

Simulation and parameter estimation with rxode2 and nlmixr²

Rxode2/nlmixr2 PopSim Course Copenhagen 2024

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Course outline

- Introduction to rxode2 simulation
- Introduction to nlmixr² and parameter estimation
- Hands on with the warfarin PK models (part 1)
- Advanced capabilities nlmixr²
- Hands on with the warfarin PK and PKPD models (part 2)

rxode2 simulation software in R

- rxode2 is pharmacometric simulation software using ordinary differential equations (ODEs) as an open-source R package
- Rewritten by Matt Fidler after Wenping Wang's original RxODE package, available on CRAN^a and GitHub^b, and described in a tutorial in CPT:PSP^c and with online documentation^d
- Simulation of ODEs was already possible in R (using deSolve), but was slow and virtually impossible to code with flexible dosing history
- rxode2 has rapid execution due to compilation in C
- rxode2 allows fully flexible dosing history
- Stable and mature software for Windows, OS X (in docker), Linux
- Requires external compilers (provided by Rtools on Windows)
- rxode2 is an evolution of the original RxODE package: after a full re-write of the code backward compatibility could not be guaranteed

[a] CRAN: <https://cran.r-project.org/web/packages/rxode2>

[b] GitHub: <https://github.com/nlmixr2/rxode2>

[c] Wang W et al. CPT:PSP (2016) 5, 3–10.

[d] RxODE packagedown: <https://nlmixr2.github.io/rxode2>

Basic example load the library and define the ODEs

```
library(rxode2)

## set up the system of differential equations (ODEs)
odeKA1 <- "
d/dt(depot) = -ka*depot;                      # This is compartment number 1 (depot)
d/dt(central) = ka*depot-(cl/v)*central; # This is compartment number 2 (central)
C1=central/v;                                # Calculates concentration from amount
"
```

Compile the model and set the parameter values

```
library(rxode2)

## set up the system of differential equations (ODEs)
odeKA1 <- "
d/dt(depot) = -ka*depot;                      # This is compartment number 1 (depot)
d/dt(central) = ka*depot-(cl/v)*central; # This is compartment number 2 (central)
C1=central/v;                                # Calculates concentration from amount
"

## compile the model
modKA1 <- rxode2(model = odeKA1)

## provide the parameter values to be simulated:
Params <-
  c(ka = log(2)/0.5, # 1/h (absorption half-life of 30 minutes)
    cl = 0.135,      # L/h
    v = 8)           # L
```

Create an eventTable that defines the doses and the sampling times

```
library(rxode2)
## set up the system of differential equations (ODEs)
odeKA1 <- "
d/dt(depot) = -ka*depot;                      # This is compartment number 1 (depot)
d/dt(central) = ka*depot-(cl/v)*central; # This is compartment number 2 (central)
C1=central/v;                                # Calculates concentration from amount
"
## compile the model
modKA1 <- rxode2(model = odeKA1)
## provide the parameter values to be simulated:
Params <-
  c(ka = log(2)/0.5, # 1/h (absorption half-life of 30 minutes)
    cl = 0.135,      # L/h
    v = 8)           # L

## create an empty event table that stores both dosing and sampling information :
ev <- eventTable()

## add a dose to the event table:
ev$add.dosing(dose = 500) #mg

## add time points to the event table where concentrations will be simulated
## these actions are cumulative
ev$add.sampling(seq(0, 120, 0.1))
```

Solve the equations and plot the results

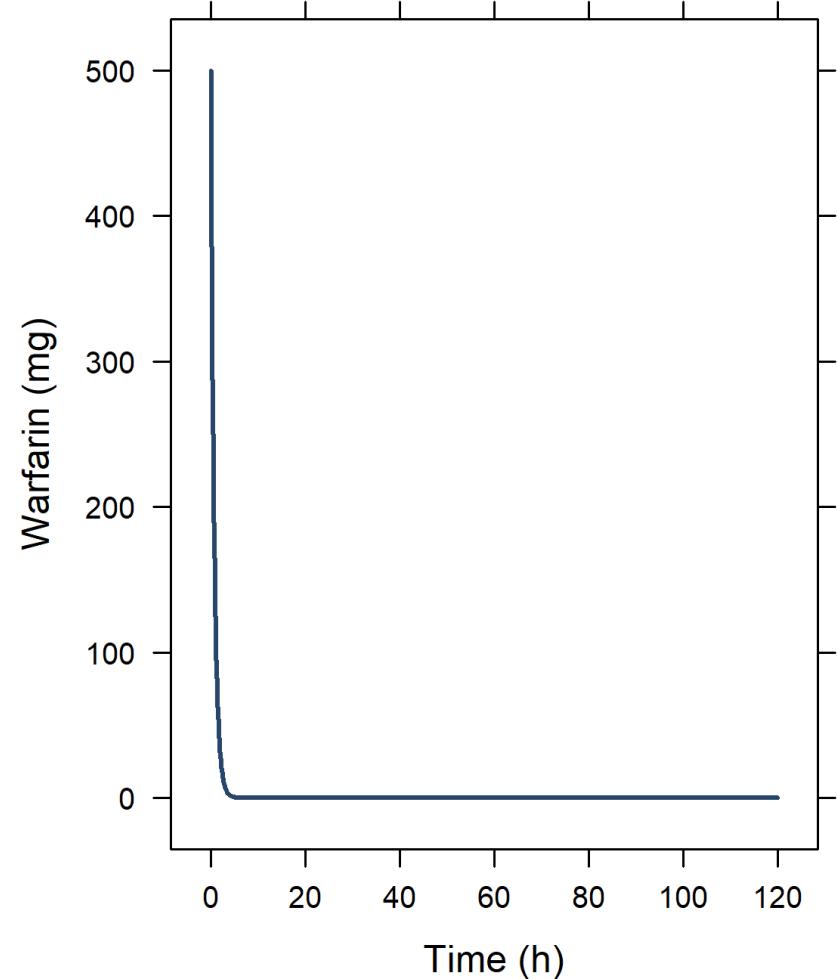
```
library(rxode2)
## set up the system of differential equations (ODEs)
odeKA1 <- "
  d/dt(depot) = -ka*depot;                      # This is compartment number 1 (depot)
  d/dt(central) = ka*depot-(c1/v)*central; # This is compartment number 2 (central)
  C1=central/v;                                # Calculates concentration from amount
"
## compile the model
modKA1 <- rxode2(model = odeKA1)
## provide the parameter values to be simulated:
Params <-
  c(ka = log(2)/0.5, # 1/h (absorption half-life of 30 minutes)
    c1 = 0.135,      # L/h
    v = 8)           # L

## create an empty event table that stores both dosing and sampling information :
ev <- eventTable()
## add a dose to the event table:
ev$add.dosing(dose = 500) #mg
## add time points to the event table where concentrations will be simulated
## these actions are cumulative
ev$add.sampling(seq(0, 120, 0.1))

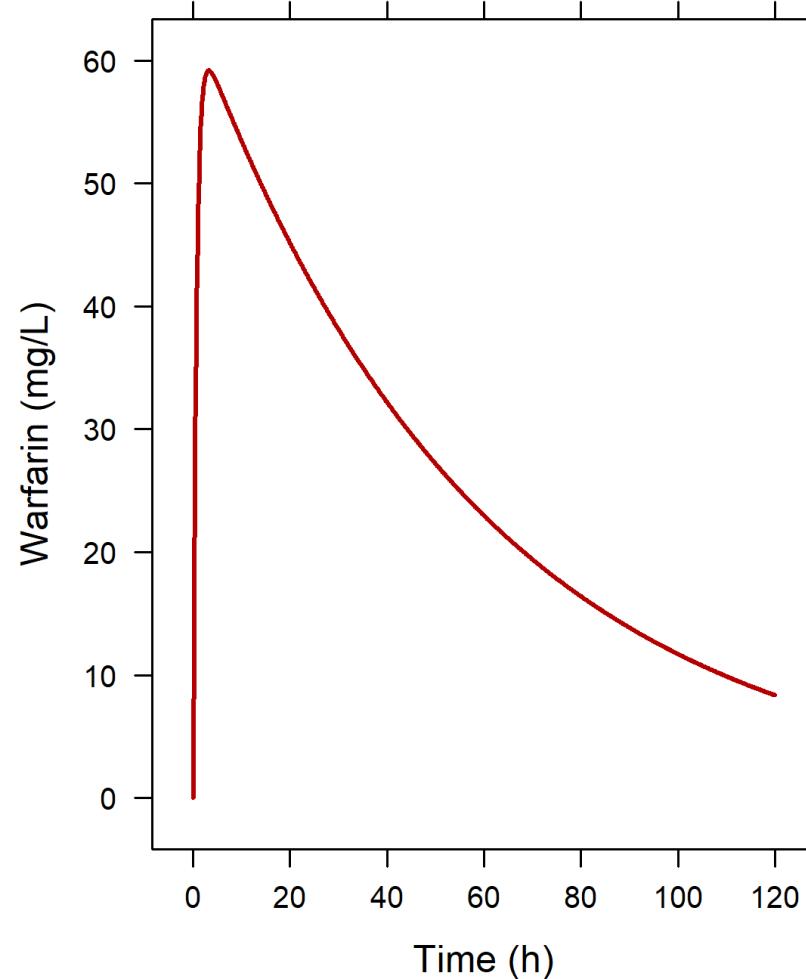
## Then solve the system
## The output from rxSolve is a solved RxODE object,
## By making it a data.frame only the simulated values are retained:
Res <- data.frame(rxSolve(modKA1, Params, ev))
```

Single bolus dose in the first (depot) compartment

Depot compartment amounts



Central compartment concentrations



Adding extra doses (expand the existing eventTable): three additional infusions in the central compartment

```
## Extend the eventTable by adding three infusions to the central compartment
## Remember: updates to the eventTable are cumulative

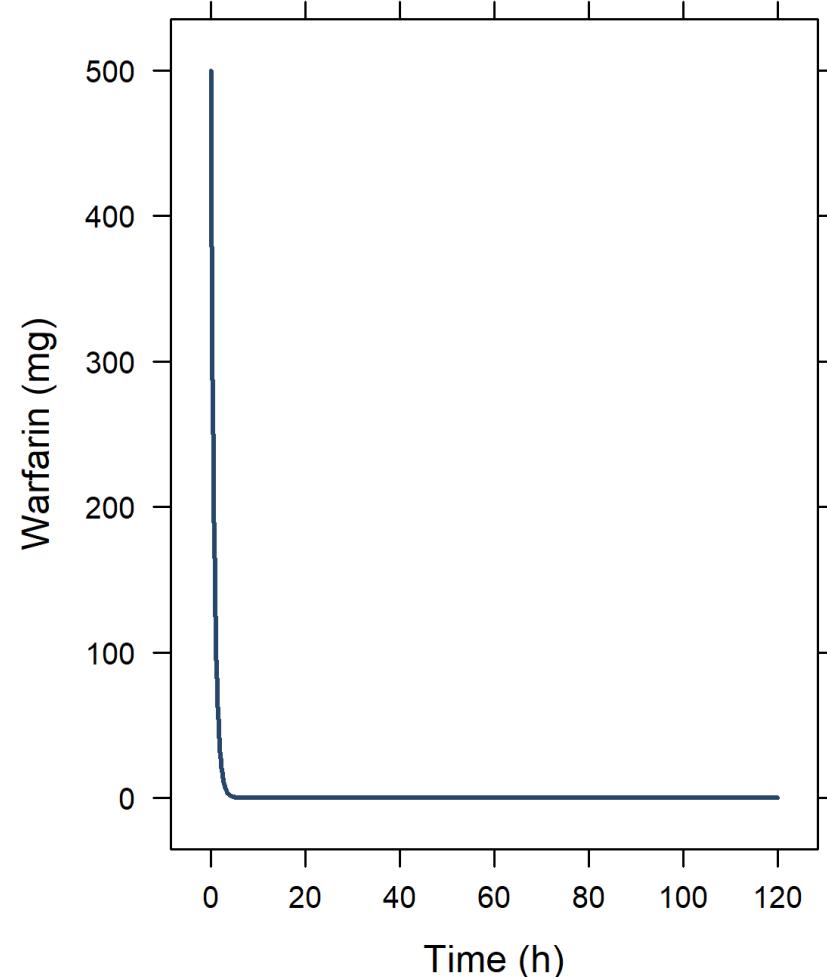
ev$add.dosing(
  dose = 250,           #mg
  nbr.doses = 3,        #add three doses
  dosing.to = 2,         #add them to the second ODE in the model (=central)
  dosing.interval = 12, #h; set the doses 12 hours apart
  rate = 125,            #mg/h; infuse at a rate of 125 mg/h, resulting in 2-hour infusions
  start.time = 36        #h; have the three doses start at 36h
)

Res <- data.frame(rxSolve(modKA1, Params, ev))
```

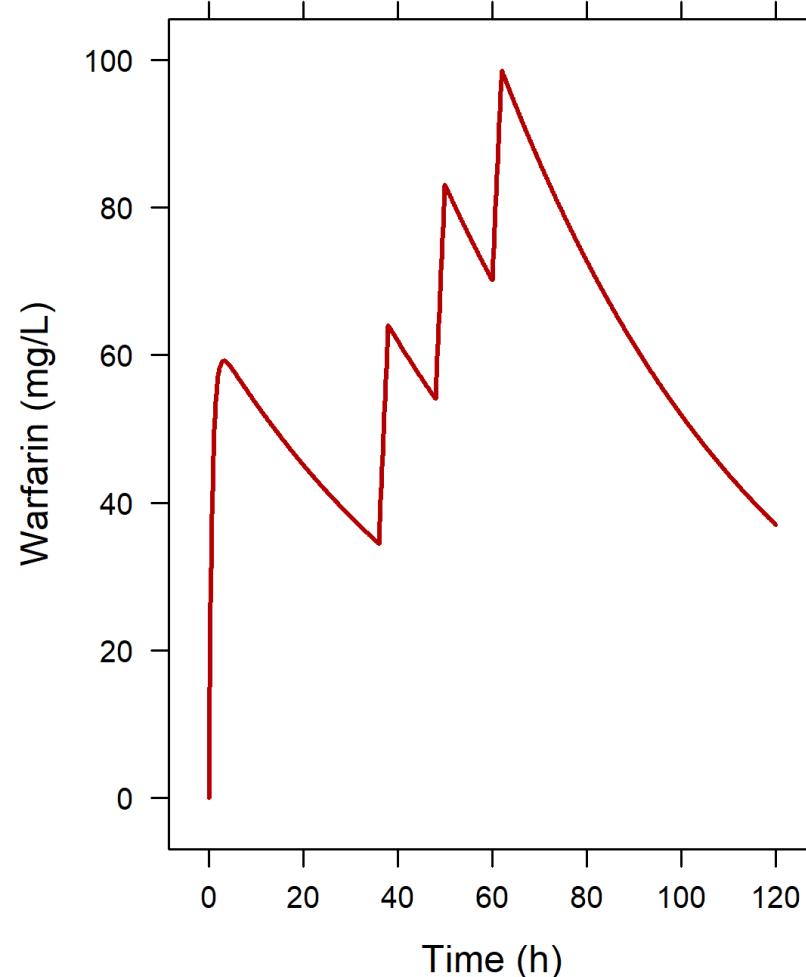
Multiple dose in different compartments

Only the first dose goes into the depot (first) compartment

Depot compartment amounts



Central compartment concentrations



Extend the model: add a transit compartment...

```
odeKA1trans <- "
  d/dt(depot) = -ka*depot;
  d/dt(central) = ktr*trans-(cl/v)*central; # update to central: input from trans
  d/dt(trans) = ka*depot-ktr*trans;        # transit compartment between depot and central
  C1=central/v;
"

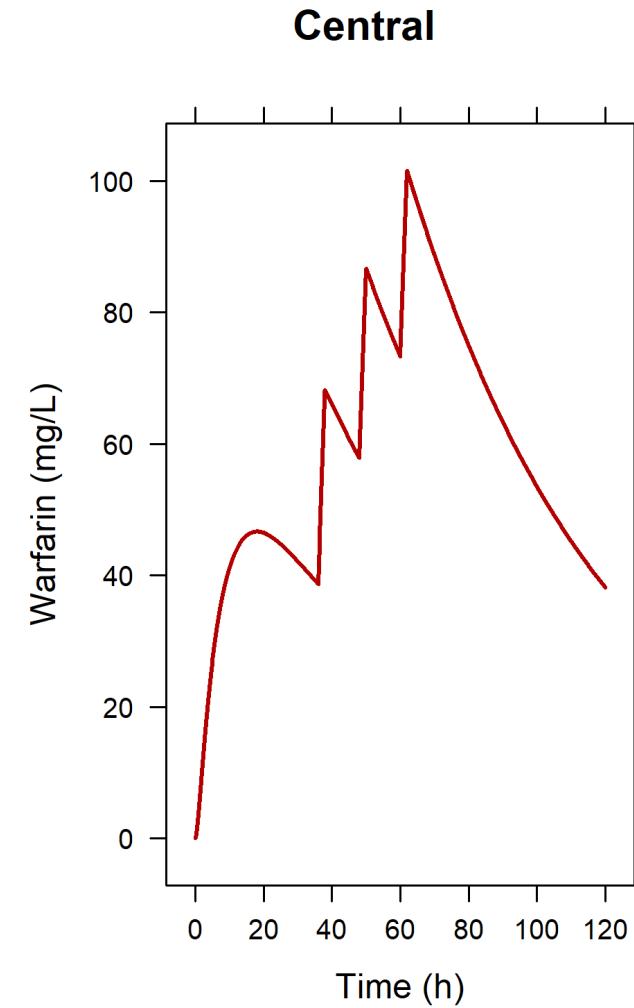
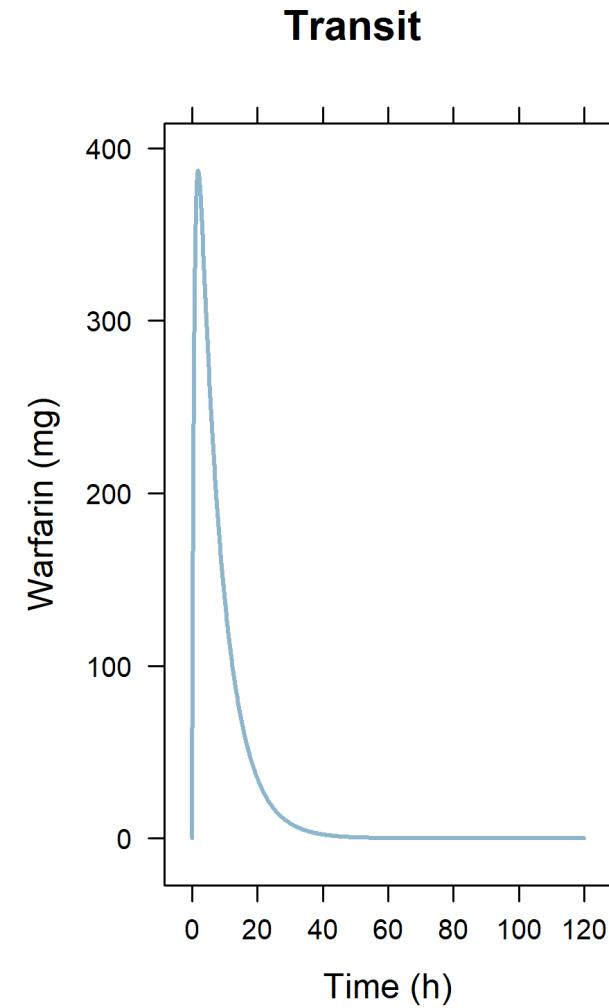
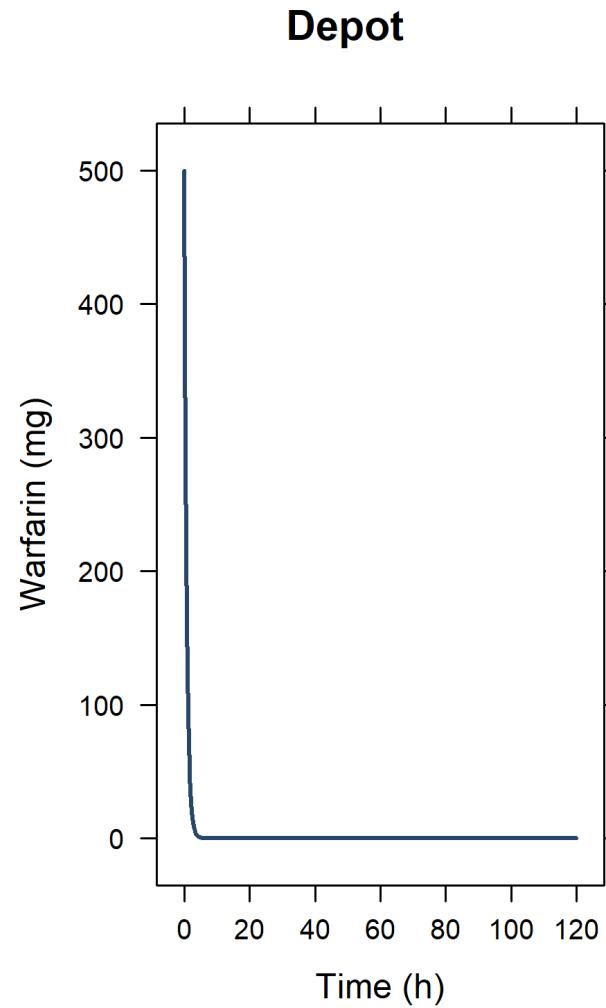
## compile the model
modKA1trans <- rxode2(model = odeKA1trans)

## provide the extra ktr parameter:
Params2 <- c(
  ka = log(2)/0.5, # 1/h (absorption half-life of 30 minutes)
  cl = 0.135,       # L/h
  v = 8,            # L
  ktr = log(2)/5   # 1/h (transit half-life of 5 hours)

## the eventTable does not have to change
Res <- data.frame(rxSolve(modKA1trans, Params2, ev))

## if the trans compartment had been put as second compartment above,
## the eventTable would need an update to infuse in compartment 3 instead
```

...adding a transit compartment between depot and central



Or with five transit compartments and only bolus doses in the depot...

```
odeKA5trans <- "
d/dt(depot) = -ktr*depot;
d/dt(central) = ktr*trans5-(cl/v)*central; # update to central: input from trans5
d/dt(trans1) = ktr*depot-ktr*trans1;      # use same constant for every compartment
d/dt(trans2) = ktr*trans1-ktr*trans2;
d/dt(trans3) = ktr*trans2-ktr*trans3;
d/dt(trans4) = ktr*trans3-ktr*trans4;
d/dt(trans5) = ktr*trans4-ktr*trans5;
C1=central/v;
"

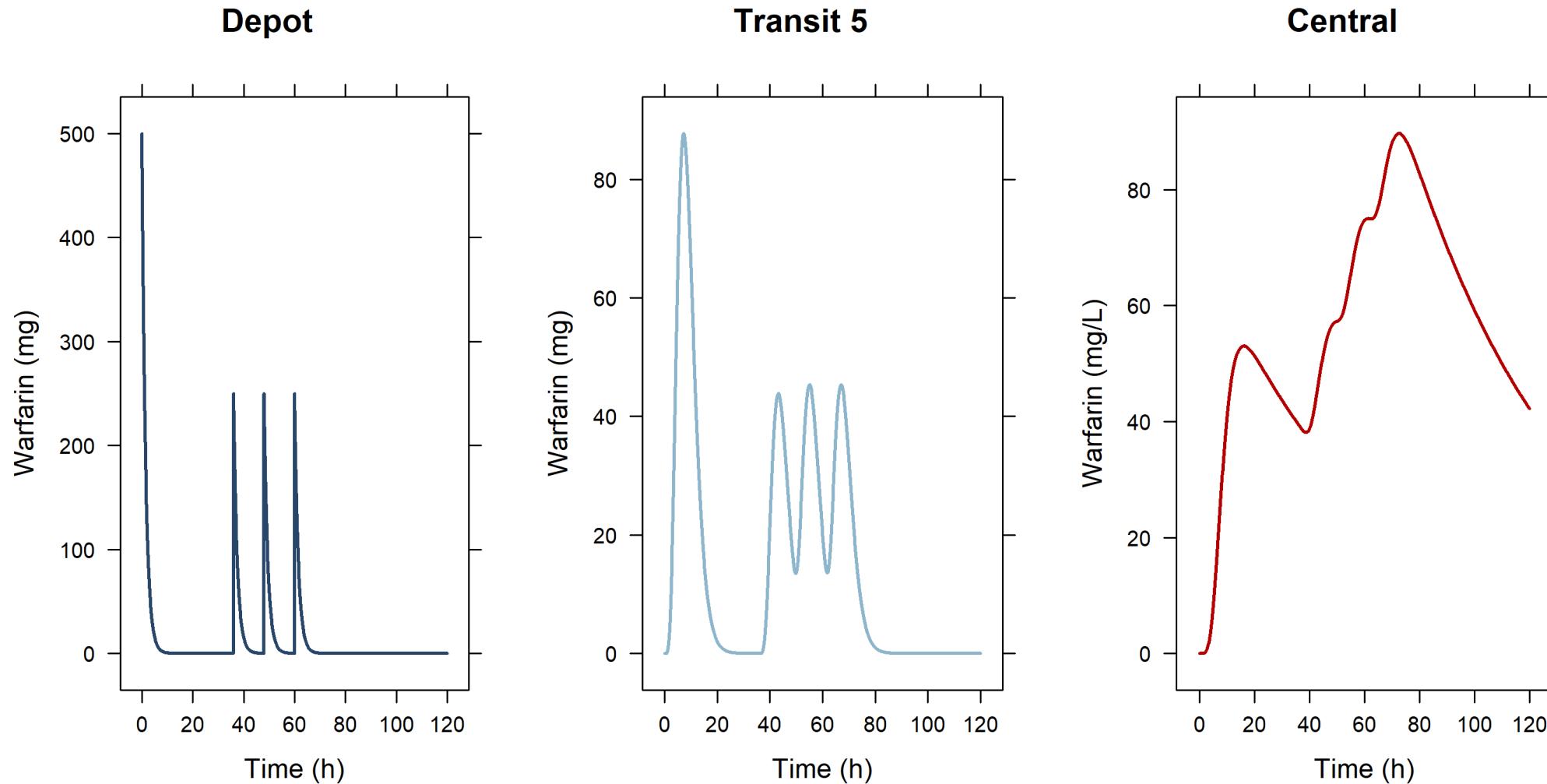
ev3 <- eventTable()
ev3$add.dosing(dose = 500) # mg; 1st bolus
ev3$add.dosing(
  dose = 250,           # mg
  nbr.doses = 3,        # 3 additional doses (bolusses because rate is absent so rate=0)
  dosing.interval = 12, # h; at 12 hour intervals
  dosing.to = 1,         # dosed into depot (compartment 1)
  start.time = 36       # h; starting at 36 hours
)
ev3$add.sampling(seq(0, 120, 0.1))

Params3 <-
  c(ktr = log(2)/1, # use same constant for every compartment
    cl = 0.135,
    v = 8)

modKA5trans <- rxode2(model = odeKA5trans)

Res <- data.frame(rxSolve(modKA5trans, Params3, ev3))
```

**...adding 5 transit compartments between depot and central
and giving 4 bolus doses in the 1st (depot) compartment**



Alternatively: use NONMEM-style dataset as input

- Instead of eventTables you can also use a NONMEM dataset structure to simulate

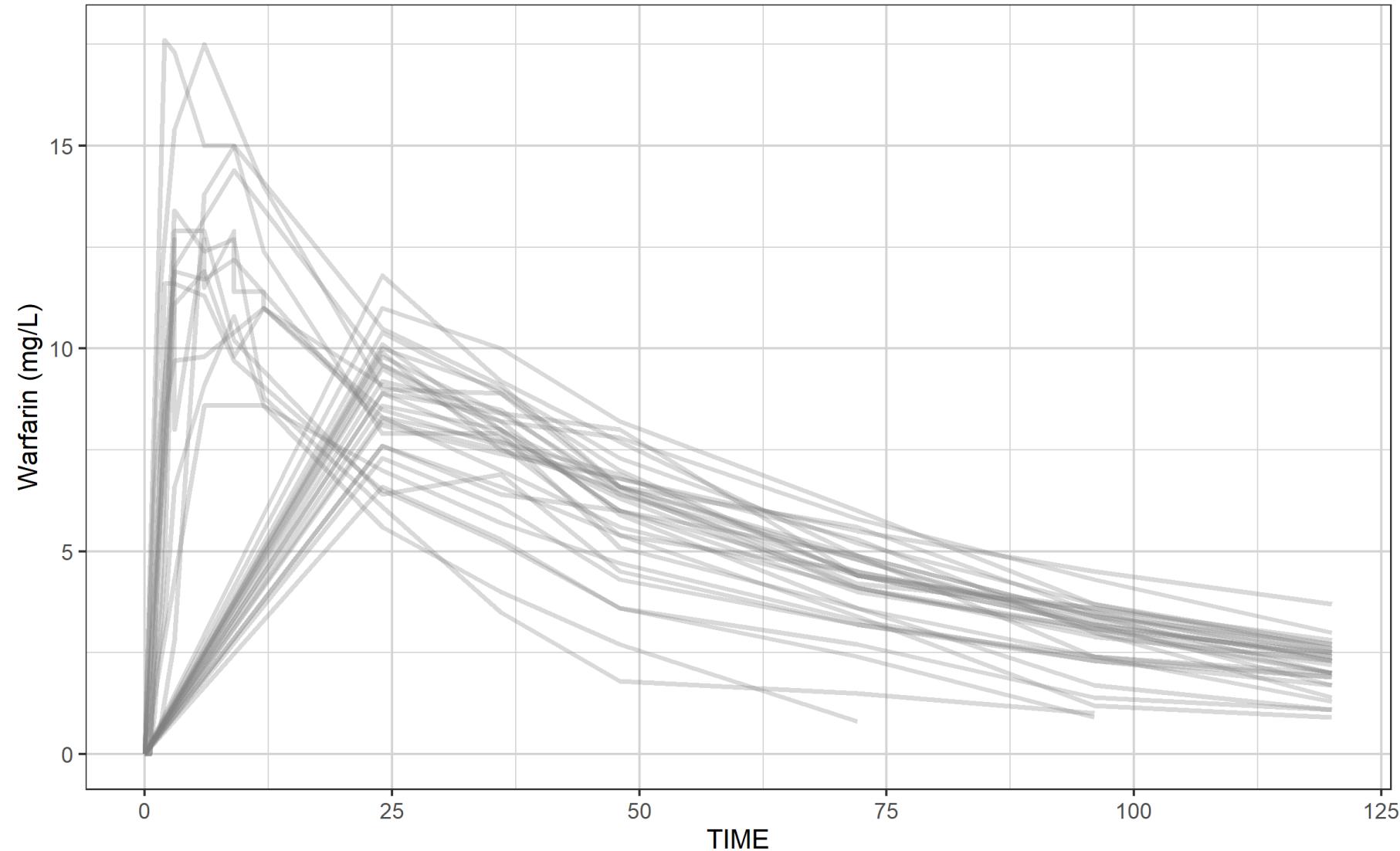
Hands-on session I: rxode2 simulations

- Examine the code in HandsOn_1.R to run pre-programmed simulations and try out your own variations

