T-012 *nlmixr:* an open-source package for pharmacometric modeling in R

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Introduction

nlmixr is a free open-source R package available on GitHub[1], and soon to appear on CRAN. It builds on RxODE[2], a fast and efficient R package for simulating nonlinear mixed effect models using ordinary differential equations (ODEs). It provides an efficient and versatile way to specify pharmacometric models and dosing scenarios, with rapid execution due to compilation in C. By combining the RxODE core with population-type estimation routines, a versatile R-based pharmacometric eco-system becomes feasible. Currently, estimation routines comprise the nlme[3] package in R, and a Stochastic Approximation Expectation Maximization (SAEM) algorithm[4]. Implementation of First-Order Conditional Estimation with Interaction (FOCE-I)[5], as well as adaptive Gaussian quadrature for odd-type data is under active development. Both closed-form and ODE model definitions are included in nlmixr.

A valuable update is provided by the unified user interface that allows a consistent definition of models, parameters, and parameterizations across estimation routines.

Methods

Richly sampled profiles were simulated for 4 different dose levels (10, 30, 60 and 120 mg) of 30 subjects each as single dose (over 72h), multiple dose (4 daily doses), single and multiple dose combined, and steady state dosing, for a range of test models: 1- and 2-compartment disposition, with and without 1st order absorption, with either linear or Michaelis-Menten (MM) clearance (MM without steady state dosing). This provided a total of 42 test cases. All inter-individual variabilities (IIVs) were set at 30%, residual error at 20% and overlapping PK parameters were the same for all models. A similar set of models was previously used to compare NONMEM and Monolix[6].

Additionally, a sparse data estimation situation was investigated where 500 datasets of 600 subjects each (150 per dose) were generated consisting of 4 random time point samples in 24 hours per subject, using a first-order absorption, 1-compartment disposition, linear elimination model. NONMEM®[5] with FOCE-I was used as a comparator to test the nlme and SAEM estimation routines implemented in nlmixr.

