Comparison of pharmacokinetic parameters estimated by the experimental R package 'nlmixr' and MONOLIX

Elvira Erhardt (1), Tom Jacobs (2), Mauro Gasparini (1)

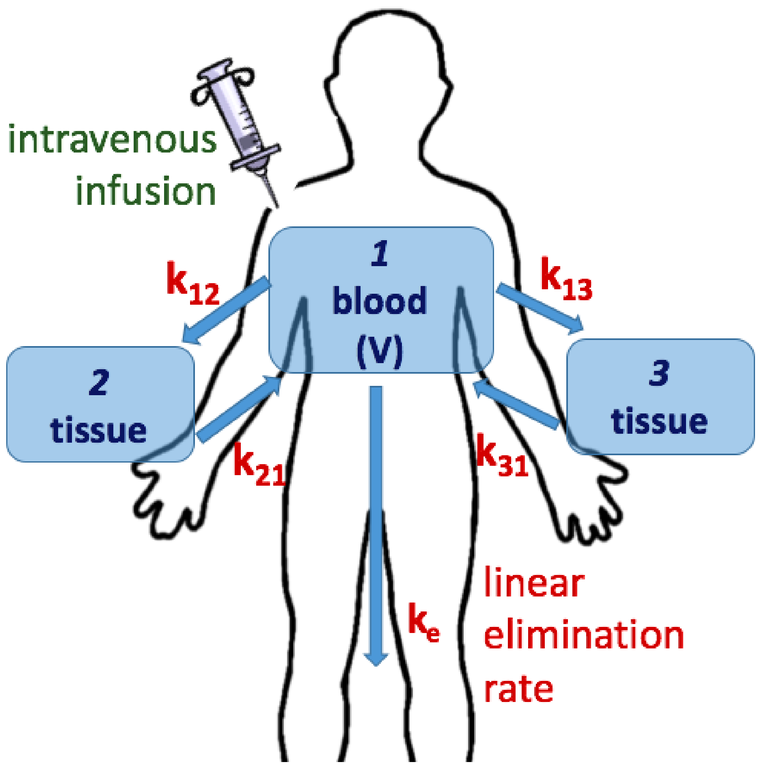
(1) Politecnico di Torino, Turin, Italy, (2) Janssen Pharmaceutica NV, Beerse, Belgium.

INTRODUCTION

The aim of this work was to model in-vivo pharmacokinetic (PK) data using a three-compartment model with first-order elimination. The parameters of the compartmental model were estimated by non-linear mixed models in R and MONOLIX. The fit of the resulting models was compared to the individual intravenous (IV) infusion data.

METHODS

- To examine the drug's PK, the mean and individual plasma concentration time profile after intravenous infusion has been measured in each of 18 subjects at 20 time points.
- Each infusion lasted 15min and contained 300 µg (=0.3 mg).
- PK processes can be simplified and visualized as compartmental models [3]:



- Mathematically, pharmacokinetic models are characterized by *non-linear models*,

$$y_{ij} = f(t_{ij}; \phi_{ij}, c_{ij}) + e_{ij}, \quad e_{ij} \sim \mathcal{N}(0, \sigma^2)$$
$$i = 1, \dots M, \quad j = 1, \dots n_i$$

- The function f can be defined as the solution to a system of:

ordinary differential equations (ODE's)

$$\begin{aligned}
\frac{dA_1(t)}{dt} &= \text{absorption - elimination} \\
&= k_{21}A_2(t) + k_{31}A_3(t) - [k_{12}A_1(t) + k_{13}A_1(t) + k_eA_1(t)] \\
\frac{dA_2(t)}{dt} &= k_{12}A_1(t) + k_{32}A_3(t) - [k_{21}A_2(t) + k_{23}A_2(t)] \\
\frac{dA_3(t)}{dt} &= k_{13}A_1(t) + k_{23}A_2(t) - [k_{31}A_3(t) + k_{32}A_3(t)]
\end{aligned}$$

- To predict the drug concentration C in the blood for any time t, the amount of drug (A) in the blood has to be divided by the *apparent volume of distribution* (V) of the blood:

$$C_1(t) = A_1(t)/V_1$$

- Data not only from one subject, but from a whole sample of 18 subjects
- Parameters are different for each subject i, thus, are the sums of population (fixed) effects and individual (random) effects [2]:

$$V_i = \beta_V + b_{V,i}, \qquad b_{V,i} \sim \mathcal{N}(0, \sigma_b^2)$$

$\Rightarrow$ **Non-linear mixed effects** modelling

- The fixed effects model was determined using nonlinear least-squares estimation in R (functions `nls()` and `optim()` (Gauss-Newton algorithm)).
- The random effects model was computed in
  - the experimental R-package `'nlmixr'` [4], applying the functions `nlme_lin_cmpt()` and `nlme_ode()`,
  - the frequentist estimation procedure of MONOLIX [1].

