Roche

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Nonlinear mixed effect models in R

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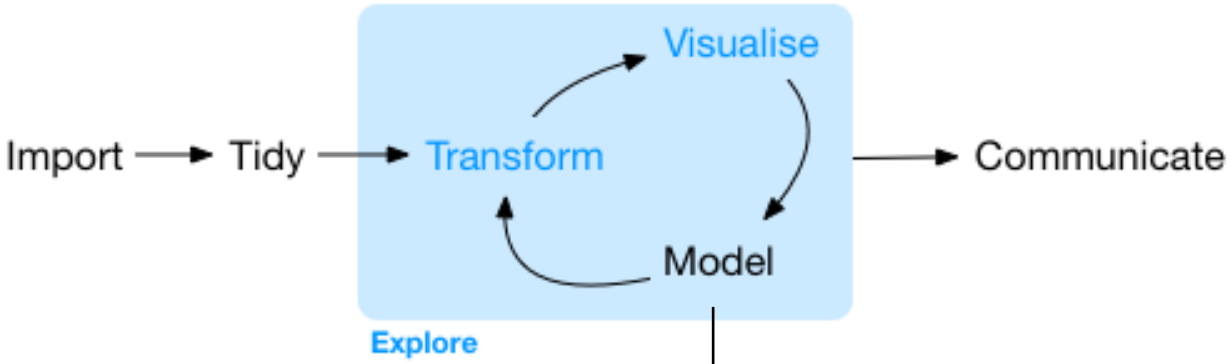
Scope & Objective



Linear models (e.g `lm()`)

Nonlinear models (e.g `nls()`)

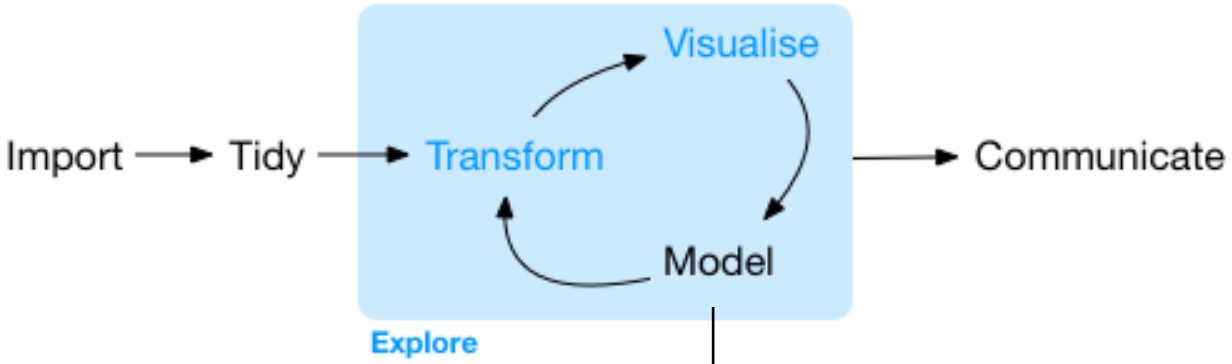
Linear mixed-effect models (e.g. `lmer()`)

Nonlinear mixed-effect models

- Ecology: fishery, tree growth
- Econometrics
- Manufacturing
- **Medicine**

⚠ Left out of this talk: polynomial functions, Bayesian approach, non continuous response variable

Scope & Objective



Linear models (e.g `lm()`)

Nonlinear models (e.g `nls()`)

Linear mixed-effect models (e.g. `lmer()`)

