Chapter 568

M×M Cross-Over Designs

Introduction

This module calculates the power for an MxM cross-over design in which each subject receives a sequence of M treatments and is measured at M periods (or time points). The 2x2 cross-over design, the simplest and most common case, is well covered by other PASS procedures. We anticipate that users will use this procedure when the number of treatments is greater than or equal to three.

MxM cross-over designs are often created from Latin-squares by letting groups of subjects follow different column of the square. The subjects are randomly assigned to different treatment sequences. The overall design is arranged so that there is balance in that each treatment occurs before and after every other treatment an equal number of times. We refer you to any book on cross-over designs or Latin-squares for more details.

The power calculations used here ignore the complexity of specifying sequence terms in the analysis. Therefore, the data may be thought of as a one-way, repeated measures design. Combining subjects with different treatment sequences makes it more reasonable to assume a simple, circular variance-covariance pattern. Hence, usually, you will assume that all correlations are equal.

This procedure computes power for both the univariate (F test and F test with Geisser-Greenhouse correction) and multivariate (Wilks' lambda, Pillai-Bartlett trace, and Hotelling-Lawley trace) approaches.

Impact of Treatment Order, Unequal Variances, and Unequal Correlations

Treatment Order

It is important to understand under what conditions the order of treatment application matters since the design will usually include subjects with different treatment arrangements, although each subject will eventually receive all treatments. Even though the cross-over design requires a *washout* period between each two treatment applications so that the effect of one treatment does not *carryover* to next treatment, it is always a good research practice to try several different treatment orders. **PASS** lets you study this by allowing you to set the means and standard deviations in any order you like.

A brief investigation showed that the order of treatment application only matters when the variances at each treatment are different. The pattern of the correlation matrix does have an impact, but only when the variances are different.

Unequal Variances

PASS lets you investigate the impact of unequal variances on power. Of course, different variance patterns lead to different powers. However, the special point to understand is that when the variances are different, different treatment orders result in different powers as well.

Unequal Correlations

PASS lets you investigate the impact of unequal correlations on power. Of course, different correlation patterns lead to different powers. However, the special point to understand is that when the variances are equal, different treatment orders do not result in different powers. Thus, when the variances are the same, the power values for different treatment orders will remain constant across different treatment orderings.

Conclusions

The above considerations result in the following strategy when using this procedure to power analyze (find the sample size) for a particular design.

1. If the variance is constant across treatments, you can analyze any order and the results will stand for all orderings. For example, for the case M = 3, there are six possible orders: ABC, ACB, BAC, BCA, CAB, and CBA. In this case, the resulting sample size will be identical for any order.
2. If the variances are different across treatments (for example, if the variances are treatments with larger means are assumed to be proportionally larger), you should analyze each order separately and then use the average sample size or the maximum sample size. The point is, you cannot simply analyze one order.

Assumptions

The following assumptions are made when using the *F* test to analyze a factorial experimental design.

1. The response variable is continuous.
2. The residuals follow the normal probability distribution with mean equal to zero and constant variance.
3. The subjects are independent.

Since in a within-subject design responses coming from the same subject are not independent, assumption 3 must be modified for responses within a subject. Independence between subjects is still assumed.

4. The within-subject covariance matrix is equal for all subjects. In this type of experiment, the repeated measurements on a subject may be thought of as a multivariate response vector having a certain covariance structure.
5. When using an *F* test, the within-subject covariance matrix is assumed to be *circular*. One way of defining circularity is that the variances of differences between any two measurements within a subject are constant for all measurements. Since responses that are close together in time (or space) often have a higher correlation than those that are far apart, it is common for this assumption to be violated. This assumption is not necessary for the validity of the three multivariate tests: Wilks' lambda, Pillai-Bartlett trace, or Hotelling-Lawley trace. In fact, their validity does not even require that the variances are equal for all treatments.

Technical Details

General Linear Multivariate Model

This section provides the technical details of the repeated measures designs that can be analyzed by ***PASS***. The approximate power calculations outlined in Muller, LaVange, Ramey, and Ramey (1992) are used. Using their notation, for *N* subjects, the usual general linear multivariate model is

$$Y = XM + R$$

where each row of the residual matrix *R* is distributed as a multivariate normal

$$row_k(R) \sim N_p(0, \Sigma)$$

Note that *p* is the number of levels of the within-subject factor, *Y* is the matrix of responses, *X* is the design matrix, *M* is the matrix of regression parameters (means), and *R* is the matrix of residuals.

Hypotheses about various sets of regression parameters are tested using

$$H_0: \Theta = \Theta_0$$

$$MD = \Theta$$

where *D* is an orthonormal contrast matrix and Θ_0 is a matrix of hypothesized values, usually zeros.

