

Chapter 571

Mixed Models (Simulation)

Introduction

This procedure power analyzes random effects designs in which the outcome (response) is continuous. Thus, as with the analysis of variance (ANOVA), the procedure is used to test hypotheses comparing various group means. Unlike ANOVA, this procedure relaxes the strict assumptions regarding the variances of the groups. Random effects models are commonly used to analyze longitudinal (repeated measures) data.

This procedure extends many of the classical statistical techniques to the case when the variances are not equal, such as

- Two-sample designs (extending the t-test)
- One-way layout designs (extending one-way ANOVA)
- Factorial designs (extending factorial GLM)
- Split-plot designs (extending split-plot GLM)
- Repeated-measures designs (extending repeated-measures GLM)
- Cross-over designs (extending GLM)

Types of Linear Mixed Models

Several linear mixed model subtypes exist that are characterized by the random effects, fixed effects, and covariance structure they involve. These include fixed effects models, random effects models, and covariance pattern models.

Fixed Effects Models

A *fixed effects model* is a model where only fixed effects are included in the model. An effect (or factor) is fixed if the levels in the study represent all levels of interest of the factor, or at least all levels that are important for inference (e.g., treatment, dose, etc.). No random components are present. The general linear model is a fixed effects model. Fixed effects models can include interactions. The fixed effects can be estimated and tested using the F-test.

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) can also be included in the model as fixed factors.

Random Effects Models

A *random effects model* includes both fixed and random terms in the model. An effect (or factor) is random if the levels of the factor represent a random subset of a larger group of levels (e.g., patients). The random effects are not tested but are included to make the model more realistic.

Longitudinal Data Models

Longitudinal data arises when more than one response is measured on each subject in the study. Responses are often measured over time at fixed time points. A time point is fixed if it is pre-specified. Various variance-matrix structures can be employed to model the variance and correlation among repeated measurements.

Types of Factors

Between-Subject Factors

Between-subject factors are those that separate the experimental subjects into groups. If twelve 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 response is measured on the same subject 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.

Technical Details

What is a Mixed Model?

In a general linear model (GLM), a random sample of the individuals in is drawn. Treatments are applied to each individual and an outcome is measured. The data so obtained are analyzed using an analysis of variance table that includes an F-test.

A mathematical model may be formulated that underlies each analysis of variance. This model expresses of the response variable as the sum of population parameters and a residual. For example, a common linear model for a two-factor experiment is

$$Y_{ijk} = \mu + a_i + b_j + (ab)_{ij} + e_{ijk}$$

where $i = 1, 2, \dots, I$ (the number of levels of factor 1), $j = 1, 2, \dots, J$ (the number of levels of factor 2), and $k = 1, 2, \dots, K$ (the number of subjects in the study). This model expresses the value of the response variable, Y , as the sum of five components:

- μ the mean.
- a_i the contribution of the i^{th} level of a factor A.
- b_j the contribution of the j^{th} level of a factor B.
- $(ab)_{ij}$ the combined contribution (or interaction) of the i^{th} level of a factor A and the j^{th} level of a factor B.
- e_{ijk} the contribution of the k^{th} individual. This is often called the *residual*.

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In this example, the linear model is made up of *fixed effects* only. An effect is fixed if the levels in the study represent all levels of the factor that are of interest, or at least all levels that are important for inference (e.g., treatment, dose, etc.).

The following assumptions are made when using the F-test in a general linear model.

1. The response variable is continuous.
2. The individuals are independent.
3. The e_{ijk} follow the normal probability distribution with mean equal to zero.
4. The variances of the e_{ijk} are equal for all values of i, j , and k .

The Linear Mixed Model (LMM)

The linear mixed model (LMM) is a natural extension of the general linear model. Mixed models extend linear models by allowing for the addition of *random effects*, where the levels of the factor represent a random subset of a larger group of all possible levels (e.g., time of administration, clinic, etc.). For example, the two-factor linear model above could be augmented to include random effects such as an adjustment for each patient, since a patient may be assumed to be a random realization from a distribution of patients. The general form of the mixed model in matrix notation is

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

where

- \mathbf{y} vector of responses
- \mathbf{X} known design matrix of the fixed effects
- $\boldsymbol{\beta}$ unknown vector of fixed effects parameters to be estimated
- \mathbf{Z} known design matrix of the random effects
- \mathbf{u} unknown vector of random effects
- $\boldsymbol{\varepsilon}$ unobserved vector of random errors

We assume

$$\begin{aligned}\mathbf{u} &\sim N(\mathbf{0}, \mathbf{G}) \\ \boldsymbol{\varepsilon} &\sim N(\mathbf{0}, \mathbf{R}) \\ \text{Cov}[\mathbf{u}, \boldsymbol{\varepsilon}] &= \mathbf{0}\end{aligned}$$

where

- \mathbf{G} variance-covariance matrix of \mathbf{u}
- \mathbf{R} variance-covariance matrix of the errors $\boldsymbol{\varepsilon}$

The variance-covariance matrix of \mathbf{y} , denoted \mathbf{V} , is

$$\begin{aligned}\mathbf{V} &= \text{Var}[\mathbf{y}] \\ &= \text{Var}[\mathbf{X}\boldsymbol{\beta} + \mathbf{Z}\mathbf{u} + \boldsymbol{\varepsilon}] \\ &= 0 + \text{Var}[\mathbf{Z}\mathbf{u} + \boldsymbol{\varepsilon}] \\ &= \mathbf{ZGZ}' + \mathbf{R}\end{aligned}$$

Individual Subject Formulation

Because of the size of the matrices that are involved in mixed model analysis, it is useful for computational purposes to reduce the dimensionality of the problem by analyzing the data one subject at a time. Because the data from different subjects are statistically independent, the log-likelihood of the data can be summed over the subjects, according to the formulas below. Before we look at the likelihood functions, we examine the linear mixed model for a particular subject:

$$\mathbf{y}_i = \mathbf{X}_i\boldsymbol{\beta} + \mathbf{Z}_i\mathbf{u}_i + \boldsymbol{\varepsilon}_i, \quad i = 1, \dots, N$$

where

\mathbf{y}_i $n_i \times 1$ vector of responses for subject i .

\mathbf{X}_i $n_i \times p$ design matrix of fixed effects for subject i (p is the number of columns in \mathbf{X}).

$\boldsymbol{\beta}$ $p \times 1$ vector of regression parameters.

\mathbf{Z}_i $n_i \times q$ design matrix of the random effects for subject i .

\mathbf{u}_i $q \times 1$ vector of random effects for subject i which has means of zero and covariance matrix \mathbf{G}_{sub} .

$\boldsymbol{\varepsilon}_i$ $n_i \times 1$ vector of errors for subject i with zero mean and covariance \mathbf{R}_i .

n_i number of repeated measurements on subject i .

N number of subjects.

The following definitions will also be useful.

\mathbf{e}_i vector of residuals for subject i ($\mathbf{e}_i = \mathbf{y}_i - \mathbf{X}_i\boldsymbol{\beta}$).

\mathbf{V}_i $\text{Var}[\mathbf{y}_i] = \mathbf{Z}_i\mathbf{G}_{sub}\mathbf{Z}_i' + \mathbf{R}_i$

To see how the individual subject mixed model formulation relates to the general form, we have

$$\mathbf{y} = \begin{pmatrix} \mathbf{y}_1 \\ \mathbf{y}_2 \\ \vdots \\ \mathbf{y}_N \end{pmatrix}, \quad \mathbf{X} = \begin{pmatrix} \mathbf{X}_1 \\ \mathbf{X}_2 \\ \vdots \\ \mathbf{X}_N \end{pmatrix}, \quad \mathbf{Z} = \begin{pmatrix} \mathbf{Z}_1 & \mathbf{0} & \mathbf{0} \\ \mathbf{0} & \ddots & \mathbf{0} \\ \mathbf{0} & \mathbf{0} & \mathbf{Z}_N \end{pmatrix}, \quad \mathbf{u} = \begin{pmatrix} \mathbf{u}_1 \\ \mathbf{u}_2 \\ \vdots \\ \mathbf{u}_N \end{pmatrix}, \quad \boldsymbol{\varepsilon} = \begin{pmatrix} \boldsymbol{\varepsilon}_1 \\ \boldsymbol{\varepsilon}_2 \\ \vdots \\ \boldsymbol{\varepsilon}_N \end{pmatrix}$$

In order to test the parameters in $\boldsymbol{\beta}$, which is typically the goal in LMM analysis, the unknown parameters ($\boldsymbol{\beta}$, \mathbf{G} , and \mathbf{R}) must be estimated. Estimates for $\boldsymbol{\beta}$ require estimates of \mathbf{G} and \mathbf{R} . In order to estimate \mathbf{G} and \mathbf{R} , the structure of \mathbf{G} and \mathbf{R} must be specified. Details of the specific structures for \mathbf{G} and \mathbf{R} are discussed later.

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The following assumptions are made when using the F-test in a LMM.

1. The response variable is continuous.
2. The individuals are independent.
3. The responses follow the normal probability distribution with mean equal to zero and variance structure given by \mathbf{V} .

A distinct (and arguably the most important) advantage of LMM over the GLM is flexibility in random error and random effect variance component modeling (note that the equal-variance assumption of GLM is not necessary for LMM). LMM allows you to model both heterogeneous variances and correlations among observations through the specification of the covariance matrix structures for \mathbf{u} and $\boldsymbol{\varepsilon}$. The variance matrix estimates are obtained using maximum likelihood (ML) or, more commonly, restricted maximum likelihood (REML). The fixed effects in the mixed model are tested using F-tests.

Structure of the Variance-Covariance Matrix

The G Matrix

The \mathbf{G} matrix is the variance-covariance matrix for the random effects \mathbf{u} . Typically, when the \mathbf{G} matrix is used to specify the variance-covariance structure of \mathbf{y} , the structure for \mathbf{R} is simply $\sigma^2\mathbf{I}$. Caution should be used when both \mathbf{G} and \mathbf{R} are specified as complex structures, since large numbers of sometimes redundant covariance elements can result.

