ON MULTIVARIATE ANALYSES OF CROSSOVER DESIGNS

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In crossover experiments, treatments are assigned to experimental units in successive periods. Traditional analyses of crossover designs with three or more periods assume that the observations in successive periods satisfy conditions similar to those utilized in the analysis of many repeated measures experiments. The successive measurements are assumed to satisfy conditions known as the Huynh-Feldt conditions. This paper gives a test for the Huynh-Feldt conditions and discusses possible analyses of crossover experiments, including tests for carryover, when the Huynh-Feldt conditions are not satisfied.

1. Introduction

Crossover experiments are special types of repeated measures experiments where the treatments being given to an experimental unit change over time. This paper has nothing to add to traditional analysis methods for two period crossover designs, and considers only those crossover designs which involve three or more periods.

Huynh and Feldt (1970) gave conditions under which repeated measures experiments can be analyzed in the same way that split plot experiments are analyzed. These conditions have since been called the Huynh-Feldt (H-F) conditions. If one has p repeated measures and if one lets Σ represent the variance-covariance matrix of the repeated measures on a randomly selected experimental unit, the H-F conditions are said to be satisfied if there exists a constant η and a p x 1 vector γ such that $\Sigma = \eta\mathbf{I}_p+\gamma\mathbf{j}_p'+\mathbf{j}_p\gamma'$.

A test for the H-F conditions is obtained by testing $\mathbf{P}\Sigma\mathbf{P}' = \eta\mathbf{I}_{p-1}$ for some η where $\mathbf{P}$ is any p-1 x p matrix whose rows consist of orthogonal normalized contrasts. A test of whether a covariance matrix is a multiple of an identity matrix is usually called a test of sphericity in multivariate literature, and such a test is discussed in most multivariate methods books. The test is also described in the next section.

When the H-F conditions are not satisfied, there have been several alternative suggestions for analyzing repeated measures designs. Some suggestions involve making adjustments to the degrees of freedom associated with test statistics involving the repeated measures. There are two common adjustments, one given by Huynh and Feldt (1970) and one given by Greenhouse and Geisser (1959). Both of these adjustments reduce the degrees of freedom of ANOVA test statistics by multiplying their numerator and denominator degrees of freedom by an adjustment or correction factor.

A third method for analyzing repeated measures experiments, which is likely the most general approach, is to treat the vector of repeated measures as a multivariate response vector and apply multivariate analysis of variance methods to test the relevant hypotheses.

The above approaches have rarely, if ever, been applied to crossover designs in the published literature. In the next section, a test for the H-F conditions in a crossover design is given, and in the following sections, methods for analyzing crossover designs when the H-F conditions are not satisfied are proposed.

2. Testing for the H-F Conditions

Suppose a researcher has a crossover design with treatments given to experimental units in s different sequences where each sequence involves p periods. A traditional model (without carryover) for this setup is

$$y_{ijk\ell} = \mu + S_i + \delta_{i\ell} + T_j + P_k + \varepsilon_{ijk\ell} \tag{1}$$

for $i=1,2,\cdots,s$; $j=1,2,\cdots,t$; $k=1,2,\cdots,p$; $\ell=1,2,\ldots,n_i$ where μ represents an overall mean, S_i represents an effect due to the ith sequence, $\delta_{i\ell}$ represents an error which is associated with the ℓth subject in the ith sequence, T_j represents the effect of the jth treatment, P_k represents the effect of the kth period, and $\varepsilon_{ijk\ell}$ represents residual variation within the ℓth subject who received the jth treatment in the kth period of the ith sequence.

Let $\mathbf{y}_{i\ell}$ be the p x 1 vector of responses for the ℓth subject in the ith sequence and let $\boldsymbol{\varepsilon}_{i\ell}$ be the corresponding vector of errors. Let $\Sigma = \text{Cov}[\boldsymbol{\varepsilon}_{i\ell}]$, and assume the $\boldsymbol{\varepsilon}_{i\ell}$'s are distributed independently and identically multivariate normal for $i=1,\cdots,s$ and $\ell=1,\cdots,n_i$. For convenience, let $\mu_i = E[\mathbf{y}_{i\ell}]$ and note that the elements in the μ_i's are functions of the S_i's, the T_j's, and the P_k's in model (1).

Let N be the total sample size, i.e., $N=\sum_{i=1}^{s} n_i$. It is straightforward to show that

$$\hat{\boldsymbol{\mu}}_i = \frac{1}{n_i}\sum_{\ell=1}^{n_i} \boldsymbol{y}_{i\ell} \quad \text{and} \quad \hat{\boldsymbol{\Sigma}} = \frac{1}{N-s}\sum_{i=1}^{s}\sum_{\ell=1}^{n_i} (\boldsymbol{y}_{i\ell}-\hat{\boldsymbol{\mu}}_i)(\boldsymbol{y}_{i\ell}-\hat{\boldsymbol{\mu}}_i)'$$

are sufficient statistics for this problem.

It can be shown that $(N-s)\hat{\boldsymbol{\Sigma}}$ is distributed as a central Wishart distribution with N-s degrees and variance-covariance matrix Σ and that the $\hat{\mu}_i's$ are distributed independent $N(\mu_i, (1/n_i)\Sigma)$, $i=1,2,\cdots,s$. Also the $\hat{\mu}_i's$ are independent of $\hat{\boldsymbol{\Sigma}}$.

Let **P** be any p-1 x p matrix whose rows are orthogonal normalized contrasts and $\mathbf{W} = (N-s)\mathbf{P}\hat{\boldsymbol{\Sigma}}\mathbf{P}'$ then a test of the H-F conditions is based on $\Lambda = \dfrac{|\boldsymbol{W}|}{\left[\frac{1}{p-1} tr(\boldsymbol{W})\right]^{p-1}}$. A formula for approximating a p-value for this test statistic is given by Srivastava and Carter (1979, p. 327).

A SAS Analysis

A test for the H-F conditions in crossover designs can be easily obtained in SAS-GLM by using the REPEATED option with the following SAS commands where *p* represents the number of periods in each sequence and Y1,Y2,···,Y*p* represent the measurements taken in successive periods. In the SAS output, the test labeled as a test for sphericity is the test of the H-F conditions.

```
PROC GLM;
 CLASSES SEQUENCE;
 MODEL Y1--Yp = SEQUENCE;
 REPEATED PERIOD p POLYNOMIAL / PRINTE;
```

3. Alternative Analyses of Crossover Designs

In this section some different possible analyses of crossover designs are suggested for those situations where the H-F conditions are not satisfied.

3.1 Adjustments to the Degrees of Freedom

Greenhouse and Geisser (1959) and Huynh and Feldt (1970) suggested reductions in the degrees of freedom of the numerator and denominator mean squares of F ratios which involve time in repeated measures experiments. These same kinds of adjustments can be made in crossover experiments.

Again let **P** be any p-1 x p matrix whose rows are orthogonal normalized contrasts and let $\mathbf{W} = (N-s)\mathbf{P}\hat{\boldsymbol{\Sigma}}\mathbf{P}'$. Greenhouse and Geisser adjust the numerator and denominator degrees of freedom by

$$\hat{\xi}_1 = \frac{\left[\sum_{i=1}^{p-1} w_{ii}\right]^2}{(p-1)\sum_{i=1}^{p-1}\sum_{j=1}^{p-1} w_{ij}^2} ,$$

and Huynh and Feldt adjust the numerator and denominator degrees of freedom by

$$\hat{\xi}_2 = \frac{N(p-1)\hat{\xi}_1 - 2}{(p-1)(N-s-(p-1)\hat{\xi}_1)} .$$

If $\hat{\xi}_1$ or $\hat{\xi}_2$ should happen to be greater than 1, then they are replaced by 1. That is, the degrees of freedom associated with F -ratios are never increased.

