Chapter 222

Mixed Models – Repeated Measures

Introduction

This specialized Mixed Models procedure analyzes results from repeated measures designs in which the outcome (response) is continuous and measured at fixed time points. The procedure uses the standard mixed model calculation engine to perform all calculations. However, the user-interface has been simplified to make specifying the repeated measures analysis much easier.

These designs that can be analyzed by this procedure include

- Split-plot designs
- Repeated-measures designs
- Cross-over designs
- Designs with covariates

This chapter gives an abbreviated coverage of mixed models in general. We rely on the Mixed Models - General chapter for a comprehensive overview. We encourage you to look there for details of mixed models.

Types of Factors

It is important to understand between-subject factors and within-subject factors.

Between-Subject Factors

Each subject is assigned to only one category of a each between-subject factor. For example, if 12 subjects are randomly assigned to three treatment groups (four subjects per group), treatment is a between-subject factor.

Within-Subject Factors

Within-subject factors are those in which the subject's response is measured at several time points. Within-subject factors are those factors for which multiple levels of the factor are measured on the same subject. If each subject is measured at the low, medium, and high level of the treatment, treatment is a within-subject factor.
Random versus Repeated Error Formulation

The general form of the linear mixed model is

\[ \mathbf{y} = \mathbf{X}\beta + \mathbf{Z}\mathbf{u} + \mathbf{\varepsilon} \]

\[ \mathbf{u} \sim N(\mathbf{0}, \mathbf{G}) \]

\[ \mathbf{\varepsilon} \sim N(\mathbf{0}, \mathbf{R}) \]

\[ \text{Cov} [\mathbf{u}, \mathbf{\varepsilon}] = \mathbf{0} \]

\[ \mathbf{V} = \mathbf{ZGZ}' + \mathbf{R} \]

The specification of the random component of the model specifies the structure of \( \mathbf{Z}, \mathbf{u}, \) and \( \mathbf{G}. \) The specification of the repeated (error or residual) component of the model specifies the structure of \( \mathbf{\varepsilon} \) and \( \mathbf{R}. \) Most of the designs available in this procedure use only the repeated component. The exception is that a compound symmetric, random effects design can be generated that uses a diagonal repeated component.

Determining the Correct Model of the Variance-Covariance of \( \mathbf{Y} \)

Akaike Information Criterion (AIC) for Model Assessment

Akaike information criterion (AIC) is a tool for assessing model fit (Akaike, 1973, 1974). The formula is

\[ AIC = -2 \times L + 2p \]

where \( L \) is the (ML or REML) log-likelihood and \( p \) depends on the type of likelihood selected. If the ML method is used, \( p \) is the total number of parameters. If the REML method is used, \( p \) is the number of variance component parameters.

The formula is designed so that a smaller AIC value indicates a “better” model. AIC penalizes models with larger numbers of parameters. That is, if a model with a much larger number of parameters produces only a slight improvement in likelihood, the values of AIC for the two models will suggest that the more parsimonious (limited) model is still the “better” model.

As an example, suppose a researcher would like to determine the appropriate variance-covariance structure for a longitudinal model with four equal time points. The researcher uses REML as the likelihood type. The analysis is run five times, each with a different covariance pattern, and the AIC values are recorded as follows.

<table>
<thead>
<tr>
<th>Pattern</th>
<th>Number of Parameters</th>
<th>-2 log-likelihood</th>
<th>AIC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diagonal</td>
<td>1</td>
<td>214.43</td>
<td>216.43</td>
</tr>
<tr>
<td>Compound Symmetry</td>
<td>2</td>
<td>210.77</td>
<td>214.77</td>
</tr>
<tr>
<td>AR(1)</td>
<td>2</td>
<td>203.52</td>
<td>207.52</td>
</tr>
<tr>
<td>Toeplitz</td>
<td>4</td>
<td>198.03</td>
<td>206.03</td>
</tr>
<tr>
<td>Unstructured</td>
<td>7</td>
<td>197.94</td>
<td>211.94</td>
</tr>
</tbody>
</table>

The recommended variance-covariance structure among these five is the Toeplitz pattern, since it results in the smallest AIC value.
What to Do When You Encounter a Variance Estimate that is Equal to Zero

It is possible that a mixed models data analysis results in a variance component estimate that is negative or equal to zero. When this happens, the fitted model should be changed by selecting a different repeated component, by selecting a grouping factor, or by selecting different fixed factors and covariates.

Fixed Effects

A fixed effect (or factor) is a variable for which levels in the study represent all levels of interest, or at least all levels that are important for inference (e.g., treatment, dose, etc.). The fixed effects in the model include those factors for which means, standard errors, and confidence intervals will be estimated, and tests of hypotheses will be performed. Other variables for which the model is to be adjusted (that are not important for estimation or hypothesis testing) may also be included in the model as fixed factors. Fixed factors may be discrete variables or continuous covariates.

The correct model for fixed effects depends on the number of fixed factors, the questions to be answered by the analysis, and the amount of data available for the analysis. When more than one fixed factor may influence the response, it is common to include those factors in the model, along with their interactions (two-way, three-way, etc.). Difficulties arise when there are not sufficient data to model the higher-order interactions. In this case, some interactions must be omitted from the model. It is usually suggested that if you include an interaction in the model, you should also include the main effects (i.e., individual factors) involved in the interaction even if the hypothesis test for the main effects is not significant.

Covariates

Covariates are continuous measurements that are not of primary interest in the study, but potentially have an influence on the response. Two types of covariates typically arise in mixed models designs: subject covariates and within-subject covariates.

This procedure permits the user to make comparisons of fixed-effect means at specified values of covariates. Commonly, investigators wish to make comparisons of levels of a factor at low, medium, and high values of covariates.

Multiple Comparisons of Fixed Effect Levels

If there is evidence that a fixed factor of a mixed model has difference responses among its levels, it is usually of interest to perform post-hoc pair-wise comparisons of the least-squares means to further clarify those differences. It is well-known that p-value adjustments need to be made when multiple tests are performed (see Hochberg and Tamhane, 1987, or Hsu, 1996, for general discussion and details of the need for multiplicity adjustment). Such adjustments are usually made to preserve the family-wise error rate (FWER), also called the experiment-wise error rate, of the group of tests. FWER is the probability of incorrectly rejecting at least one of the pair-wise tests.

We refer you to the Mixed Models chapter for more details on multiple comparisons.
Specifying the Within-Subjects Variance-Covariance Matrix

The R Matrix

The R matrix is the variance-covariance matrix for errors, \( \varepsilon \). When the R matrix is used to specify the variance-covariance structure of \( y \), the \( G_{sub} \) matrix (the random component) is not used.

The full R matrix is made up of \( N \) symmetric R sub-matrices,

\[
R = \begin{pmatrix}
R_1 & 0 & 0 & \cdots & 0 \\
0 & R_2 & 0 & \cdots & 0 \\
0 & 0 & R_3 & \cdots & 0 \\
\vdots & \vdots & \vdots & \ddots & \vdots \\
0 & 0 & 0 & \cdots & R_N
\end{pmatrix},
\]

where \( R_1, R_2, R_3, \ldots, R_N \) are all of the same structure, but, unlike the \( G_{sub} \) matrices, differ according to the number of repeated measurements on each subject.

When the R matrix is specified in NCSS, it is assumed that there is a fixed, known set of repeated measurement times. Thus, the differences in the dimensions of the R sub-matrices occur only when some measurements for a subject are missing.

As an example, suppose an R sub-matrix is of the form

\[
R_{sub} = \begin{pmatrix}
\sigma_1^2 & \sigma_2^2 & \sigma_3^2 & \sigma_4^2 & \sigma_5^2 \\
\sigma_2^2 & \sigma_3^2 & \sigma_4^2 & \sigma_5^2 & \sigma_6^2 \\
\sigma_3^2 & \sigma_4^2 & \sigma_5^2 & \sigma_6^2 & \sigma_7^2 \\
\sigma_4^2 & \sigma_5^2 & \sigma_6^2 & \sigma_7^2 & \sigma_8^2 \\
\sigma_5^2 & \sigma_6^2 & \sigma_7^2 & \sigma_8^2 & \sigma_9^2
\end{pmatrix},
\]

where there are five time points at which each subject is intended to be measured: 1 hour, 2 hours, 5 hours, 10 hours, and 24 hours. If the first subject has measurements at all five time points, then \( n_1 = 5 \), and the sub-matrix is identical to \( R_{sub} \) above, and \( R_1 = R_{sub} \).

Suppose the second subject is measured at 1 hour, 5 hours, and 24 hours, but misses the 2-hour and 10-hour measurements. The \( R_2 \) matrix for this subject is

\[
R_2 = \begin{pmatrix}
\sigma_1^2 & \sigma_3^2 \\
\sigma_3^2 & \sigma_5^2
\end{pmatrix}.
\]

For this subject, \( n_2 = 3 \). That is, for the case when the time points are fixed, instead of having missing values in the R sub-matrices, the matrix is collapsed to accommodate the number of realized measurements.
Structures of R

There are many possible structures for the sub-matrices that make up the \( \mathbf{R} \) matrix. The \( \mathbf{R}_{\text{sub}} \) structures that can be specified in NCSS are shown below.