The \mathbf{G} matrix is made up of N symmetric \mathbf{G}_{sub} matrices,

$$\mathbf{G} = \begin{pmatrix} \mathbf{G}_{sub} & \mathbf{0} & \mathbf{0} & \cdots & \mathbf{0} \\ \mathbf{0} & \mathbf{G}_{sub} & \mathbf{0} & \cdots & \mathbf{0} \\ \mathbf{0} & \mathbf{0} & \mathbf{G}_{sub} & \cdots & \mathbf{0} \\ \vdots & \vdots & \vdots & \ddots & \vdots \\ \mathbf{0} & \mathbf{0} & \mathbf{0} & \cdots & \mathbf{G}_{sub} \end{pmatrix}$$

The dimension of \mathbf{G}_{sub} is $q \times q$, where q is the number of random effects for each subject.

Structures of \mathbf{G}_{sub}

The structure of the \mathbf{G}_{sub} matrix in this procedure is diagonal.

$$\text{Diagonal } \mathbf{G}_{sub} = \begin{pmatrix} \sigma_1^2 & & & & \\ & \sigma_2^2 & & & \\ & & \sigma_3^2 & & \\ & & & \sigma_4^2 & \\ & & & & \sigma_4^2 \end{pmatrix}$$

The R Matrix

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

The full **R** matrix is made up of N symmetric **R** sub-matrices,

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

where $\mathbf{R}_1, \mathbf{R}_2, \mathbf{R}_3, \dots, \mathbf{R}_N$ are all of the same structure.

Structures of R

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

Diagonal

Homogeneous

Heterogeneous

Correlation

$$\begin{pmatrix} \sigma^2 & & & \\ & \sigma^2 & & \\ & & \sigma^2 & \\ & & & \sigma^2 \end{pmatrix} \quad \begin{pmatrix} \sigma_1^2 & & & \\ & \sigma_2^2 & & \\ & & \sigma_3^2 & \\ & & & \sigma_4^2 \end{pmatrix} \quad \begin{pmatrix} 1 & & & \\ & 1 & & \\ & & 1 & \\ & & & 1 \end{pmatrix}$$

Compound Symmetry

Homogeneous

Heterogeneous

Correlation

$$\begin{pmatrix} \sigma^2 & \rho\sigma^2 & \rho\sigma^2 & \rho\sigma^2 \\ \rho\sigma^2 & \sigma^2 & \rho\sigma^2 & \rho\sigma^2 \\ \rho\sigma^2 & \rho\sigma^2 & \sigma^2 & \rho\sigma^2 \\ \rho\sigma^2 & \rho\sigma^2 & \rho\sigma^2 & \sigma^2 \end{pmatrix} \quad \begin{pmatrix} \sigma_1^2 & \rho\sigma_1\sigma_2 & \rho\sigma_1\sigma_3 & \rho\sigma_1\sigma_4 \\ \rho\sigma_2\sigma_1 & \sigma_2^2 & \rho\sigma_2\sigma_3 & \rho\sigma_2\sigma_4 \\ \rho\sigma_3\sigma_1 & \rho\sigma_3\sigma_2 & \sigma_3^2 & \rho\sigma_3\sigma_4 \\ \rho\sigma_4\sigma_1 & \rho\sigma_4\sigma_2 & \rho\sigma_4\sigma_3 & \sigma_4^2 \end{pmatrix} \quad \begin{pmatrix} 1 & \rho & \rho & \rho \\ \rho & 1 & \rho & \rho \\ \rho & \rho & 1 & \rho \\ \rho & \rho & \rho & 1 \end{pmatrix}$$

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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

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

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

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

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Toeplitz(2)

Homogeneous

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

Heterogeneous

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

Correlation

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

Banded(2)

Homogeneous

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

Heterogeneous

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

Correlation

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

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

Banded(3)

Homogeneous

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

Heterogeneous

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

Correlation

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

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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 groups of a between-subjects factor, a different set of **R** or **G** parameters can be specified for each group. 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.

Likelihood Formulas

There are two types of likelihood estimation methods that are generally considered in mixed model estimation: maximum likelihood (ML) and restricted maximum likelihood (REML). REML is generally favored over ML because the variance estimates using REML are unbiased for small sample sizes, whereas ML estimates are unbiased only asymptotically (see Littell et al., 2006 or Demidenko, 2004). Both estimation methods are available in **PASS**.

Maximum Likelihood

The general form -2 log-likelihood ML function is

$$-2L_{ML}(\boldsymbol{\beta}, \mathbf{G}, \mathbf{R}) = \ln|\mathbf{V}| + \mathbf{e}'\mathbf{V}^{-1}\mathbf{e} + N_T \ln(2\pi)$$

The equivalent individual subject form is

$$-2L_{ML}(\boldsymbol{\beta}, \mathbf{G}, \mathbf{R}) = \sum_{i=1}^N (\ln|\mathbf{V}_i| + \mathbf{e}_i'\mathbf{V}_i^{-1}\mathbf{e}_i) + N_T \ln(2\pi)$$

where N_T is the total number of observations, or

$$N_T = \sum_{i=1}^N n_i$$

Restricted Maximum Likelihood

The general form -2 log-likelihood REML function is

$$-2L_{REML}(\boldsymbol{\beta}, \mathbf{G}, \mathbf{R}) = \ln|\mathbf{V}| + \mathbf{e}'\mathbf{V}^{-1}\mathbf{e} + \ln|\mathbf{X}'\mathbf{V}^{-1}\mathbf{X}| + (N_T - p) \ln(2\pi)$$

The equivalent individual subject form is

$$-2L_{REML}(\boldsymbol{\beta}, \mathbf{G}, \mathbf{R}) = \sum_{i=1}^N [\ln|\mathbf{V}_i| + \mathbf{e}'_i\mathbf{V}_i^{-1}\mathbf{e}_i] + \ln \left| \sum_{i=1}^N \mathbf{X}'_i\mathbf{V}_i^{-1}\mathbf{X}_i \right| + (N_T - p) \ln(2\pi)$$

where, again, N_T is the total number of observations, or

$$N_T = \sum_{i=1}^N n_i$$

and p is the number of columns in \mathbf{X} or \mathbf{X}_i .

Estimating and Testing Fixed Effects Parameters

The estimation phase in the analysis of a mixed model produces variance and covariance parameter estimates of the elements of \mathbf{G} and \mathbf{R} , giving $\hat{\mathbf{R}}$ and $\hat{\mathbf{G}}$, and hence, $\hat{\mathbf{V}}$. The REML and ML solutions for $\hat{\boldsymbol{\beta}}$ are given by

$$\hat{\boldsymbol{\beta}} = (\mathbf{X}'\hat{\mathbf{V}}^{-1}\mathbf{X})^{-1}\mathbf{X}'\hat{\mathbf{V}}^{-1}\mathbf{y}$$

with estimated variance-covariance

$$\hat{\boldsymbol{\Sigma}} = \text{var}(\hat{\boldsymbol{\beta}}) = (\mathbf{X}'\hat{\mathbf{V}}^{-1}\mathbf{X})^{-1}$$

See, for example, Brown and Prescott (2006), Muller and Stewart (2006), or Demidenko (2004) for more details of the estimating equations.

Hypothesis tests and confidence intervals for $\boldsymbol{\beta}$ are formed using a linear combination matrix (or vector) \mathbf{L} . Although you don't have to specify \mathbf{L} , it is important that you understand how its function.

L Matrix Details

L matrices specify linear combinations of β corresponding to means or hypothesis tests of interest. Essentially, the **L** matrix defines the mean or test. The number of columns in each **L** matrix is the same as the number of elements of β . For estimating a particular mean, the **L** matrix consists of a single row. For hypothesis tests, the number of rows of **L** varies according to the test. Below are some examples of **L** matrices that arise in common analyses:

L Matrix for Testing a Single Factor (Food with 4 levels) in a Single-Factor Model

No.	Effect	Food	L1	L2	L3
1	Intercept				
2	Food	HighIron	1.0000	1.0000	1.0000
3	Food	LowIron	-1.0000		
4	Food	None		-1.0000	
5	Food	Salicyl			-1.0000

L Matrix for a Single Mean (LowIron) of a Single Factor (4 levels) in a Single-Factor Model

No.	Effect	Food	L1
1	Intercept		1.0000
2	Food	HighIron	
3	Food	LowIron	1.0000
4	Food	None	
5	Food	Salicyl	

L Matrix for Testing a Single Factor (Drug – 3 levels) in a Two-Factor Model with Interaction

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	Drug*Time	Kerlosin	0.5	0.1667	0.1667
12	Drug*Time	Kerlosin	1	0.1667	0.1667
13	Drug*Time	Kerlosin	1.5	0.1667	0.1667
14	Drug*Time	Kerlosin	2	0.1667	0.1667
15	Drug*Time	Kerlosin	2.5	0.1667	0.1667
16	Drug*Time	Kerlosin	3	0.1667	0.1667
17	Drug*Time	Laposec	0.5	-0.1667	
18	Drug*Time	Laposec	1	-0.1667	

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19	Drug*Time	Laposec	1.5	-0.1667	
20	Drug*Time	Laposec	2	-0.1667	
21	Drug*Time	Laposec	2.5	-0.1667	
22	Drug*Time	Laposec	3	-0.1667	
23	Drug*Time	Placebo	0.5		-0.1667
24	Drug*Time	Placebo	1		-0.1667
25	Drug*Time	Placebo	1.5		-0.1667
26	Drug*Time	Placebo	2		-0.1667
27	Drug*Time	Placebo	2.5		-0.1667
28	Drug*Time	Placebo	3		-0.1667

Kenward and Roger Fixed Effects Hypothesis Tests

Hypothesis tests have the general form

$$H_0: \mathbf{L}\boldsymbol{\beta} = \mathbf{0}$$

where \mathbf{L} is a linear contrast matrix of rank h corresponding to the desired comparisons to be made in the hypothesis test. Let d be the denominator degrees of freedom and q be the number of variance-covariance parameters, which is the dimension of \mathbf{W} (defined below).