3.2 A Multivariate Approach

Unfortunately, a multivariate analysis of crossover designs is not a straightforward generalization of a multivariate analysis of a repeated measures experiment. This is because the treatments are changing with respect to time in crossover experiments. That is, both time and treatments are changing in crossover experiments while only time is changing in repeated measures experiments.

To consider a multivariate approach to analyzing crossover experiments, once again let μ_i, $\hat{\boldsymbol{\mu}}_i$, and $\hat{\boldsymbol{\Sigma}}$ be defined as they were in Section 2, and for illustration purposes consider model (1). For model (1)

$$\boldsymbol{\mu}_i = \begin{bmatrix} \mu_{i1} \\ \mu_{i2} \\ \vdots \\ \mu_{ip} \end{bmatrix} = \begin{bmatrix} \mu + S_i + T_{1i} + P_1 \\ \mu + S_i + T_{2i} + P_2 \\ \vdots \\ \mu + S_i + T_{pi} + P_p \end{bmatrix}, \quad i=1,2,\cdots,s .$$

where T_{ki} represents the treatment assigned to an experimental unit in the kth period of the ith sequence, i=1,2,···,s, k=1,2,···,p.

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Let $\beta' = [\mu \ S_1 \ S_2 \ \cdots \ S_s \ T_1 \ T_2 \ \cdots \ T_t \ P_1 \ P_2 \ \cdots \ P_p]$ be the vector of the parameters in model (1). Let $\mu' = [\mu_1' \ \mu_2' \ \cdots \ \mu_s']$. Thus μ is a ps x 1 vector. Note that the elements of μ are all estimable functions and span the space of all estimable functions of β. Thus there exists a matrix $\mathbf{H}$ such that

$$\mu = \mathbf{H}\beta.$$

Suppose $\mathbf{a}'\beta$ is an estimable function of the parameters in β. Let $\mathbf{H}^-$ be the Moore-Penrose generalized inverse of $\mathbf{H}$. It can be shown that $\mathbf{a}'\beta=\mathbf{a}'\mathbf{H}^-\mu=\mathbf{b}'\mu$ where $\mathbf{b}=\mathbf{H}'^-\mathbf{a}$.

One unbiased estimator of $\mathbf{a}'\beta$ which is based on the sufficient statistics is $\boldsymbol{b}'\hat{\boldsymbol{\mu}}$, and

$$\boldsymbol{b}'\hat{\boldsymbol{\mu}} \sim N(\boldsymbol{a}'\boldsymbol{\beta}, \boldsymbol{b}'\boldsymbol{\Sigma}^*\boldsymbol{b})$$

where

$$\Sigma^* = \mathrm{COV}(\hat{\boldsymbol{\mu}}) = \begin{bmatrix} \frac{1}{n_1}\boldsymbol{\Sigma} & \mathbf{0} & \cdots & \mathbf{0} \\ \mathbf{0} & \frac{1}{n_2}\boldsymbol{\Sigma} & \cdots & \mathbf{0} \\ \vdots & \vdots & \cdots & \vdots \\ \mathbf{0} & \mathbf{0} & \cdots & \frac{1}{n_s}\boldsymbol{\Sigma} \end{bmatrix} = \boldsymbol{\Sigma} \otimes DIAG\left(\frac{1}{n_1}, \frac{1}{n_2}, \cdots, \frac{1}{n_s}\right).$$

Let $\mathbf{b}' = [\mathbf{b}_1' \ \mathbf{b}_2' \ \cdots \ \mathbf{b}_s']$ where each $\mathbf{b}_i$ is a p x 1 vector, then

$$\boldsymbol{b}'\hat{\mu} = \sum_{i=1}^{s} \boldsymbol{b}_i'\hat{\mu}_i \quad \text{and VAR} \quad (\boldsymbol{b}'\hat{\boldsymbol{\mu}}) = \sum_{i=1}^{s} \frac{1}{n_i}\boldsymbol{b}_i'\boldsymbol{\Sigma}\boldsymbol{b}_i .$$

It must be noted that there may be other unbiased estimators of $\mathbf{a}'\beta$ which depend on the sufficient statistics, so it cannot be guaranteed that the one given by $\boldsymbol{b}'\hat{\boldsymbol{\mu}}$ is the best. It should, however, be a PDG (pretty darn good) estimator of $\mathbf{a}'\beta$.

$$\text{Now let V} = \frac{\boldsymbol{b}'\hat{\boldsymbol{\mu}} - \boldsymbol{a}'\boldsymbol{\beta}}{\sqrt{\sum_{i=1}^{s} \frac{1}{n_i}\boldsymbol{b}_i'\hat{\boldsymbol{\Sigma}}\boldsymbol{b}_i}} . \tag{2}$$

The result in (2) can be used to make inferences about $\mathbf{a}'\beta$ if each of the samples sizes corresponding to each possible sequence of treatments is sufficiently large. In this case, one can assume the distribution of V is approximately N(0,1). But what can be done for small sample sizes?

For small sample sizes, one might try to approximate the distribution of V with a t - distribution. Since the numerator and denominator of V are stochastically independent, one might try to use a Satterthwaite approximation to the degrees of freedom of V.

By Satterthwaite's method, one would try to find υ so that

$$U=\frac{\upsilon\left[\sum_{i=1}^{s}\frac{1}{n_i}\boldsymbol{b}_i'\hat{\boldsymbol{\Sigma}}\boldsymbol{b}_i\right]}{\sum_{i=1}^{s}\frac{1}{n_i}\boldsymbol{b}_i'\boldsymbol{\Sigma}\boldsymbol{b}_i} \quad \text{is approximately distributed } \chi^2(\upsilon)$$

by equating the variance of U to 2υ, the variance of the chi-square distribution with υ degrees of freedom, and solving for υ. However, at this point in time, the variance of U has not been obtained.

Since (N-s) $\hat{\boldsymbol{\Sigma}}$ has a Wishart distribution with N-s degrees of freedom, one might conjecture that the degrees of freedom of V will be approximately equal to N-s. We believe this to be a reasonable conjecture and, in fact, there appears to be some reason to believe that this is what Satterthwaite's method will eventually give. The evaluation of this conjecture has not yet been done.

3.3 A Mixed Models Approach

Consider a model for a crossover experiment which is based on the sufficient statistics. This model can be written as

$$\hat{\boldsymbol{\mu}} = \boldsymbol{H}\boldsymbol{\beta} + \boldsymbol{\varepsilon}^* \tag{2}$$

where $\varepsilon^* \sim N(\mu,\Sigma^*)$. If Σ^* were known, the uniformly minimum variance unbiased estimator of an estimable function $\mathbf{a}'\beta$ is

$$\mathbf{a}'\hat{\boldsymbol{\beta}}_G \quad \text{where} \quad \hat{\boldsymbol{\beta}}_G = (\boldsymbol{H}'\boldsymbol{\Sigma}^{*-1}\boldsymbol{H})^-\boldsymbol{H}'\boldsymbol{\Sigma}^{*-1}\hat{\boldsymbol{\mu}} \quad .$$

In addition,

$$\mathbf{a}'\hat{\boldsymbol{\beta}}_G \sim N(\mathbf{a}'\boldsymbol{\beta}, \mathbf{a}'(\boldsymbol{H}'\boldsymbol{\Sigma}^{*-1}\boldsymbol{H})^-\boldsymbol{a}) \quad .$$

Unfortunately, Σ^* is unknown, but it can be estimated by $\hat{\boldsymbol{\Sigma}}\otimes DIAG(\frac{1}{n_1},\frac{1}{n_2},\cdots,\frac{1}{n_s})$. Then the estimated mixed model estimator of $\mathbf{a}'\beta$ is

$$\mathbf{a}'\hat{\boldsymbol{\beta}}_{EG} \quad \text{where} \quad \hat{\boldsymbol{\beta}}_{EG} = (\boldsymbol{H}'\hat{\boldsymbol{\Sigma}}^{*-1}\boldsymbol{H})^-\boldsymbol{H}'\hat{\boldsymbol{\Sigma}}^{*-1}\hat{\boldsymbol{\mu}} \quad .$$

Inferences about $\mathbf{a}'\beta$ based on $\mathbf{a}'\boldsymbol{\beta}_{EG}$ can be made using critical points from the standard normal distribution in those cases when all of the n_i's are large and perhaps by using critical points from the t - distribution with N-s degrees of freedom when the sample sizes are small. The suitability of these approximations are in the process of being examined.

