Chapter 3 - Kuehl

3.1 Treatment comparisons answer research questions

Often questions arise regarding specific treatment means. These may be simply comparing pairs of treatment means, or more complex comparisons among groups of treatment means.

3.2 Linear functions of observations & contrasts

Linear functions of observations (Appendix 3A)

Let \( y_1, \ldots, y_n \) be a sample of random variables.

\[ c = \sum_{i=1}^{n} k_i y_i = k_1 y_1 + \ldots + k_n y_n \] is a linear function of the random variables.

- \( E[y_i] = \mu_i \)
- \( V[y_i] = \sigma_i^2 \)
- \( \text{Cov}(y_i, y_j) = \sigma_{ij} \)

\[ M_c = E(c) = E[\sum_{i}^{n} k_i y_i] = \sum_{i=1}^{n} E[k_i y_i] = \sum_{i=1}^{n} k_i E[y_i] = \sum_{i=1}^{n} k_i \mu_i \]

\[ \sigma_c^2 = V(c) = V[\sum_{i}^{n} k_i y_i] = \sum_{i=1}^{n} k_i^2 V[y_i] + 2 \sum_{i=1}^{n} \sum_{j=i+1}^{n} k_i k_j \text{Cov}(y_i, y_j) \]

\[ = \sum_{i=1}^{n} k_i^2 \sigma_i^2 + 2 \sum_{i=1}^{n} \sum_{j=i+1}^{n} k_i k_j \sigma_{ij} \]
Special Cases

Sample Mean

\[ \overline{Y}_i = \frac{\sum_{i=1}^{n_i} \overline{Y}_i}{n} \]

\[ \mu_e = \frac{1}{n} \sum_{i=1}^{n_i} \bar{Y}_i \]

\[ \sigma^2_e = \frac{1}{n} \sum_{i=1}^{n_i} \sigma_i^2 + 2 \left( \frac{1}{n} \right) \sum_{i=1}^{n_i} \sum_{j=i+1}^{n_i} \sigma_{ij} \]

If this represents a sample of independent observations from a Normal distribution with mean \( \mu \), variance \( \sigma^2 \):

\[ \mu_e = \mu \neq \bar{Y}_i, \quad \sigma^2_e = \sigma^2 \neq \sigma_i^2 = 0 \neq \sigma_{ij} \]

AND sampling dist of \( \overline{Y} \) is normal:

\[ \mu_e = \frac{1}{n} \sum_{i=1}^{n_i} \mu_i = \frac{1}{n} (nm) = \mu \]

\[ \sigma^2_e = \frac{1}{n} \sum_{i=1}^{n_i} \sigma_i^2 = \frac{1}{n} [ \sigma^2 + \sigma^2 ] = \sigma^2 \]

Linear Functions of Sample Means (Independent Sample)

\[ \overline{Y}_i = \text{Sample mean from population } i, \text{ based on sample of } Y_i \]

\[ X = \frac{1}{n} \sum_{i=1}^{n} k_i \overline{Y}_i \]

\[ \mu_e = \frac{1}{n} \sum_{i=1}^{n} k_i \mu_i = \frac{1}{n} \sum_{i=1}^{n} k_i \mu_i \]

\[ \sigma^2_e = \frac{1}{n} \sum_{i=1}^{n} k_i^2 \sigma_i^2 = \frac{1}{n} \sum_{i=1}^{n} k_i^2 \sigma_i^2 \]

Note: \( \text{Cor}(\overline{Y}_i, \overline{Y}_j) = 0 \) when samples are independent as they are in the Completely Randomized Design
Contrasts of Means

Contrasts of Means are linear functions of Means such that the coefficients sum to 0.

Notation:
- Upper case letters = contrast of population means.
- Lower case letters = contrast of sample means.

\[
C = \sum_{i=1}^{t} K_i \bar{\mu}_i \quad \Rightarrow \quad \sum_{i=1}^{t} K_i = 0
\]

\[
C = \sum_{i=1}^{t} K_i \bar{y}_i \quad \Rightarrow \quad \sum_{i=1}^{t} K_i = 0
\]

Note: \( C = \sum_{i=1}^{t} K_i \bar{\mu}_i \) is an unknown parameter that we wish to make inferences about.

Estimator:
\[
C = \sum_{i=1}^{t} K_i \bar{y}_i. \quad \bar{y}_i \sim N(\mu_i, \frac{\sigma^2}{n_i}) \quad \text{under null}
\]

\[
E[C] = E\left[\sum_{i=1}^{t} K_i \bar{y}_i\right] = \sum_{i=1}^{t} K_i E(\bar{y}_i) = \sum_{i=1}^{t} K_i \mu_i
\]

\[
V[C] = V\left[\sum_{i=1}^{t} K_i \bar{y}_i\right] = \sum_{i=1}^{t} K_i^2 \cdot V[\bar{y}_i] = \sum_{i=1}^{t} \frac{K_i^2 \sigma^2}{n_i}
\]

Balanced Data (\( r_1 = r_2 = \cdots = r_t = r \))

\[
\Rightarrow V(C) = \frac{r^2 \sum_{i=1}^{t} K_i^2}{r^2}
\]
Estimated Variance: \( \hat{S}_e^2 = \frac{\hat{S}_e^2}{\frac{1}{t} \sum_{i=1}^{t} k_i^2} \)

Estimated Standard Error: \( \hat{S}_e = \sqrt{\hat{S}_e^2} \)

Interval Estimates for Contrasts

\[ C \pm t_{\frac{\alpha}{2}, N-t} \cdot \hat{S}_e \]

Sum of Squares Partition for Contrast

\[ SSC = \frac{\sum_{i=1}^{t} (\bar{Y}_i - \bar{Y})^2}{\bar{Y}} \]

If Design is Balanced: \( SSC = \bar{Y} \frac{\sum_{i=1}^{t} k_i^2}{N} \)

Hypothesis Tests Regarding Contrasts

\( H_0: C = \sum_{i=1}^{t} k_i m_i = 0 \)

