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

Uppsala University Presentation

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The nlmixr development team:

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nlmixr is an open-source R package

- Written by Wenping Wang and available on GitHub:
  - builds on RxODE, an R package for simulation of nonlinear mixed effect models using ODEs
  - combined with nlme, an R package for parameter estimation in nonlinear mixed effect models
  - but also gnlmm and SAEM estimation routines…
- nlmixr provides an efficient and versatile way to specify pharmacometric models (closed-form and ODEs) and dosing scenarios, with rapid execution due to compilation in C

- NONMEM® with first-order conditional estimation with interaction was used as a comparator to test nlmixr

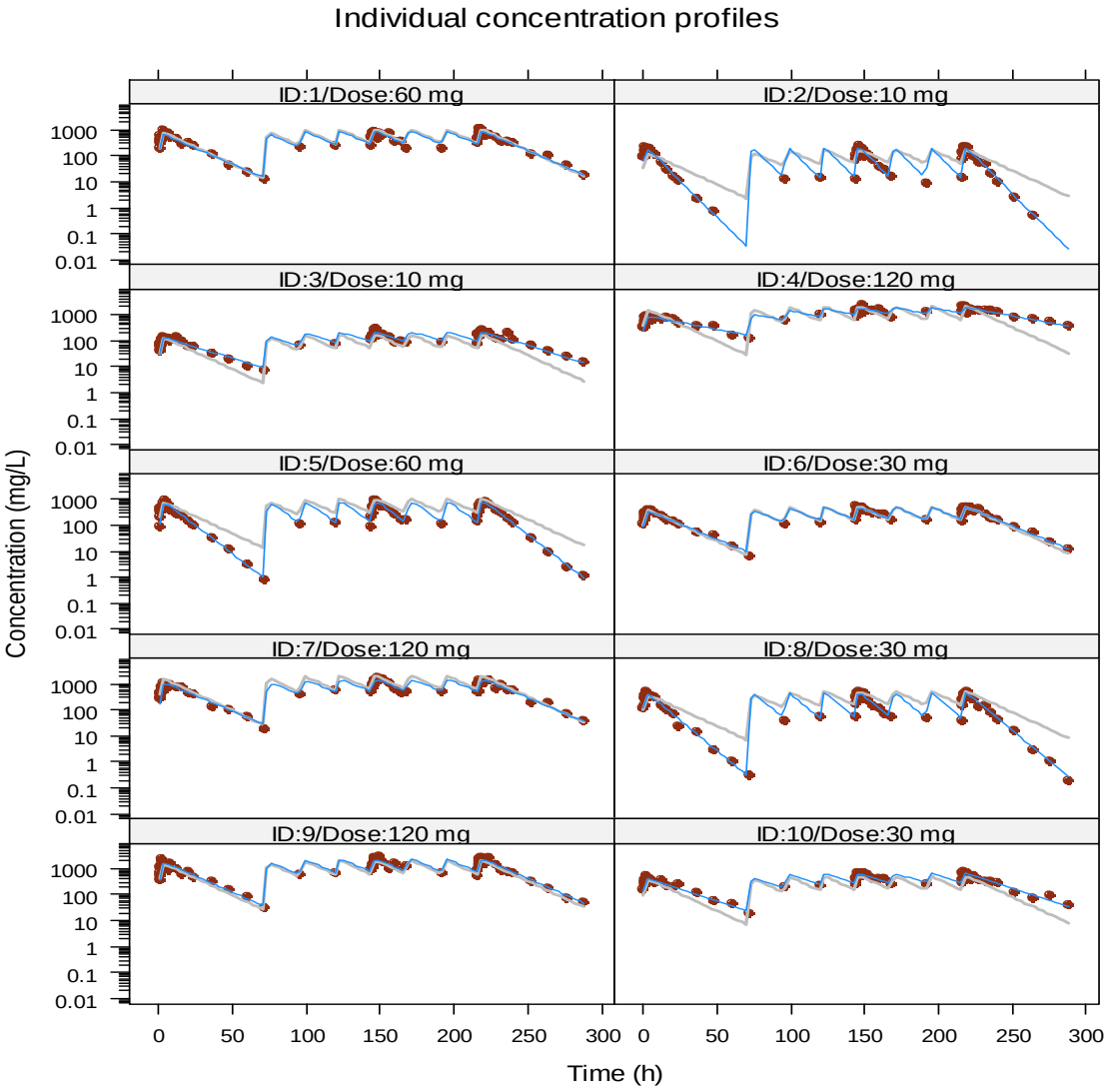
Example syntax

```
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))
```

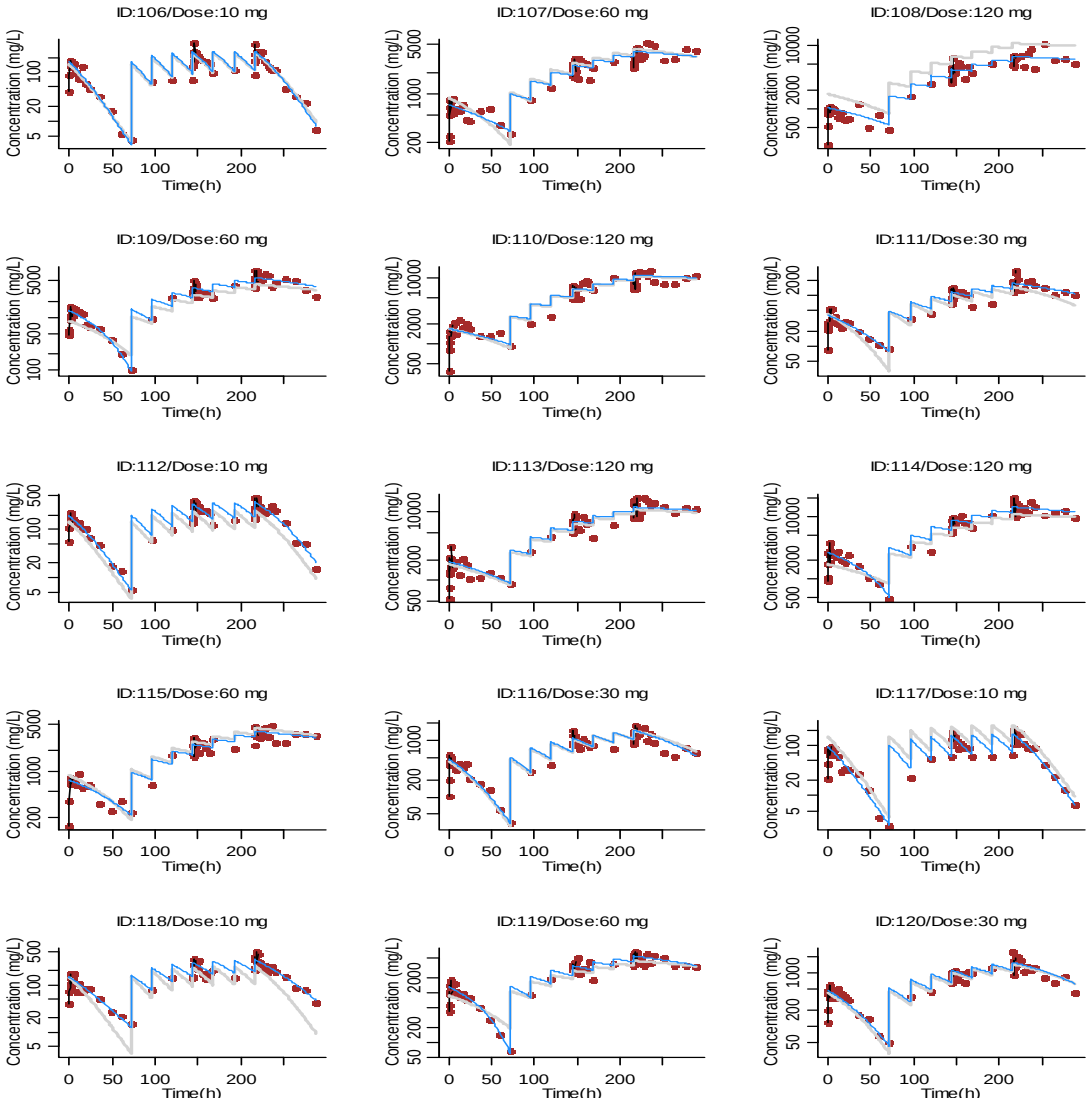
Rich data sets

- 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
- Range of test models:
  - 1- and 2-compartment disposition
  - with and without 1st order absorption
  - linear or Michaelis-Menten (MM) clearance
- A total of 42 test cases
  - all IIVs were set at 30%, residual error at 20%
  - overlapping PK parameters were the same for all models

Example full profiles (linear elimination)



Example full profiles (MM elimination)



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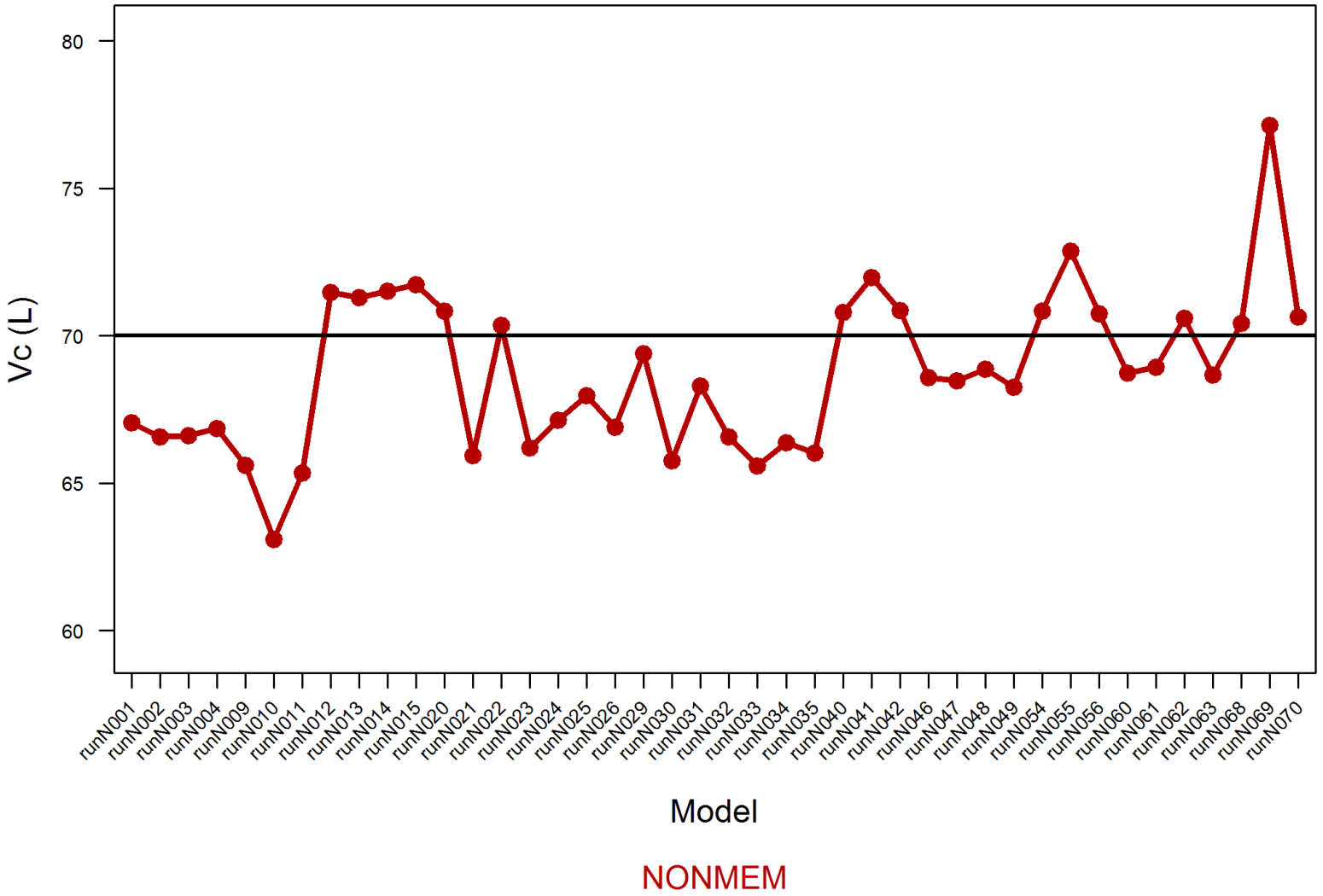
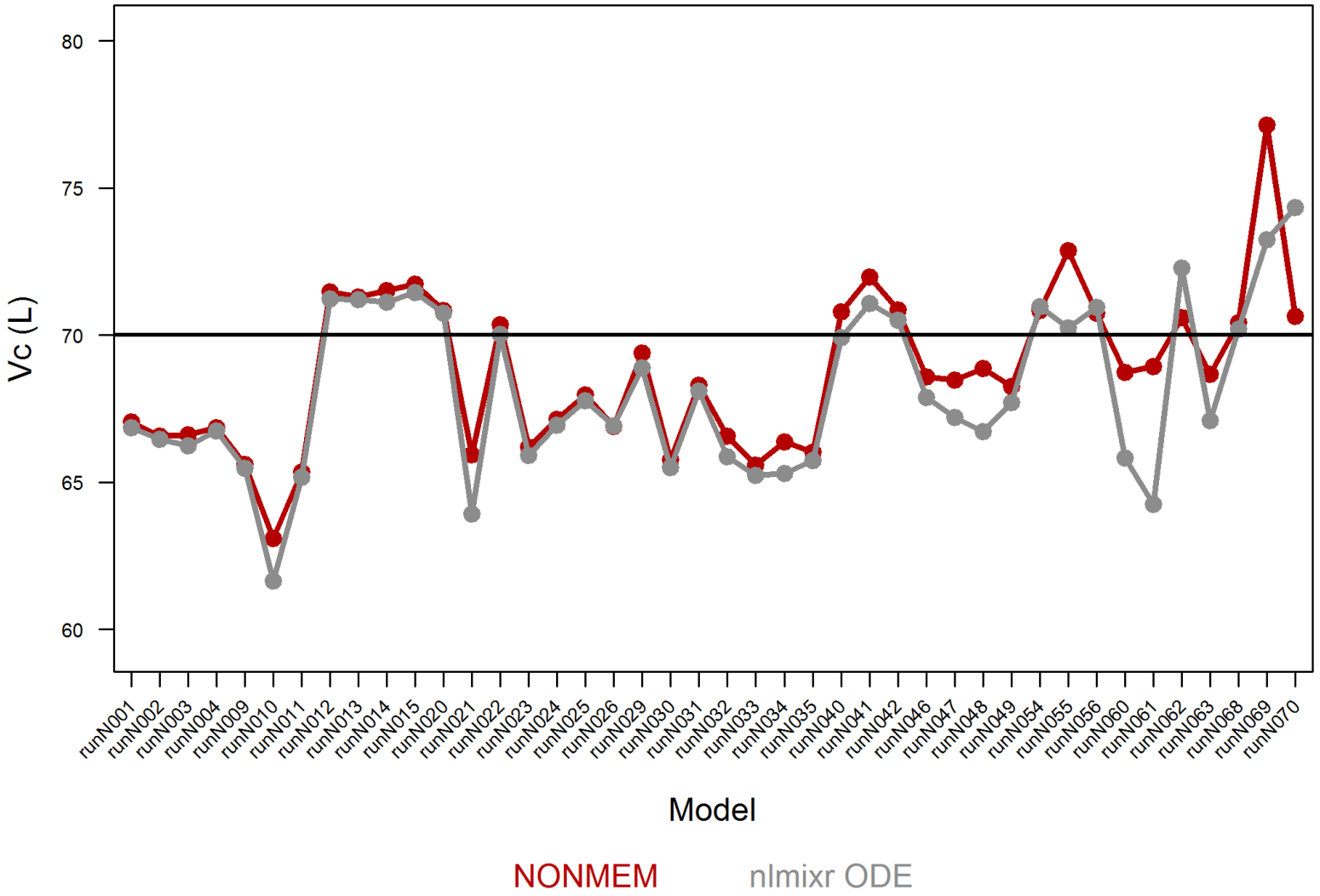
Vc is available in all models: Theta estimates using NONMEM

