

A pragmatic approach to handling data below the lower limit of quantification in complex pharmacokinetic models

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Background and objectives

Adequate handling of data below the lower limit of quantification (BLQ) is key for parameter estimation in population pharmacokinetic (PK) analyses. The M3 method¹ is the gold standard,^{2,3} but has limitations such as minimization issues,^{4,5} and has mostly been evaluated on simpler scenarios.

Other commonly used methods impute or exclude data BLQ. All these methods may introduce bias,^{4,6} and of note, the standard imputation methods do not account for the fact that imputed values carry additional uncertainty compared to observed ones, which may increase bias.

Objective: To assess the stability and accuracy of BLQ handling methods in a complex PK model.

Methods

We compared six BLQ handling methods¹:

- M1: Excludes BLQ data
- M3: Considers BLQ data as censored and computes the likelihood of the data being BLQ
- M6: Imputes the BLQ samples closest before and after the maximum to half of the lower limit of quantification (LLOQ), discarding the rest
- M6+: Modification of M6 including extra additive error (i.e., LLOQ/2) for imputed data
- M7: Imputes 0 for all BLQ data
- M7+: Modification of M7 including extra additive error (i.e., LLOQ/2) for imputed data

Evaluation of the methods on real data:

- Isoniazid PK data for 100 individuals from the study TRUST⁷ (Fig. 1)
- Utilized a previously developed NONMEM model (ADVAN14): two-compartment disposition with transit compartment absorption, first-order elimination with hepatic extraction and a mixture model to assign N-acetyltransferase 2 metabolizer status (affecting clearance) as this data was missing. Residual error was described by a combined error model. M3 was estimated using Laplace, the other methods with FOCE-I.
- Parallel retries were run (n=10) with 30% tweaking of initial estimates and the resulting OFVs were used to compare **stability** between the BLQ handling methods.⁸

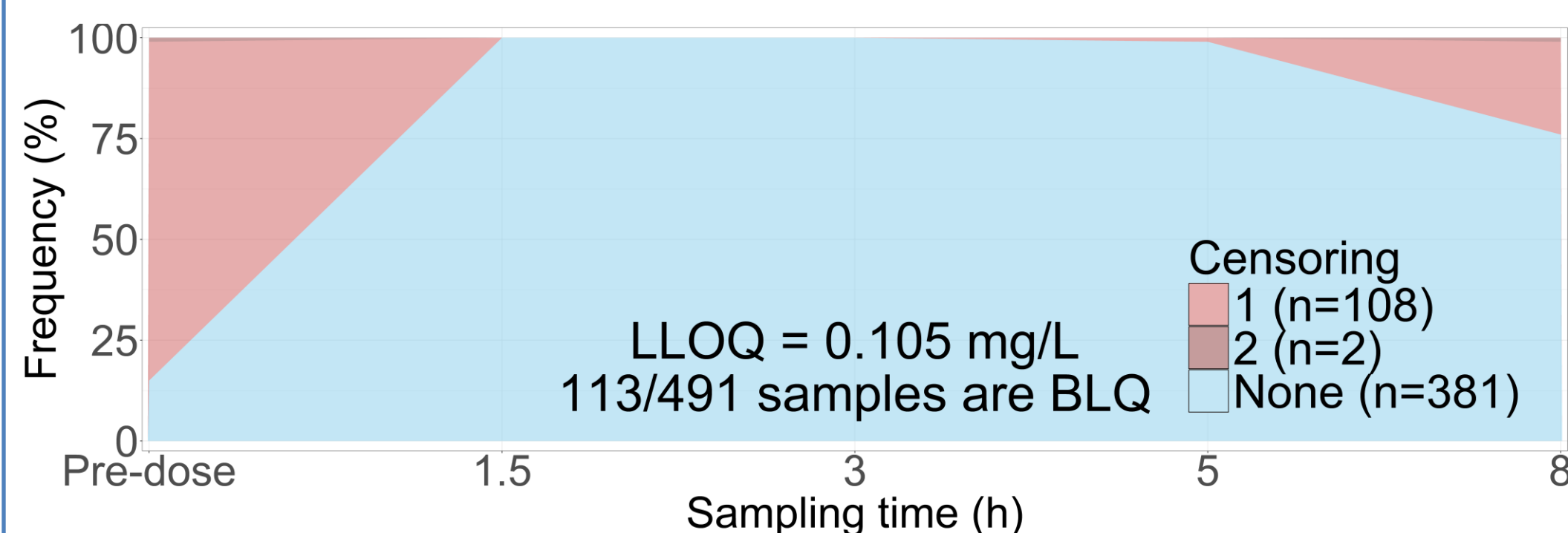


Figure 1: Proportion of BLQ data at each sampling point in the **real** data. Censoring = 1 and 2 are BLQ, and 2 are discarded in M6/M6+.

