Package 'RxODE'

March 23, 2022

Version 1.1.5

Title Facilities for Simulating from ODE-Based Models

Maintainer Wenping Wang <wwang8198@gmail.com>

Depends R (>= 4.0.0)

Suggests spelling, Matrix, DT, covr, crayon, curl, data.table (>= 1.12.4), digest, dplyr (>= 0.8.0), ggrepel, gridExtra, htmltools, knitr, learnr, microbenchmark, nlme, remotes, rlang, rmarkdown, scales, shiny, stringi, symengine, testthat, tidyr, usethis, vdiffr, xgxr, pillar, tibble, units (>= 0.6-0), rsconnect, devtools, patchwork

Imports PreciseSums (>= 0.3), Rcpp (>= 0.12.3), assertthat, backports, checkmate, cli (>= 2.0.0), dparser (>= 0.1.8), ggplot2, inline, lotri (>= 0.3.0), magrittr, memoise, methods, rex, qs, sys, tools, utils

Description Facilities for running simulations from ordinary differential equation ('ODE') models, such as pharmacometrics and other compartmental models. A compilation manager translates the ODE model into C, compiles it, and dynamically loads the object code into R for improved computational efficiency. An event table object facilitates the specification of complex dosing regimens (optional) and sampling schedules. NB: The use of this package requires both C and Fortran compilers, for details on their use with R please see Section 6.3, Appendix A, and Appendix D in the ``R Administration and Installation'' manual. Also the code is mostly released under GPL. The 'VODE' and 'LSODA' are in the public domain. The information is available in the inst/COPYRIGHTS.

BugReports https://github.com/nlmixrdevelopment/RxODE/issues/

NeedsCompilation yes

VignetteBuilder knitr

License GPL (>= 3)

URL https://nlmixrdevelopment.github.io/RxODE/, https://github.com/nlmixrdevelopment/RxODE/

RoxygenNote 7.1.2

Biarch true

LinkingTo dparser (>= 1.3.1-0), PreciseSums (>= 0.3), RcppEigen (>= 0.3.3.3.0), RcppArmadillo (>= 0.9.300.2.0), sitmo, StanHeaders (>= 2.21.0), BH

Encoding UTF-8

LazyData true

Language en-US

Author Matthew L. Fidler [aut] (<https://orcid.org/0000-0001-8538-6691>),
Melissa Hallow [aut],
Wenping Wang [aut, cre],
Zufar Mulyukov [ctb],
Alan Hindmarsh [ctb],
Awad H. Al-Mohy [ctb],
Matt Dowle [ctb],
Cleve Moler [ctb],
David Cooley [ctb],
Drew Schmidt [ctb],
Arun Srinivasan [ctb],
Ernst Hairer [ctb],
Gerhard Wanner [ctb],
Goro Fuji [ctb],
Hadley Wickham [ctb],
Jack Dongarra [ctb],
Linda Petzold [ctb],
Martin Maechler [ctb],
Matteo Fasiolo [ctb],
Morwenn [ctb],
Nicholas J. Higham [ctb],
Roger B. Sidje [ctb],
Simon Frost [ctb],
Kevin Ushey [ctb],
Yu Feng [ctb]

Repository CRAN

Date/Publication 2022-03-23 01:10:12 UTC

R topics documented:

`.rxGenFoce` *Generate FOCE without interaction*

Description

Generate FOCE without interaction

Usage

```
.rxGenFoce(
  obj,
  predfn,
  pkpars = NULL,
  errfn = NULL,
  init = NULL,
  pred.minus.dv = TRUE,
  sum.prod = FALSE,
  optExpression = TRUE,
  promoteLinSens = TRUE,
  theta = FALSE,
  addProp = c("combined2", "combined1")
)
```

Arguments

`obj`	RxODE object
`predfn`	Prediction function
`pkpars`	Pk Pars function
`errfn`	Error function
`init`	Initialization parameters for scaling.
`pred.minus.dv`	Boolean stating if the FOCEi objective function is based on PRED-DV (like NONMEM). Default TRUE.
`sum.prod`	A boolean determining if RxODE should use more numerically stable sums/products.
`optExpression`	Optimize the model text for computer evaluation.
`promoteLinSens`	Promote solved linear compartment systems to sensitivity-based solutions.
`theta`	Calculate THETA derivatives instead of ETA derivatives. By default FALSE
`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

Value

RxODE/symengine environment

Author(s)

Matthew Fidler

`.rxWithOptions` *Temporarily set options then restore them while running code*

Description

Temporarily set options then restore them while running code

Usage

```
.rxWithOptions(ops, code)
```

Arguments

`ops`	list of options that will be temporarily set for the `code`
`code`	The code to run during the sink

Value

value of code

Examples

```
.rxWithOptions(list(digits = 21), {
  print(pi)
})

print(pi)
```

.rxWithWd *Temporarily set options then restore them while running code*

Description

Temporarily set options then restore them while running code

Usage

```
.rxWithWd(wd, code)
```

Arguments

wd	working directory to temporarily set the system to while evaluating the code
code	The code to run during the sink

Value

value of code

Examples

```
.rxWithWd(tempdir(), {
  getwd()
})

getwd()
```

.setWarnIdSort *Turn on/off warnings for ID sorting.*

Description

Turn on/off warnings for ID sorting.

Usage

```
.setWarnIdSort(warnIdSort = TRUE)
```

Arguments

warnIdSort	Boolean for if the sorting warning is turned on or off.

Value

Nothing

Author(s)

Matthew Fidler

`add.dosing` *Add dosing to eventTable*

Description

This adds a dosing event to the event table. This is provided for piping syntax through magrittr. It can also be accessed by `eventTable$add.dosing(...)`

Usage

```
add.dosing(
  eventTable,
  dose,
  nbr.doses = 1L,
  dosing.interval = 24,
  dosing.to = 1L,
  rate = NULL,
  amount.units = NA_character_,
  start.time = 0,
  do.sampling = FALSE,
  time.units = NA_character_,
  ...
)
```

Arguments

`eventTable`	eventTable object; When accessed from object it would be eventTable$
`dose`	numeric scalar, dose amount in `amount.units`;
`nbr.doses`	integer, number of doses;
`dosing.interval`	required numeric scalar, time between doses in `time.units`, defaults to 24 of `time.units="hours"`;
`dosing.to`	integer, compartment the dose goes into (first compartment by default);
`rate`	for infusions, the rate of infusion (default is `NULL`, for bolus dosing;
`amount.units`	optional string indicating the dosing units. Defaults to `NA` to indicate as per the original `EventTable` definition.
`start.time`	required dosing start time;
`do.sampling`	logical, should observation sampling records be added at the dosing times? Defaults to `FALSE`.
`time.units`	optional string indicating the time units. Defaults to `"hours"` to indicate as per the original `EventTable` definition.
`...`	Other parameters passed to `et()`.

Value

eventTable with updated dosing (note the event table will be updated anyway)

Author(s)

Matthew L. Fidler

Matthew L Fidler, Wenping Wang

References

Wang W, Hallow K, James D (2015). "A Tutorial on RxODE: Simulating Differential Equation Pharmacometric Models in R." CPT: Pharmacometrics \& Systems Pharmacology, 5(1), 3-10. ISSN 2163-8306, <URL: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4728294/>.

See Also

eventTable, add.sampling, add.dosing, et, etRep, etRbind, RxODE

Examples

```
library(RxODE)
library(units)

## Model from RxODE tutorial
mod1 <-RxODE({
    KA=2.94E-01;
    CL=1.86E+01;
    V2=4.02E+01;
    Q=1.05E+01;
    V3=2.97E+02;
    Kin=1;
    Kout=1;
    EC50=200;
    C2 = centr/V2;
    C3 = peri/V3;
    d/dt(depot) =-KA*depot;
    d/dt(centr) = KA*depot - CL*C2 - Q*C2 + Q*C3;
    d/dt(peri)  =                    Q*C2 - Q*C3;
    d/dt(eff)  = Kin - Kout*(1-C2/(EC50+C2))*eff;
});

## These are making the more complex regimens of the RxODE tutorial

## bid for 5 days
bid <- et(timeUnits="hr") %>%
       et(amt=10000,ii=12,until=set_units(5, "days"))

## qd for 5 days
```

```
qd <- et(timeUnits="hr") %>%
      et(amt=20000,ii=24,until=set_units(5, "days"))

## bid for 5 days followed by qd for 5 days

et <- seq(bid,qd) %>% et(seq(0,11*24,length.out=100));

bidQd <- rxSolve(mod1, et)

plot(bidQd, C2)


## Now Infusion for 5 days followed by oral for 5 days

##  note you can dose to a named compartment instead of using the compartment number
infusion <- et(timeUnits = "hr") %>%
      et(amt=10000, rate=5000, ii=24, until=set_units(5, "days"), cmt="centr")


qd <- et(timeUnits = "hr") %>% et(amt=10000, ii=24, until=set_units(5, "days"), cmt="depot")

et <- seq(infusion,qd)

infusionQd <- rxSolve(mod1, et)

plot(infusionQd, C2)

## 2wk-on, 1wk-off

qd <- et(timeUnits = "hr") %>% et(amt=10000, ii=24, until=set_units(2, "weeks"), cmt="depot")

et <- seq(qd, set_units(1,"weeks"), qd) %>%
     add.sampling(set_units(seq(0, 5.5,by=0.005),weeks))

wkOnOff <- rxSolve(mod1, et)

plot(wkOnOff, C2)

## You can also repeat the cycle easily with the rep function

qd <-et(timeUnits = "hr") %>% et(amt=10000, ii=24, until=set_units(2, "weeks"), cmt="depot")

et <- etRep(qd, times=4, wait=set_units(1,"weeks")) %>%
     add.sampling(set_units(seq(0, 12.5,by=0.005),weeks))

repCycle4 <- rxSolve(mod1, et)

plot(repCycle4, C2)
```

`add.sampling` *Add sampling to eventTable*

Description

This adds a dosing event to the event table. This is provided for piping syntax through magrittr. It can also be accessed by `eventTable$add.sampling()`

Usage

```
add.sampling(eventTable, time, time.units = NA)
```

Arguments

`eventTable`	An eventTable object. When accessed from object it would be eventTable$
`time`	a vector of time values (in `time.units`).
`time.units`	an optional string specifying the time units. Defaults to the units specified when the `EventTable` was initialized.

Value

eventTable with updated sampling. (Note the event table will be updated even if you don't reassign the eventTable)

Author(s)

Matthew L Fidler, Wenping Wang

References

Wang W, Hallow K, James D (2015). "A Tutorial on RxODE: Simulating Differential Equation Pharmacometric Models in R." CPT: Pharmacometrics \& Systems Pharmacology, 5(1), 3-10. ISSN 2163-8306, <URL: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4728294/>.

See Also

`eventTable`, `add.sampling`, `add.dosing`, `et`, `etRep`, `etRbind`, `RxODE`

Examples

```
library(RxODE)
library(units)

## Model from RxODE tutorial
mod1 <-RxODE({
```

```
    KA=2.94E-01;
    CL=1.86E+01;
    V2=4.02E+01;
    Q=1.05E+01;
    V3=2.97E+02;
    Kin=1;
    Kout=1;
    EC50=200;
    C2 = centr/V2;
    C3 = peri/V3;
    d/dt(depot) =-KA*depot;
    d/dt(centr) = KA*depot - CL*C2 - Q*C2 + Q*C3;
    d/dt(peri)  =                   Q*C2 - Q*C3;
    d/dt(eff)  = Kin - Kout*(1-C2/(EC50+C2))*eff;
});

## These are making the more complex regimens of the RxODE tutorial

## bid for 5 days
bid <- et(timeUnits="hr") %>%
       et(amt=10000,ii=12,until=set_units(5, "days"))

## qd for 5 days
qd <- et(timeUnits="hr") %>%
      et(amt=20000,ii=24,until=set_units(5, "days"))

## bid for 5 days followed by qd for 5 days

et <- seq(bid,qd) %>% et(seq(0,11*24,length.out=100));

bidQd <- rxSolve(mod1, et)

plot(bidQd, C2)


## Now Infusion for 5 days followed by oral for 5 days

##  note you can dose to a named compartment instead of using the compartment number
infusion <- et(timeUnits = "hr") %>%
      et(amt=10000, rate=5000, ii=24, until=set_units(5, "days"), cmt="centr")


qd <- et(timeUnits = "hr") %>% et(amt=10000, ii=24, until=set_units(5, "days"), cmt="depot")

et <- seq(infusion,qd)

infusionQd <- rxSolve(mod1, et)

plot(infusionQd, C2)

## 2wk-on, 1wk-off

qd <- et(timeUnits = "hr") %>% et(amt=10000, ii=24, until=set_units(2, "weeks"), cmt="depot")
```

```
et <- seq(qd, set_units(1,"weeks"), qd) %>%
     add.sampling(set_units(seq(0, 5.5,by=0.005),weeks))

wkOnOff <- rxSolve(mod1, et)

plot(wkOnOff, C2)

## You can also repeat the cycle easily with the rep function

qd <-et(timeUnits = "hr") %>% et(amt=10000, ii=24, until=set_units(2, "weeks"), cmt="depot")

et <- etRep(qd, times=4, wait=set_units(1,"weeks")) %>%
     add.sampling(set_units(seq(0, 12.5,by=0.005),weeks))

repCycle4 <- rxSolve(mod1, et)

plot(repCycle4, C2)
```

`as.et` *Coerce object to data.frame*

Description

Coerce object to data.frame

Usage

```
as.et(x, ...)

## Default S3 method:
as.et(x, ...)
```

Arguments

`x`	Object to coerce to et.
`...`	Other parameters

Value

An event table

cvPost *Sample a covariance Matrix from the Posterior Inverse Wishart distribution.*

Description

Note this Inverse wishart rescaled to match the original scale of the covariance matrix.

Usage

```
cvPost(
  nu,
  omega,
  n = 1L,
  omegaIsChol = FALSE,
  returnChol = FALSE,
  type = c("invWishart", "lkj", "separation"),
  diagXformType = c("log", "identity", "variance", "nlmixrSqrt", "nlmixrLog",
    "nlmixrIdentity")
)
```

Arguments

nu	Degrees of Freedom (Number of Observations) for covariance matrix simulation.
omega	Either the estimate of covariance matrix or the estimated standard deviations in matrix form each row forming the standard deviation simulated values
n	Number of Matrices to sample. By default this is 1. This is only useful when omega is a matrix. Otherwise it is determined by the number of rows in the input omega matrix of standard deviations
omegaIsChol	is an indicator of if the omega matrix is in the Cholesky decomposition. This is only used when codetype="invWishart"
returnChol	Return the Cholesky decomposition of the covariance matrix sample. This is only used when codetype="invWishart"
type	The type of covariance posterior that is being simulated. This can be: • invWishart The posterior is an inverse wishart; This allows for correlations between parameters to be modeled. All the uncertainty in the parameter is captured in the degrees of freedom parameter. • lkj The posterior separates the standard deviation estimates (modeled outside and provided in the omega argument) and the correlation estimates. The correlation estimate is simulated with the rLKJ1(). This simulation uses the relationship eta=(nu-1)/2. This is relationship based on the proof of the relationship between the restricted LKJ-distribution and inverse wishart distribution (XXXXXX). Once the correlation posterior is calculated, the estimated standard deviations are then combined with the simulated correlation matrix to create the covariance matrix.

- `separation` Like the `lkj` option, this separates out the estimation of the correlation and standard deviation. Instead of using the `LKJ` distribution to simulate the correlation, it simulates the inverse wishart of the identity matrix and converts the result to a correlation matrix. This correlation matrix is then used with the standard deviation to calculate the simulated covariance matrix.

`diagXformType` Diagonal transformation type. These could be:

- `log` The standard deviations are log transformed, so the actual standard deviations are exp(omega)
- `identity` The standard deviations are not transformed. The standard deviations are not transformed; They should be positive.
- `variance` The variances are specified in the `omega` matrix; They are transformed into standard deviations.
- `nlmixrSqrt` These standard deviations come from an nlmixr omega matrix where diag(chol(inv(omega))) = x^2
- `nlmixrLog` These standard deviations come from a nlmixr omega matrix omega matrix where diag(chol(solve(omega))) = exp(x)
- `nlmixrIdentity` These standard deviations come from a nlmixr omega matrix omega matrix where diag(chol(solve(omega))) = x

The nlmixr transformations only make sense when there is no off-diagonal correlations modeled.

Details

If your covariance matrix is a 1x1 matrix, this uses an scaled inverse chi-squared which is equivalent to the Inverse Wishart distribution in the uni-directional case.

In general, the separation strategy is preferred for diagonal matrices. If the dimension of the matrix is below 10, `lkj` is numerically faster than `separation` method. However, the `lkj` method has densities too close to zero (XXXX) when the dimension is above 10. In that case, though computationally more expensive `separation` method performs better.

For matrices with modeled covariances, the easiest method to use is the inverse Wishart which allows the simulation of correlation matrices (XXXX). This method is more well suited for well behaved matrices, that is the variance components are not too low or too high. When modeling nonlinear mixed effects modeling matrices with too high or low variances are considered sub-optimal in describing a system. With these rules in mind, it is reasonable to use the inverse Wishart.

