

Chapter 567

M-Period Cross-Over Designs using Contrasts

Introduction

This module calculates the power for an M period cross-over design in which the analysis is done by a testing a user-supplied contrast. The test may be univariate or multivariate.

In a cross-over design, each subject receives a sequence of treatments and is measured at M periods. The number of unique treatments will usually be two or three, but can be up to M. Common designs that might be analyzed by this procedure are 3x2, 4x2, etc. The arrangement of the treatments at the M time points may be ABA, AAB, ABB, BAA, AABB, ABAB, BBAA, ABABA, etc.

Cross-over designs are often created from Latin-squares by letting groups of subjects follow different column of the square. 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 among subject. 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 simply 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 module calculates the power of a test of a contrast among the means in a one-way repeated measures design using either the multivariate test or the univariate, repeated-measures F-test as described by Maxwell and Delaney (2003) and Davis (2002).

A repeated measures design is one in which subjects are observed at a fixed set of time points. These time points do not have to be equally spaced, but they must be identical for all subjects. A hypothesis about a contrast of the means can be tested using Hotelling's T^2 test or the univariate F-test.

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.

Technical Details

The formulas used to perform a Hotelling's T^2 power analysis provide exact answers if the above assumptions are met. These formulas can be found in many places. We use the results in Davis (2002). We refer you to that reference for more details.

Technical Details for the Multivariate Test

In one-factor case, a sample of N subjects are measured at M time points. We assume that all N subjects have the same multivariate normal distribution with mean vector μ and variance covariance matrix Σ and that Hotelling's T^2 is used for testing the null hypothesis that $\sum c_i \mu_i = 0$ versus the alternative that $\sum c_i \mu_i = A \neq 0$. The value of T^2 is computed using the formula

$$F_{1,N-1} = T_{1,N-1}^2 = N \frac{(C'\bar{y})^2}{C'SC}$$

where \bar{y} is the M -dimensional vector of sample means, C is M -dimensional vector of contrast coefficients, and S is the sample variance-covariance matrix. Rather than use the T^2 distribution, we use the well-known relationship between it and the F-distribution with $df_1 = 1$ and $df_2 = (N - 1)$.

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To calculate power, we need the non-centrality parameter for this distribution. This non-centrality parameter is defined as follows

$$\lambda = N \frac{(C'\mu)^2}{C'\Sigma C} = N\Delta^2$$

We define Δ as the *effect size* because it provides an expression for the magnitude of the contrast of the means under the alternative hypothesis.

Using this non-centrality parameter, the power of the Hotelling's T^2 may be calculated for any value of the means and standard deviations. Since there is a simple relationship between the non-central T^2 and the non-central F, calculations are based on the non-central F using the formula

$$Power = 1 - P(F' > F_{1-\alpha,1,(N-1),0} | F' \sim F_{1,(N-1),\lambda})$$

Technical Details for the Univariate Test

The univariate approach calculates an F-test for testing the hypothesis using

$$F_{1,(M-1)(N-1)} = \frac{MS_C}{MS_{T \times S}}$$

where MS_C is the mean square for the contrast (including an adjustment for the sum of squared contrast coefficients) and $MS_{T \times S}$ is time period-by-subject interaction mean square.

To calculate power, we need the non-centrality parameter. This is defined as

$$\lambda = N \frac{(C'\mu)^2}{C'\Sigma C} = N\Delta^2$$

where Σ meets the compound symmetry requirement defined below. We define Δ as the *effect size* because it provides an expression for the magnitude of the contrast of the means under the alternative hypothesis.

PASS requires the input of σ_Y and ρ . These can be estimated from a repeated measures ANOVA table which provides values for MS_S (mean square of subjects) and MS_{ST} (mean square of subject-time interaction). The parameters can then be calculated as follows

$$\hat{\rho} = \frac{F - 1}{F - 1 + M}, \quad F = \frac{MS_{ST}}{MS_S}, \quad \hat{\sigma}_Y^2 = \frac{MS_{ST}}{1 - \hat{\rho}}$$

It is useful to note the following expectations

$$E(MS_{ST}) = \sigma_Y^2(1 - \rho)$$

$$E(MS_S) = \sigma_Y^2(1 + (M - 1)\rho)$$

The power is calculated using a formula similar to the one above based on the non-central F distribution

$$Power = 1 - P(F' > F_{1-\alpha,1,(M-1)(N-1),0} | F' \sim F_{1,(M-1)(N-1),\lambda})$$

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:

$$V = \begin{pmatrix} V_1 & 0 & 0 & \cdots & 0 \\ 0 & V_2 & 0 & \cdots & 0 \\ 0 & 0 & V_3 & \cdots & 0 \\ \vdots & \vdots & \vdots & \ddots & \vdots \\ 0 & 0 & 0 & \cdots & V_N \end{pmatrix},$$

where V_i is the $M \times M$ covariance submatrices corresponding to the i^{th} subject. The $\mathbf{0}$'s represent $M \times M$ matrices of zeros giving zero covariances for observations on different subjects. This routine allows the specification of four different covariance matrix types: All ρ 's Equal, 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 $\rho^t \sigma^2$. **This choice is recommended.** That is

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

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

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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.