Evaluation of the methods on simulated data:

- Slightly modified version of model and richer sampling to increase the data BLQ for better assessment of the methods (Fig. 2).
- Parallel retries were run as described to compare **stability**.
- Relative root mean squared error (rRMSE) obtained through stochastic simulation and estimation (SSE) was used to compare **bias and accuracy** in parameter estimates in 50 simulated datasets with 30% variability in initial estimates.

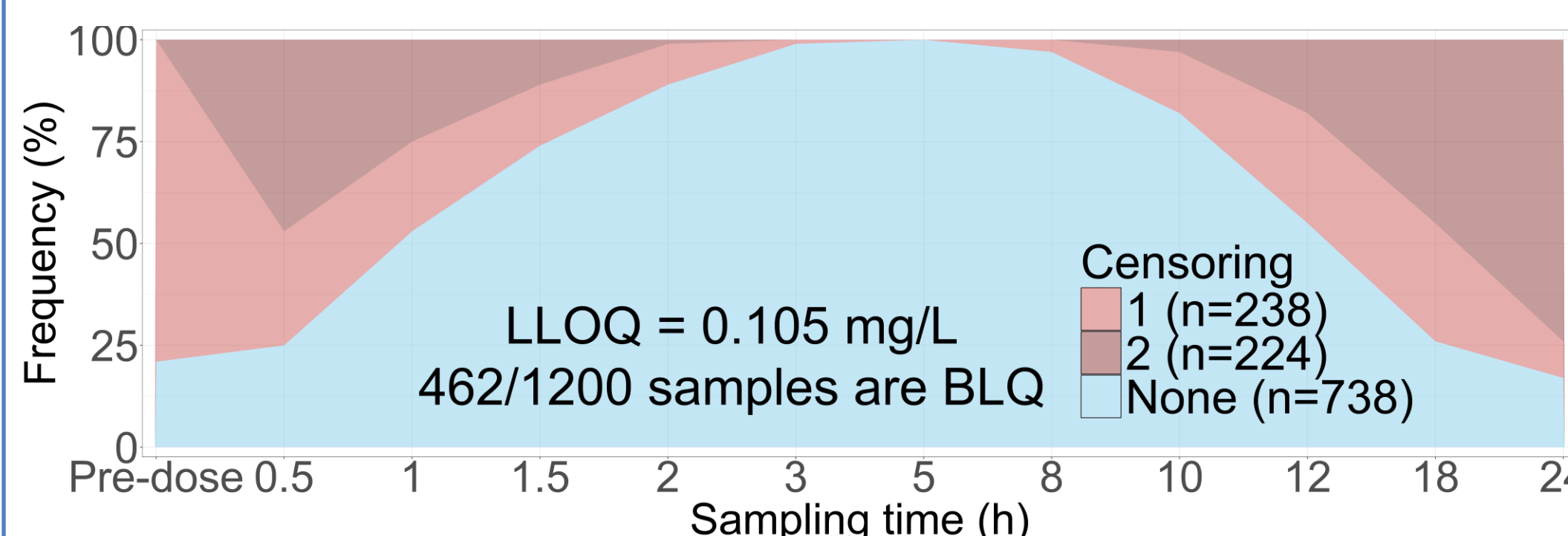


Figure 2: Proportion of BLQ data at each sampling point in the **simulated** data. Censoring = 1 and 2 are BLQ, and 2 are discarded in M6/M6+.

Results

Model stability

- M3 and M7 converged to very different solutions (OFV (Fig. 3) and parameter estimates) in each parallel retry, both on the real and simulated data.
- M1, M6, M6+, and M7+ converged to similar solutions in the parallel retries on both the real and simulated data, except for M6 getting stuck in local minima in four out of ten retries on simulated data with dOFV >3.84 (Fig. 3).