Tests of the main effect may be constructed with suitable choices for *D*. These tests are based on

$$\hat{M} = \left(X'X\right)^{-} X'Y$$

$$\hat{\Theta} = \hat{M}D$$

$$\underset{b\times b}{H} = \left(\hat{\Theta} - \Theta_0\right)' \left[C\left(X'X\right)^{-} C'\right]^{-1} \left(\hat{\Theta} - \Theta_0\right)$$

$$\underset{b\times b}{E} = D'\hat{\Sigma}D \cdot \left(N - r\right)$$

$$\underset{b\times b}{T} = H + E$$

where *r* is the rank of *X* which is, in this case, *p* - 1. Also, C is the scalar 1 and can be ignored in this case.

Geisser-Greenhouse F Test

Upon the assumption that Σ has compound symmetry, a size α test of $H_0: \Theta = \Theta_0$ is given by the *F* ratio

$$F = \frac{\mathrm{tr}(H)/(p-1)}{\mathrm{tr}(E)/[(p-1)(N-p+1)]}$$

with degrees of freedom given by

$$df_1 = p - 1$$

$$df_2 = (p-1)(N-p+1)$$

and noncentrality parameter

$$\lambda = df_1(F)$$

The assumption that Σ has compound symmetry is usually not viable. Box (1954a,b) suggested that adjusting the degrees of freedom of the above *F*-ratio could compensate for the lack of compound symmetry in Σ. His adjustment has become known as the Geisser-Greenhouse adjustment. Under this adjustment, the modified degrees of freedom and noncentrality parameter are given by

$$df_1 = (p-1)\varepsilon$$

$$df_2 = (p-1)(N-p+1)\varepsilon$$

$$\lambda = (df_1)F\varepsilon$$

where

$$\varepsilon = \frac{\mathrm{tr}\left(D'\hat{\Sigma}D\right)^2}{b\ \mathrm{tr}\left(D'\hat{\Sigma}DD'\hat{\Sigma}D\right)}$$

The range of ε is $\frac{1}{b-1}$ to 1. When $\varepsilon = 1$, the matrix is *spherical*. When $\varepsilon = \frac{1}{b-1}$, the matrix differs maximally from sphericity.

The critical value F_{Crit} is computed using the expected value of ε to adjust the degrees of freedom. That is, the degrees of freedom of F_{Crit} are given by

$$df_1 = (p-1)E(\varepsilon)$$

$$df_2 = (p-1)(N-p+1)E(\varepsilon)$$

where

$$E(\hat{\varepsilon}) = \begin{cases} \varepsilon + \frac{g_1}{N-r} & \text{if } \varepsilon > \frac{g_1}{N-r} \\ \varepsilon / 2 & \text{otherwise} \end{cases}$$

$$g_1 = \sum_{i=1}^{T} f_{ii}\xi_i^2 + \sum\sum_{i \neq j} \frac{f_i \xi_i \xi_j}{\left(\xi_i - \xi_j\right)}$$

$$f_i = \frac{\partial \varepsilon}{\partial \xi_i}$$

$$= \frac{2\sum \xi_j}{df_1 \sum \xi_j^2} - \frac{2\lambda_i \left(\sum \xi_j\right)^2}{df_1 \left(\sum \xi_j^2\right)^2}$$

$$f_{ii} = \frac{\partial^{(2)} \varepsilon}{\partial \xi_i^{(2)}}$$

$$= 2h_1 - 8h_2 + 8h_3 - 2h_4$$

$$h_1 = \frac{2}{df_1 \sum \xi_j^2}$$

$$h_2 = \frac{\xi_i \left(\sum \xi_j\right)}{df_1 \left(\sum \xi_j^2\right)^2}$$

$$h_3 = \frac{\xi_i^2 \left(\sum \xi_j\right)^2}{df_1 \left(\sum \xi_j^2\right)^3}$$

$$h_4 = \frac{\left(\sum \xi_j\right)^2}{df_1 \left(\sum \xi_j^2\right)^2}$$

where the ξ_j's are the ordered eigenvalues of $D'\Sigma D$.

Wilks' Lambda Approximate F Test

The hypothesis $H_0 : \Theta = \Theta_0$ may be tested using Wilks' likelihood ratio statistic *W*. This statistic is computed using

$$W = \left| ET^{-1} \right|$$

An *F* approximation to the distribution of *W* is given by

$$F_{df_1, df_2} = \frac{\eta / df_1}{(1 - \eta) / df_2}$$

where

$$\lambda = df_1 F_{df_1, df_2}$$

$$\eta = 1 - W$$

$$df_1 = p - 1$$

$$df_2 = N - p + 1$$

Pillai-Bartlett Trace Approximate F Test

The hypothesis $H_0 : \Theta = \Theta_0$ may be tested using the Pillai-Bartlett Trace. This statistic is computed using

$$T_{PB} = tr\left(HT^{-1} \right)$$

A non-central *F* approximation to the distribution of T_{PB} is given by

$$F_{df_1, df_2} = \frac{\eta / df_1}{(1 - \eta) / df_2}$$

where

$$\lambda = df_1 F_{df_1, df_2}$$

$$\eta = \frac{T_{PB}}{s}$$

$$s = 1$$

$$df_1 = p - 1$$

$$df_2 = N - p + 1$$

Hotelling-Lawley Trace Approximate F Test

The hypothesis $H_0 : \Theta = \Theta_0$ may be tested using the Hotelling-Lawley Trace. This statistic is computed using