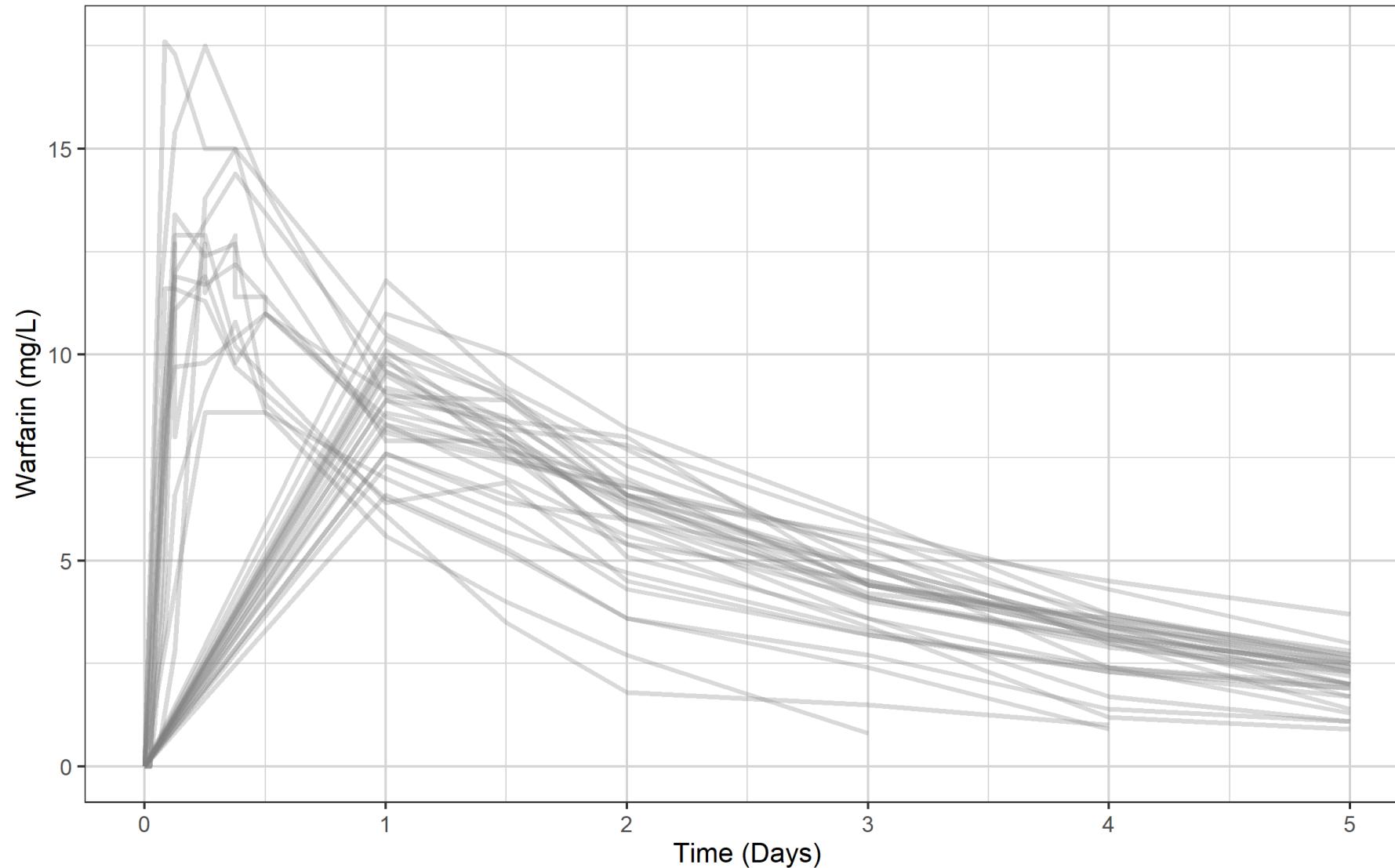
Assess the data before you start analysis

- Classic data sets used by Nick Holford in his courses:
 - O'Reilly RA, Aggeler PM. Studies on coumarin anticoagulant drugs initiation of warfarin therapy without a loading dose. *Circulation* 1968;38:169-177
 - O'Reilly RA, Aggeler PM, Leong LS. Studies of the coumarin anticoagulant drugs: The pharmacodynamics of warfarin in man. *Journal of Clinical Investigation* 1963;42(10):1542-1551
- Some simple plots to get a feel of the data
- Additional xgxr functionality to improve and summarize the profiles

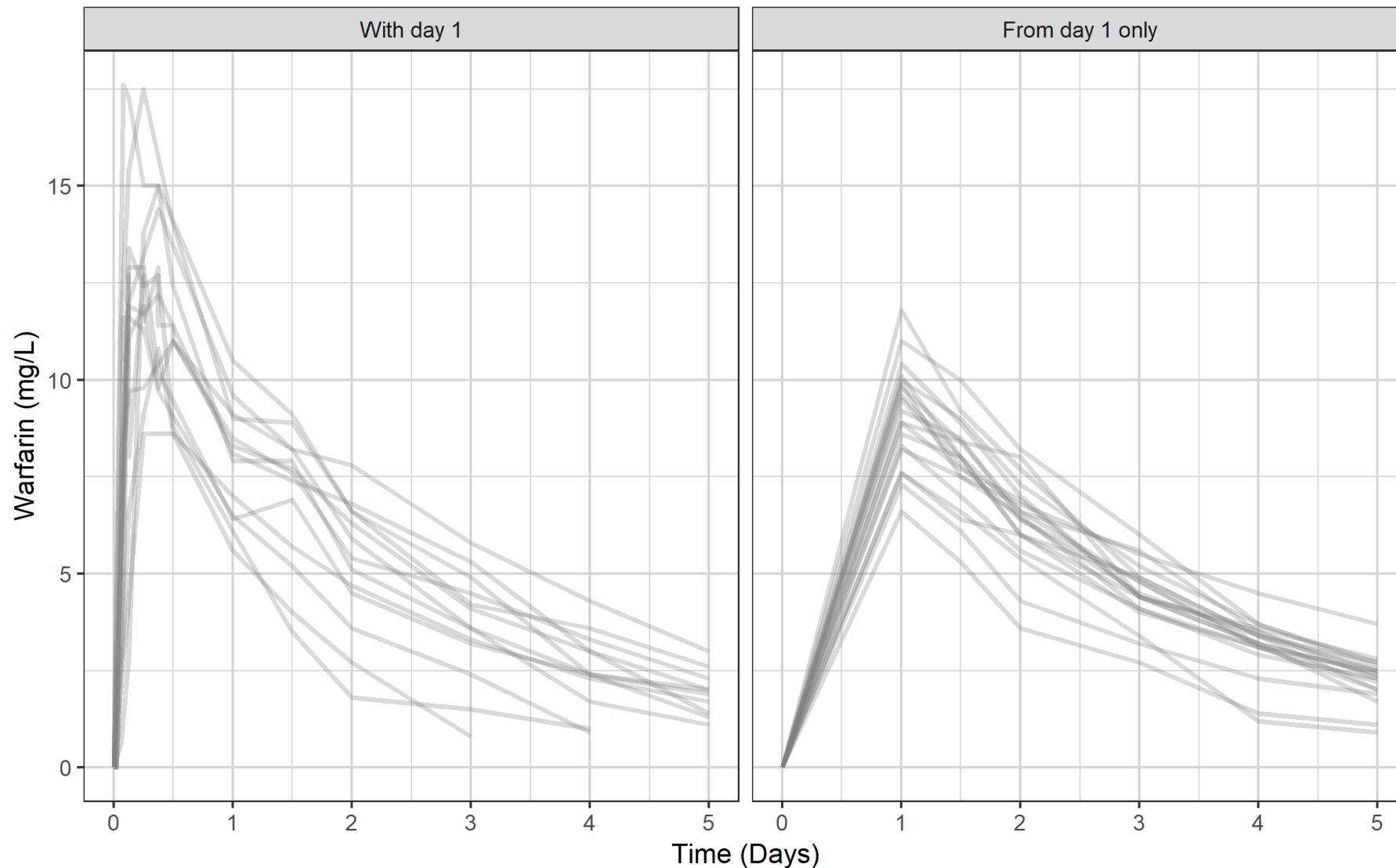
Our warfarin data file: a simple ggplot to provide an impression



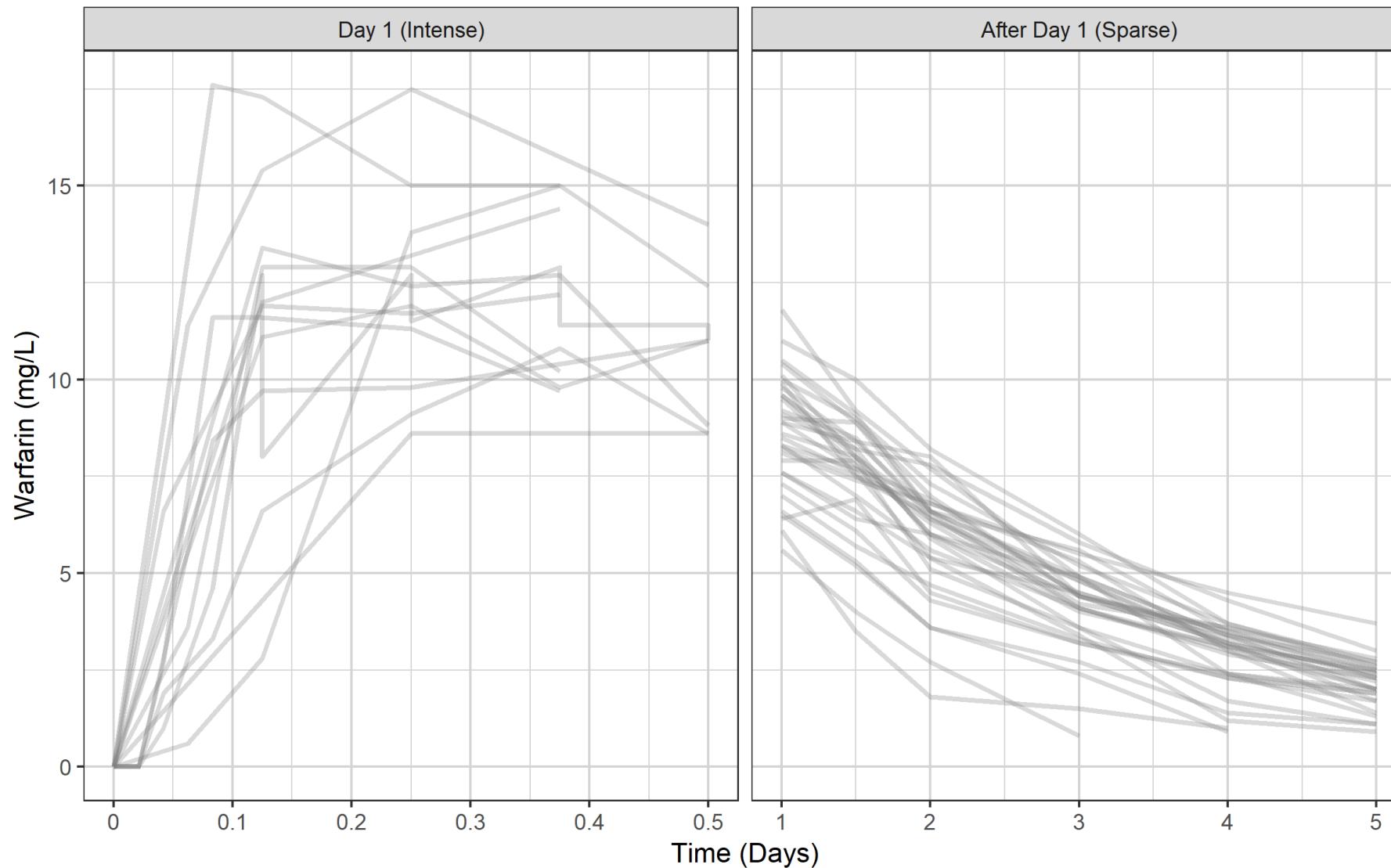
Change the x-axis from hours to days and add a proper label using the xgx helper
`xgx_scale_x_time_units(units_dataset = "hours", units_plot = "days")`



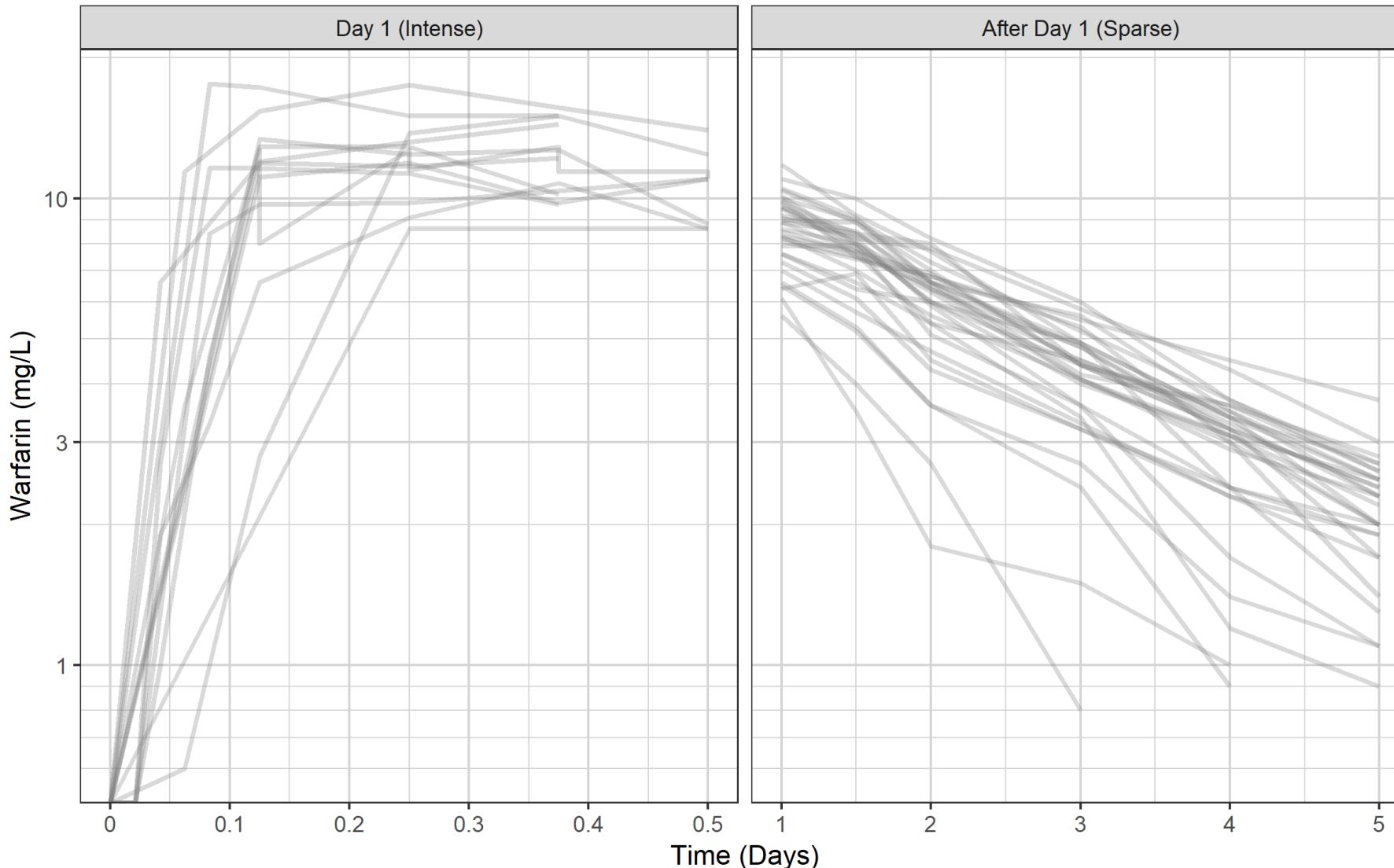
The data set has two types of profiles...



...but you can also group by rich day 1 and sparse later days...

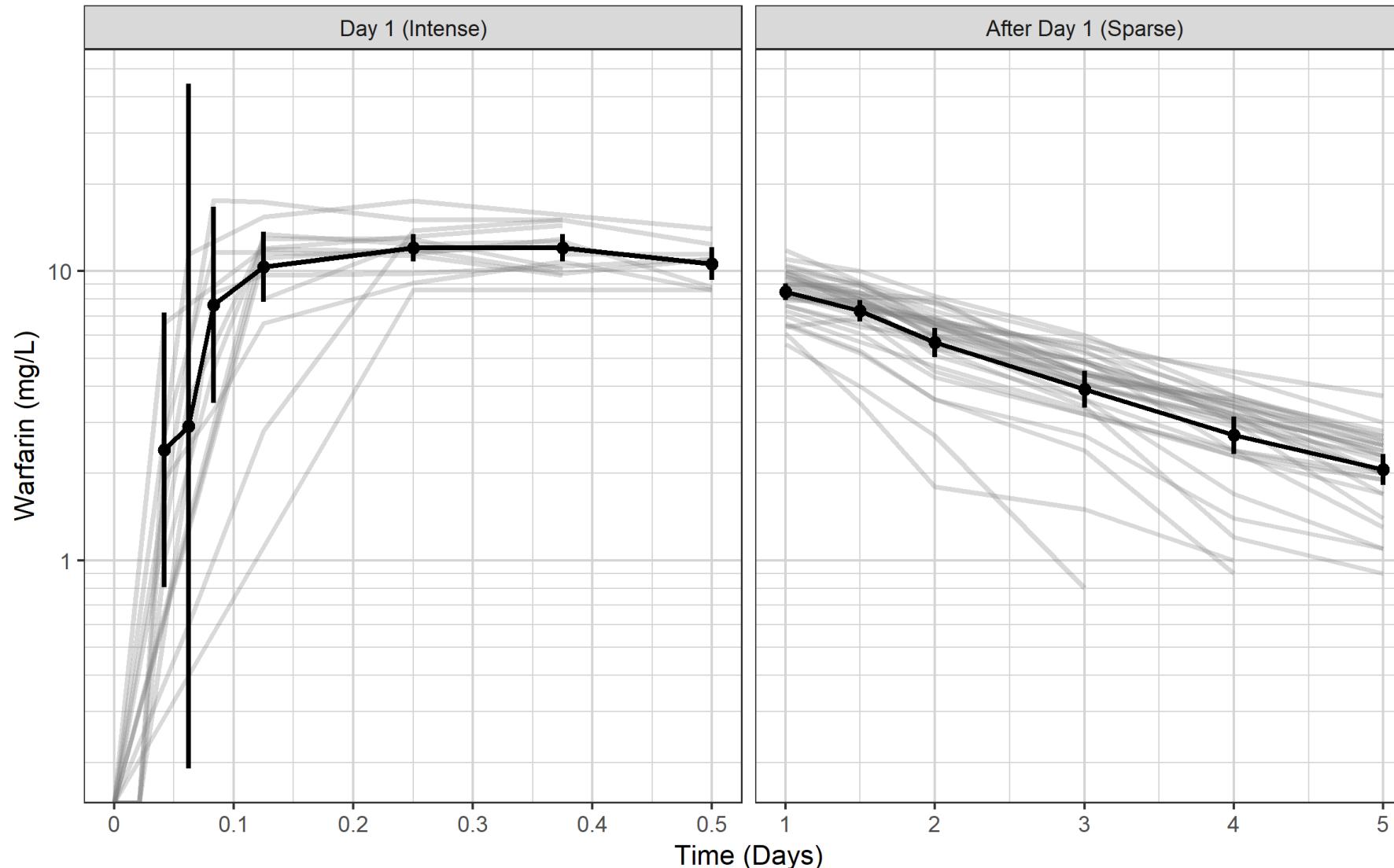


Switch to semi-log scale using xgx helper `xgx_scale_y_log10()`
Any clues to what model we should use?

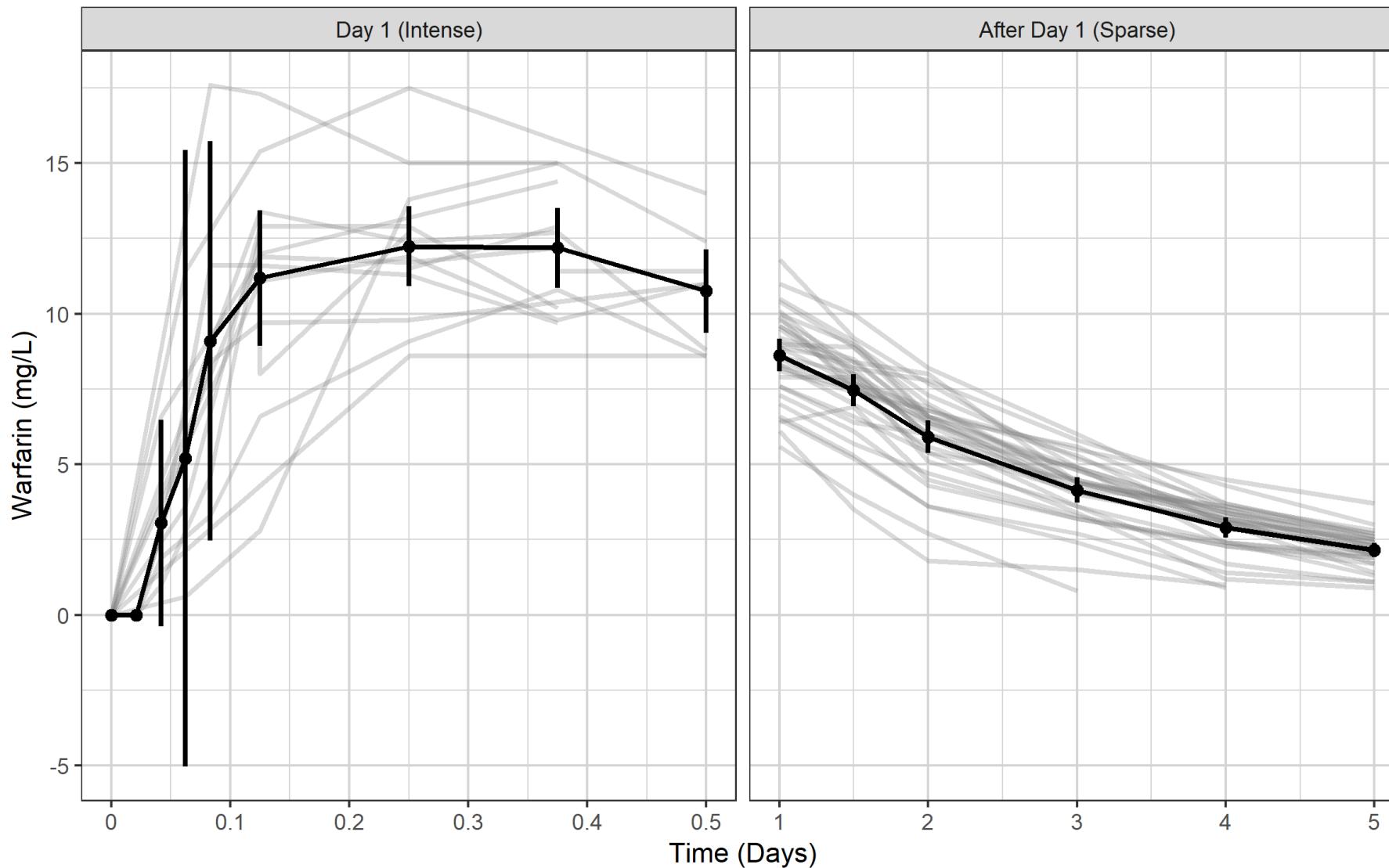


xgx can also add nice summary information if data has nominal times:
summaries of mean plus 95% CI

```
xgx_geom_ci(aes(x = TIME, color = NULL, group = NULL, shape = NULL), conf level = 0.95)
```

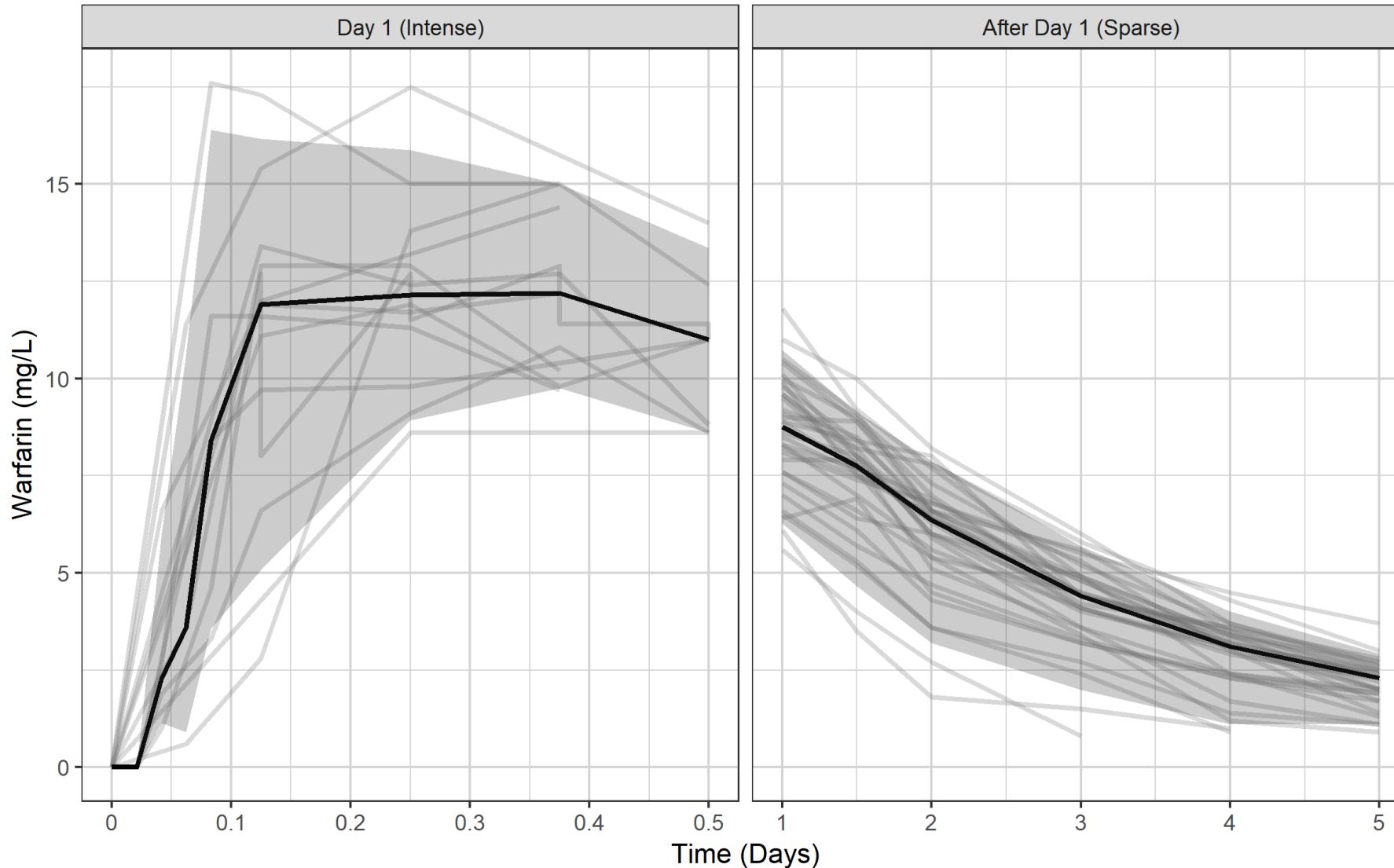


On linear scale this would result in a CI crossing zero because CIs are assumed symmetrical

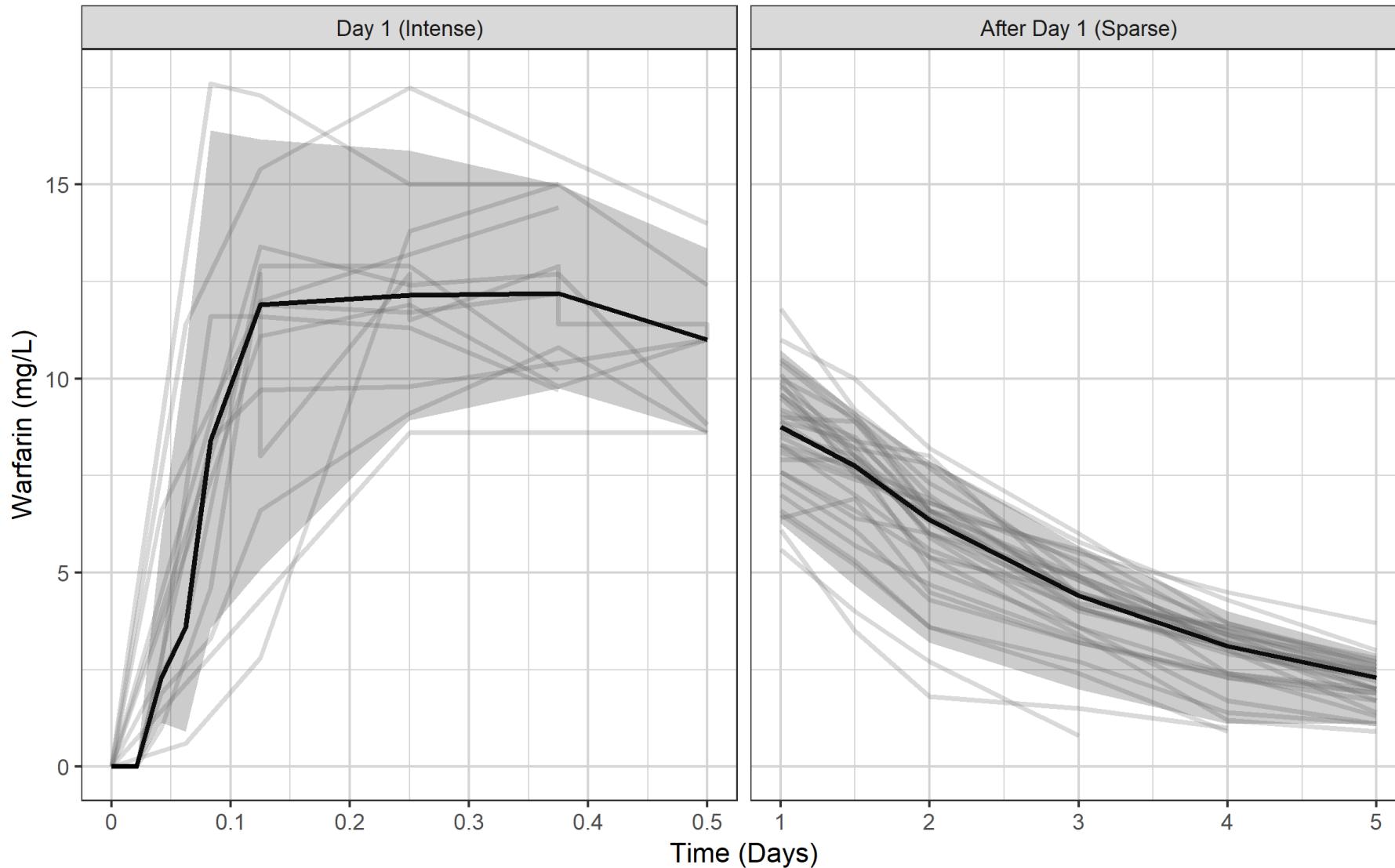


...so perhaps a median and 95% of the data would be more suitable

```
xgx_geom_pi(aes(x = TIME, color = NULL, group = NULL, shape = NULL))
```



There appears to be a delay in absorption...