Horizontal black line: value used for simulation



Grey line: nlmixr/nlme estimates using ODEs



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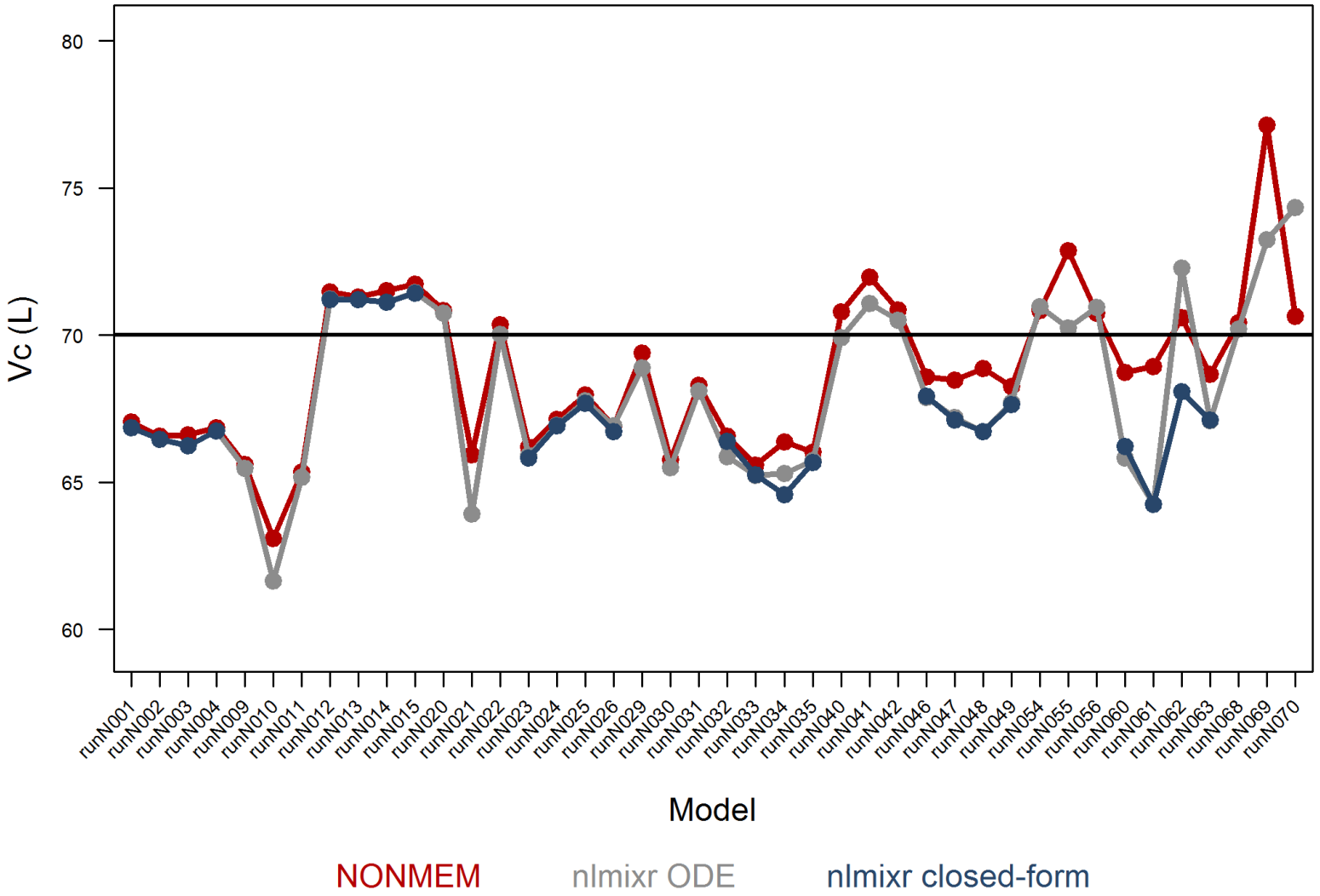
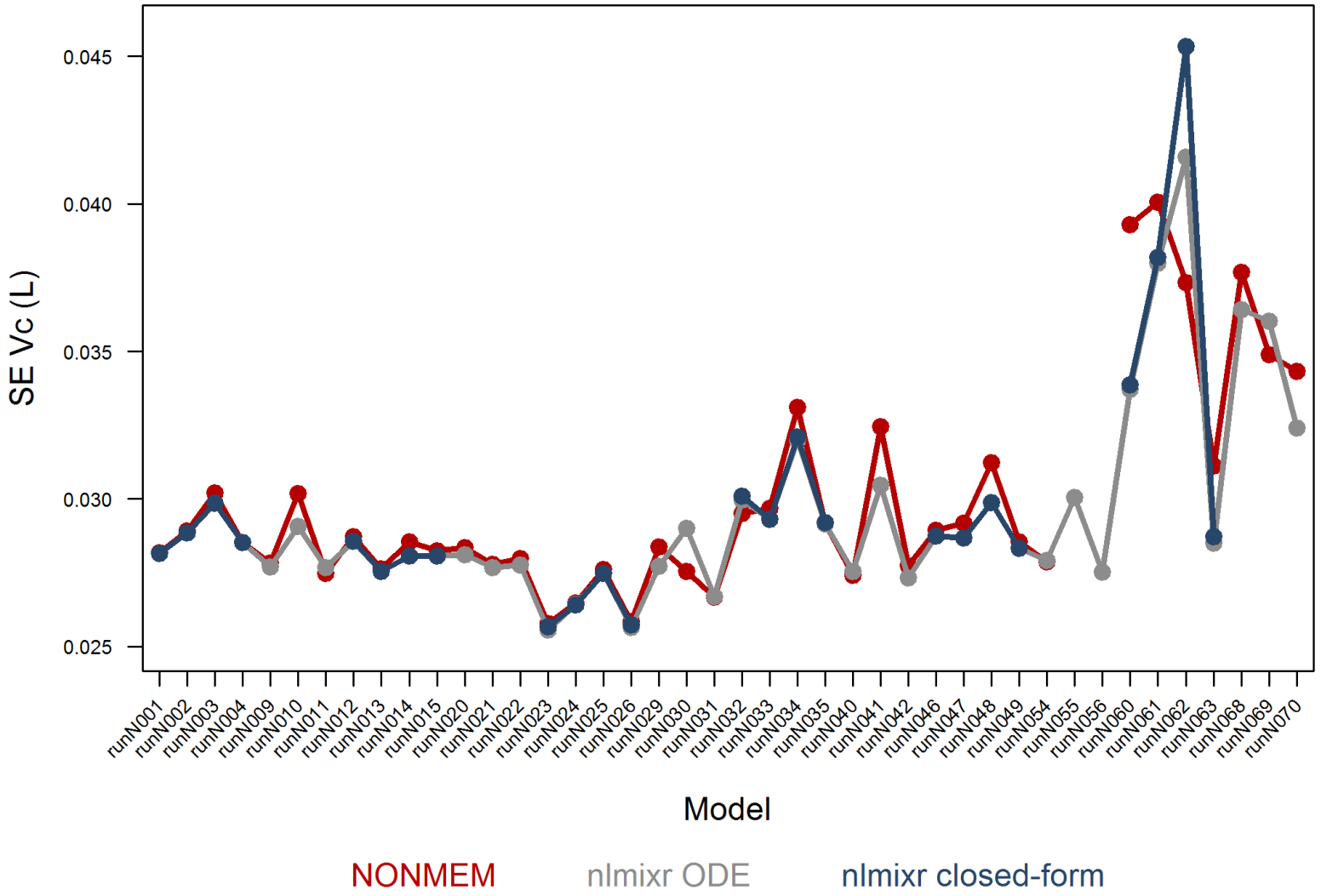
Non MM models also implemented using closed-form solutions