$$T_{HL} = tr\left(HE^{-1} \right)$$

An *F* approximation to the distribution of T_{HL} is given by

$$F_{df_1, df_2} = \frac{\eta / df_1}{(1 - \eta) / df_2}$$

where

$$\lambda = df_1 F_{df_1, df_2}$$

$$\eta = \frac{\frac{T_{HL}}{s}}{1 + \frac{T_{HL}}{s}}$$

$$s = 1$$

$$df_1 = p - 1$$

$$df_2 = N - p + 1$$

The Mean Vector

In the general linear multivariate model presented above, *M* represents a matrix of regression coefficients. Since you must provide the elements of *M*, we will discuss its meaning in more detail. Although other structures and interpretations of *M* are possible, in this module we assume that the elements of *M* are the cell means. The row of *M* represents the single group and the columns of *M* represent the within-group categories.

Consider now an example in which $p = 4$. That is, there is one group of subjects that are each measured four times. The matrix *M* would appear as follows.

$$M = [\mu_1 \quad \mu_2 \quad \mu_3 \quad \mu_4]$$

To calculate the power of this design, you would need to specify appropriate values of all four means under the alternative hypothesis.

Specifying the M Matrix

When computing the power in a repeated measures analysis of variance, the specification of the *M* matrix is one of your main tasks. The program cannot do this for you. The calculated power is directly related to your choice. So your choice for the elements of *M* must be selected carefully and thoughtfully. When authorization and approval from a government organization is sought, you should be prepared to defend your choice of *M*. In this section, we will explain how you can specify *M*.

Before we begin, it is important that you have in mind exactly what *M* is. *M* is a row of means that represent the size of the differences among the means that you want the study or experiment to detect. *M* gives the means under the alternative hypothesis. Under the null hypothesis, these means are assumed to be equal.

The D Matrix for Within-Subject Contrasts

The *D* matrix is comprised of contrasts that are applied to the columns of *M*. The choice of D does not matter as long as it is orthogonal, so an appropriate matrix is generated for you.

Power Calculations

To calculate statistical power, we must determine distribution of the test statistic under the alternative hypothesis which specifies a different value for the regression parameter matrix *B*. The distribution theory in this case has not been worked out, so approximations must be used. We use the approximations given by Mueller and Barton (1989) and Muller, LaVange, Ramey, and Ramey (1992). These approximations state that under the alternative hypothesis, F_U is distributed as a noncentral *F* random variable with degrees of freedom and noncentrality shown above. The calculation of the power of a particular test may be summarized as follows

1. Specify values of M, Σ.
2. Determine the critical value using F_{crit} = FINV (1 - α, df_1 ,df_2), where FINV ( ) is the inverse of the central *F* distribution and α is the significance level.
3. Compute the noncentrality parameter λ.
4. Compute the power as Power = 1 - NCFPROB (F_{crit}, df_1, df_2, λ), where NCFPROB ( ) is the noncentral *F* distribution.

Covariance Matrix Assumptions

The following assumptions are made when using the *F* test. These assumptions are not needed when using one of the three multivariate tests.

In order to use the *F* ratio to test hypotheses, certain assumptions are made about the distribution of the residuals e_{ijk}. Specifically, it is assumed that the residuals for each subject, $e_{ij1}, e_{ij2}, \cdots, e_{ijT}$, are distributed as a multivariate normal with means equal to zero and covariance matrix Σ_{ij}. Two additional assumptions are made about these covariance matrices. First, they are assumed to be equal for all subjects. That is, it is assumed that $\Sigma_{11} = \Sigma_{12} = \cdots = \Sigma_{Gn} = \Sigma$. Second, the covariance matrix is assumed to have a particular form called *circularity*. A covariance matrix is *circular* if there exists a matrix *A* such that

$$\Sigma = A + A' + \lambda I_T$$

where I_T is the identity matrix of order *T* and λ is a constant.

This property may also be defined as

$$\sigma_{ii} + \sigma_{jj} - 2\sigma_{ij} = 2\lambda$$

One type of matrix that is circular is one that has *compound symmetry*. A matrix with this property has all elements on the main diagonal equal and all elements off the main diagonal equal. An example of a covariance matrix with compound symmetry is

$$\Sigma = \begin{bmatrix} \sigma^2 & \rho\sigma^2 & \rho\sigma^2 & \cdots & \rho\sigma^2 \\ \rho\sigma^2 & \sigma^2 & \rho\sigma^2 & \cdots & \rho\sigma^2 \\ \rho\sigma^2 & \rho\sigma^2 & \sigma^2 & \cdots & \rho\sigma^2 \\ \vdots & \vdots & \vdots & \ddots & \vdots \\ \rho\sigma^2 & \rho\sigma^2 & \rho\sigma^2 & \cdots & \sigma^2 \end{bmatrix}$$

or, with actual numbers,

$$\begin{bmatrix} 9 & 2 & 2 & 2 \\ 2 & 9 & 2 & 2 \\ 2 & 2 & 9 & 2 \\ 2 & 2 & 2 & 9 \end{bmatrix}$$

Covariance Patterns

In a repeated measures design with N subjects, each measured M times, observations within a single subject may be correlated, and a pattern for their covariance must be specified. In this case, the overall covariance matrix will have the block-diagonal form:

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

where $\mathbf{V}_i$ is the M x M covariance submatrices corresponding to the i^{th} subject. The **0**'s represent M x M matrices of zeros giving zero covariances for observations on different subjects. This routine allows the specification of two different covariance matrix types: All ρ's Equal and AR(1), Banded(1), and Banded(2).

