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

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Introduction

nlmixr is a freely available open-source package for R [1] that does not depend on any commercial software, and is available on CRAN [2] and GitHub [3]. The package allows structural models to be implemented using a system of ordinary differential equations (ODEs), and allows fully flexible dosing definitions in terms of the type (e.g. bolus doses or infusions), the timing, the number of doses, and their amount, which can vary between individuals. nlmixr builds on RxODE [4], a fast and efficient R package for simulating nonlinear mixed effect models using ODEs, with rapid execution due to compilation in C. Comprehensive online documentation is available [5], and an nlmixr tutorial is in preparation. The package comes with its dedicated project manager shinyMixR [6] that runs in a web-browser, and is linked to xpose [7,8] for graphical exploration and goodness of fit plots.

nlmixr implements a number of parameter estimation algorithms that can be accessed through a common model definition language. These algorithms currently comprise nlme [9], stochastic approximation expectation maximization (SAEM) [10], and first-order conditional estimation with interaction (FOCEI) [11]. Further algorithms and parallel computation are in active development.

For a new tool to be accepted by the pharmacometric modelling and simulation community, it is essential that its estimation algorithms can be demonstrated to perform well and provide results comparable to widely used standards. The question is, can one switch from another package to an nlmixr estimation algorithm and obtain similar results?

Methods

Performances of the SAEM and FOCEI algorithms in nlmixr were compared to those found in the industry standards, Monolix [12] and NONMEM [11], using two scenarios: a simple model fit to 500 sparsely-sampled datasets, and a range of more complex compartmental models with linear and non-linear clearance fit to datasets with rich sampling.

Estimation with sparsely sampled data was investigated for a first-order absorption model with one-compartmental disposition and linear elimination. Single-dose data for 10,000 subjects were simulated, split into four equal-sized dose groups, and four time points were randomly sampled within the 24 hours after the dose. Using the bootstrap tool of PsN [13], 500 datasets containing 120 subjects each were resampled from these 10,000 subjects, stratified by dose so that 30 subjects in each resampled dataset received one of the four doses.

Each resampled dataset was then analysed using the same structural model that was used for simulation, using Monolix's SAEM algorithm, NONMEM's FOCEI algorithm, and nlmixr's SAEM and FOCEI algorithms, to allow a paired comparison for each simulated data set of the analysis outcomes.

Richly sampled profiles were simulated for 4 different dose levels of 30 subjects each, for a range of test models with one- or two-compartmental disposition, oral (first-order absorption), intravenous bolus, or intravenous infusion administration, with either linear or Michaelis-Menten clearance. Inter-individual variability was applied to all pharmacokinetic parameters. Data were simulated for a single administration with sampling over 72 hours (19 samples), seven repeated daily administrations, with 15 samples over 24 hours after the 4th dose, 19 samples over 72 hours after the 7th dose, and 5 trough samples, and the combined single and multiple dose profiles (58 samples). These combinations provided a total of 36 test cases. A similar set of models and data sets was previously used to compare NONMEM and Monolix [14].

Results

Single-thread computational run times were almost always lower for nlmixr/FOCEI compared to NONMEM, but higher for nlmixr/SAEM compared to Monolix (figure 1, left panel). Figure 1, right panel, illustrates that there is a near perfect match in estimated objective function values (OFV) between NONMEM/FOCEI and nlmixr/FOCEI, suggesting that the implementation of FOCEI between the two tools is practically equivalent.

Estimation results obtained from nlmixr for SAEM and FOCEI for the repeated sparse data sets matched corresponding output from Monolix/SAEM (figure 2) and NONMEM/FOCEI (figure 3) closely, both in terms of parameter estimates and associated standard errors, but nlmixr had improved capability to extract non-zero IIV estimates for ka. Results from the 36 data-rich models and data set combinations (figure 4 using Vc: the only parameter that is common to all 36 models) show that the four estimation algorithms provide highly comparable results for population typical estimates, IIV estimates, and SEs of population typical estimates.

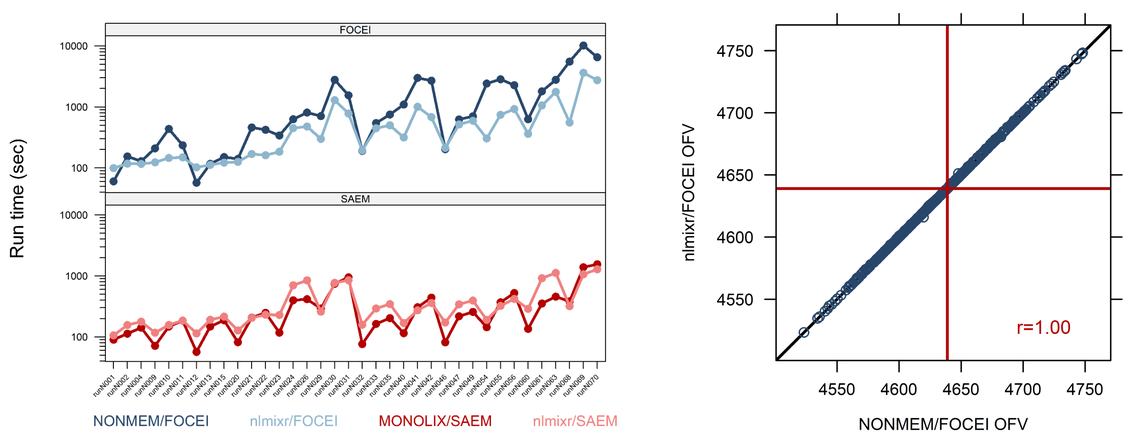

Figure 1. Left: Run times on logarithmic scale using single-thread implementation for the four different estimation algorithms (top: FOCEI, bottom: SAEM). Right: Sparse-data single-model objective function value (OFV) comparison results for nlmixr/FOCEI *vs.* NONMEM/FOCEI.

