Prediction of shrinkage of individual parameters using the Bayesian information matrix in nonlinear mixed-effect models with application in pharmacokinetics

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Outline

1. **Context**
2. **Objectives**
3. **Materials and methods**
4. **Results**
5. **Conclusion & perspectives**

Context

Non-linear mixed effect models (NLMEM)

- Individual statistical model

$$y = f(\theta, \xi) + \varepsilon \qquad \text{with } \xi = \{t_1, \dots, t_n\}$$

$$\theta = g(\mu, \eta) \qquad \eta \sim \mathcal{N}(0, \Omega)$$

$$g(\mu, \eta) = \mu + \eta \text{ or } g(\mu, \eta) = \mu e^{\eta}$$

$$\varepsilon \sim \mathcal{N}\big(0, \Sigma(\theta, \xi)\big)$$

- Fixed effects $\mu = (\mu_1, \dots, \mu_p)$
- Variance-covariance matrix from random effects $\Omega = diag\left(\omega_1^2, \dots, \omega_p^2\right)$
- Variance of residual error $\Sigma(\theta, \xi) = diag\left((\sigma_{inter} + \sigma_{slope} f(\theta, \xi))^2\right)$
- Population parameters Ψ estimated by Maximum Likelihood (ML) approach

Context

Individual parameters estimation by MAP

- In Bayesian methodology, estimating θ is similar as estimating η
- η *are* estimated as the Maximum *a posteriori* (MAP)

$$\hat{\eta} = argmax\big(p(\eta|y)\big) = argmax\left(\frac{p(y|\eta) \times p(\eta)}{p(y)}\right)$$

- Bayesian information Matrix

$$BMF(\xi) = -E_{\eta}\left(\frac{\partial^2 \, log\big(p(\eta|y)\big)}{\partial\eta\partial\eta^T}\right)$$

$$= -E_{\eta}\left(E_{y|\eta}\left(\frac{\partial^2 log\big(p(y|\eta)\big)}{\partial\eta\partial\eta^T}\right)\right) - E_{\eta}\left(\frac{\partial^2 log\big(p(\eta)\big)}{\partial\eta\partial\eta^T}\right)$$

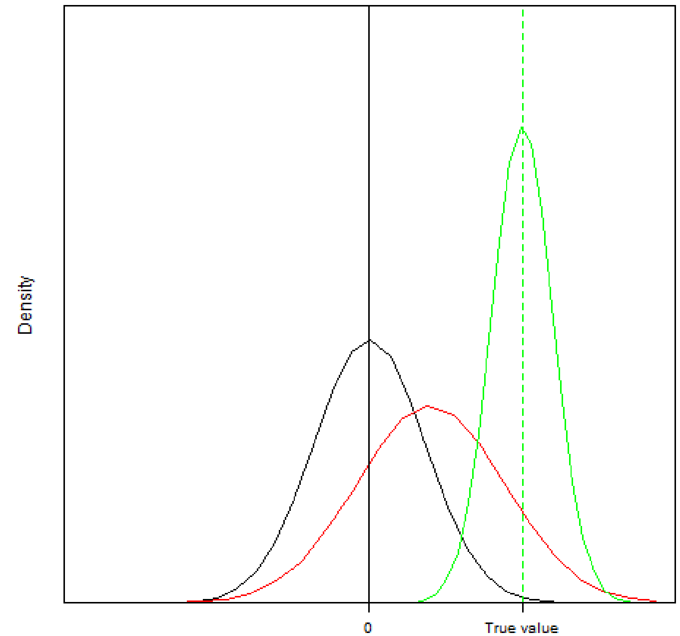
- Individual parameters are used to predict response, to select covariates and to draw diagnostics plots

Context

Shrinkage

- For each subject, $\hat{\eta}$ is influenced by the amount of individual information
  - A priori: normal distribution with zero mean
  - Rich design: *a posteriori* distribution with small standard deviation and a true mean
  - Sparse design: *a posteriori* distribution with high standard deviation and mean away from the true value

Individual *a posteriori* distribution of $\hat{\eta}_k$



A posteriori distribution

- *A priori*
- Rich design
- Sparse design

Context

Observed shrinkage

- Savic and Karlsson proposed a measure of shrinkage based on the dispersion of $\hat{\eta}_k$ in N patients

$$Sh_k = 1 - \frac{Var(\hat{\eta}_k)}{\omega_k^2}$$

  - *A priori* distribution:

    $$Var(\hat{\eta}_k) = \omega_k^2 \Leftrightarrow Sh_k = 0\ \%$$

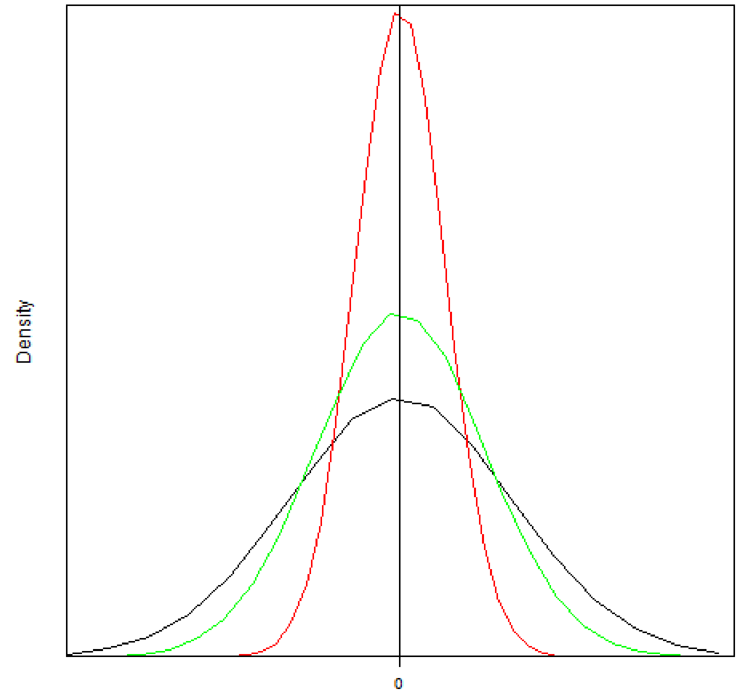
  - Rich design:

    $$Var(\hat{\eta}_k) \leq \omega_k^2 \Leftrightarrow Sh_k \leq 40\ \%$$

  - Sparse design:

    $$Var(\hat{\eta}_k) \ll \omega_k^2 \Leftrightarrow Sh_k \geq 50\ \%$$

$\hat{\eta}_k$ distribution for N subjects



- *A priori*
- Rich design
- Sparse design

Savic R, Karlsson M. Importance of shrinkage in empirical Bayes estimates for diagnostics: problems and solutions. *The AAPS J*, 2009;11(3):558-69

Context

Consequences of shrinkage

- Change of distribution shape (non-normal) of $\hat{\eta}$
- Significant change in the mean value of $\hat{\eta}$ (different from 0)
- Correlation between random effects may be hidden or induced
- Covariate relationships may be hidden or induced

⇨ Problems in individual estimates when shrinkage is over 50%

Savic R, Karlsson M. Importance of shrinkage in empirical Bayes estimates for diagnostics: problems and solutions. *The AAPS J*, 2009;11(3):558-69

Objectives

- Approximate BMF using first-order linearization
- Describe relationship between BMF and shrinkage
- Evaluate by simulation BMF and link with shrinkage

Materials and methods

Design evaluation and optimization in NLMEM

- Design evaluation and optimization based on Rao-Cramer inequality:

  MF^{-1} is the lower bound of estimation variance

- Individual estimation: Individual Fisher information Matrix

$$\mathrm{IMF}(\theta,\xi) = F(\theta,\xi)^T \Sigma(\theta,\xi)^{-1} F(\theta,\xi)$$

with $F(\theta,\xi) = \frac{\partial f(\theta,\xi)}{\partial \theta^T}$

- Population estimation: Population Fisher information Matrix (PMF)
  - evaluated using First-Order linearization (FO)
  - implemented in R in PFIM 3.2

