

## Chapter 221

# Mixed Models – No Repeated Measures

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### Introduction

This specialized Mixed Models procedure analyzes data from fixed effects, factorial designs. These designs classify subjects into one or more fixed factors and have only one measurement per subject. This procedure is especially useful when you have covariates and/or unequal variances across a factor.

The *Mixed Models - General* chapter gives a comprehensive overview of this topic. We encourage you to look there for details.

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### Fixed Effects Models

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. 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. 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. 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 several values of covariates.

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### Multiple Comparisons of Fixed Effect Levels

If there is evidence that the means of a fixed factor are, 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 comparison 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.

## Family-Wise Error Rate (FWER) Control – Bonferroni Adjustment

The Bonferroni p-value adjustment produces adjusted p-values (probability levels) for which the FWER is controlled strictly (Westfall et al, 1999). The Bonferroni adjustment is applied to all  $m$  unadjusted (raw) p-values ( $p_j$ ) as

$$\tilde{p}_j = \min(mp_j, 1).$$

That is, each p-value is multiplied by the number of tests in the set (family), and if the result is greater than one, it is set to the maximum possible p-value of one. The Bonferroni adjustment is generally considered to be a conservative method for simultaneously comparing levels of fixed effects.

## Multiple Comparisons for the Interaction of Two Main Effects

When examining a fixed effect interaction using post-hoc (or planned) multiple comparison tests, a useful method is to compare all levels of one factor at each level of the other factor. This method is termed ‘slicing’. For example, if the interaction of Factor1 and Factor2 is significant, comparing the Factor2 mean at each level of Factor1 could aid in understanding the nature of the interaction.

## Multiple Comparisons for Several Covariate Levels

When more than one covariate value is specified for *Compute Means at these Values*, the number of test used in the Bonferroni adjustment can increase dramatically. The number of tests for the Bonferroni adjustment is computed as

$$\text{Number of Tests} = \text{Number of Comparisons per Set} \times \text{Number of Covariate Sets}$$

As an example, suppose that an experiment has two covariates, and a single fixed treatment factor with three levels: Control, T1, and T2. If ‘All Pairs’ were selected as the comparison on the Comparisons tab, then the number of comparisons per set would be three (T1 – Control, T2 – Control, and T2 – T1). Suppose that the researcher desired to compute the hypothesis tests at two values for the first covariate and four values for the second. The number of covariate sets would be  $2 \times 4 = 8$ . Therefore, the number of tests used in the Bonferroni adjustment to conserve the overall error-rate would be  $3 \times 8 = 24$ . The raw p-value would have to be less than  $0.05/24 = 0.00208$  in order to declare significance at the 0.05 level.

This example illustrates that care must be taken when specifying the covariate values at which the means and analyses will be computed. As more covariate values are specified, the number of tests in the adjustment increases, which makes it more difficult to find significance.

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## Procedure Options

This section describes the options available in this procedure.

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### Variables Tab

These panels specify the variables used in the analysis, the solution type, and the model.

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#### Response Variable

##### Response

Specify the variable that contains the numeric response (measurement) for each subject. There is one measurement per subject. Hence, all responses are in a single column (variable) of the spreadsheet.

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#### Between-Subject Fixed Factors

##### 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.

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.

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- **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.

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.

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### 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.

### Model

#### 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.

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- **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 the 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

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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.

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## Maximization Tab

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

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### 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.

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### 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'.

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## 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.

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## 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.

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### 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 0.00000000001 (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.

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## 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.

### 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.

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### 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.

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## Reports Tab

The following options control which reports are displayed.

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### Select Reports

#### Run Summary

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

#### Variance Estimates

Check this box to obtain estimates of group variances.

#### Hypothesis Tests

Check this box to obtain F-Tests for all terms.

#### 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.

#### Comparisons – Sorted by Factors

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.

#### Comparisons – Sorted by Covariate Values

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.

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### L-Matrices – Comparisons

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 – Sorted by Factors

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.

### Means – Sorted by Covariate Values

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.

### L-Matrices – LS Means

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

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

### Asymptotic VC Matrix

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

### Hessian Matrix

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.

### 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.

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## 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.

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## 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.

