - MM 19.00000 11.7194181 26.386214 6.7175144 0.0000
## SS - MS 7.00000 -0.1206754 14.187423 2.4748737 0.0556
## MM - SS -1.00000 -9.0565723 7.108379 -0.3535534 1.0000
```

CI's based on Studentized estimates. var.equal = TRUE by default.

Bootstrap using boot package

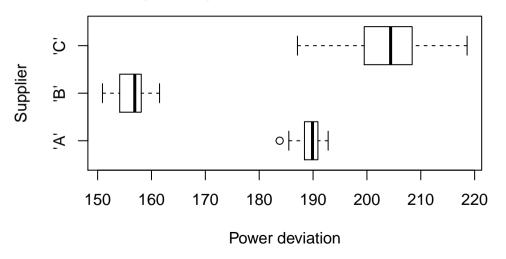
Cl's for contrasts with medians, trimmed means, and means.



Watch presentation about 'boot' package.

Contact Lenses Example

See Problem 8.27 in Ott (page 442).



Contact Lenses Example (2)

• Estimate differences in population medians: C-A, C-B, and A-B

```
bootMedDiff <- function(d,i){
    # d is a dataframe with
    # quantitative variable in column 1
    # factor variable in column 2
    meds <- tapply(d[i,1],d[,2],median)
    c( meds[3]-meds[1], meds[3]-meds[2], meds[1]-meds[2])
}</pre>
```

Contact Lenses Example (3)

44 [4] OZ O OZ O

```
boot.object <- boot(contacts, bootMedDiff, R = 5000,
                     strata = contacts$Supplier)
\# med C - med A
boot.ci(boot.object,conf = 1 - .05/3, type='bca', index=1)$bca[4:5]
## [1] 6.7 22.1
\# med C - med B
boot.ci(boot.object,conf = 1 - .05/3, type='bca', index=2)$bca[4:5]
## [1] 39.2 54.5
\# \text{ med } A - \text{ med } B \ (= 6)
boot.ci(boot.object,conf = 1 - .05/3, type='bca', index=3)$bca[4:5]
```

Contact Lenses Example (4)

For power deviations, we are 95% confident that

- Pop. median C is 6.7 to 22.1 larger than pop. median A
- Pop. median C is 39.2 to 54.5 larger than pop. median B
- Pop. median A is 27.8 to 37.8 larger than pop. median B

Statistically significant, YES. Practically significant?

Procedures for HT's

Simultaneous		Distributions	
Hypothesis Tests		Normal	Not Normal
Compare Type	All pairwise	Tukey-Kramer or Games-Howell (use REGWQ if balanced and equal variances)	Dunn Test if appropriate, other more advanced procedures such as bootstrap
	Few pairs or contrasts	F or t tests with Bonferroni- Holm adjusted p-values	Pairwise test like Mann Whitney or bootstrap tests + adjusted p-values

Sequential Procedures

- Adjust α and/or p sequentially to account for
 - number of tests remaining
 - possibly the number of means between the pair being tested
- No confidence intervals.
- Less conservative, more power!

Bonferroni-Holm Stepdown Procedure

- Compare smallest *p*-value to α/m
- Second smallest *p*-value to $\alpha/(m-1)$, etc.
- Stop at first non-rejection and do not reject any remaining hypotheses.
- Strengths: Guaranteed FWER, arbitrary contrasts, more power than Bonferroni
- Cons: still conservative

Bonferroni-Holm Example

null hyp.	p-value
H1	0.01
H2	0.04
H3	0.03
H4	0.002

Bonferroni-Holm Example - adjusted *p*-values

null hyp.	p-value
H1	0.01
H2	0.04
H3	0.03
H4	0.002

