

Improving the reproducibility of NONMEM-based pharmacometric analyses

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Background

- Pharmacometric analyses commonly support critical drug development decisions
- A high degree of traceability and reproducibility must be ensured throughout the entire analysis to as a key element for the quality and validity of the analysis
- This is especially challenging with pharmacometric analyses due to:
 - the array of tools used throughout data processing (e.g., SAS, R), data analysis (e.g., R, Monolix, NONMEM, PsN), and reporting which themselves have additional dependencies (e.g., compilers, libraries).
 - the generation of random numbers in the context of parallel computing (e.g. SAEM)

Objectives

- To illustrate common reproducibility issues and suggest solutions to address them

Methods

Model examples

- Models were implemented in NONMEM using the MU-referencing approach
- The moxonidine model example was used throughout this analysis (additional examples should be evaluated to confirm the robustness of results presented herein)

Moxonidine model

- Adapted from Karlsson *et al.* [1]
- Single dose pharmacokinetic (PK) data
- Inclusion of 476 obs. from 74 patients
- Estimation of 6 thetas, 2 omegas (+1 correlation term) and 2 sigmas

Repeatability workflow

NONMEM 7.4.3

FOCE

SAEM/IMP

1 node A
1 node B
PARSE_TYPE=2

3 nodes A
3 nodes B
PARSE_TYPE=2

6 nodes A
6 nodes B
PARSE_TYPE=2

NONMEM 7.5.0

FOCE

SAEM/IMP

1 node A
1 node B
PARSE_TYPE=2

3 nodes A
3 nodes B
PARSE_TYPE=2

6 nodes A
6 nodes B
PARSE_TYPE=2

1 node A
1 node B
PARSE_TYPE=1

3 nodes A
3 nodes B
PARSE_TYPE=1

6 nodes A
6 nodes B
PARSE_TYPE=1

1 node A
1 node B
PARSE_TYPE=1

3 nodes A
3 nodes B
PARSE_TYPE=1

6 nodes A
6 nodes B
PARSE_TYPE=1

The parameter estimates were evaluated under 2 NONMEM versions, with 2 estimation methods, with 6 parallelization settings (nodes and PARSE_TYPE*), finally each of these scenarios was repeated twice in a row (i.e., runs A/B)

*PARSE_TYPE [2] : setting in the NONMEM parafille to control load balance across nodes

- PARSE_TYPE=2 (default): automatically balance load among nodes
- PARSE_TYPE=1: evenly distribute numbers of subjects among available nodes
- Others i.e., PARSE_TYPE=0, 3 or 4

Figure 1. Moxonidine concentration-time profiles

Methods cont'd

Reproducibility across computers

- The repeatability workflow was evaluated under 3 environments with Intel CPUs
- Parameter estimates were compared across environments

- Docker enables the creation and deployment versioned containers (i.e., environment) that may contain Linux-based software. In this analysis we used IQdesktop⁺ a free qualified virtual modeling and simulation environment

Results

Repeatability

- Using FOCE, all runs were repeatable i.e., identical objective function value (OFV), parameters value and residual standard error (RSE) between runs A/B
- Using SAEM/IMP parallelized runs were not repeatable (small OFV, parameters value and RSE changes) unless PARSE_TYPE=1 or NONMEM 7.5.0 were used
- The number of nodes had no impact on the FOCE results but did impact the NONMEM 7.4.3. SAEM/IMP results as also noted by Gibiansky *et al.* [3] Of note, this issue with SAEM/IMP has been addressed in NONMEM 7.5.0

Table 1. NONMEM SAEM/IMP runs repeatability illustrated under versions 7.4.3 and 7.5.0 and using PARSE_TYPE=2 (NONMEM default). Repeatability issues are highlighted in orange. Showing estimates (RSE)