You need to simulate before you can estimate

- With simulation covered, you can start to think about estimation
- Combine the simulation core with estimation routines and you get:

nlmixr²!

nlmixr² is an open-source R package

- Written by Wenping Wang and Matt Fidler, and available on CRAN^a and GitHub^b:
 - builds on rxode2
 - combined with SAEM, and FOCEi estimation routines, provides an R package for parameter estimation in nonlinear mixed effect models
 - under very active development!
- nlmixr² is completely free and open source, and does not depend on any other commercial tool such as NONMEM or Monolix
- nlmixr² provides an efficient and versatile way to specify pharmacometric models (both closed-form and ODEs) and dosing scenarios, with rapid execution due to compilation in C

[a] <https://cran.r-project.org/web/packages/nlmixr2>

[b] <https://github.com/nlmixr2/nlmixr2>

nlmixr² is a well-embedded open-source R package

- nlmixr² is fully supported by ggPMX^a
- Additionally, xpose.nlmixr2^b written by Justin Wilkins provides linkage to the new xpose package^c, written by Ben Guiastrennec, feeding the uniform output into a highly flexible diagnostics package
- The shinyMixR^d project management tool written by Richard Hooijmaijers and Teun Post provides an interface to nlmixr² from both the R command line and a user-friendly browser-based Shiny dashboard application
- nlmixr² requires access to compilers, easily installed using Rtools on Windows^e
- Installation is very simple from CRAN:
`install.packages("nlmixr2", dependencies=TRUE)`
- Documentation is available in the form of a bookdown (nlmixr2.org)^f with a dedicated nlmixr blog (blog.nlmixr2.org)
- Runs on Windows, Linux, and OS X, and a Docker install is available

[a] <https://cran.r-project.org/web/packages/ggPMX/> and <https://github.com/ggPMXdevelopment/ggPMX>

[b] <https://github.com/nlmixr2/xpose.nlmixr2> and <https://cran.r-project.org/packages/xpose.nlmixr2>

[c] <https://cran.r-project.org/packages/xpose> and <https://uupharmacometrics.github.io/xpose/>

[d] <https://github.com/RichardHooijmaijers/shinyMixR> and <https://richardhooijmaijers.github.io/shinyMixR/articles/shinyMixR-vignette.html>

[e] <https://cran.r-project.org/bin/windows/Rtools/rtools42/rtools.html>

[f] <https://nlmixr2.github.io/nlmixr2>

... and **nlmixr²** has some amazing new features!

- **nlmixr²** can now use NONMEM for its parameter estimation when using the **babelmixr2^a** package
- Additionally, **babelmixr2** can use the PKNCA package to provide starting values for PK analysis when rich profiles are available, and can keep track of units
- The **nonmem2rx^b** package allows reading in of NONMEM output and translation of NONMEM models (with a single epsilon error component) to **nsmixr²** objects
- This allows checking of NONMEM models, additional calculation of covariance matrices where NONMEM failed, and **nsmixr²** functionality like creation of VPCs and smooth predicted individual profiles

[a] <https://cran.r-project.org/web/packages/babelmixr2/index.html>

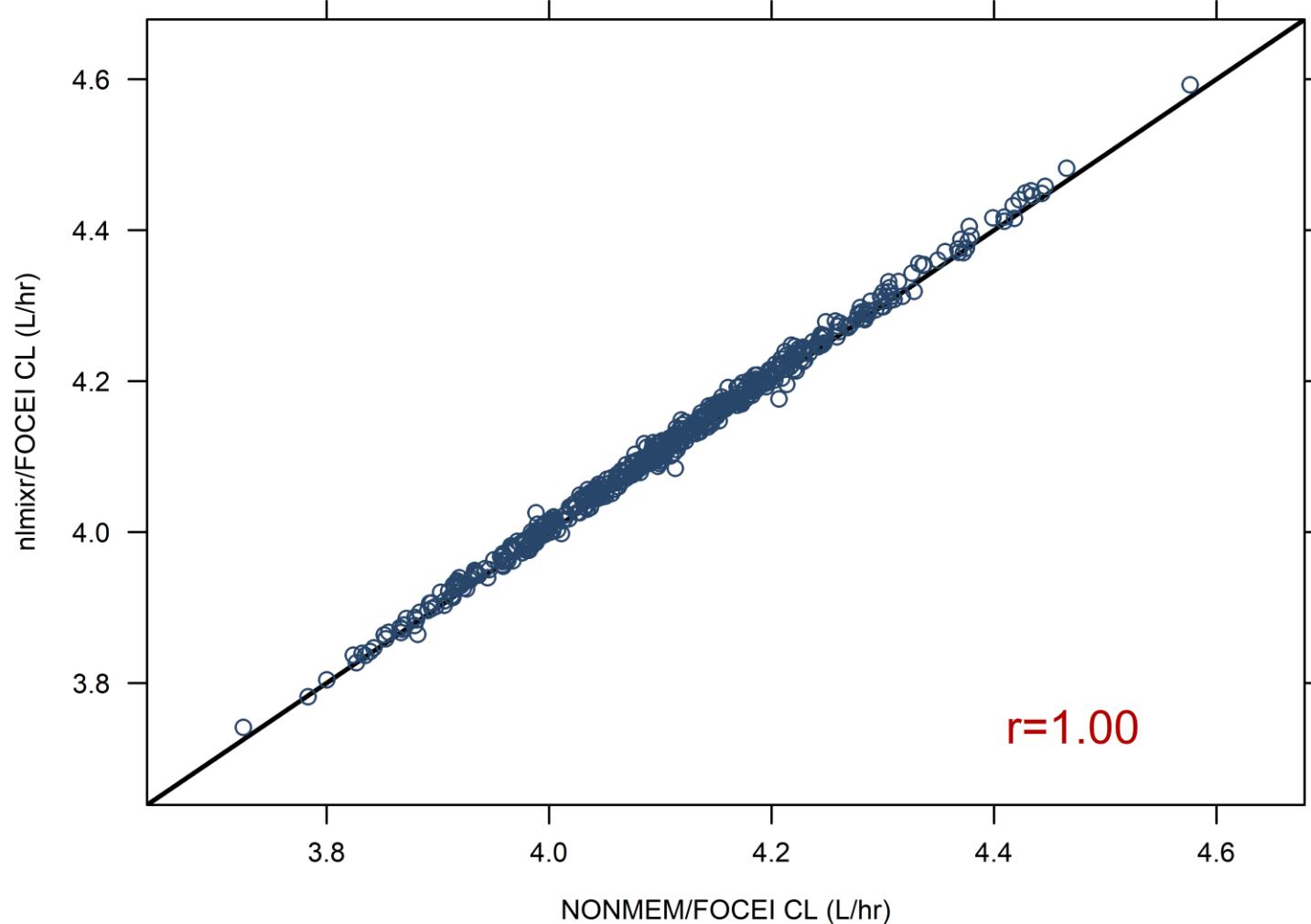
[b] <https://nsmixr2.github.io/nonmem2rx/index.html>

nlmixr performance: do I get the same results when I switch from my usual estimation tool to nlmixr?

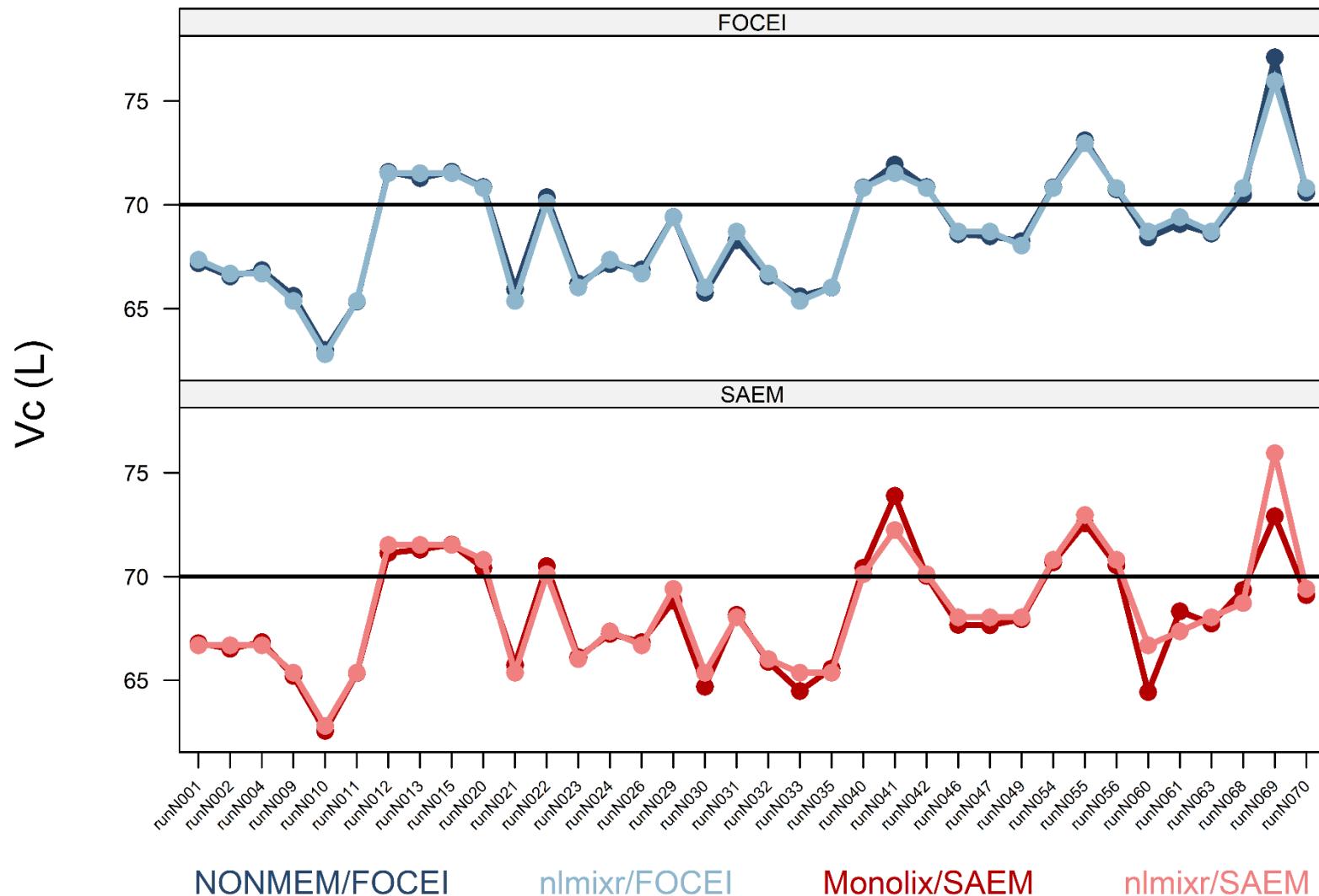
- Publication in CPT:PSP: *Performance of the SAEM and FOCEI algorithms in the open-source non-linear mixed effect modelling tool nlmixr^a*
- nlmixr/FOCEi compared to NONMEM/FOCEi
- nlmixr/SAEM compared to Monolix/SAEM
- Repeated sparse data sets for a single model
- A wide range of models and inputs using single rich data sets
- Results for both FOCEi and SAEM are perfectly comparable to NONMEM and Monolix

[a] <https://ascpt.onlinelibrary.wiley.com/doi/10.1002/psp4.12471>

500 sparse data sets are analysed using both NONMEM/FOCEi and nlmixr/FOCEi. Each marker is a single paired data set result for clearance for NONMEM on the x-axis and nlmixr/FOCEi on the y-axis: results are highly correlated ($r=1.00$), and lie on the line of identity (diagonal black line)



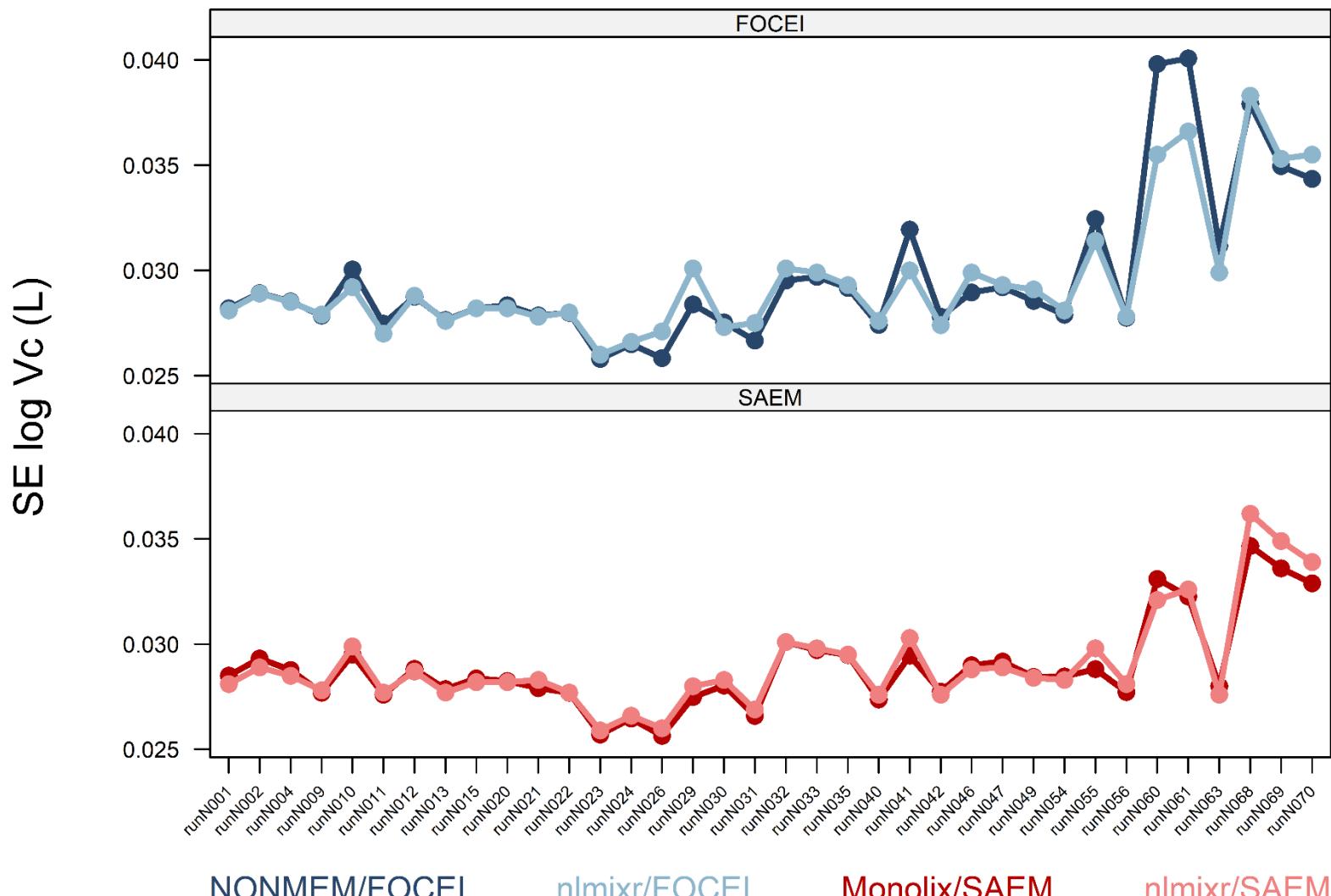
**Central volume (V_c): Top panel: FOCEi estimates, bottom panel: SAEM estimates
Dark lines: NONMEM/MONOLIX, light lines: nlmixr**



SE of theta estimates for Vc: very good match across software packages

Top panel: FOCEi estimates, bottom panel: SAEM estimates

Dark lines: NONMEM/MONOLIX, light lines: nlmixr



Defining nlmixr² models

- Models are defined using a function containing an initialisation block (**ini**) and a model definition block (**model**)

```
One.comp.KA.solved <- function() {  
  ini({  
    # Where initial conditions/variables are specified  
  })  
  model({  
    # Where the model is specified  
  })  
}
```

Defining nlmixr² models

- The **ini** block defines the parameters
 - Thetas and residual error defined using assign operators (**<-** or **=**)
 - Etas defined using a model formula (**~**)
- Parameter names, starting values, labels for thetas and errors (using **#**), bounds for some estimation routines (like FOCEI)

```
One.comp.KA.solved <- function() {  
  ini({  
    # Where initial conditions/variables are specified  
    lka <- log(1.15) #log ka (1/h)  
    lcl <- log(0.135) #log CL (L/h)  
    lv <- log(8) #log V (L)  
    prop.err <- 0.15 #proportional error (SD/mean)  
    add.err <- 0.6 #additive error (mg/L)  
    eta.ka ~ 0.5  
    eta.cl ~ 0.1  
    eta.v ~ 0.1  
  })  
  model({  
  })  
}
```

Defining nlmixr² models

- The **model** block defines
 - the relationship between thetas and etas
 - the model structure using either closed-form solutions or ODEs
 - the residual error structure, and where it is applied

```
One.comp.KA.solved <- function() {  
  ini{  
  }  
  model{  
    # Where the model is specified  
    cl <- exp(lcl + eta.cl)  
    v <- exp(lv + eta.v)  
    ka <- exp(lka + eta.ka)  
    ## solved system example  
    ## where residual error is assumed to follow proportional and additive error  
    linCmt() ~ prop(prop.err) + add(add.err)  
  }  
}
```

Running nlmixr² models: the full model

```
One.comp.KA.solved <- function() {  
  ini{  
    # Where initial conditions/variables are specified  
    lka <- log(1.15) #Log ka (1/h)  
    lcl <- log(0.135) #Log CL (L/h)  
    lv <- log(8) #Log V (L)  
    prop.err <- 0.15 #proportional error (SD/mean)  
    add.err <- 0.6 #additive error (mg/L)  
    eta.ka ~ 0.5  
    eta.cl ~ 0.1  
    eta.v ~ 0.1  
  }  
  model{  
    # Where the model is specified  
    cl <- exp(lcl + eta.cl)  
    v <- exp(lv + eta.v)  
    ka <- exp(lka + eta.ka)  
    ## solved system example  
    ## where residual error is assumed to follow proportional and additive error  
    linCmt() ~ prop(prop.err) + add(add.err)  
  }  
}
```

Running nlmixr² models: check the model code

```
## Check the model and some of the assumptions made by nlmixr

nlmixr2(One.comp.KA.solved)

> nlmixr2(one.comp.KA.solved)
i parameter labels from comments will be replaced by 'label()'
-- rxode2-based solved PK 1-compartment model with first-order absorption -----
-- Initialization: --
Fixed Effects ($theta):
  lka      lcl      lv prop.err   add.err
0.1397619 -2.0024805 2.0794415 0.1500000 0.6000000

Omega ($omega):
  eta.ka eta.cl eta.v
eta.ka  0.5  0.0  0.0
eta.cl  0.0  0.1  0.0
eta.v   0.0  0.0  0.1
-- mu-referencing ($muRefTable): --
  theta  eta level
1  lcl eta.cl  id
2  lv  eta.v   id
3  lka eta.ka  id
```

Running nlmixr² models: check the model code

```
## Check the model and some of the assumptions made by nlmixr2
```

```
nlmixr2(One.comp.KA.solved)

-- Model (Normalized Syntax): --
function() {
  ini({
    lka <- 0.139761942375159
    label("log ka (1/h)")
    lcl <- -2.00248050054371
    label("log cl (L/h)")
    lv <- 2.07944154167984
    label("log v (L)")
    prop.err <- c(0, 0.15)
    label("proportional error (SD/mean)")
    add.err <- c(0, 0.6)
    label("additive error (mg/L)")
    eta.ka ~ 0.5
    eta.cl ~ 0.1
    eta.v ~ 0.1
  })
  model({
    cl <- exp(lcl + eta.cl)
    v <- exp(lv + eta.v)
    ka <- exp(lka + eta.ka)
    lincmt() ~ prop(prop.err) + add(add.err)
  })
}
```

Running nlmixr² models with the nlmixr2 command

```
## estimate parameters using nlmixr:  
run001S <-  
  nlmixr2(  
    One.comp.KA.solved,           #the model definition  
    PKdata,                      #the data set  
    est = "saem",                 #the estimation algorithm (SAEM)  
                                #the SAEM minimisation options:  
    saemControl(nBurn = 200,       #200 SAEM burn-in iterations (the default)  
                nEm   = 300,       #300 EM iterations (the default)  
                print = 50),      #only print every 50th estimation step  
    tableControl(cwres = TRUE,     #calculates NONMEM-style conditional weighted residuals  
                  npde = TRUE)    #and npde values for diagnostics  
  )  
  
## results are stored in the nlmixr2 object and can be viewed:  
run001S
```

nlmixr² output for SAEM

```
> run001s
-- nlmixr2 SAEM OBJF by FOCEi approximation --

      OBJF      AIC      BIC Log-likelihood Condition#(cov) Condition#(cor)
FOCEi 454.9677 932.2748 960.4784     -458.1374      19.65728      1.52084

-- Time (sec run001s$time): --
setup optimize covariance saem table compress
elapsed 0.001    0.001    0.001 9.42 11.07      0.07

-- Population Parameters (run001s$parFixed or run001s$parFixedddf): --

      Parameter   Est.      SE %RSE Back-transformed(95%CI) BSV(cv%) shrink(sd)%
lka      log ka (1/h) -0.605  0.205  34     0.546 (0.365, 0.817)      54.6      46.5%
lcl      log cl (L/h) -1.99   0.0492 2.47     0.136 (0.124, 0.15)      23.4      15.5%
lv       log V (L)   2.05   0.0473 2.3      7.77 (7.08, 8.52)      16.2      35.3%
prop.err proportional error (SD/mean) 0.17
add.err      additive error (mg/L)  0.818

Covariance Type (run001s$covMethod): linFim
No correlations in between subject variability (BSV) matrix
Full BSV covariance (run001s$omega) or correlation (run001s$omegaR; diagonals=SDs)
Distribution stats (mean/skewness/kurtosis/p-value) available in run001s$shrink
Censoring (run001s$censInformation): No censoring

-- Fit Data (object run001s is a modified tibble): --
# A tibble: 251 x 26
   ID    TIME    DV EPRED   ERES   NPDE   NPD    PDE    PD   PRED   RES   WRES  IPRED   IRES   IWRES CPRED   CRES CWRES eta.ka eta.cl
   <fct> <dbl> <dbl>
1 1        0.5     0  3.57 -3.57  0.643 -2.33  0.74   0.01   3.06 -3.06 -1.76  1.45 -1.45 -1.69   2.56 -2.56 -2.28 -0.724  0.413
2 1        1       1.9  5.70 -3.80 -0.117 -1.79  0.453  0.0367  5.36 -3.46 -1.36  2.69 -0.794 -0.846  4.66 -2.76 -1.74 -0.724  0.413
3 1        2       3.3  8.49 -5.19 -1.71 -2.05  0.0433  0.02   8.38 -5.08 -1.61  4.70 -1.40 -1.22   7.74 -4.44 -1.96 -0.724  0.413
# i 248 more rows
# i 6 more variables: eta.v <dbl>, cl <dbl>, v <dbl>, ka <dbl>, tad <dbl>, dosenum <dbl>
# i Use `print(n = ...)` to see more rows
```

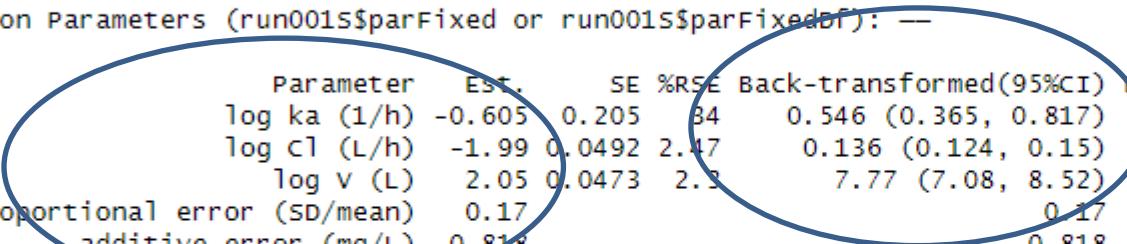
The labels in the ini block end up in the output, and the log-transformed parameters are returned with a back-transformation and 95%CIs

```
> run001s
-- nlmixr² SAEM OBJF by FOCEi approximation --

      OBJF      AIC      BIC Log-likelihood Condition#(cov) Condition#(cor)
FOCEi 454.9677 932.2748 960.4784     -458.1374      19.65728      1.52084

-- Time (sec run001s$time): --

  setup optimize covariance saem table compress
elapsed 0.001    0.001    0.001 9.42 11.07      0.07

-- Population Parameters (run001s$parFixed or run001s$parFixedBF): --


|          | Parameter                    | Est.   | SE     | %RSE | Back-transformed(95%CI) | BSV(cv%) | shrink(SD)% |
|----------|------------------------------|--------|--------|------|-------------------------|----------|-------------|
| lka      | log ka (1/h)                 | -0.605 | 0.205  | 34   | 0.546 (0.365, 0.817)    | 54.6     | 46.5%       |
| lc1      | log c1 (L/h)                 | -1.99  | 0.0492 | 2.47 | 0.136 (0.124, 0.15)     | 23.4     | 15.5%       |
| lv       | log v (L)                    | 2.05   | 0.0473 | 2.3  | 7.77 (7.08, 8.52)       | 16.2     | 35.3%       |
| prop.err | proportional error (SD/mean) | 0.17   |        |      | 0.17                    |          |             |
| add. err | additive error (mg/L)        | 0.818  |        |      | 0.818                   |          |             |


Covariance Type (run001s$covMethod): linFim
No correlations in between subject variability (BSV) matrix
Full BSV covariance (run001s$omega) or correlation (run001s$omegaR; diagonals=SDs)
Distribution stats (mean/skewness/kurtosis/p-value) available in run001s$shrink
censoring (run001s$censInformation): No censoring

-- Fit Data (object run001s is a modified tibble): --
# A tibble: 251 × 26
   ID    TIME    DV EPRED   ERES   NPDE    PDE    PD   PRED    RES   WRES  IPRED   IRES   IWRES  CPRED   CRES   CWRES eta.ka eta.cl
   <fct> <dbl> <dbl>
1 1       0.5    0  3.57 -3.57  0.643 -2.33  0.74   0.01   3.06 -3.06 -1.76  1.45 -1.45 -1.69  2.56 -2.56 -2.28 -0.724  0.413
2 1       1     1.9  5.70 -3.80 -0.117 -1.79  0.453  0.0367  5.36 -3.46 -1.36  2.69 -0.794 -0.846  4.66 -2.76 -1.74 -0.724  0.413
3 1       2     3.3  8.49 -5.19 -1.71 -2.05  0.0433  0.02   8.38 -5.08 -1.61  4.70 -1.40 -1.22  7.74 -4.44 -1.96 -0.724  0.413
# i 248 more rows
# i 6 more variables: eta.v <dbl>, c1 <dbl>, v <dbl>, ka <dbl>, tad <dbl>, dosenum <dbl>
# i Use `print(n = ...)` to see more rows
```

