Chapter 384

Mixed Models Tests for the Slope Difference in a 2-Level Hierarchical Design with Fixed Slopes

Introduction

This procedure calculates power and sample size for a two-level longitudinal design in which subjects (level-two unit) are randomly assigned to one of two groups. Each subject is measured at several time points and the goal of the study is to compare the slopes of the two groups. If the group means are identical at the beginning of the study (which they often are in a randomized trial), testing the difference in slopes is the same as testing the difference in means at the end of the study. This is a test of the time-by-treatment interaction.

All subjects in a group are assumed to have a common slope. Each subject is assigned to receive one of two possible interventions.

Note that a companion procedure power analyzes the random-slope case in which each subject has their own slope.

Technical Details

Our formulation comes from Ahn, Heo, and Zhang (2015), chapter 5, section 5.4.1, pages 159-161. The longitudinal mixed model that is adopted is

$$Y_{ij} = \beta_0 + \xi X_{ij} + \tau T_{ij} + \delta X_{ij} T_{ij} + u_i + e_{ij}$$

where

$\quad Y_{ij} \quad$ is the continuous response of the jth measurement in the ith subject.

$\quad \beta_0 \quad$ is the fixed intercept.

$\quad X_{ij} \quad$ is an indicator variable that is 1 if subject i is assigned to group 1 and 0 otherwise.

$\quad T_{ij} \quad$ is the time value. It is assumed that $T_{ij} = j - 1$ for all i and j.

$\quad \xi \quad$ is the intervention effect at baseline and is usually expected to be zero.

$\quad \delta \quad$ is the treatment-by-time effect. It is the difference between the two treatment slopes.

$\quad u_i \quad$ is a random effect (subject-specific intercept) term for the ith subject that is distributed as $N(0, \sigma_u^2)$.

$\quad e_{ij} \quad$ is a random effect for the jth measurement in the ith subject that is distributed as $N(0, \sigma_e^2)$.

$\quad \sigma_u^2 \quad$ is variance of the subject random effects.

σ_e^2 is variance of the measurement random effects.

σ^2 is the variance of Y, where $\sigma^2 = \sigma_e^2/(1-\rho)$.

ρ is the correlation between measurements on the same subject.

K_1 is the number of subjects in group 1.

K_2 is the number of subjects in group 2.

λ is K_1/K_2.

M is the number of measurements per subject.

$V(T)$ is $\sum_{j=1}^{M}\left(T_j - \bar{T}\right)^2/M$.

The test of significance of the $X_{ij}T_{ij}$ term in the mixed model analysis is the test statistic of interest. It tests the difference of the two slopes. The power calculations assume that the estimated value of δ, called $\hat{\delta}$, has an approximate normal distribution with mean δ and known variance.

The power is calculated using

$$Power = \Phi\left\{\frac{\delta}{\sigma}\sqrt{K_2 MV(T)/[(1+\lambda^{-1})(1-\rho)]} - \Phi^{-1}(1-\alpha/2)\right\}$$

The values of the other parameters when requested are found using a binary search based on this formula.

Example 1 – Calculating Power

Researchers are planning a study of the impact of a new drug on heart rate. They want to evaluate the change in heart rate between subjects who take the new drug and subjects who take a standard drug. Their experimental protocol calls for a baseline heart rate measurement, followed by administration of the drug, followed by three additional measurements ten minutes apart. They want to be able to detect a difference of 12 in the means of the heart rate across time between the two treatments. They want a sensitivity analysis by considering a range of differences from 9 to 15.

Similar studies have found a standard deviation of 9.2. These studies also showed correlation among measurements on the same individual of 0.5. The two-sided test of the slope difference parameter will be conducted at the 0.05 significance level. The desired power is 90%. They are planning on dividing subjects equally between the treatment and control groups. They want to investigate $K1 = K2$ = 5 to 25 by 5.

