

## Chapter 222

# Mixed Models – Repeated Measures

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### 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.

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### 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 as described earlier is

$$\mathbf{y} = \mathbf{X}\boldsymbol{\beta} + \mathbf{Z}\mathbf{u} + \boldsymbol{\varepsilon}$$

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

$$\boldsymbol{\varepsilon} \sim N(\mathbf{0}, \mathbf{R})$$

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

$$\mathbf{V} = \mathbf{Z}\mathbf{G}\mathbf{Z}' + \mathbf{R}$$

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.

## Mixed Models - Repeated Measures

### 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.

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## 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.

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## 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.

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## 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 $\mathbf{R}$ 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  $\mathbf{R}_1, \mathbf{R}_2, \mathbf{R}_3, \dots, \mathbf{R}_N$  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.

## Mixed Models - Repeated Measures

## Structures of R

There are many possible structures for the sub-matrices that make up the **R** matrix. The **R**<sub>Sub</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

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

## Mixed Models - Repeated Measures

**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

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

## Mixed Models - Repeated Measures

### 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

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

Heterogeneous

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

Correlation

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

Note: This is the same as Toeplitz(1).

#### Banded(3)

Homogeneous

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

Heterogeneous

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

Correlation

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

#### 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.

## Mixed Models - Repeated Measures

## Partitioning the R Matrix Parameters

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

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

If there are sixteen subjects then

$$\mathbf{R} = \begin{pmatrix} \mathbf{R}_1 & \mathbf{0} & \mathbf{0} & \cdots & \mathbf{0} \\ \mathbf{0} & \mathbf{R}_2 & \mathbf{0} & \cdots & \mathbf{0} \\ \mathbf{0} & \mathbf{0} & \mathbf{R}_3 & \cdots & \mathbf{0} \\ \vdots & \vdots & \vdots & \ddots & \vdots \\ \mathbf{0} & \mathbf{0} & \mathbf{0} & \cdots & \mathbf{R}_{16} \end{pmatrix}.$$

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

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

$$\mathbf{R}_1, \dots, \mathbf{R}_8 = \begin{pmatrix} \sigma_1^2 & \rho_{11}\sigma_1^2 & \rho_{12}\sigma_1^2 & \rho_{13}\sigma_1^2 \\ \rho_{11}\sigma_1^2 & \sigma_1^2 & \rho_{11}\sigma_1^2 & \rho_{12}\sigma_1^2 \\ \rho_{12}\sigma_1^2 & \rho_{11}\sigma_1^2 & \sigma_1^2 & \rho_{11}\sigma_1^2 \\ \rho_{13}\sigma_1^2 & \rho_{12}\sigma_1^2 & \rho_{11}\sigma_1^2 & \sigma_1^2 \end{pmatrix},$$

and

$$\mathbf{R}_9, \dots, \mathbf{R}_{16} = \begin{pmatrix} \sigma_2^2 & \rho_{21}\sigma_2^2 & \rho_{22}\sigma_2^2 & \rho_{23}\sigma_2^2 \\ \rho_{21}\sigma_2^2 & \sigma_2^2 & \rho_{21}\sigma_2^2 & \rho_{22}\sigma_2^2 \\ \rho_{22}\sigma_2^2 & \rho_{21}\sigma_2^2 & \sigma_2^2 & \rho_{21}\sigma_2^2 \\ \rho_{23}\sigma_2^2 & \rho_{22}\sigma_2^2 & \rho_{21}\sigma_2^2 & \sigma_2^2 \end{pmatrix}.$$

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  $\mathbf{R}$  is partitioned by groups.



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## Procedure Options

This section describes the options available in this procedure.

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### Variables

These panels specify the response and subject variables used.

#### Response Variable

This variable contains the numeric responses (measurements) for each of the subjects. There is one measurement per subject per time point. Hence, all responses are in a single column (variable) of the spreadsheet.

#### Subject Variable

This variable contains an identification value for each subject. Each subject must have a unique identification number (or name). In a repeated measures design, several measurements are made on each subject.

#### Times Variable

This optional variable contains the time at which each measurement is made. If this variable is omitted, the time values are assigned sequentially with the first value being '1', the next value being '2', and so on.

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### Between and Within Fixed Factors

This section lets you specify all fixed factors whether they are between or within.

#### Number

Enter the number of factors (up to 6) that you want to use. This option controls how many factor variable entry boxes are displayed and used.

Note that if you select factor variables in the boxes below, and then reduce this number so those boxes are no longer visible, the hidden factors will not be used.

#### Fixed Factor Variables

Select a fixed factor (categorical or class) variable here. Capitalization is ignored when determining unique text values.

A categorical variable has only a few unique values (text or numeric) which are used to identify the categories (groups) into which the subject falls.

#### $\neq\sigma^2$ (Unequal Group Variance)

One factor variable can have a different variance in each group. Check this box to indicate that this factor should have unequal variances. Other factors will have equal variances.

This panel is used to specify multiple comparisons or custom contrasts for factor variables.

#### Comparison

This option specifies the set of multiple comparisons that will be computed for this factor. Several predefined sets are available or you can specify up to two of your own in the Custom (1-2) options.

For interactions, these comparisons are run for each category of the second factor.

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Possible choices are:

- **First versus Each**

The multiple comparisons are each category tested against the first category. This option would be used when the first category is the control (standard) category. Note: the first is determined alphabetically.

- **2nd versus Each**

The multiple comparisons are each category tested against the second category. This option would be used when the second category is the control (standard) category.

- **3rd versus Each**

The multiple comparisons are each category tested against the third category. This option would be used when the third category is the control (standard) category.

- **Last versus Each**

The multiple comparisons are each category tested against the last category. This option would be used when the last category is the control (standard) category.

- **Baseline versus Each**

The multiple comparisons are each category tested against the baseline category. This option would be used when the baseline category is the control (standard) category. The baseline category is entered to the right.

- **Ave versus Each**

The multiple comparisons are each category tested against the average of the other categories.

- **All Pairs**

The multiple comparisons are each category tested against every other category.

- **Custom**

The multiple comparisons are determined by the coefficients entered in the two Custom boxes to the right.

### Baseline

Enter the level of the corresponding Factor Variable to which comparisons will be made. The Baseline is used only when Comparison is set to *Baseline vs Each*. The value entered here must be one of the levels of the Factor Variable. The entry is not case sensitive and values should not be entered with quotes.

### Custom 1-2

This option specifies the weights of a comparison. It is used when the *Comparison* is set to *Custom*. There are no numerical restrictions on these coefficients. They do not even have to sum to zero. However, this is recommended. If the coefficients do sum to zero, the comparison is called a CONTRAST. The significance tests anticipate that only one or two of these comparisons are run. If you run several, you should make some type of Bonferroni adjustment to your alpha value.

### Specifying the Coefficients

When you put in your own contrasts, you must be careful that you specify the appropriate number of coefficients. For example, if the factor has four levels, four coefficients must be specified, separated by blanks or commas. Extra coefficients are ignored. If too few coefficients are specified, the missing coefficients are assumed to be zero.

These comparison coefficients designate weighted averages of the level-means that are to be statistically tested. The null hypothesis is that the weighted average is zero. The alternative hypothesis is that the weighted average is nonzero. The coefficients are specified here in this box.

