Evaluation of bootstrap methods in nonlinear mixed-effects models

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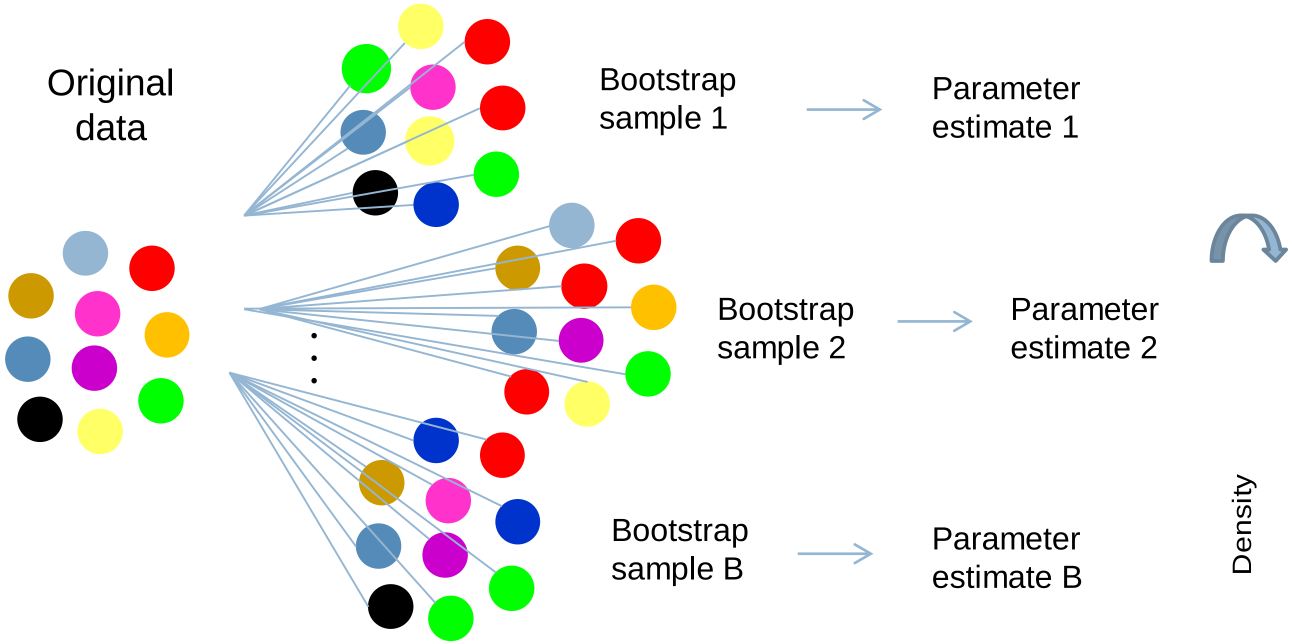
PAGE MEETING

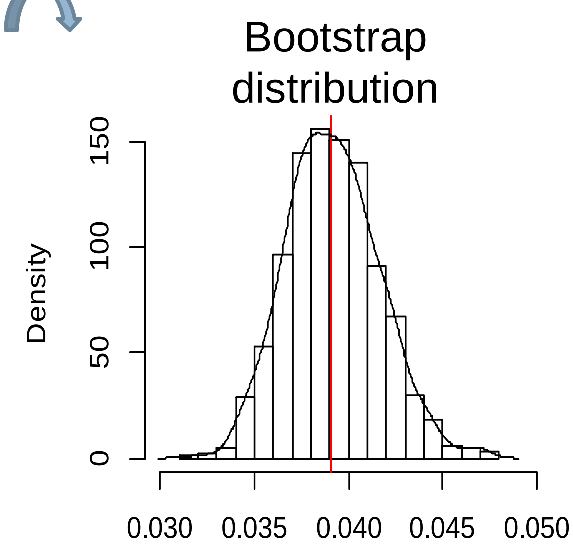
Glasgow, 14 June 2013

Principle of bootstrap (Efron 1979)[1]

- Resample with replacement the observed data to construct the distribution of an estimate or a statistic of interest
- A general bootstrap procedure in regression:

«Pull one self up with your own bootstrap»





- "Main" bootstrap methods
  - case bootstrap[2]: resample the pairs
  - residual bootstrap[1]: resample the residuals after model fitting

1. Efron B . *Annal Stat* 1979; 7: 1-26
2. Freedman D.A . *Annal Stat* 1981; 9: 1218-1228

Bootstrap in mixed-effects models (MEM)

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MEM model

$$y_i = f(\xi_i, \mu, \eta_i) + g(\xi_i, \mu, \eta_i, \sigma)\varepsilon_i$$

μ : fixed parameters

$\eta_i \sim N(0, \Omega)$

$\varepsilon_i \sim N(0,1)$

- Take into account the characteristics of MEM[1]: repeated measures, heteroscedasticity, nonlinearity
- Respect two levels of variability: interindividual and residual variabilities[2,3]

- Previous simulation study in linear MEM to compare bootstrap methods (THAI HT et al. Pharm Stat 2013; 12 (3): 129-140)
  - poor performance of bootstraps resampling only one level of variability
  - good performance of three bootstrap methods resampling two levels of variability
  - some differences between bootstrap methods when applied to a real unbalanced dataset

1. Das S, Krishen A. *J Stat Plan Inference* 1999; 75: 237-245
2. Ocana J, Halimi E. *Mathematics Preprint Series 2005;* 367
3. Leeuw J, Meijer E. *Handbook of multilevel analysis*. Springer 2008

Objective

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Evaluate the performance of bootstrap methods for estimating uncertainty of parameters in nonlinear mixed-effects models (NLMEM) using a simulation study

Bootstrap methods

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- Case bootstrap (B_{case})
- Nonparametric random effect and residual bootstrap ($B^{NP}_{\eta,\varepsilon}$)
- Parametric random effect and residual bootstrap ($B^{P}_{\eta,\varepsilon}$)