Retout S, Mentré F, Bruno R. Fisher information matrix for non-linear mixed-effets models: evaluation and application for optimal design of enoxaparin population pharmacokinetics. *Stat Med*, 2002;21:2623-39

Materials and methods

Bayesian design evaluation

- Bayesian estimation of individual random effects

$$BMF(\xi) = E_\eta\big(IMF(g(\mu,\eta),\xi)\big) + \Omega^{-1}$$

- Two methods
  - Simulate η to compute E_η by Monte-Carlo simulation (MC)
  - FO
    - for additive random effects

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

    - for exponential random effects

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

with $\mathrm{M} = \mathrm{diag}(\mu_1, \dots, \mu_p)$

Merlé Y, Mentré F. Bayesian design criteria: computation, comparison and application to a pharmacokinetic and a pharmacodynamic model. *J Pharmacokinet Biopharm*, 1995;23(1):101-25

Materials and methods

Shrinkage in linear mixed effects model

- In linear mixed effects modeling

$$y(\xi) = \mathrm{F}(\xi)\theta + \varepsilon$$

with $\theta = \mu + \eta$, $\eta \sim \mathcal{N}(0, \Omega)$, $\varepsilon \sim \mathcal{N}(0, \Sigma)$

- ML estimate of θ

$$\hat{\theta}_{ML} = IMF(\xi)^{-1} F(\xi)^T y$$

- Bayesian estimate of θ

$$\hat{\theta}_{MAP} = (IMF(\xi) + \Omega^{-1})^{-1} \left(IMF(\xi) \hat{\theta}_{ML} + \Omega^{-1} \mu \right)$$

Fedorov F. Mixed models: design of experiments. Presented at *Isaac Newton Institute for Mathematical science*, Design and Analysis of Experiment, Cambridge, UK. August 2011

Materials and methods

Shrinkage in nonlinear mixed effects model

- $\mathrm{W}(\xi) = (IMF(\xi) + \Omega^{-1})^{-1}\Omega^{-1}$

  Then $\hat{\theta}_{MAP} = W(\xi)\mu + \left(I - W(\xi)\right)\hat{\theta}_{ML}$

  $\mathrm{W}(\xi)$ quantifies the balance between prior and individual information

- For nonlinear mixed effects models, using FO

$$\mathrm{W}(\xi) = BMF(\xi)^{-1}\Omega^{-1}$$

  $\mathrm{W}(\xi)$: normalized variance of estimation

  ⇨ W used for prediction of shrinkage

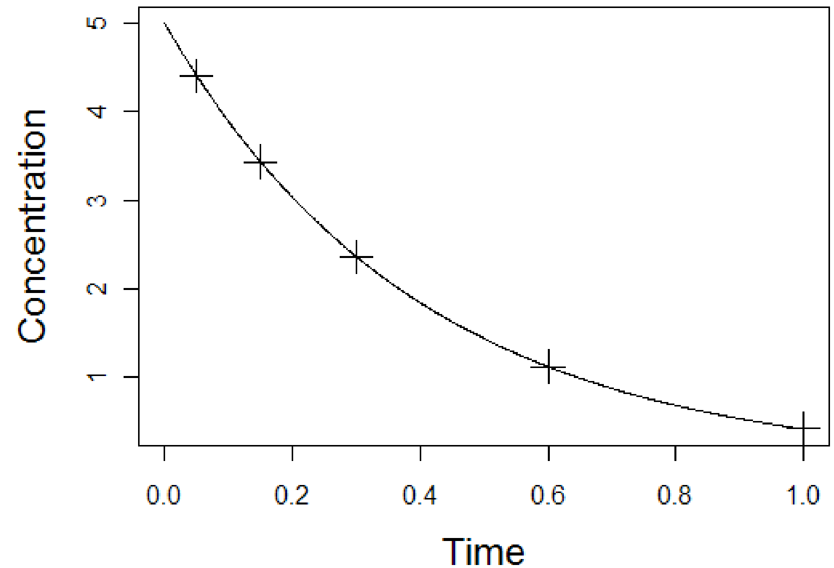
Materials and methods
Simulated example

- Monocompartimental IV PK model with non-saturable elimination
  - $\mu_V = 0.2$
  - $\mu_{CL} = 0.5$
- 6 simulated scenarios

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_{inter}	0.15	0.15	0.15	0.15	0.15	0.15
σ_{slope}	0	0.15	0	0.15	0	0.15

Materials and methods
Design

- Several designs from 2 to 5 samples
  - {0.05, 0.15, 0.3, 0.6, 1}
  - {0.05, 0.3, 0.6, 1}
  - {0.05, 0.3, 0.6}
  - {0.05, 0.3}
- For each scenario, 1000 subjects with the same design simulated
- Population parameters fixed to their true value
- Estimation of individual parameters by MAP with NONMEM 7. and MONOLIX 4.0



Materials and methods

Shrinkage investigation

- Exploration of scatterplots of individual estimates from NONMEM *vs* simulated parameters along with observed shrinkage

Validation of BMF computation and shrinkage

- Evaluation of the approximation of BMF by MC and FO
- Prediction of W from BMF
- Comparison of W *vs* observed shrinkage with NONMEM and MONOLIX

NB: Results presented for clearance

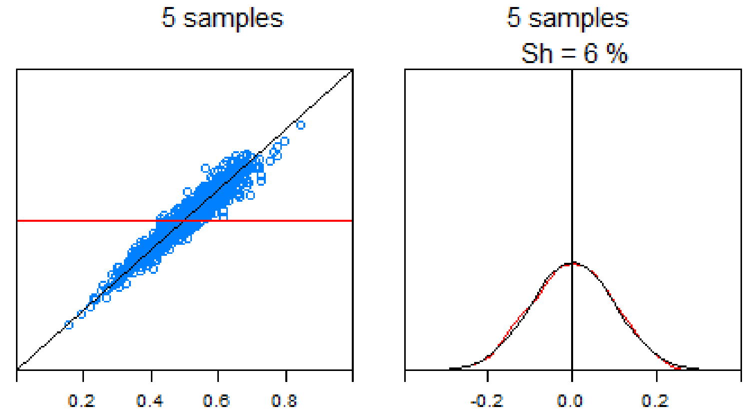
Results

Shrinkage investigation

Estimated *vs* simulated parameters and η distribution

aa

Estimated CL



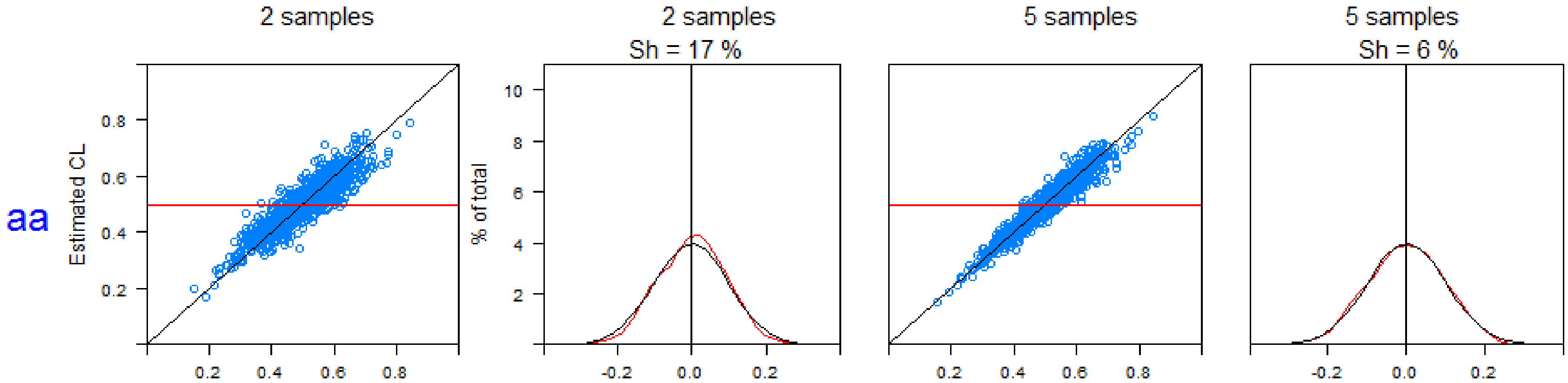
Parameter scatterplot
- Identity line
- Mean

