Prediction of precision of individual parameter estimates and of shrinkage via the Bayesian Fisher information matrix in non-linear mixed-effects models with application in pharmacokinetics

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Context

- Individual parameters in Non-Linear Mixed Effects Models (NLMEM)
  - Estimated by Bayesian methodology as Maximum *A Posteriori* (MAP)
  - Used to predict response, select covariates and draw diagnostic plots
  - Need high precision of estimation → smallest Standard Errors (SE) on parameters
- Optimal design
  - Evaluate the informativeness of the design and its influence on SE through the Fisher information Matrix
  - Prediction of SE:
    - Individual fitting → Individual information Matrix of Fisher (IMF)
    - Population fitting → Population information Matrix of Fisher (PMF) [1]
    - Individual Bayes fitting → Bayesian information Matrix (BMF) [2]
  - IMF and PMF already implemented in various softwares (PFIM, PopDES, PopED,...)
- Shrinkage of Random Effects (RE)
  - Shrunk *a posteriori* distribution of estimated η towards the population mean
  - Occurs when few information is available for each patient
  - Problems in individual parameters used for modeling (toxicity, pharmacodynamics, ...) and therapeutic drug monitoring studies

Objective

1. Explore relationship between Bayesian information Matrix and shrinkage
2. Evaluate by simulation prediction of individual parameters precision and shrinkage

Materials and methods

- Individual statistical model: $y = f(\theta, \xi) + \epsilon$, $\xi = \{t_1, ..., t_n\}$, $f(\theta, \xi)$: model
  - $\theta = g(\mu, \eta)$: individual parameters
    Fixed effects $\mu = (\mu_1, ..., \mu_p)$
    $\eta \sim N(0, \Omega)$, $\Omega = diag(\omega_1^2, ..., \omega_p^2)$
    $g(\mu, \eta) = \mu + \eta$ or $g(\mu, \eta) = \mu e^{\eta}$
  - $\epsilon \sim N(0, \Sigma(\theta, \xi))$: residual error
    $\Sigma(\theta, \xi) = diag\left(\left(\sigma_{inter} + \sigma_{slope} f(\theta, \xi)\right)^2\right)$
- Design evaluation
  - Based on Rao-Cramer inequality: the inverse of the Fisher Information Matrix (MF^{-1}) is the lower bound of estimation variance
  - For individual fitting $IMF(\theta, \xi) = F(\theta, \xi)^T \Sigma(\theta, \xi) F(\theta, \xi)$ with $F(\theta, \xi) = \frac{\partial f(\theta, \xi)}{\partial \theta^T}$
  - Evaluation of Bayesian individual design

$$BMF(\xi) = -E_\eta\left(\frac{\partial^2 log(p(\eta|y))}{\partial \eta \partial \eta^T}\right) = E_\eta\left(IMF(g(\mu, \eta), \xi)\right) + \Omega^{-1}$$

  $p(\eta|y)$ *a posteriori* distribution of η given y with known population parameters
  - Two methods to approximate BMF:
    - Monte-Carlo (MC) simulation: simulation of η
    - First-Order linearization (FO):

$$BMF(\xi) = M^T F(\mu, \xi)^T \Sigma(\mu, \xi) F(\mu, \xi) M + \Omega^{-1}$$

$M = I$ for additive RE $M = diag(\mu_1, ..., \mu_p)$ for exponential RE

- Prediction of shrinkage
  - For linear mixed effects models [3,4]:$\widehat{\theta}_{MAP} = W(\xi)\mu + (I - W(\xi))\widehat{\theta}_{ML}$
    With:
    - $W(\xi) = BMF(\xi)^{-1}\Omega^{-1}$ $\widehat{\theta}_{MAP}$ and $\widehat{\theta}_{ML}$ Bayesian and Maximum Likelihood estimate respectively
    - $W(\xi)$ quantifies the balance between prior and individual information → proposed as a measure of predicted shrinkage
- Individual prediction: $IBMF$ computed for one patient (with random effects η)

$$IBMF(\eta, \xi) = \Theta^T F(g(\mu, \eta), \xi)^T \Sigma(g(\mu, \eta), \xi) F(g(\mu, \eta), \xi) \Theta + \Omega^{-1}$$

