Package 'nlmixr'

March 27, 2022

Type Package

Title Nonlinear Mixed Effects Models in Population PK/PD

Depends R (>= 4.0)

Imports Rcpp (>= 0.12.3), brew, parallel, lbfgsb3c, dparser, methods, ggplot2, rex, minqa, Matrix, n1qn1 (>= 6.0.1-10), fastGHQuad, RxODE(>= 1.1.5), nlme, magrittr, backports, symengine

Suggests Deriv, Rvmmin, broom.mixed, crayon, knitr, data.table, devtools, digest, dotwhisker, dplyr, expm, flextable, ggtext, patchwork, gridExtra, huxtable, lattice, lbfgs, lotri, madness, matrixcalc, nloptr, officer, pkgdown, reshape2, rmarkdown, testthat, tidyr, ucminf, vpc (>= 1.1.0), xgxr, yaml, xpose, generics, tibble, checkmate, cli, qs, covr, forecast, latticeExtra

Version 2.0.7

Description Fit and compare nonlinear mixed-effects models in differential equations with flexible dosing information commonly seen in pharmacokinetics and pharmacodynamics (Almquist, Leander, and Jirstrand 2015 <doi:10.1007/s10928-015-9409-1>). Differential equation solving is by compiled C code provided in the 'RxODE' package (Wang, Hallow, and James 2015 <doi:10.1002/psp4.12052>).

License GPL (>= 2)

NeedsCompilation yes

LinkingTo dparser(>= 0.1.8), RxODE(>= 1.0.0-0), RcppEigen (>= 0.3.3.3.0), lbfgsb3c, Rcpp, BH, StanHeaders(>= 2.18.0), RcppArmadillo (>= 0.5.600.2.0)

URL https://github.com/nlmixrdevelopment/nlmixr

LazyData true

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R topics documented:

`addCovariate` *Add covariate expression to a function string*

Description

Add covariate expression to a function string

Usage

```
addCovariate(funstring, varName, covariate, theta, isLog)
```

Arguments

`funstring`	a string giving the expression that needs to be modified
`varName`	the variable to which the given string corresponds to in the model expression
`covariate`	the covariate expression that needs to be added (at the appropriate place)
`theta`	a list of names of the 'theta' parameters in the 'fit' object
`isLog`	a boolean signifying the presence of log-transformation in the funstring

Value

returns the modified string with the covariate added to function string

Author(s)

Vipul Mann, Matthew Fidler

addCovVar *Adding covariate to a given variable in an nlmixr model expression*

Description

Adding covariate to a given variable in an nlmixr model expression

Usage

```
addCovVar(
  fitobject,
  varName,
  covariate,
  norm = c("median", "mean", "autoscale"),
  norm_type = c("mul", "div", "sub", "add", "autoscale"),
  categorical = FALSE,
  isHS = FALSE,
  initialEst = 0,
  initialEstLB = -Inf,
  initialEstUB = Inf
)
```

Arguments

fitobject	an nlmixr 'fit' object
varName	a string giving the variable name to which covariate needs to be added
covariate	a string giving the covariate name; must be present in the data used for 'fit'
norm	the kind of normalization to be used while normalizing covariates; must be either 'mean' or 'median'
norm_type	a string defining operator to be used for transforming covariates using 'norm'; must be one among 'mul', 'div', 'sub', 'add'
categorical	a boolean indicating if the 'covariate' is categorical
isHS	a boolean indicating if 'covariate' is of Hockey-stick kind
initialEst	the initial estimate for the covariate parameters to be estimated; default is 0
initialEstLB	a lower bound for the covariate parameters to be estimated; default is -Inf
initialEstUB	an upper bound for the covariate parameters to be estimated; default is Inf

Value

a list with the updated model expression and data with columns corresponding to normalized covaraite(s) appended

Author(s)

Vipul Mann, Matthew Fidler

addCwres *Add CWRES*

Description

This returns a new fit object with CWRES attached

Usage

```
addCwres(fit, updateObject = TRUE, envir = parent.frame(1))
```

Arguments

fit	nlmixr fit without WRES/CWRES
updateObject	Boolean indicating if the original fit object should be updated. By default this is true.
envir	Environment that should be checked for object to update. By default this is the global environment.

Value

fit with CWRES

Author(s)

Matthew L. Fidler

Examples

```
one.cmt <- function() {
  ini({
    ## You may label each parameter with a comment
    tka <- 0.45 # Log Ka
    tcl <- log(c(0, 2.7, 100)) # Log Cl
    ## This works with interactive models
    ## You may also label the preceding line with label("label text")
    tv <- 3.45; label("log V")
    ## the label("Label name") works with all models
    eta.ka ~ 0.6
    eta.cl ~ 0.3
    eta.v ~ 0.1
    add.sd <- 0.7
  })
  model({
    ka <- exp(tka + eta.ka)
    cl <- exp(tcl + eta.cl)
```

```
    v <- exp(tv + eta.v)
    linCmt() ~ add(add.sd)
  })
}

f <- try(nlmixr(one.cmt, theo_sd, "saem"))

print(f)

# even though you may have forgotten to add the cwres, you can add it to the data.frame:

if (!inherits(f, "try-error")) {
  f <- try(addCwres(f))
  print(f)
}

# Note this also adds the FOCEi objective function
```

---

addNpde *NPDE calculation for nlmixr*

Description

NPDE calculation for nlmixr

Usage

```
addNpde(
  object,
  updateObject = TRUE,
  table = tableControl(),
  ...,
  envir = parent.frame(1)
)
```

Arguments

object	nlmixr fit object
updateObject	Boolean indicating if original object should be updated. By default this is TRUE.
table	‘tableControl()‘ list of options
...	Other ignored parameters.
envir	Environment that should be checked for object to update. By default this is the global environment.

Value

New nlmixr fit object

Author(s)

Matthew L. Fidler

Examples

```
one.cmt <- function() {
  ini({
    ## You may label each parameter with a comment
    tka <- 0.45 # Log Ka
    tcl <- log(c(0, 2.7, 100)) # Log Cl
    ## This works with interactive models
    ## You may also label the preceding line with label("label text")
    tv <- 3.45; label("log V")
    ## the label("Label name") works with all models
    eta.ka ~ 0.6
    eta.cl ~ 0.3
    eta.v ~ 0.1
    add.sd <- 0.7
  })
  model({
    ka <- exp(tka + eta.ka)
    cl <- exp(tcl + eta.cl)
    v <- exp(tv + eta.v)
    linCmt() ~ add(add.sd)
  })
}

f <- nlmixr(one.cmt, theo_sd, "saem")

# even though you may have forgotten to add the NPDE, you can add it to the data.frame:

f <- addNpde(f)
```

---

addTable *Add table information to nlmixr fit object without tables*

Description

Add table information to nlmixr fit object without tables

Usage

```
addTable(
  object,
```

```
  updateObject = FALSE,
  data = object$dataSav,
  thetaEtaParameters = .foceiThetaEtaParameters(object),
  table = tableControl(),
  keep = NULL,
  drop = NULL,
  envir = parent.frame(1)
)
```

Arguments

object	nlmixr family of objects
updateObject	Update the object (default FALSE)
data	Saved data from
thetaEtaParameters	Intenral theta/eta parameters
table	a ‘tableControl()‘ list of options
keep	Character Vector of items to keep
drop	Character Vector of items to drop or NULL
envir	ENvironment to search for updating

Value

Fit with table information attached

Author(s)

Matthew Fidler

Examples

```
one.cmt <- function() {
  ini({
    ## You may label each parameter with a comment
    tka <- 0.45 # Log Ka
    tcl <- log(c(0, 2.7, 100)) # Log Cl
    ## This works with interactive models
    ## You may also label the preceding line with label("label text")
    tv <- 3.45; label("log V")
    ## the label("Label name") works with all models
    eta.ka ~ 0.6
    eta.cl ~ 0.3
    eta.v ~ 0.1
    add.sd <- 0.7
  })
  model({
```

```
    ka <- exp(tka + eta.ka)
    cl <- exp(tcl + eta.cl)
    v <- exp(tv + eta.v)
    linCmt() ~ add(add.sd)
  })
}

# run without tables step
f <- nlmixr(one.cmt, theo_sd, "saem", control=list(calcTables=FALSE))

print(f)

# Now add the tables

f <- addTable(f)

print(f)
```

`as.dynmodel` *Convert fit to classic dynmodel object*

Description

Convert fit to classic dynmodel object

Usage

```
as.dynmodel(x)
```

Arguments

`x`	nlmixr object to convert to dynmodel object

Value

dynmodel

Author(s)

Matthew Fidler

`as.focei` *Convert fit to FOCEi style fit*

Description

Convert fit to FOCEi style fit

Usage

```
as.focei(
  object,
  uif,
  pt = proc.time(),
  ...,
  data,
  calcResid = TRUE,
  table = tableControl(),
  IDlabel = NULL
)

## S3 method for class 'nlmixrNlme'
as.focei(
  object,
  uif,
  pt = proc.time(),
  ...,
  data,
  calcResid = TRUE,
  nobs2 = 0,
  keep = NULL,
  drop = NULL,
  table = tableControl(),
  IDlabel = NULL
)
```

Arguments

`object`	Fit object to convert to FOCEi-style fit.
`uif`	Unified Interface Function
`pt`	Proc time object
`...`	Other Parameters
`data`	The data to pass to the FOCEi translation.
`calcResid`	A boolean to indicate if the CWRES residuals should be calculated
`table`	A list of table options
`IDlabel`	labels for the ID column; used to change the IDs back to their normal valuesr

nobs2	Number of observations without EVID=2
keep	Columns to keep from either the input dataset. For the input dataset, if any records are added to the data LOCF (Last Observation Carried forward) imputation is performed.
drop	Columns to drop from the output

Value

A FOCEi fit style object.

Author(s)

Matthew L. Fidler

---

backwardSearch *Backward covariate search*

Description

Backward covariate search

Usage

```
backwardSearch(
  covInfo,
  fitorig,
  fitupdated,
  pVal = 0.01,
  reFitCovars = FALSE,
  outputDir,
  restart = FALSE
)
```

Arguments

covInfo	a list containing information about each variable-covariate pair
fitorig	the original 'fit' object before forward search
fitupdated	the updatef 'fit' object, if any, after the forward search
pVal	p-value that should be used for selecting covariates in the forward search
reFitCovars	if the covariates should be added before performing backward search - useful for directly performing backward search without forward search; default is FALSE
outputDir	the name of the output directory that stores the covariate search result
restart	a boolean that controls if the search should be restarted; default is FALSE

Value

returns the updated 'fit' object at the end of the backward search and a table of information for all the covariates tested

Author(s)

Vipul Mann, Matthew Fidler

`Bolus_1CPT` *Bolus_1CPT – 1 Compartment Model Simulated Data from ACOP 2016*

Description

This is a simulated dataset from the ACOP 2016 poster. All Datasets were simulated with the following methods.

Usage

```
Bolus_1CPT
```

Format

A data frame with 7,920 rows and 14 columns

ID Simulated Subject ID

TIME Simulated Time

DV Simulated Dependent Variable

LNDV Simulated log(Dependent Variable)

MDV Missing DV data item

AMT Dosing AMT

EVID NONMEM Event ID

DOSE Dose

V Individual Simulated Volume

CL Individual Clearance

SS Steady State

II Interdose Interval

SD Single Dose Flag

CMT Compartment

Details

Richly sampled profiles were simulated for 4 different dose levels (10, 30, 60 and 120 mg) of 30 subjects each as single dose (over 72h), multiple dose (4 daily doses), single and multiple dose combined, and steady state dosing, for a range of test models: 1- and 2-compartment disposition, with and without 1st order absorption, with either linear or Michaelis-Menten (MM) clearance(MM without steady state dosing). This provided a total of 42 test cases. All inter-individual variabilities (IIVs) were set at 30 were the same for all models. A similar set of models was previously used to compare NONMEM and Monolix4. Estimates of population parameters, standard errors for fixed-effect parameters, and run times were compared both for closed-form solutions and using ODEs. Additionally, a sparse data estimation situation was investigated where 500 datasets of 600 subjects each (150 per dose) were generated consisting of 4 random time point samples in 24 hours per subject, using a first-order absorption, 1-compartment disposition, linear elimination model.

Source

Schoemaker R, Xiong Y, Wilkins J, Laveille C, Wang W. nlmixr: an open-source package for pharmacometric modelling in R. ACOP 2016

See Also

Other nlmixr datasets: `Bolus_1CPTMM`, `Bolus_2CPTMM`, `Bolus_2CPT`, `Infusion_1CPT`, `Oral_1CPT`, `Wang2007`, `pheno_sd`, `rats`, `theo_md`, `theo_sd`, `warfarin`

Bolus_1CPTMM *1 Compartment Model w/ Michaelis-Menten Elimination*

Description

This is a simulated dataset from the ACOP 2016 poster. All Datasets were simulated with the following methods.

Usage

```
Bolus_1CPTMM
```

Format

A data frame with 7,920 rows and 14 columns

ID Simulated Subject ID

TIME Simulated Time

DV Simulated Dependent Variable

LNDV Simulated log(Dependent Variable)

MDV Missing DV data item

AMT Dosing AMT

EVID NONMEM Event ID

DOSE Dose

V Individual Simulated Volume

VM Individual Vm constant

KM Individual Km constant

SD Single Dose Flag

CMT Compartment

Details

Richly sampled profiles were simulated for 4 different dose levels (10, 30, 60 and 120 mg) of 30 subjects each as single dose (over 72h), multiple dose (4 daily doses), single and multiple dose combined, and steady state dosing, for a range of test models: 1- and 2-compartment disposition, with and without 1st order absorption, with either linear or Michaelis-Menten (MM) clearance(MM without steady state dosing). This provided a total of 42 test cases. All inter-individual variabilities (IIVs) were set at 30 were the same for all models. A similar set of models was previously used to compare NONMEM and Monolix4. Estimates of population parameters, standard errors for fixed-effect parameters, and run times were compared both for closed-form solutions and using ODEs. Additionally, a sparse data estimation situation was investigated where 500 datasets of 600 subjects each (150 per dose) were generated consisting of 4 random time point samples in 24 hours per subject, using a first-order absorption, 1-compartment disposition, linear elimination model.

Source

Schoemaker R, Xiong Y, Wilkins J, Laveille C, Wang W. nlmixr: an open-source package for pharmacometric modelling in R. ACOP 2016

See Also

Other nlmixr datasets: `Bolus_1CPT`, `Bolus_2CPTMM`, `Bolus_2CPT`, `Infusion_1CPT`, `Oral_1CPT`, `Wang2007`, `pheno_sd`, `rats`, `theo_md`, `theo_sd`, `warfarin`

`Bolus_2CPT` *2 Compartment Model*

Description

This is a simulated dataset from the ACOP 2016 poster. All Datasets were simulated with the following methods.

Usage

```
Bolus_2CPT
```

Format

A data frame with 7,920 rows and 16 columns

ID Simulated Subject ID

TIME Simulated Time

DV Simulated Dependent Variable

LNDV Simulated log(Dependent Variable)

MDV Missing DV data item

AMT Dosing AMT

EVID NONMEM Event ID

DOSE Dose

V1 Individual Central Compartment Volume

CL Individual Clearance

Q Individual Between Compartment Clearance

V2 Periperial Volume

SS Steady State Flag

II Interdose interval

SD Single Dose Flag

CMT Compartment Indicator

Details

Richly sampled profiles were simulated for 4 different dose levels (10, 30, 60 and 120 mg) of 30 subjects each as single dose (over 72h), multiple dose (4 daily doses), single and multiple dose combined, and steady state dosing, for a range of test models: 1- and 2-compartment disposition, with and without 1st order absorption, with either linear or Michaelis-Menten (MM) clearance(MM without steady state dosing). This provided a total of 42 test cases. All inter-individual variabilities (IIVs) were set at 30 were the same for all models. A similar set of models was previously used to compare NONMEM and Monolix4. Estimates of population parameters, standard errors for fixed-effect parameters, and run times were compared both for closed-form solutions and using ODEs. Additionally, a sparse data estimation situation was investigated where 500 datasets of 600 subjects each (150 per dose) were generated consisting of 4 random time point samples in 24 hours per subject, using a first-order absorption, 1-compartment disposition, linear elimination model.

Source

Schoemaker R, Xiong Y, Wilkins J, Laveille C, Wang W. nlmixr: an open-source package for pharmacometric modelling in R. ACOP 2016

See Also

Other nlmixr datasets: `Bolus_1CPTMM`, `Bolus_1CPT`, `Bolus_2CPTMM`, `Infusion_1CPT`, `Oral_1CPT`, `Wang2007`, `pheno_sd`, `rats`, `theo_md`, `theo_sd`, `warfarin`

`Bolus_2CPTMM` *2 Compartment Model with Michaelis-Menten Clearance*

Description

This is a simulated dataset from the ACOP 2016 poster. All Datasets were simulated with the following methods.

Usage

```
Bolus_2CPTMM
```

Format

A data frame with 7,920 rows and 15 columns

ID Simulated Subject ID

TIME Simulated Time

DV Simulated Dependent Variable

LNDV Simulated log(Dependent Variable)

MDV Missing DV data item

AMT Dosing AMT

EVID NONMEM Event ID

DOSE Dose

V Individual Central Compartment Volume

VM Individual Vmax

KM Individual Km

Q Individual Q

V2 Individual Peripheral Compartment Volume

SD Single Dose Flag

CMT Compartment Indicator

Details

Richly sampled profiles were simulated for 4 different dose levels (10, 30, 60 and 120 mg) of 30 subjects each as single dose (over 72h), multiple dose (4 daily doses), single and multiple dose combined, and steady state dosing, for a range of test models: 1- and 2-compartment disposition, with and without 1st order absorption, with either linear or Michaelis-Menten (MM) clearance(MM without steady state dosing). This provided a total of 42 test cases. All inter-individual variabilities (IIVs) were set at 30 were the same for all models. A similar set of models was previously used to compare NONMEM and Monolix4. Estimates of population parameters, standard errors for fixed-effect parameters, and run times were compared both for closed-form solutions and using ODEs. Additionally, a sparse data estimation situation was investigated where 500 datasets of 600 subjects each (150 per dose) were generated consisting of 4 random time point samples in 24 hours per subject, using a first-order absorption, 1-compartment disposition, linear elimination model.

Source

Schoemaker R, Xiong Y, Wilkins J, Laveille C, Wang W. nlmixr: an open-source package for pharmacometric modelling in R. ACOP 2016

See Also

Other nlmixr datasets: Bolus_1CPTMM, Bolus_1CPT, Bolus_2CPT, Infusion_1CPT, Oral_1CPT, Wang2007, pheno_sd, rats, theo_md, theo_sd, warfarin

---

bootdata *Bootstrap data*

Description

Bootstrap data by sampling the same number of subjects from the original dataset by sampling with replacement.

Usage

```
bootdata(dat)
```

Arguments

dat	model data to be bootstrapped

Value

Bootstrapped data

Examples

```
specs <- list(fixed = lKA + lCL + lV ~ 1,
  random = pdDiag(lKA + lCL ~ 1),
  start = c(lKA = 0.5, lCL = -3.2, lV = -1))
set.seed(99)
nboot <- 5
cat("generating", nboot, "bootstrap samples...\n")
cmat <- matrix(NA, nboot, 3)
for (i in 1:nboot)
{
  # print(i)
  bd <- bootdata(theo_md)
  fit <- nlme_lin_cmpt(bd, par_model = specs, ncmt = 1)
  cmat[i, ] <- fit$coefficients$fixed
}
dimnames(cmat)[[2]] <- names(fit$coefficients$fixed)
print(head(cmat))
```

`bootplot` *Produce trace-plot for fit if applicable*

Description

Produce trace-plot for fit if applicable

Usage

```
bootplot(x, ...)
```

Arguments

`x`	fit object
`...`	other parameters

Value

Fit traceplot or nothing.

Author(s)

Vipul Mann, Matthew L. Fidler

`bootplot.nlmixrFitCore` *Produce trace-plot for fit if applicable*

Description

Produce trace-plot for fit if applicable

Usage

```
## S3 method for class 'nlmixrFitCore'
bootplot(x, ...)

traceplot(x, ...)

## S3 method for class 'nlmixrFitCore'
traceplot(x, ...)
```

Arguments

`x`	fit object
`...`	other parameters

Value

Fit traceplot or nothing.

Author(s)

Rik Schoemaker, Wenping Wang & Matthew L. Fidler

`bootstrapFit` *Bootstrap nlmixr fit*

Description

Bootstrap input dataset and rerun the model to get confidence bounds and aggregated parameters

Usage

```
bootstrapFit(
  fit,
  nboot = 200,
  nSampIndiv,
  stratVar,
  stdErrType = c("perc", "se"),
  ci = 0.95,
  pvalues = NULL,
  restart = FALSE,
  plotHist = FALSE,
  fitName = as.character(substitute(fit))
)
```

Arguments

`fit`	the nlmixr fit object
`nboot`	an integer giving the number of bootstrapped models to be fit; default value is 200
`nSampIndiv`	an integer specifying the number of samples in each bootstrapped sample; default is the number of unique subjects in the original dataset
`stratVar`	Variable in the original dataset to stratify on; This is useful to distinguish between sparse and full sampling and other features you may wish to keep distinct in your bootstrap
`stdErrType`	This gives the standard error type for the updated standard errors; The current possibilities are: `"perc"` which gives the standard errors by percentiles (default) or `"se"` which gives the standard errors by the traditional formula.
`ci`	Confidence interval level to calculate. Default is 0.95 for a 95% confidence interval

pvalues	a vector of pvalues indicating the probability of each subject to get selected; default value is NULL implying that probability of each subject is the same
restart	A boolean to try to restart an interrupted or incomplete boostrap. By default this is FALSE
plotHist	A boolean indicating if a histogram plot to assess how well the bootstrap is doing. By default this is turned off (FALSE)
fitName	is the fit name that is used for the name of the boostrap files. By default it is the fit provided though it could be something else.

Value

Nothing, called for the side effects; The original fit is updated with the bootstrap confidence bands

Author(s)

Vipul Mann, Matthew Fidler

Examples

```
one.cmt <- function() {
  ini({
    ## You may label each parameter with a comment
    tka <- 0.45 # Log Ka
    tcl <- 1 # Log Cl
    ## This works with interactive models
    ## You may also label the preceding line with label("label text")
    tv <- 3.45
    label("log V")
    ## the label("Label name") works with all models
    eta.ka ~ 0.6
    eta.cl ~ 0.3
    eta.v ~ 0.1
    add.sd <- 0.7
  })
  model({
    ka <- exp(tka + eta.ka)
    cl <- exp(tcl + eta.cl)
    v <- exp(tv + eta.v)
    linCmt() ~ add(add.sd)
  })
}

fit <- nlmixr(one.cmt, theo_sd, "focei")

RxODE::.rxWithWd(tempdir(), { # Run example in temp dir

bootstrapFit(fit, nboot = 5, restart = TRUE) # overwrites any of the existing data or model files
bootstrapFit(fit, nboot = 7) # resumes fitting using the stored data and model files
```

```
# Note this resumes because the total number of bootstrap samples is not 50

bootstrapFit(fit, nboot=50)

# Note the boostrap standard error and variance/covariance matrix is retained.
# If you wish to switch back you can change the covariance matrix by

setCov(fit,"r,s")

# And change it back again

setCov(fit,"boot50")

# This change will affect any simulations with uncertainty in their parameters

# You may also do a chi-square diagnostic plot check for the bootstrap with

bootplot(fit)

})
```

---

boxCox *Cox Box, Yeo Johnson and inverse transformation*

Description

Cox Box, Yeo Johnson and inverse transformation

Usage

```
boxCox(x, lambda = 1)

iBoxCox(x, lambda = 1)

yeoJohnson(x, lambda = 1)

iYeoJohnson(x, lambda = 1)
```

Arguments

x	data to transform
lambda	Cox-box lambda parameter

Value

Cox-Box Transformed Data

Author(s)

Matthew L. Fidler

Examples

```
boxCox(1:3,1) ## Normal
iBoxCox(boxCox(1:3,1))

boxCox(1:3,0) ## Log-Normal
iBoxCox(boxCox(1:3,0),0)

boxCox(1:3,0.5) ## lambda=0.5
iBoxCox(boxCox(1:3,0.5),0.5)

yeoJohnson(seq(-3,3),1) ## Normal
iYeoJohnson(yeoJohnson(seq(-3,3),1))

yeoJohnson(seq(-3,3),0)
iYeoJohnson(yeoJohnson(seq(-3,3),0),0)
```

---

calc.2LL *Log-likelihood using Gaussian Quadrature*

Description

Estimate the log-likelihood using Gaussian Quadrature (multidimensional grid)

Usage

```
calc.2LL(fit, nnodes.gq = 8, nsd.gq = 4)
```

Arguments

fit	saemFit fit
nnodes.gq	number of nodes to use for the Gaussian quadrature when computing the likelihood with this method (defaults to 1, equivalent to the Laplaclian likelihood)
nsd.gq	span (in SD) over which to integrate when computing the likelihood by Gaussian quadrature. Defaults to 3 (eg 3 times the SD)

Value

log-likelihood calculated by Gaussian Quadrature

References

Kuhn E, Lavielle M. Maximum likelihood estimation in nonlinear mixed effects models. Computational Statistics and Data Analysis 49, 4 (2005), 1020-1038.

Comets E, Lavenu A, Lavielle M. SAEMIX, an R version of the SAEM algorithm. 20th meeting of the Population Approach Group in Europe, Athens, Greece (2011), Abstr 2173.

`calc.COV` *Covariance matrix by Fisher Information Matrix via linearization*

Description

Get the covariance matrix of fixed effect estimates via calculating Fisher Information Matrix by linearization

Usage

```
calc.COV(fit0)
```

Arguments

`fit0`	saemFit fit

Value

standard error of fixed effects

References

Comets E, Lavenu A, Lavielle M. SAEMIX, an R version of the SAEM algorithm. 20th meeting of the Population Approach Group in Europe, Athens, Greece (2011), Abstr 2173.

`calcCov` *Calculate gnlmm variance-covariance matrix of fixed effects*

Description

Calculate variance-covariance matrix of fixed effects after a gnlmm() fit

Usage

```
calcCov(fit, method = 1, trace = FALSE)
```

Arguments

fit	a gnlmm fit object
method	method for calculating variance-covariance matrix
trace	logical whether to trace the iterations

Value

variance-covariance matrix of model parameters

---

cholSE *Generalized Cholesky Matrix Decomposition*

Description

Performs a (modified) Cholesky factorization of the form

Usage

```
cholSE(matrix, tol = (.Machine$double.eps)^(1/3))
```

Arguments

matrix	Matrix to be Factorized.
tol	Tolerance; Algorithm suggests (.Machine$double.eps) ^ (1 / 3), default

Details

t(P) %*% A %*% P + E = t(R) %*% R

As detailed in Schnabel/Eskow (1990)

Value

Generalized Cholesky decomposed matrix.

Note

This version does not pivot or return the E matrix

Author(s)

Matthew L. Fidler (translation), Johannes Pfeifer, Robert B. Schnabel and Elizabeth Eskow

References

matlab source: http://www.dynare.org/dynare-matlab-m2html/matlab/chol_SE.html; Slightly different return values

Robert B. Schnabel and Elizabeth Eskow. 1990. "A New Modified Cholesky Factorization," SIAM Journal of Scientific Statistical Computing, 11, 6: 1136-58.

