Power and Sample Size for the Most Common Hypotheses in Mixed Models

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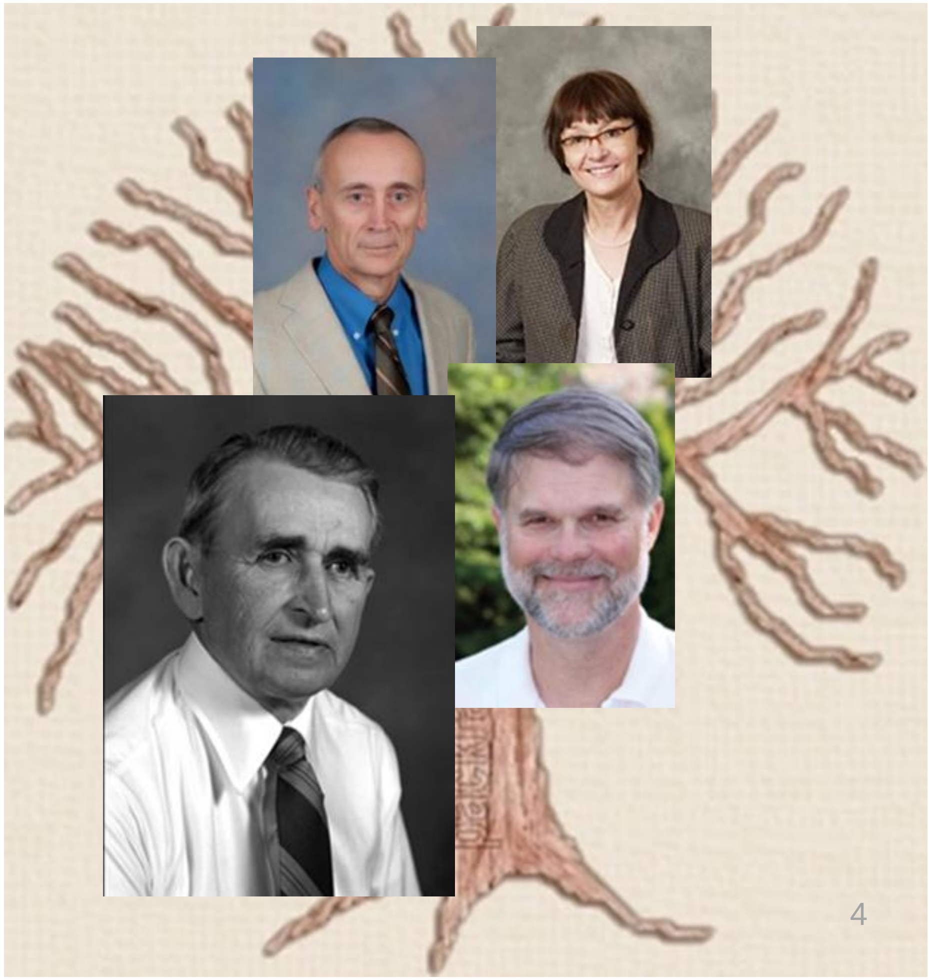
Outline

- Mixed Model (MM): Longitudinal and Multi-level Data
- Common Hypothesis Tests in the Linear MM
- **Reversibility**: Linear MM as General Linear Multivariate Model (GLMM)
- Power and Sample Size for GLMM
- **Goal**: Power and Sample Size for Fixed Effects in the Linear MM
- Missing Data
- Summary, Segue to Software Solution: GLIMMPSE

Prof. Frank Graybill's Legacy

- *Exemplary data* approach $\Rightarrow$ Noncentral F approx. for power in mixed model (O'Brien and Muller, 1993)
- Based on earlier ideas of Graybill (1976)
- Later generalized to multivariate case by Muller and Peterson (1984)



Mixed Models Commonly Used for Longitudinal and Multi-level data

- Linear MM: Laird and Ware, 1982; Demidenko, 2004; Muller and Stewart, 2007
- Nonlinear MM: Lindstrom and Bates, 1980
- Longitudinal/prospective studies - designed
  - Randomized clinical trials, individuals
  - Cluster randomized studies
- Longitudinal/prospective studies - observational
  - Cohort studies, natural history
- Multi-level - designed
  - Cluster randomized studies
- Multi-level - observational
  - Clustered +/- longitudinal

