Determination of Appropriate SIR Settings when Assessing Parameter Uncertainty

UPPSALA UNIVERSITET

Anne-Gaëlle Dosne[1], Martin Bergstrand[1], Mats O. Karlsson[1]

[1]Department of Pharmaceutical Biosciences, Uppsala University, Uppsala, Sweden

Aim

The objectives of this work were to develop diagnostics to select optimal settings for the Sampling Importance Resampling (SIR) method in terms of:

- number of initial samples
- proposal uncertainty distribution

Conclusion

- dOFV distributions and bin plots were developed as quantitative and qualitative criteria to determine whether SIR settings are optimal
- These criteria are easy to use and will facilitate reliable use of the SIR method
- SIR is readily implemented in PsN [6] and the diagnostics are being added. Automation of the choice of settings based on these criteria is under investigation

Background

SIR [1] has been proposed as a method for assessment of parameter uncertainty in nonlinear mixed effects models [2]. The advantages of SIR are:

- no repeated parameter estimations
- no distributional assumptions
- applicability to many situations in which other methods fail (limited data, meta-analysis)

SIR always constitutes an improvement over the proposal distribution, but it is only guaranteed to reflect the true uncertainty when the number of initial samples is high enough in relationship to the adequacy of the proposal density. The question of whether SIR settings are optimal, or how close the results are from the true uncertainty, needs to be addressed.

Methods

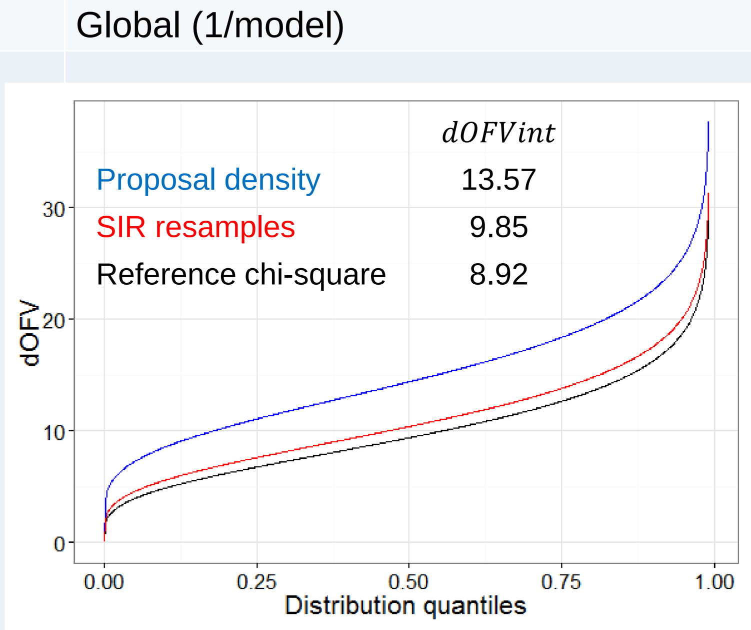
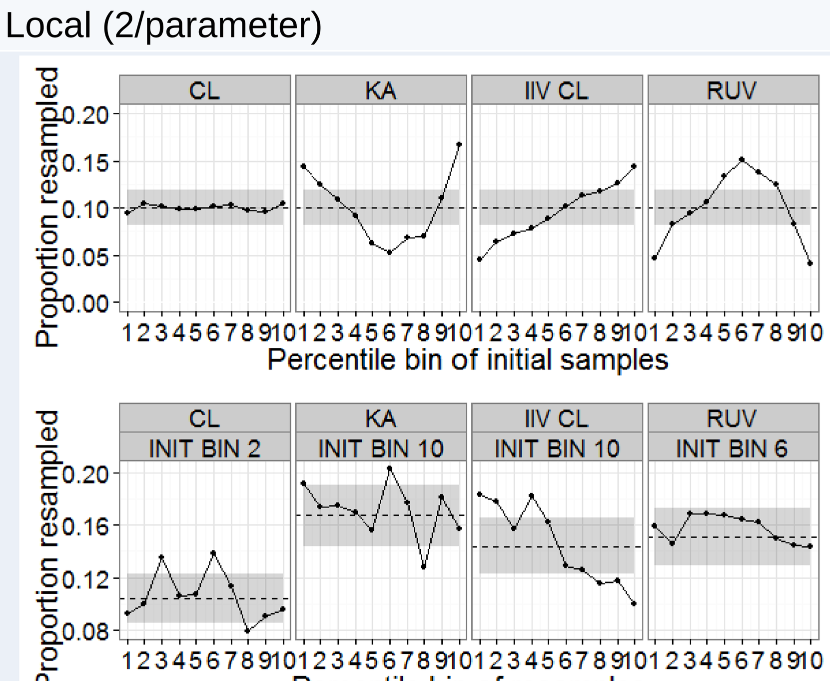
SIR principle

