

Package ‘Phxnlme’

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Type Package

Title Run Phoenix NLME and Perform Post-Processing

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Description Calls 'Phoenix NLME' (non-linear mixed effects), a population modeling and simulation software, for pharmacokinetics and pharmacodynamics analyses and conducts post-processing of the results. This includes creation of various diagnostic plots, bootstrap and visual predictive checks. See <<http://www.certara.com/software/pkpd-modeling-and-simulation/phoenix-nlme/>> for more information about 'Phoenix NLME'.

LazyLoad yes

LazyData yes

License GPL-2

Repository CRAN

Depends R (>= 2.10)

Imports ggplot2, gridExtra, manipulate, grid, lattice, testthat

SystemRequirements Phoenix NLME with Phoenix Modeling Language (PML)
license

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Phxnlme-package	<i>Package 'Phxnlme'</i>
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Description

The Phxnlme package implements the Phoenix NLME program as a nonlinear mixed effects modeling tool, for pharmacokinetic and pharmacodynamic analysis. It provides access to several Maximum Likelihood engines to perform individual, population, and pooled data analyses. Nonparametric bootstrap, visual predictive checks and diagnostic and exploratory plots are options that are also provided in this package.

Details

Package:	Phxnlme
Type:	Package
Version:	1.0
Date:	2015-10-12
License:	GPL-2

Author(s)

Chay Ngee Lim <limxx356@umn.edu>

References

Phoenix NLME User Guide
 Phoenix Modeling Language Reference Guide

Examples

```
data(ex1phxd)
phxd=ex1phxd
phxplot(phxd=phxd,plot.type="residual.scatter",outpdf=FALSE)
```

bootmodel	<i>Nonparametric bootstrap</i>
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Description

Execute model bootstrapping and collect parameter estimation results.

Usage

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

Arguments

model	a character string for name of model folder
nodes	an integer value that specifies the number of processors to use. Default is no parallel processing.
method	Phoenix NLME estimation method (for more details refer to Phoenix NLME manuals), default method is 5 (FOCE-ELS)
niter	an integer value that limits the maximum number of iterations during the mode execution (default is 1000).
nboot	an integer value that provides the number of bootstrap samples (default is 200). Maximum number of bootstrap samples is 9999.
bstrat	a character vector that provides a maximum of 3 stratification variables.
setseed	an integer value that provides a fixed seed for random resampling. If omitted, seed will be assigned automatically.
clean	a logical value. If TRUE (default), the NLME executable file will be deleted after model execution, the results cannot be updated/modified. If FALSE, it makes possible to apply other estimation/simulation functions to the same model and collect the results in the same sub-folder.
hold	a logical value that determines whether the command window closes automatically after model execution or needs to be closed manually. Default is FALSE. TRUE option is currently unavailable.

Details

`phxn1me` needs to be executed prior to `bootmodel`. Working directory should be set to the folder containing Phoenix NLME output.

Value

.csv file of bootstrap results are returned.

Author(s)

Chay Ngee Lim

References

Phoenix Modeling Language Reference Guide
 Efron, B. and Tibshirani, R. (1993) An Introduction to the Bootstrap. Chapman and Hall, New York, London.

Examples

```
if(!is.null(checkphxn1me(testchk=TRUE))){
  ## Setting working directory to Model 1
  path="C:/Program Files (x86)/Pharsight/Phoenix/application/Examples/NLME Command Line/Model 1"
  model.file="lyon04.mdl"
  cols.file="COLS04.txt"
  data="EMAX02.csv"

  ## Run model fit
  phxn1me(path=path,model.file=model.file,cols.file=cols.file,data=data)

  ## Run bootstrap
  bootmodel(model="Model 1",setseed=NULL,clean=FALSE,hold=FALSE,nboot=50)
}
```

bootsum

Bootstrap summary

Description

Summarize results from nonparametric bootstrap and produce histograms for each parameters.