η distribution
- *A priori*
- Estimated

Results

Shrinkage investigation

Estimated *vs* simulated parameters and η distribution



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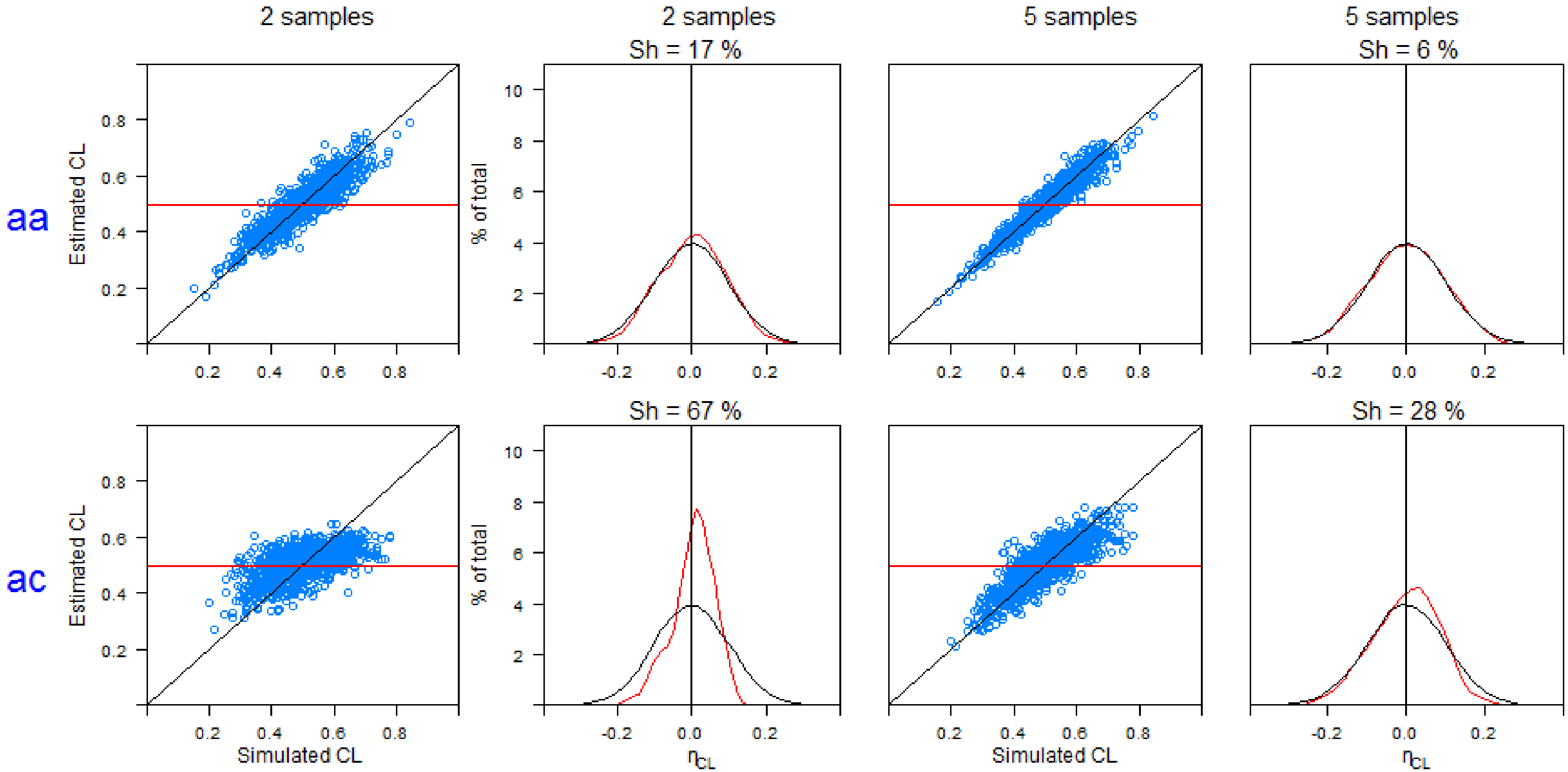
Shrinkage investigation

Estimated *vs* simulated parameters and η distribution



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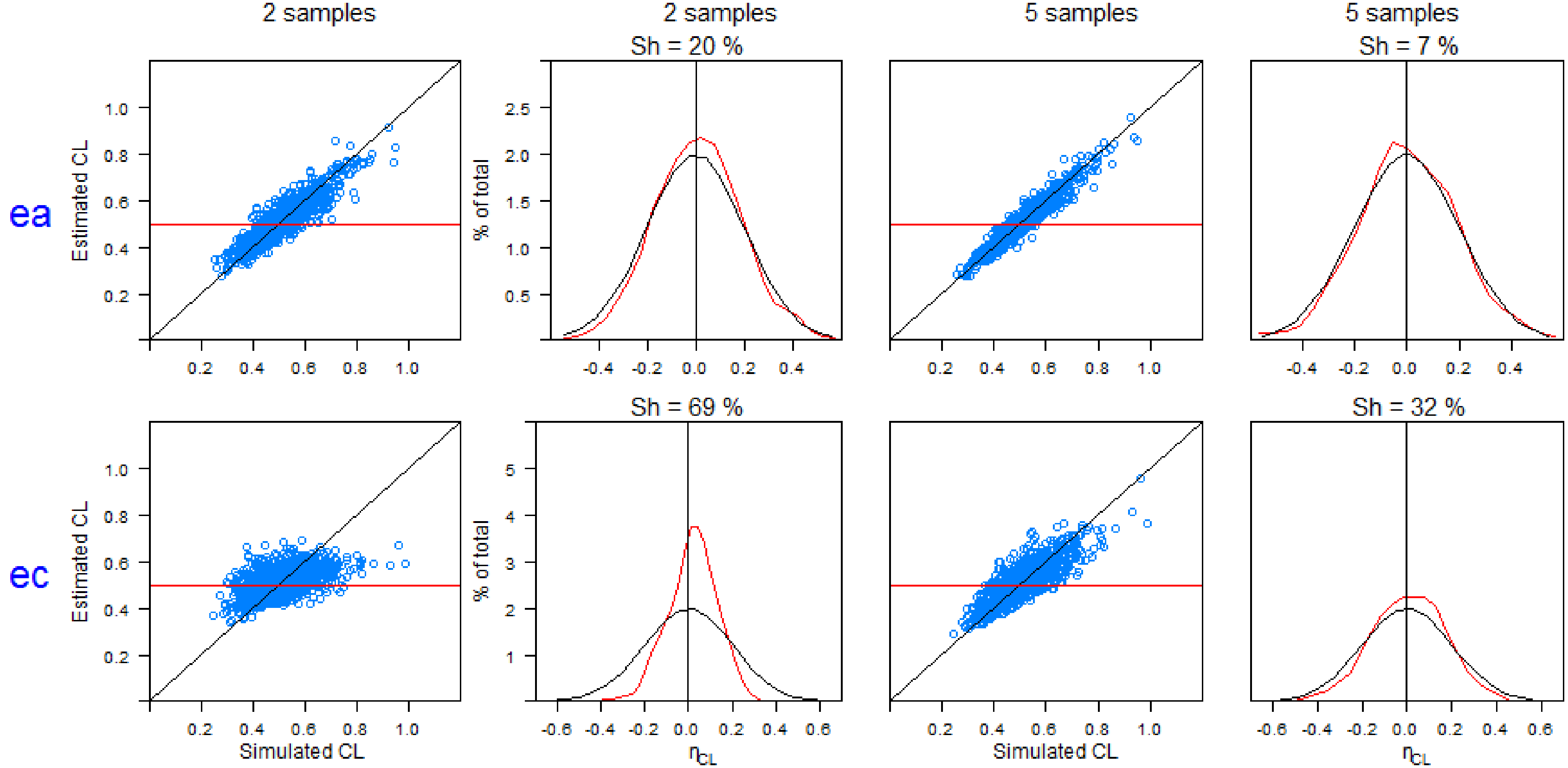
Shrinkage investigation