### Diagonal

<table>
<thead>
<tr>
<th>Homogeneous</th>
<th>Heterogeneous</th>
<th>Correlation</th>
</tr>
</thead>
</table>
| \[
\begin{pmatrix}
\sigma^2 \\
\sigma^2 \\
\sigma^2 \\
\sigma^2
\end{pmatrix}
\]
| \[
\begin{pmatrix}
\sigma_1^2 \\
\sigma_2^2 \\
\sigma_3^2 \\
\sigma_4^2
\end{pmatrix}
\]
| \[
\begin{pmatrix}
1 \\
1 \\
1 \\
1
\end{pmatrix}
\]

### Compound Symmetry

<table>
<thead>
<tr>
<th>Homogeneous</th>
<th>Heterogeneous</th>
<th>Correlation</th>
</tr>
</thead>
</table>
| \[
\begin{pmatrix}
\sigma^2 & \rho \sigma^2 & \rho \sigma^2 & \rho \sigma^2 \\
\rho \sigma^2 & \sigma^2 & \rho \sigma^2 & \rho \sigma^2 \\
\rho \sigma^2 & \rho \sigma^2 & \sigma^2 & \rho \sigma^2 \\
\rho \sigma^2 & \rho \sigma^2 & \rho \sigma^2 & \sigma^2
\end{pmatrix}
\]
| \[
\begin{pmatrix}
\sigma_1^2 & \rho \sigma_1 \sigma_2 & \rho \sigma_1 \sigma_3 & \rho \sigma_1 \sigma_4 \\
\rho \sigma_1 \sigma_2 & \sigma_2^2 & \rho \sigma_2 \sigma_3 & \rho \sigma_2 \sigma_4 \\
\rho \sigma_1 \sigma_3 & \rho \sigma_2 \sigma_3 & \sigma_3^2 & \rho \sigma_3 \sigma_4 \\
\rho \sigma_1 \sigma_4 & \rho \sigma_2 \sigma_4 & \rho \sigma_3 \sigma_4 & \sigma_4^2
\end{pmatrix}
\]
| \[
\begin{pmatrix}
1 & \rho & \rho & \rho \\
\rho & 1 & \rho & \rho \\
\rho & \rho & 1 & \rho \\
\rho & \rho & \rho & 1
\end{pmatrix}
\]

### AR(1)

<table>
<thead>
<tr>
<th>Homogeneous</th>
<th>Heterogeneous</th>
<th>Correlation</th>
</tr>
</thead>
</table>
| \[
\begin{pmatrix}
\sigma^2 & \rho \sigma^2 & \rho^2 \sigma^2 & \rho^3 \sigma^2 \\
\rho \sigma^2 & \sigma^2 & \rho^2 \sigma^2 & \rho^3 \sigma^2 \\
\rho^2 \sigma^2 & \rho \sigma^2 & \sigma^2 & \rho^2 \sigma^2 \\
\rho^3 \sigma^2 & \rho^2 \sigma^2 & \rho \sigma^2 & \sigma^2
\end{pmatrix}
\]
| \[
\begin{pmatrix}
\sigma_1^2 & \rho \sigma_1 \sigma_2 & \rho^2 \sigma_1 \sigma_3 & \rho^3 \sigma_1 \sigma_4 \\
\rho \sigma_1 \sigma_2 & \sigma_2^2 & \rho \sigma_2 \sigma_3 & \rho^2 \sigma_2 \sigma_4 \\
\rho^2 \sigma_1 \sigma_3 & \rho \sigma_2 \sigma_3 & \sigma_3^2 & \rho \sigma_3 \sigma_4 \\
\rho^3 \sigma_1 \sigma_4 & \rho^2 \sigma_2 \sigma_4 & \rho \sigma_3 \sigma_4 & \sigma_4^2
\end{pmatrix}
\]
| \[
\begin{pmatrix}
1 & \rho & \rho^2 & \rho^3 \\
\rho & 1 & \rho & \rho^2 \\
\rho^2 & \rho & 1 & \rho \\
\rho^3 & \rho^2 & \rho & 1
\end{pmatrix}
\]

### AR(Time Diff)

<table>
<thead>
<tr>
<th>Homogeneous</th>
<th>Heterogeneous</th>
<th>Correlation</th>
</tr>
</thead>
</table>
| \[
\begin{pmatrix}
\sigma^2 & \rho^{t_2-t_1} \sigma^2 & \rho^{t_3-t_1} \sigma^2 & \rho^{t_4-t_1} \sigma^2 \\
\rho^{t_2-t_1} \sigma^2 & \sigma^2 & \rho^{t_3-t_1} \sigma^2 & \rho^{t_4-t_1} \sigma^2 \\
\rho^{t_3-t_1} \sigma^2 & \rho^{t_3-t_2} \sigma^2 & \sigma^2 & \rho^{t_4-t_3} \sigma^2 \\
\rho^{t_4-t_1} \sigma^2 & \rho^{t_4-t_2} \sigma^2 & \rho^{t_4-t_3} \sigma^2 & \sigma^2
\end{pmatrix}
\]
| \[
\begin{pmatrix}
\sigma_1^2 & \rho^{t_2-t_1} \sigma_1 \sigma_2 & \rho^{t_3-t_1} \sigma_1 \sigma_3 & \rho^{t_4-t_1} \sigma_1 \sigma_4 \\
\rho^{t_2-t_1} \sigma_1 \sigma_2 & \sigma_2^2 & \rho^{t_3-t_1} \sigma_2 \sigma_3 & \rho^{t_4-t_1} \sigma_2 \sigma_4 \\
\rho^{t_3-t_1} \sigma_1 \sigma_3 & \rho^{t_3-t_2} \sigma_3 \sigma_2 & \sigma_3^2 & \rho^{t_4-t_3} \sigma_3 \sigma_4 \\
\rho^{t_4-t_1} \sigma_1 \sigma_4 & \rho^{t_4-t_2} \sigma_4 \sigma_2 & \rho^{t_4-t_3} \sigma_4 \sigma_3 & \sigma_4^2
\end{pmatrix}
\]
| \[
\begin{pmatrix}
1 & \rho^{t_2-t_1} & \rho^{t_3-t_1} & \rho^{t_4-t_1} \\
\rho^{t_2-t_1} & 1 & \rho^{t_3-t_2} & \rho^{t_4-t_2} \\
\rho^{t_3-t_1} & \rho^{t_3-t_2} & 1 & \rho^{t_4-t_3} \\
\rho^{t_4-t_1} & \rho^{t_4-t_2} & \rho^{t_4-t_3} & 1
\end{pmatrix}
\]
### Toeplitz

#### Homogeneous

\[
\begin{pmatrix}
\sigma^2 & \rho_1 \sigma^2 & \rho_2 \sigma^2 & \rho_3 \sigma^2 \\
\rho_1 \sigma^2 & \sigma^2 & \rho_1 \sigma^2 & \rho_2 \sigma^2 \\
\rho_2 \sigma^2 & \rho_1 \sigma^2 & \sigma^2 & \rho_1 \sigma^2 \\
\rho_3 \sigma^2 & \rho_2 \sigma^2 & \rho_1 \sigma^2 & \sigma^2
\end{pmatrix}
\]

#### Heterogeneous

\[
\begin{pmatrix}
\sigma_1^2 & \rho_1 \sigma_1 \sigma_2 & \rho_2 \sigma_1 \sigma_3 & \rho_3 \sigma_1 \sigma_4 \\
\rho_1 \sigma_2 \sigma_1 & \sigma_2^2 & \rho_1 \sigma_2 \sigma_3 & \rho_2 \sigma_2 \sigma_4 \\
\rho_2 \sigma_3 \sigma_1 & \rho_1 \sigma_3 \sigma_2 & \sigma_3^2 & \rho_1 \sigma_3 \sigma_4 \\
\rho_3 \sigma_4 \sigma_1 & \rho_2 \sigma_4 \sigma_2 & \rho_1 \sigma_4 \sigma_3 & \sigma_4^2
\end{pmatrix}
\]

#### Correlation

\[
\begin{pmatrix}
1 & \rho_1 & \rho_2 & \rho_3 \\
\rho_1 & 1 & \rho_1 & \rho_2 \\
\rho_2 & \rho_1 & 1 & \rho_1 \\
\rho_3 & \rho_2 & \rho_1 & 1
\end{pmatrix}
\]

Note: This is the same as Banded(2).

### Toeplitz(2)

#### Homogeneous

\[
\begin{pmatrix}
\sigma^2 & \rho_1 \sigma^2 \\
\rho_1 \sigma^2 & \sigma^2 \\
\rho_1 \sigma^2 & \sigma^2 \\
\rho_1 \sigma^2 & \sigma^2
\end{pmatrix}
\]

#### Heterogeneous

\[
\begin{pmatrix}
\sigma_1^2 & \rho_1 \sigma_1 \sigma_2 \\
\rho_1 \sigma_2 \sigma_1 & \sigma_2^2 \\
\rho_1 \sigma_3 \sigma_1 & \rho_1 \sigma_3 \sigma_2 & \sigma_3^2 \\
\rho_1 \sigma_4 \sigma_1 & \rho_1 \sigma_4 \sigma_2 & \rho_1 \sigma_4 \sigma_3 & \sigma_4^2
\end{pmatrix}
\]

#### Correlation

\[
\begin{pmatrix}
1 & \rho_1 \\
\rho_1 & 1 \\
\rho_1 & 1 \\
\rho_1 & 1
\end{pmatrix}
\]

Note: This is the same as Banded(2).

### Toeplitz(3)

#### Homogeneous

\[
\begin{pmatrix}
\sigma^2 & \rho_1 \sigma^2 & \rho_2 \sigma^2 \\
\rho_1 \sigma^2 & \sigma^2 & \rho_1 \sigma^2 \\
\rho_2 \sigma^2 & \rho_1 \sigma^2 & \sigma^2 \\
\rho_2 \sigma^2 & \rho_1 \sigma^2 & \sigma^2
\end{pmatrix}
\]

#### Heterogeneous

\[
\begin{pmatrix}
\sigma_1^2 & \rho_1 \sigma_1 \sigma_2 & \rho_2 \sigma_1 \sigma_3 \\
\rho_1 \sigma_2 \sigma_1 & \sigma_2^2 & \rho_1 \sigma_2 \sigma_3 & \rho_2 \sigma_2 \sigma_4 \\
\rho_2 \sigma_3 \sigma_1 & \rho_1 \sigma_3 \sigma_2 & \sigma_3^2 & \rho_1 \sigma_3 \sigma_4 \\
\rho_2 \sigma_4 \sigma_1 & \rho_1 \sigma_4 \sigma_2 & \rho_1 \sigma_4 \sigma_3 & \sigma_4^2
\end{pmatrix}
\]

#### Correlation

\[
\begin{pmatrix}
1 & \rho_1 & \rho_2 & \rho_3 \\
\rho_1 & 1 & \rho_1 & \rho_2 \\
\rho_2 & \rho_1 & 1 & \rho_1 \\
\rho_3 & \rho_2 & \rho_1 & 1
\end{pmatrix}
\]

### Toeplitz(4) and Toeplitz(5)

Toeplitz(4) and Toeplitz(5) follow the same pattern as Toeplitz(2) and Toeplitz(3), but with the corresponding numbers of bands.

