Graphs in the npde library, version 2.0 - A demo

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Contents

This document runs automatically a number of examples in the npde library, producing various graphs in order to assess whether the library is working properly.

1 Graphs in the npde library

1.1 Plot method

Given an object x resulting from a call to npde or autonpde, default plots can be produced using the following command:

```
plot(x)
```

Different plots are also available using the option plot.type, as in:

```
plot(x,plot.type="data")
```

Table 1 shows which plot types are available (some depend on whether for instance covariates or data below the limit of quantification are present in the dataset) for a NpdeObject object.

Plot type	Description
data	Plots the observed data in the dataset
x.scatter	Scatterplot of the npde versus the predictor X (optionally can plot pd or npd instead)
pred.scatter	Scatterplot of the npde versus the population predicted values
cov.scatter	Scatterplot of the npde versus covariates
vpc	Plots a Visual Predictive Check
loq	Plots the probability for an observation to be BQL, versus the predictor X
ecdf	Empirical distribution function of the npde(optionally pd or npd)
hist	Histogram of the npde(optionally pd or npd)
qqplot	QQ-plot of the npdeversus its theoretical distribution (optionally pd or npd)
cov.x.scatter	Scatterplot of the npde versus the predictor X, split by covariate
cov.pred.scatter	Scatterplot of the npde versus the population predicted values, split by covariate
cov.ecdf	Empirical distribution function of the npde(optionally pd or npd), split by covariate
cov.hist	Histogram of the npde(optionally pd or npd), split by covariate
cov.qqplot	QQ-plot of the npdeversus its theoretical distribution (optionally pd or npd) , split by covariate

Table 1: Plot types available.

The final five plots can also be accessed with the base plot and the option covsplit=TRUE. For instance, `plot(x,plot.type="cov.x.scatter")` is equivalent to `plot(x,plot.type="x.scatter",covsplit=TRUE)`.

1.2 Graph options

Table 2 shows the options that can be set, either by specifying them on the fly in a call to plot applied to a NpdeObject object, or by storing them in the prefs component of the object.

Parameter	Description	Default value

– *To be continued*

Table 2 – cont.

Parameter	Description	Default value
General graphical options		
new	Whether a new plot should be produced	TRUE
ask	Whether users should be prompted before each new plot (if TRUE)	FALSE
interactive	Output is produced for some plots (most notably when binning is used, this prints out the boundaries of the binning intervals) if TRUE	FALSE
xaxt	A character which specifies the x axis type. Specifying "n" suppresses plotting of the axis	empty
yaxt	A character which specifies the y axis type. Specifying "n" suppresses plotting of the axis	empty
frame.plot	If TRUE, a box is drawn around the current plot	TRUE
main	Title	empty
xlab	Label for the X-axis	empty
ylab	Label for the Y-axis	empty
xlog	Scale for the X-axis (TRUE: logarithmic scale)	FALSE
ylog	Scale for the Y-axis (TRUE: logarithmic scale)	FALSE
cex	A numerical value giving the amount by which plotting text and symbols should be magnified relative to the default	1
cex.axis	Magnification to be used for axis annotation relative to the current setting of 'cex'	1
cex.lab	Magnification to be used for x and y labels relative to the current setting of 'cex'	1
cex.main	Magnification to be used for main titles relative to the current setting of 'cex'	1
mfrow	Page layout (NA: layout set by the plot function or before)	NA
xlim	Range for the X-axis (NA: ranges set by the plot function)	NA
ylim	Range for the Y-axis (NA: ranges set by the plot function)	NA
type	Type of plot ("b": both, "p": points, "l": lines). Defaults to b for data and p for other plots	b/p
Options controlling the type of plots		
plot.type	Type of plot (see documentation for list)	default
ilist	List of subjects to include in the individual plots	1:N
smooth	Whether a smooth should be added to certain plots	FALSE
line.smooth	Type of smoothing (l=line, s=spline)	s
which.cov	Which covariates to use for the plot	all
ncat	Number of categories in which to split continuous covariates for graphs Defaults to 3, splitting in $<Q_1$, Q_1-Q_3, $>Q_3$	3
which.resplot	Type of residual plot ("res.vs.x": scatterplot versus X, "res.vs.pred": scatterplot versus predictions, "dist.hist": histogram, "dist.qqplot": QQ-plot)	c("res.vs.x","res.vs.pred", "dist.qqplot","dist.hist")
box	If TRUE, boxplots are produced instead of scatterplots	FALSE
Options for colours and line types		
col	Default symbol and line colour	black
lty	Default line type	1 (straight line)
lwd	Default line width	1
pch.pobs	Default symbol type	20 (dot)
pch.pcens	Default symbol type for censored observations	8 ()
col.pobs	Symbol colour to use for observations (points)	steelblue4
col.lobs	Symbol colour to use for observations (lines)	steelblue4
col.pcens	Symbol colour to use for censored observations	red
lty.lobs	Line type for observations	1

– To be continued

Table 2 – cont.

Parameter	Description	Default value
lwd.lobs	Line width for observations	1
col.abline	Colour of the horizontal/vertical lines added to the plots	"DarkBlue"
lty.abline	Type of the lines added to the plots	2 (dashed)
lwd.abline	Width of the lines added to the plots	2
col.fillpi	Colour used to fill histograms andprediction bands	slategray1
col.fillmed	Colour used to fill prediction band on the median (VPC, npde)	pink
col.lmed	Colour used to plot the predicted median (VPC, npde)	indianred4
col.lpi	Colour used to plot lower and upper quantiles	slategray4
lty.lmed	Line type used to plot the predicted median (VPC, npde)	2
lty.lpi	Line type used to plot lower and upper quantiles	2
lwd.lmed	Line width used to plot the predicted median (VPC, npde)	1
lwd.lpi	Line width used to plot lower and upper quantiles	1
Graphical options for VPC and residual plots		
bands	Whether prediction intervals should be plotted	TRUE
approx.pi	If TRUE, samples from $\mathcal{N}(0,1)$ are used to plot prediction intervals, while if FALSE, prediction bands are obtained using pd/npde computed for the simulated data	TRUE
vpc.method	Method used to bin points (one of "equal", "width", "user" or "optimal"); at least the first two letters of the method need to be specified	"equal"
vpc.bin	Number of binning intervals	10
vpc.interval	Size of interval	0.95
vpc.breaks	Vector of breaks used with user-defined breaks (vpc.method="user")	NULL
vpc.extreme	Can be set to a vector of 2 values to fine-tune the behaviour of the binning algorithm at the boundaries; specifying c(0.01,0.99) with the "equal" binning method and vpc.bin=10 will create 2 extreme bands containing 1% of the data on the X-interval, then divide the region within the two bands into the remaining 8 intervals each containing the same number of data; in this case the intervals will all be equal except for the two extreme intervals, the size of which is fixed by the user; complete fine-tuning can be obtained by setting the breaks with the vpc.method="user"	NULL
pi.size	Width of the prediction interval on the quantiles	0.95
vpc.lambda	Value of lambda used to select the optimal number of bins through a penalised criterion	0.3
vpc.beta	Value of beta used to compute the variance-based criterion (Jopt,beta(I)) in the clustering algorithm	0.2
bands.rep	Number of simulated datasets used to compute prediction bands	200

Table 2: Default graphical parameters. Any option not defined by the user is automatically set to its default value.

Note that not all of the graphical parameters in `par()` can be used, but it is possible for instance to use the xaxt="n" option below to suppress plotting of the X-axis, and to then add back the axis with the R function axis() to tailor the tickmarks or change colours as wanted. It is also possible of course to extract npde, fitted values or original data to produce any of these plots by hand if the flexibility provided in the library isn't sufficient.

2 Demo setup

2.1 Technical aspects

This document should be compiled from the Sweave file (extension .Rnw) into a LaTeX file using the `Sweave()` function in R; this generates a .tex file which should then compiled, eg by pdflatex (twice to get the references properly). Once the files have been successfully compiled, tables (LaTeX format) and figures (pdf format, with some exported as postscript) will be (re-)created and stored in two subdirectories (figs and tabs). Results of the npde runs will be stored in a subdirectory called results.

The library requires the mclust library (used for the *optimal* binning method).

2.2 Datasets

The three examples used to showcase the graphs and their options in this document are included in the library npde:

1. theophylline PK data

description this dataset is a well-known dataset in population pharmacokinetics; it contains the PK data from a study in 12 patients receiving the drug theophylline and is frequently used to illustrate non-linear mixed effect modelling. It is available in NONMEM, and Monolix, as well as in the dataset package in R (under the name Theoph under a slightly different format)

dataset this dataset is included in the library under the name theopp (it also appeared in version 1 of the npde library)

simulations the corresponding simulation dataset is simtheopp

2. viral load data (new)

description this dataset was simulated based on a real study of viral load in HIV patients, corresponding to the COPHAR 3 - ANRS 134 trial, a phase II clinical trial supported by the French Agency for AIDS Research (see documentation for details)

datasets 3 versions of the datasets are available, corresponding to no censoring (virload), censoring assuming the LOQ is 20 copies/mL (virload_20), and censoring assuming the LOQ is 50 copies/mL (virload_50); in the present document we will show different graphs and options for the full dataset (no censoring) and for the dataset with the highest level of censoring, corresponding to the fraction of censored data observed in the real data from the clinical trial

simulations the corresponding simulation dataset is simvirload (for the 3 versions)

3. remifentanil PK data (new)

description this dataset includes rich data from a study of remifentanil in 65 healthy volunteers, a synthetic opioid derivative, used as a major analgesic before surgery or in critical care. In the study, the subjects were given remifentanil as a continuous infusion over 4 to 20 min, and measurements were collected over a period of time varying from 45 to 230 min (mean 80 min), along with EEG measurements. The following covariates were recorded: gender, age, body weight, height, body surface area and lean body mass. The recruitment was specifically designed to investigate the effect of age, with recruitment over 3 age groups (young (20-40 yr), middle-aged (40-65 yr) and elderly (over 65 yr)). It is available in the nlme package in R (under the name Remifentanil in the groupedData format).

datasets this dataset is included in the library under the name remifent

simulations the simulation dataset for the base model without covariates is simremifent.tab

All these datasets are available in the *data* directory of the npde package, and their structure and content are described in the online help.

3 Computing npde

3.1 Theophylline data

This dataset presents a simple example, without covariates or BQL data.

```
> cat("Computing npde, observed data=",nam.obs,", simulated data=",nam.sim,"\n")
Computing npde, observed data= theopp.tab , simulated data= simtheopp.tab
> data(theopp)
> data(simtheopp)
> xtheo<-autonpde(namobs=theopp,namsim=simtheopp,
         iid=1,ix=3,iy=4,namsav="results/theo_nocov",units=list(x="hr",y="mg/L"))
-------------------------------------------
Distribution of npde :
      nb of obs: 120
           mean= 0.0668   (SE= 0.095 )
       variance= 1.074   (SE= 0.14 )
       skewness= 0.511
       kurtosis= 0.2912
-------------------------------------------

Statistical tests
  t-test                     : 0.481
  Fisher variance test       : 0.55
  SW test of normality       : 0.00273 **
Global adjusted p-value      : 0.00818 **
---
Signif. codes: '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1
-------------------------------------------


Computing npde, observed data= theopp.tab , simulated data= simtheopp.tab
-------------------------------------------
Distribution of npde :
      nb of obs: 120
           mean= 0.0668   (SE= 0.095 )
       variance= 1.074   (SE= 0.14 )
       skewness= 0.511
       kurtosis= 0.2912
-------------------------------------------

Statistical tests
  t-test                     : 0.481
  Fisher variance test       : 0.55
  SW test of normality       : 0.00273 **
Global adjusted p-value      : 0.00818 **
---
Signif. codes: '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1
-------------------------------------------
```

3.2 Cophar data - BQL

Different censoring methods are available to handle BQL data: the default censoring method (cdf) is to use the model predicted probability for an observation to be below the LOQ to impute pd, and the empirical distribution function to impute observations, using the completed dataset to build npde(see main user guide). In the npde package, different options are available to treat BQL data:

- removed from the dataset: option cens.method = "omit"