Resample the individuals

$$(\xi_i, y_i) \rightarrow (\xi_i^*, y_i^*)$$

Bootstrap methods

- Case bootstrap (B_{case})
- Nonparametric random effect and residual bootstrap ($B^{NP}_{\eta,\varepsilon}$)
- Parametric random effect and residual bootstrap ($B^{P}_{\eta,\varepsilon}$)

Fit the model to the data and estimate random effects $\hat{\eta}_i$ and standardized residuals $\hat{\varepsilon}_{ij}$

↓

Correct for shrinkage[1,2] in random effects and residuals

↓

Resample the random effects
Resample the residuals

↓

Generate the bootstrap observations

$$y_i^* = f(\xi_i, \hat{\mu}, \hat{\eta}_i^*) + g(\xi_i, \hat{\mu}, \hat{\eta}_i^*, \hat{\sigma})\varepsilon_i^*$$

1. Carpenter JR. *Appl Statist* 2003, 52: 431-443
2. Wang J et el.*Comput Methods Programs Biomed 2006*; 82: 130-143.

Bootstrap methods

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- Case bootstrap (B_{case})
- Nonparametric random effect and residual bootstrap ($B^{NP}_{\eta,\varepsilon}$)
- Parametric random effect and residual bootstrap ($B^{P}_{\eta,\varepsilon}$)

Fit the model to the data

↓

Simulate the random effects from $N(0,\hat{\Omega})$
Simulate the residuals from N(0,1)

↓

Generate the bootstrap observations

$$y_i^* = f(\xi_i, \hat{\mu}, \hat{\eta}_i^*) + g(\xi_i, \hat{\mu}, \hat{\eta}_i^*, \hat{\sigma})\varepsilon_i^*$$

Motivating example

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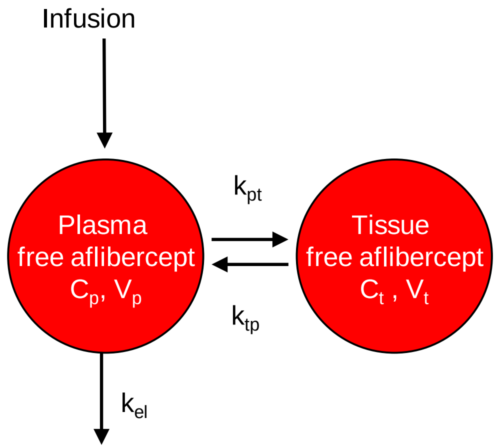
- Pharmacokinetic data: aflibercept[1], an anti-angiogenic agent
  - 2 clinical trials[2]
    - phase I TCD 6120 trial (first dose) (N_1=53, n_1=median of 9)
    - phase III VITAL trial (first two doses) (N_2=291, n_2=2)
  - two - compartment PK model with first-order elimination
    - exponential model for IIV
    - proportional model for residual error



- Model fit to the data: SAEM (MONOLIX 4.1.2)[1]

Parameter	Estimate (RSE)	IIV (%)
CL (L/hr)	0.04 (2)	28.8 (5)
V1 (L)	3.62 (2)	19.7 (10)
Q (L/hr)	0.14 (15)	111(12)
V2 (L)	2.9 (5)	-
Corr(CL,Q) (ρ)	0.90 (8)	
σ_p (%)	24.8 (4)	

1. Chu QS. *Expert Opin Biol Ther* 2009;9:263-271
2. Gaya A et al. *Cancer Treat Rev* 2012 38): 484-493
3. Lavielle M. MONOLIX. MONOLIX group, Orsay, France, 2008.

Simulation settings

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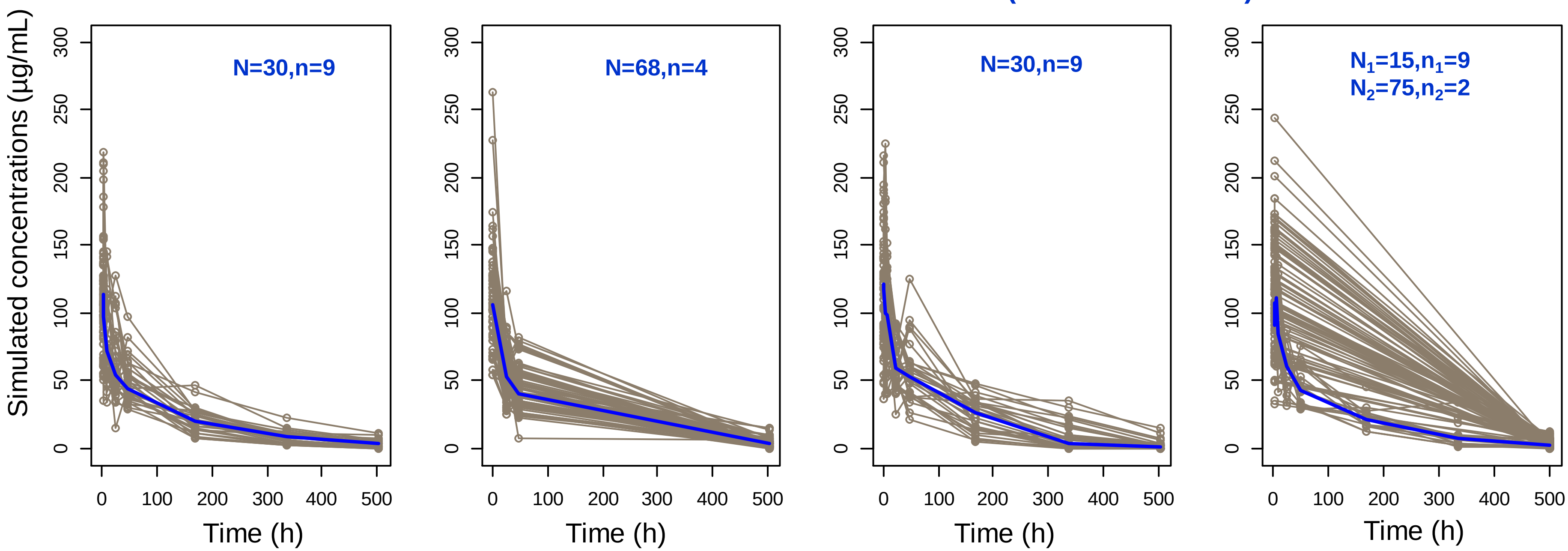
Frequent balanced design first-order | **Sparse balanced design first-order** | **Frequent balanced design mixed-order (Michaelis-Menten)** | **Unbalanced design first-order**



