nlmixr^2: Goodness of Fit plots using nlmixr^2

PSSN Conference 2023 workshop

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On behalf of the nlmixr2 development team:

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Standard Pharmacometrics goodness of fit plots (NPD or CWRES common, NPD in chart)

Plot	Shrinkage
Plot of normalized prediction distribution errors versus population predictions (NPD *vs.* EPRED)	
Plot of normalized prediction discrepancies versus time (NPD *vs.* TIME)	
Plot of individual weighted residuals versus individual predictions (IWRES *vs.* IPRED)	ε
Plot of individual weighted residuals versus time (IWRES *vs.* TIME)	ε
Visual predictive check (VPC)	
Distribution and quantile-quantile plot of IWRES	ε
Distribution and correlation structure of estimated inter-individual random effects (ETA)	η
Relationships between estimated inter-individual random effects (ETA) and covariates (before and after inclusion of covariates)	η
Plots of observations and model predictions per individual	ε
Plot of observations versus population predictions (DV *vs.* EPRED)	
Plot of observations versus individual predictions (DV *vs.* IPRED)	ε
Plot of absolute individual weighted residuals versus individual predictions (|IWRES| *vs.* IPRED)	ε

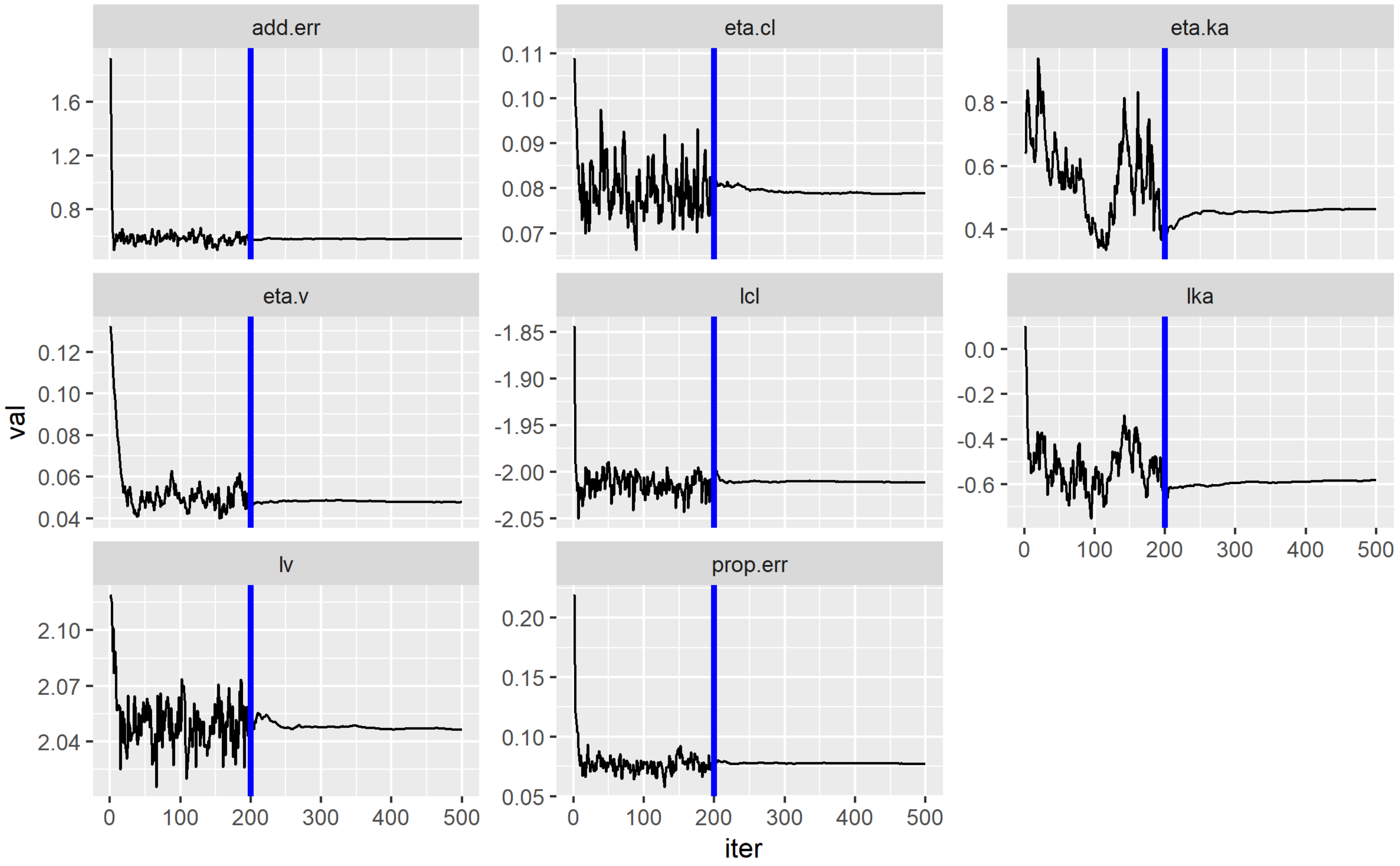
Running nlmixr^2 models: save the object, and examine parameter trace plots when using SAEM to check convergence

```r
## results are stored in the nlmixr object and can be viewed:
fitOne.comp.KA.solved_S

## and saved for future use or reference:
save(fitOne.comp.KA.solved_S, file = "fitOne.comp.KA.solved_S.Rdata")

## and for SAEM, convergence can be checked using a parameter trace plot:
traceplot(fitOne.comp.KA.solved_S)
```