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 ....**Power**
Alpha...**0.05**
K1 (Group 1 Subjects) **5 10 15 20 25**
K2 (Group 2 Subjects) **K1**
M (Measurements Per Subject) **4**
Slope Input Type...**μ1 – μ2 (Mean Difference)**
μ1 – μ2 (Mean Difference) **9 12 15**
σ (Standard Deviation).................................**9.2**
ρ (Within Subject Correlation)........................**0.5**

Output

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

Numeric Reports

Numeric Results

Solve For: Power
Groups: 1 = Treatment, 2 = Control

	Number of Subjects						Within-	
							Subject	
	Group 1	Group 2	Total	Measurements per Subject	Mean Difference	Standard Deviation	Correlation	
Power	K1	K2	K	M	μ1 - μ2	σ	ρ	Alpha
0.3709	5	5	10	4	9	9.2	0.5	0.05
0.6353	10	10	20	4	9	9.2	0.5	0.05
0.8062	15	15	30	4	9	9.2	0.5	0.05
0.9034	20	20	40	4	9	9.2	0.5	0.05
0.9541	25	25	50	4	9	9.2	0.5	0.05
0.5847	5	5	10	4	12	9.2	0.5	0.05
0.8674	10	10	20	4	12	9.2	0.5	0.05
0.9645	15	15	30	4	12	9.2	0.5	0.05
0.9915	20	20	40	4	12	9.2	0.5	0.05
0.9981	25	25	50	4	12	9.2	0.5	0.05
0.7756	5	5	10	4	15	9.2	0.5	0.05
0.9702	10	10	20	4	15	9.2	0.5	0.05
0.9970	15	15	30	4	15	9.2	0.5	0.05
0.9997	20	20	40	4	15	9.2	0.5	0.05
1.0000	25	25	50	4	15	9.2	0.5	0.05

Power	The probability of rejecting a false null hypothesis when the alternative hypothesis is true.
K	The total number of subjects.
K1 and K2	The number of subjects in groups 1 and 2, respectively.
M	The number of equally spaced measurement times.
μ1 - μ2	The difference in the two group means at the final measurement time: M - 1. $\delta = (\mu1 - \mu2) / (M - 1)$.
σ	The standard deviation of the response.
ρ	The correlation of the measurements on a subject.
Alpha	The probability of rejecting a true null hypothesis, that is, rejecting when the slopes are actually equal.

Summary Statements

A 2-group 2-level hierarchical design will have random assignment of subjects (level-2 units) to each of the 2 treatment arms (level-2 randomization), with repeated measurements (level-1 units) on each subject (over time). This design will be used to test whether the outcome trends (slopes) of the two groups are different by testing whether the 2 group means are different (μ1 - μ2) at the final time point, using the appropriate mean difference term of the linear mixed-effects model, assuming fixed slopes, with a Type I error rate (α) of 0.05. The standard deviation of Yij, assuming a fixed-slope model, is assumed to be 9.2 (this standard deviation is the square-root of the fixed-slope model variance of Yij, where the fixed-slope variance is the sum of the error term variance and the level-2 random intercept variance). The intraclass correlation coefficient of level-1 units (repeated measurements on a subject) is assumed to be 0.5. To detect a mean difference at the final time point (μ1 - μ2) of 9, with 5 subjects (level-2 units) in Group 1 and 5 subjects in Group 2, with 4 repeated measurements (level-1 units) obtained from each subject (level-2 unit), the power is 0.3709.
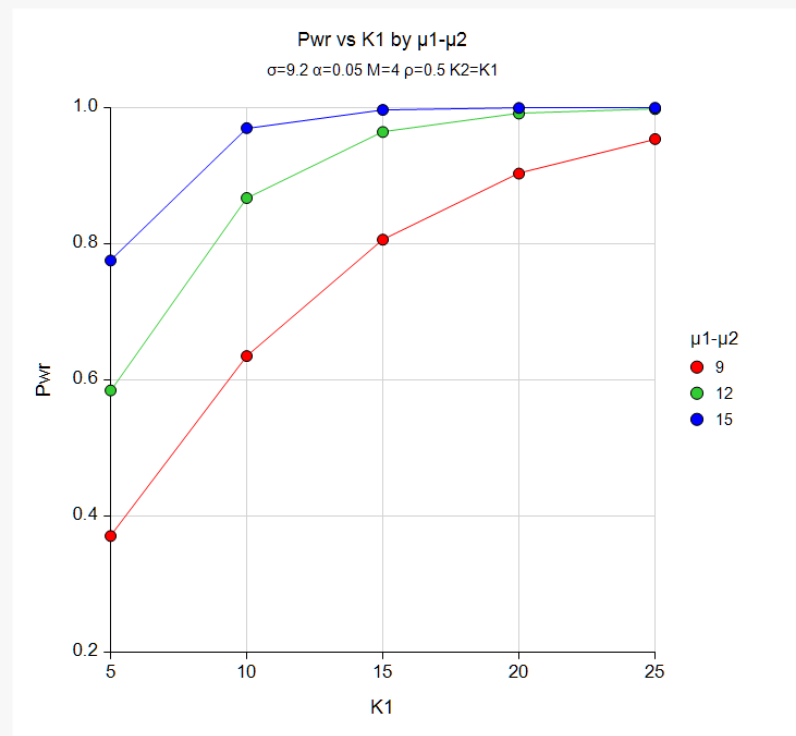
References
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Ahn, C., Heo, M., and Zhang, S. 2015. Sample Size Calculations for Clustered and Longitudinal Outcomes in
   Clinical Research. CRC Press. New York.
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This report shows the power for each of the scenarios.