- imputed to model predictions: population predictions (option cens.method = "ppred") or individual predictions (option cens.method = "ipred")
  - with the "ppred" method, population predictions are computed using the simulated datasets
  - with the "ipred" method, individual predictions for each observation obtained during the estimation process need to be included in the data file as an additional column
  - pd and npde are computed after replacing observed and simulated data by the imputed values
- imputed to a fixed value: to the LOQ value given in the dataset (option cens.method = "loq") or to a value chosen by the user (option cens.method = "fixed",loq=LOQ where LOQ is a number)
  - as in the previous method, pd and npde are computed after replacing observed and simulated data by the imputed values

```
> data(virload)
> data(virload50)
> data(simvirload)
> cat("Computing the npde for the full COPHAR dataset (no censoring)\n")
Computing the npde for the full COPHAR dataset (no censoring)
> xvir.full1<-autonpde(namobs=virload,namsim=simvirload,
  iid=1,ix=2,iy=3,icens=0,namsav="results/virload_full",units=list(x="days",y="copies/mL"))
-------------------------------------------
Distribution of npde :
      nb of obs: 300
           mean= 0.03821   (SE= 0.053 )
       variance= 0.8327   (SE= 0.068 )
       skewness= -0.04464
       kurtosis= -0.2207
-------------------------------------------

Statistical tests
  t-test                    : 0.469
  Fisher variance test      : 0.032 *
  SW test of normality      : 0.845
Global adjusted p-value     : 0.0959 .
---
Signif. codes: '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1
-------------------------------------------
> xvir.full2<-autonpde(namobs=virload,namsim=simvirload,
         iid=1,ix=2,iy=3,icens=4,boolsave=FALSE,units=list(x="days",y="copies/mL"))
-------------------------------------------
Distribution of npde :
      nb of obs: 300
           mean= 0.03821   (SE= 0.053 )
       variance= 0.8327   (SE= 0.068 )
       skewness= -0.04464
       kurtosis= -0.2207
-------------------------------------------

Statistical tests
  t-test                    : 0.469
  Fisher variance test      : 0.032 *
  SW test of normality      : 0.845
Global adjusted p-value     : 0.0959 .
---
Signif. codes: '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1
-------------------------------------------
```

```
> xvir.polar<-autonpde(namobs=virload,namsim=simvirload,
         iid=1,ix=2,iy=3,icens=0,namsav="results/virload_polar",
         units=list(x="days",y="copies/mL"),decorr.method="polar")
-------------------------------------------
Distribution of npde :
      nb of obs: 300
           mean= -0.01066   (SE= 0.053 )
       variance= 0.845   (SE= 0.069 )
       skewness= 0.009628
       kurtosis= -0.2051
-------------------------------------------

Statistical tests
  t-test                     : 0.841
  Fisher variance test       : 0.0483 *
  SW test of normality       : 0.734
Global adjusted p-value      : 0.145
---
Signif. codes: '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1
-------------------------------------------
> vec<-xvir.full1@results@res$npde-xvir.full2@results@res$npde
> cat("Checking that the npde are the same for these two objects:")
Checking that the npde are the same for these two objects:
> if(zapsmall(max(abs(vec),na.rm=T))>0) cat("ERROR\n") else cat("OK\n")
OK
> cat("Computing the npde for the COPHAR dataset with censoring=50 copies/mL\n")
Computing the npde for the COPHAR dataset with censoring=50 copies/mL
> x50<-autonpde(namobs=virload50,namsim=simvirload,iid=1,ix=2,iy=3,icens=4,
         namsav="results/virload_c50",units=list(x="days",y="copies/mL"))
-------------------------------------------
Distribution of npde :
      nb of obs: 300
           mean= -0.09555   (SE= 0.055 )
       variance= 0.9028   (SE= 0.074 )
       skewness= 0.01539
       kurtosis= 0.2781
-------------------------------------------

Statistical tests
  t-test                     : 0.0826 .
  Fisher variance test       : 0.23
  SW test of normality       : 0.598
Global adjusted p-value      : 0.248
---
Signif. codes: '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1
-------------------------------------------
> x50.omit<-autonpde(namobs=virload50,namsim=simvirload,iid=1,ix=2,iy=3,icens=4,
         namsav="results/virload_omit50",units=list(x="days",y="copies/mL"),
   cens.method="omit")
-------------------------------------------
Distribution of npde :
      nb of obs: 169
           mean= 0.1433   (SE= 0.07 )
       variance= 0.8186   (SE= 0.089 )
       skewness= -0.03812
       kurtosis= -0.3733
-------------------------------------------
```

```
Statistical tests
  t-test                     : 0.041 *
  Fisher variance test       : 0.0822 .
  SW test of normality       : 0.687
Global adjusted p-value      : 0.123
---
Signif. codes: '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1
-------------------------------------------
> x50.ipred<-autonpde(namobs=virload50,namsim=simvirload,iid=1,ix=2,iy=3,icens=4,
         namsav="results/virload_ipred50",units=list(x="days",y="copies/mL"),
         cens.method="ipred")
-------------------------------------------
Distribution of npde :
      nb of obs: 300
           mean= 0.03058   (SE= 0.062 )
       variance= 1.164   (SE= 0.095 )
       skewness= 0.04433
       kurtosis= -0.05092
-------------------------------------------

Statistical tests
  t-test                     : 0.624
  Fisher variance test       : 0.0539 .
  SW test of normality       : 0.973
Global adjusted p-value      : 0.162
---
Signif. codes: '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1
-------------------------------------------
> x50.ppred<-autonpde(namobs=virload50,namsim=simvirload,iid=1,ix=2,iy=3,icens=4,
         namsav="results/virload_ppred50",units=list(x="days",y="copies/mL"),
         cens.method="ppred")
-------------------------------------------
Distribution of npde :
      nb of obs: 300
           mean= 0.03101   (SE= 0.057 )
       variance= 0.9715   (SE= 0.079 )
       skewness= -0.006498
       kurtosis= 0.8122
-------------------------------------------

Statistical tests
  t-test                     : 0.586
  Fisher variance test       : 0.746
  SW test of normality       : 0.00121 **
Global adjusted p-value      : 0.00364 **
---
Signif. codes: '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1
-------------------------------------------
```

3.3 Remifentanil PK - covariates

```
> cat("Computing the npde for the remifentanil data\n")
Computing the npde for the remifentanil data
> xrem<-autonpde(namobs=file.path(lib.rem,"remifent.tab"),
         namsim=file.path(lib.rem,"simremifent_base.tab"),iid=1,ix=2,iy=3,icov=c(6:12),
```

```
         namsav="results/remibase",units=list(x="hr",y="ug/L",
         covariates=c("yr","-","cm","kg","m2","kg","yr")))
-------------------------------------------
Distribution of npde :
      nb of obs: 1992
           mean= -0.02578   (SE= 0.015 )
       variance= 0.4637   (SE= 0.015 )
       skewness= 0.2545
       kurtosis= 2.077
-------------------------------------------

Statistical tests
  t-test                     : 0.0912 .
  Fisher variance test       : 1.88e-102 ***
  SW test of normality       : 8e-18 ***
Global adjusted p-value      : 5.65e-102 ***
---
Signif. codes: '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1
-------------------------------------------
```

4 Graphs npde

4.1 Theophylline data - no BQL

4.1.1 Default plots

By default, the package produces and saves the four graphs shown in figure 1:

1. a quantile-quantile plot: plot of the npde versus the corresponding quantiles of a normal distribution
   - the line $y = x$ is also drawn
2. a histogram of the npde
   - the shape of the normal distribution $\mathcal{N}(0, 1)$ is also shown
3. a plot of the npde versus the independent variable X
4. a plot of the npde versus ypred
   - for these last two graphs, we plot the lines corresponding to $y = 0$ and to the critical values 5% and 95% (delimiting the 90% confidence interval in which we expect to find the bulk of the npde).

```
> plot(xtheo)
```

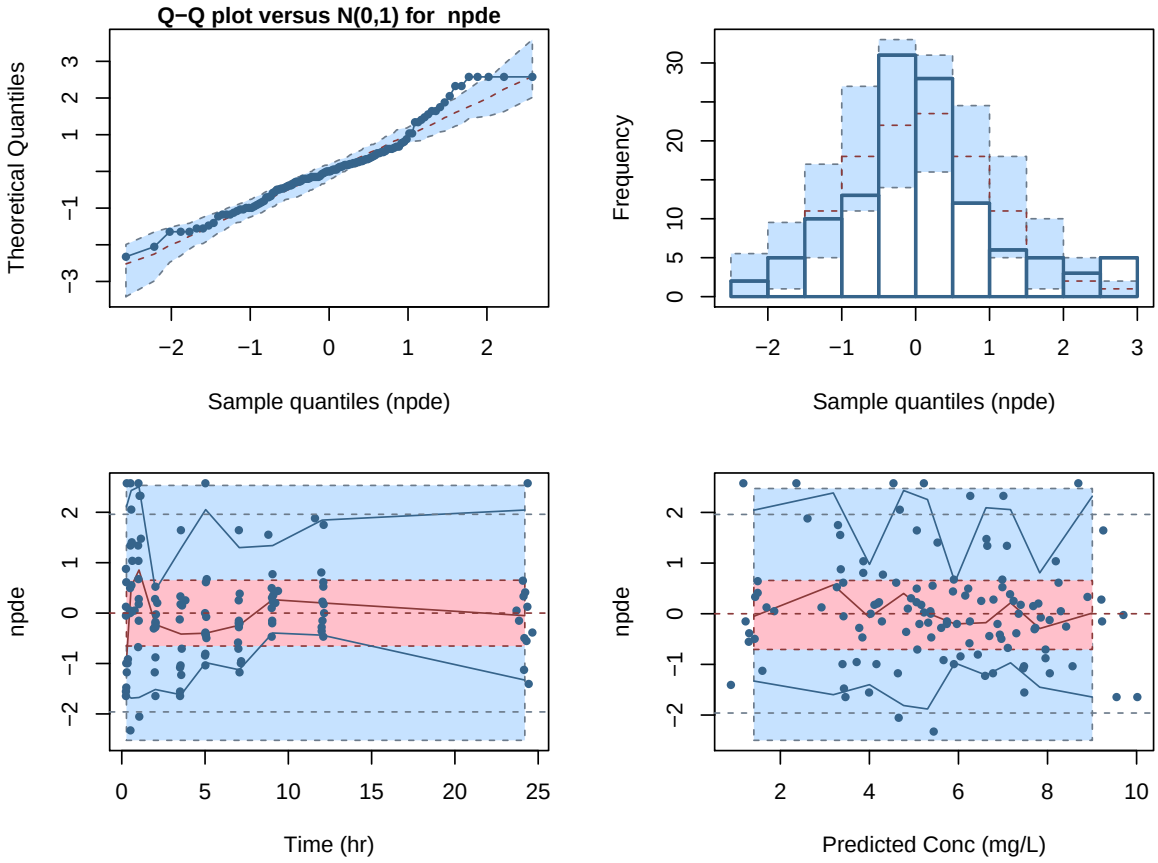

Figure 1: Default plots for xtheo.

The following commandes may be used to save the file in the postcript format (alternatively and depending on the installation of R, png, pdf or jpeg files can be requested, see the documentation for R).

```
> # Saving the graph
> postscript("figs/xtheo_default.eps",horizontal=T)
> plot(xtheo)
> x<-dev.off()
```

4.1.2 Available basic plots

Data: default plot of the data (using points and lines)

```
> plot(xtheo,plot.type="data")
```

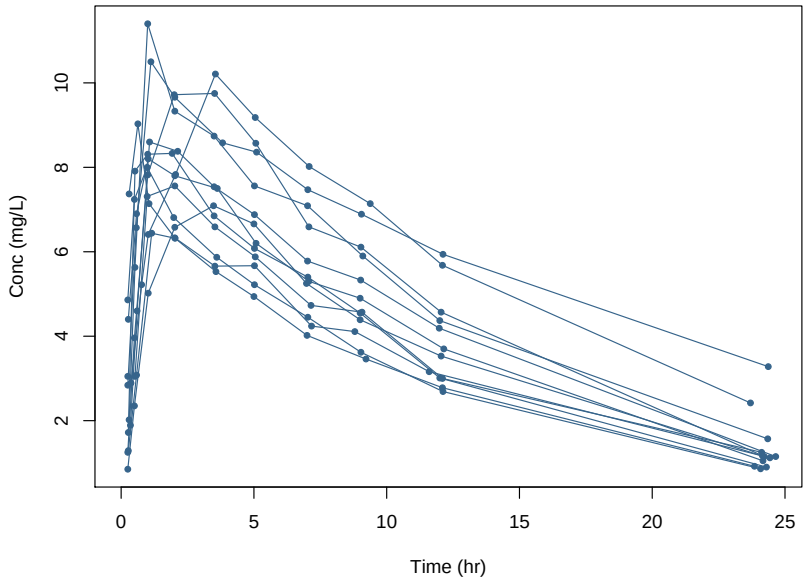

Figure 2: Default plot for xtheo - data.

