Population Design in Nonlinear Mixed Effects Multiple Response Models: extension of PFIM and evaluation by simulation with NONMEM and MONOLIX

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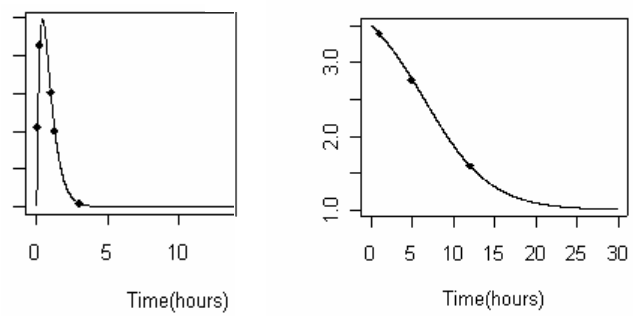
Context (1)

- **Nonlinear mixed effects models (NLEM)**
  - Handle data measured repeatedly through time and described by nonlinear models
  - Estimation of the mean parameters and their intersubject variability in the population to be treated
  - Allow sparse data

- **Nonlinear mixed effects models for multiple responses**
  - For each individual *i :* vectors of observations in time from K different types of measure (k=1, …,K)
  - Different times of measurement in case of different time scale for each type of measure
  - Examples
    - Pharmacokinetics/Pharmacodynamics (PK/PD)



    - Drug and its metabolite

Context (2)

- **Maximum likelihood estimation**
  - **No analytical expression for the likelihood**
  - **Several methods**
    - **Linearisation of the log-likelihood**
      - NONMEM [1]
        - *FO method (First Order) :* linearisation of the model around the mean of the random effects
        - *FOCE method (First Order Conditional Estimate)* [2] : linearisation of the model around individual values of the random effects
    - **Stochastic approach**
      - MONOLIX [3] *: SAEM algorithm* [4]
        - Based on the EM algorithm
        - Used Markov Chain Monte Carlo
        - Estimation by stochastic approximation

(1) Beal SL, Sheiner LB. NONMEM Project Group, *University of California,* 1992
(2) Lindstrom MJ, Bates DM. *Biometrics,* 1990
(3) MONOLIX, Version 2.1. (2007) http://software.monolix.org
(4) Khun E, Lavielle M. *Computational Statistics and Data Analysis*, 2005

Context (3)

- **Collect of data: Importance of the choice of the design**
  - Impact on the precision of estimation of the population parameters
- **Population design** Ξ
  - Model for one response
    - N subjects
    - Q groups of N_q subjects with a same elementary design $\xi_q = \{t_1, t_2, \ldots, t_{nq}\}$
      - n_q samples
      - Allocation in time

$$\Xi = \{[\xi_1, N_1]; [\xi_2, N_2]; \ldots; [\xi_Q, N_Q]\}$$

  - Model for multiple responses

$$\Xi = \{[(\xi_1^1, \xi_1^2, .., \xi_1^K), N_1]; [(\xi_2^1, \xi_2^2, .., \xi_2^K), N_2]; \ldots; [(\xi_Q^1, \xi_Q^2, .., \xi_Q^K), N_Q]\}$$

⇒ Elementary design composed of several sub-design ξ_q^k, $k = 1, \ldots, K$, associated with the k^{th} type of measurement : $\xi_i = \{\xi_i^1, \xi_i^2, .., \xi_i^K\}$

Context (4)

- **Design evaluation and optimisation**
  - **Approach based on the Fisher information matrix**
    - **For single response model**
      - Linearisation of the model using a first order Taylor expansion around the expectation of the random effects (1)
      - Relevance of this approach demonstrated on real data (2)
    - **For multiple response model**
      - Extension of M_F for multiple responses (3) (4)
        - Same method as for a model with one response
      - Computation of the matrix more complex
        - Some parameters included in several models
        - Need to be considered in the derivatives

⟹ Relevance of this extension with this first order approximation ?

(1) Mentré F, Mallet A, Baccar D. *Biometrika*, 1997
(2) Retout S, Mentré F. Bruno R. *Statistics in Medicine*, 2002
(3) Hooker A, Vicini P. *The American Association of Pharmaceutical Scientists Journal,* 2005
(4) Gueorguieva I, Aarons L, Ogungbenro K, Jorga KM, Rodgers T, Rowland M. *Journal of Pharmacokinetics and Pharmacodynamics*, 2006

Objective

- **Evaluation of the relevance of this first order extension for multiple response model by simulation**

Notation

- **Nonlinear mixed effects model for one individual *i* among *N***

$$Y_i = \left[{y_{i1}}^T, {y_{i2}}^T, \ldots, {y_{iK}}^T \right]$$

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

- $\theta_i = \beta + b_i$ *or* $\theta_i = \beta \exp(b_i)$, *as* $\theta_i = g(\beta, b_i)$ *with* $b_i \sim N(0, \Omega)$
- f_k *describing nonlinear model*
- θ_i *vector of individual parameters*

