General considerations about designs for mixed models illustrated by very simple examples and potential implications to PPK designs

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Outline

Part 1

Non-linearity and Variance Heterogeneity

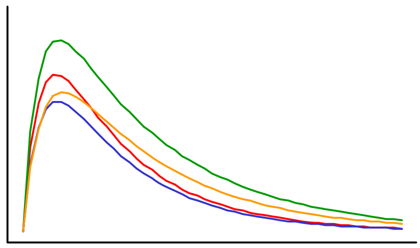
1. A General Non-linear Mixed Model
2. A Simple Example

Part 2

Design for Random Components

Example

- population pharmacokinetic curves



Part 1

Non-linearity and Variance Heterogeneity

1. A General Non-linear Mixed Model

- individual response

$$\boxed{Y_{ij} = \eta(\mathbf{x}_{ij}, \mathbf{b}_i) + \varepsilon_{ij}}$$

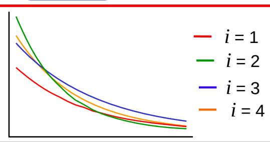
individual $i=1,\ldots,n$

replication $j=1,\ldots,m_i$

explanatory variable

error

$\varepsilon_{ij} \sim N(0,\sigma^2)$



1. A General Non-linear Mixed Model

- individual response

$$\boxed{Y_{ij} = \eta(\mathbf{x}_{ij}, \mathbf{b}_i) + \varepsilon_{ij}}$$

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error

$\varepsilon_{ij} \sim N(0,\sigma^2)$

- individual parameters:

population parameters

$$\mathbf{b}_i \sim N_p(\boldsymbol{\beta}, \mathbf{D})$$

random comp.

Linearization

- **I**: in $\boldsymbol\beta_0$

$$\boxed{Y_{ij} \approx \eta(\mathbf{x}_{ij},\boldsymbol\beta_0) + \frac{\partial \eta(\mathbf{x}_{ij},\boldsymbol\beta_0)}{\partial \boldsymbol\beta^{\mathsf{T}}}(\boldsymbol\beta-\boldsymbol\beta_0) + \frac{\partial \eta(\mathbf{x}_{ij},\boldsymbol\beta_0)}{\partial \boldsymbol\beta^{\mathsf{T}}}(\mathbf{b}_i-\boldsymbol\beta)+\varepsilon_{ij}}$$

- **II**: in $\boldsymbol\beta$

$$\boxed{Y_{ij} \approx \eta(\mathbf{x}_{ij},\boldsymbol\beta) + \frac{\partial \eta(\mathbf{x}_{ij},\boldsymbol\beta)}{\partial \boldsymbol\beta^{\mathsf{T}}}(\mathbf{b}_i-\boldsymbol\beta)+\varepsilon_{ij}}$$

Linearization

- standardized information matrix for $\boldsymbol\beta$

$$\boxed{\frac{1}{n}\sum_{i=1}^{n}\mathbf{F}_i^{\mathsf{T}}\mathbf{V}_i^{-1}\mathbf{F}_i + \mathbf{A}_n}$$

crude linearization

heteroscedasticity by non-linearity

$$\mathbf{F}_i = \left(\frac{\partial \eta(\mathbf{x}_{ij},\boldsymbol\beta)}{\partial \boldsymbol\beta^{\mathsf{T}}}\right)_{j=1,\dots,m_i} \qquad \mathbf{V}_i = \sigma^2\mathbf{I}_{m_i} + \mathbf{F}_i\mathbf{D}\mathbf{F}_i^{\mathsf{T}}$$

Linearization

$$\boxed{\frac{1}{n}\sum_{i=1}^{n}\mathbf{F}_i^{\mathsf{T}}\mathbf{V}_i^{-1}\mathbf{F}_i + \mathbf{A}_n}$$

- Nie (2007): $\boxed{\mathbf{A}_n \to \mathbf{0}}$

$$\sqrt{n}(\hat{\boldsymbol\beta}_{\mathrm{ML}}-\boldsymbol\beta) \to N_p\left(0, \lim\left(\frac{1}{n}\sum_{i=1}^{n}\mathbf{F}_i^{\mathsf{T}}\mathbf{V}_i^{-1}\mathbf{F}_i\right)^{-1}\right)$$

Proof ???