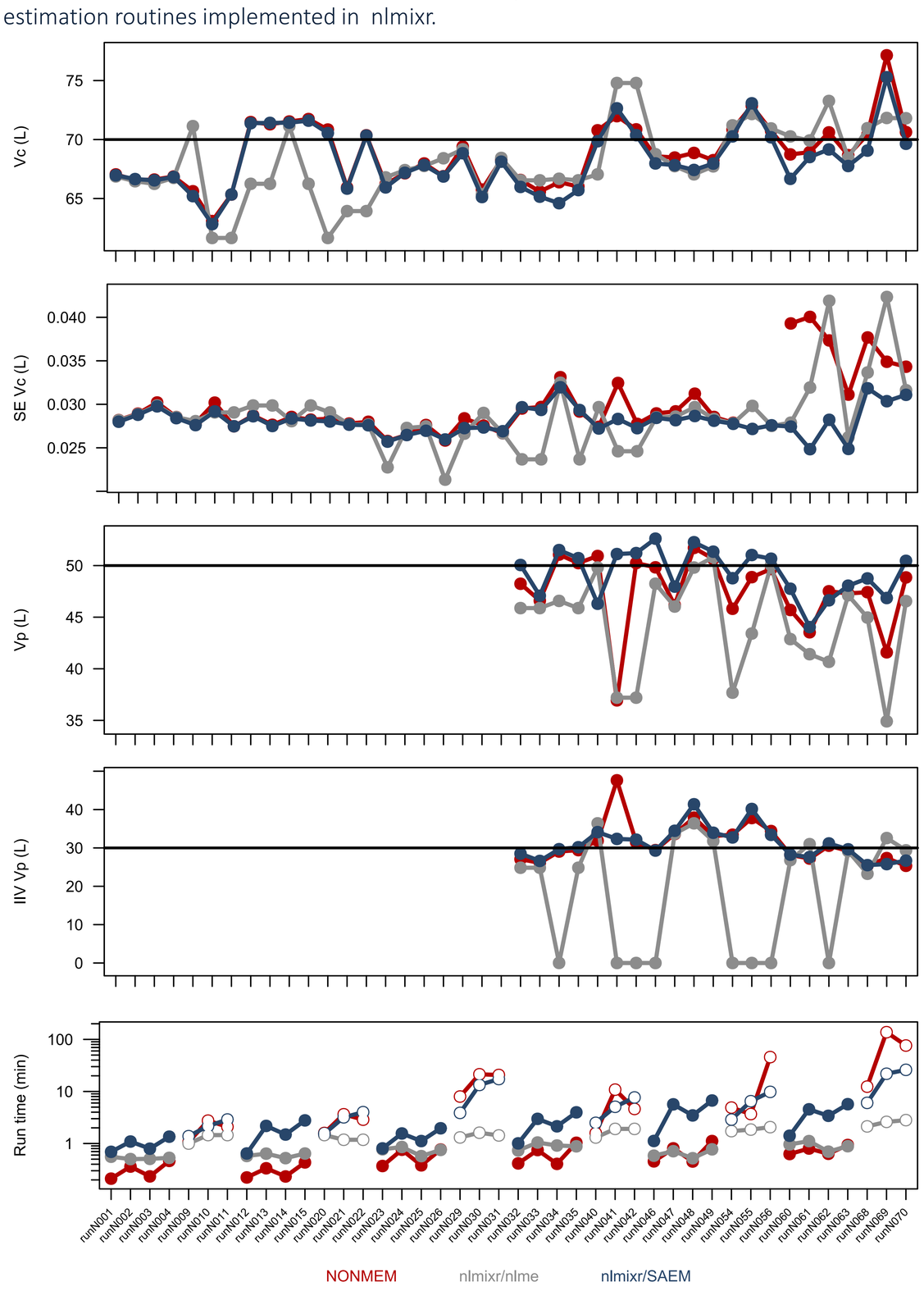

Figure 1. Rich sampling data results: theta estimates for Vc and Vp, standard errors for Vc, IIV estimates for Vp, and log run times for closed-form solution models (closed markes) and ode solution models (open markers), comparing NONMEM (red lines), nlmixr/nlme (grey lines), nlmixr/SAEM (blue lines). Horizontal line: value used for simulation.

Results

For the richly sampled profiles, theta parameter estimates and residual error estimates were comparable across estimation methods, although for some parameters, nlmixr/SAEM results seemed to be closer to the simulated values than either NONMEM or nlmixr/nlme results (see Vp results in Figure 1). Interestingly, standard errors (SEs) were obtained consistently for nlmixr/SAEM where these could not be obtained for some complex models in NONMEM, and SEs seemed to be more consistent for nlmixr/SAEM across models, with increased SEs for NONMEM and nlmixr/nlme estimates for complex models. IIV estimates were regularly estimated close to 0% with nlmixr/nlme, whereas NONMEM and nlmixr/SAEM provided estimates closer to the original simulation values (see Figure 1). For closed-form solutions, NONMEM FOCE-I was the fastest algorithm while for ODEs, NONMEM FOCE-I (single core) was the slowest.

The sparse data analyses indicated a good correlation between NONMEM Ka estimates and both nlmixr/nlme and nlmixr/SAEM estimates (see Figure 2). IIV for Ka was estimated close to zero for 91.1% of the analyses for nlmixr/nlme, for 2.2% for NONMEM, and for 0.0% of the cases for nlmixr/SAEM. These results suggest that at this stage, the nlmixr/SAEM algorithm is a viable alternative to NONMEM-based parameter estimation.