Traceplot for SAEM parameter estimates using `traceplot` command



nlmixr^2 is linked to ggPMX

```r
# Model Diagnostics with ggPMX
# The controller is first constructed
ctr <- pmx_nlmixr(fitOne.comp.KA.solved_S,
                  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
ctr %>% pmx_plot_npde_pred
#alternatively:
pmx_plot_npde_pred(ctr)
```

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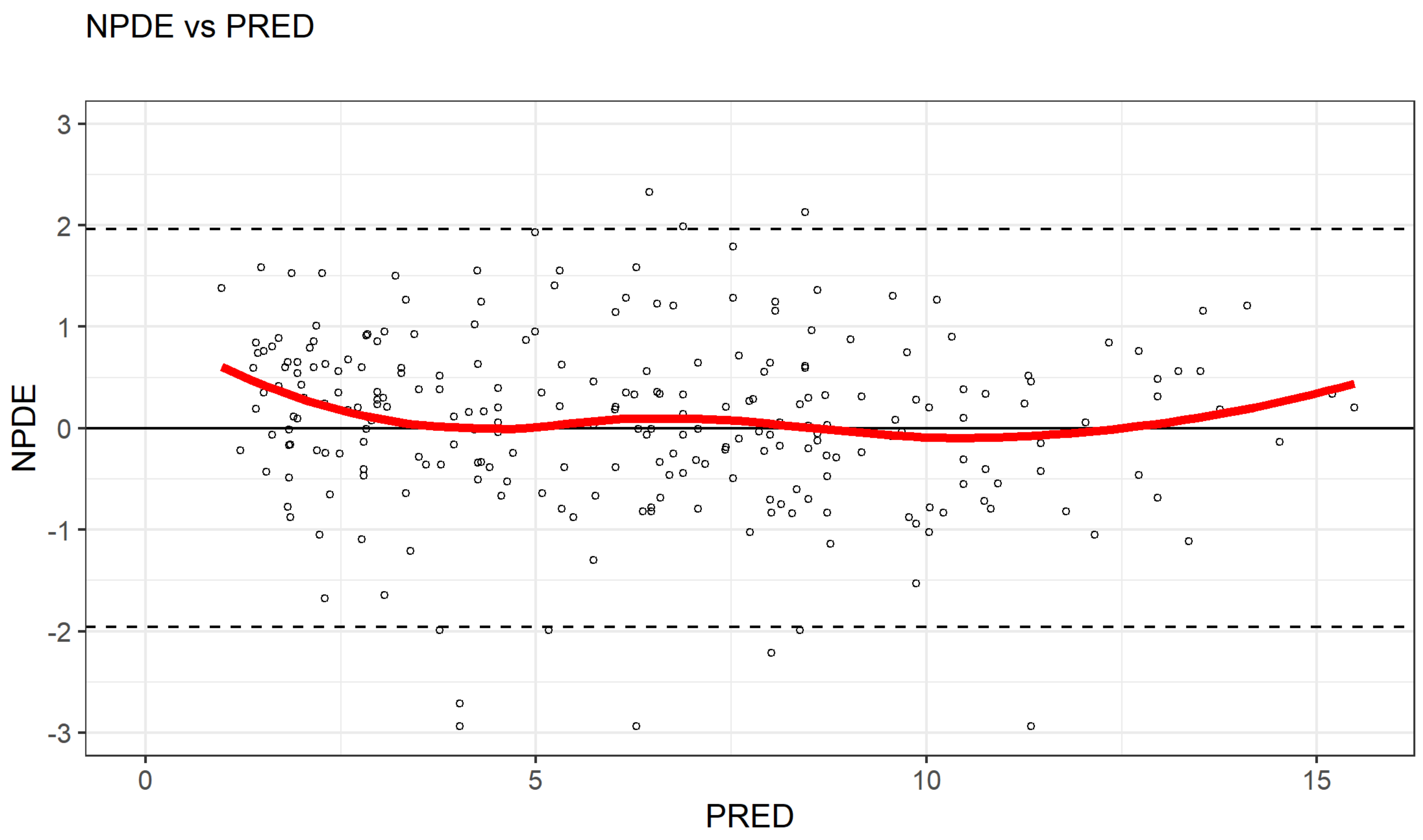