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As an example, suppose you want to compare the average of the first two levels with the average of the last two levels in a six-level factor. You would enter -1 -1 0 0 1 1.

As a second example, suppose you want to compare the average of the first two levels with the average of the last three levels in a six-level factor. The custom contrast would be -3 -3 0 2 2 2.

Note that in each example, coefficients were used that sum to zero. Ones were not used in the second example because the result would not sum to zero.

### Covariates

#### Number

Enter the number of covariates (up to 6) that you want to use. This option controls how many covariate variable entry boxes are displayed and used.

Note that if you select covariate variables in the boxes below, and then reduce this number so those boxes are no longer visible, the hidden covariates will not be used.

#### Covariate Variables

Specify a covariate variable here. The values in this variable must be numeric and should be at least ordinal. When covariates are used, the analysis is called analysis of covariance (ANCOVA).

#### Compute Means at these Values

Specify one or more values at which means and comparisons are to be calculated. A separate report is calculated for each unique set of covariate values.

#### Mean

Enter **Mean** to indicate that the covariate mean should be used as the value of the covariate in the various reports.

### Within-Subject Variance-Covariance Matrix

The repeated component is used to specify the **R** matrix in the mixed model.

#### Pattern

Specify the type of **R** (error covariance) matrix to be generated. This represents the relationship between observations from the same subject. The **R** structures that can be specified in *NCSS* are shown below. The usual type is the 'Diagonal' matrix.

The options are:

- **Unused**

No repeated component is used.

- **Diagonal**

Homogeneous

Heterogeneous across time ( $\neq \sigma^2$ )

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

Mixed Models - Repeated Measures

- Diagonal: Random**

Homogeneous                      Heterogeneous across time ( $\neq\sigma^2$ )

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

Note: A random effects model is created by adding a random subjects term to the model.

- Compound Symmetry: Repeated**

Homogeneous                      Heterogeneous across time ( $\neq\sigma^2$ )

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

- AR(1)**

Homogeneous                      Heterogeneous across time ( $\neq\sigma^2$ )

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

- 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 across time ( $\neq\sigma^2$ )

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

## Mixed Models - Repeated Measures

• **Toeplitz (All)**

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 across time ( $\neq\sigma^2$ )

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

• **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 across time ( $\neq\sigma^2$ )

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

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 across time ( $\neq\sigma^2$ )

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

• **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

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

Heterogeneous across time ( $\neq\sigma^2$ )

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

Note: This is the same as Toeplitz(1).

• **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 across time ( $\neq\sigma^2$ )

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

## Mixed Models - Repeated Measures

- **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 across time ( $\neq\sigma^2$ )

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

### Force Positive Correlations

When checked, this option forces all covariances in the Random and Repeated Components (off-diagonal elements of the R matrix) to be non-negative. When this option is not checked, covariances can be negative.

Usually, negative covariances are okay and should be allowed. However, some Repeated patterns such as Compound Symmetry assume that covariances (correlations) are positive.

---

## Model (Fixed Terms)

### Terms

This option specifies which terms (terms, powers, cross-products, and interactions) are included in the fixed portion of the mixed model.

The options are

- **1-Way**

All covariates and factors are included in the model. No interaction or power terms are included. Use this option when you just want to use the variables you have specified.

- **Up to 2-Way**

All individual variables, two-way interactions, cross-products, and squared covariates are included.

For example, if you are analyzing four factors named A, B, C, and D, this option would generate the model as:  $A + B + C + D + AB + AC + AD + BC + BD + CD$ .

- **Up to 3-Way**

All individual variables, two-way interactions, three-way interactions, squared covariates, cross-products, and cubed covariates are included in the model.

For example, if you are analyzing two covariates called X1 and X2 and a factor named A, this option would generate the model as:  $X1 + X2 + C + X1*X2 + X1*C + X2*C + X1*X1 + X2*X2 + X1*X1*C + X2*X2*C + X1*X2*C + X1*X1*X1 + X1*X1*X2 + X1*X2*X2 + X2*X2*X2$ .

- **Up to 4-Way**

All individual variables, two-way interactions, three-way interactions, and four-way interactions, along with the squares, cubics, quartics, and cross-products of covariates and their interactions are included in the model.

- **Interaction Model**

All individual variables and their interactions are included. No powers of covariates are included. This requires a dataset in which all combinations of factor variables are present.

## Mixed Models - Repeated Measures

- **Custom**

The model specified in the **Custom** box is used.

### Maximum Exponent of Covariates

This option specifies the maximum exponent of each covariate in the terms of the model. This maximum is further constrained by the setting of the **Terms** option.

### Custom Model

Specify a custom statistical model for fixed effects here. Statistical hypothesis tests will be generated for each term in this model. Variables for which hypothesis tests are to be performed should be included in this model statement. You may also include variables in this model that are solely to be used for adjustment and not important for inference or hypothesis testing. For categorical factors, each term represents a set of indicator variables in the expanded design matrix.

The components of this model come from the variables listed in the factor and covariate variables. If you want to use them, they must be listed there.

### Syntax

In the examples that follow each syntax description, A, B, C, and X represent variable names. Assume that A, B, and C are factors, and X is a covariate.

1. Specify main effects by specifying their variable names, separated by blanks or the '+' (plus) sign.
 

A+B	Main effects for A and B only
A B C	Main effects for A, B, and C only
A B X	Main effects for A and B, plus the covariate effect of X
2. Specify interactions and cross products using an asterisk (\*) between variable names, such as Fruit\*Nuts or A\*B\*C. When an interaction between a factor and a covariate is specified, a cross-product is generated for each value of the factor. For covariates, higher order (e.g. squared, cubic) terms may be added by repeating the covariate name. If X is a covariate, X\*X represents the covariate squared, and X\*X\*X represents the covariate cubed, etc. Only covariates can be repeated. Factors cannot be squared or cubed. That is, if A is a factor, you would not include A\*A nor A\*A\*A in your model.
 

A+B+A*B	Main effects for A and B plus the AB interaction
A+B+C+A*B+A*C+B*C+A*B*C	Full model for factors A, B, and C
A+B+C+A*X	Main effects for A, B, and C plus the interaction of A with the covariate X
A+X+X*X	Main Effect for A plus X and the square of X
A+B*B	Not valid since B is categorical and cannot be squared
3. Use the '|' (bar) symbol as a shorthand technique for specifying large models quickly.
 

A B = A+B+A*B
A B C = A+B+C+A*B+A*C+B*C+A*B*C
A B C X*X = A+B+A*B+C+X*X
A B C X = A+B+A*B+C+X+C*X
4. You can use parentheses for multiplication.
 

(A+B)*(C+X) = A*C+A*X+B*C+B*X
(A+B) C = A+B+C+(A+B)*C = A+B+C+A*C+B*C

## Mixed Models - Repeated Measures

5. Use the '@' (at) symbol to limit the order of interaction and cross-product terms in the model.

$$A|B|C @2 = A+B+C+A*B+A*C+B*C$$

$$A|B|X|X (@2) = A+B+X+A*B+A*X+B*X+X*X$$

### Intercept

Check this box to include the intercept in the model. Under most circumstances, you should include the intercept term in your model.

---

## Maximization Tab

This tab controls the Newton-Raphson, Fisher-Scoring, and Differential Evolution likelihood-maximization algorithms.

