

CONTEXT

- Individual parameters in nonlinear mixed effect models (NLMEM)
 - Estimated by Bayesian approach: Maximum *A Posteriori* (MAP)
 - Important for treatment optimization, sequential analysis in pharmacokinetic-pharmacodynamic studies, screening for covariates
- Precision of individual parameter estimates and shrinkage depends on sampling designs, percentage of data below the limit of quantification (LOQ) and the method for handling these data
- Design evaluation: Approach based on the Fisher information matrix (FIM)
 - Standard Individual estimation → Individual FIM (IFIM)
 - Population analysis → Population FIM, implemented in several software [1]
 - Bayesian Individual estimation → Bayesian FIM (BFIM) [2,3]
- BFIM, implemented in the R package PFIM 4.0 (www.pfim.biostat.fr), can be used to predict standard error and shrinkage [4]
- Data below LOQ are not yet taken into account in BFIM

OBJECTIVES

- Take into account possible BQL data in evaluation of IFIM and BFIM
- Evaluate the influence of design and of different levels of inter- and intra-individual variability on the precision of individual parameter estimation and shrinkage using BFIM

METHODS

NOTATIONS

Design

n_i sampling times in individual i ($i = 1, \dots, N$)

Individual design $\xi_i = (t_{i1}, \dots, t_{in_i})$

NLMEM

Individual model: $y_{ij} = f(\theta_i, \xi_i) + \varepsilon_{ij}$

Structural model f ; Individual parameters θ_i

Residual errors $\varepsilon_{ij} \sim \mathcal{N}(0, \Sigma(\theta_i, \xi_i))$

$$\Sigma(\theta_i, \xi_i) = \Sigma(\theta_i, \xi_i) = \text{diag}((\sigma_{\text{inter}} + \sigma_{\text{slope}} f(\theta_i, \xi_i))^2)$$

Random effect model $\theta_i = g(\mu, \eta_i) = \mu e^{\eta_i}$; $\eta_i \sim \mathcal{N}(0, \Omega)$; $\Omega = \text{diag}(\omega_1^2, \dots, \omega_p^2)$

Population parameters $\Psi = \{\mu_1, \dots, \mu_p, \omega_1^2, \dots, \omega_p^2, \sigma\}$

BAYESIAN FISHER INFORMATION MATRIX

$$M_{BF}(\xi) = E_{\eta} (M_{IF}(\theta, \xi)) + \Omega^{-1}$$

indice i omitted

a priori information

Individual information

$$M_{IF}(\theta, \xi) = E_y (M_{IF}(\theta, y)) = E_y \left(\frac{\partial \log L(\theta, y)}{\partial \theta} \frac{\partial \log L(\theta, y)^T}{\partial \theta} \right)$$

$E_{\eta} (M_{IF}(\theta, \xi))$ can be approximated by FO linearisation as $M_{IF}(\mu, \xi)$

Shrinkage: Ratio between predicted variance and variance *a priori* [3]

$$I - W(\xi) = M_{BF}(\xi)^{-1} \Omega^{-1}$$

HANDLING OF DATA BELOW LOQ

In presence of data below LOQ, we observe: $y_j = \begin{cases} y_j^{obs} & \text{if } y_j > LOQ \\ y_j^{cens} & \text{if } y_j \leq LOQ \end{cases}$

Likelihood function for an individual:

$$L(\theta; y) = \prod_{y_j \in y_j^{obs}} p(y_j^{obs}; \theta) \prod_{y_j \in y_j^{cens}} p(y_j^{cens}; \theta)$$

with $p(y_j^{cens}; \theta) = p(y_j \leq LOQ) = \Phi\left(\frac{LOQ - f(\theta, t_j)}{\Sigma(\theta, \xi)}\right)$, Φ : cdf $\mathcal{N}(0, 1)$

Considering a decreasing function f [5]

Probability for the $j+1$ th observation to be the first below LOQ

$$p_j = \Phi\left(\frac{LOQ - f(\theta, t_{j+1})}{\Sigma(\theta, \xi)}\right) - \Phi\left(\frac{LOQ - f(\theta, t_j)}{\Sigma(\theta, \xi)}\right)$$