### Banded(2)

#### Homogeneous

\[
\begin{pmatrix}
\sigma^2 & \rho_1 \sigma^2 \\
\rho_1 \sigma^2 & \sigma^2 \\
\rho_1 \sigma^2 & \sigma^2 \\
\rho_1 \sigma^2 & \sigma^2
\end{pmatrix}
\]

#### Heterogeneous

\[
\begin{pmatrix}
\sigma_1^2 & \rho_1 \sigma_1 \sigma_2 \\
\rho_1 \sigma_2 \sigma_1 & \sigma_2^2 \\
\rho_1 \sigma_3 \sigma_1 & \rho_1 \sigma_3 \sigma_2 & \sigma_3^2 \\
\rho_1 \sigma_4 \sigma_1 & \rho_1 \sigma_4 \sigma_2 & \rho_1 \sigma_4 \sigma_3 & \sigma_4^2
\end{pmatrix}
\]

#### Correlation

\[
\begin{pmatrix}
1 & \rho_1 \\
\rho_1 & 1 \\
\rho_1 & 1 \\
\rho_1 & 1
\end{pmatrix}
\]

Note: This is the same as Toeplitz(2).
Banded(3)

**Homogeneous**

\[
\begin{pmatrix}
\sigma^2 & \rho \sigma^2 & \rho \sigma^2 \\
\rho \sigma^2 & \sigma^2 & \rho \sigma^2 \\
\rho \sigma^2 & \rho \sigma^2 & \sigma^2
\end{pmatrix}
\]

**Heterogeneous**

\[
\begin{pmatrix}
\sigma_1^2 & \rho \sigma_1 \sigma_2 & \rho \sigma_1 \sigma_3 \\
\rho \sigma_2 \sigma_1 & \sigma_2^2 & \rho \sigma_2 \sigma_3 \\
\rho \sigma_3 \sigma_1 & \rho \sigma_3 \sigma_2 & \sigma_3^2
\end{pmatrix}
\]

**Correlation**

\[
\begin{pmatrix}
1 & \rho & \rho \\
\rho & 1 & \rho \\
\rho & \rho & 1
\end{pmatrix}
\]

Banded(4) and Banded (5)

Banded(4) and Banded(5) follow the same pattern as Banded(2) and Banded(3), but with the corresponding numbers of bands.

**Unstructured**

**Homogeneous**

\[
\begin{pmatrix}
\sigma^2 & \rho_{12} \sigma^2 & \rho_{13} \sigma^2 & \rho_{14} \sigma^2 \\
\rho_{21} \sigma^2 & \sigma^2 & \rho_{23} \sigma^2 & \rho_{24} \sigma^2 \\
\rho_{31} \sigma^2 & \rho_{32} \sigma^2 & \sigma^2 & \rho_{34} \sigma^2 \\
\rho_{41} \sigma^2 & \rho_{42} \sigma^2 & \rho_{43} \sigma^2 & \sigma^2
\end{pmatrix}
\]

**Heterogeneous**

\[
\begin{pmatrix}
\sigma_1^2 & \rho_{12} \sigma_1 \sigma_2 & \rho_{13} \sigma_1 \sigma_3 & \rho_{14} \sigma_1 \sigma_4 \\
\rho_{21} \sigma_2 \sigma_1 & \sigma_2^2 & \rho_{23} \sigma_2 \sigma_3 & \rho_{24} \sigma_2 \sigma_4 \\
\rho_{31} \sigma_3 \sigma_1 & \rho_{32} \sigma_3 \sigma_2 & \sigma_3^2 & \rho_{34} \sigma_3 \sigma_4 \\
\rho_{41} \sigma_4 \sigma_1 & \rho_{42} \sigma_4 \sigma_2 & \rho_{43} \sigma_4 \sigma_3 & \sigma_4^2
\end{pmatrix}
\]

**Correlation**

\[
\begin{pmatrix}
1 & \rho_{12} & \rho_{13} & \rho_{14} \\
\rho_{21} & 1 & \rho_{23} & \rho_{24} \\
\rho_{31} & \rho_{32} & 1 & \rho_{34} \\
\rho_{41} & \rho_{42} & \rho_{43} & 1
\end{pmatrix}
\]

Partitioning the Variance-Covariance Structure with Groups

In the case where it is expected that the variance-covariance parameters are different across group levels of the data, it may be useful to specify a different set of $R$ parameters for each level of a group variable. This produces a set of variance-covariance parameters that is different for each level of the chosen group variable, but each set has the same structure as the other groups.

Partitioning the R Matrix Parameters

Suppose the structure of $R$ in a study with four time points is specified to be Toeplitz:

\[
R = \begin{pmatrix}
\sigma^2 & \rho_1 \sigma^2 & \rho_2 \sigma^2 & \rho_3 \sigma^2 \\
\rho_1 \sigma^2 & \sigma^2 & \rho_1 \sigma^2 & \rho_2 \sigma^2 \\
\rho_2 \sigma^2 & \rho_1 \sigma^2 & \sigma^2 & \rho_1 \sigma^2 \\
\rho_3 \sigma^2 & \rho_2 \sigma^2 & \rho_1 \sigma^2 & \sigma^2 \\
\end{pmatrix}
\]

If there are sixteen subjects, then

\[
R = \begin{pmatrix}
R_1 & 0 & 0 & \cdots & 0 \\
0 & R_2 & 0 & \cdots & 0 \\
0 & 0 & R_3 & \cdots & 0 \\
\vdots & \vdots & \vdots & \ddots & \vdots \\
0 & 0 & 0 & \cdots & R_{16}
\end{pmatrix}
\]

The total number of variance-covariance parameters is four: $\sigma^2, \rho_1, \rho_2,$ and $\rho_3$. 

222-7

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Suppose now that there are two groups of eight subjects, and it is believed that the four variance parameters of the first group are different from the four variance parameters of the second group.

We now have

\[ R_1, \ldots, R_8 = \begin{pmatrix} \sigma_1^2 & \rho_{11}\sigma_1^2 & \rho_{12}\sigma_1^2 & \rho_{13}\sigma_1^2 \\ \rho_{11}\sigma_1^2 & \sigma_1^2 & \rho_{11}\sigma_1^2 & \rho_{12}\sigma_1^2 \\ \rho_{12}\sigma_1^2 & \rho_{11}\sigma_1^2 & \sigma_1^2 & \rho_{11}\sigma_1^2 \\ \rho_{13}\sigma_1^2 & \rho_{12}\sigma_1^2 & \rho_{11}\sigma_1^2 & \sigma_1^2 \end{pmatrix}, \]

and

\[ R_9, \ldots, R_{16} = \begin{pmatrix} \sigma_2^2 & \rho_{21}\sigma_2^2 & \rho_{22}\sigma_2^2 & \rho_{23}\sigma_2^2 \\ \rho_{21}\sigma_2^2 & \sigma_2^2 & \rho_{21}\sigma_2^2 & \rho_{22}\sigma_2^2 \\ \rho_{22}\sigma_2^2 & \rho_{21}\sigma_2^2 & \sigma_2^2 & \rho_{21}\sigma_2^2 \\ \rho_{23}\sigma_2^2 & \rho_{22}\sigma_2^2 & \rho_{21}\sigma_2^2 & \sigma_2^2 \end{pmatrix}. \]

The total number of variance-covariance parameters is now eight.

It is easy to see how quickly the number of variance-covariance parameters increases when \( R \) is partitioned by groups.
Example 1 – Longitudinal Design (One Between-Subject Factor, One Within-Subject Factor, One Covariate)

This example has two purposes

1. Acquaint you with the output for all output options. In only this example, each section of the output is described in detail.

2. Describe a typical analysis of a longitudinal design. A portion of this example involves the comparison of options for the Variance-Covariance Matrix pattern. There is some discussion as the output is presented and annotated, with a fuller discussion of model refinement and covariance options at the end of this example.

In a longitudinal design, subjects are measured more than once, usually over time. This example presents the analysis of a longitudinal design in which there is one between-subjects factor (Drug), one within-subjects factor (Time), and a covariate (Weight). Two drugs (Kerlosin and Laposec) are compared to a placebo for their effectiveness in reducing pain following a surgical eye procedure.

A standard pain measurement for each patient is measured at 30 minute intervals following surgery and administration of the drug (or placebo). Six measurements, with the last at Time = 3 hours, are made for each of the 21 patients (7 per group). A blood pressure measurement (Cov) of each individual at the time of pain measurement is measured as a covariate. The researchers wish to compare the drugs at Cov equal 140.

### Pain Dataset

<table>
<thead>
<tr>
<th>Drug</th>
<th>Patient</th>
<th>Time</th>
<th>Cov</th>
<th>Pain</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kerlosin</td>
<td>1</td>
<td>0.5</td>
<td>125</td>
<td>68</td>
</tr>
<tr>
<td>Kerlosin</td>
<td>1</td>
<td>1</td>
<td>196</td>
<td>67</td>
</tr>
<tr>
<td>Kerlosin</td>
<td>1</td>
<td>1.5</td>
<td>189</td>
<td>61</td>
</tr>
<tr>
<td>Kerlosin</td>
<td>1</td>
<td>2</td>
<td>135</td>
<td>57</td>
</tr>
<tr>
<td>Kerlosin</td>
<td>1</td>
<td>2.5</td>
<td>128</td>
<td>43</td>
</tr>
<tr>
<td>Kerlosin</td>
<td>1</td>
<td>3</td>
<td>151</td>
<td>37</td>
</tr>
<tr>
<td>Kerlosin</td>
<td>2</td>
<td>0.5</td>
<td>215</td>
<td>75</td>
</tr>
<tr>
<td>Kerlosin</td>
<td>2</td>
<td>1</td>
<td>151</td>
<td>68</td>
</tr>
<tr>
<td>Kerlosin</td>
<td>2</td>
<td>1.5</td>
<td>191</td>
<td>62</td>
</tr>
<tr>
<td>Kerlosin</td>
<td>2</td>
<td>2</td>
<td>212</td>
<td>47</td>
</tr>
<tr>
<td>Kerlosin</td>
<td>2</td>
<td>2.5</td>
<td>127</td>
<td>46</td>
</tr>
<tr>
<td>Kerlosin</td>
<td>2</td>
<td>3</td>
<td>133</td>
<td>42</td>
</tr>
<tr>
<td>.</td>
<td>.</td>
<td>.</td>
<td>.</td>
<td>.</td>
</tr>
<tr>
<td>.</td>
<td>.</td>
<td>.</td>
<td>.</td>
<td>.</td>
</tr>
<tr>
<td>.</td>
<td>.</td>
<td>.</td>
<td>.</td>
<td>.</td>
</tr>
<tr>
<td>Placebo</td>
<td>21</td>
<td>2</td>
<td>129</td>
<td>73</td>
</tr>
<tr>
<td>Placebo</td>
<td>21</td>
<td>2.5</td>
<td>216</td>
<td>68</td>
</tr>
<tr>
<td>Placebo</td>
<td>21</td>
<td>3</td>
<td>158</td>
<td>70</td>
</tr>
</tbody>
</table>
The following plot shows the relationship among all variables except the covariate.

