

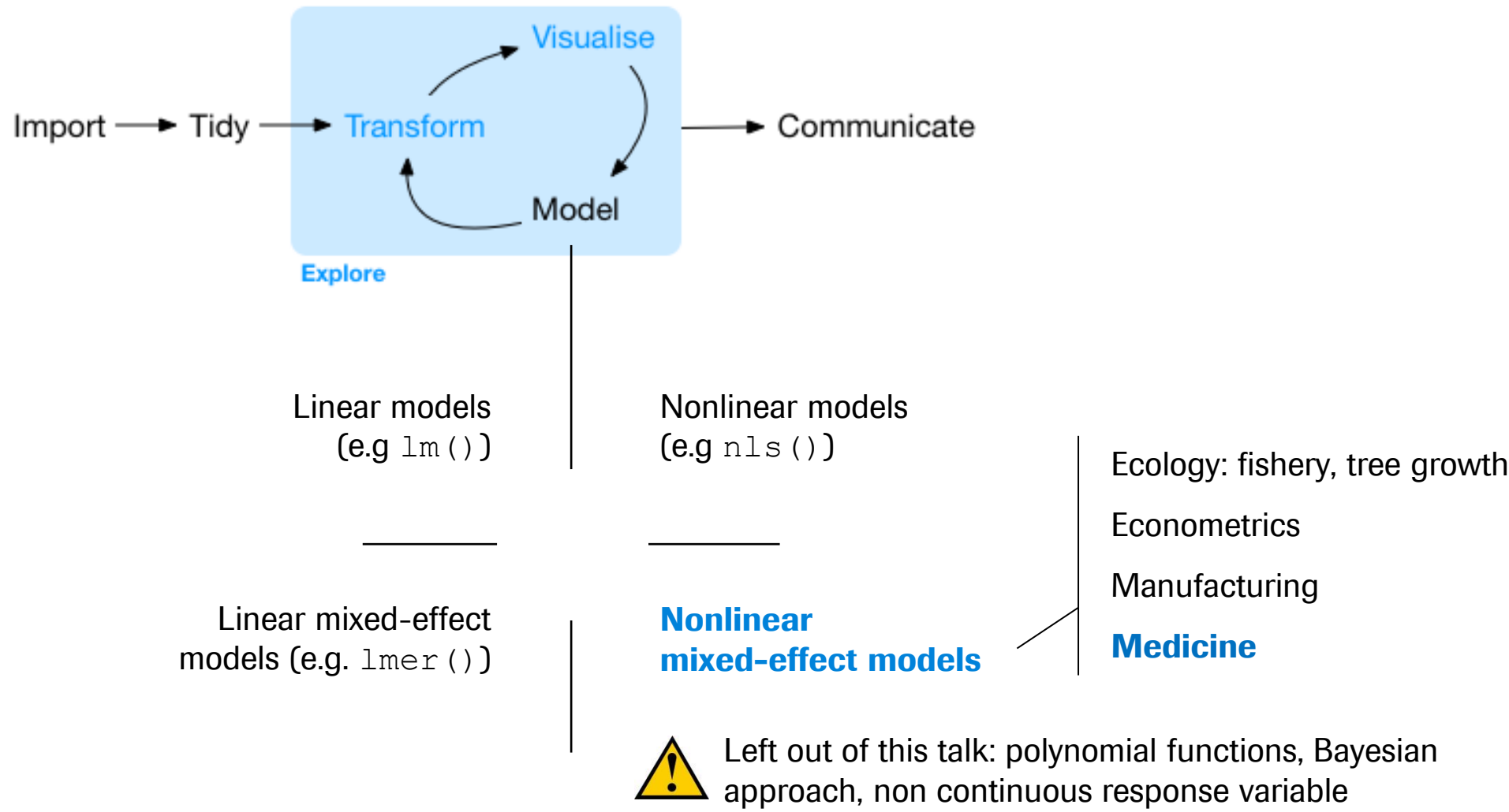
**eRum 2018**

# **Nonlinear mixed effect models in**

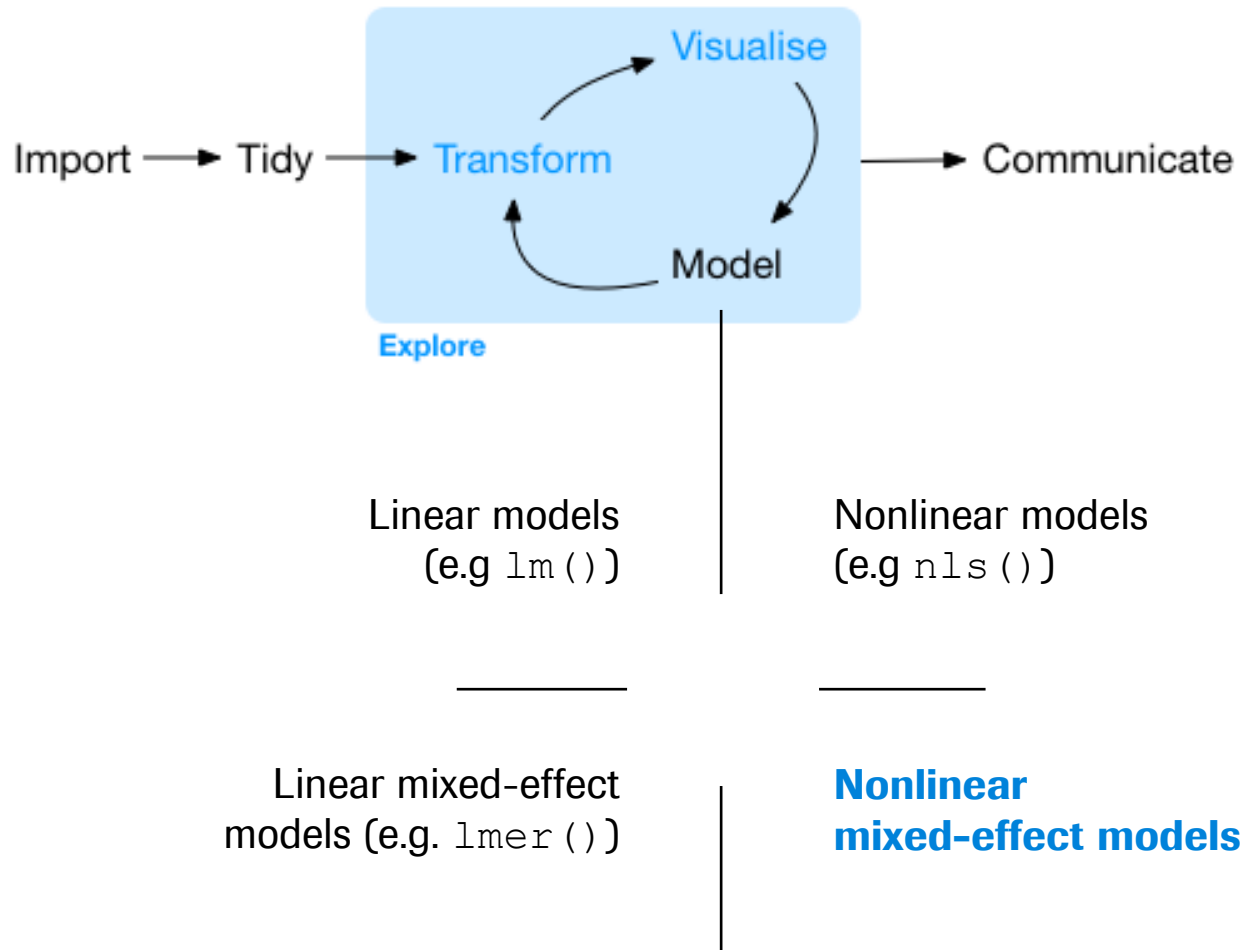
*Francois Mercier*

Pharmaceutical Sciences  
Roche Innovation Center Basel

# Scope & Objective



# Scope & Objective



**THEORY**

# Characteristics of NLMEM

- General formulation:

$$y_{ij} = f(\mathbf{x}_{ij}, \phi_{ki}) + \varepsilon_{ij}$$

$$i = 1, \dots, N$$

$$j = 1, \dots, n_i$$

jth observation in the ith cluster —●  
 Parametric function —●  
 Design matrix —●  
 Residual error —●  
 $\varepsilon_{ij} \sim N(0, \sigma^2)$   
 Fixed effect a.k.a. typical values —●  
 $\phi_{ki} = g(\mathbf{z}_i, \theta_k) + \eta_{ki}$   
 Individual parameters —●  
 Covariates —●  
 $\eta_{ki} \sim N(0, \omega_k^2)$   
 Indiv. random effect (associated with kth parameter) —●

- 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<sup>1</sup> (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<sup>2</sup> and convergence issues<sup>3</sup>. Two approaches have been proposed to overcome these issues:

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

<sup>1</sup>Lindstrom and Bates 1990 Biometrics; <sup>2</sup>Comets and Mentre 2001 J Biopharm Stat; <sup>3</sup>Plan *et al.* 2012 AAPS J. <sup>4</sup>Bates *et al.* 2015 JSS. <sup>5</sup>Dempster *et al.* 1977 JRSS-B.

