Chapter 223

Mixed Models – Random Coefficients

Introduction

This specialized Mixed Models procedure analyzes random coefficient regression models. In this case, the regression coefficients (the intercepts and slopes) are unique to each subject. Since the subjects are a random sample from a population of subjects, this technique is called random coefficients. The technique is also known as multilevel modeling or hierarchical modeling.

This procedure uses the standard mixed model calculation engine to perform all calculations. However, the user-interface has been simplified to make specifying the random coefficients analysis much easier.

Random Coefficients Models

It is often important in a study to determine the relationship between the response and time. This is often done by including the measurement time as a covariate in the model, with a corresponding slope, say β_t. It is plausible and likely that the slope will vary with subject, so it might be useful to model a separate intercept and slope for each subject in the study. This is done by fitting the subject variable as the intercept and the subject*time interaction as the slope for each patient. These two terms could reasonably be assumed to arise at random from a distribution and, thus, would be specified as random effects. This gives rise to what is called a *random coefficients model*.

A random coefficients model is one in which the subject term and a subject*time interaction term are both included as random effects in the model. This type of model is different from an ordinary random effects model because when we fit a straight line, the estimates of the slope and intercept are not independent. Thus, the subject and subject*time effects in the model are correlated. The random effects model must be adapted to this situation to allow for correlation among these random effects. This is done using the bivariate normal distribution. The bivariate random effect becomes

$$\begin{pmatrix} subject_k \\ (subject * time)_k \end{pmatrix} \sim N(0, \mathbf{G}),$$

where

$$\mathbf{G} = \begin{pmatrix} \sigma^2_{subject} & \sigma_{subject,subject*time} \\ \sigma_{subject,subject*time} & \sigma^2_{subject*time} \end{pmatrix}$$

The random coefficients model is often used if the relationship with time is of interest or if the repeated measurements do not occur at fixed intervals.

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.

Determining the Correct Model of the Variance-Covariance of Y

Akaike Information Criterion (AIC) for Model Assessment

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

$$AIC = -2 \times L + 2p$$

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

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

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

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

The recommended variance-covariance structure among these five is the Toeplitz pattern, since it results in the smallest AIC value.

What to Do When You Encounter a Variance Estimate that is Equal to Zero

It is possible that a mixed models data analysis results in a variance component estimate that is negative or equal to zero. This is particularly true in the case of random coefficients models. When this happens, the component that has a variance estimate equal to zero should be removed from the random factors model statement (or, if possible, the repeated pattern should be simplified to 'diagonal'), and the analysis should be rerun.

Fixed Effects

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

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

Covariates

Covariates are continuous measurements that may not be 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.

Time as a Fixed Effects Factor vs. Time as a Covariate

Time is an essential measurement in many mixed model designs. In some analyses, time may be considered a fixed factor, while in others it is covariate. In random coefficient models, time is considered to be a covariate.

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.

Speciying the Within-Subjects Variance-Covariance Matrix

The R Matrix

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

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

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

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

When the $\mathbf{R}$ matrix is specified in **NCSS**, it is assumed that there is a fixed, known set of repeated measurement times. (If the repeated measurement times are random, specification of the $\mathbf{G}_{sub}$ matrix with $\mathbf{R} = \sigma^2\mathbf{I}$ should be used instead for specifying covariance structure.) Thus, the differences in the dimensions of the $\mathbf{R}$ sub-matrices occur only when some measurements for a subject are missing.

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

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

where there are five time points at which each subject is intended to be measured: 1 hour, 2 hours, 5 hours, 10 hours, and 24 hours. If the first subject has measurements at all five time points, then $n_1 = 5$, and the sub-matrix is identical to $\mathbf{R}_{sub}$ above, and $\mathbf{R}_1 = \mathbf{R}_{sub}$.