Blue line: nlmixr/nlme estimates using closed-form solutions



SE of theta estimates for Vc are very comparable



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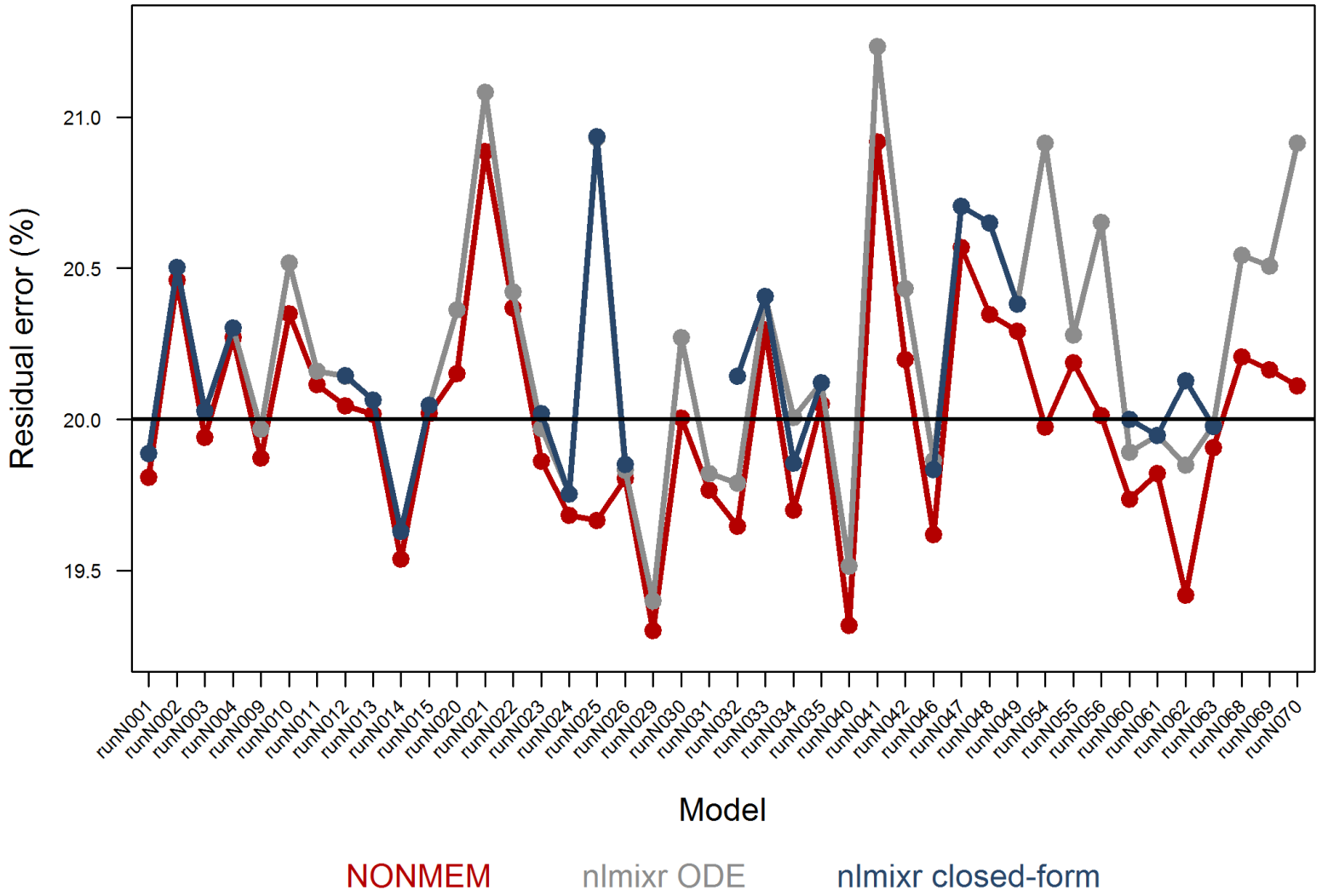
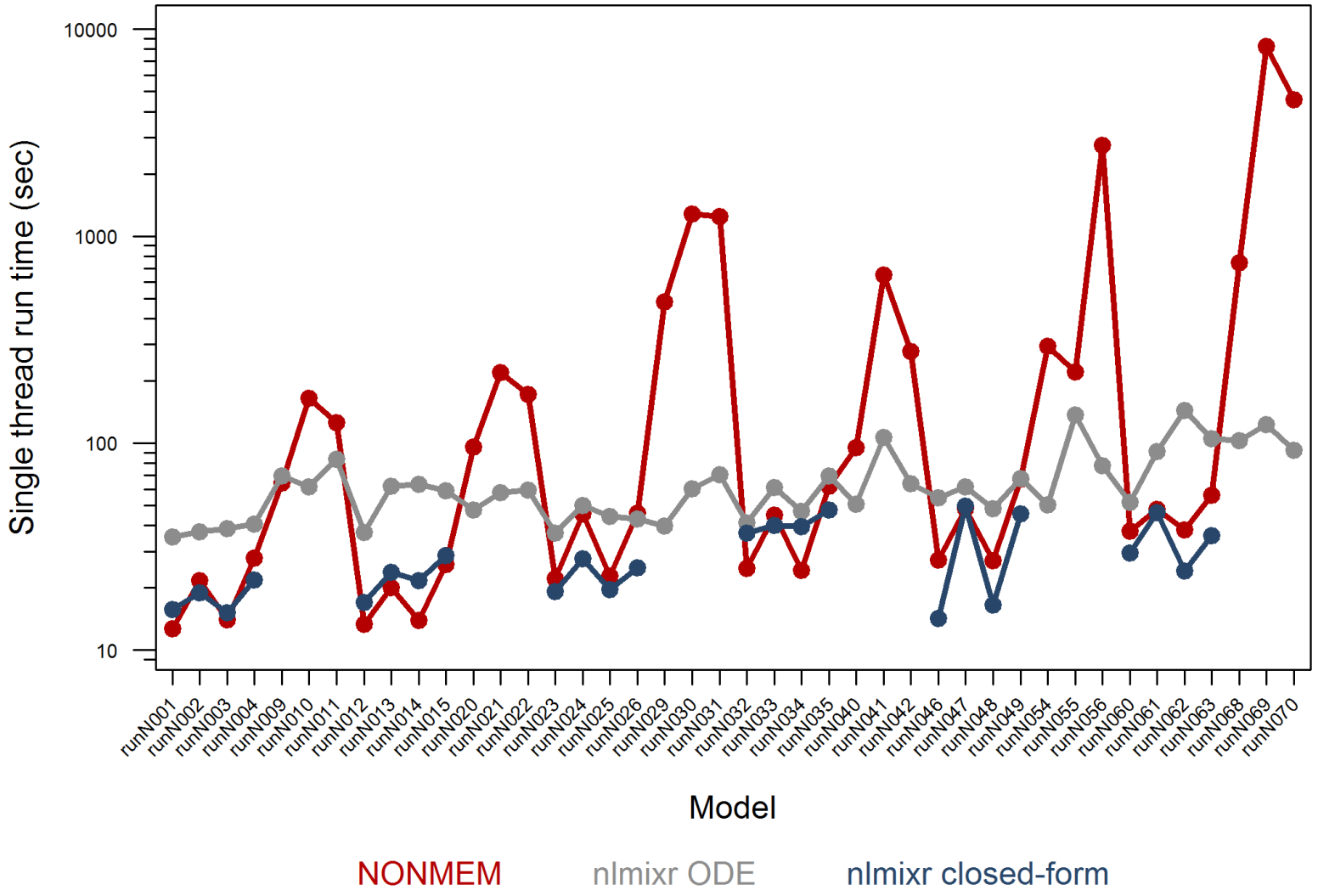
Residual error is well-estimated

Horizontal black line: value used for simulation



Run times are perfectly acceptable, and often lower than NONMEM



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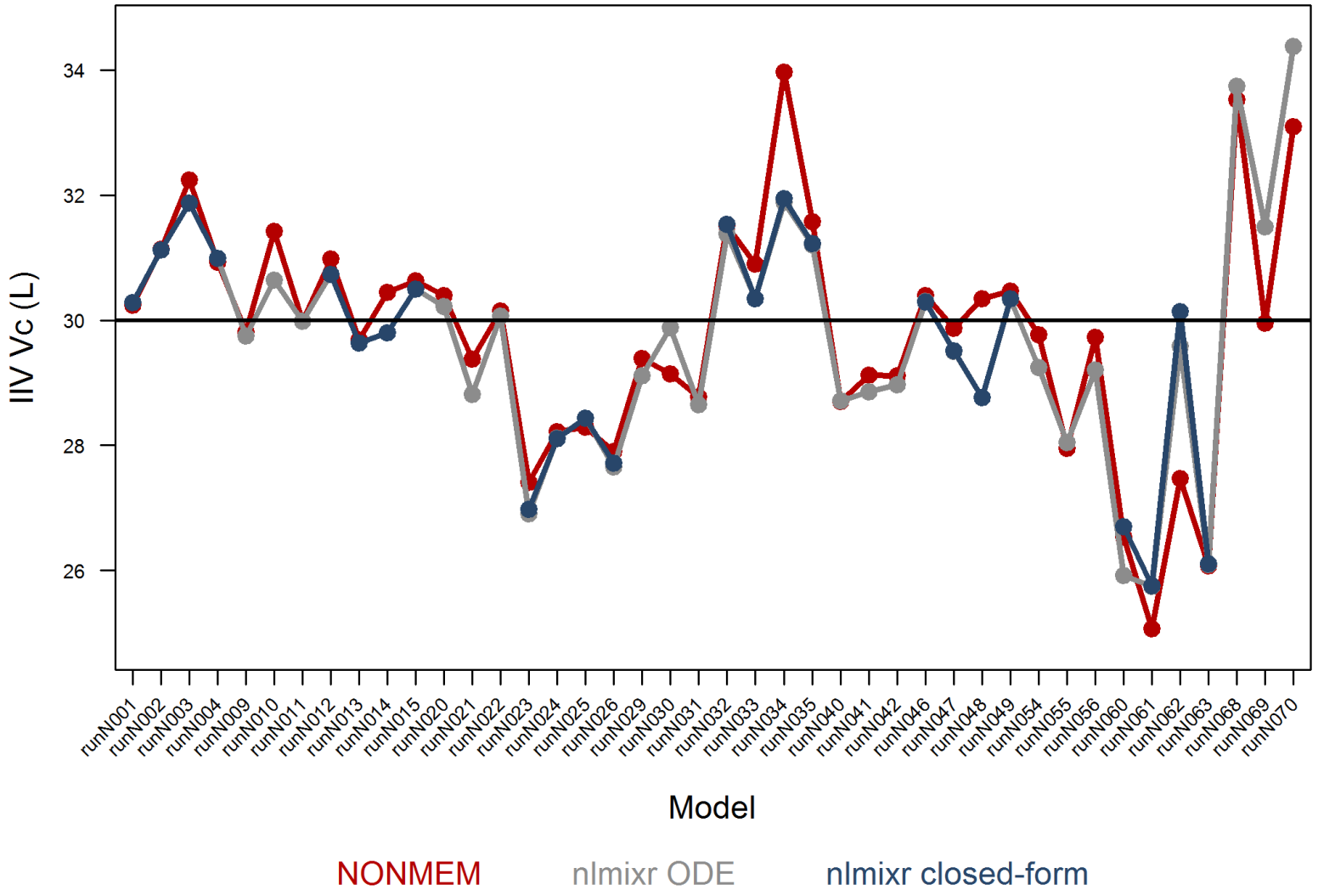
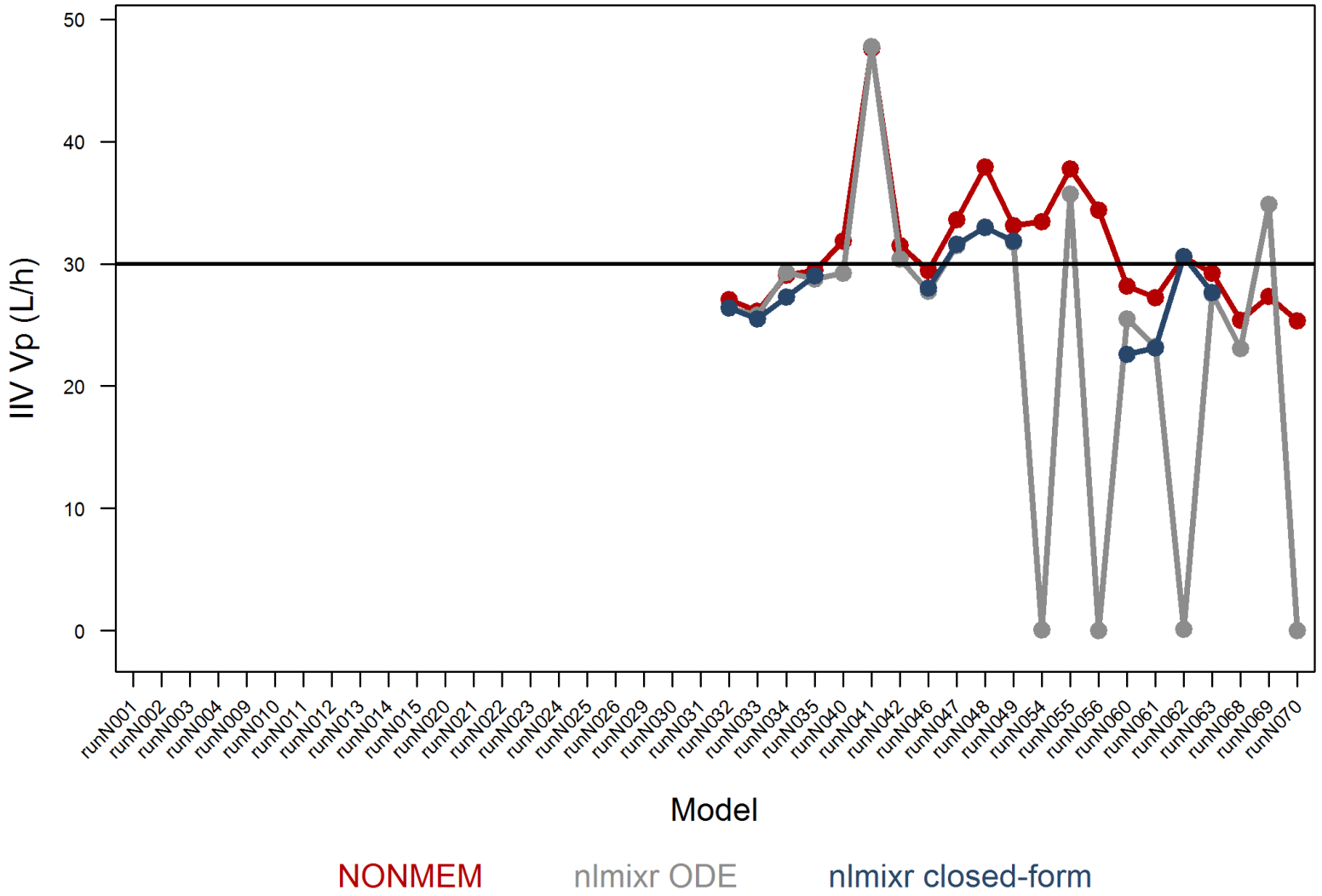
For Vc, Omega (IIV) estimates are also very comparable