The Kenward and Roger (1997) test statistic for testing H_0 is currently the most recommended method of specifying the F-ratio and its degrees of freedom. The F-ratio is

$$F_{h,d} = \frac{\lambda}{h} \hat{\boldsymbol{\beta}}' \mathbf{L}' (\mathbf{L}\mathbf{C}^* \mathbf{L}')^{-1} \mathbf{L} \hat{\boldsymbol{\beta}}$$

where

$$\mathbf{C}^* = \mathbf{C} + 2\mathbf{C} \left\{ \sum_{r=1}^q \sum_{s=1}^q \mathbf{W}_{rs} \left(\mathbf{Q}_{rs} - \mathbf{P}_r \mathbf{C} \mathbf{P}_s - \frac{1}{4} \mathbf{S}_{rs} \right) \right\} \mathbf{C}$$

$$\mathbf{C} = (\mathbf{X}' \mathbf{V}^{-1} \mathbf{X})^{-1}$$

$$\mathbf{Q}_{rs} = \mathbf{X}' \mathbf{V}^{-1} \dot{\mathbf{V}}_r \mathbf{V}^{-1} \dot{\mathbf{V}}_s \mathbf{V}^{-1} \mathbf{X} = \sum_{i=1}^N \mathbf{X}_i' \mathbf{V}_i^{-1} \dot{\mathbf{V}}_{ri} \mathbf{V}_i^{-1} \dot{\mathbf{V}}_{si} \mathbf{V}_i^{-1} \mathbf{X}_i$$

$$\mathbf{P}_r = -\mathbf{X}' \mathbf{V}^{-1} \dot{\mathbf{V}}_r \mathbf{V}^{-1} \mathbf{X} = -\sum_{i=1}^N \mathbf{X}_i' \mathbf{V}_i^{-1} \dot{\mathbf{V}}_{ri} \mathbf{V}_i^{-1} \mathbf{X}_i$$

$$\mathbf{S}_{rs} = \mathbf{X}' \mathbf{V}^{-1} \ddot{\mathbf{V}}_{rs} \mathbf{V}^{-1} \mathbf{X} = \sum_{i=1}^N \mathbf{X}_i' \mathbf{V}_i^{-1} \ddot{\mathbf{V}}_{rsi} \mathbf{V}_i^{-1} \mathbf{X}_i$$

$$\mathbf{W} = \mathbf{H}^{-1}$$

$$\{\mathbf{H}\}_{rs} = \{\text{Hessian}\}_{rs}$$

$$\dot{V}_r = \frac{\partial \mathbf{V}}{\partial \sigma_r}$$

$$\dot{V}_{rs} = \frac{\partial^2 \mathbf{V}}{\partial \sigma_r \partial \sigma_s}$$

$$\mathbf{T} = \mathbf{L}'(\mathbf{LCL}')^{-1}\mathbf{L}$$

$$a_1 = \sum_{r=1}^q \sum_{s=1}^q \mathbf{W}_{rs} \text{tr}(\mathbf{TCP}_r \mathbf{C}) \text{tr}(\mathbf{TCP}_s \mathbf{C}), \quad a_2 = \sum_{r=1}^q \sum_{s=1}^q \mathbf{W}_{rs} \text{tr}(\mathbf{TCP}_r \mathbf{C} \mathbf{TCP}_s \mathbf{C})$$

$$a_3 = \frac{a_1 + 6a_2}{2h}, \quad e = \left(1 - \frac{a_2}{h}\right)^{-1}, \quad v = \frac{2}{h} \left\{ \frac{1 + c_1 a_3}{(1 - c_2 a_3)^2 (1 - c_3 a_3)} \right\}$$

$$c_1 = \frac{g}{3h + 2(1 - g)}, \quad c_2 = \frac{h - g}{3h + 2(1 - g)}, \quad c_3 = \frac{h + 2 - g}{3h + 2(1 - g)}, \quad c_4 = \frac{v}{2e^2}$$

$$g = \frac{(h + 1)a_1 - (h + 4)a_2}{(h + 2)a_2}$$

$$d = 4 + \frac{h + 2}{c_4 h - 1}, \quad \lambda = \frac{d}{e(d - 2)}$$

Solution Algorithms

Methods for Finding Likelihood Solutions (Newton-Raphson, Fisher Scoring, MIVQUE, and Differential Evolution)

There are four techniques in the Mixed Models procedure for determining the maximum likelihood or restricted maximum likelihood solution (optimum): Newton-Raphson, Fisher Scoring, MIVQUE, and Differential Evolution.

The general steps for the Newton-Raphson, Fisher Scoring, and Differential Evolution techniques are (let θ be the overall covariance parameter vector):

1. Roughly estimate θ according to the specified structure for each.
2. Evaluate the likelihood of the model given the data and the estimates of θ .
3. Improve upon the estimates of θ using a search algorithm. (Improvement is defined as an increase in likelihood.)
4. Iterate until maximum likelihood is reached, according to some convergence criterion.
5. Use the final θ estimates to estimate β .

Newton-Raphson and Fisher Scoring

The differences in the techniques revolve around the initial estimates in Step 1, and the improvements in estimates made in Step 3. For the Newton-Raphson and Fisher Scoring techniques, Step 3 occurs as follows:

- 3a. With the estimated θ , compute the gradient vector \mathbf{g} , and the Hessian matrix \mathbf{H} .
- 3b. Compute $\mathbf{d} = -\mathbf{H}^{-1}\mathbf{g}$.
- 3c. Let $\lambda = 1$.
- 3d. Compute new estimates for θ , iteratively, using $\theta_i = \theta_{i-1} + \lambda\mathbf{d}$.
- 3e. If θ_i is a valid set of covariance parameters and improves the likelihood, continue to 3f. Otherwise, reduce λ by half and return to Step 3d.
- 3f. Check for convergence. If the convergence criteria (small change in $-2\log$ -likelihood) are met, stop. If the convergence criteria are not met, go back to Step 3a.

The gradient vector \mathbf{g} , and the Hessian matrix \mathbf{H} , used for the Newton-Raphson and Fisher Scoring techniques for solving the REML equations are shown in the following table:

REML Gradient (g) and Hessian (H)

Technique	Gradient (g)	Hessian (H)
Newton-Raphson	$\mathbf{g}_1 + \mathbf{g}_2 + \mathbf{g}_3$	$\mathbf{H}_1 + \mathbf{H}_2 + \mathbf{H}_3$
Fisher Scoring	$\mathbf{g}_1 + \mathbf{g}_2 + \mathbf{g}_3$	$-\mathbf{H}_1 + \mathbf{H}_3$

The gradient vector \mathbf{g} , and the Hessian matrix \mathbf{H} , used for the Newton-Raphson and Fisher Scoring techniques for solving the ML equations are shown in the following table:

ML Gradient (g) and Hessian (H)

Technique	Gradient (g)	Hessian (H)
Newton-Raphson	$\mathbf{g}_1 + \mathbf{g}_2$	$\mathbf{H}_1 + \mathbf{H}_2$
Fisher Scoring	$\mathbf{g}_1 + \mathbf{g}_2$	$-\mathbf{H}_1$

where $\mathbf{g}_1, \mathbf{g}_2, \mathbf{g}_3, \mathbf{H}_1, \mathbf{H}_2,$ and \mathbf{H}_3 are defined as in Wolfinger, Tobias, and Sall (1994).

Definitons

$$\dot{\mathbf{V}}_{ri} = \frac{\partial \mathbf{V}_i}{\partial \sigma_r}, \quad \ddot{\mathbf{V}}_{rsi} = \frac{\partial^2 \mathbf{V}_i}{\partial \sigma_r \partial \sigma_s}, \quad \mathbf{e}_i = \mathbf{y}_i - \mathbf{X}_i\boldsymbol{\beta}, \quad \mathbf{A}_i = \mathbf{X}'_i\mathbf{V}_i^{-1}\mathbf{X}_i, \quad \mathbf{A} = \sum_{i=1}^N \mathbf{X}'_i\mathbf{V}_i^{-1}\mathbf{X}_i = \sum_{i=1}^N \mathbf{A}_i, \quad \mathbf{C} = \mathbf{A}^{-1},$$

$$\dot{\mathbf{A}}_r = \sum \mathbf{X}'_i \left(\frac{\partial \mathbf{V}_i^{-1}}{\partial \sigma_r} \right) \mathbf{X}_i = - \sum \mathbf{X}'_i (\mathbf{V}_i^{-1} \dot{\mathbf{V}}_{ri} \mathbf{V}_i^{-1}) \mathbf{X}_i = -\mathbf{P}_r$$

$$\mathbf{X}^* = \mathbf{X}\mathbf{K}, \quad \mathbf{K}\mathbf{K}' = (\mathbf{X}'\mathbf{V}^{-1}\mathbf{X})^{-1}$$

Likelihoods

$$\mathbf{l}_1 = \frac{1}{2} \sum_{i=1}^N \ln|\mathbf{V}_i|, \quad \mathbf{l}_2 = \frac{1}{2} \sum_{i=1}^N \mathbf{e}_i' \mathbf{V}_i^{-1} \mathbf{e}_i, \quad \mathbf{l}_3 = \frac{1}{2} \ln \left| \sum_{i=1}^N \mathbf{X}_i' \mathbf{V}_i^{-1} \mathbf{X}_i \right| = \frac{1}{2} \ln \left| \sum_{i=1}^N \mathbf{A}_i \right| = \frac{1}{2} \ln|\mathbf{A}|$$