\( H_a: C \neq 0 \)

i) F-Test

\[ T.S. F_0 = \frac{MSC}{MSE} = \frac{SSC/m}{SSE/(N-t)} \]

\[ RR: F_0 \geq F_{k, 1, N-t} \]
(c) \textit{t-test}

T.S. \( t_0 = \frac{\bar{c}}{s_c} \)

\[ \text{RR: } |t_0| \geq t_{\alpha, N-t} \]

\text{Connection Between F-test and t-test}

\[ F_0 = \frac{\text{MSC}}{\text{MSE}} = \frac{\text{SSC}}{s^2} = \frac{1}{s^2} \frac{\sum (k_i \bar{q}_i)^2}{\sum k_i \bar{q}_i^2} \]

\[ t_0 = \frac{\bar{c}}{s_c} = \frac{\sum k_i \bar{q}_i}{s \sqrt{2 \sum k_i^2}} = \frac{\sqrt{F_0}}{s \sqrt{\sum k_i^2}} \]

\[ \Rightarrow t_0^2 = F_0 \]

Also: \( [t_{\alpha, N-t}]^2 = F_{\alpha, N-t} \)

\text{Orthogonal Contrasts}

Two contrasts are orthogonal if the sum of the products of their coefficients is 0 (when weighted by reciprocal of sample sizes).

\[ C = \sum_{i=1}^t k_i \bar{q}_i, \quad D = \sum_{i=1}^t d_i \bar{q}_i \]

\[ C \parallel D \text{ are orthogonal if } \frac{\sum_{i=1}^t k_i d_i}{t} = 0 \]

Note: if all \( r_i \) are =, then \( C \parallel D \) orthogonal if \[ \sum_{i=1}^t k_i d_i = 0 \]
NOTE: If we have \( k-1 \) pairwise orthogonal contrasts, their sums of squares will add up to the treatment sum of squares. That is, we can partition the treatment sum of squares into \( k-1 \) pairwise orthogonal contrasts.

**Example - Placebo Controlled Trial for Arthroscopic Knee Surgery** (assuming \( r_1 = r_2 = r_3 = r = 54 \))

**TRT 1 - Placebo** \( \bar{y}_1 = 53.6 \) \( s_1 = 22.1 \) \( r_1 = 54 \)

**TRT 2 - Lavage (Active)** \( \bar{y}_2 = 57.8 \) \( s_2 = 23.5 \) \( r_2 = 57 \)

**TRT 3 - Débridement (Active)** \( \bar{y}_3 = 53.3 \) \( s_3 = 25.4 \) \( r_3 = 51 \)

**Case 1 - Treating Data as Balanced \((r = 54)\)**

<table>
<thead>
<tr>
<th>TRT</th>
<th>( r_i )</th>
<th>( \bar{y}_i )</th>
<th>( s_i )</th>
<th>( r_i (\bar{y}<em>i - \bar{y}</em>{..})^2 )</th>
<th>( (r_i-1) s_i^2 )</th>
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<tr>
<td>1</td>
<td>54</td>
<td>53.6</td>
<td>22.1</td>
<td>91.26</td>
<td>2598.573</td>
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<td>57.8</td>
<td>23.5</td>
<td>454.14</td>
<td>2926.25</td>
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<tr>
<td>3</td>
<td>54</td>
<td>53.3</td>
<td>25.4</td>
<td>137.24</td>
<td>34193.79</td>
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</tbody>
</table>

\( \bar{y}_{..} = 54.9 \)

\( \sum_{i=1}^{k} s_i^2 = 683.64 \)

\( \sum_{i=1}^{k} (\bar{y}_i - \bar{y}_{..})^2 = 89381.46 \)

\( M_S T = \frac{\sum_{i=1}^{k} r_i}{k-1} = \frac{683.64}{21} = 34.182 \)

\( M_S E = \frac{\sum_{i=1}^{k} s_i^2}{N-k} = \frac{89381.46}{162-3} = 561.94 \)

\( F_0 = \frac{341.82}{561.94} = 0.61 \)

\( F_{0.05, 2.160} \approx 3.07 \) (Bonferroni)
Consider 2 contrasts:

**Contrast 1: Placebo vs 2 Actives**

\[ C = 2 \mu_1 - \mu_2 - \mu_3 \]

(This is equivalent to comparing \( \mu_1 \) vs mean of \( \mu_2 \) and \( \mu_3 \), but math is easier when working with integers.)

\[ k_1 = 2, \ k_2 = -1, \ k_3 = -1 \Rightarrow \sum k_i = 0 \]

\[ C = 2 \bar{y}_1 - \bar{y}_2 - \bar{y}_3 = 2(53.6) - 57.8 - 53.3 = -3.90 \]

\[ S_c^2 = \frac{\sum k_i^2}{\sum k_i^2} = 561.94 \left[ \frac{4 + 1 + 1}{54} \right] = \frac{561.94}{54} = 10.44 \]

\[ S_c = \sqrt{10.44} = 3.24 \]

95% CI for \( C = 2 \mu_1 - \mu_2 - \mu_3 \)

\[ C \pm t_{0.025, 54} \cdot S_c \Rightarrow C \pm 2.025 \cdot 3.24 \]

\[ -3.90 \pm 1.96(3.24) \Rightarrow -3.90 \pm 15.99 \Rightarrow (-19.39, 11.59) \]

\[ SSC = 9 (-3.90)^2 = 136.89 \]

Do F-test;confirm equivalence to t-test.
**ARThROSCOPIC SURGERY EXAMPLE CONTINUED**

**Contrast 2 - LAVAGE vs. DÉBRIDEMENT (Comparison of Averages)**

\[
D = \mu_2 - \mu_3 \\
d_i = 0, \ c_i = 1, \ d_i = -1, \ z_i = 0
\]

\[
d = \bar{y}_i - \bar{y}_3 = 57.8 - 53.3 = 4.5
\]

\[
s^2_d = s^2 \sum_{i=1}^{5} \frac{k_i}{n_i} = 561.94 \left[ \frac{0 + 1 + 1}{5} \right] = \frac{561.94}{2} = 20.61
\]

\[
s_d = 4.54
\]

95% CI for \( \mu_2 - \mu_3 \)

\[
d \pm 2.051 \cdot s_d \equiv 4.5 \pm 1.96 \cdot (4.54) \equiv 4.5 \pm 8.94
\]

\[
= (-4.44, 13.44)
\]

Contains 0.

\[
SSD = \frac{\sum (z_i d_i)^2}{z_i^2} = 5 \frac{(4.5)^2}{(0 + 1 + 1)} = 27 \frac{(4.5)^2}{2} = 546.75
\]

Conduct F-test and confirm equivalence to the F-test.