General Linear Mixed Model Formulation - Muller and Stewart (2007)

$$\begin{array}{rcccc} \boldsymbol{y}_i & = & \boldsymbol{X}_i\boldsymbol{\beta} & + & \boldsymbol{Z}_i\boldsymbol{d}_i + \boldsymbol{e}_i \\ & = & \boldsymbol{X}_i\boldsymbol{\beta} & + & \boldsymbol{e}_{+i} \\ & = & \text{fixed} & + & \text{random} \\ & & \uparrow & & \uparrow \\ & & \mathrm{E}(\boldsymbol{y}_i) & & \mathcal{V}(\boldsymbol{y}_i) \\ & & \text{model} & & \text{model} \end{array}$$

With Gaussian errors indicates

$$\begin{bmatrix} \boldsymbol{d}_i \\ \boldsymbol{e}_i \end{bmatrix} \sim \mathcal{N}_{m+p_i}\left\{ \begin{bmatrix} \mathbf{0} \\ \mathbf{0} \end{bmatrix}, \begin{bmatrix} \boldsymbol{\Sigma}_{di}(\boldsymbol{\tau}_d) & \mathbf{0} \\ \mathbf{0} & \boldsymbol{\Sigma}_{ei}(\boldsymbol{\tau}_e) \end{bmatrix} \right\}$$

Population average version combines the randomness:

$$\boldsymbol{y}_i = \boldsymbol{X}_i\boldsymbol{\beta} + \boldsymbol{e}_{+i}$$

Power for the Most Common Hypothesis Tests for the Linear Mixed Model

A) Power for testing fixed effects (means)

B) Power for testing random effects (covariance)

C) Power for testing fixed and random effects

General and accurate power and sample size methodology is not available.

There are, however, good methods for most of class A.

Power and Sample Size for Fixed Effects in the Linear Mixed Model

- **Key idea**: Some LMM can be recast as GLMM
- Which ones?
  – No missing data and no mistimed data
  – Unstructured covariance model across responses (a robust, safe, conservative assumption)
  – Typical clinical trial or longitudinal study in which main inference is about time by treatment interaction
- Why do we care?
  – Muller, et al (1992) show how to do power for time by treatment using GLMM framework!

Reversibility: The Linear Mixed Model as a General Linear Multivariate Model

- A General Linear Multivariate Model (GLMM) has rows (subjects) and columns (repeated measures or multiple outcomes): $\boldsymbol{Y} = \boldsymbol{X}\boldsymbol{B} + \boldsymbol{E}$

- Equations 12.1-12.7 in Muller and Stewart (2007) allow seeing the LMM as a stacked (by subject) GLMM

Reversibility: Six Steps from a GLMM to a LMM

$$\text{vec}(\boldsymbol{Y}') = \text{vec}\left[(\boldsymbol{X_M B})'\right] + \text{vec}(\boldsymbol{E}')$$

$$\begin{bmatrix} \boldsymbol{Y}_1' \\ \boldsymbol{Y}_2' \\ \vdots \\ \boldsymbol{Y}_N' \end{bmatrix} = \begin{bmatrix} (\boldsymbol{X}_{M1}\boldsymbol{B})' \\ (\boldsymbol{X}_{M2}\boldsymbol{B})' \\ \vdots \\ (\boldsymbol{X}_{MN}\boldsymbol{B})' \end{bmatrix} + \begin{bmatrix} \boldsymbol{E}_1' \\ \boldsymbol{E}_2' \\ \vdots \\ \boldsymbol{E}_N' \end{bmatrix}$$

$$\begin{bmatrix} \boldsymbol{Y}_1' \\ \boldsymbol{Y}_2' \\ \vdots \\ \boldsymbol{Y}_N' \end{bmatrix} = (\boldsymbol{X_M} \otimes \boldsymbol{I}_p)\text{vec}(\boldsymbol{B}') + \begin{bmatrix} \boldsymbol{E}_1' \\ \boldsymbol{E}_2' \\ \vdots \\ \boldsymbol{E}_N' \end{bmatrix}$$

1. Stack GLMM by Independent Sampling Unit (ISU)
2. Distribute *vec* operator
3. Summarize common Design Matrix across the $\boldsymbol{Y}_i'$

