Package 'mrgsolve'

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Type Package

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Title Simulation from ODE-Based Population PK/PD and Systems Pharmacology Models

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Description Facilitates simulation in R from hierarchical, ordinary differential equation (ODE) based models typically employed in drug development. The modeler creates a model specification file consisting of R and C++ code that is parsed, compiled, and dynamically loaded into the R session. Input data are passed in and simulated data are returned as R objects, so disk access is never required during the simulation cycle after compiling. Differential equations are solved with the DLSODA routine in ODEPACK [A. C. Hindmarsh, ``ODEPACK, A Systematized Collection of ODE Solvers," in Scientific Computing, R. S. Stepleman et al. (eds.), North-Holland, Amsterdam, 1983, pp.55-64.]. ACH and LRP are listed as authors of the DLSODA function in ODEPACK.

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Depends R (>= 3.1.2), methods

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Suggests lattice, testthat, XML

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Collate 'classes.R' 'events.R' 'Ops.R' 'RcppExports.R' 'chain.R' 'utils.R' 'compile.R' 'complog.R' 'datasets.R' 'example.R' 'mrgsims.R' 'init.R' 'knobs.R' 'lockedmod.R' 'matlist.R' 'nmxml.R' 'modspec.R' 'mrgsolve.R' 'package.R' 'param.R' 'print.R' 'simtime.R' 'specdoc.R' 'update.R' 'zchain.R'

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R topics documented:

aboutsolver	. 4
add.ev	. 5
as.init	. 5
as.locked	. 7
as.matrix.list	. 7
as.packmod	
as_bmat	
blocks	
bmat	
carry.out	
efile	
chain	. 12
emt	. 12
emtn	. 13
cmt_list-class	. 13
	. 13
complog	
cvec	. 14
data_set	. 15
design	
dllname	
ev-class	
events	
exdatasets	
expand.idata	. 20
firstonly	. 21
idata	. 21
idata_set	. 21
installed_models	
knobs	
label	
letran	
limit	
loadso	
lower2matrix	
matlist	
matlist-class	. 28
mcode	
mcRNG	
merge.list	
mod	
model	
modelparse	
modelspec	
modMATRIX	
mread	
mrgindata	. 37
mrgmod-class	. 38
mrgsim	. 39
mrgsims	. 41
mrgsims-class	. 43

4 aboutsolver

aboutsolver *ODE solver.*

Description

About the ODEPACK differential equation solver used by mrgsolve.

DLSODA

```
C-----
C This is the 12 November 2003 version of
C DLSODA: Livermore Solver for Ordinary Differential Equations, with
         Automatic method switching for stiff and nonstiff problems.
C
C This version is in double precision.
C DLSODA solves the initial value problem for stiff or nonstiff
C systems of first order ODEs,
С
     dy/dt = f(t,y), or, in component form,
С
     dy(i)/dt = f(i) = f(i,t,y(1),y(2),...,y(NEQ)) (i = 1,...,NEQ).
C
C This a variant version of the DLSODE package.
C It switches automatically between stiff and nonstiff methods.
C This means that the user does not have to determine whether the
C problem is stiff or not, and the solver will automatically choose the
C appropriate method. It always starts with the nonstiff method.
С
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C References:
C 1. Alan C. Hindmarsh, ODEPACK, A Systematized Collection of ODE
С
     Solvers, in Scientific Computing, R. S. Stepleman et al. (Eds.),
C
     North-Holland, Amsterdam, 1983, pp. 55-64.
C 2. Linda R. Petzold, Automatic Selection of Methods for Solving
     Stiff and Nonstiff Systems of Ordinary Differential Equations,
С
С
     Siam J. Sci. Stat. Comput. 4 (1983), pp. 136-148.
```

add.ev 5

add.ev

Add two events objects

Description

Add two events objects

Usage

```
add.ev(e1, e2)
```

Arguments

e1 first events object e2 second events object

as.init

Get and set model initial conditions.

Description

Calling init with the model object as the first argument will return the model initial conditions as a numericlist object. See numericlist for methods to deal with cmt_list objects.

```
##' @export
```

Usage

```
as.init(.x, ...)
## S4 method for signature 'list'
as.init(.x, ...)
## S4 method for signature 'numeric'
as.init(.x, ...)
## S4 method for signature 'cmt_list'
as.init(.x, ...)
## S4 method for signature 'missing'
as.init(.x, ...)
## S4 method for signature 'NULL''
as.init(.x, ...)
## S4 method for signature 'NULL''
as.init(.x, ...)
## S4 method for signature 'mrgmod'
init(.x, .y = list(), ..., .pat = "*")
```

6 as.init

```
## S4 method for signature 'mrgsims'
init(.x, ...)
## S4 method for signature 'missing'
init(.x, ...)
## S4 method for signature 'list'
init(.x, ...)
## S4 method for signature 'ANY'
init(.x, ...)
## S4 method for signature 'cmt_list'
show(object)
```

Arguments

. x	the model object
	passsed along
. y	list to be merged into parameter list
.pat	a regular expression (character) to be applied as a filter when printing compartments to the screen
object	to show

Details

Can be used to either get a compartment list object from a mrgmod model object or to update the compartment initial conditions in a model object. For both uses, the return value is a cmt_list object. For the former use, init is usually called to print the compartment initial conditions to the screen, but the cmt_list object can also be coreced to a list or numeric R object.

Value

```
an object of class cmt_list (see numericlist)
```

```
## example("init")
mod <- mrgsolve:::house()
init(mod)
init(mod, .pat="^C") ## may be useful for large models
class(init(mod))
init(mod)$CENT
as.list(init(mod))
as.data.frame(init(mod))</pre>
```

as.locked 7

as.locked

Corece an mrgmod object to a lockedmod object.

Description

Corece an mrgmod object to a lockedmod object.

Usage

```
as.locked(x, ...)
## S4 method for signature 'mrgmod'
as.locked(x, dllloc, dllname, src, include, ...)
```

Arguments

x mrgmod model object

... passed along

dllloc directory location for the model shared object

dllname the name of the model shared object

src directory location of the model specification file

include directory location for the header file

as.matrix.list

Coerce a list to a matrix

Description

All elements of the list must be of length 1.

Usage

```
as.matrix.list(x, ..., nrow = 1)
```

Arguments

x a named list, with each element of length 1

... not used

nrow the number of rows to make the matrix

Value

matrix with colnames set to the names of x

Author(s)

Kyle Baron

8 as_bmat

Examples

```
x <- list(a=1, b=2, c=3)
as.matrix(x,nrow=3)</pre>
```

as.packmod

Coerce an mrgmod object to packmod

Description

Coerce an mrgmod object to packmod

Usage

```
as.packmod(x, ...)
## S4 method for signature 'mrgmod'
as.packmod(x, ...)
```

Arguments

x mrgmod model object

... passed along

as_bmat

Coerce R objects to block or diagonal matrices.

Description

Coerce R objects to block or diagonal matrices.

Usage

```
as_bmat(x, ...)
## S4 method for signature 'list'
as_bmat(x, ...)
## S4 method for signature 'numeric'
as_bmat(x, pat = "*", ...)
## S4 method for signature 'data.frame'
as_bmat(x, pat = "*", ...)
## S4 method for signature 'ANY'
as_bmat(x, ...)
## S4 method for signature 'list'
```

blocks 9

```
as_dmat(x, ...)
## S4 method for signature 'ANY'
as_dmat(x, ...)
## S4 method for signature 'numeric'
as_dmat(x, pat = "*", ...)
## S4 method for signature 'data.frame'
as_dmat(x, pat = "*", ...)
```

Arguments

```
x an R object... passed alongpat regular expression, character
```

Value

A numeric matrix for list and numeric methods. For data frames, a list of matrices are returned.

See Also

bmat, dmat

Examples

blocks

Return the code blocks from a model specification file.

Description

Return the code blocks from a model specification file.

10 bmat

Usage

```
blocks(x, ...)
## S4 method for signature 'mrgmod'
blocks(x, ...)
## S4 method for signature 'character'
blocks(x, ...)
```

Arguments

```
x model object or path to model specification file... passed along
```

Examples

```
mod <- mrgsolve:::house()
mod %>% blocks
mod %>% blocks(PARAM,TABLE)
```

bmat

Create matrices from vector input

Description

Create matrices from vector input

Usage

```
bmat(..., correlation = FALSE, digits = -1)
BLOCK(..., correlation = FALSE, digits = -1)
cmat(..., digits = -1)
dmat(...)
```

Arguments

... matrix data

correlation logical; if TRUE, off diagonal elements are assumed to be correlations and converted to covariances

digits if greater than zero, matrix is passed to signif (along with digits) prior to returning

Details

bmat makes a block matrix. cmat makes a correlation matrix. dmat makes a diagonal matrix. BLOCK is a synonym for bmat.

carry.out 11

See Also

```
as_bmat
as_dmat
```

Examples

```
dmat(1,2,3)/10
bmat(0.5,0.01,0.2)
cmat(0.5, 0.87,0.2)
```

carry.out

Set the carry.out argument for mrgsim.

Description

Set the carry.out argument for mrgsim.

Usage

```
carry.out(x, ...)
```

Arguments

x model object... passed along

cfile

Return the name of the model specification file.

Description

Return the name of the model specification file.

Usage

```
cfile(x, ...)
## S4 method for signature 'mrgmod'
cfile(x, ...)
## S4 method for signature 'lockedmod'
cfile(x, ...)
```

Arguments

```
x model object ... passed along
```

12 cmt

chain

Functions for chaining commands together.

Description

Use these functions with chaining commands together with the

Details

Other functions that may be used in the chain of commands include: param, init, update,ev,limit or any other function that will take the output of the preceding command as it's first argument.

Examples

```
mod <- mrgsolve:::house()

data(exidata)
data(exTheoph)

out <- mod %>% data_set(exTheoph) %>% mrgsim()
out <- mod %>% carry.out(evid) %>% ev(amt=100, cmt=1) %>% mrgsim()
out <- mod %>% Req(CP,RESP) %>% mrgsim()
```

cmt

Get the names of model compartments.

Description

Get the names of model compartments.

Usage

```
cmt(x, ...)
## S4 method for signature 'mrgmod'
cmt(x, ...)
```

Arguments

```
x model object
... passed along
```

```
mod <- mrgsolve:::house()
cmt(mod)</pre>
```

cmtn 13

cmtn

Get the compartment number from a compartment name.

Description

Get the compartment number from a compartment name.

Usage

```
cmtn(x, ...)
## S4 method for signature 'mrgmod'
cmtn(x, tag, ...)
```

Arguments

```
x model object... passed alongtag compartment name
```

Examples

```
mod <- mrgsolve:::house()
mod %>% cmtn("CENT")
```

 ${\tt cmt_list_class}$

S4 cmt_list class

Description

```
S4 cmt_list class
```

Details

```
cmt_list is a numericlist-class
```

14 cvec

complog

Functions for viewing and manipulating the compilation log.