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## 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 ... Covariates

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 **All** to display all digits available. The number of digits displayed by this option is controlled by whether the **Precision** option is *Single* or *Double*.

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## Plots Tab

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

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### 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 by pressing the format button.

## Example 1 – Two Fixed Factors and Two Covariates

In this example, 24 males and 24 females are randomly allocated to three dose groups: low, medium, and high. The age of each subject is recorded. Their response to a certain stimuli is recorded as a pretest. Next, the assigned dose of a certain compound is administered and their response to the stimuli is measured again.

Researchers wish to investigate how the response to the stimuli is affected by the subject's age, gender, dose, and pretest score. This can be done using a two factor, two covariate mixed model. They want to allow for the possibility of a difference in variance for males versus females.

This example will run all reports and plots so that they may be documented. Usually, only a subset of the reports would be generated. Here is an excerpt of the dataset

### 2 Factor 2 Covariate Dataset

Test	Dose	Gender	PreTest	Age
64.1	Low	F	52.1	58
69.1	Low	F	56.4	57
69.5	Low	F	53.5	50
81.8	Low	F	72.5	30
82.4	Low	F	65.3	72
86.7	Low	F	73.6	24
87	Low	F	69.2	30
93.8	Low	F	78.5	61
63.8	Low	M	52.4	42
66.1	Low	M	55.9	53
67.1	Low	M	56.5	36
74.7	Low	M	62.6	44
.	.	.	.	.
.	.	.	.	.
.	.	.	.	.
99	High	M	84.6	74
99.5	High	M	76	70
99.5	High	M	77.2	36

To run the analysis using this 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 – No Repeated Measures window.

### 1 Open the 2 Factor 2 Covariate dataset.

- From the File menu of the NCSS Data window, select **Open Example Data**.
- Click on the file **2 Factor 2 Covariate.NCSS**.
- Click **Open**.

### 2 Open the Mixed Models – No Repeated Measures window.

- Using the Analysis menu or the Procedure Navigator, find and select the **Mixed Models – No 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 **Test** from the list of variables and then click **Ok**. Test will appear in the Response box.
- Set the **Number** of Fixed Factors to **2**.
- Select **Dose** as the first **Fixed Factor** variable.

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- Set the **Comparison** for Dose to **All Pairs**.
- Select **Gender** as the second **Fixed Factor** variable.
- Check the  $\neq\sigma^2$  box next to Gender to indicate that variances of this group are possibly different.
- Set the **Number** of Covariates to **2**.
- Select **Age** as the first **Covariate** variable.
- Set the **Compute Means at these Values** to **30 60**.
- Select **PreTest** as the second **Covariate** variable.
- Set the **Compute Means at these Values** to **60 80**.

### 4 Specify the Model.

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

### 5 Select the Reports.

- Select the **Reports tab**.
- Check all reports except **L Matrices – Terms**, **L Matrices – Comparisons**, and **L Matrices – LS Means**.

### 6 Select the Plots.

- Select the **Plots tab**.
- Check the Mean Plot(s) check box.

### 7 Run the procedure.

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

## Run Summary

Item	Value
Likelihood Type	Restricted Maximum Likelihood
Fixed Model	AGE+DOSE+GENDER+PRETEST
Number of Subjects	48
Solution Type	Newton-Raphson
Fisher Iterations	5 of a possible 5
Newton Iterations	2 of a possible 40
Max Retries	10
Lambda	1
Log Likelihood	-118.2766
-2 Log Likelihood	236.5532
AIC (Smaller Better)	240.5532
Convergence	Normal
Run Time (Seconds)	0.898

This report 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 that was fit to the data.

### Number of Subjects

The number of rows processed 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.

## Mixed Models – No Repeated Measures

### 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, and five was the maximum allowed (as specified on the Maximization tab).

### Newton Iterations

The '2 of a possible 40' means two Newton-Raphson iterations were 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 were 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, a good remedy is to set 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.

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## Variance Report

	Variance	Standard Deviation
Gender	$\sigma^2$	$\sigma$
F	7.7742	2.7882
M	8.9230	2.9871

This section gives the variances and standard deviations of the individual groups as designated.

### Gender

The name of the variable across which the variances vary.

### Variance

The estimated variance of this group.