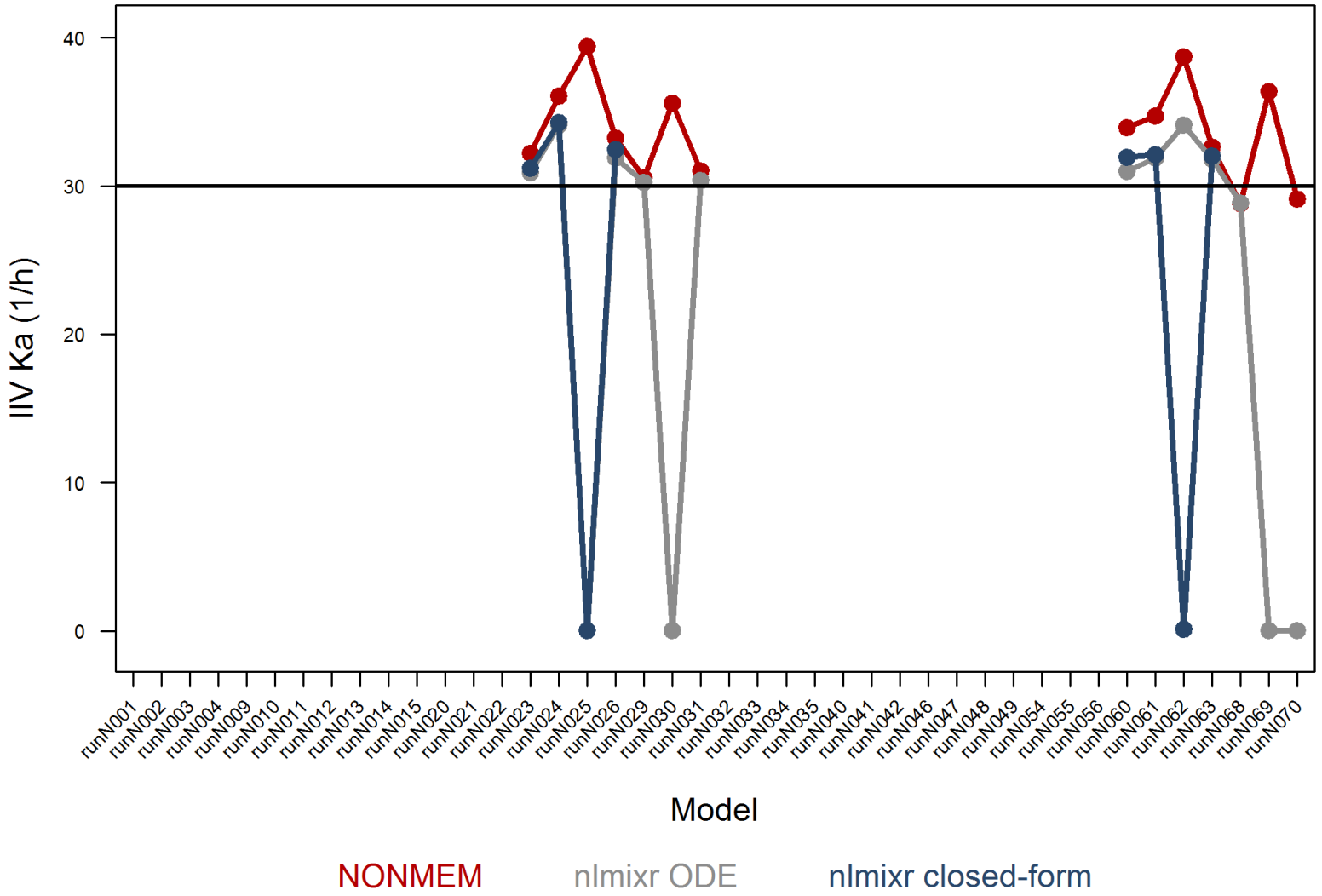
Horizontal black line: value used for simulation



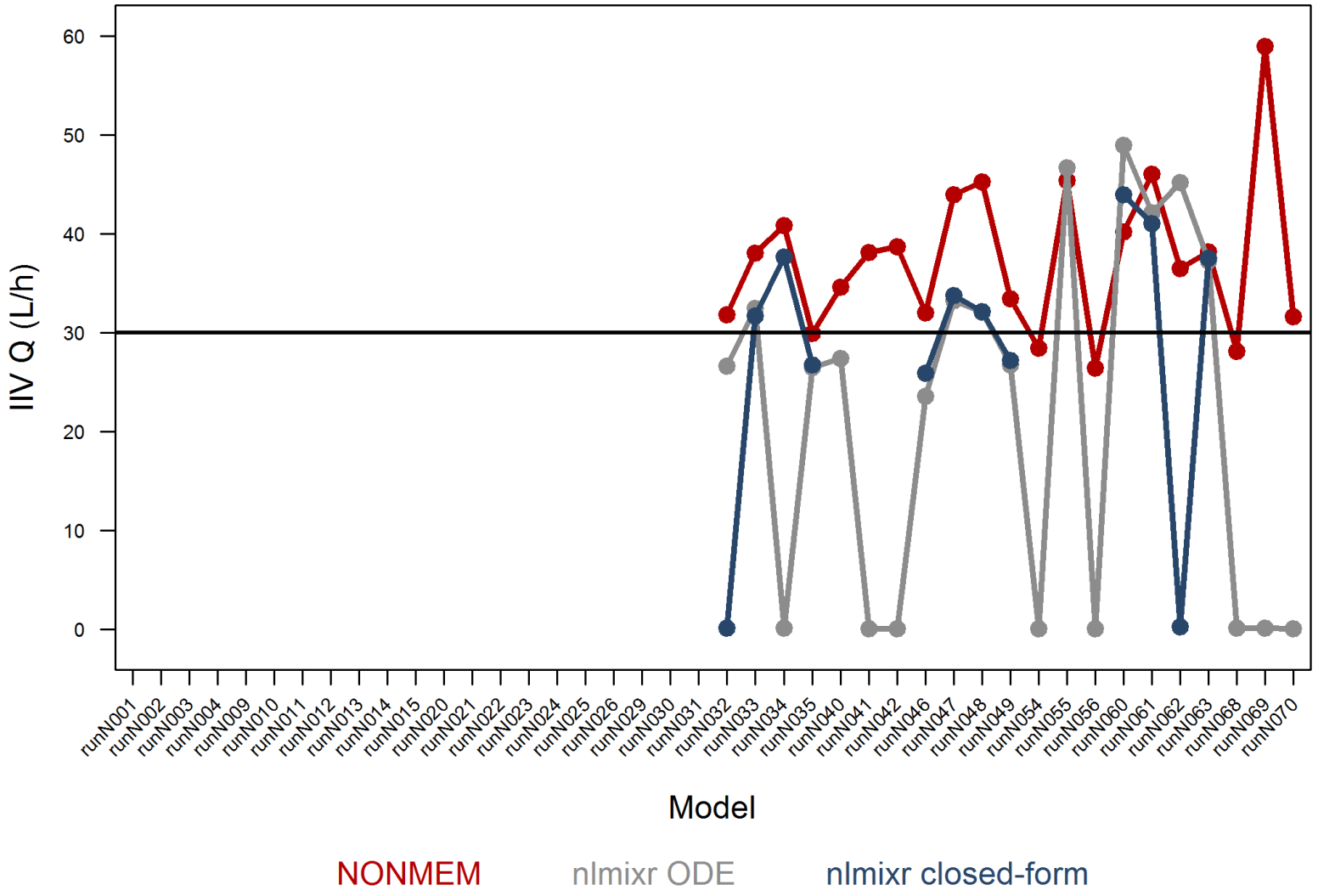
But if we examineVp…



...or Ka...


IIV Ka (1/h)
40
30
20
10
0
runN001
runN002
runN003
runN004
runN009
runN010
runN011
runN012
runN013
runN014
runN015
runN020
runN021
runN022
runN023
runN024
runN025
runN026
runN029
runN030
runN031
runN032
runN033
runN034
runN035
runN040
runN041
runN042
runN046
runN047
runN048
runN049
runN054
runN055
runN056
runN060
runN061
runN062
runN063
runN068
runN069
runN070
Model
NONMEM
nlmixr ODE
nlmixr closed-form

…or Q…
often the IIVs are estimated close to zero

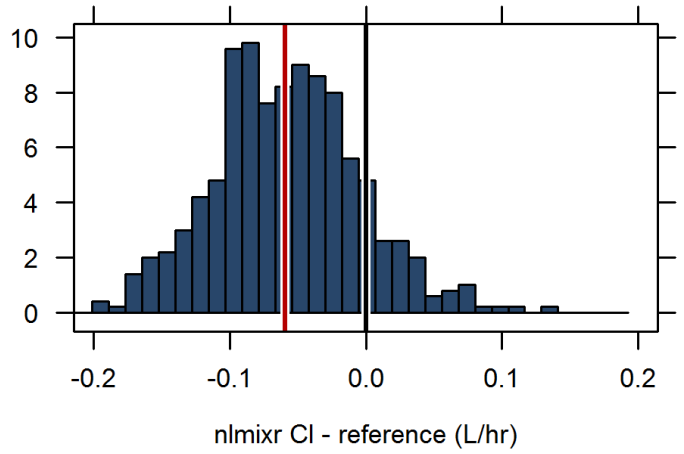


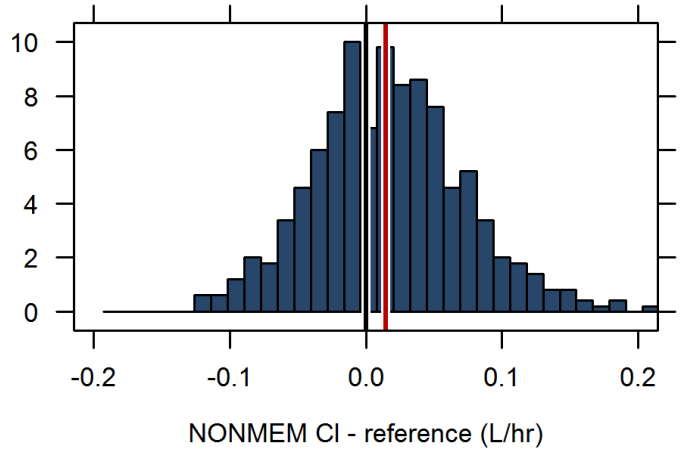
nlmixr

But what about sparse data?

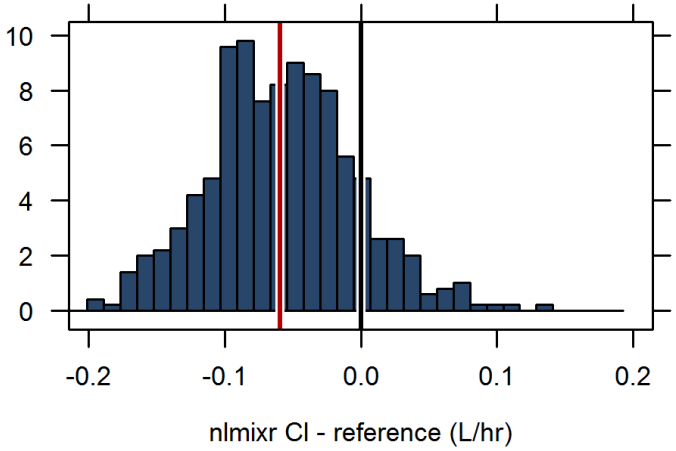
- first-order absorption, one-compartment distribution, linear elimination model
- 4 doses, 150 subjects per dose
- 4 random time point samples in 24 hours after the 7^{th} dose
- 500 datasets

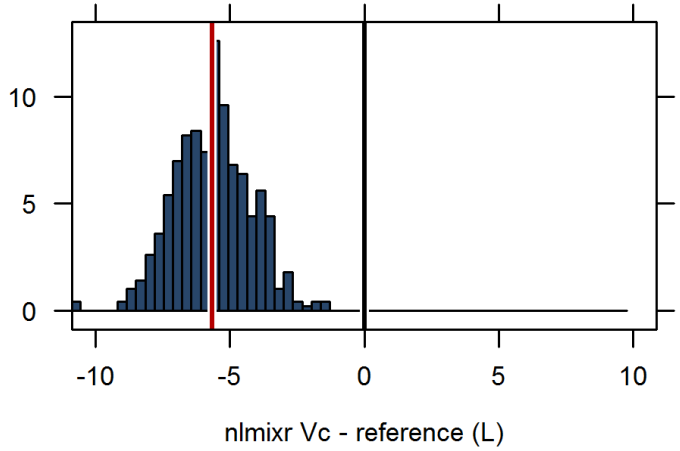
CL estimates using nlmixr (top) seem to demonstrate some bias compared to NONMEM (bottom)

