Application of **S**ampling **I**mportance **R**esampling to estimate parameter uncertainty distributions

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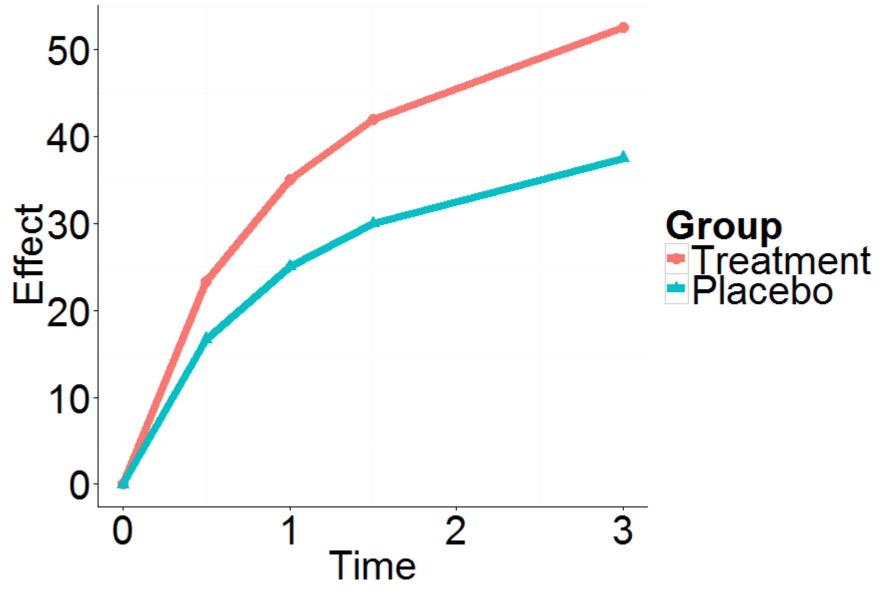
Importance of uncertainty
Uncertainty is key in decision making

Background
SIR method
Results
  simulated
  real data
Conclusion



- Model-based test to decide if treatment better than placebo
  - o Confidence intervals: *simulations*
  - o Treatment effect: *LRT, Wald test*

Parameter uncertainty

LRT: likelihood ratio test

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Available uncertainty measures
Covariance matrix, bootstrap, LLP

Covariance matrix

- Covariance step needs to be **successful**
- **Normality assumption** on uncertainty distribution, reparameterization not always straightforward

Bootstrap

- Needs high number of **estimation** steps[1]
- May be limited by **study design** (low number of patients, unbalanced designs)[2]

LLP

- Needs moderate number of **estimation** steps
- Work in progress for multidimensionality and possibility of simulating[3]

LLP: log-likelihood profiling

[1] PAGE 2013 Poster III-07, R. Leary. A fast bootstrap method using EM posteriors
[2] PAGE 2013 Poster III-47, R. Niebecker. Are datasets for NLME models large enough for a bootstrap to provide reliable parameter uncertainty distributions?
[3] PAGE 21 (2012) Abstr 2594 [www.page-meeting.org/?abstract=2594] W. Denney. N-dimensional Likelihood Profiling: An Efficient Alternative to Bootstrap

Room for improvement

Relax distribution assumption, avoid estimation

- No distribution assumption
  - Allow for asymmetric confidence intervals
- Avoid estimation
  - Convergence issues
  - No consensus on how to handle terminated runs (bootstrap)
  - Long computation times

Use **S**ampling **I**mportance **R**esampling ?

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SIR principle: 3 steps

Sampling, Importance weighting, Resampling

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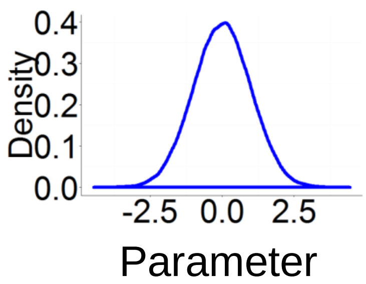
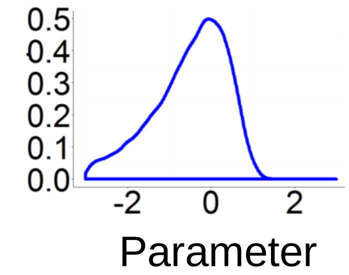
→ Approximate unknown posterior distribution by weighted known distribution[1]

