Chapter 365

Mixed Models Tests for Slope-Interaction in a 2×2 Factorial 3-Level Hierarchical Design with Random Slopes (Level-3 Randomization)

Introduction

This procedure calculates power and sample size for a three-level hierarchical mixed model which is randomized at the **third** level. 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 most cases, this design is called a *repeated measures* design. The classic example is a study in which the level-2 units are subjects which are nested in level-3 units (e.g., classes, clinics, or hospitals). 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-3 randomization, each level-3 unit is randomly assigned to one of the four treatments combinations. All level-1 and level-2 units within a specific level-3 unit receive the same interventions (treatment).

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

Technical Details

Our formulation comes from Ahn, Heo, and Zhang (2015), chapter 6, section 6.6.1, pages 218-222. The hierarchical mixed model that is adopted is

$$Y_{ij} = \beta_0 + \delta_X X_{ijk} + \delta_Z Z_{ijk} + \delta_T T_{ijk} + \delta_{XZ} X_{ijk} Z_{ijk} + \delta_{XT} X_{ijk} T_{ijk} + \delta_{ZT} Z_{ijk} T_{ijk} + \boldsymbol{\delta_{XZT} X_{ijk} Z_{ijk} T_{ijk}} + \nu_{j(i)} T_{ijk} + u_i + u_{j(i)} + e_{ijk}$$

where

Y_{ijk} is the continuous response of the k^{th} level-1 unit, within the j^{th} level-2 unit, within the i^{th} level-3 unit.

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

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

β_0 is the fixed intercept.

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**.

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

u_i is the level-3 random intercept effect for the i^{th} level-3 unit. It is distributed as $N(0, \sigma_3^2)$.

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

e_{ijk} 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 $\sigma^2 = \sigma_3^2 + \sigma_2^2 + \sigma_e^2$.

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 $r_\tau = \frac{\sigma_\tau^2}{\sigma^2}$.

$C_{0,0}$ is the number of level-3 units for which X = 0 and Z = 0.

$C_{0,1}$ is the number of level-3 units for which X = 0 and Z = 1.

$C_{1,0}$ is the number of level-3 units for which X = 1 and Z = 0.

$C_{1,1}$ is the number of level-3 units for which X = 1 and Z = 1.

K is the average number of level-2 units (subjects) per level-3 unit.

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 $H_0\colon \delta_{XZT} = 0$ vs. $H_a\colon \delta_{XZT} \neq 0$.

The power is calculated using

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

where $f = 1 - \rho_1 + r_\tau\, M\, \mathrm{Var}(T)$ and $\mathrm{Var}(T) = \sum_{j=1}^{M}\left(T_j - \bar{T}\right)^2 / M$.

Example 1 – Calculating Power

Suppose that a three-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 five measurements per subject and the four treatments will be applied to level-3 units. A range of level-2 units are planned in each treatment group. The available level-3 units will be randomly assigned on one of the four groups.

The analysis will be a mixed model of continuous data using the model given earlier in this chapter. The goal of the study is to test the regression coefficient of the XZT interaction. The following parameter settings are to be used for the power analysis: δ_{XZT} = 3; σ = 9.8; ρ1 = 0.1; r_T = 0.1; K = 5 or 10; M = 5; α = 0.05; and C00 = C01 = C10 = C11 = 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**
C00 (Group 00 Count (X=0, Z=0))	**5 10 15 20**
C01 (Group 01 Count (X=0, Z=1))	**C00**
C10 (Group 10 Count (X=1, Z=0))	**C00**
C11 (Group 11 Count (X=1, Z=1))	**C00**
K (Level 2 Units Per Level-3 Unit)	**5 10**
M (Level 1 Units Per Level-2 Unit)	**5**
δxzт (Three-Way Interaction)	**3**
σ (Standard Deviation)	**9.8**
ρ1 (Correlation Among Level-1 Units)	**0.1**
rт (V(τ) / σ²)	**0.1**