Plots Section

Plots
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Pwr vs K1 by μ1-μ2
σ=9.2 α=0.05 M=4 ρ=0.5 K2=K1

Mixed Models Tests for the Slope Difference in a 2-Level Hierarchical Design with Fixed Slopes
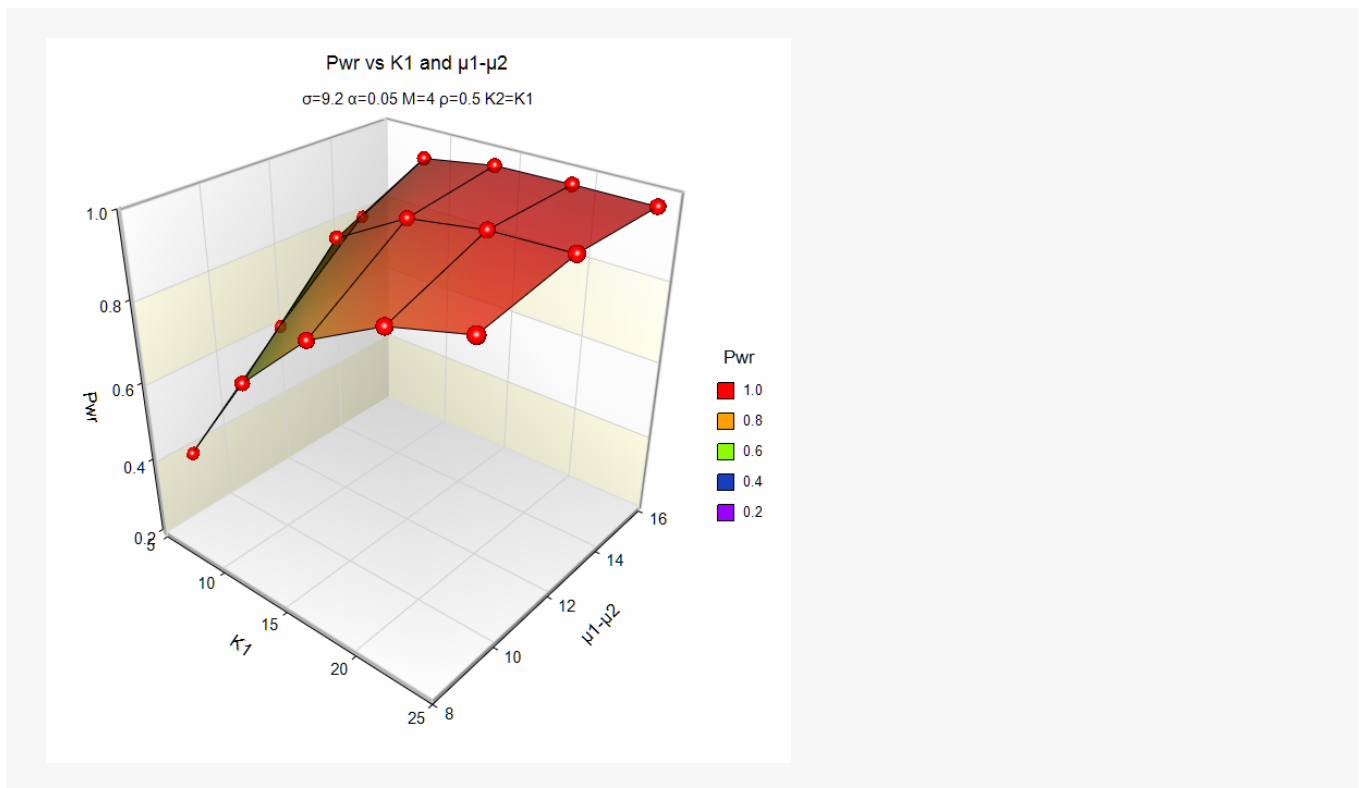
These plots show the power versus K1 for the various δ's.