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

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

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

Structures of R

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

Diagonal

Homogeneous

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

Heterogeneous

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

Correlation

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

Compound Symmetry

Homogeneous

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

Heterogeneous

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

Correlation

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

AR(1)

Homogeneous

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

Heterogeneous

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

Correlation

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

AR(Time Diff)

Homogeneous

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

Heterogeneous

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

Correlation

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

Toeplitz

Homogeneous

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

Heterogeneous

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

Correlation

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

Toeplitz(2)

Homogeneous

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

Heterogeneous

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

Correlation

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

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

Toeplitz(3)

Homogeneous

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

Heterogeneous

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

Correlation

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

Toeplitz(4) and Toeplitz(5)

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

Banded(2)

Homogeneous

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

Heterogeneous

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

Correlation

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

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

Banded(3)

Homogeneous

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

Heterogeneous

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

Correlation

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

Banded(4) and Banded (5)

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

Unstructured

Homogeneous

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

Heterogeneous

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

Correlation

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

Partitioning the Variance-Covariance Structure with Groups

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

Partitioning the R Matrix Parameters

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

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

If there are sixteen subjects, then

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

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

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

We now have

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

and

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

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

It is easy to see how quickly the number of variance-covariance parameters increases when **R** is partitioned by groups.

Example 1 – Random Coefficients Model with a Between Subjects Factor and Two, Within-Subjects Covariates

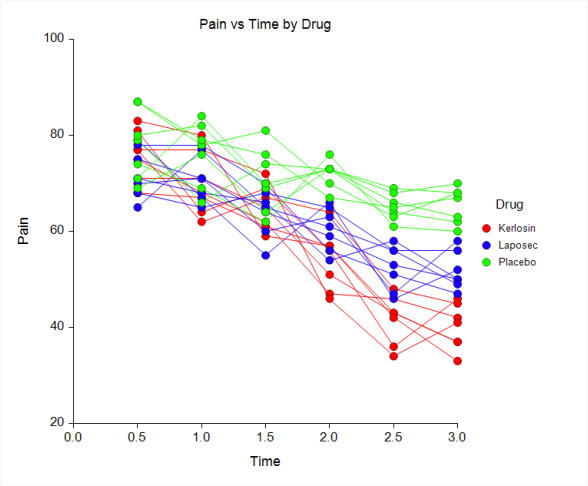
This example should acquaint the reader with the output for all output options. It presents an analysis of a longitudinal design in which there is one between-subjects factor (Drug) a time variable (Time), and a covariate (Cov). The response is a measure of pain (Pain).

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 of each individual at the time of pain measurement is measured as a covariate. The researchers wish to compare the drugs at the time value of 2.0 and the Cov value of 140.

Pain Dataset

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

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



Setup

To run this example, complete the following steps:

1 Open the Pain example dataset

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

2 Specify the Mixed Models – Random Coefficients procedure options

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

Variables Tab	
Response	**Pain**
Subjects	**Patient**
Regressions	**Linear**
Covariances	**Checked**
Number	**1**
Variable 1	**Drug**
Comparison	**All Pairs**
Number	**2**
Variable 1	**Time**
Compute Means at these Values	**2**
Variable 2	**Cov**
Compute Means at these Values	**140**

Terms ..... **Up to 2-Way**
Maximum Exponent of Covariates **1**

Reports Tab

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

3 Run the procedure

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

Run Summary Section

Run Summary

Item	Value
Likelihood Type	Restricted Maximum Likelihood
Fixed Model	TIME+COV+DRUG+TIME*COV+TIME*DRUG+COV*DRUG
Random Model	PATIENT+PATIENT*TIME
Repeated Pattern	Diagonal
Number of Rows	126
Number of Subjects	21
Solution Type	Newton-Raphson
Fisher Iterations	5 of a possible 5
Newton Iterations	40 of a possible 40
Max Retries	10
Lambda	1
Log-Likelihood	-388.9034
-2 Log-Likelihood	777.8067
AIC (Smaller Better)	785.8067
Convergence	Normal
Run Time (Seconds)	2.173

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 fixed model specified for this run. It includes fixed terms and covariates.

Random Model

The random model as specified by the Regressions setting.

Repeated Model

The pattern selected for the within-subjects variance-covariance matrix.

Number of Rows

The number of rows processed from the database.

Number of Subjects

The number of unique subjects from the database.

Solution Type

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

Fisher Iterations

Some Fisher-Scoring iterations are used as part of the Newton-Raphson algorithm. The '5 of a possible 5' means five Fisher-Scoring iterations were used, while five was the maximum that were allowed (as specified on the Maximization tab).

Newton Iterations

The '40 of a possible 40' means that all forty Newton-Raphson iterations were used. You may want to increase this value and rerun so the algorithm has a chance to converge.

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)

Parameter Number	Estimated Value	Model Term
1	9.4357	Patient
2	1.3770	Patient*Time
3	-3.6028	Patient, Patient*Time

This section gives the random component estimates.