Running nlmixr² models: save the object, and examine parameter trace plots when using SAEM to check convergence

results are stored in the nlmixr2 object and can be viewed:

```
run001S
```

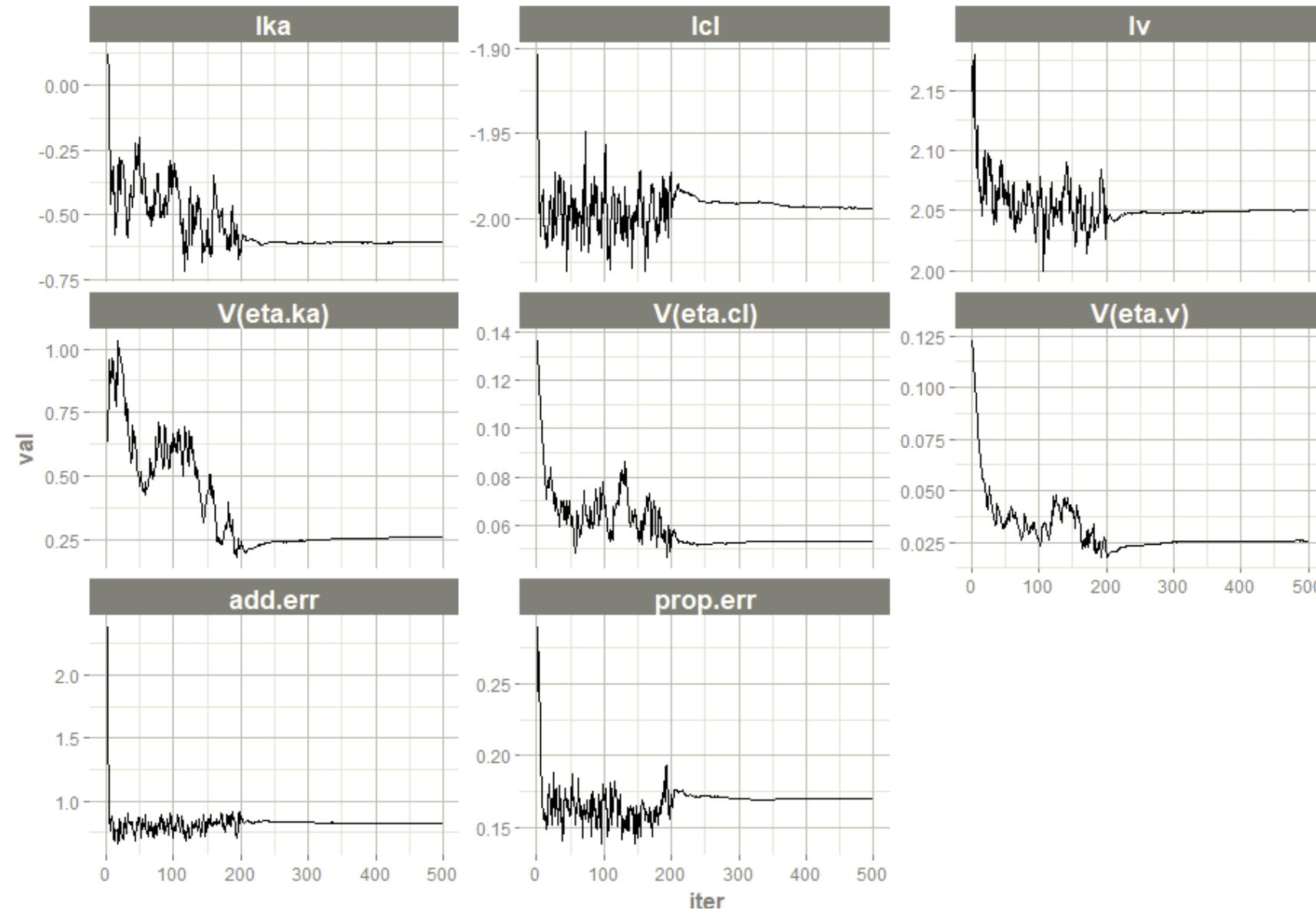
and saved for future use or reference:

```
save(run001S, file = "run001S.Rdata")
```

and for SAEM, convergence can be checked using a parameter trace plot:

```
traceplot(run001S)
```

Traceplot for SAEM parameter estimates using traceplot command



nlmixr² is linked to ggPMX

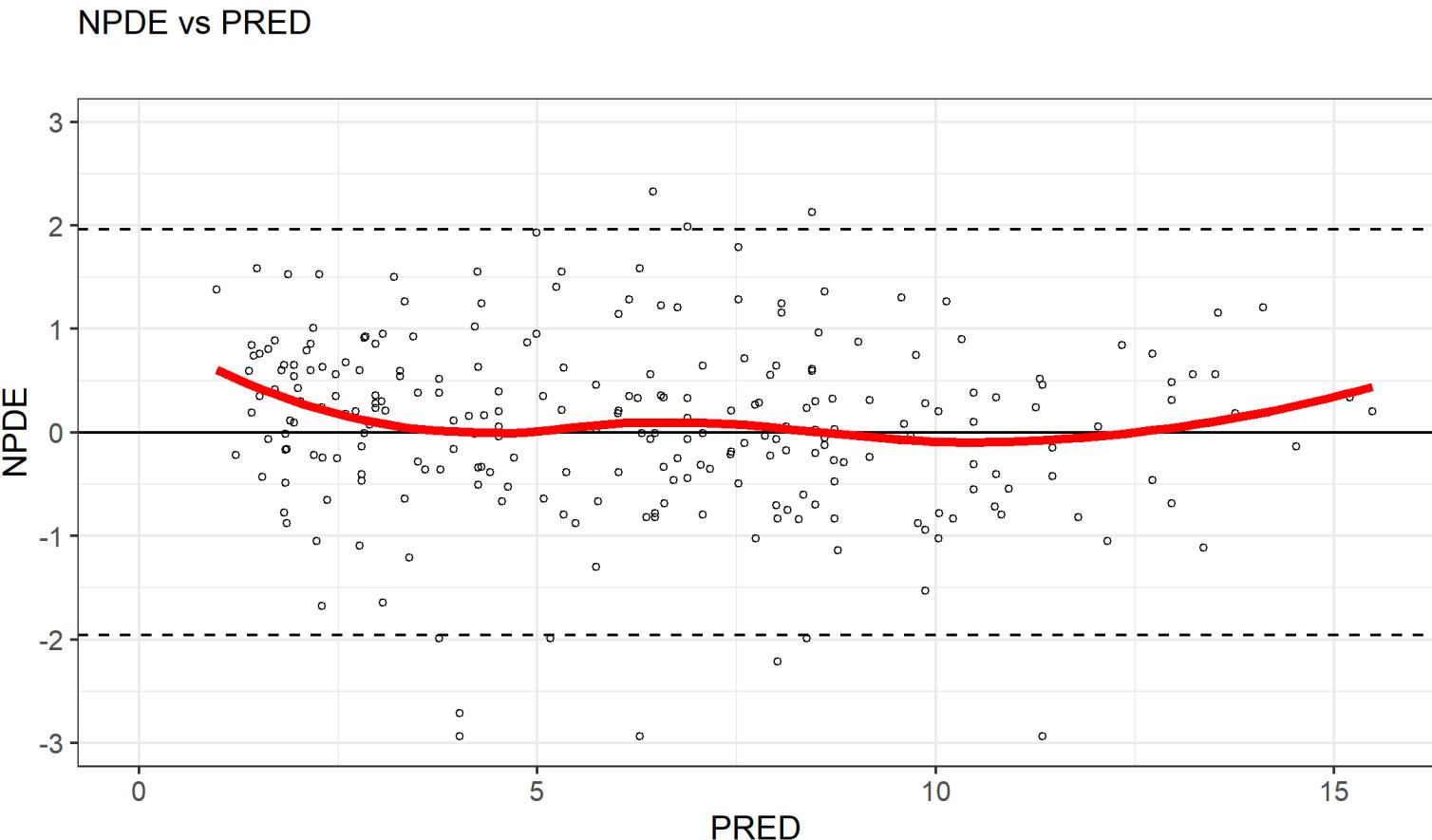
```
# Model Diagnostics with ggPMX
# The controller is first constructed
ctr001S <- pmx_nlmixr(run001S,
  conts = c("WT", "AGE"),
  cats=c("SEX", "SPARSE"),
  vpc=FALSE,
  settings=pmx_settings(is.draft=FALSE))

# and can then be piped into a specific plot
# syntax for npde vs pred plot
ctr001S %>% pmx_plot_npde_pred
#alternatively:
pmx_plot_npde_pred(ctr001S)
```

nlmixr² is linked to ggPMX

```
# Model Diagnostics with ggPMX
# The controller is first constructed
ctr001S <- pmx_nlmixr(run001S,
                        conts = c("WT", "AGE"),
                        cats=c("SEX", "SPARSE"),
                        vpc=FALSE,
                        settings=pmx_settings(is.draft=FALSE))

# and can then be piped into a specific plot
# syntax for npde vs pred plot
ctr001S %>% pmx_plot_npde_pred
#alternatively:
pmx_plot_npde_pred(ctr001S)
```



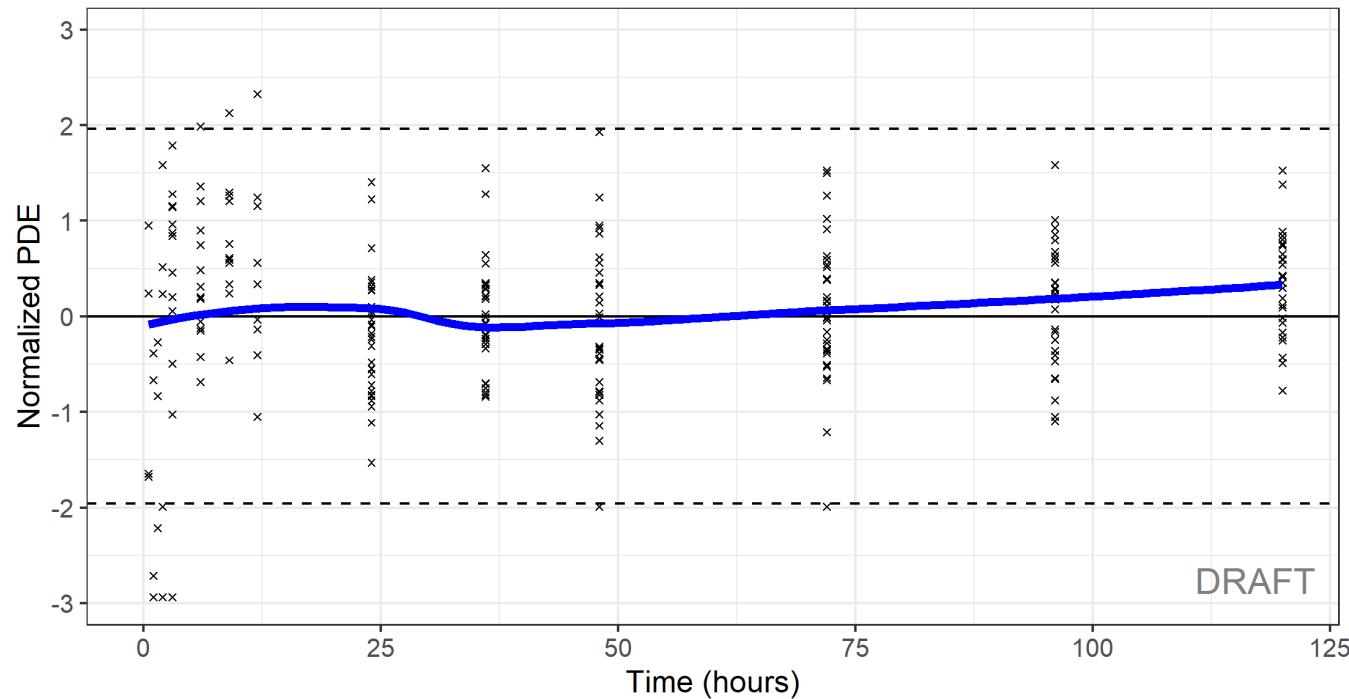
nlmixr² is linked to ggPMX

```
## Modify graphical options and add DRAFT label:  
ctr001S %>% pmx_plot_npde_time(smooth = list(color="blue"),  
                                    point = list(shape=4),  
                                    s.draft=TRUE,  
                                    labels = list(x = "Time (hours)",  
                                                y = "Normalized PDE"))
```

nlmixr² is linked to ggPMX

```
## Modify graphical options and add DRAFT label:  
ctr001S %>% pmx_plot_npde_time(smooth = list(color="blue"),  
                                   point = list(shape=4),  
                                   s.draft=TRUE,  
                                   labels = list(x = "Time (hours)",  
                                                 y = "Normalized PDE"))
```

NPDE vs TIME



nlmixr² is linked to ggPMX

```
## DV vs IPRED plot
ctr001S %>% pmx_plot_dv_ipred(scale_x_log10=TRUE, scale_y_log10=TRUE)

#You can filter to restrict the values of IPRED for instance:
ctr001S %>% pmx_plot_dv_ipred(scale_x_log10=TRUE, scale_y_log10=TRUE,filter=(IPRED>1))

## DV vs PRED plot
ctr001S %>% pmx_plot_dv_pred(scale_x_log10=TRUE, scale_y_log10=TRUE)

## Absolute individual weighted residuals to investigate the residual error model
ctr001S %>% pmx_plot_abs_iwres_ipred
#again, alternatively:
#pmx_plot_abs_iwres_ipred(ctr)

ctr001S %>% pmx_plot_iwres_dens
ctr001S %>% pmx_plot_eta_qq
ctr001S %>% pmx_plot_eta_box
ctr001S %>% pmx_plot_eta_hist
ctr001S %>% pmx_plot_eta_matrix
```

nlmixr² is linked to Ben Guiastrennec's xpose* package that uses ggplot2

```
## the nlmixr object can be transformed into an xpose object to allow diagnostics with the new xpose package
## the link between nlmixr and xpose is provided by the xpose.nlmixr package
## only xpose_data_nlmixr is from xpose.nlmixr
## all further commands (see cheatsheet) are from the xpose package

xpdb.1s <- xpose_data_nlmixr(run001S)

## this can also be used to generate trace plots (parameters vs iterations:)
prm_vs_iteration(xpdb.1s)
## to remove the path to the script from the plot use:
prm_vs_iteration(xpdb.1s,caption=NULL)
```

*<https://uupharmacometrics.github.io/xpose/>

nlmixr² is linked to Ben Guiastrennec's xpose* package that uses ggplot2

```
## the nlmixr2 object can be transformed into an xpose object to allow diagnostics with the new xpose package  
## the link between nlmixr2 and xpose is provided by the xpose.nlmixr2 package  
## only xpose_data_nlmixr is from xpose.nlmixr2  
## all further commands (see cheatsheet) are from the xpose package
```

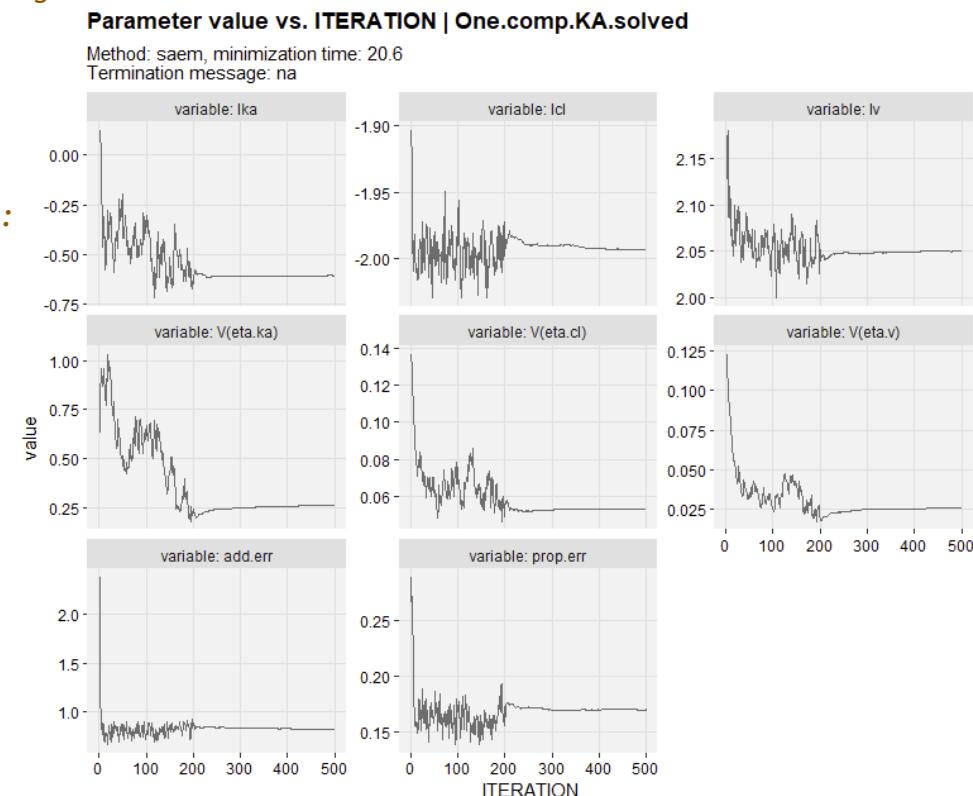
```
xpdb.1s <- xpose_data_nlmixr(run001S)
```

```
## this can also be used to generate trace plots (parameters vs iterations:
```

```
prm_vs_iteration(xpdb.1s)
```

```
## to remove the path to the script from the plot use:
```

```
prm_vs_iteration(xpdb.1s,caption=NULL)
```

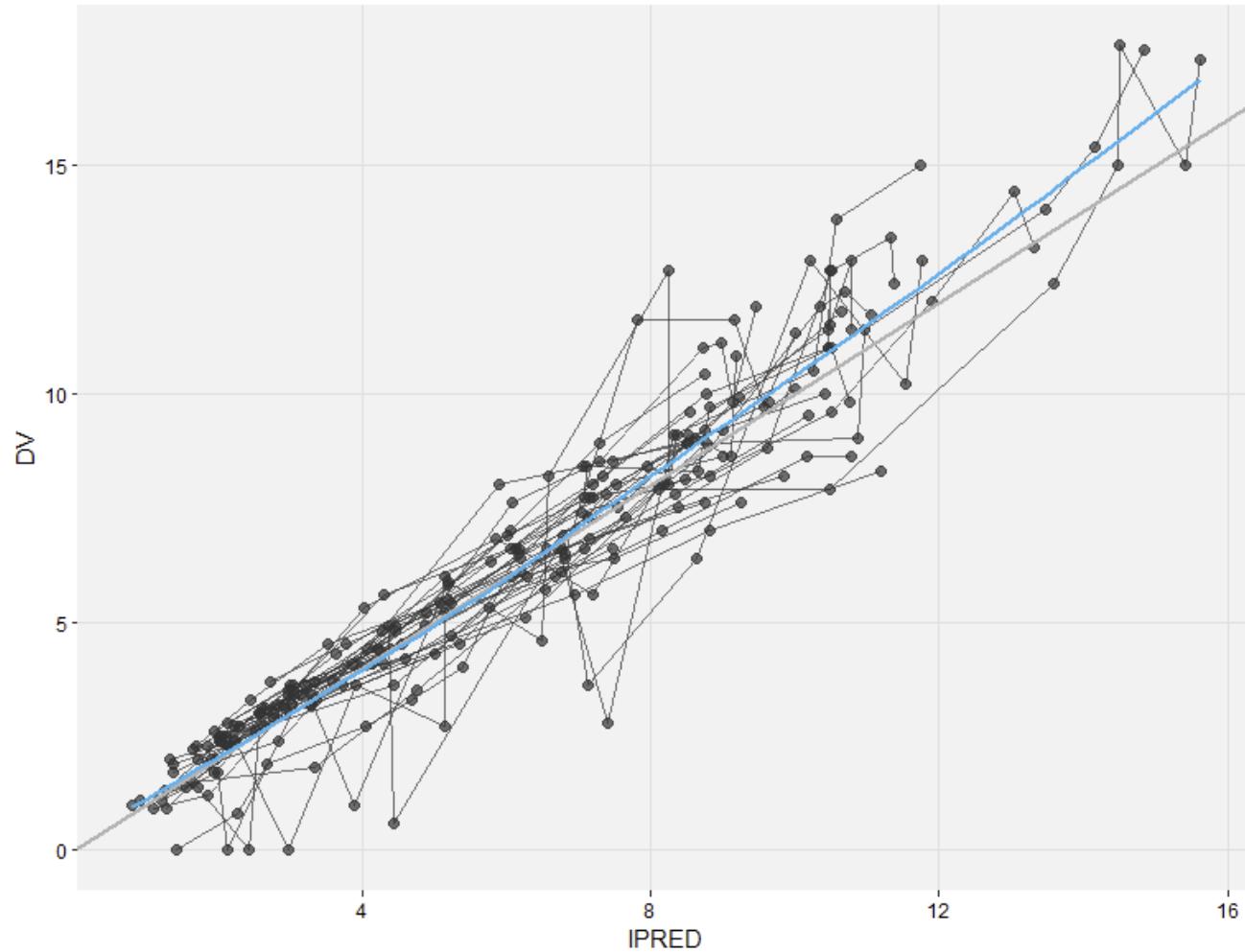


*<https://uupharmacometrics.github.io/xpose/>

DV vs IPRED using xpose

DV vs. IPRED | One.comp.KA.solved

Ofv: 455, Eps shrink: 17.1 [1]



```
xpdb.1s <- xpose_data_nlmixr(run001S)
## dv vs ipred plot:
dv_vs_ipred(xpdb.1s,
             caption = NULL)
```

nlmixr² is linked to Ron Keizer's vpc* package

```
## nlmixr2 comes with its own built-in vpc functionality that uses Ron Keizer's vpc package
## see the cheatsheet for further options

## because the data set uses nominal time points, it is nice to have the bins surround these time points
## so that each time point falls in a bin

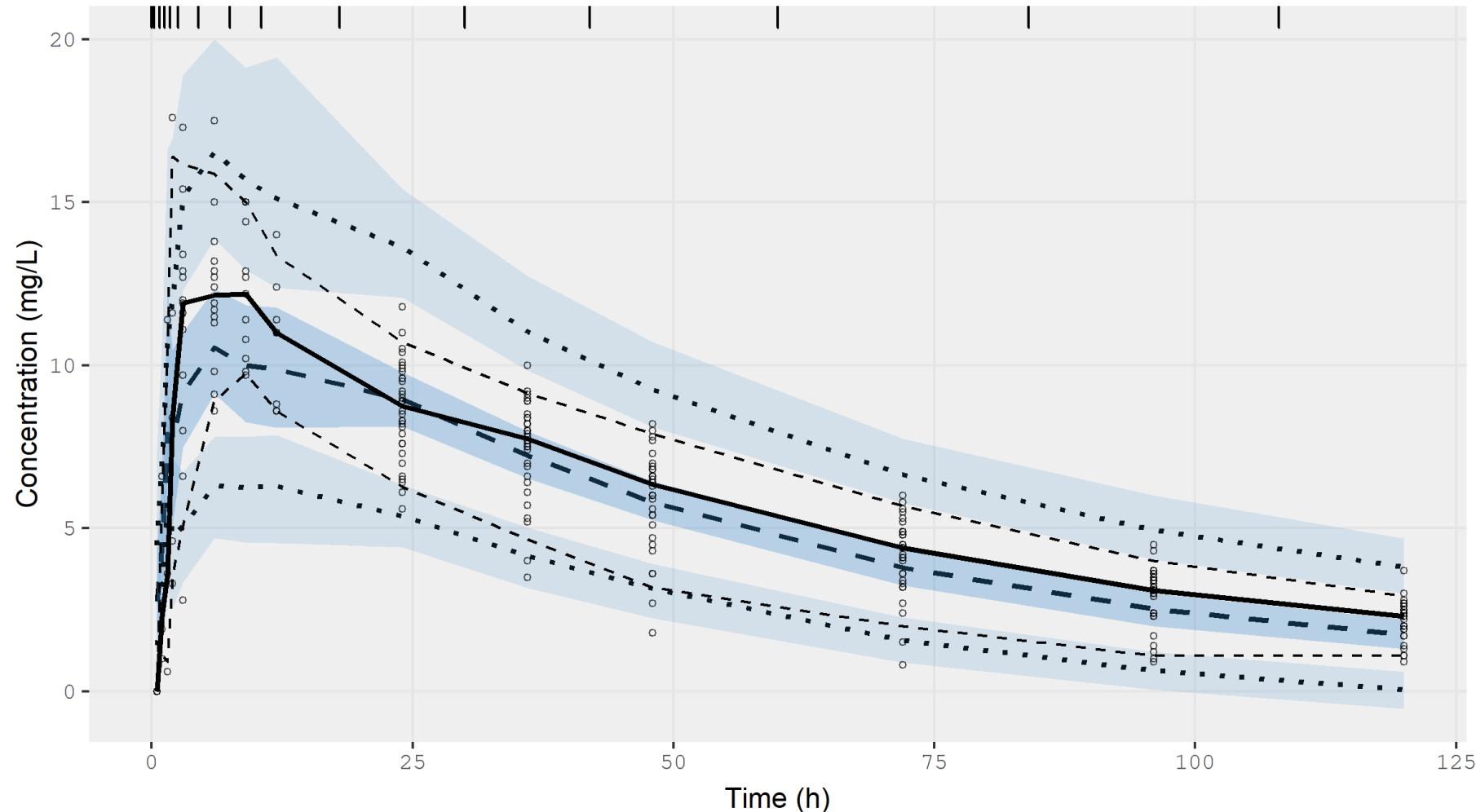
bin_mids <- sort(unique(PKdata$TIME))
bin_edges <- bin_mids - c(0, diff(bin_mids) / 2)

vpcPlot(
  run001S,                                #the nlmixr object
  n = 500,                                   #number of trials simulated
  bins = bin_edges,
  show = list(obs_dv = TRUE,                 #additional items to show, like the observations
              obs_median = TRUE,
              sim_median = TRUE,
              sim_median_ci = TRUE,
              obs_ci = TRUE,
              pi = TRUE
  ),
  xlab = "Time (h)",                         #x-axis label
  ylab = "Concentration (mg/L)",             #y-axis label
  title = "VPC for first order absorption PopPK model"
)
```

*<http://vpc.ronkeizer.com/>

VPC for the base model on linear scale...

