ST3232: Design and Analysis of Experiments

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4:00-6:00 pm, Tuesday, March 8, 2016
Graeco-Latin squares

- If, in addition to the three factors (row, column and treatment), there is another factor to be controlled, a Graeco-Latin square can be used.

- A Graeco-Latin square is obtained by imposing the levels of the additional factor on a Latin square in a way such that any level of a factor appears once and only once at each level of the other factors.

- The following gives the standard $3 \times 3$ Graeco-Latin square:

$$
\begin{array}{ccc}
A_\alpha & B_\beta & C_\gamma \\
B_\gamma & C_\alpha & A_\beta \\
C_\beta & A_\gamma & B_\alpha \\
\end{array}
$$
The following are standard $4 \times 4$ Graeco-Latin squares: $g = 4$:

$$
\begin{array}{cccc}
A\alpha & B\beta & C\gamma & D\delta \\
B\delta & A\gamma & D\beta & C\alpha \\
C\beta & D\alpha & A\delta & B\gamma \\
D\gamma & C\delta & B\alpha & A\beta \\
\end{array}
$$


Randomization of Greco-Latin squares

A random Graeco-Latin squares can be obtained from a standard square in three steps: 1) permute the rows of the standard square; 2) permute the columns of the standard square; 3) permute the Graeco letters.
Analysis

▶ The analysis of a single Graeco-Latin square is similar to that of a single Latin square. The only difference is that in the ANOVA table, there is an additional SS (i.e., the Graeco SS).

▶ Like in Latin square case, the df of the residuals of a single Graeco-Latin square is too small. Replicated squares are usually needed.

▶ Parallel to the situation in replicated Latin squares, there are corresponding two scenarios for replicated Graeco-Latin squares.

▶ The analysis of replicated Graeco-Latin squares are similar to that of Latin squares in both scenarios. The only difference is that additional main effect and interactions related to Graeco factor are included in the analysis.
Example 13.1

An experimenter is studying the effects of five different formulations of a rocket propellant.

- Each formulation is mixed from a batch of raw material that is only large enough for five formulations to be tested.
- The formulations are prepared by several operators, and there may be substantial differences in the skills and experience of the operators.
- The tests are carried out in different assemblies, which could affect the results of the experiment.

The effects of Batch, Operator and Assembly should be considered. A Graeco-Latin square design is used for the experiment. The design and data are given in the next slide.
Example 13.1: data

<table>
<thead>
<tr>
<th>Batches</th>
<th>Operators</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1</td>
</tr>
<tr>
<td>1</td>
<td>$A\alpha = -1$</td>
</tr>
<tr>
<td>2</td>
<td>$B\beta = -8$</td>
</tr>
<tr>
<td>3</td>
<td>$C\gamma = -7$</td>
</tr>
<tr>
<td>4</td>
<td>$D\delta = 1$</td>
</tr>
<tr>
<td>5</td>
<td>$E\epsilon = -3$</td>
</tr>
</tbody>
</table>
Example 13.1: R codes and ANOVA table

\begin{verbatim}
y=c(-1,-8,-7,1,-3,-5,-1,13,6,5,-6,5,1,1,-5, -1,2,2,-2,4,-1,11,-4,-3,6)
ope =factor(kronecker(1:5,rep(1,5)))
bat =factor(rep(1:5,5))
latin =factor(c(1,2,3,4,5,2,3,4,5,1,3,4,5,1,2, 4,5,1,2,3,5,1,2,3,4))
greco =factor(c(1,2,3,4,5,3,4,5,1,2,5,1,2,3,4, 2,3,4,5,1,4,5,1,2,3))
GLfit = lm(y~ope+bat+greco+latin)
anova(GLfit)
\end{verbatim}

\begin{verbatim}
Df Sum Sq  Mean Sq  F value Pr(>F)
ope  4   150    37.50   4.5455  0.032930 *
bat  4    68    17.00   2.0606  0.178311
greco 4    62    15.50   1.8788  0.207641
latin 4   330   82.50  10.0000  0.003344 **
Residuals  8    66    8.25
\end{verbatim}
Example 13.1: Inference

The inference on the significance of the formulations can be made using the ANOVA table. The test statistic has value 10 with $p$-value 0.0033. The significance can be claimed at any level $\alpha > 0.0033$.

