Package 'crmPack'

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Title Object-oriented implementation of CRM designs

LazyLoad yes

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Description Object-oriented implementation of CRM designs

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Suggests ggmcmc,
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Collate 'helpers.R'
'Data-class.R'
'Data-methods.R'
'Rules-class.R'
'Model-class.R'
'Design-class.R'
'writeModel.R'
'McmcOptions-methods.R'
'McmcOptions-class.R'
'Samples-class.R'
'mcmc.R'

'Simulations-class.R'
'Model-methods.R'
'Rules-methods.R'
'Design-methods.R'
'fromQuantiles.R'
'Samples-methods.R'
'Simulations-methods.R'
'crmPack-package.R'
'crmUpgrade.R'

R topics documented:

`crmPack-package` *Object-oriented implementation of CRM designs*

Description

Object-oriented implementation of CRM designs

Author(s)

Daniel Sabanes Bove <sabanesd@roche.com>

`approximate` *Approximate posterior with (log) normal distribution*

Description

It is recommended to use `set.seed` before, in order to be able to reproduce the resulting approximating model exactly.

Usage

```
approximate(object, model, data, ...)

## S4 method for signature 'Samples'
approximate(object, model, data, points = seq(from =
  min(data@doseGrid), to = max(data@doseGrid), length = 5L),
  refDose = median(points), logNormal = FALSE, verbose = TRUE, ...)
```

Arguments

object	the Samples object
model	the Model object
data	the Data object
points	optional parameter, which gives the dose values at which the approximation should rely on (default: 5 values equally spaced from minimum to maximum of the dose grid)
refDose	the reference dose to be used (default: median of points)
logNormal	use the log-normal prior? (not default) otherwise, the normal prior for the logistic regression coefficients is used
verbose	be verbose (progress statements and plot)? (default)
...	additional arguments (see methods)

Value

the approximation model

Methods (by class)

- Samples: Here the ... argument can transport additional arguments for Quantiles2LogisticNormal, e.g. in order to control the approximation quality, etc.

---

as.list,GeneralData-method

as.list method for the "GeneralData" class

Description

as.list method for the "GeneralData" class

Usage

```
## S4 method for signature 'GeneralData'
as.list(x, ...)
```

Arguments

x	the GeneralData object we want to convert
...	unused

Value

a list of all slots in x

biomLevel — *Compute the biomarker level for a given dose, given model and samples*

Description

Compute the biomarker level for a given dose, given model and samples

Usage

```
biomLevel(dose, model, samples, ...)

## S4 method for signature 'numeric,DualEndpoint,Samples'
biomLevel(dose, model, samples, xLevel,
  ...)
```

Arguments

dose	the dose
model	the DualEndpoint object
samples	the Samples object
xLevel	the grid index of dose
...	unused

Methods (by class)

- dose = numeric,model = DualEndpoint,samples = Samples: Here it is very easy, we just return the corresponding column (index xLevel) of the biomarker samples matrix, since we save that in the samples

CohortSize-class — *The virtual class for cohort sizes*

Description

The virtual class for cohort sizes

See Also

CohortSizeMax, CohortSizeMin, CohortSizeRange, CohortSizeDLT, CohortSizeConst, CohortSizeParts

CohortSizeConst *Initialization function for "CohortSizeConst"*

Description

Initialization function for "CohortSizeConst"

Usage

```
CohortSizeConst(size)
```

Arguments

size	see CohortSizeConst

Value

the CohortSizeConst object

CohortSizeConst-class *Constant cohort size*

Description

This class is used when the cohort size should be kept constant.

Slots

size the constant integer size

CohortSizeDLT *Initialization function for "CohortSizeDLT"*

Description

Initialization function for "CohortSizeDLT"

Usage

```
CohortSizeDLT(DLTintervals, cohortSize)
```

Arguments

DLTintervals	see CohortSizeDLT
cohortSize	see CohortSizeDLT

Value

the CohortSizeDLT object

CohortSizeDLT-class *Cohort size based on number of DLTs*

Description

Cohort size based on number of DLTs

Slots

`DLTintervals` an integer vector with the left bounds of the relevant DLT intervals

`cohortSize` an integer vector of the same length with the cohort sizes in the `DLTintervals`

CohortSizeMax *Initialization function for "CohortSizeMax"*

Description

Initialization function for "CohortSizeMax"

Usage

```
CohortSizeMax(cohortSizeList)
```

Arguments

`cohortSizeList` see `CohortSizeMax`

Value

the `CohortSizeMax` object

CohortSizeMax-class *Size based on maximum of multiple cohort size rules*

Description

This class can be used to combine multiple cohort size rules with the MAX operation.

Details

`cohortSizeList` contains all cohort size rules, which are again objects of class `CohortSize`. The maximum of these individual cohort sizes is taken to give the final cohort size.

Slots

`cohortSizeList` list of cohort size rules

CohortSizeMin *Initialization function for "CohortSizeMin"*

Description

Initialization function for "CohortSizeMin"

Usage

```
CohortSizeMin(cohortSizeList)
```

Arguments

cohortSizeList	see CohortSizeMin

Value

the CohortSizeMin object

CohortSizeMin-class *Size based on minimum of multiple cohort size rules*

Description

This class can be used to combine multiple cohort size rules with the MIN operation.

Details

cohortSizeList contains all cohort size rules, which are again objects of class CohortSize. The minimum of these individual cohort sizes is taken to give the final cohort size.

Slots

cohortSizeList	list of cohort size rules

CohortSizeParts *Initialization function for "CohortSizeParts"*

Description

Initialization function for "CohortSizeParts"

Usage

```
CohortSizeParts(sizes)
```

Arguments

sizes	see CohortSizeParts

Value

the CohortSizeParts object

CohortSizeParts-class *Cohort size based on the parts*

Description

This class is used when the cohort size should change for the second part of the dose escalation. Only works in conjunction with DataParts objects.

Slots

`sizes` the two sizes for part 1 and part 2

CohortSizeRange *Initialization function for "CohortSizeRange"*

Description

Initialization function for "CohortSizeRange"

Usage

```
CohortSizeRange(intervals, cohortSize)
```

Arguments

`intervals`	see CohortSizeRange
`cohortSize`	see CohortSizeRange

Value

the CohortSizeRange object

CohortSizeRange-class *Cohort size based on dose range*

Description

Cohort size based on dose range

Slots

`intervals` a vector with the left bounds of the relevant dose intervals

`cohortSize` an integer vector of the same length with the cohort sizes in the `intervals`

ComboLogistic *Initialization function for the "ComboLogistic" class*

Description

Initialization function for the "ComboLogistic" class

Usage

```
ComboLogistic(singlePriors, gamma, tau)
```

Arguments

singlePriors	a named list where each element is a LogisticLogNormal object, specifying the prior for this drug. The list names are the drug names.
gamma	see ComboLogistic
tau	see ComboLogistic

Value

the ComboLogistic object

ComboLogistic-class *Combo model with logistic regression*

Description

Currently, this model is for double combination dose escalation trials.

