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Introduction

- Aggregate data modelling is a method which can be used to combine summary-level data or previous existing models for pharmacometric modelling [1].
- The method allows for reusing existing data and combining multiple sources with different study designs, previously not possible with existing techniques. The modelling workflow is shown in Figure 1.
- However, the published method has a relatively slow algorithm and is not implemented for easy usability.

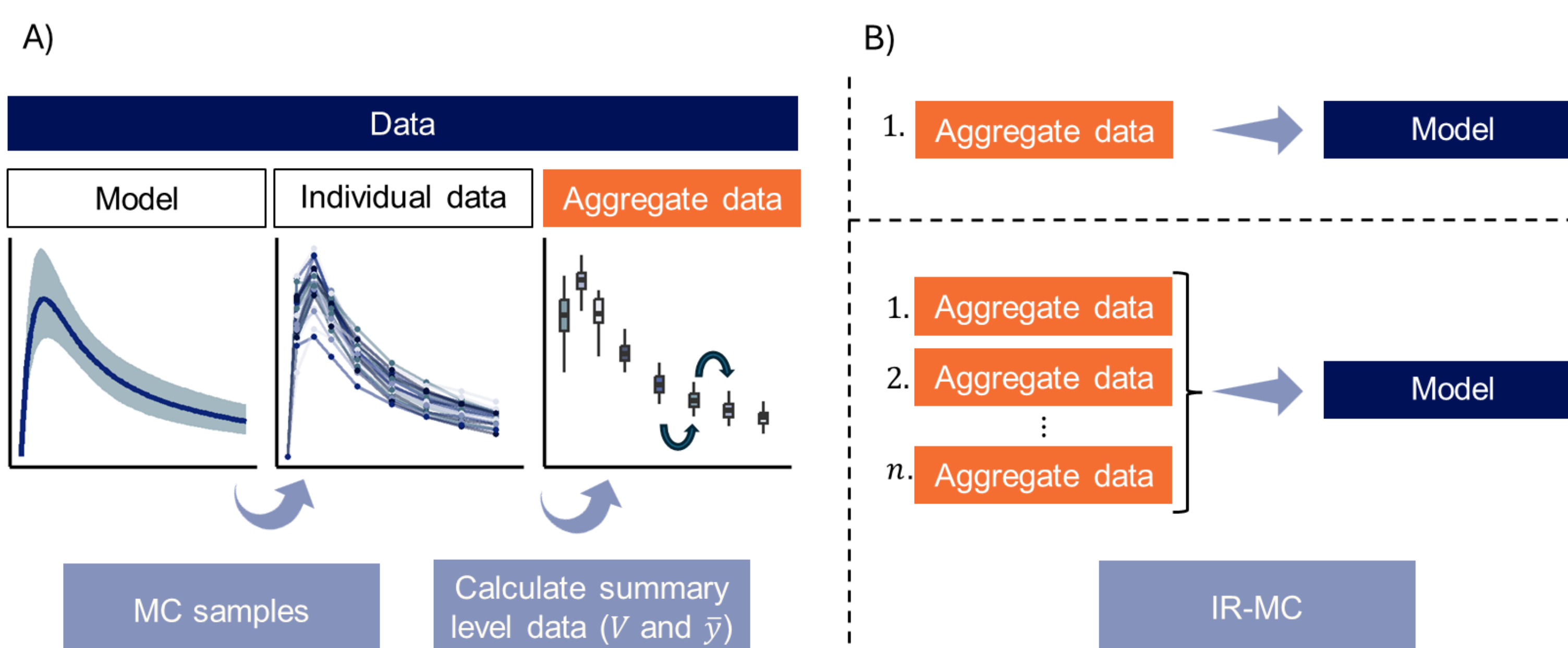


Figure 1. Modelling workflow of (A) transforming different data sources into aggregate data and (B) modelling aggregate data from one or multiple sources.

Aims

- Develop and evaluate a new estimation algorithm for aggregate data modelling.
- Apply the new aggregate data algorithm in a meta-analysis problem.

Methods

Algorithm development and evaluation

- We developed an improved algorithm based on iteratively reweighting the Monte Carlo predictions (IR-MC).

- Simulation studies were performed to compare the convergence times, bias, and precision.

Meta analysis

- A simulation was performed to show a meta-analysis using two different aggregate data sources from the distribution phase and elimination phase to jointly fit a two-compartmental PK model.
- A data set of 100 individuals was generated with dense sampling after 100 mg intravenous drug dosing using a two compartmental model with inter-individual variability.
- The parameter estimates were compared to the estimates of the individual level fit of the combined data using nlmixr2.