VPC for first order absorption PopPK model
with linear y axis

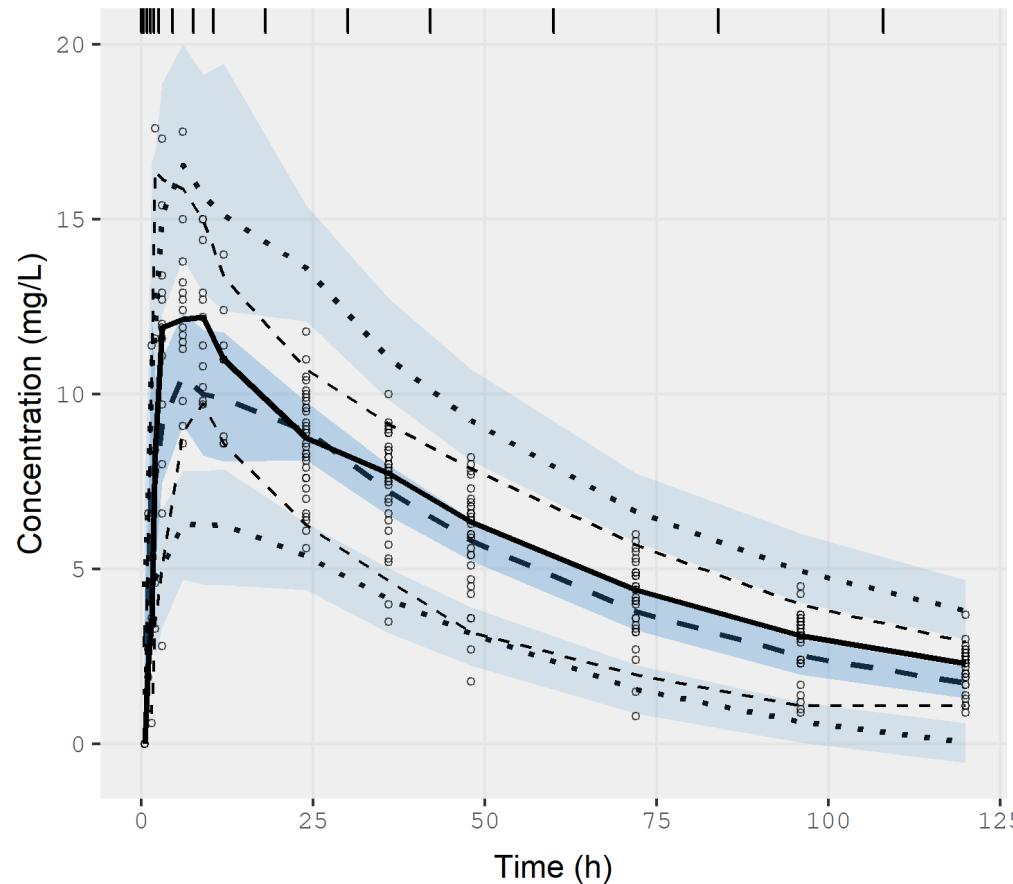


...and on log scale

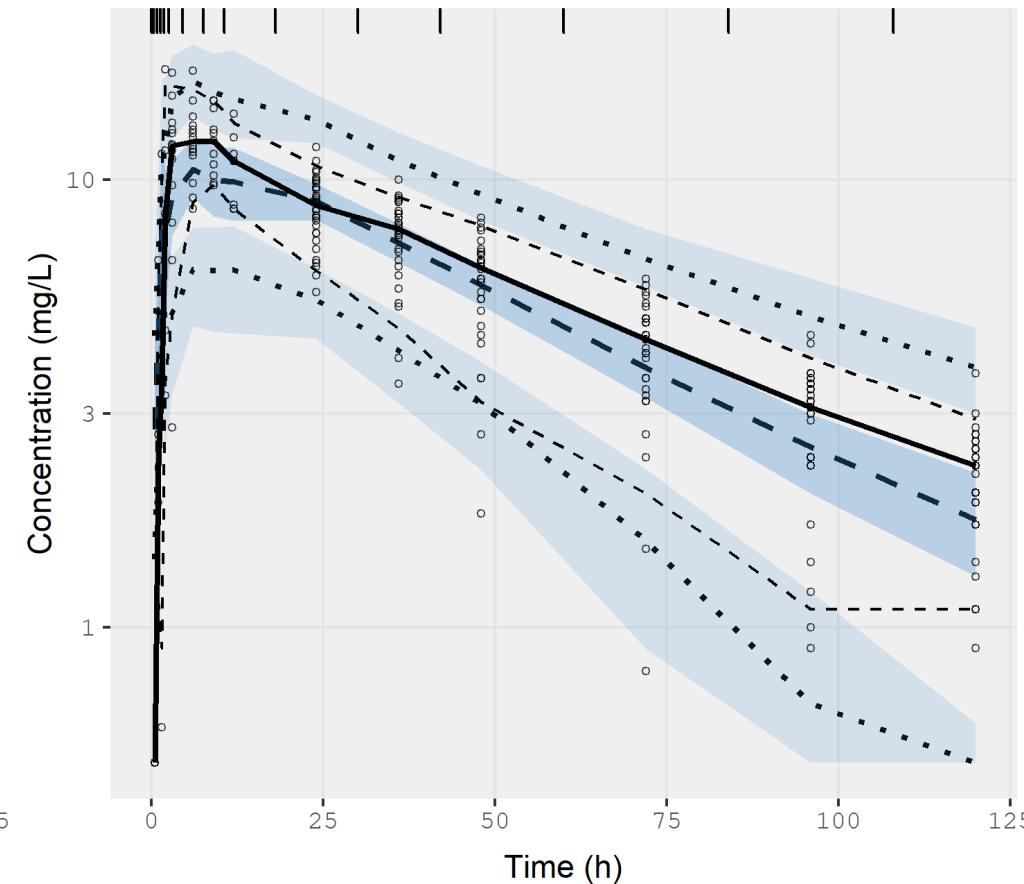
```
## or with a log y-axis starting at 0.5
vpcPlot(
  run001S,                      #the nlmixr object
  n = 500,                        #number of trials simulated
  bins = bin_edges,
  show = list(obs_dv = TRUE,       #additional items to show, like the observations
              obs_median = TRUE,
              sim_median = TRUE,
              sim_median_ci = TRUE,
              obs_ci = TRUE,
              pi = TRUE
  ),
  xlab = "Time (h)",             #x-axis label
  ylab = "Concentration (mg/L)", #y-axis label
  title = "VPC for first order absorption PopPK model"
  log_y = TRUE,                  #to request a log y-axis
  log_y_min = 0.5                #starting at 0.5
)
```

...and on log scale. It's super fast 😊

VPC for first order absorption PopPK model with linear y axis



VPC for first order absorption PopPK model with log y-axis



Alternatively using direct Ron Keizer code so you only need to simulate once

```
library(vpc)

SimVPC <- vpcSim(run001S,                      ## the nlmixr2 object
                  n = 500)

setnames(SimVPC, c("id","time","sim"), c("ID","TIME","DV"))

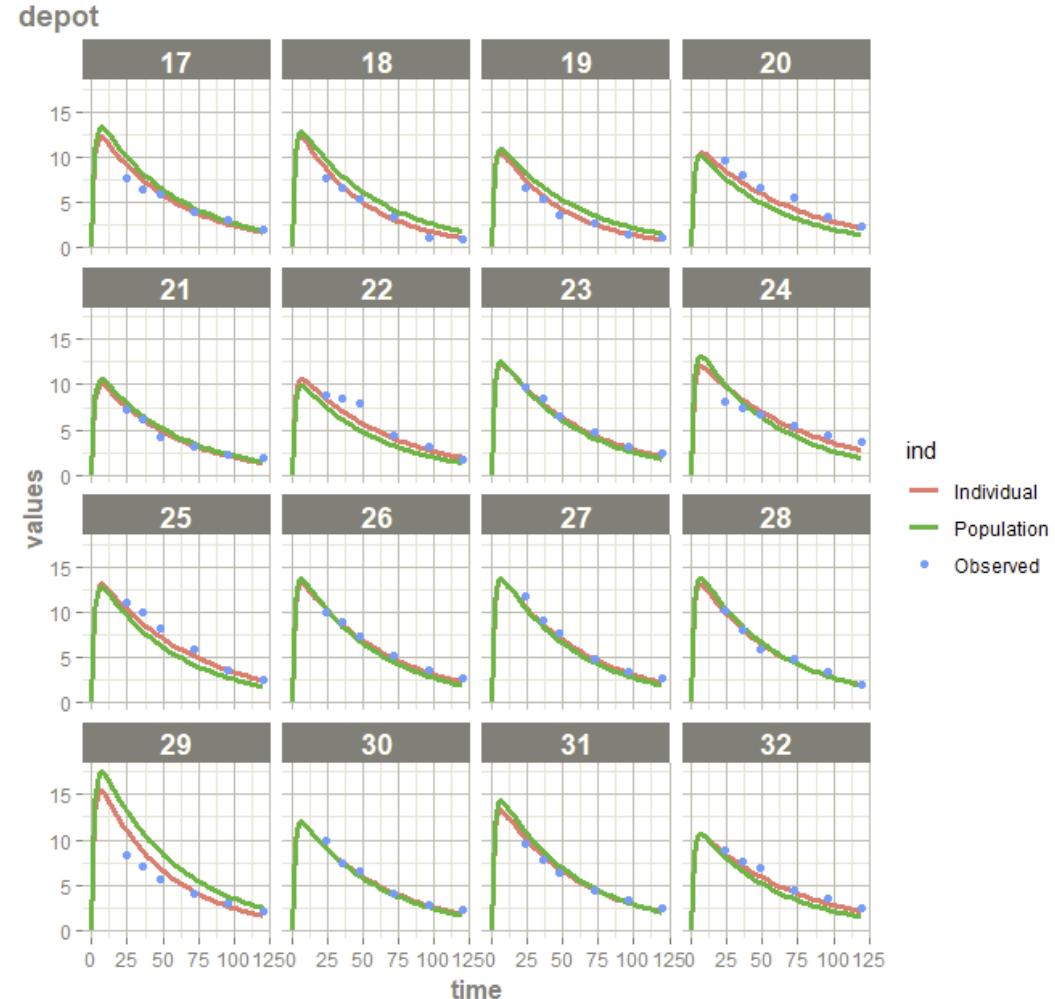
vpc_vpc(
  sim  = SimVPC,
  obs  = Pkdata,
  bins = bin_edges,
  show = list(obs_dv = TRUE,
              obs_median = TRUE,
              sim_median = TRUE,
              sim_median_ci = TRUE,
              obs_ci = TRUE,
              pi = TRUE
  ),
  xlab = "Time (h)",           #x-axis Label
  ylab = "Concentration (mg/L)", #y-axis Label
  title = "VPC for first order absorption PopPK model\nwith linear y axis"
)
```

nlmixr² can generate individual graphs using augPred

```
## Individual fits can be generated using augPred (augmented predictions)
## that provides smooth profiles by interpolating the predictions between observations:
plot(augPred(fitOne.comp.KA.solved_S))
## ...use the arrows in the plot window to examine the earlier curves
```

nlmixr² can generate individual graphs using augPred

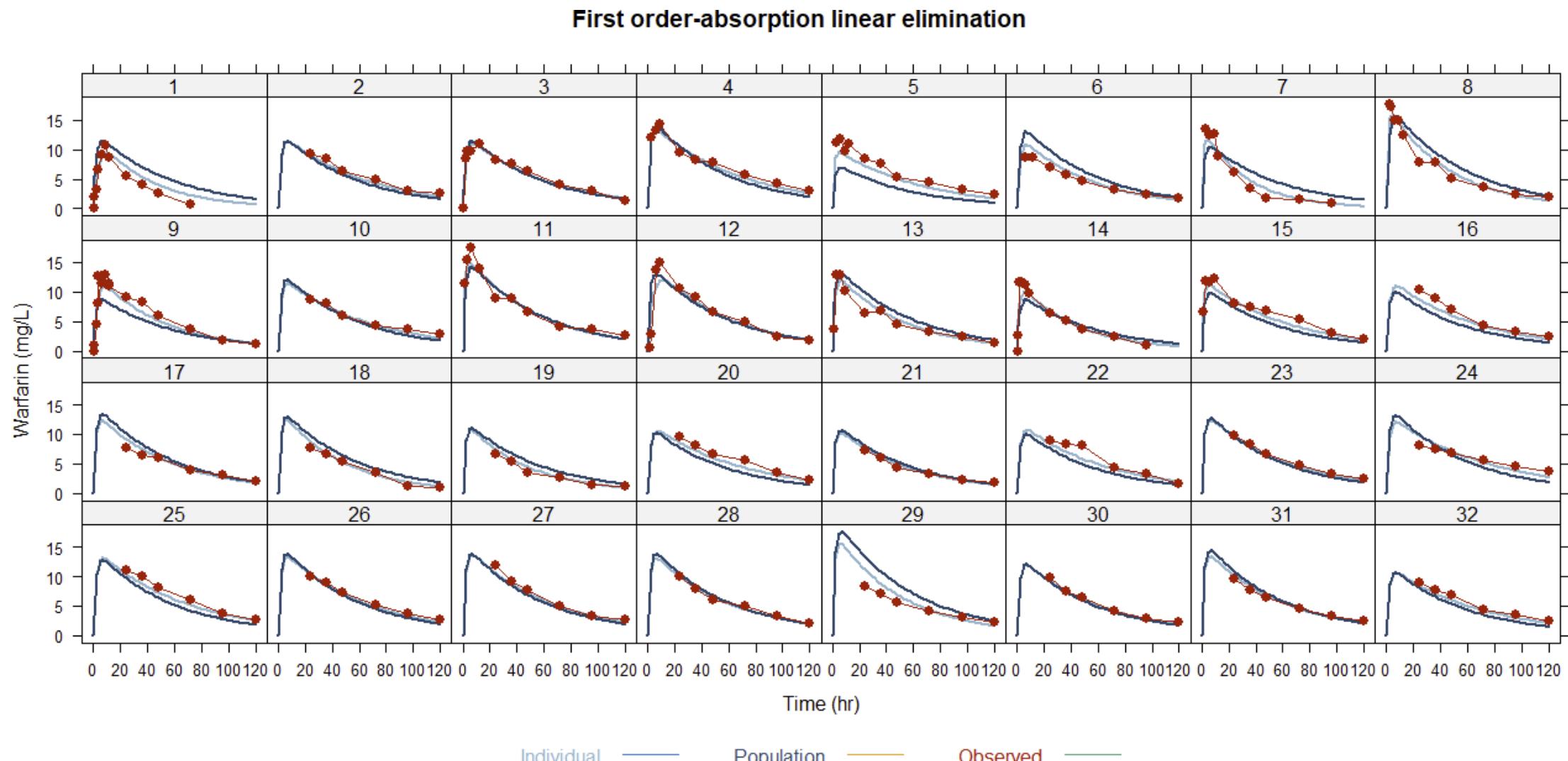
```
## Individual fits can be generated using augPred (augmented predictions)  
## that provides smooth profiles by interpolating the predictions between observations:  
plot(augPred(run001S))  
## ...use the arrows in the plot window to examine the earlier curves
```



use augPred output to plot using your favourite package...

```
#or the augPred output can be plotted to your liking, for instance using ggplot2 or the lattice function xyplot:  
indivpk<-augPred(run001S)  
nlmixCOLS <- c("#28466A", "#8DB6CD", "#B40000) ## specify array of colours for curves  
  
xyplot(  
  values~time|id,          ## plot the variable values by time and make a separate panel for each id  
  data=indivpk,            ## data source with smooth interpolated predictions and observations  
  groups=ind,              ## make separate curves by ind that separates Observed data,  
                          ## Individual predictions and Population predictions  
  layout=c(8,4),           ## arrange as 8 columns and 4 rows  
  type=c("l","l","p"),       ## represent these three by a line, a line and only markers (l=line, p=points)  
  col=nlmixCOLS[c(2,1,3)], ## colours for each curve  
  cex=c(0.1,0.1,1),         ## character size for the markers  
  lwd=c(2,2,0.1),           ## line width of the lines  
  pch=19,                  ## use closed circles as marker  
  xlab="Time (hr)\n",       ## x-axis Label  
  ylab="Warfarin (mg/L)",   ## y-axis Label  
  as.table=TRUE,             ## have the first plot at the top left (otherwise plot 1 starts at the lower left corner)  
  scales=list(alternating=1), ## have axis labels at left and bottom (and not alternating)  
  main="First order-absorption linear elimination", ## title for plot  
  auto.key=list(adj=1,col=nlmixCOLS[c(2,1,3)],columns=3,space="bottom",rectangles=FALSE,points=FALSE) ## key for curves  
)
```

..like lattice



Solved systems and ODEs...

- Using solved-system code:

```
linCmt() ~ prop(prop.err) + add(add.err)
```

- For a solved system, model structure is automatically derived (!) from the parameter names in the **ini** block

- Using ODEs:

```
# rxode2-style differential equation definition
d/dt(depot)      = -ka * depot
d/dt(central) = ka * depot - (cl / v) * central
## Concentration is calculated
cp = central / v
# And is assumed to follow proportional and additive error
cp ~ prop(prop.err) + add(add.err)
```

- ODEs are much more flexible but also more run-time consuming

Running nlmixr² for a system of ODEs using FOCEi

```
One.comp.KA.ODE <- function() {
  ini{
    # Where initial conditions/variables are specified
    lka <- log(1.15) #Log ka (/h)
    lcl <- log(0.135) #Log CL (L/hr)
    lv <- log(8) #Log V (L)
    prop.err <- 0.15 #proportional error (SD/mean)
    add.err <- 0.6 #additive error (mg/L)
    eta.ka ~ 0.5
    eta.cl ~ 0.1
    eta.v ~ 0.1
  })
  model{
    # Where the model is specified
    cl <- exp(lcl + eta.cl)
    v <- exp(lv + eta.v)
    ka <- exp(lka + eta.ka)
    # RxODE-style differential equation definition
    d/dt(gut) = -ka * depot
    d/dt(center) = ka * depot - (cl / v) * center
    ## Concentration is calculated
    cp = center / v
    ## And is assumed to follow proportional and additive error
    cp ~ prop(prop.err) + add(add.err)
  })
}

run002F <- nlmixr2(One.comp.KA.ODE, PKdata, est = "focei", foceiControl(print = 5))
```

nlmixr² output for FOCEi with ODEs

```
> run002F
— nlmixr2 FOCEi (outer: nlminb) —

      OBJF      AIC      BIC Log-likelihood Condition#(Cov) Condition#(Cor)
FOCEi 425.4509 902.758 930.9616      -443.379      25.84916      2.290799

— Time (sec run002F$time): —

  setup optimize covariance table compress other
elapsed 0.001    1.835    1.835  0.06    0.02 15.959

— Population Parameters (run002F$parFixed or run002F$parFixeddf): —

          Parameter   Est.     SE %RSE Back-transformed(95%CI)  BSV(cv%) shrink(sd)%
lka      log ka (1/h) -0.351 0.477  136     0.704 (0.276, 1.8)    100.    49.4%
lc1      log cl (L/h)    -2  0.12    6     0.136 (0.108, 0.172)    29.8    6.08%
lv       log v (L)     2.07 0.115  5.55     7.95 (6.35, 9.97)    25.0    19.1%
prop.err proportional error (SD/mean)  0.125                      0.125
add.err    additive error (mg/L)     0.657                      0.657

Covariance Type (run002F$covMethod): s
No correlations in between subject variability (BSV) matrix
Full BSV covariance (run002F$omega) or correlation (run002F$omegaR; diagonals=SDs)
Distribution stats (mean/skewness/kurtosis/p-value) available in run002F$shrink
Information about run found (run002F$runInfo):
  • gradient problems with initial estimate; see $scaleInfo
  • using S matrix to calculate covariance, can check sandwich or R matrix with $covRS and $covR
  • last objective function was not at minimum, possible problems in optimization
  • ETAs were reset to zero during optimization; (can control by foceiControl(resetEtaP=.))
  • initial ETAs were nudged; (can control by foceiControl(etaNudge=., etaNudge2=))

Censoring (run002F$censInformation): No censoring
Minimization message (run002F$message):
  false convergence (8)
In an ODE system, false convergence may mean "useless" evaluations were performed.
See https://tinyurl.com/yvrrwkce
It could also mean the convergence is poor, check results before accepting fit
You may also try a good derivative free optimization:
  nlmixr2(...,control=list(outerOpt="bobyqa"))
```

Hands-on session II: running **nlmixr²** and diagnostics

- Examine the code in HandsOn_2.R to run a pre-programmed FOCEi analysis with a solved system and its diagnostics
- Examine the code in HandsOn_2.R to run a pre-programmed FOCEi analysis with ODEs
- Examine the VPCs and implement alternative models for absorption (like one or more transit compartments...)

Running nlmixr²: 1 transit compartment

```
## 1 transit compartment
One.comp.transit <- function() {
  ini{
    # Where initial conditions/variables are specified
    lktr <- log(1.15) #log transit rate constant (/h)
    lcl <- log(0.135) #log CL (L/h)
    lv <- log(8)      #Log V (L)
    prop.err <- 0.15    #proportional error (SD/mean)
    add.err <- 0.6      #additive error (mg/L)
    eta.ktr ~ 0.5
    eta.cl ~ 0.1
    eta.v ~ 0.1
  })
  model{
    # Where the model is specified
    ktr <- exp(lktr + eta.ktr)
    cl <- exp(lcl + eta.cl)
    v <- exp(lv + eta.v)
    ## ODE example
    d/dt(depot)  =-ktr*depot
    d/dt(central) = ktr*trans - (cl/v)*central
    d/dt(trans)   = ktr*(depot - trans)
    ## where residual error is assumed to follow proportional and additive error
    central ~ prop(prop.err) + add(add.err)
  }}}
```

nlmixr² output: 1 transit compartment with ODEs using FOCEi

```
> run003F
-- nlmixr^ FOCEi (outer: nlminb) --

      OBJF      AIC      BIC Log-likelihood Condition#(cov) Condition#(cor)
FOCEi 321.1837 798.4908 826.6945     -391.2454      18.54498      1.596483

-- Time (sec run003F$time): --
setup optimize covariance table compress other
elapsed 0.017    2.688    2.688   0.06    0.03 12.867

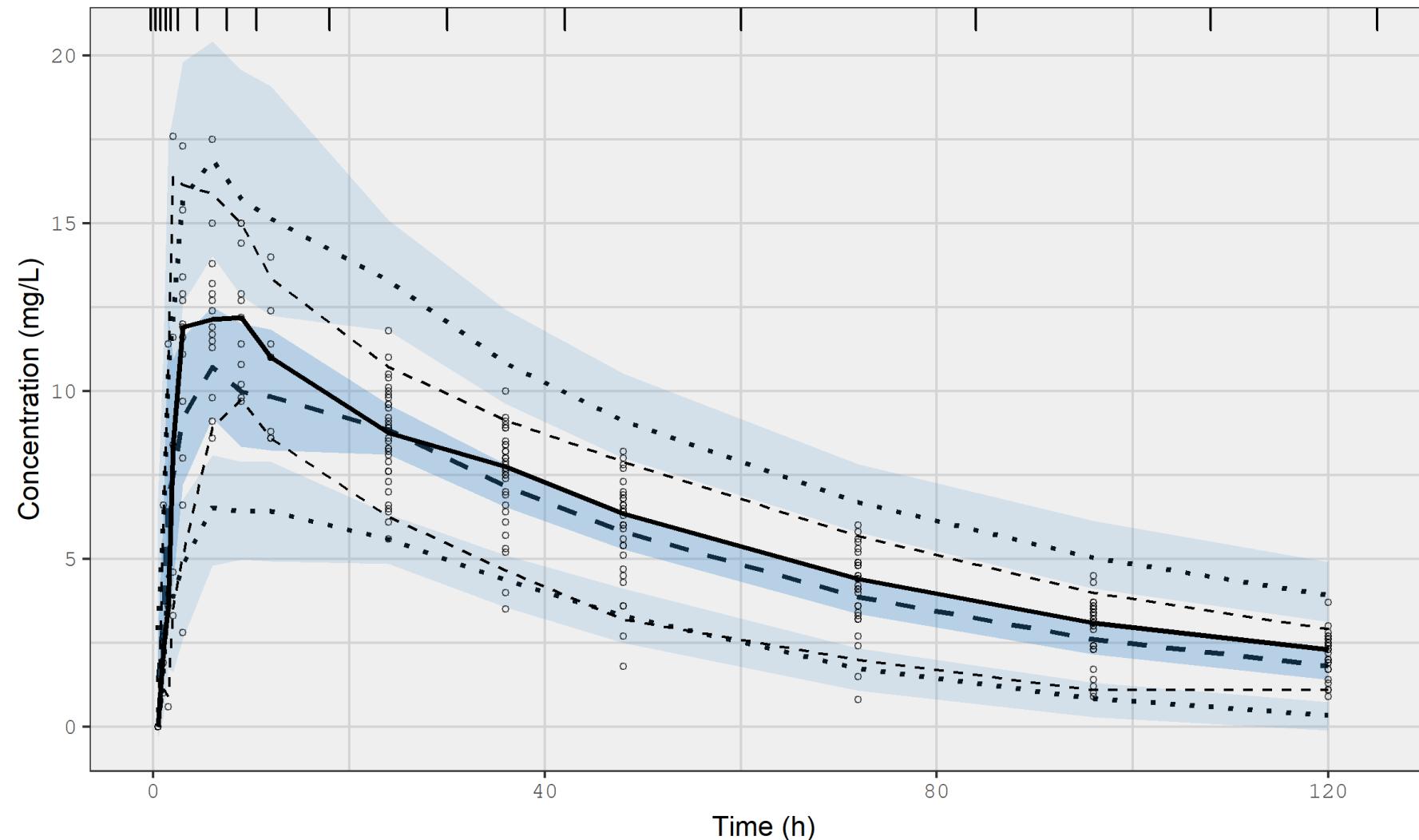
-- Population Parameters (run003F$parFixed or run003F$parFixedDF): --

          Parameter  Est.    SE  %RSE Back-transformed(95%CI)  BSV(CV%)  shrink(SD)%
lktr      log k transit (/h) 0.161  0.073  45.5      1.17 (1.02, 1.35)    64.0    45.9%
lc1      log cl (L/hr) -2.03  0.0226  1.11      0.132 (0.126, 0.138)    30.8    5.53%
lv       log v (L)  2.07  0.0179  0.862      7.94 (7.66, 8.22)    26.4    17.6%
prop.err proportional error (SD/mean) 0.099
add.err      additive error (mg/L) 0.489

Covariance Type (run003F$covMethod): r,s
No correlations in between subject variability (BSV) matrix
Full BSV covariance (run003F$omega) or correlation (run003F$omegaR; diagonals=SDs)
Distribution stats (mean/skewness/kurtosis/p-value) available in run003F$shrink
Information about run found (run003F$runInfo):
• gradient problems with initial estimate and covariance; see $scaleInfo
• last objective function was not at minimum, possible problems in optimization
• ETAs were reset to zero during optimization; (Can control by foceiControl(resetEtaP=.))
• initial ETAs were nudged; (can control by foceiControl(etaNudge=., etaNudge2=))
Censoring (run003F$censInformation): No censoring
```

VPC for one compartment model with a transit compartment using FOCEi

One transit compartment FOCEi



Running nlmixr²: 5 transit compartments

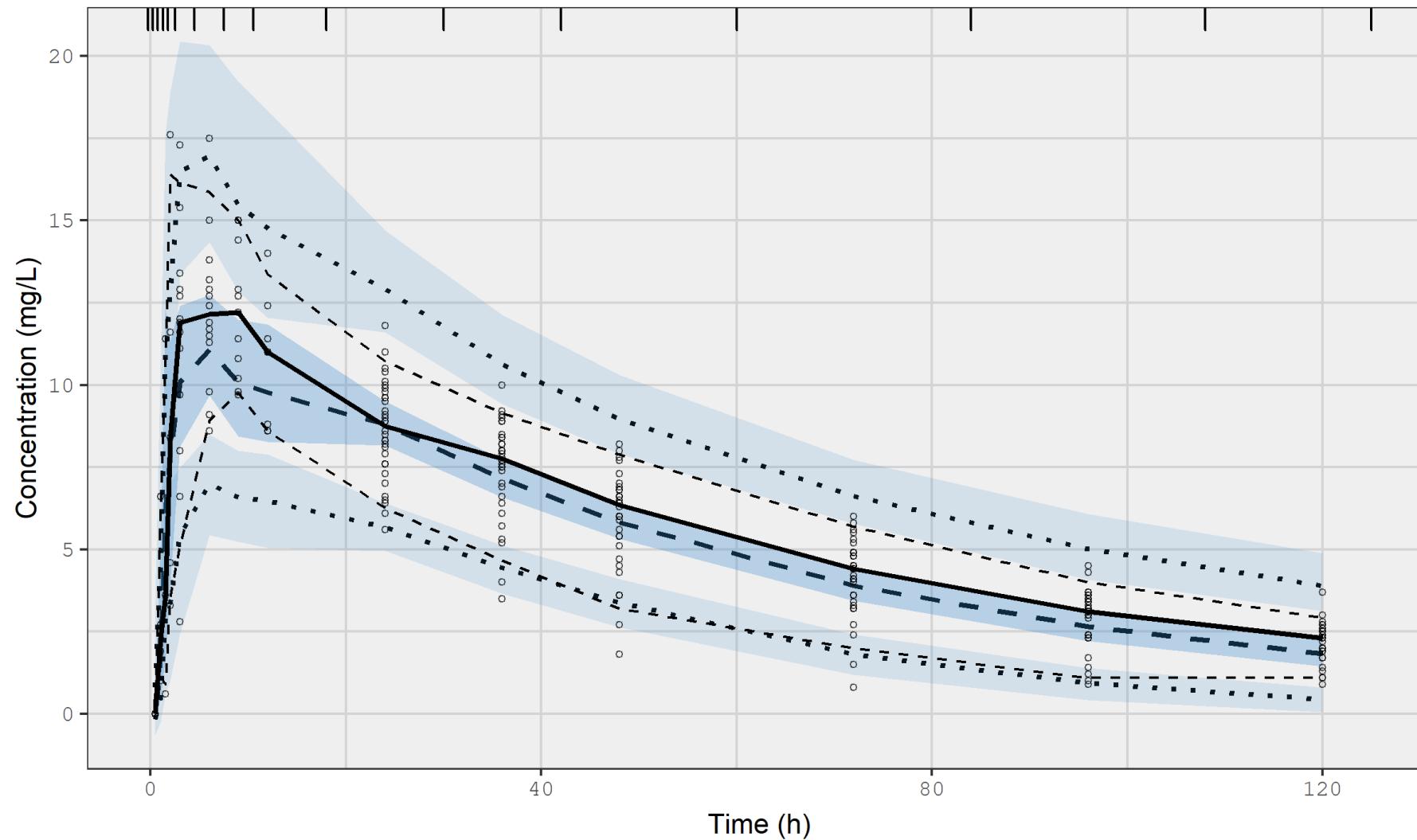
```
## 5 transit compartments
KA1tr5ode <- function() {
  ini{
    # Where initial conditions/variables are specified
    lktr <- log(1.15) #log transit rate constant (/h)
    lcl <- log(0.135) #log CL (L/h)
    lv <- log(8)      #Log V (L)
    prop.err <- 0.15    #proportional error (SD/mean)
    add.err <- 0.6     #additive error (mg/L)
    eta.ktr ~ 0.5      #IIV ktr
    eta.cl ~ 0.1       #IIV cl
    eta.v ~ 0.1        #IIV v
  })
  model{
    # Where the model is specified
    ktr <- exp(lktr + eta.ktr)
    cl <- exp(lcl + eta.cl)
    v <- exp(lv + eta.v)
    ## ODE example
    d/dt(depot)  =-ktr*depot
    d/dt(central) = ktr*transit5 - cl* central/v
    d/dt(transit1)= ktr*(depot - transit1)
    d/dt(transit2)= ktr*(transit1 - transit2)
    d/dt(transit3)= ktr*(transit2 - transit3)
    d/dt(transit4)= ktr*(transit3 - transit4)
    d/dt(transit5)= ktr*(transit4 - transit5)
    ## where residual error is assumed to follow proportional and additive error
    central ~ prop(prop.err) + add(add.err)
  }}}
```