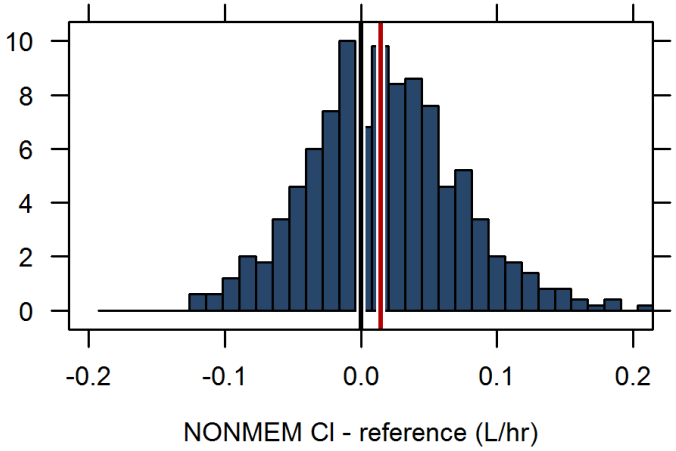


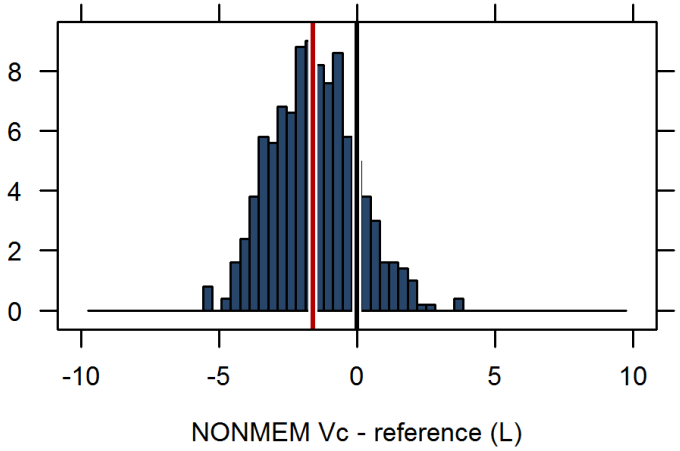


And V estimates demonstrate even larger bias…

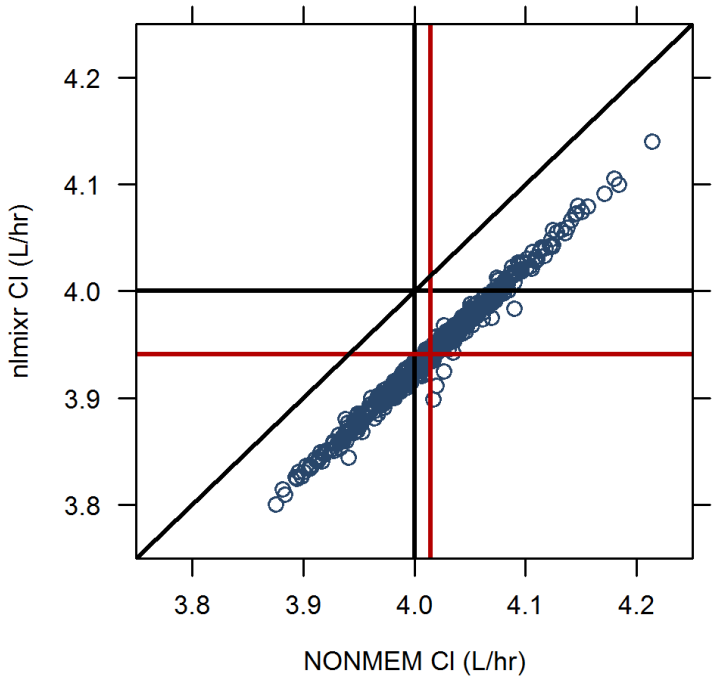


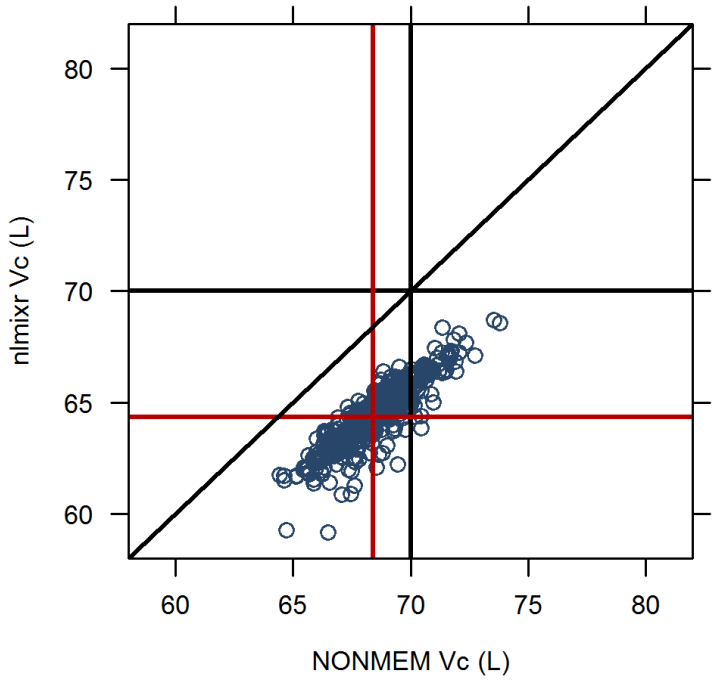




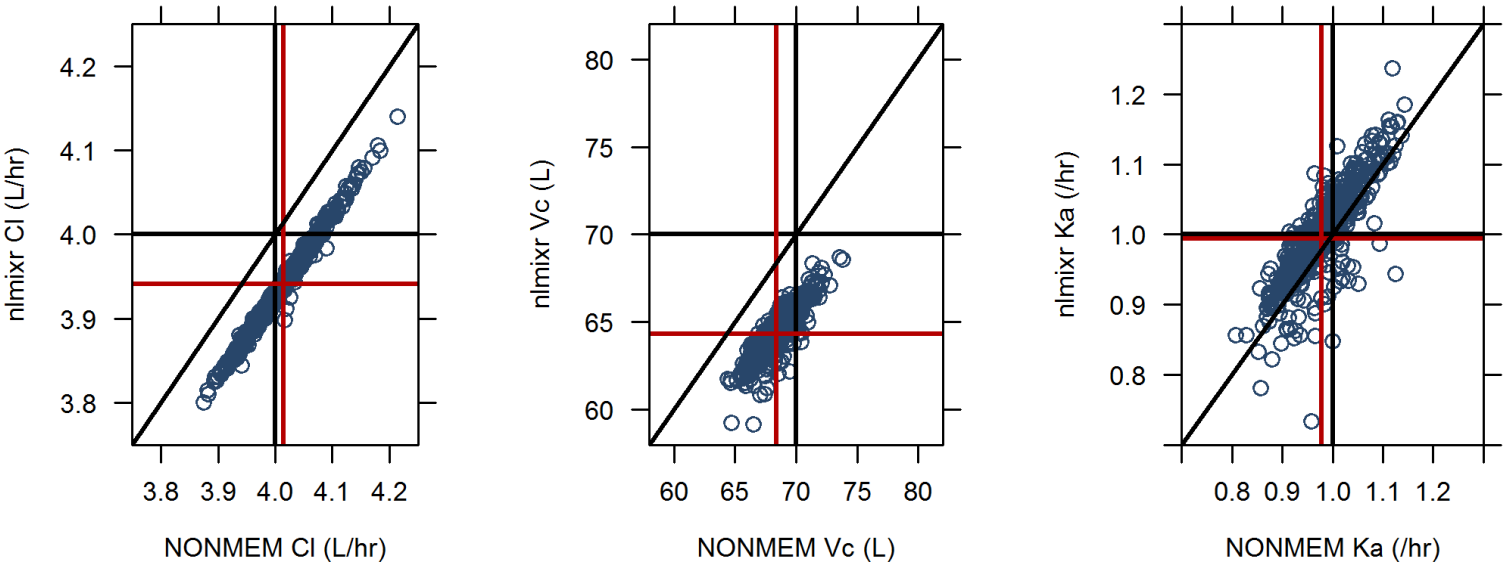


…but NONMEM and nlmixr estimates are highly correlated





This is also the case for Ka theta estimates… (right)



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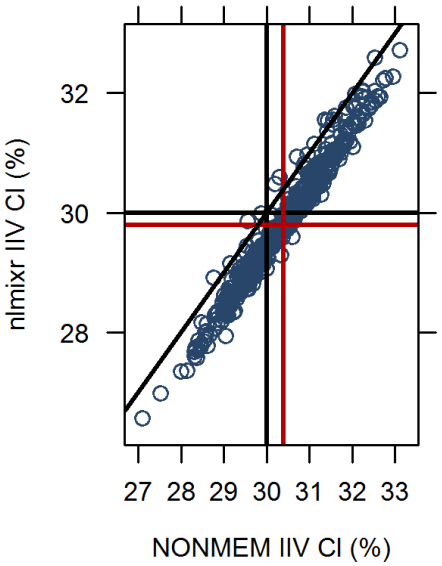
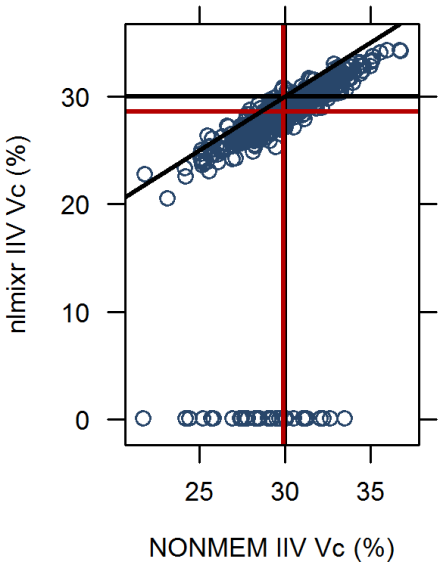
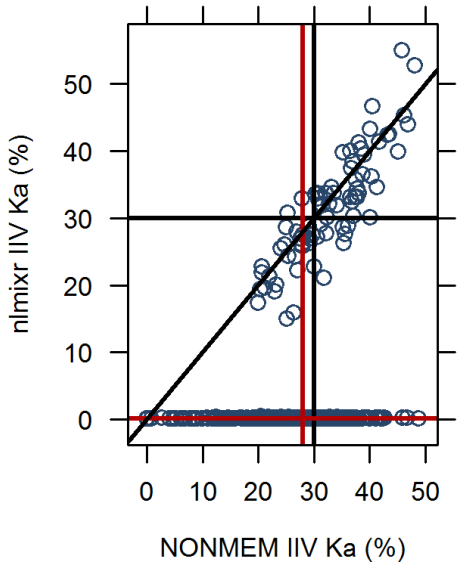
…but IIV estimates for Vc and especially for Ka clearly demonstrate a large fraction of runs with IIV=0 for nlmixr (91.1% *vs.* 2.2% for NONMEM)







Disappointing results?

- Findings are in line with earlier experience with nlme
- Bob Bauer claims nlme is somewhere beween ITS and FOCE

- However, nlme in nlmixr provides a gateway into nonlinear mixed effect modelling for statisticians…

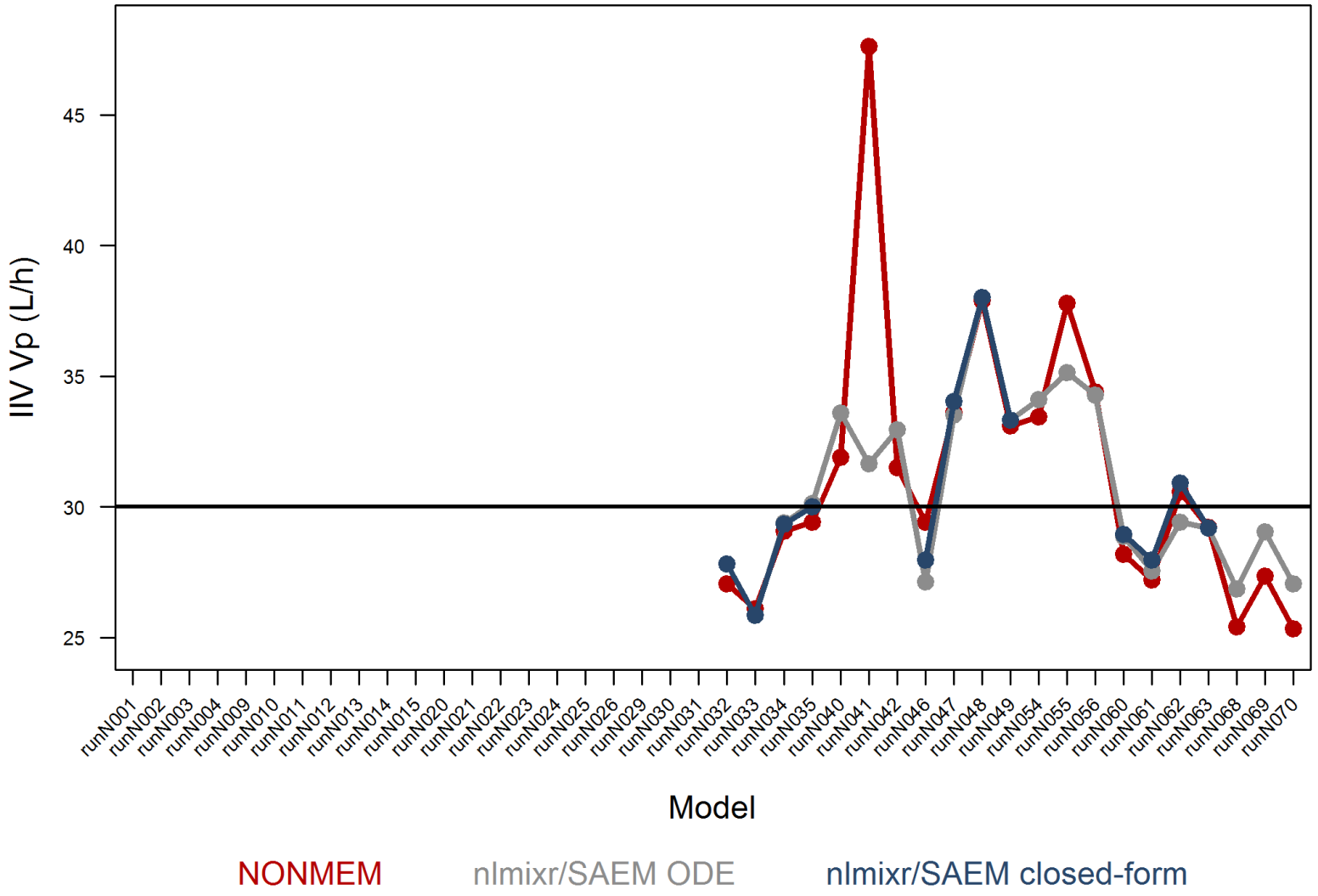
- With the machinery in place, the groundwork is laid for other/better estimation routines, like SAEM or FOCE-I…