All ρ's Equal (Compound Symmetry)

A compound symmetry covariance model assumes that all covariances are equal, and all variances on the diagonal are equal. That is

$$\Sigma = \sigma^2 \begin{pmatrix} 1 & \rho & \rho & \rho & \cdots & \rho \\ \rho & 1 & \rho & \rho & \cdots & \rho \\ \rho & \rho & 1 & \rho & \cdots & \rho \\ \rho & \rho & \rho & 1 & \cdots & \rho \\ \vdots & \vdots & \vdots & \vdots & \ddots & \vdots \\ \rho & \rho & \rho & \rho & \cdots & 1 \end{pmatrix}_{M \times M}$$

where σ^2 is the subject variance and ρ is the correlation between observations on the same subject.

AR(1)

An AR(1) (autoregressive order 1) covariance model assumes that all variances on the diagonal are equal and that covariances t time periods apart are equal to $\rho^t\sigma^2$. That is

$$\Sigma = \sigma^2 \begin{pmatrix} 1 & \rho & \rho^2 & \rho^3 & \ldots & \rho^{M-1} \\ \rho & 1 & \rho & \rho^2 & \ldots & \rho^{M-2} \\ \rho^2 & \rho & 1 & \rho & \ldots & \rho^{M-3} \\ \rho^3 & \rho^2 & \rho & 1 & \ldots & \rho^{M-4} \\ \vdots & \vdots & \vdots & \vdots & \ddots & \vdots \\ \rho^{M-1} & \rho^{M-2} & \rho^{M-3} & \rho^{M-4} & \ldots & 1 \end{pmatrix}_{M \times M}$$

where σ^2 is the residual variance and ρ is the correlation between observations on the same subject.

Banded(1)

A Banded(1) (banded order 1) covariance model assumes that all variances on the diagonal are equal, covariances for observations one time period apart are equal to $\rho\sigma^2$, and covariances for measurements greater than one time period apart are equal to zero. That is

$$\Sigma = \sigma^2 \begin{pmatrix} 1 & \rho & 0 & 0 & \cdots & 0 \\ \rho & 1 & \rho & 0 & \cdots & 0 \\ 0 & \rho & 1 & \rho & \cdots & 0 \\ 0 & 0 & \rho & 1 & \cdots & 0 \\ \vdots & \vdots & \vdots & \vdots & \ddots & \vdots \\ 0 & 0 & 0 & 0 & \cdots & 1 \end{pmatrix}_{M \times M}$$

where σ^2 is the residual variance and ρ is the correlation between observations on the same subject.

Banded(2)

A Banded(2) (banded order 2) covariance model assumes that all variances on the diagonal are equal, covariances for observations one or two time periods apart are equal to $\rho\sigma^2$, and covariances for measurements greater than two time period apart are equal to zero. That is

$$\Sigma = \sigma^2 \begin{pmatrix} 1 & \rho & \rho & 0 & \cdots & 0 \\ \rho & 1 & \rho & \rho & \cdots & 0 \\ \rho & \rho & 1 & \rho & \cdots & 0 \\ 0 & \rho & \rho & 1 & \cdots & 0 \\ \vdots & \vdots & \vdots & \vdots & \ddots & \vdots \\ 0 & 0 & 0 & 0 & \cdots & 1 \end{pmatrix}_{M \times M}$$

where σ^2 is the residual variance and ρ is the correlation between observations on the same subject.

Procedure Options

This section describes the options that are specific to this procedure. These are located on the Design tab. For more information about the options of other tabs, go to the Procedure Window chapter.

Design Tab

The Design tab contains most of the parameters and options that you will be concerned with.

Solve For

Solve For

This option specifies the parameter to be solved for. When you choose to solve for *Sample Size*, the program searches for the lowest sample size that meets the alpha and power criterion you have specified.

This parameter is displayed on the vertical axis of the plot.

Tests

Test Statistic

You should select the test statistic that will be used to analyze the data. There are two general types: univariate and multivariate. The univariate repeated measures ANOVA approach (also known as the mixed model approach) analyzes the power of the corresponding F-test. The multivariate approach uses any of three common multivariate tests. For the one-way repeated measures design, all three multivariate tests give the same result.

The test statistics are

Univariate: F Test

This test assumes that all variances are equal and all correlations are equal (a condition called compound symmetry). If you want to use this option, you must choose equal σ's and constant ρ's across time.