```
p.adjust( p = c( .01, .04, .03, .002), method = 'holm')
```

```
## [1] 0.030 0.060 0.060 0.008
```

Benjamin-Hochberg

- less conservative sequential method
- controls False Discovery Rate (FDR)
- allows more false positives, but more powerful
- use for Exploratory Analysis

Ryan Procedure (REGWQ)

- Sequential, more powerful version of Tukey Test
- Requires samples
 - are from normal distributions with equal variances
 - have (approx) equal sample sizes
- guarantees FWER
- Available in package 'mutoss', but difficult to use.
- Use downloaded regwqComp().
 - also in DS705data package.

Multiple HT with Normal Distributions

Simultaneous		Distributions	
Hypothesis Tests		Normal	Not Normal
Compare Type	All pairwise	Tukey-Kramer or Games-Howell (use REGWQ if balanced and equal variances)	Dunn Test if appropriate, other more advanced procedures such as bootstrap
	Few pairs or contrasts	F or t tests with Bonferroni- Holm adjusted p-values	Pairwise test like Mann Whitney or bootstrap tests + adjusted p-values

Which procedure?

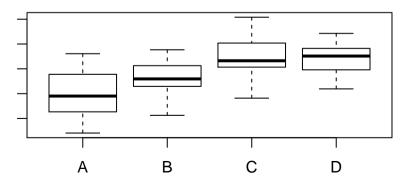
For independent samples from (approx.) normal distributions:

- approx. balanced sample sizes AND approx. equal variances
 - Tukey-Kramer or REGWQ if available
 - onewayComp() with var.equal = TRUE, or regwqComp()
- unbalanced sample sizes and/or unequal variances
 - Games-Howell
 - onewayComp() with var.equal = FALSE

Example REGWQ

4 samples from normals with $\sigma=1$ and $\mu_{A}=0, \mu_{B}=0.5, \mu_{C}=1, \mu_{D}=1.5$

```
set.seed(4321)
x <- rnorm(80)+rep(c(0,.5,1,1.5),each=20)
g <- factor(rep(LETTERS[1:4],each=20)); d <- data.frame(x,g)</pre>
```



Example REGWQ (2)

If REGWQ is not available, can use Tukey-Kramer:

```
posthoc<-onewayComp(x~g,adjust='one.step')
posthoc$comp[,c(1,6,7)]</pre>
```

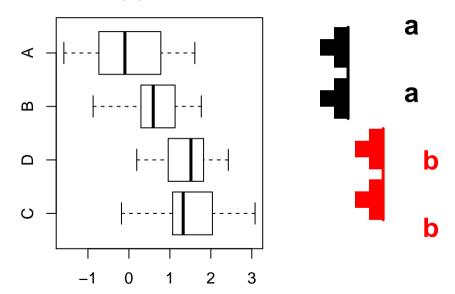
Can't separate μ_A and μ_B or μ_C and μ_D

Example REGWQ (3)

Visualize pairs with multcompBoxlot

See next slide for plot

Example REGWQ (4)



Example REGWQ (5)

source('./regwqComp.R')
posthoc<-regwqComp(x~g)</pre>

With REGWQ

D-C -0.05494531 8.234992e-01 0.02532057

Now μ_A and mu_B are also separated!

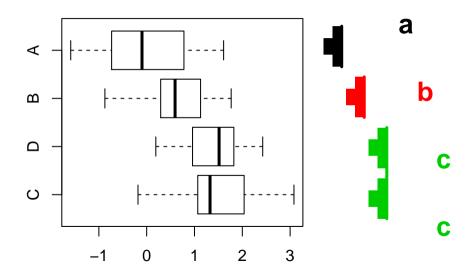
Example REGWQ (6)

Visualize pairs with multcompBoxlot

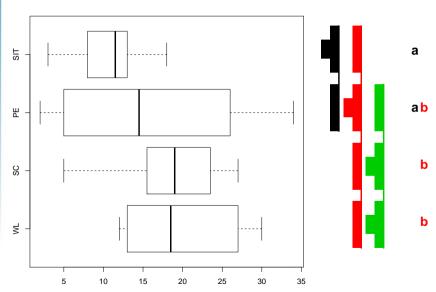
```
require(multcompView)
padj_extract <- function(formula,data){posthoc[,'p adj']}
par(mar=c(4,4,4,4))
multcompBoxplot(x~g,data=d,horizontal=TRUE,compFn="padj_extract")</pre>
```

See next slide for plot

Example REGWQ (8)



One more visualization



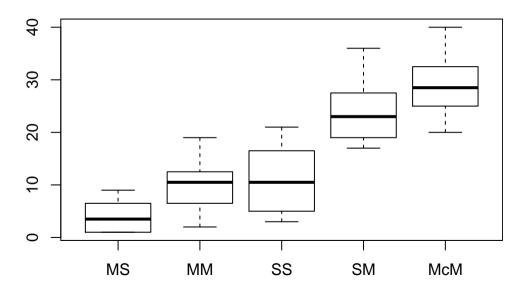
HT's for few pairs or contrasts

Simultaneous		Distributions		
Hypothesis Tests		Normal	Not Normal	
are Type	All pairwise	Tukey-Kramer or Games-Howell (use REGWQ if balanced and equal variances)	Dunn Test if appropriate, other more advanced procedures such as bootstrap	
Compare	Few pairs or contrasts	F or t tests with Bonferroni- Holm adjusted p-values	Pairwise test like Mann Whitney or bootstrap tests + adjusted p-values	

Morphine Again

- Particular comparisons of interest
 - average of MS, MM, SS vs average of SM, McM
 - MM vs McM
 - MS vs SS
 - MM vs SS

Morphine Again (2)



Morphine Again (3)

Test with one-step Bonferroni

The first two contrasts are significant. Note, the third is close ($P_{\rm adi} \approx 0.07$)

Morphine Again (4)

Test with sequential Bonferroni-Holm