Value

a matrix (n=1) or a list of matrices (n > 1)

Author(s)

Matthew L.Fidler & Wenping Wang

References

Alvarez I, Niemi J and Simpson M. (2014) *Bayesian Inference for a Covariance Matrix*. Conference on Applied Statistics in Agriculture. https://newprairiepress.org/cgi/viewcontent.cgi?article=1004&context=agstatconference

Wang1 Z, Wu Y, and Chu H. (2018) *On Equivalence of the LKJ distribution and the restricted Wishart distribution*. arXiv:1809.04746

Examples

```
## Sample a single covariance.
draw1 <- cvPost(3, matrix(c(1, .3, .3, 1), 2, 2))

## Sample 3 covariances
set.seed(42)
draw3 <- cvPost(3, matrix(c(1, .3, .3, 1), 2, 2), n = 3)

## Sample 3 covariances, but return the cholesky decomposition
set.seed(42)
draw3c <- cvPost(3, matrix(c(1, .3, .3, 1), 2, 2), n = 3, returnChol = TRUE)

## Sample 3 covariances with lognormal standard deviations via LKJ
## correlation sample
cvPost(3, sapply(1:3, function(...) {
  rnorm(10)
}), type = "lkj")

## or return cholesky decomposition
cvPost(3, sapply(1:3, function(...) {
  rnorm(10)
}),
type = "lkj",
returnChol = TRUE
)

## Sample 3 covariances with lognormal standard deviations via separation
## strategy using inverse Wishart correlation sample
cvPost(3, sapply(1:3, function(...) {
  rnorm(10)
}), type = "separation")

## or returning the cholesky decomposition
cvPost(3, sapply(1:3, function(...) {
  rnorm(10)
}),
type = "separation",
returnChol = TRUE
)
```

et *Event Table Function*

Description

Event Table Function

Usage

```
et(x, ..., envir = parent.frame())

## S3 method for class 'RxODE'
et(x, ..., envir = parent.frame())

## S3 method for class 'rxSolve'
et(x, ..., envir = parent.frame())

## S3 method for class 'rxParams'
et(x, ..., envir = parent.frame())

## Default S3 method:
et(
  x,
  ...,
  time,
  amt,
  evid,
  cmt,
  ii,
  addl,
  ss,
  rate,
  dur,
  until,
  id,
  amountUnits,
  timeUnits,
  addSampling,
  envir = parent.frame(),
  by = NULL,
  length.out = NULL
)
```

Arguments

x	This is the first argument supplied to the event table. This is named to allow et to be used in a pipe-line with arbitrary objects.

`...` Times or event tables. They can also be one of the named arguments below.

`envir` the environment in which `expr` is to be evaluated. May also be `NULL`, a list, a data frame, a pairlist or an integer as specified to `sys.call`.

`time` Time is the time of the dose or the sampling times. This can also be unspecified and is determined by the object type (list or numeric/integer).

`amt` Amount of the dose. If specified, this assumes a dosing record, instead of a sampling record.

`evid` Event ID; This can be:

Numeric Value	Description
0	An observation. This can also be specified as `evid=obs`
1	A dose observation. This can also be specified as `evid=dose`
2	A non-dose event. This can also be specified as `evid=other`
3	A reset event. This can also be specified as `evid=reset`.
4	Dose and reset event. This can also be specified as `evid=doseReset` or `evid=resetDose`

Note a reset event resets all the compartment values to zero and turns off all infusions.

`cmt` Compartment name or number. If a number, this is an integer starting at 1. Negative compartments turn off a compartment. If the compartment is a name, the compartment name is changed to the correct state/compartment number before running the simulation. For a compartment named "-cmt" the compartment is turned off.

`Can also specify `cmt` as `dosing.to`, `dose.to`, `doseTo`, `dosingTo`, and `state`.`

`ii` When specifying a dose, this is the inter-dose interval for `ss`, `addl` and `until` options (described below).

`addl` The number of additional doses at a inter-dose interval after one dose.

`ss` Steady state flag; It can be one of:

Value	Description
0	This dose is not a steady state dose
1	This dose is a steady state dose with the between/inter-dose interval of `ii`
2	Superposition steady state

When `ss=2` the steady state dose that uses the super-position principle to allow more complex steady states, like 10 mg in the morning and 20 mg at night, or dosing at 8 am 12 pm and 8 pm instead of every 12 hours. Since it uses the super positioning principle, it only makes sense when you know the kinetics are linear.

All other values of `SS` are currently invalid.

`rate` When positive, this is the rate of infusion. Otherwise:

Value	Description
0	No infusion is on this record
-1	Modeled rate (in RxODE:rate(cmt) =); Can be `et(rate=model)`.
-2	Modeled duration (in RxODE: dur(cmt) =); Can be`et(dur=model)` or `et(rate=dur)`.

When a modeled bioavailability is applied to positive rates (`rate` > 0), the duration of infusion is changed. This is because the data specify the rate and amount, the only think that modeled bioavailability can affect is duration.

If instead you want the modeled bioavailability to increase the rate of infusion instead of the duration of infusion, specify the `dur` instead or model the duration with `rate=2`.

`dur` Duration of infusion. When `amt` and `dur` are specified the rate is calculated from the two data items. When `dur` is specified instead of `rate`, the bioavailability changes will increase rate instead of duration.

`until` This is the time until the dosing should end. It can be an easier way to figure out how many additional doses are needed over your sampling period.

`id` A integer vector of IDs to add or remove from the event table. If the event table is identical for each ID, then you may expand it to include all the IDs in this vector. All the negative IDs in this vector will be removed.

`amountUnits` The units for the dosing records (`amt`)

`timeUnits` The units for the time records (`time`)

`addSampling` This is a boolean indicating if a sampling time should be added at the same time as a dosing time. By default this is `FALSE`.

`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.

Value

A new event table

Author(s)

Matthew L Fidler, Wenping Wang

References

Wang W, Hallow K, James D (2015). "A Tutorial on RxODE: Simulating Differential Equation Pharmacometric Models in R." CPT: Pharmacometrics \& Systems Pharmacology, 5(1), 3-10. ISSN 2163-8306, <URL: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4728294/>.

See Also

`eventTable`, `add.sampling`, `add.dosing`, `et`, `etRep`, `etRbind`, `RxODE`

Examples

```
library(RxODE)
library(units)

## Model from RxODE tutorial
mod1 <-RxODE({
    KA=2.94E-01;
    CL=1.86E+01;
    V2=4.02E+01;
    Q=1.05E+01;
    V3=2.97E+02;
    Kin=1;
    Kout=1;
    EC50=200;
    C2 = centr/V2;
    C3 = peri/V3;
    d/dt(depot) =-KA*depot;
    d/dt(centr) = KA*depot - CL*C2 - Q*C2 + Q*C3;
    d/dt(peri)  =                    Q*C2 - Q*C3;
    d/dt(eff)  = Kin - Kout*(1-C2/(EC50+C2))*eff;
});

## These are making the more complex regimens of the RxODE tutorial

## bid for 5 days
bid <- et(timeUnits="hr") %>%
       et(amt=10000,ii=12,until=set_units(5, "days"))

## qd for 5 days
qd <- et(timeUnits="hr") %>%
      et(amt=20000,ii=24,until=set_units(5, "days"))

## bid for 5 days followed by qd for 5 days

et <- seq(bid,qd) %>% et(seq(0,11*24,length.out=100));

bidQd <- rxSolve(mod1, et)

plot(bidQd, C2)


## Now Infusion for 5 days followed by oral for 5 days

##  note you can dose to a named compartment instead of using the compartment number
infusion <- et(timeUnits = "hr") %>%
      et(amt=10000, rate=5000, ii=24, until=set_units(5, "days"), cmt="centr")


qd <- et(timeUnits = "hr") %>% et(amt=10000, ii=24, until=set_units(5, "days"), cmt="depot")
```

```
et <- seq(infusion,qd)

infusionQd <- rxSolve(mod1, et)

plot(infusionQd, C2)

## 2wk-on, 1wk-off

qd <- et(timeUnits = "hr") %>% et(amt=10000, ii=24, until=set_units(2, "weeks"), cmt="depot")

et <- seq(qd, set_units(1,"weeks"), qd) %>%
     add.sampling(set_units(seq(0, 5.5,by=0.005),weeks))

wkOnOff <- rxSolve(mod1, et)

plot(wkOnOff, C2)

## You can also repeat the cycle easily with the rep function

qd <-et(timeUnits = "hr") %>% et(amt=10000, ii=24, until=set_units(2, "weeks"), cmt="depot")

et <- etRep(qd, times=4, wait=set_units(1,"weeks")) %>%
     add.sampling(set_units(seq(0, 12.5,by=0.005),weeks))

repCycle4 <- rxSolve(mod1, et)

plot(repCycle4, C2)
```

---

etExpand *Expand additional doses*

Description

Expand additional doses

Usage

```
etExpand(et)
```

Arguments

et	Event table to expand additional doses for.

Value

New event table with addl doses expanded

Author(s)

Matthew Fidler

Examples

```
ev <- et(amt = 3, ii = 24, until = 240)
print(ev)
etExpand(ev) # expands event table, but doesn't modify it

print(ev)

ev$expand() ## Expands the current event table and saves it in ev
```

---

etRbind *Combining event tables*

Description

Combining event tables

Usage

```
etRbind(
  ...,
  samples = c("use", "clear"),
  waitII = c("smart", "+ii"),
  id = c("merge", "unique")
)

## S3 method for class 'rxEt'
rbind(..., deparse.level = 1)
```

Arguments

`...`	The event tables and optionally time between event tables, called waiting times in this help document.
`samples`	How to handle samples when repeating an event table. The options are: • `"clear"` Clear sampling records before combining the datasets • `"use"` Use the sampling records when combining the datasets
`waitII`	This determines how waiting times between events are handled. The options are: • `"smart"` This "smart" handling of waiting times is the default option. In this case, if the waiting time is above the last observed inter-dose interval in the first combined event table, then the actual time between doses is given by the wait time. If it is smaller than the last observed inter-dose interval, the time between event tables is given by the inter-dose interval + the waiting time between event tables.

- `"+ii"` In this case, the wait time is added to the inter-dose interval no matter the length of the wait time or inter-dose interval

`id` This is how rbind will handle IDs. There are two different types of options:

- `merge` with `id="merge"`, the IDs are merged together, overlapping IDs would be merged into a single event table.
- `unique` with `id="unique"`, the IDs will be renumbered so that the IDs in all the event tables are not overlapping.

`deparse.level` The `deparse.level` of a traditional `rbind` is ignored.

Value

An event table

Author(s)

Matthew L Fidler

Matthew L Fidler, Wenping Wang

References

Wang W, Hallow K, James D (2015). "A Tutorial on RxODE: Simulating Differential Equation Pharmacometric Models in R." CPT: Pharmacometrics \& Systems Pharmacology, 5(1), 3-10. ISSN 2163-8306, <URL: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4728294/>.

See Also

`eventTable`, `add.sampling`, `add.dosing`, `et`, `etRep`, `etRbind`, `RxODE`

Examples

```
library(RxODE)
library(units)

## Model from RxODE tutorial
mod1 <-RxODE({
    KA=2.94E-01;
    CL=1.86E+01;
    V2=4.02E+01;
    Q=1.05E+01;
    V3=2.97E+02;
    Kin=1;
    Kout=1;
    EC50=200;
    C2 = centr/V2;
    C3 = peri/V3;
    d/dt(depot) =-KA*depot;
    d/dt(centr) = KA*depot - CL*C2 - Q*C2 + Q*C3;
```

```
    d/dt(peri)  =                    Q*C2 - Q*C3;
    d/dt(eff)  = Kin - Kout*(1-C2/(EC50+C2))*eff;
});

## These are making the more complex regimens of the RxODE tutorial

## bid for 5 days
bid <- et(timeUnits="hr") %>%
       et(amt=10000,ii=12,until=set_units(5, "days"))

## qd for 5 days
qd <- et(timeUnits="hr") %>%
      et(amt=20000,ii=24,until=set_units(5, "days"))

## bid for 5 days followed by qd for 5 days

et <- seq(bid,qd) %>% et(seq(0,11*24,length.out=100));

bidQd <- rxSolve(mod1, et)

plot(bidQd, C2)


## Now Infusion for 5 days followed by oral for 5 days

##  note you can dose to a named compartment instead of using the compartment number
infusion <- et(timeUnits = "hr") %>%
      et(amt=10000, rate=5000, ii=24, until=set_units(5, "days"), cmt="centr")


qd <- et(timeUnits = "hr") %>% et(amt=10000, ii=24, until=set_units(5, "days"), cmt="depot")

et <- seq(infusion,qd)

infusionQd <- rxSolve(mod1, et)

plot(infusionQd, C2)

## 2wk-on, 1wk-off

qd <- et(timeUnits = "hr") %>% et(amt=10000, ii=24, until=set_units(2, "weeks"), cmt="depot")

et <- seq(qd, set_units(1,"weeks"), qd) %>%
     add.sampling(set_units(seq(0, 5.5,by=0.005),weeks))

wkOnOff <- rxSolve(mod1, et)

plot(wkOnOff, C2)

## You can also repeat the cycle easily with the rep function

qd <-et(timeUnits = "hr") %>% et(amt=10000, ii=24, until=set_units(2, "weeks"), cmt="depot")
```

```
et <- etRep(qd, times=4, wait=set_units(1,"weeks")) %>%
     add.sampling(set_units(seq(0, 12.5,by=0.005),weeks))

repCycle4 <- rxSolve(mod1, et)

plot(repCycle4, C2)
```

---

etRep *Repeat an RxODE event table*

Description

Repeat an RxODE event table

Usage

```
etRep(
  x,
  times = 1,
  length.out = NA,
  each = NA,
  n = NULL,
  wait = 0,
  id = integer(0),
  samples = c("clear", "use"),
  waitII = c("smart", "+ii"),
  ii = 24
)

## S3 method for class 'rxEt'
rep(x, ...)
```

Arguments

x	An RxODE event table
times	Number of times to repeat the event table
length.out	Invalid with RxODE event tables, will throw an error if used.
each	Invalid with RxODE event tables, will throw an error if used.
n	The number of times to repeat the event table. Overrides times.
wait	Waiting time between each repeated event table. By default there is no waiting, or wait=0
id	A integer vector of IDs to add or remove from the event table. If the event table is identical for each ID, then you may expand it to include all the IDs in this vector. All the negative IDs in this vector will be removed.

`samples` How to handle samples when repeating an event table. The options are:

- `"clear"` Clear sampling records before combining the datasets
- `"use"` Use the sampling records when combining the datasets

`waitII` This determines how waiting times between events are handled. The options are:

- `"smart"` This "smart" handling of waiting times is the default option. In this case, if the waiting time is above the last observed inter-dose interval in the first combined event table, then the actual time between doses is given by the wait time. If it is smaller than the last observed inter-dose interval, the time between event tables is given by the inter-dose interval + the waiting time between event tables.
- `"+ii"` In this case, the wait time is added to the inter-dose interval no matter the length of the wait time or inter-dose interval

`ii` When specifying a dose, this is the inter-dose interval for `ss`, `addl` and `until` options (described below).

`...` Times or event tables. They can also be one of the named arguments below.

Value

An event table

Author(s)

Matthew L Fidler, Wenping Wang

References

Wang W, Hallow K, James D (2015). "A Tutorial on RxODE: Simulating Differential Equation Pharmacometric Models in R." CPT: Pharmacometrics \& Systems Pharmacology, 5(1), 3-10. ISSN 2163-8306, <URL: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4728294/>.

See Also

`eventTable`, `add.sampling`, `add.dosing`, `et`, `etRep`, `etRbind`, `RxODE`

Examples

```
library(RxODE)
library(units)

## Model from RxODE tutorial
mod1 <-RxODE({
    KA=2.94E-01;
    CL=1.86E+01;
    V2=4.02E+01;
    Q=1.05E+01;
```

```
    V3=2.97E+02;
    Kin=1;
    Kout=1;
    EC50=200;
    C2 = centr/V2;
    C3 = peri/V3;
    d/dt(depot) =-KA*depot;
    d/dt(centr) = KA*depot - CL*C2 - Q*C2 + Q*C3;
    d/dt(peri)  =                    Q*C2 - Q*C3;
    d/dt(eff)  = Kin - Kout*(1-C2/(EC50+C2))*eff;
});

## These are making the more complex regimens of the RxODE tutorial

## bid for 5 days
bid <- et(timeUnits="hr") %>%
       et(amt=10000,ii=12,until=set_units(5, "days"))

## qd for 5 days
qd <- et(timeUnits="hr") %>%
      et(amt=20000,ii=24,until=set_units(5, "days"))

## bid for 5 days followed by qd for 5 days

et <- seq(bid,qd) %>% et(seq(0,11*24,length.out=100));

bidQd <- rxSolve(mod1, et)

plot(bidQd, C2)


## Now Infusion for 5 days followed by oral for 5 days

##  note you can dose to a named compartment instead of using the compartment number
infusion <- et(timeUnits = "hr") %>%
      et(amt=10000, rate=5000, ii=24, until=set_units(5, "days"), cmt="centr")


qd <- et(timeUnits = "hr") %>% et(amt=10000, ii=24, until=set_units(5, "days"), cmt="depot")

et <- seq(infusion,qd)

infusionQd <- rxSolve(mod1, et)

plot(infusionQd, C2)

## 2wk-on, 1wk-off

qd <- et(timeUnits = "hr") %>% et(amt=10000, ii=24, until=set_units(2, "weeks"), cmt="depot")

et <- seq(qd, set_units(1,"weeks"), qd) %>%
     add.sampling(set_units(seq(0, 5.5,by=0.005),weeks))
```

```
wkOnOff <- rxSolve(mod1, et)

plot(wkOnOff, C2)

## You can also repeat the cycle easily with the rep function

qd <-et(timeUnits = "hr") %>% et(amt=10000, ii=24, until=set_units(2, "weeks"), cmt="depot")

et <- etRep(qd, times=4, wait=set_units(1,"weeks")) %>%
     add.sampling(set_units(seq(0, 12.5,by=0.005),weeks))

repCycle4 <- rxSolve(mod1, et)

plot(repCycle4, C2)
```

---

etSeq *Sequence of event tables*

Description

This combines a sequence of event tables.