Elizabeth Eskow and Robert B. Schnabel 1991. "Algorithm 695 - Software for a New Modified Cholesky Factorization," ACM Transactions on Mathematical Software, Vol 17, No 3: 306-312

`configsaem` *Configure an SAEM model*

Description

Configure an SAEM model by generating an input list to the SAEM model function

Usage

```
configsaem(
  model,
  data,
  inits,
  mcmc = list(niter = c(200, 300), nmc = 3, nu = c(2, 2, 2)),
  ODEopt = list(atol = 1e-06, rtol = 1e-04, method = "lsoda", transitAbs = FALSE,
    maxeval = 1e+05),
  distribution = c("normal", "poisson", "binomial"),
  addProp = c("combined2", "combined1"),
  seed = 99,
  fixed = NULL,
  DEBUG = 0,
  tol = 1e-04,
  itmax = 100L,
  type = c("nelder-mead", "newuoa"),
  lambdaRange = 3,
  powRange = 10,
  odeRecalcFactor = 10^(0.5),
  maxOdeRecalc = 5L
)
```

Arguments

`model`	a compiled saem model by gen_saem_user_fn()
`data`	input data
`inits`	initial values
`mcmc`	a list of various mcmc options
`ODEopt`	optional ODE solving options

distribution	one of c("normal","poisson","binomial")
addProp	one of "combined1" and "combined2"; These are the two forms of additive+proportional errors supported by monolix/nonmem: combined1: transform(y)=transform(f)+(a+b*f^c)*eps combined2: transform(y)=transform(f)+(a^2+b^2*f^(2c))*eps
seed	seed for random number generator
fixed	a character vector of fixed effect only parameters (no random effects attached) to be fixed
DEBUG	Integer determining if debugging is enabled
tol	This is the tolerance for the regression models used for complex residual errors (ie add+prop etc)
itmax	This is the maximum number of iterations for the regression models used for complex residual errors. The number of iterations is itmax*number of parameters
type	indicates the type of optimization for the residuals; Can be one of c("nelder-mead", "newuoa")
lambdaRange	This indicates the range that Box-Cox and Yeo-Johnson parameters are constrained to be; The default is 3 indicating the range (-3,3)
powRange	This indicates the range that powers can take for residual errors; By default this is 10 indicating the range is c(1/10, 10) or c(0.1,10)
odeRecalcFactor	The factor to increase the rtol/atol with bad ODE solving.
maxOdeRecalc	Maximum number of times to reduce the ODE tolerances and try to resolve the system if there was a bad ODE solve.

Details

Fit a generalized nonlinear mixed-effect model by he Stochastic Approximation Expectation-Maximization (SAEM) algorithm

Value

Returns a list neede for the saem fit procedure

Author(s)

Wenping Wang & Matthew Fidler

Examples

```
# In this ODE system we simply specify the ODEs

ode <- "d/dt(depot) =-KA*depot;
        d/dt(centr) = KA*depot - KE*centr;"
```

```
m1 <- RxODE(ode)


# In this ode System, we also specify the concentration as C2 = centr/V

ode <- "C2 = centr/V;
      d/dt(depot) =-KA*depot;
      d/dt(centr) = KA*depot - KE*centr;"
m2 = RxODE(ode)

PKpars <- function() {
  CL <- exp(lCL)
  V <- exp(lV)
  KA <- exp(lKA)
  KE <- CL / V
}

PRED <- function() centr / V
PRED2 <- function() C2

saem_fit <- gen_saem_user_fn(model = m1, PKpars, pred = PRED)

# Can also use PRED2
saem_fit <- gen_saem_user_fn(model=m2, PKpars, pred=PRED2)


# You can also use the nlmixr UI to run this model and call the lower level functions

one.compartment <- function() {
ini({
  tka <- 0.45 # Log Ka
  tcl <- 1 # Log Cl
  tv <- 3.45    # Log V
  eta.ka ~ 0.6
  eta.cl ~ 0.3
  eta.v ~ 0.1
  add.sd <- 0.7
  wt.est <- 0.0
})
model({
  ka <- exp(tka + eta.ka)
  cl <- exp(tcl + eta.cl)
  v <- exp(tv + eta.v + wt.est * WT)
  d/dt(depot) = -ka * depot
  d/dt(center) = ka * depot - cl / v * center
  cp = center / v
  cp ~ add(add.sd)
})
}
fit  <- nlmixr(one.compartment, theo_sd, "saem")
fit
```

`covarSearchAuto` *Stepwise Covariate Model-selection (SCM) method*

Description

Stepwise Covariate Model-selection (SCM) method

Usage

```
covarSearchAuto(
  fit,
  varsVec,
  covarsVec,
  pVal = list(fwd = 0.05, bck = 0.01),
  covInformation = NULL,
  catCovariates = NULL,
  searchType = c("scm", "forward", "backward"),
  restart = FALSE
)
```

Arguments

`fit`	an nlmixr 'fit' object
`varsVec`	a list of candidate variables to which the covariates could be added
`covarsVec`	a list of candidate covariates that need to be tested
`pVal`	a named list with names 'fwd' and 'bck' for specifying the p-values for the forward and backward searches, respectively
`covInformation`	a list containing additionl information on the variables-covariates pairs that should be passed on to addCovMultiple function
`catCovariates`	a list of covariates that should be treated as categorical
`searchType`	one of 'scm', 'forward' and 'backward' to specify the covariate search method; default is 'scm'
`restart`	a boolean that controls if the search should be restarted; default is FALSE

Value

A list summarizing the covariate selection steps and output; This list has the "summaryTable" for the overall summary of the covariate selection as well as "resFwd" for the forward selection method and "resBck" for the backward selection method.

Author(s)

Vipul Mann, Matthew Fidler

Examples

```
one.cmt <- function() {
  ini({
    ## You may label each parameter with a comment
    tka <- 0.45 # Log Ka
    tcl <- log(c(0, 2.7, 100)) # Log Cl
    ## This works with interactive models
    ## You may also label the preceding line with label("label text")
    tv <- 3.45; label("log V")
    ## the label("Label name") works with all models
    eta.ka ~ 0.6
    eta.cl ~ 0.3
    eta.v ~ 0.1
    add.sd <- 0.7
  })
  model({
    ka <- exp(tka + eta.ka)
    cl <- exp(tcl + eta.cl)
    v <- exp(tv + eta.v)
    linCmt() ~ add(add.sd)
  })
}

fit <- nlmixr(one.cmt, theo_sd,"focei")
RxODE::.rxWithWd(tempdir(), {# with temporary directory

covarSearchAuto(fit, varsVec = c("ka", "cl"),
    covarsVec = c("WT", "SEX"), catCovariates = c("SEX"))

})

## Note that this didn't include sex, add it to dataset and restart model

d <- theo_sd
d$SEX <-0
d$SEX[d$ID<=6] <-1

fit <- nlmixr(one.cmt, d, "focei")

# This would restart if for some reason the search crashed:

RxODE::.rxWithWd(tempdir(), {# with temporary directory

covarSearchAuto(fit, varsVec = c("ka", "cl"), covarsVec = c("WT", "SEX"),
                catCovariates = c("SEX"), restart = TRUE)

covarSearchAuto(fit, varsVec = c("ka", "cl"), covarsVec = c("WT", "SEX"),
                catCovariates = c("SEX"), restart = TRUE,
                searchType = "forward")
```

```
})
```

`dynmodel` *Fit a non-population dynamic model*

Description

Fit a non-population dynamic model

Usage

```
dynmodel(
  system,
  model,
  inits,
  data,
  fixPars = NULL,
  nlmixrObject = NULL,
  control = list(),
  ...
)
```

Arguments

`system`	RxODE object. See `RxODE` for more details.
`model`	Error model.
`inits`	Initial values of system parameters.
`data`	Dataset to estimate. Needs to be RxODE compatible in EVIDs.
`fixPars`	Fixed system parameters. Default is NULL.
`nlmixrObject`	nlmixr object. See `nlmixr` for more details. Default is NULL.
`control`	Control options for dynmodel `dynmodelControl` .
`...`	Other parameters (ignored)

Value

A dynmodel fit object

Author(s)

Wenping Wang, Mason McComb and Matt Fidler

Examples

```
# dynmodel example ------------------------------------------------------
ode <- "
      kel = CL/V;
      d/dt(X) = -kel*X;
      C=X/V;
      PRED = C
      "
ode_system <- RxODE(model = ode)
model_error_structure <- cp ~ C + add(0.01) + prop(0.01)
inits <- c(CL = 1, V = 10)
control <- dynmodelControl(method = "Nelder-Mead")
fit <-
  try(dynmodel(
    system = ode_system,
    model = model_error_structure,
    data = Bolus_1CPT,
    inits = inits,
    control = control
  ))

# nlmixr model example -------------------------------------------------------
model_onecmt_bolus <- function() {
  ini({
    CL <- c(0, 5, 10) # Clearance (L/hr)
    V <- c(0, 50, 100) # Volume of Distribution
    prop.err <- c(0, 0.01, 1)
  })
  model({
    kel <- CL / V
    d / dt(X) <- -kel * X
    cp <- X / V
    cp ~ prop(prop.err)
  })
}

# note on some platforms this fit is not successful
fit <- try(nlmixr(object = model_onecmt_bolus, data = Bolus_1CPT, est = "dynmodel"))

if (inherits(fit, "nlmixrDynmodel")) {
 as.dynmodel(fit)
}

# method = "focei" is slightly more flexible and well tested

fit <- try(nlmixr(object = model_onecmt_bolus, data = Bolus_1CPT, est = "focei"))
```

`dynmodel.mcmc` *Fit a non-population dynamic model using mcmc*

Description

Fit a non-population dynamic model using mcmc

Usage

```
dynmodel.mcmc(
  system,
  model,
  evTable,
  inits,
  data,
  fixPars = NULL,
  nsim = 500,
  squared = TRUE,
  seed = NULL
)
```

Arguments

`system`	an RxODE object
`model`	a list of statistical measurement models
`evTable`	an Event Table object
`inits`	initial values of system parameters
`data`	input data
`fixPars`	fixed system parameters
`nsim`	number of mcmc iterations
`squared`	if parameters be squared during estimation
`seed`	random number seed

Value

A dyn.mcmc object detailing the model fit

Author(s)

Wenping Wang

Examples

```
ode <- "
   dose=200;
   pi = 3.1415926535897931;

   if (t<=0) {
      fI = 0;
   } else {
      fI = F*dose*sqrt(MIT/(2.0*pi*CVI2*t^3))*exp(-(t-MIT)^2/(2.0*CVI2*MIT*t));
   }

   C2 = centr/V2;
   C3 = peri/V3;
   d/dt(centr) = fI - CL*C2 - Q*C2 + Q*C3;
   d/dt(peri)  =              Q*C2 - Q*C3;
"
sys1 <- RxODE(model = ode)


## ----------------------------------------------------------------------
dat <- invgaussian
mod <- cp ~ C2 + prop(.1)
inits <- c(MIT = 190, CVI2 = .65, F = .92)
fixPars <- c(CL = .0793, V2 = .64, Q = .292, V3 = 9.63)
ev <- eventTable()
ev$add.sampling(c(0, dat$time))
(fit <- dynmodel.mcmc(sys1, mod, ev, inits, dat, fixPars))
```

`dynmodelControl` *Control Options for dynmodel*

Description

Control Options for dynmodel

Usage

```
dynmodelControl(
  ...,
  ci = 0.95,
  nlmixrOutput = FALSE,
  digs = 3,
  lower = -Inf,
  upper = Inf,
  method = c("bobyqa", "Nelder-Mead", "lbfgsb3c", "L-BFGS-B", "PORT", "mma",
    "lbfgsbLG", "slsqp", "Rvmmin"),
```

```
maxeval = 999,
scaleTo = 1,
scaleObjective = 0,
normType = c("rescale2", "constant", "mean", "rescale", "std", "len"),
scaleType = c("nlmixr", "norm", "mult", "multAdd"),
scaleCmax = 1e+05,
scaleCmin = 1e-05,
scaleC = NULL,
scaleC0 = 1e+05,
atol = NULL,
rtol = NULL,
ssAtol = NULL,
ssRtol = NULL,
npt = NULL,
rhobeg = 0.2,
rhoend = NULL,
iprint = 0,
print = 1,
maxfun = NULL,
trace = 0,
factr = NULL,
pgtol = NULL,
abstol = NULL,
reltol = NULL,
lmm = NULL,
maxit = 100000L,
eval.max = NULL,
iter.max = NULL,
abs.tol = NULL,
rel.tol = NULL,
x.tol = NULL,
xf.tol = NULL,
step.min = NULL,
step.max = NULL,
sing.tol = NULL,
scale.init = NULL,
diff.g = NULL,
boundTol = NULL,
epsilon = NULL,
derivSwitchTol = NULL,
sigdig = 4,
covMethod = c("nlmixrHess", "optimHess"),
gillK = 10L,
gillStep = 4,
gillFtol = 0,
gillRtol = sqrt(.Machine$double.eps),
gillKcov = 10L,
gillStepCov = 2,
```

```
  gillFtolCov = 0,
  rxControl = NULL
)
```

Arguments

`...`	Other arguments including scaling factors for each compartment. This includes S# = numeric will scale a compartment # by a dividing the compartment amount by the scale factor, like NONMEM.
`ci`	Confidence level for some tables. By default this is 0.95 or 95% confidence.
`nlmixrOutput`	Option to change output style to nlmixr output. By default this is FALSE.
`digs`	Option for the number of significant digits of the output. By default this is 3.
`lower`	Lower bounds on the parameters used in optimization. By default this is -Inf.
`upper`	Upper bounds on the parameters used in optimization. By default this is Inf.
`method`	The method for solving ODEs. Currently this supports: • `"liblsoda"` thread safe lsoda. This supports parallel thread-based solving, and ignores user Jacobian specification. • `"lsoda"` – LSODA solver. Does not support parallel thread-based solving, but allows user Jacobian specification. • `"dop853"` – DOP853 solver. Does not support parallel thread-based solving nor user Jacobain specification • `"indLin"` – Solving through inductive linearization. The RxODE dll must be setup specially to use this solving routine.
`maxeval`	Maximum number of iterations for Nelder-Mead of simplex search. By default this is 999.
`scaleTo`	Scale the initial parameter estimate to this value. By default this is 1. When zero or below, no scaling is performed.
`scaleObjective`	Scale the initial objective function to this value. By default this is 1.
`normType`	This is the type of parameter normalization/scaling used to get the scaled initial values for nlmixr. These are used with `scaleType` of. With the exception of `rescale2`, these come from Feature Scaling. The `rescale2` The rescaling is the same type described in the OptdesX software manual. In general, all all scaling formula can be described by: v_scaled = (v_unscaled-C_1)/C_2 Where The other data normalization approaches follow the following formula v_scaled = (v_unscaled-C_1)/C_2; • `rescale2` This scales all parameters from (-1 to 1). The relative differences between the parameters are preserved with this approach and the constants are: C_1 = (max(all unscaled values)+min(all unscaled values))/2 C_2 = (max(all unscaled values) - min(all unscaled values))/2

- `rescale` or min-max normalization. This rescales all parameters from (0 to 1). As in the `rescale2` the relative differences are preserved. In this approach:
  C_1 = min(all unscaled values)
  C_2 = max(all unscaled values) - min(all unscaled values)
- `mean` or mean normalization. This rescales to center the parameters around the mean but the parameters are from 0 to 1. In this approach:
  C_1 = mean(all unscaled values)
  C_2 = max(all unscaled values) - min(all unscaled values)
- `std` or standardization. This standardizes by the mean and standard deviation. In this approach:
  C_1 = mean(all unscaled values)
  C_2 = sd(all unscaled values)
- `len` or unit length scaling. This scales the parameters to the unit length. For this approach we use the Euclidean length, that is:
  C_1 = 0
  C_2 = sqrt(v_1^2 + v_2^2 + ... + v_n^2)
- `constant` which does not perform data normalization. That is
  C_1 = 0
  C_2 = 1

`scaleType` The scaling scheme for nlmixr. The supported types are:

- `nlmixr` In this approach the scaling is performed by the following equation:
  v_scaled = (v_current - v_init)/scaleC[i] + scaleTo
  The `scaleTo` parameter is specified by the `normType`, and the scales are specified by `scaleC`.
- `norm` This approach uses the simple scaling provided by the `normType` argument.
- `mult` This approach does not use the data normalization provided by `normType`, but rather uses multiplicative scaling to a constant provided by the `scaleTo` argument.
  In this case:
  v_scaled = v_current/v_init*scaleTo
- `multAdd` This approach changes the scaling based on the parameter being specified. If a parameter is defined in an exponential block (ie exp(theta)), then it is scaled on a linearly, that is:
  v_scaled = (v_current-v_init) + scaleTo
  Otherwise the parameter is scaled multiplicatively.
  v_scaled = v_current/v_init*scaleTo

`scaleCmax` Maximum value of the scaleC to prevent overflow.

`scaleCmin` Minimum value of the scaleC to prevent underflow.

`scaleC` The scaling constant used with `scaleType=nlmixr`. When not specified, it is based on the type of parameter that is estimated. The idea is to keep the derivatives similar on a log scale to have similar gradient sizes. Hence parameters like log(exp(theta)) would have a scaling factor of 1 and log(theta) would have a scaling factor of ini_value (to scale by 1/value; ie d/dt(log(ini_value)) = 1/ini_value or scaleC=ini_value)

- For parameters in an exponential (ie exp(theta)) or parameters specifying powers, boxCox or yeoJohnson transformations , this is 1.
- For additive, proportional, lognormal error structures, these are given by 0.5*abs(initial_estimate)
- Factorials are scaled by abs(1/digamma(inital_estimate+1))
- parameters in a log scale (ie log(theta)) are transformed by log(abs(initial_estimate))*abs(initial_estim

These parameter scaling coefficients are chose to try to keep similar slopes among parameters. That is they all follow the slopes approximately on a log-scale.

While these are chosen in a logical manner, they may not always apply. You can specify each parameters scaling factor by this parameter if you wish.

`scaleC0` Number to adjust the scaling factor by if the initial gradient is zero.

`atol` a numeric absolute tolerance (1e-8 by default) used by the ODE solver to determine if a good solution has been achieved; This is also used in the solved linear model to check if prior doses do not add anything to the solution.

`rtol` a numeric relative tolerance (`1e-6` by default) used by the ODE solver to determine if a good solution has been achieved. This is also used in the solved linear model to check if prior doses do not add anything to the solution.

`ssAtol` Steady state atol convergence factor. Can be a vector based on each state.

`ssRtol` Steady state rtol convergence factor. Can be a vector based on each state.

`npt` The number of points used to approximate the objective function via a quadratic approximation for bobyqa. The value of npt must be in the interval [n+2,(n+1)(n+2)/2] where n is the number of parameters in par. Choices that exceed 2*n+1 are not recommended. If not defined, it will be set to 2*n + 1

`rhobeg` Beginning change in parameters for bobyqa algorithm (trust region). By default this is 0.2 or 20 parameters when the parameters are scaled to 1. rhobeg and rhoend must be set to the initial and final values of a trust region radius, so both must be positive with 0 < rhoend < rhobeg. Typically rhobeg should be about one tenth of the greatest expected change to a variable. Note also that smallest difference abs(upper-lower) should be greater than or equal to rhobeg*2. If this is not the case then rhobeg will be adjusted.

`rhoend` The smallest value of the trust region radius that is allowed. If not defined, then 10^(-sigdig-1) will be used.

`iprint` Print option for optimization. See `bobyqa`, `lbfgsb3c`, and `lbfgs` for more details. By default this is 0.

`print` Integer representing when the outer step is printed. When this is 0 or do not print the iterations. 1 is print every function evaluation (default), 5 is print every 5 evaluations.

`maxfun` The maximum allowed number of function evaluations. If this is exceeded, the method will terminate. See `bobyqa` for more details. By default this value is NULL.

`trace` Tracing information on the progress of the optimization is produced. See `bobyqa`, `lbfgsb3c`, and `lbfgs` for more details. By default this is 0.

`factr` Controls the convergence of the "L-BFGS-B" method. Convergence occurs when the reduction in the objective is within this factor of the machine tolerance. Default is 1e10, which gives a tolerance of about `2e-6`, approximately 4 sigdigs. You can check your exact tolerance by multiplying this value by `.Machine$double.eps`

`pgtol` is a double precision variable.

On entry pgtol >= 0 is specified by the user. The iteration will stop when:

`max(\| proj g_i \| i = 1,...,n) <= lbfgsPgtol`

where pg_i is the ith component of the projected gradient.

On exit pgtol is unchanged. This defaults to zero, when the check is suppressed.

`abstol` Absolute tolerance for nlmixr optimizer

`reltol` tolerance for nlmixr

`lmm` An integer giving the number of BFGS updates retained in the "L-BFGS-B" method, It defaults to 7.

`maxit` Maximum number of iterations for lbfgsb3c. See `lbfgsb3c` for more details. By default this is 100000L.

`eval.max` Number of maximum evaluations of the objective function

`iter.max` Maximum number of iterations allowed.

`abs.tol` Used in Nelder-Mead optimization and PORT optimization. Absolute tolerance. Defaults to 0 so the absolute convergence test is not used. If the objective function is known to be non-negative, the previous default of 1e-20 would be more appropriate.

`rel.tol` Relative tolerance before nlminb stops.

`x.tol` X tolerance for nlmixr optimizers

`xf.tol` Used in Nelder-Mead optimization and PORT optimization. false convergence tolerance. Defaults to 2.2e-14. See `nlminb` for more details.

`step.min` Used in Nelder-Mead optimization and PORT optimization. Minimum step size. By default this is 1. See `nlminb` for more details.

`step.max` Used in Nelder-Mead optimization and PORT optimization. Maximum step size. By default this is 1. See `nlminb` for more details.

`sing.tol` Used in Nelder-Mead optimization and PORT optimization. Singular convergence tolerance; defaults to rel.tol. See `nlminb` for more details.

`scale.init` Used in Nelder-Mead optimization and PORT optimization. See `nlminb` for more details.

`diff.g` Used in Nelder-Mead optimization and PORT optimization. An estimated bound on the relative error in the objective function value. See `nlminb` for more details.

`boundTol` Tolerance for boundary issues.

`epsilon` Precision of estimate for n1qn1 optimization.

`derivSwitchTol` The tolerance to switch forward to central differences.

`sigdig` Optimization significant digits. This controls:

- The tolerance of the inner and outer optimization is `10^-sigdig`

- The tolerance of the ODE solvers is `0.5*10^(-sigdig-2)`; For the sensitivity equations and steady-state solutions the default is `0.5*10^(-sigdig-1.5)` (sensitivity changes only applicable for liblsoda)
- The tolerance of the boundary check is `5 * 10 ^ (-sigdig + 1)`
- The significant figures that some tables are rounded to.

`covMethod` Method for calculating covariance. In this discussion, R is the Hessian matrix of the objective function. The S matrix is the sum of individual gradient cross-product (evaluated at the individual empirical Bayes estimates).

`gillK` The total number of possible steps to determine the optimal forward/central difference step size per parameter (by the Gill 1983 method). If 0, no optimal step size is determined. Otherwise this is the optimal step size determined.

`gillStep` When looking for the optimal forward difference step size, this is This is the step size to increase the initial estimate by. So each iteration the new step size = (prior step size)*gillStep

`gillFtol` The gillFtol is the gradient error tolerance that is acceptable before issuing a warning/error about the gradient estimates.

`gillRtol` The relative tolerance used for Gill 1983 determination of optimal step size.

`gillKcov` The total number of possible steps to determine the optimal forward/central difference step size per parameter (by the Gill 1983 method) during the covariance step. If 0, no optimal step size is determined. Otherwise this is the optimal step size determined.

`gillStepCov` When looking for the optimal forward difference step size, this is This is the step size to increase the initial estimate by. So each iteration during the covariance step is equal to the new step size = (prior step size)*gillStepCov

`gillFtolCov` The gillFtol is the gradient error tolerance that is acceptable before issuing a warning/error about the gradient estimates during the covariance step.

`rxControl` This uses RxODE family of objects, file, or model specification to solve a ODE system. See `rxControl` for more details. By default this is NULL.

Value

dynmodelControl list for options during dynmodel optimization

Author(s)

Mason McComb and Matthew L. Fidler

`focei.eta` *Get the FOCEi theta or eta specification for model.*

Description

Get the FOCEi theta or eta specification for model.

Usage

```
focei.eta(object, uif, ...)

## S3 method for class 'nlmixrNlme'
focei.eta(object, ...)
```

Arguments

object	Fit object
uif	User interface function or object
...	Other parameters

Value

List for the OMGA list in FOCEi

Author(s)

Matthew L. Fidler

---

focei.theta *Get the FOCEi theta specification for the model*

Description

Get the FOCEi theta specification for the model

Usage

```
focei.theta(object, uif, ...)

## S3 method for class 'nlmixrNlme'
focei.theta(object, uif, ...)
```

Arguments

object	Fit object
uif	User interface function or object
...	Other parameters

Value

Parameter estimates for Theta

`foceiControl` *Control Options for FOCEi*

Description

Control Options for FOCEi

Usage

```
foceiControl(
  sigdig = 3,
  ...,
  epsilon = NULL,
  maxInnerIterations = 1000,
  maxOuterIterations = 5000,
  n1qn1nsim = NULL,
  method = c("liblsoda", "lsoda", "dop853"),
  transitAbs = NULL,
  atol = NULL,
  rtol = NULL,
  atolSens = NULL,
  rtolSens = NULL,
  ssAtol = NULL,
  ssRtol = NULL,
  ssAtolSens = NULL,
  ssRtolSens = NULL,
  minSS = 10L,
  maxSS = 1000L,
  maxstepsOde = 500000L,
  hmin = 0L,
  hmax = NA_real_,
  hini = 0,
  maxordn = 12L,
  maxords = 5L,
  cores,
  covsInterpolation = c("locf", "linear", "nocb", "midpoint"),
  print = 1L,
  printNcol = floor((getOption("width") - 23)/12),
  scaleTo = 1,
  scaleObjective = 0,
  normType = c("rescale2", "mean", "rescale", "std", "len", "constant"),
  scaleType = c("nlmixr", "norm", "mult", "multAdd"),
  scaleCmax = 1e+05,
  scaleCmin = 1e-05,
  scaleC = NULL,
  scaleC0 = 1e+05,
  derivEps = rep(20 * sqrt(.Machine$double.eps), 2),
```

```
  derivMethod = c("switch", "forward", "central"),
  derivSwitchTol = NULL,
  covDerivMethod = c("central", "forward"),
  covMethod = c("r,s", "r", "s", ""),
  hessEps = (.Machine$double.eps)^(1/3),
  eventFD = sqrt(.Machine$double.eps),
  eventType = c("gill", "central", "forward"),
  centralDerivEps = rep(20 * sqrt(.Machine$double.eps), 2),
  lbfgsLmm = 7L,
  lbfgsPgtol = 0,
  lbfgsFactr = NULL,
  eigen = TRUE,
  addPosthoc = TRUE,
  diagXform = c("sqrt", "log", "identity"),
  sumProd = FALSE,
  optExpression = TRUE,
  ci = 0.95,
  useColor = crayon::has_color(),
  boundTol = NULL,
  calcTables = TRUE,
  noAbort = TRUE,
  interaction = TRUE,
  cholSEtol = (.Machine$double.eps)^(1/3),
  cholAccept = 0.001,
  resetEtaP = 0.15,
  resetThetaP = 0.05,
  resetThetaFinalP = 0.15,
  diagOmegaBoundUpper = 5,
  diagOmegaBoundLower = 100,
  cholSEOpt = FALSE,
  cholSECov = FALSE,
  fo = FALSE,
  covTryHarder = FALSE,
 outerOpt = c("nlminb", "bobyqa", "lbfgsb3c", "L-BFGS-B", "mma", "lbfgsbLG", "slsqp",
    "Rvmmin"),
  innerOpt = c("n1qn1", "BFGS"),
  rhobeg = 0.2,
  rhoend = NULL,
  npt = NULL,
  rel.tol = NULL,
  x.tol = NULL,
  eval.max = 4000,
  iter.max = 2000,
  abstol = NULL,
  reltol = NULL,
  resetHessianAndEta = FALSE,
  stateTrim = Inf,
  gillK = 10L,
```

```
  gillStep = 4,
  gillFtol = 0,
  gillRtol = sqrt(.Machine$double.eps),
  gillKcov = 10L,
  gillStepCov = 2,
  gillFtolCov = 0,
  rmatNorm = TRUE,
  smatNorm = TRUE,
  covGillF = TRUE,
  optGillF = TRUE,
  covSmall = 1e-05,
  adjLik = TRUE,
  gradTrim = Inf,
  maxOdeRecalc = 5,
  odeRecalcFactor = 10^(0.5),
  gradCalcCentralSmall = 1e-04,
  gradCalcCentralLarge = 10000,
  etaNudge = qnorm(1 - 0.05/2)/sqrt(3),
  etaNudge2 = qnorm(1 - 0.05/2) * sqrt(3/5),
  stiff,
  nRetries = 3,
  seed = 42,
  resetThetaCheckPer = 0.1,
  etaMat = NULL,
  repeatGillMax = 3,
  stickyRecalcN = 5,
  gradProgressOfvTime = 10,
  addProp = c("combined2", "combined1"),
  singleOde = TRUE,
  badSolveObjfAdj = 100
)
```

Arguments

`sigdig`	Optimization significant digits. This controls: • The tolerance of the inner and outer optimization is `10^-sigdig` • The tolerance of the ODE solvers is `0.5*10^(-sigdig-2)`; For the sensitivity equations and steady-state solutions the default is `0.5*10^(-sigdig-1.5)` (sensitivity changes only applicable for liblsoda) • The tolerance of the boundary check is `5 * 10 ^ (-sigdig + 1)` • The significant figures that some tables are rounded to.
`...`	Ignored parameters
`epsilon`	Precision of estimate for n1qn1 optimization.
`maxInnerIterations`	Number of iterations for n1qn1 optimization.
`maxOuterIterations`	Maximum number of L-BFGS-B optimization for outer problem.