<sup>6</sup>Delyon *et al.* 1999 *Annals of Stat.*

# Key features of R packages

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

<sup>1</sup>But see package *nlmeODE*; <sup>2</sup>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, Lavenue 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 ( $i = 1, \dots, 12$ ) received a single oral dose  $D$  of Theo at time  $t = 0$ . Concentration of theo  $C$  was measured in blood at 11 time points ( $j = 1, \dots, 11$ ) over 25 hours.
- Pharmacokinetics of Theo can be described by a NLMEM, specifically a one-compartment model with first-order absorption and linear elimination:

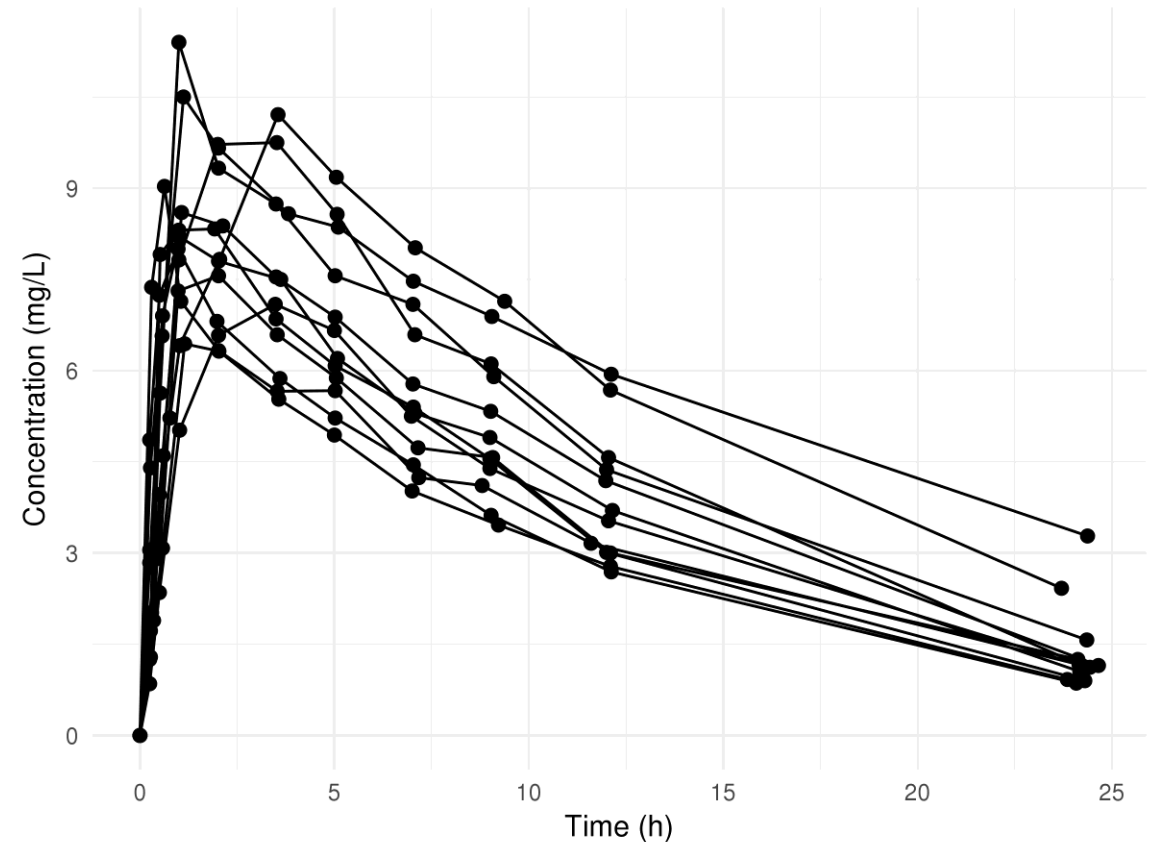
$$C_{ij} = f(t_{ij}, D_i) + \varepsilon_{ij}$$

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

$ka$ : 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"))

modellcpt<-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=modellcpt, 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