**Note:** \( \sum k_i d_i = 2(0) + (-1)(1) + (-1)(1) = 0 - 1 - 1 = -2 \) or orthogonal under equal reps “assumption.”

\[
SSC + SSD = 136.89 + 546.75 = 683.64 = SST
\]

(SST has 2 df, we have 2 orthogonal contrasts.)
CASE 2 - ACTUAL SAMPLE SIZES (UNBALANCED)

\[
\begin{array}{cccc}
\mathbf{i} & \mathbf{K_i} & \mathbf{d_i} & \mathbf{r_i} & \mathbf{\frac{K_i d_i}{r_i}} \\
1 & 2 & 0 & 54 & \frac{0}{54} \\
2 & -1 & 1 & 57 & \frac{-1}{57} \\
3 & -1 & -1 & 51 & \frac{1}{51} \\
\end{array}
\]

\[\sum_{j=1}^{3} \frac{K_i d_i}{r_i} = \frac{0(57)(51) + (-1)(54)(51) + (1)(54)(57)}{54(57)(51)} - \frac{-2754 + 3078}{156978} = \frac{324}{156978} \neq 0\]

To get an orthogonal contrast, start with the second (d) contrast and leave it as

\[d = \frac{\bar{Y}_2 - \bar{Y}_3}{\bar{Y}_2 - \bar{Y}_3}\] (d1 = 0, d2 = 1, d3 = -1)

- Now select the coefficients of the first contrast that have the same weights as their sample sizes (e.g. K1 = 57, K2 = 51). Since these are divisible by 3, we can use K1 = 19 and K2 = 17.

- Finally choose K1 so that the coefficients for contrast 1 sum to 0 (definition of contrast). This implies K1 = -(57 + 51) = -108. We could also have had K1 = 108, K2 = -57, K3 = -51.

- Checking for orthogonality (K1 = 108, K2 = -57, K3 = -51)

\[\sum_{j=1}^{3} \frac{K_i d_i}{r_i} = \frac{108(0)}{54} + \frac{(-57)(1)}{57} + \frac{(-51)(-1)}{51} = 0 - 1 + 1 = 0\]
### ANOVA for Unbalanced Data (Actual Sample Sizes)

<table>
<thead>
<tr>
<th>i</th>
<th>$n_i$</th>
<th>$\bar{y}_i$</th>
<th>$S_i$</th>
<th>$r_i(\bar{y}_i - \bar{y})^2$</th>
<th>$(r_i - 1)S_i^2$</th>
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<tbody>
<tr>
<td>1</td>
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<td>53.6</td>
<td>22.1</td>
<td>103.335</td>
<td>23885.73</td>
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<tr>
<td>3</td>
<td>51</td>
<td>53.3</td>
<td>25.4</td>
<td>144.514</td>
<td>32258.00</td>
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</table>

$$\bar{y} = \frac{54(53.6) + 57(57.8) + 51(53.3)}{54 + 57 + 51} = \frac{8907.3}{162} = 54.983$$

- Note slight changes in $SS_T$ and $SS_E$ from having treated data as balanced. Would have been much lower had the degree of unbalance been higher.

$$C_0 = \sum k_i\bar{y}_i = 108\bar{y}_1 - 57\bar{y}_2 - 51\bar{y}_3.$$  
$$= 108(53.6) - 57(57.8) - 51(53.3)$$  
$$= 5798.8 - 3294.6 - 2718.3 = 224.90$$  
$$\sum k_i^2/r_i = \frac{108^2}{54} + \frac{(-57)^2}{57} + \frac{(-51)^2}{51} = 4(54) + 57 + 51 = 324$$  
$$SSC = \frac{(-224.90)^2}{324} = 155.0025$$

- $d = \sum d_i\bar{y}_i = 0\bar{y}_1 + \bar{y}_2 - \bar{y}_3 = 57.8 - 53.3 = 4.5$  
$$\sum d_i^2/r_i = \frac{0^2}{54} + \frac{1}{57} + \frac{1}{51} = 0.037151703$$  
$$SSD = \frac{(4.5)^2}{0.037151703} = 545.0625$$  
$$SSC + SSD = 155.0025 + 545.0625 = 700.065 = SST$$
Response Curves for Quantitative Treatments

- Sometimes treatment levels are quantitative (e.g., dose of drug, amount or intensity of exposure to stimulus, density of experimental units).

- When the treatments are quantitative, it may be that a polynomial response function can describe the relationship between $E(Y) \sim X$ (treatment).

- The treatment sum of squares can be partitioned into $t-1$ orthogonal polynomials using coefficients provided in Table XI - p. 623 for various values of $t$. See plots in Kuehl (p. 52) for linear, quadratic, and cubic terms.

**Example** - Dose response studies in laboratory animals w/ $t=10$ doses ($0, 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 4.5, 5, 5.5, 6, 6.5, 7, 7.5, 8, 8.5, 9, 9.5$) and $r=6$ animals/dose.