Results

Algorithm development

- The IR-MC showed an 11-fold reduction in time compared to the MC algorithm, while achieving the same accuracy and precision. The parameter estimates of both algorithms in the meta-analysis are shown in Figure 2.

Meta analysis

- Aggregate fixed effects were 97.5%–110.0% of individual estimates, and random effects ranged from 89.3% to 123.0%, as shown in Figure 2.
- The Visual Predictive Check in Figure 3 shows that the estimates led to slightly different predicted concentration curves.

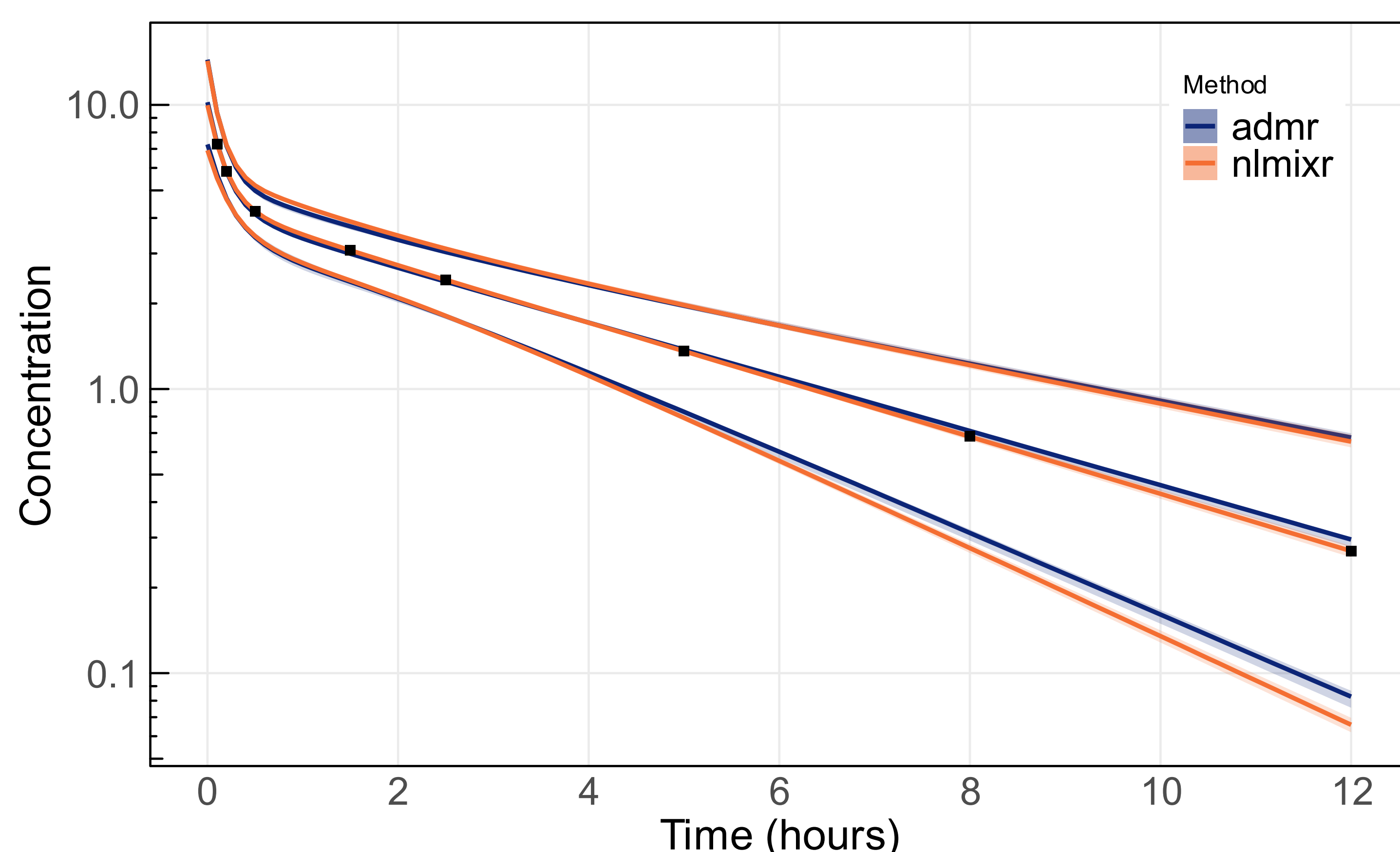


Figure 3. Visual Predictive Check of the aggregate modelling method over 20 iterations, showing the predicted median, 10th, and 90th percentile range of the population PK.

