Phxnlme: an R package that faciliates pharmacometrics workflow of Phoenix NLME analyses

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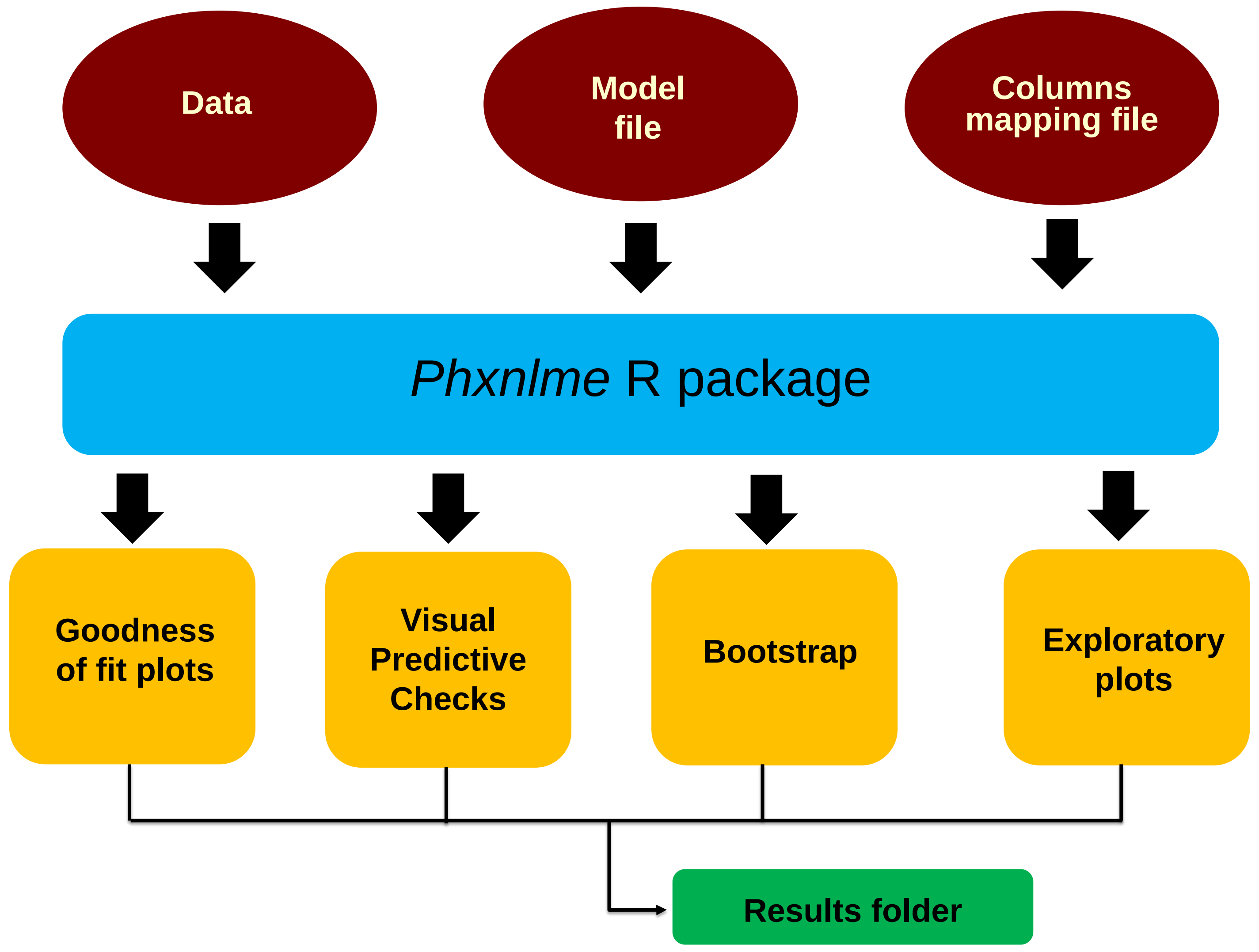
INTRODUCTION AND OBJECTIVE

