Written Examination for Linear Mixed Models (MSA650 and MVE210)

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Rules: This is a closed book exam. Only simple pocket calculators are allowed.
Grades: The written exam is worth 24 scores (80%) while the computer assignments are worth 6 scores (20%). The two add up to 30 scores (100%). Excellent (≥ 26 scores), pass (≥ 16 scores) and do not pass (< 16 scores).

1.

▷ *Marginal residuals:*

$$\begin{cases} y_i &= X_i\beta + \varepsilon_i^*, \quad \varepsilon_i^* \sim \mathcal{N}(0, Z_i D Z_i^\top + \sigma^2 \mathsf{I}_{n_i}) \\ r_i^{marg} &= y_i - X_i\widehat{\beta} \end{cases}$$

▷ These residuals predict the marginal errors ε_i^*

▷ They can be used to

* investigate misspecification of the mean structure $X_i\beta$
* validate the assumptions for the within-subjects covariance structure $Z_i D Z_i^\top + \sigma^2 \mathsf{I}_{n_i}$

▷ *Conditional residuals*

$$\begin{cases} y_i &= X_i\beta + Z_i b_i + \varepsilon_i, \quad b_i \sim \mathcal{N}(0, D), \quad \varepsilon_i \sim \mathcal{N}(0, \sigma^2 \mathsf{I}_{n_i}) \\ r_i^{cond} &= y_i - X_i\widehat{\beta} - Z_i\widehat{b}_i \end{cases}$$

▷ These residuals predict the conditional errors ε_i

▷ They can be used to

* investigate misspecification of the hierarchical mean structure $X_i\beta + Z_i b_i$
* validate the assumptions for the within-subjects variance structure σ^2

2. A model with systematic effect of treatment and period and possibly interaction (the carry-over effect) is as below. We expect observations from the same period (and patient) to be more strongly correlated when they are close in time. We also expect correlations between observations from different periods, but this is most likely not as strong. The hypotheses of interest concern the treatment and the carryover effect.

$$
\begin{aligned}
Y_{ij} &= \alpha + \beta \cdot \text{treat} + \gamma \cdot \text{period} + \delta \cdot \text{treat} * \text{period} \\
&\quad + b_i + \varepsilon_{ij}
\end{aligned}
$$

- α is the intercept.
- β is the treatment effect.
- γ is the period effect.
- δ is the carry-over effect.
- $b_i \sim N(0, \omega_B^2)$: random subject effects
- $\varepsilon_{ij} \sim N(0, \sigma_W^2)$: residuals

3.

a. Marginal model

▷ different average longitudinal evolutions per treatment group ($X\beta$ part)

▷ compound symmetry covariance matrix (V_i part)

$$
\left\{
\begin{array}{l}
\sqrt{\texttt{CD4}_{ij}} = \beta_0 + \beta_1 \texttt{Time}_{ij} + \beta_2 \{\texttt{ddI}_i \times \texttt{Time}_{ij}\} + \varepsilon_{ij}, \\
\\
\varepsilon_i \sim \mathcal{N}(0, V_i)
\end{array}
\right.
$$

b. A linear mixed model

▷ different average longitudinal evolutions per treatment group (fixed part)

▷ random intercepts & random slopes (random part)

$$
\left\{
\begin{array}{l}
\sqrt{\texttt{CD4}_{ij}} = \beta_0 + \beta_1 \texttt{Time}_{ij} + \beta_2 \{\texttt{ddI}_i \times \texttt{Time}_{ij}\} + b_{i0} + b_{i1} \texttt{Time}_{ij} + \varepsilon_{ij}, \\
\\
b_i \sim \mathcal{N}(0, D), \qquad \varepsilon_{ij} \sim \mathcal{N}(0, \sigma^2)
\end{array}
\right.
$$

c. Assumptions: The usual ones; linearity, distributional assumptions, correlations.

(4p)

4.

What is the problem? The null hypothesis for $\sigma_{b_2}^2$ is on the boundary of its corresponding parameter space

▷ statistical tests derived from standard ML theory assume the H_0 is an interior point of the parameter space

▷ **the classical asymptotic χ^2 distribution for the likelihood ratio test statistic does not apply**

5. These models are not nested and hence to compare them we use the AIC and BIC. Based on the table, both AIC and BIC suggest that the model with the nonlinear random slopes is better than the model with the linear random slopes

6.

To obtain estimates for the random effects, we typically use measures of location from this posterior distribution (e.g., mean or mode). Due to the fact that in linear mixed models we obtain a normal distribution (in which the mean and mode coincide), we use as estimates of the random effects the means of these distributions leading to the following empirical Bayes estimate.

$$\widehat{b}_i = DZ_i^\top V_i^{-1}(y_i - X_i\beta)$$

The predictions based on the marginal and mixed models are:

$$\widehat{y}_i^{marg} = X_i\widehat{\beta} \quad \text{and} \quad \widehat{y}_i^{subj} = X_i\widehat{\beta} + Z_i\widehat{b}_i$$

The difference is that

- from the marginal model we obtain predictions for the *'average'* patient having characteristics X_i (i.e., age, sex, etc.)
- from the mixed model we obtain predictions for the *'average'* patient that has characteristics X_i and observed data y_i (i.e., they have a subject-specific nature)

The predictions $X_i\widehat{\beta} + Z_i\widehat{b}_i$ we obtain from the mixed model are called the *Best Linear Unbiased Predictions (BLUPs)*

- 'linear' because they are a linear combination of $\widehat{\beta}$ and $\widehat{b}_i$
- 'unbiased' because their average equals the true subject-specific mean
- 'best' because they have the smallest variance of all linear predictors

From the graphs, we clearly observe that the subject-specific predictions are much closer to the data of each individual patient than the marginal ones