Design evaluation in nonlinear mixed effect models: influence of covariance between random effects

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Introduction

Choice of population pharmacokinetic (PK) designs

- Important on the study results (precision of parameter estimates)
- Balance between number of subjects and number of measures/subject, choice of sampling times
- Approaches to assess/optimise designs for nonlinear mixed effect models (NLMEM)

- Based on simulation: time consuming
- Based on the calculation of the Fisher information matrix (FIM) and the optimisation of its determinant (det(FIM)) [1,2]

- Several software packages including PFIM in R [3,4]

Objectives

1) To implement in PFIM an extension of FIM for NLMEM considering covariance between random effects
2) To study the impact of the size of covariance on the relative standard errors (RSE), on the amount of information and on optimal designs
3) To derive analytical prediction of the RSE in the framework of rich individual data without using the model

Data and pharmacokinetic model

- 82 children receiving an intravenous single dose of 0.1 mg/kg [5,6] (see poster Dumont et al., PAGE 2011, poster n°2160)
- 22 observations per child at sampling times 0.1, 0.2, 0.4, 0.6, 0.8, 1, 1.3, 1.6, 1.8, 2, 2.5, 3, 4, 5, 6, 7, 8, 9, 10, 12, 16 and 24 hours after dose injection
- Three compartment model with 6 parameters

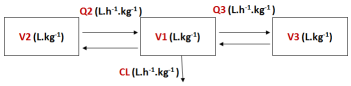

Figure 1: Structural PK model with 3 compartments

- Parameters CL and V1 with inter-individual variability and which are correlated (corr=0.78)
- Combined residual error model
- Estimated parameters used for designing are given in Table 1

Methods

Notations: N subjects $i = 1,\ldots, N$

$Y_i = F(g(\beta, b_i), \xi_i) + \varepsilon_i$: vector of observations for individual i

β: vector of the p fixed effect parameters

b_i : vector of the p random effects for individual i

$b_i \sim N(0,\Omega)$, Ω defined as a $p \times p$-non diagonal matrix

$\xi_i = (t_{i1}, t_{i2}, \ldots, t_{in_i})$: elementary design for individual i

$\theta_i = g(\beta, b_i)$ with $g(\beta, b_i) = \beta \exp(b_i)$: vector of individual parameters

$\lambda^T = (\omega_{11}^2, \ldots, \omega_{pp}^2, \omega_{21}, \omega_{31}, \omega_{32}, \ldots, \omega_{p,p-1}, \sigma_{inter}, \sigma_{slope})$: vector of the variance-covariance terms, corresponding to the vector of the lower triangular of Ω and additional error terms

$\psi^T = (\beta^T, \lambda^T)$

ε_i : vector of residual errors, $\varepsilon_i \sim N(0, \Sigma_i)$

$\Sigma_i(\beta, b_i, \sigma_{inter}, \sigma_{slope}, \xi_i) = diag(\sigma_{inter} + \sigma_{slope} \times f(g(\beta, b_i), \xi_i))^2$

1) Implementation of FIM including covariance between random effects in PFIM:

- Extension of the calculation including covariance between random effects already performed [7]
- Expression of $FIM(\psi, \xi_i)$: diagonal block matrix
  - block with fixed effects (size $p \times p$)
  - block with elements of λ (size $p(p+1)/2+$*number of error terms* if all covariance terms are different from zero)
- Implementation of FIM including covariance in PFIM for single and multiple responses
- Evaluation of implementation of FIM including covariance in PFIM:
  - Simulation of data for rich design (with 22 points) in 82 children and with a dose of 0.1 mg/kg
  - Estimation of parameters and standard errors given by NONMEM
  - Comparison of RSE predicted by PFIM with the new implementation of FIM with those observed by NONMEM

2) Impact of the size of covariance on the RSE and on the designs:

Impact of the covariance on RSE and on amount of information was tested on a range from a covariance equal to 0 to 0.12 (corr = 0.9)

- Prediction of RSE on fixed effects and on variance components assuming different values of covariance
- Evaluation of the total information through the criterion $(\det(FIM)^{1/P}$, P being the total number of parameters)
- Role of covariance on optimal designs with 6 points among 12, obtained via the Federov-Wynn algorithm. Here, it is constrained that all individuals have the same design (only one group)

3) Approximation of the calculation of FIM and of the RSE in the framework of individual rich data :

- Assuming a rich design, we would have a lower bound if we had observed individual parameters which follow a log-normal distribution

$\ln(\theta_i) \sim N(\ln(\beta), \Omega)$

$$RSE(\beta_k) = \frac{1}{\sqrt{N}}\sqrt{\omega_{kk}^2} \times 100 \quad RSE(\omega_{kk}^2) = \frac{1}{\sqrt{N}}\sqrt{2} \times 100 \quad RSE(\omega_{kl}) = \frac{1}{\sqrt{N}}\frac{\sqrt{\omega_{kk}^2\omega_{ll}^2 + \omega_{kl}^2}}{\omega_{kl}} \times 100$$