Usage

```
bootsum(model = NULL,
        outpdf = TRUE,
        bootfl = "out0002.csv",
        qtype = 7,
        min = TRUE,
```

```
showmean = FALSE,  
showmedian = TRUE,  
showcinorm = FALSE,  
showci = TRUE)
```

Arguments

model	Name of folder containing model
outpdf	A logical value. If TRUE (default), graphical output will be saved as PDF file.
bootfl	A character string that provides the file name of the bootmodel output. Default is "out0002.csv".
qtype	An integer value that provides type argument for quantiles calculation (see quantilestats). Default is 7.
min	A logical value. If TRUE (default), minimization summary will be included on graphical output.
showmean	A logical value. If FALSE (default), mean line will not be displayed on graphical output.
showmedian	A logical value. If TRUE (default), median line will be displayed on graphical output.
showcinorm	A logical value. If FALSE (default), 95 percent confidence intervals based on normal assumption will not be displayed on graphical output.
showci	A logical value. If TRUE (default), 95 percent confidence intervals based on 2.5th and 97.5th percentile will be displayed on graphical output.

Value

Distribution plots and summary files are returned.

Author(s)

Chay Ngee Lim

Examples

```
## Setting working directory to Model 1  
#setwd("C:/Program Files (x86)/Pharsight/Phoenix/application/Examples/NLME Command Line/Model 1")  
  
## Create summary of bootstrap runs  
#bootsum(model="Model 1")
```

checkphxn1me	<i>Checks for installation of Phoenix NLME</i>
--------------	--

Description

The function checks for the presence of the license file within "C:/.../Pharsight/Phoenix/application/Plugins/DrugModelEffects/Executables"

Usage

```
checkphxn1me(testchk=FALSE)
```

Arguments

testchk a logical value. If FALSE (default), performs check for presence of the license file. Otherwise skips test when license file is not found.

Value

Value of 1 is returned if the file is found. Otherwise, error message is generated.

Author(s)

Chay Ngee Lim

dupmodel	<i>Duplicate a selected model.</i>
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Description

Create a copy of essential files from a selected model.

Usage

```
dupmodel(path,  
          path.new,  
          modsp.file="model.spec.csv",  
          model.file,  
          cols.file,  
          data,  
          bat.file,  
          model.file.new="test.mdl",  
          cols.file.new="cols1.txt",  
          data.new="data1.txt")
```

Arguments

path	System path for location of the model to be duplicated
path.new	System path for location of destination folder.
modsp.file	An output file from phxnlme that specifies the model file, column file, data file, and Phoenix NLME estimation method used in model run. If this file exists, the following arguments <i>model.file</i> , <i>cols.file</i> , <i>data</i> , and <i>bat.file</i> will be ignored.
model.file	Optional. A character string that provides the model file name (*.mdl). This argument will be ignored if <i>modsp.file</i> exists.
cols.file	Optional. A character string that provides the name of the columns mapping file. This is an ASCII text file that contains a series of statements that define the association between model concepts and columns in a data set (Refer to Phoenix NLME manual). This argument will be ignored if <i>modsp.file</i> exists.
data	Optional. A character string that provides the file name of the data file (*.dat, *.csv or *.txt). This argument will be ignored if <i>modsp.file</i> exists.
bat.file	Optional. A character string that provides the file name of the batch file. This argument will be ignored if <i>modsp.file</i> exists.
model.file.new	A character string that provides the model file name (*.mdl) in the destination folder. Default is "test.mdl".
cols.file.new	A character string that provides the name of the columns mapping file in the destination folder. Default is "cols1.txt".
data.new	A character string that provides the file name of the data file in the destination folder. Default is "data1.txt".

Author(s)

Shuang Liang

Examples

```
if(!is.null(checkphxnlme(testchk=TRUE))){

## When modsp.file exists, specify path and destination path
path="C:/Program Files (x86)/Pharsight/Phoenix/application/Examples/NLME Command Line/Model 3"
path.new="C:/Program Files (x86)/Pharsight/Phoenix/application/Examples/NLME
Command Line/Model 3/vpc_1"

## Duplicate model
dupmodel(path, path.new)

## When modsp.file does not exist, specify path, path.new, model.file,
## cols.file, data, and bat.file
path="C:/Program Files (x86)/Pharsight/Phoenix/application/Examples/NLME Command Line/Model 3"
path.new="C:/Program Files (x86)/Pharsight/Phoenix/application/Examples/NLME
/Command Line/Model 3/vpc_1"
model.file="fm1theo.mdl"
cols.file="colstheo.txt"
data="ThBates.csv"
```

```
bat.file="RunNLME.bat"  
  
## Duplicate model  
dupmodel(path=path,path.new=path.new,model.file=model.file,cols.file=col.file  
,data=data, bat.file=bat.file)  
}
```

ex1phxd

Example output data for plotting examples.