At this point in time, there exists no statistical software to carry out a multivariate analysis of crossover experiments (except to test for the H-F conditions). In the next section an example is given. SAS-IML has been used to carry out the multivariate analyses.

4. An Example

To illustrate the techniques discussed in the previous sections, consider the three period - three treament crossover experiment discussed in Milliken and Johnson (1984). The design used in this experiment considered all possible sequences of the three treatments. This design produces an experimental design which is balanced for carry-over effects.

Table 1 shows the six sequences in the this data set.

TABLE 1. Sequences of Treatment Assignments.

	PERIOD		
SEQUENCE	1	2	3
1	A	B	C
2	A	C	B
3	B	A	C
4	B	C	A
5	C	A	B
6	C	B	A

Let μ_{ij} represent the expected response for PERIOD j in SEQUENCE i. The usual effects model parameters without carryover for the crossover design in Table 1 is:

$$
\begin{array}{lll}
\mu_{11} = \mu+P_1+S_1+\tau_1 & \mu_{12} = \mu+P_2+S_1+\tau_2 & \mu_{13} = \mu+P_3+S_1+\tau_3 \\
\mu_{21} = \mu+P_1+S_2+\tau_1 & \mu_{22} = \mu+P_2+S_2+\tau_3 & \mu_{23} = \mu+P_3+S_2+\tau_2 \\
\mu_{31} = \mu+P_1+S_3+\tau_2 & \mu_{32} = \mu+P_2+S_3+\tau_1 & \mu_{33} = \mu+P_3+S_3+\tau_3 \\
\mu_{41} = \mu+P_1+S_4+\tau_2 & \mu_{42} = \mu+P_2+S_4+\tau_3 & \mu_{43} = \mu+P_3+S_4+\tau_1 \\
\mu_{51} = \mu+P_1+S_5+\tau_3 & \mu_{52} = \mu+P_2+S_5+\tau_1 & \mu_{53} = \mu+P_3+S_5+\tau_2 \\
\mu_{61} = \mu+P_1+S_6+\tau_3 & \mu_{62} = \mu+P_2+S_6+\tau_2 & \mu_{63} = \mu+P_3+S_6+\tau_1
\end{array}
$$

where S_i represents the effect of the ith sequence, i=1,2,3,4,5,6, T_j represents the effect of the jth treatment,

$j=1,2,3$, and P_k represents the effect of the kth period, $k=1,2,3$.

Let $\beta' = [\mu\ S_1\ S_2\ S_3\ S_4\ S_5\ S_6\ T_1\ T_2\ T_3\ P_1\ P_2\ P_3]$, and $\mu' = [\mu_1'\ \mu_2'\ \mu_3'\ \mu_4'\ \mu_5'\ \mu_6']$ where $\mu_i' = [\mu_{i1}\ \mu_{i2}\ \mu_{i3}]$ for $i=1,2,\cdots,6$.

For this example, the matrix **H** which makes $\mu = \mathbf{H}\beta$ is

$$\mathbf{H} = \begin{bmatrix}
1 & 1 & 0 & 0 & 0 & 0 & 0 & 1 & 0 & 0 & 1 & 0 & 0 \\
1 & 1 & 0 & 0 & 0 & 0 & 0 & 0 & 1 & 0 & 0 & 1 & 0 \\
1 & 1 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 1 & 0 & 0 & 1 \\
1 & 0 & 1 & 0 & 0 & 0 & 0 & 1 & 0 & 0 & 1 & 0 & 0 \\
1 & 0 & 1 & 0 & 0 & 0 & 0 & 0 & 0 & 1 & 0 & 1 & 0 \\
1 & 0 & 1 & 0 & 0 & 0 & 0 & 0 & 1 & 0 & 0 & 0 & 1 \\
1 & 0 & 0 & 1 & 0 & 0 & 0 & 0 & 1 & 0 & 1 & 0 & 0 \\
1 & 0 & 0 & 1 & 0 & 0 & 0 & 1 & 0 & 0 & 0 & 1 & 0 \\
1 & 0 & 0 & 1 & 0 & 0 & 0 & 0 & 0 & 1 & 0 & 0 & 1 \\
1 & 0 & 0 & 0 & 1 & 0 & 0 & 0 & 1 & 0 & 1 & 0 & 0 \\
1 & 0 & 0 & 0 & 1 & 0 & 0 & 0 & 0 & 1 & 0 & 1 & 0 \\
1 & 0 & 0 & 0 & 1 & 0 & 0 & 1 & 0 & 0 & 0 & 0 & 1 \\
1 & 0 & 0 & 0 & 0 & 1 & 0 & 0 & 0 & 1 & 1 & 0 & 0 \\
1 & 0 & 0 & 0 & 0 & 1 & 0 & 1 & 0 & 0 & 0 & 1 & 0 \\
1 & 0 & 0 & 0 & 0 & 1 & 0 & 0 & 1 & 0 & 0 & 0 & 1 \\
1 & 0 & 0 & 0 & 0 & 0 & 1 & 0 & 0 & 1 & 1 & 0 & 0 \\
1 & 0 & 0 & 0 & 0 & 0 & 1 & 0 & 1 & 0 & 0 & 1 & 0 \\
1 & 0 & 0 & 0 & 0 & 0 & 1 & 1 & 0 & 0 & 0 & 0 & 1
\end{bmatrix} .$$

The SAS statements used to analyze the data in Milliken and Johnson and some of the results of the SAS analyses are shown in Appendix 1. The first set of analyses assume there are no unequal carryover effects; the second set of analyses test for unequal carryover effects and give comparisons between treatments in the presence of unequal carryover effects.

First a test for the H-F conditions is produced. This test is the same regardless of whether there is carryover or not. The results of this test are shown near the middle of page 4 of the SAS output. The test is labled as a "Test for Sphericity." The test resulted in a p-value of 0.8775, and hence, the H-F conditions can not be rejected for this data. This is not surprising if one examines the correlation matrix shown on page 3 of the SAS output. The pairwise correlations between Y1 and Y2, Y1 and Y3, and Y2 and Y3 are 0.78, 0.80, and 0.74, respectively. These are nearly equal to one another, and the repeated measures seem to not only satisfy the H-F conditions, they also seem to possess compound symmetry.

The adjustment factors for the H-F and G-G adjustments to degrees of freedom are shown on page 6 of the SAS output. The value of ξ_1 is 1.2378 and the value of ξ_2 is 0.9911. Since the H-F factor is greater than 1, 1 would be used when making adjustments to degrees of freedom using a H-F adjustment. Nothing else on SAS output pages 1-6 are useful for our purposes.