Results

1) Relevance of the extension of FIM including covariance in PFIM by comparison with NONMEM

Parameters	Model without covariance: Values of parameters	RSE predicted by PFIM (%)	RSE observed by NONMEM (%)	Δ	Model with covariance: Values of parameters	RSE predicted by PFIM (%)	RSE observed by NONMEM (%)	Δ
β_{CL}	0.9	5.9	5.9	0.0	0.9	6.1	6.1	0.0
β_{V1}	0.9	4.9	4.2	0.7	0.9	5.0	4.6	0.4
β_{Q2}	0.6	6.5	5.1	1.4	0.6	6.8	6.1	0.7
β_{V2}	1.0	2.8	2.1	0.7	1.0	2.9	2.5	0.4
β_{Q3}	1.4	13.7	10.9	2.8	1.4	13.9	11.9	2.0
β_{V3}	0.4	8.3	5.3	3.0	0.4	8.4	6.2	2.2
ω_{CL}^2	0.3	15.7	13.5	2.2	0.3	15.7	13.0	2.7
ω_{V1}^2	0.1	18.9	17.8	1.1	0.1	18.4	20.1	1.7
$\omega_{(CL,V1)}$	-	-	-	-	0.1	18.2	17.3	0.9
σ_{inter}	0.3	4.5	4.0	0.5	0.3	4.6	4.1	0.5
σ_{slope}	0.1	2.6	2.0	0.6	0.1	2.6	1.9	0.7

Table 1: Comparison between RSE (%) predicted by PFIM and RSE(%) observed by NONMEM

- Predictions of PFIM similar to NONMEM results (Table 1)
- Predictions of PFIM similar to PopDes and PopED (comparison thanks to K. Ogungbenro and J. Nyberg)
- Similar RSE for fixed effects and variances with and without covariance (Table 1)

2) Influence of covariance

- Similar RSE for fixed effects and variance components whatever the value of covariance
- RSE for covariance decreases when covariance increases
- Amount of information increases when covariance increases

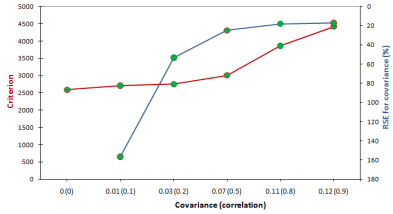

Figure 2: Influence of covariance on criterion and on RSE for covariance

- Optimal designs according to the value of covariance with only one group:

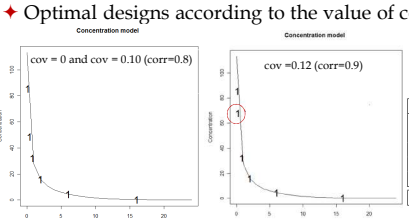

Figure 3: Optimal designs according to the value of covariance with design A (left) = 0.1, 0.4, 0.8, 2, 6, 16, and with design B (right) = 0.1, 0.2, 0.8, 2, 6, 16

Parameters	RSE (%) for design A	RSE (%) for design B
β_{CL}	5.4	5.4
β_{V1}	4.6	5.0
ω_{CL}^2	15.9	15.9
ω_{V1}^2	19.2	18.3
$\omega_{(CL,V1)}$	17.6	17.3
Criterion	1955.2	1970.7

Table 2: Evaluation of designs A and B considering the model with cov = 0.12 (corr = 0.90)

Same optimal sampling times for a correlation equal to 0 and equal to 0.8 Design slightly different with a correlation equal to 0.9 (a different optimal time) but little loss of efficiency (lower than 1%)

3) Analytical predictions of the RSE for rich individual data

Parameters	RSE (%) predicted by PFIM	Analytical RSE (%)
β_{CL}	6.1	6.1
β_{V1}	5.0	3.4
ω_{CL}^2	15.7	15.6
ω_{V1}^2	18.4	15.6
$\omega_{(CL,V1)}$	18.2	17.1

Table 3: Comparison of results obtained by the calculation with those predicted by PFIM

- Analytical RSE are similar to those given by PFIM (Table 3)

Conclusion and prospects

- Relevance of the extension of FIM taking into account covariance in PFIM: available in the next version
- Development also done for multi-responses models
- Covariance affects neither RSE of fixed effects nor RSE of variance components
- Influence on optimal design only exists for important correlation but has very low impact on efficiency
- It is possible to analytically predict the RSE in the framework of rich individual data without using the model and these RSE are lower bound of RSE that could be obtained by population approach

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