S	**SAMPLING** *Step 1*	• **Sample** *p* parameter vectors from covariance matrix
I	**IMPORTANCE WEIGTHING** *Step 2*	• **Calculate weights** based on fit to original data
R	**RESAMPLING** *Step 3*	• **Resample** *M* vectors based on weights from step 2 • Compute confidence intervals





[1] Rubin DB, Bayesian Statistics. 1988;3:395-402

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Computation of the weights

Crucial step

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- Idea: refine the uncertainty distribution by evaluating how well the sampled vectors fit the original data
- The closer the vectors are to the final parameter estimates, the better they are expected to fit the data

$$Weight = \frac{fit\ to\ data}{density\ (covariance\ matrix)}$$

fit to data: $e^{(-0.5 \cdot dOFV)}$

density (covariance matrix): pdf multivariate normal

dOFV= difference in objective function value, pdf=probability density function

Simulation settings

PK IV 1 CMT; 50 ID, 4 observations/ID

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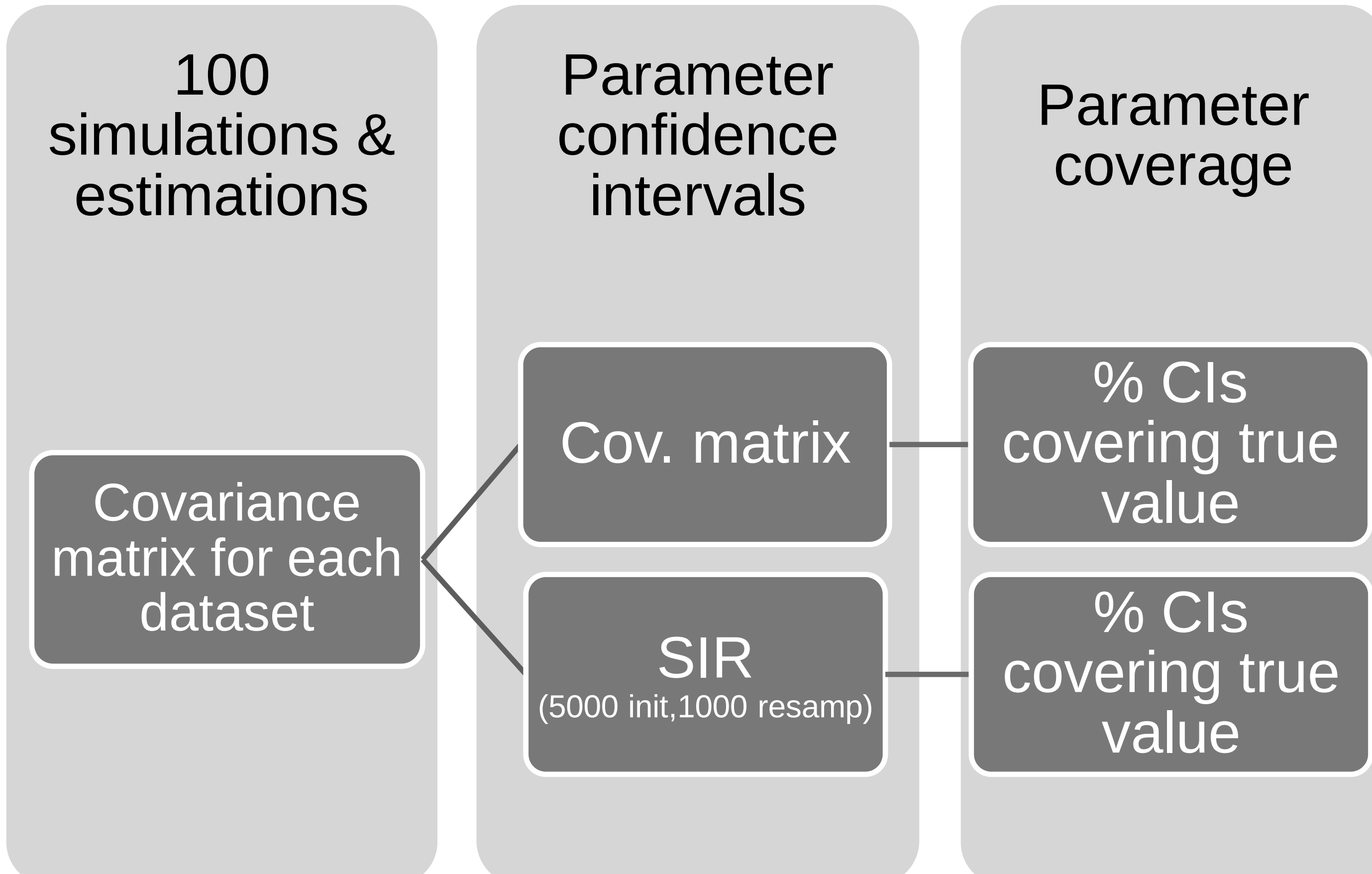