Nonlinear mixed-effect models

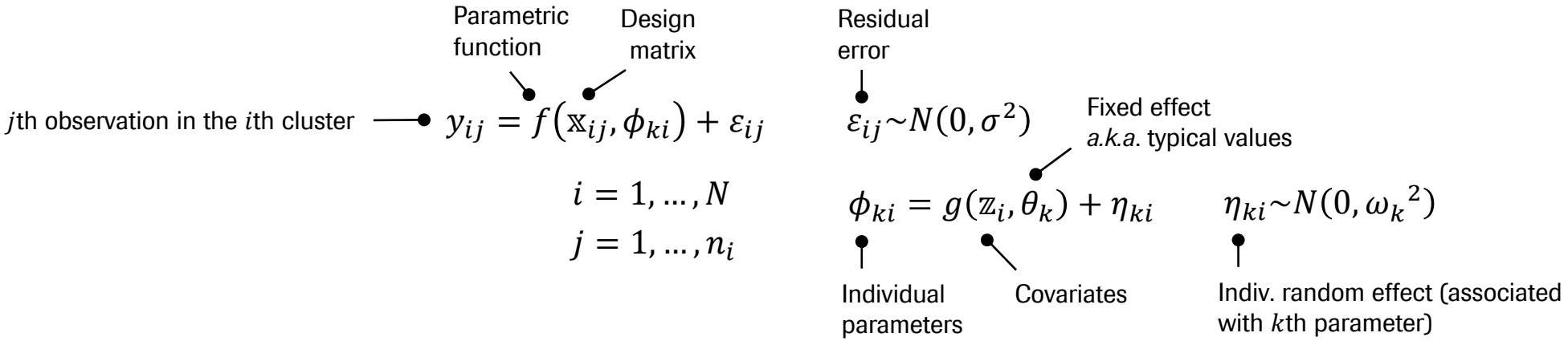
Goal of today's talk:

Review R packages available to fit NLMEM

THEORY

Characteristics of NLMEM

- General formulation:



- Mechanistic *i.e.* assumption/knowledge about the mechanism producing the response; Model parameters have a natural interpretation and models can be used for prediction, including extrapolation.
- NLMEM in medicine often describe time dynamics; Two forms: ODEs or closed-form expressions

$$\frac{dy}{dt} = \beta_1 y \quad \text{with} \quad y(0) = y_o \quad \Leftrightarrow \quad y(t) = y_o \times exp(\beta_1 \times t)$$

Note: often, ODEs don't have closed-form equivalent

Algorithms

- First Order (FO, 1970's) method – model linearization (first order Taylor development) to obtain an approximation of the likelihood. This approximation is then maximized through iterative Newton-Raphson minimization.
- Lindstrom-Bates[1] (LB, 1990): FO where linearization takes place around the current estimates at each iteration (note: LB is the algorithm implemented in SAS® PROC NLMIXED and NONMEM FOCE).

Linearization approaches have both statistical and practical shortcomings including bias estimates of variance components[2] and convergence issues[3]. Two approaches have been proposed to overcome these issues:

- Laplace approximation (equivalent to AGQ with one notch)[4]
- SA-EM approach: Stochastic approximation to the likelihood combined with an expectation-maximization[5] (EM) algorithm; quick and efficient convergence to ML estimators[6].

[1]Lindstrom and Bates 1990 Biometrics; [2]Comets and Mentre 2001 J Biopharm Stat; [3]Plan *et al.* 2012 AAPS J. [4]Bates *et al*. 2015 JSS. [5]Dempster *et al.* 1977 JRSS-B. [6]Delyon *et al.* 1999 *Annals of Stat*.

Key features of R packages

	nlme	nlmer	saemix	nlmixr
First release	2000 [1]	2011 [2]	2016 [3]	2017 [4]
Engine	R/S3 class	C++	R/S4 class[2]	C++
Algorithm	LB	Laplace?	SAEM	LB, SAEM
Allow ODE formulation	×[1]	×	×	✓
Proportional or exponential residual error	×	×	✓	✓
Weights options	✓	✓	×	×
Within-group correlation options	✓	✓	×	×
Model building	*anova(), AIC()*	*anova()*	×	×
predict()	✓	✓	VPC	VPC
residuals()	✓	✓	✓(+npde)	✓

[1]But see package *nlmeODE*; [2]Initially implemented in MATLAB;

[1] Pinheiro JC, Bates DM. 2000. *Mixed-effects models in S and S-PLUS*. Springer. 528 pages. [2] Bates DM. 2011. *Mixed models in R using the lme4 package - Part 6: Nonlinear mixed models.* Vignette. 9 pages.[3] Comets E, Lavenu A, Lavielle M. 2016. *SAEMIX, an R version of the SAEM algorithm*. PAGE meeting.[4] Schoemaker R, *et al*. 2017. *nlmixr: an open-source package for pharmacometric modeling in R*. ACoP meeting.