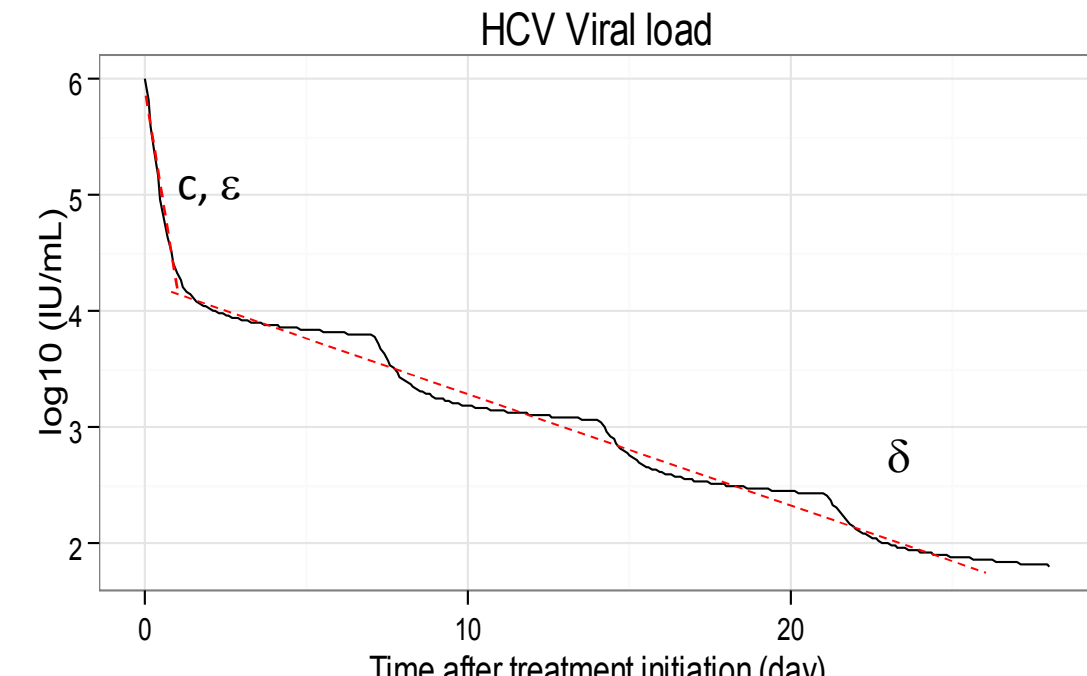
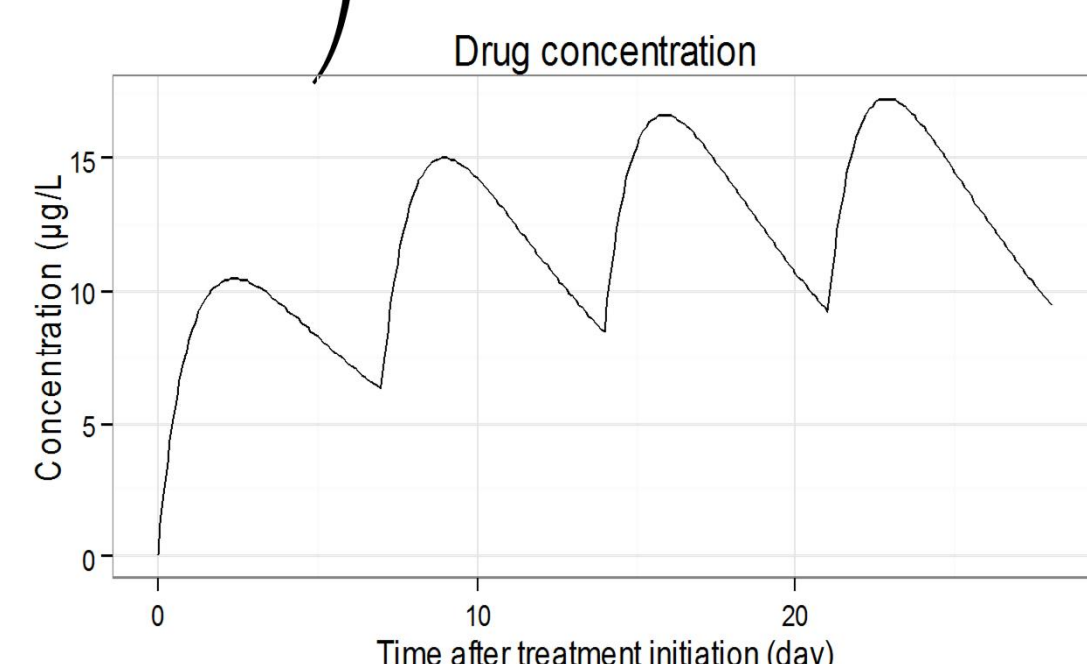