K=100 replications for each design

Bootstrap settings

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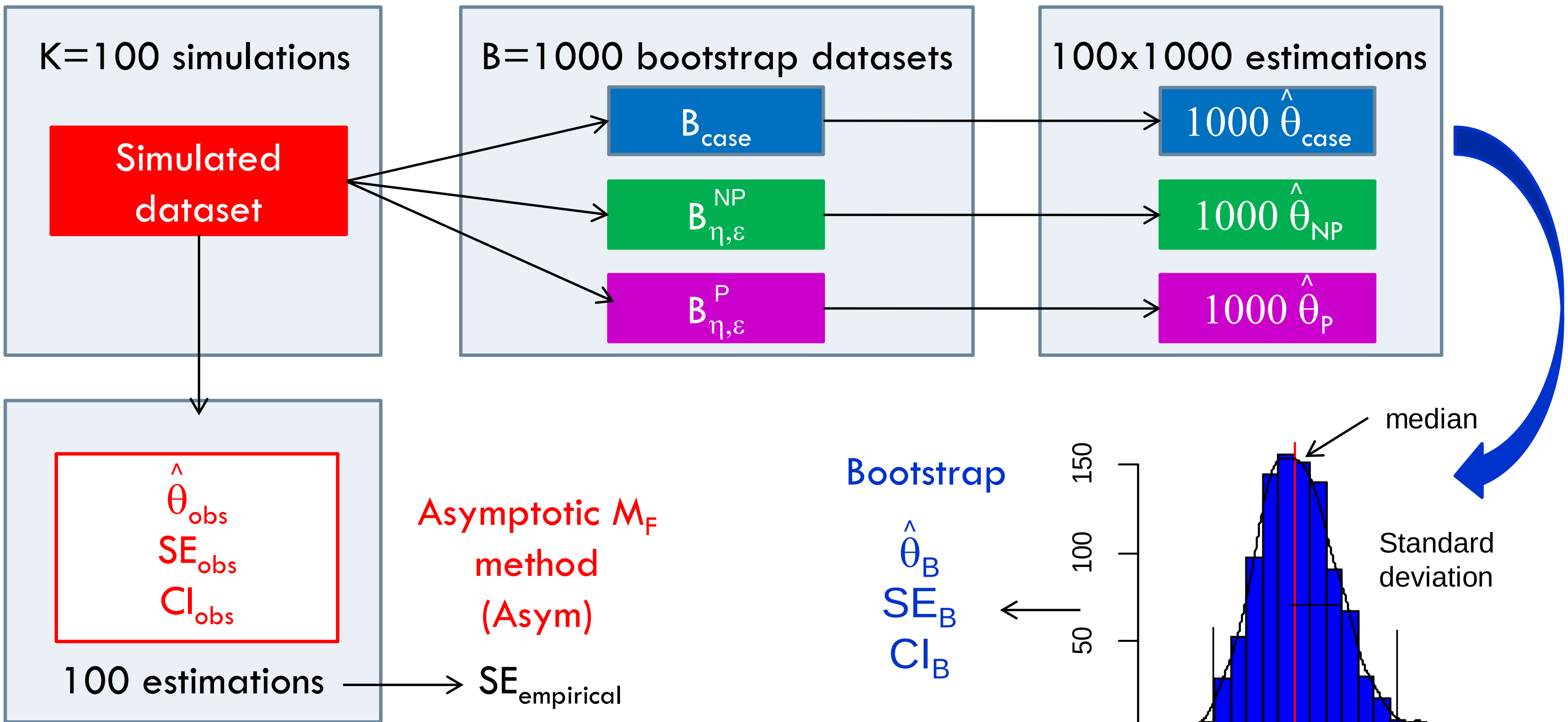
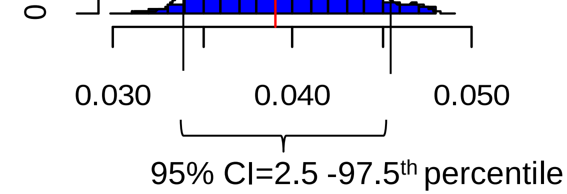
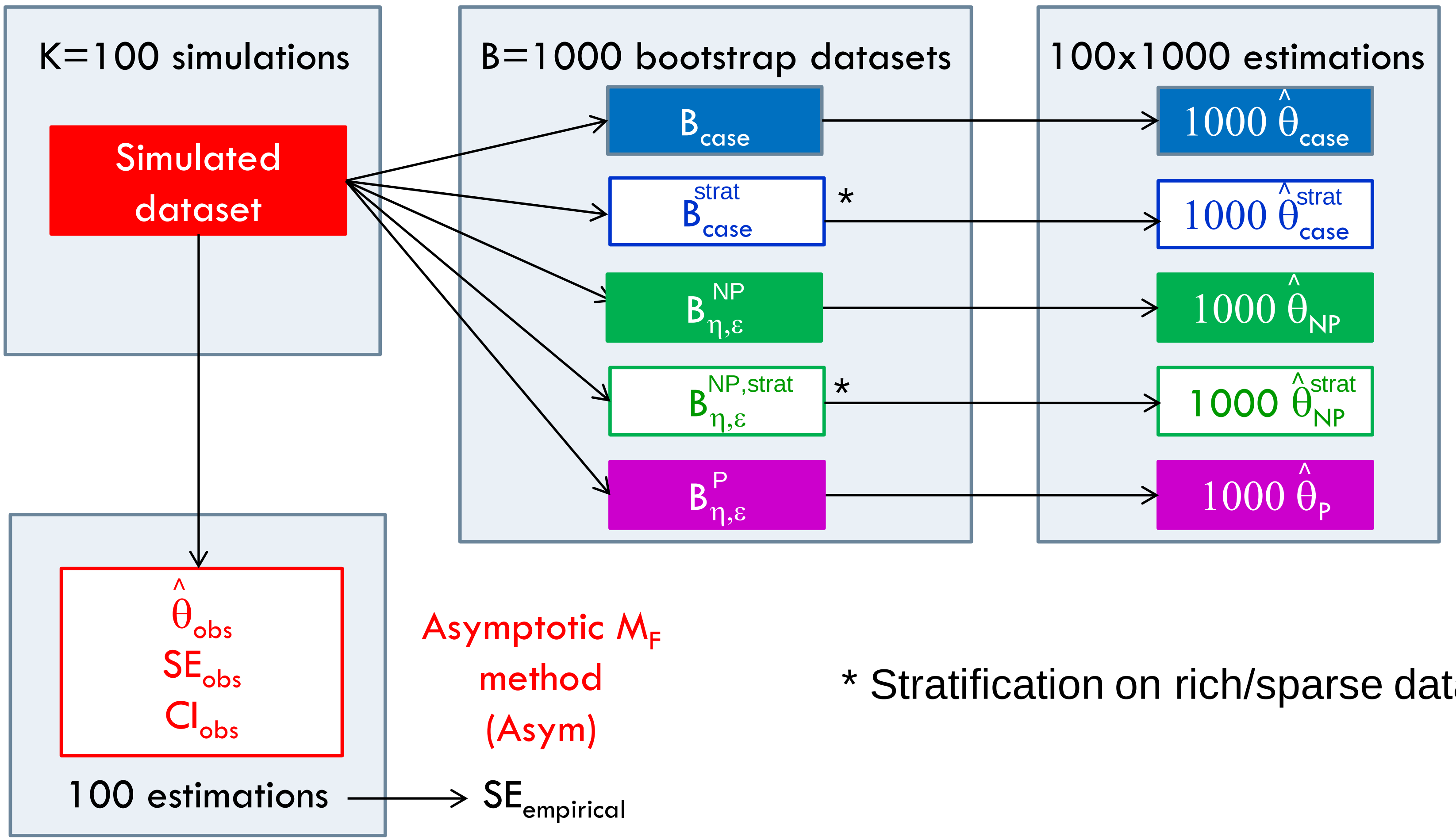