Description

Phoenix NLME output of simulated 1-compartment PK model.

Usage

```
data(ex1phxd)
```

Details

Example output data that can be used to test [phxplot](#) functions.

Examples

```
data(ex1phxd)
```

internal functions

Generic internal functions for phxnlme

Description

These are internal functions for the phxnlme package.

Details

These are internal phxnlme functions for formatting data for phxnlme-specific plots, and reading values for simulation and creation of VPCs. Not intended for direct use.

Value

Internal functions.

Author(s)

Shuang Liang and Chay Ngee Lim

phxnlme

*Run Phoenix NLME***Description**

Run the specified model file and dataset using Phoenix NLME

Usage

```
phxnlme(inst.path = NULL, path, model.file, cols.file, data, method, iterlimit)
```

Arguments

<code>inst.path</code>	Default of NULL sets the Phoenix installation path to the default of: "C:/Program Files (x86)/Pharsight/Phoenix"
<code>path</code>	System path for location of the model run folder
<code>model.file</code>	A character string that provides the model file name (*.mdl)
<code>cols.file</code>	A character string that provides the name of the columns mapping file. This is an ASCII text file that contains a series of statements that define the association between model concepts and columns in a data set (Refer to Phoenix NLME manual).
<code>data</code>	A character string that provides the file name of the data file (*.dat, *.csv or *.txt). Note that ID column needs to be the first column.
<code>method</code>	Phoenix NLME estimation method (refer to Phoenix NLME manual). 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
<code>iterlimit</code>	An integer between 0 and 10000 that specifies the maximum number of iterations to run the main optimization routine (default is 1000). If maxiterations= 0, no optimization is run but the model is evaluated at the initial solution defined in the model file or restart file.

Details

Model folder containing the model file, columns mapping file and dataset has to be set up prior to model run. Valid license for Phoenix NLME required.

Request of empirical bayes estimates of parameters required. E.g. include the following statement in the columns mapping file:

```
table(file="parmtable.csv",V,CI)
```

(see Phoenix Modeling Language Reference Guide for details)

Note

For Phoenix installation at locations other than the default, please specify its location. Example where installation path is "C:/Program Files/Pharsight/Phoenix":

```
phxnlme(inst.path="C:/Program Files/Pharsight/Phoenix",path=path,model.file=model.file,cols.file=cols.file,data=data)
```

Author(s)

Chay Ngee Lim

References

Phoenix Modeling Language Reference Guide

Examples

```
## Specify model folder path, model.file, cols.file and data
if(!is.null(checkphxnlme(testchk=TRUE))){
  path="C:/Program Files (x86)/Pharsight/Phoenix/application/Examples/NLME Command Line/Model 1"
  model.file="lyon04.mdl"
  cols.file="COLS04.txt"
  data="EMAX02.csv"

  ## Run model fit
  phxnlme(path=path,model.file=model.file,cols.file=cols.file,data=data)
}
```

phxplot

Plotting of Phoenix NLME output

Description

Several plots, selectable by the argument *plot.type* are currently available: observations versus predictions, correlation, residuals, parameter distribution, forest plots, and individual and dynamic individual fits.

Usage

```
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,
        sparsname)
```

Arguments

phxd	Phoenix NLME plot object. Default of NULL requires working directory to be set to model folder so Phoenix NLME output can be read.
plot.type	A character string specifying the type of plot needed: "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 (if applicable) "param.catcov" - Boxplots of parameters versus categorical covariates. Argument <i>cat.cov</i> has to be defined and empirical bayes estimates of parameters have to be requested (see <i>cat.cov</i> and phxnlme). "param.contcov" - Scatterplots of parameters versus continuous covariates. Argument <i>cont.cov</i> has to be defined and empirical bayes estimates of parameters have to be requested (see <i>cont.cov</i> and phxnlme). "param" - Histograms of parameters. Empirical bayes estimates of parameters have to be requested (see phxnlme). See also <i>multip</i> . "forest" - Forest/tornado plots of specified categorical covariates and parameters. Argument <i>cat.cov</i> and <i>spaname</i> need to be defined and empirical bayes estimates of parameters have to be requested (see <i>cat.cov</i> , <i>spaname</i> and phxnlme). Note: Quantiles are computed from post-hoc values of the parameters. "ind" - Individual fits. "ind.dynamic" - Dynamic plots of individual fits. Only one subject can be dynamically plotted at a time. Requires specification of ID (see <i>sel.ID</i>). "qq" - Correlation matrix plots of parameters. Argument <i>cat.cov</i> has to be defined and empirical bayes estimates of parameters have to be requested (see <i>cat.cov</i> and phxnlme). Note: Quantiles are computed from post-hoc values of the parameters.
cat.cov	A vector of character strings, specifying categorical covariates in the dataset to be plotted. Required for forest and parameters versus categorical covariate plots (see <i>plot.type</i>).
cont.cov	A vector of character strings, specifying continuous covariates in the dataset to be plotted. Required for parameters versus continuous covariate plots (see <i>plot.type</i>)