First Derivatives

$$\mathbf{g}_{1r} = \frac{\partial \mathbf{l}_1}{\partial \boldsymbol{\sigma}_r} = \frac{1}{2} \sum_{i=1}^N \text{tr}(\mathbf{V}_i^{-1} \dot{\mathbf{V}}_{ri})$$

$$\mathbf{g}_{2r} = \frac{\partial \mathbf{l}_2}{\partial \boldsymbol{\sigma}_r} = -\frac{1}{2} \sum_{i=1}^N \mathbf{e}_i' \mathbf{V}_i^{-1} \dot{\mathbf{V}}_{ri} \mathbf{V}_i^{-1} \mathbf{e}_i$$

$$\mathbf{g}_{3r} = \frac{\partial \mathbf{l}_3}{\partial \boldsymbol{\sigma}_r} = -\frac{1}{2} \text{tr}[\mathbf{H}_3^r]$$

Second Derivatives

$$\mathbf{H}_{1rs} = \frac{\partial^2 \mathbf{l}_1}{\partial \boldsymbol{\sigma}_r \partial \boldsymbol{\sigma}_s} = -\frac{1}{2} \sum_{i=1}^N \{ \text{tr}(\mathbf{V}_i^{-1} \dot{\mathbf{V}}_{rsi}) - \text{tr}(\mathbf{V}_i^{-1} \dot{\mathbf{V}}_{ri} \mathbf{V}_i^{-1} \dot{\mathbf{V}}_{si}) \}$$

$$\mathbf{H}_{2rs} = \frac{\partial^2 \mathbf{l}_2}{\partial \boldsymbol{\sigma}_r \partial \boldsymbol{\sigma}_s} = \frac{1}{2} (\mathbf{H}_2^{rs} - 2\mathbf{H}_2^{r'} \mathbf{H}_2^s)$$

$$\mathbf{H}_{3rs} = \frac{\partial^2 \mathbf{l}_3}{\partial \boldsymbol{\sigma}_r \partial \boldsymbol{\sigma}_s} = \frac{1}{2} \text{tr}(\mathbf{H}_3^{rs} - \mathbf{H}_3^r \mathbf{H}_3^s)$$

See Wolfinger, Tobias, and Sall (1994), page 1299, for details.

MIVQUE

The MIVQUE estimates of $\boldsymbol{\theta}$ in REML estimation are found by solving

$$-(\mathbf{H}_1 + \mathbf{H}_3)\boldsymbol{\theta} = -\mathbf{g}_2.$$

The MIVQUE estimates of $\boldsymbol{\theta}$ in ML estimation are found by solving

$$-\mathbf{H}_1\boldsymbol{\theta} = -\mathbf{g}_2.$$

See Wolfinger, Tobias, and Sall (1994), page 1306, for details.

Differential Evolution

The differential evolution techniques used in this procedure for the ML and REML optimization are described in Price, Storn, and Lampinen (2005). This algorithm is very slow, but it is also very robust. As it stands now, it is too slow to be used. However, as computers become faster, this algorithm will become more viable.

Specifying the Minimum Detectable Difference

The four main parameters of a power analysis are the sample size, the effect size, the significance level, and the power level. Other extraneous parameters, such as the variance, must also be specified. This section describes the specification of the effect size, or minimum detectable difference (MDD) as we choose to call it in this chapter.

Power is defined as the probability of rejecting the null hypothesis of zero difference when the actual difference is a given amount. As the size of the actual difference increases, so does the power. The MDD (or minimum effect size) is the smallest difference among the population means that will be detected by an experiment at the specified settings of the other parameters.

Typically, a longitudinal design includes a between-subjects factor, a within-subject factor, and their interaction. A MDD must be specified for each. As the number of factors grows, the number of interactions grows, and the number of MDD's that must be specified also grows. It becomes crucial that you specify these values in a meaningful and accurate way.

In the Repeated Measures module, **PASS** only requires the standard deviation of the group means. Unfortunately, this is a quantity that researchers have very little experience with. It seldom appears on any of the standard reports that are produced by commercial software. It is seldom present in the written reports of analyses. A different method is used to specify the MDD in **PASS**.

In this routine, the MDD is specified as the difference between the smallest and largest effects. For example, suppose that a factor has three levels with means 10, 15, 18. The detectable difference is $18 - 10 = 8$. This is a simply quantity that is easy to interpret.

The Effect Pattern for Factors

When there are more than two means, the minimum detectable difference does not uniquely define a set of means that can be simulated. For example, the following sets of means all have identical MDD's, but the means themselves are quite different: (10, 12, 18), (10, 14, 18), and (10, 18, 18). The following method for defining the pattern is quite informative:

1. Set the first (low) value to -0.5.
2. Set the last (high) value to 0.5.
3. Set each value in between to $(\text{Mean} - \text{Min}) / \text{MDD} - 0.5$.

Mixed Models (Simulation)

Using these steps, the three sets of means may be reduced to MDD and a pattern as follows:

Original	MDD	Pattern	MDD x Pattern
10, 12, 18	8	-0.5, -0.25, 0.5	-4, -2, 4
10, 14, 18	8	-0.5, 0.0, 0.5	-4, 0, 4
10, 18, 18	8	-0.5, 0.5, 0.5	-4, 4, 4

Thus, each set of means can be easily reduced to two components: the MDD and a pattern. This is the method that **PASS** uses to supply the sets of means. Using this method, it is easy to compare various sizes of means. You simply enter different values for the MDD, keeping the pattern the same.

The Effect Pattern for Interactions

Specifying the structure of the interactions is a little more problematic. Often, you are not interested in the interaction. When the interaction is of interest, you may have only a vague idea of its structure. Part of your analysis will be to investigate the effect of the interaction, with little or no knowledge of its pattern beforehand.

Specifying the MDD for the interaction is somewhat intuitive. The MDD defines the largest difference among the interaction effects. A difficulty still arises in that there is a very large number of possible patterns, many of which are useful. For planning purposes, we have decided to use a standard pattern in **PASS**. The interaction pattern used in *PASS* is defined as the Kronecker product of the factor patterns that make up the interaction, scaled so that the largest value is 0.5 and the smallest value is -0.5.

Example

Suppose that a two-factor interaction is made up of a three-level factor A with a pattern of -0.5, 0, 0.5 and a two-level factor B with a pattern of -0.5, 0.5. The interaction pattern would be found as follows. The Kronecker product of these two patterns is 0.25, -0.25, 0.0, 0.0, -0.25, 0.25. Rescaling so that the minimum is -0.5 and the maximum is 0.5 is achieved by doubling the values. The final interaction pattern is 0.5, -0.5, 0.0, 0.0, -0.5, 0.5. This pattern compares the difference due to factor B across the levels of factor A.

Suppose the MDD for A is set to 8, the MDD for B is set to 15, and the MDD for AB is set to 10. Suppose the overall mean is 12. The six cell means would be found by adding the individual effects as follows

Term	A1B1	A1B2	A2B1	A2B2	A3B1	A3B2
A	-4.0	-4.0	0.0	0.0	4.0	4.0
B	-7.5	7.5	-7.5	7.5	-7.5	7.5
AB	5.0	-5.0	0.0	0.0	-5.0	5.0
Total	-6.5	-1.5	-7.5	7.5	-8.5	16.5
Overall	12.0	12.0	12.0	12.0	12.0	12.0
Cell Mean	5.5	10.5	4.5	19.5	3.5	28.5

The cell means are then used to simulate the data for power and sample size calculation. This set of cell means has the MDD's and patterns specified.

Specifying the Simulated Variance-Covariance Matrix

As stated above, the variance of \mathbf{y} is $\mathbf{V} = \mathbf{ZGZ}' + \mathbf{R}$. In this PASS Mixed Models module, \mathbf{ZGZ}' is called the *random component* and \mathbf{R} is called the *residual component*. Since \mathbf{V} is block-diagonal (with one block for each subject), it is specified by specifying the random and residual components for one subject and repeating those components for each subject.

ZGZ'

When the random component is included, the model is called a *random effects model*. For a design with four time points, the structure of \mathbf{ZGZ}' is

$$\begin{pmatrix} g & g & g & g \\ g & g & g & g \\ g & g & g & g \\ g & g & g & g \end{pmatrix} = g[\mathbf{J}_4]$$

This structure only requires a single value: g .

R

The structure of \mathbf{R} is quite flexible. Since it is a variance-covariance matrix, the only stipulation is that it must be non-negative definite. Possible choices for \mathbf{R} when the variance is constant are

Diagonal

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

Constant (Compound Symetric)

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

AR(1)

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

List

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

Mixed Models (Simulation)

Possible choices for \mathbf{R} when the variance is allowed to vary are

Diagonal

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

Constant

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

AR(1)

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

List

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

ZGZ' + R

When **ZGZ'** is included and \mathbf{R} is set to diagonal as recommended, the value of \mathbf{V} becomes

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

This is the compound symmetric pattern that is assumed in the repeated measures analysis of variance (RMANOVA). This model is often used to compare LMM with RMANOVA.

Power Calculations using Computer Simulation

Computer simulation allows us to estimate the power that is actually achieved by a test procedure in situations such as LMM that are not mathematically tractable. Computer simulation was once limited to mainframe computers. But, in recent years, as computer speeds have increased, simulation studies can be completed on desktop and laptop computers in a reasonable period of time. The simulations can still be time consuming, so we have proposed some steps below that will significantly shorten the time needed to obtain answers.

The Simulation

It is important that you understand how the simulation is setup. There are three main tabs (panels or windows) that contain parameters that you will need to set. These are the Data tab, the Covariance tab, and the Fitted Model tab.

Data Tab

The Data tab contains all the parameters associated with the sample size, the effect size, and the significance level (α). The effect size parameters define the experimental design.

Covariance Tab

The Covariance tab specifies the parameters used to define the covariance of the data that is generated. Note that the covariance of the data you generate does not have to match the covariance model that you use to fit the data. In fact, since you seldom know even the structure of the true covariance matrix, it is more realistic to generate data using one type of covariance matrix and then fit the generated data with a different covariance structure.

Fitted Model Tab

The Fitted Model tab specifies the covariance matrix that is actually fit to your data. As stated above, the model does not need to coincide with the model used to generate the data. It may be more realistic if it does not.