Usage

```
etSeq(..., samples = c("clear", "use"), waitII = c("smart", "+ii"), ii = 24)

## S3 method for class 'rxEt'
seq(...)
```

Arguments

`...`	The event tables and optionally time between event tables, called waiting times in this help document.
`samples`	How to handle samples when repeating an event table. The options are: • `"clear"` Clear sampling records before combining the datasets • `"use"` Use the sampling records when combining the datasets
`waitII`	This determines how waiting times between events are handled. The options are: • `"smart"` This "smart" handling of waiting times is the default option. In this case, if the waiting time is above the last observed inter-dose interval in the first combined event table, then the actual time between doses is given by the wait time. If it is smaller than the last observed inter-dose interval, the time between event tables is given by the inter-dose interval + the waiting time between event tables.

- `"+ii"` In this case, the wait time is added to the inter-dose interval no matter the length of the wait time or inter-dose interval

`ii` If there was no inter-dose intervals found in the event table, assume that the interdose interval is given by this `ii` value. By default this is `24`.

Details

This sequences all the event tables in added in the argument list `....` By default when combining the event tables the offset is at least by the last inter-dose interval in the prior event table (or `ii`). If you separate any of the event tables by a number, the event tables will be separated at least the wait time defined by that number or the last inter-dose interval.

Value

An event table

Author(s)

Matthew L Fidler, Wenping Wang

References

Wang W, Hallow K, James D (2015). "A Tutorial on RxODE: Simulating Differential Equation Pharmacometric Models in R." CPT: Pharmacometrics \& Systems Pharmacology, 5(1), 3-10. ISSN 2163-8306, <URL: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4728294/>.

See Also

`eventTable`, `add.sampling`, `add.dosing`, `et`, `etRep`, `etRbind`, `RxODE`

Examples

```
library(RxODE)
library(units)

## Model from RxODE tutorial
mod1 <-RxODE({
    KA=2.94E-01;
    CL=1.86E+01;
    V2=4.02E+01;
    Q=1.05E+01;
    V3=2.97E+02;
    Kin=1;
    Kout=1;
    EC50=200;
    C2 = centr/V2;
    C3 = peri/V3;
    d/dt(depot) =-KA*depot;
```

```
    d/dt(centr) = KA*depot - CL*C2 - Q*C2 + Q*C3;
    d/dt(peri)  =                    Q*C2 - Q*C3;
    d/dt(eff)  = Kin - Kout*(1-C2/(EC50+C2))*eff;
});

## These are making the more complex regimens of the RxODE tutorial

## bid for 5 days
bid <- et(timeUnits="hr") %>%
       et(amt=10000,ii=12,until=set_units(5, "days"))

## qd for 5 days
qd <- et(timeUnits="hr") %>%
      et(amt=20000,ii=24,until=set_units(5, "days"))

## bid for 5 days followed by qd for 5 days

et <- seq(bid,qd) %>% et(seq(0,11*24,length.out=100));

bidQd <- rxSolve(mod1, et)

plot(bidQd, C2)


## Now Infusion for 5 days followed by oral for 5 days

##  note you can dose to a named compartment instead of using the compartment number
infusion <- et(timeUnits = "hr") %>%
      et(amt=10000, rate=5000, ii=24, until=set_units(5, "days"), cmt="centr")


qd <- et(timeUnits = "hr") %>% et(amt=10000, ii=24, until=set_units(5, "days"), cmt="depot")

et <- seq(infusion,qd)

infusionQd <- rxSolve(mod1, et)

plot(infusionQd, C2)

## 2wk-on, 1wk-off

qd <- et(timeUnits = "hr") %>% et(amt=10000, ii=24, until=set_units(2, "weeks"), cmt="depot")

et <- seq(qd, set_units(1,"weeks"), qd) %>%
     add.sampling(set_units(seq(0, 5.5,by=0.005),weeks))

wkOnOff <- rxSolve(mod1, et)

plot(wkOnOff, C2)

## You can also repeat the cycle easily with the rep function

qd <-et(timeUnits = "hr") %>% et(amt=10000, ii=24, until=set_units(2, "weeks"), cmt="depot")
```

```
et <- etRep(qd, times=4, wait=set_units(1,"weeks")) %>%
     add.sampling(set_units(seq(0, 12.5,by=0.005),weeks))

repCycle4 <- rxSolve(mod1, et)

plot(repCycle4, C2)
```

`eventTable` *Create an event table object*

Description

Initializes an object of class 'EventTable' with methods for adding and querying dosing and observation records

Usage

```
eventTable(amount.units = NA, time.units = NA)
```

Arguments

`amount.units`	string denoting the amount dosing units, e.g., "mg", "ug". Default to `NA` to denote unspecified units. It could also be a solved RxODE object. In that case, eventTable(obj) returns the eventTable that was used to solve the RxODE object.
`time.units`	string denoting the time units, e.g., "hours", "days". Default to `"hours"`.
	An `eventTable` is an object that consists of a data.frame storing ordered time-stamped events of an (unspecified) PK/PD dynamic system, units (strings) for dosing and time records, plus a list of functions to add and extract event records.
	Currently, events can be of two types: dosing events that represent inputs to the system and sampling time events that represent observations of the system with 'amount.units' and 'time.units', respectively.

Value

A modified data.frame with the following accessible functions:

- `get.EventTable()` returns the current event table
- `add.dosing()` adds dosing records to the event table.
- `get.dosing()` returns a data.frame of dosing records.
- `clear.dosing()` clears or deletes all dosing from event table
- 'add.sampling() adds sampling time observation records to the event table.
- `get.sampling()`returns a data.frame of sampled observation records.
- `clear.sampling()` removes all sampling from event table.

- `get.obs.rec()` returns a logical vector indicating whether each event record represents an observation or not.
- `get.nobs()` returns the number of observation (not dosing) records.
- `get.units()` returns a two-element character vector with the dosing and time units, respectively
- `copy()` makes a copy of the current event table. To create a copy of an event table object use `qd2 <-qd$copy()`
- `expand()` Expands the event table for multi-subject solving. This is done by `qd$expand(400)` for a 400 subject data expansion

Author(s)

Matthew Fidler, Melissa Hallow and Wenping Wang

See Also

`et()`, `RxODE()`

Examples

```
# create dosing and observation (sampling) events
# QD 50mg dosing, 5 days followed by 25mg 5 days
#
qd <- eventTable(amount.units = "mg", time.units = "days")
#
qd$add.dosing(dose = 50, nbr.doses = 5, dosing.interval = 1, do.sampling = FALSE)
#
# sample the system's drug amounts hourly the first day, then every 12 hours
# for the next 4 days
qd$add.sampling(seq(from = 0, to = 1, by = 1 / 24))
qd$add.sampling(seq(from = 1, to = 5, by = 12 / 24))
#
# print(qd$get.dosing())     # table of dosing records
print(qd$get.nobs()) # number of observation (not dosing) records
#
# BID dosing, 5 days
bid <- eventTable("mg", "days") # only dosing
bid$add.dosing(
  dose = 10000, nbr.doses = 2 * 5,
  dosing.interval = 12, do.sampling = FALSE
)
#
# Use the copy() method to create a copy (clone) of an existing
# event table (simple assignments just create a new reference to
# the same event table object (closure)).
#
bid.ext <- bid$copy() # three-day extension for a 2nd cohort
bid.ext$add.dosing(
  dose = 5000, nbr.doses = 2 * 3,
  start.time = 120, dosing.interval = 12, do.sampling = FALSE
)
```

```
# You can also use the Piping operator to create a table

qd2 <- eventTable(amount.units = "mg", time.units = "days") %>%
  add.dosing(dose = 50, nbr.doses = 5, dosing.interval = 1, do.sampling = FALSE) %>%
  add.sampling(seq(from = 0, to = 1, by = 1 / 24)) %>%
  add.sampling(seq(from = 1, to = 5, by = 12 / 24))
# print(qd2$get.dosing())     # table of dosing records
print(qd2$get.nobs()) # number of observation (not dosing) records

# Note that piping with %>% will update the original table.

qd3 <- qd2 %>% add.sampling(seq(from = 5, to = 10, by = 6 / 24))
print(qd2$get.nobs())
print(qd3$get.nobs())
```

`forderForceBase` *Force using base order for RxODE radix sorting*

Description

Force using base order for RxODE radix sorting

Usage

```
forderForceBase(forceBase = FALSE)
```

Arguments

`forceBase`	boolean indicating if RxODE should use R's `order()` for radix sorting instead of `data.table`'s parallel radix sorting.

Value

NILL; called for side effects

Examples

```
forderForceBase(TRUE) # Use base `order` for RxODE sorts
forderForceBase(FALSE) # Use `data.table` for RxODE sorts
```

gammap *Gammap: normalized lower incomplete gamma function*

Description

This is the gamma_p from the boost library

Usage

```
gammap(a, z)
```

Arguments

a	The numeric 'a' parameter in the normalized lower incomplete gamma
z	The numeric 'z' parameter in the normalized lower incomplete gamma

Details

The gamma p function is given by:

gammap = lowergamma(a, z)/gamma(a)

Value

gammap results

Author(s)

Matthew L. Fidler

Examples

```
gammap(1, 3)
gammap(1:3, 3)
gammap(1, 1:3)
```

gammapDer *gammapDer: derivative of gammap*

Description

This is the gamma_p_derivative from the boost library

Usage

```
gammapDer(a, z)
```

Arguments

a	The numeric 'a' parameter in the upper incomplete gamma
z	The numeric 'z' parameter in the upper incomplete gamma

Value

lowergamma results

Author(s)

Matthew L. Fidler

Examples

```
gammapDer(1:3, 3)

gammapDer(1, 1:3)
```

gammapInv *gammapInv and gammapInva: Inverses of normalized gammap function*

Description

gammapInv and gammapInva: Inverses of normalized gammap function

Usage

```
gammapInv(a, p)

gammapInva(x, p)
```

Arguments

a	The numeric 'a' parameter in the upper incomplete gamma
p	The numeric 'p' parameter in the upper incomplete gamma
x	The numeric 'x' parameter in the upper incomplete gamma

Details

With the equation:

p = gammap(a, x)

The 'gammapInv' function returns a value 'x' that satisfies the equation above

The 'gammapInva' function returns a value 'q' that satisfies the equation above

NOTE: gammapInva is slow

Value

inverse gammap results

Author(s)

Matthew L. Fidler

Examples

```
gammapInv(1:3, 0.5)

gammapInv(1, 1:3 / 3.1)

gammapInv(1:3, 1:3 / 3.1)

gammapInva(1:3, 1:3 / 3.1)
```

---

gammaq *Gammaq: normalized upper incomplete gamma function*

Description

This is the gamma_q from the boost library

Usage

```
gammaq(a, z)
```

Arguments

a	The numeric 'a' parameter in the normalized upper incomplete gamma
z	The numeric 'z' parameter in the normalized upper incomplete gamma

Details

The gamma q function is given by:

gammaq = uppergamma(a, z)/gamma(a)

Value

gammaq results

Author(s)

Matthew L. Fidler

Examples

```
gammaq(1, 3)
gammaq(1:3, 3)
gammaq(1, 1:3)
```

`gammaqInv` *gammaqInv and gammaqInva: Inverses of normalized gammaq function*

Description

gammaqInv and gammaqInva: Inverses of normalized gammaq function

Usage

```
gammaqInv(a, q)

gammaqInva(x, q)
```

Arguments

`a`	The numeric 'a' parameter in the upper incomplete gamma
`q`	The numeric 'q' parameter in the upper incomplete gamma
`x`	The numeric 'x' parameter in the upper incomplete gamma

Details

With the equation:

q = gammaq(a, x)

The 'gammaqInv' function returns a value 'x' that satisfies the equation above

The 'gammaqInva' function returns a value 'a' that satisfies the equation above

NOTE: gammaqInva is slow

Value

inverse gammaq results

Author(s)

Matthew L. Fidler

Examples

```
gammaqInv(1:3, 0.5)

gammaqInv(1, 1:3 / 3)

gammaqInv(1:3, 1:3 / 3.1)

gammaqInva(1:3, 1:3 / 3.1)
```

---

genShinyApp.template *Generate an example (template) of a dosing regimen shiny app*

Description

Create a complete shiny application for exploring dosing regimens given a (hardcoded) PK/PD model.

Usage

```
genShinyApp.template(
  appDir = "shinyExample",
  verbose = TRUE,
 ODE.config = list(ode = "model", params = c(KA = 0.294), inits = c(eff = 1), method =
    "lsoda", atol = 1e-08, rtol = 1e-06)
)

write.template.server(appDir)

write.template.ui(appDir, statevars)
```

Arguments

appDir	a string with a directory where to store the shiny app, by default is "shinyExample". The directory appDir will be created if it does not exist.
verbose	logical specifying whether to write messages as the shiny app is generated. Defaults to TRUE.
ODE.config	model name compiled and list of parameters sent to rxSolve().

statevars List of statevars passed to to the write.template.ui() function. This usually isn't called directly.

A PK/PD model is defined using RxODE(), and a set of parameters and initial values are defined. Then the appropriate R scripts for the shiny's user interface ui.R and the server logic server.R are created in the directory appDir.

The function evaluates the following PK/PD model by default:

```
C2 = centr/V2;
C3 = peri/V3;
d/dt(depot) =-KA*depot;
d/dt(centr) = KA*depot - CL*C2 - Q*C2 + Q*C3;
d/dt(peri)  =                   Q*C2 - Q*C3;
d/dt(eff)  = Kin - Kout*(1-C2/(EC50+C2))*eff;
```

This can be changed by the ODE.config parameter.

To launch the shiny app, simply issue the runApp(appDir) R command.

Value

None, these functions are used for their side effects.

Note

These functions create a simple, but working example of a dosing regimen simulation web application. Users may want to modify the code to experiment creating shiny applications for their specific RxODE models.

See Also

RxODE(),eventTable(), and the package **shiny** (https://shiny.rstudio.com).

Examples

```
# create the shiny app example (template)
genShinyApp.template(appDir = "myapp")
# run the shiny app
library(shiny)
# runApp("myapp") # Won't launch in environments without browsers
unlink("myapp", recursive = TRUE, force = TRUE) # remove myapp
```

---

getRxThreads *Get/Set the number of threads that RxODE uses*

Description

Get/Set the number of threads that RxODE uses

Usage

```
getRxThreads(verbose = FALSE)

setRxThreads(threads = NULL, percent = NULL, throttle = NULL)

rxCores(verbose = FALSE)
```

Arguments

verbose	Display the value of relevant OpenMP settings
threads	NULL (default) rereads environment variables. 0 means to use all logical CPUs available. Otherwise a number >= 1
percent	If provided it should be a number between 2 and 100; the percentage of logical CPUs to use. By default on startup, 50 percent.
throttle	2 (default) means that, roughly speaking, a single thread will be used when number subjects solved for is <=2, 2 threads when the number of all points is <=4, etc. The throttle is to speed up small data tasks (especially when repeated many times) by not incurring the overhead of managing multiple threads. The throttle will also suppress sorting which ID will be solved first when there are (nsubject solved)*throttle <= nthreads. In RxODE this sorting occurs to minimize the time for waiting for another thread to finish. If the last item solved is has a long solving time, all the other solving have to wait for that last costly solving to occur. If the items which are likely to take more time are solved first, this wait is less likely to have an impact on the overall solving time. In RxODE the IDs are sorted by the individual number of solving points (largest first). It also has a C interface that allows these IDs to be resorted by total time spent solving the equation. This allows packages like nlmixr to sort by solving time if needed. Overall the the number of threads is throttled (restricted) for small tasks and sorting for IDs are suppressed.

Value

number of threads that RxODE uses

---

invWR1d *One correlation sample from the Inverse Wishart distribution*

Description

This correlation is constructed by transformation of the Inverse Wishart random covariate to a correlation.

Usage

```
invWR1d(d, nu, omegaIsChol = FALSE)
```

Arguments

d	The dimension of the correlation matrix
nu	Degrees of freedom of the Wishart distribution
omegaIsChol	is an indicator of if the omega matrix is in the Cholesky decomposition. This is only used when codetype="invWishart"

Value

One correlation sample from the inverse wishart

Author(s)

Matthew Fidler

---

logit *logit and inverse logit (expit) functions*

Description

logit and inverse logit (expit) functions

Usage

```
logit(x, low = 0, high = 1)

expit(alpha, low = 0, high = 1)

logitNormInfo(mean = 0, sd = 1, low = 0, high = 1, abs.tol = 1e-06, ...)

probitNormInfo(mean = 0, sd = 1, low = 0, high = 1, abs.tol = 1e-06, ...)
```

Arguments

x	Input value(s) in range [low,high] to translate -Inf to Inf
low	Lowest value in the range
high	Highest value in the range
alpha	Infinite value(s) to translate to range of [low, high]
mean	logit-scale mean
sd	logit-scale standard deviation
abs.tol	absolute accuracy requested.
...	other parameters passed to integrate()

Details

logit is given by:

logit(p) = -log(1/p-1)

where:

p = x-low/high-low

expit is given by:

expit(p, low, high) = (high-low)/(1+exp(-alpha)) + low

The `logitNormInfo()` gives the mean, variance and coefficient of variability on the untransformed scale.