nlmixr^2 is linked to ggPMX

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

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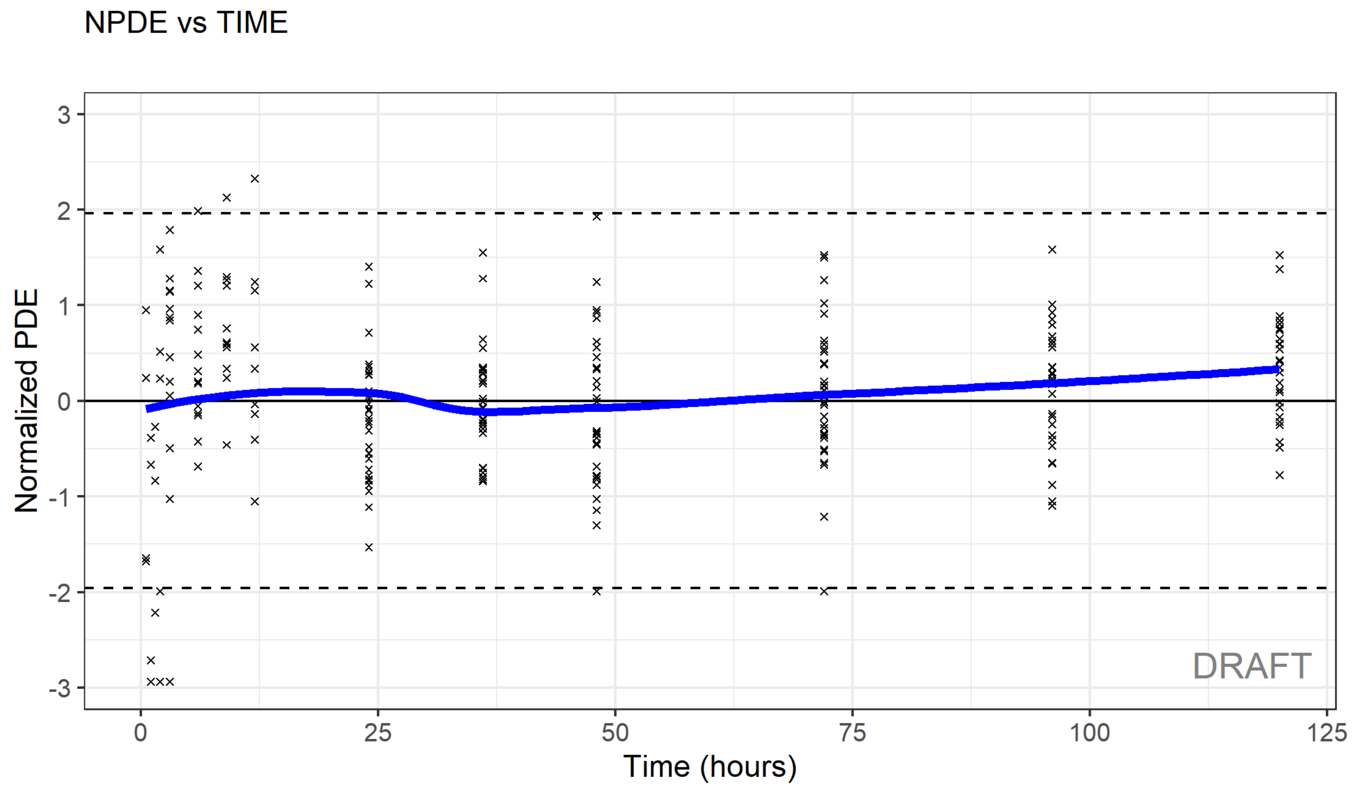

nlmixr2 is linked to ggPMX

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

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

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

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


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

nlmixr2 is linked to ggPMX

```
## generate a full report with diagnostics

ctr %>% pmx_report(name="ggPMX_report",
                   save_dir=".",
                   format="report",
                   extension="word")
```