The objective of SIR is to provide a given number *m* of parameter vectors which are representative of the true uncertainty distribution based on a given number *M* (*M* > *m*) of parameter vectors simulated from a proposal uncertainty distribution. The *m* vectors can then be used to compute confidence intervals or as input for simulation.

Step	Action
SAMPLING *Step 1*	• **Sample** *M* parameter vectors from known proposal distribution
IMPORTANCE WEIGHTING *Step 2*	• Calculate **importance ratio (IR)** for each vector
RESAMPLING *Step 3*	• **Resample** *m* vectors based on IR

$$IR_M = \frac{\exp\left(-\frac{1}{2}dOFV\right)}{relPDF} = \frac{\exp\left(-\frac{1}{2}(OFV_M - OFV_{MLE})\right)}{\frac{PDF_M}{PDF_{MLE}}}$$

Developed diagnostics

	dOFV distribution	Resampling plots
Description	Plot dOFV value versus dOFV quantile for SIR, the proposal density and the reference chi-square. Can be summarized numerically by taking the integrand of the area under the dOFV quantile curve ($dOFVint$). $dOFVint = \int_{0.025}^{0.975} dOFV\, d(q)$	Initial percentile plot : divide the parameter space defined by the initial samples into 10 equally sized percentile bins. Calculate and plot the proportion of parameters resampled by SIR in each bin. Resamples percentile plot : for the bin with highest proportion in the initial plot, calculate the proportion of resamples for 10 subsets of the resampled parameters sorted by sampling order.
Level	Global (1/model)	Local (2/parameter)
Example		
Expected behavior under the true uncertainty	The dOFV follow a χ^2-distribution with degree of freedom equal or slightly inferior to the number of estimated parameters.	The proportion of resampled parameters should be similar (up to stochastic noise) in each bin. SIR is able to compensate trends if the proportion stays similar over the resamples percentile bins.
Interpretation	$dOFVint$ higher than the reference indicates less than optimal conditions. The number of initial samples should be so that further initial samples do not change the dOFV distribution.	Trends in initial percentile plot (top panel): • Horizontal : proposal density appropriate • U-shaped : proposal density too narrow • Diagonal : presence of asymmetry • Bell-shaped : proposal density too wide. Trends in resamples percentile plot (bottom panel): • Horizontal : SIR appropriate • Diagonal descending : SIR can be improved

Methods

Application to real data examples

Three real data examples [3-5] were used to investigate the relevance of the proposed diagnostics in the choice of optimal SIR settings.