Since the H-F conditions are satisfied, one can make inferences about the treatment effects from the analyses shown on page 10. At the bottom of page 10, one finds estimates of the treatment means as well as estimates, standard errors and test statistics for making pairwise comparisons amongst the treatments. Some of the output on page 10 has lines drawn through it. We crossed these things out because SAS has not computed these statistics correctly. Using methods discussed in Chapter 28 of Milliken and Johnson (1984) one can compute corrected standard errors for the treatment means. First one must estimate the two variance components by solving $\hat{\sigma}_\varepsilon^2+3\hat{\sigma}_\delta^2=10.2593$ and $\hat{\sigma}_\varepsilon^2=1.03876$ for $\hat{\sigma}_\varepsilon^2$ and $\hat{\sigma}_\delta^2$. One gets $\hat{\sigma}_\varepsilon^2=1.03876$ and $\hat{\sigma}_\delta^2=3.0735$. Then the standard error of each of the treatment means is $\sqrt{(\hat{\sigma}_\varepsilon^2+\hat{\sigma}_\delta^2)/36}=.3380$. To construct a confidence interval for the true treatment means one must use a Satterthwaite approximation to compute an approximate degrees of freedom for a t critical point.

If it were the case that the H-F conditions were not satisfied, F-type ratios can be computed by squaring the t-ratios, then the degrees of freedom corresponding to the numerators and denominators of the F-ratios could be multiplied by ξ_1 or ξ_2, and then finally, p-values could be recomputed.

Since the H-F conditions are satisfied for this data, and the other analyses presented in this paper would not be necessary. However, for illustration purposes, the other two analyses are obtained by using the remaining SAS statements. On page 12 of the SAS output, one finds the estimate of Σ. On page 13, estimates of the treatment means and their standard errors are computed using the multivariate approach described in Section 3.2. Confidence intervals for the true treatment means are also given. Estimates of pairwise differences in the treatments are shown along with their standard errors, t-tests, and confidence intervals. The significance levels and confidence intevals are computed by using degrees of freedom on the t-distribution equal to N-s. Note that the estimates in this analysis are the same as those in the first analysis, but the estimated standard errors are slightly different.

The results from the mixed model analysis described in Section 3.3 are shown on page 14 of the SAS output. The significance levels are once again computed by using degrees of freedom equal to N-s. Note that the estimates as well as their estimated standard errors are slightly different than those given by the first two analyses.

The output on SAS pages 15-20 is obtained by using a model which allows for unequal carryover effects from the treatments occuring in the previous period. Page 17 gives an analysis appropriate when the H-F conditions are satisfied except for the test statistics and p-values which have been crossed out. Page 19 gives the analysis described in Section 3.2, and page 20 gives the analysis described in Section 3.3.

5. References

Huynh, H. and Feldt, L.S. (1970). Conditions under which mean square ratios in repeated measures designs have exact F-distributions. *Journal of the American Statistical Association* 65:1582-89.

Greenhouse, S.W. and Geisser, S. (1959). On methods in the analysis of profile data. *Psychometrika* 24:95-112.

Milliken, G.A and Johnson, D.E. (1984) *Analysis of Messy Data - Vol. 1: Designed Experiments*. Van Nostrand Reinhold, New York.

Srivastava, M.S. and Carter, E.M. (1983). *An Introduction to Applied Multivariate Statistics*. North-Holland, New York.

