nlmixr: an open-source package for pharmacometric modelling in R

Rik Schoemaker[1], Yuan Xiong[2], Justin Wilkins[1], Christian Laveille[3], Wenping Wang[4]
[1]Occams, The Netherlands, [2]Certara Strategic Consulting, USA, [3]Calvagone, France, [4]Novartis Pharmaceuticals, USA

Now on github!
https://github.com/nlmixrdevelopment/nlmixr

Aims

nlmixr is an open-source R package under development that builds on both *RxODE*[1], an R package for simulation of nonlinear mixed effect models using ordinary differential equations (ODEs), and the *nlme*[2] package in R, for parameter estimation in nonlinear mixed effect models. ***nlmixr*** greatly expands the utility of *nlme* by providing an efficient and versatile way to specify pharmacometric models and dosing scenarios, with rapid execution due to compilation in C++. NONMEM®[3] with first-order conditional estimation with interaction was used as a comparator to test ***nlmixr***.

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[4]. Estimates of population parameters, standard errors for fixed-effect parameters, and run times were compared both for closed-form solutions and using ODEs.

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.

Example code

```
library(nlmixr)
datr<-read.csv("BOLUS_1CPT.csv", header=TRUE)
datr$EVID<-ifelse(datr$EVID==1,101,datr$EVID)
specs<-list(fixed=lCL+lV~1,random=pdDiag(form=lCL+lV~1),start=c(lCL=1.6,lV=4.5))

#Closed-form:
fit<-nlme_lin_cmpt(datr,par_model=specs,ncmt=1,oral=FALSE,weight=varPower(fixed=c(1)))

#ODE:
ode <- "d/dt(centr)  = -(CL/V)*centr;"
mypar <- function(lCL, lV )
  {CL = exp(lCL)
   V  = exp(lV)}
fitODE<-nlme_ode(datr,model=ode,par_model=specs,par_trans=mypar,response="centr",
                 response.scaler="V", weight=varPower(fixed=c(1)),
                 control=nlmeControl(pnlsTol=.1))
```

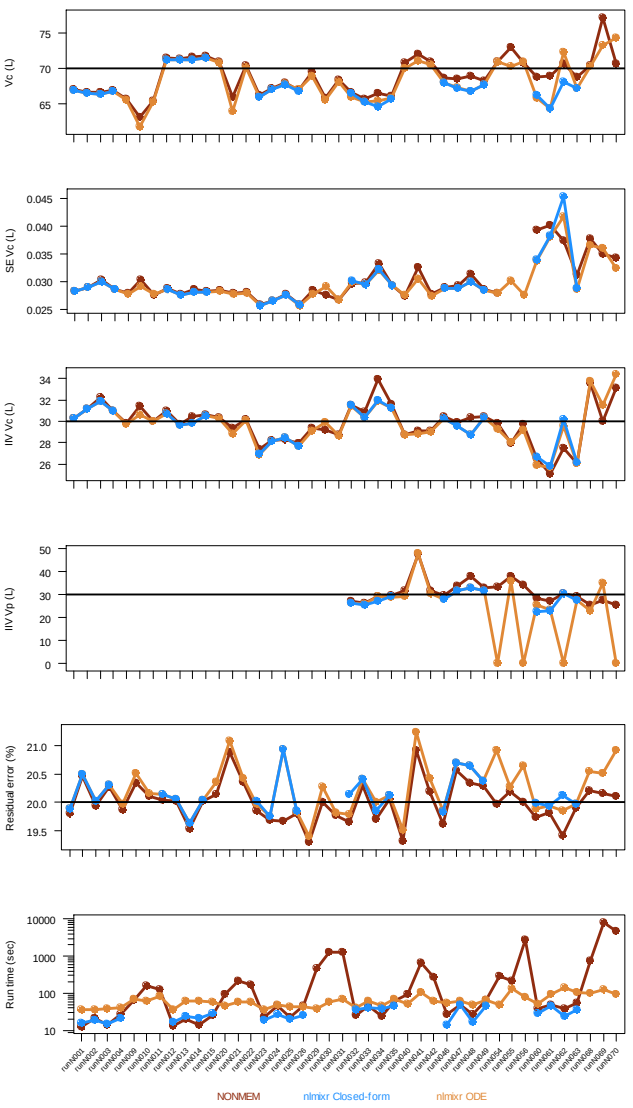

Figure 1. Theta, SE, and IIV estimates for Vc, IIV estimates for Vp, residual error, and log run times comparing NONMEM (red lines, closed form where possible), ***nlmixr*** using ODEs (orange lines) and closed-form ***nlmixr*** (blue lines). Horizontal lines: values used for simulation.

Results

Theta parameter estimates were comparable across estimation methods applied to rich data. **Figure 1** provides results for central volume of distribution (Vc) as illustration because it is the single parameter present in all models. Standard error estimates were obtained for all ***nlmixr*** models, but not all NONMEM models. IIV estimates were regularly estimated close to 0% for ill-defined model parameters like peripheral volume (Vp) in ***nlmixr***, whereas NONMEM provided estimates closer to the original simulation values. In comparison to NONMEM, ***nlmixr*** was always faster for ODEs (MM-models) and comparable for closed-form models.

The sparse data analyses indicated a bias in values for clearance (CL) and volume (Vc) both for NONMEM and for ***nlmixr***, but bias was much more pronounced for ***nlmixr*** (see **Figure 2**). IIV for absorption constant (Ka) was estimated close to zero for 91.1% of the analyses for ***nlmixr*** and only 2.2% for NONMEM.

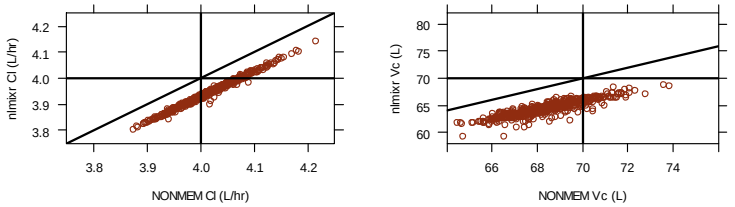

Figure 2 Population estimates for CL (left) and Vc (right) using NONMEM and ***nlmixr***. Horizontal and vertical lines: simulated value. Diagonal line: line of identity.

Conclusions

These findings suggest that nlmixr provides a viable open-source parameter estimation procedure for nonlinear mixed effects pharmacometric models within the R environment. Implementation of alternatives to the nlme estimation routine may be warranted for analysis of sparse data.

References

[1]Wang W *et al.* A Tutorial on RxODE. CPT:PSP (2016) 5, 3–10.
[2]Pinheiro J *et al.* (2016). nlme: Linear and Nonlinear Mixed Effects Models.
[3]Beal SL *et al.* 1989-2011. NONMEM Users Guides. Icon Development Solutions, USA.
[4]Laveille C *et al.* PAGE 17 (2008) Abstr 1356 [www.pagemeeting.org/?abstract=1356]

www.OCCAMS.eu