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

$$\mathbf{y} = \mathbf{X\beta} + \mathbf{Zu} + \boldsymbol{\varepsilon}$$
$$\mathbf{u} \sim N(\mathbf{0}, \mathbf{G})$$
$$\boldsymbol{\varepsilon} \sim N(\mathbf{0}, \mathbf{R})$$
$$\mathrm{Cov}[\mathbf{u}, \boldsymbol{\varepsilon}] = \mathbf{0}$$
$$\mathbf{V} = \mathbf{ZGZ}' + \mathbf{R}$$

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 $\boldsymbol{\varepsilon}$ 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 Y

Akaike Information Criterion (AIC) for Model Assessment

Akaike information criterion (AIC) is 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.

Pattern	Number of Parameters	-2 log-likelihood	AIC
Diagonal	1	214.43	216.43
Compound Symmetry	2	210.77	214.77
AR(1)	2	203.52	207.52
Toeplitz	4	198.03	206.03
Unstructured	7	197.94	211.94

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 in 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 $\mathbf{R}$ matrix is the variance-covariance matrix for errors, $\boldsymbol{\varepsilon}$. When the $\mathbf{R}$ matrix is used to specify the variance-covariance structure of $\mathbf{y}$, the $\mathbf{G}_{sub}$ matrix (the random component) is not used.

The full $\mathbf{R}$ matrix is made up of *N* symmetric $\mathbf{R}$ sub-matrices,

$$\mathbf{R} = \begin{pmatrix} \mathbf{R}_1 & \mathbf{0} & \mathbf{0} & \cdots & \mathbf{0} \\ \mathbf{0} & \mathbf{R}_2 & \mathbf{0} & \cdots & \mathbf{0} \\ \mathbf{0} & \mathbf{0} & \mathbf{R}_3 & \cdots & \mathbf{0} \\ \vdots & \vdots & \vdots & \ddots & \vdots \\ \mathbf{0} & \mathbf{0} & \mathbf{0} & \cdots & \mathbf{R}_N \end{pmatrix},$$

where $\mathbf{R}_1, \mathbf{R}_2, \mathbf{R}_3, \cdots, \mathbf{R}_N$ are all of the same structure, but, unlike the $\mathbf{G}_{sub}$ matrices, differ according to the number of repeated measurements on each subject.

When the $\mathbf{R}$ 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 $\mathbf{R}$ sub-matrices occur only when some measurements for a subject are missing.

As an example, suppose an $\mathbf{R}$ sub-matrix is of the form

$$\mathbf{R}_{sub} = \begin{pmatrix} \sigma_1^2 & & & & \\ & \sigma_2^2 & & & \\ & & \sigma_3^2 & & \\ & & & \sigma_4^2 & \\ & & & & \sigma_5^2 \end{pmatrix},$$

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 $\mathbf{R}_{sub}$ above, and $\mathbf{R}_1 = \mathbf{R}_{sub}$.

Suppose the second subject is measured at 1 hour, 5 hours, and 24 hours, but misses the 2-hour and 10-hour measurements. The $\mathbf{R}_2$ matrix for this subject is

$$\mathbf{R}_2 = \begin{pmatrix} \sigma_1^2 & & \\ & \sigma_3^2 & \\ & & \sigma_5^2 \end{pmatrix}.$$

For this subject, n_2 = 3. That is, for the case when the time points are fixed, instead of having missing values in the $\mathbf{R}$ 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 $\mathbf{R}_{sub}$ structures that can be specified in **NCSS** are shown below.

Diagonal

Homogeneous

$$\begin{pmatrix} \sigma^2 & & & \\ & \sigma^2 & & \\ & & \sigma^2 & \\ & & & \sigma^2 \end{pmatrix}$$

Heterogeneous

$$\begin{pmatrix} \sigma_1^2 & & & \\ & \sigma_2^2 & & \\ & & \sigma_3^2 & \\ & & & \sigma_4^2 \end{pmatrix}$$

Correlation

$$\begin{pmatrix} 1 & & & \\ & 1 & & \\ & & 1 & \\ & & & 1 \end{pmatrix}$$

Compound Symmetry

Homogeneous

$$\begin{pmatrix} \sigma^2 & \rho\sigma^2 & \rho\sigma^2 & \rho\sigma^2 \\ \rho\sigma^2 & \sigma^2 & \rho\sigma^2 & \rho\sigma^2 \\ \rho\sigma^2 & \rho\sigma^2 & \sigma^2 & \rho\sigma^2 \\ \rho\sigma^2 & \rho\sigma^2 & \rho\sigma^2 & \sigma^2 \end{pmatrix}$$

Heterogeneous

$$\begin{pmatrix} \sigma_1^2 & \rho\sigma_1\sigma_2 & \rho\sigma_1\sigma_3 & \rho\sigma_1\sigma_4 \\ \rho\sigma_2\sigma_1 & \sigma_2^2 & \rho\sigma_2\sigma_3 & \rho\sigma_2\sigma_4 \\ \rho\sigma_3\sigma_1 & \rho\sigma_3\sigma_2 & \sigma_3^2 & \rho\sigma_3\sigma_4 \\ \rho\sigma_4\sigma_1 & \rho\sigma_4\sigma_2 & \rho\sigma_4\sigma_3 & \sigma_4^2 \end{pmatrix}$$

Correlation

$$\begin{pmatrix} 1 & \rho & \rho & \rho \\ \rho & 1 & \rho & \rho \\ \rho & \rho & 1 & \rho \\ \rho & \rho & \rho & 1 \end{pmatrix}$$

AR(1)

Homogeneous

$$\begin{pmatrix} \sigma^2 & \rho\sigma^2 & \rho^2\sigma^2 & \rho^3\sigma^2 \\ \rho\sigma^2 & \sigma^2 & \rho\sigma^2 & \rho^2\sigma^2 \\ \rho^2\sigma^2 & \rho\sigma^2 & \sigma^2 & \rho\sigma^2 \\ \rho^3\sigma^2 & \rho^2\sigma^2 & \rho\sigma^2 & \sigma^2 \end{pmatrix}$$