Example 2 – Calculating Sample Size (Number of Subjects)

Continuing with the last example, suppose the researchers want to determine the number of subjects needed to achieve 90% power.

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
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Solve For ....**K1 (Group 1 Subjects)**
Power...**0.90**
Alpha..**0.05**
K2 (Group 2 Subjects) **K1**
M (Measurements Per Subject) **4**
Slope Input Type...**µ1 - µ2 (Mean Difference)**
µ1 - µ2 (Mean Difference)..............................**9 12 15**
σ (Standard Deviation)..................................**9.2**
ρ (Within Subject Correlation).......................**0.5**

Output

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

Numeric Results
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Solve For: K1 (Group 1 Subjects)
Groups: 1 = Treatment, 2 = Control
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| | Number of Subjects | | | | | | Within- | |
Power	Group 1 K1	Group 2 K2	Total K	Measurements per Subject M	Mean Difference µ1 - µ2	Standard Deviation σ	Subject Correlation ρ	Alpha
0.9034	20	20	40	4	9	9.2	0.5	0.05
0.9204	12	12	24	4	12	9.2	0.5	0.05
0.9302	8	8	16	4	15	9.2	0.5	0.05

This report shows the number of subjects required for each of the scenarios.

Example 3 – Validation using Ahn, Heo, and Zhang (2015)

Ahn, Heo, and Zhang (2015) page 162 provide a table in which several scenarios are reported. We will validate this procedure by duplicating the first row of their table. The following parameter settings were used: Power = 0.80; δ = 0.4; σ = 4; ρ = 0.1; M = 5; and α = 0.05. The reported value of $K1$ is 142. The achieved power is 0.802.

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 Tab

Solve For ....**K1 (Group 1 Subjects)**
Power...**0.80**
Alpha..**0.05**
K2 (Group 2 Subjects) **K1**
M (Measurements Per Subject) **5**
Slope Input Type..**δ (Slope Difference)**
δ (Slope Difference)......................................**0.4**
σ (Standard Deviation)..................................**4**
ρ (Within Subject Correlation)........................**0.1**

Output

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

Numeric Results
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Solve For: K1 (Group 1 Subjects)
Groups: 1 = Treatment, 2 = Control
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	Number of Subjects			Measurements per Subject M	Slope Difference δ	Standard Deviation σ	Within-Subject Correlation ρ	Alpha
Power	Group 1 K1	Group 2 K2	Total K					
0.802	142	142	284	5	0.4	4	0.1	0.05

PASS also calculates the value of K1 to be 142. The calculated power is also 0.802.