Value

values from logit and expit

Examples

```
logit(0.25)

expit(-1.09)

logitNormInfo(logit(0.25), sd = 0.1)

logitNormInfo(logit(1, 0, 10), sd = 1, low = 0, high = 10)
```

`lowergamma` *lowergamma: upper incomplete gamma function*

Description

This is the tgamma_lower from the boost library

Usage

```
lowergamma(a, z)
```

Arguments

a	The numeric 'a' parameter in the upper incomplete gamma
z	The numeric 'z' parameter in the upper incomplete gamma

Details

The lowergamma function is given by:

$$lowergamma(a, z) = \int_0^z t^{a-1} \cdot e^{-t} dt$$

Value

lowergamma results

Author(s)

Matthew L. Fidler

Examples

```
lowergamma(1, 3)

lowergamma(1:3, 3)

lowergamma(1, 1:3)
```

---

phi *Cumulative distribution of standard normal*

Description

Cumulative distribution of standard normal

Usage

```
phi(q)
```

Arguments

q	vector of quantiles.

Value

cumulative distribution of standard normal distribution

Author(s)

Matthew Fidler

Examples

```
# phi is equivalent to pnorm(x)
phi(3)

# See
pnorm(3)

# This is provided for NONMEM-like compatibility in RxODE models
```

probit *probit and inverse probit functions*

Description

probit and inverse probit functions

Usage

```
probit(x, low = 0, high = 1)

probitInv(x, low = 0, high = 1)
```

Arguments

x	Input value(s) in range [low,high] to translate -Inf to Inf
low	Lowest value in the range
high	Highest value in the range

Value

values from probit, probitInv and probitNormInfo

Examples

```
probit(0.25)

probitInv(-0.674)

probitNormInfo(probit(0.25), sd = 0.1)

probitNormInfo(probit(1, 0, 10), sd = 1, low = 0, high = 10)
```

rinvchisq *Scaled Inverse Chi Squared distribution*

Description

Scaled Inverse Chi Squared distribution

Usage

```
rinvchisq(n = 1L, nu = 1, scale = 1)
```

Arguments

n	Number of random samples
nu	degrees of freedom of inverse chi square
scale	Scale of inverse chi squared distribution (default is 1).

Value

a vector of inverse chi squared deviates.

Examples

```
rinvchisq(3, 4, 1) ## Scale = 1, degrees of freedom = 4
rinvchisq(2, 4, 2) ## Scale = 2, degrees of freedom = 4
```

---

rLKJ1 *One correlation sample from the LKJ distribution*

Description

One correlation sample from the LKJ distribution

Usage

```
rLKJ1(d, eta = 1, cholesky = FALSE)
```

Arguments

d	The dimension of the correlation matrix
eta	The scaling parameter of the LKJ distribution. Must be > 1. Also related to the degrees of freedom nu. eta = (nu-1)/2.
cholesky	boolean; If TRUE return the cholesky decomposition.

Value

A correlation sample from the LKJ distribution

Author(s)

Matthew Fidler (translated to RcppArmadillo) and Emma Schwager

rxAllowUnload *Allow unloading of dlls*

Description

Allow unloading of dlls

Usage

```
rxAllowUnload(allow)
```

Arguments

allow	boolean indicating if garbage collection will unload of RxODE dlls.

Value

Boolean allow; called for side effects

Author(s)

Matthew Fidler

Examples

```
# Garbage collection will not unload un-used RxODE dlls
rxAllowUnload(FALSE);

# Garbage collection will unload unused RxODE dlls
rxAllowUnload(TRUE);
```

rxAssignPtr *Assign pointer based on model variables*

Description

Assign pointer based on model variables

Usage

```
rxAssignPtr(object = NULL)
```

Arguments

object	RxODE family of objects

Value

nothing, called for side effects

`rxbeta` *Simulate beta variable from threefry generator*

Description

Care should be taken with this method not to encounter the birthday problem, described https://www.johndcook.com/blog/2016/01/29/random-number-generator-seed-mistakes/. Since the `sitmo threefry`, this currently generates one random deviate from the uniform distribution to seed the engine `threefry` and then run the code.

Usage

```
rxbeta(shape1, shape2, n = 1L, ncores = 1L)
```

Arguments

`shape1`	non-negative parameters of the Beta distribution.
`shape2`	non-negative parameters of the Beta distribution.
`n`	number of observations. If `length(n) > 1`, the length is taken to be the number required.
`ncores`	Number of cores for the simulation `rxnorm` simulates using the threefry sitmo generator; `rxnormV` uses the vandercorput generator

Details

Therefore, a simple call to the random number generated followed by a second call to random number generated may have identical seeds. As the number of random number generator calls are increased the probability that the birthday problem will increase.

The key to avoid this problem is to either run all simulations in the `RxODE` environment once (therefore one seed or series of seeds for the whole simulation), pre-generate all random variables used for the simulation, or seed the RxODE engine with `rxSetSeed()`

Also care should be made that the computer you will be running on can run the same number of cores as you are running so they can reproduce your results.

Value

beta random deviates

Examples

```
## Use threefry engine

rxbeta(0.5, 0.5, n = 10) # with rxbeta you have to explicitly state n
rxbeta(5, 1, n = 10, ncores = 2) # You can parallelize the simulation using openMP

rxbeta(1, 3)


## This example uses `rxbeta` directly in the model

rx <- RxODE({
  a <- rxbeta(2, 2)
})

et <- et(1, id = 1:2)

s <- rxSolve(rx, et)
```

---

rxbinom *Simulate Binomial variable from threefry generator*

Description

Care should be taken with this method not to encounter the birthday problem, described https://www.johndcook.com/blog/2016/01/29/random-number-generator-seed-mistakes/. Since the sitmo threefry, this currently generates one random deviate from the uniform distribution to seed the engine threefry and then run the code.

Usage

```
rxbinom(size, prob, n = 1L, ncores = 1L)
```

Arguments

size	number of trials (zero or more).
prob	probability of success on each trial.
n	number of observations. If length(n) > 1, the length is taken to be the number required.
ncores	Number of cores for the simulation rxnorm simulates using the threefry sitmo generator; rxnormV uses the vandercorput generator

Details

Therefore, a simple call to the random number generated followed by a second call to random number generated may have identical seeds. As the number of random number generator calls are increased the probability that the birthday problem will increase.

The key to avoid this problem is to either run all simulations in the RxODE environment once (therefore one seed or series of seeds for the whole simulation), pre-generate all random variables used for the simulation, or seed the RxODE engine with `rxSetSeed()`

Also care should be made that the computer you will be running on can run the same number of cores as you are running so they can reproduce your results.

Value

binomial random deviates

Examples

```
## Use threefry engine

rxbinom(10, 0.9, n = 10) # with rxbinom you have to explicitly state n
rxbinom(3, 0.5, n = 10, ncores = 2) # You can parallelize the simulation using openMP

rxbinom(4, 0.7)


## This example uses `rxbinom` directly in the model

rx <- RxODE({
  a <- rxbinom(1, 0.5)
})

et <- et(1, id = 1:2)

s <- rxSolve(rx, et)
```

---

rxcauchy *Simulate Cauchy variable from threefry generator*

Description

Care should be taken with this method not to encounter the birthday problem, described https://www.johndcook.com/blog/2016/01/29/random-number-generator-seed-mistakes/. Since the `sitmo threefry`, this currently generates one random deviate from the uniform distribution to seed the engine `threefry` and then run the code.

Usage

```
rxcauchy(location = 0, scale = 1, n = 1L, ncores = 1L)
```

Arguments

location	location and scale parameters.
scale	location and scale parameters.
n	number of observations. If length(n) > 1, the length is taken to be the number required.
ncores	Number of cores for the simulation rxnorm simulates using the threefry sitmo generator; rxnormV uses the vandercorput generator

Details

Therefore, a simple call to the random number generated followed by a second call to random number generated may have identical seeds. As the number of random number generator calls are increased the probability that the birthday problem will increase.

The key to avoid this problem is to either run all simulations in the RxODE environment once (therefore one seed or series of seeds for the whole simulation), pre-generate all random variables used for the simulation, or seed the RxODE engine with rxSetSeed()

Also care should be made that the computer you will be running on can run the same number of cores as you are running so they can reproduce your results.

Value

Cauchy random deviates

Examples

```
## Use threefry engine

rxcauchy(0, 1, n = 10) # with rxcauchy you have to explicitly state n
rxcauchy(0.5, n = 10, ncores = 2) # You can parallelize the simulation using openMP

rxcauchy(3)


## This example uses `rxcauchy` directly in the model

rx <- RxODE({
  a <- rxcauchy(2)
})

et <- et(1, id = 1:2)

s <- rxSolve(rx, et)
```

rxCbindStudyIndividual *Bind the study parameters and individual parameters*

Description

Bind the study parameters and individual parameters

Usage

```
rxCbindStudyIndividual(studyParameters, individualParameters)
```

Arguments

studyParameters	These are the study parameters, often can be generated by sampling from a population. This can be either a matrix or a data frame
individualParameters	A data frame of individual parameters

Value

Data frame that can be used in RxODE simulations

Author(s)

Matthew Fidler

Examples

```
# Function for coverting coefficient of covariance into a variance
logncv <- function(x){log((x/100)^2+1)}

set.seed(32)

nSub  <-  100
nStud  <-  10

#define theta
theta <- c(lka=log(0.5), # log ka
          lCl=log(5), # log Cl
          lV=log(300) # log V
          )

#define theta Matrix
```

```
thetaMat <- lotri(lCl ~ lognCv(5),
                  lV  ~ lognCv(5),
                  lka ~ lognCv(5))


nev <- nSub*nStud

ev1 <- data.frame(COV1=rnorm(nev,50,30),COV2=rnorm(nev,75,10),
                  COV3=sample(c(1.0,2.0),nev,replace=TRUE))


tmat <-rxRmvn(nStud, theta[dimnames(thetaMat)[[1]]], thetaMat)

rxCbindStudyIndividual(tmat, ev1)
```

---

rxChain *rxChain Chain or add item to solved system of equations*

Description

Add item to solved system of equations

Usage

```
rxChain(obj1, obj2)

## S3 method for class 'solveRxDll'
obj1 + obj2
```

Arguments

obj1	Solved object.
obj2	New object to be added/piped/chained to solved object.

Value

When newObject is an event table, return a new solved object with the new event table.

Author(s)

Matthew L. Fidler

rxchisq *Simulate chi-squared variable from threefry generator*

Description

Care should be taken with this method not to encounter the birthday problem, described https://www.johndcook.com/blog/2016/01/29/random-number-generator-seed-mistakes/. Since the sitmo threefry, this currently generates one random deviate from the uniform distribution to seed the engine threefry and then run the code.

Usage

```
rxchisq(df, n = 1L, ncores = 1L)
```

Arguments

df	degrees of freedom (non-negative, but can be non-integer).
n	number of observations. If length(n) > 1, the length is taken to be the number required.
ncores	Number of cores for the simulation rxnorm simulates using the threefry sitmo generator; rxnormV uses the vandercorput generator

Details

Therefore, a simple call to the random number generated followed by a second call to random number generated may have identical seeds. As the number of random number generator calls are increased the probability that the birthday problem will increase.

The key to avoid this problem is to either run all simulations in the RxODE environment once (therefore one seed or series of seeds for the whole simulation), pre-generate all random variables used for the simulation, or seed the RxODE engine with rxSetSeed()

Also care should be made that the computer you will be running on can run the same number of cores as you are running so they can reproduce your results.

Value

chi squared random deviates

Examples

```
## Use threefry engine

rxchisq(0.5, n = 10) # with rxchisq you have to explicitly state n
rxchisq(5, n = 10, ncores = 2) # You can parallelize the simulation using openMP
```

```
rxchisq(1)


## This example uses `rxchisq` directly in the model

rx <- RxODE({
  a <- rxchisq(2)
})

et <- et(1, id = 1:2)

s <- rxSolve(rx, et)
```

---

rxClean *Cleanup anonymous DLLs by unloading them*

Description

This cleans up any RxODE loaded DLLs

Usage

```
rxClean(wd)
```

Arguments

wd	What directory should be cleaned; (DEPRECIATED), this no longer does anything.
	This unloads all RxODE anonymous dlls.

Value

TRUE if successful

Author(s)

Matthew L. Fidler

rxCompile *Compile a model if needed*

Description

This is the compilation workhorse creating the RxODE model DLL files.

Usage

```
rxCompile(
  model,
  dir,
  prefix,
  force = FALSE,
  modName = NULL,
  package = NULL,
  ...
)

## S3 method for class 'rxModelVars'
rxCompile(
  model,
  dir = NULL,
  prefix = NULL,
  force = FALSE,
  modName = NULL,
  package = NULL,
  ...
)

## S3 method for class 'character'
rxCompile(
  model,
  dir = NULL,
  prefix = NULL,
  force = FALSE,
  modName = NULL,
  package = NULL,
  ...
)

## S3 method for class 'rxDll'
rxCompile(model, ...)

## S3 method for class 'RxODE'
rxCompile(model, ...)
```

Arguments

model	This is the ODE model specification. It can be: • a string containing the set of ordinary differential equations (ODE) and other expressions defining the changes in the dynamic system. • a file name where the ODE system equation is contained An ODE expression enclosed in \{\} (see also the filename argument). For details, see the sections "Details" and RxODE Syntax below.
dir	This is the model directory where the C file will be stored for compiling. If unspecified, the C code is stored in a temporary directory, then the model is compiled and moved to the current directory. Afterwards the C code is removed. If specified, the C code is stored in the specified directory and then compiled in that directory. The C code is not removed after the DLL is created in the same directory. This can be useful to debug the c-code outputs.
prefix	is a string indicating the prefix to use in the C based functions. If missing, it is calculated based on file name, or md5 of parsed model.
force	is a boolean stating if the (re)compile should be forced if RxODE detects that the models are the same as already generated.
modName	a string to be used as the model name. This string is used for naming various aspects of the computations, including generating C symbol names, dynamic libraries, etc. Therefore, it is necessary that modName consists of simple ASCII alphanumeric characters starting with a letter.
package	Package name for pre-compiled binaries.
...	Other arguments sent to the rxTrans() function.

Value

An rxDll object that has the following components

- dllDLL path
- modelmodel specification
- .cA function to call C code in the correct context from the DLL using the .C() function.
- .callA function to call C code in the correct context from the DLL using the .Call() function.
- argsA list of the arguments used to create the rxDll object.

Author(s)

Matthew L.Fidler

See Also

RxODE()

rxCreateCache — *This will create the cache directory for RxODE to save between sessions*

Description

When run, if the `R_user_dir` for RxODE's cache isn't present, create the cache

Usage

```
rxCreateCache()
```

Value

nothing

Author(s)

Matthew Fidler

rxD — *Add to RxODE's derivative tables*

Description

Add to RxODE's derivative tables

Usage

```
rxD(name, derivatives)
```

Arguments

`name`	Function Name
`derivatives`	A list of functions. Each function takes the same number of arguments as the original function. The first function will construct the derivative with respect to the first argument; The second function will construct the derivitive with respect to the second argument, and so on.

Value

nothing

Author(s)

Matthew Fidler

Examples

```
## Add an arbitrary list of derivative functions
## In this case the fun(x,y) is assumed to be 0.5*x^2+0.5*y^2

rxD("fun", list(
  function(x, y) {
    return(x)
  },
  function(x, y) {
    return(y)
  }
))
```

`rxDelete` *Delete the DLL for the model*

Description

This function deletes the DLL, but doesn't delete the model information in the object.

Usage

```
rxDelete(obj)
```

Arguments

`obj`	RxODE family of objects

Value

A boolean stating if the operation was successful.

Author(s)

Matthew L.Fidler

`rxDerived` *Calculate derived parameters for the 1-, 2-, and 3- compartment linear models.*

Description

This calculates the derived parameters based on what is provided in a data frame or arguments

Usage

```
rxDerived(..., verbose = FALSE, digits = 0)
```

Arguments

...	The input can be: • A data frame with PK parameters in it; This should ideally be a data frame with one pk parameter per row since it will output a data frame with one PK parameter per row. • PK parameters as either a vector or a scalar
verbose	boolean that when TRUE provides a message about the detected pk parameters and the detected compartmental model. By default this is FALSE.
digits	represents the number of significant digits for the output; If the number is zero or below (default), do not round.

Value

Return a data.frame of derived PK parameters for a 1-, 2-, or 3-compartment linear model given provided clearances and volumes based on the inferred model type.