nlmixr^2 is linked to Ben Guiastrennec's xpose* package that uses ggplot2

```r
## 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(fitOne.comp.KA.solved_S)

## 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/

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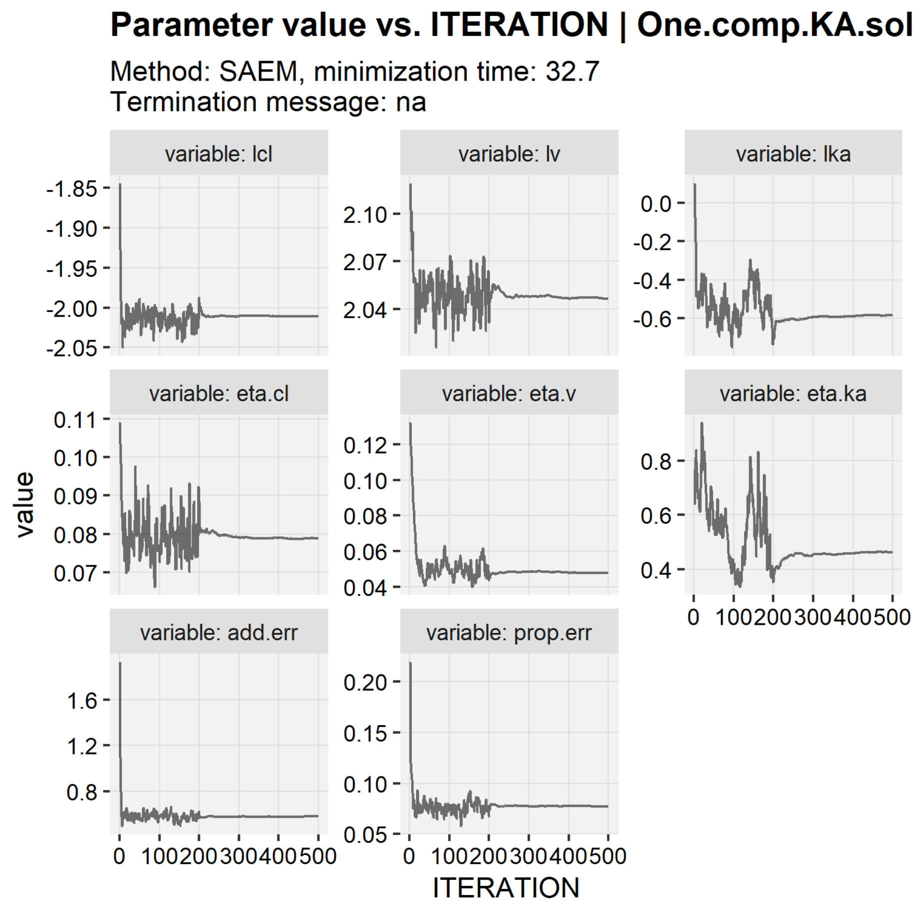