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-3 Units Group 00 C00	Group 01 C01	Group 10 C10	Group 11 C11	Total C	Number of Level-2 Units per Level-3 Unit 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
0.4191	500	5	5	5	5	20	5	5	3	9.8	0.1	0.1	0.05
0.6995	1000	5	5	5	5	20	10	5	3	9.8	0.1	0.1	0.05
0.6995	1000	10	10	10	10	40	5	5	3	9.8	0.1	0.1	0.05
0.9396	2000	10	10	10	10	40	10	5	3	9.8	0.1	0.1	0.05
0.8602	1500	15	15	15	15	60	5	5	3	9.8	0.1	0.1	0.05
0.9904	3000	15	15	15	15	60	10	5	3	9.8	0.1	0.1	0.05
0.9396	2000	20	20	20	20	80	5	5	3	9.8	0.1	0.1	0.05
0.9987	4000	20	20	20	20	80	10	5	3	9.8	0.1	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.
C00 The number of Level-3 units in Group (0,0) (the group in which X = 0 and Z = 0).
C01 The number of Level-3 units in Group (0,1) (the group in which X = 0 and Z = 1).
C10 The number of Level-3 units in Group (1,0) (the group in which X = 1 and Z = 0).
C11 The number of Level-3 units in Group (1,1) (the group in which X = 1 and Z = 1).
C The total number of Level-3 units.
K The number of Level-2 units (subjects) per Level-3 unit.
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) 3-level hierarchical design will have subjects (level-2 units) in clusters (level-3 units, e.g., classes, clinics, or hospitals), with random assignment of clusters to each of the 4 treatment arms (Groups 00, 01, 10, and 11) (level-3 randomization), and 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 Yijk, assuming a fixed-slope model, is assumed to be 9.8 (this standard deviation is the square-root of the fixed-slope model variance of Yijk (σ²), where the variance is the sum of the error term variance, the level-2 random intercept variance, and the level-3 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 Yijk, 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 0.1. To detect a three-way interaction among the subject-specific slopes (δxzτ) of at least 3, with level-3 (cluster-level) sizes of 5 clusters in Group 00 (X = 0, Z = 0), 5 clusters in Group 01 (X = 0, Z = 1), 5 clusters in Group 10 (X = 1, Z = 0), and 5 clusters in Group 11 (X = 1, Z = 1), with 5 level-2 units (subjects) in each cluster, and with 5 level-1 units (repeated measurements) obtained from each level-2 unit (for a grand total of 500 level-1 measurements), the power is 0.4191.