VPC: visual predictive check

```
> plot(xtheo,plot.type="vpc")
```

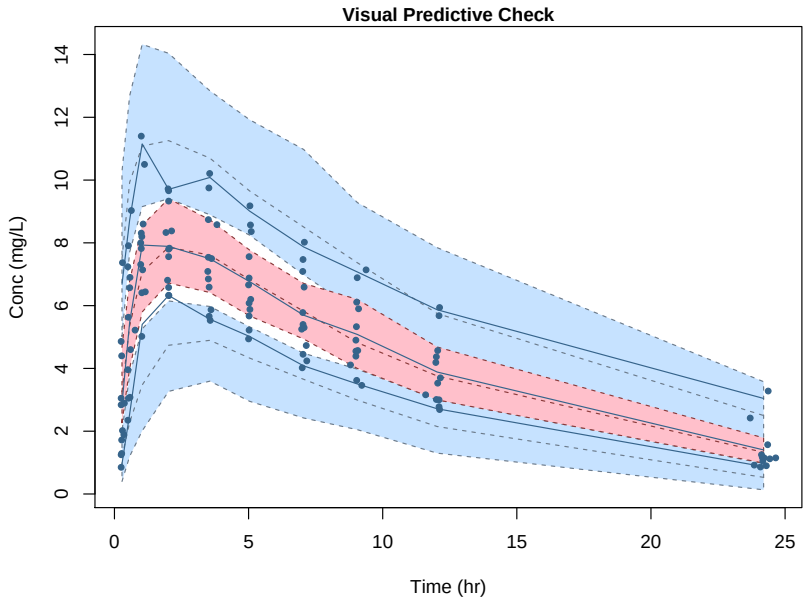

Figure 3: Default plot for xtheo - VPC.

Scatterplots: scatterplots of npde versus X or predictions

```
> plot(xtheo,plot.type="x.scatter")
```

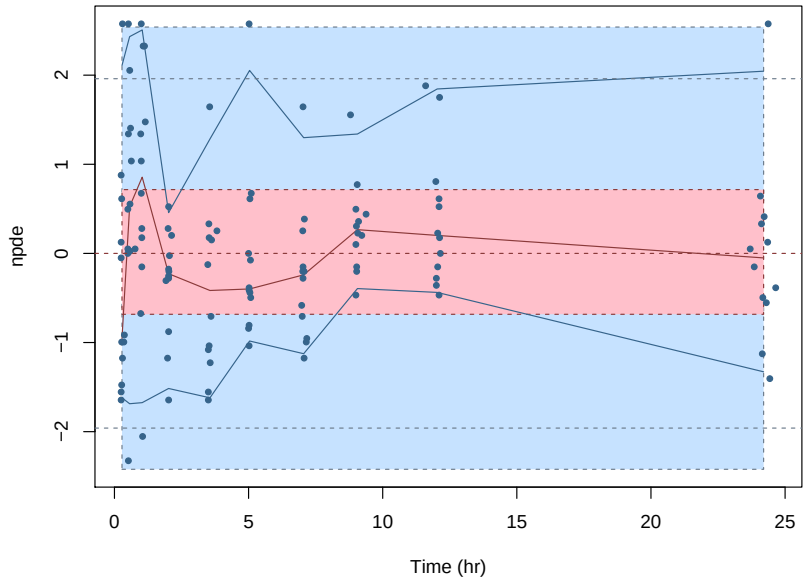

Figure 4: Default plot for xtheo - scatterplot of npde vs X.

```
> plot(xtheo,plot.type="pred.scatter")
```

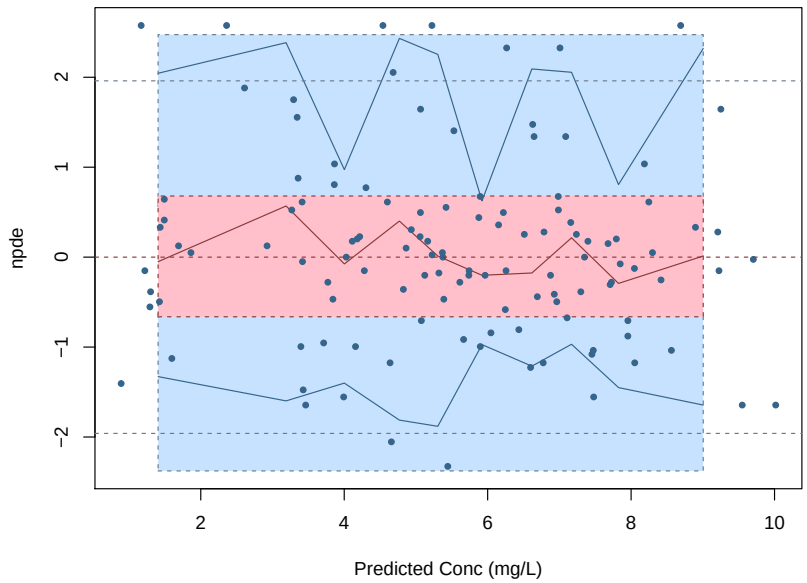

Figure 5: Default plot for xtheo - scatterplot of npde vs predictions.

Distribution plots: QQ-plot of npde versus $\mathcal{N}(0,1)$, histogram of npde, empirical cdf

```
> plot(xtheo,plot.type="qqplot")
```

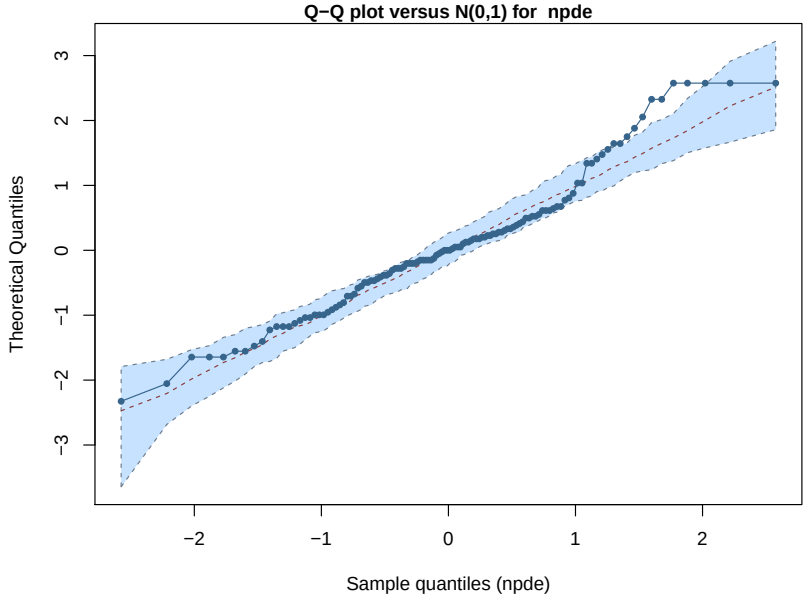

Figure 6: Default plot for xtheo - QQ-plot of npde versus $\mathcal{N}(0,1)$.

```
> plot(xtheo,plot.type="hist")
```

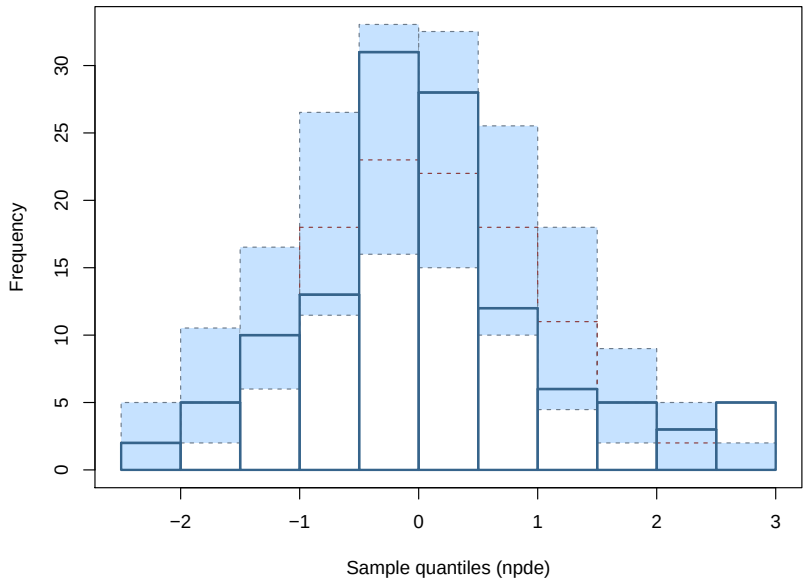

Figure 7: Default plot for xtheo - histogram of npde.

```
> plot(xtheo,plot.type="ecdf")
```

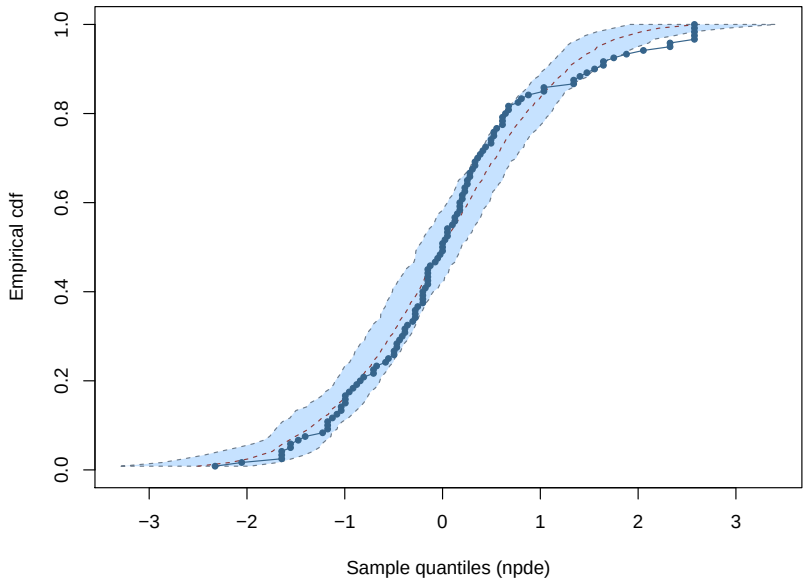

Figure 8: Default plot for xtheo - empirical cumulative distribution function of npde.

4.1.3 General plot options

General graphical settings: titles, labels, plot type and sizes can be set using similar options as the general plot function. By default, each graph is produced in a new plot window with default layout (eg, one figure per page for the plot of the data). This can be overriden by the new=FALSE option, and the graph then fits into a layout previously defined. An example is shown in figure 9, which shows side by side the default plot from figure 2 and the plot of the same data with user-defined changes.

```
> par(mfrow=c(1,2))
> plot(xtheo,plot.type="data",new=FALSE)
> plot(xtheo,plot.type="data",new=FALSE,main="Title",sub="subtitle",xlab="Label for X-axis",
        ylab="Label for Y-axis",type="p",ylog=TRUE,frame.plot=FALSE,xaxt="n",pch=2,col.pobs="
        cex=2,cex.lab=1.5,cex.main=0.8)
```

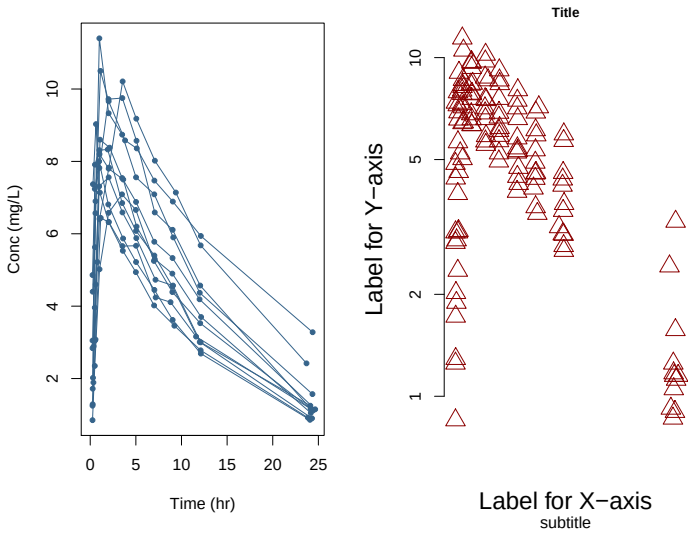

Figure 9: Default plot for xtheo - data - some options.

