

Performance of the SAEM and FOCEI algorithms in the open-source non-linear mixed effect modelling tool **nlmixr**

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nlmixr performance

- Main question:

Do I get the same results when I switch from my usual method to nlmixr?

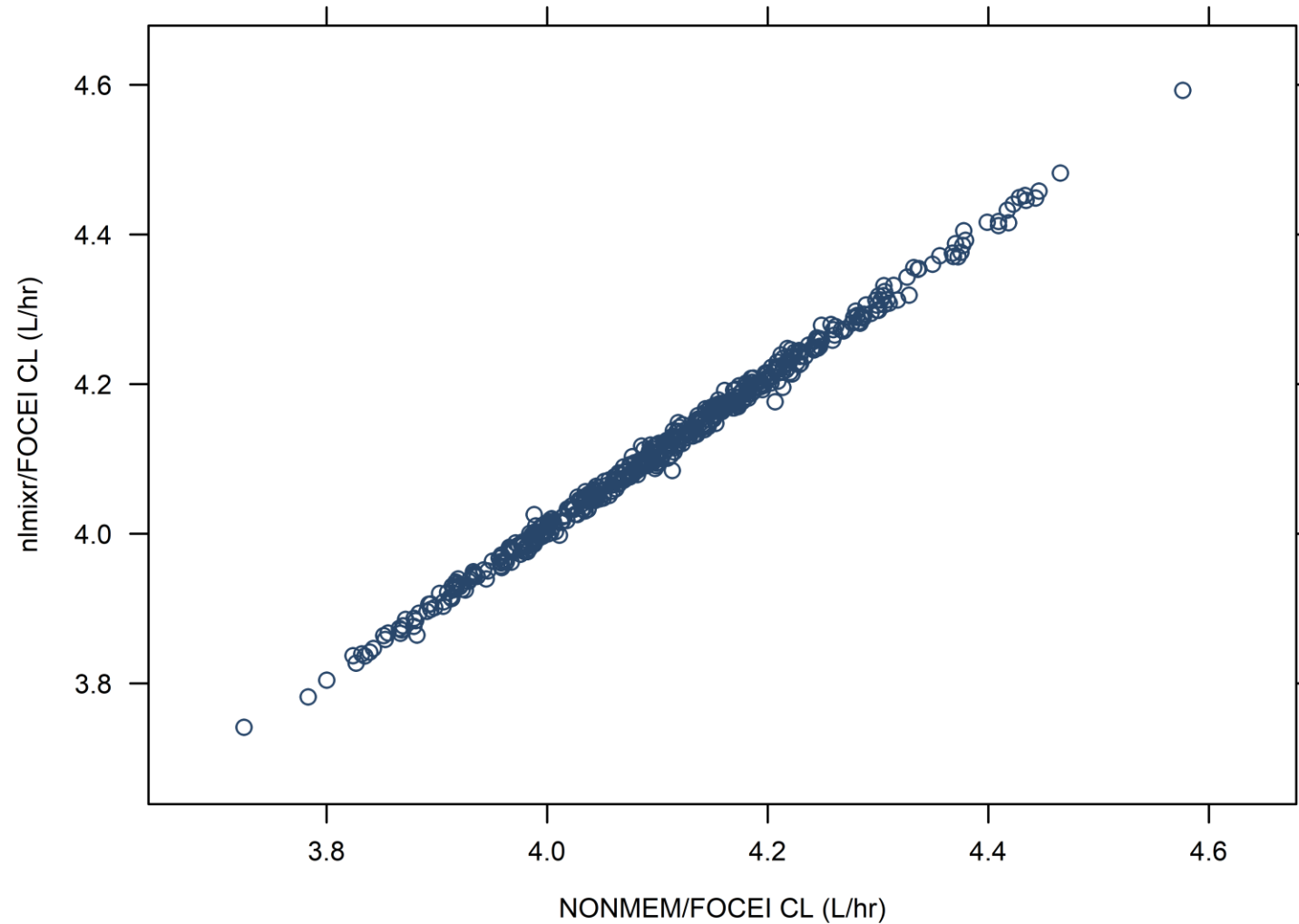
- nlmixr/FOCEI compared to NONMEM/FOCEI
- nlmixr/SAEM compared to Monolix/SAEM
- Repeated sparse data sets for a single model
- A wide range of models and inputs using single rich data sets
- Publication just published in CPT:PSP *"Performance of the SAEM and FOCEI algorithms in the open-source non-linear mixed effect modelling tool nlmixr"**

* <https://ascpt.onlinelibrary.wiley.com/doi/10.1002/psp4.12471>

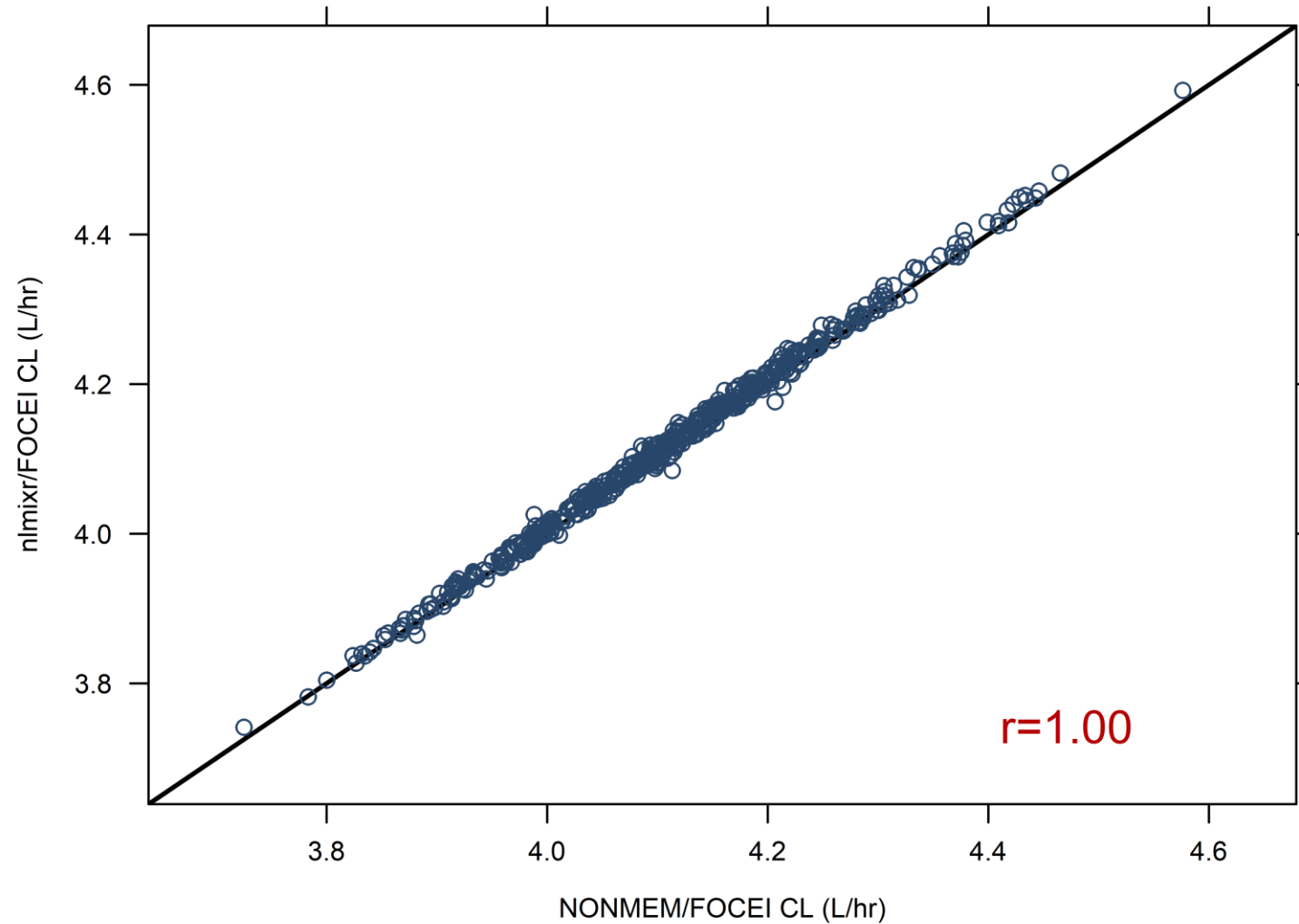
nlmixr performance: sparse data

- first-order absorption, one-compartment distribution, linear elimination model
- 4 doses, 30 subjects per dose
- 4 random time point samples in 24 hours after the 1st dose
- 500 simulated data sets
- Analysed using:
 - nlmixr/FOCEI
 - NONMEM/FOCEI
 - nlmixr/SAEM
 - Monolix/SAEM