Univariate: Geisser-Greenhouse F Test

The Geisser-Greenhouse adjustment corrects the degrees of freedom of the F-Test so that the actual significance levels are closer to the stated levels when there is a lack of compound symmetry in the variance-covariance matrix.

Multivariate: Wilks Lambda Test

Wilks' Lambda is the multivariate generalization of $1 - R^2$ in multiple regression. Because of its easy interpretation, it is the most popular of the three tests.

Multivariate: Pillai-Bartlett Test

The Pillai-Bartlett statistic calculates the amount of variance in the dependent variable accounted for by the greatest separation of the independent (design) variables. This test is considered most reliable in small sample sizes.

Multivariate: Hotelling-Lawley Trace Test

This test is usually converted to Hotelling's T^2.

Power and Alpha

Power

This option specifies one or more values for power. Power is the probability of rejecting a false null hypothesis, and is equal to one minus Beta. Beta is the probability of a type-II error, which occurs when a false null hypothesis is not rejected. In this procedure, a type-II error occurs when you fail to reject the null hypothesis of equal means when in fact the means are different.

Values must be between zero and one. Historically, the value of 0.80 (Beta = 0.20) was used for power. Now, 0.90 (Beta = 0.10) is also commonly used.

A single value may be entered here or a range of values such as *0.8 to 0.95 by 0.05* may be entered.

Alpha

This option specifies one or more values for the probability of a type-I error. A type-I error occurs when a true null hypothesis is rejected. In this procedure, a type-I error occurs when you reject the null hypothesis of equal means when in fact the means are equal.

Values must be between zero and one. Historically, the value of 0.05 has been used for alpha. This means that about one test in twenty will falsely reject the null hypothesis. You should pick a value for alpha that represents the risk of a type-I error you are willing to take in your experimental situation.

Note that this is a two-sided test.

You may enter a range of values such as *0.01 0.05 0.10* or *0.01 to 0.10 by 0.01*.

Sample Size

N (Subjects)

Enter a value for the sample size (N), the number of subjects in the study. Each subject is measured two or more times. You may enter a single value or a range of values. A separate power calculation will be made for each value of N you enter.

Examples

10 to 100 by 10

10 30 80 90

10, 30, 80, 90

Effect Size – Number of Periods and Treatments

M (Periods, Treatment)

Enter a value for the number of periods and treatments (repeated measurements) at which each subject is measured.

Effect Size – Means

These options specify the means under the alternative hypothesis, one for each treatment. The test statistic tests whether the differences among these means are all zero.

The means represent the alternative hypothesis. They are not necessarily the means you expect. Rather, they represent the magnitude of the differences that you want to detect.

μi's (μ1, μ2, …, μM)

This option specifies how you want to enter the M means for the alternative hypothesis. Your choices are List, Range, or Sequence.

μi's (μ1, μ2, …, μM) = List

Enter a set of M hypothesized means, μi, one mean for each treatment. Enter numbers separated by blanks or commas. If the number of means entered is less than M, the last mean entered will be copied forward. If too many means are entered, the extra will be ignored.

μi's (μ1, μ2, …, μM) = Range

Enter a range of values by specifying the first and the last. The other means will be generated equi-spaced between these values.

μi's (μ1, μ2, …, μM) = Sequence

Enter a set of means by specifying the first mean and a step-size (increment) to be added for each succeeding mean.

K (Mean Multiplier)

Enter one or more values for K, the mean multiplier. A separate power calculation is conducted for each value of K. In each analysis, all means are multiplied by K. In this way, you can determine how sensitive the power values are to the magnitude of the means without the need to change them all individually.

For example, if the original means are 0, 1, and 2, setting this option to '1 2' results in two sets of means used in separate analyses: 0, 1, and 2 in the first analysis and 0, 2, and 4 in the second analysis.

If you want to ignore this option, enter a one.

Effect Size – σ (Standard Deviation)

Pattern of σ's Across Time

Specify whether the σi's vary across the measurement points or are the same.

Equal: σ = σ1 = σ2 = ... = σM

The σi's are constant across time. This assumption is required by the univariate F-test.

Unequal: σ1 ≠ σ2 ≠ ... ≠ σM

The σi's can vary across time.

σ (Standard Deviation) – Equal Pattern

This is the between subject standard deviation of the response variable (Y) at a particular time point. It is assumed to be the same for all time points. As a standard deviation, the number(s) must be greater than zero.

This represents the variability from subject to subject that occurs when the subjects are treated identically.

You can enter a list of values separated by blanks or commas, in which case, a separate analysis will be calculated for each value.

σ Button

You can press the σ button and select 'Covariance Matrix' to obtain help on estimating the standard deviation from an ANOVA table.

Examples

1,4,7,10

1 4 7 10

1 to 10 by 3

σi's (σ1, σ2, …, σM) – Unequal Pattern

Specify how you want to enter the M σi's. Your choices are List, Range, or Sequence.

σi's (σ1, σ2, …, σM) = List (Unequal Pattern)

Enter a list of σi's in the box that appears to the right.