## Mixed Models – No Repeated Measures

**Standard Deviation**

The estimated standard deviation of this group.

**Term-by-Term Hypothesis Test Results**

Model Term	F-Value	Numer-ator DF	Denomi-nator DF	Prob Level
Age	2.68	1	41.5	0.1092
Dose	27.77	2	41.9	0.0000
Gender	1.14	1	41.8	0.2923
PreTest	371.29	1	40.6	0.0000

This section contains a F-test for each model term using the methods of 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).

**Numerator DF**

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

**Denominator 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.

## Mixed Models – No Repeated Measures

## Individual Comparison Tests – Sorted by Factors, Sorted by Covariates

Comparison/ Covariate(s)	Comparison Mean Difference	F-Value	Numer- ator DF	Denomi- nator DF	Raw Prob Level	Bonferroni Prob Level
<b>Dose</b>						
Age=30.0000, PreTest=60.0000		27.77	2	41.9	0.0000	0.0000 [4]
Age=30.0000, PreTest=80.0000		27.77	2	41.9	0.0000	0.0000 [4]
Age=60.0000, PreTest=60.0000		27.77	2	41.9	0.0000	0.0000 [4]
Age=60.0000, PreTest=80.0000		27.77	2	41.9	0.0000	0.0000 [4]
<b>Dose: Low - Medium</b>						
Age=30.0000, PreTest=60.0000	-3.5405	10.70	1	42.0	0.0021	0.0258 [12]
Age=30.0000, PreTest=80.0000	-3.5405	10.70	1	42.0	0.0021	0.0258 [12]
Age=60.0000, PreTest=60.0000	-3.5405	10.70	1	42.0	0.0021	0.0258 [12]
Age=60.0000, PreTest=80.0000	-3.5405	10.70	1	42.0	0.0021	0.0258 [12]
(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 F-test for the overall Dose factor. On this line, the levels of dose are compared when the age is 30 and the PreTest is 60.

**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).

**Numerator DF**

This is the numerator degrees of freedom for this comparison.

**Denominator 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.

Mixed Models – No Repeated Measures

**Least Squares (Adjusted) Means – Sorted by Factors**

Term/ Covariate(s)	Mean	Standard Error of Mean	95.0% Lower Conf. Limit for Mean	95.0% Upper Conf. Limit for Mean	DF
<b>Intercept</b>					
Age=30.0000, PreTest=60.0000	76.4756	0.6804	75.1015	77.8498	40.9
Age=30.0000, PreTest=80.0000	95.2350	0.8576	93.5041	96.9658	41.8
Age=60.0000, PreTest=60.0000	77.9188	0.6560	76.5949	79.2428	41.9
Age=60.0000, PreTest=80.0000	96.6782	0.9836	94.6906	98.6658	40.2
<b>Dose = [Low]</b>					
Age=30.0000, PreTest=60.0000	72.6032	0.9360	70.7098	74.4967	38.9
Age=30.0000, PreTest=80.0000	91.3626	1.1474	89.0454	93.6797	41.1
Age=60.0000, PreTest=60.0000	74.0464	0.8347	72.3599	75.7330	40.4
Age=60.0000, PreTest=80.0000	92.8058	1.1841	90.4162	95.1953	42.0
<b>Dose = [Medium]</b>					
Age=30.0000, PreTest=60.0000	76.1437	0.8637	74.4006	77.8868	42.0
Age=30.0000, PreTest=80.0000	94.9030	1.0516	92.7802	97.0259	41.6
Age=60.0000, PreTest=60.0000	77.5869	0.9406	75.6886	79.4852	41.9
Age=60.0000, PreTest=80.0000	96.3463	1.2285	93.8648	98.8277	40.8
(Report continues)					

This section gives the adjusted means for the levels of each fixed factor at the specified values of the covariates.

