Population design in nonlinear mixed effects multiple response models: extension of PFIM and evaluation by simulation with NONMEM and MONOLIX

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Context

- Influence of the design on the precision of population parameter estimates
  → importance of the choice of the design
- Population design evaluation and optimisation based on the Fisher information matrix (M_F)
  - **Single response model**
    - Linearisation of the model using a first order expansion [1]
    - Relevance of this approach demonstrated on real data [2]
- **Multiple response model**
  - Extension of M_F for multiple responses [3]
  - Using the same method as for a model with single response
  - Relevance never shown by repeated simulation study

Objective

- Evaluation by simulation of the relevance of the extension of M_F for multiple response model using a first order extension

Extension of PFIM for multiple responses

- **Population design Ξ for multiple responses**
  - Definition for single response $\Xi = \{[\xi_1, N_1]; [\xi_2, N_2]; \ldots; [\xi_Q, N_Q]\}$
    - N subjects divided in Q groups of N_q subjects with the same elementary design $\xi_q = \{t_1, t_2, \ldots, t_{nq}\}$: n_q samples and their allocation in time
  - Definition for multiple responses $\Xi = \{[(\xi_1^1, \xi_1^2, \ldots, \xi_1^K), N_1]; [(\xi_2^1, \xi_2^2, \ldots, \xi_2^K), N_2]; \ldots; [(\xi_Q^1, \xi_Q^2, \ldots, \xi_Q^K), N_Q]\}$
    - Elementary designs composed of several sub-design ξ_q^k, $k = 1, \ldots, K$, associated with the k^{th} type of response
- **Nonlinear mixed effects model for one individual *i* among *N***
  - Vector of observations Y_i composed of the vectors for the K responses
  - Each response described by a nonlinear function f_k depending on
    - The vector of individual parameters θ_i
    - An elementary design ξ_i

$$F(\theta_i, \xi_i) = \begin{bmatrix} f_1(\theta_i, \xi_i^1) \\ f_2(\theta_i, \xi_i^2) \\ \vdots \\ f_K(\theta_i, \xi_i^K) \end{bmatrix}$$

- **Statistical model**
  - For individual *i*, k^{th} response $y_{ik} = f_k(\theta_i^k, \xi_i^k) + \varepsilon_{ik}(\sigma_{inter_k} + \sigma_{slope_k} f_k(\theta_i^k, \xi_i^k))$
  - For individual *i*, K responses $Y_i = F(\theta_i, \xi_i) + \varepsilon_i \otimes (\sigma_{inter} + \sigma_{slope} \otimes F(\theta_i, \xi_i))$

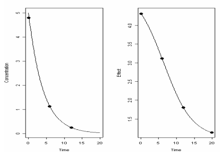
    ε_i are supposed to be independent from one type of response to the other
- **M_F for multiple responses:** linearisation of the model using a first order expansion → approximation of the variance and the expectation

$$F(g(\beta, b), \xi) \cong F(g(\beta, 0), \xi) + \left(\frac{\partial F^T(g(\beta, b), \xi)}{\partial b}\right)_{b=0} b$$

- **Implementation** of this first order extension of M_F for multiple responses in PFIM
- **Estimation methods in simultaneous approach**
  - NONMEM (FO and FOCE methods): linearisation
  - MONOLIX (SAEM algorithm): stochastic approach

PKPD example

- **PK model**
  - One compartment model
  - θ^{PK} : *Cl and V*
  - Proportional error model
- **PD model**
  - Emax model
  - θ^{PD} : *E0 , Emax and C50*
  - Additive error model
- **Population design** $\Xi = \{[(\xi^{PK}, \xi^{PD}), N]\}$
  - ξ^{PK} = {0.166,6,12}
  - ξ^{PD} = {0.166,6,12,20}
  - N =100



Evaluation method

- Computation of the predicted relative standard errors (RSE) obtained with the extension of PFIM for this PKPD example

1 Comparison to the predicted RSE obtained with *an exact method*
- Computation of M_F with the SAEM algorithm (MONOLIX 2.1) [4]
  * Louis method [5]
- Simulation of one data set with 10000 subjects in order to acquire asymptotic properties of M_F → Rescale of SE for N=100 subjects