Estimated vs simulated parameters and η distribution



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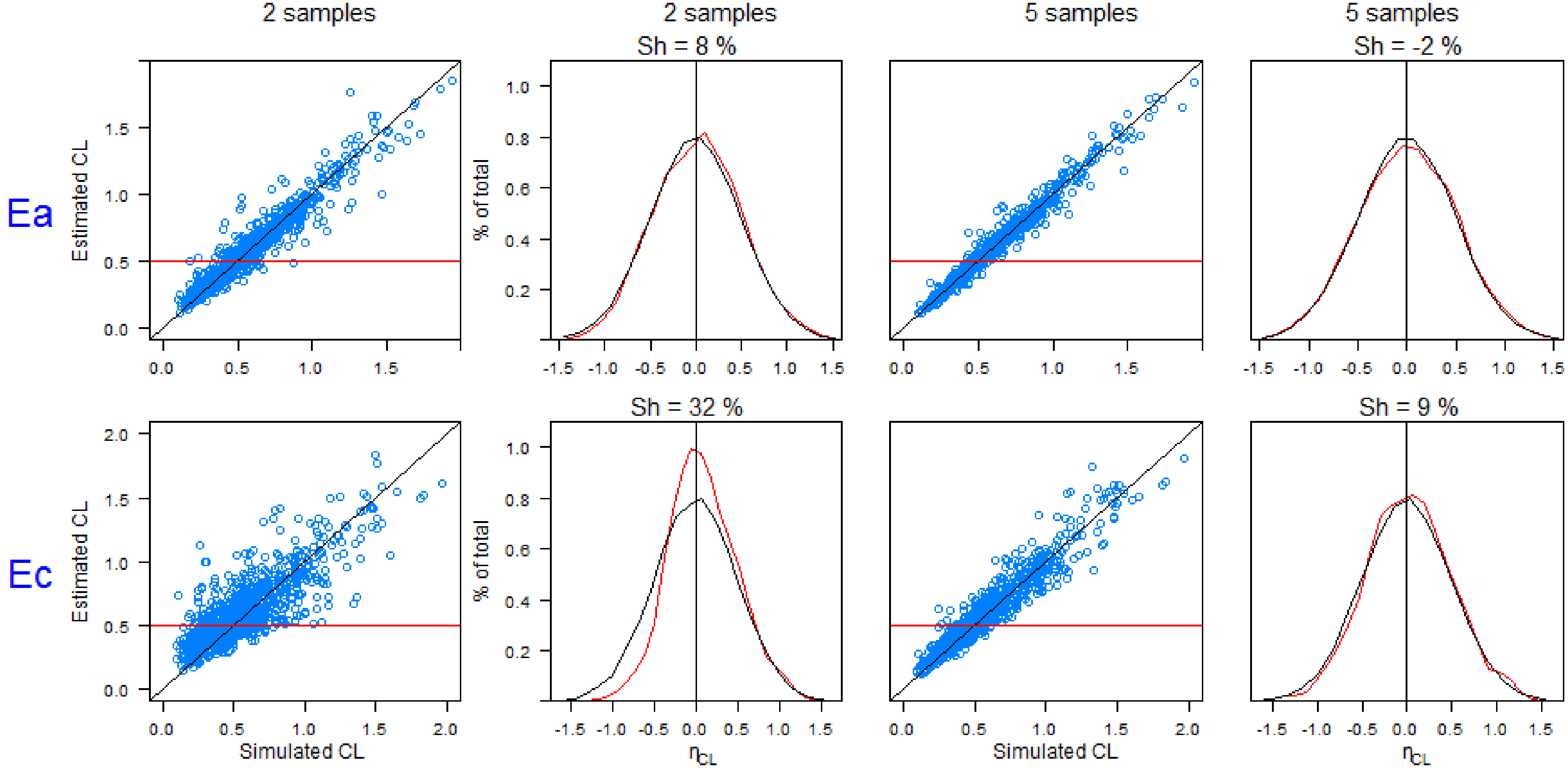
Shrinkage investigation

Estimated vs simulated parameters and η distribution



Parameter scatterplot
– Identity line
– Mean

η distribution
– *A priori*
– Estimated

Results

BMF approximation

Relative Standard Error on clearance (%)

Scenario	Number of samples	Ω	IMF^{-1}	BMF^{-1}	
				FO	MC
aa	2	20	9.0	8.2	8.4
	5	20	5.3	5.1	5.2
ac	2	20	30.8	16.5	16.3
	5	20	12.3	10.5	10.5
ea	2	20	9.0	8.2	8.5
	5	20	5.3	5.1	5.2
ec	2	20	30.8	16.5	16.5
	5	20	12.3	10.5	10.7
Ea	2	50	9.0	8.9	13.1
	5	50	5.3	5.3	6.7
Ec	2	50	30.8	25.9	27.8
	5	50	12.3	12.0	14.7

- BMF^{-1} from FO close to MC
- RSE decreases when number of samples increases
- BMF^{-1} lower than Ω and IMF^{-1}

Results

BMF approximation

Relative Standard Error on clearance (%)

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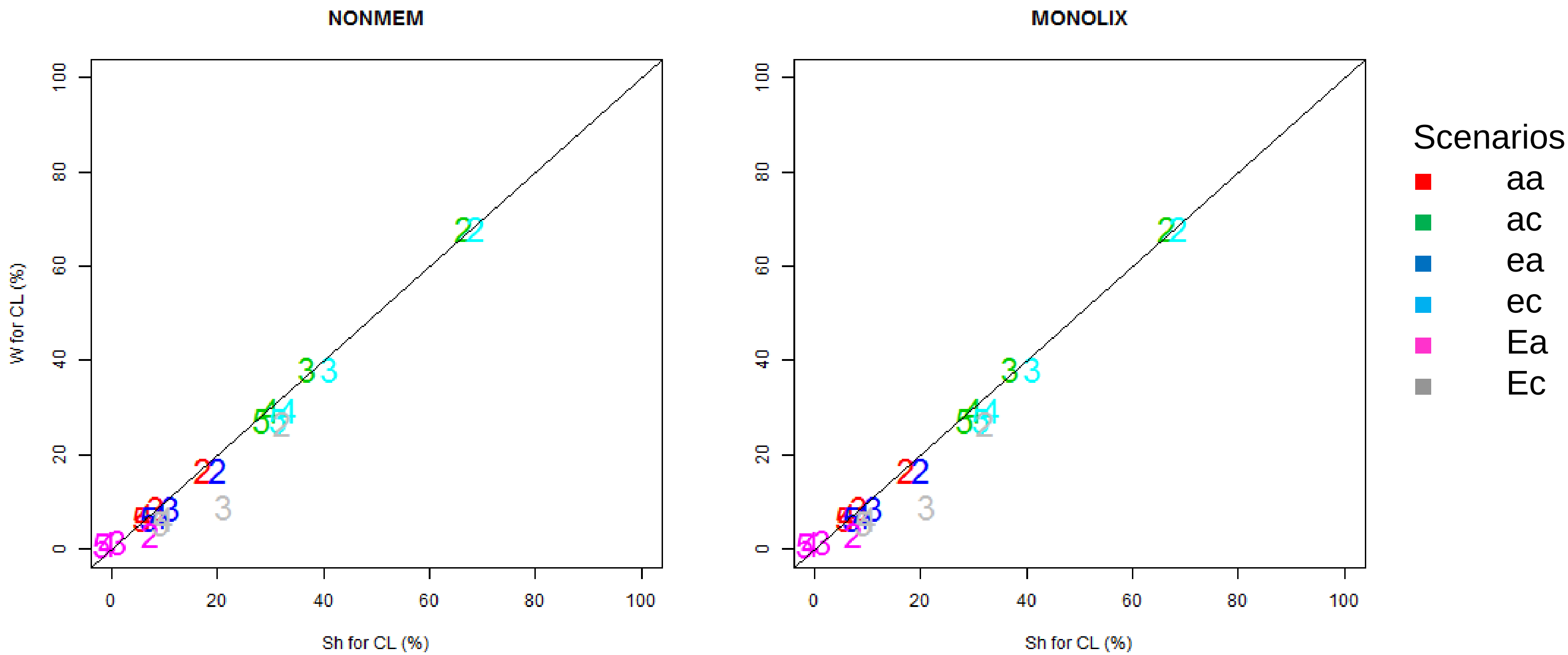
- BMF^{-1} from FO close to MC
- RSE decreases when number of samples increases
- BMF^{-1} lower than Ω and IMF^{-1}