---

### Options

#### Likelihood Type

Specify the type of likelihood equation to be solved. The options are:

- **MLE**  
The 'Maximum Likelihood' solution has become less popular.
- **REML (recommended)**  
The 'Restricted Maximum Likelihood' solution is recommended. It is the default in other software programs (such as SAS).

#### Solution Method

Specify the method to be used to solve the likelihood equations. The options are:

- **Newton-Raphson**  
This is an implementation of the popular 'gradient search' procedure for maximizing the likelihood equations. Whenever possible, we recommend that you use this method.
- **Fisher-Scoring**  
This is an intermediate step in the Newton-Raphson procedure. However, when the Newton-Raphson fails to converge, you may want to stop with this procedure.
- **MIVQUE**  
This non-iterative method is used to provide starting values for the Newton-Raphson method. For large problems, you may want to investigate the model using this method since it is much faster.
- **Differential Evolution**  
This grid search technique will often find a solution when the other methods fail to converge. However, it is painfully slow--often requiring hours to converge--and so should only be used as a last resort.
- **Read in from a Variable**  
Use this option when you want to use a solution from a previous run or from another source. The solution is read in from the variable selected in the 'Read Solution From' variable.



## Mixed Models - Repeated Measures

### Read Solution From (Variable)

This optional variable contains the variance-covariance parameter values of a solution that has been found previously. The order of the parameter values is the same as on the parameter reports.

This option is useful when problem requires a great deal of time to solve. Once you have achieved a solution, you can reuse it by entering this variable here and setting the 'Solution Method' option to 'Read in from a Variable'.

### Write Solution To (Variable)

Select an empty variable into which the solution is automatically stored. Note that any previous information in this variable will be destroyed.

This option is useful when problem requires a great deal of time to solve. Once you have achieved a solution, you can then reuse it by entering this variable in the 'Read Solution From' variable box and setting the 'Solution Method' option to 'Read in from a Variable'.

### Force Covariance to be Positive

When checked, this option forces all covariances (and correlations) in the Random Components (off-diagonal elements of the G matrix) and Repeated Components (off-diagonal elements of the R matrix) to be non-negative. When this option is not checked, some covariances can be negative.

It usually makes good sense to force these covariances (and thus the corresponding correlations) to be positive. However, occasionally you may want to allow negative covariances.

---

## Newton-Raphson / Fisher-Scoring Options

### Max Fisher Scoring Iterations

This is the maximum number of Fisher Scoring iterations that occur in the maximum likelihood finding process. When Solution Method (Variables tab) is set to 'Newton-Raphson', up to this number of Fisher Scoring iterations occur before beginning Newton-Raphson iterations.

### Max Newton-Raphson Iterations

This is the maximum number of Newton-Raphson iterations that occur in the maximum likelihood finding process. When Solution Method (Variables tab) is set to 'Newton-Raphson', Fisher-scoring iterations occur before beginning Newton-Raphson iterations.

### Lambda

Each parameter's change is multiplied by this value at each iteration. Usually, this value can be set to one. However, it may be necessary to set this value to 0.5 to implement step-halving: a process that is necessary when the Newton-Raphson diverges.

Note: this parameter only used by the Fisher-Scoring and Newton-Raphson methods.

### Convergence Criterion

This procedure uses relative Hessian convergence (or the Relative Offset Orthogonality Convergence Criterion) as described by Bates and Watts (1981).

Recommended: The default value, 1E-8, will be adequate for many problems. When the routine fails to converge, try increasing the value to 1E-6.

---

## Differential Evolution Options

### Crossover Rate

This value controls the amount of movement of the differential evolution algorithm toward the current best. Larger values accelerate movement toward the current best, but reduce the chance of locating the global maximum. Smaller values improve the chances of finding the global, rather than a local, solution, but increase the number of iterations until convergence.

RANGE: Usually, a value between .5 and 1.0 is used.

RECOMMENDED: 0.9.

### Mutation Rate

This value sets the mutation rate of the search algorithm. This is the probability that a parameter is set to a random value within the parameter space. It keeps the algorithm from stalling on a local maximum.

RANGE: Values between 0 and 1 are allowed.

RECOMMENDED: 0.9 for random coefficients (complex) models or 0.5 for random effects (simple) models.

### Minimum Relative Change

This parameter controls the convergence of the likelihood maximizer. When the relative change in the likelihoods from one generation to the next is less than this amount, the algorithm concludes that it has converged. The relative change is  $|L(g+1) - L(g)| / L(g)$  where  $L(g)$  is absolute value of the likelihood at generation 'g'. Note that the algorithm also terminates if the Maximum Generations are reached or if the number of individuals that are replaced in a generation is zero. The value 0.0000000001 (ten zeros) seems to work well in practice. Set this value to zero to ignore this convergence criterion.

### Solutions/Iteration

This is the number of trial points (solution sets) that are used by the differential evolution algorithm during each iteration. In the terminology of differential evolution, this is the population size.

RECOMMENDED: A value between 15 and 25 is recommended. More points may dramatically increase the running time. Fewer points may not allow the algorithm to converge.

### Max Iterations

Specify the maximum number of differential evolution iterations used by the differential evolution algorithm. A value between 100 and 200 is usually adequate. For large datasets, i.e., number of rows greater than 1000, you may want to reduce this number.

---

## Other Options

### Zero (Algorithm Rounding)

This cutoff value is used by the least-squares algorithm to lessen the influence of rounding error. Values lower than this are reset to zero. If unexpected results are obtained, try using a smaller value, such as 1E-32. Note that 1E-5 is an abbreviation for the number 0.00001.

RECOMMENDED: 1E-10 or 1E-12.

RANGE: 1E-3 to 1E-40.

## Mixed Models - Repeated Measures

### Variance Zero

When an estimated variance component (diagonal element) is less than this value, the variance is assumed to be zero and all reporting is terminated since the algorithm has not converged properly.

To correct this problem, remove the corresponding term from the Random Factors Model or simplify the Repeated Variance Pattern. Since the parameter is zero, why would you want to keep it?

RECOMMENDED: 1E-6 or 1E-8.

RANGE: 1E-3 to 1E-40.

### Correlation Zero

When an estimated correlation (off-diagonal element) is less than this value, the correlation is assumed to be zero and all reporting is terminated since the algorithm has not converged properly.

To correct this problem, remove the corresponding term from the Random Factors Model or simplify the Repeated Variance Pattern. Since the parameter is zero, why would you want to keep it?

RECOMMENDED: 1E-6 or 1E-8.

RANGE: 1E-3 to 1E-40.

### Max Retries

Specify the maximum number of retries to occur. During the maximum likelihood search process, the search may lead to an impossible combination of variance-covariance parameters (as defined by a matrix of variance-covariance parameters that is not positive definite). When such a combination arises, the search algorithm will begin again. Max Retries is the maximum number of times the process will re-start to avoid such combinations.

---

## Reports Tab

The following options control which reports are displayed.

---

### Select Reports

#### Run Summary Report

Check this box to obtain a summary of the likelihood type, the model, the iterations, the resulting likelihood/AIC, and run time.

#### Variance Estimates Report

Check this box to obtain estimates of random and repeated components of the model.

#### Hypothesis Tests Report

Check this box to obtain F-Tests for all terms in the Fixed (Means) Specification (see Variables tab).