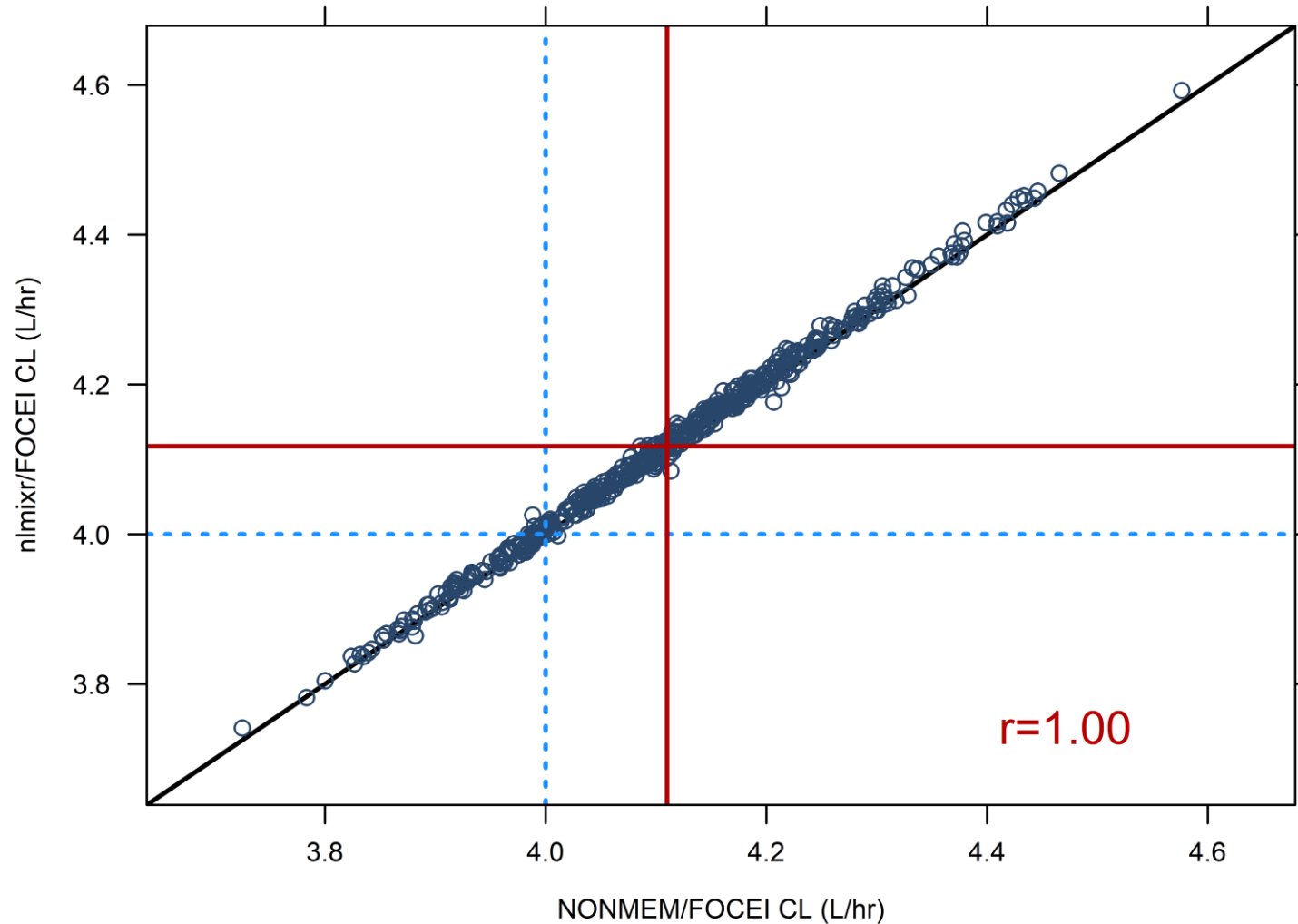
500 data sets are analysed using both NONMEM/FOCEI and **nlmixr**/FOCEI. Each marker is a single paired data set result for clearance for NONMEM on the x-axis and nlmixr/FOCEI on the y-axis



Results are highly correlated ($r=1.00$), and lie on the line of identity (diagonal black line)

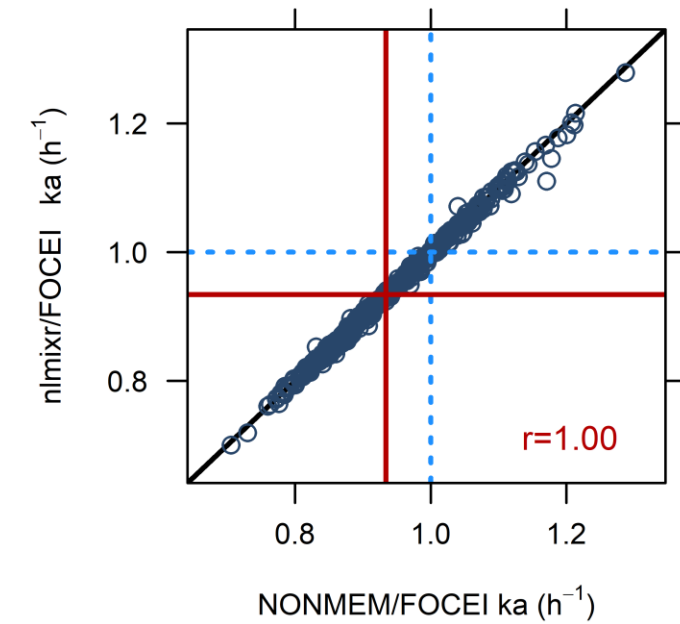
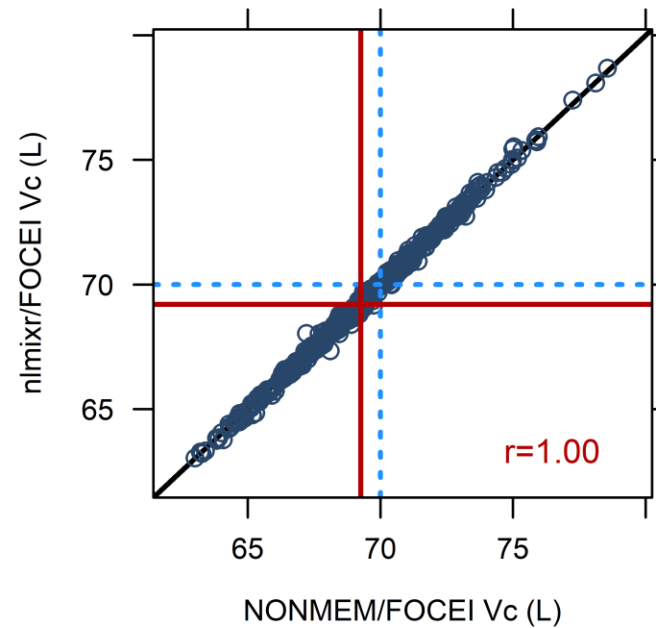
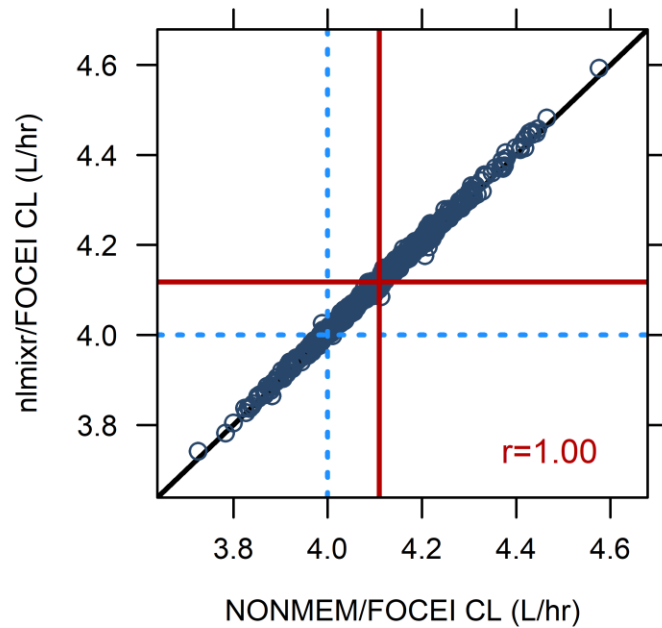


The median estimate across the 500 data sets (the red lines) is slightly higher than the value used for simulation (the blue dotted lines), but this is similar for NONMEM/FOCEI (2.8%) and **nlmixr/FOCEI (2.9%)**

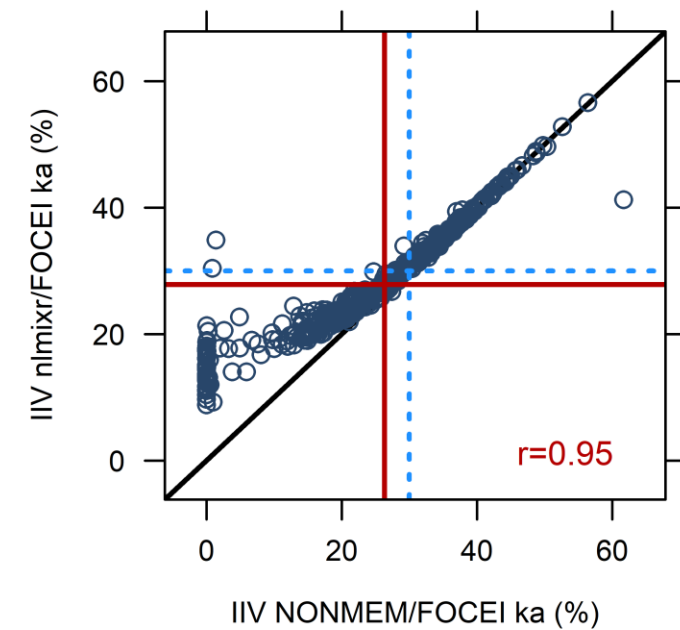
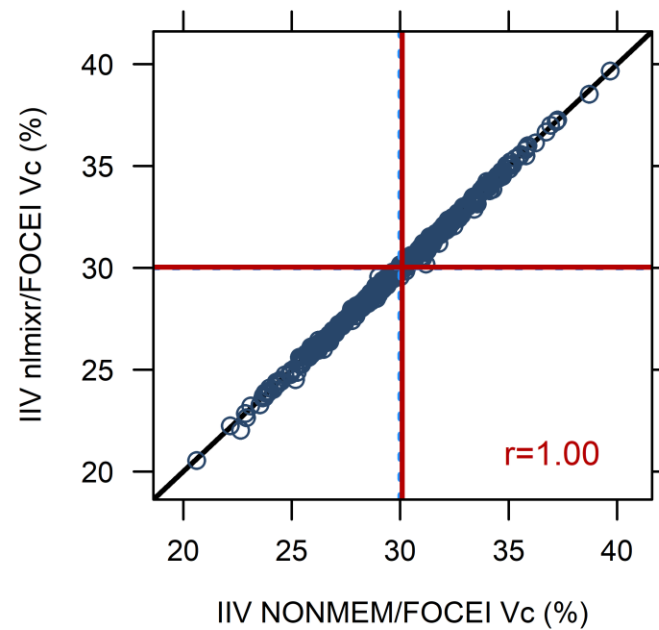
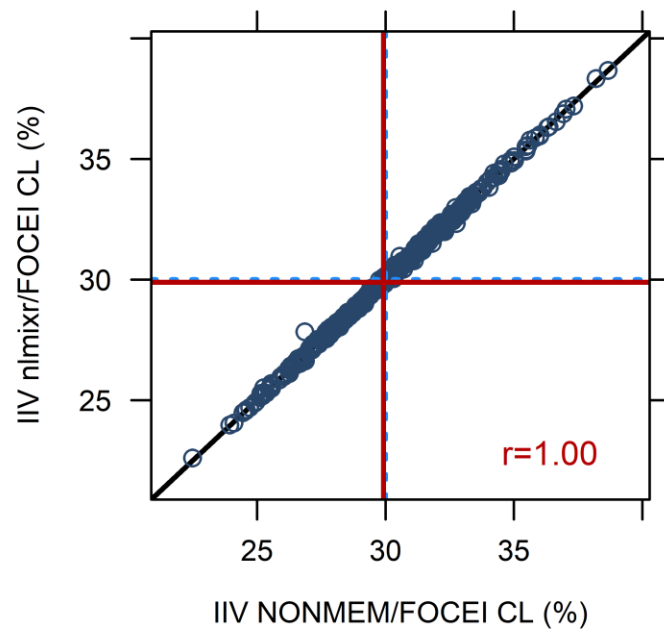