Estimation method: SAEM (Monolix 4.1.2)

Fisher information matrix (M_F) computed by linearisation

Bootstrap settings for the unbalanced design



* Stratification on rich/sparse data

Evaluation

- For each method (k=100 replicated datasets)
  - relative bias of parameter (%)

$$\mathrm{RBias}(\hat{\theta}_{\mathrm{B}}^{(l)}) = \frac{1}{K}\sum_{k=1}^{K}\left(\frac{\hat{\theta}_{\mathrm{B};k}^{(l)} - \hat{\theta}_{k}^{(l)}}{\hat{\theta}_{k}^{(l)}} \times 100\right)$$

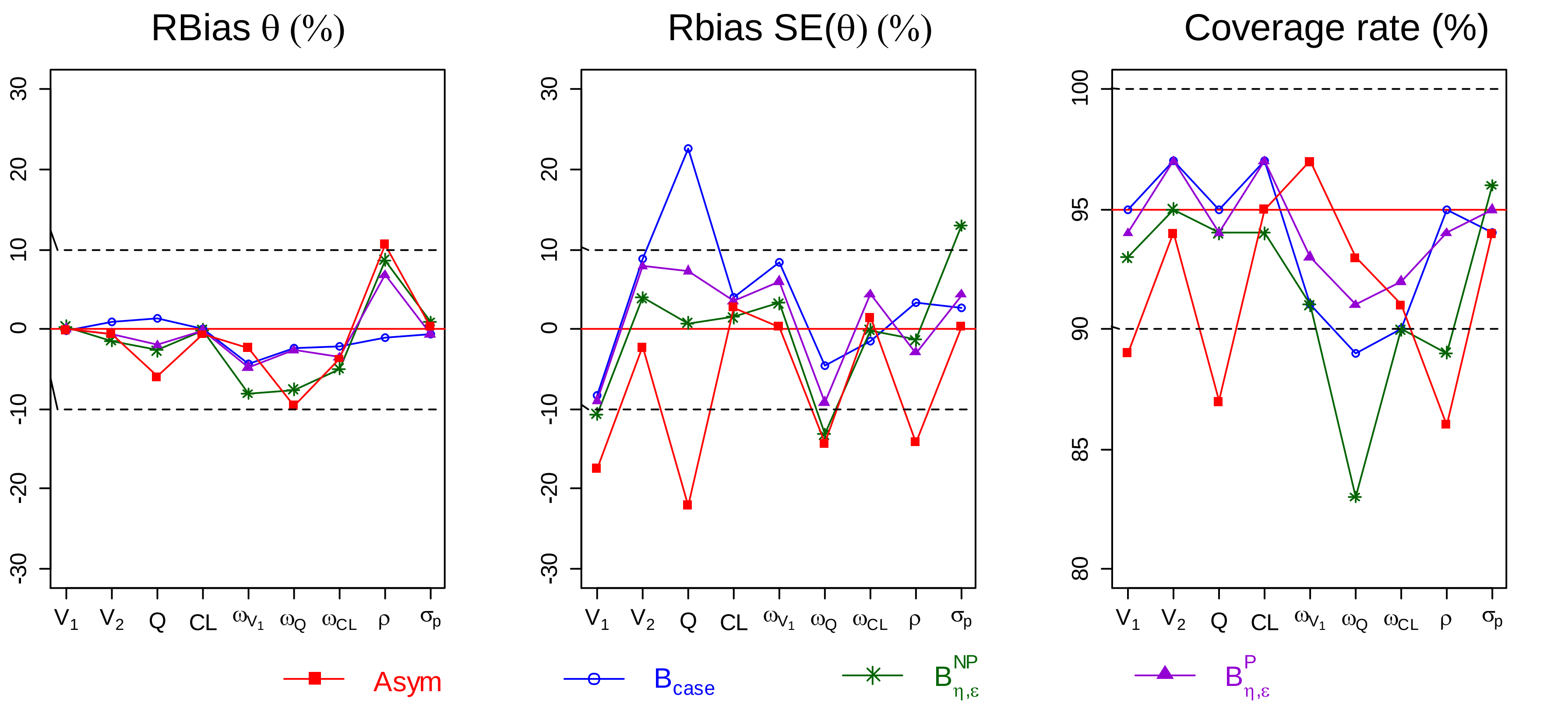
  - relative bias of SE (%)