Example 1 – Determining Sample Size

Researchers are planning a study of the impact of a new drug on heart rate. They 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, an 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. The contrast that they will use will be 0.5, 0.5, -1.0 for the treatment sequence PLH. This compares the average of the placebo and the low dose to the high dose.

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 0.6.

They decide to use the multivariate test statistic.

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

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 Tab	
Solve For	Sample Size
Test Statistic Type	Multivariate
Power.....	0.90
Alpha.....	0.05
M (Periods)	3
Means (μ 's $\mu_1, \mu_2, \dots, \mu_M$)	List
Means List	80 80 72
K (Means Multiplier).....	1
Contrast Coefficients.....	List
Contrast Coefficients List.....	0.5 0.5 -1
Pattern of σ 's Across Time.....	Equal: $\sigma = \sigma_1 = \sigma_2 = \dots = \sigma_M$
σ (Standard Deviation).....	13 15 17
Pattern of ρ 's Across Time	All ρ's Equal
ρ (Correlation).....	0.4 0.5 0.6

Output

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

Numeric Reports

Numeric Results

Solve For: [Sample Size](#)
 Test Type: Multivariate T² test
 Means: 80 80 72
 Contrast: 0.5 0.5 -1
 ρ's: All Equal
 σ's: All Equal

Power	Sample Size N	Number of Periods M	Means		Standard Deviation σ	Within- Subject Correlation ρ	Alpha
			Multiplier K	Contrast Σcμ			
0.9004	27	3	1	8	13	0.4	0.05
0.9025	23	3	1	8	13	0.5	0.05
0.9054	19	3	1	8	13	0.6	0.05
0.9065	36	3	1	8	15	0.4	0.05
0.9031	30	3	1	8	15	0.5	0.05
0.9102	25	3	1	8	15	0.6	0.05
0.9022	45	3	1	8	17	0.4	0.05
0.9035	38	3	1	8	17	0.5	0.05
0.9053	31	3	1	8	17	0.6	0.05

Power The probability of rejecting a false null hypothesis when the alternative hypothesis is true.
 N The number of subjects. Each subject is measured at two or more time points.
 M The number of time points at which each subject is measured.
 K The effect size multiplier. The original means are all multiplied by this value, resulting in a corresponding change in the effect size.
 Σcμ The linear combination of the means and the contrast coefficients. This represents the difference among the means that is being tested.
 σ The standard deviation across subjects at a given time point. It is assumed to be identical for all time points.
 ρ The (auto)correlation between observations made on a subject at the first and second time points.
 Alpha The probability of rejecting a true null hypothesis.

Summary Statements

A 3-period cross-over design will be used to test whether the contrast of the means is different from 0. The comparison will be made using a multivariate T² test using the contrast coefficients '0.5 0.5 -1', with a Type I error rate (α) of 0.05. The group means under the null hypothesis are assumed to be equal. The standard deviation across subjects at the same period is assumed to be 13. The assumed pattern of the covariance matrix is 'all correlations equal' (compound symmetry) with a correlation of 0.4 between adjacent time point measurements. To detect group means of '80 80 72' (or a contrast of means value of 8) with 90% power, the needed number of subjects is 27 (each measured 3 times).

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Dropout-Inflated Sample Size

Dropout Rate	Sample Size N	Dropout- Inflated Enrollment Sample Size N'	Expected Number of Dropouts D
20%	27	34	7
20%	23	29	6
20%	19	24	5
20%	36	45	9
20%	30	38	8
20%	25	32	7
20%	45	57	12
20%	38	48	10
20%	31	39	8

Dropout Rate	The percentage of subjects (or items) that are expected to be lost at random during the course of the study and for whom no response data will be collected (i.e., will be treated as "missing"). Abbreviated as DR.
N	The evaluable sample size at which power is computed. If N subjects are evaluated out of the N' subjects that are enrolled in the study, the design will achieve the stated power.
N'	The total number of subjects that should be enrolled in the study in order to obtain N evaluable subjects, based on the assumed dropout rate. After solving for N, N' is calculated by inflating N using the formula $N' = N / (1 - DR)$, with N' always rounded up. (See Julious, S.A. (2010) pages 52-53, or Chow, S.C., Shao, J., Wang, H., and Lohknygina, Y. (2018) pages 32-33.)
D	The expected number of dropouts. $D = N' - N$.

Dropout Summary Statements

Anticipating a 20% dropout rate, 34 subjects should be enrolled to obtain a final sample size of 27 subjects.