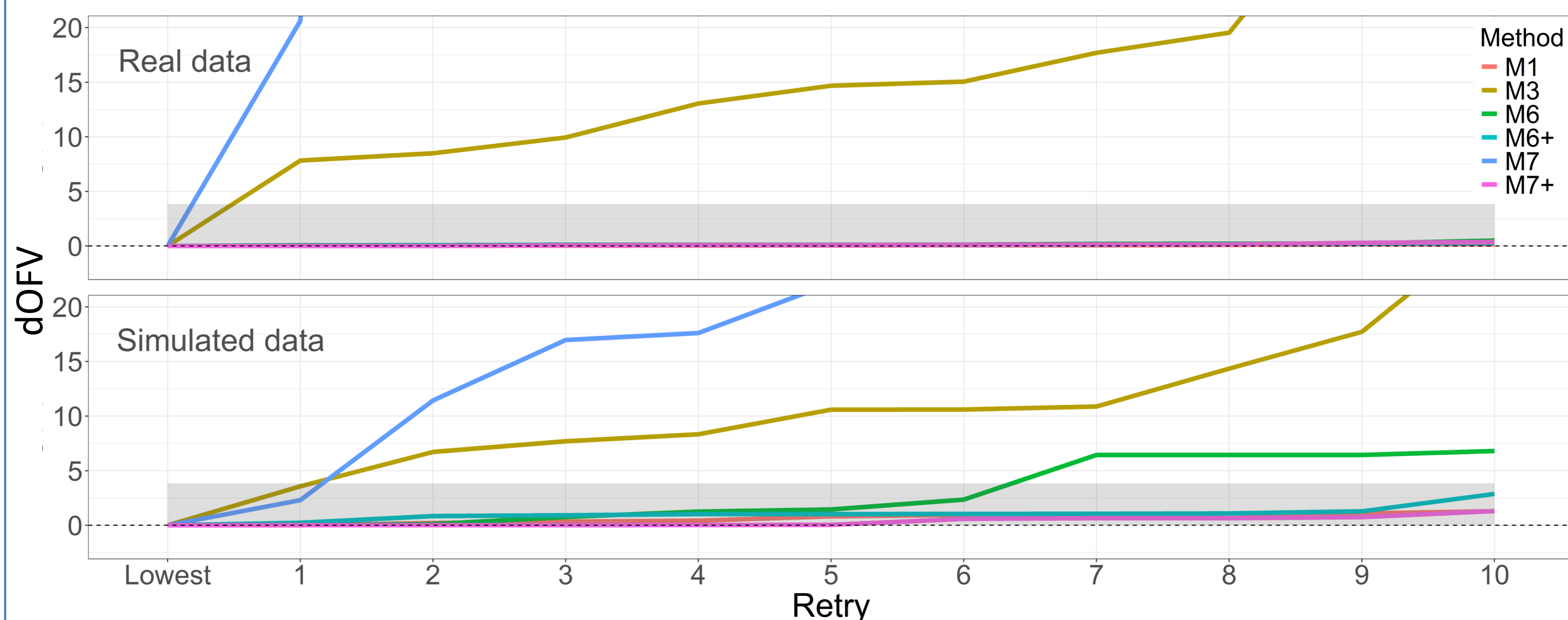


Figure 3: dOFVs with respect to the lowest dOFV for each BLQ handling method resulting from parallel retries. The dOFVs are ordered from lowest to highest dOFV within each method. The shaded area represents dOFV <= 3.84.

Bias and accuracy in parameter estimates

The cumulative rRMSE (rRMSE_{cum}) is presented excluding rRMSE for the additive error for a fairer comparison, as the M6+ and M7+ methods will have biased estimates of additive error by design due to the fixed component of the additive error.

M3 performed best with lowest rRMSE_{cum} (242%).

M6+ and M7+ performed similarly to or better than M3 in most parameters except additive error, BOVKA and the peripheral compartment (rRMSE_{cum} 333% and 381%, respectively).

M1 and M6 had rRMSE_{cum} of 441% and 829%, respectively.

M7 had very high rRMSE in most parameters, with a rRMSE_{cum} of > 10 000%.