2. A Simple "Mixed" Model

- individual linear response

$$\boxed{Y_{ij} = a_i + b_i x_{ij} + \varepsilon_{ij}}$$

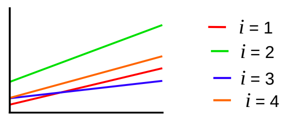
individual $i=1,\dots,n$

replication $j=1,\dots,m_i$

explanatory variable

error

$\varepsilon_{ij} \sim N(0,\sigma^2)$



2. A Simple "Mixed" Model

- individual linear response

$$\boxed{Y_{ij} = a_i + b_i x_{ij} + \cancel{\varepsilon_{ij}}}$$

individual $i=1,\dots,n$

replication $j=1,2=m_i$

explanatory variable

~~error~~

$\cancel{\varepsilon_{ij} \sim N(0,\sigma^2)}$

- individual parameters:

population parameters

$$\begin{pmatrix} a_i \\ b_i \end{pmatrix} \sim N\left(\begin{pmatrix} \alpha \\ \beta \end{pmatrix}, \begin{pmatrix} d_a & d_{ab} \\ d_{ab} & d_b \end{pmatrix}\right)$$

random comp.

Individual Observation Vector

$$\boxed{\mathbf{Y}_i = \begin{pmatrix} Y_{i1} \\ \vdots \\ Y_{im_i} \end{pmatrix} = \mathbf{F}_i\begin{pmatrix} a_i \\ b_i \end{pmatrix} = \mathbf{F}_i\begin{pmatrix} \alpha \\ \beta \end{pmatrix} + \mathbf{F}_i\begin{pmatrix} a_i-\alpha \\ b_i-\beta \end{pmatrix}}$$

- individual design matrix

$$\mathbf{F}_i = \begin{pmatrix} 1 & x_{i1} \\ \vdots & \vdots \\ 1 & x_{im_i} \end{pmatrix}$$

$\mathbf{b}_i$

$\boldsymbol\beta$

Individual Covariance Matrix

$$\boxed{\mathrm{Cov}(\mathbf{Y}_i)=\mathbf{V}_i}$$

where

$$\boxed{\mathbf{V}_i=\cancel{\sigma^2\mathbf{I}_{m_i}}+\mathbf{F}_i\,\mathbf{D}\,\mathbf{F}_i^{\mathsf{T}}}$$

- individual information matrix

$$\boxed{\mathbf{F}_i^{\mathsf{T}}\mathbf{V}_i^{-}\mathbf{F}_i=\mathbf{F}_i^{\mathsf{T}}(\mathbf{F}_i\,\mathbf{D}\,\mathbf{F}_i^{\mathsf{T}})^{-}\mathbf{F}_i=\mathbf{D}^{-1}}$$

Estimation of Population Parameters

general least squares

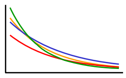
$$\boxed{\begin{aligned}\hat{\boldsymbol\beta}_{ML}&=\left(\sum\nolimits_{i=1}^{n}\mathbf{F}_i^{\mathsf{T}}\mathbf{V}_i^{-1}\mathbf{F}_i\right)^{-1}\sum\nolimits_{i=1}^{n}\mathbf{F}_i^{\mathsf{T}}\mathbf{V}_i^{-1}\mathbf{Y}_i\\&=\frac{1}{n}\sum\nolimits_{i=1}^{n}\mathbf{b}_i\end{aligned}}$$

- covariance matrix

$$\boxed{\mathrm{Cov}(\hat{\boldsymbol\beta}_{\mathrm{ML}})=\frac{1}{n}\mathbf{D}}$$