forest.ci	A vector of numeric values, specifying the required quantiles for forest plot (see <i>plot.type</i>). Default is <code>c(0.025,0.5,0.975)</code> .
multip	A logical value that specifies if multiple parameter histograms will be generated on one page. Default is TRUE.
outpdf	A logical value that specifies if output will be generated as .pdf file. Default is TRUE.
scale	A character string that specifies "log" if log scale is required for observation versus prediction plots or individual plots. Default is NULL.
sel.ID	A numeric value that specifies the subject ID for dynamic individual plot. See <i>plot.type</i>
sparname	A vector specifying the parameters to be plotted on forest plot. See <i>plot.type</i>

Details

Working directory should be set to the folder containing Phoenix NLME output. Graphical output (*.pdf) are copied to Results folder within working directory.

Value

Returns plots.

Author(s)

Chay Ngee Lim

Examples

```
## Residual plots for Model 1
## Setting working directory
#setwd("C:/Program Files (x86)/Pharsight/Phoenix/application/Examples/NLME Command Line/Model 1")
#phxplot(plot.type="residual.scatter",outpdf=FALSE)

## Residual plots for example 1
## Loading example 1 database
data(ex1phxd)
ex1=ex1phxd

phxplot(phxd=ex1,plot.type="residual.scatter",outpdf=FALSE)

## Observations versus prediction plots
phxplot(phxd=ex1,plot.type="obs.pred",outpdf=FALSE)

## Observations versus prediction plots on double log scale
phxplot(phxd=ex1,plot.type="obs.pred",scale="log",outpdf=FALSE)

## Correlation of parameters
phxplot(phxd=ex1,plot.type="correlation",outpdf=FALSE)

## Histograms of parameters
phxplot(phxd=ex1,plot.type="param",outpdf=FALSE)
```

```

phxplot(phxd=ex1,plot.type="param.contcov",cont.cov="WT",outpdf=FALSE)

## Individual fits on log y scale
phxplot(phxd=ex1,plot.type="ind",scale="log",outpdf=FALSE)

## Dynamic plot of individual fit; requires Rstudio
#phxplot(phxd=ex1,plot.type="ind.dynamic",sel.ID=39)

## QQ plots of parameters
phxplot(phxd=ex1,plot.type="qq",outpdf=FALSE)

## Forest plots and boxplots of parameters versus categorical covariates for Model 1
#setwd("C:/Program Files (x86)/Pharsight/Phoenix/application/Examples/NLME Command Line/Model 1")
#phxplot(plot.type="forest",cat.cov=c("sex","age"),sparname=c("E0","EMAX"))
#phxplot(plot.type="param.catcov",cat.cov=c("sex","dose"))

```

phxvpc.plot

Create visual predictive check plot.

Description

This function is used to create a VPC plot using the output from the *phxvpc.sim* function. The function reads in the output files created by *phxvpc.sim* and creates a plot. The dependent variable, independent variable and stratification variable are automatically determined from the *phxvpc.sim* output files.