Details

todo: Later, it will be extended to higher-order combinations. The model and code is building on the work by Simon Wandel et al (Novartis).

The regression model is defined as follows. Let $odds(p) = p/(1-p)$ be the odds transformation of the probability p, such that $logit(p) = log(odds(p))$. Let x_i be the dose of drug i=1,2, and $p(x_1, x_2)$ be the probability of DLT with doses x_1 and x_2. The reference doses for the two compounds are again denoted by stars. Then the model assumes:

$$odds(p(x_1, x_2)) = odds(p_0(x_1, x_2)) \cdot \exp(\eta x_1/x_1^* x_2/x_2^*),$$

where η is the interaction coefficient (positive values correspond to synergistic toxicity, zero corresponds to additive effect without interaction, and negative values correspond to antagonistic toxicity). A normal prior

$$\eta \sim Normal(\gamma, \tau^-1)$$

is used. Under no interaction with $\eta = 0$, this reduces the probability $\eta odds(p(x_1, x_2))$ to

$$p_0(x_1, x_2) = p(x_1) + p(x_2) - p(x_1)p(x_2) = 1 - (1 - p(x_1))(1 - p(x_2)).$$

Now for the single-agent DLT probabilities $p(x_1)$ and $p(x_2)$ we assume the logistic log-normal models (compare LogisticLogNormal):

$$logit[p(x_i)] = \alpha_i + \beta_i \cdot \log(x_i/x_i^*),$$

with prior

$$(\alpha_i, \log(\beta_i)) \sim Normal(\mu_i, \Sigma_i)$$

for $i = 1, 2$. todo: Note that in principle any model could be used for the individual agents. For now we stick to this simple, fixed implementation.

The prob function has as first argument dose, which is either a single dose combination (a vector with names specifying the drug names) or multiple dose combinations in rows of a matrix (with the column names specifying the drug names). Additional arguments are the model parameters alpha0 (intercepts, nSamples x nDrugs matrix), alpha1 (slopes, nSamples x nDrugs matrix) and eta (vector of length nSamples), containing the nSamples MCMC samples. Then prob computes the resulting samples of the probability of toxicity at that dose combination(s) (nSamples x nCombinations).

Slots

singlePriors a list with one LogisticLogNormal model per drug specifying the bivariate log normal prior described above. The names of this list are the drug names for this model - they have to be specified correctly in any interactions with the model object (e.g. when calling the prob function).

gamma the mean for the interaction parameter

tau the precision for the interaction parameter

prob function calculating the probability of toxicity for a specific dose combination, based on the model parameters (see the details above)

---

crmPackExample *Open the example pdf for crmPack*

Description

Calling this helper function should open the example.pdf document, residing in the doc subfolder of the package installation directory.

Usage

```
crmPackExample()
```

Value

nothing

Author(s)

Daniel Sabanes Bove <sabanesd@roche.com>

crmPackHelp *Open the browser with help pages for crmPack*

Description

This convenience function opens your browser with the help pages for crmPack.

Usage

```
crmPackHelp()
```

Value

nothing

Author(s)

Daniel Sabanes Bove <sabanesd@roche.com>

crmPackUpgrade *Upgrade your crmPack installation with the latest version*

Description

Executing this function upgrades your crmPack installation with the newest version available on the server. You will need connection to the Roche network (i.e. RANGE connection when you are working off-site) in order to successfully run it.

Usage

```
crmPackUpgrade(lib = NULL, devel = FALSE, force = FALSE,
  repos = structure(c(CRAN = "http://stat.ethz.ch/CRAN/")))
```

Arguments

lib	library where to install the new version (and other required packages) into. Default: same location as the last crmPack version.
devel	Should the development version from Stash be installed? (default FALSE) Otherwise and by default the latest version on the internal package repository GRAN is installed.
force	Should the installation be forced, i.e., even if you have already the latest version, should the package be re-installed?
repos	which repository to use for installing required packages (default: ETHZ in Switzerland)

Details

After installation, the new features in this version will be shown by printing the relevant parts of the NEWS file.

Value

nothing

Author(s)

Daniel Sabanes Bove <sabanesd@roche.com>

`Data` *Initialization function for the "Data" class*

Description

This is the function for initializing a "Data" class object.

Usage

```
Data(x = numeric(), y = integer(), ID = integer(), cohort = integer(),
  doseGrid = numeric(), ...)
```

Arguments

`x`	the doses for the patients
`y`	the vector of toxicity events (0 or 1 integers). You can also normal numeric vectors, but these will then be converted to integers.
`ID`	unique patient IDs (integer vector)
`cohort`	the cohort indices (sorted values from 0, 1, 2, ...)
`doseGrid`	the vector of all possible doses
`...`	not used

Details

Note that `ID` and `cohort` can be missing, then a warning will be issued and the variables will be filled with default IDs and best guesses, respectively.

Value

the initialized `Data` object

Data-class *Class for the data input*

Description

This class inherits from GeneralData.

Slots

`x` the doses for the patients

`y` the vector of toxicity events (0 or 1 integers)

`doseGrid` the vector of all possible doses (sorted), i.e. the dose grid

`nGrid` number of gridpoints

`xLevel` the levels for the doses the patients have been given

DataCombo *Initialization function for the "DataCombo" class*

Description

This is the function for initializing a "DataCombo" class object.

Usage

```
DataCombo(x, y, ID, cohort, doseGrid)
```

Arguments

`x`	the matrix with the doses for the patients. Recommendation: Use `cbind(drugA=..., drugB=...)` to create this matrix.
`y`	the vector of toxicity events (0 or 1 integers). You can also normal numeric vectors, but these will then be converted to integers.
`ID`	unique patient IDs (integer vector)
`cohort`	the cohort indices (sorted values from 0, 1, 2, ...)
`doseGrid`	the list with vectors of all possible doses for each of the drugs

Details

Note that `ID` and `cohort` can be missing, then a warning will be issued and the variables will be filled with default IDs and best guesses, respectively.

Value

the initialized DataCombo object

DataCombo-class *Class for the data input in combo trials*

Description

This class inherits from GeneralData.

Slots

x a matrix with the doses of all nDrugs drugs (columns) for the nObs patients (rows). The column names are the drugNames.

y the vector of toxicity events (0 or 1 integers)

doseGrid a list containing a vector of all possible doses (sorted) for each of the nDrugs drugs (named with drugNames).

nDrugs number of drugs

drugNames character vector with the drug names

nGrid vector with the number of gridpoints for each of the drugs

xLevel an integer matrix with the levels for the doses the patients have been given, same dimensions as x.