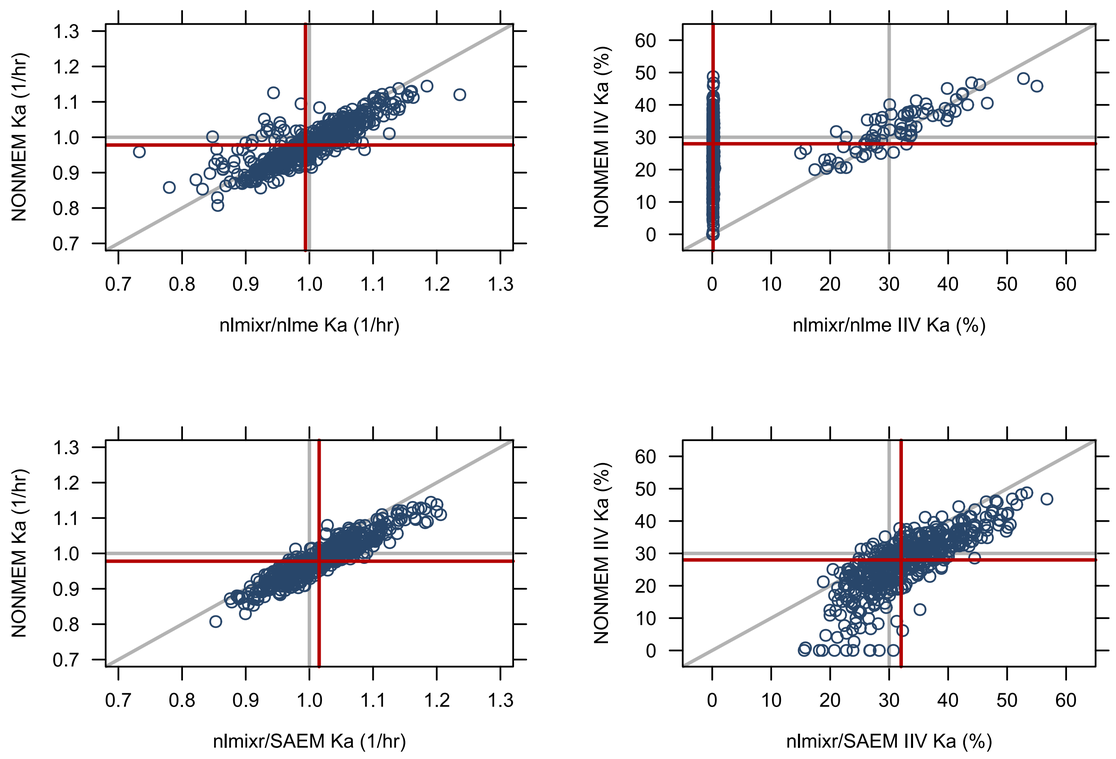

Figure 2. Sparse sampling data results: theta (left), IIV estimates (right) for Ka comparing NONMEM with nlmixr/nlme (top), and nlmixr/SAEM (bottom). Horizontal and vertical red lines: median estimate across 500 replications. Horizontal and vertical grey lines: value used for simulation.

Conclusions

These findings provide further evidence that nlmixr may provide a viable open-source parameter estimation alternative for fitting nonlinear mixed effects pharmacometric models within the R environment.

Example of unified user interface code

```
library(nlmixr)
datr <- read.csv("BOLUS_1CPT.csv", header=TRUE)
datr$EVID <- ifelse(datr$EVID==1,101,datr$EVID)

one.compartment.IV.model <- function(){
    ini({lVc <- log(90)  #log V (L)
         lCl <- 1.6      #log Cl (L/hr)
         prop.err <- c(0, 0.2, 1)
         eta.Vc ~ 0.1    #IIV V
         eta.Cl ~ 0.1    #IIV Cl
    })
    model({ Vc <- exp(lVc + eta.Vc)
            Cl <- exp(lCl + eta.Cl)
        # RxODE-style differential equations are supported
            d/dt(centr) = -(Cl / Vc) * centr;
        # Concentration is calculated
            cp = centr / Vc;
        # And is assumed to follow proportional error estimated by prop.err
            cp ~ prop(prop.err)
        # for closed form solutions, the above six lines (three lines of code) are replaced by:
        #   linCmt() ~ prop(prop.err)
        # the exact compartmental model is automatically determined by the defined parameters
    })}
# Running SAEM:
fit_saem <- nlmixr(one.compartment.IV.model,data,est="saem",control=saemControl(n.burn=200,n.em=300,print=50))
# Running nlme:
fit_nlme <- nlmixr(one.compartment.IV.model,data,est="nlme",control=nlmeControl(pnlsTol = .01))
```

References

[1]https://github.com/nlmixrdevelopment/nlmixr
[2]Wang W *et al.* A Tutorial on RxODE. CPT:PSP (2016) 5, 3–10.
[3]Pinheiro J *et al.* (2016). nlme: Linear and Nonlinear Mixed Effects Models [R package]
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[6]Laveille C *et al.* PAGE 17 (2008) Abstr 1356 [www.pagemeeting.org/?abstract=1356]

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