Reversibility: Six Steps from a GLMM to a LMM, cont'd

$$\begin{bmatrix} \boldsymbol{Y}_1' \\ \boldsymbol{Y}_2' \\ \vdots \\ \boldsymbol{Y}_N' \end{bmatrix} = (\boldsymbol{X_M} \otimes \boldsymbol{I}_p) \begin{bmatrix} \boldsymbol{B}_1' \\ \boldsymbol{B}_2' \\ \vdots \\ \boldsymbol{B}_q' \end{bmatrix} + \begin{bmatrix} \boldsymbol{E}_1' \\ \boldsymbol{E}_2' \\ \vdots \\ \boldsymbol{E}_N' \end{bmatrix}$$

4. Distribute *vec* operator on $\boldsymbol{B}_i'$

$$\begin{bmatrix} \boldsymbol{Y}_1' \\ \boldsymbol{Y}_2' \\ \vdots \\ \boldsymbol{Y}_N' \end{bmatrix} = \begin{bmatrix} x_{M11}\boldsymbol{I}_p & x_{M12}\boldsymbol{I}_p & \cdots & x_{M1q}\boldsymbol{I}_p \\ x_{M21}\boldsymbol{I}_p & x_{M22}\boldsymbol{I}_p & \cdots & x_{M2q}\boldsymbol{I}_p \\ \vdots & \vdots & \ddots & \vdots \\ x_{MN1}\boldsymbol{I}_p & x_{MN2}\boldsymbol{I}_p & \cdots & x_{MNq}\boldsymbol{I}_p \end{bmatrix} \begin{bmatrix} \boldsymbol{B}_1' \\ \boldsymbol{B}_2' \\ \vdots \\ \boldsymbol{B}_q' \end{bmatrix} + \begin{bmatrix} \boldsymbol{E}_1' \\ \boldsymbol{E}_2' \\ \vdots \\ \boldsymbol{E}_N' \end{bmatrix}$$

5. Expand Kronecker Design feature

$$\boldsymbol{Y}_i' = (\boldsymbol{X}_{Mi} \otimes \boldsymbol{I}_p)\text{vec}(\boldsymbol{B}') + \boldsymbol{E}_i'$$

6. Recognize equation for a single ISU as a *general* LMM

Reversibility: Stated Simply

Two equivalent representations for the regression equation for subject *i*:

$\boldsymbol{Y}_i' = (\boldsymbol{X}_{Mi} \otimes \boldsymbol{I}_p)\text{vec}(\boldsymbol{B}') + \boldsymbol{E}_i'$ Stacked Multivariate Model

$$\Leftrightarrow$$

$\boldsymbol{y}_i = \boldsymbol{X}_{mi}\boldsymbol{\beta} + \boldsymbol{e}_{+i}$ Population Average Mixed Model

where $\boldsymbol{X}_{Mi} \otimes \boldsymbol{I}_p = \boldsymbol{X}_{mi}$ and $\text{vec}(\boldsymbol{B}') = \boldsymbol{\beta}$

Conditions for Reversibility

- As a special case of a LMM, the defining characteristics of a GLMM are "Kronecker design" and "Kronecker covariance."
- Kronecker design requires a common design matrix for all response variables (columns of $\boldsymbol{Y}$, which may be repeated measures).
- Kronecker covariance requires a common covariance matrix for all independent sampling units (rows of $\boldsymbol{Y}$, which may be persons).
- Need to keep track of:
  - What's an ISU (often person) and what's an observation
  - Between ISU factors vs. within ISU factors