DataDual *Initialization function for the "DataDual" class*

Description

This is the function for initializing a "DataDual" class object.

Usage

```
DataDual(w = numeric(), ...)
```

Arguments

w	the continuous vector of biomarker values
...	additional parameters from Data

Value

the initialized DataDual object

DataDual-class *Class for the dual endpoint data input*

Description

This is a subclass of `Data`, so contains all slots from `Data`, and in addition biomarker values.

Slots

`w` the continuous vector of biomarker values

DataParts *Initialization function for the "DataParts" class*

Description

This is the function for initializing a `DataParts` object.

Usage

```
DataParts(part = integer(), nextPart = 1L, part1Ladder = numeric(), ...)
```

Arguments

`part`	which part does each of the patients belong to?
`nextPart`	what is the part for the next cohort? (1 or 2)
`part1Ladder`	what is the escalation ladder for part 1?
`...`	additional parameters from `Data`

Value

the initialized `DataParts` object

DataParts-class *Class for the data with two study parts*

Description

This is a subclass of `Data`, so contains all slots from `Data`, and in addition information on the two study parts.

Slots

`part` integer vector; which part does each of the patients belong to?

`nextPart` integer; what is the part for the next cohort?

`part1Ladder` sorted numeric vector; what is the escalation ladder for part 1? This shall be a subset of the `doseGrid`.

Design *Initialization function for "Design"*

Description

Initialization function for "Design"

Usage

```
Design(model, stopping, increments, ...)
```

Arguments

model	see Design
stopping	see Design
increments	see Design
...	additional arguments for RuleDesign

Value

the Design object

Design-class *Class for the CRM design*

Description

In addition to the slots in the more simple RuleDesign, objects of this class contain:

Slots

model the model to be used, an object of class Model

stopping stopping rule(s) for the trial, an object of class Stopping

increments how to control increments between dose levels, an object of class Increments

dose *Compute the doses for a given probability, given model and samples*

Description

Compute the doses for a given probability, given model and samples

Usage

```
dose(prob, model, samples, ...)

## S4 method for signature 'numeric,Model,Samples'
dose(prob, model, samples, ...)
```

Arguments

prob	the probability
model	the Model
samples	the Samples
...	unused

Methods (by class)

- prob = numeric,model = Model,samples = Samples:

DualDesign *Initialization function for "DualDesign"*

Description

Initialization function for "DualDesign"

Usage

```
DualDesign(model, data, ...)
```

Arguments

model	see DualDesign
data	see DualDesign
...	additional arguments for Design

Value

the DualDesign object

DualDesign-class *Class for the dual-endpoint CRM design*

Description

This class has special requirements for the `model` and `data` slots in comparison to the parent class `Design`:

Slots

`model` the model to be used, an object of class `DualEndpoint`

`data` what is the dose grid, any previous data, etc., contained in an object of class `DataDual`

Note that the `NextBest` slot can be of any class, this allows for easy comparison with recommendation methods that don't use the biomarker information.

DualEndpoint *Initialization function for the "DualEndpoint" class*

Description

Initialization function for the "DualEndpoint" class

Usage

```
DualEndpoint(mu, Sigma, sigma2W, rho)
```

Arguments

`mu`	see `DualEndpoint`
`Sigma`	see `DualEndpoint`
`sigma2W`	see `DualEndpoint`
`rho`	see `DualEndpoint`

Value

the `DualEndpoint` object

`DualEndpoint-class` *General class for the dual endpoint model*

Description

The idea of the dual-endpoint models is to model not only the dose-toxicity relationship, but also to model at the same time the relationship of a PD biomarker with the dose. The subclasses of this class detail how the dose-biomarker relationship is parametrized and are those to be used. This class here shall contain all the common features to reduce duplicate code. (However, this class must not be virtual, because we need to create objects of it during the construction of subclass objects.)

Details

Currently a probit regression model

$$\Phi^{-1}[p(x)] = \beta_{Z1} + \beta_{Z2} \cdot x$$

is used, where $p(x)$ is the probability of observing a DLT for a given dose x, and Φ is the standard normal cdf. This could later be generalized to have a reference dose or a log transformation for the dose. The prior is

$$\beta Z \sim Normal(\mu, \Sigma)$$

.

For the biomarker response w at a dose x, we assume

$$w(x) \sim Normal(f(x), \sigma_W^2)$$

and $f(x)$ is a function of the dose x, which is further specified in the subclasses. The biomarker variance σ_W^2 can be fixed or assigned an inverse gamma prior distribution; see the details below under slot `sigma2W`.

Finally, the two endpoints y (the binary DLT variable) and w (the biomarker) can be correlated, by assuming a correlation ρ between the underlying continuous latent toxicity variable z and the biomarker w. Again, this correlation can be fixed or assigned a prior distribution from the scaled beta family; see the details below under slot `rho`.

Please see the Hive page for more details on the model and the example vignette by typing `crmPackExample()` for a full example.

Slots

`mu` For the probit toxicity model, `mu` contains the prior mean vector

`Sigma` For the probit toxicity model, contains the prior covariance matrix

`sigma2W` Either a fixed value for the biomarker variance, or a vector with elements `a` and `b` for the inverse-gamma prior parameters.

`rho` Either a fixed value for the correlation (between -1 and 1), or a vector with elements `a` and `b` for the Beta prior on the transformation kappa = (rho + 1) / 2, which is in (0, 1). For example, `a=1,b=1` leads to a uniform prior on rho.

`useFixed` a list with logical value for each of the parameters indicating whether a fixed value is used or not; this slot is needed for internal purposes and not to be touched by the user.

See Also

Current subclasses: `DualEndpointRW`, `DualEndpointBeta`

`DualEndpointBeta` *Initialization function for the "DualEndpointBeta" class*

Description

Initialization function for the "DualEndpointBeta" class

Usage

```
DualEndpointBeta(E0, Emax, delta1, mode, refDose, ...)
```

Arguments

`E0`	see `DualEndpointBeta`
`Emax`	see `DualEndpointBeta`
`delta1`	see `DualEndpointBeta`
`mode`	see `DualEndpointBeta`
`refDose`	see `DualEndpointBeta`
`...`	additional parameters, see `DualEndpoint`

Value

the `DualEndpointBeta` object

`DualEndpointBeta-class` *Dual endpoint model with beta function for dose-biomarker relationship*

Description

This class extends the `DualEndpoint` class. Here the dose-biomarker relationship $f(x)$ is modelled by a parametric, rescaled beta density function:

Details

$$f(x) = E_0 + (E_{max} - E_0) * Beta(\delta_1, \delta_2) * (x/x^*)^{\delta_1} * (1 - x/x^*)^{\delta_2}$$

where x^* is the maximum dose (end of the dose range to be considered), δ_1 and δ_2 are the two beta parameters, and E_0 and E_{max} are the minimum and maximum levels, respectively. For ease of interpretation, we parametrize with δ_1 and the mode of the curve instead, where

$$mode = \delta_1/(\delta_1 + \delta_2),$$

and multiplying this with x^* gives the mode on the dose grid.