We will fit the first 6 polynomials (orthogonal) as that is the highest order Kuehl gives coefficients for, and these account for 99% of the treatment sum of squares.

\[ F_{0.05, 5, 50} = 2.04 \]

\[ F' = \frac{MSE}{MVT} = \frac{27506.94}{g} \]

\[ SSE = (6.1 - \bar{x})^2 \times \frac{706.90}{g} \]

\[ SS\bar{y} = 6.1 \times (y_{\bar{y}}^2) = 27506.94 \]

<table>
<thead>
<tr>
<th>( y_i )</th>
<th>( y_{\bar{y}} )</th>
<th>( y_{\bar{y}} - y_i )</th>
<th>( (y_{\bar{y}} - y_i)^2 )</th>
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<td>7.04</td>
<td>10.04</td>
<td>3.00</td>
<td>9.00</td>
</tr>
</tbody>
</table>

\[ \sum (y_{\bar{y}} - y_i)^2 = 27506.94 \]

\[ \bar{y} = \frac{\sum y_i}{n} = 7.04 \]

\[ S = 2.00 \]

\[ \sum (y_{\bar{y}} - y_i)^2 = 27506.94 \]

\[ S = 2.00 \]

\[ n = 10 \]

\[ \sum (y_{\bar{y}} - y_i)^2 = 27506.94 \]

\[ S = 2.00 \]

\[ n = 10 \]
### Orthogonal Polynomial Coefficients ($P_{ij}$)

<table>
<thead>
<tr>
<th>Dose ($x_i$)</th>
<th>$Y_i$</th>
<th>$\text{MEAN}$</th>
<th>$\text{LINEAR} \ P_{ij}$</th>
<th>$\text{QUADRATIC} \ P_{ij}$</th>
<th>$\text{CUBIC} \ P_{ij}$</th>
<th>$\text{QUARTIC} \ P_{ij}$</th>
<th>$\text{QUINTIC} \ P_{ij}$</th>
<th>$\text{SEXTIC} \ P_{ij}$</th>
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<td>18</td>
<td>6</td>
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</tr>
</tbody>
</table>

$\bar{Y} = \frac{\sum Y_i}{n}$

$\sum Y_i = 506.40 \quad 1172.10 \quad (-13.10) \quad (-12.10) \quad (-64.43) \quad 69.70 \quad 210.90 \quad 105.30 \quad 660$

$\overline{P_{ij}} = \frac{\sum P_{ij}Y_i}{\sum Y_i}$

$\overline{P_{ij}^2} = \frac{\sum P_{ij}^2}{\sum Y_i}$

$\sum P_{ij}^2 = 2491.30 \quad 190.72 \quad 8.51 \quad 342.14 \quad 985.88$

$\sum P_{ij}Y_i = 506.40 \quad 3.55 \quad -0.10 \quad -0.19 \quad 0.022 \quad 0.27 \quad 0.16$

$\sum P_{ij}^2 = 5.2$
Analysis of Variance (up to Sextic Terms)

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<thead>
<tr>
<th>Source</th>
<th>df</th>
<th>SS</th>
<th>MS</th>
<th>F</th>
<th>F_{0.05}</th>
<th>F_{0.01}</th>
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<tbody>
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<td>Dose</td>
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<tr>
<td>Error</td>
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<table>
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<tbody>
<tr>
<td>Linear</td>
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<td>24991.30</td>
<td>24991.30</td>
<td>415.97</td>
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<tr>
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<td>7.80</td>
<td>0.13</td>
<td>4.04</td>
<td></td>
</tr>
<tr>
<td>Cubic</td>
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<td>1890.72</td>
<td>31.47</td>
<td>4.04</td>
<td></td>
</tr>
<tr>
<td>Quartic</td>
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<td>8.51</td>
<td>8.51</td>
<td>0.14</td>
<td>4.04</td>
<td></td>
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<tr>
<td>Quintic</td>
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<td>342.14</td>
<td>342.14</td>
<td>5.69</td>
<td>4.04</td>
<td></td>
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<tr>
<td>Sextic</td>
<td>1</td>
<td>98.90</td>
<td>98.90</td>
<td>1.65</td>
<td>4.04</td>
<td></td>
</tr>
</tbody>
</table>

All other terms sum to 27506.94 - 27210.47 = 266.47, so it is highly unlikely any high order terms are significant. Why?

Obtaining predicted values for the 10 doses:

\[ \hat{y}_i = \hat{y}_0 + \sum_{j=1}^{6} \hat{\alpha}_j p_j; \quad i = 1, \ldots, 10 \]

For dose 0:

\[ \hat{y}_0 = 50.64 + 3.55(-9) + (-0.10)(6) + (-0.19)(-12) \]
\[ + 0.022(18) + 0.22(-6) + 0.16(3) \]
\[ = 50.64 - 31.95 - 0.60 + 7.98 + 0.40 - 1.44 + 0.16 = 25.33 \]

(Fitted values for all doses are given on p. 3.10)
Dose Response Study – Orthogonal Polynomial Contrasts

![Graph showing dose response study with 6th and 5th degree polynomial contrasts.](image)
\[ \text{Var}(\hat{\alpha}_c) = \text{Var}\left( \frac{\sum p_{c_i} \bar{Y}_{c_i}}{\sum p_{c_i}} \right) = \left[ \frac{1}{\sum p_{c_i}} \right]^2 \sum p_{c_i}^2 \text{Var}(\bar{Y}_{c_i}) \]

\[ = \left[ \frac{1}{\sum p_{c_i}} \right]^2 \left( \sum p_{c_i} \right) \frac{s^2}{r} = \frac{s^2}{\sum p_{c_i}} \]

\[ \Rightarrow S_{\hat{\alpha}_c}^2 = \frac{s^2}{\sum p_{c_i}} \]

\[ s_{\hat{\alpha}_i}^2 = S_{\hat{\alpha}_i}^2 + \sum_{j=1}^{6} p_{c_i}^2 s_{\hat{\alpha}_j}^2 \quad i = 1, \ldots, 6 \]

Don't need to worry about covariances since these are orthogonal polynomials.

\[ \text{Note:} \quad S^2 = \text{MSE} = 60.08 \quad r = 6 \quad S_{\hat{\theta}_i}^2 = \frac{s^2}{r} = \frac{60.08}{6} \approx 10 \]