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 values of the three variance components.

Model Term

The name of the random term being presented on this line.

Repeated Component Parameter Estimates (R Matrix)

Repeated Component Parameter Estimates (R Matrix)

Parameter Number	Estimated Value	Parameter Type
1	27.6148	Diagonal (Variance)

This section gives the repeated component estimates according to the Repeated Variance Pattern specifications of the Variables 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 27.6148 is the estimated residual (error) variance.

Parameter Type

The parameter type describes the structure of the R matrix.

Term-by-Term Hypothesis Test Results

Term-by-Term Hypothesis Test Results

Model Term	F-Value	Num DF	Denom DF	Prob Level
Time	3.0716	1	30.4	0.089767
Cov	1.3193	1	86.7	0.253883
Drug	2.0662	2	55.4	0.136315
Time*Cov	2.5462	1	29.8	0.121126
Time*Drug	25.3246	2	9.5	0.000155
Cov*Drug	0.7537	2	48.0	0.476088

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

This section contains an F-test for each fixed term in the model according to the methods described by Kenward and Roger (1997).

Model Term

This is the name of the term in the model.

F-Value

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

Num DF

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

Denom DF

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

Prob Level

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

Individual Comparison Hypothesis Test Results

Individual Comparison Hypothesis Test Results by Covariate Values

Covariates: Time = 2.0000, Cov = 140.0000

Comparison/ Covariate(s)	Comparison Mean Difference	F-Value	Num DF	Denom DF	Raw Prob Level	Bonferroni Prob Level
Drug						
Drug		61.5654	2	4.3	0.000666	
Drug: Kerlosin - Laposec	-4.9155	11.0898	1	4.5	0.024422	0.073266 [3]
Drug: Kerlosin - Placebo	-16.0780	117.3785	1	4.2	0.000318	0.000954 [3]
Drug: Laposec - Placebo	-11.1625	56.8153	1	4.3	0.001242	0.003727 [3]

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

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

Comparison/Covariate(s)

This is the comparison being made. The first line is 'Drug'. On this line, the levels of drug are compared when the covariate is equal to 140. The second line is 'Drug: Placebo – Kerlosin'. On this line, Kerlosin is compared to Placebo when the covariate is equal to 140.

Comparison Mean Difference

This is the difference in the least squares means for each comparison.

F-Value

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

Num DF

This is the numerator degrees of freedom for this comparison.

Denom DF

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

Raw Prob Level

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

Bonferroni Prob Level

The Bonferroni Prob Level is adjusted for multiple tests. The number of tests adjusted for is enclosed in brackets following each Bonferroni Prob Level. For example, 0.073266 [3] signifies that the probability the means are equal, given the data, is 0.073266, after adjusting for 3 tests.

Least Squares (Adjusted) Means

Least Squares (Adjusted) Means by Covariate Values

Covariates: Time = 2.0000, Cov = 140.0000

Name	Mean	Standard Error of Mean	95.0% Lower Conf. Limit for Mean	95.0% Upper Conf. Limit for Mean	DF
Intercept					
Intercept	61.5145	0.6054	59.8674	63.1615	4.2
Drug					
Kerlosin	54.5166	1.0426	51.7155	57.3178	4.4
Laposec	59.4322	1.0436	56.6756	62.1887	4.6
Placebo	70.5946	1.0558	67.6454	73.5439	3.9

This section gives the adjusted means for the levels of each fixed factor when Cov = 140 and Time = 2.

Name

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

Mean

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

Standard Error of Mean

This is the standard error of the mean.

95.0% Lower (Upper) Conf. Limit for Mean

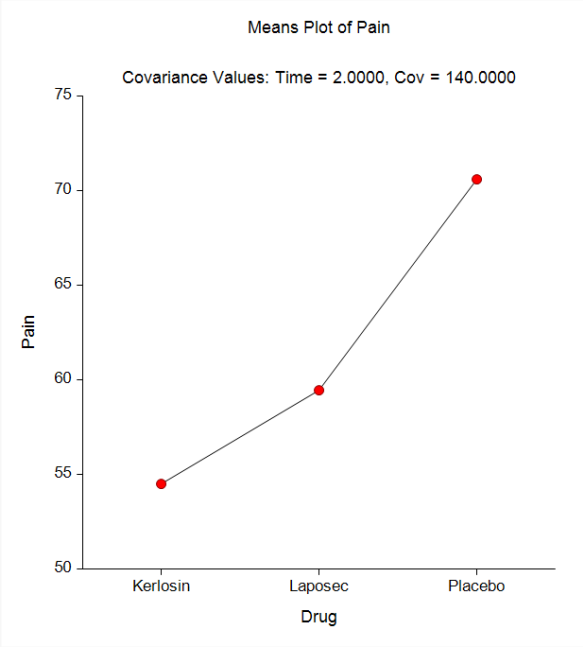
These limits give a 95% confidence interval for the mean.