All parameters can currently be assigned uniform distributions or be fixed in advance.

Slots

`E0` either a fixed number or the two uniform distribution parameters

`Emax` either a fixed number or the two uniform distribution parameters

`delta1` either a fixed number or the two uniform distribution parameters

`mode` either a fixed number or the two uniform distribution parameters

`refDose` the reference dose x^*

`DualEndpointEmax` *Initialization function for the "DualEndpointEmax" class*

Description

Initialization function for the "DualEndpointEmax" class

Usage

```
DualEndpointEmax(E0, Emax, ED50, refDose, ...)
```

Arguments

`E0`	see `DualEndpointEmax`
`Emax`	see `DualEndpointEmax`
`ED50`	see `DualEndpointEmax`
`refDose`	see `DualEndpointEmax`
`...`	additional parameters, see `DualEndpoint`

Value

the `DualEndpointEmax` object

`DualEndpointEmax-class`

Dual endpoint model with emax function for dose-biomarker relationship

---

Description

This class extends the `DualEndpoint` class. Here the dose-biomarker relationship $f(x)$ is modelled by a parametric EMAX function:

Details

$$f(x) = E_0 + \frac{(E_{max} - E_0) * (x/x^*)}{ED_{50} + (x/x^*)}$$

where x^* is a reference dose, E_0 and E_{max} are the minimum and maximum levels for the biomarker and ED_{50} is the dose achieving half of the maximum effect $0.5 * E_{max}$.

All parameters can currently be assigned uniform distributions or be fixed in advance.

Slots

`E0` either a fixed number or the two uniform distribution parameters

`Emax` either a fixed number or the two uniform distribution parameters

`ED50` either a fixed number or the two uniform distribution parameters

`refDose` the reference dose x^*

`DualEndpointRW` *Initialization function for the "DualEndpointRW" class*

Description

Initialization function for the "DualEndpointRW" class

Usage

```
DualEndpointRW(sigma2betaW, smooth = c("RW1", "RW2"), ...)
```

Arguments

`sigma2betaW`	see `DualEndpointRW`
`smooth`	either "RW1" (default) or "RW2", for specifying the random walk prior on the biomarker level.
`...`	additional parameters, see `DualEndpoint`

Value

the `DualEndpointRW` object

`DualEndpointRW-class` *Dual endpoint model with RW prior for biomarker*

Description

This class extends the `DualEndpoint` class. Here the dose-biomarker relationship $f(x)$ is modelled by a non-parametric random-walk of first (RW1) or second order (RW2) (todo: warning: at the moment only the first order random walk produces useful results).

Details

That means, for the RW1 we assume

$$\beta_{W,i} - \beta_{W,i-1} \sim Normal(0, \sigma^2_{\beta_W}),$$

where $\beta_{W,i} = f(x_i)$ is the biomarker mean at the i-th dose gridpoint x_i. For the RW2, the second-order differences instead of the first-order differences of the biomarker means follow the normal distribution.

The variance parameter $\sigma^2_{\beta_W}$ is important because it steers the smoothness of the function f(x): if it is large, then f(x) will be very wiggly; if it is small, then f(x) will be smooth. This parameter can either be fixed or assigned an inverse gamma prior distribution.

Usually this modelling will only make sense if a regular dose grid is used, with equidistant grid points ensuring that the distance $x_i - x_{i-1}$ is the same for all grid positions i.

Slots

`sigma2betaW` Contains the prior variance factor of the random walk prior for the biomarker model. If it is not a single number, it can also contain a vector with elements `a` and `b` for the inverse-gamma prior on `sigma2betaW`.

`useRW1` for specifying the random walk prior on the biomarker level: if `TRUE`, RW1 is used, otherwise RW2.

`DualSimulations` *Initialization function for "DualSimulations"*

Description

Initialization function for "DualSimulations"

Usage

```
DualSimulations(rhoEst, sigma2West, fitBiomarker, ...)
```

Arguments

`rhoEst`	see `DualSimulations`
`sigma2West`	see `DualSimulations`
`fitBiomarker`	see `DualSimulations`
`...`	additional parameters from `Simulations`

Value

the `DualSimulations` object

`DualSimulations-class` *Class for the simulations output from dual-endpoint model based designs*

Description

This class captures the trial simulations from dual-endpoint model based designs. In comparison to the parent class `Simulations`, it contains additional slots to capture the dose-biomarker fits, and the sigma2W and rho estimates.

Slots

`rhoEst` the vector of final posterior median rho estimates

`sigma2West` the vector of final posterior median sigma2W estimates

`fitBiomarker` list with the final dose-biomarker curve fits

DualSimulationsSummary-class

Class for the summary of dual-endpoint simulations output

Description

In addition to the slots in the parent class SimulationsSummary, it contains two slots for the biomarker model fit information.

Details

Note that objects should not be created by users, therefore no initialization function is provided for this class.

Slots

`biomarkerFitAtDoseMostSelected` fitted biomarker level at dose most often selected

`meanBiomarkerFit` list with the average, lower (2.5 quantiles of the mean fitted biomarker level at each dose level

examine

Obtain hypothetical trial course table for a design

Description

This generic function takes a design and generates a dataframe showing the beginning of several hypothetical trial courses under the design. This means, from the generated dataframe one can read off: - how many cohorts are required in the optimal case (no DLTs observed) in order to reach the highest dose of the specified dose grid - assuming no DLTs are observed until a certain dose level, what the next recommended dose is for all possible number of DLTs observed - the actual relative increments that will be used in these cases - whether the trial would stop at a certain cohort Examining the "single trial" behavior of a dose escalation design is the first important step in evaluating a design, and cannot be replaced by studying solely the operating characteristics in "many trials". The cohort sizes are also taken from the design, assuming no DLTs occur until the dose listed.

Usage

```
examine(object, ...)

## S4 method for signature 'Design'
examine(object, mcmcOptions = McmcOptions(), ...)

## S4 method for signature 'RuleDesign'
examine(object, ...)
```

Arguments

object	the design (Design or RuleDesign object) we want to examine
mcmcOptions	object of class McmcOptions, giving the MCMC options for each evaluation in the trial. By default, the standard options are used
...	additional arguments (see methods)

Value

The data frame

Methods (by class)

- Design: Examine a model-based CRM
- RuleDesign: Examine a rule-based design

---

fit *Fit method for the Samples class*

Description

Note this new generic function is necessary because the fitted function only allows the first argument object to appear in the signature. But we need also other arguments in the signature.