$\Theta = I$ for additive RE $\Theta = diag(\{\theta_1, ..., \theta_p\})$ for exponential RE

The simulation study

- **Simple PK model** inspired from Mentré *et al* [5], describing a one compartment model ($V = 0.2$) with elimination ($CL = 0.5$), with $\sigma_{inter} = 0.15$
  Simulation of 1000 patients following the same design (varying from 5 to 2 samples per patient) with R 2.14 under several scenarios: variation of variance of RE and residual error

Scenario	*aa*	*ac*	*ea*	*ec*	*Ea*	*Ec*
	Random effects					
Form	Add	Add	Exp	Exp	Exp	Exp
ω_V^2	0.0016	0.0016	0.04	0.04	0.25	0.25
ω_{CL}^2	0.01	0.01	0.04	0.04	0.25	0.25
	Residual error					
σ_{slope}	0	0.15	0	0.15	0	0.15

- **Illustration model** inspired from the structure of a published PK model of a real drug [6] with rounded fixed effect values and modified variabilities for simplification purposes
  Two-hours perfusions every 4 weeks at 8 mg/kg
  2 compartments with linear and non-linear elimination and RE on CL, V_1, V_2 and V_m
  Simulation of 1800 patients following the same design (varying from 10, 9, 4 or 2 samples per patient)

Fixed effects		Random effects	
CL (L/d)	0.3	ω^2	0.09
V_2 (L)	4	**Residual error**	
$Q(L/d)$	0.15	σ_{inter} $(\mu g/mL)$	0.5
V_2 (L)	3	σ_{slope} (%)	0.3
V_m (mg/d)	6		
K_m $(\mu g/mL)$	2		

- **Evaluation methods**
  - Individual parameters and their SE estimated with 2 softwares:
    - NONMEM 7.0 with MAXEVAL = 0 and FOCEI
    - MONOLIX 4.0 with population parameters fixed to their true values and SAEM algorithm
  - Observed shrinkage defined by Savic *et al* [7] on estimated $\widehat{\eta}$:

$$Sh = 1 - \frac{Var(\widehat{\eta}_i)}{\omega^2},\ i = 1, ..., N$$

  - Predicted shrinkage computed as $W(\xi)$ using BMF FO
  - Predicted SE computed with $IBMF$ using simulated η

Results

- **Simple PK model** (Results for clearance only, similar for volume)

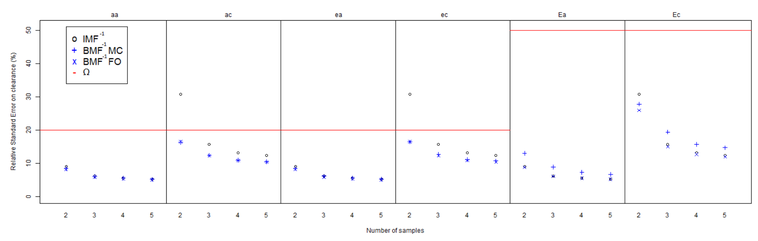

Figure 1: RSE for CL (%) predicted with IMF, BMF FO or BMF MC

- BMF FO close to BMF MC values
- Decrease of predicted RSE with increase of information
- RSE from BMF predictions below those from IMF or Ω

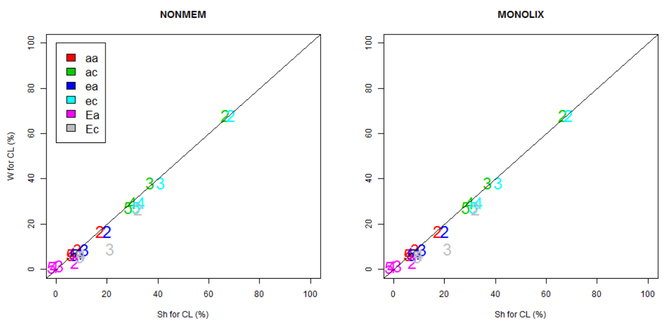

Figure 2: Expected (W) *vs* observed shrinkage (Sh) for CL (%), for each scenario and design
Number stands for the design and color for the scenario