σi's (σ1, σ2, …, σM) = Range (Unequal Pattern)

Enter a range of σi's by specifying the first and the last. The other σi's will be generated between these values using a straight-line trend.

σi's (σ1, σ2, …, σM) = Sequence (Unequal Pattern)

Enter a range of σi's by specifying the first and the step-size (increment) to be added for each succeeding σi.

h (σi Multiplier)

Enter a list of h values. A separate analysis is made for each value of h. For each analysis, the σi's entered above are all multiplied by h. Thus σ1, σ2, ..., σM become hσ1, hσ2, ..., hσM. Hence, using this parameter, you can perform a sensitivity analysis about the value(s) of the standard deviation.

Note that the resulting values must all be positive, so all h's must be greater than 0.

If you want to ignore this option, enter a 1.

Effect Size – ρ (Correlation Between Measurements)

Pattern of ρ's Across Time

Specify the correlation structure of the covariance matrix. The number of diagonal elements in the matrix is equal to M.

Possible options are

- **All ρ's Equal**
  All variances on the diagonal of the within-subject variance-covariance matrix are equal to σ^2, and all covariances are equal to $\rho\sigma^2$.

$$\Sigma = \sigma^2 \begin{pmatrix} 1 & \rho & \rho & \rho & \cdots & \rho \\ \rho & 1 & \rho & \rho & \cdots & \rho \\ \rho & \rho & 1 & \rho & \cdots & \rho \\ \rho & \rho & \rho & 1 & \cdots & \rho \\ \vdots & \vdots & \vdots & \vdots & \ddots & \vdots \\ \rho & \rho & \rho & \rho & \cdots & 1 \end{pmatrix}_{M \times M}$$

- **AR(1)**
  All variances on the diagonal of the within-subject variance-covariance matrix are equal to σ^2, and the covariance between observations *t* time periods apart is $\rho^t\sigma^2$.

$$\Sigma = \sigma^2 \begin{pmatrix} 1 & \rho & \rho^2 & \rho^3 & \dots & \rho^{M-1} \\ \rho & 1 & \rho & \rho^2 & \dots & \rho^{M-2} \\ \rho^2 & \rho & 1 & \rho & \dots & \rho^{M-3} \\ \rho^3 & \rho^2 & \rho & 1 & \dots & \rho^{M-4} \\ \vdots & \vdots & \vdots & \vdots & \ddots & \vdots \\ \rho^{M-1} & \rho^{M-2} & \rho^{M-3} & \rho^{M-4} & \dots & 1 \end{pmatrix}_{M \times M}$$

- **Banded(1)**
  All variances on the diagonal of the within-subject variance-covariance matrix are equal to σ^2, and the covariance between observations one time period apart is $\rho\sigma^2$. Covariances between observations more than one time period apart are equal to zero.

$$\Sigma = \sigma^2 \begin{pmatrix} 1 & \rho & 0 & 0 & \cdots & 0 \\ \rho & 1 & \rho & 0 & \cdots & 0 \\ 0 & \rho & 1 & \rho & \cdots & 0 \\ 0 & 0 & \rho & 1 & \cdots & 0 \\ \vdots & \vdots & \vdots & \vdots & \ddots & \vdots \\ 0 & 0 & 0 & 0 & \cdots & 1 \end{pmatrix}_{M \times M}$$

- **Banded(2)**

  All variances on the diagonal of the within-subject variance-covariance matrix are equal to σ^2, and the covariance between observations one or two time periods apart are $\rho\sigma^2$. Covariances between observations more than two time periods apart are equal to zero.

$$\Sigma = \sigma^2 \begin{pmatrix} 1 & \rho & \rho & 0 & \cdots & 0 \\ \rho & 1 & \rho & \rho & \cdots & 0 \\ \rho & \rho & 1 & \rho & \cdots & 0 \\ 0 & \rho & \rho & 1 & \cdots & 0 \\ \vdots & \vdots & \vdots & \vdots & \ddots & \vdots \\ 0 & 0 & 0 & 0 & \cdots & 1 \end{pmatrix}_{M \times M}$$

ρ (Correlation)

This is the correlation, ρ, between measurements on the same subject taken at the first and second time points.

At least one value must be entered. If multiple values are entered, a separate analysis is performed for each value.

Range

$0 < \rho < 1$ (negative values are not used). A value near 0 indicates low correlation. A value near 1 indicates high correlation.

Recommended

The value of this parameter depends on time or location pattern at which measurements are taken. In their book on sample size, Machin and Campbell comment that values between 0.60 and 0.75 are typical. Some authors recommend using 0.2 when nothing is known about the actual value.

Examples

0.5

0.5 0.6 0.7

0 to 0.9 by 0.1

Example 1 – Determining Sample Size

Researchers are planning a study of the impact of a new drug on heart rate. The want to investigate three treatments: placebo (P), low dose (L), and higher dose (H) of the new drug. They decide to use a 3x3 cross-over design with six possible treatment sequences: PLH, PHL, HPL, HLP, LPH, and LHP. They will assign an equal number of subjects to each sequence. Hence, the final sample size will be the next multiple of six above the N found by PASS. For example, and N of 32 would be rounded up to 36.