#### L-Matrices – Terms Report

Check this box to obtain L matrices for each term in the model. Each L matrix describes the linear combination of the betas that is used to test the corresponding term in the model.

Caution: Selecting this option can generate a very large amount of output, as the L matrices can be very numerous and lengthy.

## Mixed Models - Repeated Measures

### Comparisons by Fixed Effects Report

Check this box to obtain planned comparison tests, comparing levels of the fixed effects. Details of the comparisons to be made are specified under the Comparisons and Covariates tabs. When more than one covariate value is specified under the Covariates tab, the comparisons are grouped such that for each fixed effect, comparisons for all covariate(s) values are displayed.

Compare to Comparisons by Covariate Values.

### Comparisons by Covariate Values Report

Check this box to obtain planned comparison tests, comparing levels of the fixed effects. Details of the comparisons to be made are specified under the Comparisons and Covariates tabs. When more than one covariate value is specified under the Covariates tab, the comparisons are grouped such that for each value of the covariate(s), a new set of comparisons is displayed.

Compare to Comparisons by Fixed Effects.

### L-Matrices – Comparisons Report

Check this box to obtain L matrices for each planned comparison. Each L matrix describes the linear combination of the betas that is used to test the corresponding comparison.

Caution: Selecting this option can generate a very large amount of output, as the L matrices can be very numerous and lengthy.

### Means by Fixed Effects Report

Check this box to obtain means and confidence limits for each fixed effect level. When more than one covariate value is specified under the Covariates tab, the means are grouped such that for each fixed effect, means for all covariate(s) values are displayed.

Compare to Means by Covariate Values.

### Means by Covariate Values Report

Check this box to obtain means and confidence limits for each fixed effect level. When more than one covariate value is specified under the Covariates tab, the means are grouped such that for each value of the covariate(s), a new set of means is displayed.

Compare to Means by Fixed Effects.

### L-Matrices – LS Means Report

Check this box to obtain L matrices for each least squares mean (of the fixed effects). Each L matrix describes the linear combination of the betas that is used to generate the least squares mean.

Caution: Selecting this option can generate a very large amount of output, as the L matrices can be very numerous and lengthy.

### Fixed Effects Solution Report

Check this box to obtain estimates, P-values and confidence limits of the fixed effects and covariates (betas).

### Asymptotic VC Matrix Report

Check this box to obtain the asymptotic variance-covariance matrix of the random (and repeated) components of the model.

### Vi Matrices (1st 3 Subjects) Report

Check this box to display the Vi matrices of the first three subjects.

### Hessian Matrix Report

Check this box to obtain the Hessian matrix. The Hessian matrix is directly associated with the variance-covariance matrix of the random (and repeated) components of the model.

## Mixed Models - Repeated Measures

### Show Report Definitions

Indicate whether to show the definitions at the end of reports. Although these definitions are helpful at first, they may tend to clutter the output. This option lets you omit them.

---

### Select Reports – Alpha

#### Alpha

Specify the alpha value (significance level) used for F-tests, T-tests, and confidence intervals. Alpha is the probability of rejecting the null hypothesis of equal means when it is actually true. Usually, an alpha of 0.05 is used. Typical choices for alpha range from 0.001 to 0.200.

---

### Report Options

#### Stagger label and output of label length is $\geq$

When writing a row of information to a report, some variable names/labels may be too long to fit in the space allocated. If the name (or label) contains more characters than entered here, the rest of the output for that line is moved down to the next line. Most reports are designed to hold a label of up to 15 characters. Enter “1” when you always want each row's output to be printed on two lines. Enter “100” when you want each row printed on only one line. Note that this may cause some columns to be mis-aligned.

---

### Report Options – Decimal Places

#### Precision

Specifies whether unformatted numbers are displayed as single (7-digit) or double (13-digit) precision numbers in the output. All calculations are performed in double precision regardless of the Precision selected here.

#### Single

Unformatted numbers are displayed with 7-digits. This is the default setting. All reports have been formatted for single precision.

#### Double

Unformatted numbers are displayed with 13-digits. This option is most often used when the extremely accurate results are needed for further calculation. For example, double precision might be used when you are going to use the Multiple Regression model in a transformation.

#### Double Precision Format Misalignment

Double precision numbers require more space than is available in the output columns, causing column alignment problems. The double precision option is for those instances when accuracy is more important than format alignment.

#### Effects/Betas ... DF Denominator

Specify the number of digits after the decimal point to display on the output of values of this type. Note that this option in no way influences the accuracy with which the calculations are done.

Enter 'General' to display all digits available. The number of digits displayed by this option is controlled by whether the PRECISION option is SINGLE or DOUBLE.

## Plots Tab

These options specify the plots of group means and subjects. Click the plot format button to change the plot settings.

---

### Select Plots

#### Means Plots

Check this box to obtain plots of means for each fixed effects term of the model. Details of the appearance of the plots are specified under the Means Plots and Symbols tabs.

#### Subject Plots

Check this box to obtain plots of the repeated values for each subject. Plots comparing main effects for each subject are also given. The repeated values for each subject are ordered according to the order the values appear in the data set. Details of the appearance of the plots are specified under the Subject Plots and Symbols tabs.

#### Y-Axis Scaling

Specify the method for calculating the minimum and maximum along the vertical axis. *Separate* means that each plot is scaled independently. *Uniform* means that all plots use the overall minimum and maximum of the data. This option is ignored if a minimum or maximum is specified.

These options specify the subject plots.

## 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.

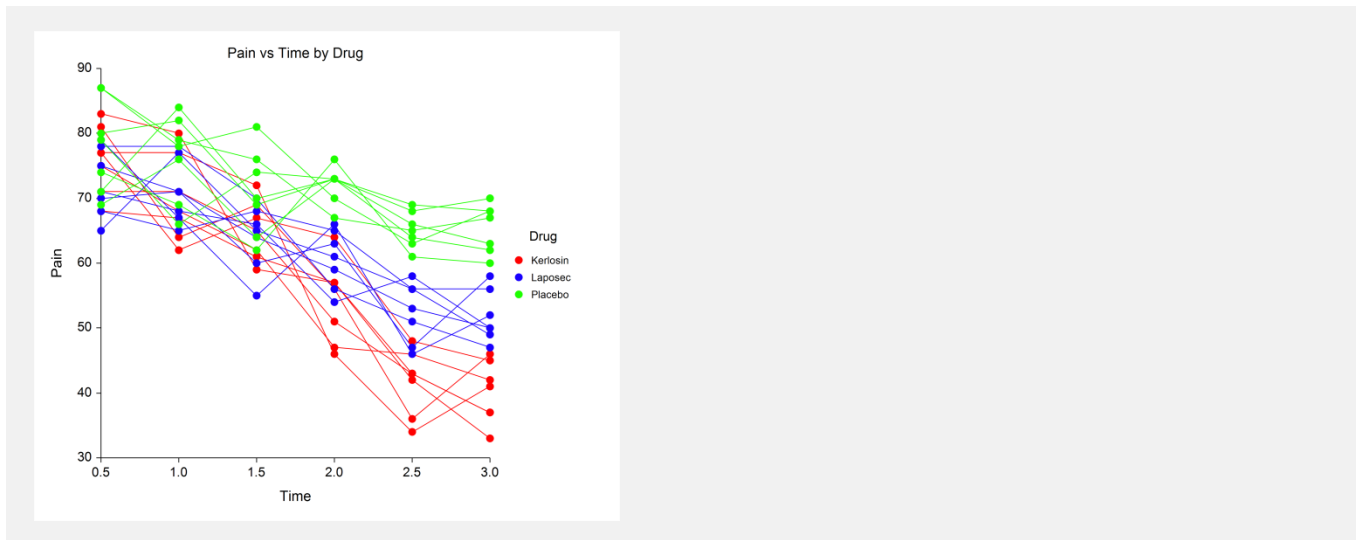
A standard pain measurement for each patient is measured at 30 minute intervals following surgery and administration of the drug (or placebo). Six measurements, with the last at Time = 3 hours, are made for each of the 21 patients (7 per group). A blood pressure measurement (Cov) of each individual at 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

## Mixed Models - Repeated Measures

The following plot shows the relationship among all variables except the covariate.