Usage

```
fit(object, model, data, ...)

## S4 method for signature 'Samples,Model,Data'
fit(object, model, data,
  points = data@doseGrid, quantiles = c(0.025, 0.975), middle = mean, ...)

## S4 method for signature 'Samples,DualEndpoint,DataDual'
fit(object, model, data,
  quantiles = c(0.025, 0.975), middle = mean, ...)

## S4 method for signature 'Samples,ComboLogistic,DataCombo'
fit(object, model, data,
  focus = head(names(model@singlePriors), 2L),
  points = as.matrix(expand.grid(data@doseGrid[focus])),
  quantiles = c(0.025, 0.975), middle = mean, ...)
```

Arguments

object	the Samples object
model	the Model object
data	the Data object
points	at which dose levels is the fit requested? default is the dose grid
quantiles	the quantiles to be calculated (default: 0.025 and 0.975)
middle	the function for computing the middle point. Default: mean

focus	two drug names of this combo for which the model fit should be produced. Defaults to the first two drugs.
...	unused
points	matrix with the dose combos at which the fit is requested. Default is the expanded dose grid of the focus drugs.
quantiles	the quantiles to be calculated (default: 0.025 and 0.975)
middle	the function for computing the middle point. Default: mean

Value

the data frame with required information (see method details)

Methods (by class)

- object = Samples,model = Model,data = Data: This method returns a data frame with dose, middle, lower and upper quantiles for the dose-toxicity curve
- object = Samples,model = DualEndpoint,data = DataDual: This method returns a data frame with dose, and middle, lower and upper quantiles, for both the dose-tox and dose-biomarker (suffix "Biomarker") curves, for all grid points (Note that currently only the grid points can be used, because the DualEndpointRW models only allow that)
- object = Samples,model = ComboLogistic,data = DataCombo: This method returns a data frame with doses for the two focus drugs, middle, lower and upper quantiles for the dose-toxicity surface

---

GeneralData-class *Class for general data input*

Description

Class for general data input

Slots

ID unique patient IDs (integer vector)

cohort the cohort indices (sorted values from 0, 1, 2, ...)

nObs number of observations

GeneralModel-class *General class for model input*

Description

This is the general model class, from which all other specific models inherit.

Details

The `datamodel` must obey the convention that the data input is called exactly as in the corresponding data class. All prior distributions for parameters should be contained in the model function `priormodel`. The background is that this can be used to simulate from the prior distribution, before obtaining any data.

Slots

`datamodel` a function representing the BUGS data model specification (see the details above)

`priormodel` a function representing the BUGS prior specification (see the details above)

`datanames` The names of all data slots that are used in the `datamodel` and/or `priormodel` definition. Note that you cannot specify more variables than those that are really used in the model!

`modelspecs` a function computing the list of the data model and prior model specifications that are required for fully specifying them (e.g. prior parameters, reference dose, etc.), based on the data slots that are then required as arguments of this function. This will then be passed to BUGS for the computations.

`init` a function computing the list of starting values for parameters required to be initialized in the MCMC sampler, based on the data slots that are then required as arguments of this function

`sample` names of all parameters from which you would like to save the MCMC samples.

See Also

`Model`, `ComboLogistic`

GeneralSimulations *Initialization function for "GeneralSimulations"*

Description

Initialization function for "GeneralSimulations"

Usage

```
GeneralSimulations(data, doses, seed)
```

Arguments

`data`	see `GeneralSimulations`
`doses`	see `GeneralSimulations`
`seed`	see `GeneralSimulations`

Value

the GeneralSimulations object

GeneralSimulations-class

General class for the simulations output

Description

This class captures trial simulations.

Details

Here also the random generator state before starting the simulation is saved, in order to be able to reproduce the outcome. For this just use set.seed with the seed as argument before running simulate,Design-method.

Slots

data list of produced Data objects

doses the vector of final dose recommendations

seed random generator state before starting the simulation

GeneralSimulationsSummary-class

Class for the summary of general simulations output

Description

Note that objects should not be created by users, therefore no initialization function is provided for this class.

Slots

target target toxicity interval

targetDoseInterval corresponding target dose interval

nsim number of simulations

propDLTs proportions of DLTs in the trials

meanToxRisk mean toxicity risks for the patients

doseSelected doses selected as MTD

toxAtDosesSelected true toxicity at doses selected

propAtTarget Proportion of trials selecting target MTD

doseMostSelected dose most often selected as MTD

obsToxRateAtDoseMostSelected observed toxicity rate at dose most often selected

nObs number of patients overall

nAboveTarget number of patients treated above target tox interval

doseGrid the dose grid that has been used

get,Samples,character-method

Get specific parameter samples and produce a data.frame

Description

Here you have to specify with pos which parameter you would like to extract from the Samples object

Usage

```
## S4 method for signature 'Samples,character'
get(x, pos = -1L, envir = NULL, mode = NULL,
  inherits = NULL)
```

Arguments

x	the Samples object
pos	the name of the parameter
envir	for vectorial parameters, you can give the indices of the elements you would like to extract. If NULL, the whole vector samples will be returned
mode	not used
inherits	not used

Value

the data frame suitable for use with ggmcmc

getMinInfBeta

Get the minimal informative unimodal beta distribution

Description

As defined in Neuenschwander et al (2008), this function computes the parameters of the minimal informative unimodal beta distribution, given the request that the p-quantile should be q, i.e. X ~ Be(a, b) with Pr(X <= q) = p.

Usage

```
getMinInfBeta(p, q)
```

Arguments

p	the probability (> 0 and < 1)
q	the quantile (> 0 and < 1)

Value

the two resulting beta parameters a and b in a list

Increments-class *The virtual class for controlling increments*

Description

The virtual class for controlling increments

See Also

IncrementsRelative, IncrementsRelativeDLT, IncrementsRelativeParts

IncrementsRelative *Initialization function for "IncrementsRelative"*

Description

Initialization function for "IncrementsRelative"

Usage

```
IncrementsRelative(intervals, increments)
```

Arguments

intervals	see IncrementsRelative
increments	see IncrementsRelative

Value

the IncrementsRelative object

IncrementsRelative-class *Increments control based on relative differences in intervals*

Description

Note that `intervals` is to be read as follows. If for example, we want to specify three intervals: First 0 to less than 50, second at least 50 up to less than 100 mg, and third at least 100 mg, then we specify `intervals` to be `c(0, 50, 100)`. That means, the right bound of the intervals are exclusive to the interval, and the last interval goes from the last value until infinity.