Heterogeneous

$$\begin{pmatrix} \sigma_1^2 & \rho\sigma_1\sigma_2 & \rho^2\sigma_1\sigma_3 & \rho^3\sigma_1\sigma_4 \\ \rho\sigma_2\sigma_1 & \sigma_2^2 & \rho\sigma_2\sigma_3 & \rho^2\sigma_2\sigma_4 \\ \rho^2\sigma_3\sigma_1 & \rho\sigma_3\sigma_2 & \sigma_3^2 & \rho\sigma_3\sigma_4 \\ \rho^3\sigma_4\sigma_1 & \rho^2\sigma_4\sigma_2 & \rho\sigma_4\sigma_3 & \sigma_4^2 \end{pmatrix}$$

Correlation

$$\begin{pmatrix} 1 & \rho & \rho^2 & \rho^3 \\ \rho & 1 & \rho & \rho^2 \\ \rho^2 & \rho & 1 & \rho \\ \rho^3 & \rho^2 & \rho & 1 \end{pmatrix}$$

AR(Time Diff)

Homogeneous

$$\begin{pmatrix} \sigma^2 & \rho^{t_2-t_1}\sigma^2 & \rho^{t_3-t_1}\sigma^2 & \rho^{t_4-t_1}\sigma^2 \\ \rho^{t_2-t_1}\sigma^2 & \sigma^2 & \rho^{t_3-t_2}\sigma^2 & \rho^{t_4-t_2}\sigma^2 \\ \rho^{t_3-t_1}\sigma^2 & \rho^{t_3-t_2}\sigma^2 & \sigma^2 & \rho^{t_4-t_3}\sigma^2 \\ \rho^{t_4-t_1}\sigma^2 & \rho^{t_4-t_2}\sigma^2 & \rho^{t_4-t_3}\sigma^2 & \sigma^2 \end{pmatrix}$$

Heterogeneous

$$\begin{pmatrix} {\sigma_1}^2 & \rho^{t_2-t_1}\sigma_1\sigma_2 & \rho^{t_3-t_1}\sigma_1\sigma_3 & \rho^{t_4-t_1}\sigma_1\sigma_4 \\ \rho^{t_2-t_1}\sigma_2\sigma_1 & {\sigma_2}^2 & \rho^{t_3-t_2}\sigma_2\sigma_3 & \rho^{t_4-t_2}\sigma_2\sigma_4 \\ \rho^{t_3-t_1}\sigma_3\sigma_1 & \rho^{t_3-t_2}\sigma_3\sigma_2 & {\sigma_3}^2 & \rho^{t_4-t_3}\sigma_3\sigma_4 \\ \rho^{t_4-t_1}\sigma_4\sigma_1 & \rho^{t_4-t_2}\sigma_4\sigma_2 & \rho^{t_4-t_3}\sigma_4\sigma_3 & {\sigma_4}^2 \end{pmatrix}$$

Correlation

$$\begin{pmatrix} 1 & \rho^{t_2-t_1} & \rho^{t_3-t_1} & \rho^{t_4-t_1} \\ \rho^{t_2-t_1} & 1 & \rho^{t_3-t_2} & \rho^{t_4-t_2} \\ \rho^{t_3-t_1} & \rho^{t_3-t_2} & 1 & \rho^{t_4-t_3} \\ \rho^{t_4-t_1} & \rho^{t_4-t_2} & \rho^{t_4-t_3} & 1 \end{pmatrix}$$

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

$$\begin{pmatrix} 1 & \rho_1 & \rho_2 & \rho_3 \\ \rho_1 & 1 & \rho_1 & \rho_2 \\ \rho_2 & \rho_1 & 1 & \rho_1 \\ \rho_3 & \rho_2 & \rho_1 & 1 \end{pmatrix}$$

Toeplitz(2)

Homogeneous

$$\begin{pmatrix} \sigma^2 & \rho_1\sigma^2 & & \\ \rho_1\sigma^2 & \sigma^2 & \rho_1\sigma^2 & \\ & \rho_1\sigma^2 & \sigma^2 & \rho_1\sigma^2 \\ & & \rho_1\sigma^2 & \sigma^2 \end{pmatrix}$$

Heterogeneous

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

Correlation

$$\begin{pmatrix} 1 & \rho_1 & & \\ \rho_1 & 1 & \rho_1 & \\ & \rho_1 & 1 & \rho_1 \\ & & \rho_1 & 1 \end{pmatrix}$$

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

Toeplitz(3)

Homogeneous

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

Heterogeneous

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

Correlation

$$\begin{pmatrix} 1 & \rho_1 & \rho_2 & \\ \rho_1 & 1 & \rho_1 & \rho_2 \\ \rho_2 & \rho_1 & 1 & \rho_1 \\ & \rho_2 & \rho_1 & 1 \end{pmatrix}$$

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

$$\begin{pmatrix} \sigma^2 & \rho_1\sigma^2 & & \\ \rho_1\sigma^2 & \sigma^2 & \rho_1\sigma^2 & \\ & \rho_1\sigma^2 & \sigma^2 & \rho_1\sigma^2 \\ & & \rho_1\sigma^2 & \sigma^2 \end{pmatrix}$$

Heterogeneous

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

Correlation

$$\begin{pmatrix} 1 & \rho_1 & & \\ \rho_1 & 1 & \rho_1 & \\ & \rho_1 & 1 & \rho_1 \\ & & \rho_1 & 1 \end{pmatrix}$$

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

Banded(3)

Homogeneous

$$\begin{pmatrix} \sigma^2 & \rho\sigma^2 & \rho\sigma^2 & \\ \rho\sigma^2 & \sigma^2 & \rho\sigma^2 & \rho\sigma^2 \\ \rho\sigma^2 & \rho\sigma^2 & \sigma^2 & \rho\sigma^2 \\ & \rho\sigma^2 & \rho\sigma^2 & \sigma^2 \end{pmatrix}$$