The model parameters that will be provided in the data frame are:

- vc: Central Volume (for 1-, 2- and 3- compartment models)
- kel: First-order elimination rate (for 1-, 2-, and 3-compartment models)
- k12: First-order rate of transfer from central to first peripheral compartment; (for 2- and 3-compartment models)
- k21: First-order rate of transfer from first peripheral to central compartment, (for 2- and 3-compartment models)
- k13: First-order rate of transfer from central to second peripheral compartment; (3-compartment model)
- k31: First-order rate of transfer from second peripheral to central compartment (3-compartment model)
- vp: Peripheral Volume (for 2- and 3- compartment models)
- vp2: Peripheral Volume for 3rd compartment (3- compartment model)
- vss: Volume of distribution at steady state; (1-, 2-, and 3-compartment models)
- t12alpha: $t_{1/2,\alpha}$; (1-, 2-, and 3-compartment models)
- t12beta: $t_{1/2,\beta}$; (2- and 3-compartment models)
- t12gamma: $t_{1/2,\gamma}$; (3-compartment model)
- alpha: α; (1-, 2-, and 3-compartment models)
- beta: β; (2- and 3-compartment models)
- gamma: β; (3-compartment model)
- A: true A; (1-, 2-, and 3-compartment models)
- B: true B; (2- and 3-compartment models)
- C: true C; (3-compartment model)
- fracA: fractional A; (1-, 2-, and 3-compartment models)
- fracB: fractional B; (2- and 3-compartment models)
- fracC: fractional C; (3-compartment model)

Author(s)

Matthew Fidler and documentation from Justin Wilkins, <justin.wilkins@occams.com>

References

Shafer S. L. CONVERT.XLS

Rowland M, Tozer TN. Clinical Pharmacokinetics and Pharmacodynamics: Concepts and Applications (4th). Clipping Williams & Wilkins, Philadelphia, 2010.

Examples

```
## Note that RxODE parses the names to figure out the best PK parameter

params <- rxDerived(cl = 29.4, v = 23.4, Vp = 114, vp2 = 4614, q = 270, q2 = 73)

## That is why this gives the same results as the value before

params <- rxDerived(CL = 29.4, V1 = 23.4, V2 = 114, V3 = 4614, Q2 = 270, Q3 = 73)

## You may also use micro-constants alpha/beta etc.

params <- rxDerived(k12 = 0.1, k21 = 0.2, k13 = 0.3, k31 = 0.4, kel = 10, v = 10)

## or you can mix vectors and scalars

params <- rxDerived(CL = 29.4, V = 1:3)

## If you want, you can round to a number of significant digits
## with the `digits` argument:

params <- rxDerived(CL = 29.4, V = 1:3, digits = 2)
```

---

rxDfdy *Jacobian and parameter derivatives*

Description

Return Jacobain and parameter derivatives

Usage

```
rxDfdy(obj)
```

Arguments

obj	RxODE family of objects

Value

A list of the jacobian parameters defined in this RxODE object.

Author(s)

Matthew L. Fidler

`rxEvid` *EVID formatting for tibble and other places.*

Description

This is to make an EVID more readable by non pharmacometricians. It displays what each means and allows it to be displayed in a tibble.

Usage

```
rxEvid(x)

as.rxEvid(x)

## S3 method for class 'rxEvid'
c(x, ...)

## S3 method for class 'rxEvid'
x[...]

## S3 method for class 'rxEvid'
as.character(x, ...)

## S3 method for class 'rxEvid'
x[[...]]

## S3 method for class 'rxRateDur'
c(x, ...)

## S3 method for class 'rxEvid'
format(x, ...)

## S3 method for class 'rxRateDur'
format(x, ...)

## S3 method for class 'rxEvid'
print(x, ...)
```

Arguments

x	Item to be converted to a RxODE EVID specification.
...	Other parameters

Value

rxEvid specification

Examples

```
rxEvid(1:7)
```

---

rxexp *Simulate exponential variable from threefry generator*

Description

Care should be taken with this method not to encounter the birthday problem, described https://www.johndcook.com/blog/2016/01/29/random-number-generator-seed-mistakes/. Since the sitmo threefry, this currently generates one random deviate from the uniform distribution to seed the engine threefry and then run the code.

Usage

```
rxexp(rate, n = 1L, ncores = 1L)
```

Arguments

rate	vector of rates.
n	number of observations. If length(n) > 1, the length is taken to be the number required.
ncores	Number of cores for the simulation
	rxnorm simulates using the threefry sitmo generator; rxnormV uses the vandercorput generator

Details

Therefore, a simple call to the random number generated followed by a second call to random number generated may have identical seeds. As the number of random number generator calls are increased the probability that the birthday problem will increase.

The key to avoid this problem is to either run all simulations in the RxODE environment once (therefore one seed or series of seeds for the whole simulation), pre-generate all random variables used for the simulation, or seed the RxODE engine with rxSetSeed()

Also care should be made that the computer you will be running on can run the same number of cores as you are running so they can reproduce your results.

Value

exponential random deviates

Examples

```
## Use threefry engine

rxexp(0.5, n = 10) # with rxexp you have to explicitly state n
rxexp(5, n = 10, ncores = 2) # You can parallelize the simulation using openMP

rxexp(1)


## This example uses `rxexp` directly in the model

rx <- RxODE({
  a <- rxexp(2)
})

et <- et(1, id = 1:2)

s <- rxSolve(rx, et)
```

---

rxf *Simulate F variable from threefry generator*

Description

Care should be taken with this method not to encounter the birthday problem, described https://www.johndcook.com/blog/2016/01/29/random-number-generator-seed-mistakes/. Since the sitmo threefry, this currently generates one random deviate from the uniform distribution to seed the engine threefry and then run the code.

Usage

```
rxf(df1, df2, n = 1L, ncores = 1L)
```

Arguments

df1	degrees of freedom. Inf is allowed.
df2	degrees of freedom. Inf is allowed.
n	number of observations. If length(n) > 1, the length is taken to be the number required.

ncores — Number of cores for the simulation

rxnorm simulates using the threefry sitmo generator; rxnormV uses the vandercorput generator

Details

Therefore, a simple call to the random number generated followed by a second call to random number generated may have identical seeds. As the number of random number generator calls are increased the probability that the birthday problem will increase.

The key to avoid this problem is to either run all simulations in the RxODE environment once (therefore one seed or series of seeds for the whole simulation), pre-generate all random variables used for the simulation, or seed the RxODE engine with rxSetSeed()

Also care should be made that the computer you will be running on can run the same number of cores as you are running so they can reproduce your results.

Value

f random deviates

Examples

```
## Use threefry engine

rxf(0.5, 0.5, n = 10) # with rxf you have to explicitly state n
rxf(5, 1, n = 10, ncores = 2) # You can parallelize the simulation using openMP

rxf(1, 3)


## This example uses `rxf` directly in the model

rx <- RxODE({
  a <- rxf(2, 2)
})

et <- et(1, id = 1:2)

s <- rxSolve(rx, et)
```

---

rxFun — *Add user function to RxODE*

Description

This adds a user function to RxODE that can be called. If needed, these functions can be differentiated by numerical differences or by adding the derivatives to RxODE's internal derivative table with `rxD()`

Usage

```
rxFun(name, args, cCode)

rxRmFun(name)
```

Arguments

name	This gives the name of the user function
args	This gives the arguments of the user function
cCode	This is the C-code for the new function

Value

nothing

Author(s)

Matthew L. Fidler

Examples

```
## Right now RxODE is not aware of the function f
## Therefore it cannot translate it to symengine or
## Compile a model with it.

try(RxODE("a=fun(a,b,c)"))

## Note for this approach to work, it cannot interfere with C
## function names or reserved RxODE specical terms.  Therefore
## f(x) would not work since f is an alias for bioaviability.

fun <- "
double fun(double a, double b, double c) {
  return a*a+b*a+c;
}
" ## C-code for function

rxFun("fun", c("a", "b", "c"), fun) ## Added function

## Now RxODE knows how to translate this function to symengine

rxToSE("fun(a,b,c)")
```

```
## And will take a central difference when calculating derivatives

rxFromSE("Derivative(fun(a,b,c),a)")

## Of course, you could specify the derivative table manually
rxD("fun", list(
  function(a, b, c) {
    paste0("2*", a, "+", b)
  },
  function(a, b, c) {
    return(a)
  },
  function(a, b, c) {
    return("0.0")
  }
))

rxFromSE("Derivative(fun(a,b,c),a)")

# You can also remove the functions by `rxRmFun`

rxRmFun("fun")
```

---

rxgamma *Simulate gamma variable from threefry generator*

Description

Care should be taken with this method not to encounter the birthday problem, described https://www.johndcook.com/blog/2016/01/29/random-number-generator-seed-mistakes/. Since the sitmo threefry, this currently generates one random deviate from the uniform distribution to seed the engine threefry and then run the code.

Usage

```
rxgamma(shape, rate = 1/scale, scale = 1, n = 1L, ncores = 1L)
```

Arguments

shape	shape and scale parameters. Must be positive, scale strictly.
rate	an alternative way to specify the scale.
scale	shape and scale parameters. Must be positive, scale strictly.
n	number of observations. If length(n) > 1, the length is taken to be the number required.
ncores	Number of cores for the simulation rxnorm simulates using the threefry sitmo generator; rxnormV uses the vandercorput generator

Details

Therefore, a simple call to the random number generated followed by a second call to random number generated may have identical seeds. As the number of random number generator calls are increased the probability that the birthday problem will increase.

The key to avoid this problem is to either run all simulations in the RxODE environment once (therefore one seed or series of seeds for the whole simulation), pre-generate all random variables used for the simulation, or seed the RxODE engine with `rxSetSeed()`

Also care should be made that the computer you will be running on can run the same number of cores as you are running so they can reproduce your results.

Value

gamma random deviates

Examples

```
## Use threefry engine

rxgamma(0.5, n = 10) # with rxgamma you have to explicitly state n
rxgamma(5, n = 10, ncores = 2) # You can parallelize the simulation using openMP

rxgamma(1)


## This example uses `rxbeta` directly in the model

rx <- RxODE({
  a <- rxgamma(2)
})

et <- et(1, id = 1:2)

s <- rxSolve(rx, et)
```

---

rxgeom *Simulate geometric variable from threefry generator*

Description

Care should be taken with this method not to encounter the birthday problem, described https://www.johndcook.com/blog/2016/01/29/random-number-generator-seed-mistakes/. Since the `sitmo threefry`, this currently generates one random deviate from the uniform distribution to seed the engine `threefry` and then run the code.

Usage

```
rxgeom(prob, n = 1L, ncores = 1L)
```

Arguments

prob	probability of success in each trial. 0 < prob <= 1.
n	number of observations. If length(n) > 1, the length is taken to be the number required.
ncores	Number of cores for the simulation rxnorm simulates using the threefry sitmo generator; rxnormV uses the vandercorput generator

Details

Therefore, a simple call to the random number generated followed by a second call to random number generated may have identical seeds. As the number of random number generator calls are increased the probability that the birthday problem will increase.

The key to avoid this problem is to either run all simulations in the RxODE environment once (therefore one seed or series of seeds for the whole simulation), pre-generate all random variables used for the simulation, or seed the RxODE engine with rxSetSeed()

Also care should be made that the computer you will be running on can run the same number of cores as you are running so they can reproduce your results.

Value

geometric random deviates

Examples

```
## Use threefry engine

rxgeom(0.5, n = 10) # with rxgeom you have to explicitly state n
rxgeom(0.25, n = 10, ncores = 2) # You can parallelize the simulation using openMP

rxgeom(0.75)


## This example uses `rxgeom` directly in the model

rx <- RxODE({
  a <- rxgeom(0.24)
})

et <- et(1, id = 1:2)

s <- rxSolve(rx, et)
```

rxGetLin *Get the linear compartment model true function*

Description

Get the linear compartment model true function

Usage

```
rxGetLin(
  model,
  linCmtSens = c("linCmtA", "linCmtB", "linCmtC"),
  verbose = FALSE
)
```

Arguments

model	This is the ODE model specification. It can be: • a string containing the set of ordinary differential equations (ODE) and other expressions defining the changes in the dynamic system. • a file name where the ODE system equation is contained An ODE expression enclosed in \{\} (see also the filename argument). For details, see the sections "Details" and RxODE Syntax below.
linCmtSens	The method to calculate the linCmt() solutions
verbose	When TRUE be verbose with the linear compartmental model

Value

model with linCmt() replaced with linCmtA()

Author(s)

Matthew Fidler

rxGetRxODE *Get RxODE model from object*

Description

Get RxODE model from object

Usage

```
rxGetRxODE(obj)
```

Arguments

obj	RxODE family of objects

Value

RxODE model

`rxHtml` *Format rxSolve and related objects as html.*

Description

Format rxSolve and related objects as html.

Usage

```
rxHtml(x, ...)

## S3 method for class 'rxSolve'
rxHtml(x, ...)
```

Arguments

x	RxODE object
...	Extra arguments sent to kable

Value

html code for rxSolve object

Author(s)

Matthew L. Fidler

rxIndLinState *Set the preferred factoring by state*

Description

Set the preferred factoring by state

Usage

```
rxIndLinState(preferred = NULL)
```

Arguments

preferred	A list of each state's preferred factorization

Value

Nothing

Author(s)

Matthew Fidler

rxIndLinStrategy *This sets the inductive linearization strategy for matrix building*

Description

When there is more than one state in a ODE that cannot be separated this specifies how it is incorporated into the matrix exponential.

Usage

```
rxIndLinStrategy(strategy = c("curState", "split"))
```

Arguments

strategy	The strategy for inductive linearization matrix building • curState Prefer parameterizing in terms of the current state, followed by the first state observed in the term. • split Split the parameterization between all states in the term by dividing each by the number of states in the term and then adding a matrix term for each state.

Value

Nothing

Author(s)

Matthew L. Fidler

`rxInv` *Invert matrix using RcppArmadillo.*

Description

Invert matrix using RcppArmadillo.

Usage

```
rxInv(matrix)
```

Arguments

`matrix`	matrix to be inverted.

Value

inverse or pseudo inverse of matrix.

`rxIsCurrent` *Checks if the RxODE object was built with the current build*

Description

Checks if the RxODE object was built with the current build

Usage

```
rxIsCurrent(obj)
```

Arguments

`obj`	RxODE family of objects

Value

boolean indicating if this was built with current RxODE

rxLhs *Left handed Variables*

Description

This returns the model calculated variables

Usage

```
rxLhs(obj)
```

Arguments

obj	RxODE family of objects

Value

a character vector listing the calculated parameters

Author(s)

Matthew L.Fidler

See Also

RxODE

rxLock *Lock/unlocking of RxODE dll file*

Description

Lock/unlocking of RxODE dll file

Usage

```
rxLock(obj)

rxUnlock(obj)
```

Arguments

obj	A RxODE family of objects

Value

nothing; called for side effects

rxNorm *Get the normalized model*

Description

This get the syntax preferred model for processing

Usage

```
rxNorm(obj, condition = NULL, removeInis, removeJac, removeSens)
```

Arguments

obj	RxODE family of objects
condition	Character string of a logical condition to use for subsetting the normalized model. When missing, and a condition is not set via rxCondition, return the whole code with all the conditional settings intact. When a condition is set with rxCondition, use that condition.
removeInis	A boolean indicating if parameter initialization will be removed from the model
removeJac	A boolean indicating if the Jacobians will be removed.
removeSens	A boolean indicating if the sensitivities will be removed.

Value

Normalized Normal syntax (no comments)

Author(s)

Matthew L. Fidler

rxnorm *Simulate random normal variable from threefry/vandercorput generator*

Description

Simulate random normal variable from threefry/vandercorput generator

Usage

```
rxnorm(mean = 0, sd = 1, n = 1L, ncores = 1L)

rxnormV(mean = 0, sd = 1, n = 1L, ncores = 1L)
```

Arguments

mean	vector of means.
sd	vector of standard deviations.
n	number of observations
ncores	Number of cores for the simulation
	rxnorm simulates using the threefry sitmo generator; rxnormV uses the vandercorput generator

Value

normal random number deviates

Examples

```
## Use threefry engine

rxnorm(n = 10) # with rxnorm you have to explicitly state n
rxnorm(n = 10, ncores = 2) # You can parallelize the simulation using openMP

rxnorm(2, 3) ## The first 2 arguments are the mean and standard deviation


## This example uses `rxnorm` directly in the model

rx <- RxODE({
  a <- rxnorm()
})

et <- et(1, id = 1:2)

s <- rxSolve(rx, et)

## Use vandercorput generator

rxnormV(n = 10) # with rxnorm you have to explicitly state n
rxnormV(n = 10, ncores = 2) # You can parallelize the simulation using openMP

rxnormV(2, 3) ## The first 2 arguments are the mean and standard deviation


## This example uses `rxnormV` directly in the model

rx <- RxODE({
  a <- rxnormV()
})

et <- et(1, id = 1:2)

s <- rxSolve(rx, et)
```

RxODE *Create an ODE-based model specification*

Description

Create a dynamic ODE-based model object suitably for translation into fast C code

Usage

```
RxODE(
  model,
  modName = basename(wd),
  wd = getwd(),
  filename = NULL,
  extraC = NULL,
  debug = FALSE,
  calcJac = NULL,
  calcSens = NULL,
  collapseModel = FALSE,
  package = NULL,
  ...,
  linCmtSens = c("linCmtA", "linCmtB", "linCmtC"),
  indLin = FALSE,
  verbose = FALSE
)
```

Arguments

model	This is the ODE model specification. It can be: • a string containing the set of ordinary differential equations (ODE) and other expressions defining the changes in the dynamic system. • a file name where the ODE system equation is contained An ODE expression enclosed in \{\} (see also the filename argument). For details, see the sections "Details" and RxODE Syntax below.
modName	a string to be used as the model name. This string is used for naming various aspects of the computations, including generating C symbol names, dynamic libraries, etc. Therefore, it is necessary that modName consists of simple ASCII alphanumeric characters starting with a letter.
wd	character string with a working directory where to create a subdirectory according to modName. When specified, a subdirectory named after the "modName.d" will be created and populated with a C file, a dynamic loading library, plus various other working files. If missing, the files are created (and removed) in the temporary directory, and the RxODE DLL for the model is created in the current directory named rx_????_platform, for example rx_129f8f97fb94a87ca49ca8dafe691e1e_i386.dll

filename	A file name or connection object where the ODE-based model specification resides. Only one of model or filename may be specified.
extraC	Extra c code to include in the model. This can be useful to specify functions in the model. These C functions should usually take double precision arguments, and return double precision values.
debug	is a boolean indicating if the executable should be compiled with verbose debugging information turned on.
calcJac	boolean indicating if RxODE will calculate the Jacobain according to the specified ODEs.
calcSens	boolean indicating if RxODE will calculate the sensitivities according to the specified ODEs.
collapseModel	boolean indicating if RxODE will remove all LHS variables when calculating sensitivities.
package	Package name for pre-compiled binaries.
...	ignored arguments.
linCmtSens	The method to calculate the linCmt() solutions
indLin	Calculate inductive linearization matrices and compile with inductive linearization support.
verbose	When TRUE be verbose with the linear compartmental model

Details

The Rx in the name RxODE is meant to suggest the abbreviation *Rx* for a medical prescription, and thus to suggest the package emphasis on pharmacometrics modeling, including pharmacokinetics (PK), pharmacodynamics (PD), disease progression, drug-disease modeling, etc.