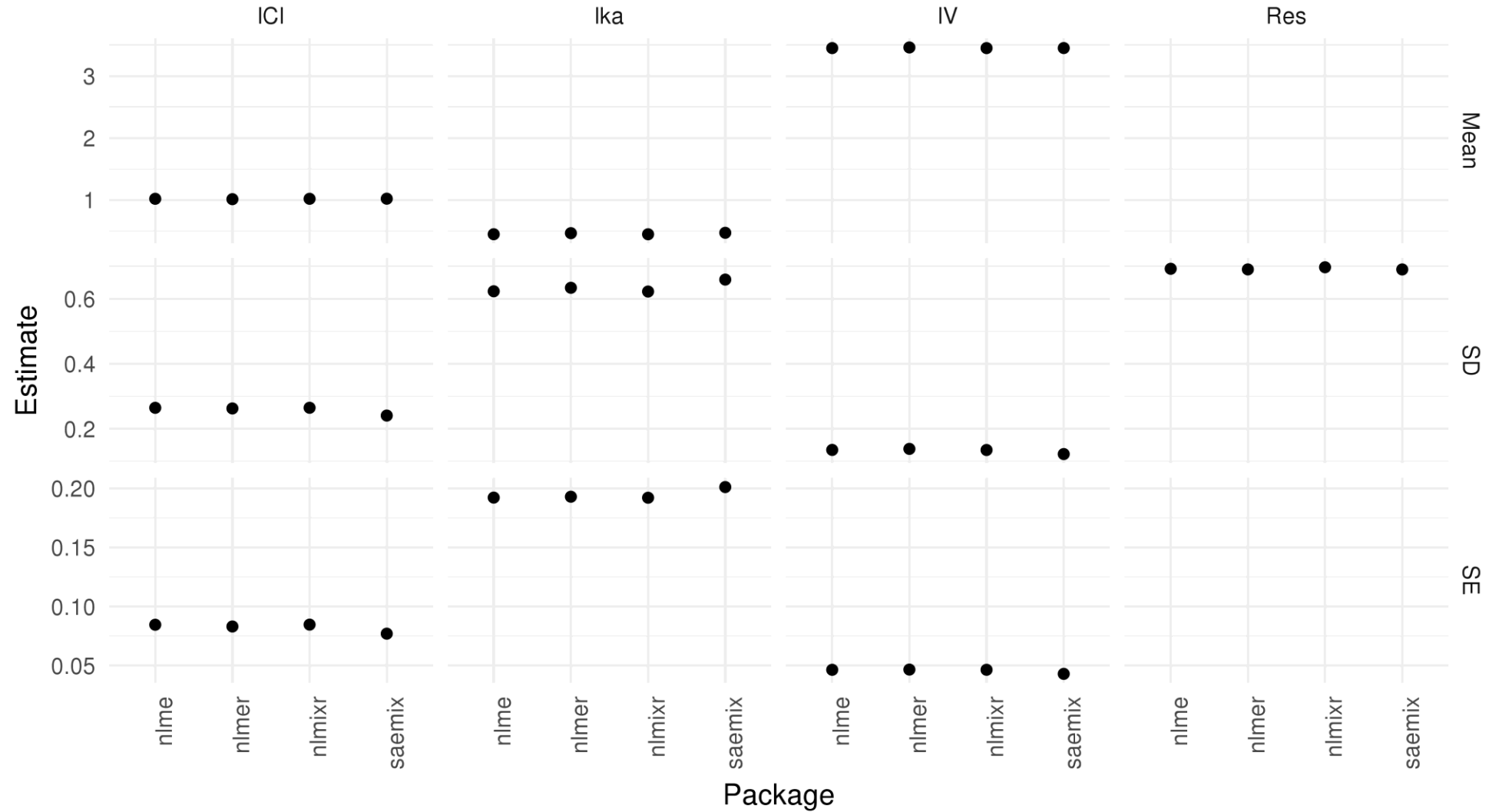
```
uif1 <- function() {  
  ini({  
    tka <- .5  
    tcl <- -3.2  
    tv  <- -1  
    eta.ka ~ 1  
    eta.cl ~ 2  
    eta.v  ~ 1  
    add.err <- 0.1  })  
  model({  
    ka <- exp(tka + eta.ka)  
    cl <- exp(tcl + eta.cl)  
    v <- exp(tv + eta.v)  
    linCmt() ~ add(add.err)  })  
}
```