Init = initial samples, resamp = resamples, CI = confidence interval

Simulation results

SIR achieves satisfactory coverage

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- **simulated**
- real data

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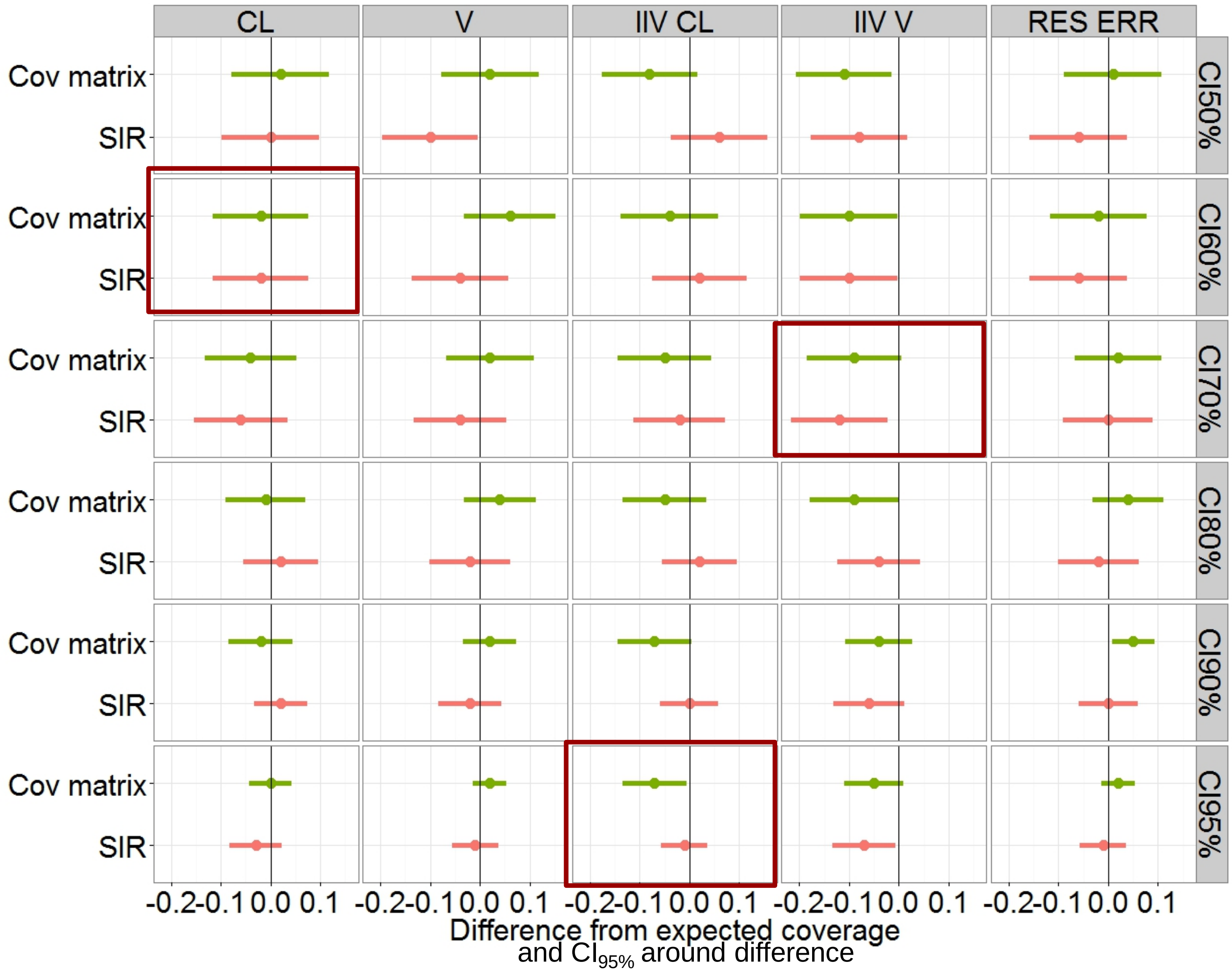