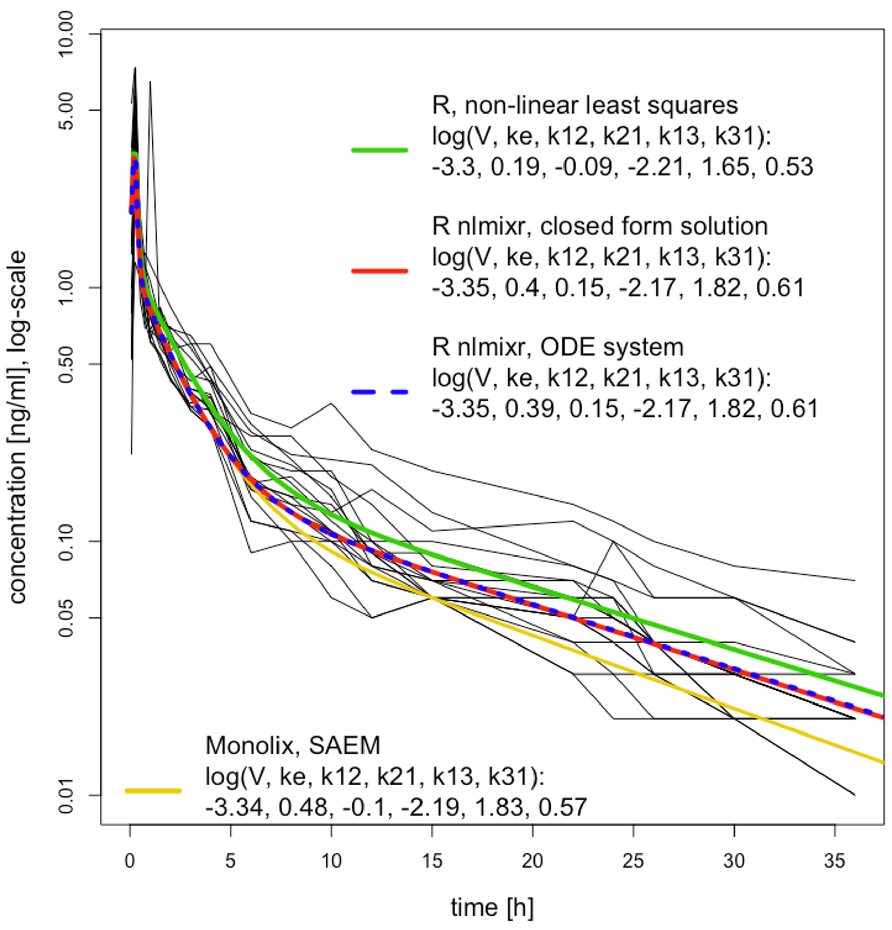
NLMIXR CODE

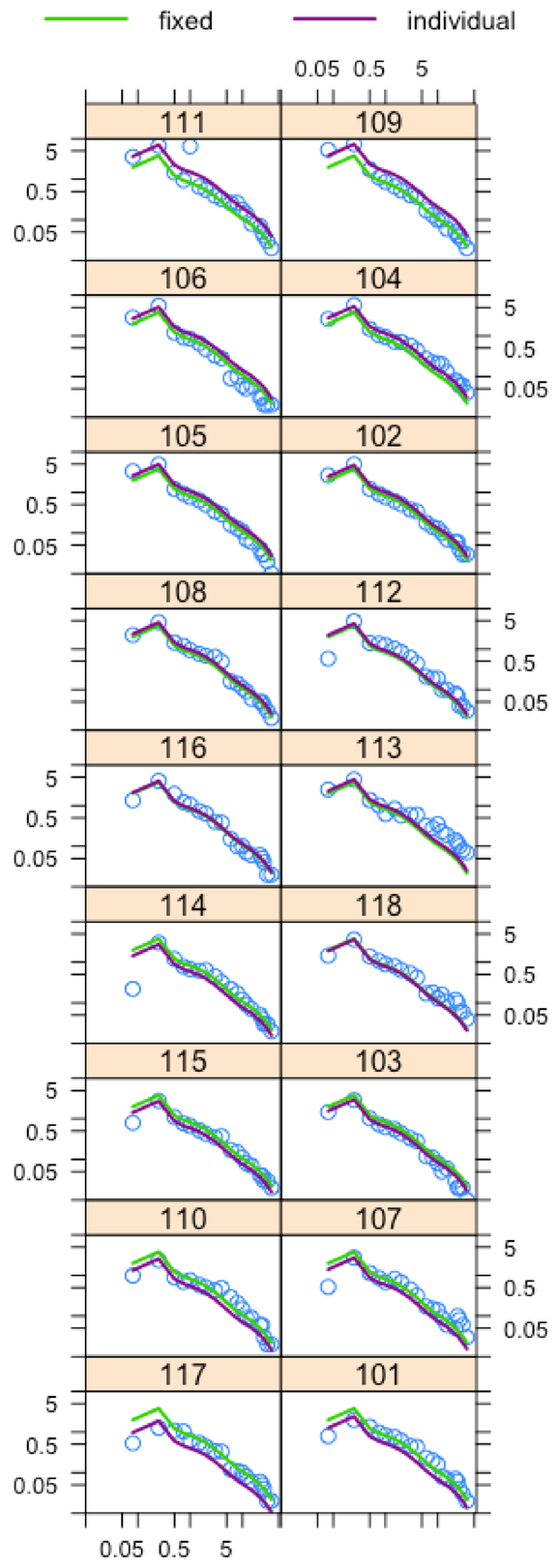
```
#1) NLME_LIN_CMPT (closed form solution)
specs.1 <- list(fixed = lV+lKE+lK12+lK21+lK13+lK31 ~ 1, random = lV~1|ID, start = c(...))
Mixr.1 <- nlme_lin_cmpt(data, par_model=specs.1, ncmt=3, oral=F, infusion=TRUE, parameterization=2, control = ...)

#2) NLME_ODE (ODE system)
ode <- "   d/dt(centr) = K21*periph+K31*periph2-K12*centr-K13*centr-KE*centr;
           d/dt(periph) =-K21*periph+K12*centr;
           d/dt(periph2)=-K31*periph2+K13*centr;  "
mypar <- function(lV, lKE, lK12, lK21, lK13, lK31)
            { V  = exp(lV); KE = exp(lKE); K12= exp(lK12); K21 = exp(lK21); K13= exp(lK13); K31 = exp(lK31) }
specs.ODE1 <- list(fixed = lV+lKE+lK12+lK21+lK13+lK31 ~ 1, random = lV~1|ID, start = c(...))
MixrODE.1 <- nlme_ode(data, model=ode, par_model=specs.ODE1, par_trans=mypar, response="centr",  control = ...,
                      response.scaler="V")
```

RESULTS

For reasons of convergence and lower AIC, only the random effect for V has been included.
The result of the fixed effects model served as initial values for the mixed effects models.





		R		Monolix
	NLS	NLME_LIN_CMPT	NLME_ODE	SAEM
log(V) FE	-3.30 (0.10)	-3.34 (0.11)	-3.34 (0.11)	-3.34
log(V) RE	-	SD: 0.375	SD: 0.375	SD: 0.389
log(ke)	0.19 (0.45)	0.40 (0.29)	0.39 (0.20)	0.48
log(k12)	-0.09 (0.74)	0.15 (0.44)	0.15 (0.45)	-0.10
log(k21)	-2.21 (1.74)	-2.17 (1.05)	-2.17 (0.93)	-2.19
log(k13)	1.65 (0.23)	1.82 (0.15)	1.82 (0.15)	1.83