```
## ave2 -ave3 18.16667 9.9502931 9.657362e-12 3.862945e-11 1 1 ## McM - MM 19.00000 6.7175144 8.872312e-08 2.661693e-07 1 ## SS - MS 7.00000 2.4748737 1.831864e-02 3.663728e-02 1 ## MM - SS -1.00000 -0.3535534 7.257945e-01 7.257945e-01 0
```

The first three contrasts are significant.

Morphine Again (5)

Test with sequential Benjamin-Hochberg (controls FDR)

```
## ave2 -ave3 18.16667 9.9502931 9.657362e-12 3.862945e-11 1 ## McM - MM 19.00000 6.7175144 8.872312e-08 1.774462e-07 1 ## SS - MS 7.00000 2.4748737 1.831864e-02 2.442485e-02 1 ## MM - SS -1.00000 -0.3535534 7.257945e-01 7.257945e-01 0
```

The first three contrasts are significant.

HT's for non-normal distributions

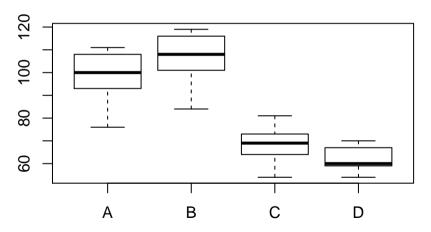
Simultaneous		Distributions		
Hypothesis Tests		Normal	Not Normal	
Compare Type	All pairwise	Tukey-Kramer or Games-Howell (use REGWQ if balanced and equal variances)	Dunn Test if appropriate, other more advanced procedures such as bootstrap	
	Few pairs or contrasts	F or t tests with Bonferroni- Holm adjusted p-values	Pairwise test like Mann Whitney or bootstrap tests + adjusted p-values	

Dunn Test

- nonparametric posthoc pairwise test of location for Kruskal-Wallis Test
- requires same conditions as Kruskal-Wallis Test
- independent samples from distributions
 - with same shape and scale
 - possibly shifted
- p-values still need to be adjusted for multiple comparisons
- p-values are compared to $\alpha/2$ not α

Rain Example

4 cities A,B,C,D have monthly rainfall (mm) recorded for 6 different months



Some skewness, similar shapes and scales \Rightarrow Kruskal-Wallis and Dunn Test OK.

Rain Example (2)

```
require(dunn.test) # install package 'dunn.test' if needed
dunn.test(rainfall,city,method='holm',alpha=.05)
```