GLMM $\Rightarrow$ LMM: Start with GLMM

Y_1	Y_2	Y_3	X_1	X_2	X_3	X_4	E1	E2	E3
$Y_{1,1,1}$	$Y_{1,2,1}$	$Y_{1,3,1}$	1	0	0	0	$E_{1,1,1}$	$E_{1,2,1}$	$E_{1,3,1}$
$Y_{2,1,1}$	$Y_{2,2,1}$	$Y_{2,3,1}$	1	0	0	0	$E_{2,1,1}$	$E_{2,2,1}$	$E_{2,3,1}$
.	.	.	1	0	0	0	.	.	.
$Y_{n1,1,1}$	$Y_{n1,2,1}$	$Y_{n1,3,1}$	1	0	0	0	$E_{n1,1,1}$	$E_{n1,2,1}$	$E_{n1,3,1}$
$Y_{1,1,2}$	$Y_{1,2,2}$	$Y_{1,3,2}$	0	1	0	0	$E_{1,1,2}$	$E_{1,2,2}$	$E_{1,3,2}$
$Y_{2,1,2}$	$Y_{2,2,2}$	$Y_{2,3,2}$	0	1	0	0	$E_{2,1,2}$	$E_{2,2,2}$	$E_{2,3,2}$
.	.	.	0	1	0	0	.	.	.
$Y_{n2,1,2}$	$Y_{n2,2,2}$	$Y_{n2,3,2}$	0	1	0	0	$E_{n2,1,2}$	$E_{n2,2,2}$	$E_{n2,3,2}$
$Y_{1,1,3}$	$Y_{1,2,3}$	$Y_{1,3,3}$	0	0	1	0	$E_{1,1,3}$	$E_{1,2,3}$	$E_{1,3,3}$
$Y_{2,1,3}$	$Y_{2,2,3}$	$Y_{2,3,3}$	0	0	1	0	$E_{2,1,3}$	$E_{2,2,3}$	$E_{2,3,3}$
.	.	.	0	0	1	0	.	.	.
$Y_{n3,1,3}$	$Y_{n3,2,3}$	$Y_{n3,3,3}$	0	0	1	0	$E_{n3,1,3}$	$E_{n3,2,3}$	$E_{n3,3,3}$
$Y_{1,1,4}$	$Y_{1,2,4}$	$Y_{1,3,4}$	0	0	0	1	$E_{1,1,4}$	$E_{1,2,4}$	$E_{1,3,4}$
$Y_{2,1,4}$	$Y_{2,2,4}$	$Y_{2,3,4}$	0	0	0	1	$E_{2,1,4}$	$E_{2,2,4}$	$E_{2,3,4}$
.	.	.	0	0	0	1	.	.	.
$Y_{n4,1,4}$	$Y_{n4,2,4}$	$Y_{n4,3,4}$	0	0	0	1	$E_{n4,1,4}$	$E_{n4,2,4}$	$E_{n4,3,4}$

GLMM ⇒ LMM: Steps 1 - 3

vec(Y′)	$X_M \otimes I_p$												vec(E′)
	X_1	X_2	X_3	X_4	X_5	X_6	X_7	X_8	X_9	X_{10}	X_{11}	X_{12}	
$Y_{1,1,1}$	1	0	0	0	0	0	0	0	0	0	0	0	$E_{1,1,1}$
$Y_{1,2,1}$	0	1	0	0	0	0	0	0	0	0	0	0	$E_{1,2,1}$
$Y_{1,3,1}$	0	0	1	0	0	0	0	0	0	0	0	0	$E_{1,3,1}$
$Y_{2,1,1}$	1	0	0	0	0	0	0	0	0	0	0	0	$E_{2,1,1}$
$Y_{2,2,1}$	0	1	0	0	0	0	0	0	0	0	0	0	$E_{2,2,1}$
$Y_{2,3,1}$	0	0	1	0	0	0	0	0	0	0	0	0	$E_{2,3,1}$
.	.	.	.	.	.	.	.	.	.	.	.	.	.
$Y_{2,1,2}$	0	0	0	1	0	0	0	0	0	0	0	0	$E_{1,1,2}$
$Y_{2,2,2}$	0	0	0	0	1	0	0	0	0	0	0	0	$E_{1,2,2}$
$Y_{2,3,2}$	0	0	0	0	0	1	0	0	0	0	0	0	$E_{1,3,2}$
.	.	.	.	.	.	.	.	.	.	.	.	.	.
$Y_{1,1,3}$	0	0	0	0	0	0	1	0	0	0	0	0	$E_{1,1,3}$
$Y_{1,2,3}$	0	0	0	0	0	0	0	1	0	0	0	0	$E_{1,2,3}$
$Y_{1,3,3}$	0	0	0	0	0	0	0	0	1	0	0	0	$E_{1,3,3}$
.	.	.	.	.	.	.	.	.	.	.	.	.	.
$Y_{1,1,4}$	0	0	0	0	0	0	0	0	0	1	0	0	$E_{1,1,4}$
$Y_{1,2,4}$	0	0	0	0	0	0	0	0	0	0	1	0	$E_{1,2,4}$
$Y_{1,3,4}$	0	0	0	0	0	0	0	0	0	0	0	1	$E_{1,3,4}$
.	.	.	.	.	.	.	.	.	.	.	.	.	.

