Chapter 361

Mixed Models Tests for Slope-Interaction in a 2×2 Factorial 2-Level Hierarchical Design with Random Slopes (Level-2 Randomization)

Introduction

This procedure calculates power and sample size for a two-level hierarchical mixed model which is randomized at the **second** level (subjects). The associated **longitudinal** study uses a 2-by-2 factorial design with two binary factors X and Z, each with two possible values (0 and 1). This results in four treatment arms. The goal of the study is to test whether the slopes of subjects across time are different from what would be expected if the effect of the two factors were additive. That is, one wants to test the three-way interaction between the two binary factors and time.

In many cases, this design is called a *repeated measures* design. The classic example is a study in which the level-2 units are subjects, and the level-1 units are time points at which measurements are taken. This factor is nested in the level-2 units.

This procedure is for longitudinal studies in which each subject is measured two or more times.

In this case of level-2 randomization, each level-2 unit (subject) is randomly assigned to one of the four treatments combinations.

Each subject is assumed to have a separate, *random* slope.

Technical Details

Our formulation comes from Ahn, Heo, and Zhang (2015), chapter 5, section 5.6, pages 172-176. The linear mixed model that is adopted is

$$Y_{ij} = \beta_0 + \delta_X X_{ij} + \delta_Z Z_{ij} + \delta_T T_{ij} + \delta_{XZ} X_{ij} Z_{ij} + \delta_{XT} X_{ij} T_{ij} + \delta_{ZT} Z_{ij} T_{ij} + \boldsymbol{\delta_{XZT} X_{ij} Z_{ij} T_{ij}} + \nu_i T_{ij} + u_i + e_{ij}$$

where

Y_{ij} is the continuous response of the j^{th} level-1 unit, within the i^{th} level-2 unit.

X_{ij} is an indicator variable that is equal to "1" if the i^{th} level-2 unit is assigned to receive intervention X and "0" otherwise. Thus, $X_{ij} = Xi$ for all *i*.

Z_{ij} is an indicator variable that is equal to "1" if the i^{th} level-2 unit is assigned to receive intervention Z and "0" otherwise. Thus, $Z_{ij} = Zi$ for all *i*.

β_0 is the fixed intercept.

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δ_X is the treatment effect of factor X.

δ_Z is the treatment effect of factor Z.

δ_{XZ} is the interaction effect of factors X and Z.

δ_{XT} is the interaction effect of factors X and Z.

δ_{ZT} is the interaction effect of factors X and Z.

δ_{XZT} is the 3-way interaction effect of X, Z, and time. **This is the coefficient of interest**.

ν_i is the random slope of the i^{th} level-2 unit. It is distributed as $N(0, \sigma_\tau^2)$.

u_i is the random intercept for the i^{th} level-2 unit. It is distributed as $N(0, \sigma_2^2)$.

e_{ij} is the level-1 random intercept effect that is distributed as $N(0, \sigma_e^2)$.

σ_τ^2 is variance of the subject-specific random slopes.

σ^2 is the variance of *Y* when slopes are fixed, where $\sigma^2 = \sigma_2^2 + \sigma_e^2$.

ρ_1 is the correlation among level-1 units which are in a particular level-2 unit.

r_τ is the ratio of the random-slope variance to the sum of the other variances. So $r_\tau = \frac{\sigma_\tau^2}{\sigma^2}$.

$K_{0,0}$ is the number of level-2 units for which X = 0 and Z = 0.

$K_{0,1}$ is the number of level-2 units for which X = 0 and Z = 1.

$K_{1,0}$ is the number of level-2 units for which X = 1 and Z = 0.

$K_{1,1}$ is the number of level-2 units for which X = 1 and Z = 1.

M is the number of level-1 units per level-2 unit. It is the number of measurement times.

The test of significance of the product $X_{ijk}Z_{ijk}T_{ijk}$ is the interaction effect of X, Z, and Time. This is the test statistic of interest. It tests whether the subject-specific slopes behave the same across all treatment combinations.

Assume that δ_{XZT} is to be tested using a Wald test. The statistical hypotheses are H_0: $\delta_{XZT} = 0$ vs. H_a: $\delta_{XZT} \neq 0$.