For dose 0:

\[ S_{\hat{\alpha}_0}^2 = S_{\hat{\theta}_0}^2 + p_{1c}^2 S_{\hat{\theta}_1}^2 + p_{2c}^2 S_{\hat{\theta}_2}^2 + p_{3c}^2 S_{\hat{\theta}_3}^2 + p_{4c}^2 S_{\hat{\theta}_4}^2 + p_{5c}^2 S_{\hat{\theta}_5}^2 + p_{6c}^2 S_{\hat{\theta}_6}^2 \]

\[ = 1.00 + (-0.1)^2(0.0303) + 6^2(0.0759) + (-4)^2(0.0003) + 18^2(0.0035) \]

\[ + (-6)^2(0.0128) + 3^2(0.0157) = \]

\[ = 1.00 + 0.0265 + 2.73 + 2.12 + 1.08 + 0.46 + 0.14 = 10.03 \quad \Rightarrow S_{\hat{\theta}_0}^2 = 3.17 \]

(Std. errors for all fitted values are given on Table on p.3.12)
3.4 Multiple Comparisons Affect Error Rates

- \( \alpha_c \) is the comparison-wise error rate for a single comparison.
- With \( t \) trt means, there are \( \binom{t}{2} \) possible comparisons. We can make up to \( \binom{t}{2} \) type I errors if all \( t \) means are equal.
- \( \alpha_E \) is experiment-wise error rate = accumulated risks for the individual comparisons.

Obtaining the maximum error rate

\[
N = \binom{t}{2} \text{ tests of the form } t_0 = \frac{\bar{Y}_i - \bar{Y}_j}{\sqrt{\frac{S_i^2}{n_i} + \frac{S_j^2}{n_j}}}
\]

(Note: These tests are not independent since they share common variance estimates and sample means.)

- Upper limit for Type I error rate (experiment-wise) can be obtained assuming independence.
- Assume \( H_0: \mu_i - \mu_j = 0 \) is true \( \forall (i, j) \)
- \( \Pr \{ \text{Type I error} \} = \alpha_c \Rightarrow \Pr \{ \text{Correct decision} \} = 1 - \alpha_c \)
- Let \( X \) = # of Type I errors: \( X \sim \text{Bin}(N, \alpha_c) \)
- \( \Rightarrow \Pr(X = x) = \binom{N}{x} \alpha_c^x (1-\alpha_c)^{N-x} \quad x = 0, 1, \ldots, N \)
- \( \Rightarrow \Pr \{ \text{No Type I errors} \} = \Pr(0) = (1-\alpha_c)^N \)
- \( \Rightarrow \Pr \{ \text{At least 1 Type I error} \} = 1 - (1-\alpha_c)^N = \alpha_E \)
- \( \Rightarrow \) Solving for \( \alpha_c \) that gives prescribed \( \alpha_E \): \( \alpha_c = 1 - (1-\alpha_E)^{1/N} \)
2 Types of Experimentwise Error Rate

1. Weak Sense - Defined under configuration $M_1 = \ldots = M_c$
2. Strong Sense - Probability of at least one wrong decision overall parameter configurations.

Strang: Error RATE = $\sup_{\{M\}} \left[ \text{at least one incorrect decision} \right]$

Weak $\leq$ Strong when supremum occurs $\hat{M}_1 = M_1 = \ldots = M_c$

3.5 Simultaneous Statistical Inference

Types of Contrasts Constructed

- Planned Contrasts among treatment means
- Orthogonal Polynomial Contrasts
- Multiple Comparisons with the best treatment
- "..." Control
- All pairwise comparisons

Strength of Inference (Each will give levels of confidence)

Strong
- Simultaneous Confidence Intervals $\Rightarrow$ direction & magnitude
- Confident Directions $\Rightarrow$ Direction only ($C_i \geq 0, C_i < 0$)
- Confident Inequalities $\Rightarrow$ Inequality only ($C_i \neq 0$)

Weak
- Individual comparisons $\Rightarrow$ Ignore Simultaneity of inference

We will focus on simultaneous 2-sided CIs, the strongest inferences.
Bonferroni's Inequality (very general approach to simultaneous inference)

- \( \alpha_e = \sum_{i=1}^{n} \alpha_{ci} = n \alpha_c \) when there are \( n \) comparisons, each conducted at level \( \alpha = \alpha_c \)

- \( \Rightarrow \) for a chosen experimentwise error rate \( \alpha_e \), conduct each at \( \alpha_c = \frac{\alpha_e}{n} \) (conservative due to inequality above)

<table>
<thead>
<tr>
<th>( n )</th>
<th>( \alpha_e )</th>
<th>( \alpha_c )</th>
</tr>
</thead>
<tbody>
<tr>
<td>3</td>
<td>0.05</td>
<td>0.0167</td>
</tr>
<tr>
<td>3</td>
<td>0.01</td>
<td>0.0033</td>
</tr>
<tr>
<td>4</td>
<td>0.05</td>
<td>0.0125</td>
</tr>
<tr>
<td>4</td>
<td>0.01</td>
<td>0.0025</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>0.05</td>
<td>0.0050</td>
</tr>
<tr>
<td>10</td>
<td>0.01</td>
<td>0.0010</td>
</tr>
</tbody>
</table>

Table V pp. 595-6

Give \( \xi_{k,v} \) for:
\( \alpha = 0.01, 0.05 \)
\( k = \# of comparisons \) (C51)
\( v = \text{Error df} \)
(degree of freedom associated with \( s^2 \)).