`n1qn1nsim` Number of function evaluations for n1qn1 optimization.

`method` The method for solving ODEs. Currently this supports:

- `"liblsoda"` thread safe lsoda. This supports parallel thread-based solving, and ignores user Jacobian specification.
- `"lsoda"` – LSODA solver. Does not support parallel thread-based solving, but allows user Jacobian specification.
- `"dop853"` – DOP853 solver. Does not support parallel thread-based solving nor user Jacobain specification
- `"indLin"` – Solving through inductive linearization. The RxODE dll must be setup specially to use this solving routine.

`transitAbs` boolean indicating if this is a transit compartment absorption

`atol` a numeric absolute tolerance (1e-8 by default) used by the ODE solver to determine if a good solution has been achieved; This is also used in the solved linear model to check if prior doses do not add anything to the solution.

`rtol` a numeric relative tolerance (`1e-6` by default) used by the ODE solver to determine if a good solution has been achieved. This is also used in the solved linear model to check if prior doses do not add anything to the solution.

`atolSens` Sensitivity atol, can be different than atol with liblsoda. This allows a less accurate solve for gradients (if desired)

`rtolSens` Sensitivity rtol, can be different than rtol with liblsoda. This allows a less accurate solve for gradients (if desired)

`ssAtol` Steady state absolute tolerance (atol) for calculating if steady-state has been archived.

`ssRtol` Steady state relative tolerance (rtol) for calculating if steady-state has been achieved.

`ssAtolSens` Sensitivity absolute tolerance (atol) for calculating if steady state has been achieved for sensitivity compartments.

`ssRtolSens` Sensitivity relative tolerance (rtol) for calculating if steady state has been achieved for sensitivity compartments.

`minSS` Minimum number of iterations for a steady-state dose

`maxSS` Maximum number of iterations for a steady-state dose

`maxstepsOde` Maximum number of steps for ODE solver.

`hmin` The minimum absolute step size allowed. The default value is 0.

`hmax` The maximum absolute step size allowed. When `hmax=NA` (default), uses the average difference + hmaxSd*sd in times and sampling events. The `hmaxSd` is a user specified parameter and which defaults to zero. When `hmax=NULL` RxODE uses the maximum difference in times in your sampling and events. The value 0 is equivalent to infinite maximum absolute step size.

`hini` The step size to be attempted on the first step. The default value is determined by the solver (when `hini = 0`)

`maxordn` The maximum order to be allowed for the nonstiff (Adams) method. The default is 12. It can be between 1 and 12.

`maxords` The maximum order to be allowed for the stiff (BDF) method. The default value is 5. This can be between 1 and 5.

`cores` Number of cores used in parallel ODE solving. This is equivalent to calling `setRxThreads()`

`covsInterpolation`

specifies the interpolation method for time-varying covariates. When solving ODEs it often samples times outside the sampling time specified in `events`. When this happens, the time varying covariates are interpolated. Currently this can be:

- `"linear"` interpolation, which interpolates the covariate by solving the line between the observed covariates and extrapolating the new covariate value.
- `"constant"` – Last observation carried forward (the default).
- `"NOCB"` – Next Observation Carried Backward. This is the same method that NONMEM uses.
- `"midpoint"` Last observation carried forward to midpoint; Next observation carried backward to midpoint.

`print` Integer representing when the outer step is printed. When this is 0 or do not print the iterations. 1 is print every function evaluation (default), 5 is print every 5 evaluations.

`printNcol` Number of columns to printout before wrapping parameter estimates/gradient

`scaleTo` Scale the initial parameter estimate to this value. By default this is 1. When zero or below, no scaling is performed.

`scaleObjective` Scale the initial objective function to this value. By default this is 1.

`normType` This is the type of parameter normalization/scaling used to get the scaled initial values for nlmixr. These are used with `scaleType` of.

With the exception of `rescale2`, these come from Feature Scaling. The `rescale2` The rescaling is the same type described in the OptdesX software manual.

In general, all all scaling formula can be described by:

v_scaled = (v_unscaled-C_1)/C_2

Where

The other data normalization approaches follow the following formula

v_scaled = (v_unscaled-C_1)/C_2;

- `rescale2` This scales all parameters from (-1 to 1). The relative differences between the parameters are preserved with this approach and the constants are:
  C_1 = (max(all unscaled values)+min(all unscaled values))/2
  C_2 = (max(all unscaled values) - min(all unscaled values))/2
- `rescale` or min-max normalization. This rescales all parameters from (0 to 1). As in the `rescale2` the relative differences are preserved. In this approach:
  C_1 = min(all unscaled values)
  C_2 = max(all unscaled values) - min(all unscaled values)
- `mean` or mean normalization. This rescales to center the parameters around the mean but the parameters are from 0 to 1. In this approach:
  C_1 = mean(all unscaled values)
  C_2 = max(all unscaled values) - min(all unscaled values)

- `std` or standardization. This standardizes by the mean and standard deviation. In this approach:
  C_1 = mean(all unscaled values)
  C_2 = sd(all unscaled values)
- `len` or unit length scaling. This scales the parameters to the unit length. For this approach we use the Euclidean length, that is:
  C_1 = 0
  C_2 = sqrt(v_1^2 + v_2^2 + ... + v_n^2)
- `constant` which does not perform data normalization. That is
  C_1 = 0
  C_2 = 1

`scaleType` The scaling scheme for nlmixr. The supported types are:

- `nlmixr` In this approach the scaling is performed by the following equation:
  v_scaled = (v_current - v_init)/scaleC[i] + scaleTo
  The `scaleTo` parameter is specified by the `normType`, and the scales are specified by `scaleC`.
- `norm` This approach uses the simple scaling provided by the `normType` argument.
- `mult` This approach does not use the data normalization provided by `normType`, but rather uses multiplicative scaling to a constant provided by the `scaleTo` argument.
  In this case:
  v_scaled = v_current/v_init*scaleTo
- `multAdd` This approach changes the scaling based on the parameter being specified. If a parameter is defined in an exponential block (ie exp(theta)), then it is scaled on a linearly, that is:
  v_scaled = (v_current-v_init) + scaleTo
  Otherwise the parameter is scaled multiplicatively.
  v_scaled = v_current/v_init*scaleTo

`scaleCmax` Maximum value of the scaleC to prevent overflow.

`scaleCmin` Minimum value of the scaleC to prevent underflow.

`scaleC` The scaling constant used with `scaleType=nlmixr`. When not specified, it is based on the type of parameter that is estimated. The idea is to keep the derivatives similar on a log scale to have similar gradient sizes. Hence parameters like log(exp(theta)) would have a scaling factor of 1 and log(theta) would have a scaling factor of ini_value (to scale by 1/value; ie d/dt(log(ini_value)) = 1/ini_value or scaleC=ini_value)

- For parameters in an exponential (ie exp(theta)) or parameters specifying powers, boxCox or yeoJohnson transformations , this is 1.
- For additive, proportional, lognormal error structures, these are given by 0.5*abs(initial_estimate)
- Factorials are scaled by abs(1/digamma(inital_estimate+1))
- parameters in a log scale (ie log(theta)) are transformed by log(abs(initial_estimate))*abs(initial_estim

These parameter scaling coefficients are chose to try to keep similar slopes among parameters. That is they all follow the slopes approximately on a log-scale.

While these are chosen in a logical manner, they may not always apply. You can specify each parameters scaling factor by this parameter if you wish.

`scaleC0` Number to adjust the scaling factor by if the initial gradient is zero.

`derivEps` Forward difference tolerances, which is a vector of relative difference and absolute difference. The central/forward difference step size h is calculated as:

`h = abs(x)*derivEps[1] + derivEps[2]`

`derivMethod` indicates the method for calculating derivatives of the outer problem. Currently supports "switch", "central" and "forward" difference methods. Switch starts with forward differences. This will switch to central differences when abs(delta(OFV)) <= derivSwitchTol and switch back to forward differences when abs(delta(OFV)) > derivSwitchTol.

`derivSwitchTol` The tolerance to switch forward to central differences.

`covDerivMethod` indicates the method for calculating the derivatives while calculating the covariance components (Hessian and S).

`covMethod` Method for calculating covariance. In this discussion, R is the Hessian matrix of the objective function. The S matrix is the sum of individual gradient cross-product (evaluated at the individual empirical Bayes estimates).

- `"r,s"` Uses the sandwich matrix to calculate the covariance, that is: `solve(R) %*% S %*% solve(R)`
- `"r"` Uses the Hessian matrix to calculate the covariance as `2 %*% solve(R)`
- `"s"` Uses the cross-product matrix to calculate the covariance as `4 %*% solve(S)`
- `""` Does not calculate the covariance step.

`hessEps` is a double value representing the epsilon for the Hessian calculation.

`eventFD` Finite difference step for forward or central difference estimation of event-based gradients

`eventType` Event gradient type for dosing events; Can be "gill", "central" or "forward"

`centralDerivEps`

Central difference tolerances. This is a numeric vector of relative difference and absolute difference. The central/forward difference step size h is calculated as:

`h = abs(x)*derivEps[1] + derivEps[2]`

`lbfgsLmm` An integer giving the number of BFGS updates retained in the "L-BFGS-B" method, It defaults to 7.

`lbfgsPgtol` is a double precision variable.

On entry pgtol >= 0 is specified by the user. The iteration will stop when:

`max(\| proj g_i \| i = 1,...,n) <= lbfgsPgtol`

where pg_i is the ith component of the projected gradient.

On exit pgtol is unchanged. This defaults to zero, when the check is suppressed.

`lbfgsFactr` Controls the convergence of the "L-BFGS-B" method. Convergence occurs when the reduction in the objective is within this factor of the machine tolerance. Default is 1e10, which gives a tolerance of about `2e-6`, approximately 4 sigdigs. You can check your exact tolerance by multiplying this value by `.Machine$double.eps`

`eigen` A boolean indicating if eigenvectors are calculated to include a condition number calculation.

`addPosthoc` Boolean indicating if posthoc parameters are added to the table output.

`diagXform` This is the transformation used on the diagonal of the `chol(solve(omega))`. This matrix and values are the parameters estimated in FOCEi. The possibilities are:

- `sqrt` Estimates the sqrt of the diagonal elements of `chol(solve(omega))`. This is the default method.
- `log` Estimates the log of the diagonal elements of `chol(solve(omega))`
- `identity` Estimates the diagonal elements without any transformations

`sumProd` Is a boolean indicating if the model should change multiplication to high precision multiplication and sums to high precision sums using the PreciseSums package. By default this is `FALSE`.

`optExpression` Optimize the RxODE expression to speed up calculation. By default this is turned on.

`ci` Confidence level for some tables. By default this is 0.95 or 95% confidence.

`useColor` Boolean indicating if focei can use ASCII color codes

`boundTol` Tolerance for boundary issues.

`calcTables` This boolean is to determine if the foceiFit will calculate tables. By default this is `TRUE`

`noAbort` Boolean to indicate if you should abort the FOCEi evaluation if it runs into troubles. (default TRUE)

`interaction` Boolean indicate FOCEi should be used (TRUE) instead of FOCE (FALSE)

`cholSEtol` tolerance for Generalized Cholesky Decomposition. Defaults to suggested (.Machine$double.eps)^(1/3)

`cholAccept` Tolerance to accept a Generalized Cholesky Decomposition for a R or S matrix.

`resetEtaP` represents the p-value for reseting the individual ETA to 0 during optimization (instead of the saved value). The two test statistics used in the z-test are either chol(omega^-1) %*% eta or eta/sd(allEtas). A p-value of 0 indicates the ETAs never reset. A p-value of 1 indicates the ETAs always reset.

`resetThetaP` represents the p-value for reseting the population mu-referenced THETA parameters based on ETA drift during optimization, and resetting the optimization. A p-value of 0 indicates the THETAs never reset. A p-value of 1 indicates the THETAs always reset and is not allowed. The theta reset is checked at the beginning and when nearing a local minima. The percent change in objective function where a theta reset check is initiated is controlled in `resetThetaCheckPer`.

`resetThetaFinalP` represents the p-value for reseting the population mu-referenced THETA parameters based on ETA drift during optimization, and resetting the optimization one final time.

`diagOmegaBoundUpper` This represents the upper bound of the diagonal omega matrix. The upper bound is given by diag(omega)*diagOmegaBoundUpper. If `diagOmegaBoundUpper` is 1, there is no upper bound on Omega.

`diagOmegaBoundLower`
: This represents the lower bound of the diagonal omega matrix. The lower bound is given by diag(omega)/diagOmegaBoundUpper. If `diagOmegaBoundLower` is 1, there is no lower bound on Omega.

`cholSEOpt`
: Boolean indicating if the generalized Cholesky should be used while optimizing.

`cholSECov`
: Boolean indicating if the generalized Cholesky should be used while calculating the Covariance Matrix.

`fo`
: is a boolean indicating if this is a FO approximation routine.

`covTryHarder`
: If the R matrix is non-positive definite and cannot be corrected to be non-positive definite try estimating the Hessian on the unscaled parameter space.

`outerOpt`
: optimization method for the outer problem

`innerOpt`
: optimization method for the inner problem (not implemented yet.)

`rhobeg`
: Beginning change in parameters for bobyqa algorithm (trust region). By default this is 0.2 or 20 parameters when the parameters are scaled to 1. rhobeg and rhoend must be set to the initial and final values of a trust region radius, so both must be positive with 0 < rhoend < rhobeg. Typically rhobeg should be about one tenth of the greatest expected change to a variable. Note also that smallest difference abs(upper-lower) should be greater than or equal to rhobeg*2. If this is not the case then rhobeg will be adjusted.

`rhoend`
: The smallest value of the trust region radius that is allowed. If not defined, then 10^(-sigdig-1) will be used.

`npt`
: The number of points used to approximate the objective function via a quadratic approximation for bobyqa. The value of npt must be in the interval [n+2,(n+1)(n+2)/2] where n is the number of parameters in par. Choices that exceed 2*n+1 are not recommended. If not defined, it will be set to 2*n + 1

`rel.tol`
: Relative tolerance before nlminb stops.

`x.tol`
: X tolerance for nlmixr optimizers

`eval.max`
: Number of maximum evaluations of the objective function

`iter.max`
: Maximum number of iterations allowed.

`abstol`
: Absolute tolerance for nlmixr optimizer

`reltol`
: tolerance for nlmixr

`resetHessianAndEta`
: is a boolean representing if the individual Hessian is reset when ETAs are reset using the option `resetEtaP`.

`stateTrim`
: Trim state amounts/concentrations to this value.

`gillK`
: The total number of possible steps to determine the optimal forward/central difference step size per parameter (by the Gill 1983 method). If 0, no optimal step size is determined. Otherwise this is the optimal step size determined.

`gillStep`
: When looking for the optimal forward difference step size, this is This is the step size to increase the initial estimate by. So each iteration the new step size = (prior step size)*gillStep

`gillFtol`
: The gillFtol is the gradient error tolerance that is acceptable before issuing a warning/error about the gradient estimates.

`gillRtol` The relative tolerance used for Gill 1983 determination of optimal step size.

`gillKcov` The total number of possible steps to determine the optimal forward/central difference step size per parameter (by the Gill 1983 method) during the covariance step. If 0, no optimal step size is determined. Otherwise this is the optimal step size determined.

`gillStepCov` When looking for the optimal forward difference step size, this is This is the step size to increase the initial estimate by. So each iteration during the covariance step is equal to the new step size = (prior step size)*gillStepCov

`gillFtolCov` The gillFtol is the gradient error tolerance that is acceptable before issuing a warning/error about the gradient estimates during the covariance step.

`rmatNorm` A parameter to normalize gradient step size by the parameter value during the calculation of the R matrix

`smatNorm` A parameter to normalize gradient step size by the parameter value during the calculation of the S matrix

`covGillF` Use the Gill calculated optimal Forward difference step size for the instead of the central difference step size during the central difference gradient calculation.

`optGillF` Use the Gill calculated optimal Forward difference step size for the instead of the central difference step size during the central differences for optimization.

`covSmall` The covSmall is the small number to compare covariance numbers before rejecting an estimate of the covariance as the final estimate (when comparing sandwich vs R/S matrix estimates of the covariance). This number controls how small the variance is before the covariance matrix is rejected.

`adjLik` In nlmixr, the objective function matches NONMEM's objective function, which removes a 2*pi constant from the likelihood calculation. If this is TRUE, the likelihood function is adjusted by this 2*pi factor. When adjusted this number more closely matches the likelihood approximations of nlme, and SAS approximations. Regardless of if this is turned on or off the objective function matches NONMEM's objective function.

`gradTrim` The parameter to adjust the gradient to if the |gradient| is very large.

`maxOdeRecalc` Maximum number of times to reduce the ODE tolerances and try to resolve the system if there was a bad ODE solve.

`odeRecalcFactor`
The factor to increase the rtol/atol with bad ODE solving.

`gradCalcCentralSmall`
A small number that represents the value where |grad| < gradCalcCentralSmall where forward differences switch to central differences.

`gradCalcCentralLarge`
A large number that represents the value where |grad| > gradCalcCentralLarge where forward differences switch to central differences.

`etaNudge` By default initial ETA estimates start at zero; Sometimes this doesn't optimize appropriately. If this value is non-zero, when the n1qn1 optimization didn't perform appropriately, reset the Hessian, and nudge the ETA up by this value; If the ETA still doesn't move, nudge the ETA down by this value. By default this value is qnorm(1-0.05/2)*1/sqrt(3), the first of the Gauss Quadrature numbers

times by the 0.95% normal region. If this is not successful try the second eta nudge number (below). If +-etaNudge2 is not successful, then assign to zero and do not optimize any longer

`etaNudge2` This is the second eta nudge. By default it is qnorm(1-0.05/2)*sqrt(3/5), which is the n=3 quadrature point (excluding zero) times by the 0.95% normal region

`stiff` a logical (`TRUE` by default) indicating whether the ODE system is stiff or not.

```
For stiff ODE systems (`stiff = TRUE`), `RxODE` uses the
LSODA (Livermore Solver for Ordinary Differential Equations)
Fortran package, which implements an automatic method switching
for stiff and non-stiff problems along the integration
interval, authored by Hindmarsh and Petzold (2003).

For non-stiff systems (`stiff = FALSE`), `RxODE` uses
DOP853, an explicit Runge-Kutta method of order 8(5, 3) of
Dormand and Prince as implemented in C by Hairer and Wanner
(1993).

If stiff is not specified, the `method` argument is used instead.
```

`nRetries` If FOCEi doesn't fit with the current parameter estimates, randomly sample new parameter estimates and restart the problem. This is similar to 'PsN' resampling.

`seed` seed for random number generator

`resetThetaCheckPer`
represents objective function % percentage below which resetThetaP is checked.

`etaMat` Eta matrix for initial estimates or final estimates of the ETAs.

`repeatGillMax` If the tolerances were reduced when calculating the initial Gill differences, the Gill difference is repeated up to a maximum number of times defined by this parameter.

`stickyRecalcN` The number of bad ODE solves before reducing the atol/rtol for the rest of the problem.

`gradProgressOfvTime`
This is the time for a single objective function evaluation (in seconds) to start progress bars on gradient evaluations

`addProp` one of "combined1" and "combined2"; These are the two forms of additive+proportional errors supported by monolix/nonmem:

combined1: transform(y)=transform(f)+(a+b*f^c)*eps

combined2: transform(y)=transform(f)+(a^2+b^2*f^(2c))*eps

`singleOde` This option allows a single ode model to include the PK parameter information instead of splitting it into a function and a RxODE model

`badSolveObjfAdj`
The objective function adjustment when the ODE system cannot be solved. It is based on each individual bad solve.

Details

Note this uses the R's L-BFGS-B in optim for the outer problem and the BFGS n1qn1 with that allows restoring the prior individual Hessian (for faster optimization speed).

However the inner problem is not scaled. Since most eta estimates start near zero, scaling for these parameters do not make sense.

This process of scaling can fix some ill conditioning for the unscaled problem. The covariance step is performed on the unscaled problem, so the condition number of that matrix may not be reflective of the scaled problem's condition-number.

Value

The control object that changes the options for the FOCEi family of estimation methods

Author(s)

Matthew L. Fidler

See Also

optim

n1qn1

rxSolve

---

foceiFit *FOCEi fit*

Description

FOCEi fit

Usage

```
foceiFit(data, ...)

focei.fit(data, ...)

## S3 method for class 'data.frame'
foceiFit(data, ...)

## S3 method for class 'data.frame0'
foceiFit(
  data,
  inits,
  PKpars,
  model = NULL,
  pred = NULL,
```

```
  err = NULL,
  lower = -Inf,
  upper = Inf,
  fixed = NULL,
  skipCov = NULL,
  control = foceiControl(),
  thetaNames = NULL,
  etaNames = NULL,
  etaMat = NULL,
  ...,
  env = NULL,
  keep = NULL,
  drop = NULL
)
```

Arguments

data	Data to fit; Needs to be RxODE compatible and have DV, AMT, EVID in the dataset.
...	Ignored parameters
inits	Initialization list
PKpars	Pk Parameters function
model	The RxODE model to use
pred	The Prediction function
err	The Error function
lower	Lower bounds
upper	Upper Bounds
fixed	Boolean vector indicating what parameters should be fixed.
skipCov	Boolean vector indicating what parameters should be fixed when calculating covariances
control	FOCEi options Control list. See foceiControl
thetaNames	Names of the thetas to be used in the final object.
etaNames	Eta names to be used in the final object.
etaMat	Eta matrix for initial estimates or final estimates of the ETAs.
env	An environment used to build the FOCEi or nlmixr object.
keep	Columns to keep from either the input dataset. For the input dataset, if any records are added to the data LOCF (Last Observation Carried forward) imputation is performed.
drop	Columns to drop from the output

Value

A focei fit or nlmixr fit object

FOCEi fit object

Author(s)