EXAMPLE

Theophylline (Theo) PK – Data and equation

- 12 patients (i =1, …, 12) received a single oral dose D of Theo at time t =0. Concentration of theo C was measured in blood at 11 time points (j=1, …, 11) over 25 hours.
- Pharmacokinetics of Theo can be described by a NLMEM, specifically a one-compartment model with first-order absorption and linear elimination:

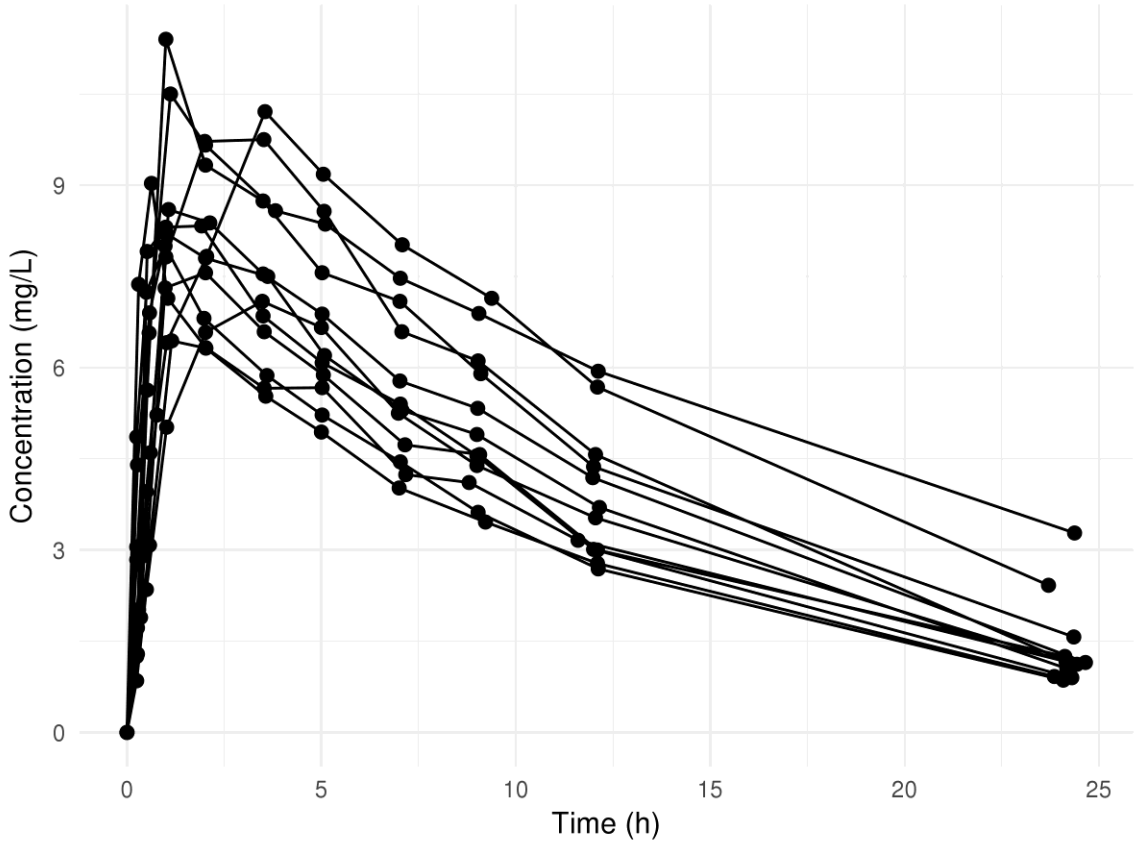
$$C_{ij} = f(t_{ij}, D_i) + \varepsilon_{ij}$$

$$f(t_{ij}, D_i) = \frac{D_i \times ka_i}{V_i \times \left(ka_i - \frac{CL_i}{V_i}\right)} \times \left(e^{-\frac{CL_i}{V_i} \times t_{ij}} - e^{-ka_i \times t_{ij}}\right)$$

ka: first-order absorption rate (1/h)

V: volume of distribution (L)

CL: clearance (L/h)