Usage

```

phxvpc.plot(vpcpath="",
            xlab=NULL,
            ylab=NULL,
            xlab.cex=1.3,
            ylab.cex=1.3,
            x.cex=1.3,
            y.cex=1.3,
            main.title=NULL,
            main.cex=1.3,
            xlim=NULL,
            ylim=NULL,
            obs.pt=FALSE,
            obs.pch=16,
            logY=FALSE,
            Q.obs.line=TRUE,
            Q.pred.line=TRUE,
            CI.Q.pred="area",
            CI.Q.pred.area1="pink",
            CI.Q.pred.area2="grey",

```

```

ppp=4,
legend=T,
result.path=NULL,
pred.corr=FALSE,
data.obs=NULL,
data.Q.obs=NULL,
data.Q.pred=NULL,
data.Q.CI.pred=NULL)

```

Arguments

vpcpath	A system directory where vpc simulation results are stored. It should be the same directory as specified in the <i>vpcpath</i> argument in <i>phxvpc.sim</i>
xlab	A title for the x-axis.
ylab	A title for the y-axis.
xlab.cex	Font size for the x-axis title.
ylab.cex	Font size for the y-axis title.
x.cex	Font size for the x-axis label.
y.cex	Font size for the y-axis label.
main.title	A title for the vpc plot.
main.cex	Font size for the vpc plot main title.
xlim	A numerical vector specifying x-axis limits
ylim	A numerical vector specifying y-axis limits
obs.pt	A logical value indicating whether observed data points will be presented. Default is FALSE.
obs.pch	A numerical value specifying the symbol to use when plotting observation data points.
logY	A logical value indicating whether y-axis should be log transformed. Default is FALSE.
Q.obs.line	A logical value indicating whether lines for observation percentiles will be presented. Default is TRUE.
Q.pred.line	A logical value indicating whether lines for prediction percentiles will be presented. Default is TRUE.
CI.Q.pred	A string of either "lines" or "area" (default) specifying whether the confidence intervals of prediction percentiles (as lines or a shaded area) should be added to the plot. NULL means no confidence intervals for prediction percentiles.
CI.Q.pred.area1	A string specifying the color of the shaded area of the confidence intervals for 50th prediction percentile.
CI.Q.pred.area2	A string specifying the color of the shaded area of the confidence intervals for 5th and 95th prediction percentiles.
ppp	Panel per page. Either 1 or 4 (default) specifying the number of panels per page when multiple panels are generated as a result of stratification.

legend	A logical value indicating whether figure legend will be presented. Default is TRUE.
result.path	A system directory where vpc plot will be stored. If NULL (default), it will be set as "../Results", in which ".." is the parent folder of the vpcpath folder.
pred.corr	Prediction corrected VPC is not yet implemented in this function.
data.obs	Optional. Default is NULL. Observed data points.
data.Q.obs	Optional. Default is NULL. Data of bserveation quantiles.
data.Q.pred	Optional. Default is NULL. Data of predicted quantiles.
data.Q.CI.pred	Optional. Default is NULL. Data of confidence intervals for predicted quantiles.

Details

[phxvpc.sim](#) must be first executed. The vpc plot will be a pdf file with the same name as the folder that contains *phxvpc.sim* output. The pdf plot will be stored in the folder specified by the *result.path* argument.

Value

A plot or a list of plots.

Author(s)

Shuang Liang

Examples

```
## Note: before plotting, first run model fit using phxnlme,
## next perform VPC simulation using either phxvpc.sim or simmodel.
#setwd("C:/Program Files (x86)/Pharsight/Phoenix/application/Examples/NLME Command Line/Model 3")
#phxvpc.plot(vpcpath="vpc_1")
## or
#phxvpc.plot(vpcpath="C:/Program Files (x86)/Pharsight/Phoenix
#/application/Examples/NLME Command Line/Model 3/vpc_1")

## without showing lines for percentiles of the observation data points
#phxvpc.plot(vpcpath="vpc_1", Q.obs.line=F)

## showing lines for predicted percentiles
#phxvpc.plot(vpcpath="vpc_1", Q.pred.line=T)

## using lines instead of shaded area to indicate the confidence
## intervals for the predicted percentiles
#phxvpc.plot(vpcpath="vpc_1", CI.Q.pred="lines")

## changing color of shaded area
#phxvpc.plot(vpcpath="vpc_1", CI.Q.pred="area", CI.Q.pred.area1="green", CI.Q.pred.area2="yellow")

## changing x-axis limits
#phxvpc.plot(vpcpath="vpc_1", xlim=c(0,10))
```

phxvpc.sim	<i>Visual predictive check data simulation using Phoenix NLME based on final parameter estimates.</i>
------------	---

Description

Use final parameter estimates of a model to simulate data, calculate statistics for visual predictive check, and collect the results.