Setup

To run this example, complete the following steps:

1. **Open the Pain example dataset**
   - From the File menu of the NCSS Data window, select Open Example Data.
   - Select Pain and click OK.

2. **Specify the Mixed Models – Repeated Measures procedure options**
   - Find and open the Mixed Models – Repeated Measures procedure using the menus or the Procedure Navigator.
   - The settings for this example are listed below and are stored in the Example 1 settings file. To load these settings to the procedure window, click Open Example Settings File in the Help Center or File menu.

Variables Tab

<table>
<thead>
<tr>
<th>Response</th>
<th>Pain</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subjects</td>
<td>Patient</td>
</tr>
<tr>
<td>Times</td>
<td>Time</td>
</tr>
<tr>
<td>Number</td>
<td>2</td>
</tr>
<tr>
<td>Variable 1</td>
<td>Drug</td>
</tr>
<tr>
<td>Comparison</td>
<td>All Pairs</td>
</tr>
<tr>
<td>Variable 2</td>
<td>Time</td>
</tr>
<tr>
<td>Comparison</td>
<td>Baseline vs Each</td>
</tr>
<tr>
<td>Baseline</td>
<td>0.5</td>
</tr>
<tr>
<td>Number</td>
<td>1</td>
</tr>
<tr>
<td>Variable 1</td>
<td>Cov</td>
</tr>
<tr>
<td>Compute Means at these Values</td>
<td>140</td>
</tr>
<tr>
<td>Terms</td>
<td>Interaction Model</td>
</tr>
</tbody>
</table>
3 Run the procedure

- Click the Run button to perform the calculations and generate the output.

### Run Summary

<table>
<thead>
<tr>
<th>Item</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Likelihood Type</td>
<td>Restricted Maximum Likelihood</td>
</tr>
<tr>
<td>Fixed Model</td>
<td>COV+DRUG+TIME+COV<em>DRUG+COV</em>TIME+DRUG<em>TIME+COV</em>DRUG*TIME</td>
</tr>
<tr>
<td>Random Model</td>
<td>PATIENT</td>
</tr>
<tr>
<td>Repeated Pattern</td>
<td>Diagonal</td>
</tr>
<tr>
<td>Number of Rows</td>
<td>126</td>
</tr>
<tr>
<td>Number of Subjects</td>
<td>21</td>
</tr>
<tr>
<td>Solution Type</td>
<td>Newton-Raphson</td>
</tr>
<tr>
<td>Fisher Iterations</td>
<td>3 of a possible 5</td>
</tr>
<tr>
<td>Newton Iterations</td>
<td>1 of a possible 40</td>
</tr>
<tr>
<td>Max Retries</td>
<td>10</td>
</tr>
<tr>
<td>Lambda</td>
<td>1</td>
</tr>
<tr>
<td>Log-Likelihood</td>
<td>-369.1552</td>
</tr>
<tr>
<td>-2 Log-Likelihood</td>
<td>738.3104</td>
</tr>
<tr>
<td>AIC (Smaller Better)</td>
<td>742.3104</td>
</tr>
<tr>
<td>Convergence</td>
<td>Normal</td>
</tr>
<tr>
<td>Run Time (Seconds)</td>
<td>0.905</td>
</tr>
</tbody>
</table>

This section provides a summary of the model and the iterations toward the maximum log likelihood.
Likelihood Type
This value indicates that restricted maximum likelihood was used rather than maximum likelihood.

Fixed Model
The model shown is that entered as the Fixed Factors Model of the Variables tab. The model includes fixed terms and covariates.

Random Model
The model shown is that entered as the Random Factors Model of the Variables tab.

Repeated Model
The pattern shown is that entered as the Repeated (Time) Variance Pattern of the Variables tab.

Number of Rows
The number of rows processed from the database.

Number of Subjects
The number of subjects.

Solution Type
The solution type is method used for finding the maximum (restricted) maximum likelihood solution. Newton-Raphson is the recommended method.

Fisher Iterations
Some Fisher-Scoring iterations are used as part of the Newton-Raphson algorithm. The ‘4 of a possible 10’ means four Fisher-Scoring iterations were used, while ten was the maximum that were allowed (as specified on the Maximization tab).

Newton Iterations
The ‘1 of a possible 40’ means one Newton-Raphson iteration was used, while forty was the maximum allowed (as specified on the Maximization tab).

Max Retries
The maximum number of times that lambda was changed, and new variance-covariance parameters found during an iteration was ten. If the values of the parameters result in a negative variance, lambda is divided by two and new parameters are generated. This process continues until a positive variance occurs or until Max Retries is reached.

Lambda
Lambda is a parameter used in the Newton-Raphson process to specify the amount of change in parameter estimates between iterations. One is generally an appropriate selection. When convergence problems occur, reset this to 0.5.

If the values of the parameters result in a negative variance, lambda is divided by two and new parameters are generated. This process continues until a positive variance occurs or until Max Retries is reached.
Log-Likelihood
This is the log of the likelihood of the data given the variance-covariance parameter estimates. When a maximum is reached, the algorithm converges.

-2 Log-Likelihood
This is minus 2 times the log of the likelihood. When a minimum is reached, the algorithm converges.

AIC
The Akaike Information Criterion is used for comparing covariance structures in models. It gives a penalty for increasing the number of covariance parameters in the model.

Convergence
‘Normal’ convergence indicates that convergence was reached before the limit.

Run Time (Seconds)
The run time is the amount of time used to solve the problem and generate the output.

Random Component Parameter Estimates (G Matrix)

<table>
<thead>
<tr>
<th>Component Number</th>
<th>Parameter Number</th>
<th>Estimated Value</th>
<th>Model Term</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1</td>
<td>1.6343</td>
<td>Patient</td>
</tr>
</tbody>
</table>

This section gives the random component estimates according to the Random Factors Model specifications of the Variables tab.

Component Number
A number is assigned to each random component. The first component is the one specified on the variables tab. Components 2-5 are specified on the More Models tab.

Parameter Number
When the random component model results in more than one parameter for the component, the parameter number identifies parameters within the component.

Estimated Value
The estimated value 1.6343 is the estimated patient variance component.

Model Term
Patient is the name of the random term being estimated.
Repeated Component Parameter Estimates (R Matrix)

<table>
<thead>
<tr>
<th>Component Number</th>
<th>Parameter Number</th>
<th>Estimated Value</th>
<th>Parameter Type</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1</td>
<td>23.5867</td>
<td>Diagonal (Variance)</td>
</tr>
</tbody>
</table>

This section gives the repeated component estimates according to the Repeated Variance Pattern specifications of the Variables tab.

Component Number

A number is assigned to each repeated component. The first component is the one specified on the variables tab. Components 2-5 are specified on the More Models tab.

Parameter Number

When the repeated pattern results in more than one parameter for the component, the parameter number identifies parameters within the component.

Estimated Value

The estimated value 23.5867 is the estimated residual (error) variance.

Parameter Type

The parameter type describes the structure of the R matrix that is estimated, and is specified by the Repeated Component Pattern of the Variables tab.

Term-by-Term Hypothesis Test Results

<table>
<thead>
<tr>
<th>Model Term</th>
<th>F-Value</th>
<th>Num DF</th>
<th>Denom DF</th>
<th>Prob Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cov</td>
<td>3.3021</td>
<td>1</td>
<td>87.1</td>
<td>0.072631</td>
</tr>
<tr>
<td>Drug</td>
<td>1.8217</td>
<td>2</td>
<td>89.0</td>
<td>0.167729</td>
</tr>
<tr>
<td>Time</td>
<td>0.9780</td>
<td>5</td>
<td>88.4</td>
<td>0.435775</td>
</tr>
<tr>
<td>Cov*Drug</td>
<td>0.7698</td>
<td>2</td>
<td>86.8</td>
<td>0.466228</td>
</tr>
<tr>
<td>Cov*Time</td>
<td>1.2171</td>
<td>5</td>
<td>88.5</td>
<td>0.307773</td>
</tr>
<tr>
<td>Drug*Time</td>
<td>0.8627</td>
<td>10</td>
<td>87.0</td>
<td>0.570795</td>
</tr>
<tr>
<td>Cov<em>Drug</em>Time</td>
<td>1.0691</td>
<td>10</td>
<td>87.0</td>
<td>0.394694</td>
</tr>
</tbody>
</table>

These F-Values test Type-III (adjusted last) hypotheses.

This section contains a F-test for each component of the Fixed Component Model according to the methods described by Kenward and Roger (1997).

Model Term

This is the name of the term in the model.
**F-Value**

The F-Value corresponds to the L matrix used for testing this term in the model. The F-Value is based on the F approximation described in Kenward and Roger (1997).

**Num DF**

This is the numerator degrees of freedom for the corresponding term.

**Denom DF**

This is the approximate denominator degrees of freedom for this comparison as described in Kenward and Roger (1997).

**Prob Level**

The Probability Level (or P-value) gives the strength of evidence (smaller Prob Level implies more evidence) that a term in the model has differences among its levels, or a slope different from zero in the case of covariate. It is the probability of obtaining the corresponding F-Value (or greater) if the null hypothesis of equal means (or no slope) is true.

### Individual Comparison Hypothesis Test Results

<table>
<thead>
<tr>
<th>Individual Comparison Hypothesis Test Results by Covariate Values</th>
</tr>
</thead>
<tbody>
<tr>
<td>Covariates: Cov = 140.0000</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td><strong>Comparison/ Covariate(s)</strong></td>
</tr>
<tr>
<td>Drug</td>
</tr>
<tr>
<td>Drug: Kerlosin - Laposec</td>
</tr>
<tr>
<td>Drug: Kerlosin - Placebo</td>
</tr>
<tr>
<td>Drug: Laposec - Placebo</td>
</tr>
<tr>
<td>Time</td>
</tr>
<tr>
<td>Time: 0.5 - 1</td>
</tr>
<tr>
<td>Time: 0.5 - 1.5</td>
</tr>
<tr>
<td>Time: 0.5 - 2</td>
</tr>
<tr>
<td>Time: 0.5 - 2.5</td>
</tr>
<tr>
<td>Time: 0.5 - 3</td>
</tr>
<tr>
<td>Drug*Time</td>
</tr>
<tr>
<td>Drug = Kerlosin, Time: 0.5 - 1</td>
</tr>
</tbody>
</table>

These F-Values test Type-III (adjusted last) hypotheses.
This section shows the F-tests for comparisons of the levels of the fixed terms of the model according to the methods described by Kenward and Roger (1997). The individual comparisons are grouped into subsets of the fixed model terms.