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 (environment) with various member functions (see Section *Value* below).

For evaluating RxODE models, two types of inputs may be provided: a required set of time points for querying the state of the ODE system and an optional set of doses (input amounts). These inputs are combined into a single *event table* object created with the function eventTable() or et().

An RxODE model specification consists of one or more statements optionally terminated by semicolons ; and optional comments (comments are delimited by # and an end-of-line).

A block of statements is a set of statements delimited by curly braces, { ... }.

Statements can be either assignments, conditional if/else if/else, while loops (can be exited by break), special statements, or printing statements (for debugging/testing)

Assignment statements can be:

- **simple** assignments, where the left hand is an identifier (i.e., variable)
- special **time-derivative** assignments, where the left hand specifies the change of the amount in the corresponding state variable (compartment) with respect to time e.g., d/dt(depot):

- special **initial-condition** assignments where the left hand specifies the compartment of the initial condition being specified, e.g. `depot(0) = 0`
- special model event changes including **bioavailability** (`f(depot)=1`), **lag time** (`alag(depot)=0`), **modeled rate** (`rate(depot)=2`) and **modeled duration** (`dur(depot)=2`). An example of these model features and the event specification for the modeled infusions the RxODE data specification is found in RxODE events vignette.
- special **change point syntax, or model times**. These model times are specified by `mtime(var)=time`
- special **Jacobian-derivative** assignments, where the left hand specifies the change in the compartment ode with respect to a variable. For example, if `d/dt(y) = dy`, then a Jacobian for this compartment can be specified as `df(y)/dy(dy) = 1`. There may be some advantage to obtaining the solution or specifying the Jacobian for very stiff ODE systems. However, for the few stiff systems we tried with LSODA, this actually slightly slowed down the solving.

Note that assignment can be done by =, <- or ~.

When assigning with the ~ operator, the **simple assignments** and **time-derivative** assignments will not be output.

Special statements can be:

- **Compartment declaration statements**, which can change the default dosing compartment and the assumed compartment number(s) as well as add extra compartment names at the end (useful for multiple-endpoint nlmixr models); These are specified by `cmt(compartmentName)`
- **Parameter declaration statements**, which can make sure the input parameters are in a certain order instead of ordering the parameters by the order they are parsed. This is useful for keeping the parameter order the same when using 2 different ODE models. These are specified by `param(par1,par2,...)`

An example model is shown below:

```
# simple assignment
C2 = centr/V2;

# time-derivative assignment
d/dt(centr) = F*KA*depot - CL*C2 - Q*C2 + Q*C3;
```

Expressions in assignment and `if` statements can be numeric or logical, however, no character nor integer 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`, `abs`).

You may also access the R's functions in the R math libraries, like `lgammafn` for the log gamma function.

The `RxODE` syntax is case-sensitive, i.e., `ABC` is different than `abc`, `Abc`, `ABc`, etc.

Identifiers:

Like R, Identifiers (variable names) may consist of one or more alphanumeric, underscore _ or period . characters, but the first character cannot be a digit or underscore _.

Identifiers in a model specification can refer to:

- State variables in the dynamic system (e.g., compartments in a pharmacokinetics model).

- Implied input variable, t (time), tlast (last time point), and podo (oral dose, in the undocumented case of absorption transit models).
- Special constants like pi or R's predefined constants.
- Model parameters (e.g., ka rate of absorption, CL clearance, etc.)
- Others, as created by assignments as part of the model specification; these are referred as *LHS* (left-hand side) variable.

Currently, the RxODE modeling language only recognizes system state variables and "parameters", thus, any values that need to be passed from R to the ODE model (e.g., age) should be either passed in the params argument of the integrator function rxSolve() or be in the supplied event data-set.

There are certain variable names that are in the RxODE event tables. To avoid confusion, the following event table-related items cannot be assigned, or used as a state but can be accessed in the RxODE code:

- cmt
- dvid
- addl
- ss
- rate
- id

However the following variables are cannot be used in a model specification:

- evid
- ii

Sometimes RxODE generates variables that are fed back to RxODE. Similarly, nlmixr generates some variables that are used in nlmixr estimation and simulation. These variables start with the either the rx or nlmixr prefixes. To avoid any problems, it is suggested to not use these variables starting with either the rx or nlmixr prefixes.

Logical Operators:

Logical operators support the standard R operators ==, != >= <= > and <. Like R these can be in if() or while() statements, ifelse() expressions. Additionally they can be in a standard assignment. For instance, the following is valid:

```
cov1 = covm*(sexf == "female") + covm*(sexf != "female")
```

Notice that you can also use character expressions in comparisons. This convenience comes at a cost since character comparisons are slower than numeric expressions. Unlike R, as.numeric or as.integer for these logical statements is not only not needed, but will cause an syntax error if you try to use the function.

Value

An object (environment) of class RxODE (see Chambers and Temple Lang (2001)) consisting of the following list of strings and functions:

```
* `model` a character string holding the source model specification.
* `get.modelVars`a function that returns a list with 3 character
    vectors, `params`, `state`, and `lhs` of variable names used in the model
```

specification. These will be output when the model is computed (i.e., the ODE solved by integration).

* `solve`{this function solves (integrates) the ODE. This
    is done by passing the code to [rxSolve()].
    This is as if you called `rxSolve(RxODEobject, ...)`,
    but returns a matrix instead of a rxSolve object.

    `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);

    `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).

    `trans_abs`: a logical (`FALSE` by default) indicating
    whether to fit a transit absorption term
    (TODO: need further documentation and example);

    `atol`: a numeric absolute tolerance (1e-08 by default);

    `rtol`: a numeric relative tolerance (1e-06 by default).e

    The output of \dQuote{solve} is a matrix with as many rows as there
    are sampled time points and as many columns as system variables
    (as defined by the ODEs and additional assignments in the RxODE model
        code).}

* `isValid` a function that (naively) checks for model validity,
    namely that the C object code reflects the latest model

```
    specification.
* `version` a string with the version of the `RxODE`
    object (not the package).
* `dynLoad` a function with one `force = FALSE` argument
    that dynamically loads the object code if needed.
* `dynUnload` a function with no argument that unloads
    the model object code.
* `delete` removes all created model files, including C and DLL files.
    The model object is no longer valid and should be removed, e.g.,
    `rm(m1)`.
* `run` deprecated, use `solve`.
* `get.index` deprecated.
* `getObj` internal (not user callable) function.
```

Author(s)

Melissa Hallow, Wenping Wang and Matthew Fidler

References

Chamber, J. M. and Temple Lang, D. (2001) *Object Oriented Programming in R*. R News, Vol. 1, No. 3, September 2001. https://cran.r-project.org/doc/Rnews/Rnews_2001-3.pdf.

Hindmarsh, A. C. *ODEPACK, A Systematized Collection of ODE Solvers*. Scientific Computing, R. S. Stepleman et al. (Eds.), North-Holland, Amsterdam, 1983, pp. 55-64.

Petzold, L. R. *Automatic Selection of Methods for Solving Stiff and Nonstiff Systems of Ordinary Differential Equations*. Siam J. Sci. Stat. Comput. 4 (1983), pp. 136-148.

Hairer, E., Norsett, S. P., and Wanner, G. *Solving ordinary differential equations I, nonstiff problems*. 2nd edition, Springer Series in Computational Mathematics, Springer-Verlag (1993).

Plevyak, J. dparser, http://dparser.sourceforge.net. Web. 12 Oct. 2015.

See Also

eventTable(), et(), add.sampling(), add.dosing()

Examples

```
# Step 1 - Create a model specification
ode <- "
   # A 4-compartment model, 3 PK and a PD (effect) compartment
   # (notice state variable names 'depot', 'centr', 'peri', 'eff')

   C2 = centr/V2;
   C3 = peri/V3;
   d/dt(depot) =-KA*depot;
   d/dt(centr) = KA*depot - CL*C2 - Q*C2 + Q*C3;
   d/dt(peri)  =                    Q*C2 - Q*C3;
   d/dt(eff)  = Kin - Kout*(1-C2/(EC50+C2))*eff;
"
```

```
m1 <- RxODE(model = ode)
print(m1)

# Step 2 - Create the model input as an EventTable,
# including dosing and observation (sampling) events

# QD (once daily) dosing for 5 days.

qd <- eventTable(amount.units = "ug", time.units = "hours")
qd$add.dosing(dose = 10000, nbr.doses = 5, dosing.interval = 24)

# Sample the system hourly during the first day, every 8 hours
# then after

qd$add.sampling(0:24)
qd$add.sampling(seq(from = 24 + 8, to = 5 * 24, by = 8))

# Step 3 - set starting parameter estimates and initial
# values of the state

theta <-
  c(
    KA = .291, CL = 18.6,
    V2 = 40.2, Q = 10.5, V3 = 297.0,
    Kin = 1.0, Kout = 1.0, EC50 = 200.0
  )

# init state variable
inits <- c(0, 0, 0, 1)
# Step 4 - Fit the model to the data

qd.cp <- m1$solve(theta, events = qd, inits)

head(qd.cp)

# This returns a matrix.  Note that you can also
# solve using name initial values. For example:

inits <- c(eff = 1)
qd.cp <- solve(m1, theta, events = qd, inits)
print(qd.cp)

plot(qd.cp)
```

---

rxOptExpr *Optimize RxODE for computer evaluation*

Description

This optimizes RxODE code for computer evaluation by only calculating redundant expressions once.

Usage

```
rxOptExpr(x, msg = "model")
```

Arguments

x	RxODE model that can be accessed by rxNorm
msg	This is the name of type of object that RxODE is optimizing that will in the message when optimizing. For example "model" will produce the following message while optimizing the model: finding duplicate expressions in model...

Value

Optimized RxODE model text. The order and type lhs and state variables is maintained while the evaluation is sped up. While parameters names are maintained, their order may be modified.

Author(s)

Matthew L. Fidler

---

rxParams *Parameters specified by the model*

Description

This returns the model's parameters that are required to solve the ODE system, and can be used to pipe parameters into an RxODE solve

Usage

```
rxParams(obj, ...)

## S3 method for class 'RxODE'
rxParams(
  obj,
  constants = TRUE,
  ...,
  params = NULL,
  inits = NULL,
  iCov = NULL,
  keep = NULL,
  thetaMat = NULL,
```

```
  omega = NULL,
  dfSub = NULL,
  sigma = NULL,
  dfObs = NULL,
  nSub = NULL,
  nStud = NULL
)

## S3 method for class 'rxSolve'
rxParams(
  obj,
  constants = TRUE,
  ...,
  params = NULL,
  inits = NULL,
  iCov = NULL,
  keep = NULL,
  thetaMat = NULL,
  omega = NULL,
  dfSub = NULL,
  sigma = NULL,
  dfObs = NULL,
  nSub = NULL,
  nStud = NULL
)

## S3 method for class 'rxEt'
rxParams(
  obj,
  ...,
  params = NULL,
  inits = NULL,
  iCov = NULL,
  keep = NULL,
  thetaMat = NULL,
  omega = NULL,
  dfSub = NULL,
  sigma = NULL,
  dfObs = NULL,
  nSub = NULL,
  nStud = NULL
)

rxParam(obj, ...)
```

Arguments

obj	RxODE family of objects

...	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.
constants	is a boolean indicting if constants should be included in the list of parameters. Currently RxODE parses constants into variables in case you wish to change them without recompiling the RxODE model.
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;
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);
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.
thetaMat	Named theta matrix.
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.
dfSub	Degrees of freedom to sample the between subject variability matrix from the inverse Wishart distribution (scaled) or scaled inverse chi squared distribution.
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.
dfObs	Degrees of freedom to sample the unexplained variability matrix from the inverse Wishart distribution (scaled) or scaled inverse chi squared distribution.
nSub	Number between subject variabilities (ETAs) simulated for every realization of the parameters.
nStud	Number virtual studies to characterize uncertainty in estimated parameters.

Value

When extracting the parameters from an RxODE model, a character vector listing the parameters in the model.

Author(s)

Matthew L.Fidler

rxPkg *Creates a package from compiled RxODE models*

Description

Creates a package from compiled RxODE models

Usage

```
rxPkg(
  ...,
  package,
  wd = getwd(),
  action = c("install", "build", "binary", "create"),
  license = c("gpl3", "lgpl", "mit", "agpl3"),
  name = "Firstname Lastname",
  fields = list()
)
```

Arguments

...	Models to build a package from
package	String of the package name to create
wd	character string with a working directory where to create a subdirectory according to modName. When specified, a subdirectory named after the "modName.d" will be created and populated with a C file, a dynamic loading library, plus various other working files. If missing, the files are created (and removed) in the temporary directory, and the RxODE DLL for the model is created in the current directory named rx_????_platform, for example rx_129f8f97fb94a87ca49ca8dafe691e1e_i386.dll
action	Type of action to take after package is created
license	is the type of license for the package.
name	Full name of author
fields	A named list of fields to add to DESCRIPTION, potentially overriding default values. See use_description() for how you can set personalized defaults using package options

Value

this function returns nothing and is used for its side effects

Author(s)

Matthew Fidler

rxpois *Simulate random Poisson variable from threefry generator*

Description

Care should be taken with this method not to encounter the birthday problem, described https://www.johndcook.com/blog/2016/01/29/random-number-generator-seed-mistakes/. Since the sitmo threefry, this currently generates one random deviate from the uniform distribution to seed the engine threefry and then run the code.

Usage

```
rxpois(lambda, n = 1L, ncores = 1L)
```

Arguments

lambda	vector of (non-negative) means.
n	number of random values to return.
ncores	Number of cores for the simulation rxnorm simulates using the threefry sitmo generator; rxnormV uses the vandercorput generator

Details

Therefore, a simple call to the random number generated followed by a second call to random number generated may have identical seeds. As the number of random number generator calls are increased the probability that the birthday problem will increase.

The key to avoid this problem is to either run all simulations in the RxODE environment once (therefore one seed or series of seeds for the whole simulation), pre-generate all random variables used for the simulation, or seed the RxODE engine with rxSetSeed()

Also care should be made that the computer you will be running on can run the same number of cores as you are running so they can reproduce your results.

Value

poission random number deviates

Examples

```
## Use threefry engine

rxpois(lambda = 3, n = 10) # with rxpois you have to explicitly state n
rxpois(lambda = 3, n = 10, ncores = 2) # You can parallelize the simulation using openMP

rxpois(4) ## The first arguments are the lambda parameter
```

```
## This example uses `rxpois` directly in the model

rx <- RxODE({
  a <- rxpois(3)
})

et <- et(1, id = 1:2)

s <- rxSolve(rx, et)
```

---

rxPp *Simulate a from a Poisson process*

Description

Simulate a from a Poisson process

Usage

```
rxPp(
  n,
  lambda,
  gamma = 1,
  prob = NULL,
  t0 = 0,
  tmax = Inf,
  randomOrder = FALSE
)
```

Arguments

n	Number of time points to simulate in the Poisson process
lambda	Rate of Poisson process
gamma	Asymmetry rate of Poisson process. When gamma=1.0, this simulates a homogenous Poisson process. When gamma<1.0, the Poisson process has more events early, when gamma > 1.0, the Poisson process has more events late in the process. When gamma is non-zero, the tmax should not be infinite but indicate the end of the Poisson process to be simulated. In most pharamcometric cases, this will be the end of the study. Internally this uses a rate of: l(t) = lambda*gamma*(t/tmax)^(gamma-1)
prob	When specified, this is a probability function with one argument, time, that gives the probability that a Poisson time t is accepted as a rejection time.
t0	the starting time of the Poisson process

tmax	the maximum time of the Poisson process
randomOrder	when TRUE randomize the order of the Poisson events. By default (FALSE) it returns the Poisson process is in order of how the events occurred.