Slots

`intervals` a vector with the left bounds of the relevant intervals

`increments` a vector of the same length with the maximum allowable relative increments in the `intervals`

IncrementsRelativeDLT *Initialization function for "IncrementsRelativeDLT"*

Description

Initialization function for "IncrementsRelativeDLT"

Usage

```
IncrementsRelativeDLT(DLTintervals, increments)
```

Arguments

DLTintervals	see IncrementsRelativeDLT
increments	see IncrementsRelativeDLT

Value

the IncrementsRelativeDLT object

IncrementsRelativeDLT-class *Increments control based on relative differences in terms of DLTs*

Description

Note that DLTintervals is to be read as follows. If for example, we want to specify three intervals: First 0 DLTs, second 1 or 2 DLTs, and third at least 3 DLTs, then we specify DLTintervals to be c(0, 1, 3). That means, the right bound of the intervals are exclusive to the interval – the vector only gives the left bounds of the intervals. The last interval goes from 3 to infinity.

Slots

DLTintervals an integer vector with the left bounds of the relevant DLT intervals

increments a vector of the same length with the maximum allowable relative increments in the DLTintervals

IncrementsRelativeParts *Initialization function for "IncrementsRelativeParts"*

Description

Initialization function for "IncrementsRelativeParts"

Usage

```
IncrementsRelativeParts(dltStart, cleanStart, ...)
```

Arguments

dltStart	see IncrementsRelativeParts
cleanStart	see IncrementsRelativeParts
...	additional slots from IncrementsRelative

Value

the IncrementsRelativeParts object

IncrementsRelativeParts-class *Increments control based on relative differences in intervals, with special rules for part 1 and beginning of part 2*

Description

Note that this only works in conjunction with DataParts objects. If the part 2 will just be started in the next cohort, then the next maximum dose will be either dltStart (e.g. -1) shift of the last part 1 dose in case of a DLT in part 1, or cleanStart shift (e.g. 0) in case of no DLTs in part 1. If part 1 will still be on in the next cohort, then the next dose level will be the next higher dose level in the part1Ladder of the data object. If part 2 has been started before, the usual relative increment rules apply, see IncrementsRelative.

Slots

dltStart integer giving the dose level increment for starting part 2 in case of a DLT in part 1

cleanStart integer giving the dose level increment for starting part 2 in case of a DLT in part 1. If this is less or equal to 0, then the part 1 ladder will be used to find the maximum next dose. If this is larger than 0, then the relative increment rules will be applied to find the next maximum dose level.

initialize,DualEndpointOld-method *Initialization method for the "DualEndpointOld" class*

Description

Initialization method for the "DualEndpointOld" class

Usage

```
## S4 method for signature 'DualEndpointOld'
initialize(.Object, mu, Sigma, sigma2betaW, sigma2W,
  rho, smooth = c("RW1", "RW2"), ...)
```

Arguments

.Object	the DualEndpointOld we want to initialize
mu	see DualEndpointOld
Sigma	see DualEndpointOld
sigma2betaW	see DualEndpointOld
sigma2W	see DualEndpointOld
rho	see DualEndpointOld
smooth	either “RW1” (default) or “RW2”, for specifying the random walk prior on the biomarker level.
...	not used

LogisticKadane *Initialization function for the "LogisticKadane" class*

Description

Initialization function for the "LogisticKadane" class

Usage

```
LogisticKadane(theta, xmin, xmax)
```

Arguments

theta	the target toxicity probability
xmin	the minimum of the dose range
xmax	the maximum of the dose range

Value

the LogisticKadane

LogisticKadane-class *Reparametrized logistic model*

Description

This is the logistic model in the parametrization of Kadane et al. (1980).

Details

Let $\rho_0 = p(x_{min})$ be the probability of a DLT and the minimum dose x_{min}, and let γ be the dose with target toxicity probability θ, i.e. $p(\gamma) = \theta$. Then it can easily be shown that the logistic regression model has intercept

$$\frac{\gamma logit(\rho_0) - x_{min} logit(\theta)}{\gamma - x_{min}}$$

and slope

$$\frac{logit(theta) - logit(\rho_0)}{\gamma - x_{min}}$$

The prior is a uniform distribution for γ between x_{min} and x_{max}, and for ρ_0 as well a uniform distribution between 0 and θ.

The slots of this class, required for creating the model, are the target toxicity, as well as the minimum and maximum of the dose range. Note that these can be different from the minimum and maximum of the dose grid in the data later on.

Slots

`theta` the target toxicity probability θ

`xmin` the minimum of the dose range x_{min}

`xmax` the maximum of the dose range x_{max}

LogisticLogNormal *Initialization function for the "LogisticLogNormal" class*

Description

Initialization function for the "LogisticLogNormal" class

Usage

```
LogisticLogNormal(mean, cov, refDose)
```

Arguments

`mean`	the prior mean vector
`cov`	the prior covariance matrix
`refDose`	the reference dose

Value

the `LogisticLogNormal` object

LogisticLogNormal-class *Standard logistic model with bivariate (log) normal prior*

Description

This is the usual logistic regression model with a bivariate normal prior on the intercept and log slope.

Details

The covariate is the natural logarithm of the dose x divided by the reference dose x^*:

$$logit[p(x)] = \alpha + \beta \cdot \log(x/x^*)$$

where $p(x)$ is the probability of observing a DLT for a given dose x.

The prior is

$$(\alpha, \log(\beta)) \sim Normal(\mu, \Sigma)$$

The slots of this class contain the mean vector and the covariance matrix of the bivariate normal distribution, as well as the reference dose.

Note that the parametrization inside the class uses alpha0 and alpha1. alpha0 is identical to the intercept α above and is the log-odds for a DLT at the reference dose x*. Therefore, the prior mean for alpha0 is the expected log-odds at the reference dose x* before observing any data. Note that the expected odds is not just the exp of the prior mean of alpha0, because the non-linearity of the exp transformation. The log-normal distribution on Wikipedia gives the formula for computing the prior mean of exp(alpha0). alpha0 is the log(alpha) in the Neuenschwander et al. (2008) paper. alpha1 is identical to $\log(\beta)$ above and equals the beta in the Neuenschwander et al paper. exp(alpha1) gives the odds-ratio for DLT between two doses that differ by the factor exp(1) ~ 2.7. alpha1 has a log-normal distribution in the LogisticLogNormal model in order to ensure positivity of alpha1 and thus exp(alpha1) > 1.

