Performance of *nlmixr* vs NONMEM for the Estimation of Pharmacometrics Models with Different Degrees of Non-linearity; an AMGEN experience

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Background & Objectives

nlmixr is freely available R package designed to fit nonlinear pharmacometrics models in a nonlinear mixed effect (NLME) modeling statistical framework [1]. Detailed comparison of pharmacokinetic parameters estimated between *nlmixr* and MONOLIX as well as quantification of its performance in estimating parameters using SAEM and FOCE has been shown previously[1]. Here, we continue the exercise of validating nlmxir by sharing our experiences on how the *nlmixr* package compares with NONMEM [2] for the estimation of pharmacometrics models with different degrees of non-linearity.

Methods

Three pharmacometrics models with different degrees of non-linearity were selected for this exercise. These models were: linear and nonlinear two compartment models and TMDD model. All models were originally fit using simulated NONMEM data for which the true values are known (Table 1). The models were translated into nlmxir script and fit to the same dataset. A detailed comparison of precision of parameter estimates as well as execution time was performed.

Simulation Setup

Following simulation scenarios were considered:

- 6 dose groups (5 subjects per dose group)
- Dense sampling following 1st and 3rd dose following by trough sampling.
- True values of population PK parameters are reported in [3,4] and summarized in Table 1.
- Residual error was assumed to follow proportional error model
- No IIV was assumed on inter-compartment clearance (Q)

Table 1: Typical values of PK parameters used for the comparison study

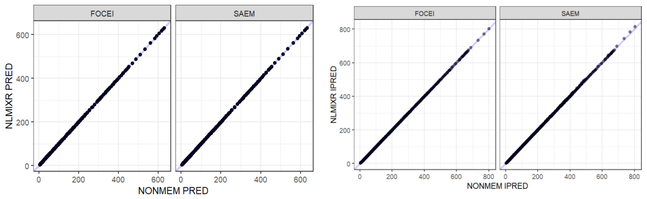
True PK parameters	Two compartment linear model	Two compartment non-linear model	TMDD model
CL (L/d)	0.4	0.4	0.4
V1 (L)	4.0	4.0	4.0
Q (L/d)	1.2	1.2	1.2
V2 (L)	3.0	3.0	3.0
Vmax (mg/d)		18	
Km (mg/L)		5	
KINT (1/d)			0.034
KDEG (mg/L)			0.03
KSS (mg/L)			0.02
KSYN (mg/L/d)			0.06
ω^2_{CL}	0.09	0.09	0.09
ω^2_{V1}	0.09	0.09	0.09
ω^2_{V2}	0.09	0.09	0.09
ω^2_{Vmax}		0.09	
ω^2_{Km}		0.09	
ω^2_{Kint}			0.00
ω^2_{Kdeg}			0.09
ω^2_{Kss}			0.00
ω^2_{Ksyn}			0.09
σ^2	0.04	0.04	0.04

Linear/non-linear pk model – comparison

Both NONMEM and *nlmixr* produced comparable results for linear and non-linear PK model

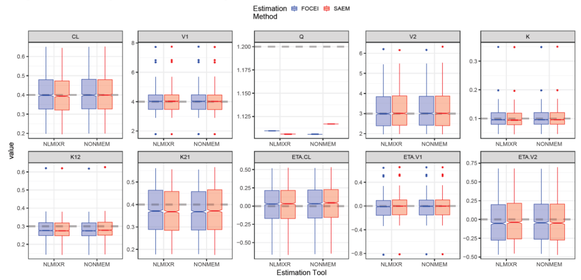
- Predicted values of concentrations from both the estimation tools were close to the line of unity. Figure 1 presents comparison for nonlinear PK model

Figure 1: PRED/IPRED comparison for non-linear PK



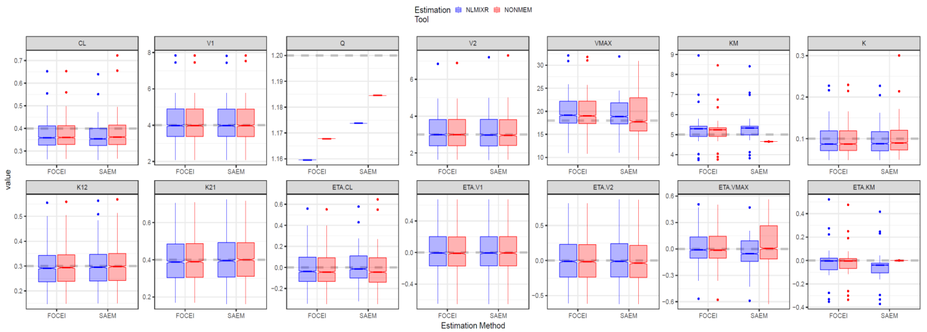
- For linear PK model, all PK estimates from both NONMEM and *nlmixr* were close to the true values (Figure 2).

Figure 2: PK parameter comparison for linear PK



- For non-linear PK model, minor differences in parameter estimates from both NONMEM and *nlmixr* were found. Some parameters estimates and random effects were either over- or under-estimated. These differences were not significant (Figure 3).

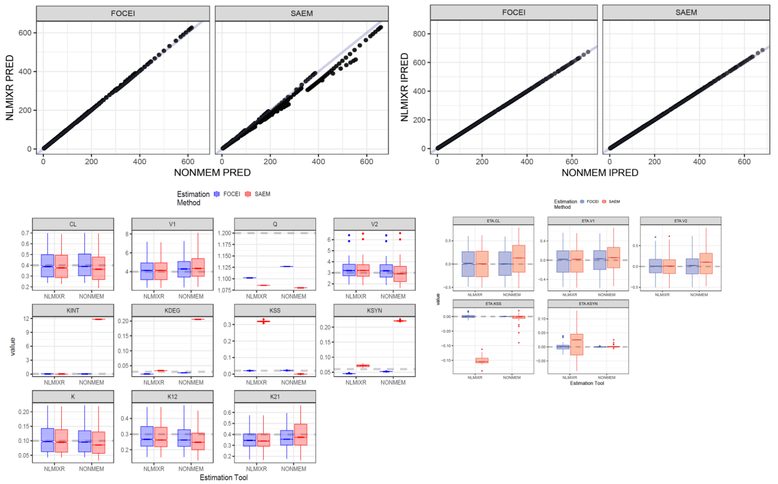
Figure 3: PK parameter comparison for non-linear PK



TMDD model – comparison

- Differences in predicted PK-concentrations between NONMEM and *nlmixr* were found for both FOCE and SAEM methods (Figure 4).

Figure 4: Comparison for TMDD model



Conclusion

- **For linear/nonlinear 2 compartment models:** Predicted PK concentrations were comparable between NONMEM and *nlmixr*. For non-linear PK model some parameters estimates, and random effects were either over- or under-estimated.
- **TMDD model:** By using SAEM, all the parameters except for K_{int} and ω^2_{Kss} were reasonably estimated through NONMEM and *nlmixr*. In general, SAEM within NONMEM produced less accurate estimation of the PK parameters than SAEM implemented in *nlmixr*.
- In general, as the degree of non-linearity of pharmacometrics models increases, both software NONMEM and *nlmixr* struggle to estimate accurately random effect parameters whilst the main parameters of the model are reasonably well estimated.

References

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