Theophylline PK – Code (1/3)

nlme

```
startvec1<-c(lKa=0.5, lCl=0.75, lV=3.45)

nform<- ~(Dose*exp(lKa)*(exp(-(exp(lCl)/exp(lV))*Time)-exp(-exp(lKa)*Time)))/(exp(lV)*(exp(lKa)-
(exp(lCl)/exp(lV))))

nlme.theomod<-deriv(nform, namevec=c("lKa", "lCl", "lV"), function.arg=c("Dose", "Time", "lKa", "lCl",
"lV"))

Theo.nlme<-nlme(Concentration ~ nlme.theomod(Dose, Time, lKa, lCl, lV),
        data=groupedData(Concentration~Time|Id, data=theodf),
        fixed=list(lKa~1, lCl~1, lV~1),
        random=pdDiag(lKa+lCl+lV~1), start = startvec1)

summary(Theo.nlme)
```

nlmer

```
Theo.nlmer<-nlmer(Concentration~nlme.theomod(Dose, Time, lKa, lCl , lV)~(lKa|Id)+(lCl|Id)+(lV|Id),
        data=theodf, start=list(nlpars=startvec1))
```

Theophylline PK – Code (2/3)

saemix

```
saemix.data<-saemixData(name.data=theodf, name.group=c("Id"), name.predictors=c("Dose", "Time"),
name.response=c("Concentration"))

model1cpt<-function(psi,id,xidep) {
   dose<-xidep[,1]
   tim<-xidep[,2]
   ka<-psi[id,1]
   V<-psi[id,2]
   CL<-psi[id,3]
   k<-CL/V
   ypred<-dose*ka/(V*(ka-k))*(exp(-k*tim)-exp(-ka*tim))
   return(ypred)
}

saemix.model<-saemixModel(model=model1cpt, description="Theomodel",
        psi0=matrix(c(1., 20, 0.5, 0.1, 0, -0.01),
                    ncol=3, byrow=TRUE, dimnames=list(NULL, c("ka","V","CL"))),
        transform.par=c(1, 1, 1))

saemix.options<-list(seed=632545, save=FALSE, save.graphs=FALSE)

saemix.fit<-saemix(saemix.model, saemix.data, saemix.options)
```

Theophylline PK – Code (3/3)

nlmixr

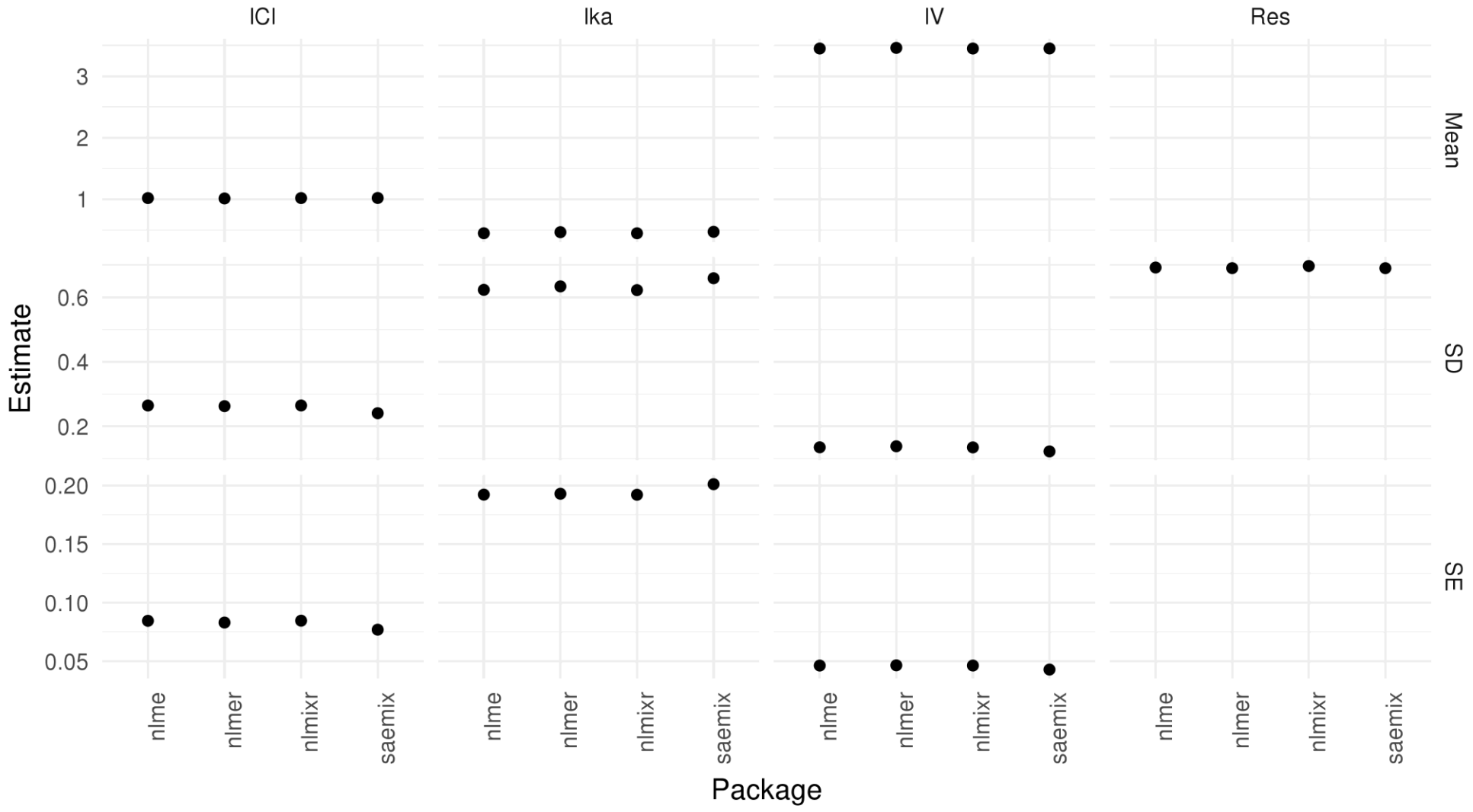
```
uif1 <- function() {
  ini({
     tka <- .5
     tcl <- -3.2
     tv  <- -1
     eta.ka ~ 1
     eta.cl ~ 2
     eta.v  ~ 1
     add.err <- 0.1  })
   model({
     ka <- exp(tka + eta.ka)
     cl <- exp(tcl + eta.cl)
     v <- exp(tv + eta.v)
     linCmt() ~ add(add.err)  })
}

nlmxir.fit1<-nlmixr(uif1, indf, est="nlme", calc.resid=FALSE)
```