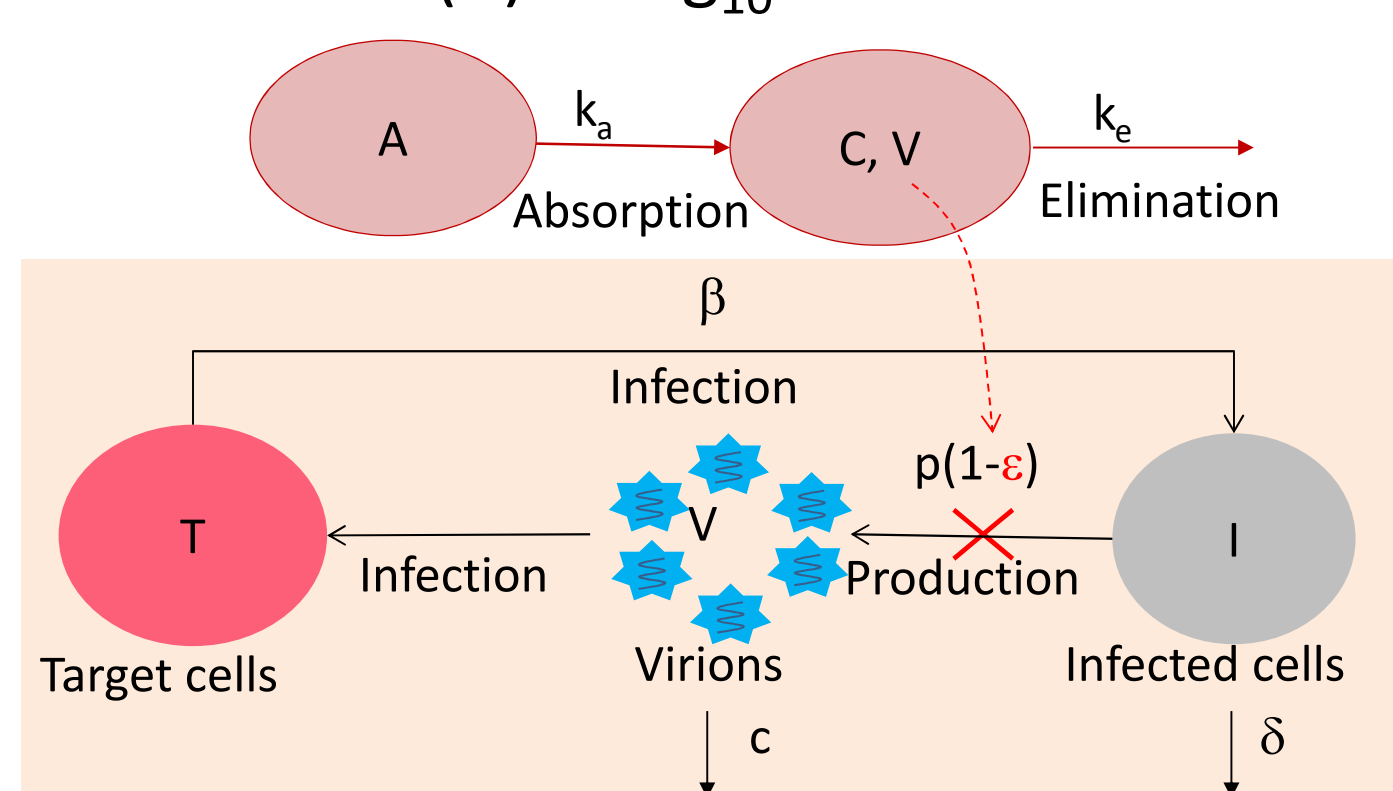
Individual information