Steps in Conducting a Simulation Analysis

Simulation Steps

The steps to a simulation study are

1. Specify the design that will be studied. Enter the sample size, MDD's, and variance covariance matrix. Specify the covariance matrix of the model that is fitted to the data.
2. Generate random samples from the design specified. Calculate the F-tests from the simulated data and determine if the null hypothesis is accepted or rejected. Tabulate the number of rejections and use this to calculate the test's power.

Mixed Models (Simulation)

3. Repeat step 2 several hundred or more times, tabulating the number of times the simulated data leads to a rejection of the null hypothesis. The power is the proportion of simulated samples in step 2 that lead to rejection.
4. Additionally, you can run a separate simulation to determine if the significance level (alpha) of the F-test matches the significance level you have selected. This is done by setting the MDD's to zero.

Saving Simulation Time

Simulations for large models or large sample sizes take several hours to run. The simulation time can be reduced by running the simulation in two steps.

1. Specify a reasonable range for the group sample sizes. For example, you may want to try group sample sizes of 5, 10, 30, 80, and 120. Set the number of simulations to 300 or 500. Although these are not a large enough simulation size to give you definitive results, you can study the confidence intervals for power provided in the reports and plots to determine a reduced range of sample sizes.
2. Reduce the range of the sample size values, increase the number of simulations to 1000 or 2000, and rerun the simulations. These simulations may run for a while, so be prepared for running times of several minutes or hours. The power values that come from these simulations should be very precise.

Generating the Random Numbers

The simulation proceeds by generating the normal random deviates in groups that are the size of the number of time points. That is, a set of normals are generated for a single subject. This set of normals is transformed into a set of normals having the desired covariance structure using the commonly known technique of multiplying the generated unit normals by the square root of the variance-covariance matrix. The square root is taken using the Choleski decompositions. The resulting response vector matrix has the desired covariance matrix.

Symbolically, suppose there are t time points and further suppose that the desired variance-covariance matrix of the data to be simulated is given by \mathbf{V} . Find a matrix \mathbf{W} such that $\mathbf{V} = \mathbf{W}\mathbf{W}'$. Note that, by construction, \mathbf{W} is lower triangular. If we generate t unit random normal deviates and place them in a vector \mathbf{z} , the vector $\mathbf{y} = \mathbf{W}\mathbf{z}$ has variance-covariance matrix $\mathbf{W}\mathbf{W}' = \mathbf{V}$. Finally, the appropriate cell mean (based on the minimum detectable differences) is added to the \mathbf{y} to obtain the simulation data with the desired properties. Once all of the data required for a complete experiment is generated, the mixed model is solved using the mixed model algorithm coded for **NCSS's** mixed model procedure.

Example 1 – Power of a Two Factor Repeated Measures Design

Researchers are planning a study of the impact of a drug on heart rate. They want to evaluate the differences in heart rate among two age groups: 20-55 and over 55. Their experimental protocol calls for a baseline heart rate measurement, followed by administration of a certain level of the drug, followed by an additional measurement 30 minutes later. They want to be able to detect a 10% difference in heart rate among the age groups. They want to detect 5% difference in heart rate within an individual across time. They decide the experiment should detect interaction effects of the same magnitude as the within-subject factor. From a heart rate of 93, a 10% reduction gives 84, a difference of 9. Similarly, a 5% reduction within a subject would result in a heart rate of 88, a difference of 5.

They plan to analyze the data using a random effects model, setting the significance level at 0.05. Similar studies have found an average heart rate of 93, a subject variance of 11, and a residual variance of 11.

They want to look at the power for group sizes of 3, 5, 7, and 9.

Setup

If the procedure window is not already open, use the PASS Home window to open it. The parameters 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.

Design: Effect Size Tab

n (Subjects Per Group)	3 5 7 9
= n's	Checked
Alpha.....	0.05
Simulations	100
Random Seed.....	5988945 (for Reproducibility)
Specify Effects Using.....	Effect Patterns, etc.
Between Factor A Levels.....	2
Between Factor A Effects Pattern.....	Linear Up
Between Factor A Detectable Difference.....	9
Within Factor C Levels.....	2
Within Factor C Effects Pattern.....	Linear Up
Within Factor C Detectable Difference.....	5
AC Interaction	Checked
AC Interaction Detectable Difference.....	5
Baseline Mean	93

Mixed Models (Simulation)

Design: Covariance Tab

Grouping Factor..... **None**
 Include G..... **Checked**
 g (Subject σ^2)..... **11**
 Specify R Using..... **Variiances Only**
 Times..... **STEP 0 1**
 Pattern..... **Constant in σ^2 for R**
 σ^2 for R..... **11**

Fitted Model Tab

G Estimation..... **G (Random Effects for Subjects)**
 Groups..... **None**
 R Estimation..... **Diagonal**
 Groups..... **None**
 Force Positive Covariances..... **Unchecked**
 Likelihood Type..... **REML (Recommended)**
 Solution Method..... **Newton-Raphson**

Output

Click the Calculate button to perform the calculations and generate the following output.

Power Report for Each Design

Power by Design

Model Term	Power	95% Confidence Interval Limits for Power		N(1)	N	Minimum Detectable Difference	Alpha	Number of Simulation Samples	Factor Pattern
		Lower	Upper						
A (2)	0.52	0.41779	0.62099	3	6	9	0.05	100	Linear Up
C (2)	0.47	0.36941	0.57242	3	6	5	0.05	100	Linear Up
AC	0.52	0.41779	0.62099	3	6	5	0.05	100	
A (2)	0.88	0.79976	0.93643	5	10	9	0.05	100	Linear Up
C (2)	0.89	0.81170	0.94379	5	10	5	0.05	100	Linear Up
AC	0.80	0.70816	0.87334	5	10	5	0.05	100	
A (2)	0.99	0.94554	0.99975	7	14	9	0.05	100	Linear Up
C (2)	0.90	0.82378	0.95100	7	14	5	0.05	100	Linear Up
AC	0.97	0.91482	0.99377	7	14	5	0.05	100	
A (2)	0.99	0.94554	0.99975	9	18	9	0.05	100	Linear Up
C (2)	0.99	0.94554	0.99975	9	18	5	0.05	100	Linear Up
AC	0.98	0.92962	0.99757	9	18	5	0.05	100	

Mixed Models (Simulation)

Simulation Time	3.65 seconds
Random Seed	5988945 (User-Entered)
Power	The probability of rejecting a false null hypothesis. It was determined by simulation.
Lower and Upper 95% C.L. for Power	The lower and upper confidence limits of a 95% confidence interval for the power. This is an exact confidence interval based solely on the binomial distribution.
N(1)	The sample size of the first group.
N	The total sample size found by summing the individual group sample sizes.
Minimum Detectable Difference	The effect size that is just detected by this design at the power probability specified. Note that this is a set value that represents how accuracy of the design and is not the difference that is actually anticipated.
Alpha	The probability of rejecting a true null hypothesis.
Number of Simulation Samples	The number of simulation samples (iterations) that converged. Those samples that did not converge are omitted from this count.
Factor Pattern	The name of the pattern that was used to generate cell means that are simulated.

This report gives the simulated power for each term in the design for each value of N , one design at a time. It is useful when you want to compare the powers of the terms in the design at a specific sample size.

The definitions of each of the columns of the report are as follows.

Model Term

This column contains the identifying label of the term. The number of levels for a factor is given in parentheses.

Power

This is the simulated power for the term.

Lower and Upper 95% Confidence Interval Limits for Power

These are the lower and upper confidence limits of a 95% confidence interval for the simulated power. These are exact, distribution-free, confidence limits based on the binomial distribution.

N(1)

The value of the number of subjects per group.

N

The value of N is the total number of subjects in the study.

Minimum Detectable Difference

This is the value of the minimum detectable difference that was entered (or calculated) for this term. This is a measure of the magnitude of the effect size.

Alpha

Alpha is the significance level of the F-test for this term.

Number of Simulation Samples

This is the number of simulation samples for which the mixed model algorithm converged.

Factor Pattern

This is the type of factor pattern that was used with the detectable difference to form the group means.