Colours: the overall colour for graphs can be set by the option col, while specific colours can be changed by a number of graphical settings (see documentation).

```
> plot(xtheo,plot.type="data",col="blue")
```

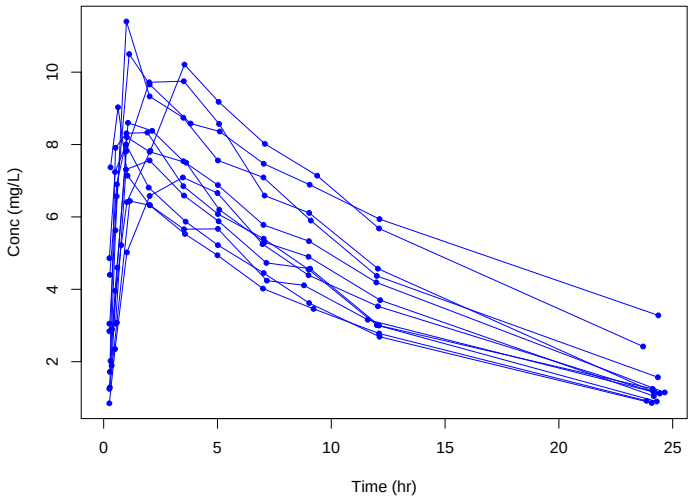

Figure 10: Default plot for xtheo - data - some options.

Warning: global options like col will affect most colour settings, unless these are specified in addition. For instance, using col="blue" will change all colours to blue, while using both options col="blue",col.pobs="red" will have the effect of setting all colours to blue except the observed data (non-censored) which will be printed in red. Here in addition we plot only the first 5 subjects in the dataset.

```
> plot(xtheo,plot.type="data",col="blue",col.pobs="red",ilist=1:5)
```

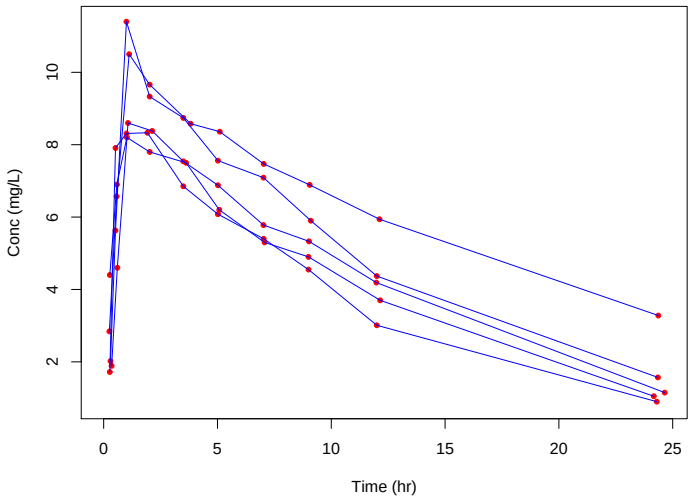

Figure 11: Default plot for xtheo - data - changing colours.

Line types and width: line types and widths can be set by the global options lty and lwd, or as previously individual line types and widths can be specified. In the plot below, we use lty.lobs and lwd.lobs to change the aspect of the lines connecting individual observations, although in this case since this is the only line in the plot the global options could be used instead. We also use the cex options to enlarge the size of the plotting symbols.

```
> plot(xtheo,plot.type="data",lty.lobs=2,lwd.lobs=3,col.lobs="DarkBlue",cex=2)
```

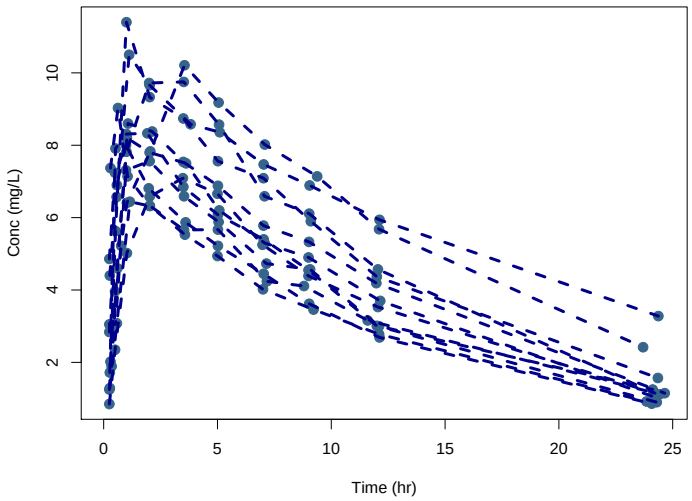

Figure 12: Default plot for xtheo - data - some options.

4.1.4 Binning methods:

Several binning methods are available to bin on the X-axis. These methods can be used in all plots which include prediction bands (scatterplots and VPC).

```
> par(mfrow=c(2,2))
> plot(xtheo,plot.type="vpc",new=FALSE,main='Method=default (=equal)')
> plot(xtheo,plot.type="vpc",new=FALSE,main='Method=width',vpc.method="width")
> plot(xtheo,plot.type="vpc",new=FALSE,main='Method=optimal',vpc.method="optimal")
> plot(xtheo,plot.type="vpc",new=FALSE,main='Method=user',vpc.method="width",
        vpc.breaks=c(0,0.4,0.8,1.5,3,6,8,10,20))
```

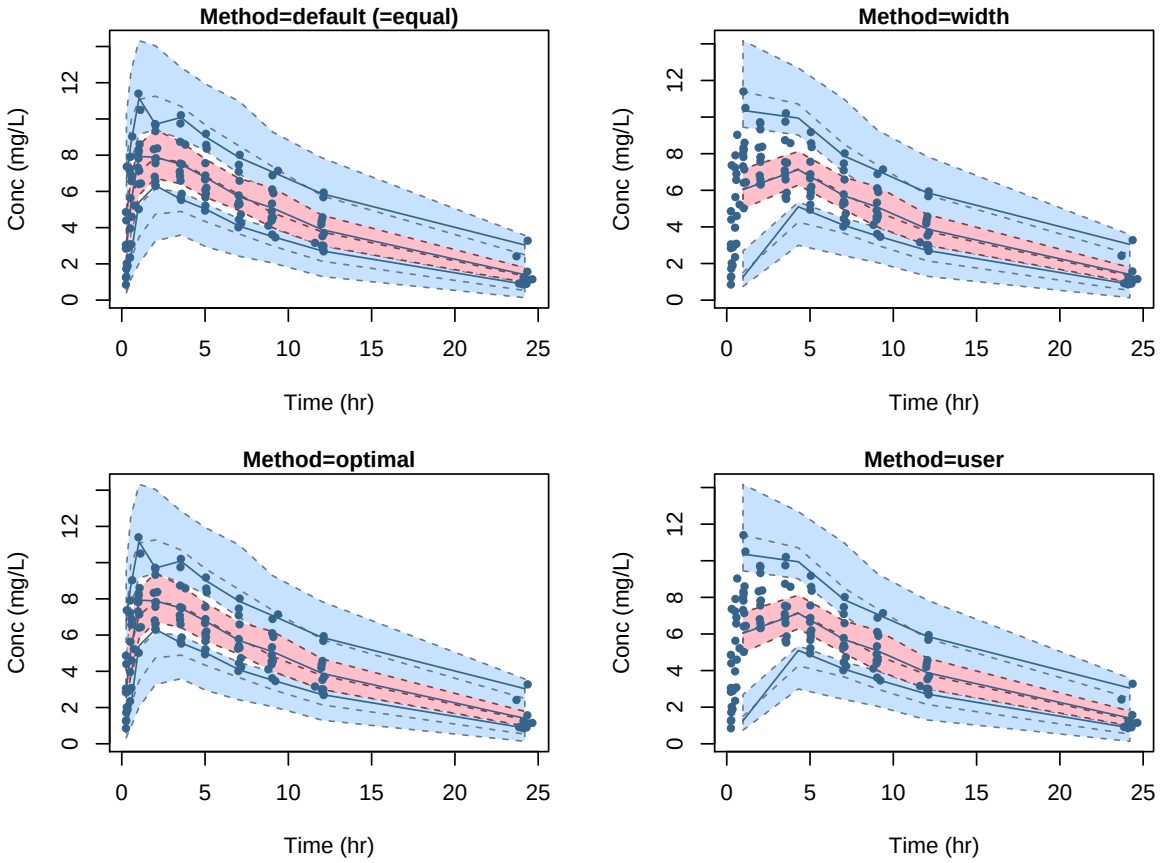

Figure 13: Plots with prediction bands for xtheo - binning method (VPC).

The figure below shows some of the other options, including the interactive=TRUE which displays the binning intervals and the number of observations in each interval. All these options also apply to the other scatterplots with prediction bands, such as scatterplots of npde versus X or predictions.

```
> par(mfrow=c(2,2))
> plot(xtheo,plot.type="vpc",new=FALSE,main='Default binning, log-scale',ylog=TRUE)
> plot(xtheo,plot.type="vpc",new=FALSE,main='Default binning, 15 bins',vpc.bin=15)
> plot(xtheo,plot.type="vpc",new=FALSE,main='Method=width, forcing boundaries',
        vpc.method="width",vpc.extreme=c(0.01,0.95))
> plot(xtheo,plot.type="vpc",new=FALSE,main='Method=optimal',vpc.method="optimal",
        interactive=TRUE, vpc.bin=15)
Method used for binning: clustering algorithm , dividing into the following 10 intervals
   Interval     Centered.On Nb.obs
1  [0.25-0.3]    0.27        10
2  [0.35-0.77]   0.53        14
3  [0.98-1.15]   1.03        12
4  [1.92-2.13]   2.02        12
5  [3.48-3.82]   3.56        12
6  [5-5.1]       5.04        12
7  [6.98-7.17]   7.05        12
8  [8.8-9.38]    9.06        12
9  [11.6-12.15] 12.03        12
10 [23.7-24.65] 24.20        12
```

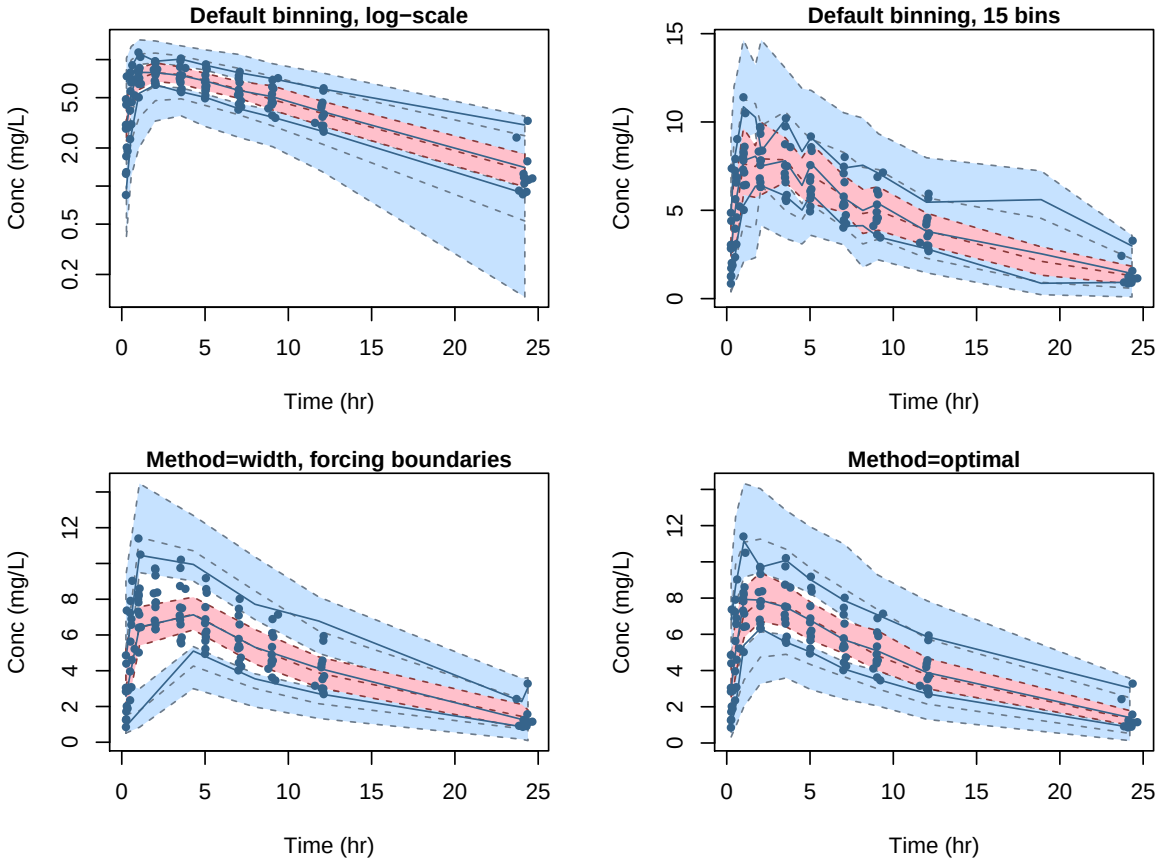

Figure 14: Plots with prediction bands for xtheo - binning options (VPC).