Slots

`mean` the prior mean vector μ

`cov` the prior covariance matrix Σ

`refDose` the reference dose x^*

LogisticLogNormalSub *Initialization function for the "LogisticLogNormalSub" class*

Description

Initialization function for the "LogisticLogNormalSub" class

Usage

```
LogisticLogNormalSub(mean, cov, refDose)
```

Arguments

mean	the prior mean vector
cov	the prior covariance matrix
refDose	the reference dose

Value

the LogisticLogNormalSub object

LogisticLogNormalSub-class

Standard logistic model with bivariate (log) normal prior with substractive dose standardization

---

Description

This is the usual logistic regression model with a bivariate normal prior on the intercept and log slope.

Details

The covariate is the dose x minus the reference dose x^*:

$$logit[p(x)] = \alpha + \beta \cdot (x - x^*)$$

where $p(x)$ is the probability of observing a DLT for a given dose x.

The prior is

$$(\alpha, \log(\beta)) \sim Normal(\mu, \Sigma)$$

The slots of this class contain the mean vector and the covariance matrix of the bivariate normal distribution, as well as the reference dose.

Slots

mean the prior mean vector μ

cov the prior covariance matrix Σ

refDose the reference dose x^*

LogisticNormal *Initialization function for the "LogisticNormal" class*

Description

Initialization function for the "LogisticNormal" class

Usage

```
LogisticNormal(mean, cov, refDose)
```

Arguments

mean	the prior mean vector
cov	the prior covariance matrix
refDose	the reference dose

Value

the LogisticNormal object

LogisticNormal-class *Standard logistic model with bivariate normal prior*

Description

This is the usual logistic regression model with a bivariate normal prior on the intercept and slope.

Details

The covariate is the natural logarithm of the dose x divided by the reference dose x^*:

$$logit[p(x)] = \alpha + \beta \cdot \log(x/x^*)$$

where $p(x)$ is the probability of observing a DLT for a given dose x.

The prior is

$$(\alpha, \beta) \sim Normal(\mu, \Sigma)$$

The slots of this class contain the mean vector, the covariance and precision matrices of the bivariate normal distribution, as well as the reference dose.

Slots

mean the prior mean vector μ

cov the prior covariance matrix Σ

prec the prior precision matrix Σ^{-1}

refDose the reference dose x^*

LogisticNormalFixedMixture

Initialization function for the "LogisticNormalFixedMixture" class

Description

Initialization function for the "LogisticNormalFixedMixture" class

Usage

```
LogisticNormalFixedMixture(components, weights, refDose, logNormal = FALSE)
```

Arguments

components	the specifications of the mixture components: a list with one list of mean and cov for each bivariate (log) normal prior
weights	the weights of the components, these must be positive and will be normalized to sum to 1
refDose	the reference dose
logNormal	should a log normal prior be specified, such that the mean vectors and covariance matrices are valid for the intercept and log slope? (not default)

Value

the LogisticNormalFixedMixture object

LogisticNormalFixedMixture-class

Standard logistic model with fixed mixture of multiple bivariate (log) normal priors

Description

This is standard logistic regression model with a mixture of multiple bivariate (log) normal priors on the intercept and slope parameters. The weights of the normal priors are fixed, hence no additional model parameters are introduced. This type of prior is often used to better approximate a given posterior distribution, or when the information is given in terms of a mixture.

Details

The covariate is the natural logarithm of the dose x divided by the reference dose x^*:

$$logit[p(x)] = \alpha + \beta \cdot \log(x/x^*)$$

where $p(x)$ is the probability of observing a DLT for a given dose x.

The prior is

$$(\alpha, \beta) \sim \sum_{j=1}^{K} w_j Normal(\mu_j, \Sigma_j)$$

if a normal prior is used and

$$(\alpha, \log(\beta)) \sim \sum_{j=1}^{K} w_j Normal(\mu_j, \Sigma_j)$$

if a log normal prior is used.

The weight w_j of the components are fixed and sum to 1.

The (additional) slots of this class comprise two lists, containing the mean vector, the covariance and precision matrices of the two bivariate normal distributions each, the parameters of the beta prior for the first component weight, as well as the reference dose. Moreover, a slot specifies whether a log normal prior is used.

Slots

`components` a list with one entry per component of the mixture. Each entry is a list with `mean`, `cov` and `prec` for the bivariate normal prior

`weights` the weights of the components, these must be positive and sum to 1

`refDose` the reference dose x^*

`logNormal` is a log normal prior specified for each of the components?

`LogisticNormalMixture` *Initialization function for the "LogisticNormalMixture" class*

Description

Initialization function for the "LogisticNormalMixture" class

Usage

```
LogisticNormalMixture(comp1, comp2, weightpar, refDose)
```

Arguments

`comp1`	the specifications of the first component: a list with `mean` and `cov` for the first bivariate normal prior
`comp2`	the specifications of the second component
`weightpar`	the beta parameters for the weight of the first component
`refDose`	the reference dose

Value

the `LogisticNormalMixture` object

LogisticNormalMixture-class

Standard logistic model with flexible mixture of two bivariate normal priors

Description

This is standard logistic regression model with a mixture of two bivariate normal priors on the intercept and slope parameters. The weight of the two normal priors is a model parameter, hence it is a flexible mixture. This type of prior is often used with a mixture of a minimal informative and an informative component, in order to make the CRM more robust to data deviations from the informative component.

Details

The covariate is the natural logarithm of the dose x divided by the reference dose x^*:

$$logit[p(x)] = \alpha + \beta \cdot \log(x/x^*)$$

where $p(x)$ is the probability of observing a DLT for a given dose x.

The prior is

$$(\alpha, \beta) \sim w * Normal(\mu_1, \Sigma_1) + (1 - w) * Normal(\mu_2, \Sigma_2)$$

The weight w for the first component is assigned a beta prior B(a, b).

The slots of this class comprise two lists, containing the mean vector, the covariance and precision matrices of the two bivariate normal distributions each, the parameters of the beta prior for the first component weight, as well as the reference dose.

Slots

`comp1` the specifications of the first component: a list with `mean`, `cov` and `prec` for the first bivariate normal prior

`comp2` the specifications of the second component

`weightpar` the beta parameters for the weight of the first component

`refDose` the reference dose x^*

logit

Shorthand for logit function

Description

Shorthand for logit function

Usage

```
logit(x)
```

Arguments

x	the function argument

Value

the logit(x)

`maxDose` *Determine the maximum possible next dose*

Description

Determine the upper limit of the next dose based on the increments rule.

Usage

```
maxDose(increments, data, ...)

## S4 method for signature 'IncrementsRelative,Data'
maxDose(increments, data, ...)

## S4 method for signature 'IncrementsRelativeParts,DataParts'
maxDose(increments, data, ...)

## S4 method for signature 'IncrementsRelativeDLT,Data'
maxDose(increments, data, ...)
```

Arguments

`increments`	The rule, an object of class `Increments`
`data`	The data input, an object of class `Data`
`...`	further arguments

Details

This function outputs the maximum possible next dose, based on the corresponding rule `increments` and the `data`.