Important Note: in the current version of phxvpc.sim, the model.file (.mdl) must follow a specific format.

See the **Details** section: **Instruction on model file.**

Usage

```
phxvpc.sim(path,
            vpcpath=NULL,
            ivar="t",
            nsim=200,
            pstrat=NULL,
            setseed=NULL,
            pred.corr=NULL,
            var.corr=FALSE,
            pi=c(0.025,0.5, 0.975),
            pi.ci=c(0.025, 0.975),
            bin.option=NULL,
            bin.bound=NULL,
            bin.center=NULL,
            modsp.file="model.spec.csv",
            out.file="out0001.txt",
            clean=FALSE,
            hold=FALSE)
```

Arguments

path	System directory for location of the model run folder
vpcpath	System directory where vpc simulation results will be stored. If NULL(default), a subfolder vpc n will be created under the model run folder (path), in which n is a number. If vpc n subfolder already exists, n will automatically increase by 1 until no identical existing folder can be found.
ivar	Independent variable (x-axis). Default is "t", which is the independent variable when the structure model is set to any of Phoenix build-in PK models. Other options include "TAD", "PRED", or any user specified input. If user specified input is used, this variable must be in data set and defined in cols.file for model fit.
nsim	An integer value specifying the number of simulation replicates. Default is 200.

pstrat	A character vector that provides a maximum of 3 stratification variables. The vpc will stratify the data on unique values of the specified variable, and perform separate analyses on each set. Variables must be in data set and defined in cols.file for model fit. (Refer to Phoenix NLME manual for additional details regarding cols.file)
setseed	An integer value that provides a fixed seed for random resampling. If omitted, a random seed will be assigned automatically.
pred.corr	Optional. A character string specifying the options of how prediction correction is performed on dependent variable values before computing vpc results. Options are "proportional" or "additive", which can be shorten, with the minimal length of "prop" and "add", respectively. Not case sensitive. Default is NULL.
var.corr	A logical value. If TRUE, perform variability correction on dependent variable values before computing VPC results. Default is FALSE. Note: this option is only functional when the argument <i>pred.corr</i> is used.
pi	Default is c(0.025,0.5, 0.975). A vector of values that describe the prediction percentile that should be calculated. The prediction percentiles are displayed by the Q.pred.line option in phxvpc.plot
pi.ci	Default is c(0.025, 0.975). A vector of two values that describe the confidence interval of the prediction percentile that should be calculated. These values are used to specify the boundaries of the CI.Q.pred option in phxvpc.plot
bin.option	A character string that provide the binning options for simulation. Default is NULL. Alternative options are "K-means", "centers", and "boundaries", which can be shorten, with the minimal length of "k", "cent", and "bound", respectively. Not case sensitive.
bin.bound	A numeric vector that provides binning boundaries when bin.option "boundaries" is used. This option will be ignored when other bin.option is selected. Default is NULL.
bin.center	A numeric vector that provides centers for all bins when bin.option "centers" is used. This option will be ignored when other bin.option is selected. Default is NULL.
clean	A logical value. Default is FALSE. If TRUE, the NLME executable file in the vpcpath folder will be deleted after model execution, the results cannot be updated/modified. If FALSE, it makes possible to apply other estimation/simulation functions in the same folder.
hold	A logical value that determines command window behavior. Currently, it is not implemented.
modsp.file	An output file from phxnlme that specifies the model file, column file, data file, and Phoenix NLME estimation method used in model run. This file is required.
out.file	An output file from phxnlme that contains the final parameter estimates of model run. This file is required so that final parameter estimates can be obtained to simulate data.

Details

[phxnlme](#) must be executed before using [phxvpc.sim](#).