DF

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

Means Plots

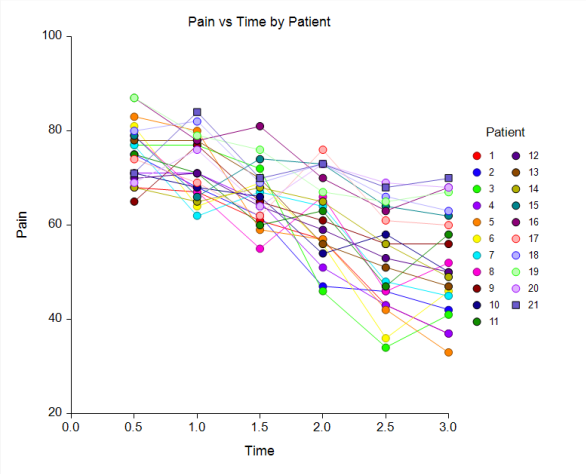
Means Plots

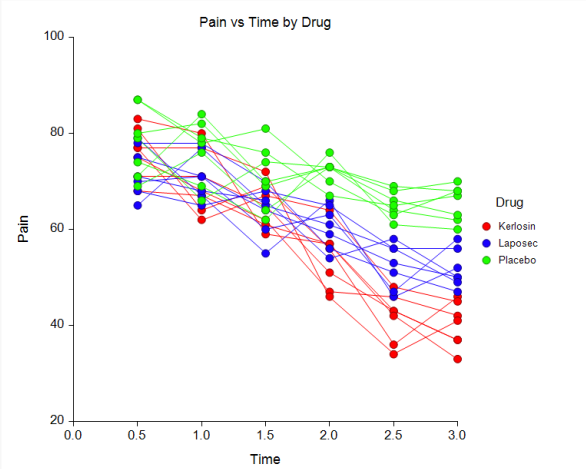


These plots show the means broken up into the categories of the fixed effects of the model. Some general trends that can be seen are those of pain decreasing with time and lower pain for the two drugs after two hours.

Subject Plots

Subject Plots





Each set of connected dots of the Subject plots show the response trajectory of particular subject.

Solution for Fixed Effects

Solution for Fixed Effects

Effect Name	Effect Estimate (Beta)	Effect Standard Error	Prob Level	95.0% Lower Conf. Limit of Beta	95.0% Upper Conf. Limit of Beta	DF	Effect No.
Intercept	75.3756	6.8605	0.000000	61.7020	89.0493	72.8	1
Time	-0.5691	3.1987	0.860185	-7.1478	6.0096	25.7	2
Cov	0.0340	0.0419	0.419993	-0.0495	0.1174	77.5	3
(Drug="Kerlosin")	7.7959	7.1744	0.282843	-6.6441	22.2359	46.1	4
(Drug="Laposec")	-7.9409	7.2768	0.279642	-22.5052	6.6233	58.3	5
(Drug="Placebo")	0.0000	0.0000					6
Time*Cov	-0.0300	0.0188	0.121126	-0.0684	0.0084	29.8	7
Time*(Drug="Kerlosin")	-10.6849	1.5189	0.000048	-14.0966	-7.2731	9.4	8
Time*(Drug="Laposec")	-3.7308	1.5091	0.034477	-7.1245	-0.3371	9.4	9
Time*(Drug="Placebo")	0.0000	0.0000					10
Cov*(Drug="Kerlosin")	-0.0179	0.0388	0.647188	-0.0963	0.0606	39.0	11
Cov*(Drug="Laposec")	0.0303	0.0401	0.453369	-0.0502	0.1108	49.7	12
Cov*(Drug="Placebo")	0.0000	0.0000					13

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

Effect Name

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

Effect Estimate (Beta)

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

Effect Standard Error

This is the standard error for the corresponding effect.

Prob Level

The Prob Level tests whether the effect is zero.