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

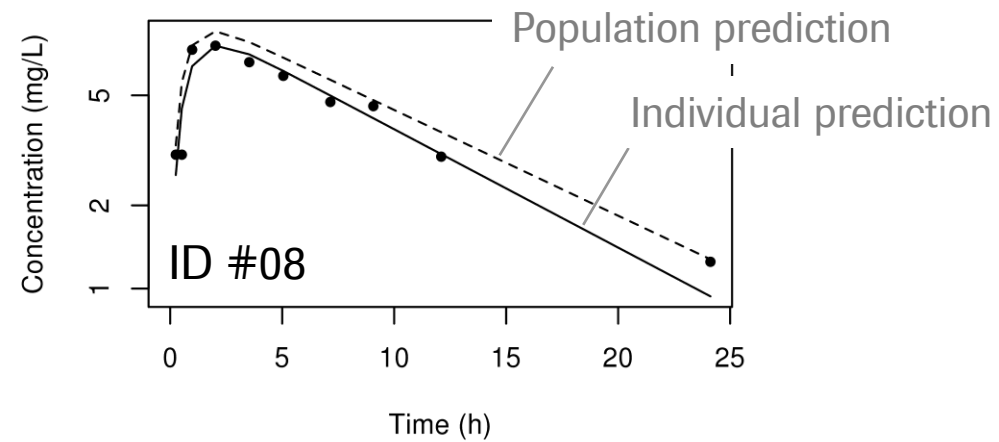
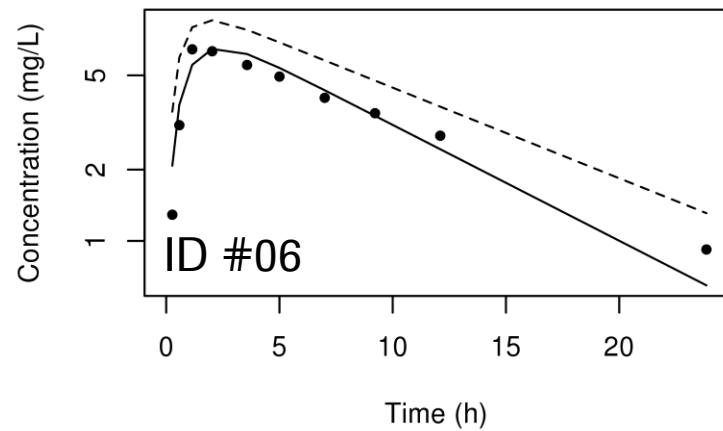
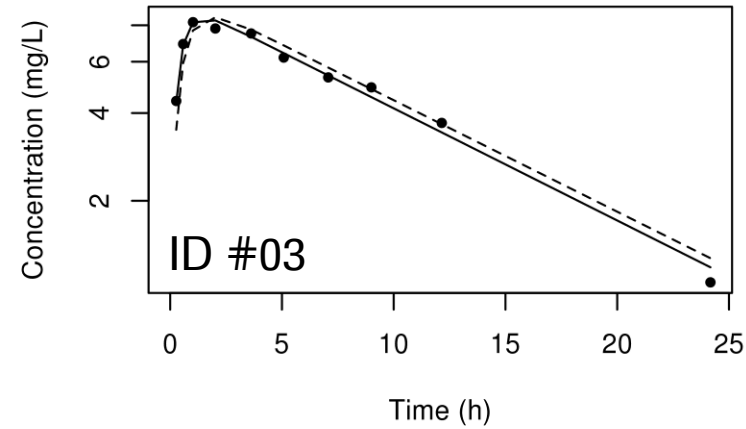
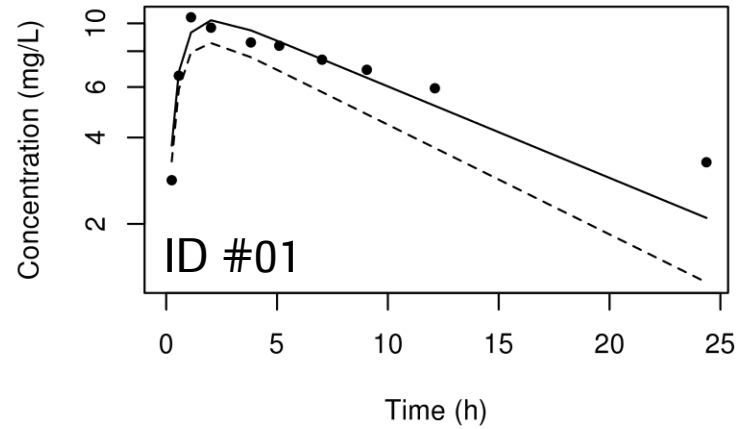
## *Alternative using ODEs:*

```
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)  })
```