$$M_{IF}(\theta, \xi) = \sum_{j=1}^n p_j E_y (M_{IF}(\theta, (y_{1...j}, y_{j+1...n})))$$

$$= \sum_{j=1}^n p_j \left(M_{IF}(\theta, \xi_{1...j}) + \sum_{k=j+1}^n M_{IF}(\theta, y_k^{cens}) \right) \quad \text{with } \xi_{1...j} = (t_1, \dots, t_j)$$

ILLUSTRATIVE EXAMPLE

- Pharmacokinetic – Viral kinetic model [6]:
 - Peg-IFN concentration (C), once-a-week subcutaneous administration
 - Viral load (V) in $\log_{10}$ scale



- Sampling protocol
 - ξ_{5-7} , with $\xi_{PK} = (1, 3, 7, 14, 28)$ and $\xi_{VK} = (0, 1, 3, 7, 14, 28)$
 - ξ_{3-5} , with $\xi_{PK} = (1, 3, 7)$; $\xi_{VK} = (0, 1, 3, 7, 28)$
 - ξ_{2-3} , with $\xi_{PK} = (1, 7)$; $\xi_{VK} = (0, 7, 28)$

SIMULATION STUDY FOR EVALUATION OF BFIM WITH LOQ

- Standard scenarios: $\omega = 30\%$, $\sigma = (\sigma_{\text{inter_PK}}, \sigma_{\text{inter_VK}}) = (0.5, 0.15)$
- No LOQ or LOQ = 2 $\log_{10}$ viral load
- Evaluation of the prediction of BFIM
 - Simulation of $N = 1000$ individuals
 - Estimation of individual parameters by MAP, Ψ fixed at simulation values (MONOLIX 4.3)
 - Comparison of RSE and shrinkage predicted by BFIM and simulation

Table 1. Parameters of PK-VK model [6]

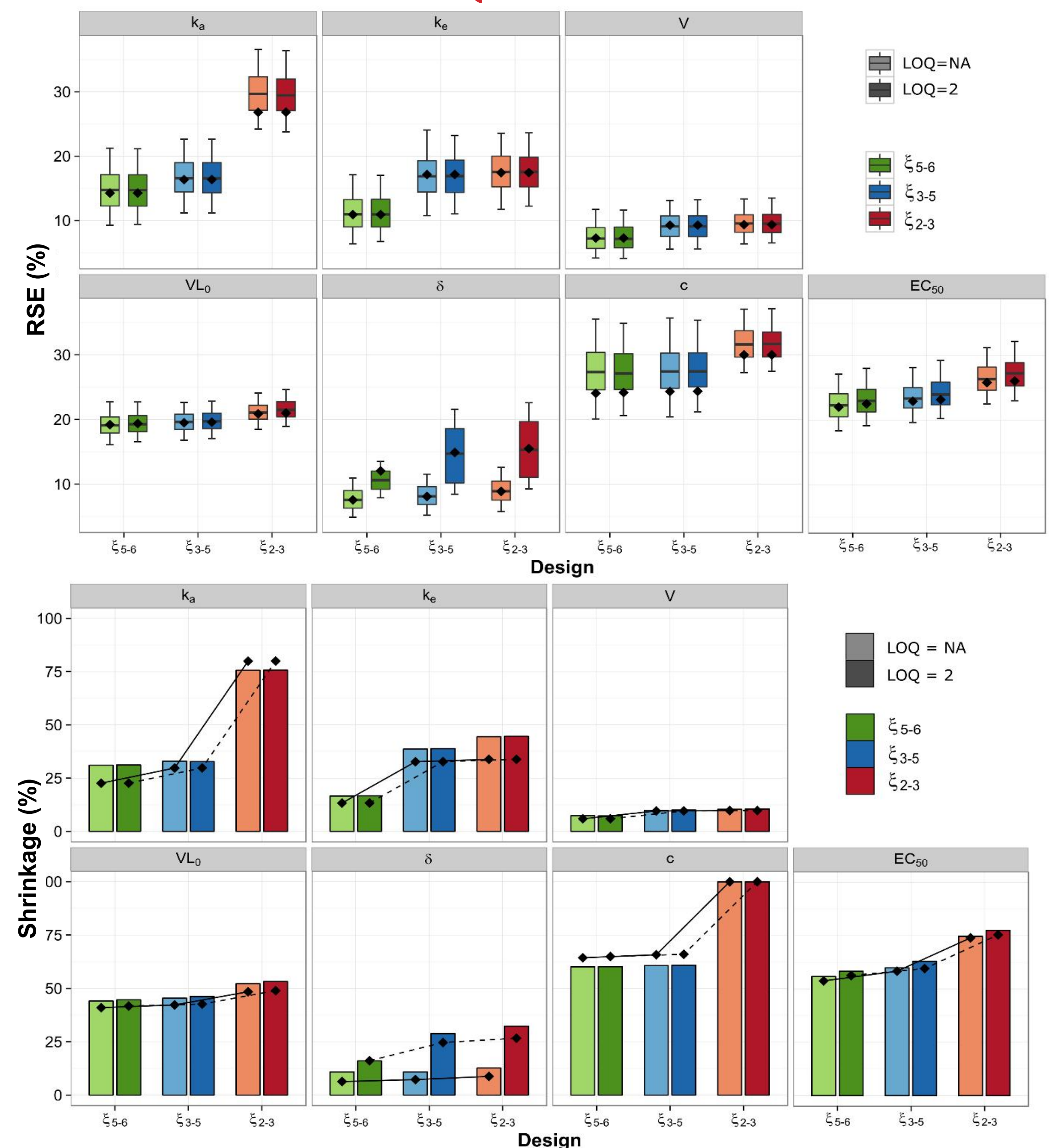
	Unit	Fixed effect	SD
k_a	day ⁻¹	0.9	ω
k_e	day ⁻¹	0.15	ω
V	L	12	ω
EC_{50}	µg/L	0.15	ω
VL_0	IU/mL	10 ⁶	ω
δ	day ⁻¹	0.2	ω
c	day ⁻¹	6	ω
β	day ⁻¹ .cell ⁻¹	5.6 10 ⁻⁷	0
p	day ⁻¹	10	0