log(k31)	0.53 (0.32)	0.61 (0.20)	0.61 (0.16)	0.57

	R		Monolix
	NLME_LIN_CMPT	NLME_ODE	SAEM
AIC	373.21	373.21	373.49
BIC	403.89	403.89	380.62
logLik	-178.60	-178.60	-178.75

Note: In the individual plots the time-axis has been log-scaled for improved visibility.
SD: standard deviation. Table: values in brackets are standard errors.

DISCUSSION

As can be seen in the left graph, the estimated PK parameters - by R as well as by MONOLIX - lie very close together, fit the individual concentration curves well and make biologically sense. The random effects models are preferred over the NLS-estimation as they incorporate also the individual effects. The parameters estimated in R fit the observed data better based on visual inspection of the individual profiles.

REFERENCES

[1] Lixoft. *Monolix 2016R1 User guide*. http://monolix.lixoft.com/single-page/. Last visit on: 15 June, 2016.

[2] J. Pinheiro and D. Bates. *Mixed-Effects Models in S and S-PLUS*. Statistics and Computing. Springer New York, 2000.

[3] S. Rosenbaum. *Basic Pharmacokinetics and Pharmacodynamics: An Integrated Textbook and Computer Simulations*. Wiley, 2011.

[4] W. Wang. nlmixr: an r package for fitting pk and pkpd models. https://github.com/nlmixrdevelopment/nlmixr/blob/master/inst/nlmixr-intro.pdf, 2016. [Online; accessed 20-February-2017].

June 8, 2017
elvira.erhardt@polito.it
http://www.ideas-itn.eu

This project has received funding from the European Unions Horizon 2020 research and innovation programme under the Marie Sklodowska-Curie grant agreement No 633567.