Appendix 1. SAS Analyses

The following statements were used to test for the H-F conditions for the experiment discussed in Section 4.

```
options ls=72 nodate pagesize=66;
dm 'log; clear; output; clear';
DATA one;
  INPUT seq subject y1 y2 y3 @@;
  IF seq=1 THEN trt1='A';  IF seq=1 THEN trt2='B';  IF seq=1
THEN trt3='C';
  IF seq=2 THEN trt1='A';  IF seq=2 THEN trt2='C';  IF seq=2
THEN trt3='B';
  IF seq=3 THEN trt1='B';  IF seq=3 THEN trt2='A';  IF seq=3
THEN trt3='C';
  IF seq=4 THEN trt1='B';  IF seq=4 THEN trt2='C';  IF seq=4
THEN trt3='A';
  IF seq=5 THEN trt1='C';  IF seq=5 THEN trt2='A';  IF seq=5
THEN trt3='B';
  IF seq=6 THEN trt1='C';  IF seq=6 THEN trt2='B';  IF seq=6
THEN trt3='A';
CARDS;
1  1 20.1 20.3 25.6   1  2 23.3 24.8 28.7   1  3 23.4 24.8 28.3
1  4 19.7 21.3 25.7   1  5 19.2 20.9 25.9   1  6 22.2 22.0 26.2
2  7 24.7 29.4 27.5   2  8 23.8 28.7 24.1   2  9 23.6 26.4 25.0
2 10 20.2 26.2 21.4   2 11 19.8 23.7 23.3   2 12 21.5 25.5 20.8
3 13 24.3 23.2 30.1   3 14 26.4 26.4 32.3   3 15 19.9 23.7 25.5
3 16 23.9 26.8 30.8   3 17 20.5 23.2 26.3   3 18 21.8 23.6 29.1
4 19 20.9 27.5 24.3   4 20 21.9 28.6 23.1   4 21 22.0 27.4 24.5
4 22 23.3 30.7 26.6   4 23 18.8 27.9 24.6   4 24 24.6 29.8 26.6
5 25 24.0 21.8 21.6   5 26 25.9 23.7 23.9   5 27 25.5 22.0 23.4
5 28 27.9 25.4 24.4   5 29 25.3 26.4 25.8   5 30 25.7 24.7 24.9
6 31 23.2 18.9 23.8   6 32 23.9 21.5 25.4   6 33 28.0 25.3 28.1
6 34 24.6 22.7 23.8   6 35 27.7 23.5 25.6   6 36 21.5 18.1 22.8
RUN;

PROC GLM DATA=one OUTSTAT=two;
  CLASS seq;
  MODEL y1--y3 = seq / NOUNI;
  REPEATED period 3 POLYNOMIAL / PRINTE;
  RUN;

DATA sigma;  SET two;
  IF _TYPE_='ERROR';
  column1 = y1/df;
  column2 = y2/df;
  column3 = y3/df;
  KEEP column1--column3;
  RUN;

DATA df;  SET two;
  IF _TYPE_ = 'ERROR';
```

```
  IF _NAME_ = 'Y1';
  KEEP DF;
  RUN;

DATA a;  SET one;  DROP y1-y3 trt1-trt3;
  period=1; y=y1; trt=trt1; priortrt='0';  OUTPUT;
  period=2; y=y2; trt=trt2; priortrt=trt1; OUTPUT;
  period=3; y=y3; trt=trt3; priortrt=trt2; OUTPUT;
  RUN;

PROC PRINT DATA=a;

PROC GLM DATA=a;
  CLASSES seq subject trt period;
  MODEL y = seq subject(seq) trt period;

  ESTIMATE 'Trt A LSM' intercept 6 seq 1 1 1 1 1 1 trt 6 0 0
    period 2 2 2/DIVISOR=6;
  ESTIMATE 'Trt B LSM' intercept 6 seq 1 1 1 1 1 1 trt 0 6 0
    period 2 2 2/DIVISOR=6;
  ESTIMATE 'Trt C LSM' intercept 6 seq 1 1 1 1 1 1 trt 0 0 6
    period 2 2 2/DIVISOR=6;

  ESTIMATE 'Trt A-Trt B' trt 1 -1 0;
  ESTIMATE 'Trt A-Trt C' trt 1 0 -1;
  ESTIMATE 'Trt B-Trt C' trt 0 1 -1;

  CONTRAST 'Trt A LSM' intercept 6 seq 1 1 1 1 1 1 trt 6 0 0
    period 2 2 2;
  CONTRAST 'Trt B LSM' intercept 6 seq 1 1 1 1 1 1 trt 0 6 0
    period 2 2 2;
  CONTRAST 'Trt C LSM' intercept 6 seq 1 1 1 1 1 1 trt 0 0 6
    period 2 2 2;

  CONTRAST 'Trt A-Trt B' trt 1 -1 0;
  CONTRAST 'Trt A-Trt C' trt 1 0 -1;
  CONTRAST 'Trt B-Trt C' trt 0 1 -1;
 RANDOM subject(seq);
  RUN;

PROC SORT DATA=a;
  BY seq period;

PROC MEANS DATA=a NOPRINT;
  BY seq period;  VAR y;
  OUTPUT OUT=b  MEAN=ybar N=n;

DATA means;  SET b;
  KEEP ybar;
  RUN;
```

```
DATA size;  SET b;
  IF period=1;
  k = 1/n;
  KEEP n k;
  RUN;


    /*          No  Carryover  Model     */;

PROC IML;
RESET nolog;

USE sigma;
READ ALL INTO sigmahat; PRINT ,,sigmahat;

USE df;
READ ALL INTO df;

USE means;
READ ALL INTO means;
muhat = means[,1];

USE size;
READ ALL INTO size;
n=size[,1] ;  k=size[,2];
d = DIAG(k);

sigmastr = d @ sigmahat;

        H = { 1  1 0 0 0 0 0  1 0 0   1 0 0 ,
              1  1 0 0 0 0 0  0 1 0   0 1 0 ,
              1  1 0 0 0 0 0  0 0 1   0 0 1 ,
              1  0 1 0 0 0 0  1 0 0   1 0 0 ,
              1  0 1 0 0 0 0  0 0 1   0 1 0 ,
              1  0 1 0 0 0 0  0 1 0   0 0 1 ,
              1  0 0 1 0 0 0  0 1 0   1 0 0 ,
              1  0 0 1 0 0 0  1 0 0   0 1 0 ,
              1  0 0 1 0 0 0  0 0 1   0 0 1 ,
              1  0 0 0 1 0 0  0 1 0   1 0 0 ,
              1  0 0 0 1 0 0  0 0 1   0 1 0 ,
              1  0 0 0 1 0 0  1 0 0   0 0 1 ,
              1  0 0 0 0 1 0  0 0 1   1 0 0 ,
              1  0 0 0 0 1 0  1 0 0   0 1 0 ,
              1  0 0 0 0 1 0  0 1 0   0 0 1 ,
              1  0 0 0 0 0 1  0 0 1   1 0 0 ,
              1  0 0 0 0 0 1  0 1 0   0 1 0 ,
              1  0 0 0 0 0 1  1 0 0   0 0 1 };

PRINT / 'No  Carryover  Model';
P              R              I              N              T
,,,'--------------------------------------------------------------
----';
```

```
PRINT 'Multivariate Approach';
P                R                I                N                T
'--------------------------------------------------------------
-';

a = { 6   1 1 1 1 1 1   6 0 0   2 2 2,
      6   1 1 1 1 1 1   0 6 0   2 2 2,
      6   1 1 1 1 1 1   0 0 6   2 2 2,
      0   0 0 0 0 0 0   6 -6 0   0 0 0,
      0   0 0 0 0 0 0   6 0 -6   0 0 0,
      0   0 0 0 0 0 0   0 6 -6   0 0 0}/6;

DO I=1 TO 6;
  b = GINV(H`)*a[i,]`;
  estimate = b` * muhat; stderr = SQRT( b` * sigmastr * b);
  t = estimate/stderr;  alpha=2*(1-PROBT(ABS(t),df));
     alpha = max(.0001,alpha);

  tcrit=tinv(.975,df);
   LCL=estimate-stderr*tcrit; UCL=estimate+stderr*tcrit;

  IF I=1 THEN;
   PRINT,, 'Trt A LSM ' estimate stderr t alpha, 'A 95% CI is'
LCL  UCL;
  IF I=2 THEN;
   PRINT,, 'Trt B LSM ' estimate stderr t alpha, 'A 95% CI is'
LCL UCL;
  IF I=3 THEN;
   PRINT,, 'Trt C LSM ' estimate stderr t alpha, 'A 95% CI is'
LCL  UCL;
  IF I=4 THEN;
   PRINT,, 'Trt A-Trt B' estimate stderr t alpha, 'A 95% CI is'
LCL UCL;
  IF I=5 THEN;
   PRINT,, 'Trt A-Trt C' estimate stderr t alpha, 'A 95% CI is'
LCL UCL;
  IF I=6 THEN;
   PRINT,, 'Trt B-Trt C' estimate stderr t alpha, 'A 95% CI is'
LCL UCL;
END;

P                R                I                N                T
/'-------------------------------------------------------------
-----';
PRINT 'Mixed Model Approach';
P                R                I                N                T
'--------------------------------------------------------------
----';

beta_eg = GINV(H` * INV(sigmastr) * H) * H` * INV(sigmastr) *
muhat;
```

```
DO I=1 TO 6;
  estimate = a[i,] * beta_eg;
  stderr = SQRT( a[i,] *  GINV( H` * INV(sigmastr) * H ) *
a[i,]` );
  t = estimate/stderr;   alpha = 2 * (1 - PROBT(ABS(t),df) );
     alpha = max(.0001,alpha);

  tcrit=tinv(.975,df);
  LCL = estimate - stderr*tcrit;  UCL = estimate + stderr*tcrit;

  IF I=1 THEN;
   PRINT,, 'Trt A LSM ' estimate stderr t alpha, 'A 95% CI is'
LCL  UCL;
  IF I=2 THEN;
   PRINT,, 'Trt B LSM ' estimate stderr t alpha, 'A 95% CI is'
LCL UCL;
  IF I=3 THEN;
   PRINT,, 'Trt C LSM ' estimate stderr t alpha, 'A 95% CI is'
LCL  UCL;
  IF I=4 THEN;
   PRINT,, 'Trt A-Trt B' estimate stderr t alpha, 'A 95% CI is'
LCL UCL;
  IF I=5 THEN;
   PRINT,, 'Trt A-Trt C' estimate stderr t alpha, 'A 95% CI is'
LCL UCL;
  IF I=6 THEN;
   PRINT,, 'Trt B-Trt C' estimate stderr t alpha, 'A 95% CI is'
LCL UCL;
END;


     /*      Model with Carryover      */  ;

PROC GLM DATA=a;
  CLASSES seq subject trt period priortrt;
  MODEL y = seq subject(seq) trt period priortrt/E;
  CONTRAST 'Carryover Effect' priortrt 1 -1 0 0,
                              priortrt 1 0 -1 0;
  ESTIMATE 'Trt A LSM' intercept 18 seq 3 3 3 3 3 3  trt 18 0 0
                       period 6 6 6 priortrt 4 4 4 6/DIVISOR=18;
  ESTIMATE 'Trt B LSM' intercept 18 seq 3 3 3 3 3 3  trt 0 18 0
                       period 6 6 6 priortrt 4 4 4 6/DIVISOR=18;
  ESTIMATE 'Trt C LSM' intercept 18 seq 3 3 3 3 3 3  trt 0 0 18
                       period 6 6 6 priortrt 4 4 4 6/DIVISOR=18;

  ESTIMATE 'Trt A-Trt B' trt 1 -1 0;
  ESTIMATE 'Trt A-Trt C' trt 1 0 -1;
  ESTIMATE 'Trt B-Trt C' trt 0 1 -1;
  ESTIMATE 'Carryover A-B' priortrt 1 -1 0 0;
  ESTIMATE 'Carryover A-C' priortrt 1 0 -1 0;
  ESTIMATE 'Carryover B-C' priortrt 0 1 -1 0;
```

```
  CONTRAST 'Trt A LSM' intercept 18 seq 3 3 3 3 3 3  trt 18 0 0
                       period 6 6 6 priortrt 4 4 4 6;
  CONTRAST 'Trt B LSM' intercept 18 seq 3 3 3 3 3 3  trt 0 18 0
                       period 6 6 6 priortrt 4 4 4 6;
  CONTRAST 'Trt C LSM' intercept 18 seq 3 3 3 3 3 3  trt 0 0 18
                       period 6 6 6 priortrt 4 4 4 6;

  CONTRAST 'Trt A-Trt B' trt 1 -1 0;
  CONTRAST 'Trt A-Trt C' trt 1 0 -1;
  CONTRAST 'Trt B-Trt C' trt 0 1 -1;
  CONTRAST 'Carryover A-B' priortrt 1 -1 0 0;
  CONTRAST 'Carryover A-C' priortrt 1 0 -1 0;
  CONTRAST 'Carryover B-C' priortrt 0 1 -1 0;
 RANDOM subject(seq);
 RUN;


PROC IML;
RESET nolog;

USE sigma;
READ ALL INTO sigmahat;

USE df;
READ ALL INTO df;
USE means;
READ ALL INTO means;
muhat = means[,1];
USE size;
READ ALL INTO size;
n=size[,1] ;  k=size[,2];
d = DIAG(k);
sigmastr = d @ sigmahat;

       H  = { 1  1 0 0 0 0 0  1 0 0   1 0 0   0 0 0 1,
              1  1 0 0 0 0 0  0 1 0   0 1 0   1 0 0 0,
              1  1 0 0 0 0 0  0 0 1   0 0 1   0 1 0 0,
              1  0 1 0 0 0 0  1 0 0   1 0 0   0 0 0 1,
              1  0 1 0 0 0 0  0 0 1   0 1 0   1 0 0 0,
              1  0 1 0 0 0 0  0 1 0   0 0 1   0 0 1 0,
              1  0 0 1 0 0 0  0 1 0   1 0 0   0 0 0 1,
              1  0 0 1 0 0 0  1 0 0   0 1 0   0 1 0 0,
              1  0 0 1 0 0 0  0 0 1   0 0 1   1 0 0 0,
              1  0 0 0 1 0 0  0 1 0   1 0 0   0 0 0 1,
              1  0 0 0 1 0 0  0 0 1   0 1 0   0 1 0 0,
              1  0 0 0 1 0 0  1 0 0   0 0 1   0 0 1 0,
              1  0 0 0 0 1 0  0 0 1   1 0 0   0 0 0 1,
              1  0 0 0 0 1 0  1 0 0   0 1 0   0 0 1 0,
              1  0 0 0 0 1 0  0 1 0   0 0 1   1 0 0 0,
              1  0 0 0 0 0 1  0 0 1   1 0 0   0 0 0 1,
              1  0 0 0 0 0 1  0 1 0   0 1 0   0 0 1 0,
              1  0 0 0 0 0 1  1 0 0   0 0 1   0 1 0 0};
```

```
PRINT  'Model with Carryover';
P              R              I              N              T
'-------------------------------------------------------------
-';
PRINT 'Multivariate Approach';
P             R             I             N             T
'-------------------------------------------------------------
-';

a = { 18  3 3 3 3 3 3  18 0 0   6 6 6  4 4 4 6,
      18  3 3 3 3 3 3  0 18 0   6 6 6  4 4 4 6,
      18  3 3 3 3 3 3  0 0 18   6 6 6  4 4 4 6,
       0  0 0 0 0 0 0  18 -18 0  0 0 0  0 0 0 0,
       0  0 0 0 0 0 0  18 0 -18  0 0 0  0 0 0 0,
       0  0 0 0 0 0 0  0 18 -18  0 0 0  0 0 0 0,
       0  0 0 0 0 0 0  0 0 0  0 0 0  18 -18 0 0,
       0  0 0 0 0 0 0  0 0 0  0 0 0  18 0 -18 0,
       0  0 0 0 0 0 0  0 0 0  0 0 0  0 18 -18 0}/18;

DO I=1 TO 9;
  b = GINV(H`)*a[i,]`;
  estimate = b` * muhat;
  stderr = SQRT( b` * sigmastr * b);
  t = estimate/stderr;
  alpha = 2 * (1 - PROBT(ABS(t),df));  alpha = max(.0001,alpha);

  tcrit=tinv(.975,df);
  LCL = estimate - stderr*tcrit;  UCL = estimate + stderr*tcrit;

  IF I=1 THEN;
   PRINT,, 'Trt A LSM ' estimate stderr t alpha, 'A 95% CI is'
LCL  UCL;
  IF I=2 THEN;
   PRINT,, 'Trt B LSM ' estimate stderr t alpha, 'A 95% CI is'
LCL UCL;
  IF I=3 THEN;
   PRINT,, 'Trt C LSM ' estimate stderr t alpha, 'A 95% CI is'
LCL  UCL;
  IF I=4 THEN;
   PRINT,, 'Trt A-Trt B' estimate stderr t alpha, 'A 95% CI is'
LCL UCL;
  IF I=5 THEN;
   PRINT,, 'Trt A-Trt C' estimate stderr t alpha, 'A 95% CI is'
LCL UCL;
  IF I=6 THEN;
   PRINT,, 'Trt B-Trt C' estimate stderr t alpha, 'A 95% CI is'
LCL UCL;
  IF I=7 THEN;
   PRINT,, 'Carryover A - Carryover B ' estimate stderr t alpha;
  IF I=8 THEN;
   PRINT,, 'Carryover A - Carryover C ' estimate stderr t alpha;
```

```
  IF I=9 THEN;
   PRINT,, 'Carryover B - Carryover C ' estimate stderr t alpha;
END;

PRINT/'-------------------------------------------------------------
-----------';
PRINT 'Mixed Model Approach';
P              R              I              N              T
'-------------------------------------------------------------
----';

beta_eg = GINV(H` * INV(sigmastr) * H) * H` * INV(sigmastr) *
muhat;

DO I=1 TO 9;
  estimate = a[i,] * beta_eg;
  stderr = SQRT( a[i,] *  GINV( H` * INV(sigmastr) * H ) *
a[i,]` );
  t = estimate/stderr;   alpha = 2 * (1 - PROBT(ABS(t),df) );
      alpha = max(.0001,alpha);

  tcrit=tinv(.975,df);
  LCL  =  estimate  -  stderr*tcrit;      UCL  =  estimate  +
stderr*tcrit;

  IF I=1 THEN;
   PRINT,, 'Trt A LSM ' estimate stderr t alpha, 'A 95% CI is'
LCL  UCL;
  IF I=2 THEN;
   PRINT,, 'Trt B LSM ' estimate stderr t alpha, 'A 95% CI is'
LCL UCL;
  IF I=3 THEN;
   PRINT,, 'Trt C LSM ' estimate stderr t alpha, 'A 95% CI is'
LCL  UCL;
  IF I=4 THEN;
   PRINT,, 'Trt A-Trt B' estimate stderr t alpha, 'A 95% CI is'
LCL UCL;
  IF I=5 THEN;
   PRINT,, 'Trt A-Trt C' estimate stderr t alpha, 'A 95% CI is'
LCL UCL;
  IF I=6 THEN;
   PRINT,, 'Trt B-Trt C' estimate stderr t alpha, 'A 95% CI is'
LCL UCL;
  IF I=7 THEN;
   PRINT,, 'Carryover A - Carryover B ' estimate stderr t alpha;
  IF I=8 THEN;
   PRINT,, 'Carryover A - Carryover C ' estimate stderr t alpha;
  IF I=9 THEN;
   PRINT,, 'Carryover B - Carryover C ' estimate stderr t alpha;
END;
```