EVALUATION WITH IFIM/BFIM OF THE INFLUENCE OF DESIGN, VARIABILITIES ON PRECISION & SHRINKAGE OF INDIVIDUAL PARAMETERS

- Several scenarios with $\omega = 30\%$ or 50% , $\sigma = (0.5, 0.15)$ or $\sigma = (1, 0.3)$
- Prediction of RSE and/or shrinkage from BFIM and IFIM in absence of BQL data
- Comparison of RSE predicted by BFIM and IFIM

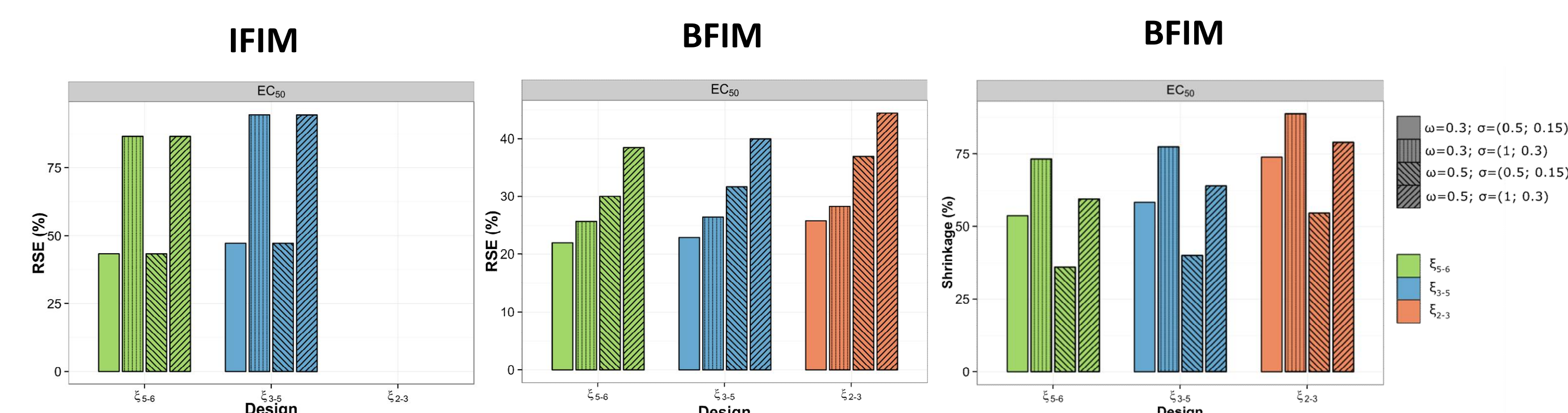
RESULTS

EVALUATION OF BFIM WITH DATA BELOW LOQ



- Good agreement between the predictions of BFIM (◆) and the simulation results for both RSE (boxplot) and shrinkage (barplot)
- The method proposed to take into account data below LOQ predict correctly the increase of RSE and shrinkage of δ in presence of data below LOQ

INFLUENCE OF DESIGN, VARIABILITY ON PRECISION AND SHRINKAGE



- NLMEM and MAP allow for better estimation of individual parameter estimates
- RSE increases when ω and/or σ increases
- Shrinkage increases when σ increases but decreases when ω increases

CONCLUSIONS

- BFIM predicts efficiently RSE and shrinkage of individual parameters
 - ⇒ Avoid intensive simulations
 - ⇒ BFIM is available in the R package PFIM 4.0 and now available in PFIM Interface 4.0, released in June 2015 (www.pfim.biostat.fr)
- Data below LOQ can influence the choice of design. The proposed method to take into account these data can correctly predict RSE and shrinkage of individual parameters
- Impact of design, inter- & intra-individual variability
 - Advantage of NLMEM and of MAP compared to individual regression
 - Importance of a careful choice of a reduced sampling design

References

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- Merlé et al. *J Pharmacokinet Biopharm*, 1995.
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