nlmixr2 output: 5 transit compartments with ODEs using FOCEi

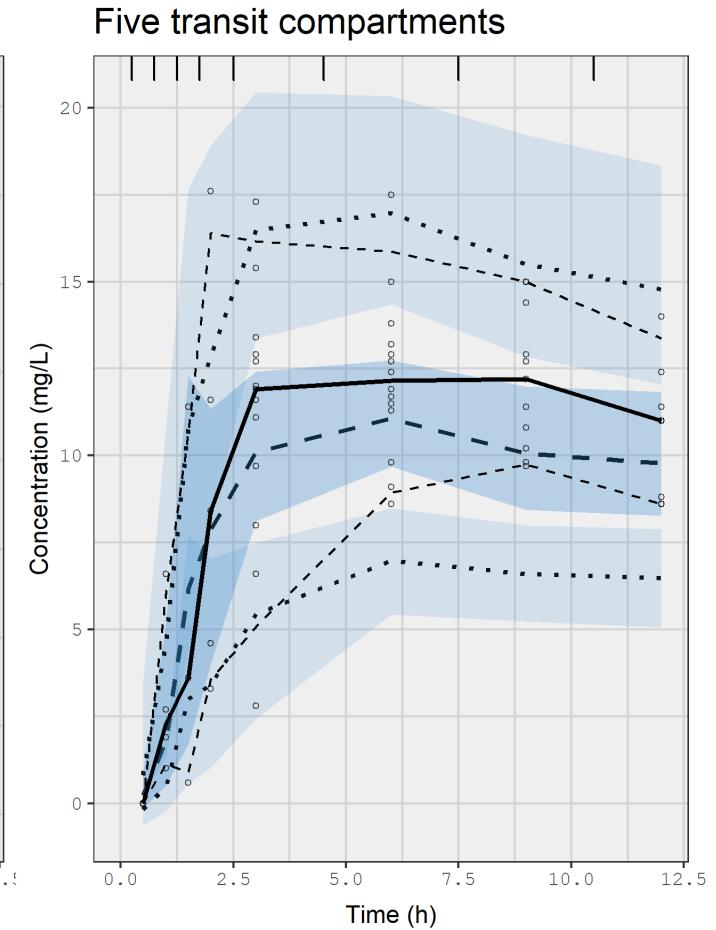
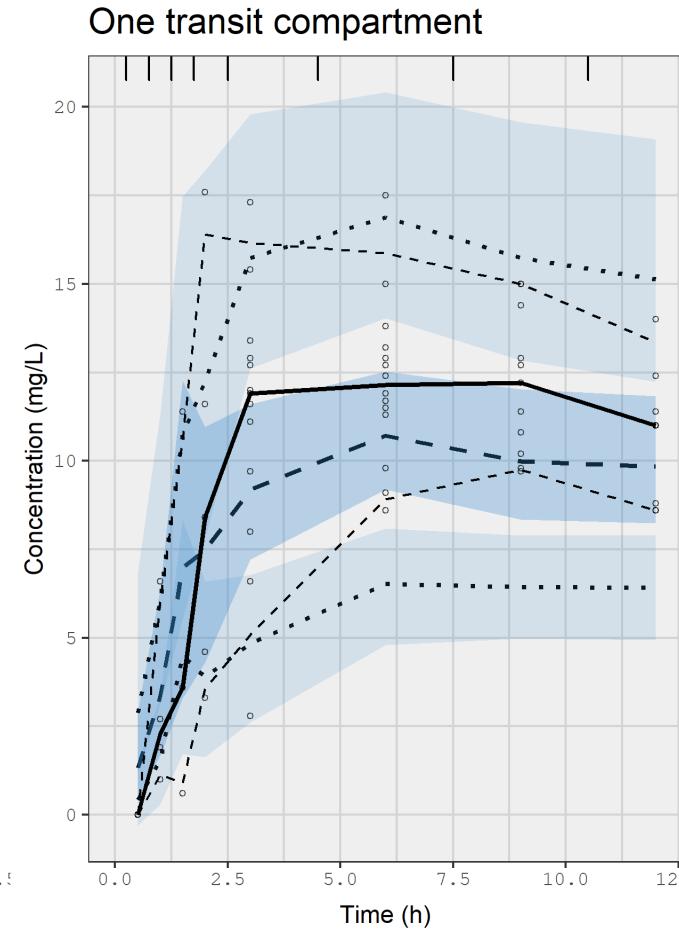
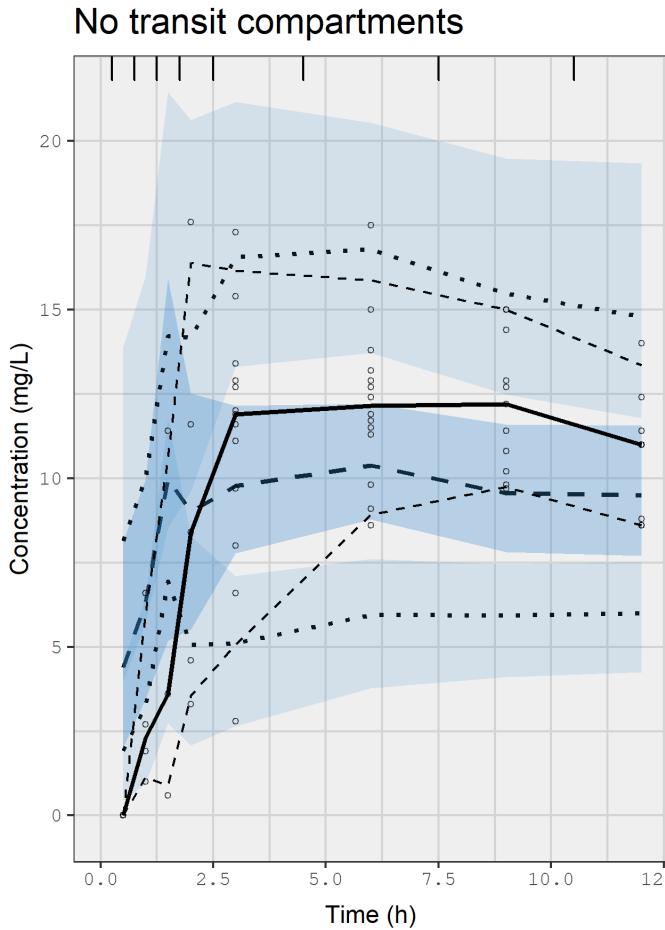
```
> run004F
— nlmixr² FOCEi (outer: nlminb) —  
  
    OBJF      AIC      BIC Log-likelihood Condition#(cov) Condition#(cor)  
FOCEi 230.5818 707.8889 736.0925     -345.9445      54.22588      3.848696  
  
— Time (sec run004F$time): —  
  
    setup optimize covariance table compress other  
elapsed 0.001   4.453    4.453  0.05    0.03 16.243  
  
— Population Parameters (run004F$parFixed or run004F$parFixeddf): —  
  
          Parameter   Est.    SE %RSE Back-transformed(95%CI)  BSV(cv%) shrink(SD)%  
lktr    log transit rate constant (/h)  1.37  0.139 10.2        3.94 (3, 5.17)    53.2    46.0%  
lc1      log cl (L/h)   -2.04 0.0285 1.4       0.13 (0.123, 0.138)    30.2    1.69%  
lv        log V (L)    2.08  0.0302 1.45       8 (7.54, 8.49)    22.9    6.38%  
prop.err  proportional error (SD/mean) 0.0759                      0.0759  
add. err    additive error (mg)    0.361                      0.361  
  
Covariance Type (run004F$covMethod): r,s  
No correlations in between subject variability (BSV) matrix  
Full BSV covariance (run004F$omega) or correlation (run004F$omegaR; diagonals=SDs)  
Distribution stats (mean/skewness/kurtosis/p-value) available in run004F$shrink  
Information about run found (run004F$runInfo):  
• gradient problems with initial estimate and covariance; see $scaleInfo  
• last objective function was not at minimum, possible problems in optimization  
• ETAs were reset to zero during optimization; (can control by foceiControl(resetEtaP=.))  
• initial ETAs were nudged; (can control by foceiControl(etaNudge=., etaNudge2=))  
Censoring (run004F$censInformation): No censoring
```

VPC for first order absorption with 5 transit compartments using FOCEi

Five transit compartments FOCEi



Comparing the VPCs for the first 12 hours to see if absorption is described better using zero, one, or five transit compartments



- For future reference, the code is provided in HandsOn_3.R

nlmixr² can read in NONMEM output and create nlmixr² models to simulate and re-estimate using nonmem2rx and babelmixr2

```
library(nlmixr2)
library(babelmixr2)
library(nonmem2rx)

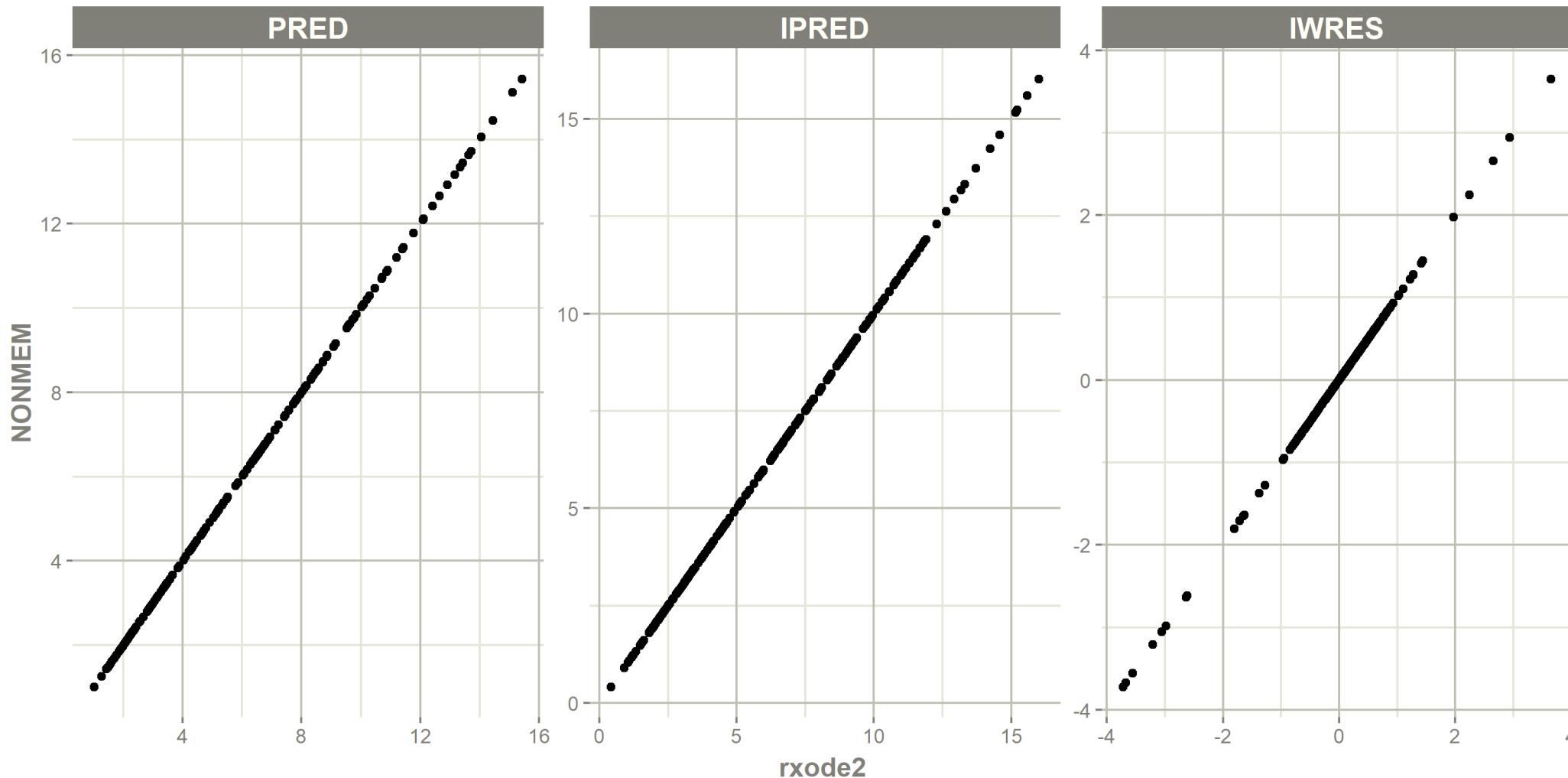
## Read in NONMEM results -in this case from run005- into an rxode2 object
## Models read in correctly if Uppsala-style residual errors are used
## with SIGMA fixed to 1 and with only a single SIGMA
## Example with combined additive and proportional error:

mod5 <- nonmem2rx("run005.ctl", lst=".res", save=FALSE)

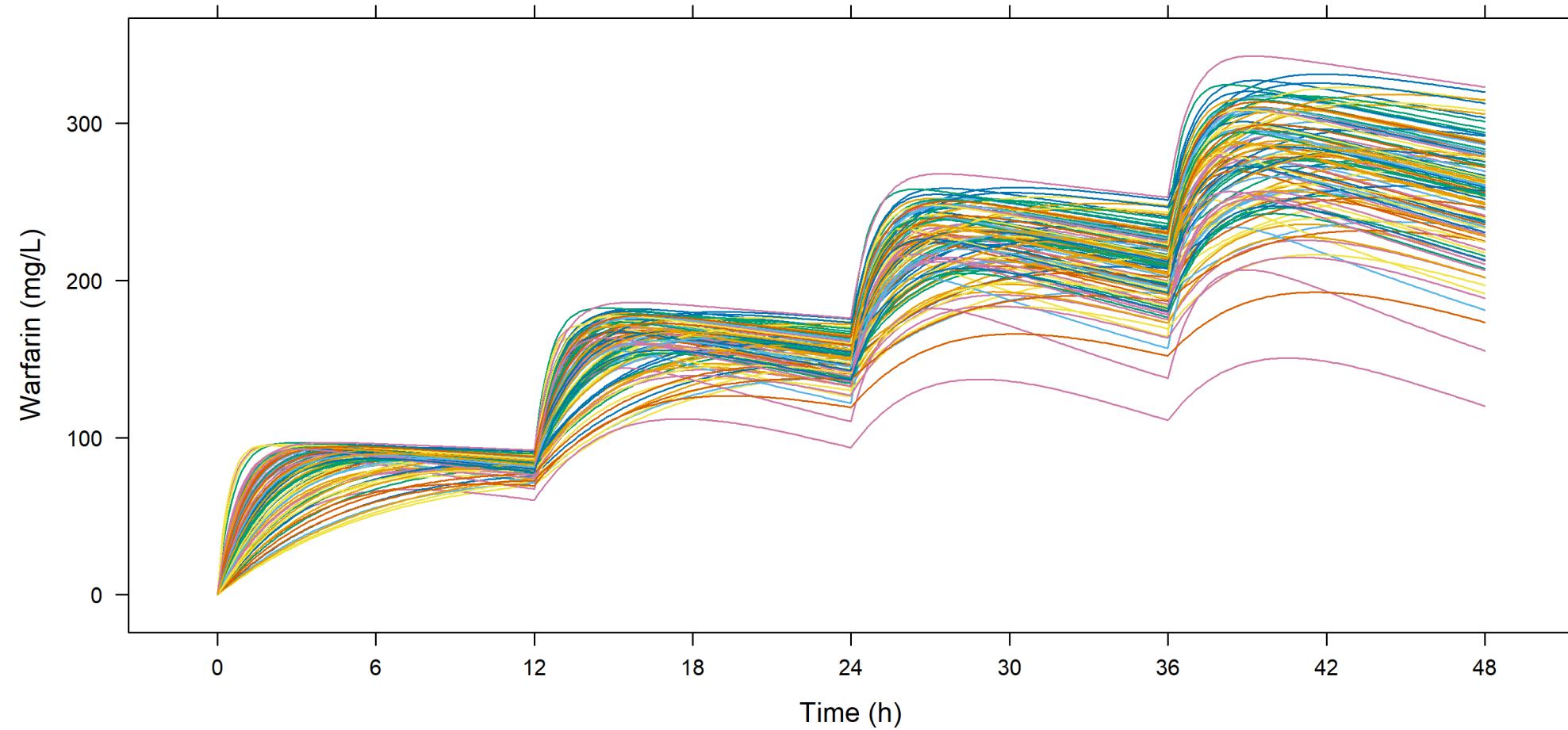
## to check if the model has been implemented correctly, NONMEM PRED, IPRED, and IWRES are
## compared with the rxode2 generated values after conversion

plot(mod5)
```

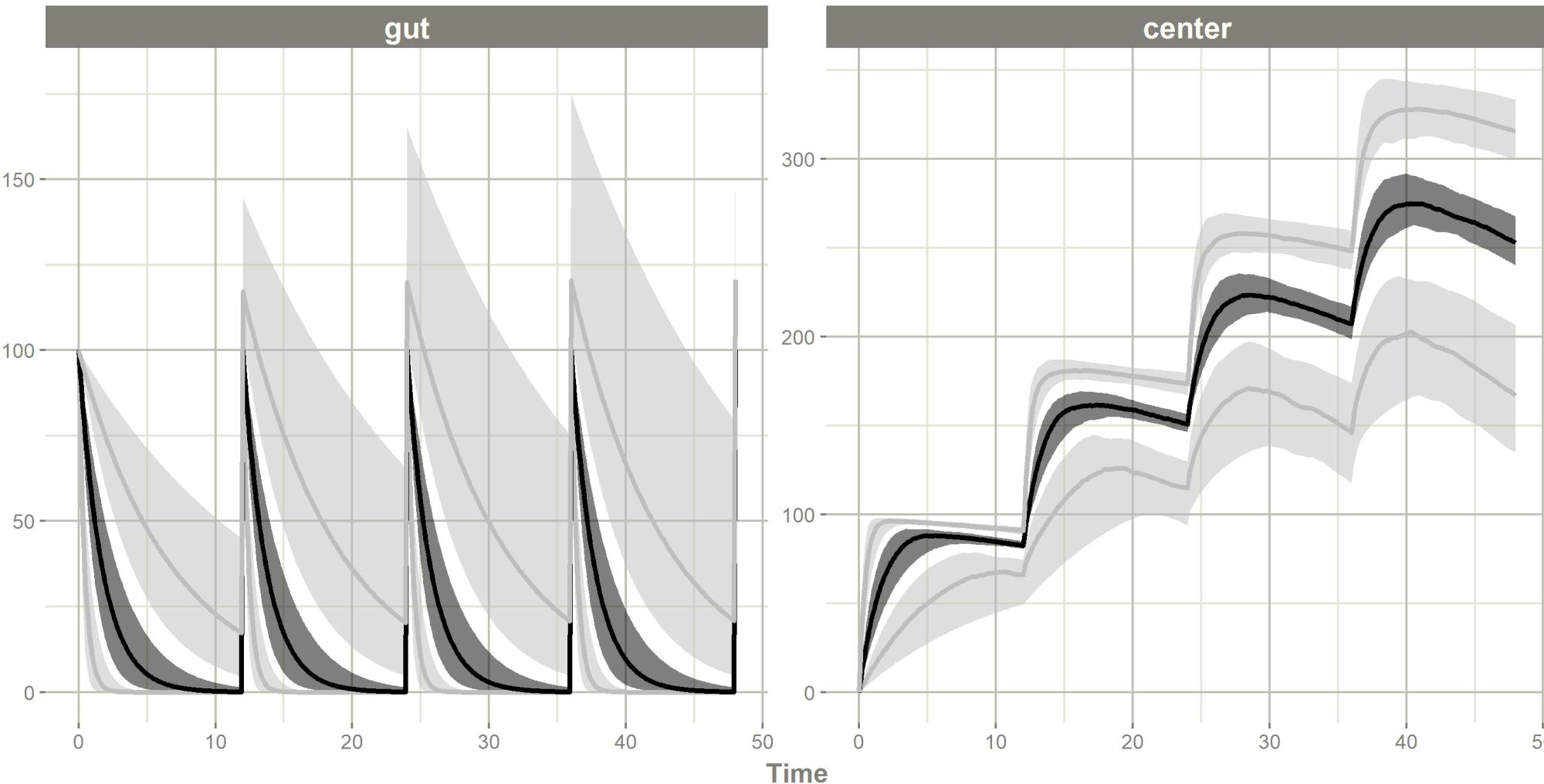
Check to see if the NONMEM-generated PRED, IPRED and IWRES values match the values when the model is used to simulate using rxode2



The rxode2 object can be used to simulate new regimens:
e.g. four doses of 100 mg at 12 hours apart using 100 subjects

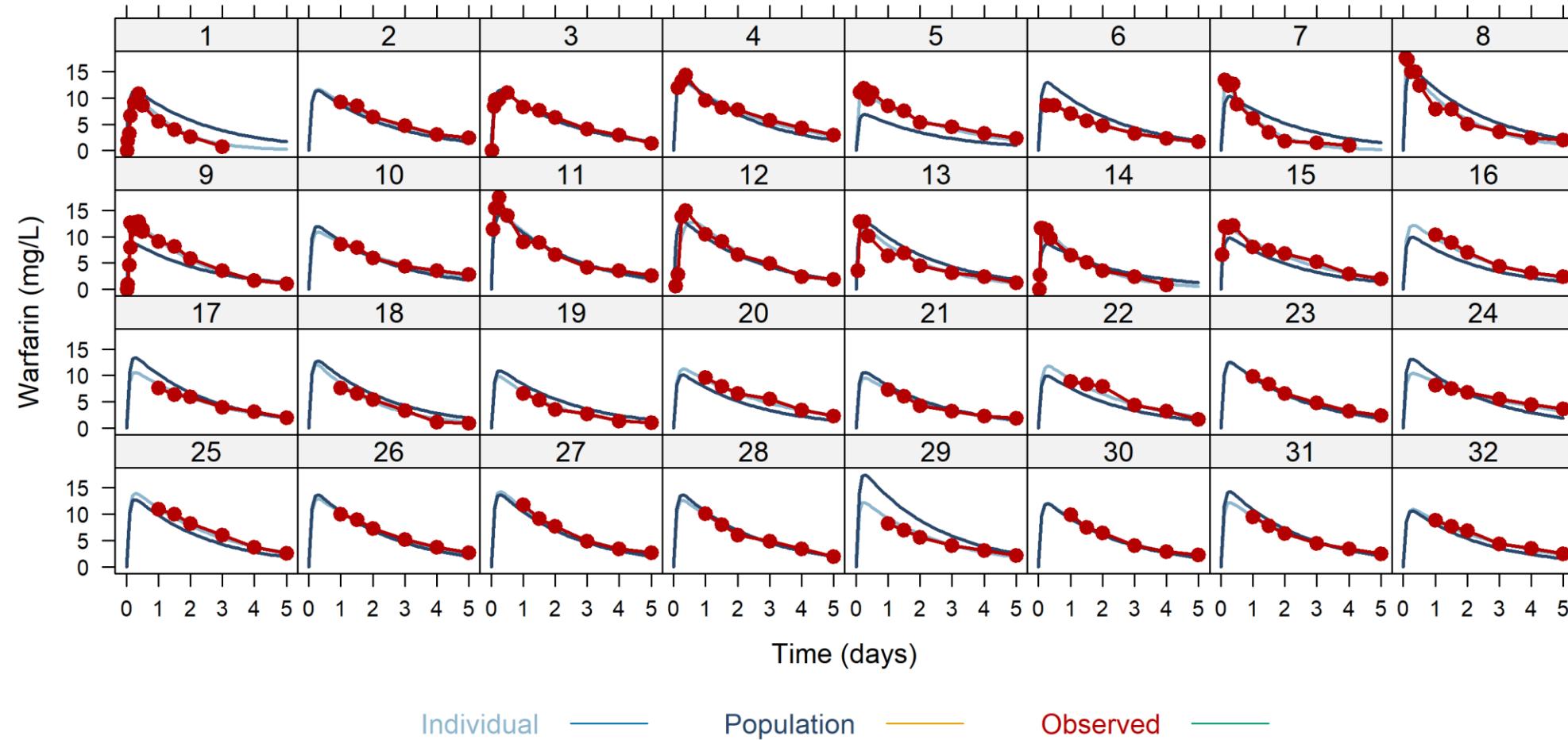


Or simulate 100 studies with these NONMEM parameters to capture uncertainty in theta estimates

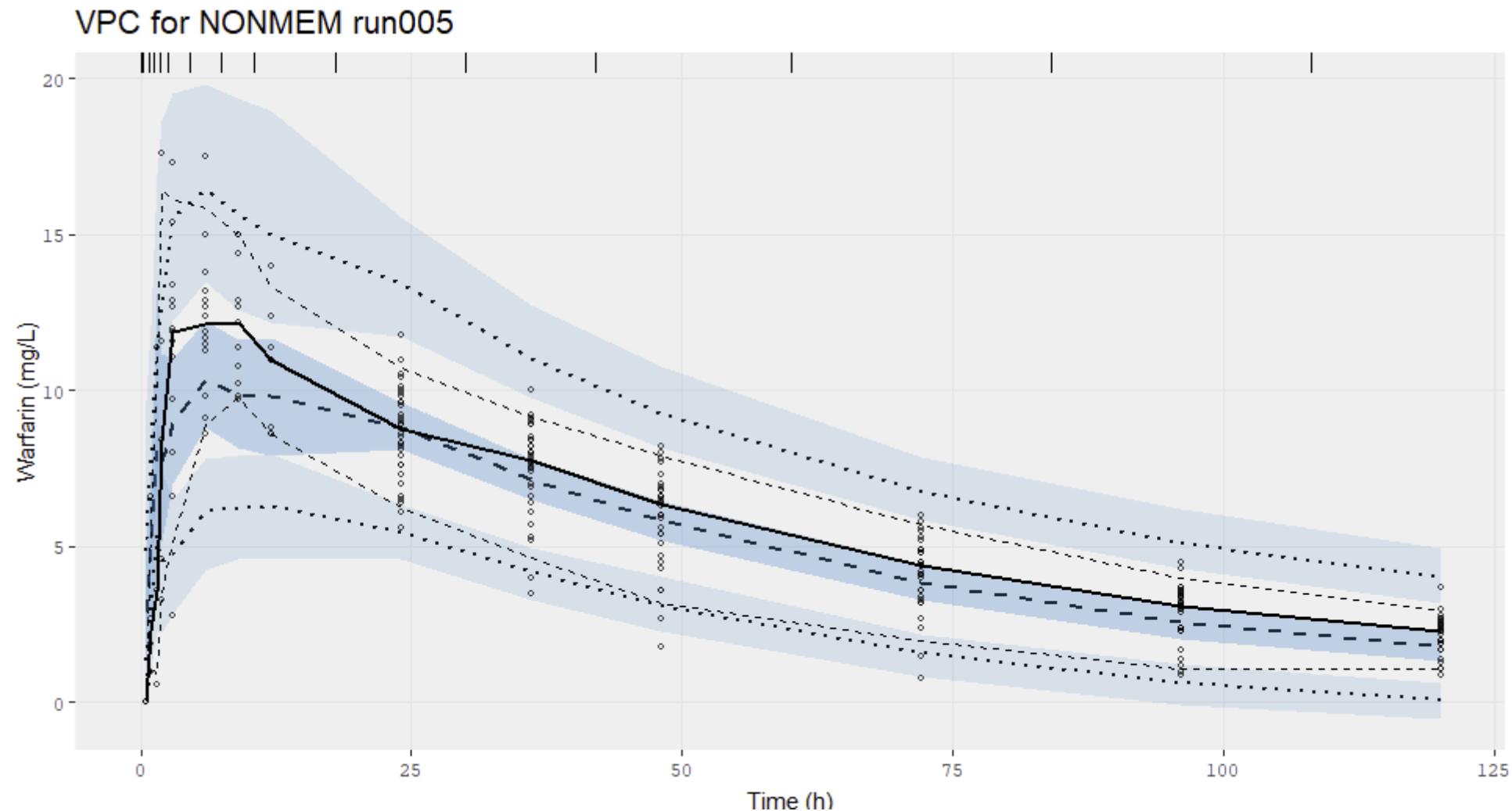


The rxode2 object can be translated to an nlmixr2 object to create individual plots

```
run005NM <- as.nlmixr2(mod5)
indivs5 <- augPred (run005NM)
```



The rxode2 object can be translated to an nlmixr2 object to create VPCs



The results of run005 as generated by NONMEM and read in using nonmem2rx

```

> #results for the NONMEM-translated model
> run005NM
— nlmixr# nonmem2rx reading NONMEM ver 7.5.0 —

          OBJF      AIC      BIC Log-likelihood Condition#(cov) Condition#(cor)
nonmem2rx -37.97987 439.3273 467.5309      -211.6636      143.2888      7.453375

— Time (sec run005NM$time): —

      setup table compress NONMEM as.nlmixr2
elapsed 0.03  0.06    0.03   9.65     5.04

— Population Parameters (run005NM$parFixed or run005NM$parFixeddf): —

      Parameter    Est.      SE %RSE Back-transformed(95%CI)  BSV(cv%) shrink(sd)%
theta1      log ka -0.569  0.246 43.3 -0.569 (-1.05, -0.0866)
theta2      log cl -2.01  0.0538 2.68    -2.01 (-2.11, -1.9)
theta3      log v  2.06  0.046 2.23     2.06 (1.97, 2.15)
EPS_prop    EPS_prop 0.117                               0.117
EPS_pkadd   EPS_pkadd 0.722                               0.722
ETA_ka                                78.0      45.8%
ETA_cl                                28.7      3.74%
ETA_v       22.2      13.4%