- **Statistical model**

$$y_{ik} = f_k(\theta_i, \xi_i^k) + \varepsilon_{ik}(\sigma_{\text{inter}_k} + \sigma_{slope_k} f_k(\theta_i, \xi_i^k))$$

$$Y_i = F(\theta_i, \xi_i) + \varepsilon_i \otimes (\sigma_{\text{inter}} + \sigma_{slope} \otimes F(\theta_i, \xi_i))$$

ε_i are supposed independent from one type of measurement to the other.

Choice of a model

- **Evaluation by simulation :** PK/PD model

  - PK model

$$f_{PK}(\theta^{PK},\xi^{PK}) = \frac{Dose}{V} \times \exp(\frac{-Cl}{V} \times \xi^{PK})$$

    - θ^{PK} : Cl et V
    - *Proportional error model*

  - PD model

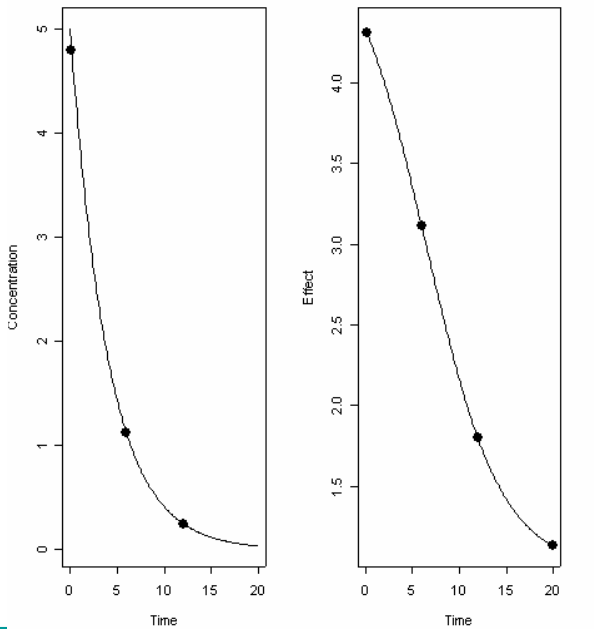
$$f_{PD}(\theta^{PK},\theta^{PD},\xi^{PD}) = E_0 + \frac{E_{\max} \times f_{PK}(\theta^{PK},\xi^{PD})}{C_{50} + f_{PK}(\theta^{PK},\xi^{PD})}$$