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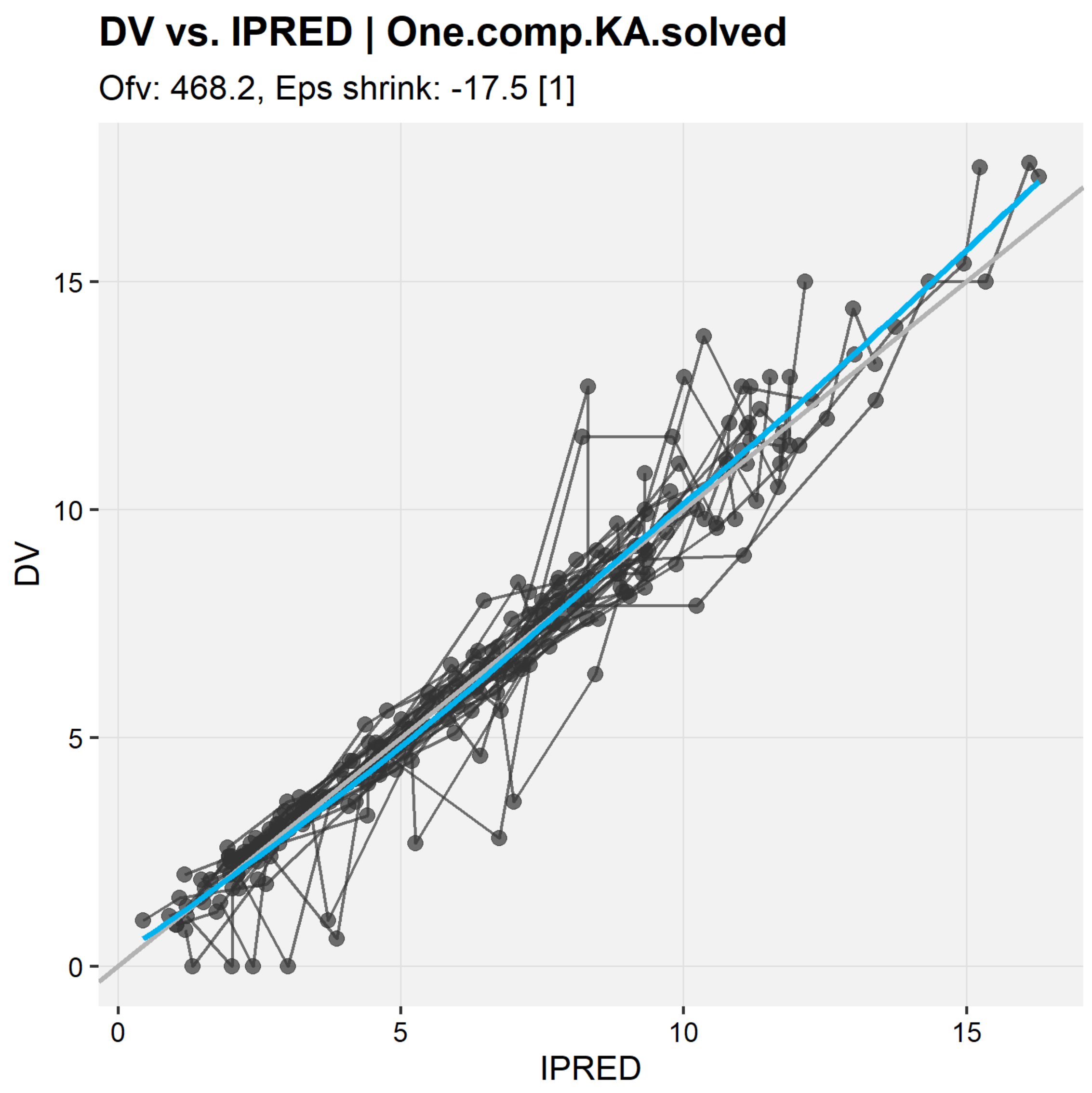
DV vs IPRED using xpose



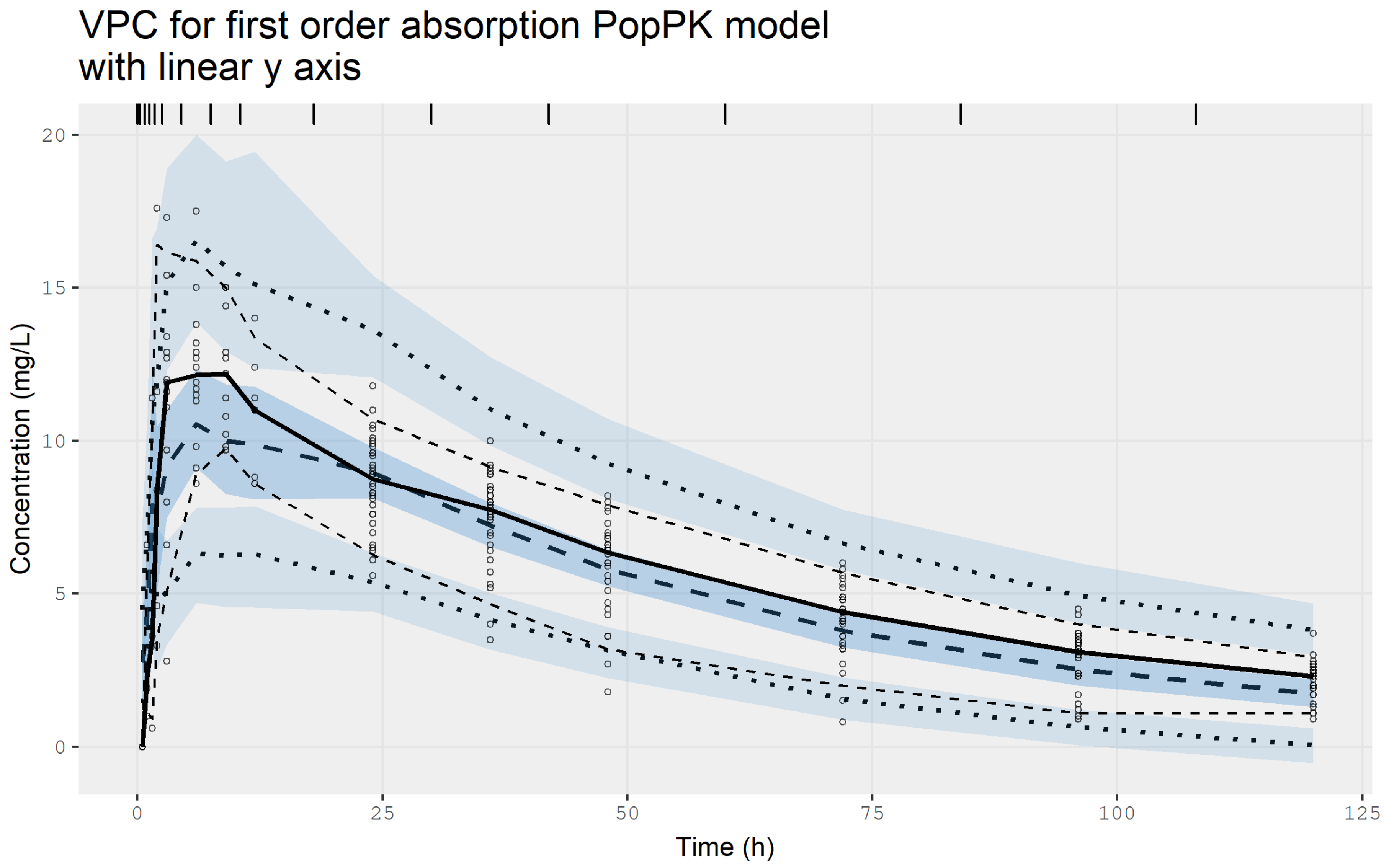
```
xpdb.1s <- xpose_data_nlmixr(fitOne.comp.KA.solved_F)
## dv vs ipred plot:
dv_vs_ipred(xpdb.1s,
            caption = NULL)
```

nlmixr2 is linked to Ron Keizer's vpc* package