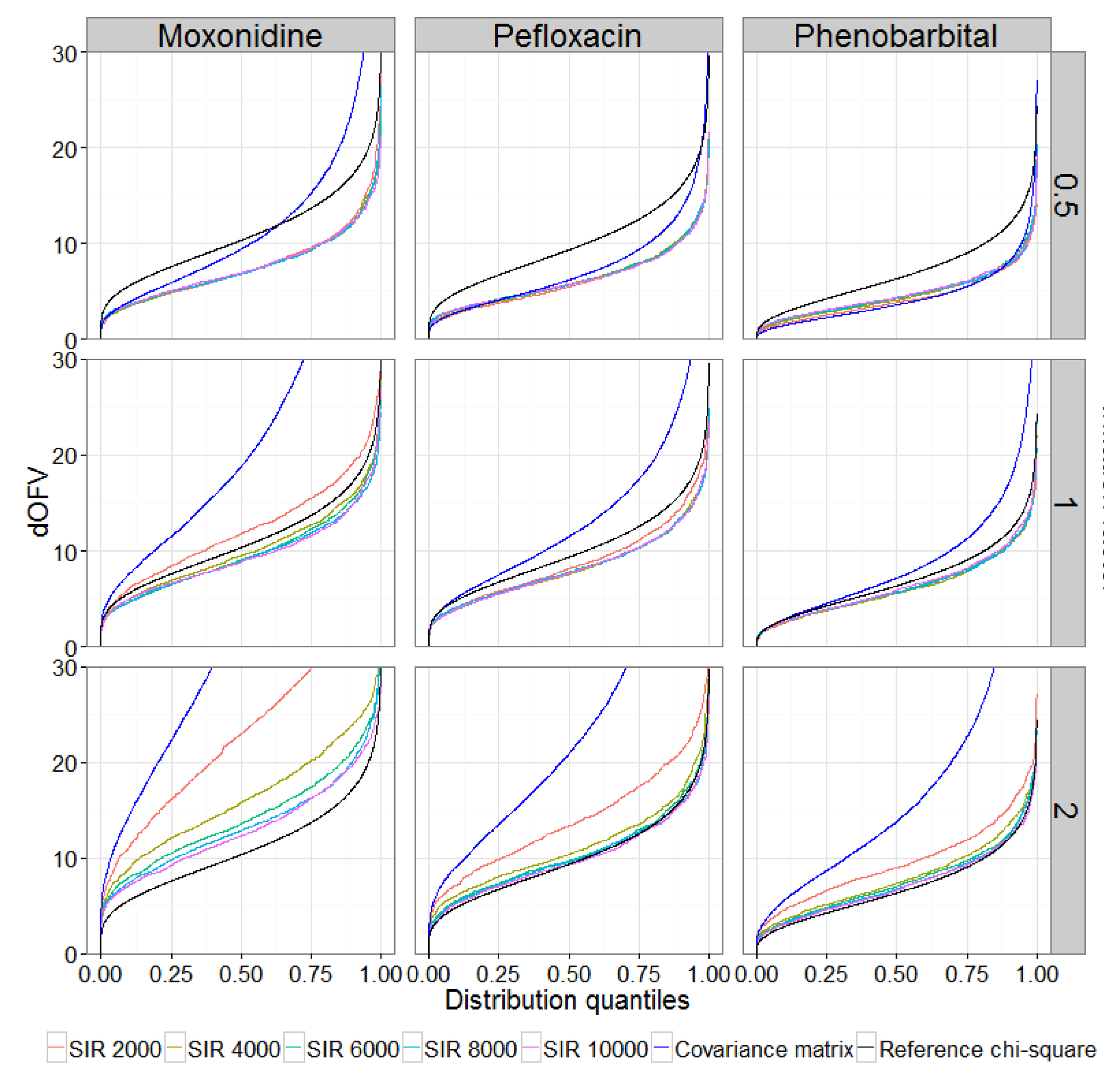
Table 1 Summary of investigated SIR settings and diagnostics used to select the most appropriate ones

SIR setting	Alternatives tested	Diagnostics
Number of initial samples	200, 4000, 6000, 8000, 10000	dOFV distribution
Proposal uncertainty distribution	0.5, 0.75, 1, 1.5, 2 *COV	Resampling plots

COV is the asymptotic variance-covariance matrix

Results

Number of initial samples



- SIR dOFV stabilized after a number of initial samples dependent on the proposal density (between 4000 and 8000 when starting from the uninflated covariance matrix)
- The level of stabilization was dependent on the proposal density
- Stabilization of the dOFV curves correlated well with stabilization of the 95% confidence intervals at the parameter level (data not shown)

Figure 1. Comparative dOFV quantile distributions for the proposal density (blue), SIR with increasing number of initial samples (colors) and the reference chi-square (black) for the three real data examples.