Description

complog displays all of the models in the compilation log. comp_forget removes models from the compilation log and attempts to unload the corresponding shared object.

Usage

```
complog(full = FALSE)
comp_forget(x)
```

Arguments

full show a full display x not used

cvec

Create create character vectors.

Description

Create create character vectors.

Usage

```
cvec(x, ...)
## S4 method for signature 'character'
cvec(x)
ch(...)
s(...)
```

Arguments

```
x comma-separated quoted string (for cvec)... unquoted strings (for ch)
```

```
cvec("A,B,C")
ch(A,B,C)
s(A,B,C)
```

data_set 15

data_set

Set the data argument for mrgsim.

Description

Set the data argument for mrgsim.

Usage

```
data_set(x, data, ...)
## S4 method for signature 'mrgmod,data.frame'
data_set(x, data, subset = TRUE,
    select = TRUE, ...)
## S4 method for signature 'mrgmod,ANY'
data_set(x, data, ...)
```

Arguments

x	model object
data	data set
	passed along
subset	passed to dplyr::filter_; retain only certain rows in the data set
select	passed to dplyr::select_; retain only certain columns in the data set

Details

Input data sets are R data frames that can include columns with any valid name, however columns with selected names are recognized by mrgsolve and incorporated into the simulation.

ID specifies the subject ID and is required for every input data set.

When columns have the same name as parameters (\$PARAM in the model specification file), the values in those columns will be used to update the corresponding parameter as the simulation progresses.

Input data set may include the following columns related to PK dosing events: time, cmt, amt, rate, ii, addl, ss. time and cmt (and ID) are required columns in the input data set. time is the observation or event time, cmt is the compartment number (see init), amt is the dosing amount, rate is the infusion rate, ii is the dosing interval, addl specifies additional doses to administer, and ss is a flag for steady state dosing. These column names operate similarly to other non-linear mixed effects modeling software, but note that (except for ID) the column names related to PK dosing must be lower case.

Only numeric data can be brought in to the problem. Any non-numeric data columns will be dropped with warning.

See exdatasets for different example data sets.

16 dllname

Examples

```
data <- expand.ev(ID=1:3, amt=c(10,20))
data <- expand.ev(amt=c(10,20), rate=c(1,2))</pre>
```

design

Set observation designs for the simulation.

Description

Set observation designs for the simulation.

Usage

```
design(x, descol = character(0), ..., deslist = list())
```

Arguments

x model object

descol the idata column name for design assignment ... tgrid or tgrids objects or numeric vector

 ${\tt deslist} \qquad \qquad {\tt a \ list \ of \ tgrid \ or \ tgrids \ objects \ or \ numeric \ vector \ to \ be \ used \ in \ place \ of \ ...}$

dllname

Return the model name.

Description

Return the model name.

Usage

```
dllname(x, ...)
## S4 method for signature 'mrgmod'
dllname(x, ...)
```

Arguments

```
x model object... passed along
```

See Also

mode1

ev-class 17

Examples

```
mod <- mrgsolve:::house()
dllname(mod)</pre>
```

ev-class

S4 events class

Description

S4 events class

Slots

data a data frame of events

events

Get model events

Description

An accessor function for the events model attribute.

Events can either be specified when the model object is created (with mrgmod) or by updating an existing model object (with update).

Usage

```
events(x, ...)
## S4 method for signature 'mrgmod'
events(x, ...)
## S4 method for signature 'mrgsims'
events(x, ...)

ev(x, ...)
## S4 method for signature 'missing'
ev(evid = 1, time = 0, ID = numeric(0), cmt = 1,
    replicate = TRUE, until = NULL, ...)
## S4 method for signature 'ev'
ev(x, ...)
## S4 method for signature 'mrgmod'
ev(x, ...)
## S4 method for signature 'mrgmod'
ev(x, ...)
```

18 events

```
## S4 method for signature 'data.frame'
as.ev(x, ...)
## S4 method for signature 'ev'
as.matrix(x, ...)
## S4 method for signature 'ev'
as.data.frame(x, row.names = NULL, optional = FALSE, ...)
## S4 method for signature 'ev'
show(object)
```

Arguments

X	mrgmodel object
	passed on
evid	event ID
time	event time
ID	subject ID
cmt	compartment
replicate	logical; if TRUE, events will be replicated for each individual in ID
until	the expected maximum observation time for this regimen
row.names	passed to as.data.frame
optional	passed to as.data.frame
object	passed to show

Details

- Required input for creating events objects include time and cmt
- If not supplied, evid is assumed to be 1
- If not supplied, cmt is assumed to be 1
- If not supplied, time is assumed to be 0
- ID may be specified as a vector
- if replicate is TRUE (default), thenthe events regimen is replicated for each ID; otherwise, the number of event rows must match the number of IDs entered

Value

Returns a user-defined data frame of events that should be suitable for passing into 1soda. If events are stored as a data frame, events returns the data frame. If events are stored as a function that generates the data frame, events calls the function and passes return back to the user.

an object of class ev

Author(s)

Kyle Baron

exdatasets 19

Examples

```
mod <- mrgsolve:::house()
mod <- mod %>% ev(amt=1000, time=0, cmt=1)
events(mod)

loading <- ev(time=0, cmt=1, amt=1000)
maint <- ev(time=12, cmt=1, amt=500, ii=12, addl=10)
loading + maint

ev(ID=1:10, cmt=1, time=0, amt=100)</pre>
```

exdatasets

Example input data sets

Description

Example input data sets

Usage

```
data(exidata)
data(extran1)
data(extran2)
data(extran3)
data(exTheoph)
data(exBoot)
```

Details

- exidata holds individual-level parameters and other data items, one per row
- extran1 is a "condensed" data set
- extran2 is a full dataset
- extran3 is a full dataset with parameters
- exTheoph is the theophylline data set, ready for input into mrgsolve
- exBoot a set of bootstrap parameter estimates

```
mod <- mrgsolve:::house() %>% update(end=240) %>% Req(CP)
## Full data set
data(exTheoph)
```

20 expand.idata

```
out <- mod %>% data_set(exTheoph) %>% mrgsim
out
plot(out)
## Condensed: mrgsolve fills in the observations
data(extran1)
out <- mod %>% data_set(extran1) %>% mrgsim
out
plot(out)
## Add a parameter to the data set
stopifnot(require(dplyr))
data <- extran1 %>% distinct(ID) %>% select(ID) %>%
  mutate(CL=exp(log(1.5) + rnorm(nrow(.), 0,sqrt(0.1)))) %>%
data
out <- mod %>% data_set(data) %>% carry.out(CL) %>% mrgsim
out
plot(out)
## idata
data(exidata)
out <- mod %>% idata_set(exidata) %>% ev(amt=100,ii=24,addl=10) %>% mrgsim
plot(out, CP~time|ID)
```

expand.idata

Create data sets.

Description

Create data sets.

Usage

```
expand.idata(...)
expand.ev(...)
```

Arguments

... passed to expand.grid

Details

An ID column is added as 1:nrow(ans)

```
idata <- expand.idata(CL=c(1,2,3), VC=c(10,20,30))
doses <- expand.ev(amt=c(300,100), ii=c(12,24), cmt=1)</pre>
```

firstonly 21

firstonly

This function is deprecated.

Description

This function is deprecated.

Usage

```
firstonly()
```

idata

Create an idata data set

Description

Create an idata data set

Usage

```
idata(..., KEEP.OUT.ATTRS = FALSE, stringsAsFactors = FALSE)
```

Arguments

```
... passed to expand.grid
KEEP.OUT.ATTRS passed to expand.grid
stringsAsFactors
passed to expand.grid
```

idata_set

Set the idata argument for mrgsim.

Description

Set the idata argument for mrgsim.

Usage

```
idata_set(x, data, ...)
## S4 method for signature 'mrgmod,data.frame'
idata_set(x, data, subset = TRUE,
    select = TRUE, ...)
## S4 method for signature 'mrgmod,ANY'
idata_set(x, data, ...)
```

22 knobs

Arguments

```
x model object
data a data set coercable to data.frame
... passed along
subset passed to dplyr::filter_
select passed to dplyr::select_
```

installed_models

Get path to example models

Description

Get path to example models

Usage

```
installed_models()
```

knobs

Run sensitivity analysis on model settings

Description

Knobs can be parameter values or PK dosing items (e.g. amt). By design, all combinations of specified knob/values are simulated.

Usage

```
knobs(x, y, ...)
## S4 method for signature 'mrgmod,missing'
knobs(x, ..., carry.out = character(0),
    drop = c("default", "none", "all"), update = list())
## S4 method for signature 'mrgmod,batch_mrgsims'
knobs(x, y, ...)
## S4 method for signature 'batch_mrgsims'
as.data.frame(x, row.names = NULL,
    optional = FALSE, ...)
## S4 method for signature 'batch_mrgsims'
as.matrix(x, y, ...)
batch(x, ...)
```

knobs 23

```
## S4 method for signature 'batch_mrgsims'
batch(x, ...)

## S4 method for signature 'batch_mrgsims,ANY'
knobs(x, y, ...)

## S4 method for signature 'batch_mrgsims'
moving(x, ...)

## S4 method for signature 'batch_mrgsims'
show(object)
```

Arguments

X	the model object
У	batch_mrgsims object
•••	knobs: named numeric vectors that identify knob names and knob values for a batch run. See details.
carry.out	passed to mrgsim
drop	defines which knobs to drop in the matrix of simulated data; with drop = "none", the values of all knobs appear in the simulated data matrix; with drop = "all", no knob names appear in the simulated data matrix; when drop is "default", selected non-moving columns related to PK dosing are dropped: cmt, time, addl, ii, ss, evid. In every case, the simulation run settings can be retreived with the batch method for the batch_mrgsims output object.
update	a list of arguments that are passed to update prior to running the knobs
row.names	passed to as.data.frame
optional	passed to as.data.frame

Details

object

Valid knob names include: any parameter name (in param(mod)), time variables (start, end, delta), PK dosing items (amt, ii, rate, and others ...), and solver settings (atol, hmax, etc...).

Value

An object of class batch_mrgsims. Most methods for mrgsims objects also work on batch_mrgsims object.