```
## nlmixr 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(
  fitOne.comp.KA.solved_S,        #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/

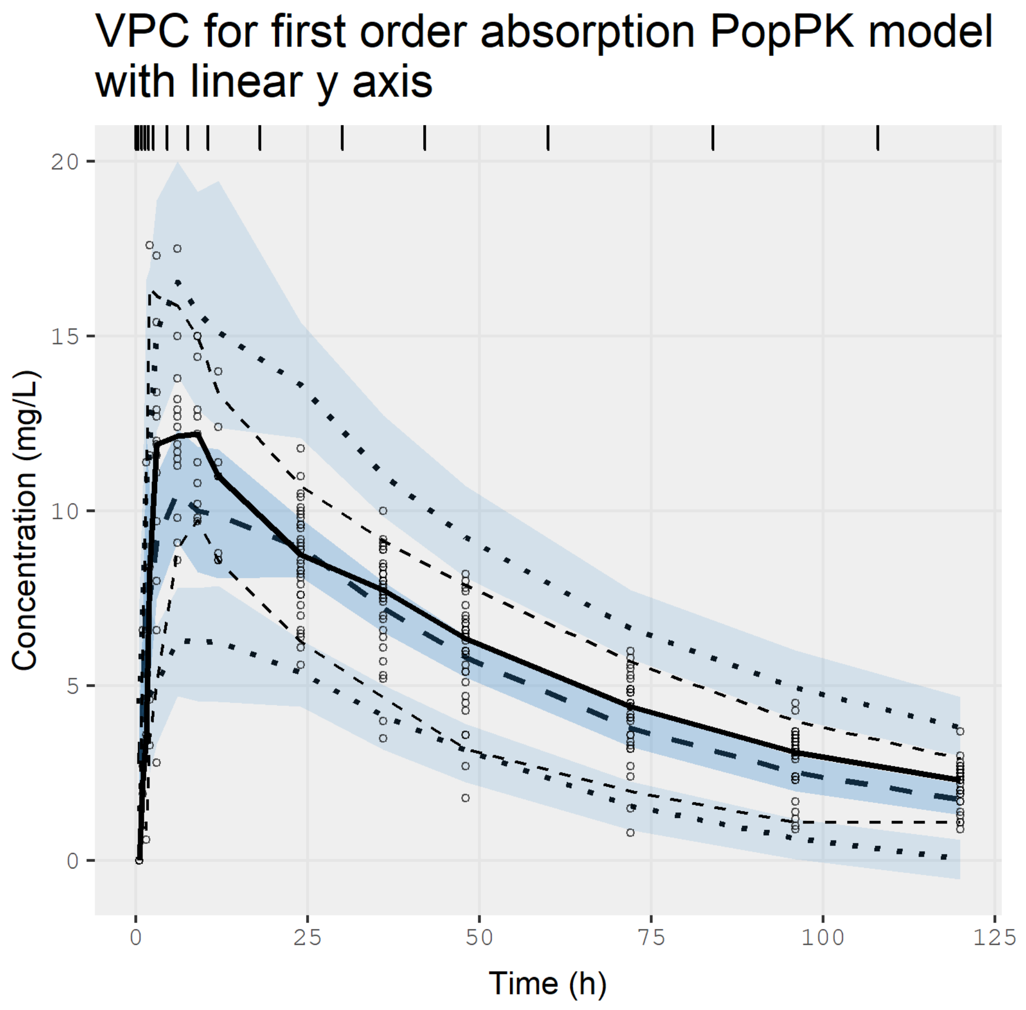
VPC for the base model on linear scale...