The power is calculated using

$$Power = \Phi\left\{\left|\frac{\delta_{XZT}}{\sigma}\right|\sqrt{\frac{K_{0,0}M\ \mathrm{Var}(T)}{f\left(\frac{1}{K_{0,0}}+\frac{1}{K_{1,1}}+\frac{1}{K_{1,0}}+\frac{1}{K_{0,1}}\right)}} - \Phi^{-1}(1-\alpha/2)\right\}$$

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Example 1 – Calculating Power

Suppose that a two-level hierarchical design is planned in which there will be two interventions. Each intervention will be whether one of two drugs is administered. There will be only one measurement per subject and the four treatments will be applied to whole clusters (level-two units). The analysis will be a mixed model of continuous data using the model given earlier in this chapter. The following parameter settings are to be used for the power analysis: $\delta_{xz\tau}$ = 7; σ = 9.7; ρ_1 = 0.06; r_τ = 0.1; M = 5 or 10; α = 0.05; and K00 = K01 = K10 = K11 = 5 to 20 by 5. Find the power of each combination of parameter settings.

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**
K00 (Group 00 Count (X=0, Z=0)) **5 10 15 20**
K01 (Group 01 Count (X=0, Z=1)) **K00**
K10 (Group 10 Count (X=1, Z=0)) **K00**
K11 (Group 11 Count (X=1, Z=1)) **K00**
M (Level 1 Units Per Level-2 Unit) **5 10**
$\delta_{xz\tau}$ (Three-Way Interaction)......................... **7**
σ (Standard Deviation).................................. **9.7**
ρ1 (Correlation Among Level-1 Units)............ **0.06**
r_τ ($V(\tau)$ / σ²) **0.1**

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Output

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

Numeric Reports

Numeric Results

Solve For: Power

Power	Total Sample Size N	Number of Level-2 Units Group 00 K00	Group 01 K01	Group 10 K10	Group 11 K11	Total K	Number of Level-1 Units per Level-2 Unit M	Three-Way Interaction δxzτ	Standard Deviation σ	Correlation Among Level-1 Units ρ1	V(τ) / σ² rτ	Alpha
0.4490	100	5	5	5	5	20	5	7	9.7	0.06	0.1	0.05
0.6763	200	5	5	5	5	20	10	7	9.7	0.06	0.1	0.05
0.7359	200	10	10	10	10	40	5	7	9.7	0.06	0.1	0.05
0.9277	400	10	10	10	10	40	10	7	9.7	0.06	0.1	0.05
0.8874	300	15	15	15	15	60	5	7	9.7	0.06	0.1	0.05
0.9870	600	15	15	15	15	60	10	7	9.7	0.06	0.1	0.05
0.9558	400	20	20	20	20	80	5	7	9.7	0.06	0.1	0.05
0.9980	800	20	20	20	20	80	10	7	9.7	0.06	0.1	0.05

Power The probability of rejecting a false null hypothesis when the alternative hypothesis is true.
N The total number of Level-1 units in the study.
K00 The number of Level-2 units in Group (0,0) (the group in which X = 0 and Z = 0).
K01 The number of Level-2 units in Group (0,1) (the group in which X = 0 and Z = 1).
K10 The number of Level-2 units in Group (1,0) (the group in which X = 1 and Z = 0).
K11 The number of Level-2 units in Group (1,1) (the group in which X = 1 and Z = 1).
K The total number of Level-2 units in the study.
M The number of Level-1 units per Level-2 unit (i.e., the number of time points).
δxzτ The three-way interaction among the subject-specific slopes (β11 - β10) - (β01 - β00) at which the power is calculated.
σ The standard deviation of the Yijk assuming a fixed-slope model.
ρ1 The correlation among Level-1 units in a particular Level-2 unit.
rτ The ratio of the subject-specific slope variance, V(τ), to σ².
Alpha The probability of rejecting a true null hypothesis.