Examples

```
## example("knobs")

mod <- mrgsolve:::house(end=72)

events <- ev(amt=1000, cmt=1, addl=3, ii=12)

out <- mod %>% ev(events) %>% knobs(CL=c(1,2,3))
plot(out)

out
```

passed to show

24 Ictran

```
moving(out)
batch(out)
out <- mod %>% ev(events) %>% knobs(CL=c(1,2,3), VC=c(5,20,50))
plot(out)
plot(out,CP~.)
plot(out, CP~time|VC, groups=CL, lty=2)
out <- knobs(mod, amt=c(100,300,500), cmt=1,time=0)
plot(out)
out <- mod %>% knobs(amt=c(100,300), CL=c(1,3),VC=c(5,20), cmt=1, time=0)
plot(out)
plot(out, CP~.)
plot(out, CP~time|CL*VC, groups=Amt)
out <- knobs(mod, CL=c(1,2,3), drop="all")</pre>
out
out <- knobs(mod, CL=c(1,2,3), drop="none")</pre>
out
```

label

Label simulation output.

Description

Attaches a named column to the simulation output with a single numeric value

Usage

```
label(x, ...)
## S4 method for signature 'mrgsims'
label(x, ...)
```

Arguments

x mrgsims object

... name=value pairs; value must be numeric.

lctran

Convert select upper case column names to lower case to conform to mrgsolve data expectations.

Description

Convert select upper case column names to lower case to conform to mrgsolve data expectations.

limit 25

Usage

```
lctran(data)
```

Arguments

data

an nmtran-like data frame

Details

Columns that will be renamed with lower case versions: AMT, II, SS, CMT, ADDL, RATE, EVID, TIME. If a lower case version of these names exist in the data set, the column will not be renamed.

Value

A data frame with renamed columns.

limit

Limit the scope of simulated output

Description

Limit the scope of simulated output

Usage

```
limit(x, ...)
## S4 method for signature 'mrgsims'
limit(x, subset, select = TRUE, ...)
```

Arguments

```
x mrgsims or batch mrgsims object
```

passed along
subset rows to keep
select columns to keep

26 lower2matrix

loadso

Load the model shared object.

Description

Load the model shared object.

Usage

```
loadso(x, ...)
## S4 method for signature 'mrgmod'
loadso(x, ...)
```

Arguments

x the model object... passed along

lower2matrix

Create a square numeric matrix from the lower-triangular elements

Description

Create a square numeric matrix from the lower-triangular elements

Usage

```
lower2matrix(x, prefix = NULL)
```

Arguments

x numeric data

prefix used to generate column names

Value

a square symmetric numeric matrix with column names

matlist 27

matlist

Various functions for and properties of matlist objects.

Description

Various functions for and properties of matlist objects.

Usage

```
zero.re(.x, ...)
## S4 method for signature 'mrgmod'
zero.re(.x, ...)
drop.re(.x, ...)
## S4 method for signature 'mrgmod'
drop.re(.x, ...)
## S4 method for signature 'matlist'
as.list(x, ...)
## S4 method for signature 'matlist'
as.matrix(x, ...)
## S4 method for signature 'matlist'
names(x)
## S4 method for signature 'matlist'
length(x)
## S4 method for signature 'matlist'
dim(x)
## S4 method for signature 'matlist'
nrow(x)
## S4 method for signature 'matlist'
show(object)
```

Arguments

```
.x a matlist object... passed alongx a matlist objectobject passed to showmatlist
```

28 mcode

matlist-class

S4 class matlist.

Description

S4 class matlist.

mcode

Write, compile, and load model code.

Description

This is a convenience function that ultimately calls mread.

Usage

```
mcode(model, code, project = tempdir(), ...)
```

Arguments

model model name

code character string specifying a mrgsolve model

project project name
... passed to mread

Details

Note that the arguments are in slightly different order than mread. The default project is tempdir().

```
code <- '
$CMT DEPOT CENT
$ADVAN2
$MAIN
pred_CL = 1;
pred_VC= 20;
'
mod <- mcode("example",code)</pre>
```

mcRNG 29

mcRNG

Set RNG to use L'Ecuyer-CMRG.

Description

Set RNG to use L'Ecuyer-CMRG.

Usage

mcRNG()

merge.list

Merge two lists

Description

Merge two lists

Usage

```
## S3 method for class 'list'
merge(x, y, ..., strict = TRUE, warn = TRUE,
   context = "object", wild = "...")
```

Arguments

Χ	the original list
---	-------------------

y the new list for merging

... not used

strict logical indicating whether or not new items should be allowed in the list upon

merging.

warn issue warning if nothing found to update

context description of usage context wild wild-card name; see details

Details

Wild-card names (wild) are always retained in x and are brought along from y only when !strict.

30 model

mod

Return the model object.

Description

Return the model object.

Usage

```
mod(x, \ldots) ## S4 method for signature 'mrgsims' mod(x, \ldots)
```

Arguments

x mrgsims object... passed along

model

Return the model name.

Description

Return the model name.

Usage

```
model(x, ...)
## S4 method for signature 'mrgmod'
model(x, ...)
```

Arguments

```
x model object... passed along
```

```
mod <- mrgsolve:::house()
model(mod)</pre>
```

modelparse 31

Description

Parse model specification text

Usage

```
modelparse(txt, split = FALSE, ...)
```

Arguments

txt model specification text split logical

... arguments passed along

modelspec Model Specification File

Description

Model Specification File

CODE BLOCKS

The following list gives the names and usage for different code blocks in the mrgsolve model specification file. All code blocks start with \$.

- \$PROB include a description of the model; the value supplied here must resolve to a valid character string when parsed by the R parser
- \$PARAM name/value pairs for parameters; these name/value pairs for inits must be valid input for list() when parsed. Parameters listed in \$PARAM are numeric variables that can be used in \$MAIN, \$ODE, \$TABLE, or \$CAPTURE and, importantly, can be updated from R without recompiling the model.
- \$FIXED include name/value pairs exactly as you would in \$PARAM. However, these values are declared as constant doubles in the C++ code and are not able to be updated from the R side. This is usually only implemented when there are a very large number of parameters, some of which are never updated. Moving these parameters to \$FIXED will decrease the "active" number of parameters resulting in minor efficiency gains during simulation but much better clarity when looking at the parameter list with param. A call to param will only show name/value pairs declared in \$PARAM. Call allparam to get all name/values declared in \$PARAM and \$FIXED.
- \$INIT name/value pars for compartments / initial conditions; these name/value pairs for inits must be valid input for list() when parsed.
- \$CMT an alternative to \$INIT; specify compartment names only; enter unquoted strings; may be separated by whitespace, comma, or newline. Initial conditions are assumed to be zero and result is stored and accessed as \$INIT would be.

32 modelspec

• \$SET run settings, as name/value pairs; these name/value pairs must be valid input for list() when parsed; value must be a scalar numeric or logical value; modify settings for simulation start or end time, simulation time interval, solver settings (e.g. tolerances or max step size), number of significant digits in output, etc.

- \$GLOBAL code that will get executed upon compile, outside of any other block; must be valid C++ code, may use C++ VARIABLES and MACROS provided by mrgsolve
- \$MAIN main function (like NONMEM \$PK); must be valid C++ code.
- \$0DE differential equations (like NONMEM \$DES); must be valid C++ code, may use C++ VARIABLES and MACROS provided by mrgsolve
- \$TABLE table function (like NONMEM \$ERROR + \$TABLE); must be valid C++ code, may use C++ VARIABLES and MACROS provided by mrgsolve
- \$ADVAN2 implement one-compartment PK model with first-order absorption, where compartment amounts are calculated from algebraic equations rather than ODEs. Initialize two compartments in \$CMT, where the first compartment is the dosing depot. Set pred_CL, prec_VC, and pred_KA in \$MAIN.
- \$ADVAN4 implement two-compartment PK model with first-order absorption, where compartment amounts are calculated from algebraic equations rather than ODEs. Initialize three compartments in \$CMT, where the first compartment is the dosing depot and the second is the central compartment. Set pred_CL, pred_V2, pred_Q, pred_V3, and pred_KA in \$MAIN.
- \$NMXML read in NONMEM modeling results; provide either project directory with run number or the full path to the .xml results file. Will read in final THETAs and add those to the parameter list. See nmxml for options that can be set in \$NMXML. To load model elements directly from a NONMEM run with \$NMXML, it is required to have the XML package installed in your packages library.
- \$THETA numeric values that will be added to the parameter list.
- \$OMEGA a matrix for subject-level random effects. See modMATRIX for options that can be set in \$OMEGA.
- \$SIGMA a matrix for residual unexplained variability. See modMATRIX for options that can be set in \$SIGMA.
- \$ENV environment variables; referencing environment variables is currently only implemented in \$NMXML.
- \$CMTN To get the number of specific compartments (CMT), specify names here as unquoted comma-separated list; they will be made available in the C++ code as _N_CMT.
- \$CAPTURE names of C++ variables to capture in simulated output; separate by comma, space or newline. Each variable listed in this block will be passed to the capture macro discussed below.
- \$SUBROUTINES an options-only block; valid options are advan and trans. Use these to select structure and parameterization for PK models with analytical solutions. Set advan to 1 or 2 for one-compartment model (without or with first-order absorption) or 3 or 4 for two-compartment model (without or with first-order absorption.

Variables

- parameters are accessible by name as specified in param(mod); readonly except in main block iniated by BEGIN_mainW; TYPE: double
- amount in a compartment is accessible by compartment name as specified in init(mod);
 readonly. TYPE: double

modelspec 33

• for the nth compartment CMT, set the bioavailability fraction to F_CMT. This is an alias to _F(n) (see below).

- for the nth compartment CMT, set the dosing lag time to ALAG_CMT. This is an alias to _ALAG(n) (see below).
- for the nth compartment CMT, set the infusion rate to R_CMT. This is an alias to _R(n) (see below).
- for the nth compartment CMT, set the infusion duration to D_CMT. This is an alias to _D(n) (see below).
- the initial amount in compartment CMT is accessible by CMT_0. TYPE: double
- EVID: event id (0: observation, 1: dosing event; 2: other type event; 3: reset; 8: replace). TYPE: int
- TIME: the time value of current record. TYPE: double
- SOLVERTIME: the current value of time within the ode solver. TYPE: double
- NEWIND: new individual flag (0: first record of data set; 1: first record of current individual; 2: subsequent records after and NEWIND 1 record). TYPE: int
- ID: current subject ID. TYPE: double.

Macros

- _F(n) bioavailability fraction for nth compartment; may be read or written to in main code block. See F_CMT above.
- _ALAG(n) dosing event (evid=1) lag time. See ALAG_CMT above.
- _R(n) infusion rate into the nth compartment. See R_CMT above.
- _D(n) infusion duration into the nth compartment. See D_CMT above.
- table(name) = value; save value to the output simulation matrix with name text; readonly. Only available in table code block.
- ETA(n) the value of the nth ETA drawn from normal distribution with mean zero and variance-covariance matrix omega; readonly.
- EPS(n) the value of the nth EPS drawn from normal distribution with mean zero and variance-covariance matrix sigma; readonly.
- SYSTEMSTOPADVANCING() stop advancing the problem for current individual; all compartments will retain the same value for all subsequent simulation times, and the table block will not be called. System will always be advancing when a new individual problem is started.
- SYSTEMNOTADAVANCING() returns bool (logical) if system is not currently advancing.
- _nEQ the number of compartments / differential equations in the problem
- capture(var) writes the C++ variable var to the table of simulated output.