Real data examples: pefloxacin

Application of SIR

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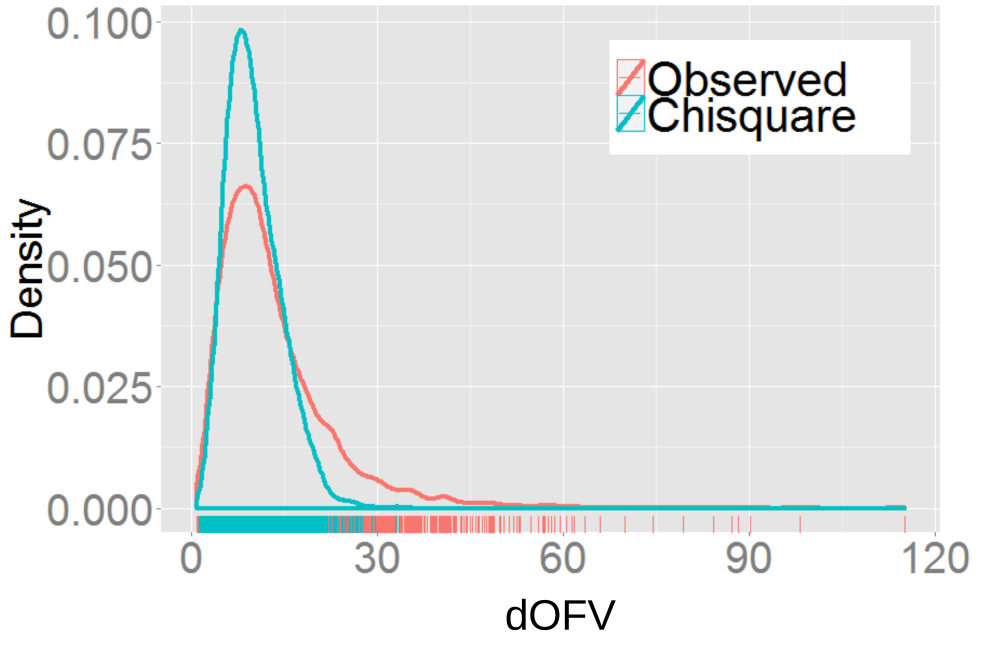
- **Step 1**: simulation from cov. matrix (4000)
- **Step 2**: evaluation on original data → observed dOFV ≠ chi-square distribution