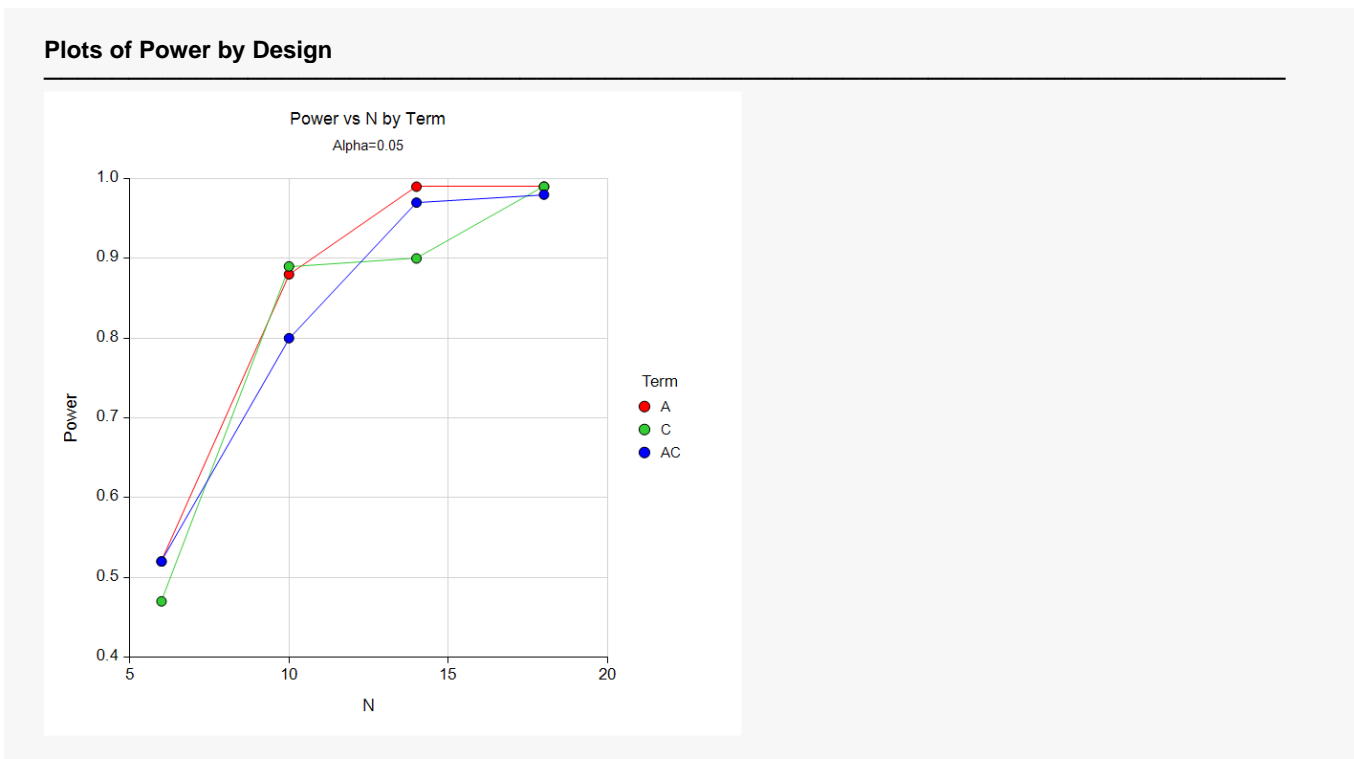
Term Reports

Power by Term									
Model Term	Power	95% Confidence Interval Limits for Power		N(1)	N	Minimum Detectable Difference	Alpha	Number of Simulation Samples	Factor Pattern
		Lower	Upper						
A (2)	0.52	0.41779	0.62099	3	6	9	0.05	100	Linear Up
A (2)	0.88	0.79976	0.93643	5	10	9	0.05	100	Linear Up
A (2)	0.99	0.94554	0.99975	7	14	9	0.05	100	Linear Up
A (2)	0.99	0.94554	0.99975	9	18	9	0.05	100	Linear Up
C (2)	0.47	0.36941	0.57242	3	6	5	0.05	100	Linear Up
C (2)	0.89	0.81170	0.94379	5	10	5	0.05	100	Linear Up
C (2)	0.90	0.82378	0.95100	7	14	5	0.05	100	Linear Up
C (2)	0.99	0.94554	0.99975	9	18	5	0.05	100	Linear Up
AC	0.52	0.41779	0.62099	3	6	5	0.05	100	
AC	0.80	0.70816	0.87334	5	10	5	0.05	100	
AC	0.97	0.91482	0.99377	7	14	5	0.05	100	
AC	0.98	0.92962	0.99757	9	18	5	0.05	100	

Simulation Time 2.53 seconds
Random Seed 5988945 (User-Entered)

This report provides the same information as the previous Design report, so the item definitions are the same. It is sorted by term, to make comparison of powers across various sample sizes easier.

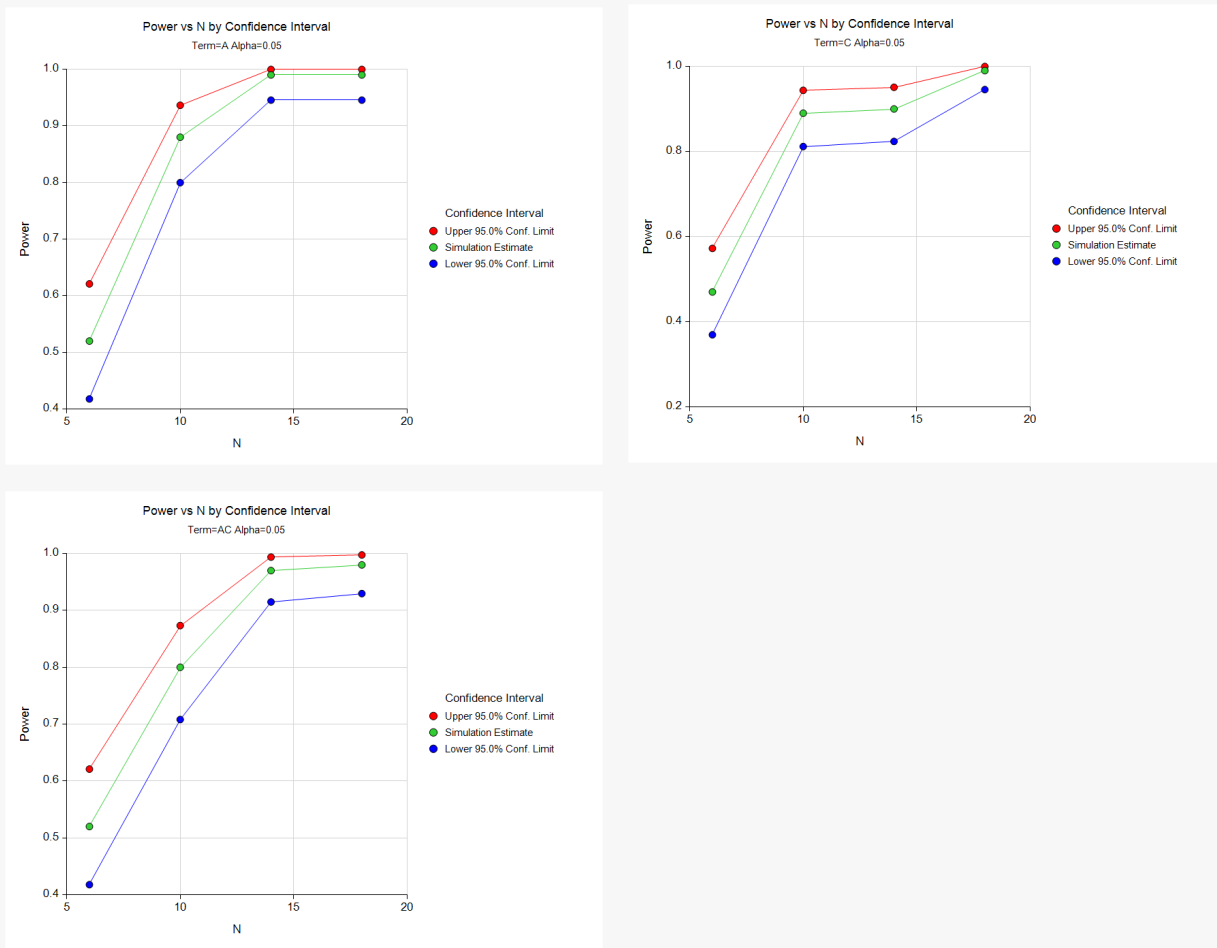
Whole Design Power Plots



This plot shows the power values on the vertical axis and the sample sizes across the horizontal axis. The plot symbols represent different model terms.

Confidence Interval Power Plots

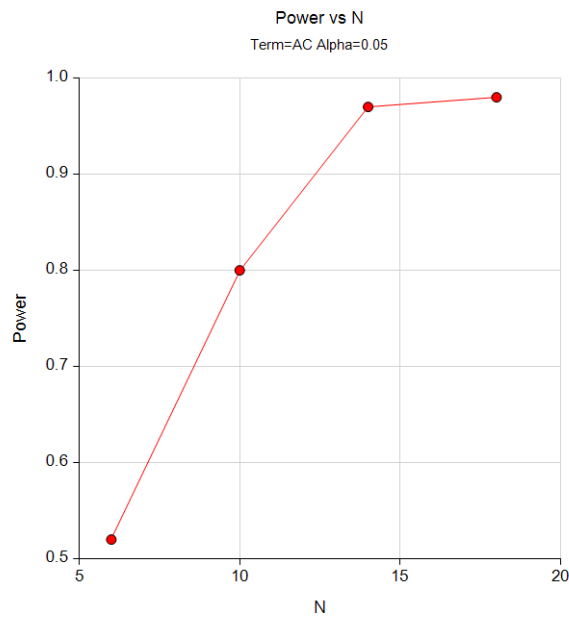
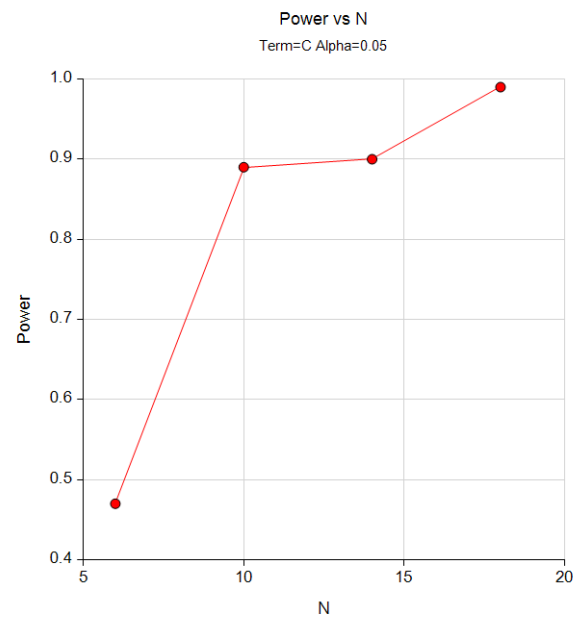
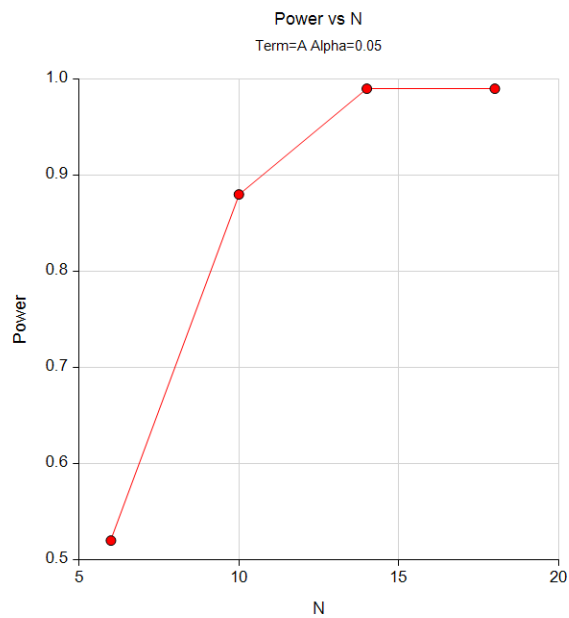
Plots of Confidence Interval Power



These plots show the confidence limits for the power for each term across the various sample sizes. Using these plots, you can quickly see for which sample sizes you might want to run a more precise (larger) simulation.