A Simple Non-linear “Mixed” Model

$$\boxed{Y_{ij}=\eta(a_i+b_i x_{ij})}$$



$\eta'>0$ e.g. $\eta(t)=\exp(t)$

- standardized information matrix for β

$$\mathbf{D}^{-1}+\mathbf{A}_n$$

- linearization **I** in β_0: $\mathbf{A}_n=\mathbf{0}$
- linearization **II** in β: $\mathbf{A}_n>\mathbf{0}$

No Heterogeneity by Non-linearity

- maximum likelihood for β

$$\hat{\boldsymbol\beta}_{ML}=\left(\sum\nolimits_{i=1}^{n}\mathbf{F}_i^{\mathsf{T}}\mathbf{V}_i^{-1}\mathbf{F}_i\right)^{-1}\sum\nolimits_{i=1}^{n}\mathbf{F}_i^{\mathsf{T}}\mathbf{V}_i^{-1}\begin{pmatrix}\eta^{-1}(Y_{i1})\\ \eta^{-1}(Y_{i2})\end{pmatrix}$$

$$=\frac{1}{n}\sum\nolimits_{i=1}^{n}\mathbf{b}_i\sim\underline{\underline{N(\boldsymbol\beta,\mathbf{D}/n)}}$$

- no heterogeneity

$$\boxed{\mathbf{A}_n=\mathbf{0}}\qquad !!!$$

Part 2

Design for Random Coefficients

Design for Random Components

Norell (2006), van Breukelen et al. (2007)

- only one treatment

$$\boxed{Y_{ij}=\mu+a_i+\varepsilon_{ij}}$$

$i=1,\ldots,n,\quad j=1,\ldots,m_i$

$\varepsilon_{ij}\sim N(0,\sigma^2)$

$a_i\sim N(0,\sigma_a^2)$

$\tau=\sigma_a^2/\sigma^2$

- design criterion $N=\sum_i m_i$ fixed

$$\boxed{\det\mathrm{Info}(\sigma^2,\sigma_a^2)\propto N\sum\nolimits_i\left(\frac{m_i}{1+\tau\cdot m_i}\right)^2-\left(\sum\nolimits_i\frac{m_i}{1+\tau\cdot m_i}\right)^2}$$

Optimal Number of Replications

number of individuals n fixed

- intra-individual correlation $\rho = \frac{\tau}{1+\tau}$ large:

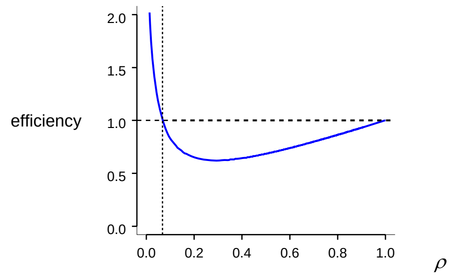
$\rho \ge \frac{n}{N}$ $\boxed{m_1^* = \dots = m_n^* = \frac{N}{n}}$ balanced

- ρ small: $\rho \le \frac{1}{N-n+2}$ unbalanced

$\boxed{m_1^* = \dots = m_{n-1}^* = 1,\ m_n^* = N-n+1}$

Balanced vs. Unbalanced Design

- efficiency of the most unbalanced design



Optimal Number of Individuals

- ρ large: $\rho \ge 1 - \frac{1}{N+2}$ balanced

large $\boxed{n^* = \frac{N}{2}}$ $\boxed{m_1^* = \dots = m_n^* = 2}$

- ρ small: $\rho \le \frac{1}{N+1}$ unbalanced

small $\boxed{n^* = 2}$ $\boxed{m_1^* = 1,\ m_2^* = N-1}$

Optimal Design

- imbalance results carry over to the whole parameter vector
  (variance components **and** population parameters),
  for small intra-class correlation

References

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- Norell (2006): Optimal design for maximum likelihood estimators in the one-way random model. *U.U.D.M. Report* 2006:24, Uppsala.
- van Breukelen, Candel, Berger (2007): Relative efficiency of unequal cluster sizes for variance component estimation in cluster randomized and multicentr trials. *Statist. Methods Medical Research* (to appear).