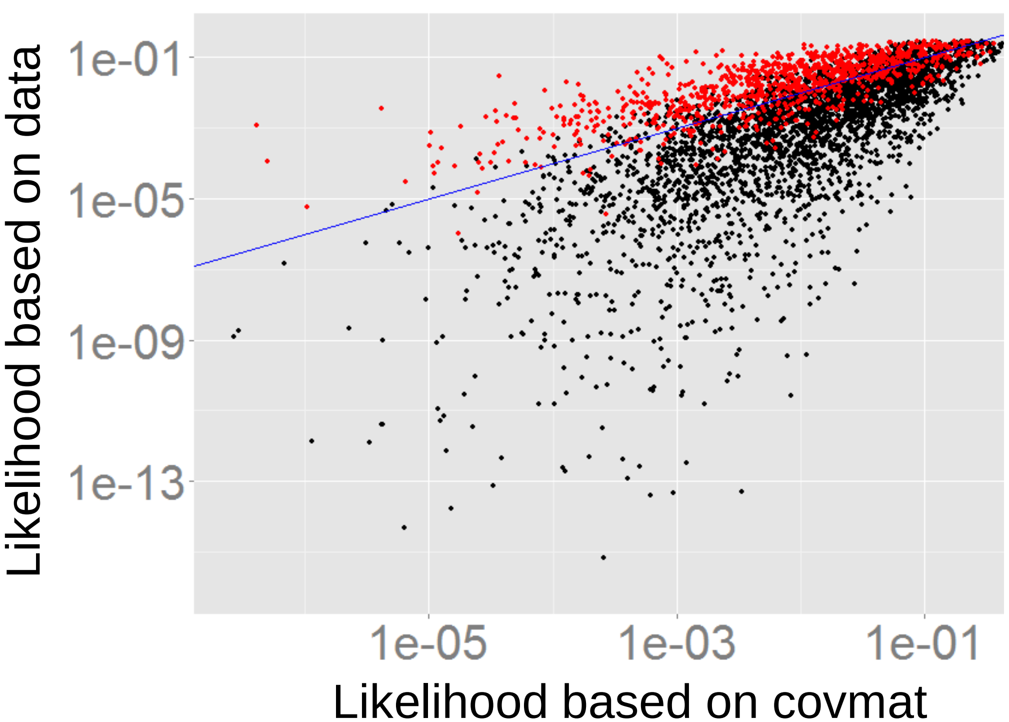


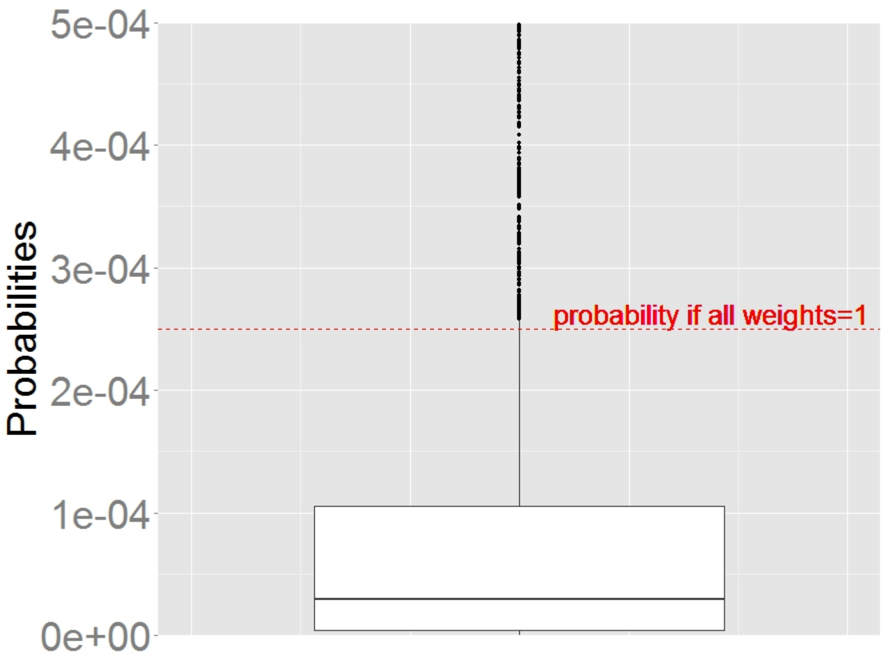
Pefloxacin model: Wählby et al., Br J Clin Pharmacol. 2004;58(4):367-77

Pefloxacin

Step 2: Importance weighting

- Many vectors do not fit as well as expected
- Wide SIR probability distribution
- Resampling of vectors above identity line