The important parts of the output obtained from the preceding SAS commands is shown next. All of the output can be obtained by executing the preceding commands.

```
                              SAS                                    4
                  General Linear Models Procedure
                Repeated Measures Analysis of Variance

          Partial Correlation Coefficients from the Error SS&CP Matrix
 of the Variables Defined by the Specified Transformation / Prob > |r|

                    DF = 29      PERIOD.1  PERIOD.2
                    PERIOD.1     1.000000  0.050046
                                   0.0       0.7892
                    PERIOD.2     0.050046  1.000000
                                   0.7892    0.0

             Test for Sphericity: Mauchly's Criterion = 0.9910303
              Chisquare Approximation = 0.2612936 with 2 df
                         Prob > Chisquare = 0.8775

              Manova Test Criteria and Exact F Statistics for
                   the Hypothesis of no PERIOD Effect
    H = Type III SS&CP Matrix for PERIOD   E = Error SS&CP Matrix

                         S=1    M=0    N=13.5

 Statistic                 Value          F     Num DF   Den DF   Pr > F

 Wilks' Lambda           0.18884865   62.2811       2        29   0.0001
 Pillai's Trace          0.81115135   62.2811       2        29   0.0001
 Hotelling-Lawley Trace  4.29524555   62.2811       2        29   0.0001
 Roy's Greatest Root     4.29524555   62.2811       2        29   0.0001

               Manova Test Criteria and F Approximations for
                   the Hypothesis of no PERIOD*SEQ Effect
   H = Type III SS&CP Matrix for PERIOD*SEQ   E = Error SS&CP Matrix

                         S=2    M=1    N=13.5

 Statistic                 Value          F     Num DF   Den DF   Pr > F

 Wilks' Lambda           0.01748514   38.0625      10        58   0.0001
 Pillai's Trace           1.7330847   38.9581      10        60   0.0001
 Hotelling-Lawley Trace  13.2652621   37.1427      10        56   0.0001
 Roy's Greatest Root     7.66493366   45.9896       5        30   0.0001

      NOTE: F Statistic for Roy's Greatest Root is an upper bound.
             NOTE: F Statistic for Wilks' Lambda is exact.


                              SAS                                    5

                   General Linear Models Procedure
                Repeated Measures Analysis of Variance
             Tests of Hypotheses for Between Subjects Effects

Source                    DF   Type III SS   Mean Square  F Value     Pr > F

SEQ                        5       53.1885       10.6377     1.04     0.4142

Error                     30      307.7789       10.2593
```