Conclusions

The FOCEI and SAEM algorithms in nlmixr provide near-identical results to those obtained from NONMEM and Monolix for the same models and data. These results indicate that nlmixr may provide a viable alternative to existing tools for pharmacometric parameter estimation.

References

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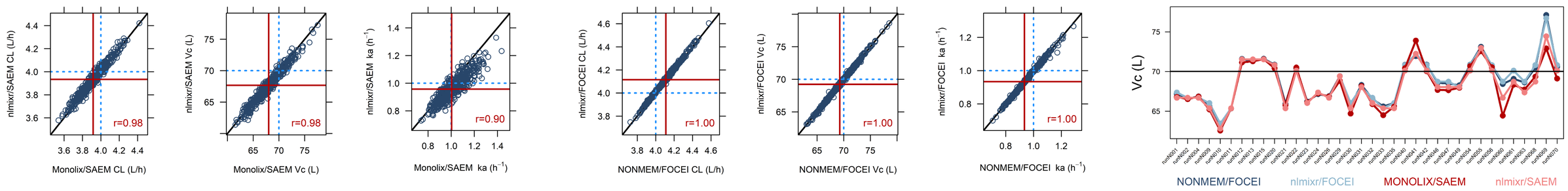

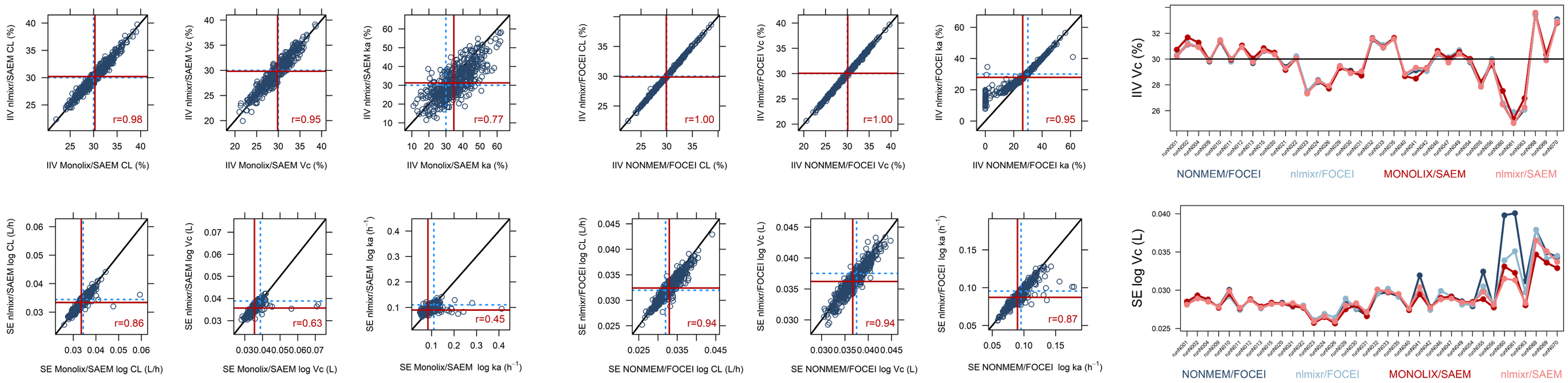

Figure 2. Sparse data analysis results for nlmixr/SAEM *vs.* Monolix/SAEM
Clearance (CL, left column), central volume (Vc, middle column), and absorption rate contant (ka, right column), for population typical parameters (top row), their inter individual variability (IIV, middle row), and the standard error (SE) of their log estimate (bottom row). Dark blue markers: individual paired outcomes for each of the 500 analyses; red lines: median estimated parameter value; blue dotted lines: reference values; black diagonal lines: line of identity.

Figure 3. Sparse data analysis results for nlmixr/FOCEI *vs.* NONMEM/FOCEI
Clearance (CL, left column), central volume (Vc, middle column), and absorption rate contant (ka, right column), for population typical parameters (top row), their inter individual variability (IIV, middle row), and the standard error (SE) of their log estimate (bottom row). Dark blue markers: individual paired outcomes for each of the 500 analyses; red lines: median estimated parameter value; blue dotted lines: reference values; black diagonal lines: line of identity.

Figure 4. Results for central volume (Vc) for 36 models with richly-sampled data sets and multiple models and inputs. Model complexity increases from left to right. Population typical parameters (top), their inter individual variability (IIV, middle), and the standard error (SE) of their log estimate (bottom). Horizontal black line: values used in simulation.