FO method used to compute $W(\xi)$ to predict shrinkage

Results

Shrinkage prediction

Predicted *vs* observed shrinkage



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

Conclusion

- Shrinkage influenced by
  - number of samples
  - error model
  - variability of parameters
- Shrinkage reflects distortions in $\hat{\eta}$ distribution
- Computation of BMF by FO adequate
- New formula to predict shrinkage from BMF

Perspectives

- Further evaluations are needed on more "extreme" models: high variances of random effects or high residual error
- Ongoing developments on a more complex Target-Mediated Drug Disposition model
- Use of BMF for individual design optimization for MAP

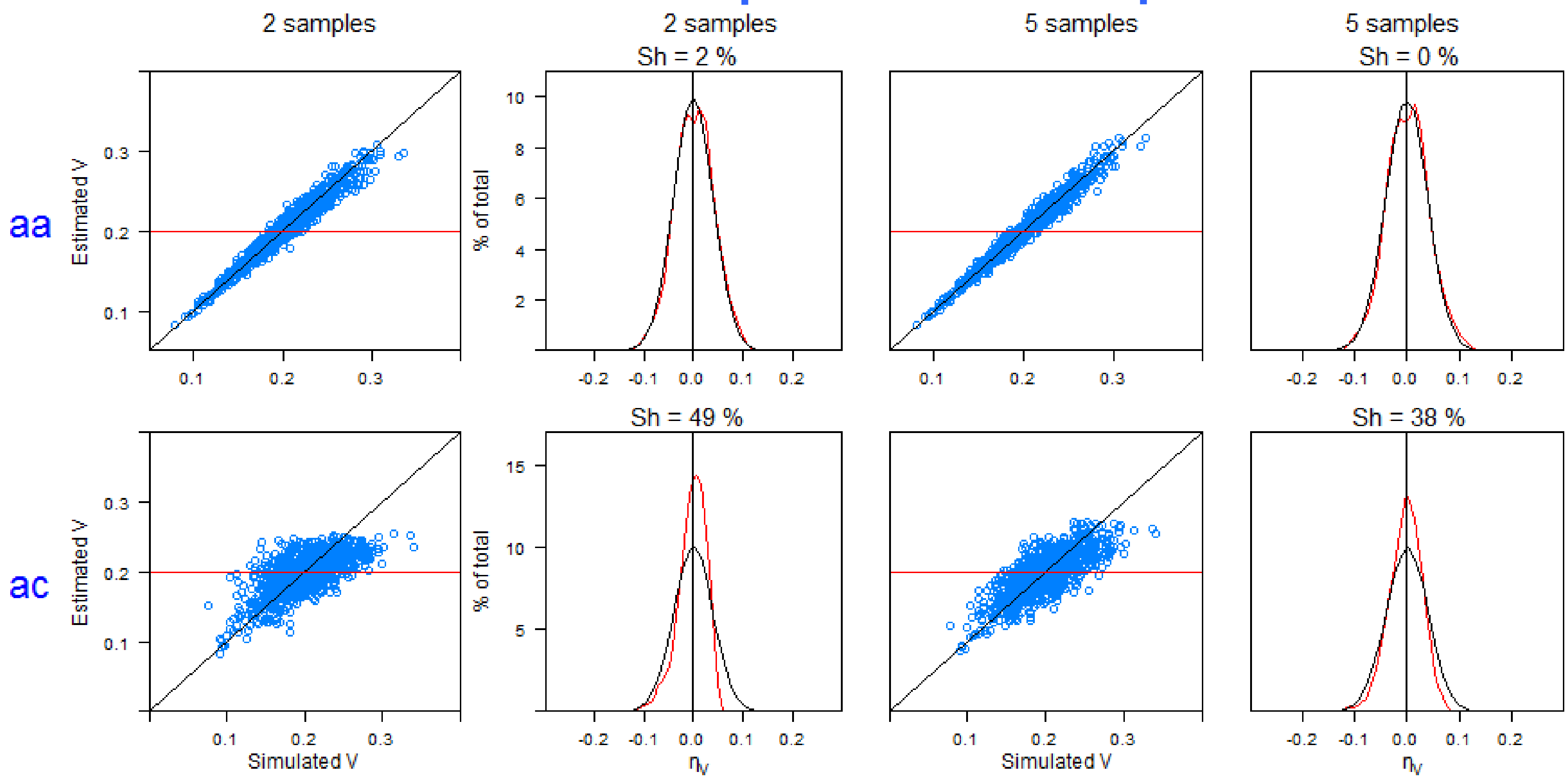
Frey N, Grange S, Woodworth T. Population pharmacokinetics analysis of tocilizumab in patients with rheumatoid arthritis. *J Clin Pharmacol*, 2010;50(7):754-66

Backup slides

Results

Shrinkage investigation

Estimated vs simulated parameters and η distribution



Parameter scatterplot
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η distribution
– *A priori*
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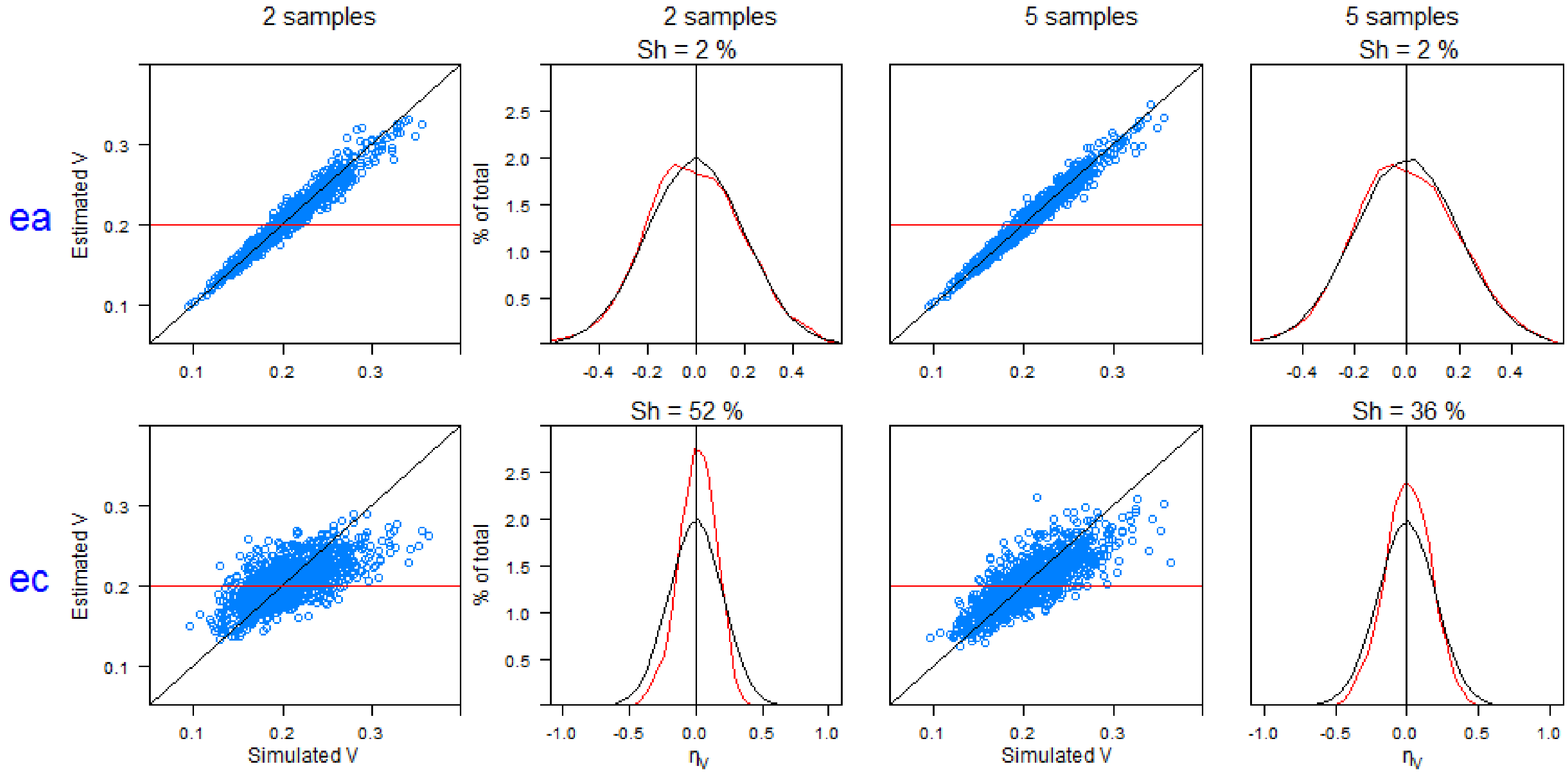
Results