Instruction on model file Model file (.mdl) must follow a certain format for phxvpc.sim to use final model estimates for simulation. First, the following blocks (fixed, ranef, stparm, error, observe) must be in the order of fixed->ranef(optional)->stparm->error->observe. Second, if the ranef block only contains diagonal elements, each element must be in a separate row. Examples are as following:

##correct format of model file:

```
test(){
  covariate(FEMALE)
  covariate(DOSE)      ##no restriction for covariate
  fixef(
    tvE0      = c(, 20,)
    tvEMAX    = c(, 120,)
    ED50MALE  = c(, 15,)
    ED50FACTOR = c(, 1,)
  )
  ranef(
    ## each element must be in a separate row
  diag(nE0, nEMAX, nED50) = c(1,
                                1,
                                1)
  )
  stparm(
    E0      = tvE0      * exp(nE0)
    EMAX    = tvEMAX    * exp(nEMAX)
    ED50    = ED50MALE * exp(nED50) * ED50FACTOR^FEMALE
  )
  E = E0 + EMAX * DOSE / (DOSE + ED50)
  error (EPS1 = 10)
  observe(EOBS = E + EPS1)
}
```

Author(s)

Shuang Liang

Examples

```
## Note: .mdl file must be in the format as specified in the details section.
## Alternatively, use simmodel for VPC simulation.
## Note that pheno2.mdl needs to be modified to follow the specified format prior to
## running examples below

if(!is.null(checkphxnlme(testchk=TRUE))){
  path="C:/Program Files (x86)/Pharsight/Phoenix/application/Examples/NLME Command Line/Model 5"
  model.file="pheno2.mdl"
  cols.file="colspheeno2.txt"
  data="pheno2.csv"

  ## Run model fit
  phxnlme(path=path,model.file=model.file,cols.file=cols.file,data=data)
```

```

## VPC simulation
#phxvpc.sim(path)
}

## Change confidence interval of prediction percentiles
#phxvpc.sim(path, pi.ci=c(0.05, 0.95))

## Bin by boundaries
#phxvpc.sim(path, bin.option="bound", bin.bound=c(0, 0.5, 4, 8, 12))

## Note: lyon04.mdl needs to be modified to specified format prior to running example below
## For models not using build-in PK structure model
## Run model fit
if(!is.null(checkphxnlme(testchk=TRUE))){
path="C:/Program Files (x86)/Pharsight/Phoenix/application/Examples/NLME Command Line/Model 1"
model.file="lyon04.mdl"
cols.file="COLS04.txt"
data="EMAX02.csv"
phxnlme(path=path,model.file=model.file,cols.file=cols.file,data=data)

#phxvpc.sim(path, ivar="DOSE")

## Stratified VPC, 1 covariate
#phxvpc.sim(path, ivar="DOSE", pstrat="FEMALE")

## Stratified VPC, 3 covariates (covariates must be included in bot data and cols.file)
#phxvpc.sim(path, pstrat=c("SEX", "AGE", "DOSE"))
}

```

simmodel

Visual predictive check data simulation using Phoenix NLME based on user-provided parameter values.

Description

Users need to provide values for fixed and random effect parameters to simulate data, calculate statistics for visual predictive check, and collect the results. Arguments in this function are similar to those in [phxvpc.sim](#). In contrast to [phxvpc.sim](#), there is no restriction on model file format. However, users will need to change the initial values of parameters to model final estimates, execute [phxnlme](#) before executing *simmodel*. See the **Examples** section for details.

Usage

```

simmodel(vpcpath,
         nsim=200,
         pstrat=NULL,
         setseed=NULL,
         pred.corr=NULL,

```

```

var.corr=FALSE,
pi=c(0.025,0.5, 0.975),
pi.ci=c(0.025, 0.975),
bin.option=NULL,
bin.bound=NULL,
bin.center=NULL,
clean=FALSE,
hold=FALSE,
ivar="t",
model.file="test.mdl",
cols.file="cols1.txt",
data="data1.txt")