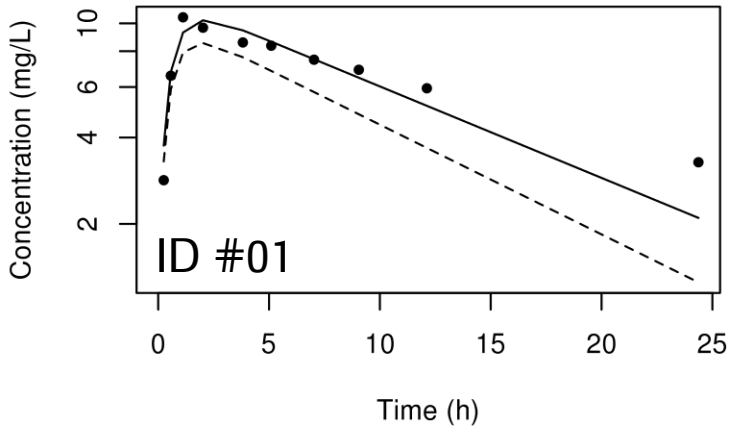
Alternative using ODEs:

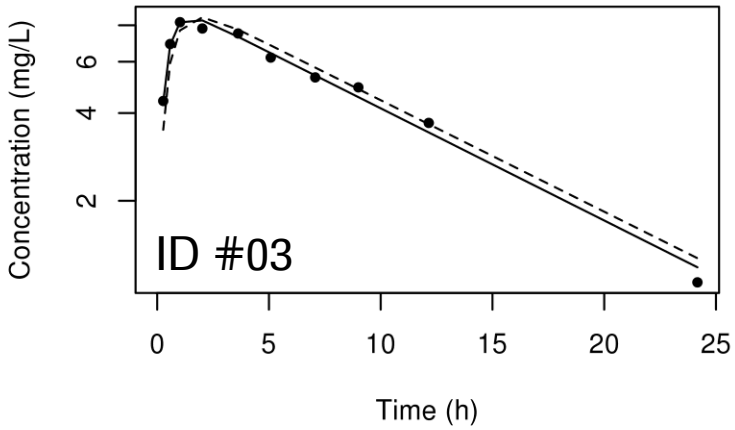
```
model({
  ka <- exp(tka + eta.ka)
  cl <- exp(tcl + eta.cl)
  v <- exp(tv + eta.v)
  d/dt(depot) = -ka * depot
  d/dt(center) = ka * depot - cl / v * center
  cp = center / v
  cp ~ add(add.err)  })
```