SAS 6

General Linear Models Procedure
Repeated Measures Analysis of Variance
Univariate Tests of Hypotheses for Within Subject Effects

Source: PERIOD

DF	Type III SS	Mean Square	F Value	Pr > F	Adj Pr > F G - G	Adj Pr > F H - F
2	106.64518519	53.32259259	58.52	0.0001	0.0001	0.0001

Source: PERIOD*SEQ

DF	Type III SS	Mean Square	F Value	Pr > F	Adj Pr > F G - G	Adj Pr > F H - F
10	365.94037037	36.59403704	40.16	0.0001	0.0001	0.0001

Source: Error(PERIOD)

DF	Type III SS	Mean Square
60	54.66777778	0.91112963

Greenhouse-Geisser Epsilon = 0.9911
Huynh-Feldt Epsilon = 1.2378

SAS 10

General Linear Models Procedure

Dependent Variable: Y

Source	DF	Sum of Squares	Mean Square	F Value	Pr > F
Model	39	817.58500	20.96372	20.18	0.0001
Error	68	70.63574	1.03876		
Corrected Total	107	888.22074			

R-Square	C.V.	Root MSE	Y Mean
0.920475	4.170071	1.0192	24.44074

Source	DF	Type I SS	Mean Square	F Value	Pr > F
SEQ	5	53.18852	10.63770	~~10.24~~	~~0.0001~~
SUBJECT(SEQ)	30	307.77889	10.25930	9.88	0.0001
TRT	2	349.97241	174.98620	168.46	0.0001
PERIOD	2	106.64519	53.32259	51.33	0.0001

Source	DF	Type III SS	Mean Square	F Value	Pr > F
SEQ	5	53.18852	10.63770	~~10.24~~	~~0.0001~~
SUBJECT(SEQ)	30	307.77889	10.25930	9.88	0.0001
TRT	2	349.97241	174.98620	168.46	0.0001
PERIOD	2	106.64519	53.32259	51.33	0.0001

Contrast	DF	Contrast SS	Mean Square	F Value	Pr > F
Trt A LSM	1	20145.071	20145.071	~~19393.37~~	~~0.0001~~
Trt B LSM	1	18609.507	18609.507	~~17915.10~~	~~0.0001~~
Trt C LSM	1	26109.174	26109.174	~~25134.92~~	~~0.0001~~
Trt A-Trt B	1	15.217	15.217	14.65	0.0003
Trt A-Trt C	1	193.061	193.061	185.86	0.0001
Trt B-Trt C	1	316.681	316.681	304.86	0.0001

Parameter	Estimate	T for H0: Parameter=0	Pr > |T|	Std Error of Estimate
Trt A LSM	23.65555556	~~139.26~~	~~0.0001~~	~~0.16986603~~
Trt B LSM	22.73611111	~~133.85~~	~~0.0001~~	~~0.16986603~~
Trt C LSM	26.93055556	~~158.54~~	~~0.0001~~	~~0.16986603~~
Trt A-Trt B	0.91944444	3.83	0.0003	0.24022685
Trt A-Trt C	-3.27500000	-13.63	0.0001	0.24022685
Trt B-Trt C	-4.19444444	-17.46	0.0001	0.24022685

```
                              SAS                              12

                 SIGMAHAT
                4.3508889 3.2581111 3.2118889
                3.2581111 3.9822222 2.8781667
                3.2118889 2.8781667 3.7484444


                              SAS                              13

                    No  Carryover  Model

   ----------------------------------------------------------------
                     Multivariate Approach
   ----------------------------------------------------------------

              ESTIMATE    STDERR         T     ALPHA
   Trt A LSM  23.655556 0.3344641 70.726734    0.0001

                                LCL       UCL
              A 95% CI is 22.972489 24.338622

              ESTIMATE    STDERR         T     ALPHA
   Trt B LSM  22.736111 0.3344641 67.977726    0.0001

                                LCL       UCL
              A 95% CI is 22.053044 23.419178

              ESTIMATE    STDERR         T     ALPHA
   Trt C LSM  26.930556 0.3344641 80.518516    0.0001

                                LCL       UCL
              A 95% CI is 26.247489 27.613622

               ESTIMATE    STDERR         T     ALPHA
   Trt A-Trt B 0.9194444 0.2249851 4.0866897 0.0003007

                                LCL       UCL
              A 95% CI is 0.4599635 1.3789254

               ESTIMATE    STDERR         T     ALPHA
   Trt A-Trt C    -3.275 0.2249851 -14.55652    0.0001

                                LCL       UCL
              A 95% CI is -3.734481 -2.815519

               ESTIMATE    STDERR         T     ALPHA
   Trt B-Trt C -4.194444 0.2249851 -18.64321    0.0001

                                LCL       UCL
              A 95% CI is -4.653925 -3.734963


                              SAS                              14

                    No  Carryover  Model

  ------------------------------------------------------------------
                     Mixed Model Approach
  ------------------------------------------------------------------

              ESTIMATE    STDERR         T     ALPHA
   Trt A LSM  23.666882 0.3342378 70.808514    0.0001

                                LCL       UCL
              A 95% CI is 22.984278 24.349487
```

```
                 ESTIMATE    STDERR          T     ALPHA
Trt B LSM   22.745525 0.3342378 68.051922     0.0001

                            LCL        UCL
          A 95% CI is 22.062921  23.42813

                 ESTIMATE    STDERR          T     ALPHA
Trt C LSM   26.909814 0.3342378 80.510983     0.0001

                            LCL        UCL
          A 95% CI is  26.22721 27.592419

                  ESTIMATE    STDERR          T     ALPHA
Trt A-Trt B  0.921357 0.2239738 4.1136812 0.0002791

                            LCL        UCL
          A 95% CI is 0.4639414 1.3787726

                  ESTIMATE    STDERR          T     ALPHA
Trt A-Trt C -3.242932 0.2239738 -14.47907     0.0001

                            LCL        UCL
          A 95% CI is -3.700348 -2.785516

                  ESTIMATE    STDERR          T     ALPHA
Trt B-Trt C -4.164289 0.2239738 -18.59275     0.0001

                            LCL        UCL
          A 95% CI is -4.621705 -3.706873
```