Value

This returns a vector of the Poisson process times; If the dropout is >= tmax, then all the rest of the times are = tmax to indicate the dropout is equal to or after tmax.

Author(s)

Matthew Fidler

Examples

```
## Sample homogenous Poisson process of rate 1/10
rxPp(10, 1 / 10)

## Sample inhomogenous Poisson rate of 1/10

rxPp(10, 1 / 10, gamma = 2, tmax = 100)

## Typically the Poisson process times are in a sequential order,
## using randomOrder gives the Poisson process in random order

rxPp(10, 1 / 10, gamma = 2, tmax = 10, randomOrder = TRUE)

## This uses an arbitrary function to sample a non-homogenous Poisson process

rxPp(10, 1 / 10, prob = function(x) {
  1 / x
})
```

---

rxProgress *RxODE progress bar functions*

Description

rxProgress sets up the progress bar

Usage

```
rxProgress(num, core = 0L)

rxTick()

rxProgressStop(clear = TRUE)

rxProgressAbort(error = "Aborted calculation")
```

Arguments

num	Tot number of operations to track
core	Number of cores to show. If below 1, don't show number of cores
clear	Boolean telling if you should clear the progress bar after completion (as if it wasn't displayed). By default this is TRUE
error	With rxProgressAbort this is the error that is displayed

Details

rxTick is a progress bar tick

rxProgressStop stop progress bar

rxProgressAbort shows an abort if rxProgressStop wasn't called.

Value

All return NULL invisibly.

Author(s)

Matthew L. Fidler

Examples

```
f <- function() {
  on.exit({
    rxProgressAbort()
  })
  rxProgress(100)
  for (i in 1:100) {
    rxTick()
    Sys.sleep(1 / 100)
  }
  rxProgressStop()
}

f()
```

---

rxRandNV *Create a random "normal" matrix using vandercorput generator*

Description

Create a random "normal" matrix using vandercorput generator

Usage

```
rxRandNV(nrow = 1, ncol = 1)
```

Arguments

nrow	Number of rows
ncol	Number of Columns

Value

Matrix of random numbers

Author(s)

Matthew Fidler

Examples

```
rxRandNV(1, 1)
rxRandNV(3, 2)
```

---

rxRateDur *Creates a rxRateDur object*

Description

This is primarily to display information about rate

Usage

```
rxRateDur(x)

## S3 method for class 'rxRateDur'
x[...]

as.rxRateDur(x)

## S3 method for class 'rxRateDur'
as.character(x, ...)

## S3 method for class 'rxRateDur'
x[[...]]
```

Arguments

x	rxRateDur data
...	Other parameters

Value

rxRateDur object

`rxReservedKeywords` *A list and description of Rode supported reserved keywords*

Description

A list and description of Rode supported reserved keywords

Usage

```
rxReservedKeywords
```

Format

A data frame with 3 columns and 98 or more rows

Reserved Name Reserved Keyword Name

Meaning Reserved Keyword Meaning

Alias Keyword Alias

`rxRmvn` *Simulate from a (truncated) multivariate normal*

Description

This is simulated with the fast, thread-safe threefry simulator and can use multiple cores to generate the random deviates.

Usage

```
rxRmvn(
  n,
  mu = NULL,
  sigma,
  lower = -Inf,
  upper = Inf,
  ncores = 1,
  isChol = FALSE,
  keepNames = TRUE,
  a = 0.4,
  tol = 2.05,
  nlTol = 1e-10,
  nlMaxiter = 100L
)
```

Arguments

n	Number of random row vectors to be simulated OR the matrix to use for simulation (faster).
mu	mean vector
sigma	Covariance matrix for multivariate normal or a list of covariance matrices. If a list of covariance matrix, each matrix will simulate n matrices and combine them to a full matrix
lower	is a vector of the lower bound for the truncated multivariate norm
upper	is a vector of the upper bound for the truncated multivariate norm
ncores	Number of cores used in the simulation
isChol	A boolean indicating if sigma is a cholesky decomposition of the covariance matrix.
keepNames	Keep the names from either the mean or covariance matrix.
a	threshold for switching between methods; They can be tuned for maximum speed; There are three cases that are considered: case 1: a < l < u case 2: l < u < -a case 3: otherwise where l=lower and u = upper
tol	When case 3 is used from the above possibilities, the tol value controls the acceptance rejection and inverse-transformation; When abs(u-l)>tol, uses accept-reject from randn
nlTol	Tolerance for newton line-search
nlMaxiter	Maximum iterations for newton line-search

Value

If n==integer (default) the output is an (n x d) matrix where the i-th row is the i-th simulated vector.

If is.matrix(n) then the random vector are store in n, which is provided by the user, and the function returns NULL invisibly.

Author(s)

Matthew Fidler, Zdravko Botev and some from Matteo Fasiolo

References

John K. Salmon, Mark A. Moraes, Ron O. Dror, and David E. Shaw (2011). Parallel Random Numbers: As Easy as 1, 2, 3. D. E. Shaw Research, New York, NY 10036, USA.

The thread safe multivariate normal was inspired from the mvnfast package by Matteo Fasiolo https://CRAN.R-project.org/package=mvnfast

The concept of the truncated multivariate normal was taken from Zdravko Botev Botev (2017) doi: 10.1111/rssb.12162 and Botev and L'Ecuyer (2015) doi: 10.1109/WSC.2015.7408180 and converted to thread safe simulation;

Examples

```
## From mvnfast
## Unlike mvnfast, uses threefry simulation

d <- 5
mu <- 1:d

# Creating covariance matrix
tmp <- matrix(rnorm(d^2), d, d)
mcov <- tcrossprod(tmp, tmp)


set.seed(414)
rxRmvn(4, 1:d, mcov)

set.seed(414)
rxRmvn(4, 1:d, mcov)

set.seed(414)
rxRmvn(4, 1:d, mcov, ncores = 2) # r.v. generated on the second core are different

###### Here we create the matrix that will hold the simulated
#  random variables upfront.
A <- matrix(NA, 4, d)
class(A) <- "numeric" # This is important. We need the elements of A to be of class "numeric".

set.seed(414)
rxRmvn(A, 1:d, mcov, ncores = 2) # This returns NULL ...
A # ... but the result is here

## You can also simulate from a truncated normal:

rxRmvn(10, 1:d, mcov, lower = 1:d - 1, upper = 1:d + 1)


# You can also simulate from different matrices (if they match
# dimensions) by using a list of matrices.

matL <- lapply(1:4, function(...) {
  tmp <- matrix(rnorm(d^2), d, d)
  tcrossprod(tmp, tmp)
})


rxRmvn(4, setNames(1:d, paste0("a", 1:d)), matL)
```

---

rxS *Load a model into a symengine environment*

Description

Load a model into a symengine environment

Usage

```
rxS(x, doConst = TRUE, promoteLinSens = FALSE)
```

Arguments

x	RxODE object
doConst	Load constants into the environment as well.
promoteLinSens	Promote solved linear compartment systems to sensitivity-based solutions.

Value

RxODE/symengine environment

Author(s)

Matthew Fidler

---

rxSetIni0 *Set Initial conditions to time zero instead of the first observed/dosed time*

Description

Set Initial conditions to time zero instead of the first observed/dosed time

Usage

```
rxSetIni0(ini0 = TRUE)
```

Arguments

ini0	When TRUE (default), set initial conditions to time zero. Otherwise the initial conditions are the first observed time.

Value

the boolean ini0, though this is called for its side effects

rxSetProd *Defunct setting of product*

Description

Defunct setting of product

Usage

```
rxSetProd(type = c("long double", "double", "logify"))
```

Arguments

type	used to be type of product

Value

nothing

rxSetProgressBar *Set timing for progress bar*

Description

Set timing for progress bar

Usage

```
rxSetProgressBar(seconds = 1)
```

Arguments

seconds	This sets the number of seconds that need to elapse before drawing the next segment of the progress bar. When this is zero or below this turns off the progress bar.

Value

nothing, used for side effects

Author(s)

Matthew Fidler

`rxSetSeed` *Set the parallel seed for RxODE random number generation*

Description

This sets the seed for the RxODE parallel random number generation. If set, then whenever a seed is set for the threefry or vandercorput simulation engine, it will use this seed, increment for the number of seeds and continue with the sequence the next time the random number generator is called.

Usage

```
rxSetSeed(seed)
```

Arguments

`seed`	An integer that represents the RxODE parallel and internal random number generator seed. When positive, use this seed for random number generation and increment and reseed any parallel or new engines that are being called. When negative, turn off the RxODE seed and generate a seed from the R's uniform random number generator. Best practice is to set this seed.

Details

In contrast, when this is not called, the time that the vandercorput or threefry simulation engines are seeded it comes from a uniform random number generated from the standard R random seed. This may cause a duplicate seed based on the R seed state. This means that there could be correlations between simulations that do not exist This will avoid the birthday problem picking exactly the same seed using the seed state of the R random number generator. The more times the seed is called, the more likely this becomes.

Value

Nothing, called for its side effects

Author(s)

Matthew Fidler

References

JD Cook. (2016). Random number generator seed mistakes. https://tinyurl.com/m62v3kv9

Examples

```
rxSetSeed(42)

# seed with generator 42
rxnorm()

# Use R's random number generator
rnorm(1)

rxSetSeed(42)

# reproduces the same number
rxnorm()

# But R's random number is not the same

rnorm(1)

# If we reset this to use the R's seed
# (internally RxODE uses a uniform random number to span seeds)
# This can lead to duplicate sequences and seeds

rxSetSeed(-1)

# Now set seed works for both.

# This is not recommended, but illustrates the different types of
# seeds that can be generated.

set.seed(42)

rxnorm()

rnorm(1)

set.seed(42)

rxnorm()

rnorm(1)
```

`rxSetSum` *Defunct setting of sum*

Description

Defunct setting of sum

Usage

```
rxSetSum(type = c("pairwise", "fsum", "kahan", "neumaier", "c"))
```

Arguments

type	used to be type of product

Value

nothing

---

rxShiny *Use Shiny to help develop an RxODE model*

Description

Use Shiny to help develop an RxODE model

Usage

```
rxShiny(
  object,
  params = NULL,
  events = NULL,
  inits = NULL,
  ...,
  data = data.frame()
)

## S3 method for class 'rxSolve'
rxShiny(
  object,
  params = NULL,
  events = NULL,
  inits = NULL,
  ...,
  data = data.frame()
)

## Default S3 method:
rxShiny(
  object = NULL,
  params = NULL,
  events = NULL,
  inits = NULL,
  ...,
  data = data.frame()
)
```

Arguments

object	A RxODE family of objects. If not supplied a 2-compartment indirect effect model is used. If it is supplied, use the model associated with the RxODE object for the model exploration.
params	Initial parameters for model
events	Event information (currently ignored)
inits	Initial estimates for model
...	Other arguments passed to rxShiny. Currently doesn't do anything.
data	Any data that you would like to plot. If the data has a time variable as well as a compartment or calculated variable that matches the RxODE model, the data will be added to the plot of a specific compartment or calculated variable.

Value

Nothing; Starts a shiny server

Author(s)

Zufar Mulyukov and Matthew L. Fidler

---

rxSimThetaOmega *Simulate Parameters from a Theta/Omega specification*

Description

Simulate Parameters from a Theta/Omega specification

Usage

```
rxSimThetaOmega(
  params = NULL,
  omega = NULL,
  omegaDf = NULL,
  omegaLower = as.numeric(c(R_NegInf)),
  omegaUpper = as.numeric(c(R_PosInf)),
  omegaIsChol = FALSE,
  omegaSeparation = "auto",
  omegaXform = 1L,
  nSub = 1L,
  thetaMat = NULL,
  thetaLower = as.numeric(c(R_NegInf)),
  thetaUpper = as.numeric(c(R_PosInf)),
  thetaDf = NULL,
  thetaIsChol = FALSE,
  nStud = 1L,
```

```
  sigma = NULL,
  sigmaLower = as.numeric(c(R_NegInf)),
  sigmaUpper = as.numeric(c(R_PosInf)),
  sigmaDf = NULL,
  sigmaIsChol = FALSE,
  sigmaSeparation = "auto",
  sigmaXform = 1L,
  nCoresRV = 1L,
  nObs = 1L,
  dfSub = 0,
  dfObs = 0,
  simSubjects = TRUE
)
```

Arguments

params	Named Vector of RxODE model parameters
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.
omegaLower	Lower bounds for simulated ETAs (by default -Inf)
omegaUpper	Upper bounds for simulated ETAs (by default Inf)
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.

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

thetaMat — Named theta matrix.

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

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

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.

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.

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

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

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

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.

`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.

`nObs` Number of observations to simulate (with `sigma` matrix)

`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.

`simSubjects` boolean indicated RxODE should simulate subjects in studies (`TRUE`, default) or studies (`FALSE`)

Value

a data frame with the simulated subjects

Author(s)

Matthew L.Fidler

`rxSolve` *Solving & Simulation of a ODE/solved system (and solving options) equation*

Description

This uses RxODE family of objects, file, or model specification to solve a ODE system. There are many options for a solved RxODE model, the first are the required `object`, and `events` with the some-times optional `params` and `inits`.

Usage

```
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,
  maxwhile = 1e+05
)

## Default S3 method:
rxSolve(
  object,
  params = NULL,
  events = NULL,
  inits = NULL,
  ...,
  theta = NULL,
  eta = NULL
)

## S3 method for class 'rxSolve'
update(object, ...)

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

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

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

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

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

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

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

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

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

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

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

rxControl(..., params = NULL, events = NULL, inits = NULL)
```

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.
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.

`...` 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.

`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 withmethod="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`.

`maxwhile` represents the maximum times a while loop is evaluated before exiting. By default this is 100000

`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

Details

The rest of the document focus on the different ODE solving methods, followed by the core solving method's options, RxODE event handling options, RxODE's numerical stability options, RxODE's output options, and finally internal RxODE options or compatibility options.

Value

An "rxSolve" solve object that stores the solved value in a special data.frame or other type as determined by `returnType`. By default this has as many rows as there are sampled time points and as many columns as system variables (as defined by the ODEs and additional assignments in the

RxODE model code). It also stores information about the call to allow dynamic updating of the solved object.

The operations for the object are similar to a data-frame, but expand the $ and [[""]] access operators and assignment operators to resolve based on different parameter values, initial conditions, solver parameters, or events (by updating the `time` variable).

You can call the `eventTable()` methods on the solved object to update the event table and resolve the system of equations.

Author(s)

Matthew Fidler, Melissa Hallow and Wenping Wang

References

"New Scaling and Squaring Algorithm for the Matrix Exponential", by Awad H. Al-Mohy and Nicholas J. Higham, August 2009

Roger B. Sidje (1998). EXPOKIT: Software package for computing matrix exponentials. ACM - Transactions on Mathematical Software *24*(1), 130-156.

Hindmarsh, A. C. *ODEPACK, A Systematized Collection of ODE Solvers*. Scientific Computing, R. S. Stepleman et al. (Eds.), North-Holland, Amsterdam, 1983, pp. 55-64.

Petzold, L. R. *Automatic Selection of Methods for Solving Stiff and Nonstiff Systems of Ordinary Differential Equations*. Siam J. Sci. Stat. Comput. 4 (1983), pp. 136-148.

Hairer, E., Norsett, S. P., and Wanner, G. *Solving ordinary differential equations I, nonstiff problems*. 2nd edition, Springer Series in Computational Mathematics, Springer-Verlag (1993).

See Also

`RxODE()`

`rxStack` *Stack a solved object for things like ggplot*

Description

Stack a solved object for things like ggplot

Usage

```
rxStack(Data, vars = NULL)
```

Arguments

`Data`	is a RxODE object to be stacked.
`vars`	Variables to include in stacked data; By default this is all the variables when vars is NULL.

Value

Stacked data with `value` and `trt`, where value is the values and `trt` is the state and `lhs` variables.

Author(s)

Matthew Fidler

`rxState` *State variables*

Description

This returns the model's compartments or states.

Usage

```
rxState(obj = NULL, state = NULL)
```

Arguments

`obj`	RxODE family of objects
`state`	is a string indicating the state or compartment that you would like to lookup.

Value

If state is missing, return a character vector of all the states.

If state is a string, return the compartment number of the named state.

Author(s)

Matthew L.Fidler

See Also

`RxODE()`

rxSumProdModel *Recast model in terms of sum/prod*

Description

Recast model in terms of sum/prod

Usage

```
rxSumProdModel(model, expand = FALSE, sum = TRUE, prod = TRUE)
```

Arguments

model	RxODE model
expand	Boolean indicating if the expression is expanded.
sum	Use sum(...)
prod	Use prod(...)

Value

model string with prod(.) and sum(.) for all these operations.