$$\mathrm{RBias}(\widehat{SE}_{\mathrm{B}}^{(l)}) = \frac{\frac{1}{K}\sum_{k=1}^{K}\widehat{SE}_{\mathrm{B;k}}^{(l)} - \widehat{SE}_{\mathrm{empirical}}^{(l)}}{\widehat{SE}_{\mathrm{empirical}}^{(l)}} \times 100$$

  - coverage rate of 95% CI: % bootstrap CI contain the true value of parameter

- "Good" bootstrap
  - relative bias of parameters and SE: unbiased (±10%)
  - coverage rate of 95% CI: good (90-100%)

Frequent balanced design with first-order elimination



✓ Parametric bootstrap had the best performance

✓ Asymptotic approach performed slightly less well than the bootstrap methods

Three balanced designs

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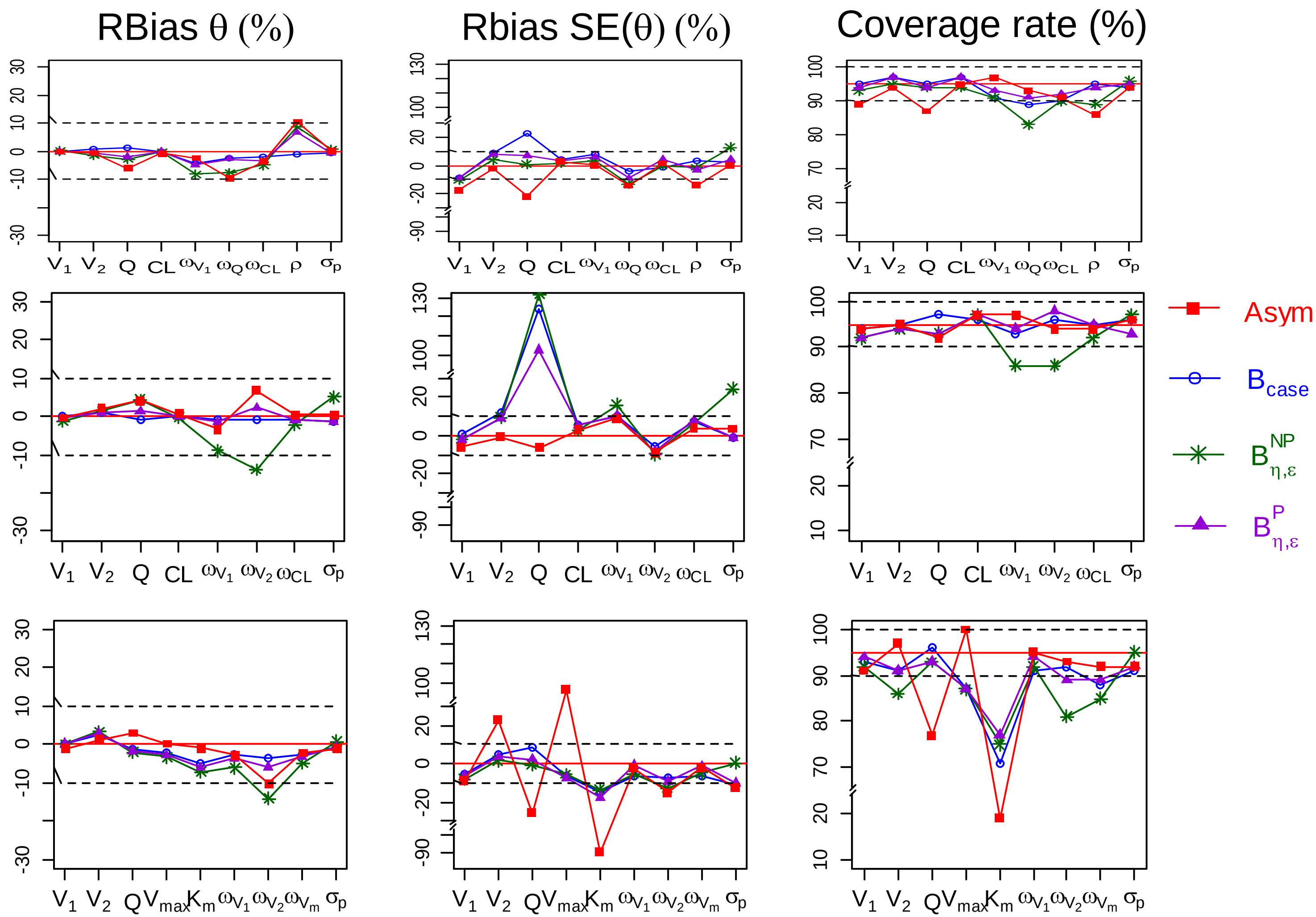
Frequent design
first order
(N=30, n=9)

Sparse design
first order
(N=68, n=4)

Frequent design
mixed-order
(N=30, n=9)