    - θ^{PD} : E_0 , E_{max} et C_{50}
    - *Additive error model*

  - Population design

$$\Xi = \left\{\left[\left(\xi^{PK},\xi^{PD}\right), N\right]\right\}$$

    - ξ^{PK} = {0.166,6,12}
    - ξ^{PD} = {0.166,6,12,20}
    - N =100

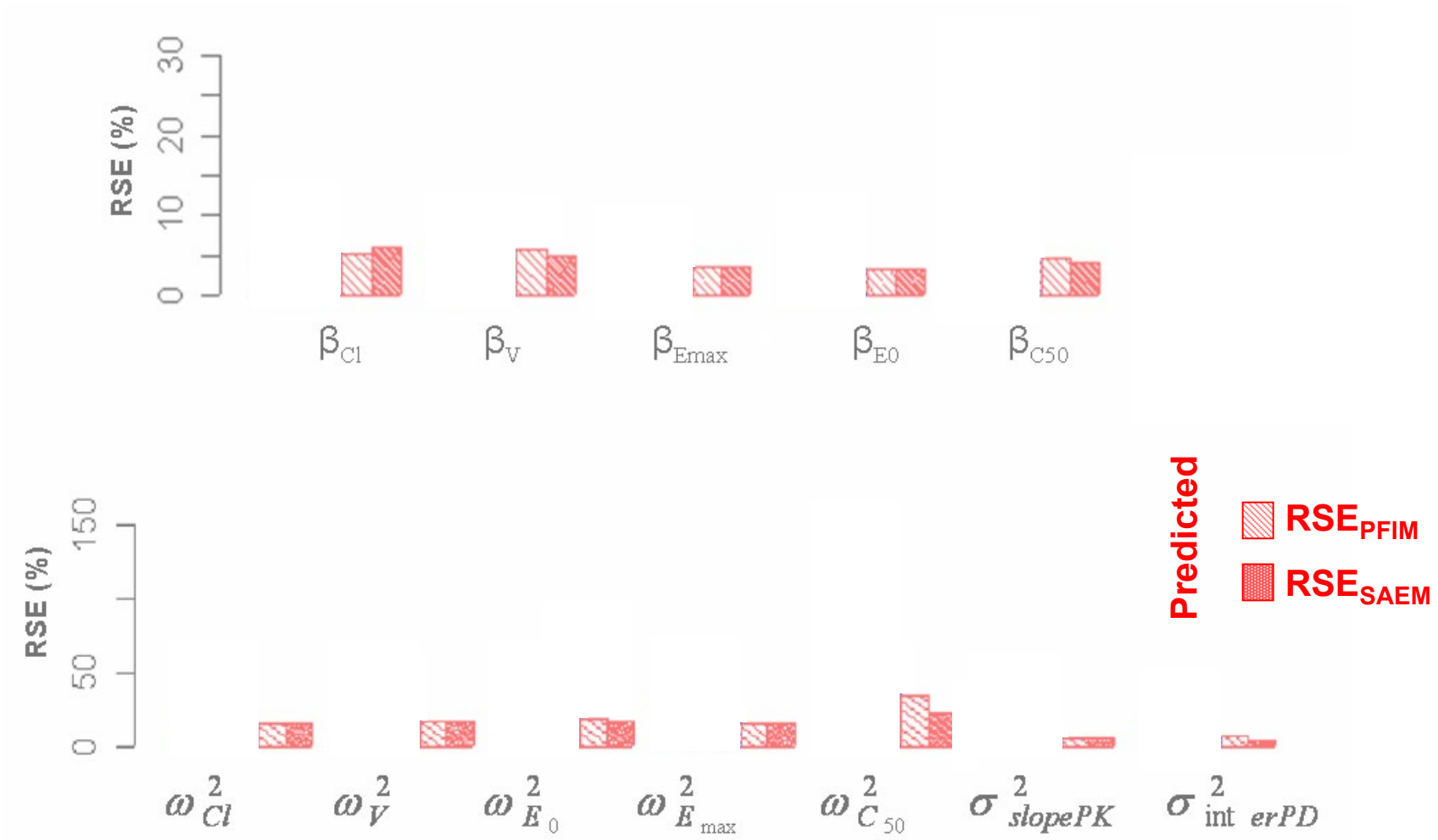


Exponential random effects for all the parameters

Evaluation : Method (1)

- **Implementation of this extension in PFIM**
- **Computation of the predicted standard errors with the extension of PFIM**
  - Relative standard errors : RSE_{PFIM}
- **Comparison to the predicted SE obtained with an "exact method"**
  - Computation of M_F by the SAEM algorithm (MONOLIX)
    - Louis method
  - Exact method without linearisation ⟹ "**gold standard**"
    - Simulation of one data set with 10000 subjects
      - Asymptotic properties of M_F
    - Rescale of the SE for N=100 subjects