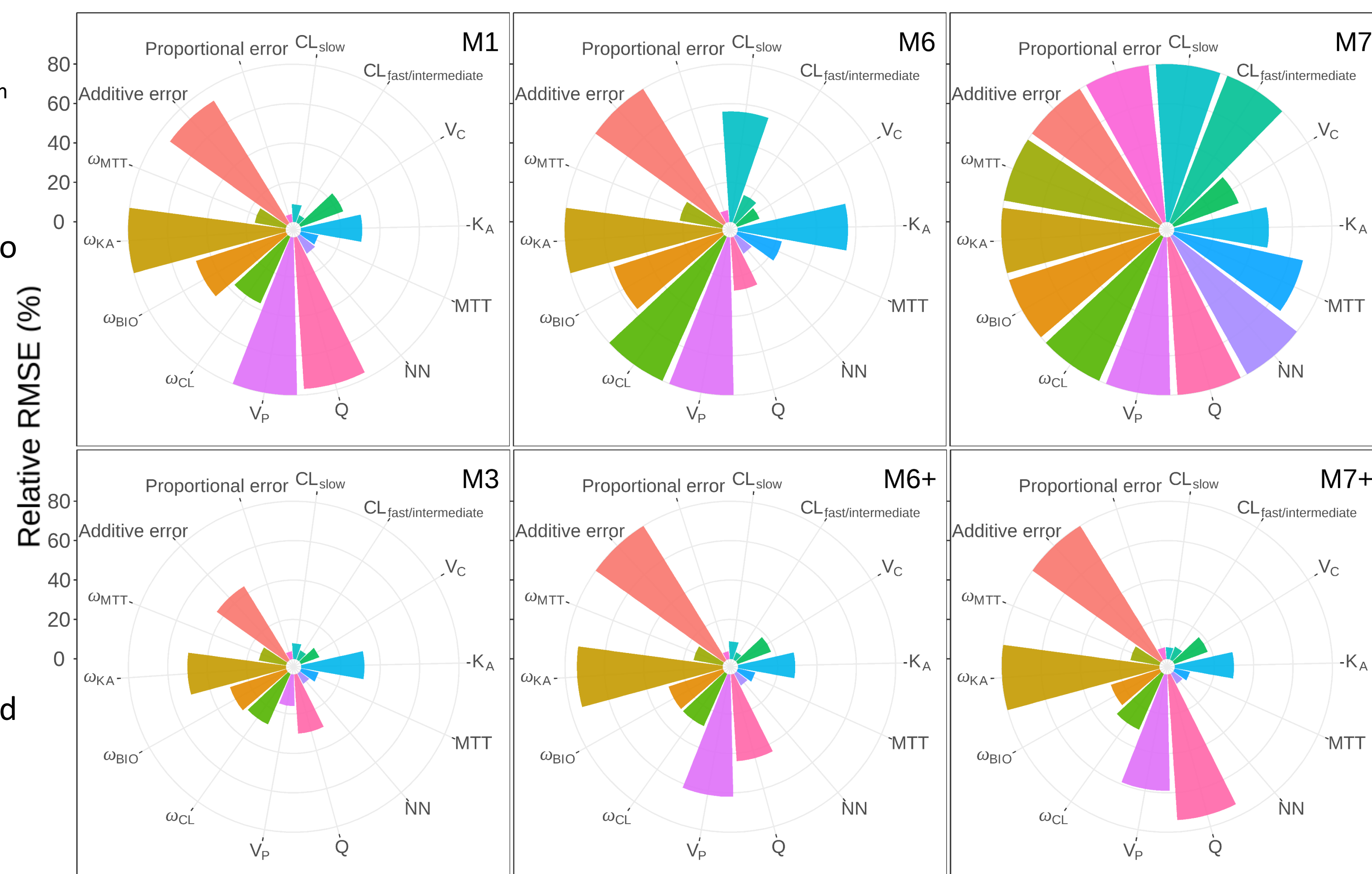


Figure 4: rRMSEs for each BLQ handling method in each estimated parameter. The length of each coloured arm are proportional to the magnitude of the rRMSE, with shorter length indicating lower rRMSE. Any parameter with rRMSE > 80% have been cut off at 80%.

Discussion and conclusion

- Although M3 is the gold standard and demonstrated the best accuracy in this analysis, it is suboptimal for model development when dealing with complex models, due to its inconsistency in converging towards a stable solution. This makes it challenging to use drop in OFV as a measure of significance for covariates.
- The imputation methods (except M7) showed superior stability in both the real and simulated data but may introduce bias and the imputation method should be chosen carefully.
- Including extra additive error** as in M6+ and M7+ **mitigates the impact of the imputation**, with major improvements in both stability and accuracy of parameter estimates compared to when the extra additive error is not included.
- In summary, **we suggest M6+ and M7+ as attractive alternatives to M3 when developing complex models**, as they perform similarly to M3 in terms of accuracy but with significantly improved model stability.

References

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