Unbalanced design with first-order elimination

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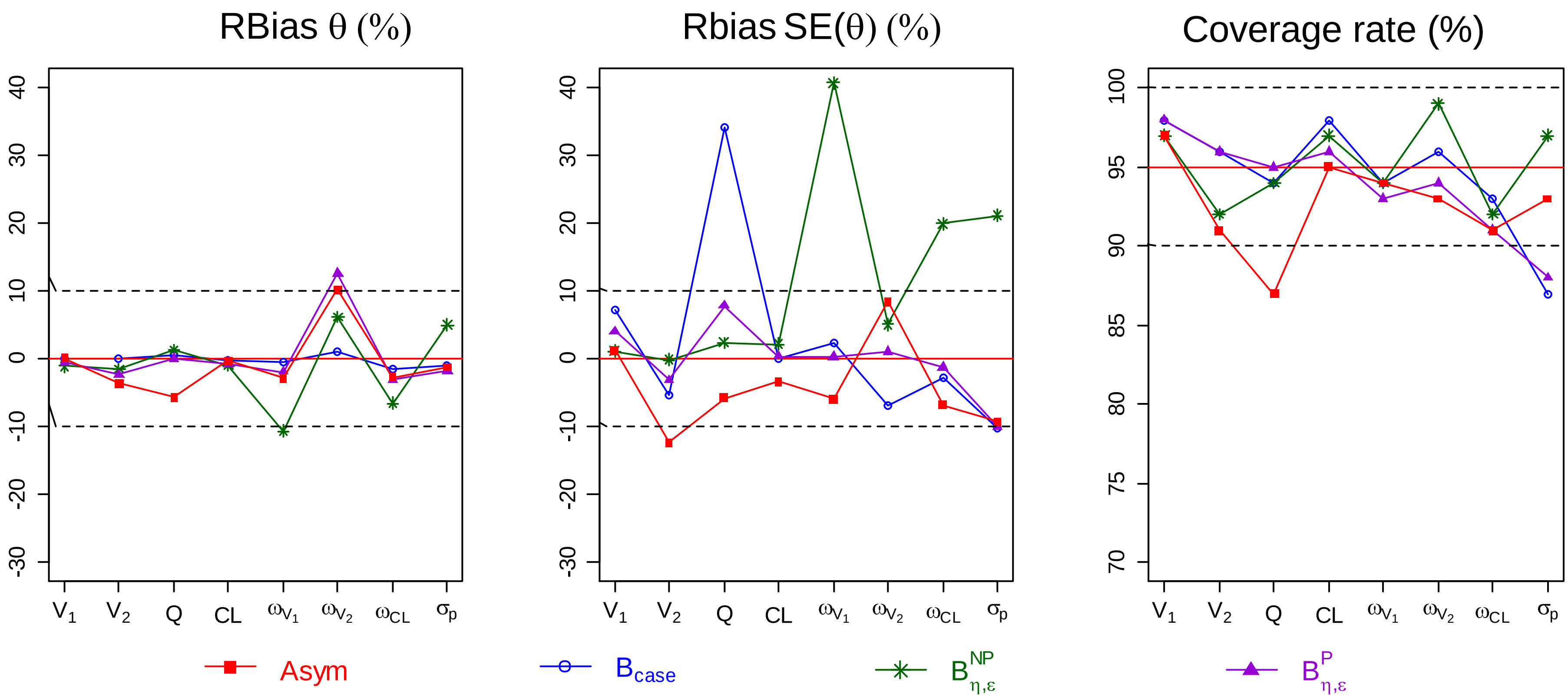

✓ Asymptotic approach and parametric bootstrap performed reasonably well and better than other bootstrap methods

Unbalanced design with first-order elimination

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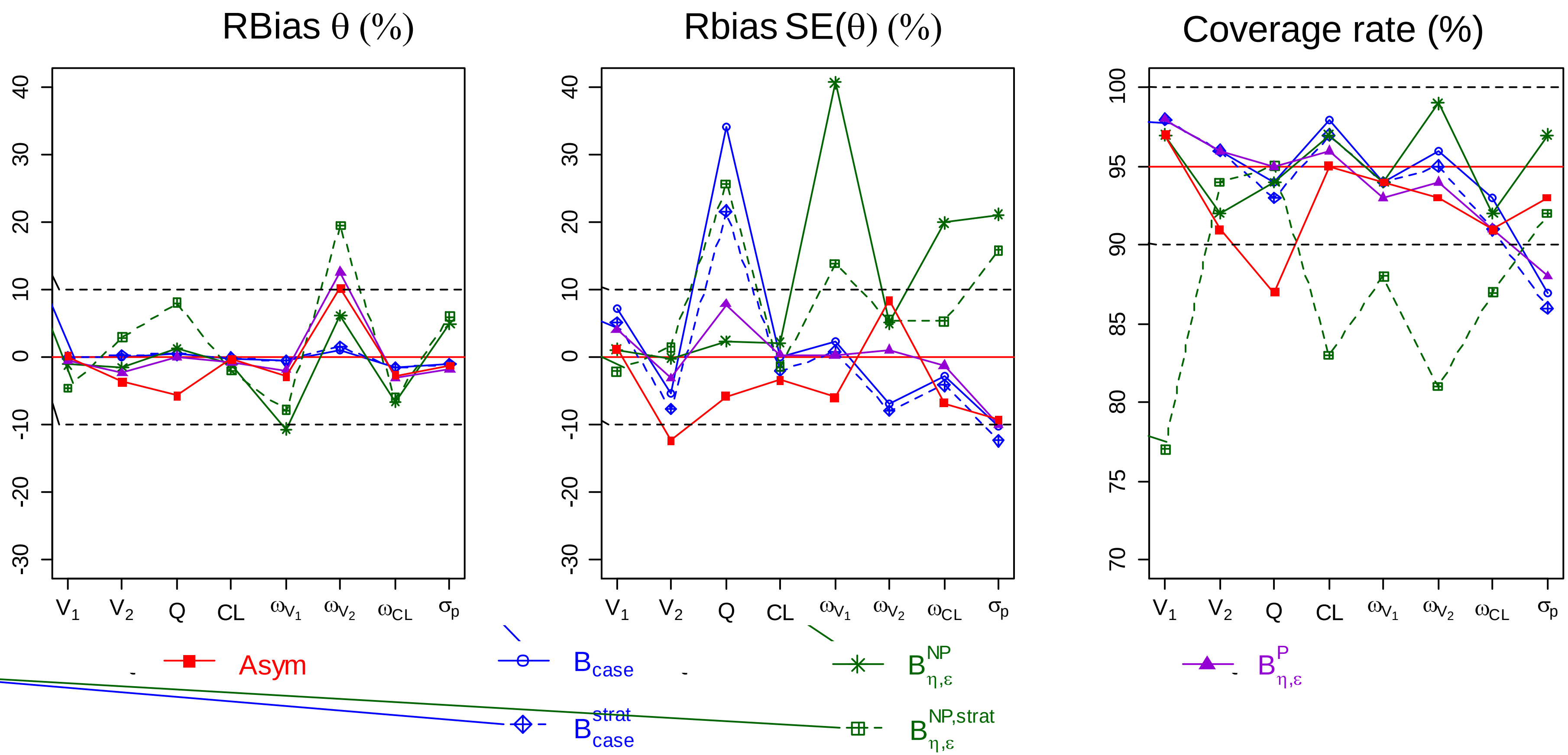