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Pefloxacin

Step 3: asymmetry for selected variances

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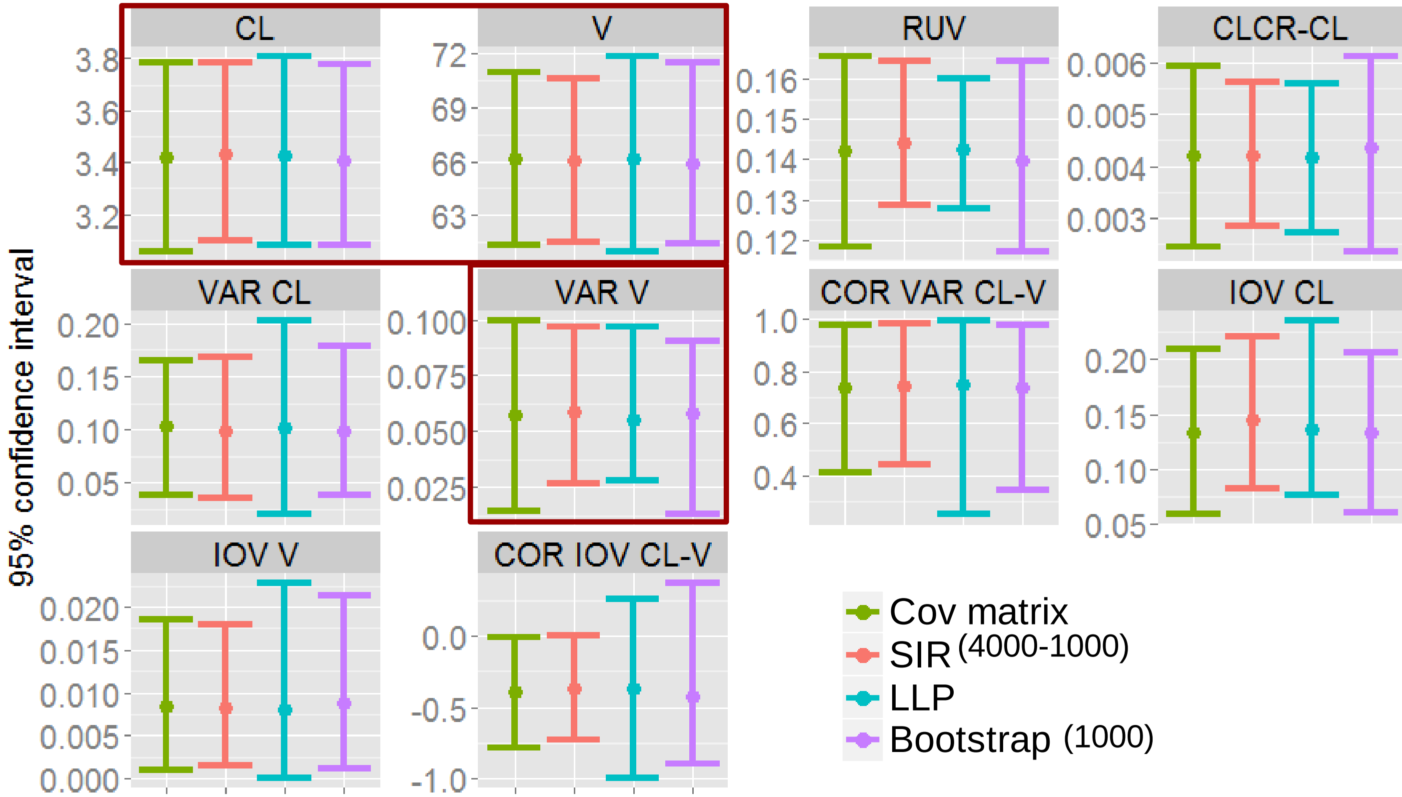

- SIR: asymmetry for VAR V & RUV, upward shift for IOV CL, narrowing of covariate CI
- NB: ½ bootstrap runs have correlation estimates near boundary (excluded)