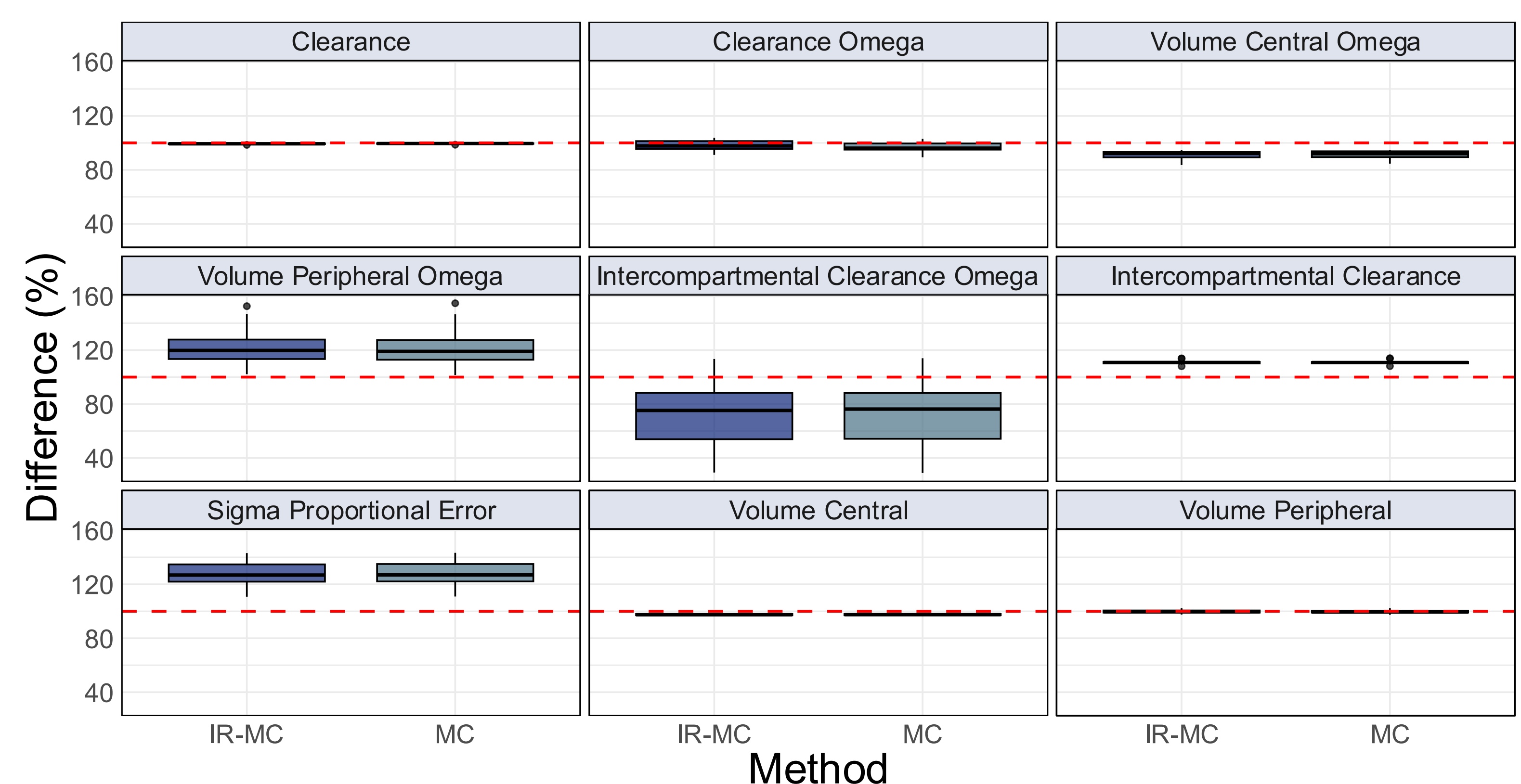


Figure 2. Parameter estimates of the aggregate data modelling algorithms as percentage of the individual data fit (nlmixr2) estimates.

Conclusions

- The ability to combine summary-level data from different data sources and with structurally different models makes it a valuable and unique tool for meta-analysis.
- We have extended the aggregate data modelling framework with a more efficient algorithm, which ensures scalability of this method.
- Finally, we developed an R package with the complete workflow to enable practical application of the method.

References

- P. A. J. Väitalo, “Pharmacometric estimation methods for aggregate data, including data simulated from other pharmacometric models,” J. Pharmacokinet. Pharmacodyn., vol. 48, no. 5, pp. 623–638, Oct. 2021, doi: 10.1007/s10928-021-09760-1.