GLMM ⇒ LMM: Steps 5 and 6

y_i	X_m												e_i
	X_1	X_2	X_3	X_4	X_5	X_6	X_7	X_8	X_9	X_{10}	X_{11}	X_{12}	
$y_{1,1,1}$	1	0	0	0	0	0	0	0	0	0	0	0	$e_{1,1,1}$
$y_{1,2,1}$	0	1	0	0	0	0	0	0	0	0	0	0	$e_{1,2,1}$
$y_{1,3,1}$	0	0	1	0	0	0	0	0	0	0	0	0	$e_{1,3,1}$
$y_{2,1,1}$	1	0	0	0	0	0	0	0	0	0	0	0	$e_{2,1,1}$
$y_{2,2,1}$	0	1	0	0	0	0	0	0	0	0	0	0	$e_{2,2,1}$
$y_{2,3,1}$	0	0	1	0	0	0	0	0	0	0	0	0	$e_{2,3,1}$
.	.	.	.	.	.	.	.	.	.	.	.	.	.
$y_{2,1,2}$	0	0	0	1	0	0	0	0	0	0	0	0	$e_{2,1,2}$
$y_{2,2,2}$	0	0	0	0	1	0	0	0	0	0	0	0	$e_{2,2,2}$
$y_{2,3,2}$	0	0	0	0	0	1	0	0	0	0	0	0	$e_{2,3,2}$
.	.	.	.	.	.	.	.	.	.	.	.	.	.
$y_{1,1,3}$	0	0	0	0	0	0	1	0	0	0	0	0	$e_{1,1,3}$
$y_{1,2,3}$	0	0	0	0	0	0	0	1	0	0	0	0	$e_{1,2,3}$
$y_{1,3,3}$	0	0	0	0	0	0	0	0	1	0	0	0	$e_{1,3,3}$
.	.	.	.	.	.	.	.	.	.	.	.	.	.
$y_{1,1,4}$	0	0	0	0	0	0	0	0	0	1	0	0	$e_{1,1,4}$
$y_{1,2,4}$	0	0	0	0	0	0	0	0	0	0	1	0	$e_{1,2,4}$
$y_{1,3,4}$	0	0	0	0	0	0	0	0	0	0	0	1	$e_{1,3,4}$
.	.	.	.	.	.	.	.	.	.	.	.	.	.

Power and Sample Size for Fixed Effects in a Linear Mixed Model

To be reversible to a GLMM, a mixed model must:

- Have a Balanced Design within ISU; no repeated covariates; saturated between-within
- Have an Unstructured Covariance Model
- Use Wald test for inference about Fixed Effects
- Use Kenward-Rogers df approximation for Wald tests

Power and Sample Size for GLMM

- Muller, LaVange, Ramey and Ramey (1992)
- Multivariate approach to repeated measures and MANOVA, “multivariate”: MULTIREP uses 1 of 4 test statistics: HLT, WLK, PBT, RLR
- “Univariate” approach to repeated measures, UNIREP uses 1 of 4 test statistics: UN, HF, GG, Box (Muller, Edwards, Simpson Taylor, 2007)

Examples of Common Fixed Effects Hypothesis Tests for the LMM

- Pure between-group comparisons - actually univariate analysis and power, so skipped here

- Treatment by Time Interaction examples:
  - Parkinson's Disease Progression and Exercise; 3 intervention groups at baseline, 4 10, 16 months

Unbalanced Designs - Missing Data

- Catellier and Muller (2000) conducted extensive simulations evaluating impact of missing data on 3 MULTIREP tests and 4 UNIREP tests based on unstructured covariance model and ML estimation

- **Results**: HLT requires aggressive sample size adjustment to approximately control Type I error rate: replace N with N_* = minimum number of non-missing pairs

- Recall that Reversible LMM + Wald test + KR correction + no missing or mistimed data ⇔ HLT in GLMM

- **Implication**: Tells us how to adjust sample size for power with missing data

Ongoing Work on Missing Data

- **Work in progress**: Formula for expected value of N_*
- Some crude approximations useful for the consulting setting:
  - Complete data power is an upper bound
  - Power for N = (100% - % missing) x # ISUs appears conservative, requires assuming MAR
- Attrition model is the next target

Summary

- Under widely applicable restrictions a LMM can be expressed as a GLMM, i.e. a LMM is reversible.

- Power and sample size for both univariate and multivariate repeated measures tests for the GLMM provide exact or very good approximations for corresponding LMM fixed effect tests.

- Straightforward adjustments can be made for missing data as long as MAR holds.

- **Bonus**: FREE software is available soon to implement the methods - GLIMMPSE - next!