Predicted RSE (%): PFIM/SAEM



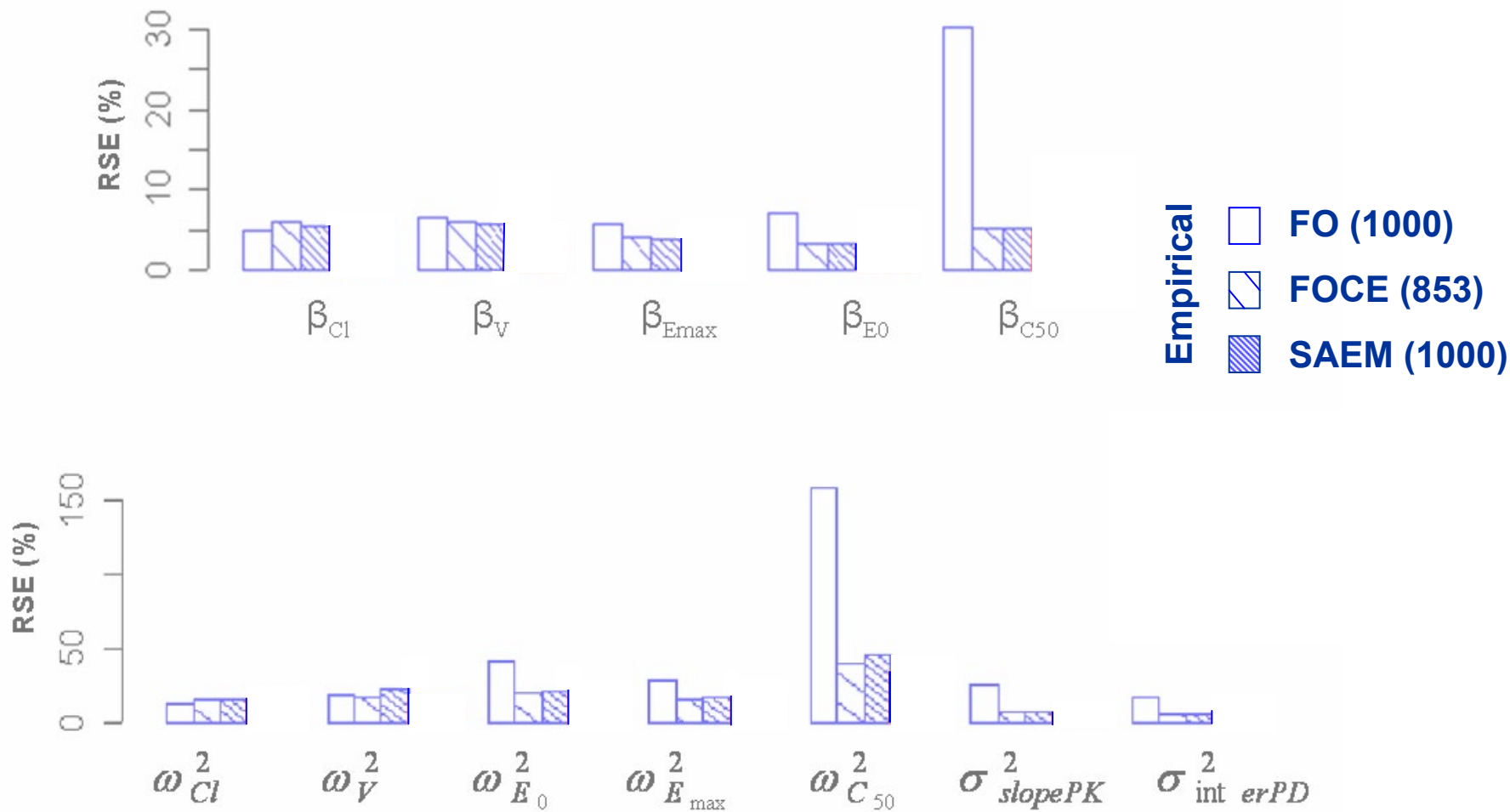
Evaluation : Method (2)