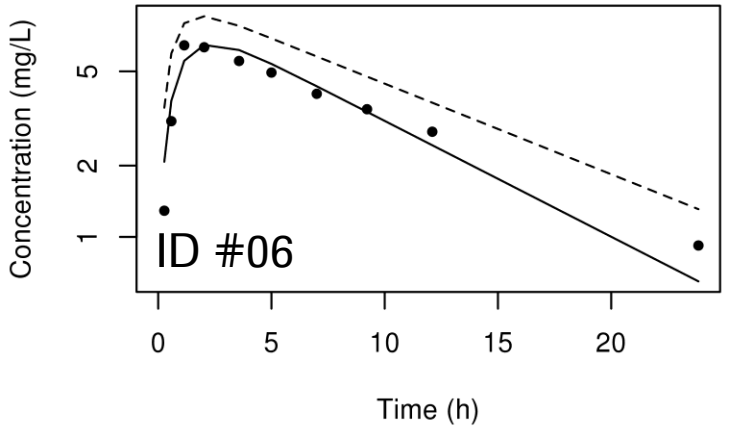
Theophylline – Comparing parameter estimates

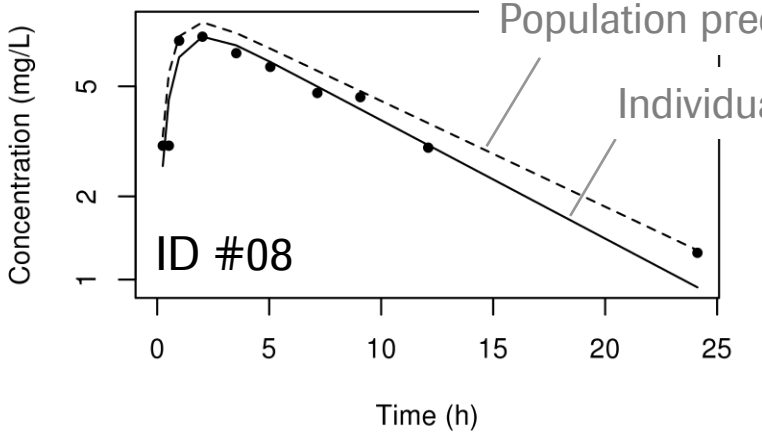


Individual goodness-of-fit





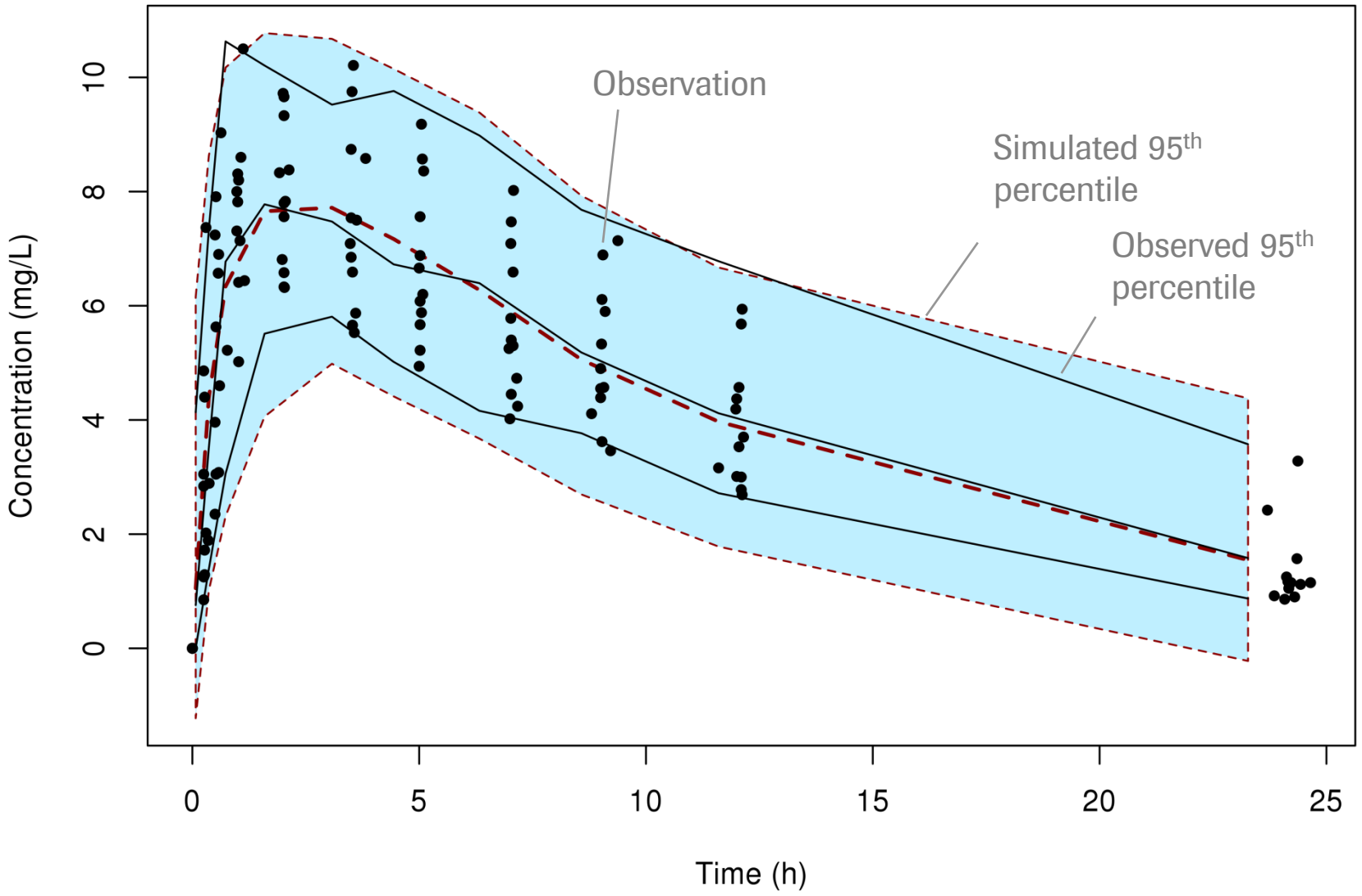




Population prediction

Individual prediction

Internal model validation (a.k.a 'Visual predictive check')



Simulated individual profiles obtained by:

- Bootstrapping from design matrix (sampling times, covariates if any)

- Sampling from IIV (random effects) to obtain individual estimates of model parameters

Overall comparison

	nlme	nlmer	saemix	nlmixr
Relative speed	1	10	100	10
Handling - ease of coding	Easy	Easy	Moderate	Hard
Technical details	Highly accessible	Brief and technical	Rich and technical	Brief
Documentation	Abundant	Nearly absent	Abundant	Nascent
Support from developers	Good	Null	Good	Outstanding
(Published) Testing for accuracy	Reference	No	Extensive	Extensive
Flexibility - types of models you can fit	Large	Limited	Extensive	Extensive+ (ODE)

ACKNOWLEDGMENTS

Authors and contributors to the R packages: *nlme*, *nlmer*, *saemix* and *nlmixr*