Shrinkage investigation

Estimated vs simulated parameters and η distribution



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Shrinkage investigation

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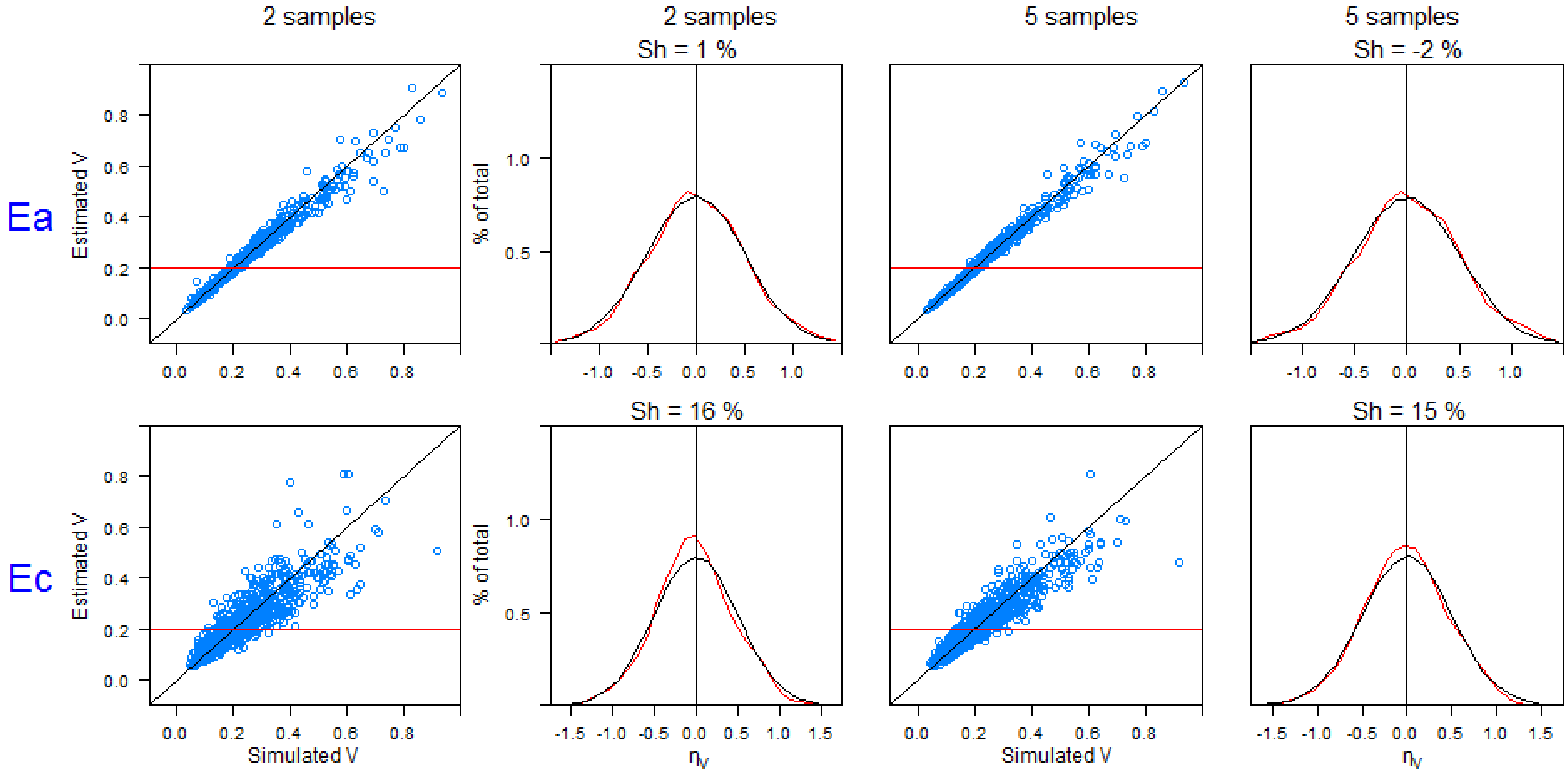

Parameter scatterplot
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– Mean

η distribution
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– Estimated

Results

BMF approximation

Relative Standard Error on Volume (%)

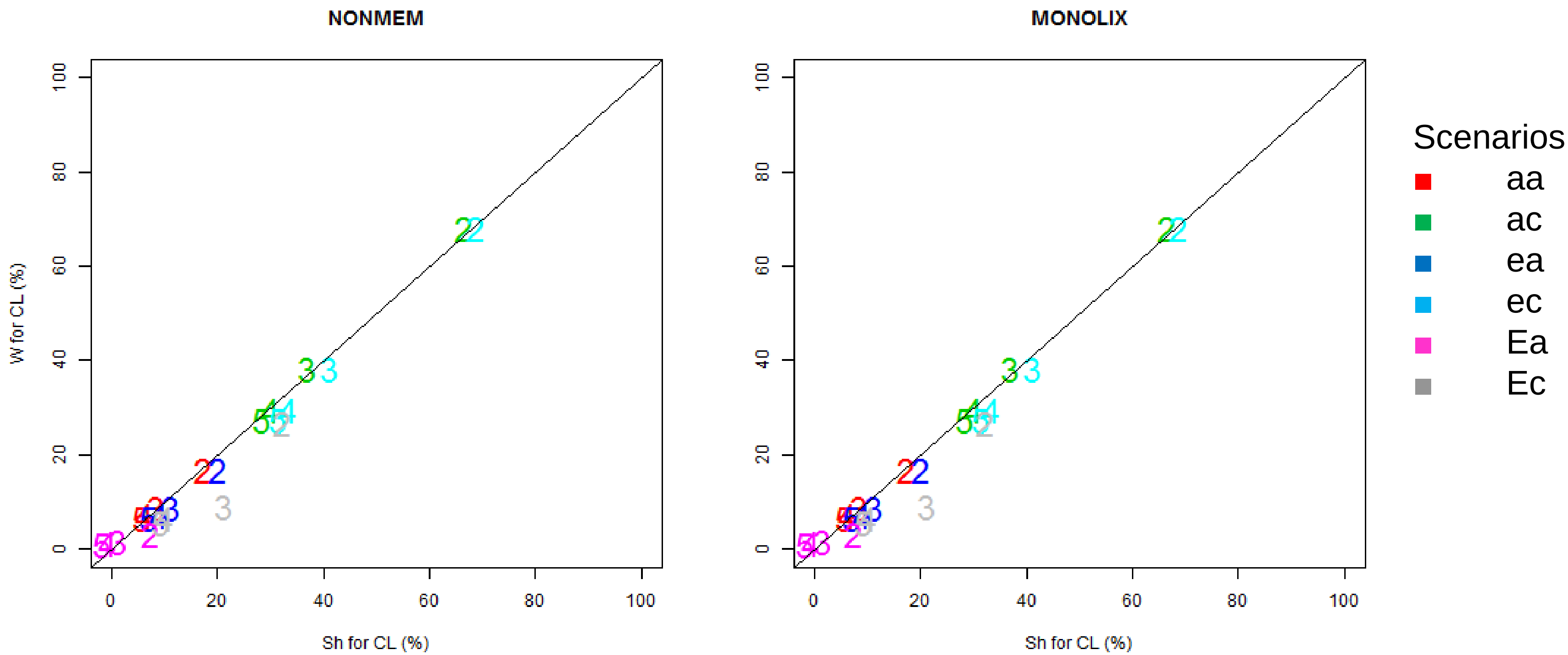
Scenario	Number of samples	Ω	IMF^{-1}	BMF^{-1}	
				FO	MC
aa	2	20	4.3	4.1	4.3
	5	20	3.5	3.4	3.6
ac	2	20	22.5	14.5	14.2
	5	20	15.0	12.0	11.8
ea	2	20	4.3	4.1	4.2
	5	20	3.5	3.4	3.5
ec	2	20	22.5	14.5	14.4
	5	20	15.0	12.0	12.1
Ea	2	50	4.3	4.2	5.3
	5	50	3.5	3.5	4.1
Ec	2	50	22.5	20.1	19.7
	5	50	15.0	14.3	15.4