User-defined variables

Users may define any valid C++ variable in the \$GLOBAL code block. These variables will be global to the problem and may be read or written to in any other code block. User may also declare and use the C++ variables double, int, and bool in the \$MAIN, \$ODE, and \$TABLE code blocks. These user variables will be declared in the global environment so that they will also be global to the problem. To use a varible that is local to one of these code blocks, use type localdouble, localint, and localbool for double, int, and bool, respectively, or create your own typedefs to avoid declaring the variables as double, int or bool.

34 modelspec

Comments

• a double forward slash (//) will comment to the end of the line in any code block. This is the preferred commenting mechanism.

Reserved words

A listing of reserved words can be printed to the R console with the function reserved.

```
code <- '
$PROB 1-cmt model with first order absorption
$SET delta =0.1, end=120, verbose=TRUE
preclean=TRUE
$OMEGA block=TRUE
0.1
0.001 0.3
$OMEGA corr=TRUE
0.67 0.2
$SIGMA
1 0.1
$PARAM
CL=1, VC=10, KA=0.1
$INIT GUT=0
CENT=1
$GLOBAL
bool cool=true;
#define KE (CL/VC)
double CP = CENT/VC;
dxdt_GUT = -KA*GUT;
dxdt_CENT = KA*GUT - KE*CENT;
$TABLE
table(ke) = CL/VC;
capture(CP);
mod <- mread(code=code, project=tempdir())</pre>
```

modMATRIX 35

```
smat(mod)
omat(mod)
as.matrix(omat(mod))
see(mod)
code <- '
PARAM CL = 1.5, VC=35, KA=1.2
$CMT DEPOT CENT
$ADVAN2
$MAIN
pred_CL = CL;
pred_VC = VC;
pred_KA = KA;
mod <- mread(code=code, "ADVAN2", tempdir())</pre>
mod %>%
  ev(amt=100,ii=24, addl=9) %>%
 mrgsim(delta=0.1,end=240) %>%
 plot
```

modMATRIX

Create a matrix.

Description

Create a matrix.

Usage

```
modMATRIX(x, name = "", use = TRUE, block = FALSE, correlation = FALSE,
  digits = -1, ...)
```

Arguments

x data for building the matrix. Data in x are assumed to be on-diagonal elements if block is FALSE and lower-triangular elements if block is TRUE

name name

use logical; if FALSE, all matrix elements are set to 0

block logical; if TRUE, try to make a block matrix; diagonal otherwise

36 mread

correlation logical; if TRUE, off diagonal elements are assumed to be correlations and con-

verted to covariances; if correlation is TRUE, then block is set to TRUE

digits if value of this argument is greater than zero, the matrix is passed to signif (along

with digits) prior to returning

... passed along

Examples

```
modMATRIX("1 2.2 333")
modMATRIX("1 1.1 2.2", block=TRUE)
modMATRIX("23 234 234 5234", use=FALSE)

ans <- modMATRIX("1.1 0.657 2.2", correlation=TRUE, block=TRUE)
ans
cov2cor(ans)</pre>
```

mread

Read a model specification file

Description

Read a model specification file

Usage

```
mread(model = character(0), project = getwd(), code = NULL, udl1 = TRUE,
  ignore.stdout = TRUE, raw = FALSE, compile = TRUE, audit = FALSE,
  quiet = getOption("mrgsolve_mread_quiet", FALSE), check.bounds = FALSE,
  warn = TRUE, soloc = tempdir(), preclean = FALSE, ...)
```

Arguments

model model name
project working directory

code a character string with model specification code

udll use unique name for shared object

ignore.stdout passed to system call for compiling model

raw if TRUE, return a list of raw output

compile try to compile the model and load the shared object

audit check the model specification file for errors quiet don't print messages when compiling

check bounds check boundaries of parameter list

warn logical; if TRUE, print warning messages that may arise

soloc directory where model shared object is stored

preclean logical; if TRUE, compilation artifacts are cleaned up first

... passed along

mrgindata 37

Examples

```
code <- '
$PARAM CL = 1, VC = 5
$CMT CENT
$ODE dxdt_CENT = -(CL/VC)*CENT;
'
mod <- mread(code=code)
mod
mod %>% init(CENT=1000) %>% mrgsim %>% plot
```

mrgindata

Prepare input data.frame or matrix

Description

Prepare input data.frame or matrix

Usage

```
mrgindata(x, ...)
## S3 method for class 'data.frame'
mrgindata(x, m = NULL, verbose = FALSE,
    quiet = FALSE, ...)
## S3 method for class 'matrix'
mrgindata(x, verbose = FALSE, ...)
```

Arguments

```
    x data.frame or matrix
    ... additional arguments
    m object that inherits from mrgmod
    verbose logical
    quiet if TRUE, messages will be suppressed
```

Value

a matrix with non-numeric columns dropped; if x is a data.frame with character cmt column comprised of valid compartment names and m is a model object, the cmt column will be converted to the corresponding compartment number.

38 mrgmod-class

mrgmod-class

S4 class for mrgsolve model object

Description

S4 class for mrgsolve model object

Slots

```
model model name <character>
project working directory; must be writeable with no spaces <character>
start simulation start time < numeric>
end simulation end time < numeric>
delta simulation time interval <numeric>
add additional simulation times <numeric-vector>
param parameter_list
fixed a parameter_list of fixed value parameters; these are not updatable from R
init cmt_list
events events object
digits significant digits in simulated output; negative integer means ignore <numeric>
hmin passed to dlsoda <numeric>
hmax passed to dlsoda <numeric>
mxhnil passed to dlsoda <numeric>
ixpr passed to dlsoda <numeric>
atol passed to dlsoda <numeric>
rtol passed to dlsoda <numeric>
maxsteps passed to dlsoda <numeric>
preclean passed to R CMD SHLIB during compilation <logical>
verbose print run information to screen <logical>
tscale used to scale time in simulated output <numeric>
omega matlist for simulating individual-level random effects
sigma matlist for simulating residual error variates
func character vector of length 2 specifying symbol name and package for ode function; this is not
     normally set by the user
init_fun character vector of length 2 specifying symbol name and package for main function; this
     is not normally set by the user
table_fun character vector of length 2 specifying symbol name and package for table function;
     this is not normally set by the user
args <list> of arguments to be passed to mrgsim
advan either 2, 4, or 13 < numeric>
trans either 1, 2, 4, or 11
request vector of compartments to request <character>
soloc directory path for storing the model shared object <character>
mindt minimum time between simulation records <numeric>
```

mrgsim 39

Notes

• Spaces in paths (project and soloc) are prohibited.

mrgsim

Simulate from a model object.

Description

This function sets up the simulation run from data stored in the model object as well as arguments passed in. Note that there are many non-formal arguments to this function that can be used to customize the simulation run and it's output.

Usage

```
mrgsim(x, ...)
## S4 method for signature 'mrgmod'
mrgsim(x, data = NULL, idata = NULL, nid = 1, ...)
## S4 method for signature 'mrgsims'
mrgsim(x, ...)
```

Arguments

```
x the model objects
... passed to update
data NMTRAN-like data set
idata a matrix or data frame of model parameters, one parameter per row
nid integer number of individuals to simulate; only used if idata and data are missing
```

Details

- Both data and idata will be coreced to numeric matrix
- carry.out can be used to insert data columns into the output data set. This is partially dependent on the nature of the data brought into the problem.
- When using data and idata together, an error is generated if an ID occurs in data but not idata. Also, when looking up data in idata, ID in idata is assumed to be uniquely keyed to ID in data. No error is generated if ID is duplicated in data; parameters will be used from the first occurrence found in idata.
- carry.out: idata is assumed to be individual-level and variables that are carried from idata are repeated throughout the invidivual's simulated data. Variables carried from data are carried via last-observation carry forward. NA is returned from observations that are inserted into simulated output that occur prior to the first record in data.

Value

```
an object of class mrgsims
```

40 mrgsim

Additional arguments

• mtime numeric vector of times where the model is evaluated (with solver reset), but results are not included in simulated output

- trequest a vector of names of table data items to take in simulated ouput
- Trequest same as trequest, except that when Trequest is specified, all model compartments (in request) are dropped; this is just a shorter syntax for saying request="", trequest="name1,name2"
- Request a vector of compartment or table names to take in simulated output; if this is specified, request, trequest, and Trequest are ignored
- obsonly omit records with evid != 0 from simulated output
- obsaug logical; when TRUE and a full data set is used, the simulated output is augmented with an observation at each time in stime(). When using obsaug, a flag indicating augmented observations can be requested by including a.u.g in carry.out
- recsort Default value is 1. Possible values are 1,2,3,4: 1 and 2 put doses in a data set after padded observations at the same time; 3 and 4 put those doses before padded observations at the same time. 2 and 4 will put doses scheduled through add1 after observations at the same time; 1 and 3 put doses scheduled through add1 before observations at the same time. recsort will not change the order of your input data set if both doses and observations are given.
- filbak For each ID, carry the first record data backward to start of the simulation
- mindt The minimum allowable difference between tto and tfrom; if (tto-tfrom)/denom < mindt where denom is tfrom if tfrom is > 0 and 1 otherwise, then tto is set to tfrom. This adjustment is usually helpful when there are infusions in the problem and the end of an infusion is very close to an observation time. When this is the case, the solver may fail with the message DLSODA- TOUT(=R1) too close to T(=R2) to start integration. When mindt==0 the adjustment is not attempted.

```
## example("mrgsim")

mod <- mrgsolve:::house() %>% ev(amt=1000, cmt=1)
out <- mrgsim(mod)
plot(out)

out <- mrgsim(mod, end=22)
out

data(exTheoph)

out <- mrgsim(mod, data=exTheoph)
out

out <- mrgsim(mod, data=exTheoph, obsonly=TRUE)
out

out <- mrgsim(mod, data=exTheoph, obsaug=TRUE, carry.out="a.u.g")
out

out <- mrgsim(mod, data=exTheoph, obsaug=TRUE, carry.out="a.u.g")
out

out <- mrgsim(mod, req="CENT")
out</pre>
```

mrgsims 41

```
out <- mrgsim(mod, Req="CP,RESP")
out</pre>
```

mrgsims

Methods for working with mrgsims objects.

Description

These methods help the user view simulation output and extract simulated data to work with further. The methods listed here for the most part have generics defined by R or other R packages. See the seealso section for other methods defined by mrgsolve that have their own documentation pages.