**Comparison/Covariate(s)**
This is the comparison being made. The first line is ‘Drug’. On this line, the levels of drug are compared when the covariate is equal to 140. The second line is ‘Drug: Placebo – Kerlosin’. On this line, Kerlosin is compared to Placebo when the covariate is equal to 140.

**Comparison Mean Difference**
This is the difference in the least squares means for each comparison.

**F-Value**
The F-Value corresponds to the L matrix used for testing this comparison. The F-Value is based on the F approximation described in Kenward and Roger (1997).

**Num DF**
This is the numerator degrees of freedom for this comparison.

**Denom DF**
This is the approximate denominator degrees of freedom for this comparison as described in Kenward and Roger (1997).

**Raw Prob Level**
The Raw Probability Level (or Raw P-value) gives the strength of evidence for a single comparison, unadjusted for multiple testing. It is the single test probability of obtaining the corresponding difference if the null hypothesis of equal means is true.

**Bonferroni Prob Level**
The Bonferroni Prob Level is adjusted for multiple tests. The number of tests adjusted for is enclosed in brackets following each Bonferroni Prob Level. For example, 0.8674 [15] signifies that the probability the means are equal, given the data, is 0.8674, after adjusting for 15 tests.
Least Squares (Adjusted) Means

This section gives the adjusted means for the levels of each fixed factor when Cov = 140.

Name
This is the level of the fixed term that is estimated on the line.

Mean
The mean is the estimated least squares (adjusted or marginal) mean at the specified value of the covariate.

Standard Error of Mean
This is the standard error of the mean.

95.0% Lower (Upper) Conf. Limit for Mean
These limits give a 95% confidence interval for the mean.

DF
The degrees of freedom used for the confidence limits are calculated using the method of Kenward and Roger (1997).
Means Plots

These plots show the means broken up into the categories of the fixed effects of the model. Some general trends that can be seen are those of pain decreasing with time and lower pain for the two drugs after two hours.
Subject Plots

Each set of connected dots of the Subject plots show the repeated measurements on the same subject. The second plot is perhaps the most telling, as it shows a separation of pain among drugs after 2 hours.
### Solution for Fixed Effects

<table>
<thead>
<tr>
<th>Effect Name</th>
<th>Effect Estimate (Beta)</th>
<th>Effect Standard Error</th>
<th>Prob Level</th>
<th>95.0% Lower Conf. Limit of Beta</th>
<th>95.0% Upper Conf. Limit of Beta</th>
<th>DF</th>
<th>Effect No.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intercept</td>
<td>66.8296</td>
<td>7.4693</td>
<td>0.000000</td>
<td>51.9900</td>
<td>81.6692</td>
<td>89.8</td>
<td>1</td>
</tr>
<tr>
<td>Cov (Drug=&quot;Kerlosin&quot;)</td>
<td>-0.0089</td>
<td>0.0461</td>
<td>0.846662</td>
<td>-10.004</td>
<td>0.0826</td>
<td>89.6</td>
<td>2</td>
</tr>
<tr>
<td>(Drug=&quot;Laposec&quot;)</td>
<td>-9.4849</td>
<td>11.9162</td>
<td>0.428154</td>
<td>-33.1595</td>
<td>14.1898</td>
<td>89.7</td>
<td>3</td>
</tr>
<tr>
<td>(Drug=&quot;Placebo&quot;)</td>
<td>-16.5164</td>
<td>14.6176</td>
<td>0.261539</td>
<td>-45.5591</td>
<td>12.5264</td>
<td>89.5</td>
<td>4</td>
</tr>
<tr>
<td>(Time=0.5)</td>
<td>23.0382</td>
<td>12.0137</td>
<td>0.058369</td>
<td>-0.8336</td>
<td>46.9099</td>
<td>88.8</td>
<td>5</td>
</tr>
<tr>
<td>(Time=1)</td>
<td>-4.9520</td>
<td>10.5394</td>
<td>0.639641</td>
<td>-25.9029</td>
<td>15.9988</td>
<td>86.2</td>
<td>6</td>
</tr>
<tr>
<td>(Time=1.5)</td>
<td>16.5033</td>
<td>12.3512</td>
<td>0.184968</td>
<td>-8.0451</td>
<td>41.0518</td>
<td>87.2</td>
<td>7</td>
</tr>
<tr>
<td>(Time=2)</td>
<td>10.8739</td>
<td>14.7800</td>
<td>0.463980</td>
<td>-18.5236</td>
<td>40.2714</td>
<td>82.9</td>
<td>8</td>
</tr>
<tr>
<td>(Time=2.5)</td>
<td>3.0828</td>
<td>12.5528</td>
<td>0.806621</td>
<td>-21.8933</td>
<td>28.0589</td>
<td>81.0</td>
<td>9</td>
</tr>
<tr>
<td>(Time=3)</td>
<td>0.0000</td>
<td>0.0000</td>
<td>0.0000</td>
<td>0.0000</td>
<td>0.0000</td>
<td>5</td>
<td>10</td>
</tr>
<tr>
<td>Cov*(Drug=&quot;Kerlosin&quot;)</td>
<td>-0.1056</td>
<td>0.0761</td>
<td>0.168318</td>
<td>-0.2568</td>
<td>0.0455</td>
<td>89.6</td>
<td>12</td>
</tr>
<tr>
<td>Cov*(Drug=&quot;Laposec&quot;)</td>
<td>0.0180</td>
<td>0.0929</td>
<td>0.846522</td>
<td>-0.1665</td>
<td>0.2026</td>
<td>89.3</td>
<td>13</td>
</tr>
<tr>
<td>Cov*(Drug=&quot;Placebo&quot;)</td>
<td>0.0000</td>
<td>0.0000</td>
<td>0.0000</td>
<td>0.0000</td>
<td>0.0000</td>
<td>5</td>
<td>14</td>
</tr>
</tbody>
</table>

This section shows the model estimates for all the model terms (betas).

**Effect Name**

The Effect Name is the level of the fixed effect that is examined on the line.

**Effect Estimate (Beta)**

The Effect Estimate is the beta-coefficient for this effect of the model. For main effects terms the number of effects per term is the number of levels minus one. An effect estimate of zero is given for the last effect(s) of each term. There may be several zero estimates for effects of interaction terms.

**Effect Standard Error**

This is the standard error for the corresponding effect.

**Prob Level**

The Prob Level tests whether the effect is zero.

**95.0% Lower (Upper) Conf. Limit of Beta**

These limits give a 95% confidence interval for the effect.
DF
The degrees of freedom used for the confidence limits and hypothesis tests are calculated using the method of Kenward and Roger (1997).

Effect No.
This number identifies the effect of the line.

Asymptotic Variance-Covariance Matrix of Variance Estimates

<table>
<thead>
<tr>
<th>Parameter</th>
<th>G(1,1)</th>
<th>R(1,1)</th>
</tr>
</thead>
<tbody>
<tr>
<td>G(1,1)</td>
<td>4.5645</td>
<td>-2.6362</td>
</tr>
<tr>
<td>R(1,1)</td>
<td>-2.6362</td>
<td>15.0707</td>
</tr>
</tbody>
</table>

This section gives the asymptotic variance-covariance matrix of the variance components of the model. Here, the variance of the Patient variance component is 4.5645. The variance of the residual variance is 15.0707.

Parm
Parm is the heading for both the row variance parameters and column variance parameters.

G(1,1)
The two elements of G(1,1) refer to the component number and parameter number of the covariance parameter in G.

R(1,1)
The two elements of R(1,1) refer to the component number and parameter number of the covariance parameter in R.

Estimated Vi Matrix of Subject = X

<table>
<thead>
<tr>
<th>Vi</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>25.2210</td>
<td>1.6343</td>
<td>1.6343</td>
<td>1.6343</td>
<td>1.6343</td>
<td>1.6343</td>
</tr>
<tr>
<td>2</td>
<td>1.6343</td>
<td>25.2210</td>
<td>1.6343</td>
<td>1.6343</td>
<td>1.6343</td>
<td>1.6343</td>
</tr>
<tr>
<td>3</td>
<td>1.6343</td>
<td>1.6343</td>
<td>25.2210</td>
<td>1.6343</td>
<td>1.6343</td>
<td>1.6343</td>
</tr>
<tr>
<td>4</td>
<td>1.6343</td>
<td>1.6343</td>
<td>1.6343</td>
<td>25.2210</td>
<td>1.6343</td>
<td>1.6343</td>
</tr>
<tr>
<td>5</td>
<td>1.6343</td>
<td>1.6343</td>
<td>1.6343</td>
<td>1.6343</td>
<td>25.2210</td>
<td>1.6343</td>
</tr>
<tr>
<td>6</td>
<td>1.6343</td>
<td>1.6343</td>
<td>1.6343</td>
<td>1.6343</td>
<td>1.6343</td>
<td>25.2210</td>
</tr>
</tbody>
</table>
Estimated Vi Matrix of Subject = 2

<table>
<thead>
<tr>
<th>Vi</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>25.2210</td>
<td>1.6343</td>
<td>1.6343</td>
<td>1.6343</td>
<td>1.6343</td>
<td>1.6343</td>
</tr>
<tr>
<td>2</td>
<td>1.6343</td>
<td>25.2210</td>
<td>1.6343</td>
<td>1.6343</td>
<td>1.6343</td>
<td>1.6343</td>
</tr>
<tr>
<td>3</td>
<td>1.6343</td>
<td>1.6343</td>
<td>25.2210</td>
<td>1.6343</td>
<td>1.6343</td>
<td>1.6343</td>
</tr>
<tr>
<td>4</td>
<td>1.6343</td>
<td>1.6343</td>
<td>1.6343</td>
<td>25.2210</td>
<td>1.6343</td>
<td>1.6343</td>
</tr>
<tr>
<td>5</td>
<td>1.6343</td>
<td>1.6343</td>
<td>1.6343</td>
<td>1.6343</td>
<td>25.2210</td>
<td>1.6343</td>
</tr>
<tr>
<td>6</td>
<td>1.6343</td>
<td>1.6343</td>
<td>1.6343</td>
<td>1.6343</td>
<td>1.6343</td>
<td>25.2210</td>
</tr>
</tbody>
</table>

Estimated Vi Matrix of Subject = 3

<table>
<thead>
<tr>
<th>Vi</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>25.2210</td>
<td>1.6343</td>
<td>1.6343</td>
<td>1.6343</td>
<td>1.6343</td>
<td>1.6343</td>
</tr>
<tr>
<td>2</td>
<td>1.6343</td>
<td>25.2210</td>
<td>1.6343</td>
<td>1.6343</td>
<td>1.6343</td>
<td>1.6343</td>
</tr>
<tr>
<td>3</td>
<td>1.6343</td>
<td>1.6343</td>
<td>25.2210</td>
<td>1.6343</td>
<td>1.6343</td>
<td>1.6343</td>
</tr>
<tr>
<td>4</td>
<td>1.6343</td>
<td>1.6343</td>
<td>1.6343</td>
<td>25.2210</td>
<td>1.6343</td>
<td>1.6343</td>
</tr>
<tr>
<td>5</td>
<td>1.6343</td>
<td>1.6343</td>
<td>1.6343</td>
<td>1.6343</td>
<td>25.2210</td>
<td>1.6343</td>
</tr>
<tr>
<td>6</td>
<td>1.6343</td>
<td>1.6343</td>
<td>1.6343</td>
<td>1.6343</td>
<td>1.6343</td>
<td>25.2210</td>
</tr>
</tbody>
</table>

This section gives the estimated variance-covariance matrix for each of the first three subjects.