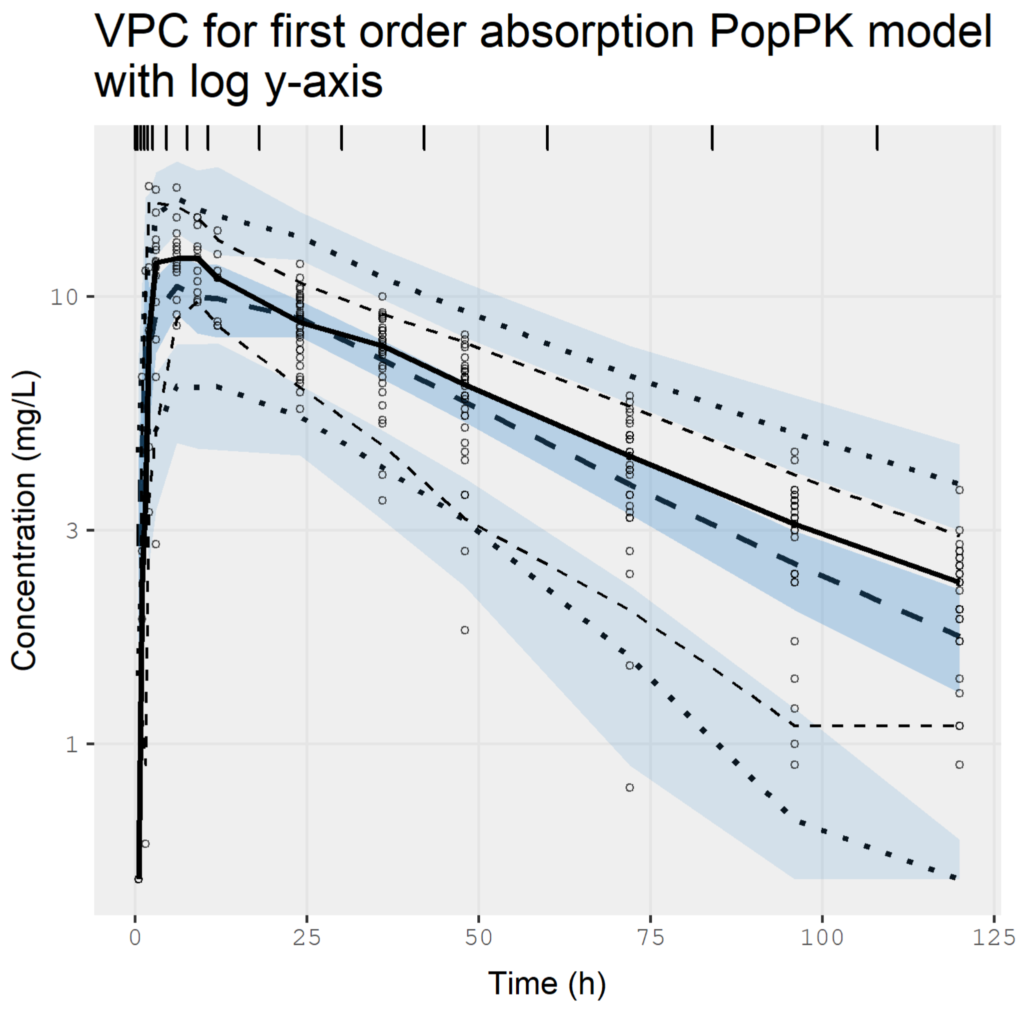


...and on log scale

```r
## or with a log y-axis starting at 0.5
vpcPlot(
  fitOne.comp.KA.solved_S,        #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 ☺





nlmixr^2 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
```