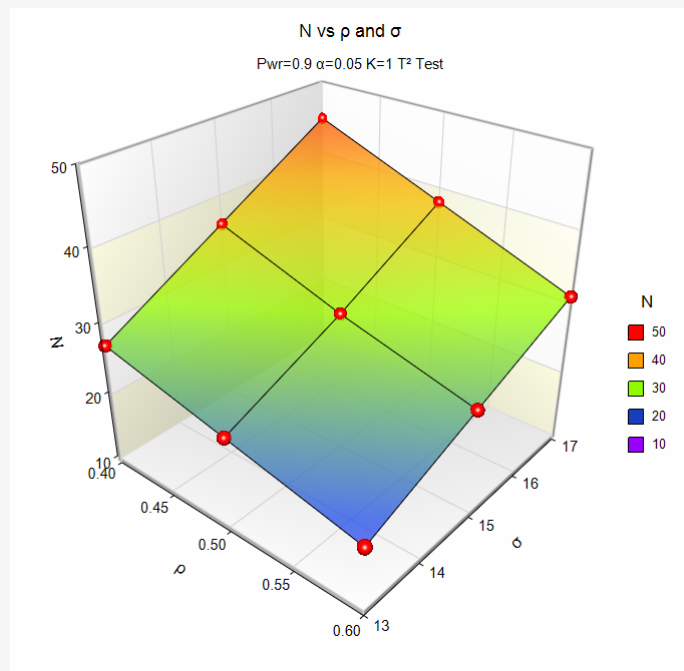
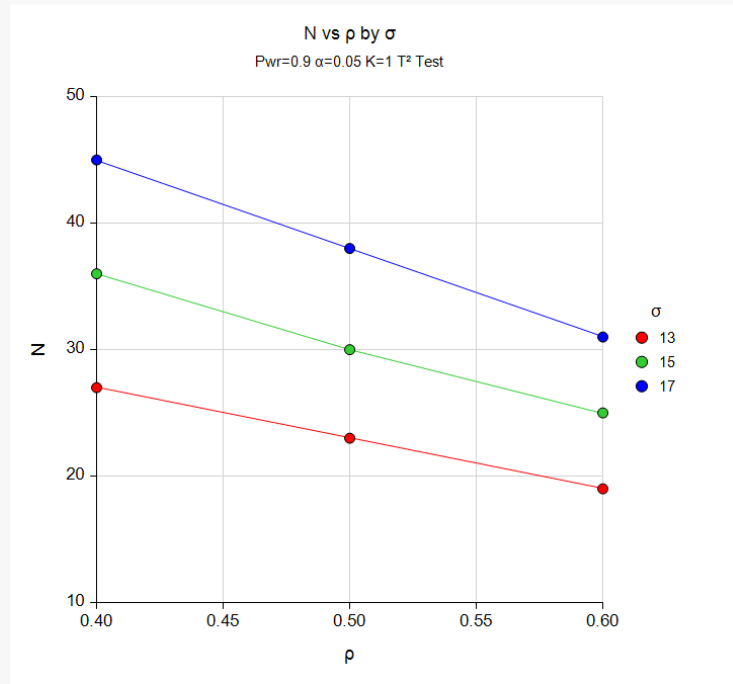
References

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- Vonesh, E.F. and Schork, M.A. 1986. 'Sample Sizes in the Multivariate Analysis of Repeated Measurements.' Biometrics, Volume 42, pages 601-610.
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This report gives the power for each value of the other parameters. The definitions are shown in the report.

Plots Section

Plots



The plots show the relationship among N , σ , and ρ when the other parameters in the design are held constant.

Example 2 – Validation using Hand Calculations

We will compute the following example by hand and then compare that with the results that PASS obtains. Here are the settings:

Test Statistic	Multivariable T^2
M	3
Means	1, 2, 3
K	1
Coefficients	-2, 1, 1
σ	5
ρ	0.5
Covariance Type	AR(1)
Alpha	0.05
N	100

Using these values, we find the following

$C'\mu$	3
$C'\Sigma C$	100
Δ	0.3
$F_{0.95,1,99}$	3.9371169
Non-Centrality	9

Power = 0.8439

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 Tab
-----
Solve For ..... Power
Test Statistic Type ..... Multivariate
Alpha..... 0.05
N (Subjects)..... 100
M (Periods) ..... 3
Means ( $\mu$ 's  $\mu_1, \mu_2, \dots, \mu_M$ ) ..... List
Means List ..... 1 2 3
K (Means Multiplier)..... 1
Contrast Coefficients..... List
Contrast Coefficients List..... -2 1 1
Pattern of  $\sigma$ 's Across Time..... Equal:  $\sigma = \sigma_1 = \sigma_2 = \dots = \sigma_M$ 
 $\sigma$  (Standard Deviation)..... 5
Pattern of  $\rho$ 's Across Time..... AR(1)
 $\rho$  (Correlation)..... 0.5
    
```

Output

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

Numeric Results

Solve For: **Power**
 Test Type: Multivariate T² test
 Means: 1 2 3
 Contrast: -2 1 1
 ρ 's: AR(1)
 σ 's: All Equal

	Sample Size N	Number of Periods M	Means		Standard Deviation σ	Within-Subject Correlation ρ	Alpha
			Multiplier K	Contrast $\Sigma\mu$			
Power	100	3	1	3	5	0.5	0.05

Note that **PASS's** power of 0.8439 matches what we obtained above by hand.