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

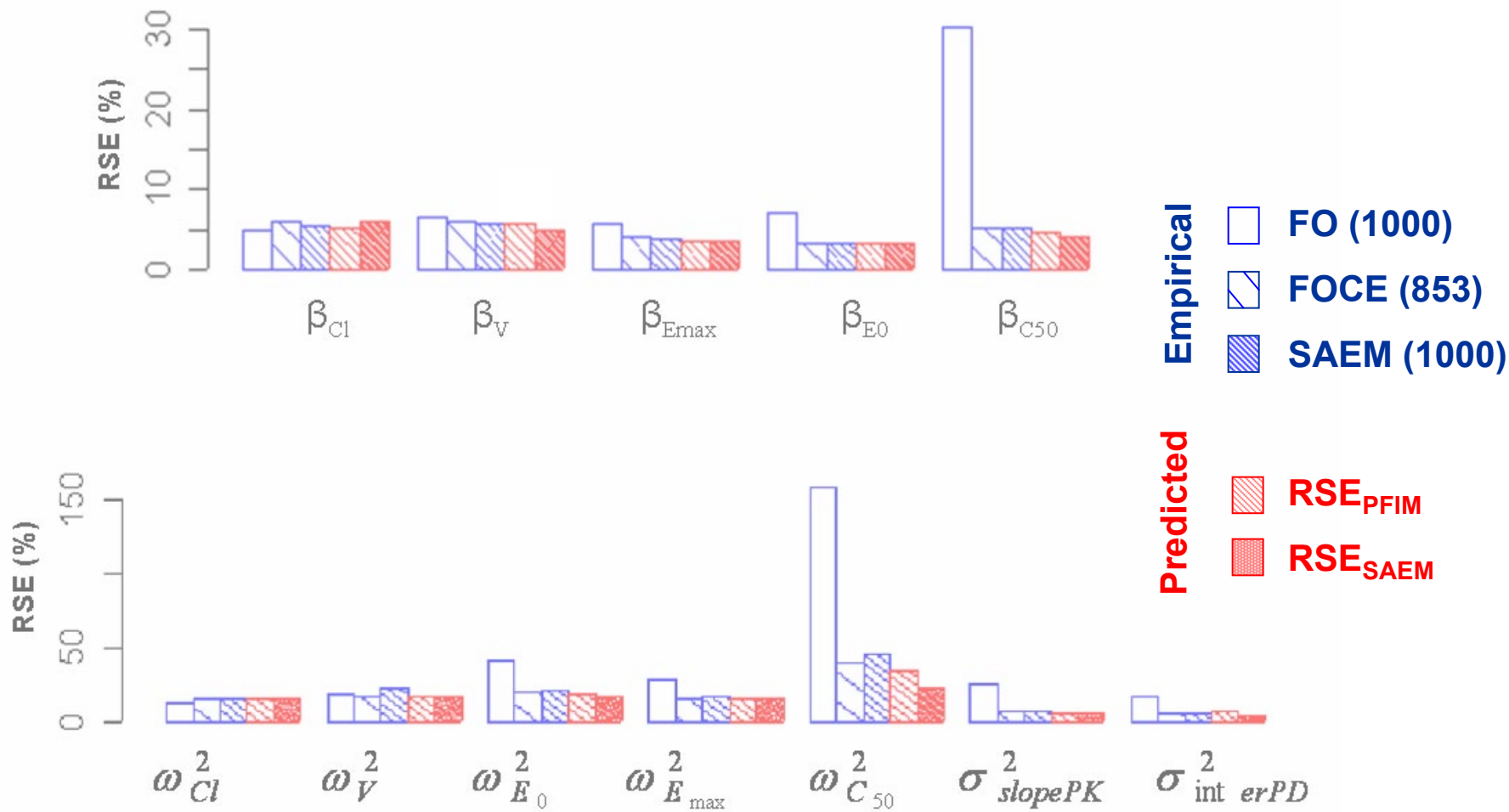
Data sets convergence

- **On the 1000 data sets**
  - Convergence obtained for
    - FO : 1000 data sets
    - FOCE : 853 data sets
    - SAEM : 1000 data sets

Empirical RSE (%)



Empirical and predicted RSE (%)



Evaluation : Method (2)

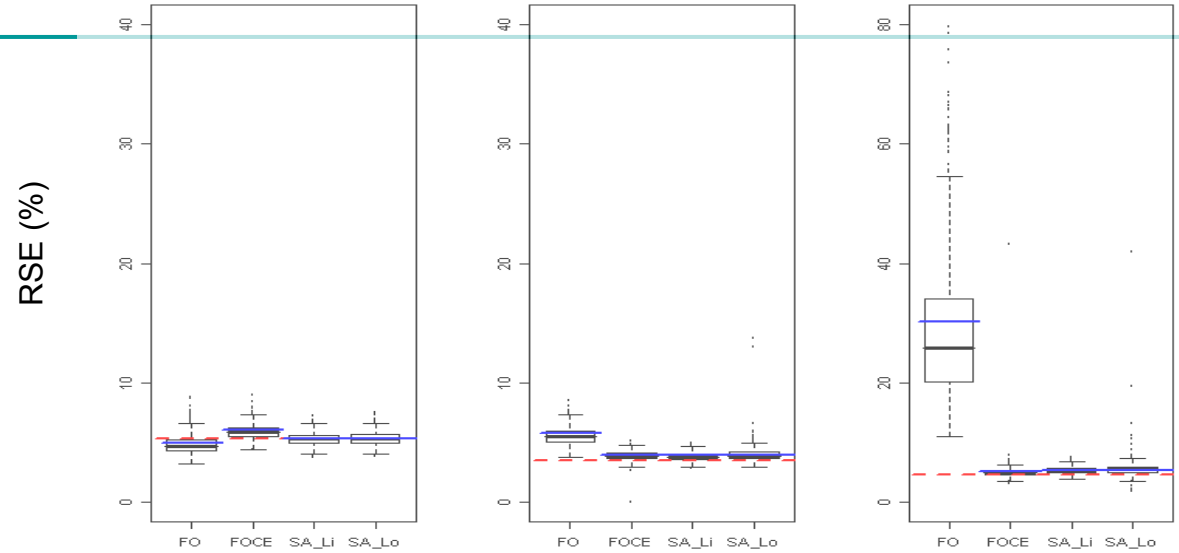
- **Comparison to the distribution of the relative standard errors obtained on each data set for each parameter**
  - NONMEM (FO et FOCE)
  - MONOLIX : SAEM
    - Computation of the SE
      - Linearisation
        around the individual parameters estimated by SAEM without linearisation
      - Louis method
  - **Comparison with RSE_{PFIM} and the empirical RSE**

Data sets convergence (%)

- **On the 1000 data sets**
  - Convergence obtained for :
    - FO : 1000 data sets
    - FOCE : 853 data sets
    - SAEM : 1000 data sets

Variance covariance matrix obtained for :