Usage

```
## S4 method for signature 'mrgsims'
x$name
## S4 method for signature 'mrgsims'
tail(x, ...)
## S4 method for signature 'mrgsims'
head(x, ...)
## S4 method for signature 'mrgsims'
dim(x)
## S4 method for signature 'mrgsims'
names(x)
## S4 method for signature 'mrgsims'
as.data.frame(x, row.names = NULL, optional = FALSE,
## S3 method for class 'mrgsims'
as.tbl(x, ...)
## S3 method for class 'mrgsims'
filter_(.data, ..., .dots)
## S3 method for class 'mrgsims'
group_by_(.data, ..., .dots, add = FALSE)
## S3 method for class 'mrgsims'
mutate_(.data, ..., .dots)
summarise.each(.data, funs, ...)
```

42 mrgsims

```
## S3 method for class 'mrgsims'
summarise_(.data, ..., .dots)
## S3 method for class 'mrgsims'
do_(.data, ..., .dots)
## S3 method for class 'mrgsims'
select_(.data, ..., .dots)
## S3 method for class 'mrgsims'
slice_(.data, ...)
## S4 method for signature 'mrgsims'
as.matrix(x, ...)
## S4 method for signature 'mrgsims'
subset(x, ...)
## S4 method for signature 'mrgsims'
summary(object, ...)
## S4 method for signature 'mrgsims'
show(object)
```

Arguments

X	mrgsims object
name	name of column of simulated output to retain
	passed to other functions
row.names	passed to as.data.frame
optional	passed to as.data.frame
.data	passed to various dplyr functions
.dots	passed to various dplyr functions
add	passed to dplyr::group_by_
funs	passed to dplyr::summarise_each
object	passed to show

Details

Most methods should behave as expected according to other method commonly used in R (e.g. head, tail, as.data.frame, etc ...)

- subset coreces simulated output to data.frame and passes to subset.data.frame
- \$ selects a column in the simulated data and returns numeric
- head see head.matrix; returns simulated data
- tail see tail.matrix; returns simulated data
- dim, nrow, ncol returns dimensions, number of rows, and number of columns in simulated data
- as.data.frame coreces simulated data to data.frame and returns the data.frame

mrgsims-class 43

- as.matrix returns matrix of simulated data
- as.tbl coreces simulated to tbl_df; requires dplyr
- summary coreces simulated data to data.frame and passes to summary.data.frame
- plot plots simulated data; see plot_mrgsims

See Also

mod request variables label limit stime

Examples

```
## example("mrgsims")
mod <- mrgsolve:::house() %>% init(GUT=100)
out <- mrgsim(mod)</pre>
class(out)
out
head(out)
tail(out)
mod(out)
dim(out)
names(out)
mat <- as.matrix(out)</pre>
df <- as.data.frame(out)</pre>
df <- subset(out, time < 12) ## a data frame</pre>
out$CP
plot(out)
plot(out, CP~.)
plot(out, CP+RESP~time, scales="same", xlab="Time", main="Model sims")
out <- label(out, DOSE=100)</pre>
head(out)
```

mrgsims-class

S4 class for mrgsolve simulation output

Description

S4 class for mrgsolve simulation output

Slots

request character vector of compartments requested in simulated output outnames character vector of column names in simulated output coming from table step data matrix of simulated data mod the mrgmod model object

44 mrgsolve

mrgsolve

mrgsolve

Description

mrgsolve is an R package maintained under the auspices of Metrum Research Group, LLC, that facilitates simulation from models based on systems of ordinary differential equations (ODE) that are typically employed for understanding pharmacokinetics, pharmacodynamics, and systems biology and pharmacology. mrgsovle consists of computer code written in the R and C++ languages, providing an interface to the DLSODA differential equation solver (written in FORTRAN) provided through ODEPACK - A Systematized Collection of ODE Solvers.

Help with model specification file

See this help page: modelspec.

Example models

See mrgsolve_example to export example models into your own, writeable project directory.

Input data sets

See data_set for help creating input data sets. See exdatasets for example input data sets.

Package help

- Package index, including a listing of all functions
- Macros and variables in the model specification file: model spec
- Reserved words in mrgsolve: reserved

About the model object

The model object has class mrgmod.

Handling simulated output

See mrgsims for methods to use with simulated output.

Operations between mrgsolve objects

See mrgsolve_Ops for details.

About the solver used by mrgsolve

See: aboutsolver

mrgsolve 45

```
## example("mrgsolve")
mod <- mrgsolve:::house(delta=0.1) %>% param(CL=0.5)
events <- ev(amt=1000, cmt=1, addl=5, ii=24)
mod
cfile(mod)
see(mod)
events
stime(mod)
param(mod)
init(mod)
out <- mod %>% ev(events) %>% mrgsim(end=168)
out <- label(out, TRT=1)</pre>
out
head(out)
tail(out)
dim(out)
mod(out)
param(out)
plot(out, GUT+CP~.)
sims <- as.data.frame(out)</pre>
t72 <- subset(sims, time==72)
str(t72)
idata \leftarrow data.frame(ID=c(1,2,3), CL=c(0.5,1,2),VC=12)
out <- mod %>% ev(events) %>% mrgsim(end=168, idata=idata, req="")
plot(out)
out <- mod %>% ev(events) %>% mrgsim(carry.out="amt,evid,cmt,CL")
head(out)
out <- mod %>% ev() %>% knobs(CL=c(0.5, 1,2), amt=c(100,300,1000), cmt=1,end=48)
plot(out, CP~., scales="same")
\verb"plot(out, RESP+CP"-time|CL, groups=Amt")"
ev1 <- ev(amt=500, cmt=2,rate=10)</pre>
ev2 <- ev(amt=100, cmt=1, time=54, ii=8, addl=10)
events <- ev1+ev2
events
out <- mod %>% ev(ev1+ev2) %>% mrgsim(end=180, req="")
```

46 mrgsolve

```
plot(out)
## Full NMTRAN data set
data(exTheoph)
head(exTheoph)
mod <- mrgsolve:::house(delta=0.1)</pre>
out <- mod %>% data_set(exTheoph) %>% mrgsim
plot(out,CP~time|factor(ID),type='b', scales="same")
## "Condensed" data set
data(extran1)
extran1
out <- mod %>% data_set(extran1) %>% mrgsim(end=200)
plot(out,CP~time|factor(ID))
## idata
data(exidata)
exidata
out <- mod %>% ev(amt=1000, cmt=1) %>% idata_set(exidata) %>% mrgsim(end=72)
plot(out, CP~., as="log10")
code <- '
$PARAM CL=1, VC=10, KA=1.1
$INIT GUT=0, CENT=0
$SET end=48, delta=0.25
$MAIN
double CLi = CL*exp(ETA(1));
double VCi = VC*exp(ETA(2));
double ke = CLi/VCi;
$OMEGA corr=TRUE
0.04 0.6 0.09
$ODE
dxdt_GUT = -KA*GUT;
dxdt_CENT = KA*GUT - ke*CENT;
$TABLE
table(CP) = CENT/VC;
```

mrgsolve_example 47

```
mod <- mread(code=code) %>% ev(amt=1000, cmt=1, addl=2, ii=8)
out <- mod %>% mrgsim
out
plot(out)
```

mrgsolve_example

Extract example model from system library

Description

Extract example model from system library

Usage

```
mrgsolve_example(model = c("pkExample", "pkpdExample", "firstmodeExample",
   "viralExample", "popExample"), project = getwd(), overwrite = FALSE,
   quiet = FALSE, ...)
```

Arguments

```
model name of model
project working directory
overwrite passed to file.copy
quiet don't print any status messages to the screen
... additional arguments
```

```
## example("mrgsolve_example", package="mrgsolve")
mrgsolve_example("pkpdExample", project=getwd())
mod <- mread("pkpdExample", project=getwd()) %>% ev(amt=1000, time=0, cmt=1)
see(mod)
out <- mod %>% mrgsim(end=48,delta=0.1)
out
plot(out)
out <- mod %>%
    ev(amt=1000, ii=24, cmt=1, addl=10) %>%
    mrgsim(end=300)
```

48 mrgsolve_Ops

```
plot(out)
plot(out, CP~time)
```

mrgsolve_models

Get the package models directory.

Description

Get the package models directory.

Usage

```
mrgsolve_models()
```

mrgsolve_Ops

Operations for ev objects.

Description

Operations for ev objects.

Usage

```
## S4 method for signature 'ev,ev'
e1 + e2

## S4 method for signature 'mrgmod,ev'
e1 + e2

## S4 method for signature 'mrgmod,data.frame'
e1 + e2

## S4 method for signature 'mrgmod,cmt_list'
e1 + e2

## S4 method for signature 'mrgmod,parameter_list'
e1 + e2

## S4 method for signature 'ev,ev'
e1 %then% e2

## S4 method for signature 'ev,ev'
e1 %then% e2

## S4 method for signature 'ev,numeric'
e1 + e2
```

mrgsolve_template 49

Arguments

e1	object on left hand side of operator (lhs)
e2	object on right hand side of operator (rhs)

Details

All operations involving mrgmod objects have been deprecated.

 $mrgsolve_template$

Create model specification file from template

Description

Create model specification file from template

Usage

```
mrgsolve_template(model = "template", project = getwd(),
    writeable = FALSE, overwrite = FALSE)
```

Arguments

model name of the model to create

project working directory

writeable logical; if TRUE, parameters may be overwritten in the main block overwrite logical; if TRUE, an existing file with same stem will be overwritten

mvgauss

Simulate from a multivariate normal distribution with mean zero.

Description

Simulate from a multivariate normal distribution with mean zero.

Usage

```
mvgauss(mat, n = 10, seed = NULL)
```

Arguments

n number of variates to simulate seed if not null, passed to set.seed

50 nmxml

neq

Return the number of compartments / equations.

Description

Return the number of compartments / equations.

Usage

```
meq(x, ...)
## S4 method for signature 'mrgmod'
meq(x, ...)
```

Arguments

```
x model object... passed along
```

Examples

```
mod <- mrgsolve:::house()
neq(mod)</pre>
```

nmxml

Get THETA, OMEGA and SIGMA from a completed NONMEM run

Description

Get THETA, OMEGA and SIGMA from a completed NONMEM run

Usage

```
nmxml(run = numeric(0), project = character(0), file = character(0),
  theta = TRUE, omega = FALSE, sigma = FALSE, olabels = NULL,
  slabels = NULL, oprefix = "", sprefix = "", tname = "THETA",
  oname = "...", sname = "...", ...)
```

Arguments

run	run number
project	project directory
file	the complete path to the run.xml file
theta	logical; if TRUE, the \$THETA vector is returned
omega	logical; if TRUE, the $OMEGA$ matrix is returned
sigma	logical; if TRUE, the \$SIGMA matrix is returned
olabels	labels for \$OMEGA

numeric2diag 51

slabels	labels for \$SIGMA
oprefix	prefix for \$0MEGA labels
sprefix	prefix for \$SIGMA labels
tname	name for \$THETA
oname	name for \$0MEGA
sname	name for \$SIGMA
	passed along

Details

If run and project are supplied, the .xml file is assumed to be located in run.xml, in directory run off the project directory. If file is supplied, run and project arguments are ignored.