Vc and ka show the same near-perfect correspondence

CL (left column), Vc (middle column), and ka (right column)



Inter-individual variability (IIV) estimates are also highly correlated, but for k_a some IIV values are estimated to be close zero with NONMEM/FOCEI (7.8%), while with **nlmixr**/FOCEI all IIV estimates are non-zero: superiority of **nlmixr**

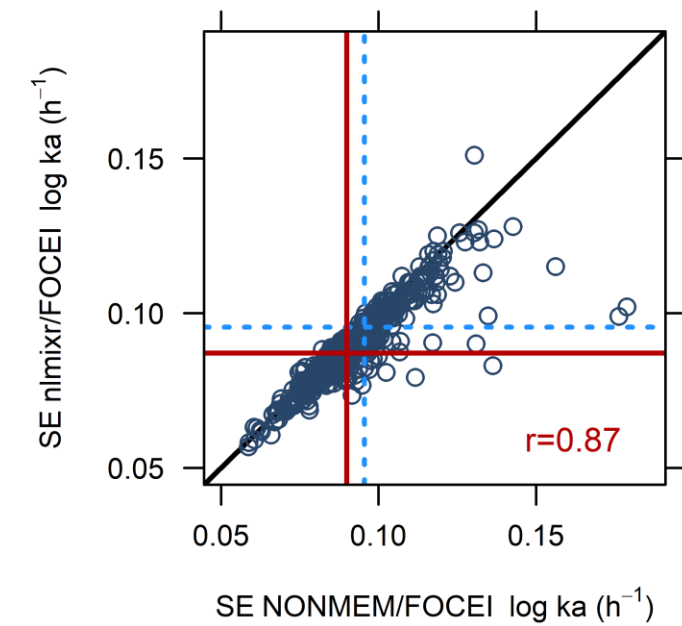
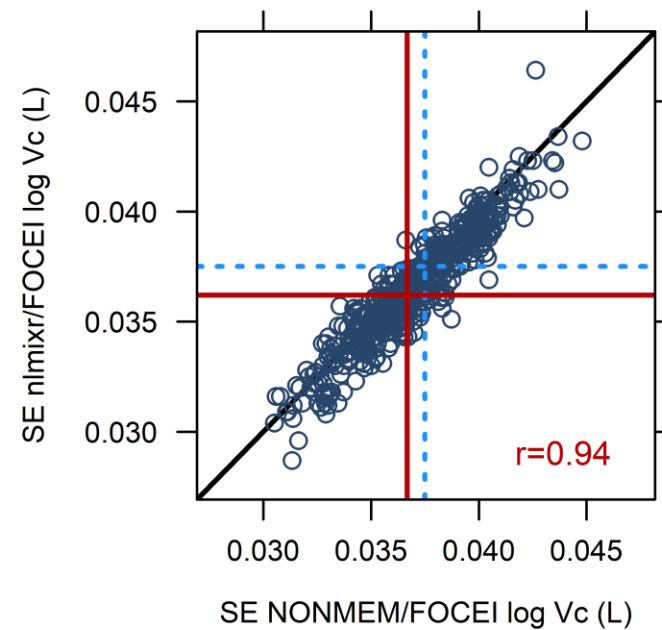
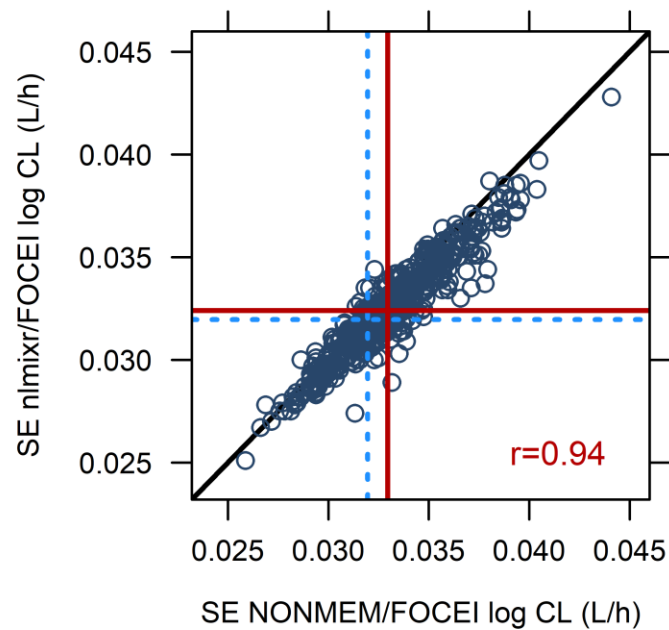


'True' standard errors (SEs) of population parameters can be obtained by estimating the standard deviation of the 500 obtained population estimates

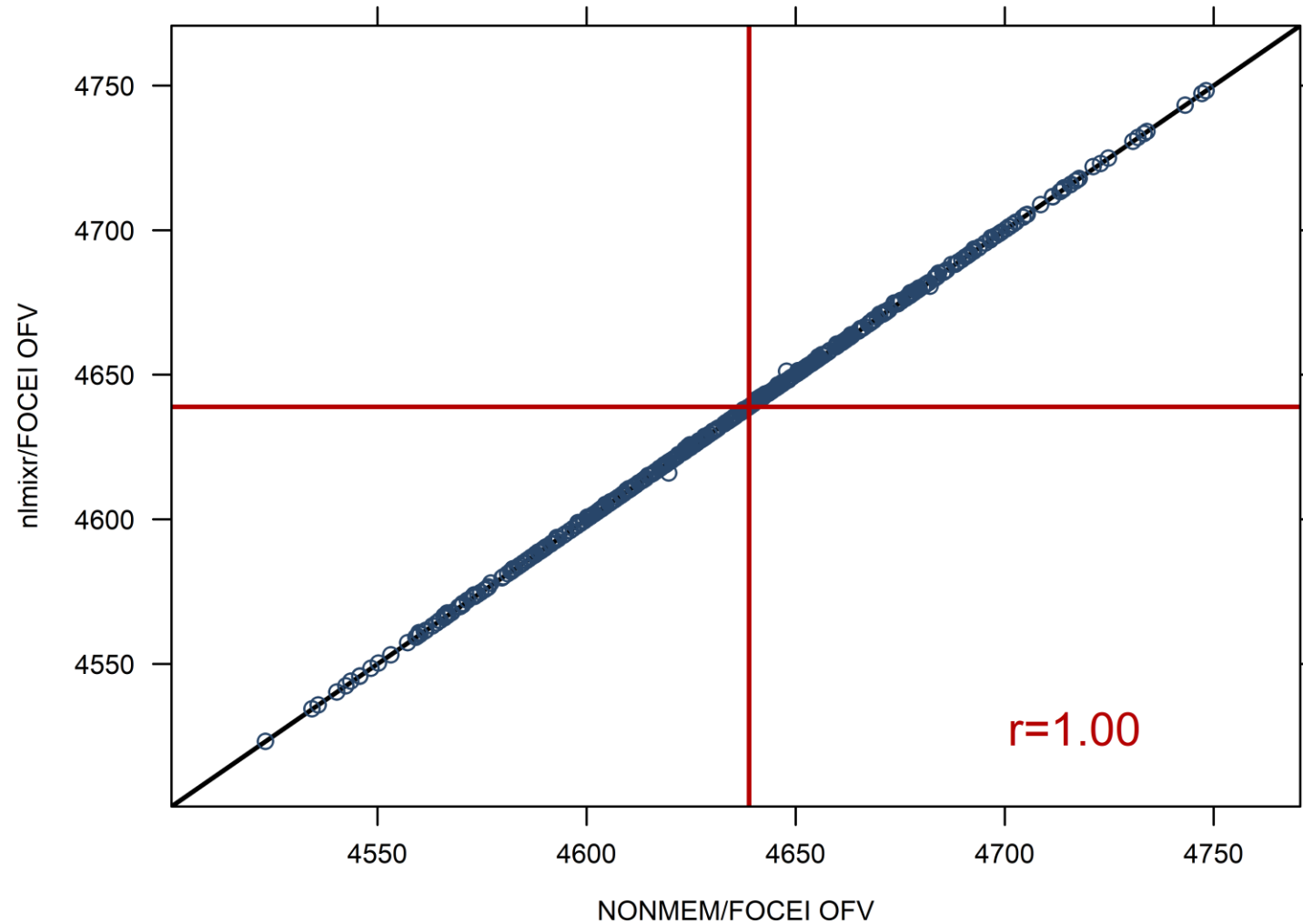
Analysis	SE CL	SE V	SE KA
Monolix/SAEM	0.0344	0.0388	0.1101
nlmixr/SAEM	0.0334	0.0381	0.0986
NONMEM/FOCEI	0.0320	0.0375	0.0955
nlmixr/FOCEI	0.0322	0.0379	0.0952