- FO : 997 data sets
- FOCE : 798 data sets
- SAEM : 1000 data sets



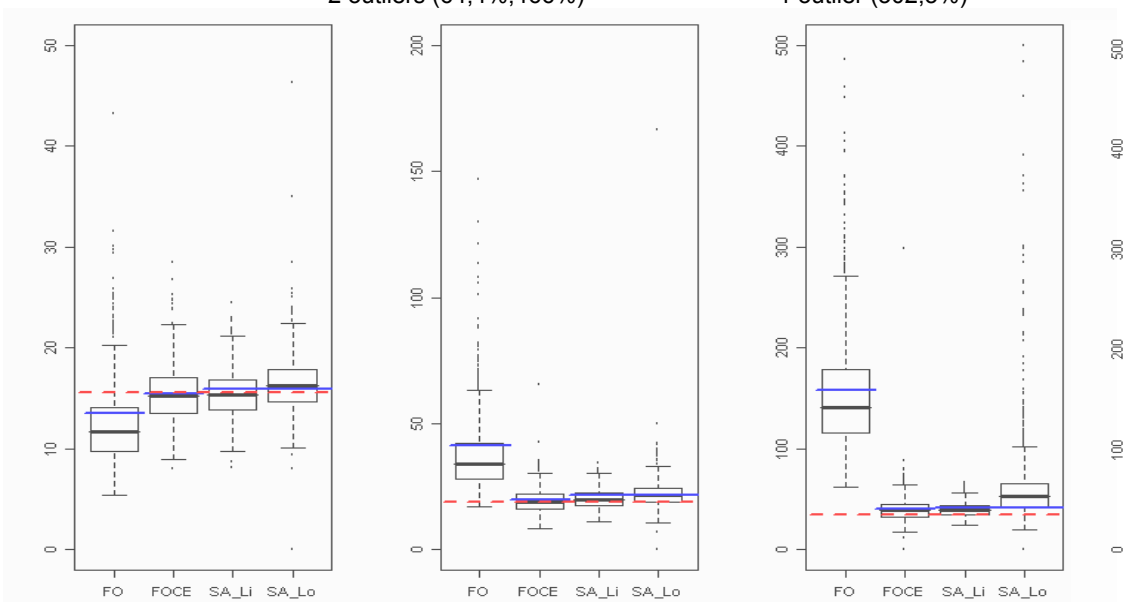
β_{Cl} β_{Emax} β_{C50}

RSE_{PFIM}

RSE_{emp}

FO
FOCE

2 outliers (64,4%,466%) 1 outlier (302,5%) 3 outliers (86,9%, 80,7%, 131,7%)
1 outlier(84,8%)

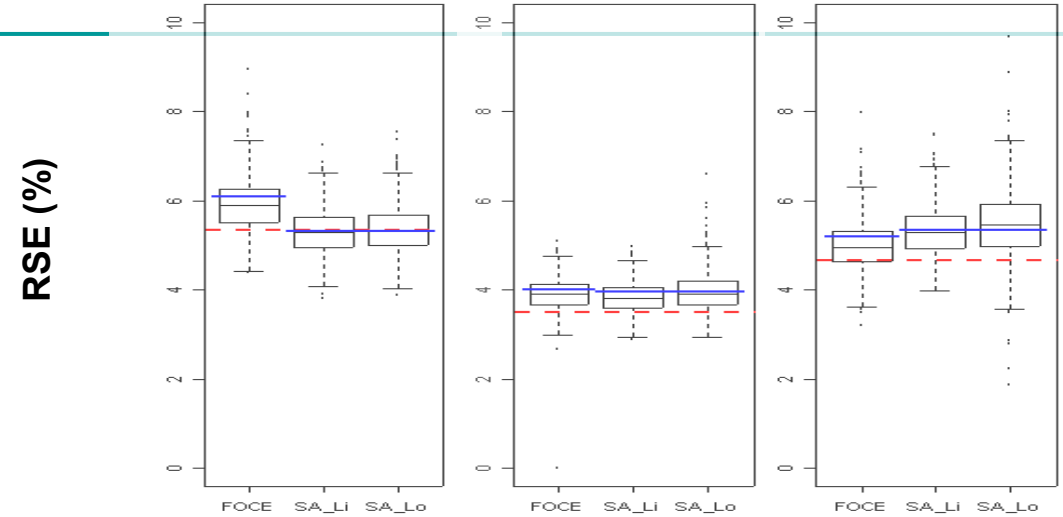


ω_{Cl}^2 ω_{Emax}^2 ω_{C50}^2 $\sigma_{slopePK}^2$ $\sigma_{interPD}^2$

FO
FOCE
SA_Lo

3 outliers(532.2%,596.6%,1200%)

2 oultiers(98.8%)
1 outlier (122.1%) 1 outlier(209,4%)