95.0% Lower (Upper) Conf. Limit of Beta

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

DF

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

Effect No.

This number identifies the effect of the line.

Asymptotic Variance-Covariance Matrix of Variance Estimates

Asymptotic Variance-Covariance Matrix of Variance Estimates

Parameter	G(1,1)	G(1,2)	G(1,3)	R(1,1)
G(1,1)	155.0994	35.0388	-72.6433	-16.9227
G(1,2)	35.0388	14.3116	-21.5071	-4.4822
G(1,3)	-72.6433	-21.5071	39.1741	7.9258
R(1,1)	-16.9227	-4.4822	7.9258	18.9471

This section gives the asymptotic variance-covariance matrix of the variance components of the model. Note that the component number is always ‘1’ in this procedure.

Parm

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

G(1,1)

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

R(1,1)

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

Estimated Vi Matrix of Subject = X

Estimated Vi Matrix of Subject = 1

Vi	1	2	3	4	5	6
1	33.7920	4.7200	3.2628	1.8057	0.3485	-1.1087
2	4.7200	31.2219	2.4942	1.3813	0.2684	-0.8445
3	3.2628	2.4942	29.3404	0.9569	0.1882	-0.5804
4	1.8057	1.3813	0.9569	28.1473	0.1081	-0.3163
5	0.3485	0.2684	0.1882	0.1081	27.6428	-0.0522
6	-1.1087	-0.8445	-0.5804	-0.3163	-0.0522	27.8268

Estimated Vi Matrix of Subject = 2

Vi	1	2	3	4	5	6
1	33.7920	4.7200	3.2628	1.8057	0.3485	-1.1087
2	4.7200	31.2219	2.4942	1.3813	0.2684	-0.8445
3	3.2628	2.4942	29.3404	0.9569	0.1882	-0.5804
4	1.8057	1.3813	0.9569	28.1473	0.1081	-0.3163
5	0.3485	0.2684	0.1882	0.1081	27.6428	-0.0522
6	-1.1087	-0.8445	-0.5804	-0.3163	-0.0522	27.8268

Estimated Vi Matrix of Subject = 3

Vi	1	2	3	4	5	6
1	33.7920	4.7200	3.2628	1.8057	0.3485	-1.1087
2	4.7200	31.2219	2.4942	1.3813	0.2684	-0.8445
3	3.2628	2.4942	29.3404	0.9569	0.1882	-0.5804
4	1.8057	1.3813	0.9569	28.1473	0.1081	-0.3163
5	0.3485	0.2684	0.1882	0.1081	27.6428	-0.0522
6	-1.1087	-0.8445	-0.5804	-0.3163	-0.0522	27.8268

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.

Hessian Matrix of Variance Estimates

Hessian Matrix of Variance Estimates

Parameter	G(1,1)	G(1,2)	G(1,3)	R(1,1)
G(1,1)	0.0937	0.1820	0.2710	0.0134
G(1,2)	0.1820	0.7529	0.7450	0.0290
G(1,3)	0.2710	0.7450	0.9313	0.0287
R(1,1)	0.0134	0.0290	0.0287	0.0596

The Hessian Matrix is directly related to the asymptotic variance-covariance matrix of the variance estimates. Note that the component number is always '1' in this procedure.

Parm

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

G(1,1)

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

R(1,1)

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

L Matrices

L Matrix for Cov

No.	Effect	Drug	L1
1	Intercept		
2	Time		
3	Cov		1.0000
4	Drug	Kerlosin	
5	Drug	Laposec	
6	Drug	Placebo	
7	Time*Cov		
8	Time*Drug	Kerlosin	
9	Time*Drug	Laposec	
10	Time*Drug	Placebo	
11	Cov*Drug	Kerlosin	0.3333
12	Cov*Drug	Laposec	0.3333
13	Cov*Drug	Placebo	0.3333

L Matrix for Drug

No.	Effect	Drug	L1	L2
1	Intercept			
2	Time			
3	Cov			
4	Drug	Kerlosin	1.0000	1.0000
5	Drug	Laposec	-1.0000	
6	Drug	Placebo		-1.0000
7	Time*Cov			
8	Time*Drug	Kerlosin		
9	Time*Drug	Laposec		
10	Time*Drug	Placebo		
11	Cov*Drug	Kerlosin		
12	Cov*Drug	Laposec		
13	Cov*Drug	Placebo		

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 the second report 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.