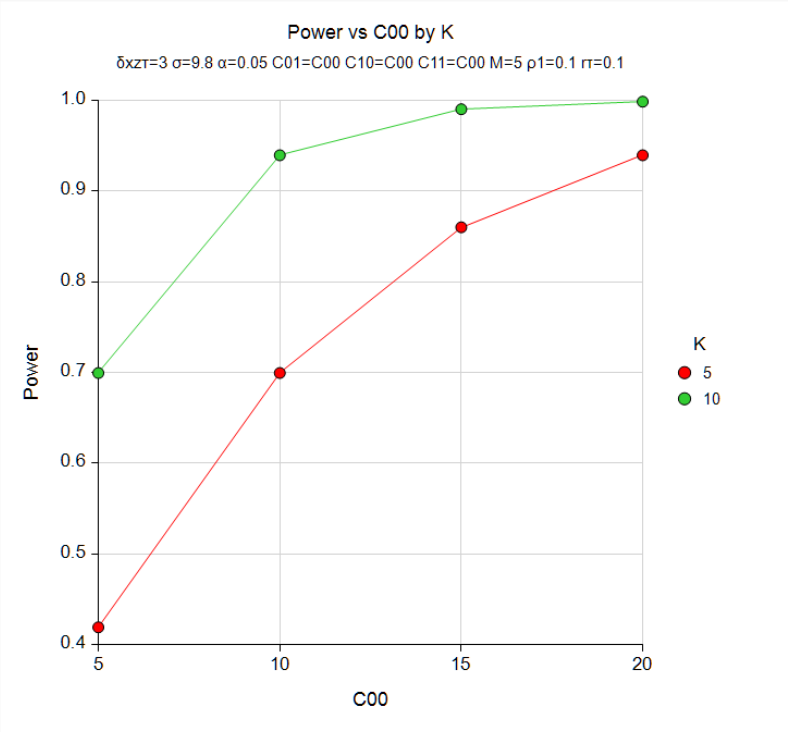
References

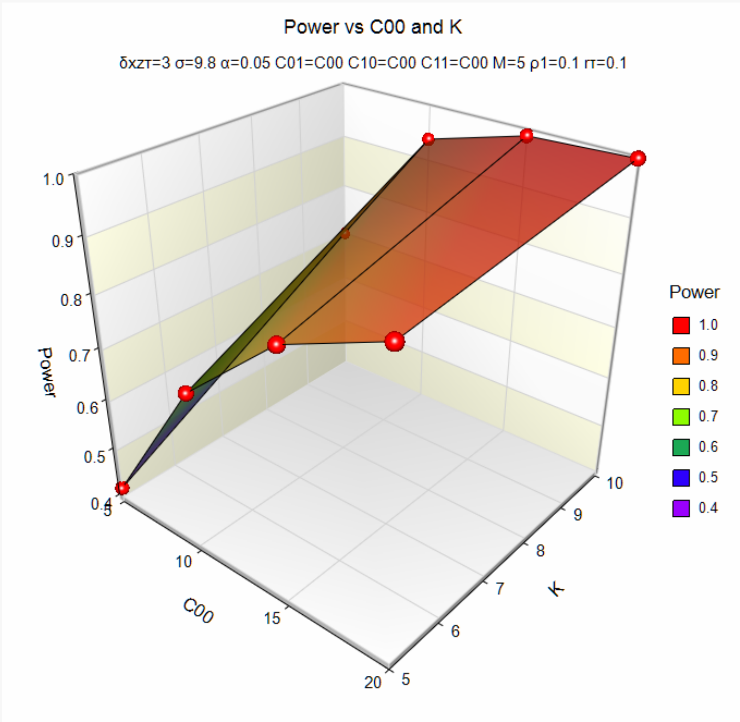
Ahn, C., Heo, M., and Zhang, S. 2015. Sample Size Calculations for Clustered and Longitudinal Outcomes in Clinical Research. CRC Press. New York.

This report shows the power for each of the scenarios.

Plots Section

Plots





These plots show the power for the various parameter settings.

Example 2 – Calculating Sample Size (C00)

Continuing with the last example, suppose the researchers want to determine the value of C00 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 .... **C00 (Group 00 Count (X=0, Z=0))**
Power... **0.90**
Alpha... **0.05**
C01 (Group 01 Count (X=0, Z=1)) **C00**
C10 (Group 10 Count (X=1, Z=0)) **C00**
C11 (Group 11 Count (X=1, Z=1)) **C00**
K (Level 2 Units Per Level-3 Unit)................. **5 10**
M (Level 1 Units Per Level-2 Unit) **5**
δxzτ (Three-Way Interaction)........................ **3**
σ (Standard Deviation).................................. **9.8**
ρ1 (Correlation Among Level-1 Units)........... **0.1**
rτ (V(τ) / σ²) **0.1**

Output

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

Numeric Results

Solve For: C00 (Group 00 Count (X=0, Z=0))

Power	Total Sample Size N	Number of Level-3 Units: Group 00 C00	Group 01 C01	Group 10 C10	Group 11 C11	Total C	Number of Level-2 Units per Level-3 Unit 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
0.9149	1800	18	18	18	18	72	5	5	3	9.8	0.1	0.1	0.05
0.9149	1800	9	9	9	9	36	10	5	3	9.8	0.1	0.1	0.05

This report shows the required C00 count for each of the scenarios.

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

Ahn, Heo, and Zhang (2015) page 222 provide a table in which several scenarios are reported. We will validate this procedure by duplicating the seventh row. The following parameter settings are used for the power analysis: Power = 0.80; δ_{XZT} = 0.3; σ = 4; ρ1 = 0.1; rτ = 0.1; *M* = 5; K = 8; and *α* = 0.05. The values of C00, C01, C10, C11 are found to be 133 and the resulting power is 0.801.

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 .... **C00 (Group 00 Count (X=0, Z=0))**
Power... **0.80**
Alpha.. **0.05**
C01 (Group 01 Count (X=0, Z=1)) **C00**
C10 (Group 10 Count (X=1, Z=0)) **C00**
C11 (Group 11 Count (X=1, Z=1)) **C00**
K (Level 2 Units Per Level-3 Unit)................. **8**
M (Level 1 Units Per Level-2 Unit) **5**
δxzτ (Three-Way Interaction)......................... **0.3**
σ (Standard Deviation).................................. **4**
ρ1 (Correlation Among Level-1 Units)........... **0.1**
rτ (V(τ) / σ²) **0.1**

Output

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

Numeric Results

Solve For: C00 (Group 00 Count (X=0, Z=0))

	Total	Number of Level-3 Units					Number	Number			Correlation		
Power	Total Sample Size N	Group 00 C00	Group 01 C01	Group 10 C10	Group 11 C11	Total C	Number of Level-2 Units per Level-3 Unit 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
0.8013	21280	133	133	133	133	532	8	5	0.3	4	0.1	0.1	0.05

PASS also calculates C00 to be 133 and the power to be 0.8013.