- SAEM currently also available in nlmixr

Example nlmixr/SAEM syntax

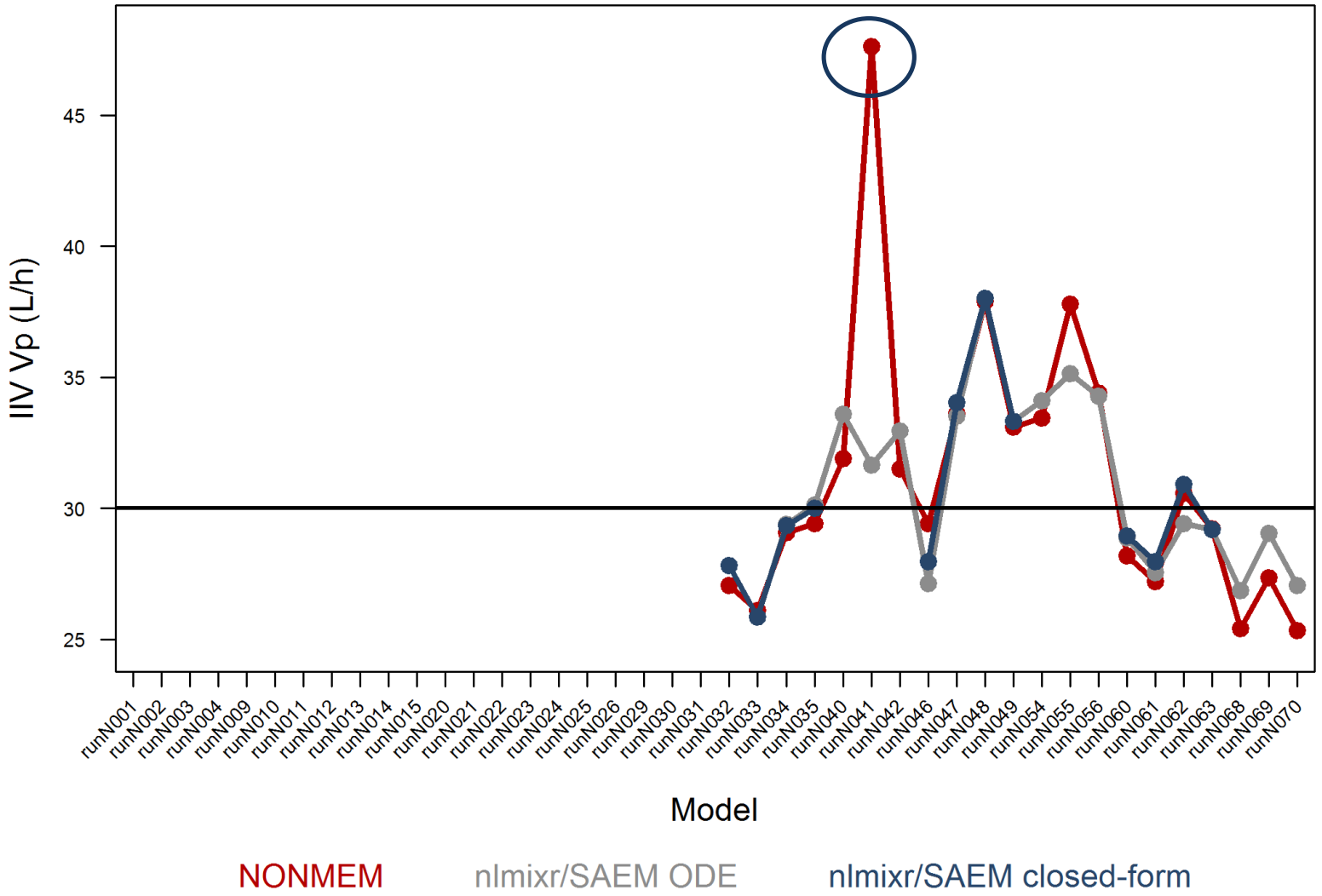
```
library(nlmixr)
datr<-read.csv("BOLUS_1CPT.csv", header=TRUE)
datr$EVID<-ifelse(datr$EVID==1,101,datr$EVID)
#temporary work-around for specifying covariates
datr$WT<-1

#Closed-form:
saem_fit <- gen_saem_user_fn(model=lincmt(ncmt=1, oral=FALSE))
#ODE:
ode <- "d/dt(centr)  = -(CL/V)*centr;"
m3 = RxODE(ode, modName="m3")
PRED = function() centr / V
mypar <- function(lCL, lV )
 {CL = exp(lCL)
  V  = exp(lV)}
saem_fit <- gen_saem_user_fn(model=m3, PKpars=mypar, pred=PRED)

#run SAEM:
model = list(saem_mod=saem_fit, res.mod=2,covars="WT")
inits = list(theta=c(5,90),omega=c(0.1,0.1),bres=0.2)
cfg   = configsaem(model, datr, inits)
cfg$print = 50
fit = saem_fit(cfg)
```

IIVs for nlmixr/SAEM for Vp show none of the close to zero behaviour

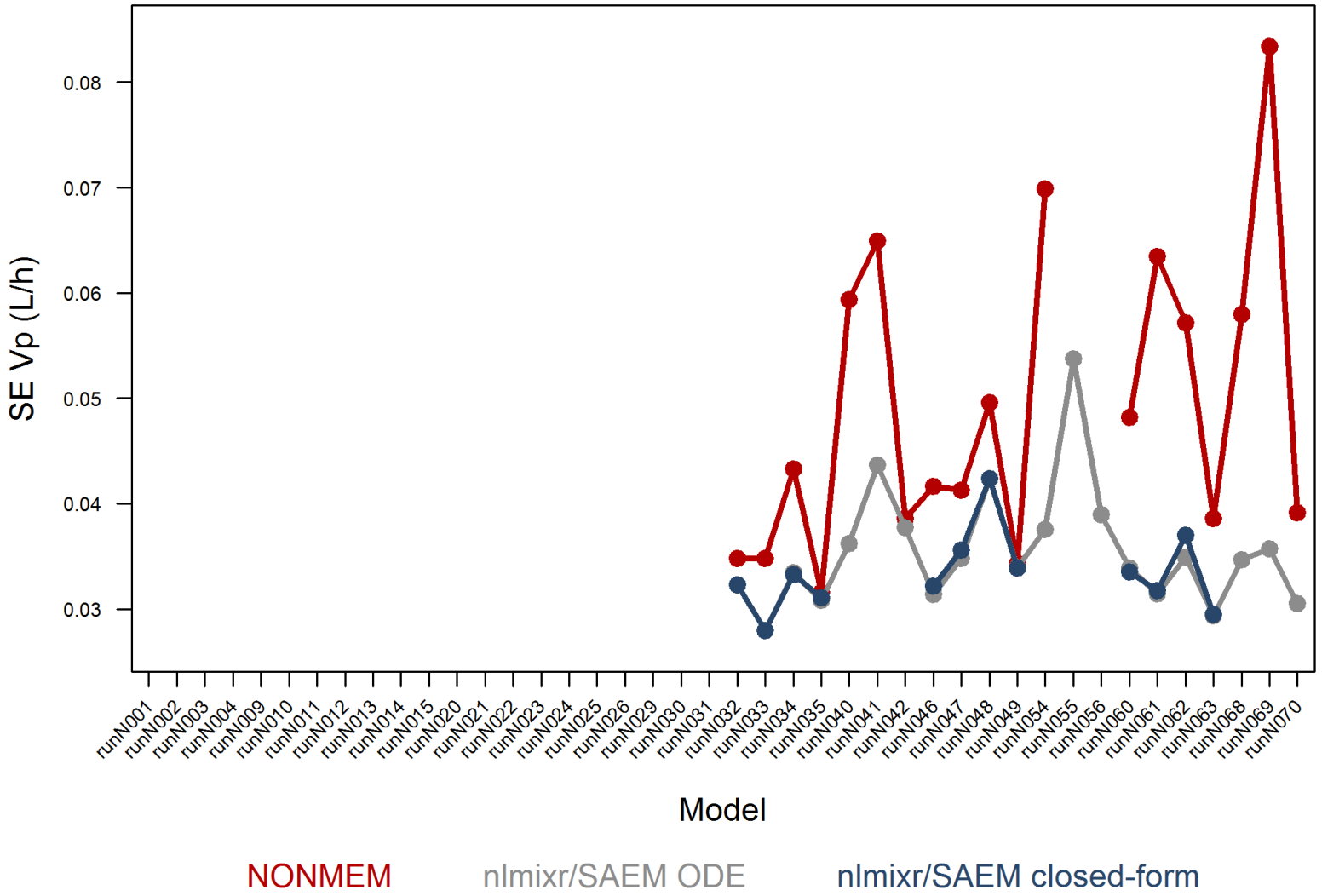


IIVs for nlmixr/SAEM for Vp show none of the close to zero behaviour

And some estimates seem better behaved…



…and could this also be the case for SEs for Vp…?



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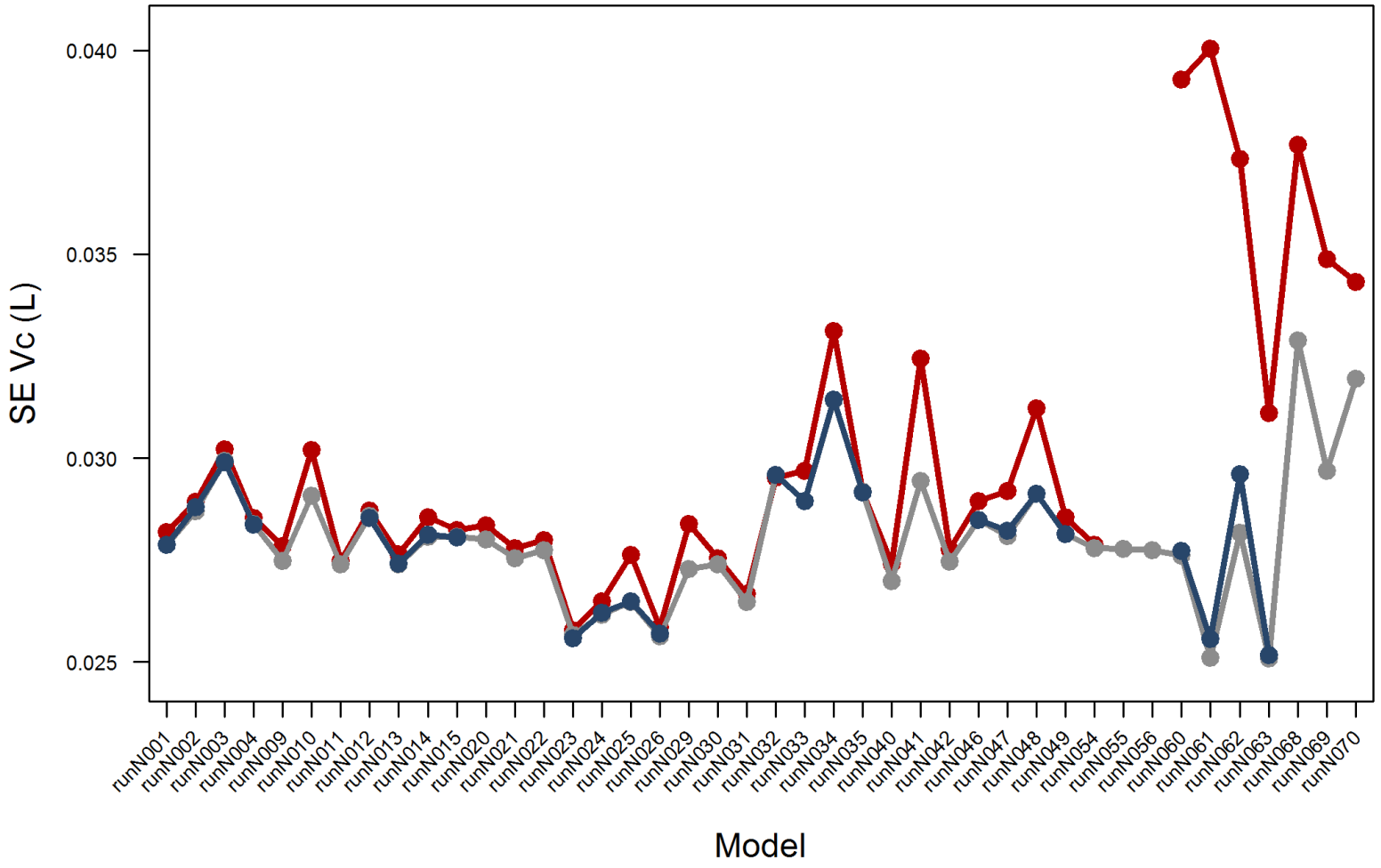
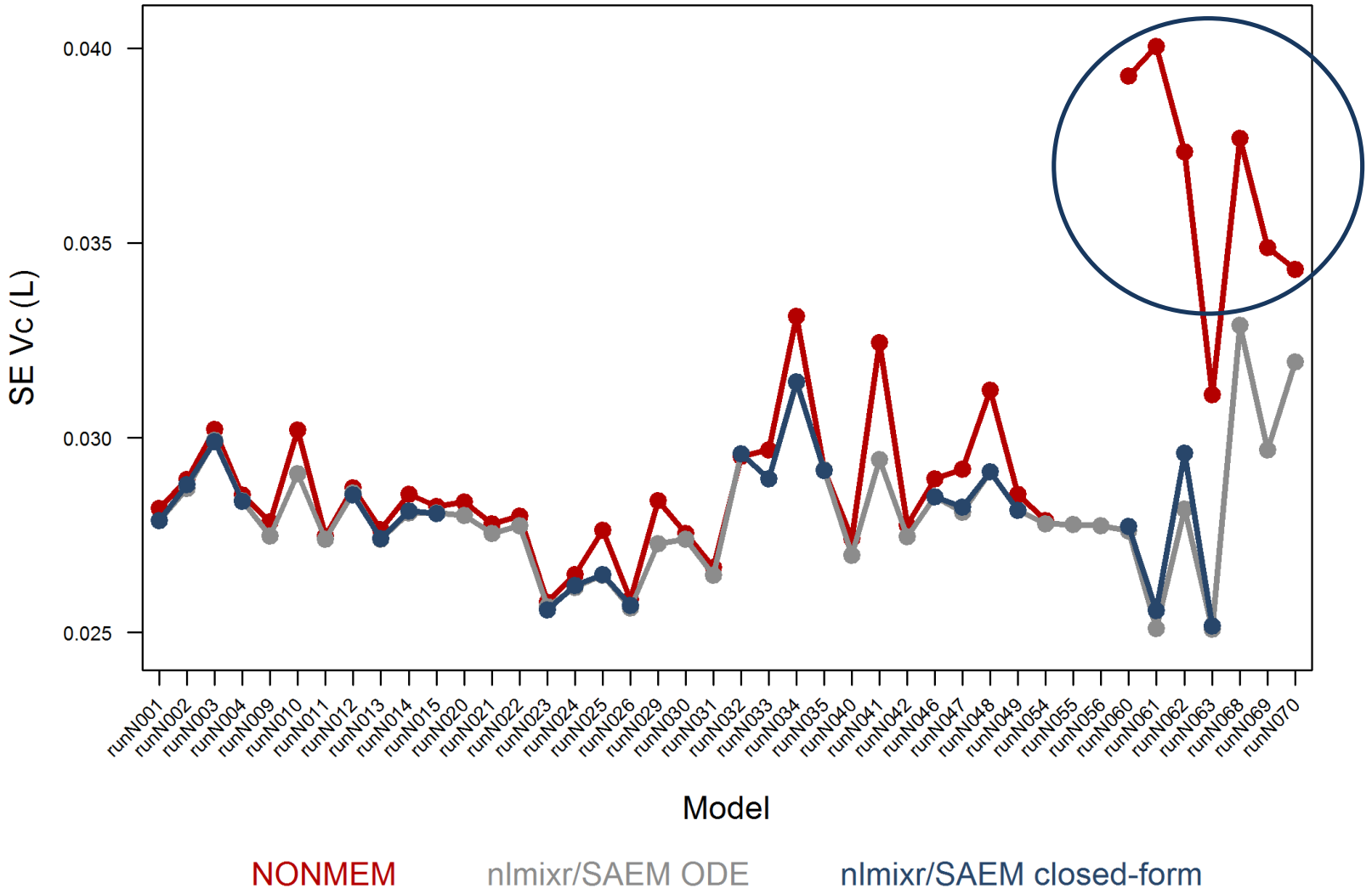
...and Vc...?