Value

a list with theta, omega and sigma elements, depending on what was requested

numeric2diag Create a diagonal numeric matrix from diagonal elements

Description

Create a diagonal numeric matrix from diagonal elements

Usage

```
numeric2diag(x, prefix = NULL)
```

Arguments

x numeric data

prefix used to generate column names

Value

a numeric diagonal matrix

52 numericlist

numericlist

Methods for numericlist

Description

These methods can be used to corece param and init objects into common R data structures.

Usage

```
## S4 method for signature 'numericlist'
as.list(x, ...)
## S4 method for signature 'numericlist'
as.numeric(x)
## S4 method for signature 'numericlist'
as.data.frame(x, row.names = NULL, optional = FALSE, ...)
## S4 method for signature 'numericlist'
length(x)
## S4 method for signature 'numericlist'
names(x)
## S4 method for signature 'numericlist'
x$name
## S4 method for signature 'numericlist'
x[i, j, ..., drop = TRUE]
```

Arguments

```
object
Х
                  passed along to other methods
. . .
                  passed to as.data.frame
row.names
                  passed to as.data.frame
optional
name
                  column to take; used with $
i
                  elements to keep
j
                  not used
drop
                  not used
```

```
## Not run:
  mod <- mrgmod(...)
  as.list(param(mod))
  as.numeric(init(mod))
## End(Not run)</pre>
```

numericlist-class 53

Description

S4 class numeric list.

Arguments

data list of data

pattern character of length 1 containing regular expression to be used as a filter when

printing data to the console

obsaug

Set the obsaug argument for mrgsim.

Description

Set the obsaug argument for mrgsim.

Usage

```
obsaug(x, value = TRUE, ...)
```

Arguments

x model object

value the value for obsaug

... passed along

obsonly

Set the obsonly argument for mrgsim.

Description

Set the obsonly argument for mrgsim.

Usage

```
obsonly(x, value = TRUE, ...)
```

Arguments

x model object

value the value for obsonly

... passed along

54 omega

omega

Manipulate OMEGA matrices.

Description

The primary function is omat that can be used to both get the \$OMEGA matrices out of a model object and to update \$OMEGA matrices in a model object.

Usage

```
omat(.x, ...)
## S4 method for signature 'missing'
omat(.x, ...)
## S4 method for signature 'matrix'
omat(.x, ..., labels = list())
## S4 method for signature 'list'
omat(.x, ...)
## S4 method for signature 'omegalist'
omat(.x, ...)
## S4 method for signature 'mrgmod'
omat(.x, ..., make = FALSE, strict = TRUE)
## S4 method for signature 'mrgsims'
omat(.x, make = FALSE, ...)
```

Arguments

```
.x a matrix, list of matrices or matlist object
... passed to other functions, including modMATRIX
labels character vector of names for $OMEGA elements; must be equal to number of rows/columns in the matrix
make logical; if TRUE, matrix list is rendered into a single matrix
strict passed to merge.list
x matlist object
```

```
## example("omega")
mat1 <- matrix(1)
mat2 <- diag(c(1,2,3))
mat3 <- matrix(c(0.1, 0.002, 0.002, 0.5), 2,2)
mat4 <- dmat(0.1, 0.2, 0.3, 0.4)

omat(mat1)
omat(mat1, mat2, mat3)</pre>
```

param 55

```
omat(A=mat1, B=mat2, C=mat3)
mod <- mrgsolve:::house() %>% omat(mat4)
omat(mod)
omat(mod, make=TRUE)
## Not run:
$OMEGA
1 2 3
$OMEGA block=TRUE
1 0.1 2
$OMEGA cor=TRUE
prefix="ETA_"
labels=s(CL,VC,KA)
0.1
0.67 0.2
0 0 0.3
## End(Not run)
```

param

Get and set model parameters

Description

An accessor function for the param model attribute.

See numericlist for methods to deal with parameter_list objects.

Usage

```
param(.x, ...)
## S4 method for signature 'mrgmod'
param(.x, .y = list(), ..., .pat = "*")
## S4 method for signature 'mrgsims'
param(.x, ...)
## S4 method for signature 'missing'
param(.x, ...)
## S4 method for signature 'list'
param(.x, ...)
## S4 method for signature 'ANY'
param(.x, ...)
```

56 param

```
as.param(.x, ...)
## S4 method for signature 'list'
as.param(.x, ...)
## S4 method for signature 'numeric'
as.param(.x, ...)
## S4 method for signature 'parameter_list'
as.param(.x, ...)
## S4 method for signature 'missing'
as.param(.x, ...)
## S4 method for signature 'parameter_list'
show(object)
```

Arguments

. X	the model object
	passed along or name/value pairs to update the parameters in a model object
. У	list to be merged into parameter list
.pat	a regular expression (character) to be applied as a filter for which parameters to show when printing
object	passed to show

Details

Can be used to either get a parameter list object from a mrgmod model object or to update the parameters in a model object. For both uses, the return value is a parameter_list object. For the former use, param is usually called to print the parameters to the screen, but the parameter_list object can also be coreced to a list or numeric R object.

Value

An object of class parameter_list (see numericlist).

```
## example("param")
mod <- mrgsolve:::house()

param(mod)
param(mod, .pat="^(C|F)") ## may be useful when large number of parameters

class(param(mod))

param(mod)$KA

as.list(param(mod))
as.data.frame(param(mod))</pre>
```

parameter_list-class 57

Description

S4 parameter_list class

Details

```
parameter_list is a numericlist-class
```

pars

Return the names of model parameters.

Description

Return the names of model parameters.

Usage

```
pars(x, ...)
## S4 method for signature 'mrgmod'
pars(x, ...)
```

Arguments

```
x model object... passed along
```

```
mod <- mrgsolve:::house()
pars(mod)</pre>
```

58 plot_mrgsims

```
{\it plot}, {\it batch\_mrgsims}, {\it missing-method} \\ {\it Plot\ method\ for\ mrgsims\ objects}.
```

Description

Plot method for mrgsims objects.

Usage

Arguments

```
mrsims object
Х
yval
                   variables to plot
                   maximum number of yval to plot
limit
                   arguments passed to xyplot
. . .
                   a formula passed to xyplot
У
show.grid
                   print grid in the plot
lwd
                   passed to xyplot
type
                   passed to xyplot
                   transformation for every yval that is plotted
as
                   passed to xyplot
auto.key
                   passed to xyplot
scales
```

plot_mrgsims

Generate a quick plot of simulated data.

Description

Generate a quick plot of simulated data.

Usage

```
## S4 method for signature 'mrgsims,missing'
plot(x, limit = 16, ...)

## S4 method for signature 'mrgsims,formula'
plot(x, y, limit = 16, show.grid = TRUE,
    as = "raw", outer = TRUE, type = "l", lwd = 2, ylab = "raw value",
    groups = ID, scales = list(y = list(relation = "free")), ...)
```

plus.ev 59

Arguments

mrgsims object
limit the the number of panels to create
other arguments passed to xyplot
formula used for plotting
logical indicating whether or not to draw panel.grid
transformations for plotting simulated values
passed to xyplot

Details

Values for as argument: ; raw: raw simulated output; frac: each observation normalized to baseline value; cfb: change (difference) from baseline; cfblog: change from baseline of log10-transformed values; log10y: log10 transformation; lny: natural log transformed.

Examples

```
mod <- mrgsolve:::house(end=48, delta=0.2) %>% init(GUT=1000)
out <- mrgsim(mod)
plot(out)
plot(out, subset=time <=24)
plot(out, GUT+CP~.)
plot(out, CP+RESP~time, col="black", scales="same", lty=2)</pre>
```

plus.ev

Add an events object to a mrgmod object

Description

Add an events object to a mrgmod object

Usage

```
plus.ev(e1, e2)
```

Arguments

```
e1 mrgmod object
e2 events object
```

60 relocate

project

Return the name of the project directory.

Description

Return the name of the project directory.

Usage

```
project(x, ...)
## S4 method for signature 'mrgmod'
project(x, ...)
## S4 method for signature 'packmod'
project(x, ...)
## S4 method for signature 'mrgsims'
project(x, ...)
```

Arguments

```
x model object or mrgsims object... passed along
```

Examples

```
mod <- mrgsolve:::house()
project(mod)</pre>
```

relocate

Update model *or* project *in an* mrgmod *object*.

Description

Update model or project in an mrgmod object.

Usage

```
relocate(x, ...)
## S4 method for signature 'mrgmod'
relocate(x, model = NULL, project = NULL)
```

Arguments

```
x mrgmod object... passed alongmodel nameproject directory
```

Req 61

Value

updated model object

Req

Set the Request argument for mrgsim.

Description

Set the Request argument for mrgsim.

Usage

```
Req(x, ...)
## S4 method for signature 'mrgmod'
Req(x, ...)
req(x, ...)
## S4 method for signature 'mrgmod'
req(x, ...)
```

Arguments

x model object

... unquoted names of compartments or tabled items

Examples

```
mod <- mrgsolve:::house()
mod %>% Req(CP,RESP) %>% ev(amt=1000) %>% mrgsim
```

request

Return the requested compartments from a simulation run.

Description

Return the requested compartments from a simulation run.

Usage

```
request(x, ...)
## S4 method for signature 'mrgsims'
request(x, ...)
```

62 revar

Arguments

```
x mrgsims object... passed along
```

See Also

```
variables
```

reserved

Reserved words in mrgsolve.

Description

Reserved words in mrgsolve.

Usage

```
reserved()
```

Details

Note: this function is not exported; you must go into the mrgsolve namespace by using the mrgsolve::: prefix.

Examples

```
mrgsolve:::reserved()
```

revar

Get model random effect variances and covariancnes.

Description

Get model random effect variances and covariancnes.

Usage

```
revar(x, ...)
## S4 method for signature 'mrgmod'
revar(x, ...)
## S4 method for signature 'mrgsims'
revar(x, ...)
```

Arguments

```
x model object... passed along
```

see 63

see

Print model code to the console.

Description

Print model code to the console.

Usage

```
see(x, ...)
## S4 method for signature 'mrgmod'
see(x, ...)
```

Arguments

```
x model object... passed along
```

Value

invisible NULL

shlib

Return information about model compilation.

Description

Return information about model compilation.

Usage

```
shlib(x, ...)
## S4 method for signature 'mrgmod'
shlib(x, ...)
```

Arguments

```
x model object... passed along
```

64 sigma

show, mrgmod-method

Print model details

Description

Print model details

Usage

```
## S4 method for signature 'mrgmod'
show(object)
```

Arguments

object

the model object

sigma

Manipulate SIGMA matrices.