nlmixr^2 can generate individual graphs using `augPred`

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## 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))
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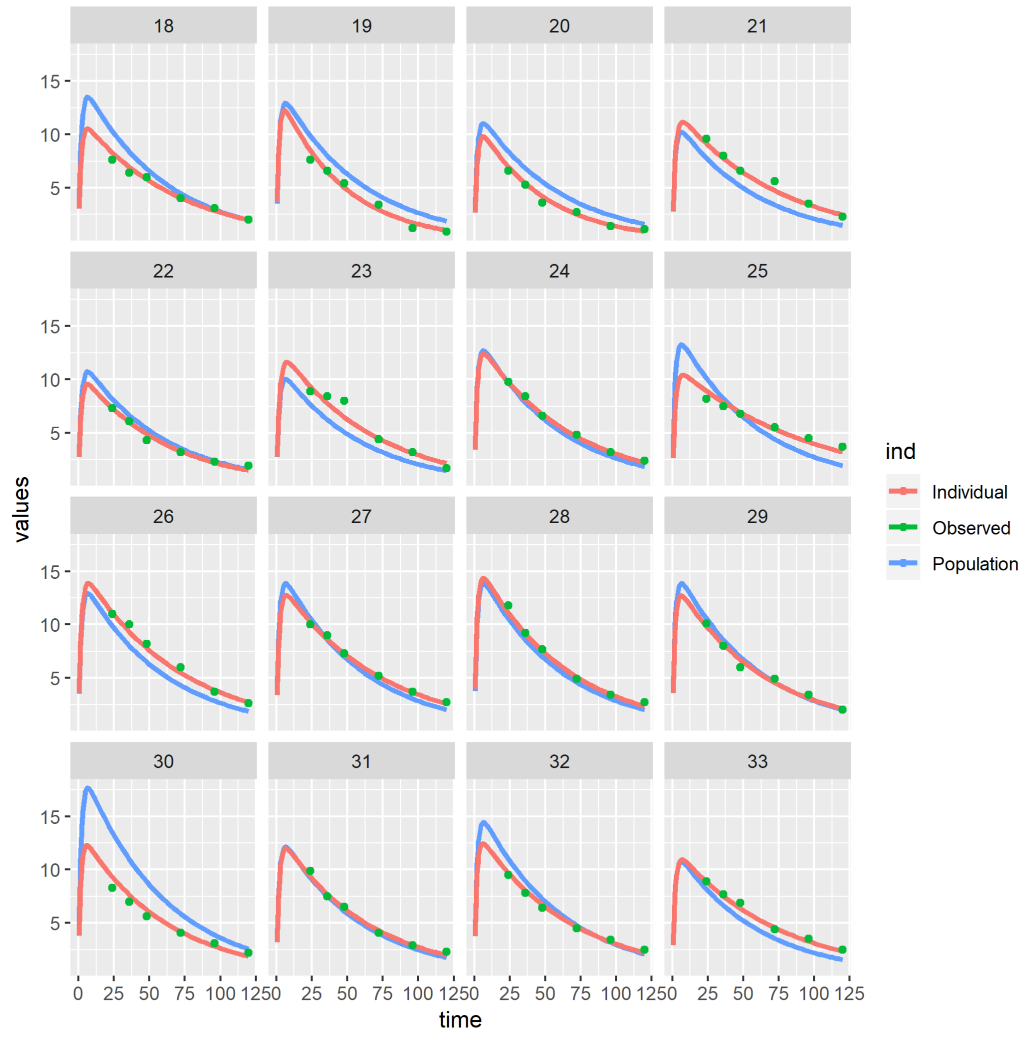
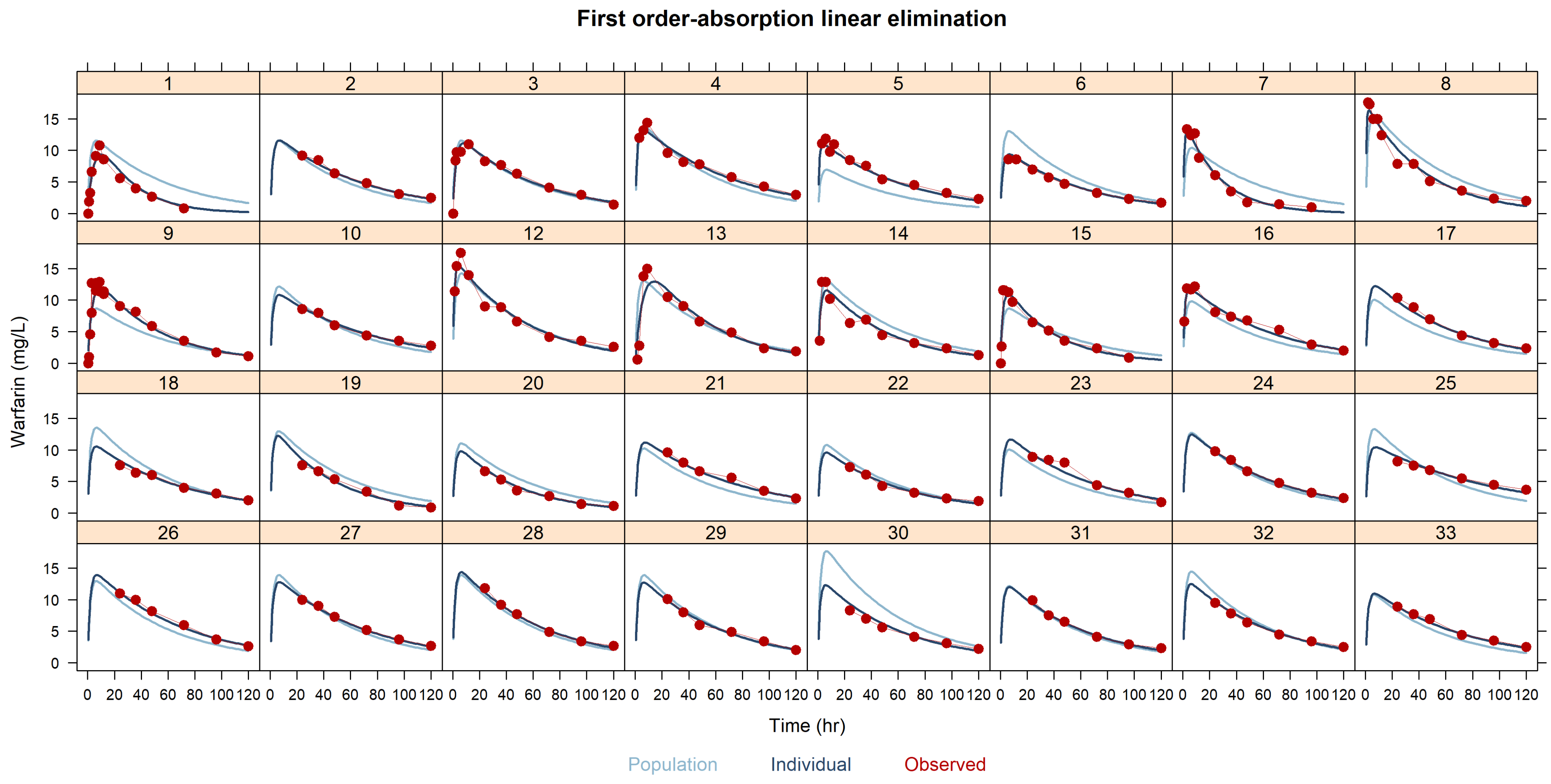


use augPred output to plot using your favourite package...

```
#or the augPred output can be plotted to your liking, for instance using ggplot2 or the lattice function xyplot:
indivpk<-augPred(fitOne.comp.KA.solved_S)
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



nlmixr²