Proposal density

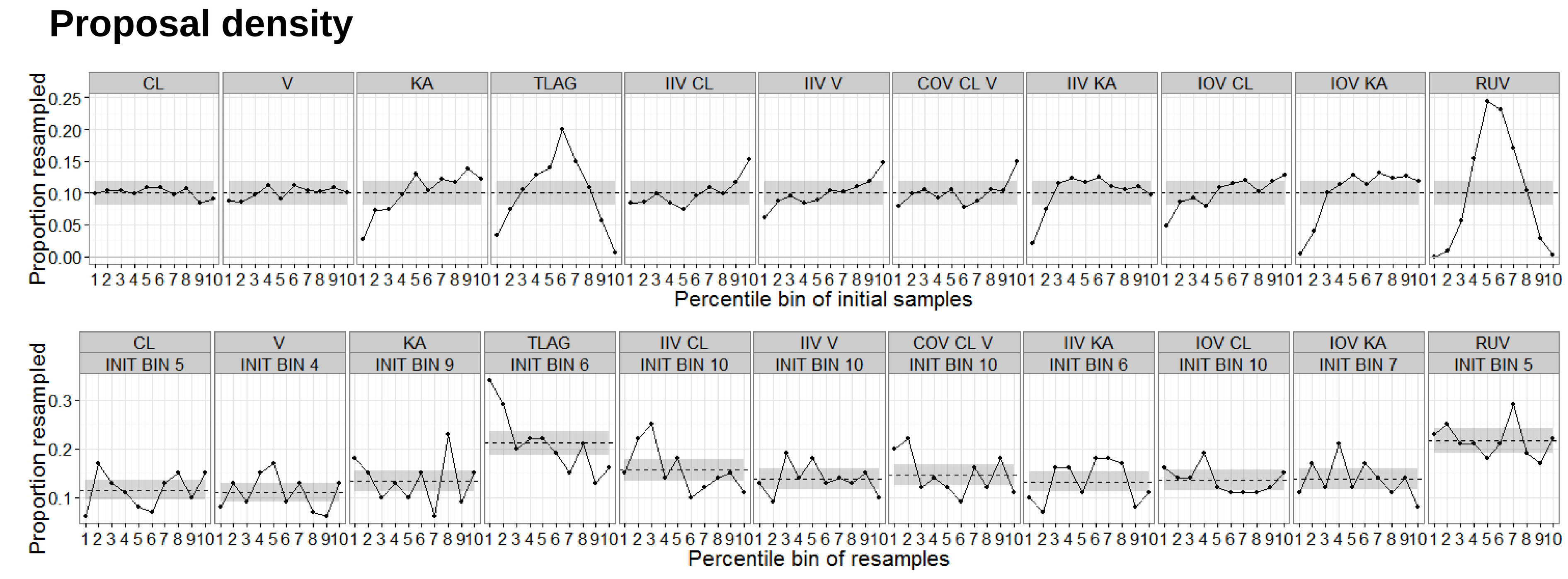


Figure 2. Resampling plots (initial in top panel, resamples in bottom panel) for the moxonidine example using SIR settings of no inflation and 10,000 initial samples. The horizontal lines are the expected proportions, the grey shaded areas are the stochastic noise.

- The appropriateness of the proposal density is parameter dependent
- Deviations from the proposal density were observed for KA, TLAG and random effects
- SIR was able to compensate these deviations except for TLAG

Proposed workflow

1. Perform SIR using the best available proposal density and a number of initial samples 5 to 10 times the desired number of resamples.
2. Based on the dOFV distribution, judge whether the number of initial samples is appropriate, i.e. whether convergence is achieved. Based on the initial percentile plot, check if the proposal density is appropriate for the parameters. If not, check the resamples percentile plot to see if SIR could compensate.
3. If SIR could not compensate for the inadequacy of the proposal density, perform SIR with an updated proposal density and/or increased number of initial samples. Updating the proposal density appeared most efficient in the investigated examples.

References

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annegaelle.dosne@farmbio.uu.se

Department of Pharmaceutical Biosciences, Uppsala University PO Box 591 - 751 24 Uppsala - Sweden