Heterogeneous

$$\begin{pmatrix} \sigma_1^2 & \rho\sigma_1\sigma_2 & \rho\sigma_1\sigma_3 & \\ \rho\sigma_2\sigma_1 & \sigma_2^2 & \rho\sigma_2\sigma_3 & \rho\sigma_2\sigma_4 \\ \rho\sigma_3\sigma_1 & \rho\sigma_3\sigma_2 & \sigma_3^2 & \rho\sigma_3\sigma_4 \\ & \rho\sigma_4\sigma_2 & \rho\sigma_4\sigma_3 & \sigma_4^2 \end{pmatrix}$$

Correlation

$$\begin{pmatrix} 1 & \rho & \rho & \\ \rho & 1 & \rho & \rho \\ \rho & \rho & 1 & \rho \\ & \rho & \rho & 1 \end{pmatrix}$$

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 $\mathbf{R}$ 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 $\mathbf{R}$ in a study with four time points is specified to be Toeplitz:

$$\boldsymbol{R} = \begin{pmatrix} \sigma^2 & \rho_1\sigma^2 & \rho_2\sigma^2 & \rho_3\sigma^2 \\ \rho_1\sigma^2 & \sigma^2 & \rho_1\sigma^2 & \rho_2\sigma^2 \\ \rho_2\sigma^2 & \rho_1\sigma^2 & \sigma^2 & \rho_1\sigma^2 \\ \rho_3\sigma^2 & \rho_2\sigma^2 & \rho_1\sigma^2 & \sigma^2 \end{pmatrix}.$$

If there are sixteen subjects, then

$$\boldsymbol{R} = \begin{pmatrix} \boldsymbol{R_1} & \mathbf{0} & \mathbf{0} & \cdots & \mathbf{0} \\ \mathbf{0} & \boldsymbol{R_2} & \mathbf{0} & \cdots & \mathbf{0} \\ \mathbf{0} & \mathbf{0} & \boldsymbol{R_3} & \cdots & \mathbf{0} \\ \vdots & \vdots & \vdots & \ddots & \vdots \\ \mathbf{0} & \mathbf{0} & \mathbf{0} & \cdots & \boldsymbol{R}_{16} \end{pmatrix}.$$

The total number of variance-covariance parameters is four: σ^2, ρ_1, ρ_2, and ρ_3.

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

$$\boldsymbol{R_1, \cdots, R_8} = \begin{pmatrix} \sigma_1^2 & \rho_{11}\sigma^2 & \rho_{12}\sigma^2 & \rho_{13}\sigma^2 \\ \rho_{11}\sigma^2 & \sigma_1^2 & \rho_{11}\sigma^2 & \rho_{12}\sigma^2 \\ \rho_{12}\sigma^2 & \rho_{11}\sigma^2 & \sigma_1^2 & \rho_{11}\sigma^2 \\ \rho_{13}\sigma^2 & \rho_{12}\sigma^2 & \rho_{11}\sigma^2 & \sigma_1^2 \end{pmatrix},$$

and

$$\boldsymbol{R_9, \cdots, R_{16}} = \begin{pmatrix} \sigma_2^2 & \rho_{21}\sigma^2 & \rho_{22}\sigma^2 & \rho_{23}\sigma^2 \\ \rho_{21}\sigma^2 & \sigma_2^2 & \rho_{21}\sigma^2 & \rho_{22}\sigma^2 \\ \rho_{22}\sigma^2 & \rho_{21}\sigma^2 & \sigma_2^2 & \rho_{21}\sigma^2 \\ \rho_{23}\sigma^2 & \rho_{22}\sigma^2 & \rho_{21}\sigma^2 & \sigma_2^2 \end{pmatrix}.$$

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 $\mathbf{R}$ 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.

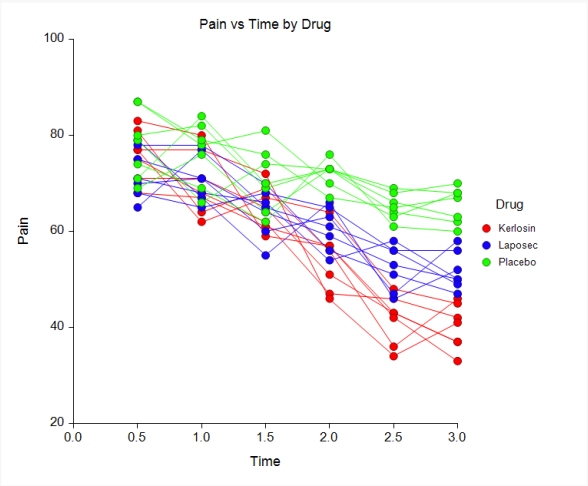
In a longitudinal design, subjects are measured more than once, usually over time. This example presents the analysis of a longitudinal design in which there is one between-subjects factor (Drug), one within-subjects factor (Time), and a covariate (Weight). Two drugs (Kerlosin and Laposec) are compared 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

Drug	Patient	Time	Cov	Pain
Kerlosin	1	0.5	125	68
Kerlosin	1	1	196	67
Kerlosin	1	1.5	189	61
Kerlosin	1	2	135	57
Kerlosin	1	2.5	128	43
Kerlosin	1	3	151	37
Kerlosin	2	0.5	215	75
Kerlosin	2	1	151	68
Kerlosin	2	1.5	191	62
Kerlosin	2	2	212	47
Kerlosin	2	2.5	127	46
Kerlosin	2	3	133	42
.	.	.	.	.
.	.	.	.	.
.	.	.	.	.
Placebo	21	2	129	73
Placebo	21	2.5	216	68
Placebo	21	3	158	70