```

Arguments

vpcpath	System directory where vpc simulation results will be stored. Users must specify this argument.
ivar	Independent variable (x-axis). Default is "t", which is the independent variable when the structure model is set to any of Phoenix build-in PK models. Other options include "TAD", "PRED", or any user specified input. If user specified input is used, this variable must be in data set and defined in cols.file for model fit.
nsim	An integer value specifying the number of simulation replicates. Default is 200.
pstrat	A character vector that provides a maximum of 3 stratification variables. The vpc will stratify the data on unique values of the specified variable, and perform separate analyses on each set. Variables must be in data set and defined in cols.file for model fit. (Refer to Phoenix NLME manual for additional details regarding cols.file)
setseed	An integer value that provides a fixed seed for random resampling. If omitted, a random seed will be assigned automatically.
pred.corr	Optional. A character string specifying the options of how prediction correction is performed on dependent variable values before computing vpc results. Options are "proportional" or "additive", which can be shorten, with the minimal length of "prop" and "add", respectively. Not case sensitive. Default is NULL.
var.corr	A logical value. If TRUE, perform variability correction on dependent variable values before computing vpc results. Default is FALSE. Note: this option is only functional when the argument <i>pred.corr</i> is used.
pi	Default is c(0.025,0.5, 0.975). A vector of values that describe the prediction percentile that should be calculated. The prediction percentiles are displayed by the Q.pred.line option in phxvpc.plot
pi.ci	Default is c(0.025, 0.975). A vector of two values that describe the confidence interval of the prediction percentile that should be calculated. These values are used to specify the boundaries of the CI.Q.pred option in phxvpc.plot
bin.option	A character string that provide the binning options for simulation. Default is NULL. Alternative options are "K-means", "centers", and "boundaries", which can be shorten, with the minimal length of "k", "cent", and "bound", respectively. Not case sensitive.

bin.bound	A numeric vector that provides binning boundaries when bin.option "boundaries" is used. This option will be ignored when other bin.option is selected. Default is NULL.
bin.center	A numeric vector that provides centers for all bins when bin.option "centers" is used. This option will be ignored when other bin.option is selected. Default is NULL.
model.file	A character string that provides the model file name (*.mdl). Default is "test.mdl".
cols.file	A character string that provides the name of the columns mapping file. This is an ASCII text file that contains a series of statements that define the association between model concepts and columns in a data set (Refer to Phoenix NLME manual).Default is "cols.txt".
data	A character string that provides the file name of the data file. This is an ASCII text file(*.txt). Default is "data.txt".
clean	A logical value. Default is FALSE. If TRUE, the NLME executable file in the vpcpath folder will be deleted after model execution, the results cannot be updated/modified. If FALSE, it makes possible to apply other estimation/simulation functions in the same folder.
hold	A logical value that determines command window behavior. Currently, it is not implemented.

Details

In order to perform visual predictive check, final model estimates must be applied as initial estimates in the model control file. [phxnlme](#) must be executed before using [simmodel](#).

Author(s)

Shuang Liang

Examples

```
## Run model fit
if(!is.null(checkphxnlme(testchk=TRUE))){

path="C:/Program Files (x86)/Pharsight/Phoenix/application/Examples/NLME Command Line/Model 5"
model.file="pheno2.mdl"
cols.file="colspheo2.txt"
data="pheno2.csv"
phxnlme(path=path,model.file=model.file,cols.file=cols.file,data=data)

## Manually create directory for duplicate model
dir.create(paste("C:/Program Files (x86)/Pharsight/Phoenix/application/"
,"Examples/NLME Command Line/Model 3/vpc_1",sep=""))

## Duplicate the model
path.new=paste("C:/Program Files (x86)/Pharsight/Phoenix/application/"
,"Examples/NLME Command Line/Model 3/vpc_1",sep="")
dupmodel(path, path.new)
```

```
## After duplicating model, change parameter initial values in .mdl file
## to the final parameter estimates obtained from running model fit.

simmodel(vpcpath=path.new)

## Change confidence interval of prediction percentiles
simmodel(vpcpath=path.new, pi.ci=c(0.05, 0.95))

## Bin by boundaries
simmodel(vpcpath=path.new, bin.option="bound", bin.bound=c(0, 0.5, 4, 8, 12))
}

if(!is.null(checkphxnlme(testchk=TRUE))){

## For models not using build-in PK structure model
## Run model fit
path="C:/Program Files (x86)/Pharsight/Phoenix/application/Examples/NLME Command Line/Model 1"
model.file="lyon04.mdl"
cols.file="COLS04.txt"
data="EMAX02.csv"
phxnlme(path=path,model.file=model.file,cols.file=cols.file,data=data)

dupmodel(path, path.new)

## After duplicating model, change parameter initial values in .mdl file
## to the final parameter estimates obtained from running model fit.
simmodel(vpcpath=path.new, ivar="DOSE")

## Stratified VPC, 1 covariate
simmodel(path, ivar="DOSE", pstrat="FEMALE")

## Stratified VPC, 3 covariates (covariates must be included in data and cols.file)
simmodel(path, pstrat=c("SEX", "AGE", "DOSE"))
}
```

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