Summary Statements

A 2×2 factorial (X = 0,1 and Z = 0,1) 2-level design will have random assignment of subjects (level-2 units) to each of the 4 treatment arms (Groups 00, 01, 10, and 11), with repeated measurements (level-1 units) on each subject (over time). This design will be used to test whether the outcome trends (slopes) are different for each of the treatment combinations (or, equivalently, whether the group combination mean differences change across time). This hypothesis will be evaluated by testing the three-way interaction term (X × Z × time) of the linear mixed-effects model, assuming random slopes, with a Type I error rate (α) of 0.05. This interaction is formed from the four group slopes across time using the following formula: δxzτ = (β11 - β10) - (β01 - β00). The standard deviation of Yij, assuming a fixed-slope model, is assumed to be 9.7 (this standard deviation is the square-root of the fixed-slope model variance of Yij (σ²), where the variance is the sum of the error term variance and the level-2 random intercept variance). The ratio of the subject-specific random slope variance to σ² (V(τ) / σ²) is assumed to be 0.1 (the variance of Yij, assuming a random-slope model, is σ² + V(τ) × T[k]²). The intraclass correlation coefficient of level-1 units (repeated measurements on a subject) is assumed to be 0.06. To detect a three-way interaction among the subject-specific slopes (δxzτ) of at least 7, with level-2 (subject-level) sample sizes of 5 in Group 00 (X = 0, Z = 0), 5 in Group 01 (X = 0, Z = 1), 5 in Group 10 (X = 1, Z = 0), and 5 in Group 11 (X = 1, Z = 1), with 5 level-1 units (repeated measurements) obtained from each level-2 unit (subject) (for a grand total of 100 level-1 measurements), the power is 0.449.

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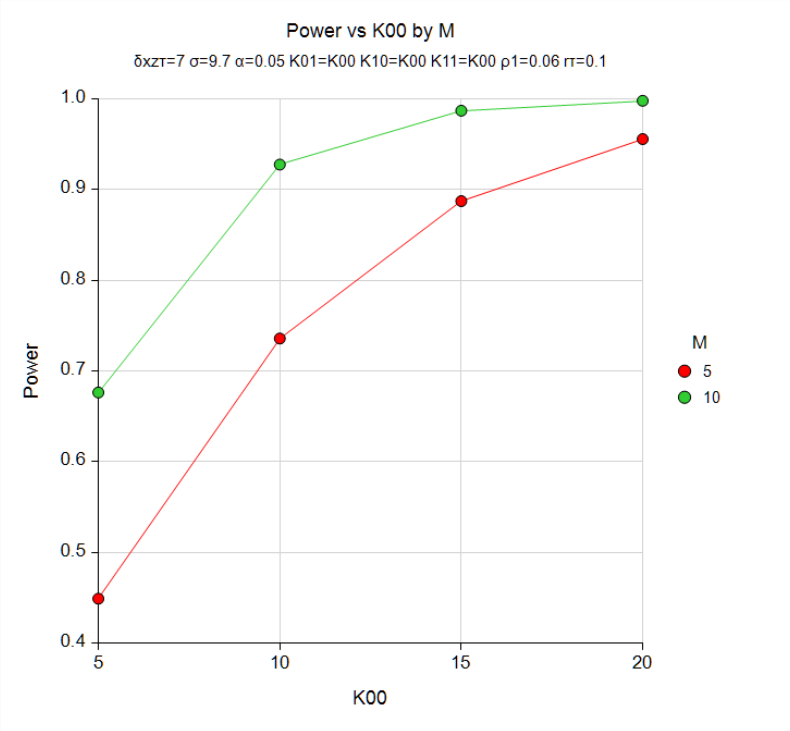
References

Ahn, C., Heo, M., and Zhang, S. 2015. Sample Size Calculations for Clustered and Longitudinal Outcomes in Clinical Research. CRC Press. New York.

This report shows the power for each of the scenarios.