4.2 Cophar data - BQL

4.2.1 Default plots

```
> plot(xvir.full1)
```

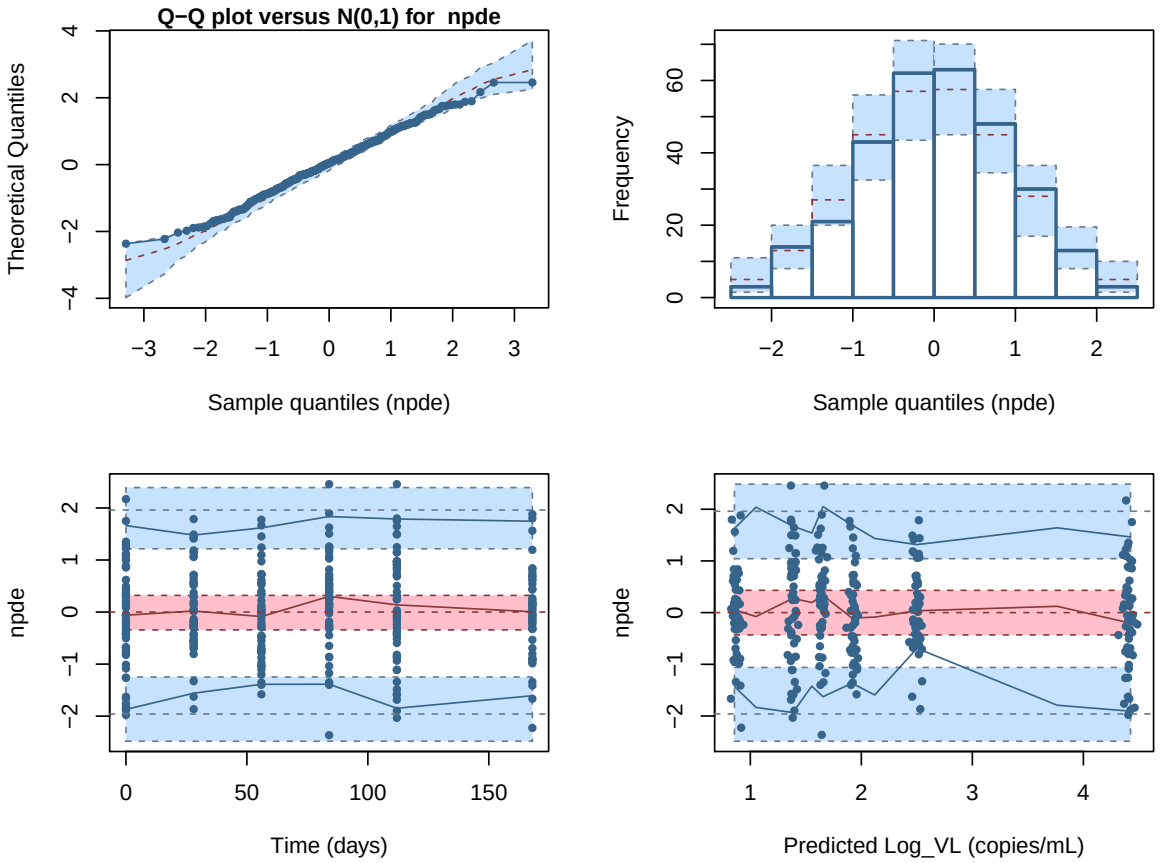

Figure 15: Default plots for COPHAR, no censored data.

```
> plot(x50.omit)
```

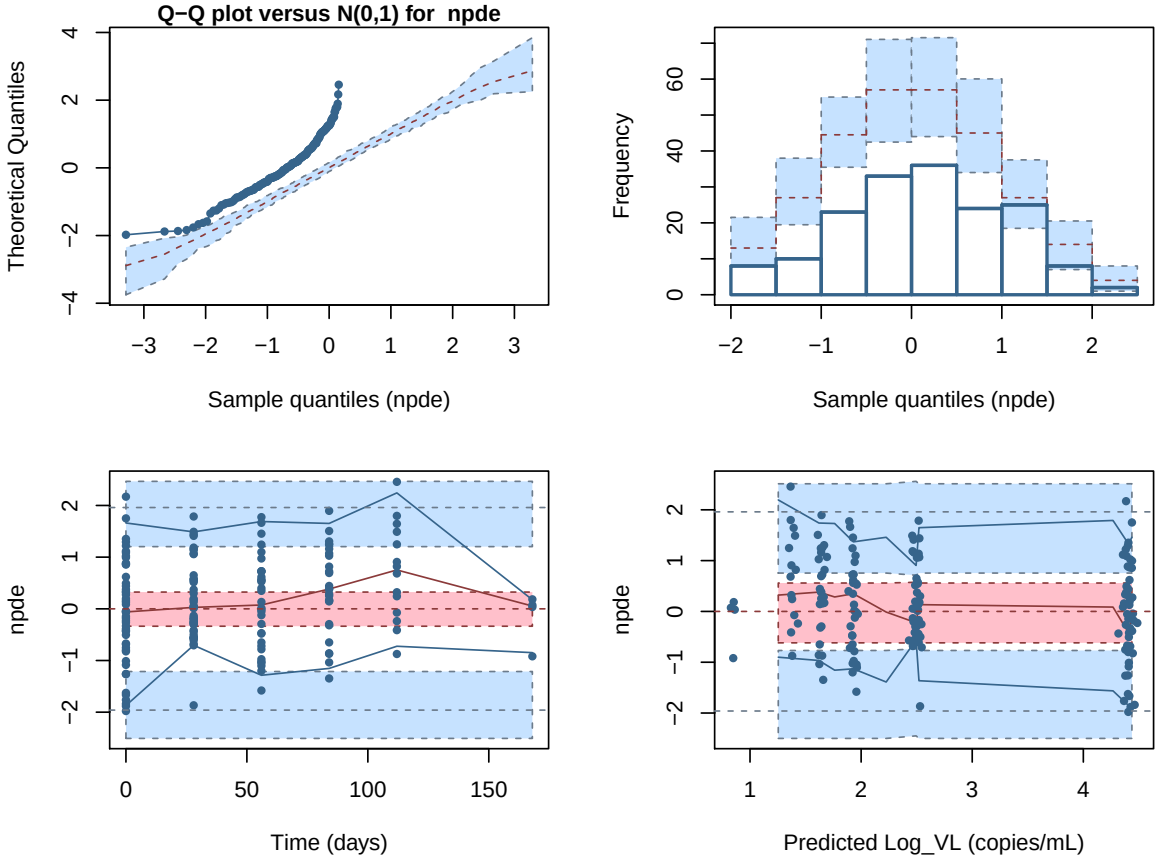

Figure 16: Default plots for COPHAR, censoring 50 copies/mL, censoring method "cdf" (default).

4.2.2 Available plots

We now show the different plot types for x50 (using imputation to handle BQL data).

```
> plot(x50,plot.type="data")
```

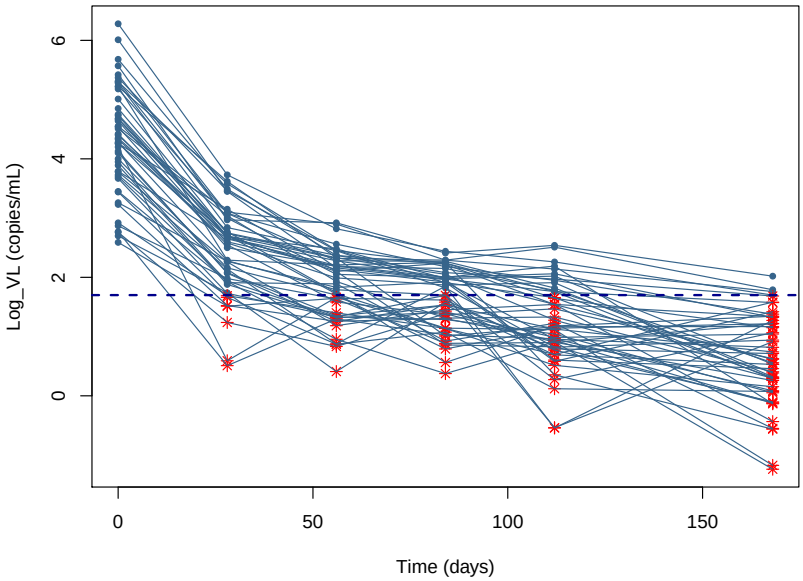

Figure 17: Default plots - data.

```
> plot(x50,plot.type="vpc")
```

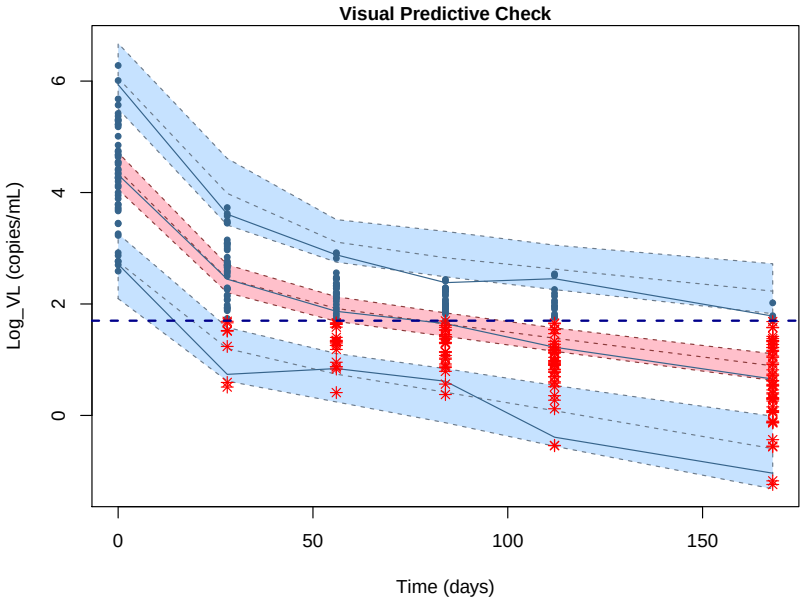

Figure 18: Default plots - VPC.

```
> plot(x50,plot.type="x.scatter")
```

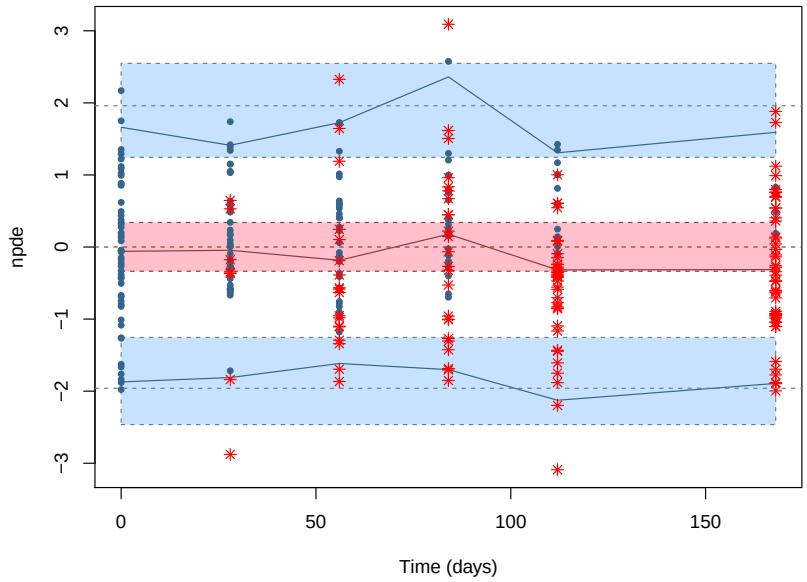

Figure 19: Default plots - scatterplot of npde versus X-axis.

```
> plot(x50,plot.type="pred.scatter")
```