1 – 6

Each of the 6 levels shown here represents one of the time values. That is 1 is for 0.5 hours, 2 is for 1 hour, 3 is for 1.5 hours, and so on. The number 25.2210 is calculated by adding the two variance estimates together, 1.6343 + 23.5867 = 25.2210.

Hessian Matrix of Variance Estimates

<table>
<thead>
<tr>
<th>Parameter</th>
<th>G(1,1)</th>
<th>R(1,1)</th>
</tr>
</thead>
<tbody>
<tr>
<td>G(1,1)</td>
<td>0.2437</td>
<td>0.0426</td>
</tr>
<tr>
<td>R(1,1)</td>
<td>0.0426</td>
<td>0.0738</td>
</tr>
</tbody>
</table>

The Hessian Matrix is directly related to the asymptotic variance-covariance matrix of the variance estimates.

Parm

Parm is the heading for both the row variance parameters and column variance parameters.

G(1,1)

The two elements of G(1,1) refer to the component number and parameter number of the covariance parameter in G.
R(1,1)
The two elements of R(1,1) refer to the component number and parameter number of the covariance parameter in R.

### L Matrices

<table>
<thead>
<tr>
<th>No.</th>
<th>Effect</th>
<th>Drug</th>
<th>Time</th>
<th>L1</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Intercept</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>Cov</td>
<td></td>
<td></td>
<td>1.0000</td>
</tr>
<tr>
<td>3</td>
<td>Drug</td>
<td>Kerlosin</td>
<td>0.5</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>Drug</td>
<td>Laposec</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>Drug</td>
<td>Placebo</td>
<td>1.5</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>Time</td>
<td>2</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>Time</td>
<td>2.5</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>Cov*Drug</td>
<td>Kerlosin</td>
<td>0.5</td>
<td>0.3333</td>
</tr>
<tr>
<td>9</td>
<td>Cov*Drug</td>
<td>Laposec</td>
<td>1</td>
<td>0.3333</td>
</tr>
<tr>
<td>10</td>
<td>Cov*Drug</td>
<td>Placebo</td>
<td>1.5</td>
<td>0.3333</td>
</tr>
<tr>
<td>11</td>
<td>Cov*Time</td>
<td>0.5</td>
<td>2</td>
<td>0.1667</td>
</tr>
<tr>
<td>12</td>
<td>Cov*Time</td>
<td>1</td>
<td>2.5</td>
<td>0.1667</td>
</tr>
<tr>
<td>13</td>
<td>Cov*Time</td>
<td>1.5</td>
<td>3</td>
<td>0.1667</td>
</tr>
<tr>
<td>14</td>
<td>Cov*Time</td>
<td>2</td>
<td>3</td>
<td>0.1667</td>
</tr>
<tr>
<td>15</td>
<td>Drug*Time</td>
<td>Kerlosin</td>
<td>0.5</td>
<td></td>
</tr>
<tr>
<td>16</td>
<td>Drug*Time</td>
<td>Kerlosin</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>17</td>
<td>Drug*Time</td>
<td>Kerlosin</td>
<td>1.5</td>
<td></td>
</tr>
<tr>
<td>18</td>
<td>Drug*Time</td>
<td>Kerlosin</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>19</td>
<td>Drug*Time</td>
<td>Kerlosin</td>
<td>2.5</td>
<td></td>
</tr>
<tr>
<td>20</td>
<td>Drug*Time</td>
<td>Kerlosin</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>21</td>
<td>Drug*Time</td>
<td>Laposec</td>
<td>0.5</td>
<td></td>
</tr>
<tr>
<td>22</td>
<td>Drug*Time</td>
<td>Laposec</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>23</td>
<td>Drug*Time</td>
<td>Laposec</td>
<td>1.5</td>
<td></td>
</tr>
<tr>
<td>24</td>
<td>Drug*Time</td>
<td>Laposec</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>25</td>
<td>Drug*Time</td>
<td>Laposec</td>
<td>2.5</td>
<td></td>
</tr>
<tr>
<td>26</td>
<td>Drug*Time</td>
<td>Laposec</td>
<td>3</td>
<td></td>
</tr>
</tbody>
</table>

The L matrices are used to form a linear combination of the betas corresponding to a specific hypothesis test or mean estimate. The L matrix in this example is used for testing whether there is a difference among the three levels of Drug.

**No.**
This number is used for identifying the corresponding beta term.

**Effect**
This column gives the model term.
Factor Variables (e.g. Drug, Time)

These columns identify the level of each fixed effect to which the coefficients of the L matrix of the same line correspond.

L1, L2, L3, ...

L1, L2, L3, ... are a group of column vectors that combine to form an L matrix. The L matrix in this example is used for testing whether there is a difference among the three levels of Drug.

Discussion of Example 1 Results

The output shown for this example to this point has been for the full model with all interactions. It has been shown to illustrate the several sections of output that are available. In practice, when dealing with covariates, this model should be refined before making conclusions concerning the two drugs in question. The original F-test results are repeated below.

<table>
<thead>
<tr>
<th>Term</th>
<th>F-Value</th>
<th>Num DF</th>
<th>Denom DF</th>
<th>Prob Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cov</td>
<td>3.3021</td>
<td>1</td>
<td>87.1</td>
<td>0.072631</td>
</tr>
<tr>
<td>Drug</td>
<td>1.8217</td>
<td>2</td>
<td>89.0</td>
<td>0.167729</td>
</tr>
<tr>
<td>Time</td>
<td>0.9780</td>
<td>5</td>
<td>88.4</td>
<td>0.435775</td>
</tr>
<tr>
<td>Cov*Drug</td>
<td>0.7698</td>
<td>2</td>
<td>86.8</td>
<td>0.466228</td>
</tr>
<tr>
<td>Cov*Time</td>
<td>1.2171</td>
<td>5</td>
<td>88.5</td>
<td>0.307773</td>
</tr>
<tr>
<td>Drug*Time</td>
<td>0.8627</td>
<td>10</td>
<td>87.0</td>
<td>0.570795</td>
</tr>
<tr>
<td>Cov<em>Drug</em>Time</td>
<td>1.0691</td>
<td>10</td>
<td>87.0</td>
<td>0.394694</td>
</tr>
</tbody>
</table>

These F-Values test Type-III (adjusted last) hypotheses.

Using a hierarchical step-down approach to model improvement, we begin by removing the highest order term, the three-way interaction (F-Value = 1.07, Prob Level = 0.3947). The F-test results for this new model are as follows.

<table>
<thead>
<tr>
<th>Term</th>
<th>F-Value</th>
<th>Num DF</th>
<th>Denom DF</th>
<th>Prob Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cov</td>
<td>1.7686</td>
<td>1</td>
<td>98.9</td>
<td>0.186615</td>
</tr>
<tr>
<td>Drug</td>
<td>4.1700</td>
<td>2</td>
<td>96.8</td>
<td>0.018315</td>
</tr>
<tr>
<td>Time</td>
<td>1.3419</td>
<td>5</td>
<td>98.0</td>
<td>0.253118</td>
</tr>
<tr>
<td>Cov*Drug</td>
<td>2.2336</td>
<td>2</td>
<td>92.4</td>
<td>0.112895</td>
</tr>
<tr>
<td>Cov*Time</td>
<td>2.3667</td>
<td>5</td>
<td>98.0</td>
<td>0.045036</td>
</tr>
<tr>
<td>Drug*Time</td>
<td>7.4394</td>
<td>10</td>
<td>84.1</td>
<td>0.000000</td>
</tr>
</tbody>
</table>

These F-Values test Type-III (adjusted last) hypotheses.

Since all interaction Prob Levels are now quite small, this model appears to be reasonable. Some researchers might argue to continue refinement by removing the Drug*Cov interaction (F-Value = 2.23, Prob Level = 0.1129). Such an argument is also reasonable, but this is not the course that is pursued here, since a moderately low prob level indicates there may be a mild Drug*Cov interaction effect.
The dominant prob level is the one associated with the Drug*Time interaction (F-Value = 7.44, Prob Level = 0.0000). This interaction can be clearly seen in the following scatter plot of the individual subjects. Note that the Placebo group does not decrease as rapidly as the Kerlosin group.

This interaction can be examined in greater detail by comparing the three levels of Drug at each time point (at the covariate value of 140).