To run the analysis using the Mixed Models - Repeated Measures procedure, you can enter the values according to the instructions below (beginning with Step 3) or load the completed template **Example 1** by clicking on Open Example Template from the File menu of the Mixed Models - Repeated Measures window.

### 1 Open the Pain dataset.

- From the File menu of the NCSS Data window, select **Open Example Data**.
- Click on the file **Pain.NCSS**.
- Click **Open**.

### 2 Open the Mixed Models - Repeated Measures window.

- Using the Analysis menu or the Procedure Navigator, find and select the **Mixed Models - Repeated Measures** procedure.
- On the menus, select **File**, then **New Template**. This will fill the procedure with the default template.

### 3 Specify the variables.

- Select the **Variables tab**.
- Double-click in the **Response** text box. This will bring up the variable selection window.
- Select **Pain** from the list of variables and then click **Ok**. 'Pain' will appear in the Response box.
- Double-click in the **Subjects** text box. This will bring up the variable selection window.
- Select **Patient** from the list of variables and then click **Ok**. 'Patient' will appear in the Subjects box.
- Select **Time** in the **Times** box.
- Set the **Number** of fixed factors to **2**.
- Set **Drug** as the first Fixed Factor Variable.
- Set the **Comparison** for **Drug** to **All Pairs**.
- Set **Time** as the second Fixed Factor Variable.
- Set the **Comparison** for Time to **Baseline vs Each**.
- Enter **0.5** as the **Baseline**.
- Set the **Number** of covariates to **1**.
- Set **Cov** as the Covariate Variable.
- Enter **140** under **Compute Means at these Values**

### 4 Specify the model.

- Set **Terms** to **Interaction Model**.



## Mixed Models - Repeated Measures

**5 Specify the reports.**

- Select the **Reports tab**.
- Check all report checkboxes except **L Matrices – Comparisons**, **L Matrices – LS Means**, and **Show Report Definitions**.

**6 Run the procedure.**

- From the Run menu, select **Run Procedure**. Alternatively, just click the green Run button.

---

## Run Summary

Parameter	Value
Likelihood Type	Restricted Maximum Likelihood
Fixed Model	DRUG+TIME+COV+DRUG*TIME+DRUG*COV+TIME*COV+ DRUG*TIME*COV
Random Model	PATIENT
Repeated Model	Diagonal
Number of Rows	126
Number of Subjects	21
Solution Type	Newton-Raphson
Fisher Iterations	4 of a possible 10
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)	1.03 (this will vary based on computer speed)

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.

## Mixed Models - Repeated Measures

### 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.

## Mixed Models - Repeated Measures

### 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

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.

## Mixed Models - Repeated Measures

### 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						
Covariates: Cov=140.00						
Comparison/ Covariate(s)	Comparison Mean Difference	F-Value	Num DF	Denom DF	Raw Prob Level	Bonferroni Prob Level
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		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		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]

(report continues)

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.

## Mixed Models - Repeated Measures

### 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					
Covariates: Cov=140.00					
Name	Mean	Standard Error of Mean	95.0% Lower Conf. Limit for Mean	95.0% Upper Conf. Limit for Mean	DF
<b>Intercept</b>					
Intercept	64.11	0.66	62.78	65.45	33.5
<b>Drug</b>					
Kerlosin	58.43	1.14	56.11	60.74	32.9
Laposec	61.89	1.24	59.38	64.40	42.3
Placebo	72.02	1.03	69.91	74.14	24.8
<b>Time</b>					
0.5	75.08	1.39	72.32	77.85	89.8
1	72.27	1.99	68.32	76.22	89.9
1.5	66.89	1.22	64.46	69.32	89.3
2	63.79	1.63	60.55	67.02	90.0
2.5	53.82	1.37	51.09	56.55	89.7
3	52.82	1.20	50.43	55.22	89.2
<b>Drug*Time</b>					
Kerlosin, 0.5	76.07	2.60	70.90	81.23	89.8
Kerlosin, 1	69.02	2.64	63.78	74.26	90.0
Kerlosin, 1.5	66.02	2.05	61.94	70.10	89.2
Kerlosin, 2	56.36	3.78	48.85	63.88	89.9
Kerlosin, 2.5	41.78	1.90	38.00	45.55	88.6
Kerlosin, 3	41.30	1.99	37.34	45.27	89.0
Laposec, 0.5	69.44	2.37	64.73	74.15	89.8
Laposec, 1	71.92	5.00	61.99	81.85	89.5
Laposec, 1.5	62.50	2.18	58.17	66.82	89.4
Laposec, 2	62.48	2.28	57.96	67.01	89.8
Laposec, 2.5	53.42	1.97	49.50	57.34	88.9
Laposec, 3	51.59	2.21	47.20	55.98	89.6
Placebo, 0.5	79.74	2.25	75.27	84.22	89.6
Placebo, 1	75.87	1.91	72.08	79.67	88.6
Placebo, 1.5	72.16	2.13	67.93	76.39	89.3
Placebo, 2	72.52	2.09	68.37	76.67	89.3
Placebo, 2.5	66.27	3.08	60.14	72.39	90.0
Placebo, 3	65.58	2.05	61.50	69.65	89.1