They anticipate little difference between the placebo and the low dose. However, they expect that the high dose will reduce the heart rate about 10%. They decide to use the mean values of 80, 80, and 72.

Similar studies have found a standard deviation of 15. To allow for a sensitivity analysis of the standard deviation, they will use three standard deviations: 13, 15, and 17.

The researchers assume that all correlations among the measurements at different time points within a subject will be equal to 0.5. To allow for a sensitivity analysis of the correlation, they will use three correlations: 0.4, 0.5, and 06.

They decide to use the F test statistic with the Geisser-Greenhouse correction.

The test will be conducted at the 0.05 significance level. What sample size is necessary to achieve 90% power over a range of possible means and standard deviations?

Setup

This section presents the values of each of the parameters needed to run this example. First, from the PASS Home window, load the **MxM Cross-Over Designs** procedure window by expanding **Means**, then **Cross-Over (Higher-Order) Design**, then **Test (Inequality)**, and then clicking on **MxM Cross-Over Designs**. You may then make the appropriate entries as listed below, or open **Example 1** by going to the **File** menu and choosing **Open Example Template**.

Option	Value
Design Tab	
Solve For	**Sample Size**
Test Statistic	**Univariate: Geisser-Greenhouse F Test**
Power	**0.90**
Alpha	**0.05**
M (Periods, Treatments)	**3**
Means	**List**
Means – List Values	**80 80 72**
K (Means Multiplier)	**1**
Pattern of σ's Across Time	**Equal**
σ (Standard Deviation)	**13 15 17**
Pattern of ρ's Across Time	**All ρ's Equal**
ρ (Correlation)	**0.4 0.5 0.6**

Annotated Output

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

Numeric Results

Numeric Results for M-Period, M-Treatment Cross-Over Design
Test: Geisser-Greenhouse Corrected F Test
μi's: 80 80 72
σi's: All Equal
ρ's: All Equal

Power	N	Treatments and Periods M	Mean Multiplier K	Standard Deviation of Means σm	Standard Deviation σ	Corr ρ	Alpha
0.9011	32	3	1.0	3.77	13.00	0.40	0.05
0.9014	27	3	1.0	3.77	13.00	0.50	0.05
0.9017	22	3	1.0	3.77	13.00	0.60	0.05
0.9012	42	3	1.0	3.77	15.00	0.40	0.05
0.9073	36	3	1.0	3.77	15.00	0.50	0.05
0.9054	29	3	1.0	3.77	15.00	0.60	0.05
0.9045	54	3	1.0	3.77	17.00	0.40	0.05
0.9024	45	3	1.0	3.77	17.00	0.50	0.05
0.9078	37	3	1.0	3.77	17.00	0.60	0.05

References
Jones, B. and Kenward, M.G. 2015. Design and Analysis of Cross-Over Trials, 3rd Edition. CRC Press. Boca Raton, Florida.
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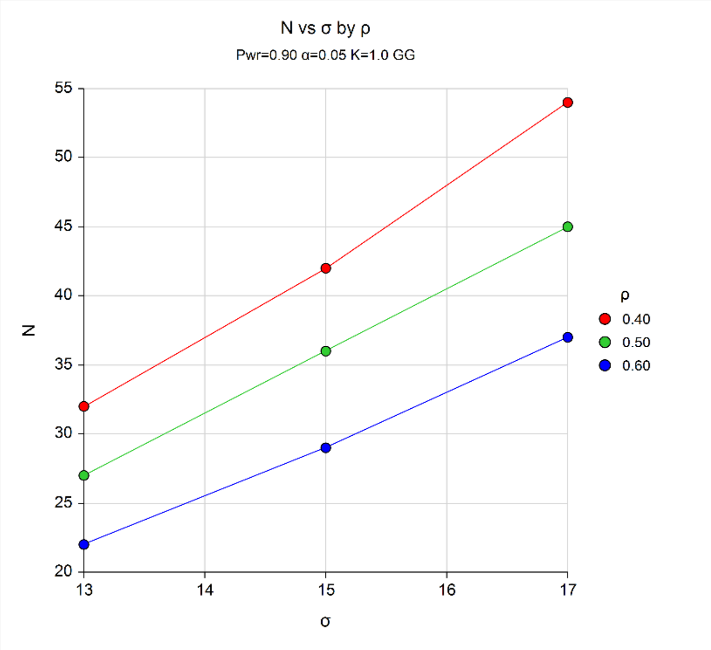
Rencher, Alvin C. 1998. Multivariate Statistical Inference and Applications. John Wiley. New York, New York.
Muller, K. E., and Barton, C. N. 1989. 'Approximate Power for Repeated-Measures ANOVA Lacking Sphericity.' Journal of the American Statistical Association, Volume 84, No. 406, pages 549-555.
Muller, K. E., LaVange, L.E., Ramey, S.L., and Ramey, C.T. 1992. 'Power Calculations for General Linear Multivariate Models Including Repeated Measures Applications.' Journal of the American Statistical Association, Volume 87, No. 420, pages 1209-1226.