*Example of multiple comparison: Dunnet’s procedure*

```r
b = GLfit$coef[14:17]
v = vcov(GLfit)[14:17,14:17]
b/sqrt(diag(v))
```

<table>
<thead>
<tr>
<th>latin2</th>
<th>latin3</th>
<th>latin4</th>
<th>latin5</th>
</tr>
</thead>
<tbody>
<tr>
<td>-4.6240478</td>
<td>-3.4129877</td>
<td>0.6605783</td>
<td>-1.4312529</td>
</tr>
</tbody>
</table>

One-sided $d_{0.05}(4, 8) = 2.55$; Two-sided $d_{0.05}(4, 8) = 3.02$. $\beta_2 = \mu_2 - \mu_1$ and $\beta_3 = \mu_3 - \mu_1$ are significant at level 0.05.
Crossover study

- A crossover design is a scheme such that different treatments are applied in a random order to the same subject sequentially over time.

- E.g., in a study for the comparison of three treatments A, B and C, for a particular subject, the treatments are applied in the order B-C-A sequentially.

- A washout period is imposed in between any two subsequent treatments to avoid the carry-over of the effect of the previous treatment to the subsequent period.

- As many different orders of the treatments as possible are considered. The number of subjects administered with different orders are made as equal as possible.

- E.g., with three treatments, the ideal scheme is to apply all the following orders with equal number of subjects for each order: A-B-C, A-C-B, B-A-C, B-C-A, C-A-B, C-B-A.
Pros and cons of crossover design

- Crossover study is only applicable in the situation where (i) The effect of treatments can be measured after a short period of administration; (ii) The effect of any treatment does not last too long (it is possible to have a short washout period).

- In crossover study, each subject serves as its own control. This effectively controls all non-treatment factors associated with the subjects.

- The major pitfall of crossover study is that the carry-over effects, if not effectively washed out in the washout period, may either ruin the whole study if the data is not analyzed with caution or waste the resource put into the study. This is especially the case when there are only two treatments to consider.
Crossover study with more than two treatments

Goodies of crossover study with more than two treatments

- In two-period crossover studies, the treatment effect can be analyzed only when the crossover effects of the treatments are equal.

- If there are more than two treatments, crossover studies can be designed such that the treatment effects can be analyzed no matter whether or not the carry-over effects are equal under the assumption that the effect of any treatment can only carry over to the immediate next period.

- The proper designs are the special Latin square designs with the property: each treatment follows each of the others the same number of times.
Special Latin square designs

Latin squares with the desired property can be obtained by:

- Let the first row of the square be
  \[1, 2, g, 3, g - 1, 4, \ldots\]

- Each subsequent row is obtained from the preceding one by adding 1 to each integer; the integer \(g + 1\) is replaced by 1. Thus the second and third rows are obtained as
  \[2, 3, 1, 4, g, 5, \ldots\]
  \[3, 4, 2, 5, 1, 6, \ldots\]

- The process continues until \(g\) rows are obtained.

- When \(g\) is even, the above process assures that each treatment follows each of the others exactly once within the square. When \(g\) is odd, the mirror image of the square must be used in tandem with the generated square, then each treatment follows each of the others exactly twice within the pair of squares.
Examples of the special Latin squares

▶ $g = 3$:

\[
\begin{bmatrix}
1 & 2 & 3 \\
2 & 3 & 1 \\
3 & 1 & 2
\end{bmatrix}
\begin{bmatrix}
3 & 2 & 1 \\
1 & 3 & 2 \\
2 & 1 & 3
\end{bmatrix}
\]

▶ $g = 5$:

\[
\begin{bmatrix}
1 & 2 & 5 & 3 & 4 \\
2 & 3 & 1 & 4 & 5 \\
3 & 4 & 2 & 5 & 1 \\
4 & 5 & 3 & 1 & 2 \\
5 & 1 & 4 & 2 & 3
\end{bmatrix}
\begin{bmatrix}
4 & 3 & 5 & 2 & 1 \\
5 & 4 & 1 & 3 & 2 \\
1 & 5 & 2 & 4 & 3 \\
2 & 1 & 3 & 5 & 4 \\
3 & 2 & 4 & 1 & 5
\end{bmatrix}
\]

▶ Randomized squares of the desired property can be obtained from the above squares by first permuting the rows and followed by permuting the numerals.