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	
Response	**Pain**
Subjects	**Patient**
Times	**Time**
Number	**2**
Variable 1	**Drug**
Comparison	**All Pairs**
Variable 2	**Time**
Comparison	**Baseline vs Each**
Baseline	**0.5**
Number	**1**
Variable 1	**Cov**
Compute Means at these Values	**140**
Terms	**Interaction Model**

Reports Tab

Run Summary	**Checked**
Variance Estimates	**Checked**
Hypothesis Tests	**Checked**
L Matrices - Terms	**Checked**
Comparisons by Fixed Effects	**Checked**
Comparisons by Covariate Values	**Checked**
L Matrices - Comparisons	**Unchecked**
Means by Fixed Effects	**Checked**
Means by Covariate Values	**Checked**
L Matrices - LS Means	**Unchecked**
Fixed Effects Solution	**Checked**
Asymptotic VC Matrix	**Checked**
Vi Matrices (1st 3 Subjects)	**Checked**
Hessian Matrix	**Checked**
Show Report Definitions	**Unchecked**

3 Run the procedure

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

Run Summary

Run Summary

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

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)

Random Component Parameter Estimates (G Matrix)

Component Number	Parameter Number	Estimated Value	Model Term
1	1	1.6343	Patient

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)

Repeated Component Parameter Estimates (R Matrix)

Component Number	Parameter Number	Estimated Value	Parameter Type
1	1	23.5867	Diagonal (Variance)

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

Term-by-Term Hypothesis Test Results

Model Term	F-Value	Num DF	Denom DF	Prob Level
Cov	3.3021	1	87.1	0.072631
Drug	1.8217	2	89.0	0.167729
Time	0.9780	5	88.4	0.435775
Cov*Drug	0.7698	2	86.8	0.466228
Cov*Time	1.2171	5	88.5	0.307773
Drug*Time	0.8627	10	87.0	0.570795
Cov*Drug*Time	1.0691	10	87.0	0.394694

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

Individual Comparison Hypothesis Test Results by Covariate Values

Covariates: Cov = 140.0000

Comparison/ Covariate(s)	Comparison Mean Difference	F-Value	Num DF	Denom DF	Raw Prob Level	Bonferroni Prob Level
Drug						
Drug		43.1757	2	32.8	0.000000	
Drug: Kerlosin - Laposec	-3.4655	4.2279	1	37.7	0.046734	0.140202 [3]
Drug: Kerlosin - Placebo	-13.5972	78.7500	1	28.9	0.000000	0.000000 [3]
Drug: Laposec - Placebo	-10.1316	39.4701	1	33.8	0.000000	0.000001 [3]
Time						
Time		46.5094	5	82.3	0.000000	
Time: 0.5 - 1	2.8138	1.3602	1	87.0	0.246695	1.000000 [5]
Time: 0.5 - 1.5	8.1935	20.2334	1	82.7	0.000022	0.000111 [5]
Time: 0.5 - 2	11.2966	29.2190	1	79.6	0.000001	0.000003 [5]
Time: 0.5 - 2.5	21.2629	122.1178	1	83.6	0.000000	0.000000 [5]
Time: 0.5 - 3	22.2608	152.6565	1	81.0	0.000000	0.000000 [5]
Drug*Time						
Drug*Time		5.3797	10	81.1	0.000005	
Drug = Kerlosin, Time: 0.5 - 1	7.0448	3.6965	1	86.3	0.057827	0.867407 [15]
.	.	.	.	.	.	.
.	.	.	.	.	.	.
.	.	.	.	.	.	.

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

Least Squares (Adjusted) Means by Covariate Values

Covariates: Cov = 140.0000

Name	Mean	Standard Error of Mean	95.0% Lower Conf. Limit for Mean	95.0% Upper Conf. Limit for Mean	DF
Intercept					
Intercept	64.1132	0.6578	62.7756	65.4508	33.5
Drug					
Kerlosin	58.4256	1.1375	56.1112	60.7400	32.9
Laposec	61.8912	1.2437	59.3819	64.4005	42.3
Placebo	72.0228	1.0266	69.9077	74.1380	24.8
Time					
0.5	75.0845	1.3928	72.3172	77.8517	89.8
1	72.2707	1.9886	68.3199	76.2216	89.9
1.5	66.8910	1.2243	64.4584	69.3235	89.3
2	63.7879	1.6286	60.5523	67.0235	90.0
2.5	53.8216	1.3744	51.0909	56.5522	89.7
3	52.8237	1.2048	50.4299	55.2175	89.2
Drug*Time					
Kerlosin, 0.5	76.0661	2.5993	70.9021	81.2302	89.8
Kerlosin, 1	69.0213	2.6391	63.7782	74.2644	90.0
Kerlosin, 1.5	66.0203	2.0542	61.9387	70.1019	89.2
Kerlosin, 2	56.3645	3.7835	48.8479	63.8812	89.9
.	.	.	.	.	.
.	.	.	.	.	.
.	.	.	.	.	.

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

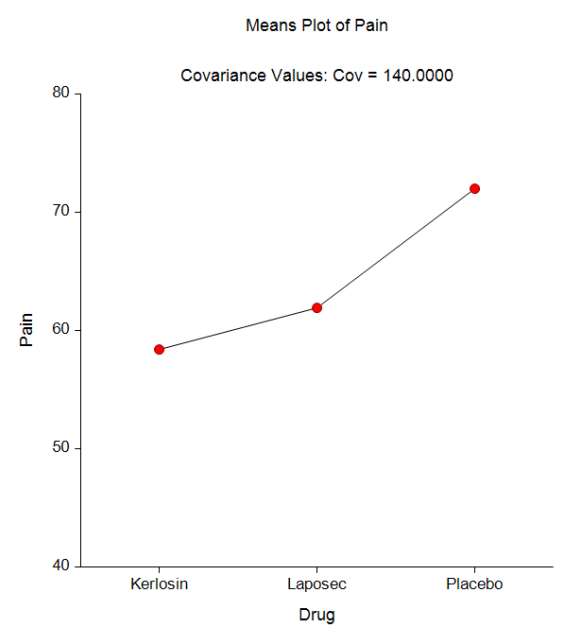
These limits give a 95% confidence interval for the mean.