Matthew L. Fidler and Wenping Wang

Examples

```
## Comparison to Wang2007 objective functions

mypar2 = function ()
{
    k = theta[1] * exp(eta[1]);
}

mod <- RxODE({
    ipre = 10 * exp(-k * t)
})
pred <- function() ipre

errProp <- function(){
  return(prop(0.1))
}

inits <- list(THTA=c(0.5),
              OMGA=list(ETA[1] ~ 0.04));

w7 <- Wang2007

w7$DV <- w7$Y
w7$EVID <- 0
w7$AMT <- 0

## Wang2007 prop error OBF 39.458 for NONMEM FOCEi, nlmixr matches.
fitPi <- foceiFit(w7, inits, mypar2,mod,pred,errProp,
     control=foceiControl(maxOuterIterations=0,covMethod=""))

print(fitPi$objective)

## Wang2007 prop error OBF 39.207 for NONMEM FOCE; nlmixr matches.
fitP <- foceiFit(w7, inits, mypar2,mod,pred,errProp,
     control=foceiControl(maxOuterIterations=0,covMethod="",
     interaction=FALSE))

print(fitP$objective)

## Wang 2007 prop error OBF 39.213 for NONMEM FO; nlmixr matches
fitPfo <- foceiFit(w7, inits, mypar2,mod,pred,errProp,
     control=foceiControl(maxOuterIterations=0,covMethod="",
     fo=TRUE))

print(fitPfo$objective)
```

```
## Note if you have the etas you can evaluate the likelihood
## of an arbitrary model.  It doesn't have to be solved by
## FOCEi

etaMat <- matrix(fitPi$eta[,-1])

fitP2 <- foceiFit(w7, inits, mypar2,mod,pred,errProp, etaMat=etaMat,
      control=foceiControl(maxOuterIterations=0,maxInnerIterations=0,
      covMethod=""))


errAdd <- function(){
  return(add(0.1))
}

## Wang2007 add error of -2.059 for NONMEM FOCE=NONMEM FOCEi;
## nlmixr matches.
fitA <- foceiFit(w7, inits, mypar2,mod,pred,errAdd,
     control=foceiControl(maxOuterIterations=0,covMethod=""))

## Wang2007 add error of 0.026 for NONMEM FO; nlmixr matches

fitAfo <- foceiFit(w7, inits, mypar2,mod,pred,errAdd,
     control=foceiControl(maxOuterIterations=0,fo=TRUE,covMethod=""))

## Extending Wang2007 to add+prop with same dataset
errAddProp <- function(){
  return(add(0.1) + prop(0.1));
}

fitAP <- foceiFit(w7, inits, mypar2,mod,pred,errAddProp,
     control=foceiControl(maxOuterIterations=0,covMethod=""))

## Checking lognormal

errLogn <- function(){
   return(lnorm(0.1));
}

## First run the fit with the nlmixr lnorm error

fitLN <- foceiFit(w7, inits, mypar2,mod,pred,errLogn,
     control=foceiControl(maxOuterIterations=0,covMethod=""))


## Next run on the log-transformed space
w72 <- w7; w72$DV <- log(w72$DV)

predL <- function() log(ipre)

fitLN2 <- foceiFit(w72, inits, mypar2,mod,predL,errAdd,
     control=foceiControl(maxOuterIterations=0,covMethod=""))
```

```
## Correct the fitLN2's objective function to be on the normal scale
print(fitLN2$objective + 2*sum(w72$DV))

## Note the objective function of the lognormal error is on the normal scale.
print(fitLN$objective)

mypar2 <- function ()
{
    ka <- exp(THETA[1] + ETA[1])
    cl <- exp(THETA[2] + ETA[2])
    v  <- exp(THETA[3] + ETA[3])
}

mod <- RxODE({
    d/dt(depot) <- -ka * depot
    d/dt(center) <- ka * depot - cl / v * center
    cp <- center / v
})

pred <- function() cp

err <- function(){
    return(add(0.1))
}

inits <- list(THTA=c(0.5, -3.2, -1),
              OMGA=list(ETA[1] ~ 1, ETA[2] ~ 2, ETA[3] ~ 1));

## Remove 0 concentrations (should be lloq)

d <- theo_sd[theo_sd$EVID==0 & theo_sd$DV>0 | theo_sd$EVID>0,];

fit1 <- foceiFit(d, inits, mypar2,mod,pred,err)

## you can also fit lognormal data with the objective function on the same scale

errl <- function(){
    return(lnorm(0.1))
}

fit2 <- foceiFit(d, inits, mypar2,mod,pred,errl)

## You can also use the standard nlmixr functions to run FOCEi

library(data.table);
datr <- Infusion_1CPT;
datr$EVID<-ifelse(datr$EVID==1,10101,datr$EVID)
datr<-data.table(datr)
datr<-datr[EVID!=2]
datro<-copy(datr)
datIV<-datr[AMT>0][,TIME:=TIME+AMT/RATE][,AMT:=-1*AMT]
datr<-rbind(datr,datIV)
```

```
one.compartment.IV.model <- function(){
  ini({ # Where initial conditions/variables are specified
    # '<-' or '=' defines population parameters
    # Simple numeric expressions are supported
    lCl <- 1.6      #log Cl (L/hr)
    lVc <- 4.5  #log V (L)
    # Bounds may be specified by c(lower, est, upper), like NONMEM:
    # Residuals errors are assumed to be population parameters
    prop.sd <- 0.3
    # Between subject variability estimates are specified by '~'
    # Semicolons are optional
    eta.Vc ~ 0.1   #IIV V
    eta.Cl ~ 0.1; #IIV Cl
  })
  model({ # Where the model is specified
    # The model uses the ini-defined variable names
    Vc <- exp(lVc + eta.Vc)
    Cl <- exp(lCl + eta.Cl)
    # RxODE-style differential equations are supported
    d / dt(centr) = -(Cl / Vc) * centr;
    ## Concentration is calculated
    cp = centr / Vc;
    # And is assumed to follow proportional error estimated by prop.err
    cp ~ prop(prop.sd)
   })}

fitIVp <- nlmixr(one.compartment.IV.model, datr, "focei");

## You can also use the Box-Cox Transform of both sides with
## proportional error (Donse 2016)

one.compartment.IV.model <- function(){
ini({ # Where initial conditions/variables are specified
    ## '<-' or '=' defines population parameters
    ## Simple numeric expressions are supported
    lCl <- 1.6      #log Cl (L/hr)
    lVc <- 4.5  #log V (L)
    ## Bounds may be specified by c(lower, est, upper), like NONMEM:
    ## Residuals errors are assumed to be population parameters
    prop.err <- 0.3
    add.err <- 0.01
    lambda <- c(-2, 1, 2)
    zeta <- c(0.1, 1, 10)
    ## Between subject variability estimates are specified by '~'
    ## Semicolons are optional
    eta.Vc ~ 0.1   #IIV V
    eta.Cl ~ 0.1; #IIV Cl
})
model({ ## Where the model is specified
    ## The model uses the ini-defined variable names
    Vc <- exp(lVc + eta.Vc)
    Cl <- exp(lCl + eta.Cl)
```

```
    ## RxODE-style differential equations are supported
    d / dt(centr) = -(Cl / Vc) * centr;
    ## Concentration is calculated
    cp = centr / Vc;
    ## And is assumed to follow proportional error estimated by prop.err
    cp ~ pow(prop.err, zeta) + add(add.err) + boxCox(lambda)
   ## This is proportional to the untransformed f; You can use the transformed f by using powT()
})}

fitIVtbs <- nlmixr(one.compartment.IV.model, datr, "focei")

## If you want to use a variance normalizing distribution with
## negative/positive data you can use the Yeo-Johnson transformation
## as well.  This is implemented by the yeoJohnson(lambda) function.
one.compartment.IV.model <- function(){
ini({ # Where initial conditions/variables are specified
    ## '<-' or '=' defines population parameters
    ## Simple numeric expressions are supported
    lCl <- 1.6      #log Cl (L/hr)
    lVc <- 4.5  #log V (L)
    ## Bounds may be specified by c(lower, est, upper), like NONMEM:
    ## Residuals errors are assumed to be population parameters
    prop.err <- 0.3
    delta <- c(0.1, 1, 10)
    add.err <- 0.01
    lambda <- c(-2, 1, 2)
    ## Between subject variability estimates are specified by '~'
    ## Semicolons are optional
    eta.Vc ~ 0.1   #IIV V
    eta.Cl ~ 0.1; #IIV Cl
})
model({ ## Where the model is specified
    ## The model uses the ini-defined variable names
    Vc <- exp(lVc + eta.Vc)
    Cl <- exp(lCl + eta.Cl)
    ## RxODE-style differential equations are supported
    d / dt(centr) = -(Cl / Vc) * centr;
    ## Concentration is calculated
    cp = centr / Vc;
    ## And is assumed to follow proportional error estimated by prop.err
    cp ~ pow(prop.err, delta) + add(add.err) + yeoJohnson(lambda)
})}

fitIVyj <- nlmixr(one.compartment.IV.model, datr, "focei")

## In addition to using L-BFGS-B for FOCEi (outer problem) you may
## use other optimizers.  An example is below

one.cmt <- function() {
  ini({
      tka <- .44   # log Ka
      tcl <- log(c(0, 2.7, 100)) # log Cl
      tv <- 3.45    # log V
```

```
      eta.ka ~ 0.6
      eta.cl ~ 0.3
      eta.v ~ 0.1
      add.err <- 0.7
  })
  model({
      ka <- exp(tka + eta.ka)
      cl <- exp(tcl + eta.cl)
      v <- exp(tv + eta.v)
      linCmt() ~ add(add.err)
  })
}

fit <- nlmixr(one.cmt, theo_sd, "focei", foceiControl(outerOpt="bobyqa"))

## You may also make an arbitrary optimizer work by adding a wrapper function:

newuoa0 <- function(par, fn, gr, lower = -Inf, upper = Inf, control = list(), ...){
  ## The function requires par, fn, gr, lower, upper and control
  ##
  ## The par, fn, gr, lower and upper and sent to the function from nlmixr's focei.
  ## The  control is the foceiControl list
  ##
  ##  The following code modifies the list control list for no warnings.
  .ctl <- control;
  if (is.null(.ctl$npt)) .ctl$npt <- length(par) * 2 + 1
  ## nlmixr will print information this is to suppress the printing from the
  ## optimizer
  .ctl$iprint <- 0L;
  .ctl <- .ctl[names(.ctl) %in% c("npt", "rhobeg", "rhoend", "iprint", "maxfun")];
  ## This does not require gradient and is an unbounded optimization:
  .ret <- minqa::newuoa(par, fn, control=.ctl);
  ## The return statement must be a list with:
  ##    - x for the final parameter message
  ##    - message for a minimization message
  ##    - convergence for a convergence code
  .ret$x <- .ret$par;
  .ret$message <- .ret$msg;
  .ret$convergence <- .ret$ierr
  ## you can access the final list from the optimization by fit$optReturn
  return(.ret);
}

fit <- nlmixr(one.cmt, theo_sd, "focei", foceiControl(outerOpt=newuoa0))
```

---

forwardSearch *Forward covariate search*

Description

Forward covariate search

Usage

```
forwardSearch(covInfo, fit, pVal = 0.05, outputDir, restart = FALSE)
```

Arguments

covInfo	a list containing information about each variable-covariate pair
fit	an nlmixr 'fit' object
pVal	p-value that should be used for selecting covariates in the forward search
outputDir	the name of the output directory that stores the covariate search result
restart	a boolean that controls if the search should be restarted; default is FALSE

Value

returns the updated 'fit' object at the end of the forward search and a table of information for all the covaraites tested

Author(s)

Vipul Mann, Matthew Fidler

---

frwd_selection *Forward covariate selection for nlme-base non-linear mixed effect models*

Description

Implements forward covariate selection for nlme-based non-linear mixed effect models

Usage

```
frwd_selection(base, cv, dat, cutoff = 0.05)
```

Arguments

base	base model
cv	a list of candidate covariate to model parameters
dat	model data
cutoff	significance level

Value

an nlme object of the final model

Examples

```
dat <- theo_md
dat$LOGWT <- log(dat$WT)
dat$TG <- (dat$ID < 6) + 0 # dummy covariate

specs <- list(
  fixed = list(lKA = lKA ~ 1, lCL = lCL ~ 1, lV = lV ~ 1),
  random = pdDiag(lKA + lCL ~ 1),
  start = c(0.5, -3.2, -1)
)
fit0 <- nlme_lin_cmpt(dat, par_model = specs, ncmt = 1)
cv <- list(lCL = c("WT", "TG"), lV = c("WT"))
fit <- frwd_selection(fit0, cv, dat)
print(summary(fit))
```

---

gauss.quad *Sets nodes and weights of Gauss-Hermite quadrature*

Description

Sets nodes and weights of Gauss-Hermite quadrature

Usage

```
gauss.quad(n)
```

Arguments

n	number of nodes

Value

a list of nodes and weights of Gauss-Hermite quadrature

Examples

```
gauss.quad(5)
```

getOMEGA *Calculate gnlmm variance-covariance matrix of random effects*

Description

Calculate variance-covariance matrix of random effects after a gnlmm() fit

Usage

```
getOMEGA(fit)
```

Arguments

fit	a gnlmm fit object

Value

variance-covariance matrix of random effects

gnlmm *Fit a generalized nonlinear mixed-effect model*

Description

Fit a generalized nonlinear mixed-effect model by adaptive Gaussian quadrature (AQD)

Usage

```
gnlmm(
  llik,
  data,
  inits,
  syspar = NULL,
  system = NULL,
  diag.xform = c("sqrt", "log", "identity"),
  ...,
  control = list()
)

gnlmm2(
  llik,
  data,
  inits,
  syspar = NULL,
  system = NULL,
  diag.xform = c("sqrt", "log", "identity"),
```

```
  ...,
  control = list()
)
```

Arguments

llik	log-likelihood function
data	data to be fitted
inits	initial values
syspar	function: calculation of PK parameters
system	an optional (compiled) RxODE object
diag.xform	transformation to diagonal elements of OMEGA during fitting
...	additional options
control	additional optimization options

Details

Fit a generalized nonlinear mixed-effect model by adaptive Gaussian quadrature (AGQ)

Value

gnlmm fit object

Author(s)

Wenping Wang

Examples

```
if (FALSE) {
llik <- function() {
  lp <- THETA[1] * x1 + THETA[2] * x2 + (x1 + x2 * THETA[3]) * ETA[1]
  p <- pnorm(lp)
  dbinom(x, m, p, log = TRUE)
}
inits <- list(THTA = c(1, 1, 1), OMGA = list(ETA[1] ~ 1))

try(gnlmm(llik, rats, inits, control = list(nAQD = 1)))

llik <- function() {
  if (group == 1) {
    lp <- THETA[1] + THETA[2] * logtstd + ETA[1]
  } else {
    lp <- THETA[3] + THETA[4] * logtstd + ETA[1]
  }
  lam <- exp(lp)
  dpois(y, lam, log = TRUE)
}
```

```
inits <- list(THTA = c(1, 1, 1, 1), OMGA = list(ETA[1] ~ 1))

fit <- try(gnlmm(llik, pump, inits,
  control = list(
    reltol.outer = 1e-4,
    optim.outer = "nmsimplex",
    nAQD = 5
  )
))



ode <- "
d/dt(depot) =-KA*depot;
d/dt(centr) = KA*depot - KE*centr;
"
sys1 <- RxODE(ode)

pars <- function() {
  CL <- exp(THETA[1] + ETA[1]) # ; if (CL>100) CL=100
  KA <- exp(THETA[2] + ETA[2]) # ; if (KA>20) KA=20
  KE <- exp(THETA[3])
  V <- CL / KE
  sig2 <- exp(THETA[4])
}
llik <- function() {
  pred <- centr / V
  dnorm(DV, pred, sd = sqrt(sig2), log = TRUE)
}
inits <- list(THTA = c(-3.22, 0.47, -2.45, 0))
inits$OMGA <- list(ETA[1]+ETA[2]~c(.027, .01, .37))

theo <- theo_md

fit <- try(gnlmm(llik, theo, inits, pars, sys1,
  control = list(trace = TRUE, nAQD = 1)
))

fit2 <- try(gnlmm2(llik, theo, inits, pars, sys1,
  control = list(trace = TRUE, nAQD = 1)
))

if (inherits(fit, "gnlmm.fit")) {
 cv <- calcCov(fit)
 cbind(fit$par[fit$nsplt == 1], sqrt(diag(cv)))
}
}
```

---

gof *Plot of a non-population dynamic model fit*

Description

Plot of a non-population dynamic model fit

Usage

```
gof(x, ...)

## S3 method for class 'dyn.ID'
plot(x, ...)
```

Arguments

x	a dynamodel fit object
...	additional arguments

Value

nothing, displays a goodness of fit plot for dynmodely

`Infusion_1CPT` *Infusion_1CPT – 1 Compartment Model Simulated Data from ACOP 2016*

Description

This is a simulated dataset from the ACOP 2016 poster. All Datasets were simulated with the following methods.

Usage

```
Infusion_1CPT
```

Format

A data frame with 7,920 rows and 14 columns

ID Simulated Subject ID

TIME Simulated Time

DV Simulated Dependent Variable

LNDV Simulated log(Dependent Variable)

MDV Missing DV data item

AMT Dosing AMT

EVID NONMEM Event ID

DOSE Dose

V Individual Simulated Volume

CL Individual Clearance

SS Steady State

II Interdose Interval

SD Single Dose Flag

RATE NONMEM Rate

CMT Compartment

Details

Richly sampled profiles were simulated for 4 different dose levels (10, 30, 60 and 120 mg) of 30 subjects each as single dose (over 72h), multiple dose (4 daily doses), single and multiple dose combined, and steady state dosing, for a range of test models: 1- and 2-compartment disposition, with and without 1st order absorption, with either linear or Michaelis-Menten (MM) clearance(MM without steady state dosing). This provided a total of 42 test cases. All inter-individual variabilities (IIVs) were set at 30 were the same for all models. A similar set of models was previously used to compare NONMEM and Monolix4. Estimates of population parameters, standard errors for fixed-effect parameters, and run times were compared both for closed-form solutions and using ODEs. Additionally, a sparse data estimation situation was investigated where 500 datasets of 600 subjects each (150 per dose) were generated consisting of 4 random time point samples in 24 hours per subject, using a first-order absorption, 1-compartment disposition, linear elimination model.

Source

Schoemaker R, Xiong Y, Wilkins J, Laveille C, Wang W. nlmixr: an open-source package for pharmacometric modelling in R. ACOP 2016

See Also

Other nlmixr datasets: `Bolus_1CPTMM`, `Bolus_1CPT`, `Bolus_2CPTMM`, `Bolus_2CPT`, `Oral_1CPT`, `Wang2007`, `pheno_sd`, `rats`, `theo_md`, `theo_sd`, `warfarin`

---

ini *nlmixr ini block handling*

Description

The ini block controls initial conditions for 'theta' (fixed effects), 'omega' (random effects), and 'sigma' (residual error) elements of the model.

Usage

```
ini(ini, ...)
```

Arguments

`ini`	Ini block or nlmixr model object
`...`	Other arguments parsed by nlmixr

Details

'theta' and 'sigma' can be set using either <- or = such as tvCL <-1 or equivalently tvCL = 1. 'omega' can be set with a ~.

Parameters can be named or unnamed (though named parameters are preferred). A named parameter is set using the name on the left of the assignment while unnamed parameters are set without an assignment operator. tvCL <-1 would set a named parameter of tvCL to 1. Unnamed parameters are set using just the value, such as 1.

For some estimation methods, lower and upper bounds can be set for 'theta' and 'sigma' values. To set a lower and/or upper bound, use a vector of values. The vector is c(lower,estimate,upper). The vector may be given with just the estimate (c(estimate)), the lower bound and estimate (c(lower,estimate)), or all three (c(lower,estimate,upper)). To set an estimate and upper bound without a lower bound, set the lower bound to -Inf, c(-Inf,estimate,upper). When an estimation method does not support bounds, the bounds will be ignored with a warning.

'omega' values can be set as a single value or as the values of a lower-triangular matrix. The values may be set as either a variance-covariance matrix (the default) or as a correlation matrix for the off-diagonals with the standard deviations on the diagonals. Names may be set on the left side of the ~. To set a variance-covariance matrix with variance values of 2 and 3 and a covariance of -2.5 use ~c(2,2.5,3). To set the same matrix with names of iivKa and iivCL, use iivKa + iivCL~c(2,2.5,3). To set a correlation matrix with standard deviations on the diagonal, use cor() like iivKa + iivCL~cor(2,-0.5,3).

Values may be fixed (and therefore not estimated) using either the name fixed at the end of the assignment or by calling fixed() as a function for the value to fix. For 'theta' and 'sigma', either the estimate or the full definition (including lower and upper bounds) may be included in the fixed setting. For example, the following are all effectively equivalent to set a 'theta' or 'sigma' to a fixed value (because the lower and upper bounds are ignored for a fixed value): tvCL <-fixed(1), tvCL <-fixed(0,1), tvCL <-fixed(0,1,2), tvCL <-c(0,fixed(1),2), or tvCL <-c(0,1,fixed). For 'omega' assignment, the full block or none of the block must be set as fixed. Examples of setting an 'omega' value as fixed are: iivKa~fixed(1), iivKa + iivCL~fixed(1,2,3), or iivKa + iivCL~c(1,2,3,fixed). Anywhere that fixed is used, FIX, FIXED, or fix may be used equivalently.

For any value, standard mathematical operators or functions may be used to define the value. For example, exp(2) and 24*30 may be used to define a value anywhere that a number can be used (e.g. lower bound, estimate, upper bound, variance, etc.).

Values may be labeled using the label() function after the assignment. Labels are are used to make reporting easier by giving a human-readable description of the parameter, but the labels do not have any effect on estimation. The typical way to set a label so that the parameter tvCL has a label of "Typical Value of Clearance (L/hr)" is tvCL <-1; label("Typical Value of Clearance (L/hr)").

nlmixr will attempt to determine some back-transformations for the user. For example, CL <-exp(tvCL) will detect that tvCL must be back-transformed by exp() for easier interpretation. When you want to control the back-transformation, you can specify the back-transformation using backTransform() after the assignment. For example, to set the back-transformation to exp(), you can use tvCL <-1; backTransform(exp()).

Value

bounds expression or parsed ui object

Author(s)

Matthew L. Fidler

`initializeCovars` *Initializing covariates before estimation*

Description

Initializing covariates before estimation

Usage

```
initializeCovars(
  fitobject,
  fstring,
  covNames,
  initialEst,
  initialEstLB,
  initialEstUB
)
```

Arguments

`fitobject`	an nlmixr 'fit' object
`fstring`	a string giving the entire expression for the model function string
`covNames`	a list of covariate names (parameters) that need to be estimates
`initialEst`	the initial estimate for the covariate parameters to be estimated; default is 0
`initialEstLB`	a lower bound for the covariate parameters to be estimated; default is -Inf
`initialEstUB`	an upper bound for the covariate parameters to be estimated; default is Inf

Value

updated model object with the modified initial values

Author(s)

Vipul Mann, Matthew Fidler

instant.stan.extension *instant.stan.extension.*

Description

instant.stan.extension

Usage

```
instant.stan.extension(ode_str = NULL, covar = NULL)
```

Arguments

ode_str	ODE equations in a string
covar	a character vector of covariates

Value

Nothing, called for its side effects

invgaussian *Inverse Guassian absorption model*

Description

Inverse Guassian absorption model

Usage

```
invgaussian
```

Format

A data frame with 32 rows and 6 columns

time Time of observation

cp Concentration

Source

D'Argenio DZ, Schumitzky A, and Wang X (2009). "ADAPT 5 User's Guide: Pharmacokinetic/Pharmacodynamic Systems Analysis Software".

lin_cmt *concentrations from a linear compartment model*

Description

concentrations from a linear compartment model by close-form solutions

Usage

```
lin_cmt(
  obs_time,
  dose_time,
  dose,
  Tinf,
  params,
  oral,
  infusion,
  ncmt,
  parameterization
)
```

Arguments

obs_time	times at which an observation is desired
dose_time	times at which doses are given
dose	a vector of doses
Tinf	a vector of infusion duration
params	model-appropriate parameters per parameterization
oral	logical, whether oral absorption is true
infusion	logical, whether infusion is true
ncmt	number of compartments
parameterization	type of parameterization, 1=clearance/volume, 2=micro-constants

Details

This is used by some of the internal nlmixr routines, for example the low level nlme estimation with nlmixr. With the nlmixr functions you should use ‘linCmt()‘ instead. It is documented at https://nlmixrdevelopment.github.io/RxODE/articles/RxODE-model-types.html#solved-compartment-models

Value

calculated concentrations

makeDummies *Create categorical covariates*

Description

Create categorical covariates

Usage

```
makeDummies(data, covariate, varName)
```

Arguments

data	a dataframe containing the dataset that needs to be used
covariate	the covariate that needs to be converted to categorical; must be present in the data
varName	the variable name to which the given covariate is to be added

Value

a list of updated data with covariates added, an expression that needs to be added to the model expression, the list of covariate names, and the column names corresponding to the categorical covariates

Author(s)

Vipul Mann, Matthew Fidler

makeHockeyStick *Creating Hockey-stick covariates*

Description

Creating Hockey-stick covariates

Usage

```
makeHockeyStick(data, covariate, varName)
```

Arguments

data	a dataframe containing the dataset that needs to be used
covariate	the covariate that needs to be converted to hockey-stick; must be present in the data
varName	the variable name to which the given covariate is to be added

Value

a list of updated data with covariates added, an expression that needs to be added to the model expression, the list of covariate names, and the column names corresponding to the hockey-stick covariates

Author(s)

Vipul Mann, Matthew Fidler

`metabolite` *Parent/Metabolite dataset*

Description

Parent/Metabolite dataset

Usage

```
metabolite
```

Format

A data frame with 32 rows and 6 columns

time Time of observation

y1 Parent Concentration

y2 Metabolite Concentration

Source

D'Argenio DZ, Schumitzky A, and Wang X (2009). "ADAPT 5 User's Guide: Pharmacokinetic/Pharmacodynamic Systems Analysis Software".

`model` *nlmixr model block*

Description

nlmixr model block

Usage

```
model(model, ..., .lines = NULL)
```

Arguments

model	Model specification
...	Other arguments to model object parsed by nlmixr
.lines	This is an internal argument when codemodel is being called recursively and should not be used.

Value

Parsed UI object

Author(s)

Matthew L. Fidler

---

nlme_gof *GOF plots for nlme-based mixed-effect models*

Description

Generates basic goodness-of-fit plots for nlme-based mixed-effect models

Usage

```
nlme_gof(fit, ...)
```

Arguments

fit	nlme fit object
...	optional additional arguments

Value

nothing, displays plots

nlme_lin_cmpt *Fit nlme-based linear compartment mixed-effect model using closed form solution*

Description

'nlme_lin_cmpt' fits a linear one to three compartment model with either first order absorption, or i.v. bolus, or i.v. infusion. A user specifies the number of compartments, route of drug administrations, and the model parameterization. 'nlmixr' supports the clearance/volume parameterization and the micro constant parameterization, with the former as the default. Specification of fixed effects, random effects and initial values follows the standard nlme notations.

Usage

```
nlme_lin_cmpt(
  dat,
  parModel,
  ncmt,
  oral = TRUE,
  infusion = FALSE,
  tlag = FALSE,
  parameterization = 1,
  parTrans = .getParfn(oral, ncmt, parameterization, tlag),
  mcCores = 1,
  ...
)

nlmeLinCmpt(
  dat,
  parModel,
  ncmt,
  oral = TRUE,
  infusion = FALSE,
  tlag = FALSE,
  parameterization = 1,
  parTrans = .getParfn(oral, ncmt, parameterization, tlag),
  mcCores = 1,
  ...
)

nlmeLinCmt(
  dat,
  parModel,
  ncmt,
  oral = TRUE,
  infusion = FALSE,
  tlag = FALSE,
```

```
  parameterization = 1,
  parTrans = .getParfn(oral, ncmt, parameterization, tlag),
  mcCores = 1,
  ...
)
```

Arguments

dat	data to be fitted
parModel	list: model for fixed effects, randoms effects and initial values using nlme-type syntax.
ncmt	numerical: number of compartments: 1-3
oral	logical
infusion	logical
tlag	logical
parameterization	numerical: type of parameterization, 1=clearance/volume, 2=micro-constants
parTrans	function: calculation of PK parameters
mcCores	number of cores used in fitting (only for Linux)
...	additional nlme options

Value

A nlmixr nlme fit object

Author(s)

Wenping Wang

Examples

```
library(nlmixr)

specs <- list(fixed=lKA+lCL+lV~1, random = pdDiag(lKA+lCL~1),
              start=c(lKA=0.5, lCL=-3.2, lV=-1))
fit <- nlme_lin_cmpt(theo_md, par_model=specs, ncmt=1, verbose=TRUE)
#plot(augPred(fit,level=0:1))
summary(fit)
```

nlme_ode *Fit nlme-based mixed-effect model using ODE implementation*

Description

'nlme_ode' fits a mixed-effect model described using ordinary differential equation (ODEs). The ODE-definition follows RxODE syntax. Specification of fixed effects, random effects and initial values follows the standard nlme notations.

Usage

```
nlme_ode(
  dat.o,
  model,
  parModel,
  parTrans,
  response,
  responseScaler = NULL,
  transitAbs = FALSE,
  atol = 1e-08,
  rtol = 1e-08,
  maxsteps = 5000,
  hmin = 0,
  hmax = NA_real_,
  hini = 0,
  maxordn = 12,
  maxords = 5,
  debugODE = FALSE,
  mcCores = 1,
  ...
)

nlmeOde(
  dat.o,
  model,
  parModel,
  parTrans,
  response,
  responseScaler = NULL,
  transitAbs = FALSE,
  atol = 1e-08,
  rtol = 1e-08,
  maxsteps = 5000,
  hmin = 0,
  hmax = NA_real_,
  hini = 0,
  maxordn = 12,
```

```
  maxords = 5,
  debugODE = FALSE,
  mcCores = 1,
  ...
)
```

Arguments

dat.o	data to be fitted
model	a string containing the set of ordinary differential equations (ODE) and other expressions defining the changes in the dynamic system. For details, see the sections "Details" and "RxODE Syntax" below.
parModel	list: model for fixed effects, randoms effects and initial values.
parTrans	function: calculation of PK parameters
response	names of the response variable
responseScaler	optional response variable scaler. default is NULL
transitAbs	boolean indicating if this is a transit compartment absorption
atol	a numeric absolute tolerance (1e-8 by default) used by the ODE solver to determine if a good solution has been achieved; This is also used in the solved linear model to check if prior doses do not add anything to the solution.
rtol	a numeric relative tolerance (1e-6 by default) used by the ODE solver to determine if a good solution has been achieved. This is also used in the solved linear model to check if prior doses do not add anything to the solution.
maxsteps	maximum number of (internally defined) steps allowed during one call to the solver. (5000 by default)
hmin	The minimum absolute step size allowed. The default value is 0.
hmax	The maximum absolute step size allowed. When hmax=NA (default), uses the average difference + hmaxSd*sd in times and sampling events. The hmaxSd is a user specified parameter and which defaults to zero. When hmax=NULL RxODE uses the maximum difference in times in your sampling and events. The value 0 is equivalent to infinite maximum absolute step size.
hini	The step size to be attempted on the first step. The default value is determined by the solver (when hini = 0)
maxordn	The maximum order to be allowed for the nonstiff (Adams) method. The default is 12. It can be between 1 and 12.
maxords	The maximum order to be allowed for the stiff (BDF) method. The default value is 5. This can be between 1 and 5.
debugODE	a logical if debugging is enabled
mcCores	number of cores used in fitting (only for Linux)
...	additional nlme options

Details

The ODE-based model specification may be coded inside a character string or in a text file, see Section *RxODE Syntax* below for coding details. An internal RxODE compilation manager object translates the ODE system into C, compiles it, and dynamically loads the object code into the current R session. The call to RxODE produces an object of class RxODE which consists of a list-like structure (closure) with various member functions (see Section *Value* below).