- Visualization, modeling, simulation, and reporting are integral parts of the pharmacometrics workflow. Currently, tools such as *Xpose* [1], *metrumrg* [2] and *saemix* [3] provide population model building support by facilitating this process, for NONMEM and Monolix respectively, via an R interface.
- With the exponential growth of the R user and package developer community, one main advantage is that it allows these integral processes of population model building to be conducted on a freely available flexible platform, that is already frequently used for data exploration and visualization. Furthermore, the use of an R interface allows one to tap into the plethora of existing functionalities available in other R packages.
- The goal of this project was to build a comprehensive and flexible platform for the implementation of Phoenix® NLME modeling, performance of model diagnostics, visualization and simulations, through the development of an R package, *Phxnlme*.

METHODS AND RESULTS

Phxnlme is developed in R, and utilizes other R packages such as *ggplot2* and *lattice* for static graphics and *manipulate* for interactive graphics.

Figure 1: *Phxnlme* workflow



Data

Model file

Columns mapping file

Phxnlme R package

Goodness of fit plots

Visual Predictive Checks

Bootstrap

Exploratory plots

Results folder

Modeling

Executes Phoenix NLME model run on R interface

phxnlme(path, model.file, cols.file, data, method, iterlimit)

Arguments

path System path for location of the model run folder

model.file A character string that provides the model file name (*.mdl)

cols.file A character string that provides the name of the columns mapping file.

data A character string that provides the file name of the data file (*.dat, *.csv or *.txt).

method 1=QRPEM (Quasi-Random Parametric expectation-maximization)
2=IT2S-EM (Iterated 2-stage expectation-maximization)
3=FOCE L-B (First-Order Conditional Estimation, Lindstrom-Bates)
4=FO (First Order)
5=General likelihood engine. Default method is FOCE-ELS
6=Naive pooled

Visualization

1. Plotting of NLME model output

Several post-analysis visualization can be selected using the argument *plot.type*

phxplot(phxd = NULL, plot.type, cat.cov, cont.cov, forest.ci = c(0.025, 0.5, 0.975), multip = TRUE, outpdf = TRUE, scale = NULL, sel.ID, sparname)