- Results are consistent across estimation methods and software packages

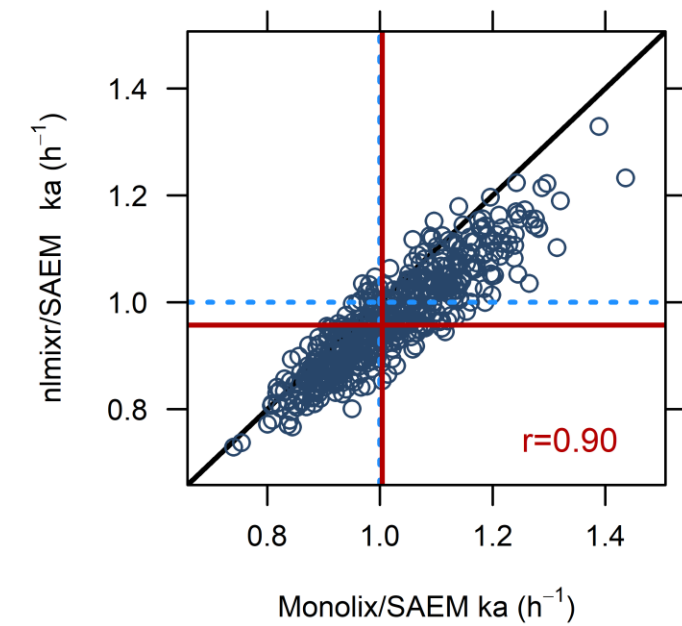
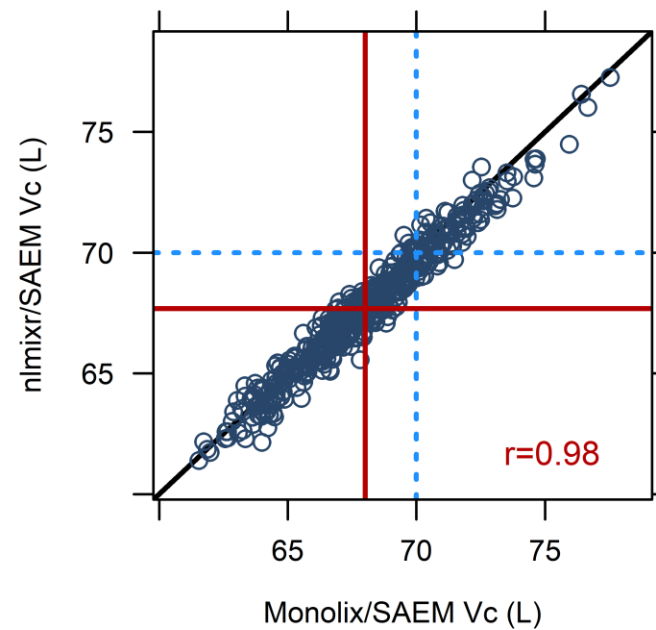
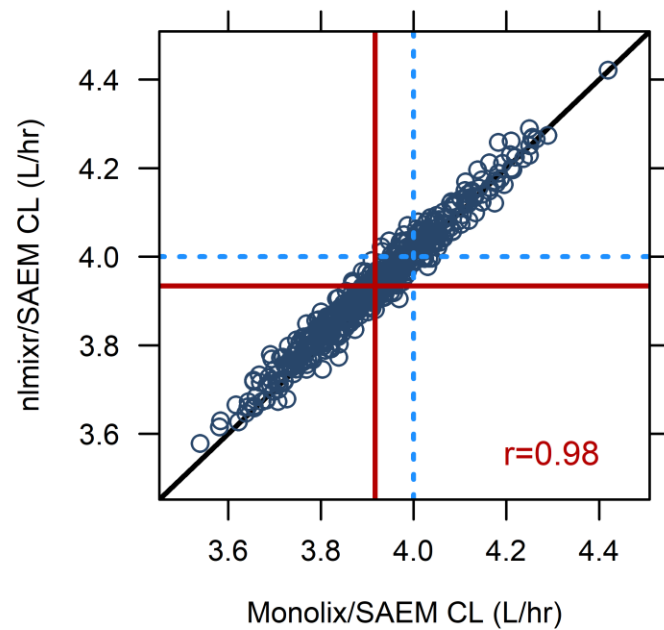
Standard errors for population parameters are also highly correlated, with some outliers for NONMEM/FOCEI



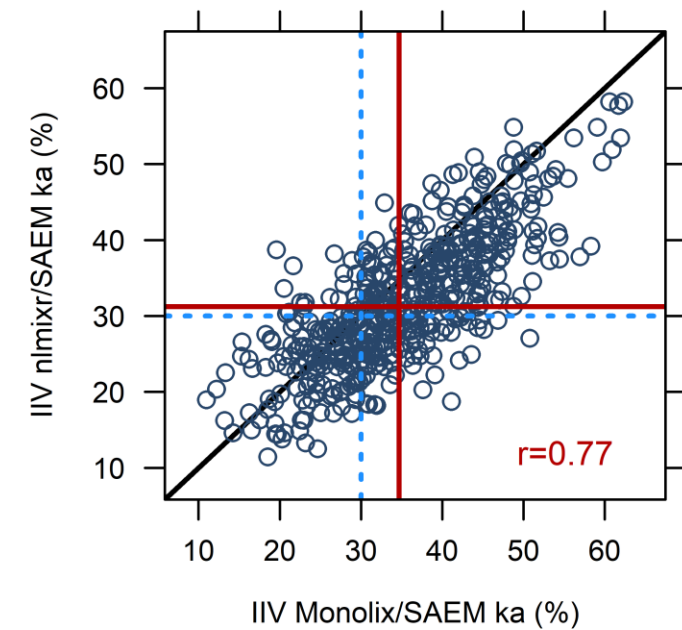
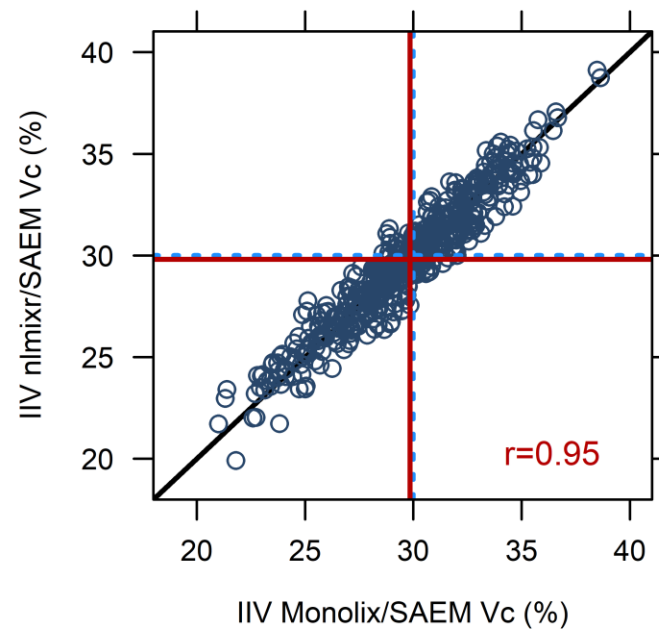
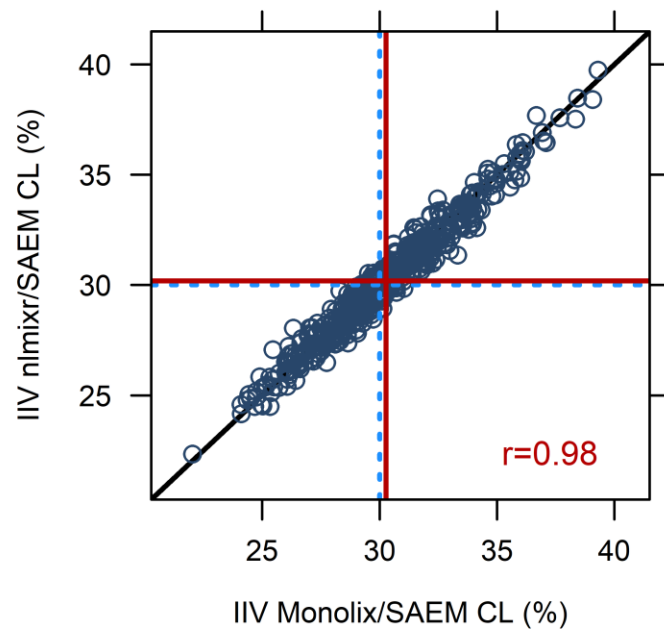
There is a near perfect match for OFV values as well



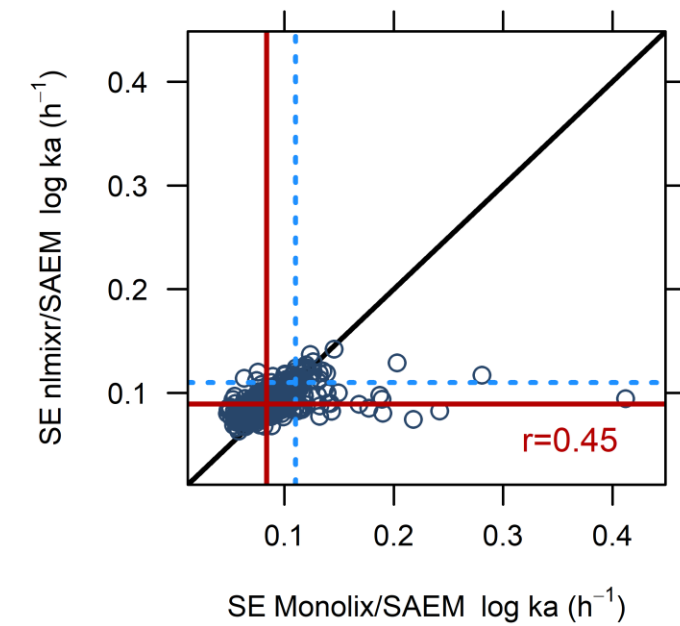
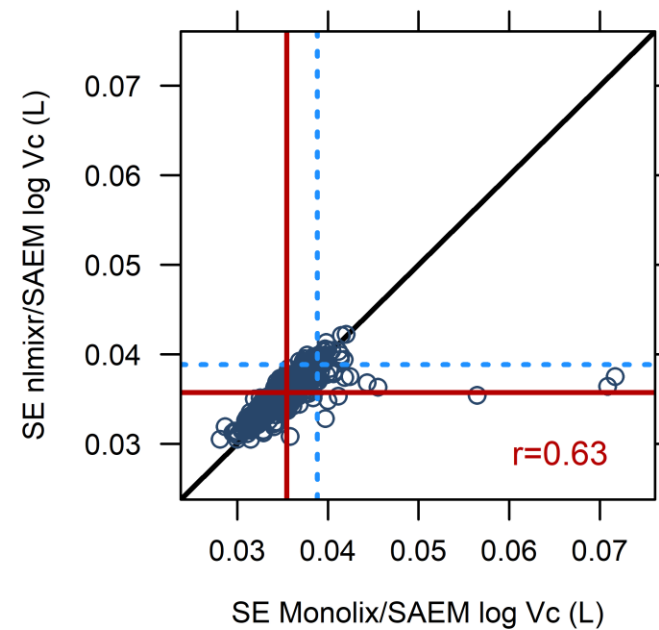
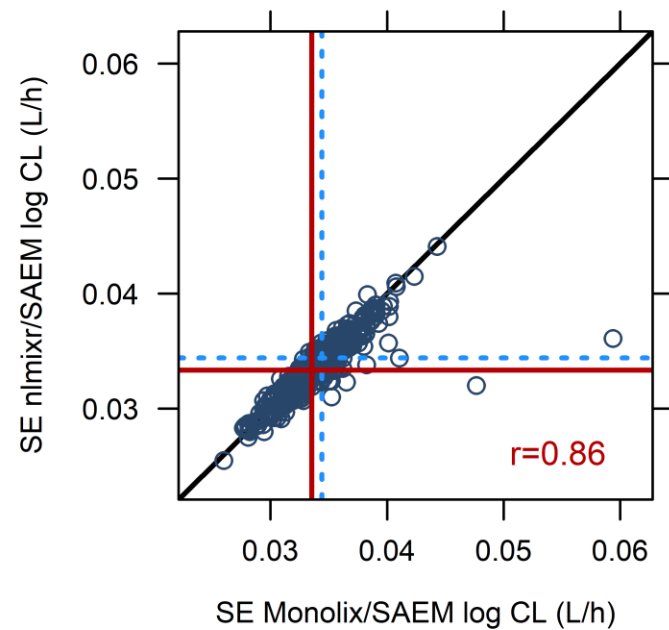
Comparison of nlmixr/SAEM with Monolix/SAEM: high correspondence again, but this time, there is a negative bias in CL that is again similar for Monolix/SAEM (-2.1%) and nlmixr/SAEM (-1.7%)
CL (left column), Vc (middle column), and ka (right column)