Value

nlmixr nlme fit

RxODE Syntax

An RxODE model specification consists of one or more statements terminated by semi-colons, ';', and optional comments (comments are delimited by # and an end-of-line marker). **NB:** Comments are not allowed inside statements.

A block of statements is a set of statements delimited by curly braces, '{ ... }'. Statements can be either assignments or conditional if statements. Assignment statements can be either "simple" assignments, where the left hand is an identifier (i.e., variable), or special "time-derivative" assignments, where the left hand specifies the change of that variable with respect to time e.g., d/dt(depot).

Expressions in assignment and 'if' statements can be numeric or logical (no character expressions are currently supported). Numeric expressions can include the following numeric operators ('+', '-', '*', '/', '^'), and those mathematical functions defined in the C or the R math libraries (e.g., fabs, exp, log, sin). (Note that the modulo operator '%' is currently not supported.)

Identifiers in an RxODE model specification can refer to:

- state variables in the dynamic system (e.g., compartments in a pharmacokinetic/pharmacodynamic model);
- implied input variable, t (time), podo (oral dose, for absorption models), and tlast (last time point);
- model parameters, (ka rate of absorption, CL clearance, etc.);
- others, as created by assignments as part of the model specification.

Identifiers consist of case-sensitive alphanumeric characters, plus the underscore '_' character. **NB:** the dot '.' character is **not** a valid character identifier.

The values of these variables at pre-specified time points are saved as part of the fitted/integrated/solved model (see eventTable, in particular its member function add.sampling that defines a set of time points at which to capture a snapshot of the system via the values of these variables).

The ODE specification mini-language is parsed with the help of the open source tool *DParser*, Plevyak (2015).

Author(s)

Wenping Wang, Mathew Fidler

Examples

```
library(nlmixr)
ode <- "
d/dt(depot) =-KA*depot;
d/dt(centr) = KA*depot - KE*centr;
"
mypar <- function(lKA, lKE, lCL)
{
    KA=exp(lKA)
    KE=exp(lKE)
    CL=exp(lCL)
    V = CL/KE
}

specs <- list(fixed=lKA+lKE+lCL~1,
     random = pdDiag(lKA+lCL~1),
     start=c(lKA=0.5, lKE=-2.5, lCL=-3.2))

fit <- nlme_ode(theo_md, model=ode, par_model=specs, par_trans=mypar,
     response="centr", response.scaler="V",control=nlmeControl(pnlsTol=0.9))
```

---

nlmixr *nlmixr fits population PK and PKPD non-linear mixed effects models.*

Description

nlmixr is an R package for fitting population pharmacokinetic (PK) and pharmacokinetic-pharmacodynamic (PKPD) models.

Usage

```
nlmixr(
  object,
  data,
  est = NULL,
  control = list(),
  table = tableControl(),
  ...,
  save = NULL,
  envir = parent.frame()
)

## S3 method for class '`function`'
nlmixr(
  object,
  data,
```

```
  est = NULL,
  control = list(),
  table = tableControl(),
  ...,
  save = NULL,
  envir = parent.frame()
)

## S3 method for class 'nlmixrFitCore'
nlmixr(
  object,
  data,
  est = NULL,
  control = list(),
  table = tableControl(),
  ...,
  save = NULL,
  envir = parent.frame()
)

## S3 method for class 'nlmixrUI'
nlmixr(
  object,
  data,
  est = NULL,
  control = list(),
  ...,
  save = NULL,
  envir = parent.frame()
)
```

Arguments

object	Fitted object or function specifying the model.
data	Dataset to estimate. Needs to be RxODE compatible (see https://nlmixrdevelopment.github.io/RxODE/articles/RxODE-event-types.html for detailed dataset requirements).
est	Estimation method
control	Estimation control options. They could be nlmeControl, saemControl or foceiControl
table	A list controlling the table options (i.e. CWRES, NPDE etc). See tableControl.
...	Other parameters
save	Boolean to save a nlmixr object in a rds file in the working directory. If NULL, uses option "nlmixr.save"
envir	Environment that nlmixr is evaluated in.

Details

The nlmixr generalized function allows common access to the nlmixr estimation routines.

Value

Either a nlmixr model or a nlmixr fit object

nlmixr modeling mini-language

Rationale

nlmixr estimation routines each have their own way of specifying models. Often the models are specified in ways that are most intuitive for one estimation routine, but do not make sense for another estimation routine. Sometimes, legacy estimation routines like `nlme` have their own syntax that is outside of the control of the nlmixr package.

The unique syntax of each routine makes the routines themselves easier to maintain and expand, and allows interfacing with existing packages that are outside of nlmixr (like `nlme`). However, a model definition language that is common between estimation methods, and an output object that is uniform, will make it easier to switch between estimation routines and will facilitate interfacing output with external packages like Xpose.

The nlmixr mini-modeling language, attempts to address this issue by incorporating a common language. This language is inspired by both R and NONMEM, since these languages are familiar to many pharmacometricians.

Initial Estimates and boundaries for population parameters

nlmixr models are contained in a R function with two blocks: `ini` and `model`. This R function can be named anything, but is not meant to be called directly from R. In fact if you try you will likely get an error such as `Error: could not find function "ini"`.

The `ini` model block is meant to hold the initial estimates for the model, and the boundaries of the parameters for estimation routines that support boundaries (note nlmixr's `saem` and `nlme` do not currently support parameter boundaries).

To explain how these initial estimates are specified we will start with an annotated example:

```
f <- function(){ ## Note the arguments to the function are currently
                 ## ignored by nlmixr
    ini({
        ## Initial conditions for population parameters (sometimes
        ## called theta parameters) are defined by either `<-` or '='
        lCl <- 1.6      #log Cl (L/hr)
        ## Note that simple expressions that evaluate to a number are
        ## OK for defining initial conditions (like in R)
        lVc = log(90)  #log V (L)
        ## Also a comment on a parameter is captured as a parameter label
        lKa <- 1 #log Ka (1/hr)
        ## Bounds may be specified by c(lower, est, upper), like NONMEM:
        ## Residuals errors are assumed to be population parameters
        prop.err <- c(0, 0.2, 1)
    })
    ## The model block will be discussed later
    model({})
}
```

As shown in the above examples:

- Simple parameter values are specified as a R-compatible assignment
- Boundaries my be specified by `c(lower,est,upper)`.
- Like NONMEM, `c(lower,est)` is equivalent to `c(lower,est,Inf)`
- Also like NONMEM, `c(est)` does not specify a lower bound, and is equivalent to specifying the parameter without R's 'c' function.
- The initial estimates are specified on the variance scale, and in analogy with NONMEM, the square roots of the diagonal elements correspond to coefficients of variation when used in the exponential IIV implementation

These parameters can be named almost any R compatible name. Please note that:

- Residual error estimates should be coded as population estimates (i.e. using an '=' or '<-' statement, not a '~').
- Naming variables that start with "_" are not supported. Note that R does not allow variable starting with "_" to be assigned without quoting them.
- Naming variables that start with "`rx_`" or "`nlmixr_`" is not supported since RxODE and nlmixr use these prefixes internally for certain estimation routines and calculating residuals.
- Variable names are case sensitive, just like they are in R. "`CL`" is not the same as "`Cl`".

Initial Estimates for between subject error distribution (NONMEM's $OMEGA)

In mixture models, multivariate normal individual deviations from the population parameters are estimated (in NONMEM these are called `eta` parameters). Additionally the variance/covariance matrix of these deviations is also estimated (in NONMEM this is the OMEGA matrix). These also have initial estimates. In nlmixr these are specified by the '~' operator that is typically used in R for "modeled by", and was chosen to distinguish these estimates from the population and residual error parameters.

Continuing the prior example, we can annotate the estimates for the between subject error distribution

```
f <- function(){
    ini({
        lCl <- 1.6      #log Cl (L/hr)
        lVc = log(90)  #log V (L)
        lKa <- 1 #log Ka (1/hr)
        prop.err <- c(0, 0.2, 1)
        ## Initial estimate for ka IIV variance
        ## Labels work for single parameters
        eta.ka ~ 0.1 # BSV Ka

        ## For correlated parameters, you specify the names of each
        ## correlated parameter separated by a addition operator `+`
        ## and the left handed side specifies the lower triangular
        ## matrix initial of the covariance matrix.
        eta.cl + eta.vc ~ c(0.1,
                            0.005, 0.1)
```

```
        ## Note that labels do not currently work for correlated
        ## parameters.  Also do not put comments inside the lower
        ## triangular matrix as this will currently break the model.
    })
    ## The model block will be discussed later
    model({})
}
```

As shown in the above examples:

- Simple variances are specified by the variable name and the estimate separated by '~'.
- Correlated parameters are specified by the sum of the variable labels and then the lower triangular matrix of the covariance is specified on the left handed side of the equation. This is also separated by '~'.

Currently the model syntax does not allow comments inside the lower triangular matrix.

Model Syntax for ODE based models (NONMEM's $PK, $PRED, $DES and $ERROR)

Once the initialization block has been defined, you can define a model in terms of the defined variables in the `ini` block. You can also mix in RxODE blocks into the model.

The current method of defining a nlmixr model is to specify the parameters, and then possibly the RxODE lines:

Continuing describing the syntax with an annotated example:

```
f <- function(){
    ini({
        lCl <- 1.6      #log Cl (L/hr)
        lVc <- log(90)   #log Vc (L)
        lKA <- 0.1      #log Ka (1/hr)
        prop.err <- c(0, 0.2, 1)
        eta.Cl ~ 0.1 ## BSV Cl
        eta.Vc ~ 0.1 ## BSV Vc
        eta.KA ~ 0.1 ## BSV Ka
    })
    model({
        ## First parameters are defined in terms of the initial estimates
        ## parameter names.
        Cl <- exp(lCl + eta.Cl)
        Vc = exp(lVc + eta.Vc)
        KA <- exp(lKA + eta.KA)
        ## After the differential equations are defined
        kel <- Cl / Vc;
        d/dt(depot)    = -KA*depot;
        d/dt(centr)  =  KA*depot-kel*centr;
        ## And the concentration is then calculated
        cp = centr / Vc;
        ## Last, nlmixr is told that the plasma concentration follows
        ## a proportional error (estimated by the parameter prop.err)
```

```
        cp ~ prop(prop.err)
    })
}
```

A few points to note:

- Parameters are defined before the differential equations. Currently directly defining the differential equations in terms of the population parameters is not supported.
- The differential equations, parameters and error terms are in a single block, instead of multiple sections.
- State names, calculated variables cannot start with either "`rx_`" or "`nlmixr_`" since these are used internally in some estimation routines.
- Errors are specified using the '~'. Currently you can use either `add(parameter)` for additive error, prop(parameter) for proportional error or `add(parameter1) + prop(parameter2)` for additive plus proportional error. You can also specify `norm(parameter)` for the additive error, since it follows a normal distribution.
- Some routines, like `saem` require parameters in terms of `Pop.Parameter + Individual.Deviation.Parameter + Covariate*Covariate.Parameter`. The order of these parameters do not matter. This is similar to NONMEM's mu-referencing, though not quite so restrictive.
- The type of parameter in the model is determined by the initial block; Covariates used in the model are missing in the `ini` block. These variables need to be present in the modeling dataset for the model to run.

Model Syntax for solved PK systems

Solved PK systems are also currently supported by nlmixr with the 'linCmt()' pseudo-function. An annotated example of a solved system is below:

##'

```
f <- function(){
    ini({
        lCl <- 1.6      #log Cl (L/hr)
        lVc <- log(90)   #log Vc (L)
        lKA <- 0.1      #log Ka (1/hr)
        prop.err <- c(0, 0.2, 1)
        eta.Cl ~ 0.1 ## BSV Cl
        eta.Vc ~ 0.1 ## BSV Vc
        eta.KA ~ 0.1 ## BSV Ka
    })
    model({
        Cl <- exp(lCl + eta.Cl)
        Vc = exp(lVc + eta.Vc)
        KA <- exp(lKA + eta.KA)
        ## Instead of specifying the ODEs, you can use
        ## the linCmt() function to use the solved system.
        ##
        ## This function determines the type of PK solved system
        ## to use by the parameters that are defined.  In this case
```

```
        ## it knows that this is a one-compartment model with first-order
        ## absorption.
        linCmt() ~ prop(prop.err)
    })
}
```

A few things to keep in mind:

- Currently the solved systems support either oral dosing, IV dosing or IV infusion dosing and does not allow mixing the dosing types.
- While RxODE allows mixing of solved systems and ODEs, this has not been implemented in nlmixr yet.
- The solved systems implemented are the one, two and three compartment models with or without first-order absorption. Each of the models support a lag time with a tlag parameter.
- In general the linear compartment model figures out the model by the parameter names. nlmixr currently knows about numbered volumes, Vc/Vp, Clearances in terms of both Cl and Q/CLD. Additionally nlmixr knows about elimination micro-constants (ie K12). Mixing of these parameters for these models is currently not supported.

Checking model syntax

After specifying the model syntax you can check that nlmixr is interpreting it correctly by using the `nlmixr` function on it.

Using the above function we can get:

```
> nlmixr(f)
## 1-compartment model with first-order absorption in terms of Cl
## Initialization:
################################################################################
Fixed Effects ($theta):
    lCl     lVc     lKA
1.60000 4.49981 0.10000

Omega ($omega):
     [,1] [,2] [,3]
[1,]  0.1  0.0  0.0
[2,]  0.0  0.1  0.0
[3,]  0.0  0.0  0.1

## Model:
################################################################################
Cl <- exp(lCl + eta.Cl)
Vc = exp(lVc + eta.Vc)
KA <- exp(lKA + eta.KA)
## Instead of specifying the ODEs, you can use
## the linCmt() function to use the solved system.
##
## This function determines the type of PK solved system
```

```
## to use by the parameters that are defined.  In this case
## it knows that this is a one-compartment model with first-order
## absorption.
linCmt() ~ prop(prop.err)
```

In general this gives you information about the model (what type of solved system/RxODE), initial estimates as well as the code for the model block.

Using the model syntax for estimating a model

Once the model function has been created, you can use it and a dataset to estimate the parameters for a model given a dataset.

This dataset has to have RxODE compatible events IDs. Both Monolix and NONMEM use a different dataset description. You may convert these datasets to RxODE-compatible datasets with the `nmDataConvert` function. Note that steady state doses are not supported by RxODE, and therefore not supported by the conversion function.

As an example, you can use a simulated rich 1-compartment dataset.

```
d <- Oral_1CPT
d <- d[,names(d) != "SS"];
d <- nmDataConvert(d);
```

Once the data has been converted to the appropriate format, you can use the `nlmixr` function to run the appropriate code.

The method to estimate the model is:

```
fit <- nlmixr(model.function, rxode.dataset, est="est",control=estControl(options))
```

Currently `nlme` and `saem` are implemented. For example, to run the above model with `saem`, we could have the following:

```
> f <- function(){
    ini({
        lCl <- 1.6      #log Cl (L/hr)
        lVc <- log(90)   #log Vc (L)
        lKA <- 0.1      #log Ka (1/hr)
        prop.err <- c(0, 0.2, 1)
        eta.Cl ~ 0.1 ## BSV Cl
        eta.Vc ~ 0.1 ## BSV Vc
        eta.KA ~ 0.1 ## BSV Ka
    })
    model({
        ## First parameters are defined in terms of the initial estimates
        ## parameter names.
        Cl <- exp(lCl + eta.Cl)
        Vc = exp(lVc + eta.Vc)
        KA <- exp(lKA + eta.KA)
        ## After the differential equations are defined
```

```
        kel <- Cl / Vc;
        d/dt(depot)    = -KA*depot;
        d/dt(centr)  =  KA*depot-kel*centr;
        ## And the concentration is then calculated
        cp = centr / Vc;
        ## Last, nlmixr is told that the plasma concentration follows
        ## a proportional error (estimated by the parameter prop.err)
        cp ~ prop(prop.err)
    })
}
> fit.s <- nlmixr(f,d,est="saem",control=saemControl(n.burn=50,n.em=100,print=50));
Compiling RxODE differential equations...done.
c:/Rtools/mingw_64/bin/g++ -I"c:/R/R-34~1.1/include" -DNDEBUG   -I"d:/Compiler/gcc-4.9.3/local330/i
In file included from c:/R/R-34~1.1/library/RCPPAR~1/include/armadillo:52:0,
           from c:/R/R-34~1.1/library/RCPPAR~1/include/RcppArmadilloForward.h:46,
                from c:/R/R-34~1.1/library/RCPPAR~1/include/RcppArmadillo.h:31,
                 from saem3090757b4bd1x64.cpp:1:
c:/R/R-34~1.1/library/RCPPAR~1/include/armadillo_bits/compiler_setup.hpp:474:96: note: #pragma messa
  #pragma message ("WARNING: use of OpenMP disabled; this compiler doesn't support OpenMP 3.0+")
                                                                                               ^
c:/Rtools/mingw_64/bin/g++ -shared -s -static-libgcc -o saem3090757b4bd1x64.dll tmp.def saem3090757b4b
done.
1:    1.8174   4.6328   0.0553   0.0950   0.0950   0.0950   0.6357
50:    1.3900   4.2039   0.0001   0.0679   0.0784   0.1082   0.1992
100:    1.3894   4.2054   0.0107   0.0686   0.0777   0.1111   0.1981
150:    1.3885   4.2041   0.0089   0.0683   0.0778   0.1117   0.1980
Using sympy via SnakeCharmR
## Calculate ETA-based prediction and error derivatives:
Calculate Jacobian...................done.
Calculate sensitivities.......
done.
## Calculate d(f)/d(eta)
## ...
## done
## ...
## done
The model-based sensitivities have been calculated
Calculating Table Variables...
done
```

The options for saem are controlled by saemControl. You may wish to make sure the minimization is complete in the case of saem. You can do that with traceplot which shows the iteration history with the divided by burn-in and EM phases. In this case, the burn in seems reasonable; you may wish to increase the number of iterations in the EM phase of the estimation. Overall it is probably a semi-reasonable solution.

nlmixr output objects

In addition to unifying the modeling language sent to each of the estimation routines, the outputs currently have a unified structure.

You can see the fit object by typing the object name:

```
> fit.s
 -- nlmixr SAEM fit (ODE); OBJF calculated from FOCEi approximation -------------
      OBJF      AIC      BIC Log-likelihood Condition Number
  62337.09 62351.09 62399.01      -31168.55          82.6086

 -- Time (sec; fit.s$time): -----------------------------------------------------
           saem setup Likelihood Calculation covariance table
 elapsed 430.25 31.64                   1.19          0  3.44

 -- Parameters (fit.s$par.fixed): -----------------------------------------------
              Parameter Estimate     SE
 lCl      log Cl (L/hr)     1.39 0.0240  1.73       4.01 (3.83, 4.20)    26.6
 lVc         log Vc (L)     4.20 0.0256 0.608       67.0 (63.7, 70.4)    28.5
 lKA      log Ka (1/hr)  0.00924 0.0323  349.      1.01 (0.947, 1.08)    34.3
 prop.err      prop.err    0.198                              19.8
          Shrink(SD)
 lCl          0.248
 lVc           1.09
 lKA           4.19
 prop.err      1.81

   No correlations in between subject variability (BSV) matrix
  Full BSV covariance (fit.s$omega) or correlation (fit.s$omega.R; diagonals=SDs)
   Distribution stats (mean/skewness/kurtosis/p-value) available in fit.s$shrink

 -- Fit Data (object fit.s is a modified data.frame): ---------------------------
 # A tibble: 6,947 x 22
   ID     TIME    DV  PRED    RES    WRES IPRED  IRES  IWRES CPRED   CRES
 * <fct> <dbl> <dbl> <dbl>  <dbl>   <dbl> <dbl> <dbl>  <dbl> <dbl>  <dbl>
 1 1      0.25  205.  198.   6.60  0.0741  189.  16.2  0.434  198.   6.78
 2 1      0.5   311.  349. -38.7  -0.261   330. -19.0 -0.291  349. -38.3
 3 1      0.75  389.  464. -74.5  -0.398   434. -45.2 -0.526  463. -73.9
 # ... with 6,944 more rows, and 11 more variables: CWRES <dbl>, eta.Cl <dbl>,
 #   eta.Vc <dbl>, eta.KA <dbl>, depot <dbl>, centr <dbl>, Cl <dbl>, Vc <dbl>,
```

This example shows what is typical printout of a nlmixr fit object. The elements of the fit are:

- The type of fit (nlme, saem, etc)
- Metrics of goodness of fit (AIC, BIC, and logLik).
  - To align the comparison between methods, the FOCEi likelihood objective is calculated regardless of the method used and used for goodness of fit metrics.
  - This FOCEi likelihood has been compared to NONMEM's objective function and gives the same values (based on the data in Wang 2007)
  - Also note that saem does not calculate an objective function, and the FOCEi is used as the only objective function for the fit.

  - Even though the objective functions are calculated in the same manner, caution should be used when comparing fits from various estimation routines.
- The next item is the timing of each of the steps of the fit.
  - These can be also accessed by (`fit.s$time`).
  - As a mnemonic, the access for this item is shown in the printout. This is true for almost all of the other items in the printout.
- After the timing of the fit, the parameter estimates are displayed (can be accessed by `fit.s$par.fixed`)
  - While the items are rounded for R printing, each estimate without rounding is still accessible by the '$' syntax. For example, the '$Untransformed' gives the untransformed parameter values.
  - The Untransformed parameter takes log-space parameters and back-transforms them to normal parameters. Not the CIs are listed on the back-transformed parameter space.
  - Proportional Errors are converted to
- Omega block (accessed by `fit.s$omega`)
- The table of fit data. Please note:
  - A nlmixr fit object is actually a data frame. Saving it as a Rdata object and then loading it without nlmixr will just show the data by itself. Don't worry; the fit information has not vanished, you can bring it back by simply loading nlmixr, and then accessing the data.
  - Special access to fit information (like the `$omega`) needs nlmixr to extract the information.
  - If you use the `$` to access information, the order of precedence is:
    * Fit data from the overall data.frame
    * Information about the parsed nlmixr model (via `$uif`)
    * Parameter history if available (via `$par.hist` and `$par.hist.stacked`)
    * Fixed effects table (via `$par.fixed`)
    * Individual differences from the typical population parameters (via `$eta`)
    * Fit information from the list of information generated during the post-hoc residual calculation.
    * Fit information from the environment where the post-hoc residual were calculated
    * Fit information about how the data and options interacted with the specified model (such as estimation options or if the solved system is for an infusion or an IV bolus).
  - While the printout may displays the data as a `data.table` object or `tbl` object, the data is NOT any of these objects, but rather a derived data frame.
  - Since the object *is* a data.frame, you can treat it like one.

In addition to the above properties of the fit object, there are a few additional that may be helpful for the modeler:

- `$theta` gives the fixed effects parameter estimates (in NONMEM the `thetas`). This can also be accessed in `fixed.effects` function. Note that the residual variability is treated as a fixed effect parameter and is included in this list.
- `$eta` gives the random effects parameter estimates, or in NONMEM the `etas`. This can also be accessed in using the `random.effects` function.

Author(s)

Matthew L. Fidler, Rik Schoemaker

Examples

```
f_ode <- function(){
    ini({
        lCl <- 1.6      #log Cl (L/hr)
        lVc <- log(80)   #log Vc (L)
        lKA <- 0.3      #log Ka (1/hr)
        prop.err <- c(0, 0.2, 1)
        eta.Cl ~ 0.3 ## BSV Cl
        eta.Vc ~ 0.2 ## BSV Vc
        eta.KA ~ 0.1 ## BSV Ka
    })
    model({
        ## First parameters are defined in terms of the initial estimates
        ## parameter names.
        Cl <- exp(lCl + eta.Cl)
        Vc = exp(lVc + eta.Vc)
        KA <- exp(lKA + eta.KA)
        ## After the differential equations are defined
        kel <- Cl / Vc;
        d/dt(depot)    = -KA*depot;
        d/dt(centr)  =  KA*depot-kel*centr;
        ## And the concentration is then calculated
        cp = centr / Vc;
        ## Last, nlmixr is told that the plasma concentration follows
        ## a proportional error (estimated by the parameter prop.err)
        cp ~ prop(prop.err)
    })
}
f_linCmt <- function(){
    ini({
        lCl <- 1.6      #log Cl (L/hr)
        lVc <- log(90)   #log Vc (L)
        lKA <- 0.1      #log Ka (1/hr)
        prop.err <- c(0, 0.2, 1)
        add.err <- c(0, 0.01)
        eta.Cl ~ 0.1 ## BSV Cl
        eta.Vc ~ 0.1 ## BSV Vc
        eta.KA ~ 0.1 ## BSV Ka
    })
    model({
        Cl <- exp(lCl + eta.Cl)
        Vc = exp(lVc + eta.Vc)
        KA <- exp(lKA + eta.KA)
        ## Instead of specifying the ODEs, you can use
        ## the linCmt() function to use the solved system.
        ##
        ## This function determines the type of PK solved system
        ## to use by the parameters that are defined.  In this case
        ## it knows that this is a one-compartment model with first-order
```

```
        ## absorption.
        linCmt() ~ add(add.err) + prop(prop.err)
    })
}

# Use nlme algorithm
fit_linCmt_nlme <- try(nlmixr(f_ode, Oral_1CPT, est="nlme",
               control=nlmeControl(maxstepsOde = 50000, pnlsTol=0.4)))
if (!inherits(fit_linCmt_nlme, "try-error")) print(fit_linCmt_nlme)

# Use Focei algorithm
fit_linCmt_focei <- try(nlmixr(f_linCmt, Oral_1CPT, est="focei"))
if (!inherits(fit_linCmt_focei, "try-error")) print(fit_linCmt_focei)

# The ODE model can be fitted using the saem algorithm, more
# iterations should be used for real applications

fit_ode_saem <- try(nlmixr(f_ode, Oral_1CPT, est = "saem",
        control = saemControl(n.burn = 50, n.em = 100, print = 50)))
if (!inherits(fit_ode_saem, "try-error")) print(fit_ode_saem)
```

`nlmixrAugPred` *Augmented Prediction for nlmixr fit*

Description

Augmented Prediction for nlmixr fit

Usage

```
nlmixrAugPred(
  object,
  ...,
  covsInterpolation = c("locf", "linear", "nocb", "midpoint"),
  primary = NULL,
  minimum = NULL,
  maximum = NULL,
  length.out = 51L
)

## S3 method for class 'nlmixrFitData'
augPred(
  object,
  primary = NULL,
  minimum = NULL,
  maximum = NULL,
  length.out = 51,
```

```
  ...
)
```

Arguments

object	Nlmixr fit object
...	some methods for the generic may require additional arguments.
covsInterpolation	specifies the interpolation method for time-varying covariates. When solving ODEs it often samples times outside the sampling time specified in events. When this happens, the time varying covariates are interpolated. Currently this can be: • "linear" interpolation, which interpolates the covariate by solving the line between the observed covariates and extrapolating the new covariate value. • "constant" – Last observation carried forward (the default). • "NOCB" – Next Observation Carried Backward. This is the same method that NONMEM uses. • "midpoint" Last observation carried forward to midpoint; Next observation carried backward to midpoint.
primary	an optional one-sided formula specifying the primary covariate to be used to generate the augmented predictions. By default, if a covariate can be extracted from the data used to generate object (using getCovariate), it will be used as primary.
minimum	an optional lower limit for the primary covariate. Defaults to min(primary).
maximum	an optional upper limit for the primary covariate. Defaults to max(primary).
length.out	an optional integer with the number of primary covariate values at which to evaluate the predictions. Defaults to 51.

Value

Stacked data.frame with observations, individual/population predictions.

Author(s)

Matthew L. Fidler

---

nlmixrBounds *Extract the nlmixr bound information from a function.*

Description

Extract the nlmixr bound information from a function.