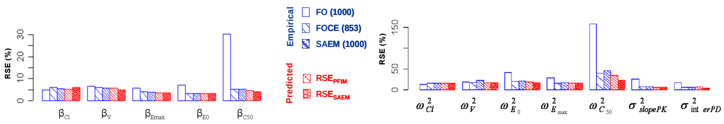
2 Comparison to the empirical RSE (NONMEM V and MONOLIX 2.1)
- Simulation of 1000 data sets (R software)
- Estimation of the population parameters
  * NONMEM V (FO and FOCE) * MONOLIX 2.1 (SAEM)
- For each method of estimation
  * Computation of the empirical RSE defined as the standard deviation on the 1000 estimates of each parameter

3 Comparison to the distribution of the RSE obtained on each data set for each parameter with :
- NONMEM V (FO and FOCE) and MONOLIX 2.1 (SAEM)
  * Computation of the SE
    - Linearisation - Louis method

4 Computation of bias and RMSE (%)
- Comparison of the three estimation methods FO, FOCE and SAEM

Results

1 2 *Barplot of the predicted and empirical relative standard errors (RSE)(%) for fixed effects (left part), variances of the random effects and of the residual errors (right part).*

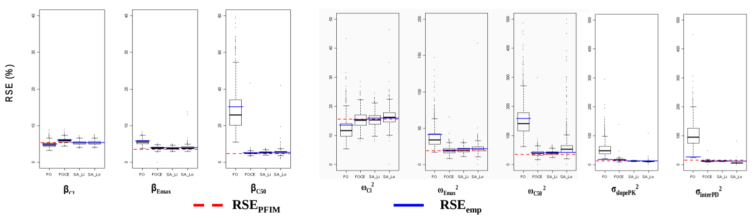


- RSE predicted by PFIM equivalent to those predicted by SAEM
- Empirical RSE
  - PFIM, FOCE*, SAEM in the same range
  - Larger RSE for FO, especially on β_{C50} and ω^2_{C50}

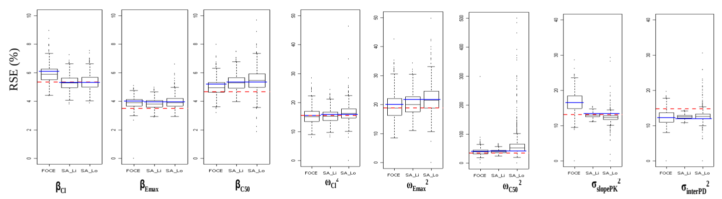
**Convergence only for 853 data files*

3 *Boxplots of the RSE (%) for the fixed effects, variances of the random effects and of the residual errors estimated from 1000 replicates by :*

➢ FO, FOCE and the two methods of computation of the SE in SAEM (linearisation SA_{Li} and Louis method SA_{Lo})

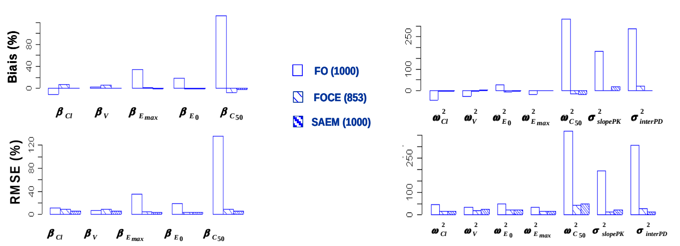


➢ FOCE and the two methods of computation of the SE in SAEM



- For FO, range of RSE and empirical RSE much larger than:
  - RSE predicted by PFIM
  - RSE with FOCE and SAEM
- Close distribution of RSE for FOCE and for the linearisation method of SAEM
  - Predicted RSE of PFIM in accordance with empirical RSE

4 *Bias (%) (upper part) and RMSE (%) (lower part) for the fixed effects, the variances of the random effects and of the residual errors with the three methods of estimation.*



- Large bias and RMSE for the FO method
- Reasonable bias and RMSE for FOCE* and SAEM

**Convergence only for 853 data files*

Conclusion

- Relevance of the SE computed from M_F using a first order extension for multiple response model
  → extension of PFIM : **PFIM3.0 [6]** will be available at www.pfim.biostat.fr
- Despite linearisation, predicted SE close to SE obtained with FOCE and SAEM but not with FO.

Acknowledgment

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