Author(s)

Matthew L. Fidler

rxSupportedFuns *Get list of supported functions*

Description

Get list of supported functions

Usage

```
rxSupportedFuns()
```

Value

list of supported functions in RxODE

Examples

```
rxSupportedFuns()
```

`rxSuppressMsg` *Respect suppress messages*

Description

This turns on the silent REprintf in C when `suppressMessages()` is turned on. This makes the `REprintf` act like `messages` in R, they can be suppressed with `suppressMessages()`

Usage

```
rxSuppressMsg()
```

Value

Nothing

Author(s)

Matthew Fidler

Examples

```
# rxSupressMsg() is called with RxODE()

# Note the errors are output to the console

try(RxODE("d/dt(matt)=/3"), silent = TRUE)

# When using suppressMessages, the output is suppressed

suppressMessages(try(RxODE("d/dt(matt)=/3"), silent = TRUE))

# In RxODE, we use REprintf so that interrupted threads do not crash R
# if there is a user interrupt. This isn't captured by R's messages, but
# This interface allows the `suppressMessages()` to suppress the C printing
# as well

# If you  want to suppress messages from RxODE in other packages, you can use
# this function
```

rxSymInvChol *Get Omega^-1 and derivatives*

Description

Get Omega^-1 and derivatives

Usage

```
rxSymInvChol(
  invObjOrMatrix,
  theta = NULL,
  type = "cholOmegaInv",
  thetaNumber = 0L
)
```

Arguments

invObjOrMatrix	Object for inverse-type calculations. If this is a matrix, setup the object for inversion rxSymInvCholCreate() with the default arguments and return a reactive s3 object. Otherwise, use the inversion object to calculate the requested derivative/inverse.
theta	Thetas to be used for calculation. If missing (NULL), a special s3 class is created and returned to access Omega^1 objects as needed and cache them based on the theta that is used.
type	The type of object. Currently the following types are supported: • cholOmegaInv gives the Cholesky decomposition of the Omega Inverse matrix. • omegaInv gives the Omega Inverse matrix. • d(omegaInv) gives the d(Omega^-1) withe respect to the theta parameter specified in thetaNumber. • d(D) gives the d(diagonal(Omega^-1)) with respect to the theta parameter specified in the thetaNumber parameter
thetaNumber	For types d(omegaInv) and d(D), the theta number that the derivative is taken against. This must be positive from 1 to the number of thetas defining the Omega matrix.

Value

Matrix based on parameters or environment with all the matrixes calculated in variables omega, omegaInv, dOmega, dOmegaInv.

Author(s)

Matthew L. Fidler

rxSyncOptions *Sync options with RxODE variables*

Description

Accessing RxODE options via getOption slows down solving. This allows the options to be synced with variables.

Usage

```
rxSyncOptions(setDefaults = c("none", "permissive", "strict"))
```

Arguments

setDefaults	This will setup RxODE's default solving options with the following options: • "none" leave the options alone • "permissive" This is a permissive option set similar to R language specifications. • "strict" This is a strict option set similar to the original RxODE(). It requires semicolons at the end of lines and equals for assignment

Value

nothing; called for side effects

Author(s)

Matthew L. Fidler

rxSyntaxFunctions *A list and description of Rode supported syntax functions*

Description

A list and description of Rode supported syntax functions

Usage

```
rxSyntaxFunctions
```

Format

A data frame with 3 columns and 98 or more rows

Function Reserved function Name

Description Description of function

Aliases Function Aliases

rxt *Simulate student t variable from threefry generator*

Description

Care should be taken with this method not to encounter the birthday problem, described https://www.johndcook.com/blog/2016/01/29/random-number-generator-seed-mistakes/. Since the sitmo threefry, this currently generates one random deviate from the uniform distribution to seed the engine threefry and then run the code.

Usage

```
rxt(df, n = 1L, ncores = 1L)
```

Arguments

df	degrees of freedom (> 0, maybe non-integer). df = Inf is allowed.
n	number of observations. If length(n) > 1, the length is taken to be the number required.
ncores	Number of cores for the simulation rxnorm simulates using the threefry sitmo generator; rxnormV uses the vandercorput generator

Details

Therefore, a simple call to the random number generated followed by a second call to random number generated may have identical seeds. As the number of random number generator calls are increased the probability that the birthday problem will increase.

The key to avoid this problem is to either run all simulations in the RxODE environment once (therefore one seed or series of seeds for the whole simulation), pre-generate all random variables used for the simulation, or seed the RxODE engine with rxSetSeed()

Also care should be made that the computer you will be running on can run the same number of cores as you are running so they can reproduce your results.

Value

t-distribution random numbers

Examples

```
## Use threefry engine

rxt(df = 3, n = 10) # with rxt you have to explicitly state n
rxt(df = 3, n = 10, ncores = 2) # You can parallelize the simulation using openMP
```

```
rxt(4) ## The first argument is the df parameter


## This example uses `rxt` directly in the model

rx <- RxODE({
  a <- rxt(3)
})

et <- et(1, id = 1:2)

s <- rxSolve(rx, et)
```

`rxTempDir` *Get the RxODE temporary directory*

Description

Get the RxODE temporary directory

Usage

```
rxTempDir()
```

Value

RxODE temporary directory.

`rxTheme` *rxTheme is the RxODE theme for plots*

Description

rxTheme is the RxODE theme for plots

Usage

```
rxTheme(
  base_size = 11,
  base_family = "",
  base_line_size = base_size/22,
  base_rect_size = base_size/22,
  grid = TRUE
)
```

Arguments

base_size	base font size, given in pts.
base_family	base font family
base_line_size	base size for line elements
base_rect_size	base size for rect elements
grid	a Boolean indicating if the grid is on (TRUE) or off (FALSE). This could also be a character indicating x or y.

Value

ggplot2 theme used in RxODE

---

rxToSE *RxODE to symengine environment*

Description

RxODE to symengine environment

Usage

```
rxToSE(x, envir = NULL, progress = FALSE, promoteLinSens = TRUE)

.rxToSE(x, envir = NULL, progress = FALSE)

rxFromSE(x, unknownDerivatives = c("forward", "central", "error"))

.rxFromSE(x)
```

Arguments

x	expression
envir	default is NULL; Environment to put symengine variables in.
progress	shows progress bar if true.
promoteLinSens	Promote solved linear compartment systems to sensitivity-based solutions.
unknownDerivatives	When handling derivatives from unknown functions, the translator will translate into different types of numeric derivatives. The currently supported methods are: - `forward` for forward differences - `central` for central differences - `error` for throwing an error for unknown derivatives

Value

An rxode symengine environment

Author(s)

Matthew L. Fidler

`rxTrans` *Translate the model to C code if needed*

Description

This function translates the model to C code, if needed

Usage

```
rxTrans(
  model,
  modelPrefix = "",
  md5 = "",
  modName = NULL,
  modVars = FALSE,
  ...
)

## Default S3 method:
rxTrans(
  model,
  modelPrefix = "",
  md5 = "",
  modName = NULL,
  modVars = FALSE,
  ...
)

## S3 method for class 'character'
rxTrans(
  model,
  modelPrefix = "",
  md5 = "",
  modName = NULL,
  modVars = FALSE,
  ...
)
```

Arguments

model	This is the ODE model specification. It can be: • a string containing the set of ordinary differential equations (ODE) and other expressions defining the changes in the dynamic system. • a file name where the ODE system equation is contained An ODE expression enclosed in \{\} (see also the filename argument). For details, see the sections "Details" and RxODE Syntax below.
modelPrefix	Prefix of the model functions that will be compiled to make sure that multiple RxODE objects can coexist in the same R session.
md5	Is the md5 of the model before parsing, and is used to embed the md5 into DLL, and then provide for functions like rxModelVars().
modName	a string to be used as the model name. This string is used for naming various aspects of the computations, including generating C symbol names, dynamic libraries, etc. Therefore, it is necessary that modName consists of simple ASCII alphanumeric characters starting with a letter.
modVars	returns the model variables instead of the named vector of translated properties.
...	Ignored parameters.

Value

a named vector of translated model properties including what type of jacobian is specified, the C function prefixes, as well as the C functions names to be called through the compiled model.

Author(s)

Matthew L.Fidler

See Also

RxODE(), rxCompile().

---

rxunif *Simulate uniform variable from threefry generator*

Description

Care should be taken with this method not to encounter the birthday problem, described https://www.johndcook.com/blog/2016/01/29/random-number-generator-seed-mistakes/. Since the sitmo threefry, this currently generates one random deviate from the uniform distribution to seed the engine threefry and then run the code.

Usage

```
rxunif(min = 0, max = 1, n = 1L, ncores = 1L)
```

Arguments

min	lower and upper limits of the distribution. Must be finite.
max	lower and upper limits of the distribution. Must be finite.
n	number of observations. If length(n) > 1, the length is taken to be the number required.
ncores	Number of cores for the simulation
	rxnorm simulates using the threefry sitmo generator; rxnormV uses the vandercorput generator

Details

Therefore, a simple call to the random number generated followed by a second call to random number generated may have identical seeds. As the number of random number generator calls are increased the probability that the birthday problem will increase.

The key to avoid this problem is to either run all simulations in the RxODE environment once (therefore one seed or series of seeds for the whole simulation), pre-generate all random variables used for the simulation, or seed the RxODE engine with rxSetSeed()

Also care should be made that the computer you will be running on can run the same number of cores as you are running so they can reproduce your results.

Value

uniform random numbers

Examples

```
## Use threefry engine

rxunif(min = 0, max = 4, n = 10) # with rxunif you have to explicitly state n
rxunif(min = 0, max = 4, n = 10, ncores = 2) # You can parallelize the simulation using openMP

rxunif()


## This example uses `rxunif` directly in the model

rx <- RxODE({
  a <- rxunif(0, 3)
})

et <- et(1, id = 1:2)

s <- rxSolve(rx, et)
```

rxUnloadAll *Unloads all RxODE compiled DLLs*

Description

Unloads all RxODE compiled DLLs

Usage

```
rxUnloadAll()
```

Value

List of RxODE dlls still loaded

boolean of if all RxODE dlls have been unloaded

Examples

```
print(rxUnloadAll())
```

rxUse *Use model object in your package*

Description

Use model object in your package

Usage

```
rxUse(obj, overwrite = TRUE, compress = "bzip2", internal = FALSE)
```

Arguments

obj	model to save.
overwrite	By default, use_data() will not overwrite existing files. If you really want to do so, set this to TRUE.
compress	Choose the type of compression used by save(). Should be one of "gzip", "bzip2", or "xz".
internal	If this is run internally. By default this is FALSE

Value

Nothing; This is used for its side effects and shouldn't be called by a user

`rxValidate` *Validate RxODE This allows easy validation/qualification of nlmixr by running the testing suite on your system.*

Description

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

Usage

```
rxValidate(type = NULL)

rxTest(type = NULL)
```

Arguments

`type`	Type of test or filter of test type

Value

nothing

Author(s)

Matthew L. Fidler

`rxweibull` *Simulate Weibull variable from threefry generator*

Description

Care should be taken with this method not to encounter the birthday problem, described https://www.johndcook.com/blog/2016/01/29/random-number-generator-seed-mistakes/. Since the `sitmo threefry`, this currently generates one random deviate from the uniform distribution to seed the engine `threefry` and then run the code.

Usage

```
rxweibull(shape, scale = 1, n = 1L, ncores = 1L)
```

Arguments

shape	shape and scale parameters, the latter defaulting to 1.
scale	shape and scale parameters, the latter defaulting to 1.
n	number of observations. If length(n) > 1, the length is taken to be the number required.
ncores	Number of cores for the simulation rxnorm simulates using the threefry sitmo generator; rxnormV uses the vandercorput generator

Details

Therefore, a simple call to the random number generated followed by a second call to random number generated may have identical seeds. As the number of random number generator calls are increased the probability that the birthday problem will increase.

The key to avoid this problem is to either run all simulations in the RxODE environment once (therefore one seed or series of seeds for the whole simulation), pre-generate all random variables used for the simulation, or seed the RxODE engine with rxSetSeed()

Also care should be made that the computer you will be running on can run the same number of cores as you are running so they can reproduce your results.

Value

Weibull random deviates

Examples

```
## Use threefry engine

# with rxweibull you have to explicitly state n
rxweibull(shape = 1, scale = 4, n = 10)

# You can parallelize the simulation using openMP
rxweibull(shape = 1, scale = 4, n = 10, ncores = 2)

rxweibull(3)


## This example uses `rxweibull` directly in the model

rx <- RxODE({
  a <- rxweibull(1, 3)
})

et <- et(1, id = 1:2)

s <- rxSolve(rx, et)
```

rxWinSetup *Setup Windows components for RxODE*

Description

Setup Windows components for RxODE

Usage

```
rxWinSetup(rm.rtools = TRUE)
```

Arguments

rm.rtools	Remove the Rtools from the current path specs.

Value

nothing, used for its side effects

Author(s)

Matthew L. Fidler

stat_amt *Dosing/Amt geom/stat*

Description

This is a dosing geom that shows the vertical lines where a dose occurs

Usage

```
stat_amt(
  mapping = NULL,
  data = NULL,
  position = "identity",
  show.legend = NA,
  inherit.aes = TRUE,
  ...
)

geom_amt(
  mapping = NULL,
  data = NULL,
  position = "identity",
  show.legend = NA,
```

```
  inherit.aes = TRUE,
  ...
)
```

Arguments

mapping	Set of aesthetic mappings created by aes() or aes_(). If specified and inherit.aes = TRUE (the default), it is combined with the default mapping at the top level of the plot. You must supply mapping if there is no plot mapping.
data	The data to be displayed in this layer. There are three options: If NULL, the default, the data is inherited from the plot data as specified in the call to ggplot(). A data.frame, or other object, will override the plot data. All objects will be fortified to produce a data frame. See fortify() for which variables will be created. A function will be called with a single argument, the plot data. The return value must be a data.frame, and will be used as the layer data. A function can be created from a formula (e.g. ~ head(.x,10)).
position	Position adjustment, either as a string, or the result of a call to a position adjustment function.
show.legend	logical. Should this layer be included in the legends? NA, the default, includes if any aesthetics are mapped. FALSE never includes, and TRUE always includes. It can also be a named logical vector to finely select the aesthetics to display.
inherit.aes	If FALSE, overrides the default aesthetics, rather than combining with them. This is most useful for helper functions that define both data and aesthetics and shouldn't inherit behaviour from the default plot specification, e.g. borders().
...	Other arguments passed on to layer(). These are often aesthetics, used to set an aesthetic to a fixed value, like colour = "red" or size = 3. They may also be parameters to the paired geom/stat.

Details

Requires the following aesthetics:

- x representing the x values, usually time
- amt representing the dosing values; They are missing or zero when no dose is given

Value

This returns a stat_amt in context of a ggplot2 plot

stat_cens *Censoring geom/stat*

Description

This is a censoring geom that shows the left or right censoring specified in the nlmixr input data-set or fit

Usage

```
stat_cens(
  mapping = NULL,
  data = NULL,
  position = "identity",
  show.legend = NA,
  inherit.aes = TRUE,
  width = 0.01,
  ...
)

geom_cens(
  mapping = NULL,
  data = NULL,
  position = "identity",
  show.legend = NA,
  inherit.aes = TRUE,
  width = 0.01,
  ...
)
```

Arguments

mapping	Set of aesthetic mappings created by aes() or aes_(). If specified and inherit.aes = TRUE (the default), it is combined with the default mapping at the top level of the plot. You must supply mapping if there is no plot mapping.
data	The data to be displayed in this layer. There are three options: If NULL, the default, the data is inherited from the plot data as specified in the call to ggplot(). A data.frame, or other object, will override the plot data. All objects will be fortified to produce a data frame. See fortify() for which variables will be created. A function will be called with a single argument, the plot data. The return value must be a data.frame, and will be used as the layer data. A function can be created from a formula (e.g. ~ head(.x,10)).
position	Position adjustment, either as a string, or the result of a call to a position adjustment function.

show.legend	logical. Should this layer be included in the legends? NA, the default, includes if any aesthetics are mapped. FALSE never includes, and TRUE always includes. It can also be a named logical vector to finely select the aesthetics to display.
inherit.aes	If FALSE, overrides the default aesthetics, rather than combining with them. This is most useful for helper functions that define both data and aesthetics and shouldn't inherit behaviour from the default plot specification, e.g. borders().
width	represents the width (in \ censoring box
...	Other arguments passed on to layer(). These are often aesthetics, used to set an aesthetic to a fixed value, like colour = "red" or size = 3. They may also be parameters to the paired geom/stat.

Details

Requires the following aesthetics:

- x Represents the independent variable, often the time scale
- y represents the dependent variable
- CENS for the censoring information; (-1 right censored, 0 no censoring or 1 left censoring)
- LIMIT which represents the corresponding limit ()

Will add boxes representing the areas of the fit that were censored.

Value

This returns a ggplot2 stat

---

summary.RxODE *Print expanded information about the RxODE object.*

Description

This prints the expanded information about the RxODE object.

Usage

```
## S3 method for class 'RxODE'
summary(object, ...)
```

Arguments

object	RxODE object
...	Ignored parameters

Value

object is returned

Author(s)

Matthew L.Fidler

`uppergamma` *uppergamma: upper incomplete gamma function*

Description

This is the tgamma from the boost library

Usage

```
uppergamma(a, z)
```

Arguments

a	The numeric 'a' parameter in the upper incomplete gamma
z	The numeric 'z' parameter in the upper incomplete gamma

Details

The uppergamma function is given by:
$uppergamma(a, z) = \int_z^\infty t^{a-1} \cdot e^{-t} dt$

Value

uppergamma results

Author(s)

Matthew L. Fidler

Examples

```
uppergamma(1, 3)

uppergamma(1:3, 3)

uppergamma(1, 1:3)
```

Index