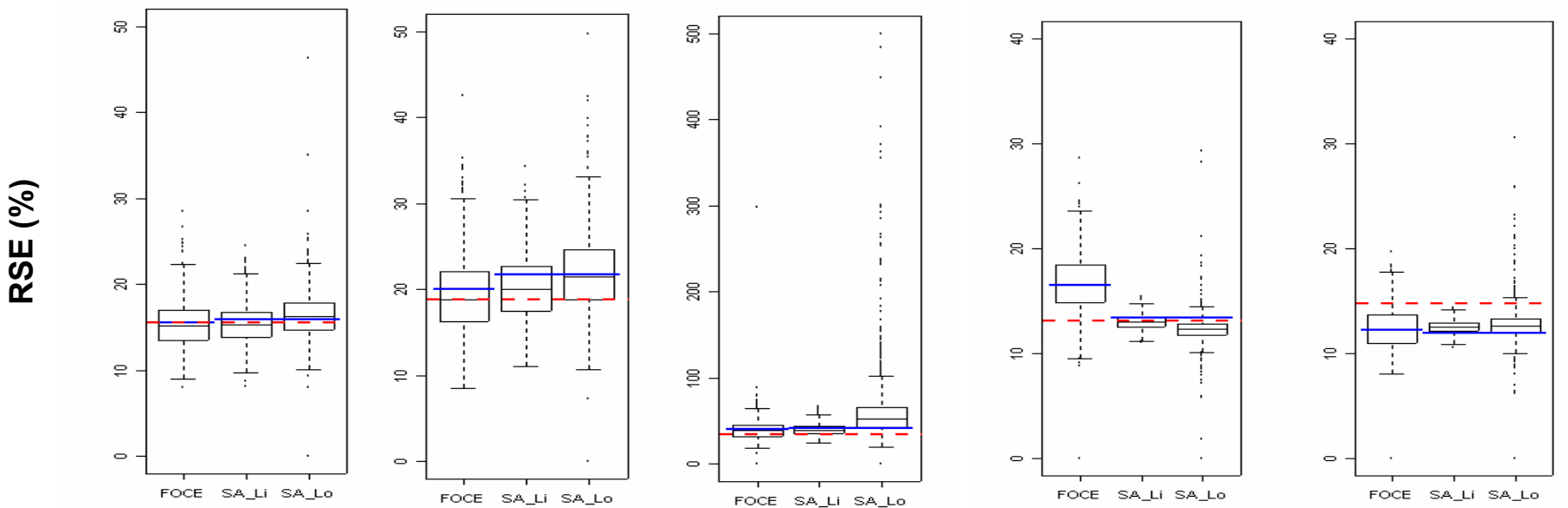


RSE_{PFIM}

RSE_{emp}

β_{Cl} | β_{Emax} | β_{C50}

	β_{Cl}	β_{Emax}	β_{C50}
FOCE	2 outliers (64.4%,466,0%)	1 oultier (45%)	2 outliers (84.6%,43.2%)
SA_Lo	17 files with NA +	2 outliers (12.9%,13.7%)	7 outliers [10.6% : 41.8%]



ω_{Cl}^2 | ω_{Emax}^2 | ω_{C50}^2 | $\sigma_{slopePK}^2$ | $\sigma_{interPD}^2$

	ω_{Cl}^2	ω_{Emax}^2	ω_{C50}^2	$\sigma_{slopePK}^2$	$\sigma_{interPD}^2$
FOCE	1 outlier (98;8%)	1 oultier (132;2%)		2 outliers(45.6%,138.8%)	1 outlier (48.4%)
SA_Lo	1 outlier (122,1%)	1 outlier(209,4%)	25 outliers [500%-10^18%]	1 outlier (109,5%)	2 outliers (153.3%,163.3%)