**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.

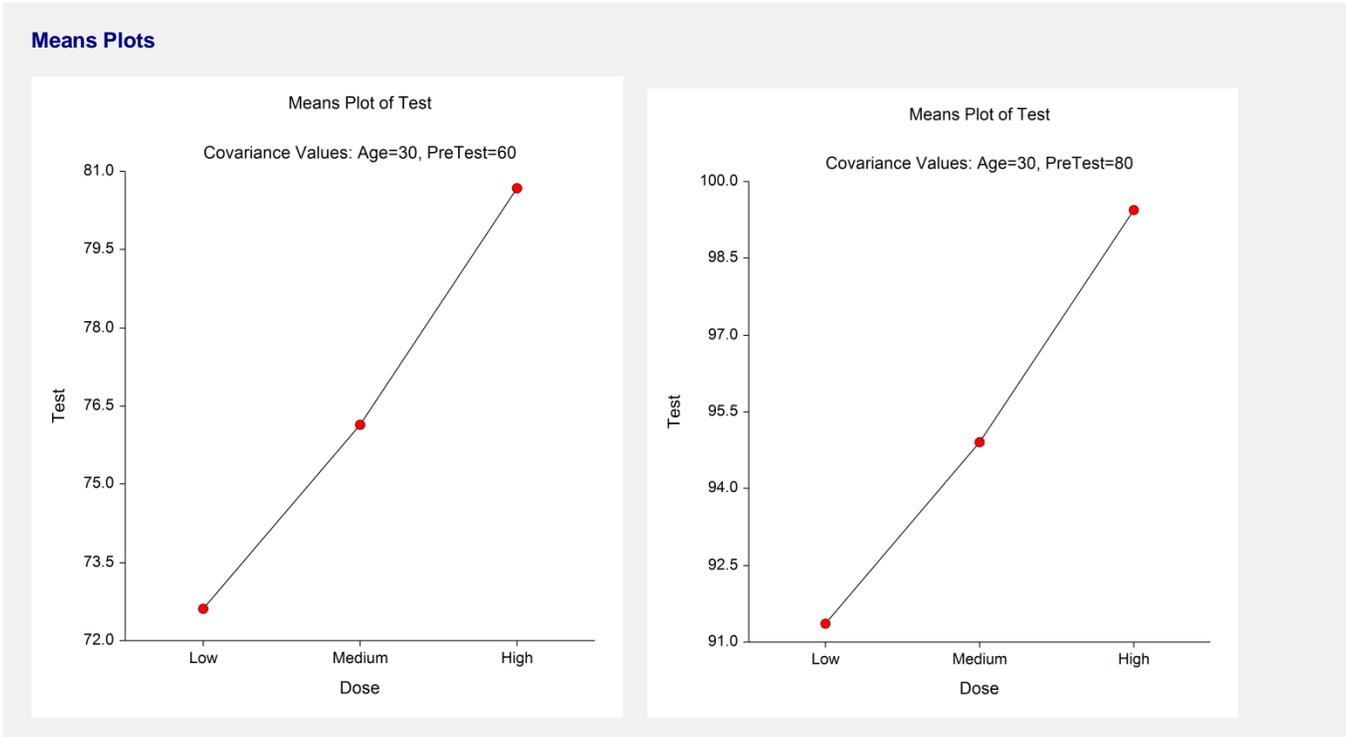
**95.0% Lower (Upper) Conf. Limit for Mean**

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.

## 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	22.4743	3.8707	0.0000	14.6519	30.2968	40.1	1
Age	0.0481	0.0294	0.1092	-0.0112	0.1074	41.5	2
(Dose="Low")	-8.0767	1.0866	0.0000	-10.2697	-5.8838	42.0	3
(Dose="Medium")	-4.5362	1.0817	0.0001	-6.7196	-2.3529	41.8	4
(Dose="High")	0.0000	0.0000					5
(Gender="F")	0.9687	0.9082	0.2923	-0.8643	2.8018	41.8	6
(Gender="M")	0.0000	0.0000					7
PreTest	0.9380	0.0487	0.0000	0.8396	1.0363	40.6	8

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.

## Mixed Models – No Repeated Measures

### 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.

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## Asymptotic Variance-Covariance Matrix of Variance Estimates

Parm	R(1,1,1)	R(1,1,2)
R(1,1,1)	5.7409	-0.0009
R(1,1,2)	-0.0009	7.6050

This section gives the asymptotic variance-covariance matrix of the variance components of the model.

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## Hessian Matrix of Variance Estimates

Parm	R(1,1,1)	R(1,1,2)
R(1,1,1)	0.17418787	0.00002123
R(1,1,2)	0.00002123	0.13149167

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