- BMF^{-1} from FO close to MC
- RSE decreases when number of samples increases
- BMF^{-1} lower than Ω and IMF^{-1}

Results

Shrinkage prediction

Predicted *vs* observed shrinkage

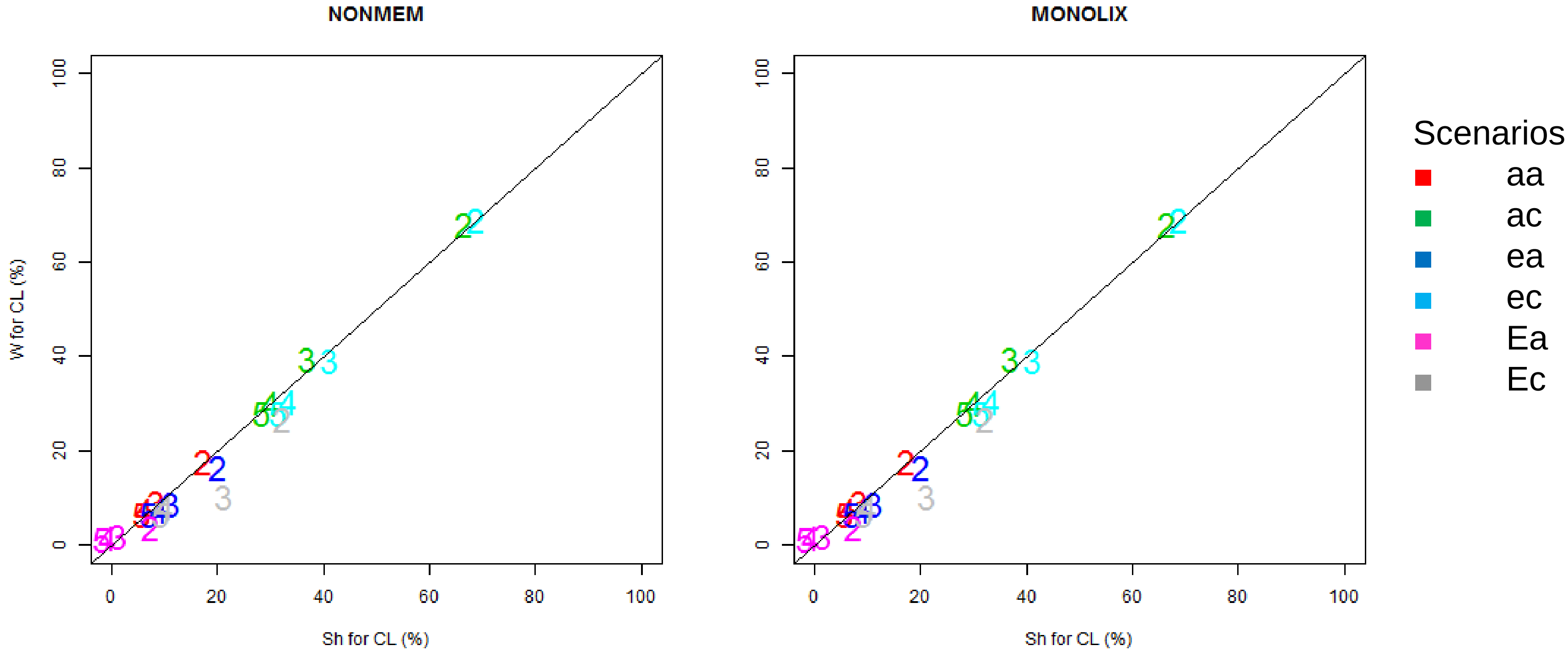


- Similar values of observed shrinkage with NONMEM and MONOLIX
- Scatterplot close to the identity line

Results

Shrinkage prediction (BMF by MC)

Predicted vs observed shrinkage

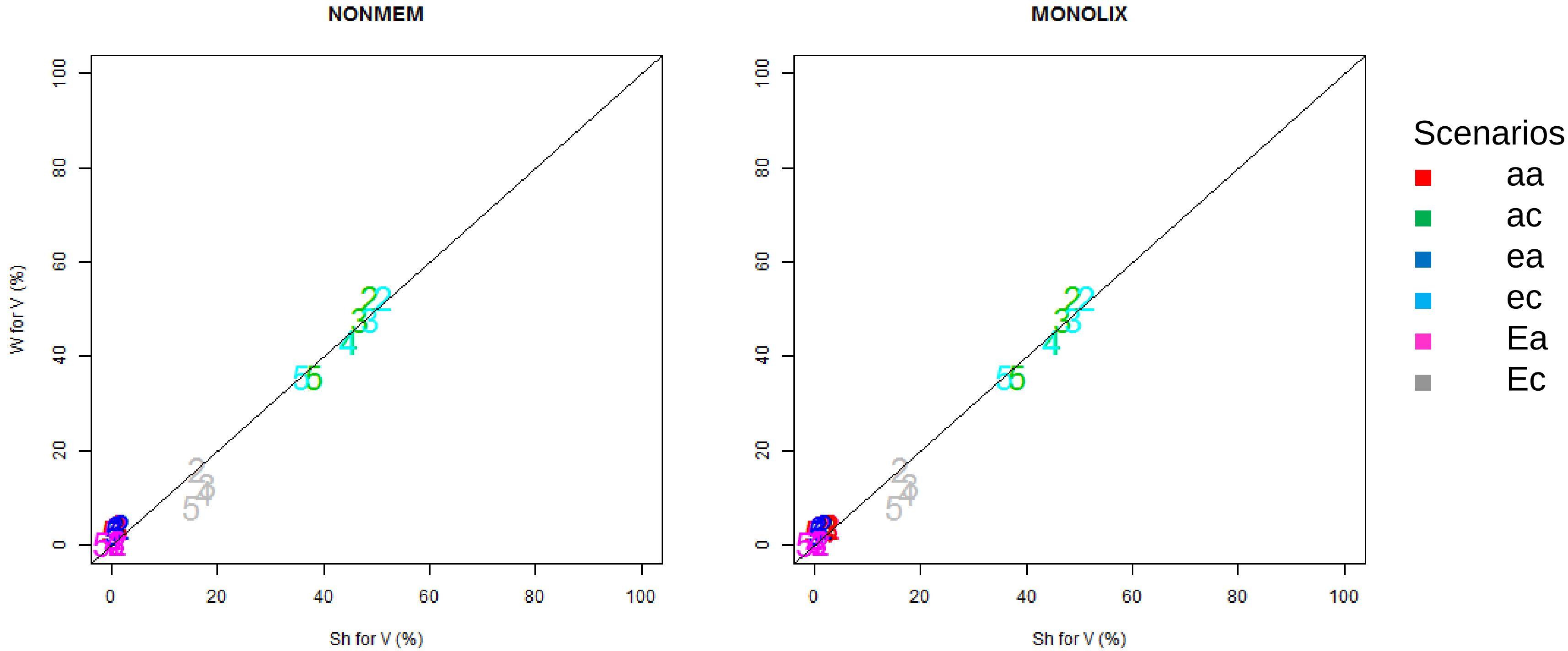


- Similar values of shrinkage for NONMEM and MONOLIX
- Scatterplot close to the identity line