✓Stratification improved slightly the performance of case bootstrap and but degraded that of nonparametric random effect and residual bootstrap in term of coverage rate

Conclusions

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- Better estimation of uncertainty by the bootstrap methods than the asymptotic method in NLMEM with high nonlinearity
- Caution with bootstrap methods in presence of large fluctuations in parameter estimates between bootstrap samples
- The choice of bootstrap methods in NLMEM
  - parametric bootstrap: best description of uncertainty

    ⟶ study robustness in case of model misspecification
  - case bootstrap: fast, simple and robust (e.g heteroscedasticity, missing data)

    ⟶ evaluate stratification for complex designs
  - nonparametric random effect and residual bootstrap: maintain the same design as the original dataset

    ⟶ improve correction for shrinkage in unbalanced designs

Acknowlegements

- Sanofi for financial support

Annexes

Correction for variance underestimation

- Correction for random effects[1,2]
  - center: $\tilde{\eta}_i = \hat{\eta}_i - \bar{\eta}_i$
  - transform: by the ratio between empricial vs estimated variance-covariance (A_η)
    - Cholesky decomposition: matrice Ω_R positive
    - EVD (*Eigen Value Decomposition*): matrice Ω_R semi-positive

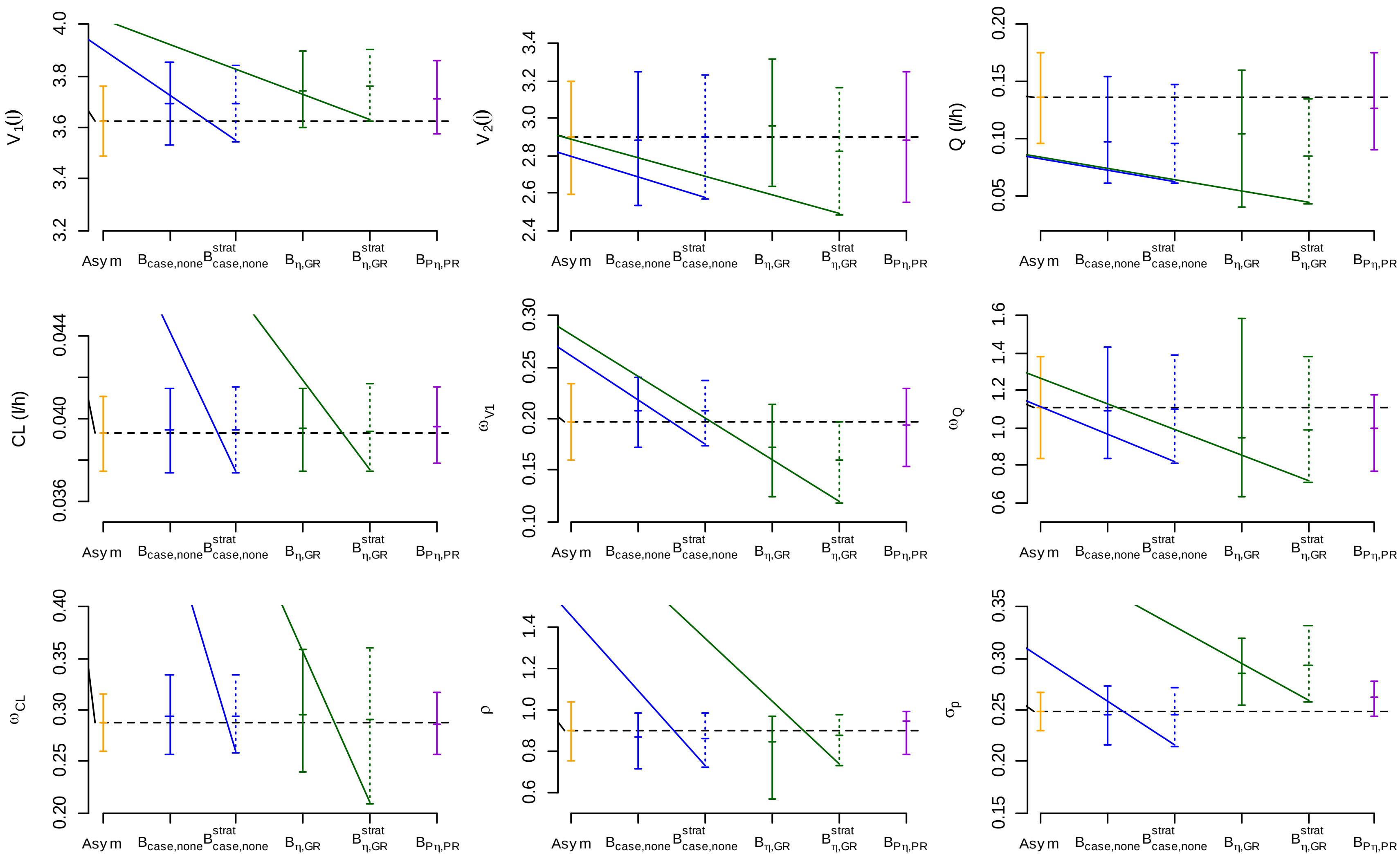
$$\hat{\eta}_i' = \tilde{\eta}_i \times A_\eta$$