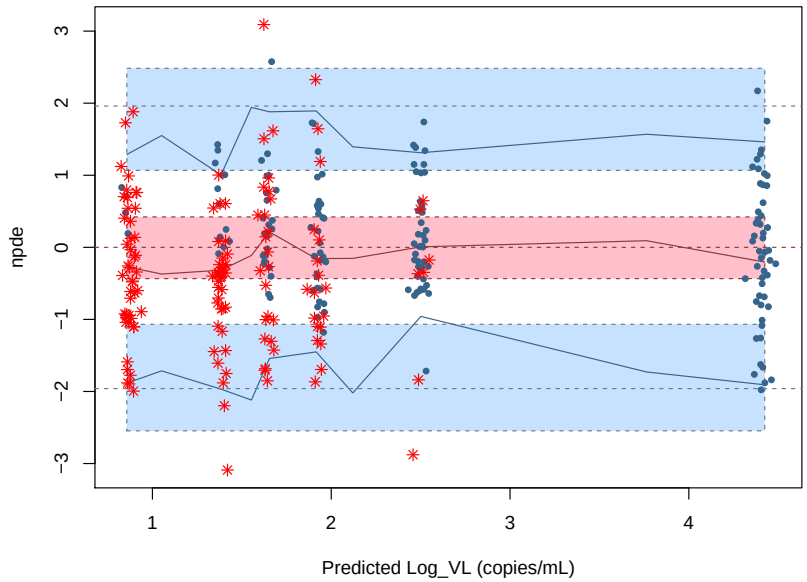

Figure 20: Default plots - scatterplot of npde versus predictions.

```
> plot(x50,plot.type="loq")
```

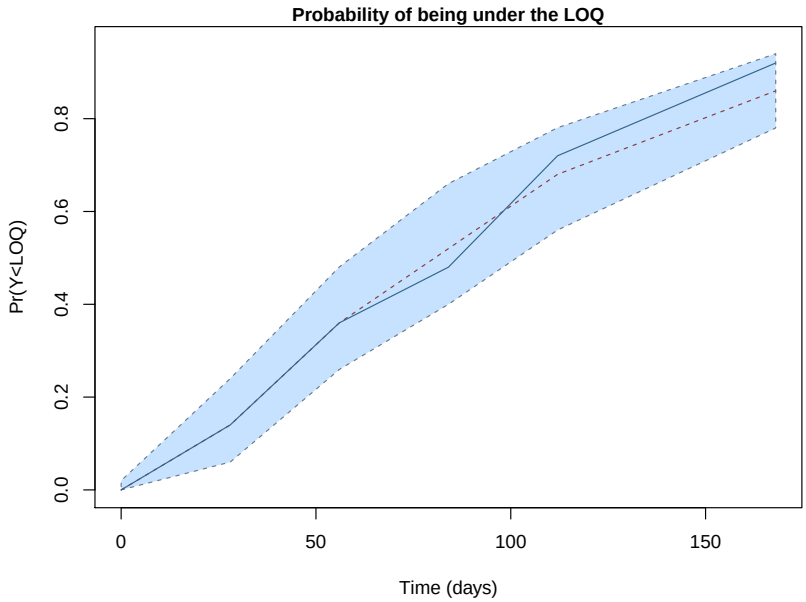

Figure 21: Default plots - fraction of data below LOQ.

4.2.3 Options for plots

```
> plot(x50,plot.type="data",main="Raw data",col.pobs="DarkRed",col.lobs="DarkRed",
        col.pcens="blue", pch.pobs=2,pch.pcens=20,lty.lobs=2,xlab="The X-axis",
        ylab="The Y-axis",sub="Some changes",cex=0.8, cex.lab=1.5)
```

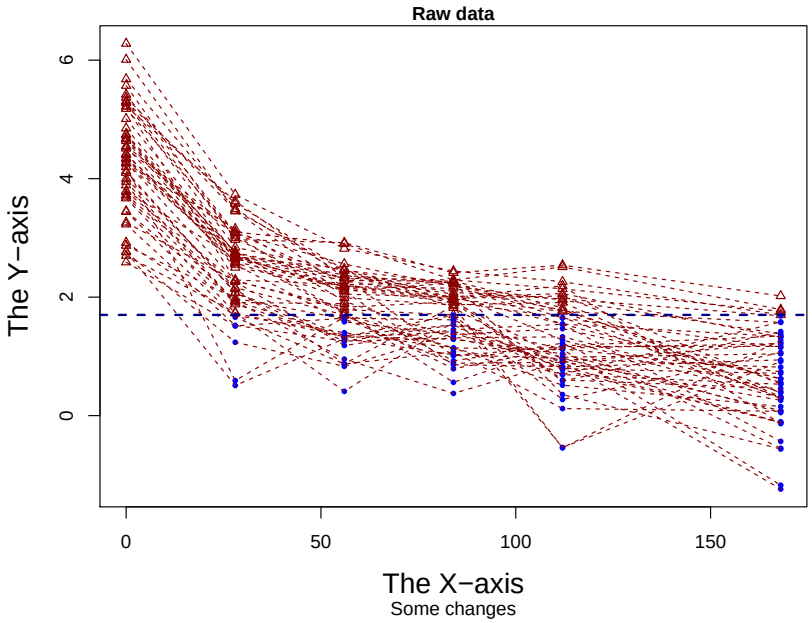

Figure 22: Plots - options for data.

```
> plot(x50,plot.type="ecdf",main="Cophar",col.pobs="DarkRed",col.lobs="DarkRed",
        col.pcens="blue",pch.pobs=2,pch.pcens=20,lty.lobs=2,xlab="The X-axis",
        ylab="The Y-axis",sub="Some changes",cex=0.8, cex.lab=1.5,bands=TRUE,
        col.fillpi="lightgreen",col.lpi="green")
```

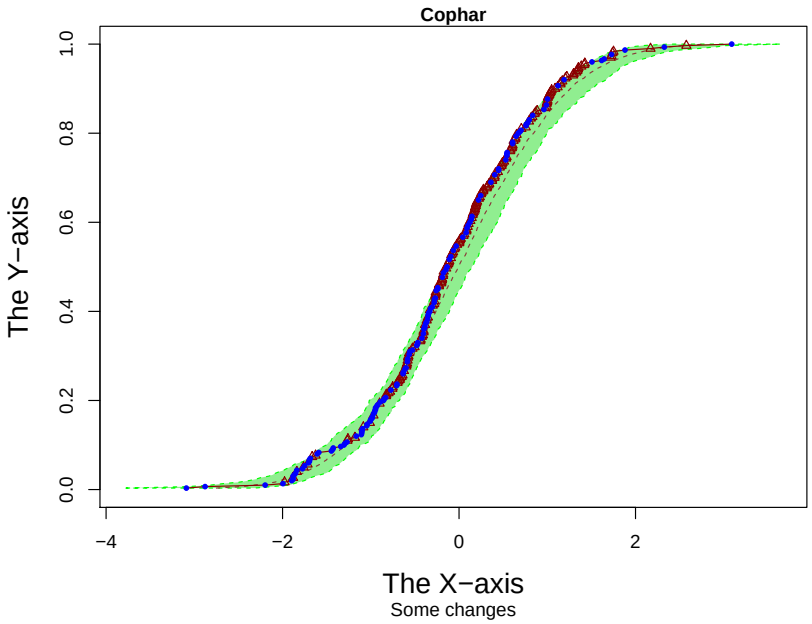

Figure 23: Plots - options for ecdf

```
> plot(x50,plot.type="vpc",main="VPC Cophar data", sub="Options", col.pobs="DarkRed",
        col.lobs="DarkRed", col.pcens="blue", pch.pobs=2,pch.pcens=20,lty.lobs=2,
        xlab="The X-axis",ylab="The Y-axis",sub="Some changes",cex=0.8, cex.lab=1.2,vpc.bin=3
        vpc.interval=0.8,vpc.method="width",col.fillmed="lightblue",col.fillpi="pink",
        lty.lmed=4,lty.lpi=3,lwd.lmed=1,lwd.lpi=3,col.lpi="red")
```

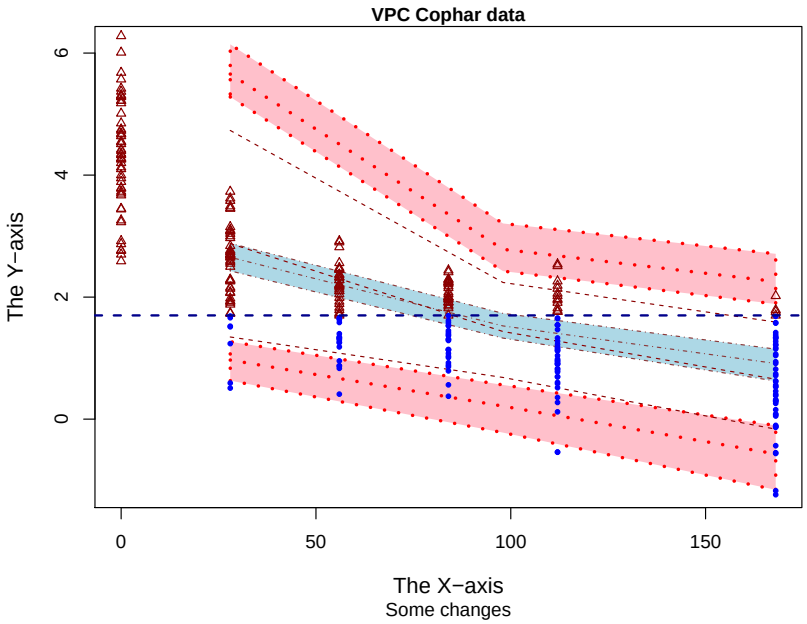

Figure 24: Plots - options for VPC.

```
> plot(x50,plot.type="vpc",main="VPC Cophar data", sub="Options", col.pobs="DarkRed",
        col.lobs="DarkRed", col.pcens="blue", pch.pobs=2,pch.pcens=20,lty.lobs=2,
        xlab="The X-axis",ylab="The Y-axis",sub="Some changes",cex=0.8, cex.lab=1.2,vpc.bin=8
        vpc.interval=0.8,vpc.method="width",col.fillmed="lightblue",col.fillpi="pink",
        lty.lmed=4,lty.lpi=3,lwd.lmed=1,lwd.lpi=3,col.lpi="red",xlog=T,ylog=T)
```

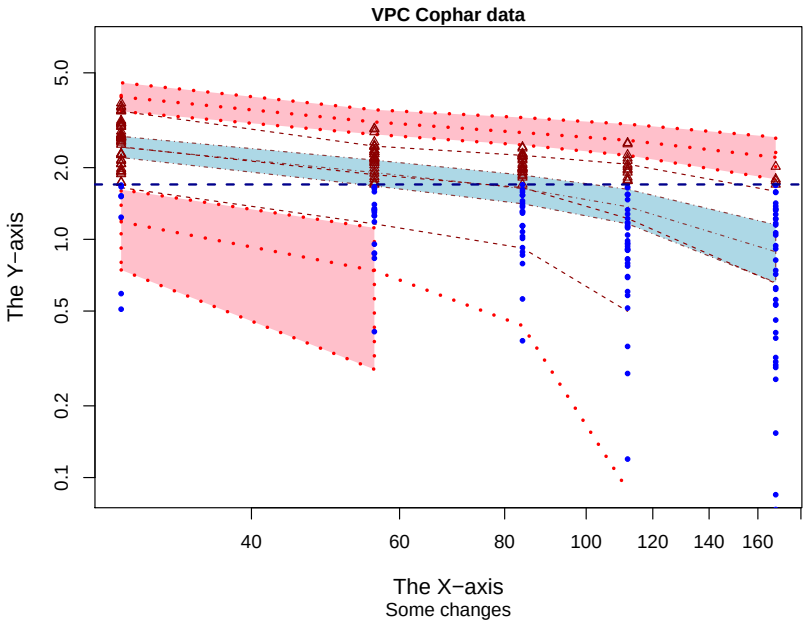

Figure 25: Plots - options for VPC. Note that the lower prediction band is truncated because the Y-axis is in log-scale but the lower boundary of the band is negative.

```
> plot(x50,plot.type="vpc",vpc.method="optimal")
```