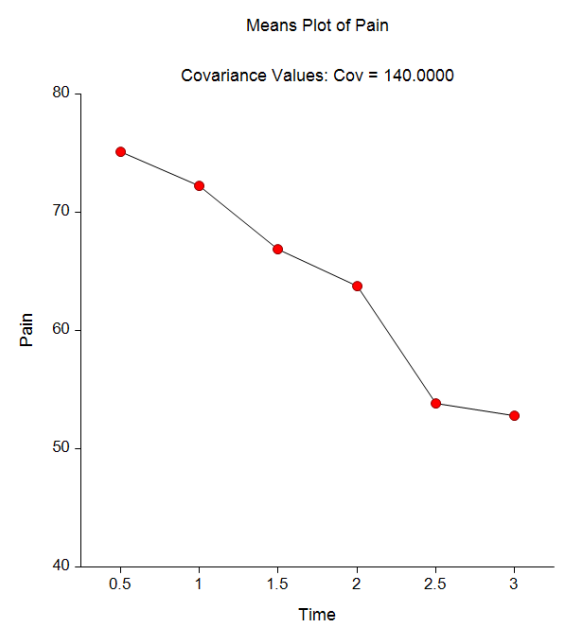
DF

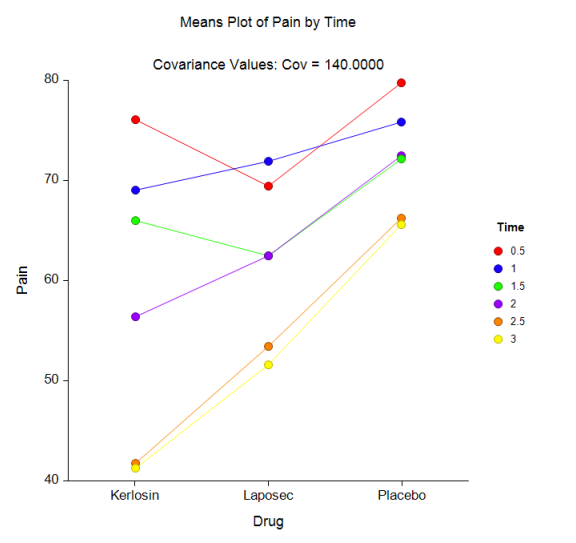
The degrees of freedom used for the confidence limits are calculated using the method of Kenward and Roger (1997).

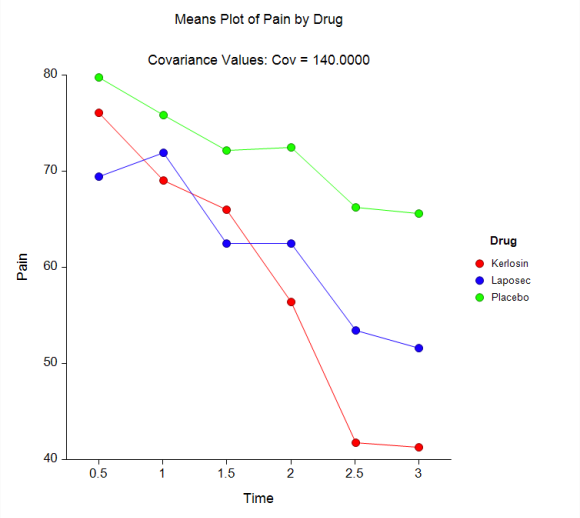
Means Plots

Means Plots





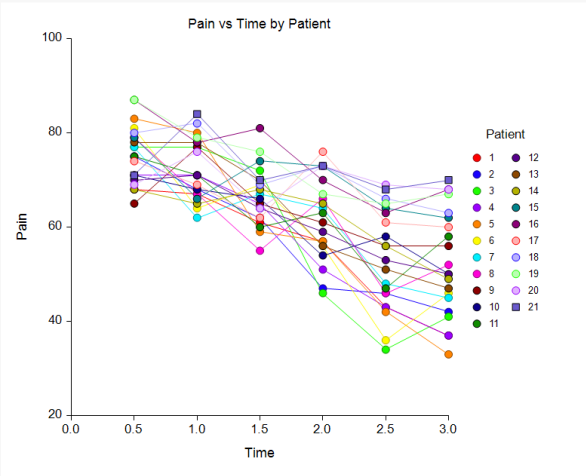


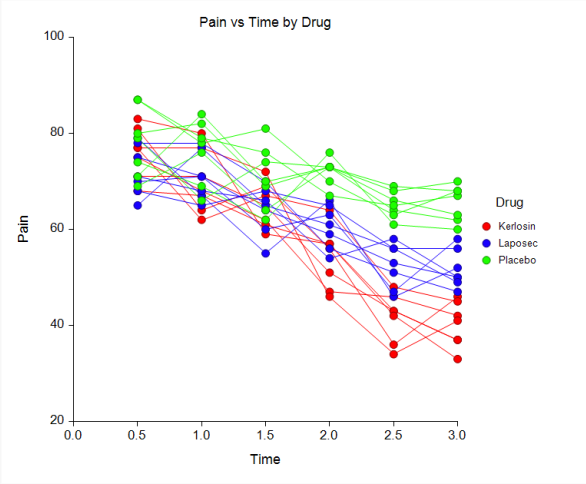


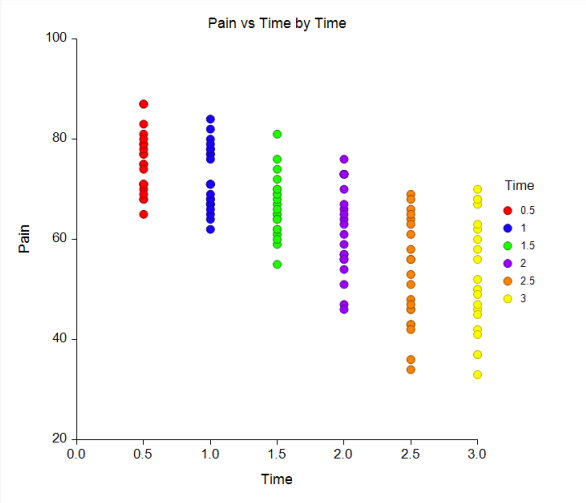
These plots show the means broken up into the categories of the fixed effects of the model. Some general trends that can be seen are those of pain decreasing with time and lower pain for the two drugs after two hours.