Plots Section

Plots



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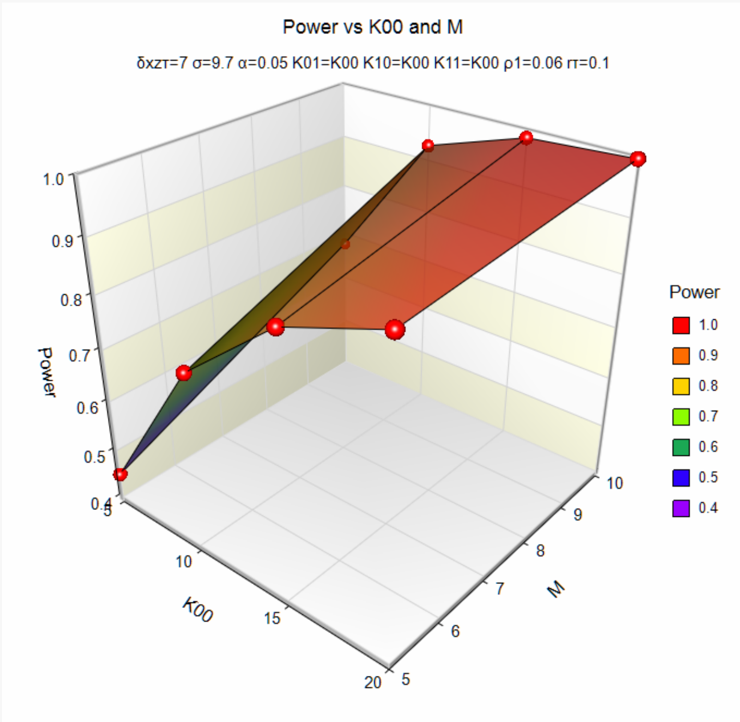

These plots show the power for the various parameter settings.

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Example 2 – Calculating Sample Size (K00)

Continuing with the last example, suppose the researchers want to determine the value of K00 needed to achieve 90% power for both values of M.

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 .... **K00 (Group 00 Count (X=0, Z=0))**
Power... **0.90**
Alpha.. **0.05**
K01 (Group 01 Count (X=0, Z=1)) **K00**
K10 (Group 10 Count (X=1, Z=0)) **K00**
K11 (Group 11 Count (X=1, Z=1)) **K00**
M (Level 1 Units Per Level-2 Unit) **5 10**
δxzτ (Three-Way Interaction)......................... **7**
σ (Standard Deviation).................................. **9.7**
ρ1 (Correlation Among Level-1 Units)........... **0.06**
rτ (V(τ) / σ²) **0.1**

Output

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

Numeric Results

Solve For: K00 (Group 00 Count (X=0, Z=0))

		Number of Level-2 Units										
Power	Total Sample Size N	Group 00 K00	Group 01 K01	Group 10 K10	Group 11 K11	Total K	Number of Level-1 Units per Level-2 Unit M	Three-Way Interaction δxzτ	Standard Deviation σ	Correlation Among Level-1 Units ρ1	V(τ) / σ² rτ	Alpha
0.9061	320	16	16	16	16	64	5	7	9.7	0.06	0.1	0.05
0.9003	360	9	9	9	9	36	10	7	9.7	0.06	0.1	0.05

This report shows the power for each of the scenarios.

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

Ahn, Heo, and Zhang (2015) page 176 provide a table in which several scenarios are reported. We will validate this procedure by duplicating the fifth row. The following parameter settings are to be used for the power analysis: $\delta_{xz\tau}$ = 0.4; σ = 4; ρ_1 = 0.1; r_τ = 0.1; M = 5; power = 0.8; and α = 0.05. The reported value of K00, K01, K10, K11 is 597 and the attained power at 0.800.

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 .... **K00 (Group 00 Count (X=0, Z=0))**
Power.. **0.80**
Alpha... **0.05**
K01 (Group 01 Count (X=0, Z=1)) **K00**
K10 (Group 10 Count (X=1, Z=0)) **K00**
K11 (Group 11 Count (X=1, Z=1)) **K00**
M (Level 1 Units Per Level-2 Unit) **5**
$\delta_{xz\tau}$ (Three-Way Interaction)......................... **0.4**
σ (Standard Deviation).................................. **4**
ρ_1 (Correlation Among Level-1 Units)............ **0.1**
r_τ ($V(\tau)$ / σ²) **0.1**

Output

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

Numeric Results

Solve For: K00 (Group 00 Count (X=0, Z=0))

Power	Total Sample Size N	Number of Level-2 Units Group 00 K00	Group 01 K01	Group 10 K10	Group 11 K11	Total K	Number of Level-1 Units per Level-2 Unit M	Three-Way Interaction $\delta_{xz\tau}$	Standard Deviation σ	Correlation Among Level-1 Units ρ_1	$V(\tau)$ / σ² r_τ	Alpha
0.8003	11940	597	597	597	597	2388	5	0.4	4	0.1	0.1	0.05

PASS also calculates the value of K00 to be 597 and the power as 0.8003.

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