Usage

```
nlmixrBounds(fun)
```

Arguments

fun	Function to extract bound information from.

Value

a data.frame with bound information.

Author(s)

Bill Denney and Matthew L. Fidler

See Also

Other nlmixrBounds: nlmixrBoundsParser()

---

nlmixrBounds.eta.names

Get ETA names

Description

Get ETA names

Usage

```
nlmixrBounds.eta.names(obj)
```

Arguments

obj	UI object

Value

ETA names

Author(s)

Matthew L. Fidler

`nlmixrBounds.focei.upper.lower` *Get upper/lower/names for THETAs*

Description

Get upper/lower/names for THETAs

Usage

```
nlmixrBounds.focei.upper.lower(obj, type = c("upper", "lower", "name", "err"))
```

Arguments

`obj`	Bounds object
`type`	type of object extracted

Value

lower/upper/name vector

Author(s)

Matthew L. Fidler

`nlmixrBoundsParser` *Functions to assist with setting initial conditions and boundaries*

Description

These functions are not intended to be called by a user. They are intended to be internal to nlmixr

Usage

```
nlmixrBoundsParser(x)

## S3 method for class '`('
nlmixrBoundsParser(x)
```

Arguments

`x`	the object to attempt extraction from

Value

A list with how the object will be used

Methods (by class)

- (: For function bodies and similar.

See Also

Other nlmixrBounds: `nlmixrBounds()`

`nlmixrDynmodelConvert` *Converting nlmixr objects to dynmodel objects*

Description

Convert nlmixr Objects to dynmodel objects for use in fitting non-population dynamic models

Usage

```
nlmixrDynmodelConvert(.nmf)
```

Arguments

`.nmf`	nlmixr object

Value

list containing inputs for the dynmodel()

- `$fixPars` - fixed parameters defined as `fixed()` in the nlmixr object
- `$sigma` - error model parameters
- `$inits` - initial estimates for parameters in the model
- `$lower` - lower boundaries for estimated parameters
- `$upper` - upper boundaries for estimated parameters
- `$system` - RxODE object that defines the structural model
- `$model` - error model

Author(s)

Mason McComb and Matt Fidler

`nlmixrEst` *Generic for nlmixr estimation methods*

Description

Generic for nlmixr estimation methods

Usage

```
nlmixrEst(env, ...)

## S3 method for class 'saem'
nlmixrEst(env, ...)

## S3 method for class 'nlme'
nlmixrEst(env, ...)

## S3 method for class 'nlme.mu'
nlmixrEst(env, ...)

## S3 method for class 'nlme.mu.cov'
nlmixrEst(env, ...)

## S3 method for class 'nlme.free'
nlmixrEst(env, ...)

## S3 method for class 'posthoc'
nlmixrEst(env, ...)

## S3 method for class 'focei'
nlmixrEst(env, ...)

## S3 method for class 'foce'
nlmixrEst(env, ...)

## S3 method for class 'fo'
nlmixrEst(env, ...)

## S3 method for class 'foi'
nlmixrEst(env, ...)

## S3 method for class 'posthoc'
nlmixrEst(env, ...)

## S3 method for class 'dynmodel'
nlmixrEst(env, ...)
```

```
## S3 method for class 'nlmixrEst'
nlmixrEst(env, ...)
```

Arguments

env	Environment for nlmixr estimation routines
...	Extra arguments sent to estimation routine

Details

This is a S3 generic that allows others to use the nlmixr environment to do their own estimation routines

Value

nlmixr estimation object

Author(s)

Matthew Fidler

---

nlmixrGill83 *Get the optimal forward difference interval by Gill83 method*

Description

Get the optimal forward difference interval by Gill83 method

Usage

```
nlmixrGill83(
  what,
  args,
  envir = parent.frame(),
  which,
  gillRtol = sqrt(.Machine$double.eps),
  gillK = 10L,
  gillStep = 2,
  gillFtol = 0
)
```

Arguments

what	either a function or a non-empty character string naming the function to be called.
args	a *list* of arguments to the function call. The names attribute of args gives the argument names.

envir	an environment within which to evaluate the call. This will be most useful if what is a character string and the arguments are symbols or quoted expressions.
which	Which parameters to calculate the forward difference and optimal forward difference interval
gillRtol	The relative tolerance used for Gill 1983 determination of optimal step size.
gillK	The total number of possible steps to determine the optimal forward/central difference step size per parameter (by the Gill 1983 method). If 0, no optimal step size is determined. Otherwise this is the optimal step size determined.
gillStep	When looking for the optimal forward difference step size, this is This is the step size to increase the initial estimate by. So each iteration the new step size = (prior step size)*gillStep
gillFtol	The gillFtol is the gradient error tolerance that is acceptable before issuing a warning/error about the gradient estimates.

Value

A data frame with the following columns:

- infoGradient evaluation/forward difference information
- hfForward difference final estimate
- dfDerivative estimate
- df22nd Derivative Estimate
- errError of the final estimate derivative
- aEpsAbsolute difference for forward numerical differences
- rEpsRelative Difference for backward numerical differences
- aEpsCAbsolute difference for central numerical differences
- rEpsCRelative difference for central numerical differences

The info returns one of the following:

- Not AssessedGradient wasn't assessed
- GoodSuccess in Estimating optimal forward difference interval
- High Grad ErrorLarge error; Derivative estimate error fTol or more of the derivative
- Constant GradFunction constant or nearly constant for this parameter
- Odd/Linear GradFunction odd or nearly linear, df = K, df2 ~ 0
- Grad changes quicklydf2 increases rapidly as h decreases

Author(s)

Matthew Fidler

Examples

```
## These are taken from the numDeriv::grad examples to show how
## simple gradients are assessed with nlmixrGill83

nlmixrGill83(sin, pi)

nlmixrGill83(sin, (0:10)*2*pi/10)

func0 <- function(x){ sum(sin(x))  }
nlmixrGill83(func0 , (0:10)*2*pi/10)

func1 <- function(x){ sin(10*x) - exp(-x) }
curve(func1,from=0,to=5)

x <- 2.04
numd1 <- nlmixrGill83(func1, x)
exact <- 10*cos(10*x) + exp(-x)
c(numd1$df, exact, (numd1$df - exact)/exact)

x <- c(1:10)
numd1 <- nlmixrGill83(func1, x)
exact <- 10*cos(10*x) + exp(-x)
cbind(numd1=numd1$df, exact, err=(numd1$df - exact)/exact)

sc2.f <- function(x){
  n <- length(x)
   sum((1:n) * (exp(x) - x)) / n
}

sc2.g <- function(x){
  n <- length(x)
  (1:n) * (exp(x) - 1) / n
}

x0 <- rnorm(100)
exact <- sc2.g(x0)

g <- nlmixrGill83(sc2.f, x0)

max(abs(exact - g$df)/(1 + abs(exact)))
```

`nlmixrHess` *Calculate Hessian*

Description

Unlike ‘stats::optimHess‘ which assumes the gradient is accurate, nlmixrHess does not make as strong an assumption that the gradient is accurate but takes more function evaluations to calculate the Hessian. In addition, this procedures optimizes the forward difference interval by `nlmixrGill83`

Usage

```
nlmixrHess(par, fn, ..., envir = parent.frame())
```

Arguments

par	Initial values for the parameters to be optimized over.
fn	A function to be minimized (or maximized), with first argument the vector of parameters over which minimization is to take place. It should return a scalar result.
...	Extra arguments sent to nlmixrGill83
envir	an environment within which to evaluate the call. This will be most useful if what is a character string and the arguments are symbols or quoted expressions.

Details

If you have an analytical gradient function, you should use 'stats::optimHess'

Value

Hessian matrix based on Gill83

Author(s)

Matthew Fidler

References

https://v8doc.sas.com/sashtml/ormp/chap5/sect28.htm

See Also

nlmixrGill83, optimHess

Examples

```
 func0 <- function(x){ sum(sin(x))  }
 x <- (0:10)*2*pi/10
 nlmixrHess(x, func0)

fr <- function(x) {   ## Rosenbrock Banana function
    x1 <- x[1]
    x2 <- x[2]
    100 * (x2 - x1 * x1)^2 + (1 - x1)^2
}
grr <- function(x) { ## Gradient of 'fr'
    x1 <- x[1]
    x2 <- x[2]
    c(-400 * x1 * (x2 - x1 * x1) - 2 * (1 - x1),
       200 *      (x2 - x1 * x1))
}
```

```
h1 <- optimHess(c(1.2,1.2), fr, grr)

h2 <- optimHess(c(1.2,1.2), fr)

## in this case h3 is closer to h1 where the gradient is known

h3 <- nlmixrHess(c(1.2,1.2), fr)
```

`nlmixrLogo` *Messages the nlmixr logo...*

Description

Messages the nlmixr logo...

Usage

```
nlmixrLogo(str = "", version = sessionInfo()$otherPkgs$nlmixr$Version)
```

Arguments

`str`	String to print
`version`	Version information (by default use package version)

Value

nothing; Called to display version information

Author(s)

Matthew L. Fidler

`nlmixrPred` *Predict a nlmixr solved system*

Description

Predict a nlmixr solved system

Usage

```
nlmixrPred(object, ..., ipred = FALSE)

## S3 method for class 'nlmixrFitData'
predict(object, ...)
```

Arguments

object	is a either a RxODE family of objects, or a file-name with a RxODE model specification, or a string with a RxODE model specification.
...	Other arguments including scaling factors for each compartment. This includes S# = numeric will scale a compartment # by a dividing the compartment amount by the scale factor, like NONMEM.
ipred	Flag to calculate individual predictions. When ipred is TRUE, calculate individual predictions. When ipred is FALSE, set calculate typical population predations. When ipred is NA, calculate both individual and population predictions.

Value

an RxODE solved data frame with the predictions

---

nlmixrSim *Simulate a nlmixr solved system*

Description

This takes the uncertainty in the model parameter estimates and to simulate a number of theoretical studies. Each study simulates a realization of the parameters from the uncertainty in the fixed parameter estimates. In addition the omega and sigma matrices are simulated from the uncertainty in the Omega/Sigma matrices based on the number of subjects and observations the model was based on.

Usage

```
nlmixrSim(object, ...)

## S3 method for class 'nlmixrFitData'
rxSolve(
  object,
  params = NULL,
  events = NULL,
  inits = NULL,
  scale = NULL,
  method = c("liblsoda", "lsoda", "dop853", "indLin"),
  transitAbs = NULL,
  atol = 1e-08,
  rtol = 1e-06,
  maxsteps = 70000L,
  hmin = 0,
  hmax = NA_real_,
  hmaxSd = 0,
  hini = 0,
  maxordn = 12L,
```

```
  maxords = 5L,
  ...,
  cores,
  covsInterpolation = c("locf", "linear", "nocb", "midpoint"),
  addCov = FALSE,
  matrix = FALSE,
  sigma = NULL,
  sigmaDf = NULL,
  sigmaLower = -Inf,
  sigmaUpper = Inf,
  nCoresRV = 1L,
  sigmaIsChol = FALSE,
  sigmaSeparation = c("auto", "lkj", "separation"),
  sigmaXform = c("identity", "variance", "log", "nlmixrSqrt", "nlmixrLog",
    "nlmixrIdentity"),
  nDisplayProgress = 10000L,
  amountUnits = NA_character_,
  timeUnits = "hours",
  stiff,
  theta = NULL,
  thetaLower = -Inf,
  thetaUpper = Inf,
  eta = NULL,
  addDosing = FALSE,
  stateTrim = Inf,
  updateObject = FALSE,
  omega = NULL,
  omegaDf = NULL,
  omegaIsChol = FALSE,
  omegaSeparation = c("auto", "lkj", "separation"),
  omegaXform = c("variance", "identity", "log", "nlmixrSqrt", "nlmixrLog",
    "nlmixrIdentity"),
  omegaLower = -Inf,
  omegaUpper = Inf,
  nSub = 1L,
  thetaMat = NULL,
  thetaDf = NULL,
  thetaIsChol = FALSE,
  nStud = 1L,
  dfSub = 0,
  dfObs = 0,
  returnType = c("rxSolve", "matrix", "data.frame", "data.frame.TBS", "data.table",
    "tbl", "tibble"),
  seed = NULL,
  nsim = NULL,
  minSS = 10L,
  maxSS = 1000L,
  infSSstep = 12,
```

```
  strictSS = TRUE,
  istateReset = TRUE,
  subsetNonmem = TRUE,
  maxAtolRtolFactor = 0.1,
  from = NULL,
  to = NULL,
  by = NULL,
  length.out = NULL,
  iCov = NULL,
  keep = NULL,
  indLinPhiTol = 1e-07,
  indLinPhiM = 0L,
  indLinMatExpType = c("expokit", "Al-Mohy", "arma"),
  indLinMatExpOrder = 6L,
  drop = NULL,
  idFactor = TRUE,
  mxhnil = 0,
  hmxi = 0,
  warnIdSort = TRUE,
  warnDrop = TRUE,
  ssAtol = 1e-08,
  ssRtol = 1e-06,
  safeZero = TRUE,
  sumType = c("pairwise", "fsum", "kahan", "neumaier", "c"),
  prodType = c("long double", "double", "logify"),
  sensType = c("advan", "autodiff", "forward", "central"),
  linDiff = c(tlag = 1.5e-05, f = 1.5e-05, rate = 1.5e-05, dur = 1.5e-05, tlag2 =
    1.5e-05, f2 = 1.5e-05, rate2 = 1.5e-05, dur2 = 1.5e-05),
 linDiffCentral = c(tlag = TRUE, f = TRUE, rate = TRUE, dur = TRUE, tlag2 = TRUE, f2 =
    TRUE, rate2 = TRUE, dur2 = TRUE),
  resample = NULL,
  resampleID = TRUE
)

## S3 method for class 'nlmixrFitData'
simulate(object, nsim = 1, seed = NULL, ...)

## S3 method for class 'nlmixrFitData'
solve(a, b, ...)
```

Arguments

object	nlmixr object
...	Other arguments sent to rxSolve
params	a numeric named vector with values for every parameter in the ODE system; the names must correspond to the parameter identifiers used in the ODE specification;

`events` an `eventTable` object describing the input (e.g., doses) to the dynamic system and observation sampling time points (see `eventTable()`);

`inits` a vector of initial values of the state variables (e.g., amounts in each compartment), and the order in this vector must be the same as the state variables (e.g., PK/PD compartments);

`scale` a numeric named vector with scaling for ode parameters of the system. The names must correspond to the parameter identifiers in the ODE specification. Each of the ODE variables will be divided by the scaling factor. For example `scale=c(center=2)` will divide the center ODE variable by 2.

`method` The method for solving ODEs. Currently this supports:

- `"liblsoda"` thread safe lsoda. This supports parallel thread-based solving, and ignores user Jacobian specification.
- `"lsoda"` – LSODA solver. Does not support parallel thread-based solving, but allows user Jacobian specification.
- `"dop853"` – DOP853 solver. Does not support parallel thread-based solving nor user Jacobain specification
- `"indLin"` – Solving through inductive linearization. The RxODE dll must be setup specially to use this solving routine.

`transitAbs` boolean indicating if this is a transit compartment absorption

`atol` a numeric absolute tolerance (1e-8 by default) used by the ODE solver to determine if a good solution has been achieved; This is also used in the solved linear model to check if prior doses do not add anything to the solution.

`rtol` a numeric relative tolerance (`1e-6` by default) used by the ODE solver to determine if a good solution has been achieved. This is also used in the solved linear model to check if prior doses do not add anything to the solution.

`maxsteps` maximum number of (internally defined) steps allowed during one call to the solver. (5000 by default)

`hmin` The minimum absolute step size allowed. The default value is 0.

`hmax` The maximum absolute step size allowed. When `hmax=NA` (default), uses the average difference + hmaxSd*sd in times and sampling events. The `hmaxSd` is a user specified parameter and which defaults to zero. When `hmax=NULL` RxODE uses the maximum difference in times in your sampling and events. The value 0 is equivalent to infinite maximum absolute step size.

`hmaxSd` The number of standard deviations of the time difference to add to hmax. The default is 0

`hini` The step size to be attempted on the first step. The default value is determined by the solver (when `hini = 0`)

`maxordn` The maximum order to be allowed for the nonstiff (Adams) method. The default is 12. It can be between 1 and 12.

`maxords` The maximum order to be allowed for the stiff (BDF) method. The default value is 5. This can be between 1 and 5.

`cores` Number of cores used in parallel ODE solving. This is equivalent to calling `setRxThreads()`

`covsInterpolation`
: specifies the interpolation method for time-varying covariates. When solving ODEs it often samples times outside the sampling time specified in `events`. When this happens, the time varying covariates are interpolated. Currently this can be:

  - `"linear"` interpolation, which interpolates the covariate by solving the line between the observed covariates and extrapolating the new covariate value.
  - `"constant"` – Last observation carried forward (the default).
  - `"NOCB"` – Next Observation Carried Backward. This is the same method that NONMEM uses.
  - `"midpoint"` Last observation carried forward to midpoint; Next observation carried backward to midpoint.

`addCov`
: A boolean indicating if covariates should be added to the output matrix or data frame. By default this is disabled.

`matrix`
: A boolean indicating if a matrix should be returned instead of the RxODE's solved object.

`sigma`
: Named sigma covariance or Cholesky decomposition of a covariance matrix. The names of the columns indicate parameters that are simulated. These are simulated for every observation in the solved system.

`sigmaDf`
: Degrees of freedom of the sigma t-distribution. By default it is equivalent to `Inf`, or a normal distribution.

`sigmaLower`
: Lower bounds for simulated unexplained variability (by default -Inf)

`sigmaUpper`
: Upper bounds for simulated unexplained variability (by default Inf)

`nCoresRV`
: Number of cores used for the simulation of the sigma variables. By default this is 1. To reproduce the results you need to run on the same platform with the same number of cores. This is the reason this is set to be one, regardless of what the number of cores are used in threaded ODE solving.

`sigmaIsChol`
: Boolean indicating if the sigma is in the Cholesky decomposition instead of a symmetric covariance

`sigmaSeparation`
: separation strategy for sigma;

  Tells the type of separation strategy when simulating covariance with parameter uncertainty with standard deviations modeled in the `thetaMat` matrix.

  - `"lkj"` simulates the correlation matrix from the `rLKJ1` matrix with the distribution parameter `eta` equal to the degrees of freedom `nu` by `(nu-1)/2`
  - `"separation"` simulates from the identity inverse Wishart covariance matrix with `nu` degrees of freedom. This is then converted to a covariance matrix and augmented with the modeled standard deviations. While computationally more complex than the `"lkj"` prior, it performs better when the covariance matrix size is greater or equal to 10
  - `"auto"` chooses `"lkj"` when the dimension of the matrix is less than 10 and `"separation"` when greater than equal to 10.

`sigmaXform`
: When taking `sigma` values from the `thetaMat` simulations (using the separation strategy for covariance simulation), how should the `thetaMat` values be turned int standard deviation values:

- identity This is when standard deviation values are directly modeled by the params and thetaMat matrix
- variance This is when the params and thetaMat simulates the variance that are directly modeled by the thetaMat matrix
- log This is when the params and thetaMat simulates log(sd)
- nlmixrSqrt This is when the params and thetaMat simulates the inverse cholesky decomposed matrix with the x^2 modeled along the diagonal. This only works with a diagonal matrix.
- nlmixrLog This is when the params and thetaMat simulates the inverse cholesky decomposed matrix with the exp(x^2) along the diagonal. This only works with a diagonal matrix.
- nlmixrIdentity This is when the params and thetaMat simulates the inverse cholesky decomposed matrix. This only works with a diagonal matrix.

nDisplayProgress
: An integer indicating the minimum number of c-based solves before a progress bar is shown. By default this is 10,000.

amountUnits
: This supplies the dose units of a data frame supplied instead of an event table. This is for importing the data as an RxODE event table.

timeUnits
: This supplies the time units of a data frame supplied instead of an event table. This is for importing the data as an RxODE event table.

stiff
: a logical (TRUE by default) indicating whether the ODE system is stiff or not.

```
For stiff ODE systems (`stiff = TRUE`), `RxODE` uses the
LSODA (Livermore Solver for Ordinary Differential Equations)
Fortran package, which implements an automatic method switching
for stiff and non-stiff problems along the integration
interval, authored by Hindmarsh and Petzold (2003).

For non-stiff systems (`stiff = FALSE`), `RxODE` uses
DOP853, an explicit Runge-Kutta method of order 8(5, 3) of
Dormand and Prince as implemented in C by Hairer and Wanner
(1993).

If stiff is not specified, the `method` argument is used instead.
```

theta
: A vector of parameters that will be named THETA\[#\] and added to parameters

thetaLower
: Lower bounds for simulated population parameter variability (by default -Inf)

thetaUpper
: Upper bounds for simulated population unexplained variability (by default Inf)

eta
: A vector of parameters that will be named ETA\[#\] and added to parameters

addDosing
: Boolean indicating if the solve should add RxODE EVID and related columns. This will also include dosing information and estimates at the doses. Be default, RxODE only includes estimates at the observations. (default FALSE). When addDosing is NULL, only include EVID=0 on solve and exclude any model-times or EVID=2. If addDosing is NA the classic RxODE EVID events are returned. When addDosing is TRUE add the event information in NONMEM-style format; If subsetNonmem=FALSE RxODE will also include extra event types (EVID) for ending infusion and modeled times:

- EVID=-1 when the modeled rate infusions are turned off (matches rate=-1)
- EVID=-2 When the modeled duration infusions are turned off (matches rate=-2)
- EVID=-10 When the specified rate infusions are turned off (matches rate>0)
- EVID=-20 When the specified dur infusions are turned off (matches dur>0)
- EVID=101,102,103,... Modeled time where 101 is the first model time, 102 is the second etc.

stateTrim When amounts/concentrations in one of the states are above this value, trim them to be this value. By default Inf. Also trims to -stateTrim for large negative amounts/concentrations. If you want to trim between a range say c(0,2000000) you may specify 2 values with a lower and upper range to make sure all state values are in the reasonable range.

updateObject This is an internally used flag to update the RxODE solved object (when supplying an RxODE solved object) as well as returning a new object. You probably should not modify it's FALSE default unless you are willing to have unexpected results.

omega Estimate of Covariance matrix. When omega is a list, assume it is a block matrix and convert it to a full matrix for simulations.

omegaDf The degrees of freedom of a t-distribution for simulation. By default this is NULL which is equivalent to Inf degrees, or to simulate from a normal distribution instead of a t-distribution.

omegaIsChol Indicates if the omega supplied is a Cholesky decomposed matrix instead of the traditional symmetric matrix.

omegaSeparation

Omega separation strategy

Tells the type of separation strategy when simulating covariance with parameter uncertainty with standard deviations modeled in the thetaMat matrix.

- "lkj" simulates the correlation matrix from the rLKJ1 matrix with the distribution parameter eta equal to the degrees of freedom nu by (nu-1)/2
- "separation" simulates from the identity inverse Wishart covariance matrix with nu degrees of freedom. This is then converted to a covariance matrix and augmented with the modeled standard deviations. While computationally more complex than the "lkj" prior, it performs better when the covariance matrix size is greater or equal to 10
- "auto" chooses "lkj" when the dimension of the matrix is less than 10 and "separation" when greater than equal to 10.

omegaXform When taking omega values from the thetaMat simulations (using the separation strategy for covariance simulation), how should the thetaMat values be turned int standard deviation values:

- identity This is when standard deviation values are directly modeled by the params and thetaMat matrix
- variance This is when the params and thetaMat simulates the variance that are directly modeled by the thetaMat matrix
- log This is when the params and thetaMat simulates log(sd)

- `nlmixrSqrt` This is when the `params` and `thetaMat` simulates the inverse cholesky decomposed matrix with the `x^2` modeled along the diagonal. This only works with a diagonal matrix.
- `nlmixrLog` This is when the `params` and `thetaMat` simulates the inverse cholesky decomposed matrix with the `exp(x^2)` along the diagonal. This only works with a diagonal matrix.
- `nlmixrIdentity` This is when the `params` and `thetaMat` simulates the inverse cholesky decomposed matrix. This only works with a diagonal matrix.

`omegaLower` Lower bounds for simulated ETAs (by default -Inf)

`omegaUpper` Upper bounds for simulated ETAs (by default Inf)

`nSub` Number between subject variabilities (`ETAs`) simulated for every realization of the parameters.

`thetaMat` Named theta matrix.

`thetaDf` The degrees of freedom of a t-distribution for simulation. By default this is `NULL` which is equivalent to `Inf` degrees, or to simulate from a normal distribution instead of a `t`-distribution.

`thetaIsChol` Indicates if the `theta` supplied is a Cholesky decomposed matrix instead of the traditional symmetric matrix.

`nStud` Number virtual studies to characterize uncertainty in estimated parameters.

`dfSub` Degrees of freedom to sample the between subject variability matrix from the inverse Wishart distribution (scaled) or scaled inverse chi squared distribution.

`dfObs` Degrees of freedom to sample the unexplained variability matrix from the inverse Wishart distribution (scaled) or scaled inverse chi squared distribution.

`returnType` This tells what type of object is returned. The currently supported types are:

- `"rxSolve"` (default) will return a reactive data frame that can change easily change different pieces of the solve and update the data frame. This is the currently standard solving method in RxODE, is used for `rxSolve(object,...)`, `solve(object,...)`,
- `"data.frame"` – returns a plain, non-reactive data frame; Currently very slightly faster than `returnType="matrix"`
- `"matrix"` – returns a plain matrix with column names attached to the solved object. This is what is used `object$run` as well as `object$solve`
- `"data.table"` – returns a `data.table`; The `data.table` is created by reference (ie `setDt()`), which should be fast.
- `"tbl"` or `"tibble"` returns a tibble format.