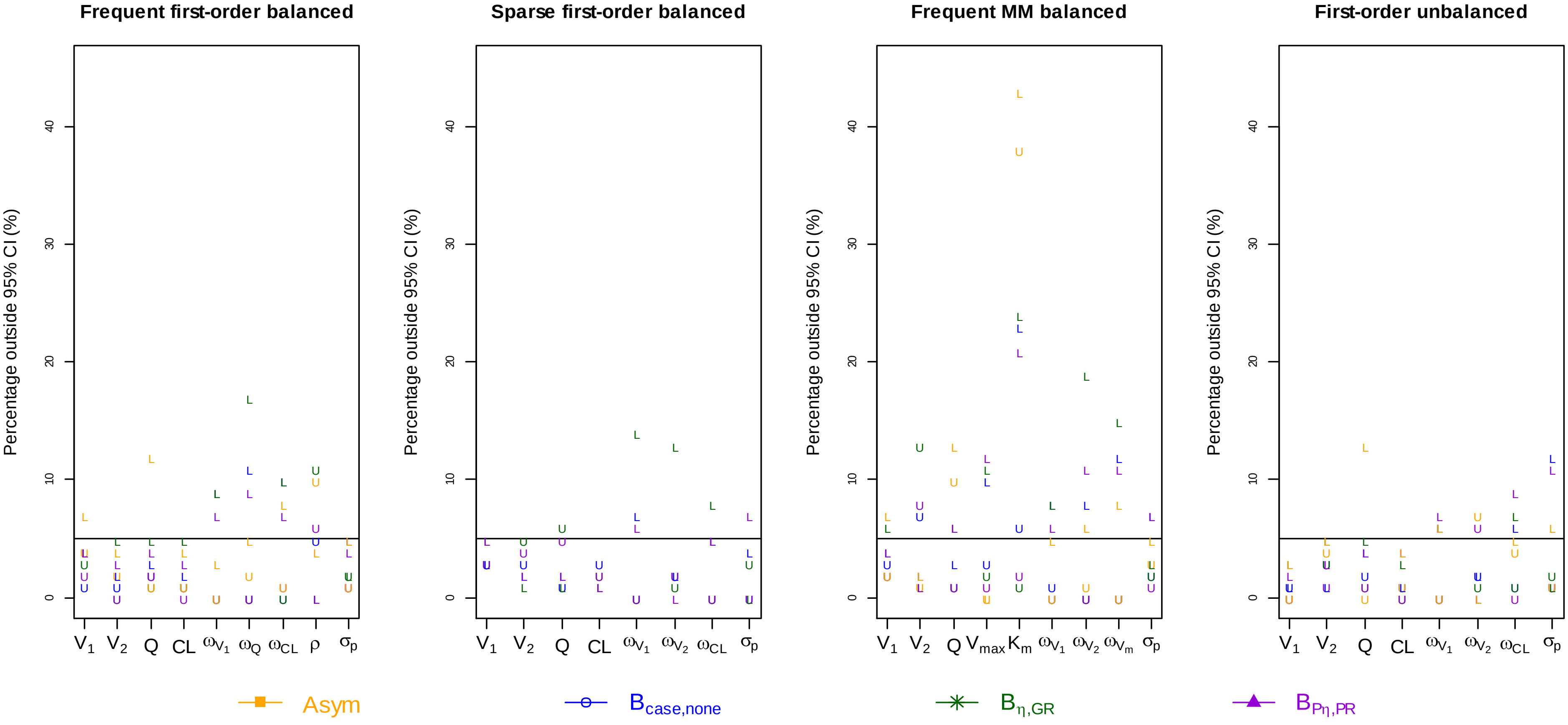
- Correction for residuals[1,2]
  - center: $\tilde{\epsilon}_{ij} = \hat{\epsilon}_{ij} - \bar{\epsilon}_{ij}$
  - transform: by the ratio between empirical vs estimated variance-covariance(A_σ)
    - homoscedastic error: $A_\sigma = \hat{\sigma} / sd(\tilde{\epsilon}_{ij})$
    - heteroscedastic error: $A_\sigma = 1$ / SD(standardized residuals)

$$\hat{\epsilon}_{ij}' = \tilde{\epsilon}_{ij} \times A_\sigma$$

1. Carpenter JR. *Appl Statist* 2003, 52: 431-443
2. Wang J et al.*Comput Methods Programs Biomed 2006*; 82: 130-143.

Application to aflibercept data





Frequent first-order balanced
Sparse first-order balanced
Frequent MM balanced
First-order unbalanced
Percentage outside 95% CI (%)
0
10
20
30
40
V_1 V_2 Q CL ω_{V_1} ω_Q ω_{CL} ρ σ_p
V_1 V_2 Q CL ω_{V_1} ω_{V_2} ω_{CL} σ_p
V_1 V_2 Q V_{max} K_m ω_{V_1} ω_{V_2} ω_{V_m} σ_p
V_1 V_2 Q CL ω_{V_1} ω_{V_2} ω_{CL} σ_p
Asym
$B_{case,none}$
$B_{\eta,GR}$
$B_{P\eta,PR}$