Results

Shrinkage prediction

Predicted vs observed shrinkage



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Shrinkage prediction (BMF by MC)

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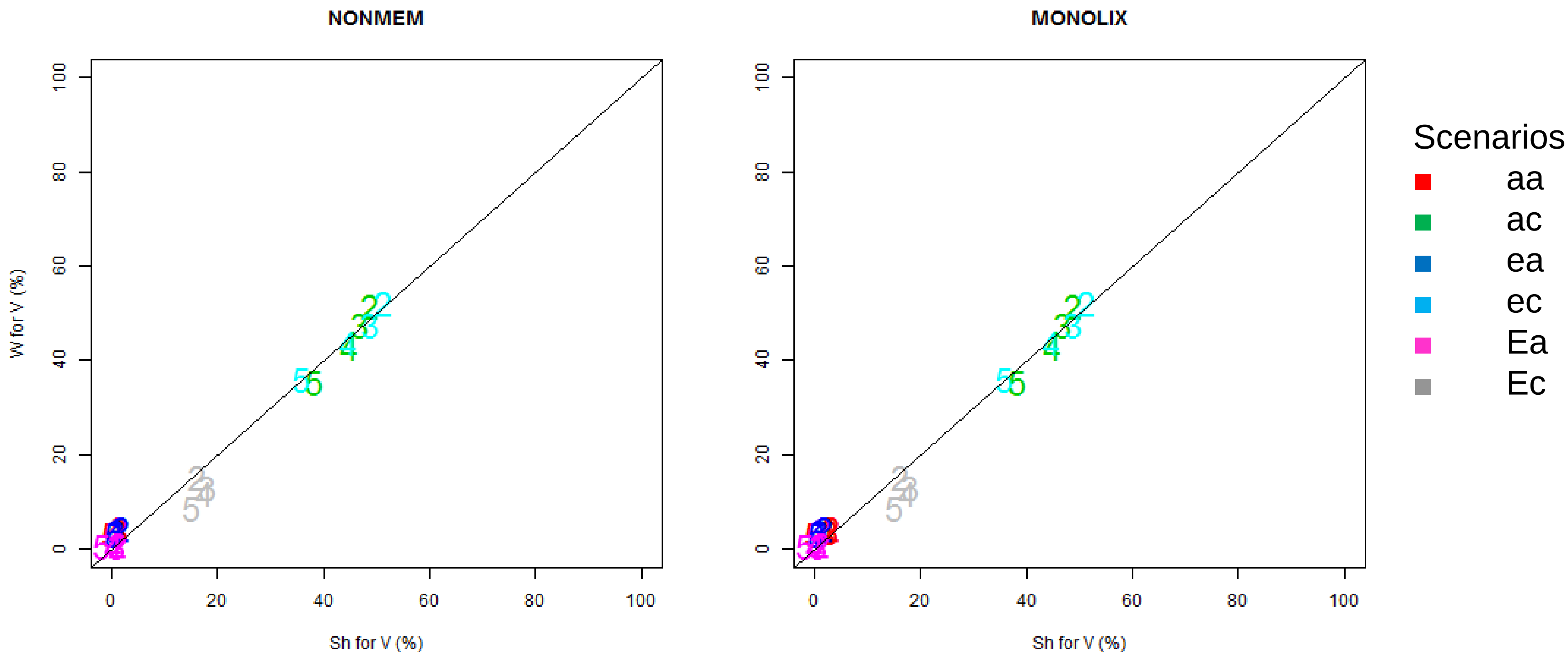

- Similar values of shrinkage for NONMEM and MONOLIX
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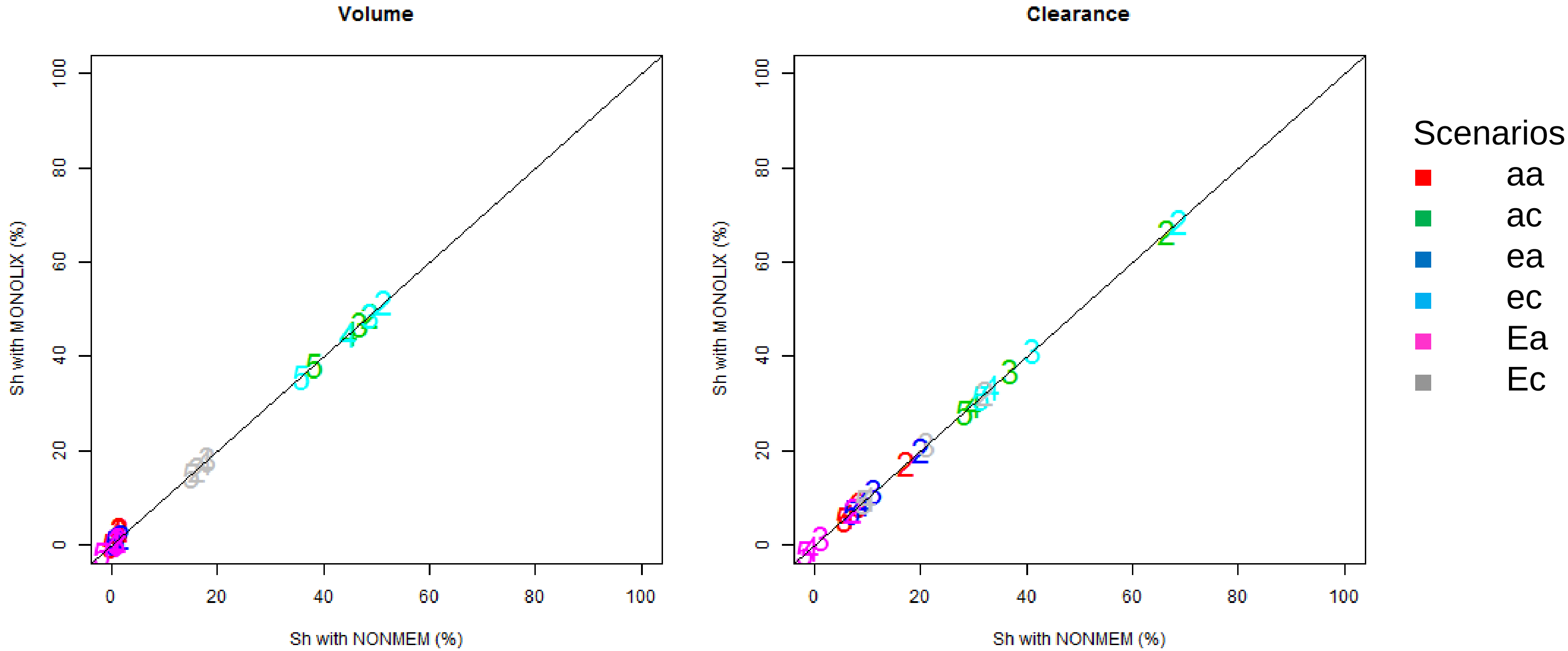
Results

Shrinkage comparison

NONMEM vs MONOLIX observed shrinkage



- Similar values of shrinkage for NONMEM and MONOLIX