Individual Term Power Plots

Plots of Individual Term Power



These plots show the power for each term across the various sample sizes without including the confidence limits.

Detectable Differences for Each Term

Detectable Differences for Each Term

Combination Number	A	C	AC
1	9	5	5

This report shows the values of the Minimum Detectable Differences for each term. It is used to identify each combination of parameter values when you have entered multiple detectable differences for more than one term.

This report shows the values of the Minimum Detectable Differences for each term. It is particularly useful to identify each combination when you enter several different values for various terms, so that there are several combinations.

Effect Pattern Section

Effect Pattern Section

A		C		AC	
Levels	Value	Levels	Value	Levels	Value
1	-0.5	1	-0.5	1,1	0.5
2	0.5	2	0.5	1,2	-0.5
				2,1	-0.5
				2,2	0.5

This report shows the patterns of the effect sizes of each of the active terms in the model. These values are multiplied by the corresponding minimum detectable differences to form the effect sizes associated with each term.

This report shows the patterns of each of the active terms in the model. These values are multiplied by the corresponding minimum detectable differences to form the effects associated with each term

Expanded Effect Pattern Section

Expanded Effect Pattern Section

A		C		AC	
Levels	Value	Levels	Value	Levels	Value
1,1	-0.5	1,1	-0.5	1,1	0.5
1,2	-0.5	1,2	0.5	1,2	-0.5
2,1	0.5	2,1	-0.5	2,1	-0.5
2,2	0.5	2,2	0.5	2,2	0.5

This report shows the patterns of the effect sizes of each of the cells in the model. These values are multiplied by the corresponding minimum detectable difference and summed to form the cell means for each group in the design.

This report shows the effect patterns of each of the cells in the model. These values are multiplied by the corresponding minimum detectable difference and summed to form the cell means for each group in the design.

Hypothesized Means Matrix for Detectable Differences Combination 1

Hypothesized Means Matrix for Detectable Differences Combination 1

Factors	A1	A2
C1	88.5	92.5
C2	88.5	102.5

This report shows the hypothesized means matrix for each combination of detectable differences. The Hypothesized Means Matrix for Detectable Differences is created by multiplying the Detectable Differences for Each Term by the Expanded Effect Pattern Section values and summing them. Then the overall mean is added. The between factors are represented across the columns of the report and the within factors are represented down the rows.

This report shows hypothesized means matrix for each combination of detectable differences. Note that the between factors are represented across the columns of the report and the within factors are represented down its rows.

Variance-Covariance Matrix

Variance-Covariance Matrix of Y

Factors	C1	C2
C1	22	11
C2	11	22

This report shows the within-subject variance-covariance matrix, $V(Y)$. It is calculated using $ZGZ' + R$.

This report shows the variance-covariance matrix used to generate the data. You should check that they are correct.

Variance and Autocorrelations

Variations and Autocorrelations

Factors	C1	C2
C1	22.0	0.5
C2	0.5	22.0

This report shows the within-subject variances on the diagonal and the autocorrelations on the off diagonal.

This report shows the variances on the diagonal and the autocorrelations on the off diagonal. You should check that they are correct.

Example 2 – Repeated Measures - Validation using Brown and Prescott (2006)

Brown and Prescott (2006) pages 268-269 present the following example of determining a sample size for a repeated measures design that is analyzed using a linear mixed model. Note that this analytic procedure is provided in PASS as the procedure entitled *Inequality Test for Two Means in a Repeated Measures Design*. That procedure is sometimes called the *time-averaged difference*.

In this example, a group size of 31 is found to achieve 80% power when the residual variance is 76, the autocorrelation is 0.53, the minimum detectable difference of a single between-subject factor is 5, the number of repeated measurements is 4, and the significance level is 0.05.

In this example, because of the long running time, the number of simulation samples will be set to 100. You can increase this to 500 or 1000 to obtain greater precision.

For reproducibility, we'll use a random seed of 5326608.

Setup

If the procedure window is not already open, use the PASS Home window to open it. The parameters for this example are listed below and are stored in the **Example 2** settings file. To load these settings to the procedure window, click **Open Example Settings File** in the Help Center or File menu.

Design: Effect Size Tab

n (Subjects Per Group)	31
= n's	Checked
Alpha.....	0.05
Simulations	100
Random Seed.....	5326608 (for Reproducibility)
Specify Effects Using.....	Effect Patterns, etc.
Between Factor A Levels.....	2
Between Factor A Effects Pattern.....	Linear Up
Between Factor A Detectable Difference.....	5
Within Factor C Levels.....	4
Within Factor C Effects Pattern.....	Linear Up
Within Factor C Detectable Difference.....	5
AC Interaction	Unchecked
Baseline Mean	93

Mixed Models (Simulation)

Design: Covariance Tab

Grouping Factor..... **None**
 Include G..... **Unchecked**
 Specify R Using..... **Variations and Autocorrelations**
 Times..... **STEP 0 1**
 Pattern..... **Constant in σ^2 for R**
 σ^2 for R..... **76**
 Pattern..... **Constant in ρ**
 ρ **0.53**
 If Time >..... **100**
 Then $\rho =$ **0**

Fitted Model Tab

G Estimation..... **G (Random Effects for Subjects)**
 Groups..... **None**
 R Estimation..... **Diagonal**
 Groups..... **None**
 Force Positive Covariances..... **Unchecked**
 Likelihood Type..... **REML (Recommended)**
 Solution Method..... **Newton-Raphson**

Output

Click the Calculate button to perform the calculations and generate the following output.

Power by Design

Model Term	Power	95% Confidence Interval Limits for Power		N(1)	N	Minimum Detectable Difference	Alpha	Number of Simulation Samples	Factor Pattern
		Lower	Upper						
A (2)	0.8	0.70816	0.87334	31	62	5	0.05	100	Linear Up
C (4)	1.0	0.96378	1.00000	31	62	5	0.05	100	Linear Up

Simulation Time 3.90 seconds
 Random Seed 5326608 (User-Entered)

Note that for just 100 simulations, the power has come out equal to the actual value of 0.8 given by Brown and Prescott (2006). The confidence interval, 0.70816 to 0.87334, is wide and could be run with a larger number of simulations to obtain a more precise answer.

Example 3 – Validation using Repeated Measures ANOVA

For balanced designs, LMM and Repeated Measures ANOVA can be used to analyze the same data. Although they both produce F-tests, the values of the F-test are different for the two tests. It is instructive to compare the power of these competing procedures.

In this example, we will determine the power for group sizes of 3, 9, and 15 when the random effects (subject) variance is 2, the residual variance is 2, the minimum detectable differences of all three terms is 1.0, the number of repeated measurements is 2, and the significance level is 0.05. A random effects model will be fit. The number of simulation samples will be set to 500.

For reproducibility, we'll use a random seed of 5338912.

Setup

If the procedure window is not already open, use the PASS Home window to open it. The parameters for this example are listed below and are stored in the **Example 3** settings file. To load these settings to the procedure window, click **Open Example Settings File** in the Help Center or File menu.

Design: Effect Size Tab

n (Subjects Per Group)	3 9 15
= n's	Checked
Alpha	0.05
Simulations	500
Random Seed	5338912 (for Reproducibility)
Specify Effects Using	Effect Patterns, etc.
Between Factor A Levels	2
Between Factor A Effects Pattern	Linear Up
Between Factor A Detectable Difference	1
Within Factor C Levels	2
Within Factor C Effects Pattern	Linear Up
Within Factor C Detectable Difference	1
AC Interaction	Checked
AC Interaction Detectable Difference	1
Baseline Mean	0

Design: Covariance Tab

Grouping Factor	None
Include G	Checked
g (Subject σ^2)	2
Specify R Using	Variances Only
Times	STEP 0 1
Pattern	Constant in σ^2 for R
σ^2 for R	2

Mixed Models (Simulation)

Fitted Model Tab

G Estimation **G (Random Effects for Subjects)**
 Groups **None**
 R Estimation **Diagonal**
 Groups **None**
 Force Positive Covariances **Unchecked**
 Likelihood Type **REML (Recommended)**
 Solution Method **Newton-Raphson**

Output

Click the Calculate button to perform the calculations and generate the following output.

Power Report for Each Design

Power by Design

Model Term	Power	95% Confidence Interval Limits for Power		N(1)	N	Minimum Detectable Difference	Alpha	Number of Simulation Samples	Factor Pattern
		Lower	Upper						
A (2)	0.038	0.02303	0.05871	3	6	1	0.05	500	Linear Up
C (2)	0.176	0.14362	0.21227	3	6	1	0.05	500	Linear Up
AC	0.214	0.17883	0.25259	3	6	1	0.05	500	
A (2)	0.224	0.18818	0.26312	9	18	1	0.05	500	Linear Up
C (2)	0.482	0.43742	0.52679	9	18	1	0.05	500	Linear Up
AC	0.552	0.50721	0.59617	9	18	1	0.05	500	
A (2)	0.358	0.31593	0.40176	15	30	1	0.05	500	Linear Up
C (2)	0.752	0.71172	0.78927	15	30	1	0.05	500	Linear Up
AC	0.728	0.68672	0.76656	15	30	1	0.05	500	

Next, we will run this same design through the Repeated Measures Analysis procedure. To make it comparable, set both the between and within factors (B1 and W1) to have two levels each with σ set to 0.5. The variance-covariance matrix is set to *Constant σ and ρ* , with $\sigma = 2$ and $\rho = 0.5$.