THANK YOU

Contact: francois.mercier@roche.com

BACK-UP

sessionInfo()

```
> sessionInfo()
R version 3.4.2 (2017-09-28)
Platform: x86_64-pc-linux-gnu (64-bit)
Running under: Red Hat Enterprise Linux Server 7.2

Matrix products: default
BLAS/LAPACK: /usr/lib64/libopenblas-r0.2.20.so

locale:
 [1] LC_CTYPE=en_US.UTF-8       LC_NUMERIC=C                   LC_TIME=en_US.UTF-8        LC_COLLATE=en_US.UTF-8
 [5] LC_MONETARY=en_US.UTF-8    LC_MESSAGES=en_US.UTF-8        LC_PAPER=en_US.UTF-8       LC_NAME=C
 [9] LC_ADDRESS=C               LC_TELEPHONE=C                 LC_MEASUREMENT=en_US.UTF-8 LC_IDENTIFICATION=C

attached base packages:
[1] stats     graphics  grDevices utils     datasets  methods   base

other attached packages:
 [1] lme4_1.1-14     Matrix_1.2-12   nlmixr_0.9.0-3  bindrcpp_0.2    RxODE_0.6-2     nlme_3.1-131
 [7] saemix_2.1      forcats_0.2.0   stringr_1.2.0   dplyr_0.7.4     purrr_0.2.4     readr_1.1.1
[13] tidyr_0.7.2     tibble_1.3.4    ggplot2_2.2.1   tidyverse_1.2.1 rocheBCE_2.3
```

Doing now what patients need next