Algorithm

1. Identify \( k \) contrasts of interest: \( C_i = \sum_{j=1}^{k} C_{ij} M_j \), \( i = 1, \ldots, k \)
2. Compute \( k \) estimators: \( \hat{C}_i = \sum_{j=1}^{k} C_{ij} \overline{Y}_j \), \( i = 1, \ldots, k \)
3. Compute \( k \) standard errors: \( S_{C_i} = \sqrt{s^2 \sum_{j=1}^{k} \frac{C_{ij}^2}{n_j}} \), \( i = 1, \ldots, k \)
4. Compute \( k \) simultaneous (1-\( \alpha \))100\% confidence intervals:

\[
CI \text{ for } C_i: \hat{C}_i \pm t \frac{S_{C_i}}{\sqrt{n}} \quad i = 1, \ldots, k
\]
Scheffe's Test for all possible Comparisons (Contrasts)

- Good for all possible linear contrasts of \( \{ x_i \} \) simultaneously with \( \alpha \).

Algorithm

1. Identify \( k \) contrasts of interest: \( C_i = \sum_{j=1}^{k} c_{ij} y_j \), \( i = 1, \ldots, k \).
2. Compute \( k \) estimates: \( \hat{C}_i = \frac{1}{k} \sum_{j=1}^{k} \hat{y}_j \), \( i = 1, \ldots, k \).
3. Compute \( k \) std. errors:
   \[
   S_{C_i} = \sqrt{\frac{1}{k} \sum_{j=1}^{k} \frac{S_{y_j}^2}{\hat{y}_j}} \quad i = 1, \ldots, k.
   \]
4. Compute \( k \) simultaneous \( 100(1-\alpha \epsilon) \) % C.I's:
   \[
   C_i \pm \sqrt{k-1} \frac{F_{\alpha \epsilon, k-1, \nu}}{S_{C_i}} \quad i = 1, \ldots, k.
   \]
3.6 Multiple Comparisons of the Best TAT

Goal: To determine the best treatment (or a subset of treatments that contain the best).

Assume that high scores are good (obvious adjustment for case where low scores are good).

**Constrained MCB Algorithm** (Interval Must Contain 0)

1. Identify parameters of interest: \( M_i = \max_{j \neq i} \bar{Y}_{ij} \\quad i = 1, \ldots, t \)

   \( M_i = \max M_j > 0 \Rightarrow TAT_i \text{ best} \)

   \( M_i = \max M_j < 0 \Rightarrow TAT_i \text{ not best} \)

2. Compute sample analogues to (1)

   \( O_i = \bar{Y}_{i.} - \max_{j \neq i} \bar{Y}_{ij} \)

   \( i = 1, \ldots, t \)

3. Compute critical quantity

   \( M = d \alpha, k, v \sqrt{2 \bar{s}^2} \)

   \( k = t \text{ comparisons} \)

   \( V \text{ Error df (t(r-1))} \)

   \( d, \alpha, k, v \text{ values given in Table VI p. 597-600} \)

   \( \alpha = 0.05, 0.01 \quad 1 - \alpha \text{ 2-sided tests} \)

   Use 1-sided

4. Lower Bound:

   \( L = \begin{cases} D_i - M & \text{if } D_i - M < 0 \\ 0 & \text{otherwise} \end{cases} \)

5. Upper Bound:

   \( U = \begin{cases} D_i + M & \text{if } D_i + M > 0 \\ 0 & \text{otherwise} \end{cases} \)
(5) If interval includes 0 or has a lower bound of 0, M_i is one of the highest (t_i is one of the best). If the upper bound of interval is 0, t_i is not one of the best.

**Example - 3 Treatments for HIV**

- **Response:** Y = AREA UNDER LN(C0Y) CURVE vs. TIME CURVE (SHAPES CAN BE +/-)
  
  - t = 3 Treatments
  
  \[ \begin{align*}
  \text{TAT 1: SQuinavir, Zidovudine, Zalcitabine (3A) Week} \\
  \text{TAT 2: SQV, 210 (5Z) } & \text{TAT 3: 2108, 216 (28)}
  \end{align*} \]
  
  - \( r = 90 \) rep / treatment

<table>
<thead>
<tr>
<th>TAT</th>
<th>( \bar{y}_i )</th>
<th>( s_i )</th>
</tr>
</thead>
<tbody>
<tr>
<td>SQ2</td>
<td>90</td>
<td>12.2</td>
</tr>
<tr>
<td>S2</td>
<td>90</td>
<td>5.1</td>
</tr>
<tr>
<td>22</td>
<td>90</td>
<td>-0.3</td>
</tr>
</tbody>
</table>

\[ \bar{y} = 5.57 \]

\[ d_{0.05,3,267} \approx 2.07 \quad (\text{ inexplicably between } n=120, \infty) \]

\[ M = 2.07 \sqrt{2(3.24)} / 90 = 6.15 \]

i. \[ \frac{1}{3} (M_i - \max M_j) \quad \mathcal{U}(\cdot) \]

1. 0 (since 7.1 \leq 6.15 < 0) = 7.1 + 6.15 = 13.25
2. -7.1 - 6.15 = -13.25 0 (since -7.1 + 6.15 < 0)
3. -12.5 - 6.15 = -18.65 0 (-12.5 + 6.15 < 0)

**Conclude SQ2 is the unique best TAT**
Multiple Comparison with the Smallest Mean

- Parameter: \( M_i = \min_{j \neq i} M_j \) \( i = 1, ..., t \)
- Estimate: \( \bar{D}_i = \bar{Y}_i - \min_{j \neq i} \bar{Y}_j \) \( i = 1, ..., t \)

\[
L = \begin{cases} 
D_i - M & \text{if } D_i - M < 0 \\
0 & \text{otherwise}
\end{cases}
\]

\[
U = \begin{cases} 
D_i + M & \text{if } D_i + M > 0 \\
0 & \text{otherwise}
\end{cases}
\]

- Decision Rule: If interval includes 0 or has 0 as an upper bound, \( \bar{Y}_i \) is one of best. If interval has 0 for lower bound, \( \bar{Y}_i \) is not one of best.