Description

The primary function is smat that can be used to both get the \$SIGMA matrices out of a model object and to update \$SIGMA matrices in a model object.

Usage

```
smat(.x, ...)
## S4 method for signature 'missing'
smat(.x, ...)
## S4 method for signature 'matrix'
smat(.x, ..., labels = list())
## S4 method for signature 'list'
smat(.x, ...)
## S4 method for signature 'sigmalist'
smat(.x, ...)
## S4 method for signature 'mrgmod'
smat(.x, ..., make = FALSE, strict = TRUE)
## S4 method for signature 'mrgsims'
smat(.x, make = FALSE, ...)
```

simargs 65

Arguments

```
    .x a matrix, list of matrices or matlist object
    ... passed to other functions, including modMATRIX
    labels character vector of names for $SIGMA elements; must be equal to number of rows/columns in the matrix
    make logical; if TRUE, matrix list is rendered into a single matrix
    strict passed to merge.list
    x matlist object
```

Examples

```
## example("sigma")
mat1 <- matrix(1)
mat2 <- diag(c(1,2))
mat3 <- matrix(c(0.1, 0.002, 0.002, 0.5), 2,2)
mat4 <- dmat(0.1, 0.2, 0.3, 0.4)

smat(mat1)
smat(mat1, mat2, mat3)
smat(A=mat1, B=mat2, C=mat3)

mod <- mrgsolve:::house() %>% smat(mat1)

smat(mod)
smat(mod, make=TRUE)
```

simargs

Access or clear arguments for mrgsim.

Description

Access or clear arguments for mrgsim.

Usage

```
simargs(x, ...)
## S3 method for class 'mrgmod'
simargs(x, clear = FALSE, ...)
```

Arguments

```
x model object
... passed along
clear logical indicating whether or not clear
```

clear logical indicating whether or not clear args from the model object

Value

If clear is TRUE, the argument list is cleared and the model object is returned. Otherwise, the argument list is returned.

66 sodll

simre

Simulate random effects from model.

Description

Simulate random effects from model.

Usage

```
simre(x, ...)
## S4 method for signature 'mrgmod'
simre(x, seed = NULL, neta = 10, neps = 10, ...)
## S4 method for signature 'mrgsims'
simre(x, seed = NULL, ...)
```

Arguments

x	model object
• • •	passed along
seed	passed to set.seed
neta	number of etas to simulate
neps	number of epsilon values to simulate

sodll

Return the name of the shared object file.

Description

Return the name of the shared object file.

Usage

```
sodll(x, ...)
## S4 method for signature 'mrgmod'
sodll(x, ...)
## S4 method for signature 'lockedmod'
sodll(x, ...)
## S4 method for signature 'packmod'
sodll(x, ...)
```

Arguments

```
x model object... passed along
```

soloc 67

Examples

```
mod <- mrgsolve:::house()
sodll(mod)</pre>
```

soloc

Return the location of the model shared object.

Description

Return the location of the model shared object.

Usage

```
soloc(x, short = FALSE)
```

Arguments

```
x model object
```

short logical; if TRUE, soloc will be rendered with a short path name

Examples

```
mod <- mrgsolve:::house()
soloc(mod)</pre>
```

stime,mrgmod-method

Create a simtime object.

Description

simtime objects allow the user to specify simulation start and end times, along with the simulation time step.

```
##' @export
```

Usage

```
## S4 method for signature 'tgrids'
c(x, ..., recursive = FALSE)
## S4 method for signature 'tgrid'
stime(x, ...)
## S4 method for signature 'tgrids'
stime(x, ...)
## S4 method for signature 'numeric'
stime(x, ...)
## S4 method for signature 'tgrid,numeric'
e1 + e2
## S4 method for signature 'tgrid,numeric'
e1 * e2
## S4 method for signature 'tgrids, numeric'
## S4 method for signature 'tgrids, numeric'
e1 * e2
## S4 method for signature 'tgrid'
show(object)
## S4 method for signature 'tgrids'
show(object)
```

Arguments

x	mrgmod object
	passed on to other methods
start	simulation start time
end	simulation end time
delta	simulation time step
add	addition simulation times
.offset	the resulting set of times will be adjusted by this amount
.scale	the resulting set of times will be scaled by this factor
recursive	not used
e1	tgrid or tgrids object
e2	numeric value
object	passed to show

```
peak <- tgrid(0,6,0.2)
```

tgrid-class 69

```
sparse <- tgrid(0,24,4)

day1 <- c(peak,sparse)

design <- c(day1, day1+72, day1+240)

mod <- mrgsolve:::house()

out <- mod %>% ev(amt=1000, ii=24, addl=10) %>% mrgsim(tgrid=design)

plot(out,CP~., type='b')
```

tgrid-class

Get the times at which the model will be evaluated.

Description

Get the times at which the model will be evaluated.

Usage

```
stime(x, ...)
```

Arguments

x object of class mrgmod ... passed on

Details

Simulation times include the sequence of times created from start, end, and delta and the vector of times found in add. Making end negative will omit any start / end / delta sequence. Negative values are discarded from the result.

Value

a sorted vector of unique times

```
## example("stime", package="mrgsolve")

mod <- mrgsolve:::house(end=12, delta=2, add=c(11,13,15))

stime(mod)

out <- mrgsim(mod, end=-1, add=c(2,4,5))

stime(out)

out$time</pre>
```

70 unloadso

touch_funs

Get inits from compiled function.

Description

Get inits from compiled function.

Usage

```
touch_funs(x)
```

Arguments

Χ

mrgmod model object

tscale

Set the tscale argument for mrgsim.

Description

Set the tscale argument for mrgsim.

Usage

```
tscale(x, value = 1, ...)
```

Arguments

x model object

value value by which time will be scaled

... passed along

unloadso

Unload the model shared object.

Description

Unload the model shared object.

Usage

```
\label{eq:continuous} \begin{tabular}{lll} $\tt unloadso(x, \ldots) \\ \begin{tabular}{lll} $\tt \# S4 method for signature 'mrgmod' \\ \begin{tabular}{lll} {\tt unloadso(x, \ldots)} \\ \end{tabular}
```

Arguments

```
x model object... passed along
```

update 71

una	data
upo	date

Update the model object

Description

After the model object is created, update various attributes.

Usage

```
## S4 method for signature 'mrgmod'
update(object, ..., merge = TRUE, strict = TRUE,
    super.strict = FALSE, data = list())

## S4 method for signature 'omegalist'
update(object, y, ...)

## S4 method for signature 'sigmalist'
update(object, y, ...)

## S4 method for signature 'parameter_list'
update(object, y, ...)

## S4 method for signature 'ev'
update(object, y, ...)
```

Arguments

object	a model object
• • •	passed to other functions
merge	logical indicating to merge (rather than replace) new and existing attributes.
strict	logical; used only when merge is TRUE and parameter list or initial conditions list is being updated; if TRUE, no new items will be added; if FALSE, the parameter list may expand.
super.strict	logical; strict common area updating
data	a list of items to update; not used for now
У	another object involved in update

Details

See also mrgsolve_Ops for alternative ways to update events, parameters, and initial conditions in a model object.

Value

The updated model object is returned.

```
mod <- mrgsolve:::house()
mod <- update(mod, end=120, delta=4, param=list(CL=19.1))</pre>
```

72 %**>**%

variables	Return the requested compartments and tabled items from a simulation
	run.

Description

Return the requested compartments and tabled items from a simulation run.

Usage

```
variables(x, ...)
## S4 method for signature 'mrgsims'
variables(x, ...)
```

Arguments

```
x mrgsims object... passed along
```

See Also

request

%>%

Forward pipe.

Description

Forward pipe.

Tee.

Index

```
*Topic datasets
                                                 as.ev, data.frame-method (events), 17
    exdatasets, 19
                                                 as.init,5
*Topic events
                                                 as.init,cmt_list-method(as.init),5
    events, 17
                                                 as.init, list-method (as.init), 5
*Topic param
                                                 as.init, missing-method (as.init), 5
    param, 55
                                                 as.init, NULL-method (as.init), 5
*,tgrid,numeric-method
                                                 as.init, numeric-method (as.init), 5
        (stime, mrgmod-method), 67
                                                 as.list, matlist-method (matlist), 27
*,tgrids,numeric-method
                                                 as.list,numericlist-method
        (stime, mrgmod-method), 67
                                                          (numericlist), 52
+, ev, ev-method (mrgsolve_Ops), 48
                                                 as.locked, 7
+, ev, numeric-method (mrgsolve_Ops), 48
                                                 as.locked, mrgmod-method (as.locked), 7
+,mrgmod,cmt_list-method
                                                 as.matrix,batch_mrgsims-method(knobs),
        (mrgsolve_Ops), 48
                                                 as.matrix,ev-method (events), 17
+, mrgmod, data. frame-method
        (mrgsolve_Ops), 48
                                                 as.matrix, matlist-method (matlist), 27
+, mrgmod, ev-method (mrgsolve_Ops), 48
                                                 as.matrix,mrgsims-method(mrgsims),41
+,mrgmod,parameter_list-method
                                                 as.matrix.list, 7
        (mrgsolve_Ops), 48
                                                 as.numeric,numericlist-method
+,tgrid,numeric-method
                                                          (numericlist), 52
        (stime, mrgmod-method), 67
                                                 as.packmod, 8
+,tgrids,numeric-method
                                                 as.packmod,mrgmod-method(as.packmod), 8
        (stime, mrgmod-method), 67
                                                 as.param(param), 55
[,numericlist-method(numericlist), 52
                                                 as.param, list-method (param), 55
, mrgsims-method (mrgsims), 41
                                                 as.param, missing-method (param), 55
$, numericlist-method (numericlist), 52
                                                 as.param, numeric-method (param), 55
%T>% (%>%), 72
                                                 as.param, parameter_list-method (param),
%then% (mrgsolve_Ops), 48
                                                          55
%then%, ev, ev-method (mrgsolve_Ops), 48
                                                 as.tbl.mrgsims(mrgsims),41
%>%, <del>72</del>
                                                 as_bmat, 8
                                                 as_bmat, ANY-method (as_bmat), 8
aboutsolver, 4, 44
                                                 as_bmat,data.frame-method(as_bmat),8
add.ev, 5
                                                 as_bmat,list-method(as_bmat),8
allparam, 31
                                                 as_bmat, numeric-method (as_bmat), 8
allparam (param), 55
                                                 as_dmat(as_bmat), 8
as.data.frame, 18, 23, 42, 52
                                                 as_dmat, ANY-method (as_bmat), 8
as.data.frame,batch_mrgsims-method
                                                 as_dmat, data.frame-method (as_bmat), 8
        (knobs), 22
                                                 as_dmat, list-method (as_bmat), 8
as.data.frame, ev-method (events), 17
                                                 as_dmat, numeric-method (as_bmat), 8
as.data.frame, mrgsims-method (mrgsims),
                                                 batch (knobs), 22
as.data.frame,numericlist-method
                                                 batch, batch_mrgsims-method (knobs), 22
        (numericlist), 52
                                                 BLOCK (bmat), 10
as.ev (events), 17
                                                 blocks, 9
```