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

## Mixed Models - Repeated Measures

### 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.

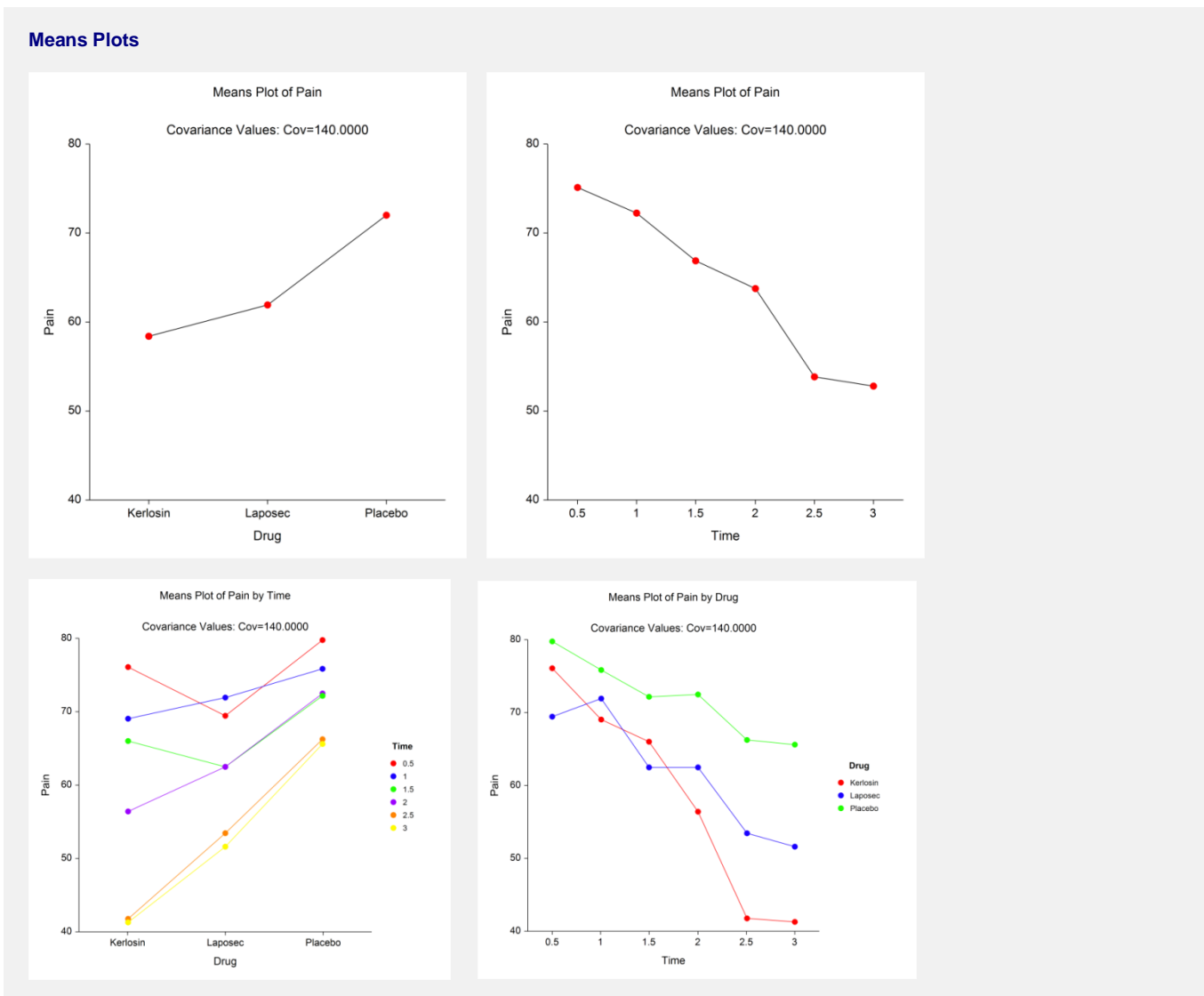
### 95.0% Lower (Upper) Conf. Limit for Mean

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).

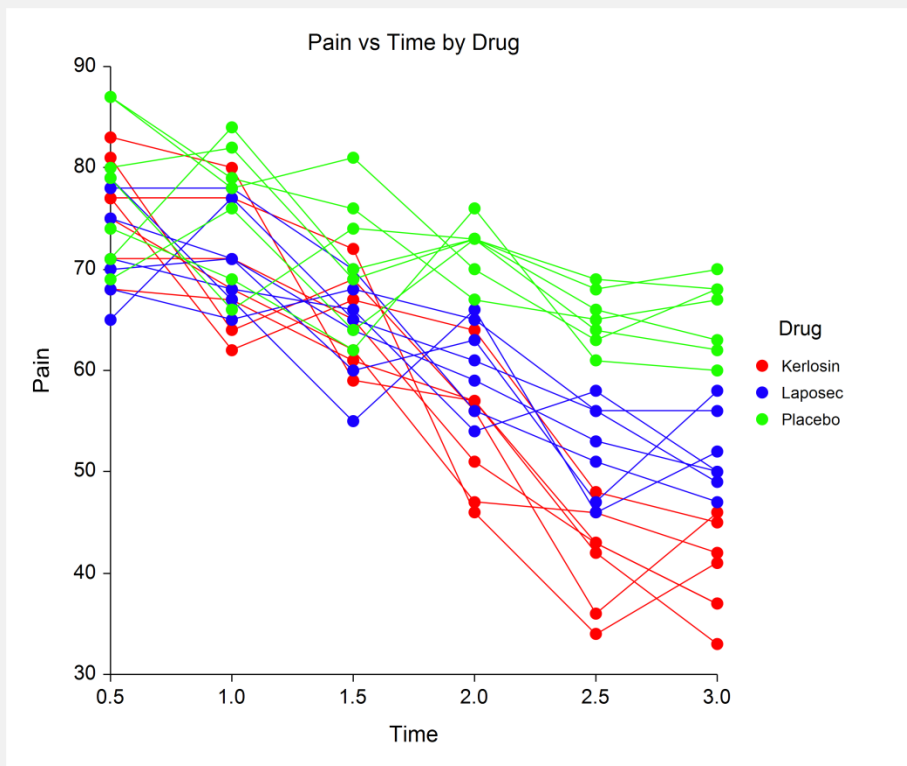
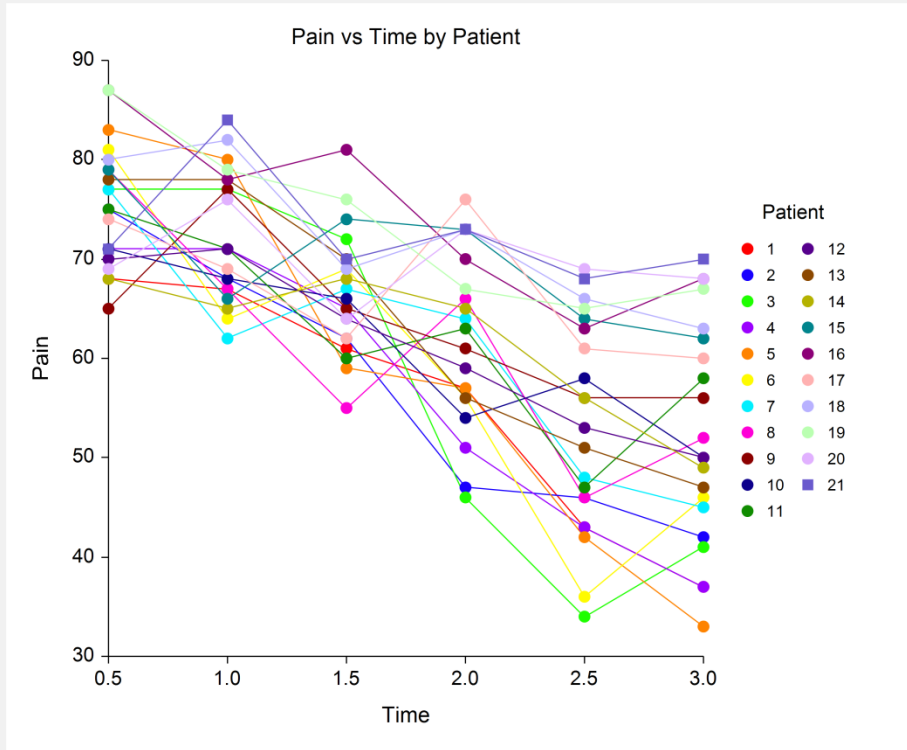
## Means Plots