Parameters	NONMEM 7.4.3 (PARSE_TYPE=2)		NONMEM 7.5.0 (PARSE_TYPE=2)	
	6 nodes [run A]	6 nodes [run B]	6 nodes [run A]	6 nodes [run B]
CL0	26.5 (4.5%)	26.5 (4.5%)	26.4 (4.3%)	26.4 (4.3%)
Vc0	103 (3.8%)	103 (3.7%)	102 (3.9%)	102 (3.9%)
kabs	8.12 (41%)	8.02 (40%)	6.88 (39%)	6.88 (39%)
Tlag1	0.311 (24%)	0.303 (24%)	0.274 (31%)	0.274 (31%)
betaCLCR	0.732 (17%)	0.683 (17%)	0.599 (18%)	0.599 (18%)
omega(CL0)	0.289 (14%)	0.286 (14%)	0.28 (13%)	0.28 (13%)
omega(Vc0)	0.226 (11%)	0.224 (11%)	0.223 (11%)	0.223 (11%)
omega(kabs)	1.4 (31%)	1.41 (28%)	1.28 (30%)	1.28 (30%)
omega(Tlag1)	0.774 (27%)	0.789 (23%)	0.863 (26%)	0.863 (26%)
corr(CL0,Vc0)	0.692 (15%)	0.7 (14%)	0.711 (13%)	0.711 (13%)
error_ADD1	0.0175 (16%)	0.017 (20%)	0.0172 (18%)	0.0172 (18%)
error_PROP1	0.15 (3.7%)	0.153 (3.7%)	0.155 (3.8%)	0.155 (3.8%)
OBJ	-1549	-1552	-1553	-1553

Conclusion

- Based on the moxonidine example, the NONMEM FOCE estimation was robust to parallelization unlike SAEM (7.4.3) for which the default parallelization settings (PARSE_TYPE=2) systematically led to non-repeatable results
- The SAEM repeatability issue could be addressed by using PARSE_TYPE=1 or switching to NONMEM 7.5.0
- Integrating the standard pharmacometric toolbox within a docker image along with the fix to the SAEM repeatability enabled near identical results across 2 physical environments under all evaluated scenarios
- With images such as IQdesktop⁺ the computing environment could be provided alongside the analysis workflow for full traceability and reproducibility of analyses

Results (cont'd)

Performances

- While PARSE_TYPE=2 (default) is performance focused, switching to PARSE_TYPE=1 in the moxonidine example only led to minor increase in runtime in comparison to the effect of increasing the number of nodes

Table 2. Impact of PARSE_TYPE on runtime with FOCE under NONMEM 7.4.3

PARSE_TYPE	Elapsed time (seconds)		
	1 node	3 nodes	6 nodes
2 (default)	31.55	21.65	17.95
1	31.55	22.35	18.05

Reproducibility across computers

- Using a pharmacometric environment inside a Docker container gave near identical results for all scenarios (only considering repeatable scenarios). However, differences were observed with FOCE when not using Docker.

Table 3. Reproducibility of non parallelized NONMEM 7.4.3 runs using FOCE across 3 work environments. Reproducibility issues are highlighted in orange. Showing estimates (RSE)

Parameter	IQdesktop ⁺ on Linux	IQdesktop ⁺ on macOS	Plain macOS
CL0	26.7 (3.4%)	26.7 (3.4%)	26.6 (0.033%)
Vc0	104 (3%)	104 (3%)	104 (0.046%)
kabs	4.35 (20%)	4.35 (20%)	4.36 (0.019%)
Tlag1	0.25 (0.00096%)	0.25 (0.00096%)	0.249 (0.014%)
betaCLCR	0.553 (16%)	0.553 (16%)	0.539 (0.013%)
omega(CL0)	0.278 (12%)	0.278 (12%)	0.268 (17%)
omega(Vc0)	0.222 (12%)	0.222 (12%)	0.236 (6.4%)
omega(kabs)	1.22 (17%)	1.22 (17%)	1.2 (0.4%)
omega(Tlag1)	0.847 (5.4%)	0.847 (5.4%)	0.963 (0.19%)
corr(CL0,Vc0)	0.713 (12%)	0.713 (12%)	0.528 (2.9%)
error_ADD1	0.0143 (1.1%)	0.0143 (1.1%)	0.0139 (3.8e-07%)
error_PROP1	0.154 (0.64%)	0.154 (0.64%)	0.153 (8.3e-08%)
OBJ	-1553	-1553	-1548

References

[1] M.O. Karlsson *et al.* *J Pharmacokinetics and Biopharmaceutics*. 26(2):207–246 (1998)

[2] R.J. Bauer NONMEM users guide. Introduction to NONMEM 7.4.3 (2019)

[3] L. Gibiansky *et al.* *J Pharmacokinet Pharmacodyn*. 39:17–35 (2012)

Acknowledgements

The authors would like to thank R.J. Bauer for his precious help about the reproducibility improvements under NONMEM 7.5.0.

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