The results of this run are presented next.

Power Report for Repeated Measures Analysis Procedure

Design Report

Solve For: Power

Term	Test	Power	Number of Subjects		Multiply Means by K	Standard Deviation of Effects σ_m	Standard Deviation σ	Effect Size σ_m / σ	Alpha
			Average Group n	Total N					
B1(2)	F	0.08588	3	6	1	0.5	1.73205	0.28868	0.05
W1(2)	F	0.15879	3	6	1	0.5	1.00000	0.50000	0.05
B1*W1	F	0.15879	3	6	1	0.5	1.00000	0.50000	0.05
B1(2)	F	0.21051	9	18	1	0.5	1.73205	0.28868	0.05
W1(2)	F	0.51336	9	18	1	0.5	1.00000	0.50000	0.05
B1*W1	F	0.51336	9	18	1	0.5	1.00000	0.50000	0.05
B1(2)	F	0.33277	15	30	1	0.5	1.73205	0.28868	0.05
W1(2)	F	0.75292	15	30	1	0.5	1.00000	0.50000	0.05
B1*W1	F	0.75292	15	30	1	0.5	1.00000	0.50000	0.05

The above results are summarized in the following table.

Comparing Linear Mixed Models and Repeated Measures Analysis Power

Power by Design

Model Term	LMM Power	95% Confidence Interval Limits for Power		RM ANOVA Power	N(1)
		Lower	Upper		
A (2)	0.038	0.02303	0.05871	0.08588	3
C (2)	0.176	0.14362	0.21227	0.15879	3
AC	0.214	0.17883	0.25259	0.15879	3
A (2)	0.224	0.18818	0.26312	0.21051	9
C (2)	0.482	0.43742	0.52679	0.51336	9
AC	0.552	0.50721	0.59617	0.51336	9
A (2)	0.358	0.31593	0.40176	0.33277	15
C (2)	0.752	0.71172	0.78927	0.75292	15
AC	0.728	0.68672	0.76656	0.75292	15

By studying the values in this table, we see that two procedures agree very well for group sample sizes of 9 and 15. However, when the group sample size is 3, the power using the Repeated Measures Analysis procedure is higher.

Example 4 – Repeated Measures with Heterogeneous Variances

One of the features offered by LMM is the ability to specify unequal group variances. This example will look at how to do this.

In this example, we will determine the power for group sizes of 6 when the random effects (subject) variance is 2 when $A=1$ and 4 with $A=2$, the residual variance is 2 when $A=1$ and 4 when $A=2$, the minimum detectable differences of all three terms is 1.0, the number of repeated measurements is 2, and the significance level is 0.05. A random effects model will be fit. The number of simulation samples will be set to 100.

Setup

If the procedure window is not already open, use the PASS Home window to open it. The parameters for this example are listed below and are stored in the **Example 4** settings file. To load these settings to the procedure window, click **Open Example Settings File** in the Help Center or File menu.

Design: Effect Size Tab

n (Subjects Per Group)	6
= n's	Checked
Alpha.....	0.05
Simulations	100
Random Seed.....	9949131 (for Reproducibility)
Specify Effects Using.....	Effect Patterns, etc.
Between Factor A Levels	2
Between Factor A Effects Pattern.....	Linear Up
Between Factor A Detectable Difference.....	1
Within Factor C Levels.....	2
Within Factor C Effects Pattern.....	Linear Up
Within Factor C Detectable Difference.....	1
AC Interaction	Checked
AC Interaction Detectable Difference.....	1
Baseline Mean	0

Design: Covariance Tab

Grouping Factor.....	A
Include G	Checked
g (Subject σ^2).....	2 4
Specify R Using	Variances Only
Times.....	STEP 0 1
Pattern	Constant in σ^2 for R
σ^2 for R.....	2 4

Mixed Models (Simulation)

Fitted Model Tab

G Estimation **G (Random Effects for Subjects)**
 Groups **A**
 R Estimation **Diagonal**
 Groups **A**
 Force Positive Covariances **Unchecked**
 Likelihood Type **REML (Recommended)**
 Solution Method **Newton-Raphson**

Output

Click the Calculate button to perform the calculations and generate the following output.

Power by Design

Model Term	Power	95% Confidence Interval Limits for Power		N(1)	N	Minimum Detectable Difference	Alpha	Number of Simulation Samples	Factor Pattern
		Lower	Upper						
A (2)	0.22	0.14330	0.31392	6	12	1	0.05	100	Linear Up
C (2)	0.32	0.23022	0.42077	6	12	1	0.05	100	Linear Up
AC	0.28	0.19479	0.37867	6	12	1	0.05	100	

Simulation Time 4.12 seconds
 Random Seed 9949131 (User-Entered)

Variance-Covariance Matrix of Y

Factors	C1	C2
A1C1	4	2
A1C2	2	4
A2C1	8	4
A2C2	4	8

Variations and Autocorrelations

Factors	C1	C2
A1C1	4.0	0.5
A1C2	0.5	4.0
A2C1	8.0	0.5
A2C2	0.5	8.0

Notice how easy it is to obtain a power analysis for the case of unequal variances.

Example 5 – T-Test with Heterogeneous Variances (Searching for n)

This example will show how to determine the power of a design that is usually analyzed with a t-test. However, in this example, the variances of the two groups are known to be very different.

In this example, the variance of the first group is 4, the variance of the second group is 9, the minimum detectable difference is set to 1.0, the significance level is 0.05, and the number of simulation samples is 100. There are no repeated measurements. Since a sample size search capability is not available in this routine, we will conduct a manual search by calculating the power for group sample sizes of 10, 20, 30, 40, 50, 60, 70, 80, 90, and 100.

Setup

If the procedure window is not already open, use the PASS Home window to open it. The parameters for this example are listed below and are stored in the **Example 5** settings file. To load these settings to the procedure window, click **Open Example Settings File** in the Help Center or File menu.

Design: Effect Size Tab

n (Subjects Per Group)	10 20 30 40 50 60 70 80 90 100
= n's	Checked
Alpha.....	0.05
Simulations	100
Random Seed.....	2299151 (for Reproducibility)
Specify Effects Using.....	Effect Patterns, etc.
Between Factor A Levels	2
Between Factor A Effects Pattern.....	Linear Up
Between Factor A Detectable Difference.....	1
Within Factor C Levels.....	0
Baseline Mean	0

Design: Covariance Tab

Grouping Factor.....	A
Include G	Unchecked
Specify R Using	Variances Only
Times	STEP 0 1
Pattern	Constant in σ^2 for R
σ^2 for R.....	4 9

Fitted Model Tab

G Estimation	None
R Estimation	Diagonal
Groups.....	A
Force Positive Covariances	Unchecked
Likelihood Type.....	REML (Recommended)
Solution Method.....	Newton-Raphson

Output

Click the Calculate button to perform the calculations and generate the following output.

Power Report for $n = 10, 20, 30, 40, 50, 60, 70, 80, 90, 100$ with Simulations = 100

Power by Term										
Model Term	Power	95% Confidence Interval Limits for Power		N(1)	N	Minimum Detectable Difference	Alpha	Number of Simulation Samples	Factor Pattern	
		Lower	Upper							
A (2)	0.24	0.16022	0.33574	10	20	1	0.05	100	Linear Up	
A (2)	0.36	0.26641	0.46212	20	40	1	0.05	100	Linear Up	
A (2)	0.47	0.36941	0.57242	30	60	1	0.05	100	Linear Up	
A (2)	0.66	0.55847	0.75178	40	80	1	0.05	100	Linear Up	
A (2)	0.78	0.68608	0.85670	50	100	1	0.05	100	Linear Up	
A (2)	0.75	0.65345	0.83122	60	120	1	0.05	100	Linear Up	
A (2)	0.83	0.74182	0.89774	70	140	1	0.05	100	Linear Up	
A (2)	0.89	0.81170	0.94379	80	160	1	0.05	100	Linear Up	
A (2)	0.89	0.81170	0.94379	90	180	1	0.05	100	Linear Up	
A (2)	0.96	0.90074	0.98900	100	200	1	0.05	100	Linear Up	

Simulation Time 12.04 seconds
Random Seed 2299151 (User-Entered)

If our goal is to achieve 90% power, it appears that we should investigate group sample sizes of 70, 75, 80, 85, and 90 using a larger simulation size, say 500. Putting these values in for n and running gives the following results.

Power Report for $n = 70, 75, 80, 85, 90$ with Simulations = 500

Power by Term										
Model Term	Power	95% Confidence Interval Limits for Power		N(1)	N	Minimum Detectable Difference	Alpha	Number of Simulation Samples	Factor Pattern	
		Lower	Upper							
A (2)	0.840	0.80487	0.87104	70	140	1	0.05	500	Linear Up	
A (2)	0.872	0.83950	0.90001	75	150	1	0.05	500	Linear Up	
A (2)	0.872	0.83950	0.90001	80	160	1	0.05	500	Linear Up	
A (2)	0.908	0.87919	0.93186	85	170	1	0.05	500	Linear Up	
A (2)	0.898	0.86807	0.92311	90	180	1	0.05	500	Linear Up	

Simulation Time 42.52 seconds
Random Seed 5168161 (User-Entered)

It appears that a group sample size of 85 or more will give us a power of 90%.

Power Report for n = 85 with Simulations = 2000

Power by Term									
Model Term	Power	95% Confidence Interval Limits for Power		N(1)	N	Minimum Detectable Difference	Alpha	Number of Simulation Samples	Factor Pattern
		Lower	Upper						
A (2)	0.912	0.89872	0.92405	85	170	1	0.05	2000	Linear Up
Simulation Time	37.30 seconds								
Random Seed	1519111 (User-Entered)								

A group sample size of 85 does indeed give us a power of 90%.