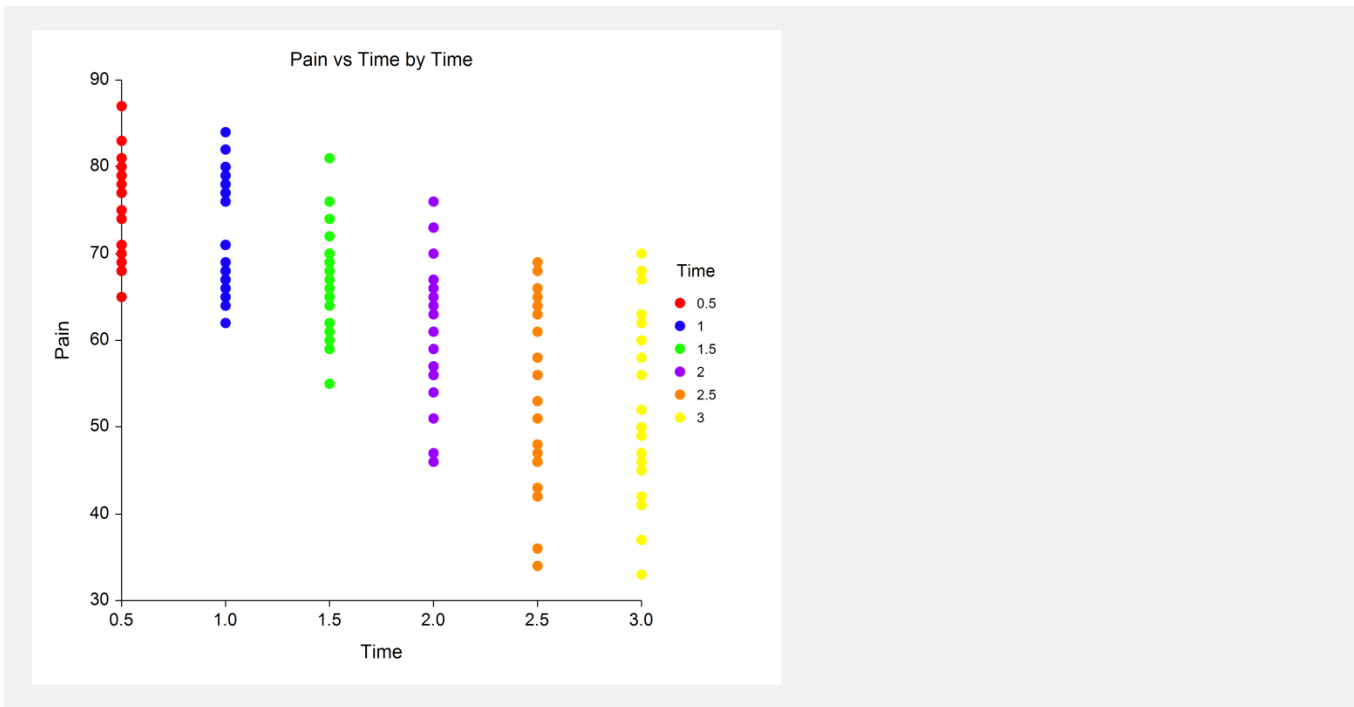
These plots show the means broken up into the categories of the fixed effects of the model. Some general trends that can be seen are those of pain decreasing with time and lower pain for the two drugs after two hours.

# Subject Plots

Subject Plots



Mixed Models - Repeated Measures



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**

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 (Drug="Kerlosin")	-0.0089	0.0461	0.846662	-0.1004	0.0826	89.6	2
(Drug="Laposec")	-9.4849	11.9162	0.428154	-33.1595	14.1898	89.7	3
(Drug="Placebo")	-16.5164	14.6176	0.261539	-45.5591	12.5264	89.5	4
	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

(report continues)

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.



## Mixed Models - Repeated Measures

### 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

Parm	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.

## Mixed Models - Repeated Measures

## 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

Parm	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.

## Mixed Models - Repeated Measures

## L Matrices

**L Matrix for Drug**

No.	Effect	Drug	Time	L1	L2
1	Intercept				
2	Drug	Kerlosin		1.0000	1.0000
3	Drug	Laposec		-1.0000	
4	Drug	Placebo			-1.0000
5	Time		0.5		
6	Time		1		
7	Time		1.5		
8	Time		2		
9	Time		2.5		
10	Time		3		
11	Cov				
12	Drug*Time	Kerlosin	0.5	0.1667	0.1667
13	Drug*Time	Kerlosin	1	0.1667	0.1667
14	Drug*Time	Kerlosin	1.5	0.1667	0.1667
15	Drug*Time	Kerlosin	2	0.1667	0.1667
16	Drug*Time	Kerlosin	2.5	0.1667	0.1667
17	Drug*Time	Kerlosin	3	0.1667	0.1667
18	Drug*Time	Laposec	0.5	-0.1667	
19	Drug*Time	Laposec	1	-0.1667	
20	Drug*Time	Laposec	1.5	-0.1667	
21	Drug*Time	Laposec	2	-0.1667	
22	Drug*Time	Laposec	2.5	-0.1667	
23	Drug*Time	Laposec	3	-0.1667	
24	Drug*Time	Placebo	0.5		-0.1667
25	Drug*Time	Placebo	1		-0.1667
26	Drug*Time	Placebo	1.5		-0.1667
27	Drug*Time	Placebo	2		-0.1667
28	Drug*Time	Placebo	2.5		-0.1667
29	Drug*Time	Placebo	3		-0.1667
.	.	.	.	.	.
.	.	.	.	.	.
.	.	.	.	.	.

(report continues with several pages of output)

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
Drug	1.82	2	89.0	0.1677
Time	0.98	5	88.4	0.4358
Cov	3.30	1	87.1	0.0726
Drug*Time	0.86	10	87.0	0.5708
Drug*Cov	0.77	2	86.8	0.4662
Time*Cov	1.22	5	88.5	0.3078
Drug*Time*Cov	1.07	10	87.0	0.3947

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.

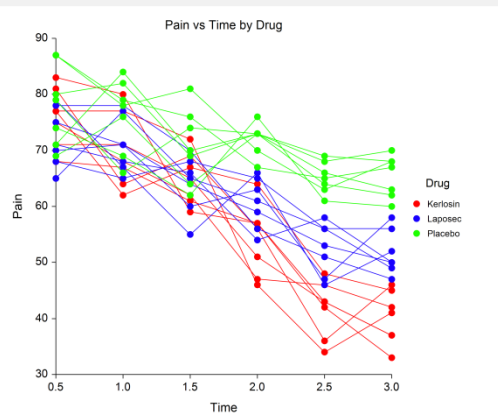
### Term-by-Term Hypothesis Test Results

Model Term	F-Value	Num DF	Denom DF	Prob Level
Drug	4.17	2	96.8	0.0183
Time	1.34	5	98.0	0.2531
Cov	1.77	1	98.9	0.1866
Drug*Time	7.44	10	84.1	0.0000
Drug*Cov	2.23	2	92.4	0.1129
Time*Cov	2.37	5	98.0	0.0450

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.