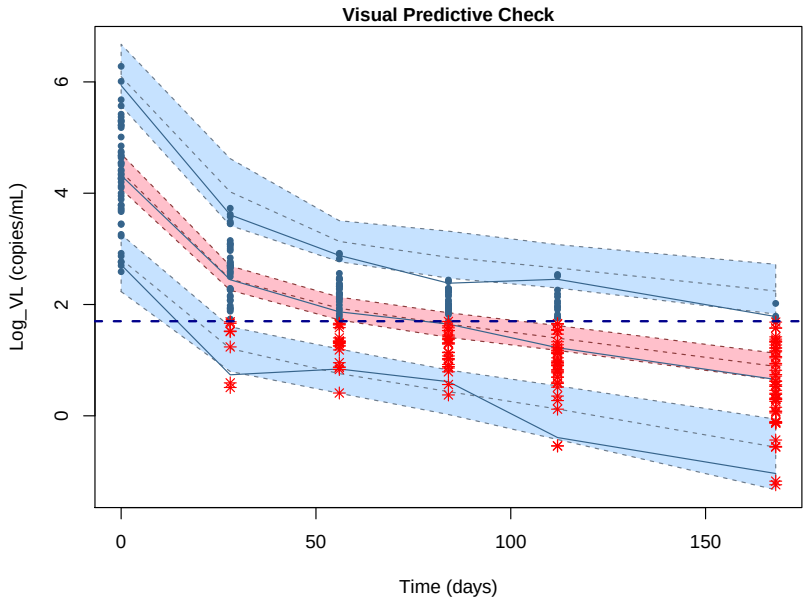

Figure 26: Plots - options for VPC - method 'optimal'.

```
> plot(x50,plot.type="vpc",vpc.method="width")
```

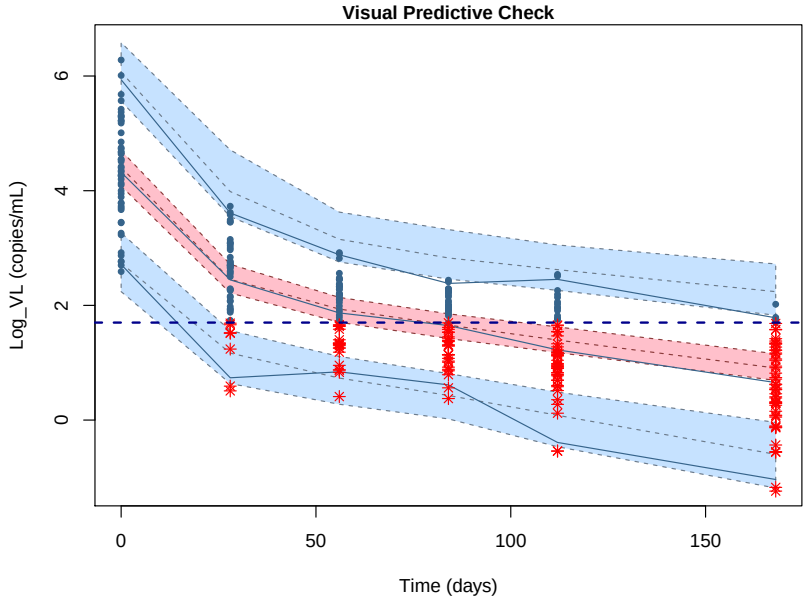

Figure 27: Plots - options for VPC - method 'width'.

4.3 Remifentanil PK - covariates

4.3.1 Default plots

Figure 28 shows the plots produced by default for the remifentanil data.

```
> plot(xrem)
```

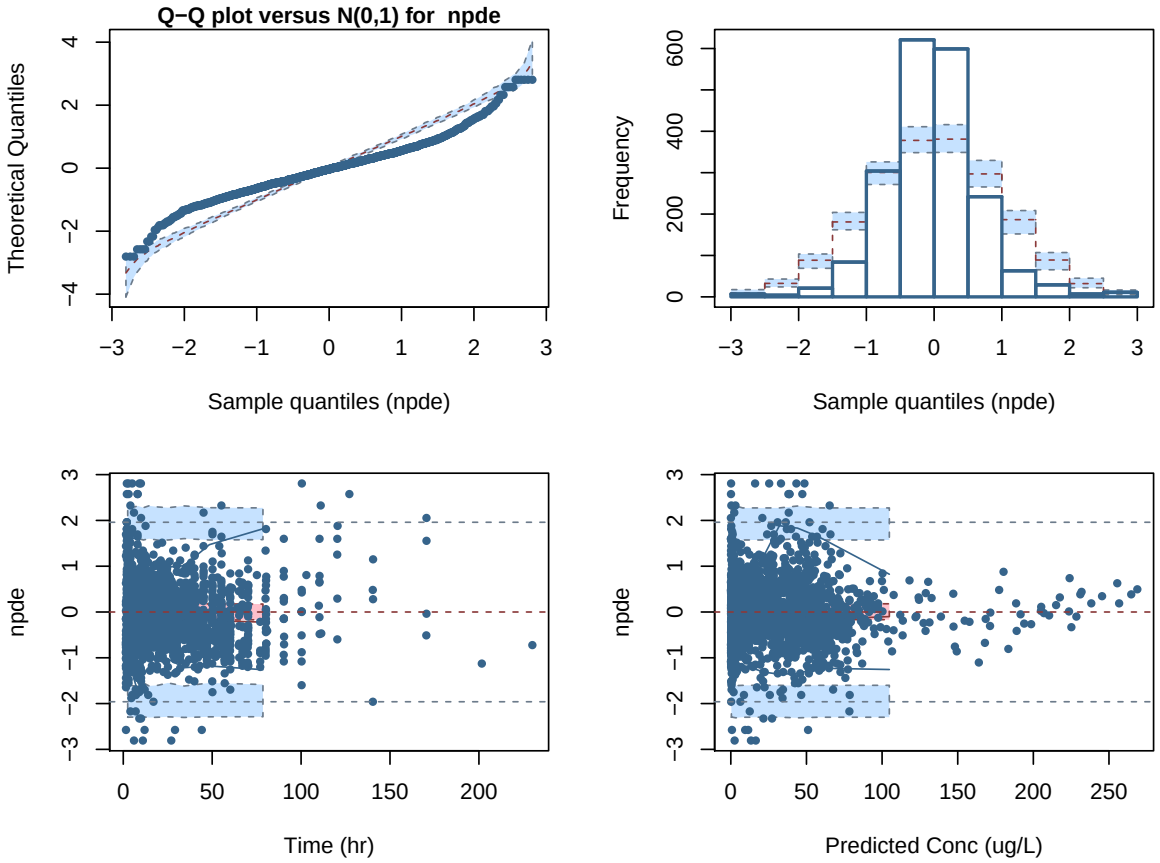

Figure 28: Default plots for remifentanil data.

Since this is a large dataset, we can get a clearer picture by removing the observations and keeping only the prediction bands and the median predictions as in fig 29. We also truncate the plot using xlim=c(0,70) to zoom on the region where there is the most data.

```
> plot(xrem,plot.type="x.scatter",xlim=c(0,70),plot.obs=FALSE)
```

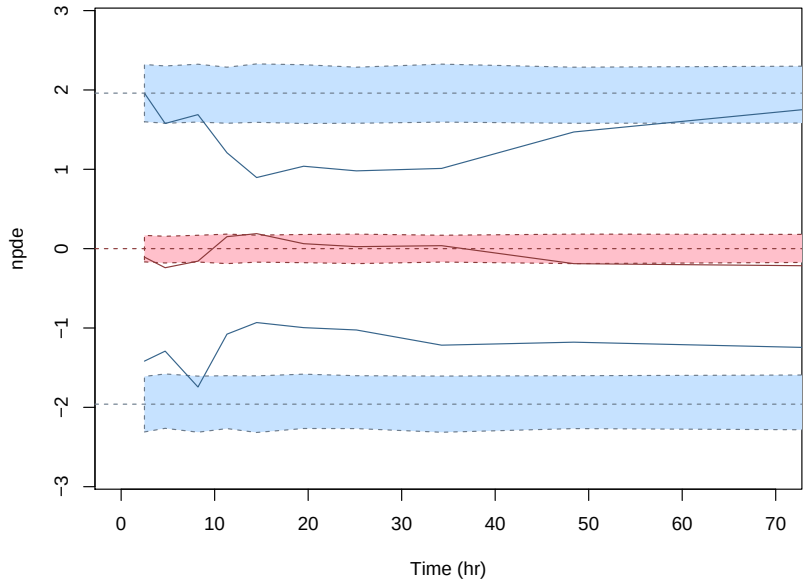

Figure 29: Remifentanil data - scatterplot of npde versus X, without observed data.

4.3.2 Covariate graphs

Scatterplot of npde versus covariates: in the presence of covariates, we can check for trends in the distribution of npde versus covariates, using the 'cov.scatter' plot type. In figure 30 there appears to be a trend towards decreasing variance of the npde with lean body mass (LBM), although the median line does not show a tendency.

```
> plot(xrem,plot.type="cov.scatter",which.cov="LBM",plot.obs=FALSE)
```

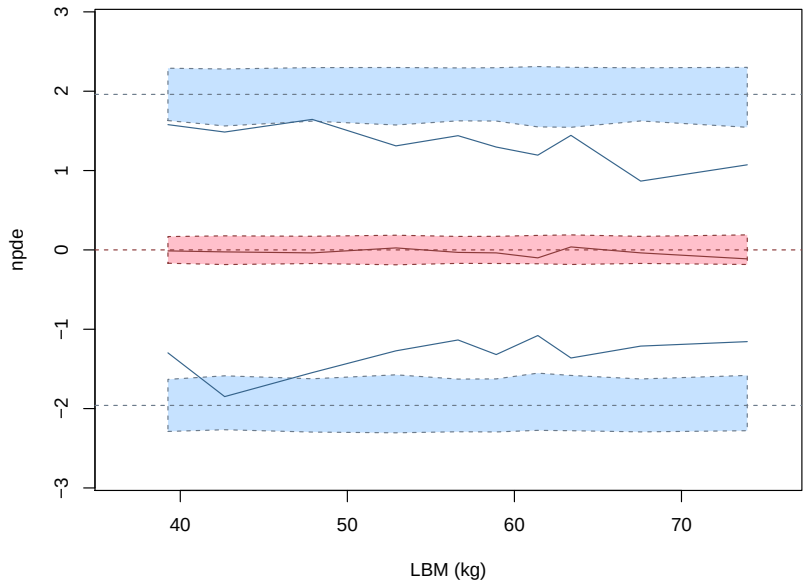

Figure 30: Remifentanil data - scatterplot of npde versus LBM, removing observations.

```
> plot(xrem,plot.type="cov.scatter",which.cov="age.grp",plot.obs=FALSE)
```

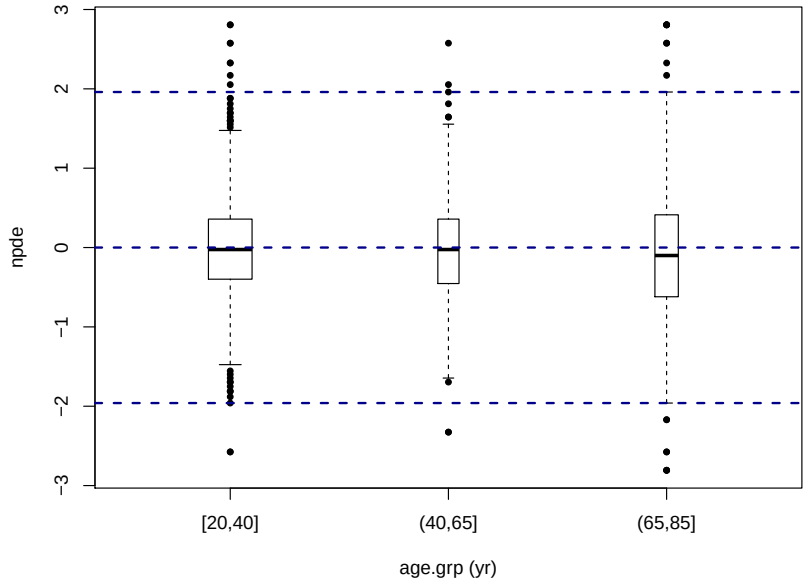

Figure 31: Remifentanil data - npde versus Age group.