`seed` an object specifying if and how the random number generator should be initialized

`nsim` represents the number of simulations. For RxODE, if you supply single subject event tables (created with [eventTable()])

`minSS` Minimum number of iterations for a steady-state dose

`maxSS` Maximum number of iterations for a steady-state dose

infSSstep Step size for determining if a constant infusion has reached steady state. By default this is large value, 420.

strictSS Boolean indicating if a strict steady-state is required. If a strict steady-state is (TRUE) required then at least minSS doses are administered and the total number of steady states doses will continue until maxSS is reached, or atol and rtol for every compartment have been reached. However, if ODE solving problems occur after the minSS has been reached the whole subject is considered an invalid solve. If strictSS is FALSE then as long as minSS has been reached the last good solve before ODE solving problems occur is considered the steady state, even though either atol, rtol or maxSS have not been achieved.

istateReset When TRUE, reset the ISTATE variable to 1 for lsoda and liblsoda with doses, like deSolve; When FALSE, do not reset the ISTATE variable with doses.

subsetNonmem subset to NONMEM compatible EVIDs only. By default TRUE.

maxAtolRtolFactor
The maximum atol/rtol that FOCEi and other routines may adjust to. By default 0.1

from When there is no observations in the event table, start observations at this value. By default this is zero.

to When there is no observations in the event table, end observations at this value. By default this is 24 + maximum dose time.

by When there are no observations in the event table, this is the amount to increment for the observations between from and to.

length.out The number of observations to create if there isn't any observations in the event table. By default this is 200.

iCov A data frame of individual non-time varying covariates to combine with the events dataset by merge.

keep Columns to keep from either the input dataset or the iCov dataset. With the iCov dataset, the column is kept once per line. For the input dataset, if any records are added to the data LOCF (Last Observation Carried forward) imputation is performed.

indLinPhiTol the requested accuracy tolerance on exponential matrix.

indLinPhiM the maximum size for the Krylov basis

indLinMatExpType
This is them matrix exponential type that is use for RxODE. Currently the following are supported:

- Al-Mohy Uses the exponential matrix method of Al-Mohy Higham (2009)
- arma Use the exponential matrix from RcppArmadillo
- expokit Use the exponential matrix from Roger B. Sidje (1998)

indLinMatExpOrder
an integer, the order of approximation to be used, for the Al-Mohy and expokit values. The best value for this depends on machine precision (and slightly on the matrix). We use 6 as a default.

drop Columns to drop from the output

idFactor — This boolean indicates if original ID values should be maintained. This changes the default sequentially ordered ID to a factor with the original ID values in the original dataset. By default this is enabled.

mxhnil — maximum number of messages printed (per problem) warning that T + H = T on a step (H = step size). This must be positive to result in a non-default value. The default value is 0 (or infinite).

hmxi — inverse of the maximum absolute value of H to are used. hmxi = 0.0 is allowed and corresponds to an infinite hmax1 (default). hminandhmximay be changed at any time, but will not take fect until the next change ofHis considered. This option is only considered with-method="liblsoda"‘.

warnIdSort — Warn if the ID is not present and RxODE assumes the order of the parameters/iCov are the same as the order of the parameters in the input dataset.

warnDrop — Warn if column(s) were supposed to be dropped, but were not present.

ssAtol — Steady state atol convergence factor. Can be a vector based on each state.

ssRtol — Steady state rtol convergence factor. Can be a vector based on each state.

safeZero — Use safe zero divide and log routines. By default this is turned on but you may turn it off if you wish.

sumType — Sum type to use for sum() in RxODE code blocks.

pairwise uses the pairwise sum (fast, default)

fsum uses Python's fsum function (most accurate)

kahan uses Kahan correction

neumaier uses Neumaier correction

c uses no correction: default/native summing

prodType — Product to use for prod() in RxODE blocks
long double converts to long double, performs the multiplication and then converts back.

double uses the standard double scale for multiplication.

sensType — Sensitivity type for linCmt() model:

advan Use the direct advan solutions

autodiff Use the autodiff advan solutions

forward Use forward difference solutions

central Use central differences

linDiff — This gives the linear difference amount for all the types of linear compartment model parameters where sensitivities are not calculated. The named components of this numeric vector are:

- "lag" Central compartment lag
- "f" Central compartment bioavailability
- "rate" Central compartment modeled rate
- "dur" Central compartment modeled duration
- "lag2" Depot compartment lag
- "f2" Depot compartment bioavailability
- "rate2" Depot compartment modeled rate

- "dur2" Depot compartment modeled duration

linDiffCentral	This gives the which parameters use central differences for the linear compartment model parameters. The are the same components as linDiff
resample	A character vector of model variables to resample from the input dataset; This sampling is done with replacement. When NULL or FALSE no resampling is done. When TRUE resampling is done on all covariates in the input dataset
resampleID	boolean representing if the resampling should be done on an individual basis TRUE (ie. a whole patient is selected) or each covariate is resampled independent of the subject identifier FALSE. When resampleID=TRUE correlations of parameters are retained, where as when resampleID=FALSE ignores patient covariate correaltions. Hence the default is resampleID=TRUE.
a	when using solve(), this is equivalent to the object argument. If you specify object later in the argument list it overwrites this parameter.
b	when using solve(), this is equivalent to the params argument. If you specify params as a named argument, this overwrites the output

Value

A RxODE solved object

`nlmixrTest` *nlmixTest function for testing*

Description

nlmixTest function for testing

Usage

```
nlmixrTest(expr, silent = .isTestthat(), test = "cran")
```

Arguments

expr	Expression for testing
silent	Boolean for testing
test	this represents the test group of the test

Value

Nothing, called for its side effects

Author(s)

Matthew Fidler

nlmixrUI.dynmodelfun *Return dynmodel variable translation function*

Description

Return dynmodel variable translation function

Usage

```
nlmixrUI.dynmodelfun(object)
```

Arguments

object	nlmixr ui object

Value

nlmixr dynmodel translation

Author(s)

Matthew Fidler

nlmixrUI.dynmodelfun2 *Return dynmodel variable translation function*

Description

Return dynmodel variable translation function

Usage

```
nlmixrUI.dynmodelfun2(object)
```

Arguments

object	nlmixr ui object

Value

nlmixr dynmodel translation

Author(s)

Matthew Fidler

nlmixrUI.focei.fixed *Get parameters that are fixed*

Description

Get parameters that are fixed

Usage

```
nlmixrUI.focei.fixed(obj)
```

Arguments

obj	UI object

Value

logical vector of fixed THETA parameters

Author(s)

Matthew L. Fidler

nlmixrUI.focei.inits *Get the FOCEi initializations*

Description

Get the FOCEi initializations

Usage

```
nlmixrUI.focei.inits(obj)
```

Arguments

obj	UI object

Value

list with FOCEi style initializations

Author(s)

Matthew L. Fidler

nlmixrUI.nlme.specs *Create the nlme specs list for nlmixr nlme solving*

Description

Create the nlme specs list for nlmixr nlme solving

Usage

```
nlmixrUI.nlme.specs(object, mu.type = c("thetas", "covariates", "none"))
```

Arguments

object	UI object
mu.type	is the mu-referencing type of model hat nlme will be using.

Value

specs list for nlme

Author(s)

Matthew L. Fidler

nlmixrUI.rxode.pred *Return RxODE model with predictions appended*

Description

Return RxODE model with predictions appended

Usage

```
nlmixrUI.rxode.pred(object)
```

Arguments

object	UI object

Value

String or NULL if RxODE is not specified by UI.

Author(s)

Matthew L. Fidler

nlmixrUI.saem.ares *Get initial estimate for ares SAEM.*

Description

Get initial estimate for ares SAEM.

Usage

```
nlmixrUI.saem.ares(obj)
```

Arguments

obj	UI model

Value

SAEM model$ares spec

Author(s)

Matthew L. Fidler

nlmixrUI.saem.bres *Get initial estimate for bres SAEM.*

Description

Get initial estimate for bres SAEM.

Usage

```
nlmixrUI.saem.bres(obj)
```

Arguments

obj	UI model

Value

SAEM model$ares spec

Author(s)

Matthew L. Fidler

nlmixrUI.saem.cres *Get initial estimate for bres SAEM.*

Description

Get initial estimate for bres SAEM.

Usage

```
nlmixrUI.saem.cres(obj)
```

Arguments

obj	UI model

Value

SAEM model$ares spec

Author(s)

Matthew L. Fidler

nlmixrUI.saem.distribution *Get SAEM distribution*

Description

Get SAEM distribution

Usage

```
nlmixrUI.saem.distribution(obj)
```

Arguments

obj	UI object

Value

Character of distribution

Author(s)

Matthew L. Fidler

nlmixrUI.saem.eta.trans *Get the eta->eta.trans for SAEM*

Description

Get the eta->eta.trans for SAEM

Usage

```
nlmixrUI.saem.eta.trans(obj)
```

Arguments

obj	ui object

Value

list of eta to eta.trans

Author(s)

Matthew L. Fidler

nlmixrUI.saem.fit *Generate saem.fit user function.*

Description

Generate saem.fit user function.

Usage

```
nlmixrUI.saem.fit(obj)
```

Arguments

obj	UI object

Value

saem user function

Author(s)

Matthew L. Fidler

nlmixrUI.saem.fixed *Get parameters that are fixed for SAEM*

Description

Get parameters that are fixed for SAEM

Usage

```
nlmixrUI.saem.fixed(obj)
```

Arguments

obj	UI object

Value

List of parameters that are fixed.

Author(s)

Matthew L. Fidler

nlmixrUI.saem.init *Get saem initilization list*

Description

Get saem initilization list

Usage

```
nlmixrUI.saem.init(obj)
```

Arguments

obj	nlmixr UI object

Value

Return SAEM inits list.

Author(s)

Matthew L. Fidler

`nlmixrUI.saem.init.omega` *SAEM's init$omega*

Description

SAEM's init$omega

Usage

```
nlmixrUI.saem.init.omega(obj, names = FALSE)
```

Arguments

`obj`	nlmixr UI object
`names`	When `TRUE` return the omega names. By default this is `FALSE`.

Value

Return initial matrix

Author(s)

Matthew L. Fidler

`nlmixrUI.saem.init.theta` *Generate SAEM initial estimates for THETA.*

Description

Generate SAEM initial estimates for THETA.

Usage

```
nlmixrUI.saem.init.theta(obj)
```

Arguments

`obj`	nlmixr UI object

Value

SAEM theta initial estimates

Author(s)

Matthew L. Fidler

nlmixrUI.saem.log.eta *Get model$log.eta for SAEM*

Description

Get model$log.eta for SAEM

Usage

```
nlmixrUI.saem.log.eta(obj)
```

Arguments

obj	UI model

Value

SAEM model$log.eta

Author(s)

Matthew L. Fidler

nlmixrUI.saem.model *Generate SAEM model list*

Description

Generate SAEM model list

Usage

```
nlmixrUI.saem.model(obj)
```

Arguments

obj	nlmixr UI object

Value

SAEM model list

Author(s)

Matthew L. Fidler

`nlmixrUI.saem.model.omega` *Get the SAEM model Omega*

Description

Get the SAEM model Omega

Usage

```
nlmixrUI.saem.model.omega(obj)
```

Arguments

`obj`	UI model

Value

SAEM model$omega spec

Author(s)

Matthew L. Fidler

`nlmixrUI.saem.res.mod` *Get the SAEM model$res.mod code*

Description

Get the SAEM model$res.mod code

Usage

```
nlmixrUI.saem.res.mod(obj)
```

Arguments

`obj`	UI model

Value

SAEM model$res.mod spec

Author(s)

Matthew L. Fidler

nlmixrUI.saem.res.name *Get error names for SAEM*

Description

Get error names for SAEM

Usage

```
nlmixrUI.saem.res.name(obj)
```

Arguments

obj	SAEM user interface function.

Value

Names of error estimates for SAEM

Author(s)

Matthew L. Fidler

nlmixrUI.saem.rx1 *Return RxODE model with predictions appended*

Description

Return RxODE model with predictions appended

Usage

```
nlmixrUI.saem.rx1(object)
```

Arguments

object	UI object

Value

Combined focei model text for RxODE

Author(s)

Matthew L. Fidler

nlmixrUI.saem.theta.name *Get THETA names for nlmixr's SAEM*

Description

Get THETA names for nlmixr's SAEM

Usage

```
nlmixrUI.saem.theta.name(uif)
```

Arguments

uif	nlmixr UI object

Value

SAEM theta names

Author(s)

Matthew L. Fidler

nlmixrUI.theta.pars *Get the Parameter function with THETA/ETAs defined*

Description

Get the Parameter function with THETA/ETAs defined

Usage

```
nlmixrUI.theta.pars(obj)
```

Arguments

obj	UI object

Value

parameters function defined in THETA[#] and ETA[#]s.

Author(s)

Matthew L. Fidler

nlmixrValidate *Validate nlmixr*

Description

This allows easy vaildation/qualification of nlmixr by running the testing suite on your system.

Usage

```
nlmixrValidate(type = NULL, check = FALSE)

nmTest(type = NULL, check = FALSE)
```

Arguments

type	of test to be run
check	Use devtools::check to run checks

Value

Nothing, called for its side effects

Author(s)

Matthew L. Fidler

nlmixrVersion *Display nlmixr's version*

Description

Display nlmixr's version

Usage

```
nlmixrVersion()
```

Value

Nothing, called for its side effects

Author(s)

Matthew L. Fidler

`nlmixr_fit` *Fit a nlmixr model*

Description

Fit a nlmixr model

Usage

```
nlmixr_fit(
  uif,
  data,
  est = NULL,
  control = list(),
  ...,
  sum.prod = FALSE,
  table = tableControl(),
  keep = NULL,
  drop = NULL,
  save = NULL,
  envir = parent.frame()
)
```

Arguments

`uif`	Parsed nlmixr model (by `nlmixr(mod.fn)`).
`data`	Dataset to estimate. Needs to be RxODE compatible (see https://nlmixrdevelopment.github.io/RxODE/articles/RxODE-event-types.html for detailed dataset requirements).
`est`	Estimation method
`control`	Estimation control options. They could be `nlmeControl`, `saemControl` or `foceiControl`
`...`	Parameters passed to estimation method.
`sum.prod`	Take the RxODE model and use more precise products/sums. Increases solving accuracy and solving time.
`table`	A list controlling the table options (i.e. CWRES, NPDE etc). See `tableControl`.
`keep`	Columns to keep from either the input dataset. For the input dataset, if any records are added to the data LOCF (Last Observation Carried forward) imputation is performed.
`drop`	Columns to drop from the output
`save`	This option determines if the fit will be saved to be reloaded if already run. If NULL, get the option from `options("nlmixr.save")`;
`envir`	Environment that nlmixr is evaluated in.

Value

nlmixr fit object

Author(s)

Matthew L. Fidler

---

nmDocx *Create a run summary word document*

Description

Create a run summary word document

Usage

```
nmDocx(
  x,
  docxOut = NULL,
  docxTemplate = NULL,
  plot = TRUE,
  titleStyle = getOption("nlmixr.docx.title", "Title"),
  subtitleStyle = getOption("nlmixr.docx.subtitle", "Subtitle"),
  normalStyle = getOption("nlmixr.docx.normal", "Normal"),
  headerStyle = getOption("nlmixr.docx.heading1", "Heading 1"),
  centeredStyle = getOption("nlmixr.docx.centered", "centered"),
 preformattedStyle = getOption("nlmixr.docx.preformatted", "HTML Preformatted"),
  width = getOption("nlmixr.docx.width", 69),
  save = FALSE
)

nmSave(x, ..., save = TRUE)
```

Arguments

x	nlmixr fit object.
docxOut	Output file for run information document. If not specified it is the name of R object where the fit is located with the -YEAR-MONTH-DAY.docx appended. If it is NULL the document is not saved, but the officer object is returned.
docxTemplate	This is the document template. If not specified it defaults to option("nlmixr.docx.template"). If option("nlmixr.docx.template") is not specified it uses the included nlmixr document template. When docxTemplate=NULL it uses the officer blank document.
plot	Boolean indicating if the default goodness of fit plots are added to the document. By default TRUE

titleStyle	This is the word style name for the nlmixr title; Usually this is nlmixr version (R object). Defaults to option("nlmixr.docx.title") or Title
subtitleStyle	This is the word style for the subtitle which is nlmixr model name and date. Defaults to option("nlmixr.docx.subtitle") or Subtitle
normalStyle	This is the word style for normal text. Defaults to option("nlmixr.docx.normal") or Normal
headerStyle	This is the word style for heading text. Defaults to option("nlmixr.docx.heading1") or Heading 1
centeredStyle	This is the word style for centered text which is used for the figures. Defaults to option("nlmixr.docx.centered") or centered
preformattedStyle	This is the preformatted text style for R output lines. Defaults to option("nlmixr.docx.preformatted" or HTML Preformatted
width	Is an integer representing the number of characters your preformatted style supports. By default this is option("nlmixr.docx.width") or 69
save	Should the docx be saved in a zip file with the R rds data object for the fit? By default this is FALSE with nmDocx and TRUE with nmSave
...	when using 'nmSave' these arguments are passed to 'nmDocx'

Value

An officer docx object

Author(s)

Matthew Fidler

Examples

```
 library(nlmixr)
pheno <- function() {
    # Pheno with covariance
  ini({
    tcl <- log(0.008) # typical value of clearance
    tv <-  log(0.6)   # typical value of volume
    ## var(eta.cl)
    eta.cl + eta.v ~ c(1,
                       0.01, 1) ## cov(eta.cl, eta.v), var(eta.v)
                      # interindividual variability on clearance and volume
    add.err <- 0.1    # residual variability
  })
  model({
    cl <- exp(tcl + eta.cl) # individual value of clearance
    v <- exp(tv + eta.v)    # individual value of volume
    ke <- cl / v            # elimination rate constant
    d/dt(A1) = - ke * A1    # model differential equation
    cp = A1 / v             # concentration in plasma
```

```
    cp ~ add(add.err)       # define error model
  })
}

fit.s <- nlmixr(pheno, pheno_sd, "saem")

## Save output information into a word document
RxODE::.rxWithWd(tempdir(), # Put document in temporary directory
  nmDocx(fit.s)
)
```

`nmLst` *Create a large output based on a nlmixr fit*

Description

Create a large output based on a nlmixr fit

Usage

```
nmLst(x, lst = NULL)
```

Arguments

`x`	nlmixr fit object
`lst`	Listing file. If not specified, it is determined by the day and the model/R-object name. If it is specified as `NULL` the listing output is displayed on the screen.

Value

invisibly returns fit

Author(s)

Matthew Fidler

nmsimplex *Nelder-Mead simplex search*

Description

Nelder-Mead simplex search

Usage

```
nmsimplex(start, fr, rho = NULL, control = list())
```

Arguments

start	initials
fr	objective function
rho	evaluation environment
control	additional optimization options

Value

a list of ...

ofv *Return the objective function*

Description

Return the objective function

Usage

```
ofv(x, type, ...)
```

Arguments

x	object to return objective function value
type	Objective function type value to retrieve or add. • focei For most models you can specify "focei" and it will add the focei objective function. • nlme This switches/chooses the nlme objective function if applicable. This objective function cannot be added if it isn't present. • fo FO objective function value. Cannot be generated • foce FOCE object function value. Cannot be generated

- laplace# This adds/retrieves the Laplace objective function value. The # represents the number of standard deviations requested when expanding the Gaussian Quadrature. This can currently only be used with saem fits.
- gauss#.# This adds/retrieves the Gaussian Quadrature approximation of the objective function. The first number is the number of nodes to use in the approximation. The second number is the number of standard deviations to expand upon.

... Other arguments sent to ofv for other methods.

Value

Objective function value

Author(s)

Matthew Fidler

`Oral_1CPT` *Oral_1CPT – 1 Compartment Model with Oral Absorption Simulated Data from ACOP 2016*

Description

This is a simulated dataset from the ACOP 2016 poster. All Datasets were simulated with the following methods.

Usage

```
Oral_1CPT
```

Format

A data frame with 7,920 rows and 15 columns

ID Simulated Subject ID

TIME Simulated Time

DV Simulated Dependent Variable

LNDV Simulated log(Dependent Variable)

MDV Missing DV data item

AMT Dosing AMT

EVID NONMEM Event ID

DOSE Dose

V Individual Simulated Volume

CL Individual Clearance

KA Individual Ka

SS Steady State

II Interdose Interval

SD Single Dose Flag

CMT Compartment

Details

Richly sampled profiles were simulated for 4 different dose levels (10, 30, 60 and 120 mg) of 30 subjects each as single dose (over 72h), multiple dose (4 daily doses), single and multiple dose combined, and steady state dosing, for a range of test models: 1- and 2-compartment disposition, with and without 1st order absorption, with either linear or Michaelis-Menten (MM) clearance(MM without steady state dosing). This provided a total of 42 test cases. All inter-individual variabilities (IIVs) were set at 30 were the same for all models. A similar set of models was previously used to compare NONMEM and Monolix4. Estimates of population parameters, standard errors for fixed-effect parameters, and run times were compared both for closed-form solutions and using ODEs. Additionally, a sparse data estimation situation was investigated where 500 datasets of 600 subjects each (150 per dose) were generated consisting of 4 random time point samples in 24 hours per subject, using a first-order absorption, 1-compartment disposition, linear elimination model.

Source

Schoemaker R, Xiong Y, Wilkins J, Laveille C, Wang W. nlmixr: an open-source package for pharmacometric modelling in R. ACOP 2016

See Also

Other nlmixr datasets: `Bolus_1CPTMM`, `Bolus_1CPT`, `Bolus_2CPTMM`, `Bolus_2CPT`, `Infusion_1CPT`, `Wang2007`, `pheno_sd`, `rats`, `theo_md`, `theo_sd`, `warfarin`

---

performNorm *Perform normalization of the covariate*

Description

Perform normalization of the covariate

Usage

```
performNorm(
  data,
  covariate,
  varName,
  normOp,
  normValVec,
  isLog = FALSE,
```

```
  isCat = FALSE,
  isHS = FALSE
)
```

Arguments

data	a dataframe consisting the covariates added
covariate	a string giving the covariate name; must be present in the data used for 'fit'
varName	the variable name to which the covariate is being added
normOp	an operator indicating the kind transformation to be done on the covariate
normValVec	a numeric value to be used for normalization of the covariate
isLog	a boolean indicating the presence of log-transformation in the funstring; default is FALSE
isCat	a boolean indicating if the covariate is categorical; default is FALSE
isHS	a boolean indicating if the covariate is of Hockey-stick kind; default is FALSE

Value

a list comprising the update dataframe, the expression for covariate, and a list of covariate names

Author(s)

Vipul Mann, Matthew Fidler

---

pheno_sd *Single Dose Phenobarbitol PK/PD*

Description

This is from a PK study in neonatal infants. They received multiple doses of phenobarbital for seizure prevention.

Usage

```
pheno_sd
```

Format

A data frame with 744 rows and 8 columns

ID Infant ID

TIME Time of (hr)

AMT Dose in (ug/kg)

WT Weight in kg

APGR A 5-minute Apgar score to measure infant health

DV The concentration of phenobarbitol in the serum (ug/mL)

MDV If the dependent variable (DV) is missing; 0 for observations, 1 for doses

EVID Event ID

Details

The data were originally given in Grasela and Donn(1985) and are analyzed in Boeckmann, Sheiner and Beal (1994), in Davidian and Giltinan (1995), and in Littell et al. (1996).

Source

Pinheiro, J. C. and Bates, D. M. (2000), Mixed-Effects Models in S and S-PLUS, Springer, New York. (Appendix A.23)

Davidian, M. and Giltinan, D. M. (1995), Nonlinear Models for Repeated Measurement Data, Chapman and Hall, London. (section 6.6)

Grasela and Donn (1985), Neonatal population pharmacokinetics of phenobarbital derived from routine clinical data, Developmental Pharmacology and Therapeutics, 8, 374-383.

Boeckmann, A. J., Sheiner, L. B., and Beal, S. L. (1994), NONMEM Users Guide: Part V, University of California, San Francisco.

Littell, R. C., Milliken, G. A., Stroup, W. W. and Wolfinger, R. D. (1996), SAS System for Mixed Models, SAS Institute, Cary, NC.

See Also

Other nlmixr datasets: `Bolus_1CPTMM`, `Bolus_1CPT`, `Bolus_2CPTMM`, `Bolus_2CPT`, `Infusion_1CPT`, `Oral_1CPT`, `Wang2007`, `rats`, `theo_md`, `theo_sd`, `warfarin`

---

plot.dyn.mcmc *Plot of a non-population dynamic model fit using mcmc*

Description

Plot of a non-population dynamic model fit using mcmc

Usage

```
## S3 method for class 'dyn.mcmc'
plot(x, ...)
```

Arguments

x	a dynmodel fit object
...	additional arguments

Value

nothing, called to produce goodness of fits

plot.nlmixrFitData *Plot a nlmixr data object*

Description

Plot some standard goodness of fit plots for the focei fitted object

Usage

```
## S3 method for class 'nlmixrFitData'
plot(x, ...)
```

Arguments

x	a focei fit object
...	additional arguments

Value

Nothing, called for its side effects

Author(s)

Wenping Wang & Matthew Fidler

plot.saemFit *Plot an SAEM model fit*

Description

Plot an SAEM model fit

Usage

```
## S3 method for class 'saemFit'
plot(x, ...)
```

Arguments

x	a saemFit object
...	others

Value

a list

preCondInv — *Calculate the inverse preconditioning matrix*

Description

Calculate the inverse preconditioning matrix

Usage

```
preCondInv(Rin)
```

Arguments

Rin	The R matrix input

Value

The inverse preconditioning matrix

preconditionFit — *Linearly re-parameterize the model to be less sensitive to rounding errors*

Description

Linearly re-parameterize the model to be less sensitive to rounding errors

Usage

```
preconditionFit(fit, estType = c("full", "posthoc", "none"), ntry = 10L)
```

Arguments

fit	A nlmixr fit to be preconditioned
estType	Once the fit has been linearly reparametrized, should a "full" estimation, "posthoc" estimation or simply a estimation of the covariance matrix "none" before the fit is updated
ntry	number of tries before giving up on a pre-conditioned covariance estimate

Value

A nlmixr fit object that was preconditioned to stabilize the variance/covariance calculation

References

Aoki Y, Nordgren R, Hooker AC. Preconditioning of Nonlinear Mixed Effects Models for Stabilisation of Variance-Covariance Matrix Computations. AAPS J. 2016;18(2):505-518. doi:10.1208/s12248-016-9866-5

`prediction` *Prediction after a gnlmm fit*

Description

Generate predictions after a generalized non-linear mixed effect model fit

Usage

```
prediction(fit, pred, data = NULL, mc.cores = 1)
```

Arguments

`fit`	a gnlmm fit object
`pred`	prediction function
`data`	new data
`mc.cores`	number of cores (for Linux only)

Value

observed and predicted

Examples

```
if (FALSE) {
ode <- "
d/dt(depot) =-KA*depot;
d/dt(centr) = KA*depot - KE*centr;
"
sys1 <- RxODE(ode)

pars <- function() {
  CL <- exp(THETA[1] + ETA[1]) # ; if (CL>100) CL=100
  KA <- exp(THETA[2] + ETA[2]) # ; if (KA>20) KA=20
  KE <- exp(THETA[3])
  V <- CL / KE
  sig2 <- exp(THETA[4])
}
llik <- function() {
  pred <- centr / V
  dnorm(DV, pred, sd = sqrt(sig2), log = TRUE)
}

inits <- list(THTA = c(-3.22, 0.47, -2.45, 0))

inits$OMGA <- list(ETA[1]+ETA[2]~c(.027, .01, .37))
```

```
theo <- theo_md

fit <- try(gnlmm(llik, theo, inits, pars, sys1,
  control = list(trace = TRUE, nAQD = 1)
))

if (!inherits(fit, "try-error")) {

pred <- function() {
  pred <- centr / V
}

s <- try(prediction(fit, pred))
if (!inherits(s, "try-error")) {
 plot(s$p, s$dv)
 abline(0, 1, col = "red")
}
}
}
```

`print.dyn.ID` *Print a non-population dynamic model fit object*

Description

Print a non-population dynamic model fit object

Usage

```
## S3 method for class 'dyn.ID'
print(x, ...)
```

Arguments

`x`	a dynmodel fit object
`...`	additional arguments

Value

the original object

print.gnlmm.fit *Print a gnlmm fit*

Description

Print a generalized non-linear mixed effect model fit

Usage

```
## S3 method for class 'gnlmm.fit'
print(x, ...)
```

Arguments

x	a gnlmm fit object
...	additional arguments

Value

the original object (invisibly)

print.nlmixrUI *Print UI function*

Description

Print UI function

Usage

```
## S3 method for class 'nlmixrUI'
print(x, ...)
```

Arguments

x	UI function
...	other arguments

Value

original object (invisibly)

Author(s)

Matthew L. Fidler

print.saemFit *Print an SAEM model fit summary*

Description

Print an SAEM model fit summary

Usage

```
## S3 method for class 'saemFit'
print(x, ...)
```

Arguments

x	a saemFit object
...	others

Value

a list

pump *Pump failure example dataset*

Description

The records the number of failures and operation time for groups of 10 pumps.

Usage

```
pump
```

Format

A data frame with 10 rows and 5 columns

y Number of pump failures

t Failure Time

group Continuous Operation (=1) or Intermittent Operation(=2)

ID ID for group of 10 pumps

logtstd Centeredy operation times

Source

https://support.sas.com/documentation/cdl/en/statug/63033/HTML/default/viewer.htm#statug_nlmixed_sect040.htm

References

Gaver, D. P. and O'Muircheartaigh, I. G. (1987), "Robust Empirical Bayes Analysis of Event Rates," Technometrics, 29, 1-15.

