**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 concentrations of the IV infusion were compared to the individual intravenous (IV) infusion data.
- PK processes can be simplified and visualized as compartmental models [3]:

![Diagram of a three-compartment model](image)

- Mathematically, pharmacokinetic models are characterized by non-linear models,
  \[ y_i = f(t_i; \phi_i, \gamma_i) + e_i, \quad e_i \sim \mathcal{N}(0, \sigma_i) \]
  \( i = 1, \ldots, M, \quad j = 1, \ldots, n \)
- The function \( f \) can be defined as the solution to a system of ordinary differential equations (ODEs):
  \[
  \begin{align*}
  \frac{dA_1(t)}{dt} &= K_{21}A_2(t) + K_{31}A_3(t) - K_{12}A_1(t) - K_{13}A_1(t) \\
  \frac{dA_2(t)}{dt} &= K_{12}A_1(t) + K_{13}A_1(t) - K_{21}A_2(t) - K_{23}A_2(t) \\
  \frac{dA_3(t)}{dt} &= K_{21}A_2(t) + K_{23}A_3(t) - K_{31}A_3(t) - K_{32}A_3(t)
  \end{align*}
  \]
- 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 drug:
  \[ C(t) = A(t)/V \]
- 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]:
  \[ V_j = \beta_V + b_{Vj}, \quad b_{Vj} \sim \mathcal{N}(0, \sigma^2_V) \]

**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.

![Graph showing concentration vs time](image)

**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 biological 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**


**NLMIXR CODE**

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

#2) NLMIXR_ODE (ODE system)
ode <- "\[d/dt(centr) = K21*periph+K31*periph2-K12*centr-K13*centr-KE*centr; d/dt(periph) = K12*periph+K13*centr; d/dt(periph2) = K31*periph2+K13*centr; \]
mpar <- function(IV, KE, K12, K21, K13, K31) {
  ( V = expr(IV), KE = expr(KE), K12 = expr(K12), K21 = expr(K21), K13 = expr(K13));
  specs.ODE1 <- list(fixed = lV+lKE+lK12+lK21+lK13+lK31 ~ 1, random = lV~1|ID, start = c(...))
  Mixr.ODE.1 <- nlmixr(data, model=ode, par_model=specs.D, par_trans=mpar, responses="centr", control = ...)
}
Mixr.ODE.1 <- nlmixr(data, model=ode, par_model=specs.D, par_trans=mpar, responses="centr", control = ...)
```

**DISCUSSION**

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