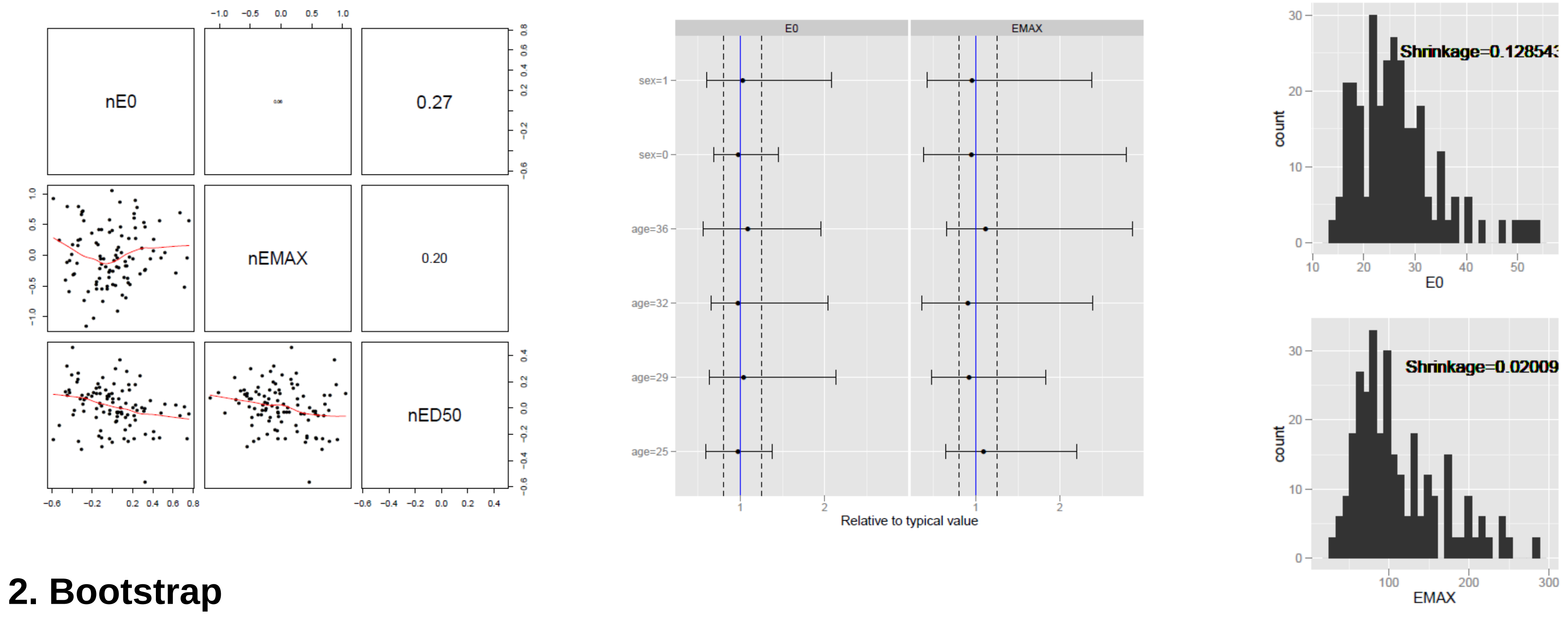
Arguments

phxd Pheonix NLME plot object. Default of NULL requires working directory to be set to model folder so Pheonix NLME output can be read.

plot.type

Options	Description
"correlation"	Correlation matrix plots of parameters
"obs.pred"	Scatterplots of observations versus prediction with loess smoothed line
"residual.scatter"	Scatterplots of weighted residual and conditional weighted versus predictions and time after dose (should be CWRED not WRED – C conditional)
"param.catcov"	Boxplots of parameters versus categorical covariates
"param.contcov"	Scatterplots of parameters versus continuous covariates
"param"	Histograms of parameters
"forest"	Forest/tornado plots of specified categorical covariates and parameters
"ind"	Individual fits
"ind.dynamic"	Dynamic plots of individual fits
"qq"	Correlation matrix plots of parameters

Figure 2: Parameter correlation, forest plot and parameter distribution plots (selected)



2. Bootstrap

Execution of nonparmateric bootstrap using *bootmodel()* and summarize results in histogram form using *bootsum()*

bootmodel(model = NULL, nodes = NULL, method = 5, niter = 1000, nboot = 500, bstrat = NULL, setseed = NULL, clean = TRUE, hold = FALSE)

bootsum(model = NULL, outpdf = TRUE, bootfl = "out0002.csv", qtype = 7, min = TRUE, showmean = FALSE, showmedian = TRUE, showcinorm = FALSE, showci = TRUE)

Various options such as the NLME estimation method, number of bootstrap samples, variables for stratification (up to 3), and other miscellaneous options such as setting of seed number and number of processors to use, are available for *bootmodel()*.

3. Visual Predictive Checks (VPC)

Take final parameter estimates from a model to perform simulation using *phxvpc.sim()* and generate plot using *phxvpc.plot()*

phxvpc.sim(path, vpcpath=NULL, ivar="t", nsim=200, pstrat=NULL, setseed=NULL, pred.corr=NULL, pi=c(0.025,0.5, 0.975), bin.option=NULL, …)

phxvpc.plot(vpcpath="", logY=FALSE, CI.Q.pred="area", obs.pch=16, …)

Options are provided in *phxvpc.sim()* for PRED/variance correction, independent variable choice, stratification (up to 3 variables), prediction intervals, various binning methods, and other miscellaneous options such as setting of seed number.

phxvpc.plot() provide functionality for easy customization of graphical features such as axis and title labels, color and size prediction intervals to create report-ready figures.