See Koch p. 102 for example of Meat Storage

3.7 Comparison of All Treatments to a Control

- Goal: Compare \( t-1 \) "active" treatments to a control.
- Can make use of 1-sided (direction chosen prior to observing data) or 2-sided simultaneous confidence intervals.
- Often helpful to identify control group as group \( t \) or group 1 (or some other group).
Algorithm

- Parameter: \( M_i - M_c \) \( i = 1, \ldots, t-1 \)
- Estimate: \( \overline{Y}_c - \overline{Y}_c \) \( i = 1, \ldots, t-1 \)
- Standard Error: \( S_{\overline{Y}_c - \overline{Y}_c} = \sqrt{\frac{\sigma^2}{n}} \) \( (r_i = r_2 = \ldots = r_t) \)
- Table value \( \alpha, k, v \) (Dunn's Table)
  
  Table VII pp. 597-600
  
  \( \alpha = .05, .01 \)
  
  \( k = \# \text{ of comparisons} = t-1 \)
  
  \( v = \text{df correction} = t(r-1) \)
  
  1-sided & 2-sided

2-Sided Simultaneous \((1-\alpha)100\%\) CI's for \( M_i - M_c \)

\[
\left( \overline{Y}_c - \overline{Y}_c \right) \pm t_{\alpha, k, v} \cdot S_{\overline{Y}_c - \overline{Y}_c} \quad (i = 1, \ldots, t-1)
\]

2-sided

Determine differences wrt control by range of values in interval

1-sided (Lower Bound) \((1-\alpha)100\%\) CI's for \( M_i - M_c \)

\[
\left[ \left( \overline{Y}_c - \overline{Y}_c \right) - \frac{d_{\alpha, k, v} \cdot S_{\overline{Y}_c - \overline{Y}_c}}{1-sided} \right]
\]

1-sided

1-sided (Upper Bound) \((1-\alpha)100\%\) CI's for \( M_i - M_c \)

\[
\left( -\infty, \left( \overline{Y}_i - \overline{Y}_c \right) + \frac{d_{\alpha, k, v} \cdot S_{\overline{Y}_c - \overline{Y}_c}}{1-sided} \right]
\]
EXAMPLE: Bovine Growth Hormone: Human Food Safety Evaluation

**Goal:** Study effect of various doses of rBGH on Body weight change (g) on male rats (85 days)

**Treatments:**
1. Control: 0 rBGH (mg/kg per day)
2. Subcutaneous: 1 rBGH injected
3. Oral: 0.1 mg/kg oral
4. **0.5**
5. **5.0**
6. **50.0**

**Research Hypotheses:**
(A) Positive effect for TTR 2 (Positive contrast)
(B) No effects among TTRS 3-6

<table>
<thead>
<tr>
<th>TTR</th>
<th>( \bar{y}_i )</th>
<th>( S_i )</th>
<th>( S_{(7,i-7,c)}^2 )</th>
<th>( S_{(7_i-7_c)^2} )</th>
<th>( 7_i-7_c )</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>30</td>
<td>39.2</td>
<td>10083.3</td>
<td>44562.56</td>
<td>8124.35</td>
</tr>
<tr>
<td>2</td>
<td>30</td>
<td>60.3</td>
<td>241203.3</td>
<td>44562.56</td>
<td>10083.3</td>
</tr>
<tr>
<td>3</td>
<td>30</td>
<td>53.0</td>
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<td>44562.56</td>
<td>10083.3</td>
</tr>
<tr>
<td>4</td>
<td>30</td>
<td>53.0</td>
<td>17763.3</td>
<td>44562.56</td>
<td>10083.3</td>
</tr>
<tr>
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<td>30</td>
<td>46.3</td>
<td>9013.3</td>
<td>44562.56</td>
<td>10083.3</td>
</tr>
<tr>
<td>6</td>
<td>30</td>
<td>43.0</td>
<td>6163.3</td>
<td>44562.56</td>
<td>10083.3</td>
</tr>
</tbody>
</table>

\[ S = 291280 \]
\[ S_{SE} = 3953.67 \]

2-Sided simultaneous 95% CI:
\[ K = k-1 = 6-1 \times 5 \]
\[ V = t(\nu-1) = \nu(30-1) = 174 \]
\[ 105.2, 174 \]

Pivotal Quantities:
\[ t_{5,0.025} = 2.25 \]

<table>
<thead>
<tr>
<th>TTR</th>
<th>( \bar{y}_i-\bar{y}_c )</th>
<th>95% CI</th>
<th>Different from Control?</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>108</td>
<td>(-76.7, 139.2)</td>
<td>Yes</td>
</tr>
<tr>
<td>3</td>
<td>3</td>
<td>(-28.2, 34.2)</td>
<td>No</td>
</tr>
<tr>
<td>5</td>
<td>-6</td>
<td>(-37.2, 25.2)</td>
<td>No</td>
</tr>
<tr>
<td>6</td>
<td>4</td>
<td>(-27.2, 35.2)</td>
<td>No</td>
</tr>
</tbody>
</table>
3.8 Pairwise Comparison of All Treatments

- **Goal:** Compare all pairs of treatment means

\[ t(\bar{x}_i - \bar{x}_j) = \frac{t(x_i - x_j)}{\sqrt{s^2_x + s^2_y}} \quad \text{for} \quad i < j \]

1. **Bonferroni's Approach**

   Choose \( k = \frac{t(x_i - x_j)}{r} \) and apply Bonferroni's method described previously.

2. **Tukey's Honestly Significant Difference**

   Studentized Range Distribution.

   Suppose \( y_1, y_2, \ldots, y_s \sim N(\mu, \sigma^2) \)

   Then \( \frac{\text{max } y_i - \text{min } y_i}{s} \sim F_{s, \nu} \)

   where \( s \) is sample size, \( \nu \) is degrees of freedom for \( s \).