Moxonidine

Step 3: asymmetry for TLAG and KA

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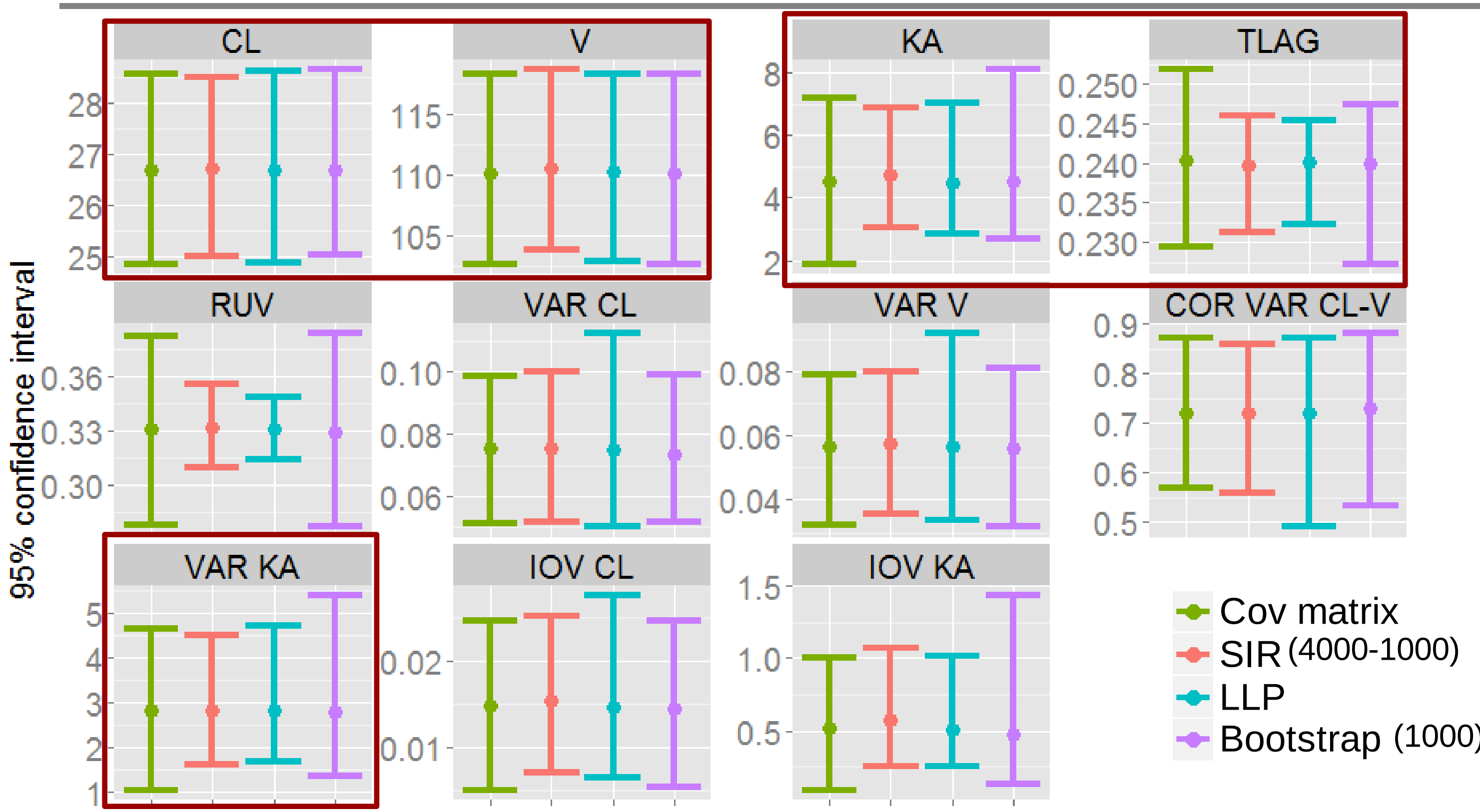

- SIR : asymmetry for KA, TLAG and variances
- Runtime : 2h (SIR 4,000 samples) vs. 3h (Boot)

Moxonidine model: Karlsson et al., J Pharmacokinet Biopharm. 1998;26(2):207-46

SIR optimization

Sampling, replacement, matrix inflation

SIR is NOT a procedure set in stone

Number of initial samples

- most robust with high number of initial samples
- but at cost of increased computation time

Resampling

- number of resamples (in relation with number of initial samples)
- with or without replacement

Inflation of sampling distribution

- trustworthiness - covariance matrix constrains investigated parameter space
- could gain e.g. from inflating variances

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Conclusion

SIR

- ✓ allows for asymmetry in uncertainty
- ✓ without the need of estimation step

⇨ Fast and stable method to assess parameter uncertainty for models with successful covariance step, in particular if:

- ✓ long estimation times
- ✓ bootstrap convergence issues
- ✓ unbalanced/small study designs

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imi Innovative Medicines Initiative

efpia

ddmore Drug Disease Model Resources