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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**  
Covariates: Cov=140.00

Comparison/ Covariate(s)	Comparison Mean Difference	F-Value	Num DF	Denom DF	Raw Prob Level	Bonferroni Prob Level
Time = 0.5, Drug: Kerlosin - Laposec	6.16	4.33	1	100.0	0.0400	0.7206 [18]
Time = 0.5, Drug: Kerlosin - Placebo	-1.05	0.13	1	100.0	0.7205	1.0000 [18]
Time = 0.5, Drug: Laposec - Placebo	-7.21	6.37	1	100.0	0.0132	0.2370 [18]
Time = 1, Drug: Kerlosin - Laposec	1.47	0.25	1	100.0	0.6161	1.0000 [18]
Time = 1, Drug: Kerlosin - Placebo	-7.29	6.21	1	99.9	0.0144	0.2583 [18]
Time = 1, Drug: Laposec - Placebo	-8.75	8.15	1	100.0	0.0052	0.0943 [18]
Time = 1.5, Drug: Kerlosin - Laposec	2.35	0.72	1	99.9	0.3987	1.0000 [18]
Time = 1.5, Drug: Kerlosin - Placebo	-5.28	3.68	1	99.8	0.0578	1.0000 [18]
Time = 1.5, Drug: Laposec - Placebo	-7.63	7.57	1	99.9	0.0070	0.1267 [18]
Time = 2, Drug: Kerlosin - Laposec	-2.48	0.63	1	100.0	0.4277	1.0000 [18]
Time = 2, Drug: Kerlosin - Placebo	-14.12	19.44	1	100.0	0.0000	0.0005 [18]
Time = 2, Drug: Laposec - Placebo	-11.64	17.64	1	99.8	0.0001	0.0010 [18]
Time = 2.5, Drug: Kerlosin - Laposec	-11.05	16.57	1	99.7	0.0001	0.0017 [18]
Time = 2.5, Drug: Kerlosin - Placebo	-27.11	70.10	1	100.0	0.0000	0.0000 [18]
Time = 2.5, Drug: Laposec - Placebo	-16.06	26.37	1	100.0	0.0000	0.0000 [18]
Time = 3, Drug: Kerlosin - Laposec	-10.80	15.65	1	99.8	0.0001	0.0026 [18]
Time = 3, Drug: Kerlosin - Placebo	-25.19	84.92	1	99.8	0.0000	0.0000 [18]
Time = 3, Drug: Laposec - Placebo	-14.40	27.54	1	99.8	0.0000	0.0000 [18]

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 **G** and the **R** used to this point have the form

$$\mathbf{G} = \begin{pmatrix} \sigma_s^2 & & & \\ & \sigma_s^2 & & \\ & & \sigma_s^2 & \\ & & & \sigma_s^2 \end{pmatrix} \quad \mathbf{R} = \begin{pmatrix} \sigma^2 & & & & \\ & \sigma^2 & & & \\ & & \sigma^2 & & \\ & & & \sigma^2 & \\ & & & & \sigma^2 \end{pmatrix}$$

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

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V =

$$\begin{pmatrix} \sigma^2 + \sigma_s^2 & \sigma_s^2 & \sigma_s^2 & \sigma_s^2 & \sigma_s^2 & \sigma_s^2 & 0 & 0 & \dots \\ \sigma_s^2 & \sigma^2 + \sigma_s^2 & \sigma_s^2 & \sigma_s^2 & \sigma_s^2 & \sigma_s^2 & 0 & 0 & \dots \\ \sigma_s^2 & \sigma_s^2 & \sigma^2 + \sigma_s^2 & \sigma_s^2 & \sigma_s^2 & \sigma_s^2 & 0 & 0 & \dots \\ \sigma_s^2 & \sigma_s^2 & \sigma_s^2 & \sigma^2 + \sigma_s^2 & \sigma_s^2 & \sigma_s^2 & 0 & 0 & \dots \\ \sigma_s^2 & \sigma_s^2 & \sigma_s^2 & \sigma_s^2 & \sigma^2 + \sigma_s^2 & \sigma_s^2 & 0 & 0 & \dots \\ \sigma_s^2 & \sigma_s^2 & \sigma_s^2 & \sigma_s^2 & \sigma_s^2 & \sigma^2 + \sigma_s^2 & 0 & 0 & \dots \\ 0 & 0 & 0 & 0 & 0 & 0 & \sigma^2 + \sigma_s^2 & \sigma_s^2 & \dots \\ 0 & 0 & 0 & 0 & 0 & 0 & \sigma_s^2 & \sigma^2 + \sigma_s^2 & \dots \\ \vdots & \vdots & \vdots & \vdots & \vdots & \vdots & \vdots & \vdots & \ddots \end{pmatrix}$$

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  $\sigma_s^2$  and  $\sigma^2$  for the model without the three-way interaction are 0.7063 and 24.6291, as shown in the output below.

Random Component Parameter Estimates (G Matrix)			
Component Number	Parameter Number	Estimated Value	Model Term
1	1	0.7063	Patient

Repeated Component Parameter Estimates (R Matrix)			
Component Number	Parameter Number	Estimated Value	Parameter Type
1	1	24.6291	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	25.3358	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

The number 25.3354 comes from adding 0.7063 and 24.6291.

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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 *Comp Sym: Repeated*. In this case, there is no **G** matrix and the **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

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

The **V** matrix now has the form

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

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

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.

## Mixed Models - Repeated Measures

## 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  $\mathbf{R}$  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  $\sigma^2$  is 25.3371 and the estimate of  $\rho$  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

To run the analysis, you may enter the values according to the instructions below (beginning with Step 3) or load the completed template **Example 2** by clicking on Open Example Template from the File menu of the Mixed Models – Repeated Measures window.

### 1 Open the Cross dataset.

- From the File menu of the NCSS Data window, select **Open Example Data**.
- Click on the file **Cross.NCSS**.
- Click **Open**.

### 2 Open the Mixed Models - Repeated Measures window.

- Using the Analysis menu or the Procedure Navigator, find and select the **Mixed Models - Repeated Measures** procedure.
- On the menus, select **File**, then **New Template**. This will fill the procedure with the default template.

### 3 Specify the variables.

- Select the **Variables** tab.
- Double-click in the **Response Variable** text box. This will bring up the variable selection window.
- Select **HR** from the list of variables and then click **Ok**. *HR* will appear in the Response Variable box.
- Double-click in the **Subject Variable** text box. This will bring up the variable selection window.
- Select **Rat** from the list of variables and then click **Ok**. *Rat* will appear in the Subject Variable box.

## Mixed Models - Repeated Measures

- The **Times** box should be left blank.
- Set the **Number of Between and Within Fixed Factors** to **2**.
- Set the first **Fixed Factor Variable** to **Period**.
- Set the second **Fixed Factor Variable** to **Trtcross**.
- Set the **Number of Covariates** to **1**.
- Select **IHR** as the first **Covariate Variable**.
- Set the **Variance-Covariance Matrix Pattern** to **Compound Symmetry: Repeated** to indicate compound symmetry.

### 4 Specify the model.

- Set **Terms** to **1-Way**.

### 5 Specify the reports.

- Leave all reports and plots at their default values.

### 6 Run the procedure.

- From the Run menu, select **Run Procedure**. Alternatively, just click the green Run button.

## 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

The F-test for Trtcross is nearly significant (F-value = 3.99, Prob Level = 0.0592) 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 = 2.00, 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.