- Similar values of observed shrinkage with NONMEM and MONOLIX
- Scatterplot close to the identity line

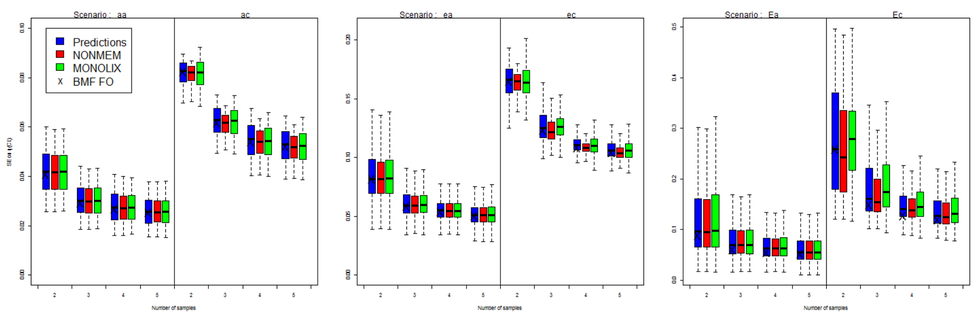

Figure 3: Predicted with $IBMF$ and estimated SE

- Similar values of estimated SE with NONMEM and MONOLIX
- Predicted SE close to the estimated SE with some small differences with MONOLIX when high variance (CV 50%) of RE is used

- **Illustration model**

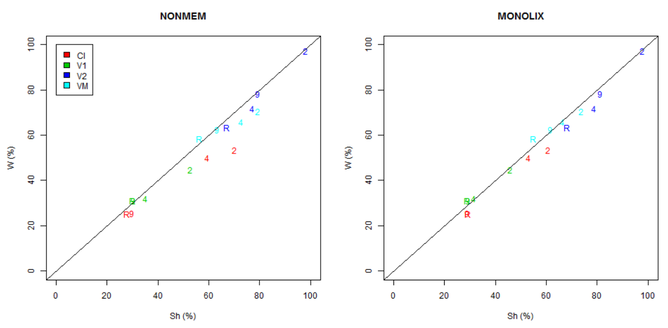

Figure 4: Expected (W) *vs* observed shrinkage (Sh)
Number stands for the design (R = 10 samples per patient) and color for the parameter

- Similar values of observed shrinkage with NONMEM and MONOLIX
- W and observed shrinkage scatterplot close to the identity line
- Highest discrepancy on CL with 17% of difference between W and observed shrinkage for 2 samples per patient

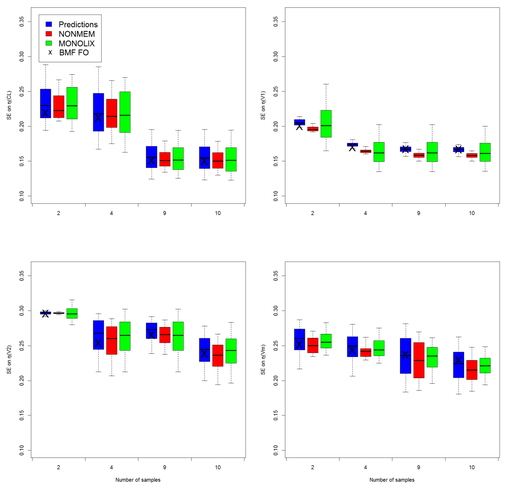

Figure 5: Predicted and estimated SE along with SE with BMF FO

- Predictions close to estimations
- Similar values of SE with NONMEM and MONOLIX
- Higher distribution for SE on V_1 with MONOLIX

Discussion

- FO computation of BMF adequate
- Development of new formula to predict shrinkage ($W = BMF^{-1}\Omega^{-1}$)
- Further explorations needed on more "extreme" models with high variances of RE or of residual error
- Perspectives:
  - Impact of precision of estimates on covariate determination
  - Link between shrinkage and power of test

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