Subject Plots

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

Solution for Fixed Effects

Effect Name	Effect Estimate (Beta)	Effect Standard Error	Prob Level	95.0% Lower Conf. Limit of Beta	95.0% Upper Conf. Limit of Beta	DF	Effect No.
Intercept	66.8296	7.4693	0.000000	51.9900	81.6692	89.8	1
Cov	-0.0089	0.0461	0.846662	-0.1004	0.0826	89.6	2
(Drug="Kerlosin")	-9.4849	11.9162	0.428154	-33.1595	14.1898	89.7	3
(Drug="Laposec")	-16.5164	14.6176	0.261539	-45.5591	12.5264	89.5	4
(Drug="Placebo")	0.0000	0.0000					5
(Time=0.5)	23.0382	12.0137	0.058369	-0.8336	46.9099	88.8	6
(Time=1)	-4.9520	10.5394	0.639641	-25.9029	15.9988	86.2	7
(Time=1.5)	16.5033	12.3512	0.184968	-8.0451	41.0518	87.2	8
(Time=2)	10.8739	14.7800	0.463980	-18.5236	40.2714	82.9	9
(Time=2.5)	3.0828	12.5528	0.806621	-21.8933	28.0589	81.0	10
(Time=3)	0.0000	0.0000					11
Cov*(Drug="Kerlosin")	-0.1056	0.0761	0.168318	-0.2568	0.0455	89.6	12
Cov*(Drug="Laposec")	0.0180	0.0929	0.846522	-0.1665	0.2026	89.3	13
Cov*(Drug="Placebo")	0.0000	0.0000					14
.	.	.	.	.	.	.	.
.	.	.	.	.	.	.	.
.	.	.	.	.	.	.	.

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 examine 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

Asymptotic Variance-Covariance Matrix of Variance Estimates

Parameter	G(1,1)	R(1,1)
G(1,1)	4.5645	-2.6362
R(1,1)	-2.6362	15.0707

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

Estimated Vi Matrix of Subject = 1

Vi	1	2	3	4	5	6
1	25.2210	1.6343	1.6343	1.6343	1.6343	1.6343
2	1.6343	25.2210	1.6343	1.6343	1.6343	1.6343
3	1.6343	1.6343	25.2210	1.6343	1.6343	1.6343
4	1.6343	1.6343	1.6343	25.2210	1.6343	1.6343
5	1.6343	1.6343	1.6343	1.6343	25.2210	1.6343
6	1.6343	1.6343	1.6343	1.6343	1.6343	25.2210

Estimated Vi Matrix of Subject = 2

Vi	1	2	3	4	5	6
1	25.2210	1.6343	1.6343	1.6343	1.6343	1.6343
2	1.6343	25.2210	1.6343	1.6343	1.6343	1.6343
3	1.6343	1.6343	25.2210	1.6343	1.6343	1.6343
4	1.6343	1.6343	1.6343	25.2210	1.6343	1.6343
5	1.6343	1.6343	1.6343	1.6343	25.2210	1.6343
6	1.6343	1.6343	1.6343	1.6343	1.6343	25.2210

Estimated Vi Matrix of Subject = 3

Vi	1	2	3	4	5	6
1	25.2210	1.6343	1.6343	1.6343	1.6343	1.6343
2	1.6343	25.2210	1.6343	1.6343	1.6343	1.6343
3	1.6343	1.6343	25.2210	1.6343	1.6343	1.6343
4	1.6343	1.6343	1.6343	25.2210	1.6343	1.6343
5	1.6343	1.6343	1.6343	1.6343	25.2210	1.6343
6	1.6343	1.6343	1.6343	1.6343	1.6343	25.2210

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

Hessian Matrix of Variance Estimates

Parameter	G(1,1)	R(1,1)
G(1,1)	0.2437	0.0426
R(1,1)	0.0426	0.0738

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

L Matrix for Cov

No.	Effect	Drug	Time	L1
1	Intercept			
2	Cov			1.0000
3	Drug	Kerlosin		
4	Drug	Laposec		
5	Drug	Placebo		
6	Time		0.5	
7	Time		1	
8	Time		1.5	
9	Time		2	
10	Time		2.5	
11	Time		3	
12	Cov*Drug	Kerlosin		0.3333
13	Cov*Drug	Laposec		0.3333
14	Cov*Drug	Placebo		0.3333
15	Cov*Time		0.5	0.1667
16	Cov*Time		1	0.1667
17	Cov*Time		1.5	0.1667
18	Cov*Time		2	0.1667
19	Cov*Time		2.5	0.1667
20	Cov*Time		3	0.1667
21	Drug*Time	Kerlosin	0.5	
22	Drug*Time	Kerlosin	1	
23	Drug*Time	Kerlosin	1.5	
24	Drug*Time	Kerlosin	2	
25	Drug*Time	Kerlosin	2.5	
26	Drug*Time	Kerlosin	3	
27	Drug*Time	Laposec	0.5	
28	Drug*Time	Laposec	1	
29	Drug*Time	Laposec	1.5	
30	Drug*Time	Laposec	2	
.	.	.	.	.
.	.	.	.	.
.	.	.	.	.

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.