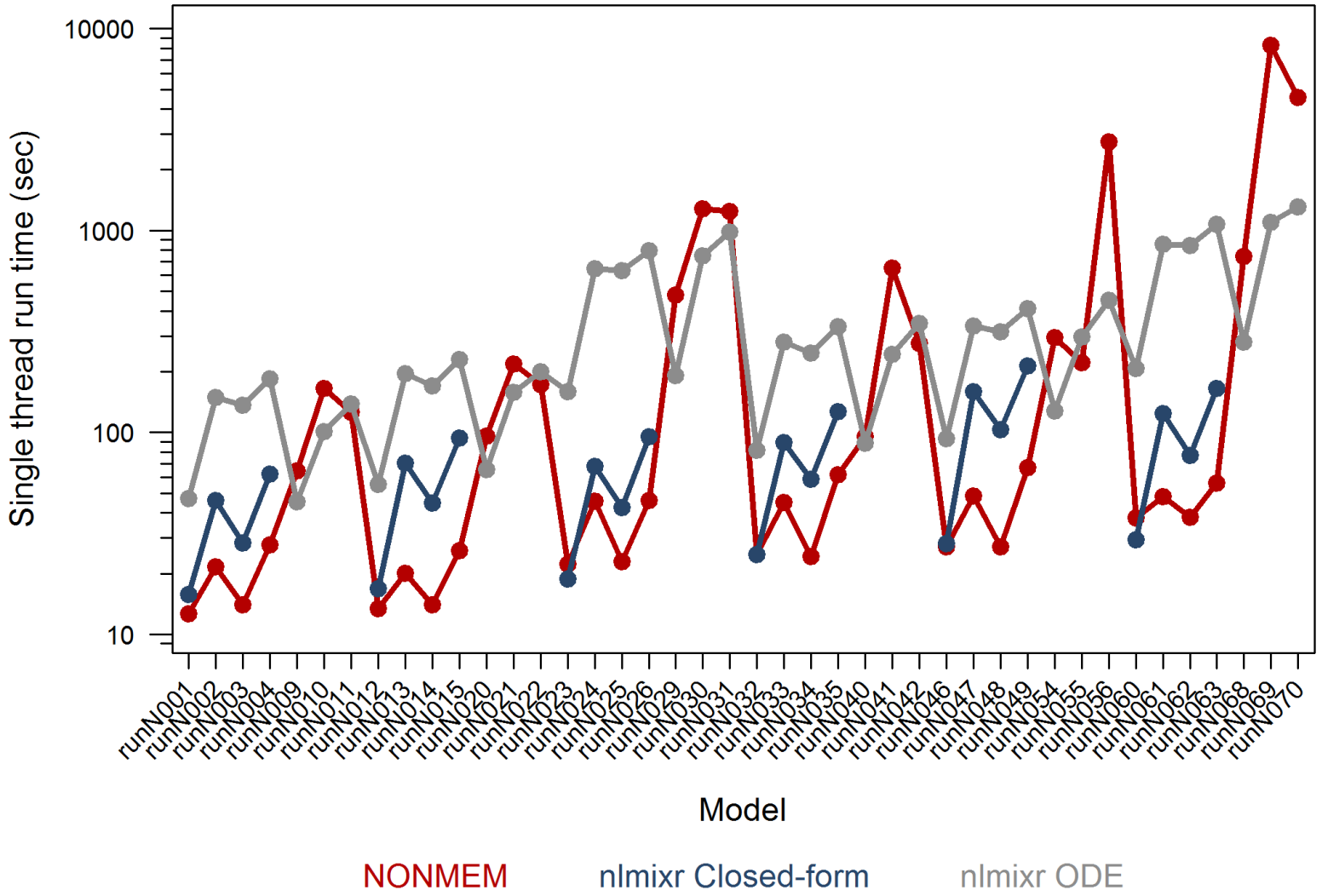
nlmixr

...and Vc...?



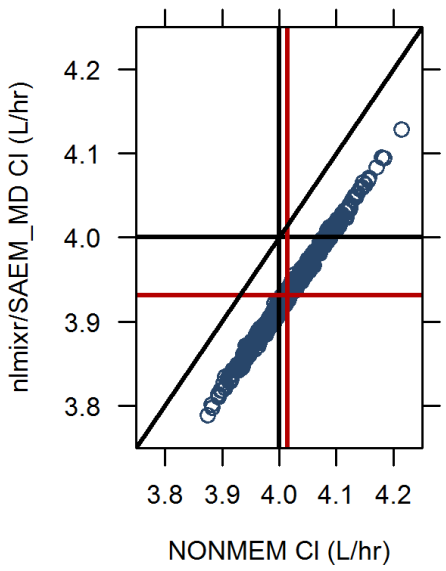
nlmixr

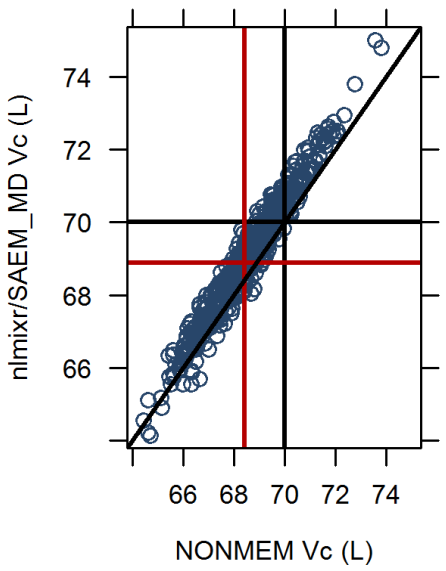
nlmixr/SAEM is slower than nlmixr/nlme but still workable

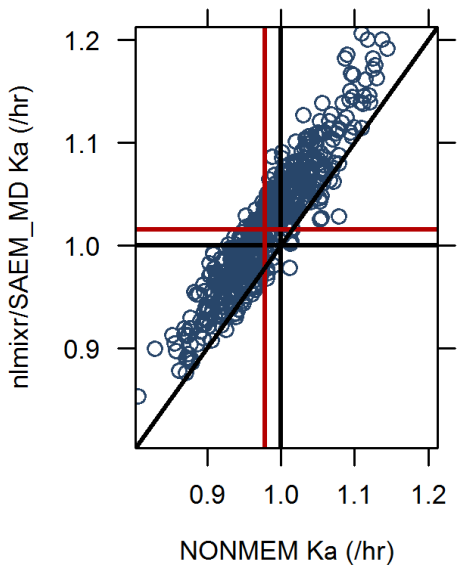


nlmixr

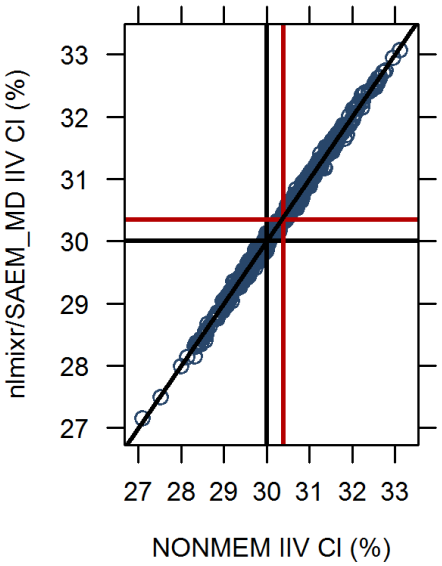
Very close correspondence for sparse sample theta estimates…

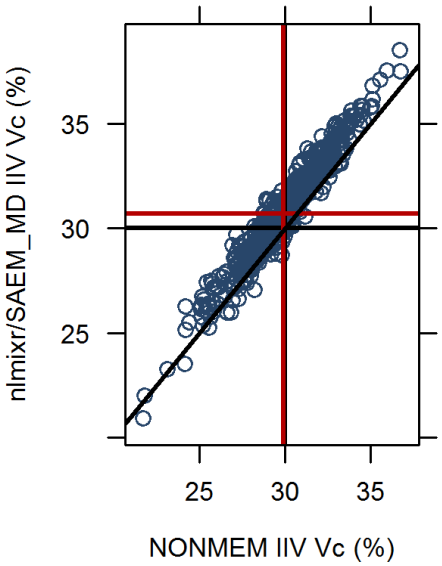


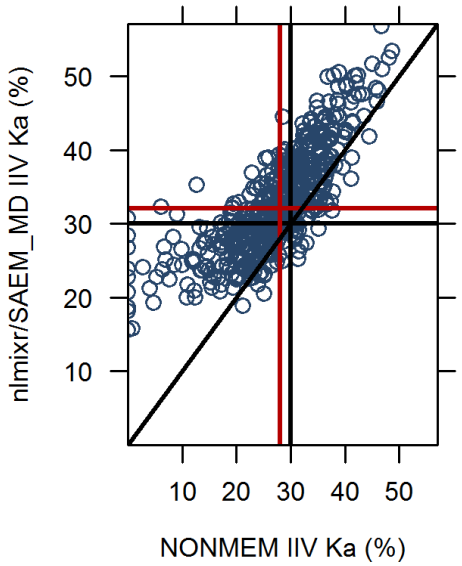




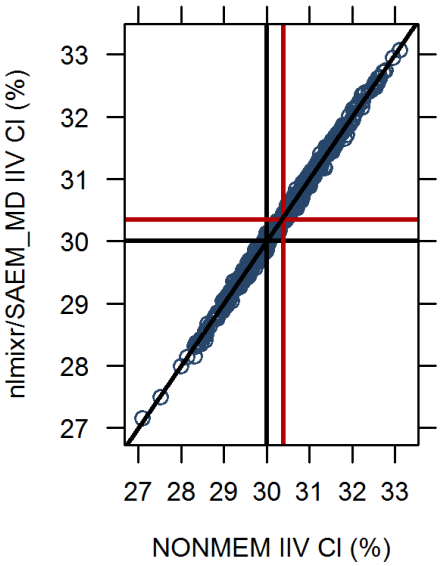
…and no close to zero IIVs for nlmixr/SAEM