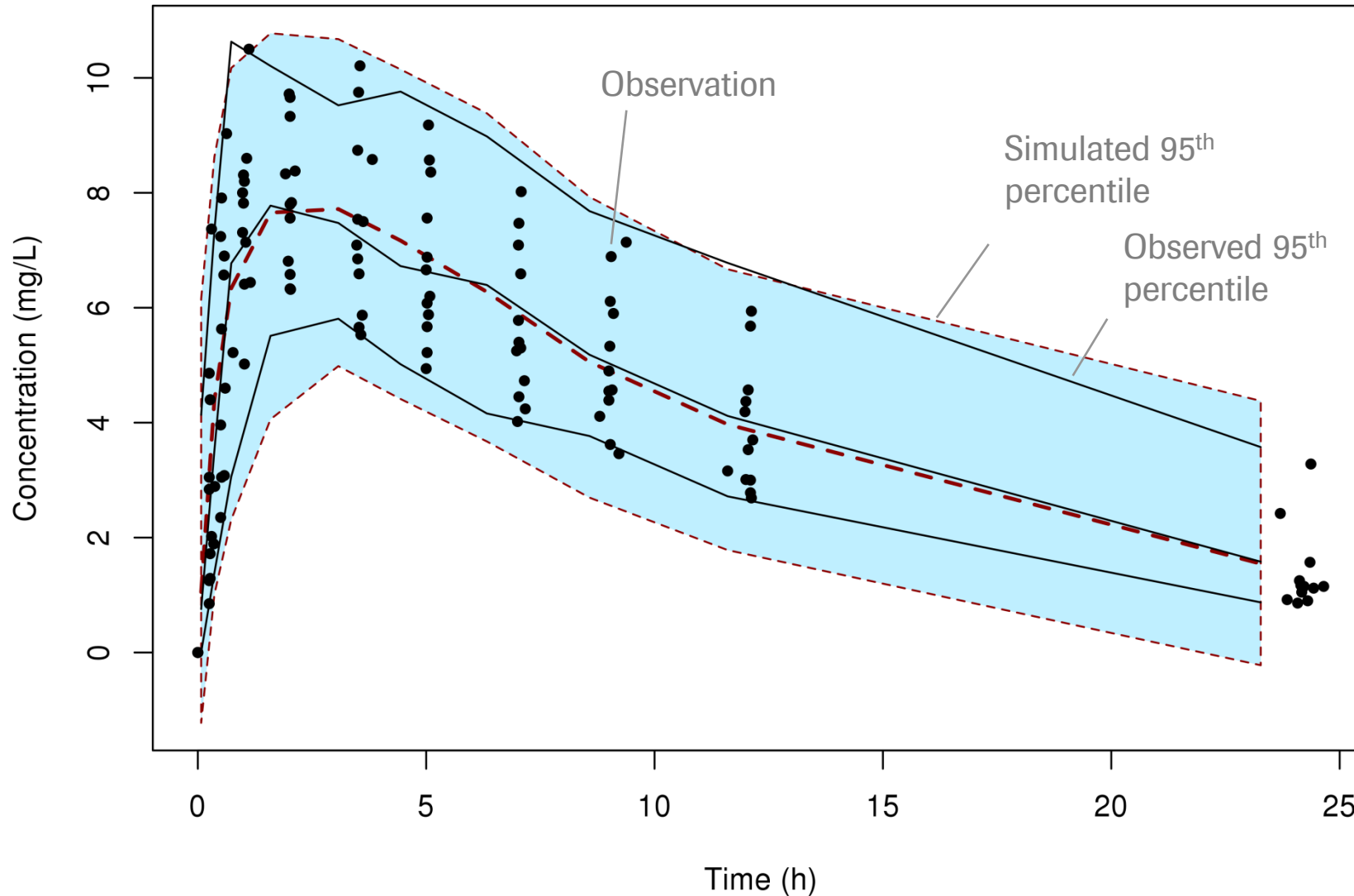
# Theophylline – Comparing parameter estimates



# Individual goodness-of-fit



# 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

|   | <b>nlme</b>       | <b>nlmer</b>        | <b>saemix</b>      | <b>nlmixr</b>    |
|---|-------------------|---------------------|--------------------|------------------|
| 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](mailto: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*