`rats` *Pregnant Rat Diet Experiment*

Description

16 pregnant rats have a control diet, and 16 have a chemically treated diet. The litter size for each rat is recorded after 4 and 21 days. This dataset is used in the SAS Probit-model with binomial data, and saved in the nlmixr package as rats.

Usage

```
rats
```

Format

A data frame with 32 rows and 6 columns

trt Treatment; c= control diet; t=treated diet

m Litter size after 4 days

x Litter size after 21 days

x1 Indicator for trt=c

x2 Indicator for trt=t

ID Rat ID

Source

https://support.sas.com/documentation/cdl/en/statug/63033/HTML/default/viewer.htm#statug_nlmixed_sect040.htm

References

Weil, C.S., 1970. Selection of the valid number of sampling units and a consideration of their combination in toxicological studies involving reproduction, teratogenesis or carcinogenesis. Fd. Cosmet. Toxicol. 8, 177-182.

Williams, D.A., 1975. The analysis of binary responses from toxicological experiments involving reproduction and teratogenicity. Biometrics 31, 949-952.

McCulloch, C. E. (1994), "Maximum Likelihood Variance Components Estimation for Binary Data," Journal of the American Statistical Association, 89, 330 - 335.

Ochi, Y. and Prentice, R. L. (1984), "Likelihood Inference in a Correlated Probit Regression Model," Biometrika, 71, 531-543.

See Also

Other nlmixr datasets: Bolus_1CPTMM, Bolus_1CPT, Bolus_2CPTMM, Bolus_2CPT, Infusion_1CPT, Oral_1CPT, Wang2007, pheno_sd, theo_md, theo_sd, warfarin

---

removeCovariate *Remove covariate expression from a function string*

Description

Remove covariate expression from a function string

Usage

```
removeCovariate(funstring, varName, covariate, theta)
```

Arguments

funstring	a string giving the expression that needs to be modified
varName	the variable to which the given string corresponds to in the model expression
covariate	the covariate expression that needs to be removed (from the appropriate place)
theta	a list of names of the 'theta' parameters in the 'fit' object

Value

returns the modified string with the covariate removed from the function string

Author(s)

Vipul Mann, Matthew Fidler

---

removeCovMultiple *Removing multiple covariates*

Description

Removing multiple covariates

Usage

```
removeCovMultiple(covInfo, fitobject)
```

Arguments

covInfo	a list containing information about each variable-covariate pair
fitobject	an nlmixr 'fit' object

Value

a list with the updated fit object, the variable-covariate pair string, and the parameter names for the corresponding covaraites removed

Author(s)

Vipul Mann, Matthew Fidler

`removeCovVar` *Remove covariate from function string*

Description

Function to remove covariates from a given variable's equation in the function string text

Usage

```
removeCovVar(fitobject, varName, covariate, categorical = FALSE, isHS = FALSE)
```

Arguments

`fitobject`	an nlmixr 'fit' object
`varName`	a string giving the variable name to which covariate needs to be added
`covariate`	a string giving the covariate name; must be present in the data used for 'fit'
`categorical`	a boolean to represent if the covariate to be added is categorical
`isHS`	a boolean to represent if the covariate to be added is hockey-stick normalized

Value

returns a list containing the updated model and the parameter names for the covariates added

Author(s)

Vipul Mann, Matthew Fidler

`residuals.nlmixrFitData` *Extract residuals from the FOCEI fit*

Description

Extract residuals from the FOCEI fit

Usage

```
## S3 method for class 'nlmixrFitData'
residuals(
  object,
  ...,
  type = c("ires", "res", "iwres", "wres", "cwres", "cpred", "cres")
)
```

Arguments

`object`	focei.fit object
`...`	Additional arguments
`type`	Residuals type fitted.

Value

residuals

Author(s)

Matthew L. Fidler

`saem.fit` *Fit an SAEM model*

Description

Fit an SAEM model using either closed-form solutions or ODE-based model definitions

Usage

```
saem.fit(
  model,
  data,
  inits,
  PKpars = NULL,
  pred = NULL,
  covars = NULL,
  mcmc = list(niter = c(200, 300), nmc = 3, nu = c(2, 2, 2)),
  ODEopt = list(atol = 1e-06, rtol = 1e-04, method = "lsoda", transitAbs = FALSE),
  distribution = c("normal", "poisson", "binomial", "lnorm"),
  seed = 99
)

saem(
  model,
  data,
  inits,
  PKpars = NULL,
  pred = NULL,
  covars = NULL,
  mcmc = list(niter = c(200, 300), nmc = 3, nu = c(2, 2, 2)),
  ODEopt = list(atol = 1e-06, rtol = 1e-04, method = "lsoda", transitAbs = FALSE),
  distribution = c("normal", "poisson", "binomial", "lnorm"),
  seed = 99
)

## S3 method for class 'fit.nlmixr.ui.nlme'
saem(
  model,
  data,
  inits,
  PKpars = NULL,
  pred = NULL,
  covars = NULL,
  mcmc = list(niter = c(200, 300), nmc = 3, nu = c(2, 2, 2)),
  ODEopt = list(atol = 1e-06, rtol = 1e-04, method = "lsoda", transitAbs = FALSE),
  distribution = c("normal", "poisson", "binomial", "lnorm"),
  seed = 99
)

## S3 method for class 'fit.function'
saem(
  model,
  data,
  inits,
  PKpars = NULL,
  pred = NULL,
```

```
  covars = NULL,
  mcmc = list(niter = c(200, 300), nmc = 3, nu = c(2, 2, 2)),
  ODEopt = list(atol = 1e-06, rtol = 1e-04, method = "lsoda", transitAbs = FALSE),
  distribution = c("normal", "poisson", "binomial", "lnorm"),
  seed = 99
)

## S3 method for class 'fit.nlmixrUI'
saem(
  model,
  data,
  inits,
  PKpars = NULL,
  pred = NULL,
  covars = NULL,
  mcmc = list(niter = c(200, 300), nmc = 3, nu = c(2, 2, 2)),
  ODEopt = list(atol = 1e-06, rtol = 1e-04, method = "lsoda", transitAbs = FALSE),
  distribution = c("normal", "poisson", "binomial", "lnorm"),
  seed = 99
)

## S3 method for class 'fit.RxODE'
saem(
  model,
  data,
  inits,
  PKpars = NULL,
  pred = NULL,
  covars = NULL,
  mcmc = list(niter = c(200, 300), nmc = 3, nu = c(2, 2, 2)),
  ODEopt = list(atol = 1e-06, rtol = 1e-04, method = "lsoda", transitAbs = FALSE),
  distribution = c("normal", "poisson", "binomial", "lnorm"),
  seed = 99
)

## S3 method for class 'fit.default'
saem(
  model,
  data,
  inits,
  PKpars = NULL,
  pred = NULL,
  covars = NULL,
  mcmc = list(niter = c(200, 300), nmc = 3, nu = c(2, 2, 2)),
  ODEopt = list(atol = 1e-06, rtol = 1e-04, method = "lsoda", transitAbs = FALSE),
  distribution = c("normal", "poisson", "binomial", "lnorm"),
  seed = 99
)
```

Arguments

model	an RxODE model or lincmt()
data	input data
inits	initial values
PKpars	PKpars function
pred	pred function
covars	Covariates in data
mcmc	a list of various mcmc options
ODEopt	optional ODE solving options
distribution	one of c("normal","poisson","binomial")
seed	seed for random number generator

Details

Fit a generalized nonlinear mixed-effect model using the Stochastic Approximation Expectation-Maximization (SAEM) algorithm

Value

saem fit object

Author(s)

Matthew Fidler & Wenping Wang

---

saemControl *Control Options for SAEM*

Description

Control Options for SAEM

Usage

```
saemControl(
  seed = 99,
  nBurn = 200,
  nEm = 300,
  nmc = 3,
  nu = c(2, 2, 2),
  atol = 1e-06,
  rtol = 1e-04,
  method = "liblsoda",
  transitAbs = FALSE,
```

```
  print = 1,
  trace = 0,
  covMethod = c("linFim", "fim", "r,s", "r", "s", ""),
  calcTables = TRUE,
  logLik = FALSE,
  nnodes.gq = 3,
  nsd.gq = 1.6,
  optExpression = FALSE,
  maxsteps = 100000L,
  adjObf = TRUE,
  sum.prod = FALSE,
  addProp = c("combined2", "combined1"),
  singleOde = TRUE,
  tol = 1e-06,
  itmax = 30,
  type = c("nelder-mead", "newuoa"),
  powRange = 10,
  lambdaRange = 3,
  loadSymengine = FALSE,
  odeRecalcFactor = 10^(0.5),
  maxOdeRecalc = 5L,
  ...
)
```

Arguments

seed	Random Seed for SAEM step. (Needs to be set for reproducibility.) By default this is 99.
nBurn	Number of iterations in the Stochastic Approximation (SA), or burn-in step. This is equivalent to Monolix's K_0 or K_b.
nEm	Number of iterations in the Expectation-Maximization (EM) Step. This is equivalent to Monolix's K_1.
nmc	Number of Markov Chains. By default this is 3. When you increase the number of chains the numerical integration by MC method will be more accurate at the cost of more computation. In Monolix this is equivalent to L
nu	This is a vector of 3 integers. They represent the numbers of transitions of the three different kernels used in the Hasting-Metropolis algorithm. The default value is c(2,2,2), representing 40 for each transition initially (each value is multiplied by 20). The first value represents the initial number of multi-variate Gibbs samples are taken from a normal distribution. The second value represents the number of uni-variate, or multi- dimensional random walk Gibbs samples are taken. The third value represents the number of bootstrap/reshuffling or uni-dimensional random samples are taken.
atol	a numeric absolute tolerance (1e-8 by default) used by the ODE solver to determine if a good solution has been achieved; This is also used in the solved linear model to check if prior doses do not add anything to the solution.

`rtol` a numeric relative tolerance (`1e-6` by default) used by the ODE solver to determine if a good solution has been achieved. This is also used in the solved linear model to check if prior doses do not add anything to the solution.

`method` The method for solving ODEs. Currently this supports:

- `"liblsoda"` thread safe lsoda. This supports parallel thread-based solving, and ignores user Jacobian specification.
- `"lsoda"` – LSODA solver. Does not support parallel thread-based solving, but allows user Jacobian specification.
- `"dop853"` – DOP853 solver. Does not support parallel thread-based solving nor user Jacobain specification
- `"indLin"` – Solving through inductive linearization. The RxODE dll must be setup specially to use this solving routine.

`transitAbs` boolean indicating if this is a transit compartment absorption

`print` The number it iterations that are completed before anything is printed to the console. By default, this is 1.

`trace` An integer indicating if you want to trace(1) the SAEM algorithm process. Useful for debugging, but not for typical fitting.

`covMethod` Method for calculating covariance. In this discussion, R is the Hessian matrix of the objective function. The S matrix is the sum of each individual's gradient cross-product (evaluated at the individual empirical Bayes estimates).

"`linFim`" Use the Linearized Fisher Information Matrix to calculate the covariance.

"`fim`" Use the SAEM-calculated Fisher Information Matrix to calculate the covariance.

"`r,s`" Uses the sandwich matrix to calculate the covariance, that is: $R^-1 \times S \times R^-1$

"`r`" Uses the Hessian matrix to calculate the covariance as $2 \times R^-1$

"`s`" Uses the crossproduct matrix to calculate the covariance as $4 \times S^-1$

"" Does not calculate the covariance step.

`calcTables` This boolean is to determine if the foceiFit will calculate tables. By default this is `TRUE`

`logLik` boolean indicating that log-likelihood should be calculate by Gaussian quadrature.

`nnodes.gq` number of nodes to use for the Gaussian quadrature when computing the likelihood with this method (defaults to 1, equivalent to the Laplaclian likelihood)

`nsd.gq` span (in SD) over which to integrate when computing the likelihood by Gaussian quadrature. Defaults to 3 (eg 3 times the SD)

`optExpression` Optimize the RxODE expression to speed up calculation. By default this is turned on.

`maxsteps` maximum number of (internally defined) steps allowed during one call to the solver. (5000 by default)

`adjObf` is a boolean to indicate if the objective function should be adjusted to be closer to NONMEM's default objective function. By default this is `TRUE`

sum.prod	Take the RxODE model and use more precise products/sums. Increases solving accuracy and solving time.
addProp	one of "combined1" and "combined2"; These are the two forms of additive+proportional errors supported by monolix/nonmem: combined1: transform(y)=transform(f)+(a+b*f^c)*eps combined2: transform(y)=transform(f)+(a^2+b^2*f^(2c))*eps
singleOde	This option allows a single ode model to include the PK parameter information instead of splitting it into a function and a RxODE model
tol	This is the tolerance for the regression models used for complex residual errors (ie add+prop etc)
itmax	This is the maximum number of iterations for the regression models used for complex residual errors. The number of iterations is itmax*number of parameters
type	indicates the type of optimization for the residuals; Can be one of c("nelder-mead", "newuoa")
powRange	This indicates the range that powers can take for residual errors; By default this is 10 indicating the range is c(1/10, 10) or c(0.1,10)
lambdaRange	This indicates the range that Box-Cox and Yeo-Johnson parameters are constrained to be; The default is 3 indicating the range (-3,3)
loadSymengine	Boolean indicating if the model should be loaded into symengine. This cause all the ODEs to be collapsed into one expression that is eventually optimized if optExpression is TRUE.
odeRecalcFactor	The factor to increase the rtol/atol with bad ODE solving.
maxOdeRecalc	Maximum number of times to reduce the ODE tolerances and try to resolve the system if there was a bad ODE solve.
...	Other arguments to control SAEM.

Value

List of options to be used in nlmixr fit for SAEM.

Author(s)

Wenping Wang & Matthew L. Fidler

---

setCov *Set the covariance type based on prior calculated covariances*

Description

Set the covariance type based on prior calculated covariances

Usage

```
setCov(fit, method)
```

Arguments

fit	nlmixr fit
method	covariance method

Value

Fit object with covariance updated

Author(s)

Matt Fidler

---

setOfv *Set/get Objective function type for a nlmixr object*

Description

Set/get Objective function type for a nlmixr object

Usage

```
setOfv(x, type)

getOfvType(x)
```

Arguments

x	nlmixr fit object
type	Type of objective function to use for AIC, BIC, and $objective

Value

Nothing

Author(s)

Matthew L. Fidler

sqrtm *Return the square root of general square matrix A*

Description

Return the square root of general square matrix A

Usage

```
sqrtm(m)
```

Arguments

m	Matrix to take the square root of.

Value

A square root general square matrix of m

summary.dyn.ID *Summary of a non-population dynamic model fit*

Description

Summary of a non-population dynamic model fit

Usage

```
## S3 method for class 'dyn.ID'
summary(object, ...)
```

Arguments

object	a dynmodel fit object
...	additional arguments

Value

original object (invisible)

summary.dyn.mcmc *Print summary of a non-population dynamic model fit using mcmc*

Description

Print summary of a non-population dynamic model fit using mcmc

Usage

```
## S3 method for class 'dyn.mcmc'
summary(object, ...)

## S3 method for class 'dyn.mcmc'
print(x, ...)
```

Arguments

...	additional arguments
x, object	a dynmodel fit object

Value

invisibly return original object

summary.saemFit *Print an SAEM model fit summary*

Description

Print an SAEM model fit summary

Usage

```
## S3 method for class 'saemFit'
summary(object, ...)
```

Arguments

object	a saemFit object
...	others

Value

a list

`tableControl` *Output table/data.frame options*

Description

Output table/data.frame options

Usage

```
tableControl(
  npde = NULL,
  cwres = NULL,
  nsim = 300,
  ties = TRUE,
  censMethod = c("truncated-normal", "cdf", "ipred", "pred", "epred", "omit"),
  seed = 1009,
  cholSEtol = (.Machine$double.eps)^(1/3),
  state = TRUE,
  lhs = TRUE,
  eta = TRUE,
  covariates = TRUE,
  addDosing = FALSE,
  subsetNonmem = TRUE,
  cores = NULL
)
```

Arguments

`npde`	When TRUE, request npde regardless of the algorithm used.
`cwres`	When TRUE, request CWRES and FOCEi likelihood regardless of the algorithm used.
`nsim`	represents the number of simulations. For RxODE, if you supply single subject event tables (created with [eventTable()])
`ties`	When ‘TRUE‘ jitter prediction-discrepancy points to discourage ties in cdf.
`censMethod`	Handle censoring method: - ‘"truncated-normal"‘ Simulates from a truncated normal distribution under the assumption of the model and censoring. - ‘"cdf"‘ Use the cdf-method for censoring with npde and use this for any other residuals (‘cwres‘ etc) - ‘"omit"‘ omit the residuals for censoring
`seed`	an object specifying if and how the random number generator should be initialized
`cholSEtol`	The tolerance for the ‘RxODE::choleSE‘ function
`state`	is a Boolean indicating if ‘state‘ values will be included (default ‘TRUE‘)

lhs	is a Boolean indicating if remaining 'lhs' values will be included (default 'TRUE')
eta	is a Boolean indicating if 'eta' values will be included (default 'TRUE')
covariates	is a Boolean indicating if covariates will be included (default 'TRUE')
addDosing	Boolean indicating if the solve should add RxODE EVID and related columns. This will also include dosing information and estimates at the doses. Be default, RxODE only includes estimates at the observations. (default FALSE). When addDosing is NULL, only include EVID=0 on solve and exclude any model-times or EVID=2. If addDosing is NA the classic RxODE EVID events are returned. When addDosing is TRUE add the event information in NONMEM-style format; If subsetNonmem=FALSE RxODE will also include extra event types (EVID) for ending infusion and modeled times: • EVID=-1 when the modeled rate infusions are turned off (matches rate=-1) • EVID=-2 When the modeled duration infusions are turned off (matches rate=-2) • EVID=-10 When the specified rate infusions are turned off (matches rate>0) • EVID=-20 When the specified dur infusions are turned off (matches dur>0) • EVID=101,102,103,... Modeled time where 101 is the first model time, 102 is the second etc.
subsetNonmem	subset to NONMEM compatible EVIDs only. By default TRUE.
cores	Number of cores used in parallel ODE solving. This is equivalent to calling setRxThreads()

Details

If you ever want to add CWRES/FOCEi objective function you can use the addCwres

If you ever want to add NPDE/EPRED columns you can use the addNpde

Value

A list of table options for nlmixr

Author(s)

Matthew L. Fidler

---

theo_md *Multiple dose theophylline PK data*

Description

This data set starts with the day 1 concentrations of the theophylline data that is included in the nlme/NONMEM. After day 7 concentrations were simulated with once a day regimen for 7 days (QD).

Usage

```
theo_md
```

Format

A data frame with 348 rows by 7 columns

ID Subject ID

TIME Time (hrs)

DV Dependent Variable, theophylline Concentration

AMT Dose Amount/kg

EVID RxODE/nlmixr event ID (not NONMEM's)

CMT Compartment number

WT Weight (kg)

Source

NONMEM/nlme

See Also

Other nlmixr datasets: `Bolus_1CPTMM`, `Bolus_1CPT`, `Bolus_2CPTMM`, `Bolus_2CPT`, `Infusion_1CPT`, `Oral_1CPT`, `Wang2007`, `pheno_sd`, `rats`, `theo_sd`, `warfarin`

---

theo_sd *Multiple dose theophylline PK data*

Description

This data set is the day 1 concentrations of the theophylline data that is included in the nlme/NONMEM.

Usage

```
theo_sd
```

Format

A data frame with 144 rows by 7 columns

ID Subject ID

TIME Time (hrs)

DV Dependent Variable, theophylline concentration

AMT Dose Amount/kg

EVID RxODE/nlmixr event ID (not NONMEM's)

CMT Compartment Number

WT Weight (kg)

Source

NONMEM/nlme

See Also

Other nlmixr datasets: Bolus_1CPTMM, Bolus_1CPT, Bolus_2CPTMM, Bolus_2CPT, Infusion_1CPT, Oral_1CPT, Wang2007, pheno_sd, rats, theo_md, warfarin

---

VarCorr.nlmixrNlme *Return VarCorr for nlmixr nlme*

Description

This returns a numeric matrix instead of character matrix

Usage

```
## S3 method for class 'nlmixrNlme'
VarCorr(x, sigma = NULL, ...)
```

Arguments

x	a fitted model object, usually an object inheriting from class "lme".
sigma	an optional numeric value used as a multiplier for the standard deviations. The default is x$sigma or 1 depending on class(x).
...	further optional arguments passed to other methods (none for the methods documented here).

Value

Extract the VarCorr from the nlmixr nlme object

Author(s)

Matthew L. Fidler

vpc *Vpc function for nlmixr*

Description

Vpc function for nlmixr

Usage

```
vpc(sim, ...)

## Default S3 method:
vpc(sim, ...)
```

Arguments

sim	Observed data frame or fit object
...	Other parameters

Value

a nlmixr composite vpc object

vpc_nlmixr_nlme *Visual predictive check (VPC) for nlmixr nlme objects*

Description

Do visual predictive check (VPC) plots for nlme-based non-linear mixed effect models

Usage

```
vpc_nlmixr_nlme(fit, nsim = 100, condition = NULL, ...)

vpcNlmixrNlme(fit, nsim = 100, condition = NULL, ...)

## S3 method for class 'nlmixrNlme'
vpc(sim, ...)
```

Arguments

fit	nlme fit object
nsim	number of simulations
condition	conditional variable
...	Additional arguments
sim	this is usually a data.frame with observed data, containing the independent and dependent variable, a column indicating the individual, and possibly covariates. E.g. load in from NONMEM using read_table_nm. However it can also be an object like a nlmixr or xpose object

Value

Called for its side effects of creating a VPC

Examples

```
specs <- list(fixed=lKA+lCL+lV~1, random = pdDiag(lKA+lCL~1), start=c(lKA=0.5, lCL=-3.2, lV=-1))
fit <- nlme_lin_cmpt(theo_md, par_model=specs, ncmt=1, verbose=TRUE)
vpc_nlmixr_nlme(fit, nsim = 100, condition = NULL)
```

---

vpc_saemFit *VPC for nlmixr saemFit objects*

Description

VPC for nlmixr saemFit objects

Usage

```
vpc_saemFit(fit, dat, nsim = 100, by = NULL, ...)

## S3 method for class 'saemFit'
vpc(sim, ...)
```

Arguments

fit	saemFit object
dat	Data to augment the saemFit vpc simulation
nsim	Number of simulations for the VPC
by	Variables to condition the VPC
...	Other arguments sent to vpc_vpc
sim	this is usually a data.frame with observed data, containing the independent and dependent variable, a column indicating the individual, and possibly covariates. E.g. load in from NONMEM using read_table_nm. However it can also be an object like a nlmixr or xpose object

Value

vpc object from the vpc_vpc package

Author(s)

Wenping Wang

---

vpc_ui *VPC based on ui model*

Description

VPC based on ui model

Usage

```
vpc_ui(
  fit,
  data = NULL,
  n = 100,
  bins = "jenks",
  n_bins = "auto",
  bin_mid = "mean",
  show = NULL,
  stratify = NULL,
  pred_corr = FALSE,
  pred_corr_lower_bnd = 0,
  pi = c(0.05, 0.95),
  ci = c(0.05, 0.95),
  uloq = NULL,
  lloq = NULL,
  log_y = FALSE,
  log_y_min = 0.001,
  xlab = NULL,
  ylab = NULL,
  title = NULL,
  smooth = TRUE,
  vpc_theme = NULL,
  facet = "wrap",
  labeller = NULL,
  vpcdb = FALSE,
  verbose = FALSE,
  ...
)

## S3 method for class 'nlmixrFitData'
vpc(sim, ...)
```

```
## S3 method for class 'nlmixrVpc'
vpc(sim, ...)

## S3 method for class 'ui'
vpc(sim, ...)
```

Arguments

fit	nlmixr fit object
data	this is the data to use to augment the VPC fit. By default is the fitted data, (can be retrieved by getData), but it can be changed by specifying this argument.
n	Number of VPC simulations. By default 100
bins	either "density", "time", or "data", "none", or one of the approaches available in classInterval() such as "jenks" (default) or "pretty", or a numeric vector specifying the bin separators.
n_bins	when using the "auto" binning method, what number of bins to aim for
bin_mid	either "mean" for the mean of all timepoints (default) or "middle" to use the average of the bin boundaries.
show	what to show in VPC (obs_dv, obs_ci, pi, pi_as_area, pi_ci, obs_median, sim_median, sim_median_ci)
stratify	character vector of stratification variables. Only 1 or 2 stratification variables can be supplied.
pred_corr	perform prediction-correction?
pred_corr_lower_bnd	lower bound for the prediction-correction
pi	simulated prediction interval to plot. Default is c(0.05, 0.95),
ci	confidence interval to plot. Default is (0.05, 0.95)
uloq	Number or NULL indicating upper limit of quantification. Default is NULL.
lloq	Number or NULL indicating lower limit of quantification. Default is NULL.
log_y	Boolean indicting whether y-axis should be shown as logarithmic. Default is FALSE.
log_y_min	minimal value when using log_y argument. Default is 1e-3.
xlab	label for x axis
ylab	label for y axis
title	title
smooth	"smooth" the VPC (connect bin midpoints) or show bins as rectangular boxes. Default is TRUE.
vpc_theme	theme to be used in VPC. Expects list of class vpc_theme created with function vpc_theme()
facet	either "wrap", "columns", or "rows"
labeller	ggplot2 labeller function to be passed to underlying ggplot object

vpcdb	Boolean whether to return the underlying vpcdb rather than the plot
verbose	show debugging information (TRUE or FALSE)
...	Args sent to rxSolve
sim	this is usually a data.frame with observed data, containing the independent and dependent variable, a column indicating the individual, and possibly covariates. E.g. load in from NONMEM using read_table_nm. However it can also be an object like a nlmixr or xpose object

Value

Simulated dataset (invisibly)

Author(s)

Matthew L. Fidler

Wang2007 *Simulated Data Set for comparing objective functions*

Description

This is a simulated dataset from Wang2007 where various NONMEM estimation methods (Laplace FO, FOCE with and without interaction) are described.

Usage

```
Wang2007
```

Format

A data frame with 20 rows and 3 columns

ID Simulated Subject ID

Time Simulated Time

Y Simulated Value

Source

Table 1 from Wang, Y *Derivation of Various NONMEM estimation methods*. J Pharmacokinet Pharmacodyn (2007) 34:575-593.

See Also

Other nlmixr datasets: Bolus_1CPTMM, Bolus_1CPT, Bolus_2CPTMM, Bolus_2CPT, Infusion_1CPT, Oral_1CPT, pheno_sd, rats, theo_md, theo_sd, warfarin

`warfarin` *Warfarin PK/PD data*

Description

Warfarin PK/PD data

Usage

```
warfarin
```

Format

A data frame with 519 rows and 9 columns

id Patient identifier (n=32)

time Time [h]

amt Total drug administered [mg]

dv Warfarin concentrations [mg/L] or PCA measurement

dvid Dependent identifier Information (cp: Dose or PK, pca: PCA, factor)

evid Event identifier

wt Weight [kg]

age Age [yr]

sex Gender (male or female, factor)

Source

Funaki T, Holford N, Fujita S (2018). Population PKPD analysis using nlmixr and NONMEM. PAGJA 2018

References

O'Reilly RA, Aggeler PM, Leong LS. Studies of the coumarin anticoagulant drugs: The pharmacodynamics of warfarin in man. Journal of Clinical Investigation 1963; 42(10): 1542-1551

O'Reilly RA, Aggeler PM. Studies on coumarin anticoagulant drugs Initiation of warfarin therapy without a loading dose. Circulation 1968; 38: 169-177.

See Also

Other nlmixr datasets: `Bolus_1CPTMM`, `Bolus_1CPT`, `Bolus_2CPTMM`, `Bolus_2CPT`, `Infusion_1CPT`, `Oral_1CPT`, `Wang2007`, `pheno_sd`, `rats`, `theo_md`, `theo_sd`

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