▶ The squares can be replicated in order to have more power.
Analysis of crossover data using linear model approach

Define dummy variables as follows:

\[ p_i = \begin{cases} 
1, & \text{if period } i, \\
0, & \text{otherwise, } i = 2, \ldots, g; 
\end{cases} \]

\[ t_j = \begin{cases} 
1, & \text{if treatment } j, \\
0, & \text{otherwise, } j = 2, \ldots, g; 
\end{cases} \]

\[ c_k = \begin{cases} 
1, & \text{if carryover } k, \\
0, & \text{otherwise, } k = 2, \ldots, g; 
\end{cases} \]

\[ s_l = \begin{cases} 
1, & \text{if subject } l, \\
0, & \text{otherwise, } l = 2, \ldots, qg. 
\end{cases} \]

The response variable \( Y \) is described by the regression model:

\[ Y = \mu + \sum_{i=2}^{g} \pi_i p_i + \sum_{j=2}^{g} \tau_j t_j + \sum_{k=2}^{g} \rho_k c_k + \sum_{l=2}^{qg} \nu_l s_l + \epsilon. \]
Let the response of Subject $l$ in period $i$ on Treatment $j$ when Treatment $k$ was given in the preceding period be denoted by $y_{ijkl}$. For the specific individual, the regression model reduces to

$$y_{ijkl} = \mu + \pi_i + \tau_j + \rho_k + \nu_l + \epsilon_{ijkl}.$$ 

Note that, where when $i = 1$, there is no carry-over effect. As a technical tool, we can take the carry over effect as $\rho_1$. (Why?)

The inferences on the various effects are boiled down to the inferences on the corresponding coefficients in the regression model.

The significance tests of the effects are done by Wald tests.

The multiple comparisons are carried out by the simultaneous tests on the corresponding linear combinations of the regression coefficients.
Example 13.2

The following table gives plague scores for 20 patients in a four-period crossover study balanced for carryover effects (numbers in parentheses is the treatment number).

<table>
<thead>
<tr>
<th>Patient</th>
<th>Period</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>86 (3)</td>
<td>77 (4)</td>
<td>102 (2)</td>
<td>122 (1)</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>79 (4)</td>
<td>110 (1)</td>
<td>77 (3)</td>
<td>106 (2)</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>77 (2)</td>
<td>90 (3)</td>
<td>105 (1)</td>
<td>120 (4)</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>52 (1)</td>
<td>85 (2)</td>
<td>69 (4)</td>
<td>73 (3)</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>74 (2)</td>
<td>73 (4)</td>
<td>83 (1)</td>
<td>105 (3)</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>96 (4)</td>
<td>97 (3)</td>
<td>94 (2)</td>
<td>113 (1)</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>83 (3)</td>
<td>87 (1)</td>
<td>91 (4)</td>
<td>104 (2)</td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>82 (1)</td>
<td>93 (2)</td>
<td>102 (3)</td>
<td>106 (4)</td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>81 (2)</td>
<td>74 (4)</td>
<td>88 (3)</td>
<td>111 (1)</td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>64 (3)</td>
<td>78 (2)</td>
<td>77 (1)</td>
<td>76 (4)</td>
<td></td>
</tr>
<tr>
<td>11</td>
<td>72 (1)</td>
<td>76 (3)</td>
<td>89 (4)</td>
<td>109 (2)</td>
<td></td>
</tr>
<tr>
<td>12</td>
<td>81 (4)</td>
<td>70 (1)</td>
<td>93 (2)</td>
<td>119 (3)</td>
<td></td>
</tr>
<tr>
<td>13</td>
<td>77 (3)</td>
<td>57 (1)</td>
<td>75 (2)</td>
<td>93 (4)</td>
<td></td>
</tr>
<tr>
<td>14</td>
<td>76 (2)</td>
<td>70 (3)</td>
<td>60 (4)</td>
<td>107 (1)</td>
<td></td>
</tr>
<tr>
<td>15</td>
<td>87 (1)</td>
<td>80 (4)</td>
<td>70 (3)</td>
<td>93 (2)</td>
<td></td>
</tr>
<tr>
<td>16</td>
<td>66 (4)</td>
<td>84 (2)</td>
<td>68 (1)</td>
<td>119 (3)</td>
<td></td>
</tr>
<tr>
<td>17</td>
<td>87 (4)</td>
<td>84 (2)</td>
<td>104 (3)</td>
<td>122 (1)</td>
<td></td>
</tr>
<tr>
<td>18</td>
<td>72 (1)</td>
<td>83 (3)</td>
<td>91 (2)</td>
<td>92 (4)</td>
<td></td>
</tr>
<tr>
<td>19</td>
<td>69 (2)</td>
<td>65 (1)</td>
<td>77 (4)</td>
<td>100 (3)</td>
<td></td>
</tr>
<tr>
<td>20</td>
<td>81 (3)</td>
<td>86 (4)</td>
<td>61 (1)</td>
<td>122 (2)</td>
<td></td>
</tr>
</tbody>
</table>
R-codes for the analysis of Example 13.2