74 INDEX

blocks, character-method (blocks), 9	expand.grid, 20
blocks, mrgmod-method(blocks), 9	expand.idata, 20
bmat, 10	exTheoph (exdatasets), 19
,	extran1 (exdatasets), 19
c,tgrid-method(stime,mrgmod-method),67	extran2 (exdatasets), 19
c,tgrids-method(stime,mrgmod-method),	extran3 (exdatasets), 19
67	(
callinit (as.init), 5	filtermrgsims(mrgsims), 41
carry.out, 11	firstonly, 21
cfile, 11	
cfile,lockedmod-method(cfile),11	<pre>group_bymrgsims (mrgsims), 41</pre>
cfile,mrgmod-method(cfile),11	band manning mathed (manning) 41
ch (cvec), 14	head, mrgsims-method (mrgsims), 41
chain, 12	head.matrix,42
cmat (bmat), 10	idata, 21
cmt, 12	idata_set, 21
cmt, mrgmod-method (cmt), 12	idata_set,mrgmod,ANY-method
cmt_list-class, 13	(idata_set), 21
cmtn, 13	idata_set,mrgmod,data.frame-method
cmtn, mrgmod-method (cmtn), 13	
comp_forget (complog), 14	(idata_set), 21
complog, 14	init, 12, 15
cvec, 14	init (as.init), 5
cvec, character-method (cvec), 14	init, ANY-method (as.init), 5
,	init, list-method (as.init), 5
data_set, 15, 44	init, missing-method (as.init), 5
data_set,mrgmod,ANY-method(data_set),	init, mrgmod-method (as.init), 5
15	init, mrgsims-method (as.init), 5
data_set,mrgmod,data.frame-method	installed_models, 22
(data_set), 15	knobs, 22
design, 16	knobs, batch_mrgsims, ANY-method (knobs),
dim, matlist-method (matlist), 27	22
dim, mrgsims-method (mrgsims), 41	knobs,mrgmod,batch_mrgsims-method
dllname, 16	
dllname, mrgmod-method (dllname), 16	(knobs), 22
dmat (bmat), 10	knobs, mrgmod, missing-method (knobs), 22
domrgsims (mrgsims), 41	label, 24
drop.re (matlist), 27	label, mrgsims-method (label), 24
drop.re,mrgmod-method(matlist), 27	lctran, 24
, ,	length, matlist-method (matlist), 27
ev, <i>12</i>	length, numericlist-method
ev (events), 17	(numericlist), 52
ev, ev-method (events), 17	limit, 12, 25
ev, missing-method (events), 17	limit, mrgsims-method (limit), 25
ev, mrgmod-method (events), 17	loadso, 26
ev-class, 17	loadso, mrgmod-method (loadso), 26
events, 17, 38	lower2matrix, 26
events, mrgmod-method (events), 17	TOWER ZINGER TX, 20
events, mrgsims-method (events), 17	matlist, 27, 38
exBoot (exdatasets), 19	matlist-class, 28
exdatasets, 15, 19, 44	mcode, 28
exidata (exdatasets), 19	mcRNG, 29
expand.ev (expand.idata), 20	merge.list, 29, 54, 65
1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1	

INDEX 75

mod, 30	param, ANY-method (param), 55
mod,mrgsims-method(mod),30	param, list-method (param), 55
model, <i>16</i> , 30	param, missing-method (param), 55
model,mrgmod-method(model),30	param, mrgmod-method (param), 55
modelparse, 31	param, mrgsims-method (param), 55
modelspec, 31, 44	parameter_list-class, 57
modMATRIX, 32, 35, 54, 65	pars, 57
moving (knobs), 22	pars, mrgmod-method (pars), 57
moving, batch_mrgsims-method(knobs), 22	plot,batch_mrgsims,formula-method
mread, 28, 36	<pre>(plot,batch_mrgsims,missing-method),</pre>
mrgindata, 37	58
mrgmod, 44, 49	plot,batch_mrgsims,missing-method,58
mrgmod-class, 38	plot,mrgsims,formula-method
mrgsim, 23, 38, 39	(plot_mrgsims), 58
mrgsim, mrgmod-method (mrgsim), 39	plot,mrgsims,missing-method
mrgsim, mrgsims-method (mrgsim), 39	(plot_mrgsims), 58
mrgsims, 39, 41, 44	plot_mrgsims, 43, 58
mrgsims-class, 43	plus.ev, 59
mrgsolve, 44	plus_mrgmod_cmt_list(mrgsolve_Ops), 48
mrgsolve-package (mrgsolve), 44	plus_mrgmod_data.frame (mrgsolve_Ops),
mrgsolve_example, 44, 47	48
mrgsolve_models, 48	plus_mrgmod_ev (mrgsolve_Ops), 48
mrgsolve_Ops, <i>44</i> , 48, <i>71</i>	plus_mrgmod_parameter_list
mrgsolve_template, 49	(mrgsolve_Ops), 48
mutatemrgsims(mrgsims), 41	project, 60
mvgauss, 49	project, mrgmod-method (project), 60
	project, mrgsims-method (project), 60
names, matlist-method (matlist), 27	project, packmod-method (project), 60
names, mrgsims-method (mrgsims), 41	[
names, numericlist-method (numericlist),	relocate, 60
52	relocate, mrgmod-method (relocate), 60
neq, 50	Reg, 61
neq, mrgmod-method (neq), 50	req (Req), 61
nmxm1, 32, 50	Req,mrgmod-method(Req), 61
nrow, matlist-method (matlist), 27	req,mrgmod-method(Req),61
numeric2diag, 51	request, 61, 72
numericlist, <i>5</i> , <i>6</i> , 52, <i>55</i> , <i>56</i>	request, mrgsims-method (request), 61
numericlist-class, 53	reserved, <i>34</i> , <i>44</i> , 62
, , , , , , , , , , , , , , , , , , , ,	revar, 62
obsaug, 53	revar, mrgmod-method (revar), 62
obsonly, 53	revar, mrgsims-method (revar), 62
omat (omega), 54	, 3
omat, list-method (omega), 54	s (cvec), 14
omat, matrix-method (omega), 54	see, 63
omat, missing-method (omega), 54	see, mrgmod-method (see), 63
omat, mrgmod-method (omega), 54	<pre>selectmrgsims (mrgsims), 41</pre>
omat, mrgsims-method (omega), 54	set.seed, 66
omat, omegalist-method (omega), 54	shlib, 63
OMEGA (omega), 54	shlib, mrgmod-method (shlib), 63
omega, 54	show, batch_mrgsims-method (knobs), 22
omegalist-class (matlist-class), 28	show, cmt_list-method (as.init), 5
	show, ev-method (events), 17
param, <i>12</i> , <i>31</i> , <i>55</i>	show, matlist-method (matlist), 27

76 INDEX

show, mrgmod-method, 64
show, mrgsims-method (mrgsims), 41
<pre>show,parameter_list-method(param), 55</pre>
show,tgrid-method
(stime, mrgmod-method), 67
show, tgrids-method
(stime, mrgmod-method), 67
SIGMA (sigma), 64
sigma, 64
sigmalist-class (matlist-class), 28
simargs, 65
simre, 66
simre, mrgmod-method (simre), 66
simre, mrgsims-method (simre), 66
slicemrgsims (mrgsims), 41
smat (sigma), 64
smat, list-method (sigma), 64
smat, matrix-method (sigma), 64
smat, missing-method (sigma), 64
smat,mrgmod-method(sigma),64
smat,mrgsims-method(sigma),64
smat, sigmalist-method (sigma), 64
sod11, 66
sodll, lockedmod-method (sodll), 66
sodll, mrgmod-method(sodll), 66
sodll, packmod-method (sodll), 66
soloc, 67
stime, <i>40</i>
stime (tgrid-class), 69
<pre>stime (tgrid-class), 69 stime,mrgmod-method, 67</pre>
stime (tgrid-class), 69 stime,mrgmod-method, 67 stime,mrgsims-method
<pre>stime (tgrid-class), 69 stime,mrgmod-method, 67 stime,mrgsims-method</pre>
<pre>stime (tgrid-class), 69 stime, mrgmod-method, 67 stime, mrgsims-method</pre>
<pre>stime (tgrid-class), 69 stime,mrgmod-method, 67 stime,mrgsims-method</pre>
<pre>stime (tgrid-class), 69 stime, mrgmod-method, 67 stime, mrgsims-method</pre>
stime (tgrid-class), 69 stime, mrgmod-method, 67 stime, mrgsims-method
stime (tgrid-class), 69 stime, mrgmod-method, 67 stime, mrgsims-method
stime (tgrid-class), 69 stime, mrgmod-method, 67 stime, mrgsims-method
stime (tgrid-class), 69 stime, mrgmod-method, 67 stime, mrgsims-method
stime (tgrid-class), 69 stime, mrgmod-method, 67 stime, mrgsims-method
stime (tgrid-class), 69 stime, mrgmod-method, 67 stime, mrgsims-method
stime (tgrid-class), 69 stime, mrgmod-method, 67 stime, mrgsims-method
stime (tgrid-class), 69 stime, mrgmod-method, 67 stime, mrgsims-method
stime (tgrid-class), 69 stime, mrgmod-method, 67 stime, mrgsims-method
stime (tgrid-class), 69 stime, mrgmod-method, 67 stime, mrgsims-method
<pre>stime (tgrid-class), 69 stime, mrgmod-method, 67 stime, mrgsims-method</pre>
<pre>stime (tgrid-class), 69 stime, mrgmod-method, 67 stime, mrgsims-method</pre>
stime (tgrid-class), 69 stime, mrgmod-method, 67 stime, mrgsims-method
<pre>stime (tgrid-class), 69 stime, mrgmod-method, 67 stime, mrgsims-method</pre>

```
tgrids_*_numeric(stime,mrgmod-method),
tgrids_+_numeric(stime,mrgmod-method),
touch_funs, 70
tscale, 70
unloadso, 70
unloadso, mrgmod-method (unloadso), 70
update, 12, 39, 71
update, ev-method (update), 71
update, mrgmod-method (update), 71
update, omegalist-method (update), 71
update,parameter_list-method(update),
        71
update, \verb|sigmalist-method| (update), 71
variables, 62,72
variables, mrgsims-method (variables), 72
zero.re(matlist), 27
zero.re,mrgmod-method(matlist),27
```