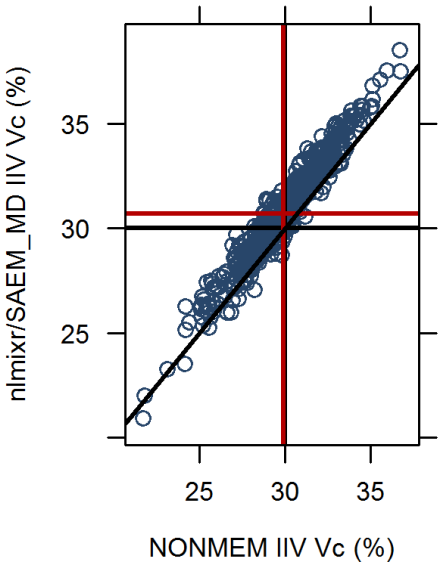


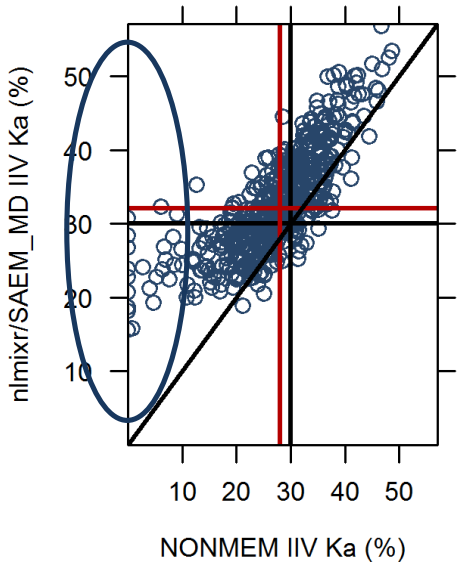




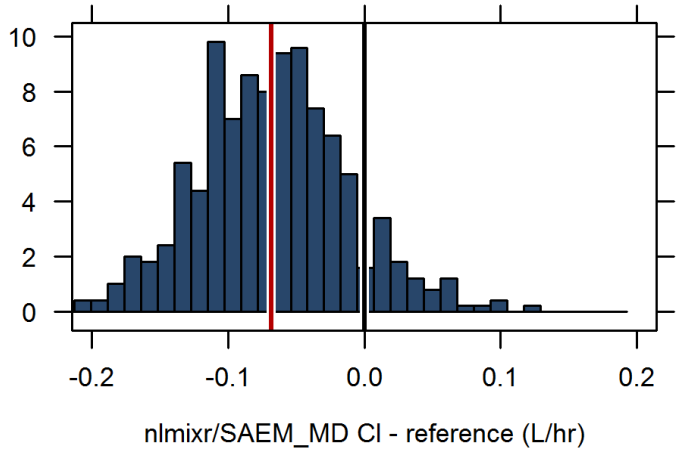
…and no close to zero IIVs for nlmixr/SAEM
and even better behaved than NONMEM

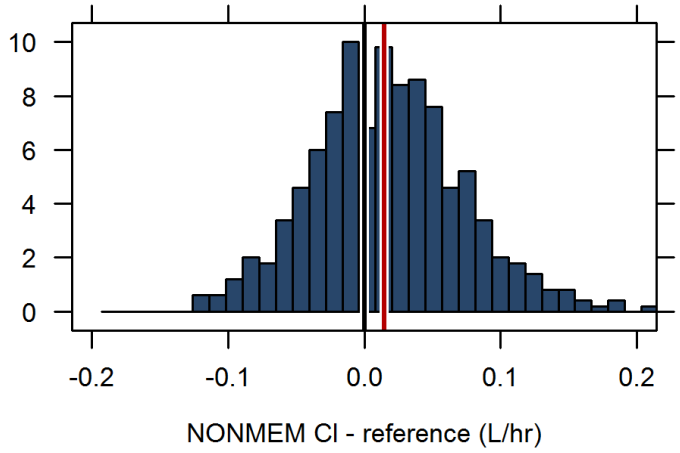


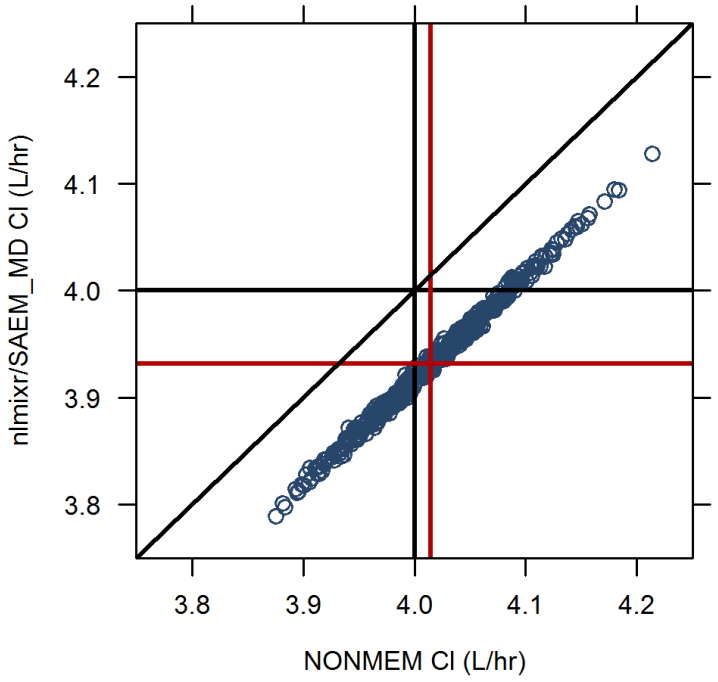




Is there an error in the algorithm in view of the systematic bias? Again that pronounced shift to the left for nlmixr…





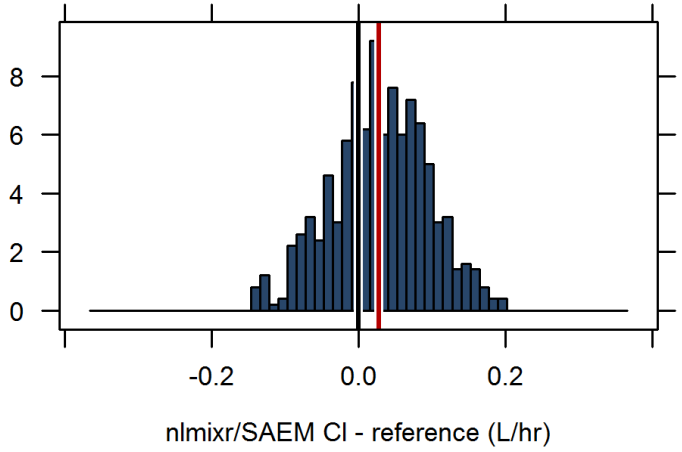


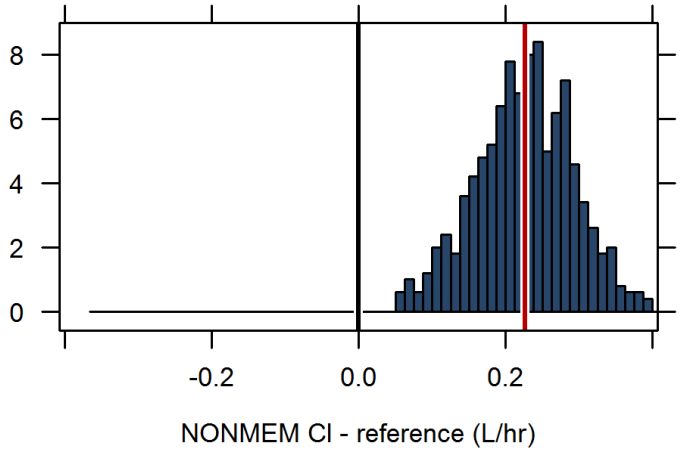
nlmixr

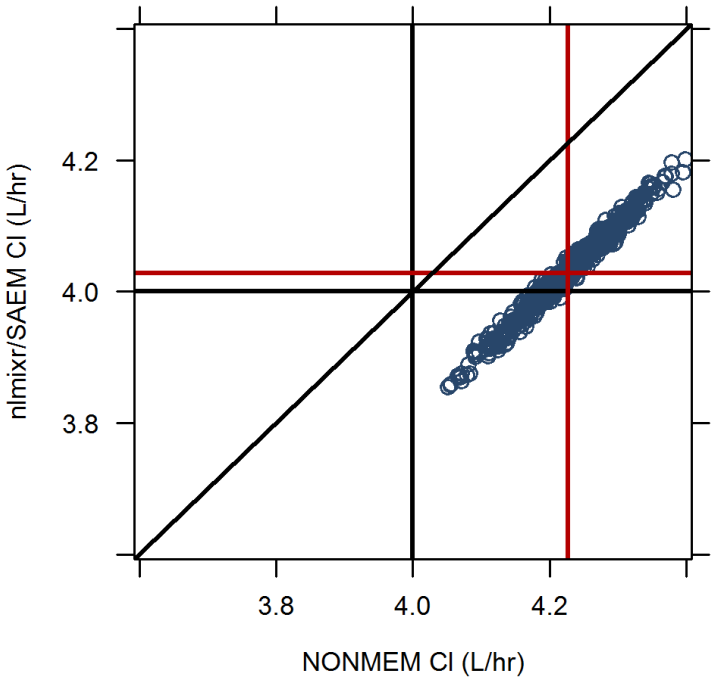
When samples are taken after the 1st dose instead of the 7th…

When samples are taken after the 1st dose instead of the 7th…

The bias is in the NONMEM estimates and nlmixr is spot on







More good news?

- nlmixr is available on GitHub at https://github.com/nlmixrdevelopment/nlmixr
- nlmixr also has an adaptive Gausian quadrature algorithm (like NONMEM's Laplace and higher) allowing fancy models
- nlmixr also has single subject dynamic models e.g. for complex system simulation and estimation (mcmc algorithm)
- Elementary implementation of VPC and bootstrap functionality

What's next?

- We need you!

- Improving computational efficiency of estimation algorithms (e.g. within-problem parallelisation)
- Implementation of FOCE-I
- Error-trapping
- Field-testing
- New features implementation
- Etc, etc…

Example nlmixr/gnlmm syntax: PK-PD model with ODE of heavy-tail data: t-distribution

```
kin.m0 <- "
C2 = centr/V2;
C3 = peri/V3;
CONC = centr/V2*1000;
Stim= EMAX*(CONC^GAM)/(CONC^GAM+EC50^GAM);
d/dt(depot) =-KA*depot;
d/dt(centr) = KA*depot - CL*C2 - Q*C2 + Q*C3;
d/dt(peri)  =                   Q*C2 - Q*C3;
d/dt(eff)   = KIN*(1-Stim) - KOUT*eff;
"
sys1 = RxODE(kin.m0)
dt_ls <- function(x, df, mu, a, log=T) {
  if (log) {
          dt((x - mu)/a, df, log=T) - log(a)
  } else {
          1/a * dt((x - mu)/a, df)
  }
}
llik <- function() {
  pred = ifelse(eff>0.01, eff, 0.01)
  sd1 = sqrt(sig2)*pred^.7
  #dnorm(DV, pred, sd=sd1, log=TRUE)
  dt_ls(DV, 4, pred, sd1, log=TRUE)
}
inits = list(THTA=c(-3, 0, 9, .7, -.4))
inits$OMGA = list(ETA[1]~.001, ETA[2]~1)
fit = gnlmm(llik, data, inits, pars, sys1,
    control=list(
    trace=TRUE,
    optim.inner = "Nelder-Mead",
    optim.outer = "nmsimplex",
    reltol.outer = 1.0e-3,
    mc.cores=4)
)
```

Example nlmixr/gnlmm syntax: PK-PD model with ODE of bounded clinical endpoint: beta-distribution

```
kin.m0 <- "
C2 = centr/V2;
C3 = peri/V3;
CONC = centr/V2*1000;
Stim= EMAX*(CONC^GAM)/(CONC^GAM+EC50^GAM);
d/dt(depot) =-KA*depot;
d/dt(centr) = KA*depot - CL*C2 - Q*C2 + Q*C3;
d/dt(peri)  =                    Q*C2 - Q*C3;
d/dt(eff)   = KIN*(1-Stim) - KOUT*eff;
"
sys1 = RxODE(kin.m0)
llik <- function() {
  mn = ifelse(eff<.0001, .0001, eff2)
  odsp = odav/mn^pwod
  shp1 = mn*odsp
  shp2 = odsp - shp1
  dbeta(DV, shp1, shp2, log=TRUE)
}

inits = list(THTA=c(-3, 2, 7.5, .7, 2.1, -.4))
inits$OMGA = list(ETA[1]~.001, ETA[2]~.8, ETA[3]~1)
fit = gnlmm(llik, x, inits, pars, sys1,
    control=list(
    trace=TRUE,
    optim.outer = "nmsimplex",
    optim.inner = "Nelder-Mead",
    reltol.outer = 1.0e-2,
    mc.cores=4)
)
```

Example nlmixr/gnlmm syntax: PK-PD model with ODE of binary data with over-dispersion: beta-binomial distribution

```
ode.bin1 <- "
C2 = centr/V2;
C3 = peri/V3;
CONC = centr/V2*1000;
d/dt(depot) =-KA*depot;
d/dt(centr) = KA*depot - CL*C2 - Q*C2 + Q*C3;
d/dt(peri)  =                   Q*C2 - Q*C3;
d/dt(eff)   = kout*(1+emax*CONC^gam/(ec50^gam+CONC^gam)) -kout*eff ;"
sys5 = RxODE(ode.bin1)


llik <- function() {
  lp = alpha+beta*eff
  pred = 1/(1+exp(-lp))
  if (do.betabinom)
    dbetabinom(DV, pred, 1, thta, log = TRUE)
  else dbinom(DV, 1, pred, log=TRUE)
}


do.betabinom = T
inits = list(
    THTA=c(2, -4, 0.3, -3, 0.2, -2, -3, 200),
    if(do.betabinom) 2 else NULL)
)
inits$OMGA = list(ETA[1]~.9, ETA[2]~.9)
fit1 = gnlmm(llik, mydat, inits, mypars, sys5,
  control=list(
    trace=TRUE,
    mc.cores=4)
)
```