```

NONMEM-reported OFV:

```
*****  
***** FIRST ORDER CONDITIONAL ESTIMATION WITH INTERACTION *****  
#OBJT:***** MINIMUM VALUE OF OBJECTIVE FUNCTION *****  
*****  
#OBJV:***** 423.327 *****
```

The results of run005 as generated by nlmixr2 after rerunning the NONMEM model imported using nonmem2rx

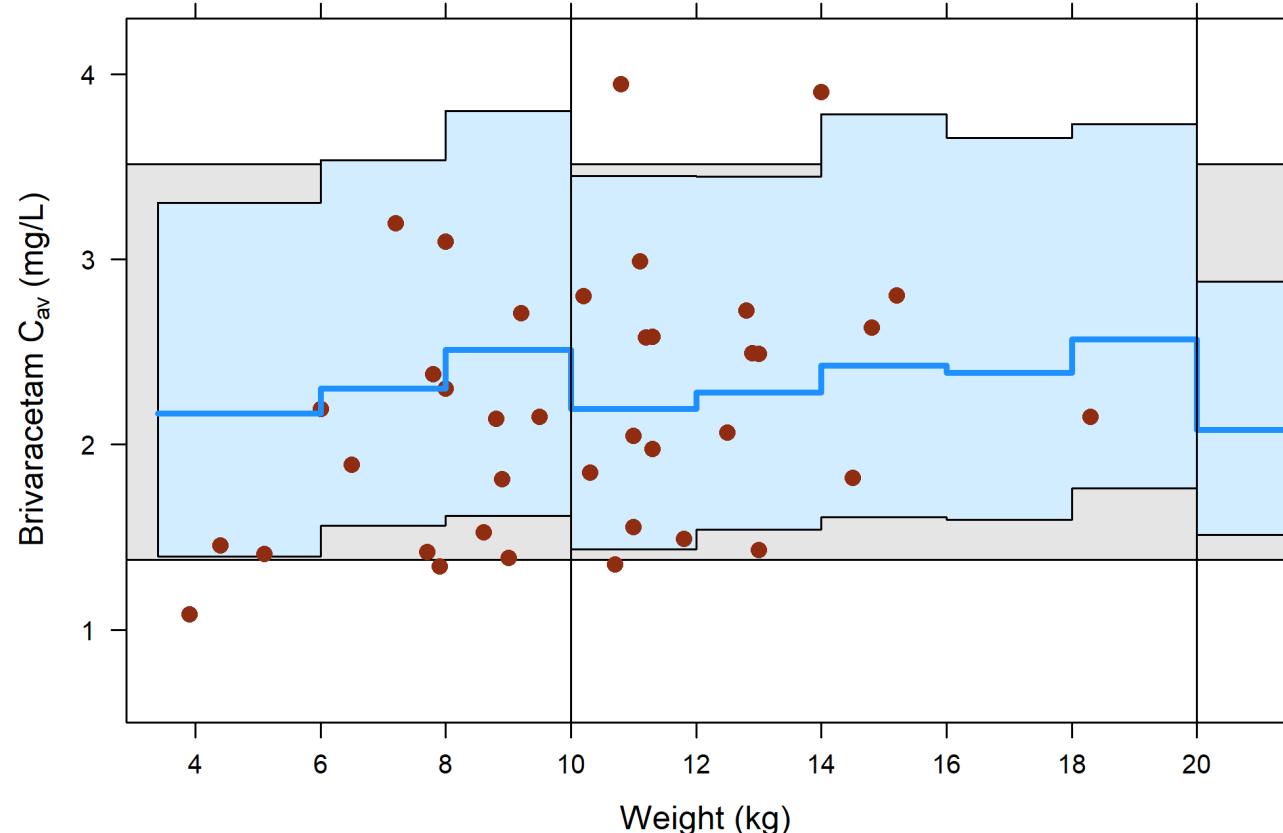
```
> #nlmixr2 results after running the NONMEM-translated model
> run005F
— nlmixr# FOCEi (outer: nlminb) —
    OBJF      AIC      BIC Log-likelihood Condition#(cov) Condition#(cor)
FOCEi 423.3296 900.6368 928.8404     -442.3184     38.37877     2.75426
— Time (sec run005F$time): —
    setup optimize covariance table compress other
elapsed 0.001     1.596      1.596   0.05     0.02 8.427
— Population Parameters (run005F$parFixed or run005F$parFixeddf): —
    Parameter    Est.      SE %RSE Back-transformed(95%CI)  BSV(cv%) shrink(sd)%
theta1    log ka -0.569  0.344 60.4    -0.569 (-1.24, 0.105)
theta2    log cl -2.01   0.0776 3.87    -2.01 (-2.16, -1.86)
theta3    log v   2.06   0.0669 3.25    2.06 (1.93, 2.19)
EPS_prop EPS_prop  0.117                   0.117
EPS_pkadd EPS_pkadd  0.722                   0.722
ETA_ka                           78.0      45.8%
ETA_c1                           28.7      3.74%
ETA_v                            22.2      13.4%
```

Hands-on session IV: read in NONMEM results using nonmem2rx and run cool stuff

- Examine and run the code in HandsOn_4.R to explore the amazing functionality of nonmem2rx

For examination at home: simulations of paediatric posology

- The course material has a subdirectory NhanesPosologyGraphs that provides a full worked example of reading in a NONMEM model and using it to simulate pediatric exposures to create the following graph:

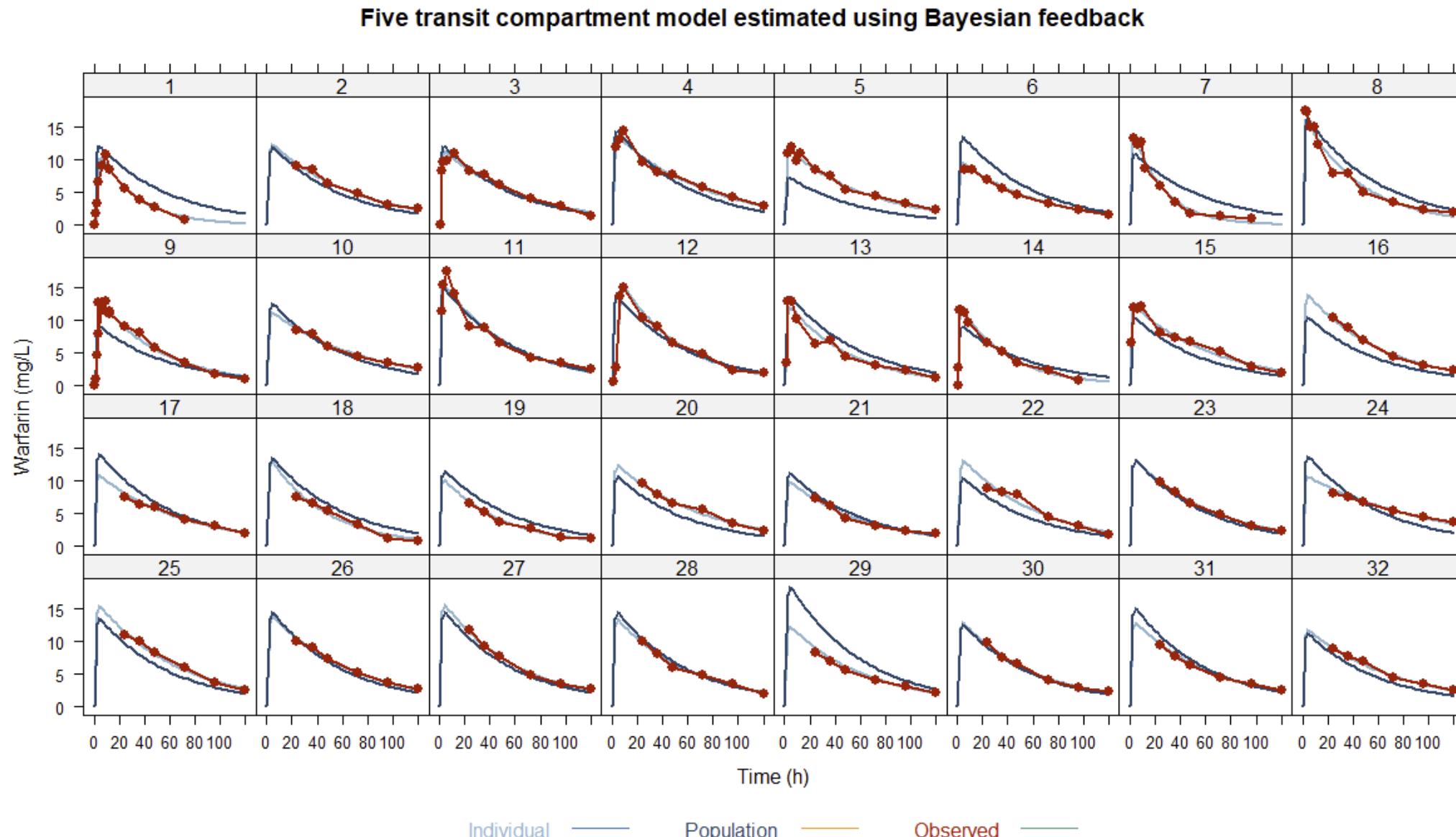


nlmixr² can generate empirical Bayes estimates for Bayesian feedback: individual EBES for a new data set using existing population parameters

```
KA1tr5posthoc <- function() {  
  ini{  
    # Specify previously obtained population estimates (e.g. from NONMEM or nlmixr)  
    lktr <- 1.18994619 #Log ktr (/h)  
    lcl <- -2.01737477 #Log CL (L/h)  
    lv <- 2.06631620 #Log V (L)  
    prop.err <- 0.07883633 #proportional error (SD/mean)  
    add.err <- 0.37249666 #additive error (mg/L)  
    eta.ktr ~ 0.2532964  
    eta.cl ~ 0.08073339  
    eta.v ~ 0.04490733  
  })  
  model{  
    cl <- exp(lcl + eta.cl)  
    v <- exp(lv + eta.v)  
    ktr <- exp(lktr + eta.ktr)  
    d/dt(trns1) = -ktr * trns1  
    d/dt(trns2) = ktr * trns1 - ktr * trns2  
    d/dt(trns3) = ktr * trns2 - ktr * trns3  
    d/dt(trns4) = ktr * trns3 - ktr * trns4  
    d/dt(trns5) = ktr * trns4 - ktr * trns5  
    d/dt(central) = ktr * trns5 - (cl/v) * central  
    cp = central/v  
    cp ~ prop(prop.err) + add(add.err)  
  })  
}  
  
run005ph <- nlmixr2(KA1tr5posthoc, PKdata,  
  est = "posthoc") # Specify posthoc as estimation method
```

- Useful in a therapeutic drug monitoring setting
- Or for generating exposure estimates with a particularly nasty model that you do not want to refit on new data ☺

Individual graphs for the five transit compartment model estimated using Bayesian feedback; perfect fit even though there was no population parameter estimation



Parameterisation and mu-referencing

- For SAEM, parameters must be defined using ‘mu-referencing’
- This means that inter-individual variability (IIV) parameters must be added onto population parameters
- This implies estimating log-parameters with the IIV added on the log-scale
- For FOCEi, mu-referencing is not strictly required, but is shown to provide superior estimation results
- For a binary covariate (e.g. sex 0/1), the back-transformed estimate is a fold-change that can be re-written as a percentage change

Corresponding nlmixr² code

```
## One compartment transit model with Sex on V
Katr1_sexV <- function() {
  ini{
    lktr <- log(1.15) #log k transit (/h)
    lcl  <- log(0.135) #log CL (L/h)
    lv   <- log(8)      #Log V (L)
    Sex_V <- 0.1          #Log Sex on v
    prop.err <- 0.15      #proportional error (SD/mean)
    add.err <- 0.6         #additive error (mg/L)
    eta.ktr ~ 0.5
    eta.cl ~ 0.1
    eta.v ~ 0.1
  })
  model{
    #Sex on volume
    cl <- exp(lcl + eta.cl)
    v  <- exp(lv + eta.v + Sex_V * SEX) #the SEX covariate is 0 or 1 in the data set
    ktr <- exp(lktr + eta.ktr)
    d/dt(depot) = -ktr * depot
    d/dt(central) = ktr * trans - (cl/v) * central
    d/dt(trans)   = ktr * depot - ktr * trans
    cp = central/v
    cp ~ prop(prop.err) + add(add.err)
  }
}
```

nlmixr² output: mu-referenced sex on V (log-scale)

```
> run006F
-- nlmixr# FOCEi (outer: nlminb) --

      OBJF      AIC      BIC Log-likelihood Condition#(Cov) Condition#(Cor)
FOCEi 303.6673 782.9744 814.7035     -382.4872      49.19971      48.1342

-- Time (sec run006F$time): --
      setup optimize covariance table compress  other
elapsed 0.001    3.844    3.844   0.06    0.02 28.441

-- Population Parameters (run006F$parFixed or run006F$parFixeddf): --

      Parameter   Est.     SE %RSE Back-transformed(95%CI)  BSV(cv%) Shrink(sd)%
lktr      log k transit (/h) 0.202 0.324 160      1.22 (0.649, 2.31)      64.8      46.0%
lc1       log CL (L/h) -2.02 0.117 5.82      0.133 (0.106, 0.167)      30.0      3.29%
lv        log V (L)  1.73 0.229 13.2      5.65 (3.61, 8.86)      15.8      14.9%
Sex_v     log Sex on v 0.404 0.24 59.3  0.404 (-0.0653, 0.874)
prop.err  proportional error (SD/mean) 0.102
add.err   additive error (mg/L) 0.451

Covariance Type (run006F$covMethod): s
No correlations in between subject variability (BSV) matrix
Full BSV covariance (run006F$omega) or correlation (run006F$omegaR; diagonals=SDs)
Distribution stats (mean/skewness/kurtosis/p-value) available in run006F$shrink
Information about run found (run006F$runInfo):
  • gradient problems with initial estimate and covariance; see $scaleInfo
  • using S matrix to calculate covariance, can check sandwich or R matrix with $covRS and $covR
  • last objective function was not at minimum, possible problems in optimization
  • ETAs were reset to zero during optimization; (can control by foceicontrol(resetEtaP=.))
  • initial ETAs were nudged; (can control by foceicontrol(etaNudge=., etaNudge2=))

Censoring (run006F$censInformation): No censoring
```

Parameterisation and mu-referencing

- For a binary covariate (e.g. sex 0/1; female/males), the back-transformed estimate is a fold-change that can be re-written as a percentage change
- The estimated 0.404 (95%CI: -0.0653/0.874) translates using

`exp(c(0.404, -0.0653, 0.874))`

to a fold-change estimate of

1.498 (95%CI: 0.937/2.397)

which corresponds to an increase of

49.9% (95%CI: -6.3%/140%)

for males compared to females

mu-referencing and allometric scaling

- For a standard allometric equation we would use:

- $CL_i = CL_{Pop} \cdot (WT_i/70)^{3/4} \cdot e^\eta$

- Take the log on both sides

- $\log[CL_i] = \log[CL_{Pop}] + \log\left[(WT_i/70)^{3/4}\right] + \log[e^\eta]$

- $\log[CL_i] = \log[CL_{Pop}] + \frac{3}{4} \cdot \log[WT_i/70] + \eta$

- And back-transforming:

- $CL_i = e^{\log[CL_{Pop}] + \frac{3}{4} \cdot \log[WT_i/70] + \eta}$

Corresponding nlmixr² code: allometric scaling

```
One.comp.transit.allo <- function() {  
  ini{  
    lktr <- log(1.15) #Log k transit (/h)  
    lcl  <- log(0.15) #log CL (L/hr)  
    lv   <- log(7)   #log V (L)  
    ALLC <- fix(0.75) #allometric exponent cl  
    ALLV <- fix(1.00) #allometric exponent v  
    prop.err <- 0.15   #proportional error (SD/mean)  
    add.err <- 0.6     #additive error (mg/L)  
    eta.ktr ~ 0.5  
    eta.cl ~ 0.1  
    eta.v ~ 0.1  
  })  
  model{  
    #Allometric scaling on weight  
    cl <- exp(lcl + eta.cl + ALLC * log(WT)70)  
    v  <- exp(lv + eta.v + ALLV * log(WT)70)  
    ktr <- exp(lktr + eta.ktr)  
    d/dt(depot) = -ktr * depot  
    d/dt(central) = ktr * trans - (cl/v) * central  
    d/dt(trans)  = ktr * depot - ktr * trans  
    cp = central/v  
    cp ~ prop(prop.err) + add(add.err)  
  })  
}
```

nlmixr² output: allometric scaling ODEs using FOCEi

Change in OFV compared to model without allometric scaling: -29.625

```
> run007F
-- nlmixr^2 FOCEi (outer: nlmInb) --

      OBJF      AIC      BIC Log-likelihood Condition#(Cov) Condition#(Cor)
FOCEi 291.5587 768.8658 797.0695     -376.4329      9.400843      5.032325

-- Time (sec run007F$time): --
      setup optimize covariance table compress other
elapsed 0.001    2.618    2.618   0.06    0.03 18.593

-- Population Parameters (run007F$parFixed or run007F$parFixeddf): --

          Parameter    Est.      SE    %RSE Back-transformed(95%CI)  BSV(CV%) shrink(SD)%
lktr      log k transit (/h) 0.0846  0.0106   12.5      1.09 (1.07, 1.11)    69.9    49.2%
lc1       log cl (L/hr)    -2.01   0.0118   0.589      0.134 (0.131, 0.137)    28.0    5.17%
lv        log v (L)        2.08   0.00579  0.278      8 (7.91, 8.09)      15.6    22.0%
ALLC     allometric exponent cl  0.75   FIXED   FIXED           0.75
ALLV     allometric exponent v   1   FIXED   FIXED           1
prop.err proportional error (SD/mean) 0.099                   0.099
add.err   additive error (mg/L)   0.442                   0.442

Covariance Type (run007F$covMethod): r,s
No correlations in between subject variability (BSV) matrix
Full BSV covariance (run007F$omega) or correlation (run007F$omegaR; diagonals=SDs)
Distribution stats (mean/skewness/kurtosis/p-value) available in run007F$shrink
Information about run found (run007F$runInfo):
  • gradient problems with initial estimate and covariance; see $scaleInfo
  • last objective function was not at minimum, possible problems in optimization
  • ETAs were reset to zero during optimization; (can control by foceiControl(resetEtaP=.))
  • initial ETAs were nudged; (can control by foceiControl(etaNudge=., etaNudge2=))
Censoring (run007F$censInformation): No censoring
```

Hands-on session V: running an `nlmixr2` posthoc analysis and implementing covariates using mu-referencing

- Examine the code in `HandsOn_5.R` to run a posthoc analysis
- Examine the code in `HandsOn _5.R` to run a covariate analysis with additive on log-scale covariate implementation
 - Binary covariate (`sex`)
 - Continuous covariate (`weight`)
- Modify the allometrically scaled model with fixed exponents to examine what happens when you set them free

nlmixr² output: allometric scaling ODEs using FOCEi Freely estimated exponents: drop of only 1.67 points

```
> run007Free
-- nlmixr2 FOCEi (outer: nlminb) --

      OBJF      AIC      BIC Log-likelihood Condition#(cov) Condition#(cor)
FOCEi 289.8876 771.1948 806.4493     -375.5974       64.6411      2.549541

-- Time (sec run007Free$time): --
      setup optimize covariance table compress other
elapsed 0.001    5.964    5.964   0.05    0.03 24.241

-- Population Parameters (run007Free$parFixed or run007Free$parFixedDF): --

      Parameter   Est.      SE  %RSE Back-transformed(95%CI)  BSV(cv%) shrink(SD)%
Tktr      log k transit (/h) 0.181  0.0348  19.3      1.2 (1.12, 1.28)    64.5    45.9%
Tc1      log c1 (L/hr) -2.01  0.00964  0.48     0.134 (0.132, 0.137)    28.1    6.26%
Tv      log v (L)  2.08   0.007  0.338      7.97 (7.86, 8.08)    14.4    21.8%
ALLC      allometric exponent c1 0.548  0.0518  9.46      0.548 (0.446, 0.65)
ALLV      allometric exponent v  0.875  0.0249  2.85      0.875 (0.827, 0.924)
prop.err  proportional error (SD/mean) 0.102
add.err    additive error (mg/L)  0.48

Covariance Type (run007Free$covMethod): r,s
No correlations in between subject variability (BSV) matrix
Full BSV covariance (run007Free$omega) or correlation (run007Free$omegaR; diagonals=SDs)
Distribution stats (mean/skewness/kurtosis/p-value) available in run007Free$shrink
Information about run found (run007Free$runInfo):
  • gradient problems with initial estimate and covariance; see $scaleInfo
  • last objective function was not at minimum, possible problems in optimization
  • ETAs were reset to zero during optimization; (can control by foceicontrol(resetEtaP=.))
  • initial ETAs were nudged; (can control by foceicontrol(etaNudge=., etaNudge2=))
Censoring (run007Free$censInformation): No censoring
```

PKPD analysis with nlmixr²: sequential estimation

- First approach: use EBEs from a previous PK model to define PK profiles and estimate PKPD relationship
- Extract EBEs from nlmixr2 object and merge to PKPD data file

```
load(file = "run007F.Rdata")
#Use the one compartment transit model to start the PD analysis
EBEs <- as.data.table(run007F)
EBEs <- EBEs[!duplicated(ID), .(ID = as.numeric(as.character(ID)),
  IKTR = ktr, ICL = cl, IV = v)]
PKPDdata <- fread("warfarin_dat.csv")

#Change variable names to upper case (not strictly necessary)
setnames(PKPDdata, names(dataF), toupper(names(dataF)))

#Generate MDV data items
PKPDdata[, MDV := ifelse(is.na(DV), 1, 0)]
PKPDdata[, MDV := ifelse(AMT > 0, 1, MDV)]

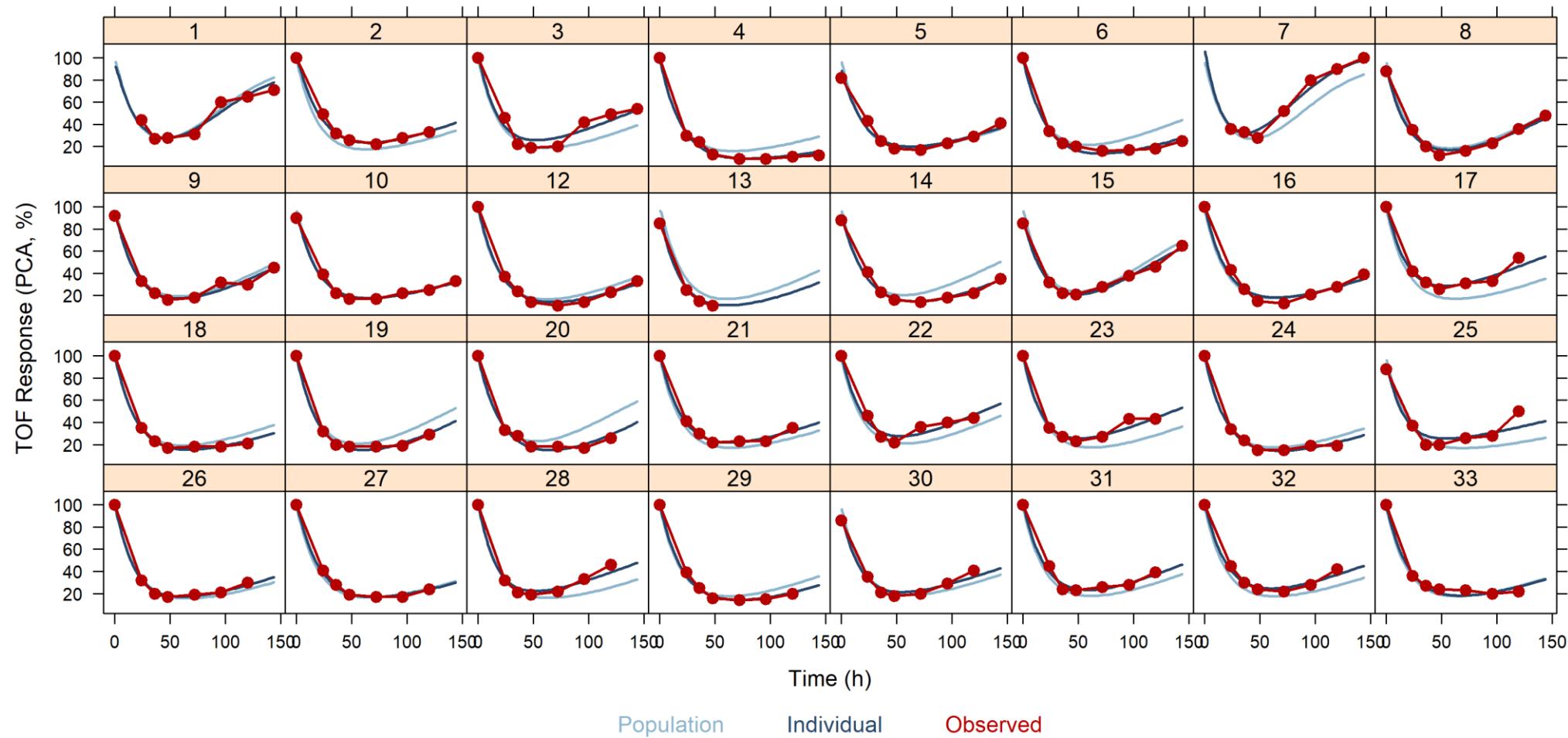
#Merge data with PK EBEs
PDdata <- merge(PKPDdata, EBEs, by = "ID", all.x = TRUE)

# remove PK measurements from file so as to not confuse the vpcPlot later on
PDdata[, DEL := ifelse(DVID == 1 & AMT == 0, 1, 0)]
Pddata <- PDdata[DEL == 0]
```

PKPD analysis with nlmixr²: define turnover model using PK EBEs

```
KA1tr1IPP_PDtoemax1 <- function() {
  ini({
    tc50 <- log(1)      #Log ec50 (mg/L)
    tkout <- log(0.05) #Log tkout (/h)
    te0   <- log(100)  #Log e0
    eta.c50 ~ .5
    eta.kout ~ .1
    eta.e0 ~ .1
    eps.pdadd <- 100
  })
  model({
    c50 = exp(tc50 + eta.c50)
    kout = exp(tkout + eta.kout)
    e0 = exp(te0 + eta.e0)
    # PK parameters from input data set
    ktr = IKTR
    cl = ICL
    v = IV
    cp = central/v
    PD = 1 - cp/(c50 + cp)
    effect(0) = e0
    kin = e0 * kout
    d/dt(depot) = -ktr * depot
    d/dt(central) = ktr * trans - cl/v * central
    d/dt(trans) = ktr * depot - ktr * trans
    d/dt(effect) = kin * PD - kout * effect
    effect ~ add(eps.pdadd)
  })
}
```

Individual graphs for turnover Emax PD model with PK using EBEs



PKPD analysis with nlmixr²: simultaneous estimation

- Second approach: estimate PK and PD simultaneously
- The source of observations is identified using a `dvid` data item
- `dvid` is coded as `central` and `effect` in the data object to identify the two types of observation as presented in the model code
- `dvid` can also coded as 1 and 2 in the data object to identify the two types of observation as presented in the model code

Immediate effect simultaneous PKPD analysis with nlmixr²: ini block

```
#Immediate effect
KA1tr1_PDimmemax1 <- function() {
  ini{
    ## PK
    tktr <- log(1) # Log ktr (/h)
    tcl  <- log(0.1) # Log CL (L/h)
    tv   <- log(8)  # Log Vc (L)
    eta.ktr ~ 1
    eta.cl ~ 0.1
    eta.v ~ 0.1
    eps.pkprop <- 0.1 #proportional error (SD/mean)
    eps.pkadd <- 0.4 #additive error (mg/L)

    ## PD
    tc50  <- log(1) #Log ec50 (mg/L)
    te0   <- log(100) #Log e0
    eta.c50 ~ .5
    eta.e0 ~ .1
    eps.pdadd <- 100
  })
  model{
  })
}
```

Immediate effect simultaneous PKPD analysis with nlmixr²: model block

```
#Immediate effect
model({
  ktr <- exp(tktr + eta.ktr)
  cl  <- exp(tcl + eta.cl)
  v   <- exp(tv + eta.v)

  c50  = exp(tc50 + eta.c50)
  e0   = exp(te0 + eta.e0)

  cp      = central/v
  d/dt(depot) = -ktr * depot
  d/dt(central)= ktr * trans - cl * cp
  d/dt(trans)  = ktr * depot - ktr * trans
  effect       = e0 * (1 - cp/(c50 + cp))

  cp ~ prop(eps.pkprop) + add(eps.pkadd) | central
  effect ~ add(eps.pdadd) | effect
})
```