   Critical values of \( q \) are given in Table VII, Pp. 601-2 for tail areas \( \alpha = .05, .01 \).
Application to multiple comparisons

\[ \overline{Y}_i \sim N(M_i, \frac{s^2}{n_i}) \quad i = 1, \ldots, k \]

(Assume \( s_i = s = \cdots = s_k \))

\[ \text{independent in CRD} \]

\[ \overline{Y}_i - M_i \sim N(0, \frac{s^2}{n_i}) \]

\[ s^2 = \text{MSE is estimate of } \sigma^2 \]

\[ \frac{s}{\sqrt{v}} = t(c-1) \text{ df} \]

\[ \Rightarrow \quad \frac{\max(\overline{Y}_i - M_i) - \min(\overline{Y}_i - M_i)}{s/\sqrt{v}} \sim F(c, v) \]

\[ \Rightarrow \quad p \leq \max(\overline{Y}_i - M_i) - \min(\overline{Y}_i - M_i) \geq q_{k,v} \cdot \sqrt{\frac{\chi^2}{v}} \]

\[ = \max(\overline{Y}_i - M_i) - \min(\overline{Y}_i - M_i) \geq q_{k,v} \cdot \sqrt{\frac{\chi^2}{v}} \]

\[ \Rightarrow \quad p \leq \max(\overline{Y}_i - M_i) - \min(\overline{Y}_i - M_i) \geq q_{k,v} \cdot \sqrt{\frac{\chi^2}{v}} \]

\[ \Rightarrow \quad p \leq \max(\overline{Y}_i - M_i) - \min(\overline{Y}_i - M_i) \geq q_{k,v} \cdot \sqrt{\frac{\chi^2}{v}} \]

\[ = 1 - \alpha \]

(since the equality holds for least difference)

\[ = \Rightarrow \quad p \leq \max(\overline{Y}_i - M_i) - \min(\overline{Y}_i - M_i) \geq q_{k,v} \cdot \sqrt{\frac{\chi^2}{v}} \]

\[ = \Rightarrow \quad p \leq q_{k,v} \cdot \sqrt{\frac{\chi^2}{v}} \]

\[ \Rightarrow \quad p \leq q_{k,v} \cdot \sqrt{\frac{\chi^2}{v}} \]

\[ \Rightarrow \quad p \leq q_{k,v} \cdot \sqrt{\frac{\chi^2}{v}} \]

\[ \Rightarrow \quad p \leq q_{k,v} \cdot \sqrt{\frac{\chi^2}{v}} \]

\[ = \Rightarrow \quad p \leq q_{k,v} \cdot \sqrt{\frac{\chi^2}{v}} \]

\[ \Rightarrow \quad (1 - \alpha) 100\% \text{ simultaneous CI's for } M_i - M_j \text{ (Tukey's HSD)} \]

\[ (\overline{Y}_i - \overline{Y}_j) \pm q_{k,v} \cdot \sqrt{\frac{s^2}{n_i}} \]

Notes:
1. Does not use \( s_i \) from Studentized Range Distribution.
2. Does not use \( s.e. (\overline{Y}_i - \overline{Y}_j) \) explicitly.
Tests of Homogeneity: \( \mu_1 = \mu_2 = \cdots = \mu_k \)

Tests set up with experimental error rates based on homogeneity (Note: Tukey's and Bonferroni's approaches are not set up under this assumption).

**Least Significant Difference (LSD)**

1. **Parameters:** \( \mu_i - \mu_j \) (i \(\neq\) j)
2. **Estimates:** \( \bar{y}_i - \bar{y}_j \), i \(\neq\) j
3. **Est. St. Error:** \( \sqrt{s^2 \left( \frac{1}{n_i} + \frac{1}{n_j} \right)} \)
4. \( \text{LSD}(\alpha) = t_{\alpha/2, n} \cdot \sqrt{s^2 \left( \frac{1}{n_i} + \frac{1}{n_j} \right)} \)
5. **Confidence Intervals**

\[
(\bar{y}_i - \bar{y}_j) \pm \text{LSD}(\alpha) \in (\bar{y}_i - \bar{y}_j) \pm t_{\alpha/2, n} \cdot \sqrt{s^2 \left( \frac{1}{n_i} + \frac{1}{n_j} \right)}
\]

6. **Tests:** Conclude \( H_0: \mu_i = \mu_j \) if
\[
|\bar{y}_i - \bar{y}_j| > \text{LSD}(\alpha)
\]

This test will tend to reject too often for large values of \( t \).

**Protected LSD (Controls weak sense experimental error rate)**

1. **Conduct the F-test of** \( H_0: \mu_1 = \cdots = \mu_k \) \( H_1: \text{Not all } \mu_i \) are equal.

   - **IF** Reject - **Conduct LSD on all pairs**
   - **IF** Fail to Reject - **STOP** (Conclude no pairs differ)
Student-Newman-Keuls (SNK) Multiple Range Test

Studentized Range Test that provides a homogeneity test in weak sense.

Algorithm

1. Order means \( \bar{y}_{(j)} \leq \bar{y}_{(j+1)} \leq \cdots \leq \bar{y}_{(k)} \)

2. Compute \( \text{SNK}(K, \sigma^2) = q_{\alpha, k, \nu} \sqrt{\frac{\sigma^2}{\nu}} \)

   where \( K \) = # of means in range \( k = 2, 3, \ldots, t \)

   \( \nu = \text{error df} = k(k-1) \)

3. Conclude \( H_0: M_i = M_j \) (vs. \( H_0: M_i = M_j \)) if

   \[ \left| \bar{y}_{(i)} - \bar{y}_{(j)} \right| \geq \text{SNK}(K, \sigma^2) \]

   where \( k \) is the number of means in range containing \( i, j \)

   \[ \frac{1}{\text{Mean diff}} \geq \frac{K}{\left| \bar{y}_{(i)} - \bar{y}_{(j)} \right|} \]

   \[ \left| \bar{y}_{(i)} - \bar{y}_{(j)} \right|, \left| \bar{y}_{(i)} - \bar{y}_{(j)} \right|, \ldots, \left| \bar{y}_{(i)} - \bar{y}_{(j)} \right|, \text{ etc.} \]

Note: All procedures that use a critical value for \( \left| \bar{y}_{(i)} - \bar{y}_{(j)} \right| \) could be used to form confidence intervals and obtain identical conclusions.