SAS 17
General Linear Models Procedure

Dependent Variable: Y

Source	DF	Sum of Squares	Mean Square	F Value	Pr > F
Model	41	822.03421	20.04961	19.99	0.0001
Error	66	66.18653	1.00283		
Corrected Total	107	888.22074			

R-Square	C.V.	Root MSE	Y Mean
0.925484	4.097307	1.0014	24.44074

Source	DF	Type III SS	Mean Square	F Value	Pr > F
SEQ	5	53.67258	10.73452	~~10.70~~	~~0.0001~~
SUBJECT(SEQ)	30	307.77889	10.25930	10.23	0.0001
TRT	2	249.72636	124.86318	124.51	0.0001
PERIOD	1	15.12500	15.12500	15.08	0.0002
PRIORTRT	2	4.44921	2.22461	2.22	0.1168

Contrast	DF	Contrast SS	Mean Square	F Value	Pr > F
Carryover Effect	2	4.449	2.225	2.22	0.1168
Trt A LSM	1	17298.308	17298.308	~~17249.56~~	~~0.0001~~
Trt B LSM	1	16108.924	16108.924	~~16063.53~~	~~0.0001~~
Trt C LSM	1	22157.857	22157.857	~~22095.41~~	~~0.0001~~
Trt A-Trt B	1	9.884	9.884	9.86	0.0025
Trt A-Trt C	1	140.188	140.188	139.79	0.0001
Trt B-Trt C	1	224.518	224.518	223.89	0.0001
Carryover A-B	1	0.596	0.596	0.59	0.4436
Carryover A-C	1	1.727	1.727	1.72	0.1940
Carryover B-C	1	4.351	4.351	4.34	0.0411

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Parameter	Estimate	T for H0: Parameter=0	Pr > |T|	Std Error of Estimate
Trt A LSM	23.67685185	~~131.34~~	~~0.0001~~	~~0.18027478~~
Trt B LSM	22.84837963	~~126.74~~	~~0.0001~~	~~0.18027478~~
Trt C LSM	26.79699074	~~148.65~~	~~0.0001~~	~~0.18027478~~
Trt A-Trt B	0.82847222	3.14	0.0025	0.26389526
Trt A-Trt C	-3.12013889	-11.82	0.0001	0.26389526
Trt B-Trt C	-3.94861111	-14.96	0.0001	0.26389526
Carryover A-B	-0.27291667	-0.77	0.4436	0.35405264
Carryover A-C	0.46458333	1.31	0.1940	0.35405264
Carryover B-C	0.73750000	2.08	0.0411	0.35405264

SAS 19

Model with Carryover

Multivariate Approach

```
           ESTIMATE    STDERR          T      ALPHA
Trt A LSM  23.676852 0.3399816 69.641567     0.0001

                      LCL        UCL
A 95% CI is 22.982517 24.371187

           ESTIMATE    STDERR          T      ALPHA
Trt B LSM   22.84838 0.3399816 67.204753     0.0001

                      LCL        UCL
A 95% CI is 22.154045 23.542715

           ESTIMATE    STDERR          T      ALPHA
Trt C LSM  26.796991 0.3399816 78.818943     0.0001

                      LCL        UCL
A 95% CI is 26.102656 27.491326

             ESTIMATE    STDERR          T      ALPHA
Trt A-Trt B 0.8284722 0.2485599 3.3330889 0.0022926

                      LCL        UCL
A 95% CI is 0.3208452 1.3360993

             ESTIMATE    STDERR          T      ALPHA
Trt A-Trt C -3.120139 0.2485599 -12.55287     0.0001

                      LCL        UCL
A 95% CI is -3.627766 -2.612512

             ESTIMATE    STDERR          T      ALPHA
Trt B-Trt C -3.948611 0.2485599 -15.88595     0.0001

                      LCL        UCL
A 95% CI is -4.456238 -3.440984

                           ESTIMATE    STDERR          T     ALPHA
Carryover A - Carryover B -0.272917 0.3446902 -0.791774 0.4347088

                           ESTIMATE    STDERR          T     ALPHA
Carryover A - Carryover C 0.4645833 0.3446902 1.3478286 0.1878041

                           ESTIMATE    STDERR          T     ALPHA
Carryover B - Carryover C    0.7375 0.3446902 2.1396024 0.0406403
```

SAS 20

Model with Carryover

Mixed Model Approach

```
             ESTIMATE    STDERR          T     ALPHA
Trt A LSM    23.68273  0.339728 69.710857    0.0001

                                LCL        UCL
           A 95% CI is 22.988913 24.376547

             ESTIMATE    STDERR          T     ALPHA
Trt B LSM  22.848954  0.339728  67.25661    0.0001

                                LCL        UCL
           A 95% CI is 22.155137 23.542771

             ESTIMATE    STDERR          T     ALPHA
Trt C LSM  26.790538  0.339728 78.858786    0.0001

                                LCL        UCL
           A 95% CI is 26.096721 27.484355

              ESTIMATE    STDERR          T     ALPHA
Trt A-Trt B 0.8337763 0.2475175 3.3685554 0.0020892

                                LCL        UCL
           A 95% CI is 0.3282782 1.3392744

              ESTIMATE    STDERR          T     ALPHA
Trt A-Trt C -3.107808 0.2475175 -12.55591    0.0001

                                LCL        UCL
           A 95% CI is -3.613306  -2.60231

              ESTIMATE    STDERR          T     ALPHA
Trt B-Trt C -3.941584 0.2475175 -15.92447    0.0001

                                LCL        UCL
           A 95% CI is -4.447082 -3.436086

                              ESTIMATE    STDERR          T     ALPHA
Carryover A - Carryover B  -0.285747 0.3437527 -0.831256 0.4123964

                              ESTIMATE    STDERR          T     ALPHA
Carryover A - Carryover C  0.4408652 0.3437527 1.2825068 0.2094864

                              ESTIMATE    STDERR          T     ALPHA
Carryover B - Carryover C  0.7266117 0.3437527 2.1137629 0.0429597
```