Inter-individual variability (IIV) estimates are also highly correlated, and do not provide the close-to-zero IIV pattern for k_a as observed for NONMEM/FOCEI



Standard errors for population parameters estimated using **nlmixr**/SAEM are sufficiently matched with **Monolix**/SAEM estimates, with some outliers for **Monolix**

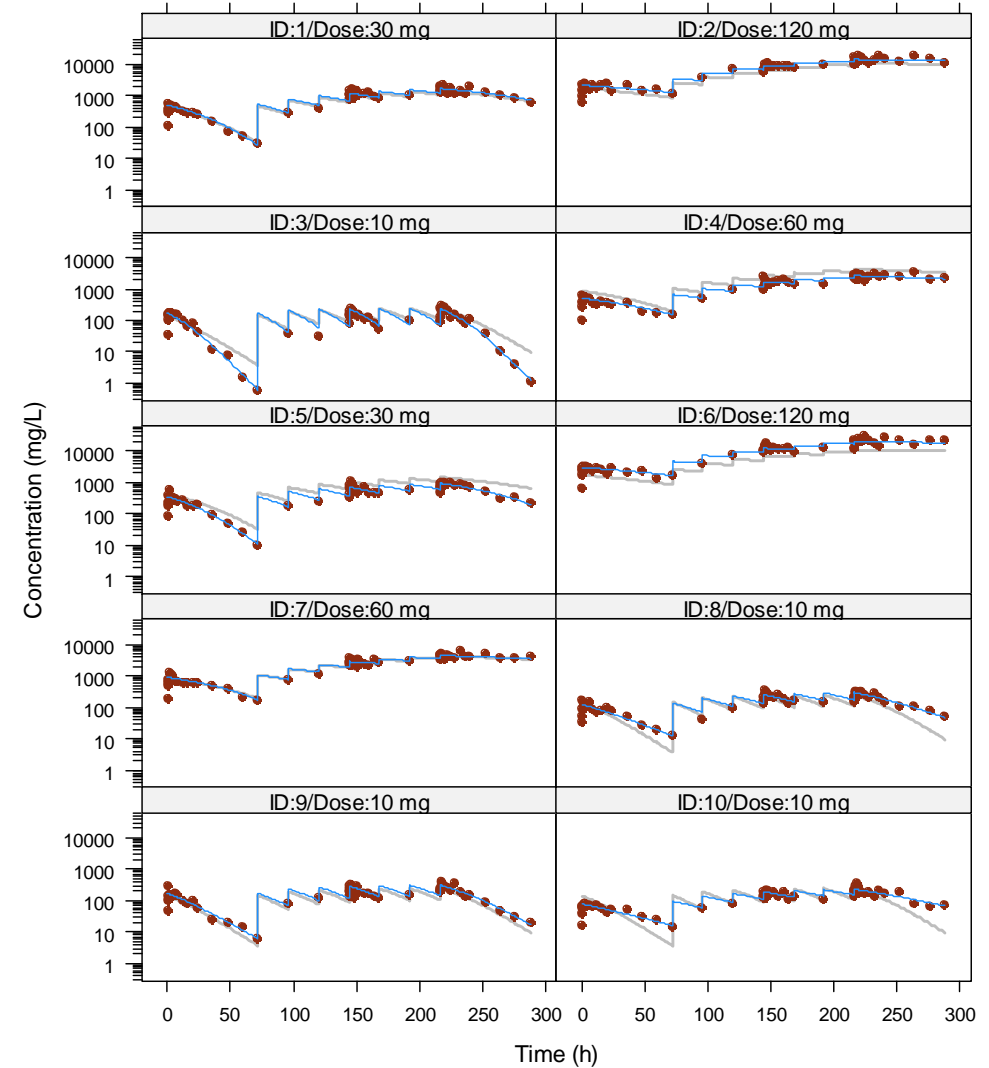
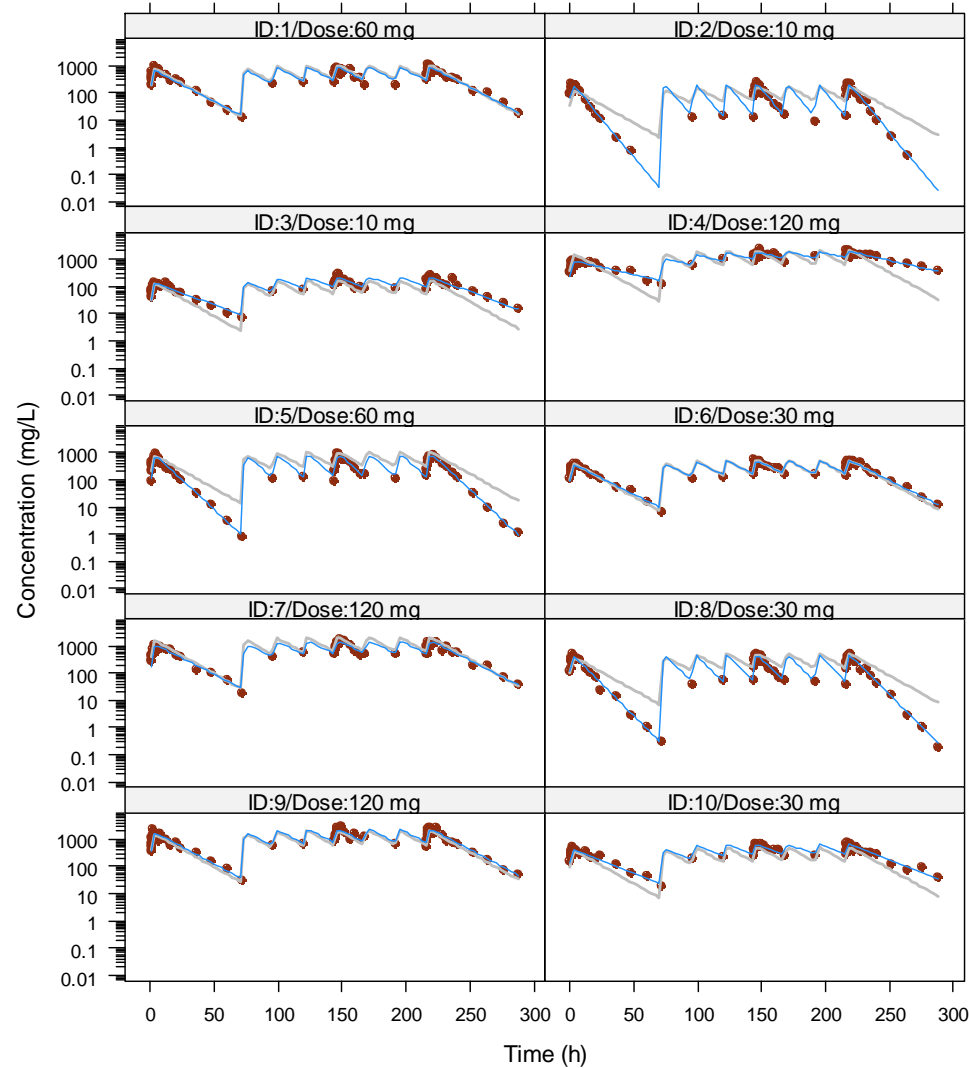