Diagnostic graphs split by covariates: diagnostic graphs can also be split according to the covariate; for continuous covariates, by default 3 groups are created (first quartile <Q1, interquartile Q1-Q3, and final quartile >Q3). Figure 32 shows this for the scatterplot of npde versus time, split by LBM, while figure 33 shows the scatterplot of npde split by the categories in age group. For continuous covariates, the option ncat can be used to change the default split.

```
> plot(xrem,plot.type="x.scatter",covsplit=TRUE,which.cov="LBM",xlim=c(0,70),plot.obs=FALSE)
```

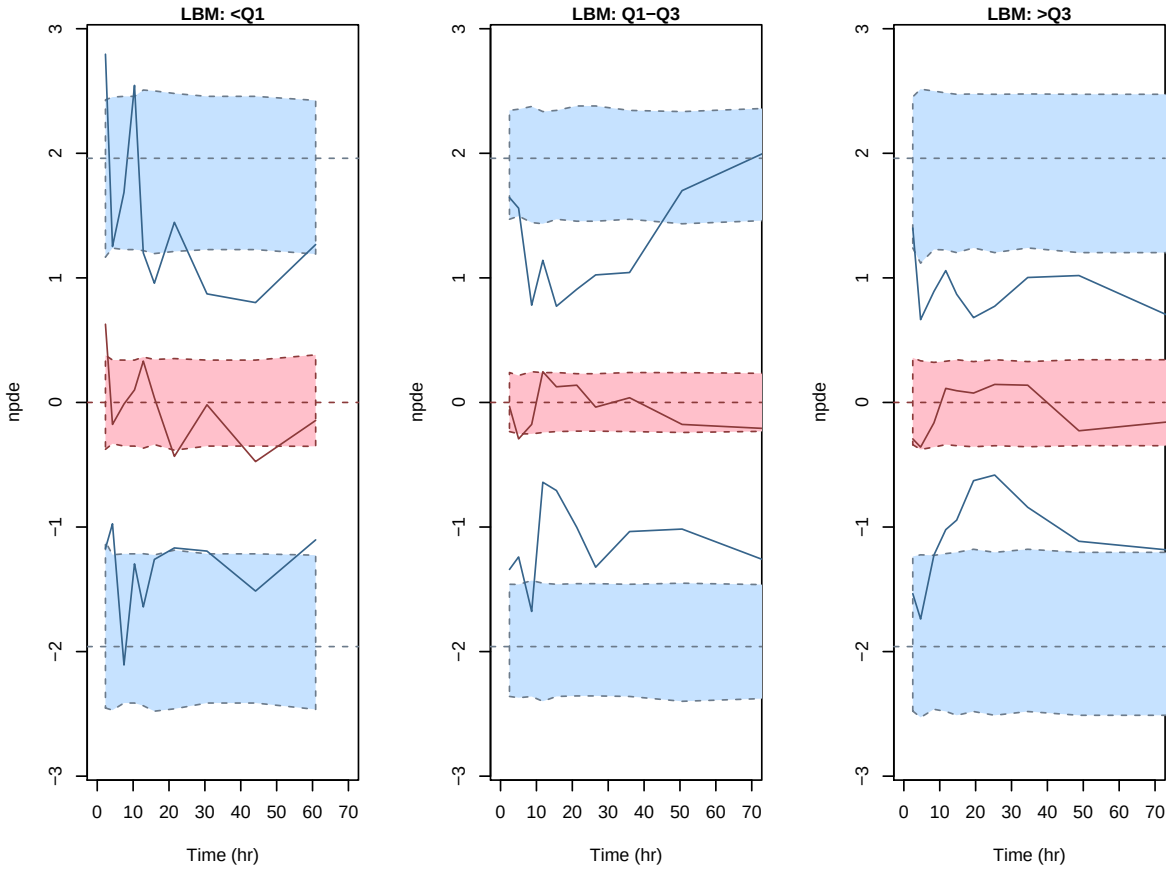

Figure 32: Remifentanil data - npde versus X, split according to LBM.

In figure 33, there is clearly a model misspecification for the lower age group (much less variability in the observed npde compared to the theoretical distribution), which could indicate that the variability is over-estimated. There is also a trend in the higher age group in the median value of npde.

```
> plot(xrem,plot.type="x.scatter",covsplit=TRUE,which.cov="age.grp",xlim=c(0,70),
      plot.obs=FALSE)
```

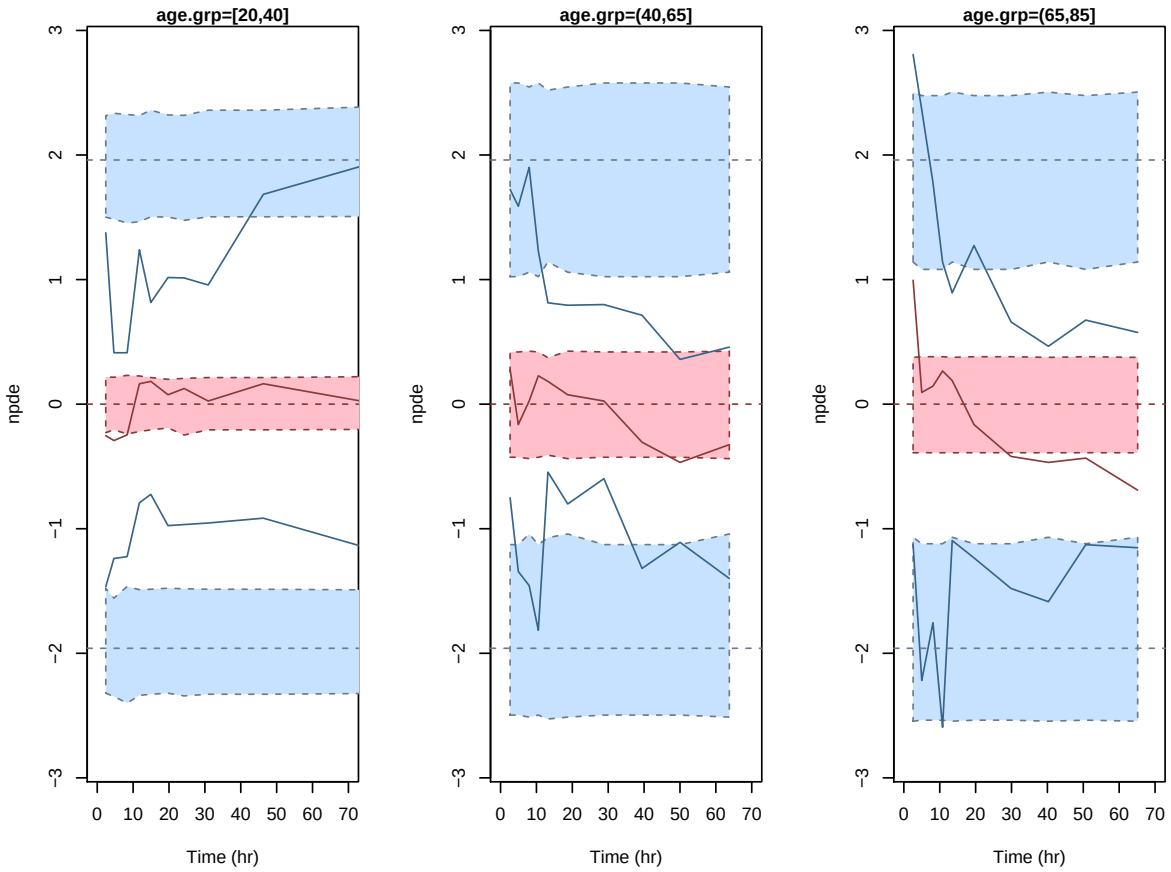

Figure 33: Remifentanil data - npde versus X, split according to Age group.

Distribution plots split by covariates:

```
> plot(xrem,plot.type="ecdf",covsplit=TRUE,which.cov="LBM",bands=TRUE,plot.obs=FALSE)
```

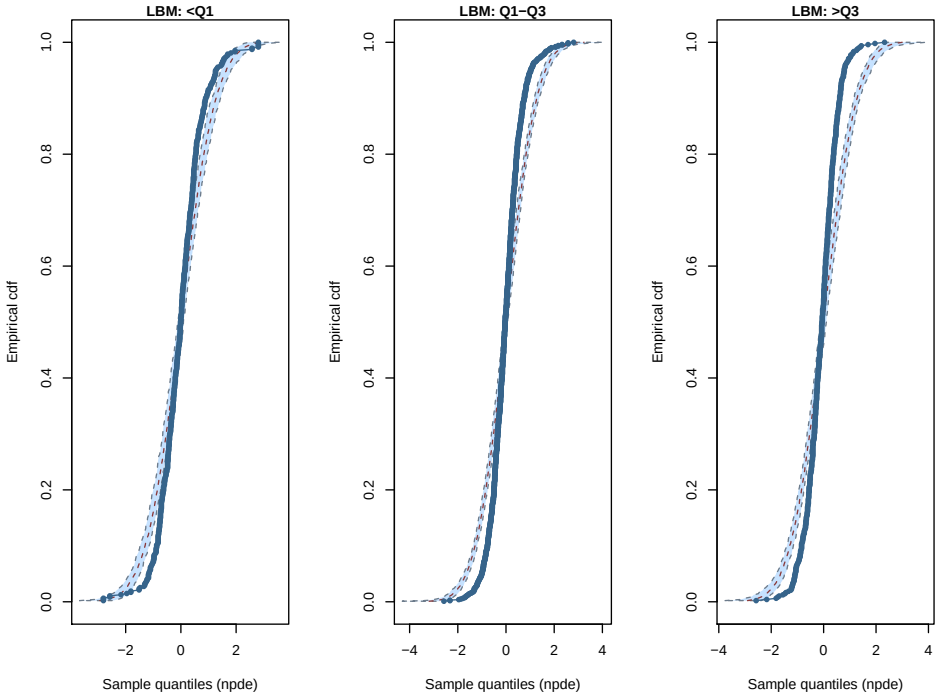

Figure 34: Remifentanil data - ecdf of npde, split according to LBM.

```
> plot(xrem,plot.type="hist",covsplit=TRUE,which.cov="age.grp",bands=TRUE,plot.obs=FALSE)
```

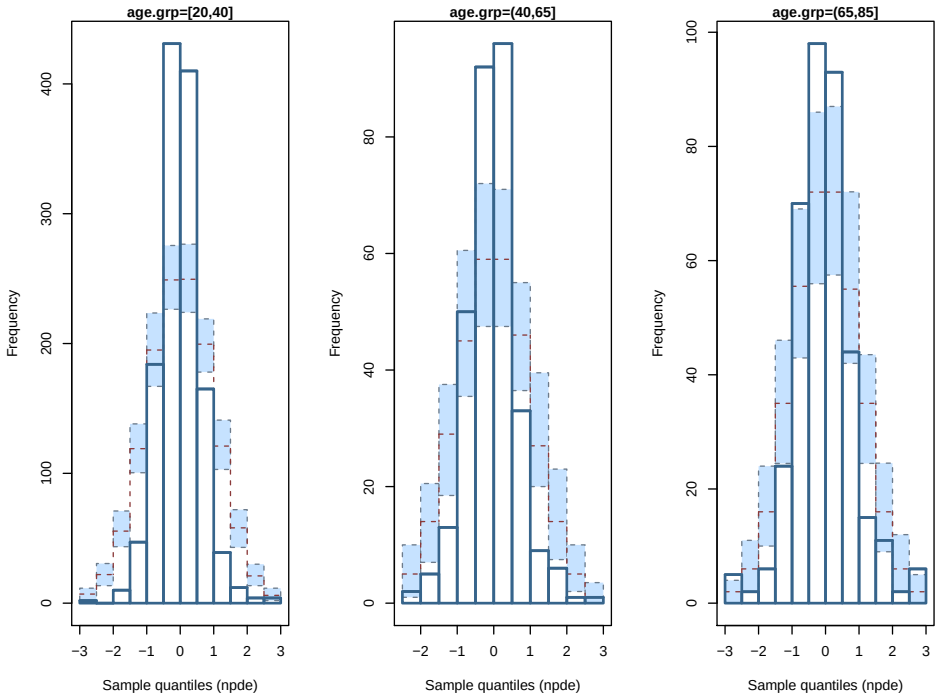

Figure 35: Remifentanil data - histogram of npde, split according to Age group.