<table>
<thead>
<tr>
<th>Code</th>
<th>Values</th>
</tr>
</thead>
<tbody>
<tr>
<td>x11</td>
<td>86, 77, 102, 122</td>
</tr>
<tr>
<td>x12</td>
<td>79, 110, 77, 106</td>
</tr>
<tr>
<td>x13</td>
<td>77, 90, 105, 120</td>
</tr>
<tr>
<td>x14</td>
<td>52, 85, 69, 73</td>
</tr>
<tr>
<td>x21</td>
<td>74, 73, 83, 105</td>
</tr>
<tr>
<td>x22</td>
<td>96, 97, 94, 113</td>
</tr>
<tr>
<td>x23</td>
<td>83, 87, 91, 104</td>
</tr>
<tr>
<td>x24</td>
<td>82, 93, 102, 106</td>
</tr>
<tr>
<td>x31</td>
<td>81, 74, 88, 111</td>
</tr>
<tr>
<td>x32</td>
<td>64, 78, 77, 76</td>
</tr>
<tr>
<td>x33</td>
<td>72, 76, 89, 109</td>
</tr>
<tr>
<td>x34</td>
<td>81, 70, 93, 119</td>
</tr>
<tr>
<td>x41</td>
<td>77, 57, 75, 93</td>
</tr>
<tr>
<td>x42</td>
<td>76, 70, 60, 107</td>
</tr>
<tr>
<td>x43</td>
<td>87, 80, 70, 93</td>
</tr>
<tr>
<td>x44</td>
<td>66, 84, 68, 119</td>
</tr>
<tr>
<td>x51</td>
<td>87, 84, 104, 122</td>
</tr>
<tr>
<td>x52</td>
<td>72, 83, 91, 92</td>
</tr>
<tr>
<td>x53</td>
<td>69, 65, 77, 100</td>
</tr>
<tr>
<td>x54</td>
<td>81, 86, 61, 122</td>
</tr>
</tbody>
</table>
R-codes for the analysis of Example 13.2 (cont.)

```r
x = c(x11, x12, x13, x14, x21, x22, x23, x24, x31, x32, x33, x34,
      x41, x42, x43, x44, x51, x52, x53, x54)
period = factor(rep(c(1:4), 20))
subject = factor(kronecker(c(1:20), c(1,1,1,1)))
tmt = c(3,4,2,1,4,1,3,2,2,3,1,4,1,2,4,3,
        2,4,1,3,4,3,2,1,3,1,4,2,1,2,3,4,
        2,4,3,1,3,2,1,4,1,3,4,2,4,1,2,3,
        3,1,2,4,2,3,4,1,1,4,3,2,4,2,1,3,
        4,2,3,1,1,3,2,4,2,1,4,3,3,4,1,2)
carryover = c(1,3,4,2,1,4,1,3,1,2,3,1,1,1,2,4,
        1,2,4,1,1,4,3,2,1,3,1,4,1,1,2,3,
        1,2,4,3,1,3,2,1,1,1,3,4,1,4,1,2,
        1,3,1,2,1,2,3,4,1,1,4,3,1,4,2,1,
        1,4,2,3,1,1,3,2,1,2,1,4,1,3,4,1)
tmt = factor(tmt)
carryover = factor(carryover)
options(contrasts=c("contr.treatment","contr.poly"))
fit.obj = lm(x ~ period + tmt + subject + carryover)
```
R-codes for the analysis of Example 13.2 (cont.)

# Compute F statistic for direct treatment effects:
b1 = fit.obj$coef[5:7]
v1 = vcov(fit.obj)[5:7,5:7]
F.T = t(b1)%*%solve(v1)%*%b1/3

# Compute F statistic for carry over treatment effects:
b2 = fit.obj$coef[27:29]
v2 = vcov(fit.obj)[27:29,27:29]
F.C = t(b2)%*%solve(v2)%*%b2/3

# Compute F statistic for period effects:
b3 = fit.obj$coef[2:4]
v3 = vcov(fit.obj)[2:4,2:4]
F.P = t(b3)%*%solve(v3)%*%b3/3