nlmixr performance: rich data

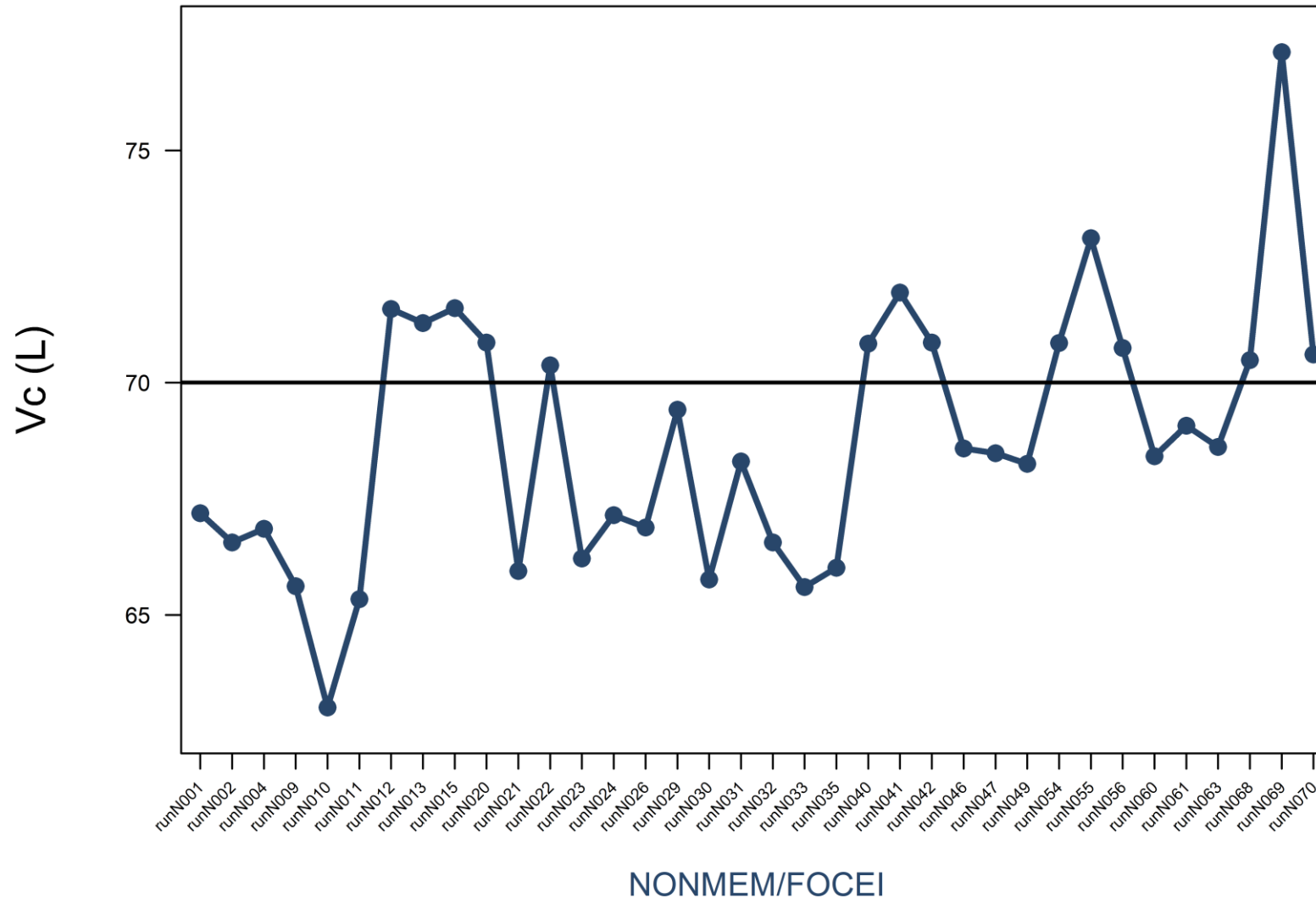
- 4 different dose levels (10, 30, 60 and 120 mg) of 30 subjects each as
 - single dose (over 72h)
 - multiple dose (6 daily doses with full profile at day 4)
 - single and multiple dose combined
- Range of test models:
 - 1- and 2-compartment disposition
 - with and without 1st order absorption
 - linear or Michaelis-Menten (MM) clearance
- A total of 36 test cases
 - all IIVs were set at 30%, residual error at 20%
 - overlapping PK parameters were the same for all models
- nlmixr/FOCEI compared to NONMEM/FOCEI
- nlmixr/SAEM compared to Monolix/SAEM

Example full profiles

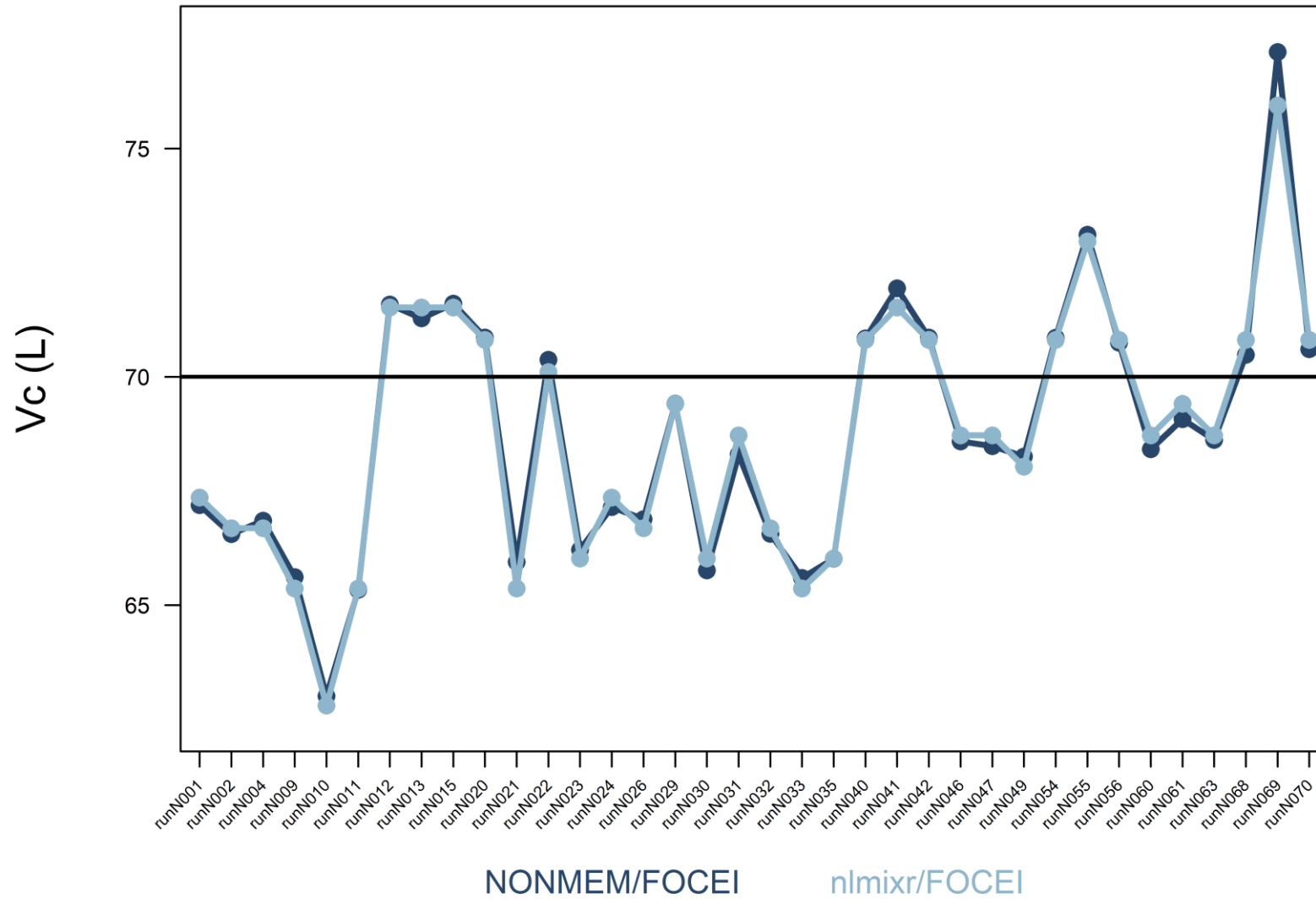
Left: linear elimination, right: MM-elimination



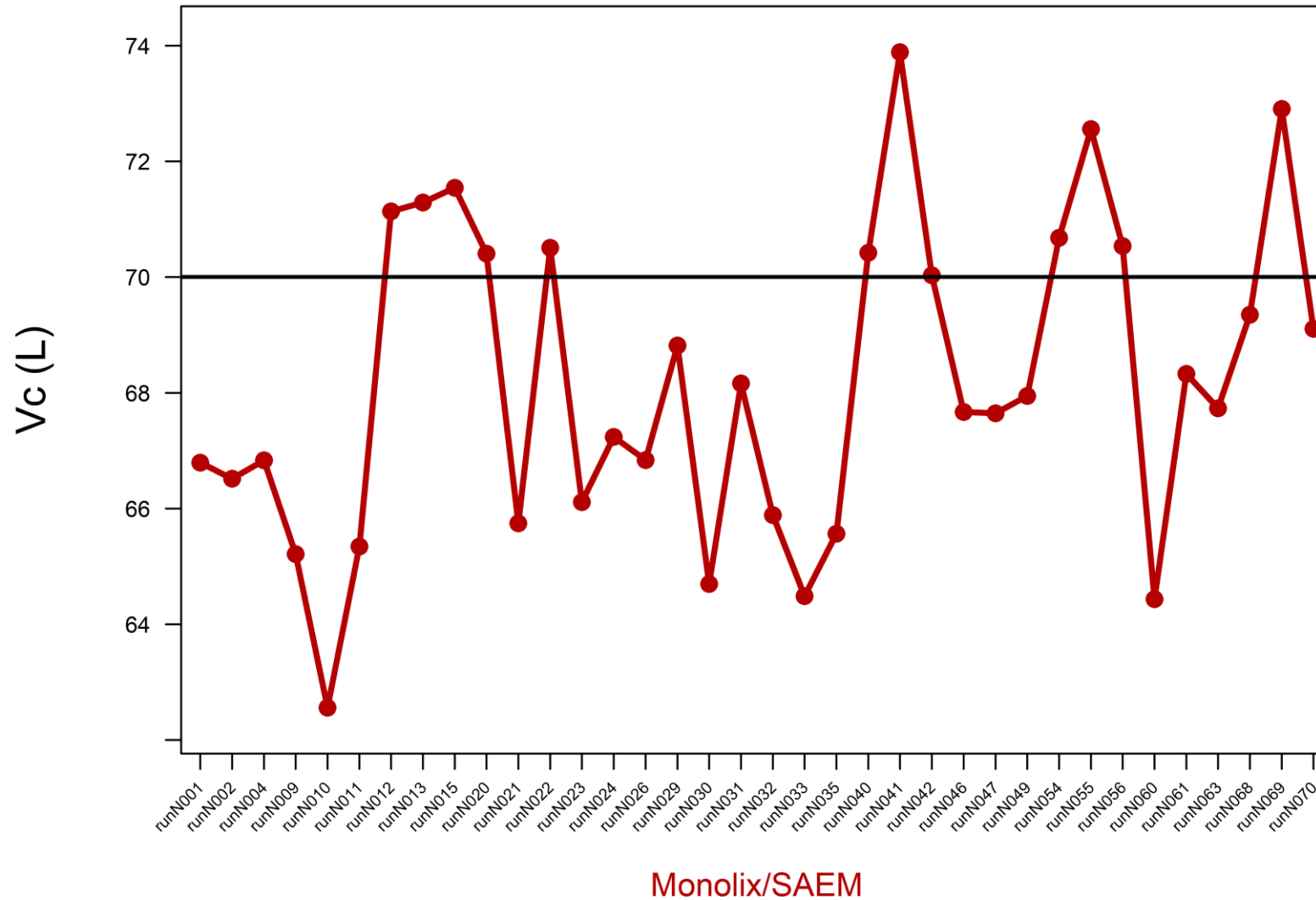
Vc is the parameter that is available in all models: theta estimates using NONMEM/FOCEI
Horizontal black line: value used for simulation