Conclusion

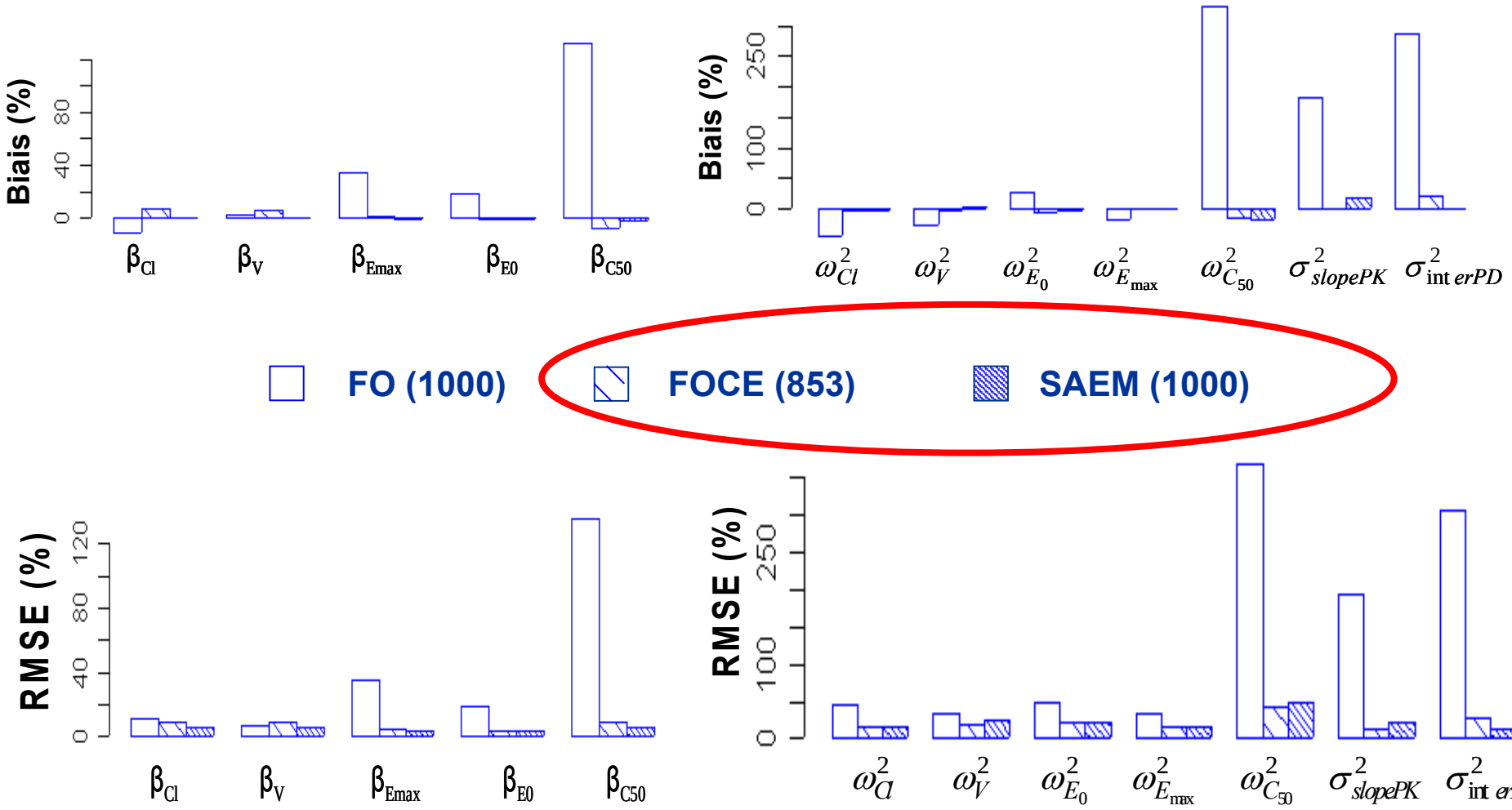
- **Relevance of the first order extension**
  - **Predicted RSE by PFIM**
    - equivalent to the RSE predicted by SAEM
    - close to the empirical RSE of FOCE and SAEM
    - concordant with the distribution of the RSE obtained with SAEM (linearisation) and FOCE

- **Although the extension of M_F for multiple response is based on a first order approximation the predicted RSE are close to those computed by FOCE and not by FO**

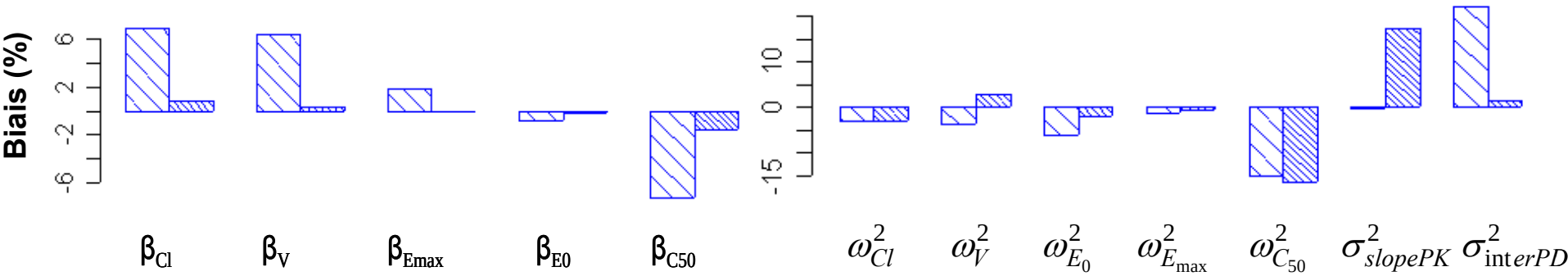
- **Extension in PFIM and PFIMOPT for K responses :**
  - **PFIM 3.0 /PFIMOPT 3.0**

Bias and RMSE: FO, FOCE and SAEM

Bias (%) and RMSE (%)



Bias (%) and RMSE (%)



FOCE (853) SAEM (1000)