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 (\(M_{ij}\))
  - Single response model
    - Linearisation of the model using a first order expansion [1]
    - Relevance of this approach demonstrated on real data [2]

Objectives

- Evaluation by simulation of the relevance of the extension of \(M_{ij}\) for multiple response model using a first order extension

Extension of PFIM for multiple responses

- Population design \(\mathcal{Z}\) for multiple responses
  - Definition for single response \(\mathcal{Z} = \{\mathcal{Z}_1, \mathcal{Z}_2, \ldots, \mathcal{Z}_N\}\)
    - \(N\) subjects divided in \(Q\) groups of \(N_i\) subjects with the same elementary design \(\mathcal{Z}_i = \{t_1, t_2, \ldots, t_{N_i}\}\) : \(N_i\) samples and their allocation in time
  - Definition for multiple responses \(\mathcal{Z} = \{\mathcal{Z}_1, \mathcal{Z}_2, \ldots, \mathcal{Z}_N\}\)
    - Elementary designs composed of several sub-design \(\mathcal{Z}_i, i = 1, \ldots, K\) 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 \(f_i\) depending on
    - The vector of individual parameters \(\theta_i\)
    - An elementary design \(\mathcal{Z}_i\)
- Statistical model
  - For individual \(i, k^{th}\) response
    \[y_{ij} = f_i(\theta_i, \mathcal{Z}_i) + \epsilon_i, \epsilon_i \sim N(0, \omega_i)\]
  - For individual \(i, K^{th}\) response
    \[y_{ij} = f_i(\theta_i, \mathcal{Z}_i) + \epsilon_i, \epsilon_i \sim N(0, \omega_i)\]
  - \(\epsilon_i\) are supposed to be independent from one type of response to the other
- \(M_{ij}\) for multiple responses: linearisation of the model using a first order expansion, approximation of the variance and the expectation
- Implementation of this first order extension of \(M_{ij}\) 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
  - \(\theta^0\) : \(C_{1/2} \land V\)
  - Proportional error model
- PD model
  - Emax model
  - \(\theta^0\) : \(E_0, \text{Emax and C50}\)
  - Additive error model

Evaluation method

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

Comparison to the predicted RSE obtained with an exact method
- Computation of \(M_{ij}\) 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 \(M_{ij}\) : Rescale of SE for \(N=100\) subjects

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

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

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

Results

- Biais (%)
- RMSE (%)

Empirical RSE
- \(\theta^0\) for \(N=100\) subjects
- For \(N=100\) subjects
  - \(RSE\) predicted by PFIM equivalent to those predicted by SAEM
  - Large RSE for \(N=100\)

Biases 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 \(S_{\text{th}}\) and Louis method \(S_{\text{L}}\))

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.

Conclusion

- Relevance of the SE computed from \(M_{ij}\) using a first order extension for multiple response model
- Despite linearisation, predicted SE close to SE obtained with FOCE and SAEM but not with FO.

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