Individual Comparison Hypothesis Test Results by Covariate Values

<table>
<thead>
<tr>
<th>Comparison/ Covariate(s)</th>
<th>Comparison Mean Difference</th>
<th>F-Value</th>
<th>Num DF</th>
<th>Denom DF</th>
<th>Raw Prob Level</th>
<th>Bonferroni Prob Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drug*Time</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Time = 0.5, Drug: Kerlosin - Laposec</td>
<td>6.1619</td>
<td>4.3285</td>
<td>1</td>
<td>100.0</td>
<td>0.040036</td>
<td>0.720656 [18]</td>
</tr>
<tr>
<td>Time = 0.5, Drug: Kerlosin - Placebo</td>
<td>-1.0451</td>
<td>0.1287</td>
<td>1</td>
<td>100.0</td>
<td>0.720543</td>
<td>1.000000 [18]</td>
</tr>
<tr>
<td>Time = 0.5, Drug: Laposec - Placebo</td>
<td>-7.2070</td>
<td>6.3717</td>
<td>1</td>
<td>100.0</td>
<td>0.013169</td>
<td>0.237046 [18]</td>
</tr>
<tr>
<td>Time = 1, Drug: Kerlosin - Laposec</td>
<td>1.4659</td>
<td>0.2530</td>
<td>1</td>
<td>100.0</td>
<td>0.616068</td>
<td>1.000000 [18]</td>
</tr>
<tr>
<td>Time = 1, Drug: Kerlosin - Placebo</td>
<td>-7.2872</td>
<td>6.2095</td>
<td>1</td>
<td>99.9</td>
<td>0.014353</td>
<td>0.258346 [18]</td>
</tr>
<tr>
<td>Time = 1, Drug: Laposec - Placebo</td>
<td>-8.7531</td>
<td>8.1482</td>
<td>1</td>
<td>100.0</td>
<td>0.005241</td>
<td>0.094336 [18]</td>
</tr>
<tr>
<td>Time = 1.5, Drug: Kerlosin - Laposec</td>
<td>2.3523</td>
<td>0.7185</td>
<td>1</td>
<td>99.9</td>
<td>0.398661</td>
<td>1.000000 [18]</td>
</tr>
<tr>
<td>Time = 1.5, Drug: Kerlosin - Placebo</td>
<td>-5.2756</td>
<td>3.6844</td>
<td>1</td>
<td>99.8</td>
<td>0.057780</td>
<td>1.000000 [18]</td>
</tr>
<tr>
<td>Time = 1.5, Drug: Laposec - Placebo</td>
<td>-7.6278</td>
<td>7.5730</td>
<td>1</td>
<td>99.9</td>
<td>0.007037</td>
<td>0.126669 [18]</td>
</tr>
<tr>
<td>Time = 2, Drug: Kerlosin - Laposec</td>
<td>-2.4751</td>
<td>0.6341</td>
<td>1</td>
<td>100.0</td>
<td>0.427746</td>
<td>1.000000 [18]</td>
</tr>
<tr>
<td>Time = 2, Drug: Kerlosin - Placebo</td>
<td>-14.1184</td>
<td>19.4393</td>
<td>1</td>
<td>100.0</td>
<td>0.000026</td>
<td>0.000471 [18]</td>
</tr>
<tr>
<td>Time = 2, Drug: Laposec - Placebo</td>
<td>-11.6433</td>
<td>17.6388</td>
<td>1</td>
<td>99.8</td>
<td>0.000058</td>
<td>0.001046 [18]</td>
</tr>
</tbody>
</table>
The first Bonferroni-adjusted significant difference among levels of treatment occurs at Time = 2 hours. At Time = 2, the Kerlosin and Laposec means are significantly different from the Placebo mean (Bonferroni Prob Levels = 0.0005 and 0.0010, respectively), but not from each other (Bonferroni Prob Level = 1.0000). At times 2.5 hours and 3 hours all levels of Drug are significantly different, with Kerlosin showing the greatest pain reduction.

### Repeated and Random Component Specification

Another issue that should be considered from the beginning of the analysis is the covariance structure of the repeated measurements over time. The specification to this point involved both random (\(G\)) and the repeated (\(R\)) components of the model. The \(G\) and the \(R\) matrices are used to form the complete variance-covariance matrix of all the responses using the formula \(V = ZGZ' + R\). The \(R\) and the \(R\) used to this point have the form

\[
G = \begin{pmatrix}
\sigma_S^2 & \sigma_S^2 \\
\sigma_S^2 & \sigma_S^2 \\
\end{pmatrix}
\quad R = \begin{pmatrix}
\sigma^2 & \sigma^2 & \sigma^2 & \sigma^2 & \sigma^2 & \sigma^2 \\
\end{pmatrix}
\]

where \(G\) has dimension 21 by 21 and \(R\) has dimension 126 by 126. The resulting variance-covariance matrix, \(V = ZGZ' + R\), has the form

\[
V = \begin{pmatrix}
\sigma^2 + \sigma_S^2 & \sigma^2 + \sigma_S^2 & \sigma^2 & \sigma^2 & \sigma^2 & \sigma^2 & 0 & 0 & \ldots \\
\sigma^2 & \sigma^2 & \sigma^2 & \sigma^2 & \sigma^2 & \sigma^2 & 0 & 0 & \ldots \\
\sigma^2 & \sigma^2 & \sigma^2 & \sigma^2 & \sigma^2 & \sigma^2 & 0 & 0 & \ldots \\
\sigma^2 & \sigma^2 & \sigma^2 & \sigma^2 & \sigma^2 & \sigma^2 & 0 & 0 & \ldots \\
\sigma^2 & \sigma^2 & \sigma^2 & \sigma^2 & \sigma^2 & \sigma^2 & 0 & 0 & \ldots \\
\sigma^2 & \sigma^2 & \sigma^2 & \sigma^2 & \sigma^2 & \sigma^2 & 0 & 0 & \ldots \\
0 & 0 & 0 & 0 & 0 & 0 & \sigma^2 & \sigma^2 & \sigma^2 & \ldots \\
0 & 0 & 0 & 0 & 0 & 0 & \sigma^2 & \sigma^2 & \sigma^2 & \ldots \\
\vdots & \vdots & \vdots & \vdots & \vdots & \vdots & \vdots & \vdots & \vdots & \vdots
\end{pmatrix}
\]

where each 6 by 6 block corresponds to a single patient. The full dimension of this matrix is 6*21 = 126 by 126.
The estimates of $\sigma^2_S$ and $\sigma^2$ for the model without the three-way interaction are 0.7066 and 24.6293, as shown in the output below.

<table>
<thead>
<tr>
<th>Component Number</th>
<th>Parameter Number</th>
<th>Estimated Value</th>
<th>Model Term</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1</td>
<td>0.7066</td>
<td>Patient</td>
</tr>
</tbody>
</table>

The resulting 6 by 6 matrix for each subject (as shown in the output) is

![Estimated Vi Matrix of Subject = 1](attachment://estimated_v_matrix.png)

The number 25.3359 comes from adding 0.7066 and 24.6293.

**Using Compound Symmetry as the Repeated Pattern Rather than Using a Random Component**

An alternative specification that yields the same results is to remove the Random Component of the Model (Patient) by changing the Variance-Covariance Matrix Pattern to **Compound Symmetry: Repeated with Force Positive Correlations** checked. In this case, there is no $G$ matrix and the $R$ matrix has the form

$$R = \begin{pmatrix}
\sigma^2 & \rho \sigma^2 & \rho \sigma^2 & \rho \sigma^2 & \rho \sigma^2 & \rho \sigma^2 \\
\rho \sigma^2 & \sigma^2 & \rho \sigma^2 & \rho \sigma^2 & \rho \sigma^2 & \rho \sigma^2 \\
\rho \sigma^2 & \rho \sigma^2 & \sigma^2 & \rho \sigma^2 & \rho \sigma^2 & \rho \sigma^2 \\
\rho \sigma^2 & \rho \sigma^2 & \rho \sigma^2 & \sigma^2 & \rho \sigma^2 & \rho \sigma^2 \\
\rho \sigma^2 & \rho \sigma^2 & \rho \sigma^2 & \rho \sigma^2 & \sigma^2 & \rho \sigma^2 \\
\rho \sigma^2 & \rho \sigma^2 & \rho \sigma^2 & \rho \sigma^2 & \rho \sigma^2 & \sigma^2 \\
\end{pmatrix}$$
The true dimension of $\mathbf{R}$ is still 126 by 126 with 21 of the above matrices along the diagonal. The Repeated Component output becomes

<table>
<thead>
<tr>
<th>Component Number</th>
<th>Parameter Number</th>
<th>Estimated Value</th>
<th>Parameter Type</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1</td>
<td>25.3358</td>
<td>Diagonal (Variance)</td>
</tr>
<tr>
<td>1</td>
<td>1</td>
<td>0.0279</td>
<td>Off-Diagonal (Correlation)</td>
</tr>
</tbody>
</table>

Here, the estimate of $\sigma^2$ is 25.3358 and the estimate of $\rho$ is 0.0279.

The V matrix now has the form

$$
\mathbf{V} =
\begin{pmatrix}
\sigma^2 & \rho \sigma^2 & \rho \sigma^2 & \rho \sigma^2 & \rho \sigma^2 & 0 & 0 & \ldots \\
\rho \sigma^2 & \sigma^2 & \rho \sigma^2 & \rho \sigma^2 & \rho \sigma^2 & \rho \sigma^2 & 0 & 0 & \ldots \\
\rho \sigma^2 & \rho \sigma^2 & \sigma^2 & \rho \sigma^2 & \rho \sigma^2 & \rho \sigma^2 & 0 & 0 & \ldots \\
\rho \sigma^2 & \rho \sigma^2 & \rho \sigma^2 & \sigma^2 & \rho \sigma^2 & \rho \sigma^2 & 0 & 0 & \ldots \\
\rho \sigma^2 & \rho \sigma^2 & \rho \sigma^2 & \rho \sigma^2 & \sigma^2 & \rho \sigma^2 & 0 & 0 & \ldots \\
0 & 0 & 0 & 0 & 0 & \sigma^2 & \rho \sigma^2 & \ldots \\
0 & 0 & 0 & 0 & 0 & 0 & \rho \sigma^2 & \sigma^2 & \ldots \\
\vdots & \vdots & \vdots & \vdots & \vdots & \vdots & \vdots & \ddots
\end{pmatrix}
$$

and the estimated block for each subject using the compound symmetry specification is

<table>
<thead>
<tr>
<th>Estimated Vi Matrix of Subject = 1</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vi 1 2 3 4 5 6</td>
</tr>
<tr>
<td>1 25.3358 0.7065 0.7065 0.7065 0.7065 0.7065</td>
</tr>
<tr>
<td>2 0.7065 25.3358 0.7065 0.7065 0.7065 0.7065</td>
</tr>
<tr>
<td>3 0.7065 0.7065 25.3358 0.7065 0.7065 0.7065</td>
</tr>
<tr>
<td>4 0.7065 0.7065 0.7065 25.3358 0.7065 0.7065</td>
</tr>
<tr>
<td>5 0.7065 0.7065 0.7065 0.7065 25.3358 0.7065</td>
</tr>
<tr>
<td>6 0.7065 0.7065 0.7065 0.7065 0.7065 25.3358</td>
</tr>
</tbody>
</table>

which is identical (to rounding error) to the previous result using random and repeated component specification.
Other Repeated Patterns (AR(1))

It is natural to expect that the covariances of measurements made closer together in time are more similar than those at more distant times. Several covariance pattern structures have been developed for such cases. We will examine one of the more common structures: AR(1).