Simultaneous PKPD analysis with nlmixr²: examine defined model

```
nlmixr2(KA1tr1_PDimmemax1) # Show initial estimates and model information:  
> nlmixr2(KA1tr1_PDimmemax1) # Show initial estimates and model  
i parameter labels from comments will be replaced by 'label()'  
-- rxode2-based free-form 3-cmt ODE model --  
-- Initialization: --  
Fixed Effects ($theta):  
    tktr      tcl      tv  eps.pkprop  eps.pkadd      tc50      te0  eps.pdadd  
0.2623643 -1.8971200  2.0794415  0.1000000  0.4000000  0.4054651  4.6051702 20.0000000  
  
Omega ($omega):  
    eta.ktr eta.cl eta.v eta.c50 eta.e0  
eta.ktr     1     0.0   0.0     0.0     0.0  
eta.cl      0     0.3   0.0     0.0     0.0  
eta.v       0     0.0   0.3     0.0     0.0  
eta.c50     0     0.0   0.0     0.5     0.0  
eta.e0      0     0.0   0.0     0.0     0.1  
  
States ($state or $statedf):  
  Compartment Number Compartment Name  
1                  1          depot  
2                  2         central  
3                  3        trans  
-- Multiple Endpoint Model ($multipleEndpoint): --  
  variable           cmt           dvid*  
1    cp ~ ... cmt='central' or cmt=2 dvid='central' or dvid=1  
2 effect ~ ... cmt='effect' or cmt=4 dvid='effect' or dvid=2  
  * If dvids are outside this range, all dvids are re-numbered sequentially, ie 1,7, 10 becomes 1,2,3 etc  
  
-- mu-referencing ($muRefTable): --  
  theta   eta level  
1  tktr eta.ktr id  
2  tcl  eta.cl id  
3  tv   eta.v  id  
4  tc50 eta.c50 id  
5  te0  eta.e0  id
```

nlmixr² output: immediate effect simultaneous PKPD model

```
> run009F
-- nlmixr2 FOCEi (outer: nlminb) --

      OBJF      AIC      BIC Log-likelihood Condition#(cov) Condition#(cor)
FOCEi 1762.228 2675.923 2730.263     -1324.961      195.1339      11.52368

-- Time (sec run009F$time): --
setup optimize covariance table compress other
elapsed 0.001   11.671    11.671   0.06    0.03 24.507

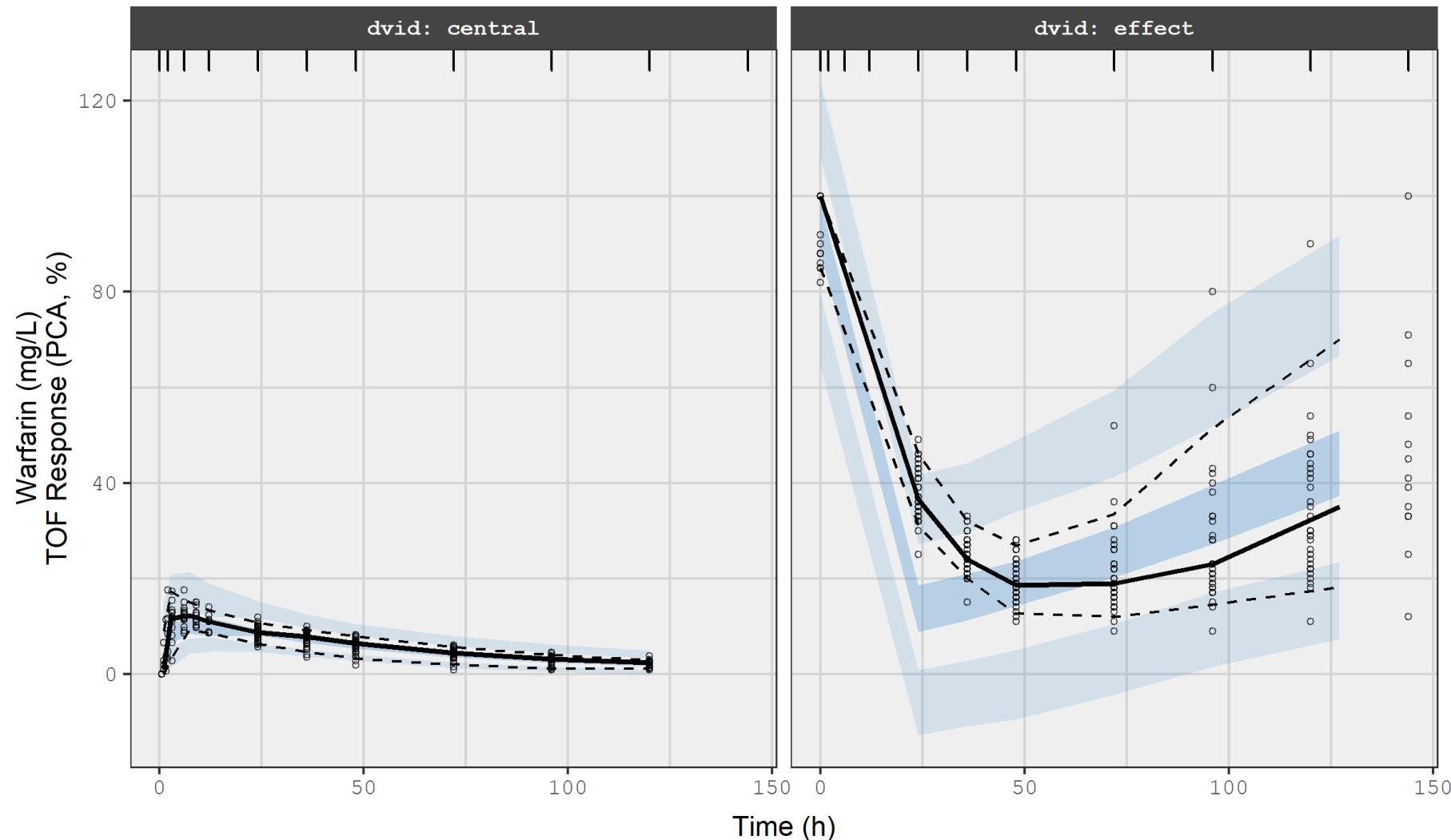
-- Population Parameters (run009F$parFixed or run009F$parFixedddf): --

      Parameter   Est.     SE   %RSE Back-transformed(95%CI)  BSV(CV%) shrink(SD)%
tktr      log ktr (/h) 0.374  0.167  44.7      1.45 (1.05, 2.02)      69.6    44.7%
tcl       log CL (L/h) -2.03  0.0436  2.15     0.132 (0.121, 0.144)     29.1    3.82%
tv        log Vc (L)   2.1   0.0529  2.52      8.16 (7.35, 9.05)      24.1    9.32%
eps.pkprop          0.104                    0.104
eps.pkadd            0.5                      0.5
tc50      log ec50 (mg/L) 0.382  0.0742  19.4      1.46 (1.27, 1.69)      28.0    40.3%
te0        log e0        4.52   0.0214  0.474      92.1 (88.3, 96)      14.3    60.9%
eps.pdadd           12.3                    12.3

Covariance Type (run009F$covMethod): r,s
No correlations in between subject variability (BSV) matrix
Full BSV covariance (run009F$omega) or correlation (run009F$omegaR; diagonals=SDs)
Distribution stats (mean/skewness/kurtosis/p-value) available in run009F$shrink
Information about run found (run009F$runInfo):
• gradient problems with initial estimate and covariance; see $scaleInfo
• last objective function was not at minimum, possible problems in optimization
• ETAs were reset to zero during optimization; (can control by foceicontrol(resetEtaP=.))
• initial ETAs were nudged; (can control by foceicontrol(etaNudge=., etaNudge2=))
Censoring (run009F$censInformation): No censoring
```

VPC for immediate effect simultaneous PKPD model

Immediate effect simultaneous PKPD model: Emax fixed to 1



Effect compartment simultaneous PKPD analysis with nlmixr²: ini block

```
#Effect compartment model
KA1tr1_PDceemax <- function() {
  ini{
    ## PK
    tktr <- log(1) # Log ktr (/h)
    tcl <- log(0.1) # Log CL (L/h)
    tv <- log(8) # Log Vc (L)
    eta.ktr ~ 1
    eta.cl ~ 0.1
    eta.v ~ 0.1
    eps.pkprop <- 0.1 #proportional error (SD/mean)
    eps.pkadd <- 0.4 #additive error (mg/L)

    ## PD
    tc50 <- log(1) #Log ec50 (mg/L)
    tkout <- log(0.05) #Log tkout (/h)
    te0 <- log(100) #Log e0
    eta.c50 ~ .5
    eta.kout ~ .1
    eta.e0 ~ .1
    eps.pdadd <- 100
  })
  model{
  }
}
```

Effect compartment simultaneous PKPD analysis with nlmixr²: model block

```
#Effect compartment model
model({
  ktr <- exp(tktr + eta.ktr)
  cl  <- exp(tcl + eta.cl)
  v   <- exp(tv + eta.v)

  c50  = exp(tc50 + eta.c50)
  kout = exp(tkout + eta.kout)
  e0   = exp(te0 + eta.e0)
  emax = 1

  cp      = central/v
  d/dt(depot) = -ktr * depot
  d/dt(central)= ktr * trans - cl * cp
  d/dt(trans)  = ktr * depot - ktr * trans
  d/dt(ce)     = kout * (cp - ce)

  effect      = e0 * (1 - emax * ce/(c50 + ce))

  cp ~ prop(eps.pkprop) + add(eps.pkadd) | central
  effect ~ add(eps.pdadd) | effect
})}
```

nlmixr² output: effect compartment simultaneous PKPD model

```
> run010F
— nlmixr2 FOCEi (outer: nlmnlb) —

      OBJF   AIC     BIC Log-likelihood Condition#(cov) Condition#(cor)
FOCEi 1523.306 2441 2503.7       -1205.5        108.638        32.47682

— Time (sec run010F$time): —

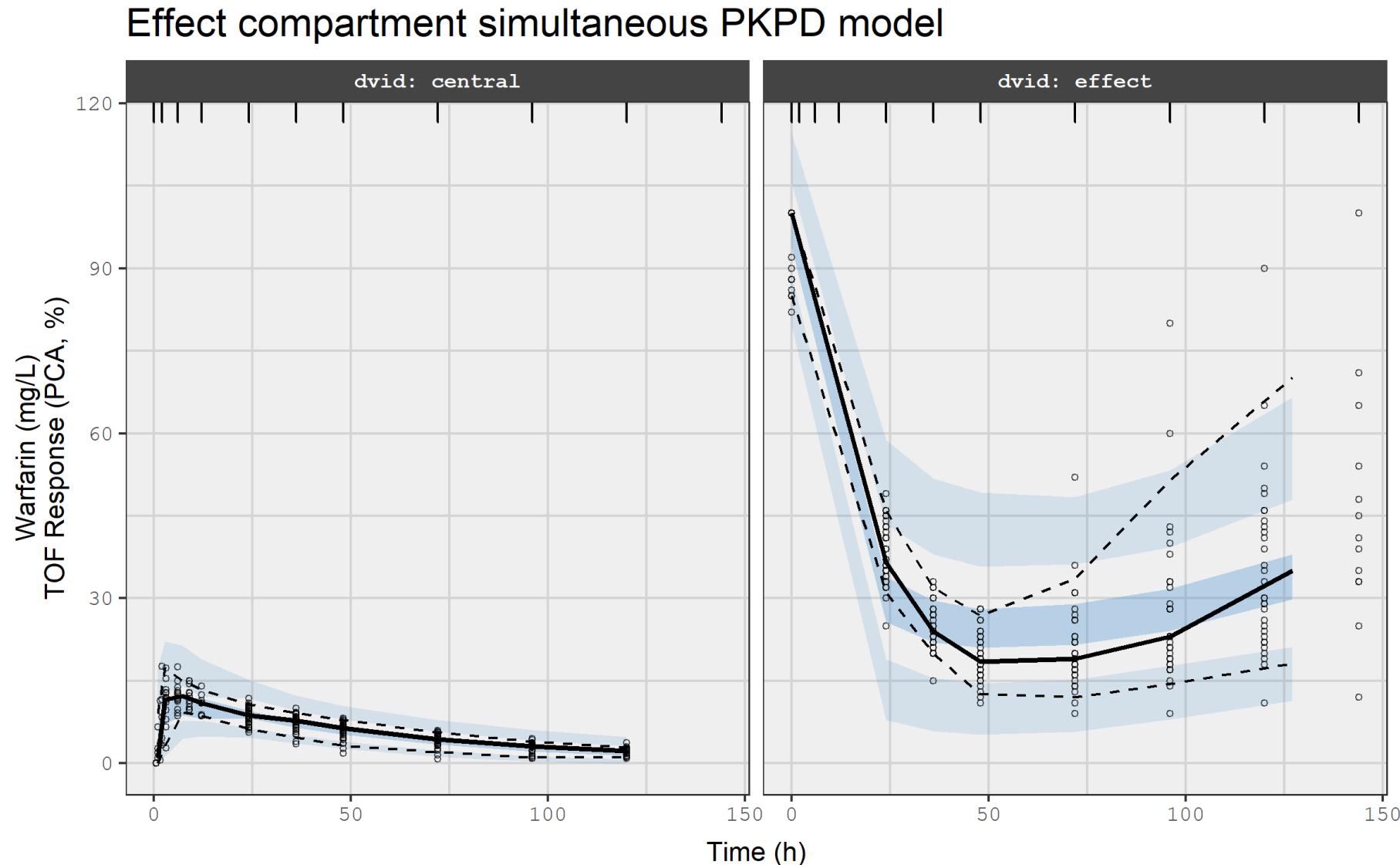
  setup optimize covariance table compress    other
elapsed 0.001   23.595    23.595  0.06     0.02 234.389

— Population Parameters (run010F$parFixed or run010F$parFixeddf): —

      Parameter   Est.     SE   %RSE Back-transformed(95%CI)  BSV(cv%) shrink(SD)%
tktr    log ktr (/h) 0.277 0.0887  32.1      1.32 (1.11, 1.57)    57.9    40.0%
tcl     log CL (L/h) -2.04 0.0542  2.66      0.13 (0.117, 0.144)    29.4    1.99%
tv      log vc (L)  2.06 0.0797  3.86      7.86 (6.72, 9.19)     23.3    9.85%
eps.pkprop          0.104                   0.104
eps.pkadd            0.495                   0.495
tc50    log ec50 (mg/L) 0.531 0.0795   15      1.7 (1.46, 1.99)    31.8    18.0%
tkout   log tkout (/h) -3.94 0.151   3.82 0.0195 (0.0145, 0.0262)    34.5    34.3%
te0      log e0        4.57 0.0273  0.597      96.8 (91.7, 102)     8.68    47.7%
eps.pdadd            6.44                    6.44

Covariance Type (run010F$covMethod): r,s
No correlations in between subject variability (BSV) matrix
Full BSV covariance (run010F$omega) or correlation (run010F$omegaR; diagonals=SDs)
Distribution stats (mean/skewness/kurtosis/p-value) available in run010F$shrink
Information about run found (run010F$runInfo):
• gradient problems with initial estimate and covariance; see $scaleInfo
• last objective function was not at minimum, possible problems in optimization
• ETAs were reset to zero during optimization; (can control by foceicontrol(resetEtaP=.))
• initial ETAs were nudged; (can control by foceicontrol(etaNudge=., etaNudge2=))
Censoring (run010F$censInformation): No censoring
```

VPC for effect compartment simultaneous PKPD model



Turnover model simultaneous PKPD analysis with nlmixr²: ini block

```
#Turnover simultaneous PKPD model
KA1tr1IPP_PDtoemax <- function() {
  ini({
    ## PK
    tktr <- log(1) # Log ktr (/h)
    tcl  <- log(0.1) # Log CL (L/h)
    tv   <- log(8)  # Log Vc (L)
    eta.ktr ~ 1
    eta.cl ~ 0.1
    eta.v ~ 0.1
    eps.pkprop <- 0.1 # proportional error (SD/mean)
    eps.pkadd <- 0.4 # additive error (mg/L)

    ## PD
    tc50  <- log(1) #Log ec50 (mg/L)
    tkout <- log(0.05) #Log tkout (/h)
    te0   <- log(100) #Log e0
    eta.c50 ~ .5
    eta.kout ~ .1
    eta.e0 ~ .1
    eps.pdadd <- 100
  })
  model({
  })
}
```

Turnover model simultaneous PKPD analysis with nlmixr²: model block

```
#Turnover simultaneous PKPD model
model({
  ktr <- exp(tktr + eta.ktr)
  cl  <- exp(tcl + eta.cl)
  v   <- exp(tv + eta.v)
  c50 = exp(tc50 + eta.c50)
  kout = exp(tkout + eta.kout)
  e0  = exp(te0 + eta.e0)
  emax = 1

  cp      = central/v
  d/dt(depot) = -ktr * depot
  d/dt(central)= ktr * trans - cl * cp
  d/dt(trans)  = ktr * depot - ktr * trans
  effect(θ)    = e0
  kin        = e0 * kout
  PD         = 1 - emax * cp/(c50 + cp)
  d/dt(effect) = kin * PD - kout * effect

  cp ~ prop(eps.pkprop) + add(eps.pkadd) | central
  effect ~ add(eps.pdadd) | effect
})}
```

nlmixr² output: turnover simultaneous PKPD model

```
> run011F
— nlmixr2 FOCEi (outer: nlminb) —

      OBJF      AIC      BIC Log-likelihood Condition#(cov) Condition#(cor)
FOCEi 1330.127 2247.821 2310.521      -1108.911      338.3274      3.064891

— Time (sec run011F$time): —

  setup optimize covariance table compress   other
elapsed 0.001    28.334    28.334  0.06     0.03 352.441

— Population Parameters (run011F$parFixed or run011F$parFixedDF): —



|            | Parameter       | Est.  | SE     | %RSE  | Back-transformed(95%CI) | BSV(cv%) | shrink(SD)% |
|------------|-----------------|-------|--------|-------|-------------------------|----------|-------------|
| tktr       | log ktr (/h)    | 0.154 | 0.181  | 118   | 1.17 (0.818, 1.66)      | 66.7     | 48.0%       |
| tcl        | log CL (L/h)    | -2    | 0.0511 | 2.55  | 0.135 (0.122, 0.149)    | 32.3     | 10.7%       |
| tv         | log vc (L)      | 2.06  | 0.0238 | 1.16  | 7.81 (7.45, 8.18)       | 27.8     | 19.4%       |
| eps.pkprop |                 | 0.104 |        |       | 0.104                   |          |             |
| eps.pkadd  |                 | 0.458 |        |       | 0.458                   |          |             |
| tc50       | log ec50 (mg/L) | 0.136 | 0.0727 | 53.3  | 1.15 (0.994, 1.32)      | 49.0     | 11.0%       |
| tkout      | log tkout (/h)  | -2.96 | 0.0208 | 0.703 | 0.052 (0.0499, 0.0541)  | 8.89     | 32.5%       |
| te0        | log e0          | 4.57  | 0.0104 | 0.227 | 96.6 (94.6, 98.5)       | 5.28     | 18.0%       |
| eps.pdadd  |                 | 3.72  |        |       | 3.72                    |          |             |



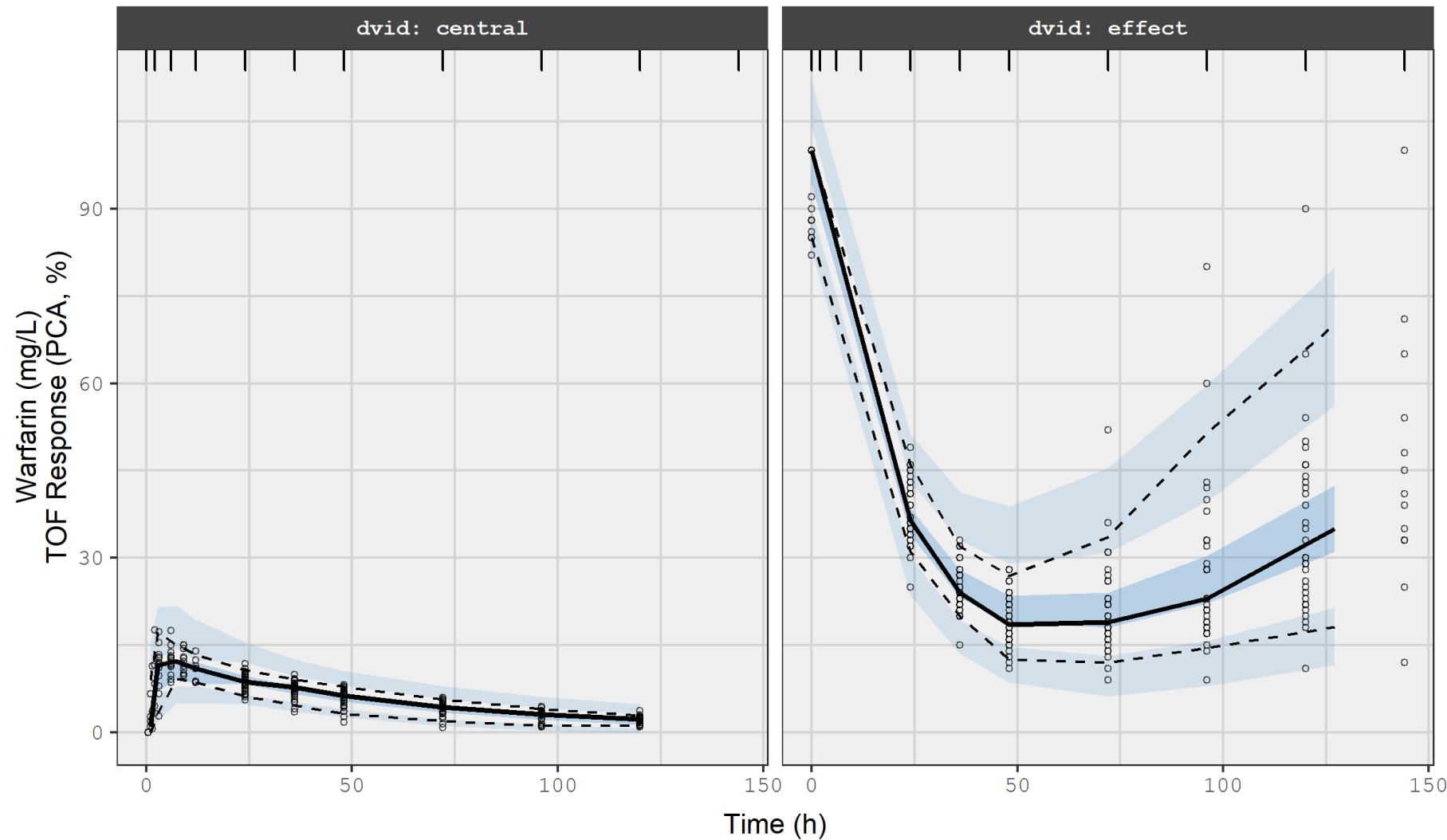
Covariance Type (run011F$covMethod): r,s
No correlations in between subject variability (bsv) matrix
Full BSV covariance (run011F$omega) or correlation (run011F$omegaR; diagonals=SDs)
Distribution stats (mean/skewness/kurtosis/p-value) available in run011F$shrink
Information about run found (run011F$runInfo):


- gradient problems with initial estimate and covariance; see $scaleInfo
- last objective function was not at minimum, possible problems in optimization
- ETAs were reset to zero during optimization; (can control by foceicontrol(resetEtaP=..))
- initial ETAs were nudged; (can control by foceicontrol(etaNudge=., etaNudge2=))


Censoring (run011F$censInformation): No censoring
```

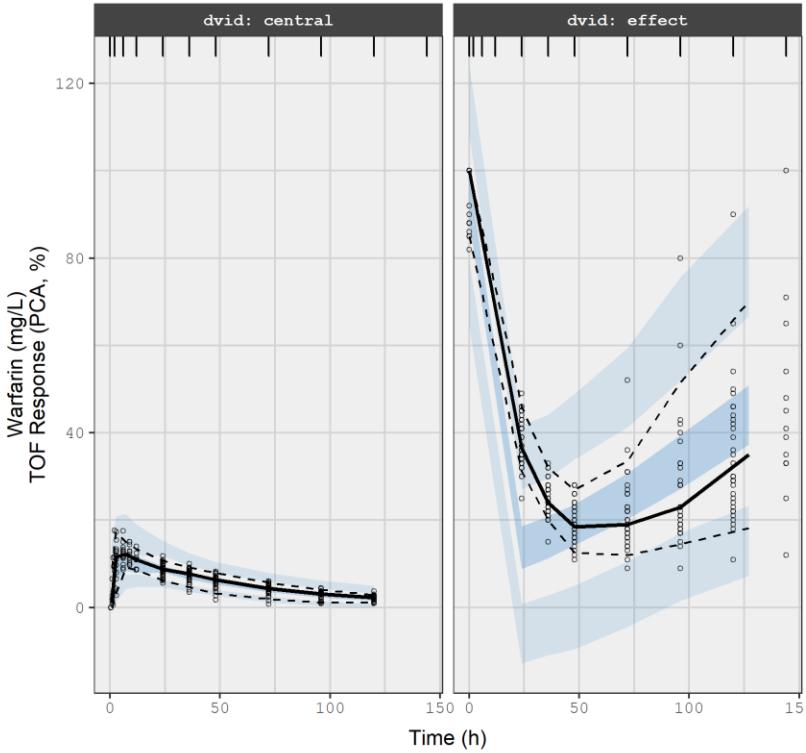
VPC for turnover simultaneous PKPD model

Turnover simultaneous PKPD model

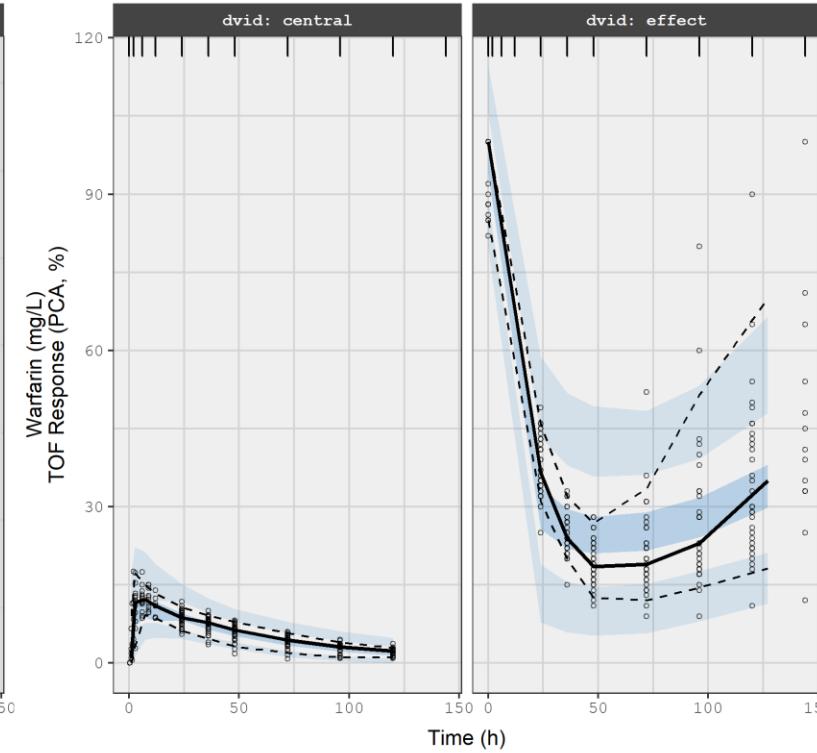


VPCs to compare the immediate effect model, the effect compartment model, and the turnover simultaneous PKPD model

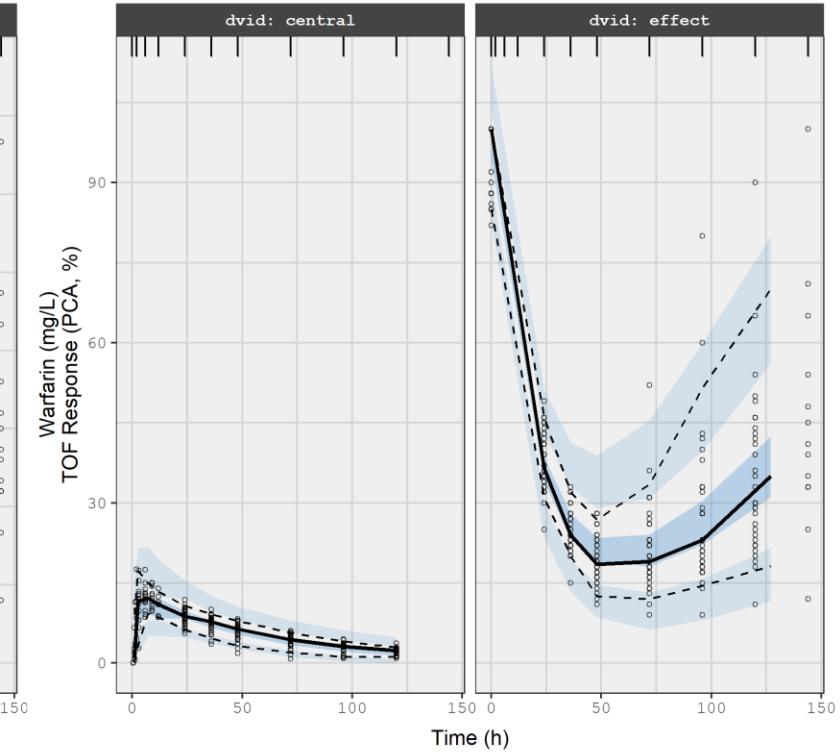
Immediate effect simultaneous PKPD model



Effect compartment simultaneous PKPD model



Turnover simultaneous PKPD model



Hands-on session VI: running nlmixr2 PKPD analysis

- Examine the code in HandsOn_6.R to run the sequential or one of the simultaneous PKPD analyses