Report Definitions
Power is the probability of rejecting a false null hypothesis.
N: The total number of subjects in the study.
M is the number of time points at which each subject is measured. This is also the number of periods and the number of treatments.
K is the effect size multiplier. The original means are all multiplied by this value, resulting in a corresponding change in the effect size.
Std Dev of Means (σm): This value represents the magnitude of differences among the hypothesized means.
σ is the standard deviation across subjects at a given time point.
ρ is the (auto)correlation between observations made on a subject at the first and second time points.
Alpha: The significance level of the test. The probability of rejecting the null hypothesis when the null hypothesis is true.

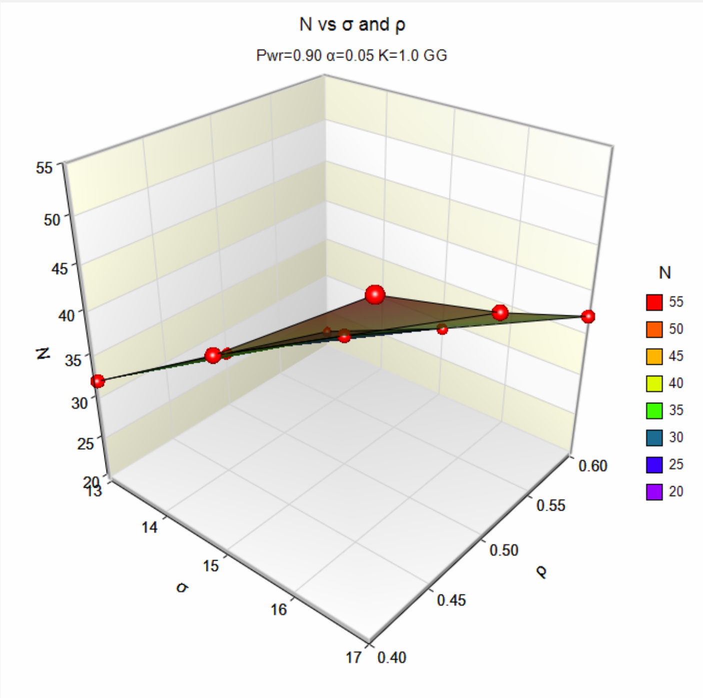
Summary Statements
A 3-period by 3-treatment cross-over design is analyzed using single-factor, repeated measures methodology. A sample of 32 subjects, measured at 3 time points, achieves 90% power to detect differences among the means using a Geisser-Greenhouse Corrected F Test at a 0.05 significance level. The standard deviation across subjects at the same time point is assumed to be 13.00. The pattern of the covariance matrix is to have all correlations equal with a correlation of 0.40 between the first and second time point measurements. The standard deviation of the hypothesized means is 3.77.

This report gives the power for each value of the other parameters. The definitions are shown in the report.

Plots Section



The chart shows the relationship between N, ρ, and σ when the other parameters in the design are held constant.



The chart shows a 3D view of the relationship between N, ρ, and σ when the other parameters in the design are held constant.

Example 2 – Validation using PASS's Repeated Measures Procedure

To validate this procedure, we will run the first scenario through PASS's Repeated Measures procedure. We did this and obtained the following report.

Design Report – Repeated Measures

Term	Test	Power	n	N	Multiply Means By K	Std Dev of Effects (σm)	Standard Deviation (σ)	Effect Size (σm/σ)	Alpha	Beta
W1(3)	GG F	0.901141	32	32	1.0	3.77	5.81	0.649	0.05	0.10

Setup

This section presents the values of each of the parameters needed to run this example. First, from the PASS Home window, load the **MxM Cross-Over Designs** procedure window by expanding **Means**, then **Cross-Over (Higher-Order) Design**, then **Test (Inequality)**, and then clicking on **MxM Cross-Over Designs**. You may then make the appropriate entries as listed below, or open **Example 2** by going to the **File** menu and choosing **Open Example Template**.

Option	Value
Design Tab	
Solve For	**Sample Size**
Test Statistic	**Univariate: Geisser-Greenhouse F Test**
Power	**0.90**
Alpha	**0.05**
M (Periods, Treatments)	**3**
Means	**List**
Means – List Values	**80 80 72**
K (Means Multiplier)	**1**
Pattern of σ's Across Time	**Equal**
σ (Standard Deviation)	**13**
Pattern of ρ's Across Time	**All ρ's Equal**
ρ (Correlation)	**0.4**

Output

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

Numeric Results

Numeric Results for M-Period, M-Treatment Cross-Over Design
Test: Geisser-Greenhouse Corrected F Test
μi's: 80 80 72
σi's: All Equal
ρ's: All Equal

Power	N	Treatments and Periods M	Mean Multiplier K	Standard Deviation of Means σm	Standard Deviation σ	Corr ρ	Alpha
0.9011	32	3	1.0	3.77	13.00	0.40	0.05

This procedure has obtained identical results with the previously validated procedure.