Using the AR(1) covariance pattern, there are only two parameters, $\sigma^2$ and $\rho$, but the coefficient of $\sigma^2$ decreases exponentially as observations are farther apart. The $R$ matrix has the form

$$
R = \begin{pmatrix}
\sigma^2 & \rho \sigma^2 & \rho^2 \sigma^2 & \rho^3 \sigma^2 & \rho^4 \sigma^2 & \rho^5 \sigma^2 \\
\rho \sigma^2 & \sigma^2 & \rho \sigma^2 & \rho^2 \sigma^2 & \rho^3 \sigma^2 & \rho^4 \sigma^2 \\
\rho^2 \sigma^2 & \rho \sigma^2 & \sigma^2 & \rho \sigma^2 & \rho^2 \sigma^2 & \rho^3 \sigma^2 \\
\rho^3 \sigma^2 & \rho^2 \sigma^2 & \rho \sigma^2 & \sigma^2 & \rho \sigma^2 & \rho^2 \sigma^2 \\
\rho^4 \sigma^2 & \rho^3 \sigma^2 & \rho^2 \sigma^2 & \rho \sigma^2 & \sigma^2 & \rho \sigma^2 \\
\rho^5 \sigma^2 & \rho^4 \sigma^2 & \rho^3 \sigma^2 & \rho^2 \sigma^2 & \rho \sigma^2 & \sigma^2
\end{pmatrix}
$$

The true dimension of $R$ is 126 by 126 with 21 of the above matrices along the diagonal.

The Repeated Component output becomes

<table>
<thead>
<tr>
<th>Component Number</th>
<th>Parameter Number</th>
<th>Estimated Value</th>
<th>Parameter Type</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1</td>
<td>25.3360</td>
<td>Diagonal (Variance)</td>
</tr>
<tr>
<td>1</td>
<td>1</td>
<td>0.0659</td>
<td>Off-Diagonal (Correlation)</td>
</tr>
</tbody>
</table>

Here, the estimate of $\sigma^2$ is 25.3360 and the estimate of $\rho$ is 0.0659.

The estimated block for each subject using the AR(1) specification is

<table>
<thead>
<tr>
<th>Vi</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>25.3360</td>
<td>1.6696</td>
<td>0.1100</td>
<td>0.0073</td>
<td>0.0005</td>
<td>0.0000</td>
</tr>
<tr>
<td>2</td>
<td>1.6696</td>
<td>25.3360</td>
<td>1.6696</td>
<td>0.1100</td>
<td>0.0073</td>
<td>0.0005</td>
</tr>
<tr>
<td>3</td>
<td>0.1100</td>
<td>1.6696</td>
<td>25.3360</td>
<td>1.6696</td>
<td>0.1100</td>
<td>0.0073</td>
</tr>
<tr>
<td>4</td>
<td>0.0073</td>
<td>0.1100</td>
<td>1.6696</td>
<td>25.3360</td>
<td>1.6696</td>
<td>0.1100</td>
</tr>
<tr>
<td>5</td>
<td>0.0005</td>
<td>0.0073</td>
<td>0.1100</td>
<td>1.6696</td>
<td>25.3360</td>
<td>1.6696</td>
</tr>
<tr>
<td>6</td>
<td>0.0000</td>
<td>0.0005</td>
<td>0.0073</td>
<td>0.1100</td>
<td>1.6696</td>
<td>25.3360</td>
</tr>
</tbody>
</table>

The estimates of the covariance parameters using this formulation are closer to 0 as the time between measurements increases.

The AIC value may be used to compare the various covariance structures. The AIC value for the AR(1) specification is 725.77. The AIC value for the compound symmetry (and random component) specification is 725.94. A smaller AIC value indicates a better model. Thus, the AR(1) specification provides a slight improvement over the compound symmetry (and random component) specification.
Example 2 – Cross-Over Design (No Between-Subject Factors, Two Within-Subject Factors, One Covariate)

In a basic two-level cross-over design, each subject receives both treatments, but (approximately) half receive the two treatments in the opposite order. In this example, researchers are comparing two drugs for their effect on heart rate in rats. Each rat is given both drugs, with a short washout period between drug administrations, but the order of the drugs is reversed in half of the rats. An initial heart rate (IHR) measurement is taken immediately before administration of each of the drugs.

### Cross Dataset

<table>
<thead>
<tr>
<th>Rat</th>
<th>Period</th>
<th>Trtcross</th>
<th>IHR</th>
<th>HR</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1</td>
<td>Drug A</td>
<td>389</td>
<td>357</td>
</tr>
<tr>
<td>1</td>
<td>2</td>
<td>Drug B</td>
<td>383</td>
<td>381</td>
</tr>
<tr>
<td>2</td>
<td>1</td>
<td>Drug B</td>
<td>372</td>
<td>409</td>
</tr>
<tr>
<td>2</td>
<td>2</td>
<td>Drug A</td>
<td>390</td>
<td>385</td>
</tr>
<tr>
<td>3</td>
<td>1</td>
<td>Drug A</td>
<td>396</td>
<td>386</td>
</tr>
<tr>
<td>3</td>
<td>2</td>
<td>Drug B</td>
<td>372</td>
<td>377</td>
</tr>
<tr>
<td>4</td>
<td>1</td>
<td>Drug B</td>
<td>389</td>
<td>376</td>
</tr>
<tr>
<td>4</td>
<td>2</td>
<td>Drug A</td>
<td>398</td>
<td>385</td>
</tr>
<tr>
<td>5</td>
<td>1</td>
<td>Drug A</td>
<td>404</td>
<td>396</td>
</tr>
<tr>
<td>5</td>
<td>2</td>
<td>Drug B</td>
<td>378</td>
<td>370</td>
</tr>
<tr>
<td>6</td>
<td>1</td>
<td>Drug B</td>
<td>394</td>
<td>394</td>
</tr>
<tr>
<td>6</td>
<td>2</td>
<td>Drug A</td>
<td>392</td>
<td>366</td>
</tr>
<tr>
<td>.</td>
<td>.</td>
<td>.</td>
<td>.</td>
<td>.</td>
</tr>
<tr>
<td>.</td>
<td>.</td>
<td>.</td>
<td>.</td>
<td>.</td>
</tr>
<tr>
<td>18</td>
<td>1</td>
<td>Drug B</td>
<td>382</td>
<td>381</td>
</tr>
<tr>
<td>18</td>
<td>2</td>
<td>Drug A</td>
<td>396</td>
<td>380</td>
</tr>
<tr>
<td>19</td>
<td>1</td>
<td>Drug A</td>
<td>380</td>
<td>391</td>
</tr>
<tr>
<td>19</td>
<td>2</td>
<td>Drug B</td>
<td>387</td>
<td>392</td>
</tr>
<tr>
<td>20</td>
<td>1</td>
<td>Drug B</td>
<td>408</td>
<td>403</td>
</tr>
<tr>
<td>20</td>
<td>2</td>
<td>Drug A</td>
<td>391</td>
<td>371</td>
</tr>
</tbody>
</table>

### Setup

To run this example, complete the following steps:

1. **Open the Cross example dataset**
   - From the File menu of the NCSS Data window, select *Open Example Data*.
   - Select *Cross* and click *OK*.

2. **Specify the Mixed Models – Repeated Measures procedure options**
   - Find and open the *Mixed Models – Repeated Measures* procedure using the menus or the Procedure Navigator.
Mixed Models - Repeated Measures

- The settings for this example are listed below and are stored in the Example 2 settings file. To load these settings to the procedure window, click Open Example Settings File in the Help Center or File menu.

```
Variables Tab

Response ........................................................ HR
Subjects .......................................................... Rat
Number ........................................................... 2
Variable 1 ....................................................... Period
Variable 2 ....................................................... Trtcross
Number ........................................................... 1
Variable 1 ....................................................... IHR
Pattern ............................................................ Compound Symmetry: Repeated
Terms ............................................................ 1-Way
```

3 Run the procedure
- Click the Run button to perform the calculations and generate the output.

Cross-Over Example Output

Repeated Component Parameter Estimates (R Matrix)

<table>
<thead>
<tr>
<th>Component Number</th>
<th>Parameter Number</th>
<th>Estimated Value</th>
<th>Parameter Type</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1</td>
<td>196.5320</td>
<td>Diagonal (Variance)</td>
</tr>
<tr>
<td>1</td>
<td>1</td>
<td>0.0352</td>
<td>Off-Diagonal (Correlation)</td>
</tr>
</tbody>
</table>

Term-by-Term Hypothesis Test Results

<table>
<thead>
<tr>
<th>Model Term</th>
<th>F-Value</th>
<th>Num DF</th>
<th>Denom DF</th>
<th>Prob Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>IHR</td>
<td>2.0014</td>
<td>1</td>
<td>35.6</td>
<td>0.165832</td>
</tr>
<tr>
<td>Period</td>
<td>0.4896</td>
<td>1</td>
<td>17.5</td>
<td>0.493296</td>
</tr>
<tr>
<td>Trtcross</td>
<td>3.9857</td>
<td>1</td>
<td>20.6</td>
<td>0.059259</td>
</tr>
</tbody>
</table>

These F-Values test Type-III (adjusted last) hypotheses.

The F-test for Trtcross is nearly significant (F-value = 3.9857, Prob Level = 0.0593) at the 0.05 level. There appears to be no period effect (F-value = 0.4896, Prob Level = 0.4933) nor relationship between the initial heart rate (F-value = 2.0014, Prob Level = 0.1658) and the response heart rate.

The advantages of using mixed models in cross-over designs are usually more pronounced when there is missing data. Missing values often occur in cross-over designs when subjects fail to appear for the second treatment. Another advantage of mixed models in cross-over designs over conventional analyses occurs when there are three or more treatments involved. In such cases, the cross-over design may be considered a repeated measures design, and specific covariate patterns can be used to model the similarity in repeated measurements. That is, measurements that are taken closer together may be expected to vary more similarly, while measurements at distant periods may not.