Term-by-Term Hypothesis Test Results

Model Term	F-Value	Num DF	Denom DF	Prob Level
Cov	3.3021	1	87.1	0.072631
Drug	1.8217	2	89.0	0.167729
Time	0.9780	5	88.4	0.435775
Cov*Drug	0.7698	2	86.8	0.466228
Cov*Time	1.2171	5	88.5	0.307773
Drug*Time	0.8627	10	87.0	0.570795
Cov*Drug*Time	1.0691	10	87.0	0.394694

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.

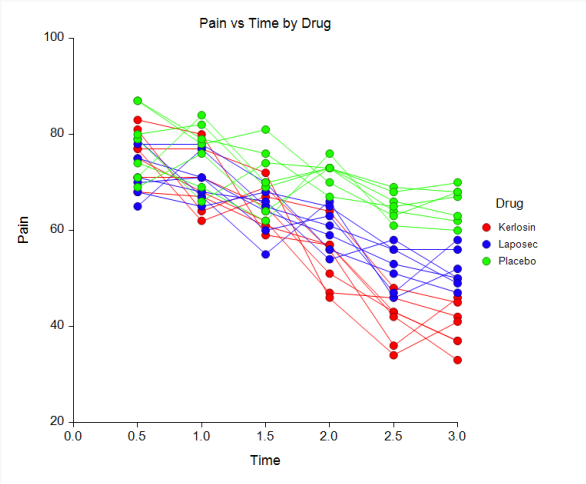
Term-by-Term Hypothesis Test Results

Model Term	F-Value	Num DF	Denom DF	Prob Level
Cov	1.7686	1	98.9	0.186615
Drug	4.1700	2	96.8	0.018315
Time	1.3419	5	98.0	0.253118
Cov*Drug	2.2336	2	92.4	0.112895
Cov*Time	2.3667	5	98.0	0.045036
Drug*Time	7.4394	10	84.1	0.000000

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

Covariates: Cov = 140.0000

Comparison/ Covariate(s)	Comparison Mean Difference	F-Value	Num DF	Denom DF	Raw Prob Level	Bonferroni Prob Level
Drug*Time						
Time = 0.5, Drug: Kerlosin - Laposec	6.1619	4.3285	1	100.0	0.040036	0.720656 [18]
Time = 0.5, Drug: Kerlosin - Placebo	-1.0451	0.1287	1	100.0	0.720543	1.000000 [18]
Time = 0.5, Drug: Laposec - Placebo	-7.2070	6.3717	1	100.0	0.013169	0.237046 [18]
Time = 1, Drug: Kerlosin - Laposec	1.4659	0.2530	1	100.0	0.616068	1.000000 [18]
Time = 1, Drug: Kerlosin - Placebo	-7.2872	6.2095	1	99.9	0.014353	0.258346 [18]
Time = 1, Drug: Laposec - Placebo	-8.7531	8.1482	1	100.0	0.005241	0.094336 [18]
Time = 1.5, Drug: Kerlosin - Laposec	2.3523	0.7185	1	99.9	0.398661	1.000000 [18]
Time = 1.5, Drug: Kerlosin - Placebo	-5.2756	3.6844	1	99.8	0.057780	1.000000 [18]
Time = 1.5, Drug: Laposec - Placebo	-7.6278	7.5730	1	99.9	0.007037	0.126669 [18]
Time = 2, Drug: Kerlosin - Laposec	-2.4751	0.6341	1	100.0	0.427746	1.000000 [18]
Time = 2, Drug: Kerlosin - Placebo	-14.1184	19.4393	1	100.0	0.000026	0.000471 [18]
Time = 2, Drug: Laposec - Placebo	-11.6433	17.6388	1	99.8	0.000058	0.001046 [18]

Time = 2.5, Drug: Kerlosin - Laposec					
-11.0499	16.5687	1	99.7	0.000094	0.001693 [18]
Time = 2.5, Drug: Kerlosin - Placebo					
-27.1071	70.0980	1	100.0	0.000000	0.000000 [18]
Time = 2.5, Drug: Laposec - Placebo					
-16.0572	26.3720	1	100.0	0.000001	0.000025 [18]
Time = 3, Drug: Kerlosin - Laposec					
-10.7977	15.6495	1	99.8	0.000143	0.002569 [18]
Time = 3, Drug: Kerlosin - Placebo					
-25.1938	84.9230	1	99.8	0.000000	0.000000 [18]
Time = 3, Drug: Laposec - Placebo					
-14.3960	27.5367	1	99.8	0.000001	0.000016 [18]

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

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 $\mathbf{V} = \mathbf{ZGZ}' + \mathbf{R}$. The **R** and the **R** used to this point have the form

$$\mathbf{G} = \begin{pmatrix} {\sigma_S}^2 & & & \\ & {\sigma_S}^2 & & \\ & & {\sigma_S}^2 & \\ & & & {\sigma_S}^2 \end{pmatrix} \qquad \mathbf{R} = \begin{pmatrix} \sigma^2 & & & & & \\ & \sigma^2 & & & & \\ & & \sigma^2 & & & \\ & & & \sigma^2 & & \\ & & & & \sigma^2 & \\ & & & & & \sigma^2 \end{pmatrix}$$

where **G** has dimension 21 by 21 and R has dimension 126 by 126. The resulting variance-covariance matrix, $\mathbf{V} = \mathbf{ZGZ}' + \mathbf{R}$, has the form