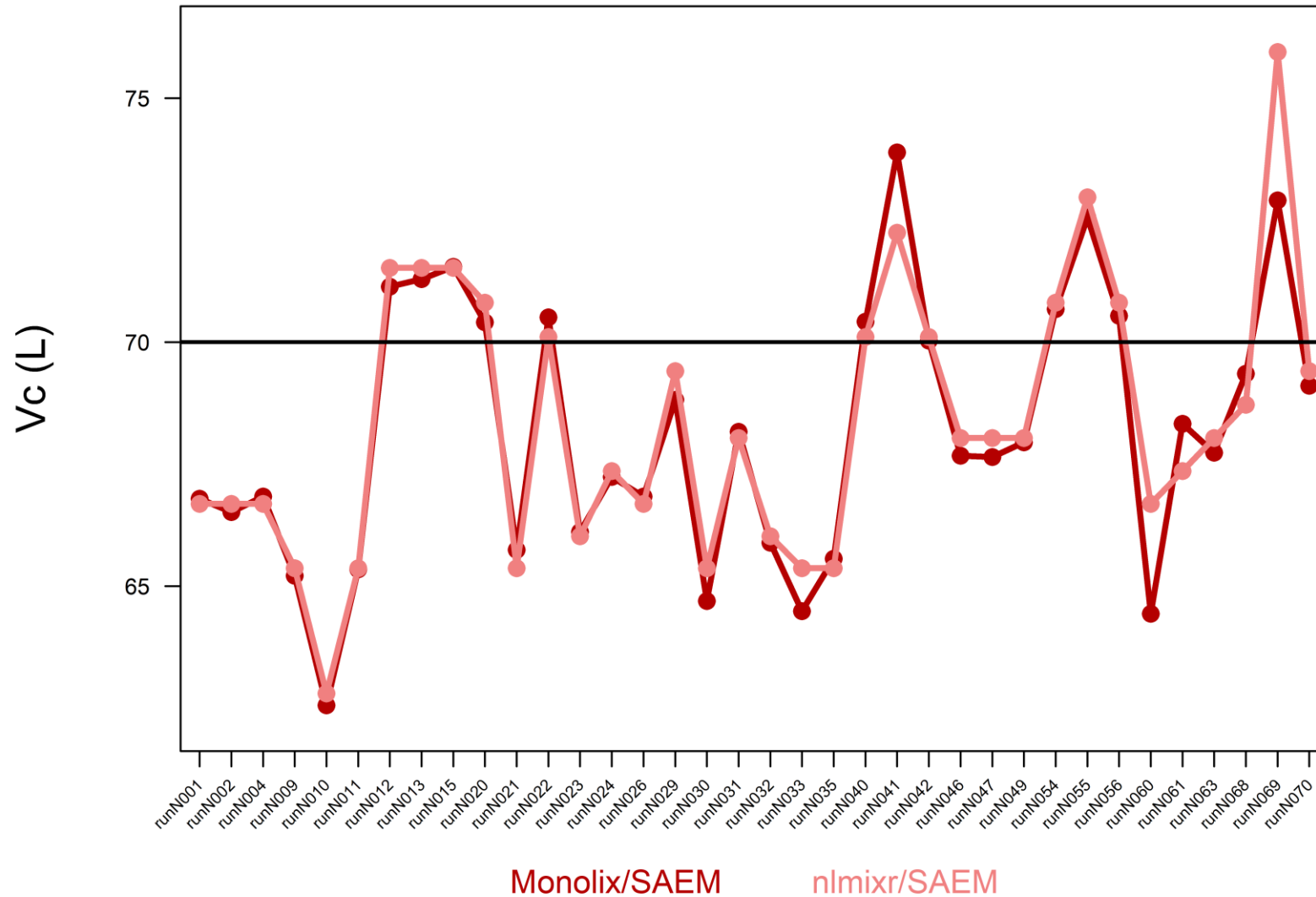
light blue line: nlmixr/FOCEI estimates: near-perfect match



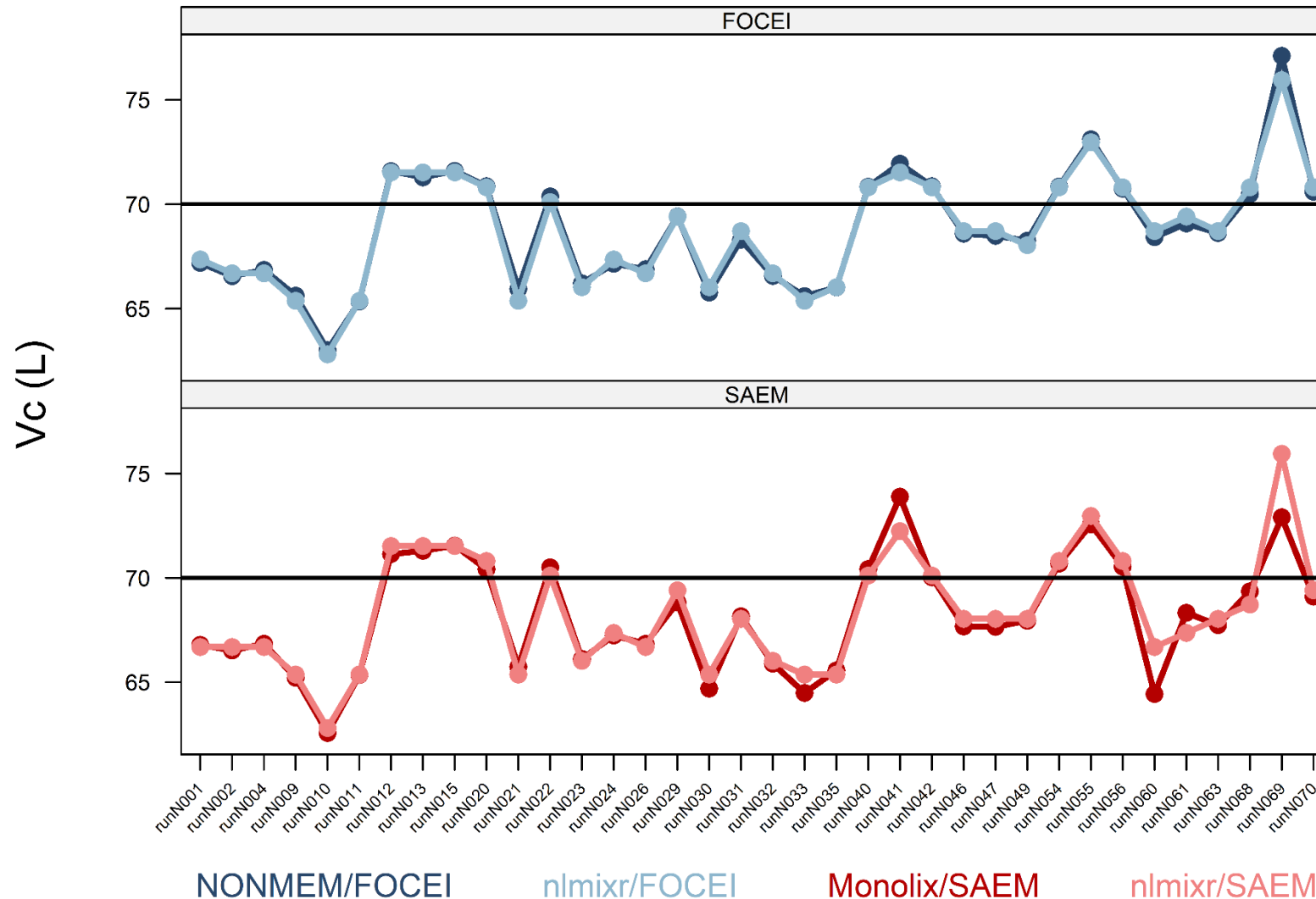
Red line: Monolix/SAEM estimates (using Monolix/SAEM defaults)