Figure 3: VPC of PK and dose-response model

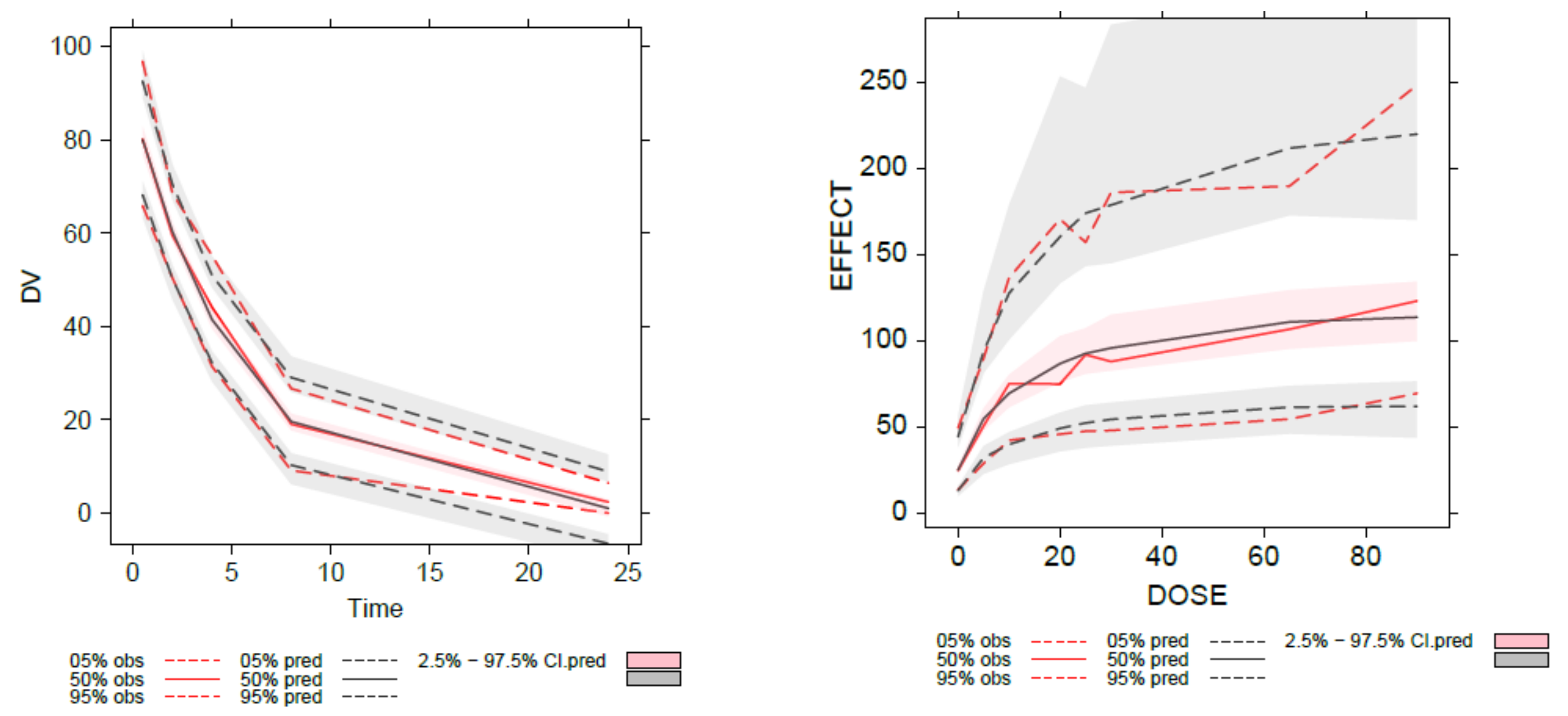
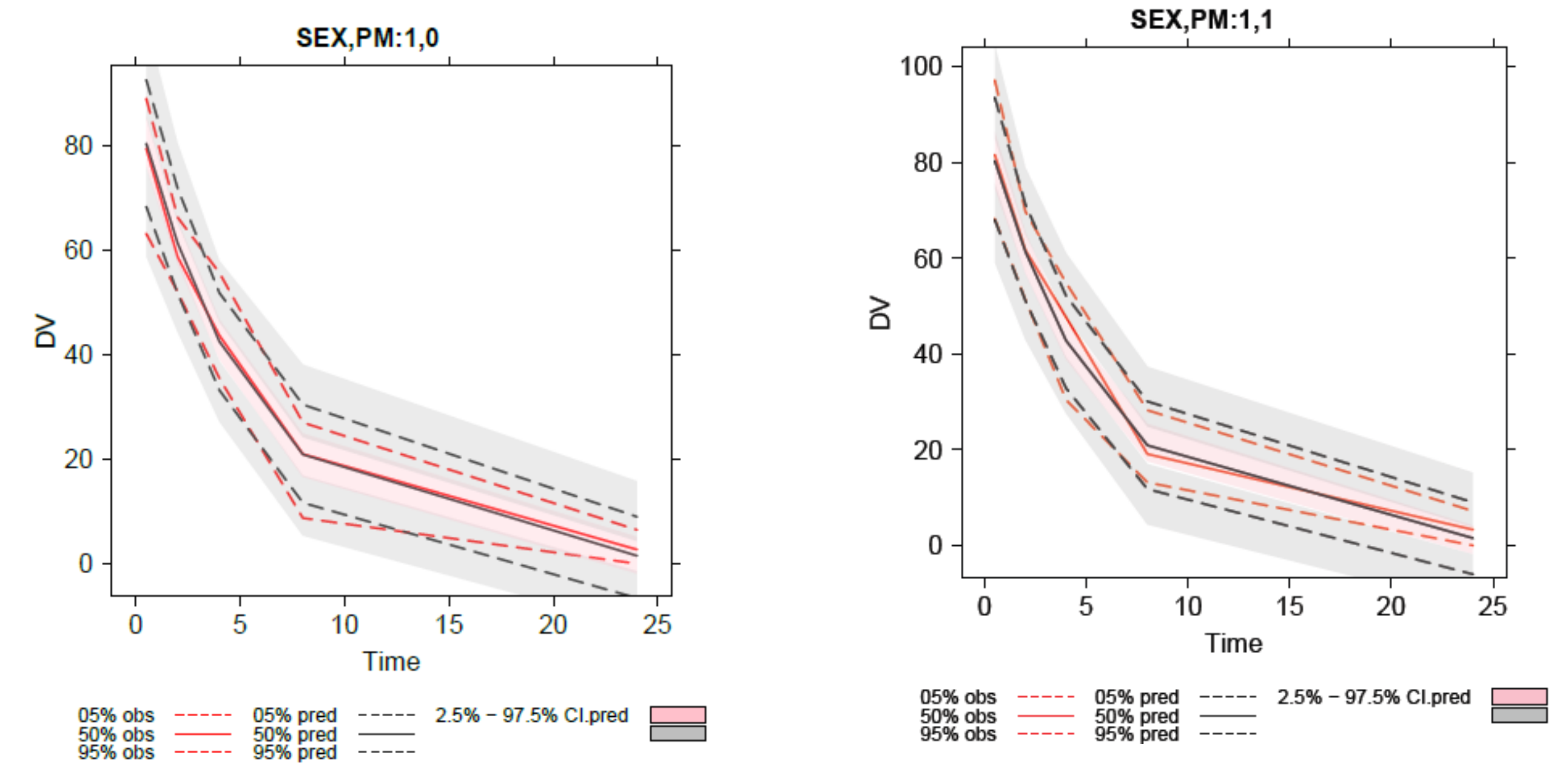


Figure 4: VPC stratified by sex and metabolizer status



CONCLUSIONS

Phxnlme is an open source package that provides users with the ability to readily implement models, simulation and bootstrap on the Phoenix NLME engine, and generate high-quality and easily customizable graphs that are currently unavailable on the Phoenix NLME graphical interface.

Phxnlme will be made freely available for download at http://cran.r-project.org/web/packages/Phxnlme/index.html.

REFERENCES

[1] http://cran.r-project.org/web/packages/xpose4/xpose4.pdf
[2] Bergsma et al., 2012 doi:10.1016/j.cmpb.2012.08.009.
[3] http://cran.r-project.org/web/packages/saemix/saemix.pdf