$$\mathbf{V} = \begin{pmatrix} \sigma^2+\sigma_S^2 & \sigma_S^2 & \sigma_S^2 & \sigma_S^2 & \sigma_S^2 & \sigma_S^2 & 0 & 0 & \cdots \\ \sigma_S^2 & \sigma^2+\sigma_S^2 & \sigma_S^2 & \sigma_S^2 & \sigma_S^2 & \sigma_S^2 & 0 & 0 & \cdots \\ \sigma_S^2 & \sigma_S^2 & \sigma^2+\sigma_S^2 & \sigma_S^2 & \sigma_S^2 & \sigma_S^2 & 0 & 0 & \cdots \\ \sigma_S^2 & \sigma_S^2 & \sigma_S^2 & \sigma^2+\sigma_S^2 & \sigma_S^2 & \sigma_S^2 & 0 & 0 & \cdots \\ \sigma_S^2 & \sigma_S^2 & \sigma_S^2 & \sigma_S^2 & \sigma^2+\sigma_S^2 & \sigma_S^2 & 0 & 0 & \cdots \\ \sigma_S^2 & \sigma_S^2 & \sigma_S^2 & \sigma_S^2 & \sigma_S^2 & \sigma^2+\sigma_S^2 & 0 & 0 & \cdots \\ 0 & 0 & 0 & 0 & 0 & 0 & \sigma^2+\sigma_S^2 & \sigma_S^2 & \cdots \\ 0 & 0 & 0 & 0 & 0 & 0 & \sigma_S^2 & \sigma^2+\sigma_S^2 & \cdots \\ \vdots & \vdots & \vdots & \vdots & \vdots & \vdots & \vdots & \vdots & \ddots \end{pmatrix}$$

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 σ_S^2 and σ^2 for the model without the three-way interaction are 0.7066 and 24.6293, as shown in the output below.

Random Component Parameter Estimates (G Matrix)

Component Number	Parameter Number	Estimated Value	Model Term
1	1	0.7066	Patient

Repeated Component Parameter Estimates (R Matrix)

Component Number	Parameter Number	Estimated Value	Parameter Type
1	1	24.6293	Diagonal (Variance)

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

Estimated Vi Matrix of Subject = 1

Vi	1	2	3	4	5	6
1	25.3359	0.7066	0.7066	0.7066	0.7066	0.7066
2	0.7066	25.3359	0.7066	0.7066	0.7066	0.7066
3	0.7066	0.7066	25.3359	0.7066	0.7066	0.7066
4	0.7066	0.7066	0.7066	25.3359	0.7066	0.7066
5	0.7066	0.7066	0.7066	0.7066	25.3359	0.7066
6	0.7066	0.7066	0.7066	0.7066	0.7066	25.3359

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 $\mathbf{G}$ matrix and the $\mathbf{R}$ matrix has the form

$$\mathbf{R} = \begin{pmatrix} \sigma^2 & \rho\sigma^2 & \rho\sigma^2 & \rho\sigma^2 & \rho\sigma^2 & \rho\sigma^2 \\ \rho\sigma^2 & \sigma^2 & \rho\sigma^2 & \rho\sigma^2 & \rho\sigma^2 & \rho\sigma^2 \\ \rho\sigma^2 & \rho\sigma^2 & \sigma^2 & \rho\sigma^2 & \rho\sigma^2 & \rho\sigma^2 \\ \rho\sigma^2 & \rho\sigma^2 & \rho\sigma^2 & \sigma^2 & \rho\sigma^2 & \rho\sigma^2 \\ \rho\sigma^2 & \rho\sigma^2 & \rho\sigma^2 & \rho\sigma^2 & \sigma^2 & \rho\sigma^2 \\ \rho\sigma^2 & \rho\sigma^2 & \rho\sigma^2 & \rho\sigma^2 & \rho\sigma^2 & \sigma^2 \end{pmatrix}$$

The true dimension of **R** is still 126 by 126 with 21 of the above matrices along the diagonal. The Repeated Component output becomes

Repeated Component Parameter Estimates (R Matrix)

Component Number	Parameter Number	Estimated Value	Parameter Type
1	1	25.3358	Diagonal (Variance)
1	1	0.0279	Off-Diagonal (Correlation)

Here, the estimate of σ^2 is 25.3358 and the estimate of ρ is 0.0279.

The V matrix now has the form

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

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

Estimated Vi Matrix of Subject = 1

Vi	1	2	3	4	5	6
1	25.3358	0.7065	0.7065	0.7065	0.7065	0.7065
2	0.7065	25.3358	0.7065	0.7065	0.7065	0.7065
3	0.7065	0.7065	25.3358	0.7065	0.7065	0.7065
4	0.7065	0.7065	0.7065	25.3358	0.7065	0.7065
5	0.7065	0.7065	0.7065	0.7065	25.3358	0.7065
6	0.7065	0.7065	0.7065	0.7065	0.7065	25.3358

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, σ^2 and ρ , but the coefficient of σ^2 decreases exponentially as observations are farther apart. The $\mathbf{R}$ matrix has the form

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

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

The Repeated Component output becomes

Repeated Component Parameter Estimates (R Matrix)

Component Number	Parameter Number	Estimated Value	Parameter Type
1	1	25.3360	Diagonal (Variance)
1	1	0.0659	Off-Diagonal (Correlation)

Here, the estimate of σ^2 is 25.3360 and the estimate of ρ is 0.0659.

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

Estimated Vi Matrix of Subject = 1

Vi	1	2	3	4	5	6
1	25.3360	1.6696	0.1100	0.0073	0.0005	0.0000
2	1.6696	25.3360	1.6696	0.1100	0.0073	0.0005
3	0.1100	1.6696	25.3360	1.6696	0.1100	0.0073
4	0.0073	0.1100	1.6696	25.3360	1.6696	0.1100
5	0.0005	0.0073	0.1100	1.6696	25.3360	1.6696
6	0.0000	0.0005	0.0073	0.1100	1.6696	25.3360

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

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

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.

- 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)

Component Number	Parameter Number	Estimated Value	Parameter Type
1	1	196.5320	Diagonal (Variance)
1	1	0.0352	Off-Diagonal (Correlation)

Term-by-Term Hypothesis Test Results

Model Term	F-Value	Num DF	Denom DF	Prob Level
IHR	2.0014	1	35.6	0.165832
Period	0.4896	1	17.5	0.493296
Trtcross	3.9857	1	20.6	0.059259

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.