Pink line: **nlmixr/SAEM** estimates: near-perfect match



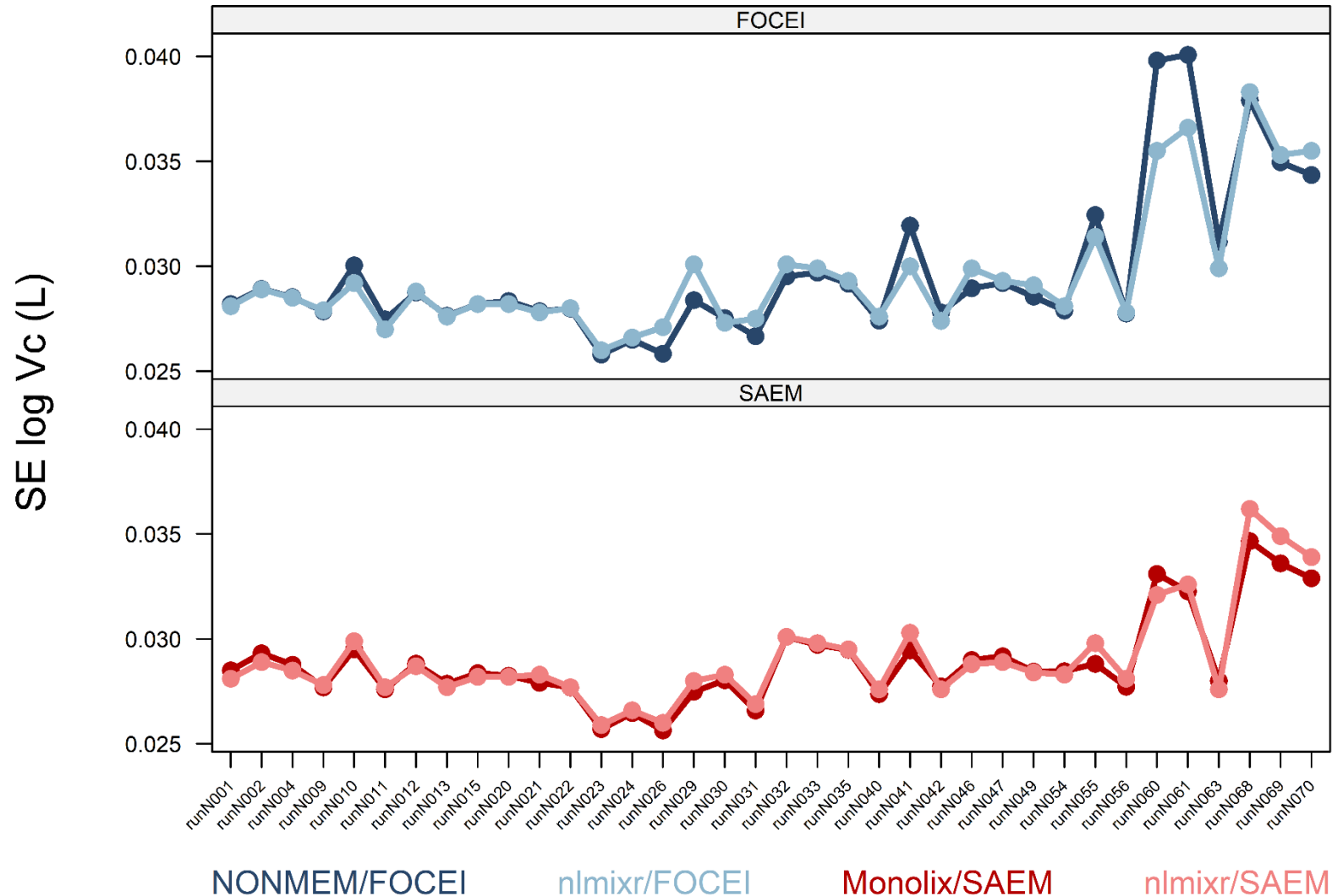
Central volume (V_c): Top panel: FOCEI estimates, bottom panel: SAEM estimates
 Dark lines: NONMEM/MONOLIX, light lines: **nlmixr**



SE of theta estimates for Vc: very good match across software packages

Top panel: FOCEI estimates, bottom panel: SAEM estimates

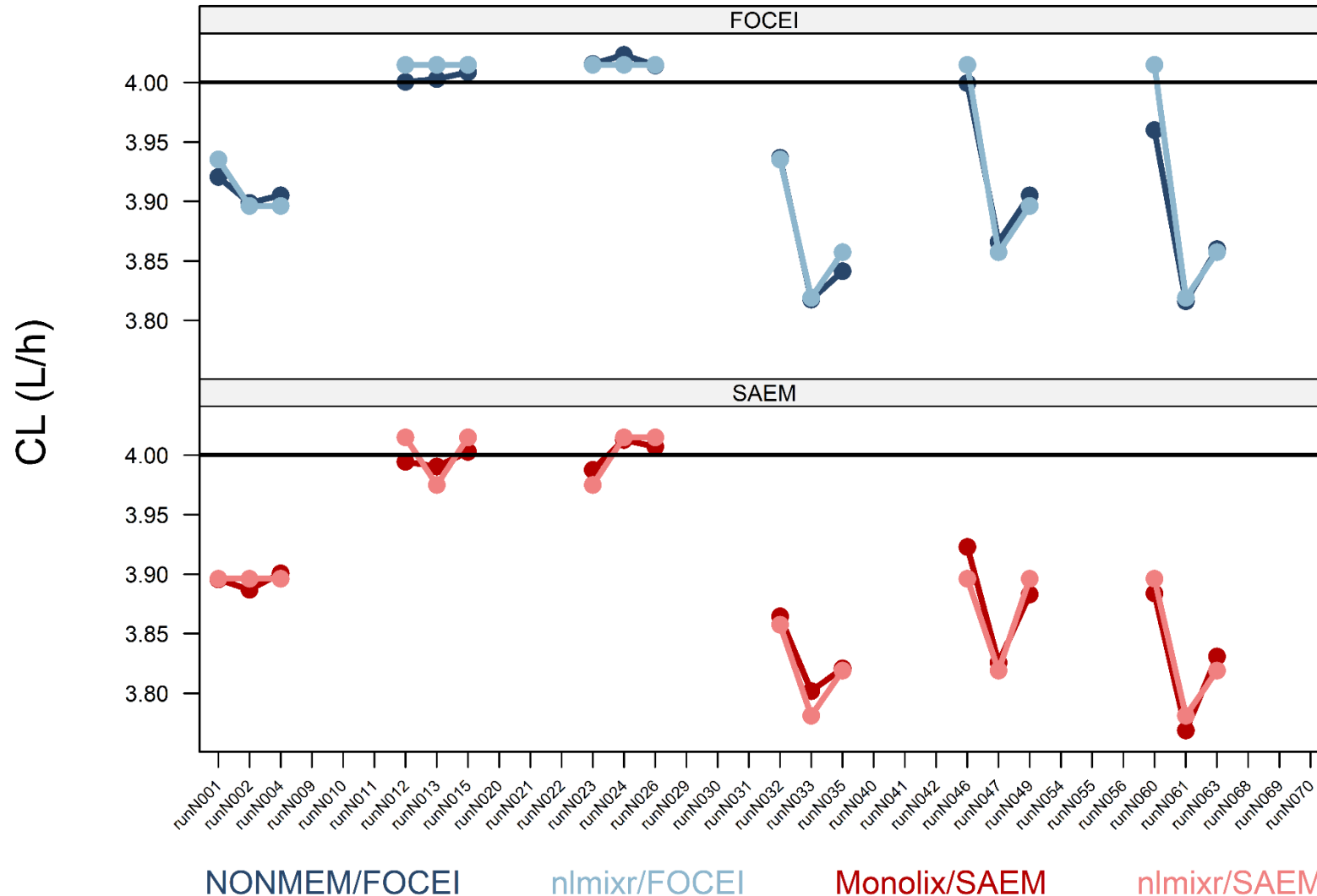
Dark lines: NONMEM/MONOLIX, light lines: **nlmixr**



Theta estimates for CL: very good match across software packages

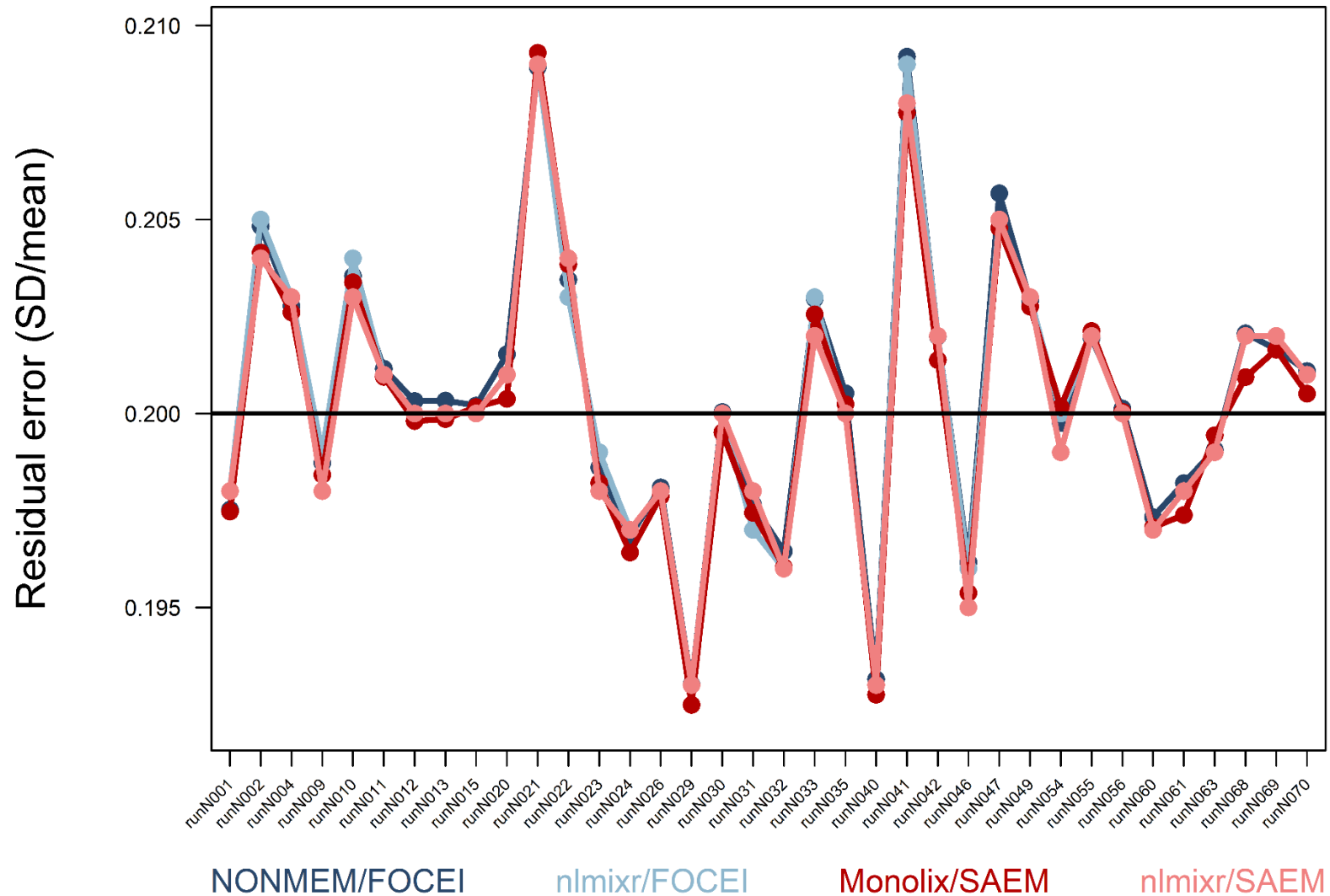
Top panel: FOCEI estimates, bottom panel: SAEM estimates

Dark lines: NONMEM/MONOLIX, light lines: **nlmixr**



Residual error is well-estimated for all algorithms

Horizontal black line: value used for simulation



Single-threaded run times are always shorter for **nlmixr**/FOCEI compared to NONMEM/FOCEI
nlmixr/SAEM is almost always faster than Monolix/SAEM
Parallel processing for **nlmixr** is actively investigated