```
## Kruskal-Wallis rank sum test
##
## data: rainfall and city
## Kruskal-Wallis chi-squared = 17.8032, df = 3, p-value = 0
```

Output continued on next slide . . .

Rain Example (3)

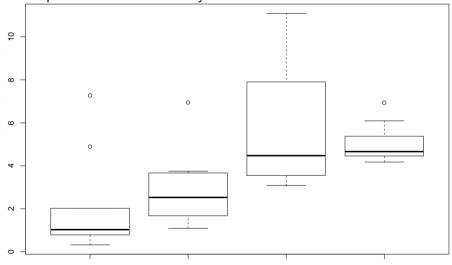
```
##
                           Comparison of rainfall by city
                                       (Holm)
##
## Col Mean-I
## Row Mean |
##
         ВΙ
               0.612772
##
                 0.2700
##
##
               -2.205979 -2.818752
##
                 0.0411 0.0096*
##
##
               -2.982158 -3.594930
                                    -0.776178
##
                 0.0072* 0.0010*
                                        0.4376
```

Non-normal distributions + few contrasts

Simultaneous		Distributions		
Hypothesis Tests		Normal	Not Normal	
Compare Type	All pairwise	Tukey-Kramer or Games-Howell (use REGWQ if balanced and equal variances)	Dunn Test if appropriate, other more advanced procedures such as bootstrap	
	Few pairs or contrasts	F or t tests with Bonferroni- Holm adjusted p-values	Pairwise test like Mann Whitney or bootstrap tests + adjusted p-values	

Synthetic Example

4 samples of size 10 from very skewed distributions.



Synthetic Example (2)

- compare mean of groups A and B to mean of groups C and D
- compare means of A and B
- compare means of C and D
- use bootstrap t-tests in onewayComp()
- can also bootstrap with 'boot' package or 'WRS' package

Synthetic Example (3)

Build the contrast matrix:

```
K = rbind('aveCD - aveAB' = c(-1/2, -1/2, 1/2, 1/2),
B - A' = c(-1, 1, 0, 0),
D - C' = c(0, 0, -1, 1))
```

Synthetic Example (4)

Reject
$$H_0$$
: $\frac{\mu_A + \mu_B}{2} = \frac{\mu_C + \mu_D}{2}$

The other contrasts are not significant.

Big data

Exploring lots of groups looking for differences? Use sequential procedures that control the FDR.

Recap

Mult	riple	Distributions	
Com	parisons	Normal	Not Normal
re Type	All pairwise (posthoc)	Tukey-Kramer, Games-Howell, REGWQ	Dunn Test + adjust, resampling with adjustment, others
Compare	Few pairs or contrasts (planned)	t-intervals + Bonferroni or sequential	Bootstrap or other with adjustment

Appendix: t-tests for contrasts

- Let k be the number of groups and N the pooled sample size.
- The formula for equal variances (next slide) is equivalent to the F
 test statistic in your textbook when all the samples are of size n
 (balanced).

Appendix: t-tests for contrasts (2)

For equal variances, use MSE from ANOVA for pooled variance estimate

$$s_p^2 = \mathsf{MSE} = (n_1 - 1)s_1^2 + (n_2 - 1)s_2^2 + \cdots$$

Now for contrast
$$\Psi = \sum_{i=1}^k a_i \mu_i$$
 we have $t = \frac{\displaystyle\sum_{i=1}^k a_i \overline{x}_i}{\sqrt{s_p^2 \sum_{i=1}^k \frac{a_i^2}{n_i}}}$ with $\mathrm{df} = N - k$.

If samples sizes are balanced with $n=n_1=n_2=\cdots=n_k$, then the square of t is the same as F in the textbook. If there are only two weights $a_m=1, a_n=-1$ this becomes the ordinary pooled t.

Appendix: t-tests for contrast (3)

For unequal variances (or quite unbalanced sample sizes). No pooled variance, but

Welch-like corrected degrees of freedom is harder.
$$t = \frac{\displaystyle\sum_{i=1}^{k} a_i \overline{x}_i}{\sqrt{\displaystyle\sum_{i=1}^{k} \frac{a_i^2 s_i^2}{n_i}}}$$

For df, set
$$w_i = \frac{a_i^2 s_i^2}{n_i}$$
, then $df = \frac{\left(\sum_{i=1}^k w_i\right)^2}{\sum_{i=1}^k \frac{w_i^2}{n_i - 1}}$.

If there are only two weights $a_m = 1$, $a_n = -1$ this becomes the ordinary unpooled t.

A Bad Idea

- It's not OK to inspect the data and then test only the groups with the largest differences
- This is called data snooping.
- You've implicitly tested all of the pairs and so you have an increased risk of Type I errors due to chance.