Value

the maximum possible next dose

Methods (by class)

- `increments = IncrementsRelative,data = Data`: Determine the maximum possible next dose based on relative increments
- `increments = IncrementsRelativeParts,data = DataParts`: Determine the maximum possible next dose based on relative increments and part 1 and 2
- `increments = IncrementsRelativeDLT,data = Data`: Determine the maximum possible next dose based on relative increments determined by DLTs so far

maxSize *"MAX" combination of cohort size rules*

Description

This function combines cohort size rules by taking the maximum of all sizes.

Usage

```
maxSize(...)

## S4 method for signature 'CohortSize'
maxSize(...)
```

Arguments

...	Objects of class CohortSize

Value

the combination as an object of class CohortSizeMax

Methods (by class)

- CohortSize: The method combining cohort size rules by taking maximum

See Also

minSize

mcmc *Obtain posterior samples for all model parameters*

Description

This is the function to actually run the MCMC machinery to produce posterior samples from all model parameters and required derived values. It is a generic function, so that customized versions may be conveniently defined for specific subclasses of GeneralData, GeneralModel, and McmcOptions input.

Usage

```
mcmc(data, model, options, ...)

## S4 method for signature 'GeneralData,GeneralModel,McmcOptions'
mcmc(data, model, options,
  program = c("JAGS", "OpenBUGS", "WinBUGS"), verbose = FALSE, ...)

## S4 method for signature 'Data,LogisticNormal,McmcOptions'
mcmc(data, model, options,
  verbose = FALSE, ...)
```

Arguments

data	The data input, an object of class GeneralData
model	The model input, an object of class GeneralModel
options	MCMC options, an object of class McmcOptions
program	the program which shall be used: either "JAGS" (default), "OpenBUGS" or "WinBUGS"
verbose	shall progress bar and messages be printed? (not default)
...	unused

Details

Reproducible samples can be obtained by setting the seed via set.seed before in the user code as usual. However, note that because the RNG sampler used is external to R, running this MCMC function will not change the seed position – that is, the repeated call to this function will then result in exactly the same output.

Value

The posterior samples, an object of class Samples.

Methods (by class)

- data = GeneralData,model = GeneralModel,options = McmcOptions: Standard method which uses JAGS/BUGS
- data = Data,model = LogisticNormal,options = McmcOptions: The fast method for the LogisticNormal class

---

McmcOptions *Initialization function for the "McmcOptions" class*

Description

Initialization function for the "McmcOptions" class

Usage

```
McmcOptions(burnin = 10000L, step = 2L, samples = 10000L)
```

Arguments

burnin	number of burn-in iterations which are not saved (default: 10,000)
step	only every step-th iteration is saved after the burn-in (default: 2)
samples	number of resulting samples (by default 10,000 will result)

Value

the McmcOptions object

McmcOptions-class *Class for the three canonical MCMC options*

Description

Class for the three canonical MCMC options

Slots

`iterations` number of MCMC iterations

`burnin` number of burn-in iterations which are not saved

`step` only every step-th iteration is saved after the burn-in

MinimalInformative *Construct a minimally informative prior*

Description

This function constructs a minimally informative prior, which is captured in a `LogisticNormal` (or `LogisticLogNormal`) object.

Usage

```
MinimalInformative(dosegrid, threshmin = 0.2, threshmax = 0.3, ...)
```

Arguments

`dosegrid`	the dose grid
`threshmin`	Any toxicity probability above this threshold would be very unlikely (5%) at the minimum dose (default: 0.2)
`threshmax`	Any toxicity probability below this threshold would be very unlikely (5%) at the maximum dose (default: 0.3)
`...`	additional arguments for computations, see `Quantiles2LogisticNormal`, e.g. `refDose` and `logNormal=TRUE` to obtain a minimal informative log normal prior.

Details

Based on the proposal by Neuenschwander et al (2008, Statistics in Medicine), a minimally informative prior distribution is constructed. The required key input is the minimum (d_1 in the notation of the Appendix A.1 of that paper) and the maximum value (d_J) of the dose grid supplied to this function. Then `threshmin` is the probability threshold q_1, such that any probability of DLT larger than q_1 has only 5% probability. Therefore q_1 is the 95% quantile of the beta distribution and hence $p_1 = 0.95$. Likewise, `threshmax` is the probability threshold q_J, such that any probability of DLT smaller than q_J has only 5% probability ($p_J = 0.05$). Subsequently, for all doses supplied in the `dosegrid` argument, beta distributions are set up from the assumption that the prior medians are linear in log-dose on the logit scale, and `Quantiles2LogisticNormal` is used to transform the resulting quantiles into an approximating `LogisticNormal` (or `LogisticLogNormal`) model. Note that the reference dose is not required for these computations.

Value

see Quantiles2LogisticNormal

---

minSize *"MIN" combination of cohort size rules*

Description

This function combines cohort size rules by taking the minimum of all sizes.

Usage

```
minSize(...)

## S4 method for signature 'CohortSize'
minSize(...)
```

Arguments

...	Objects of class CohortSize

Value

the combination as an object of class CohortSizeMin

Methods (by class)

- CohortSize: The method combining cohort size rules by taking minimum

See Also

maxSize

Model-class *Class for the model input*

Description

This is the model class for single agent dose escalation, from which all other specific models inherit. It inherits all slots from GeneralModel.

Details

The datamodel must obey the convention that the data input is called exactly as in the Data class. All prior distributions for parameters should be contained in the model function priormodel. The background is that this can be used to simulate from the prior distribution, before obtaining any data.

The dose function has as first argument prob, a scalar toxicity probability which is targeted. Additional arguments are model parameters. Then it computes, using model parameter(s) (samples), the resulting dose. Note that the model parameters are called exactly as in the model and must be included in the sample vector. The vectors of all samples for these parameters will then be supplied to the function. So your function must be able to process vectors of the model parameters, i.e. it must vectorize over them.

The prob function has as first argument dose, which is a scalar dose. Additional arguments are model parameters. Then it computes, using model parameter(s) (samples), the resulting probability of toxicity at that dose. Again here, the function must vectorize over the model parameters.

If you work with multivariate parameters, then please assume that your the two functions receive either one parameter value as a row vector, or a samples matrix where the rows correspond to the sampling index, i.e. the layout is then nSamples x dimParameter.

Note that dose and prob are the inverse functions of each other.

Slots

dose a function computing the dose reaching a specific target probability, based on the model parameters and additional prior settings (see the details above)

prob a function computing the probability of toxicity for a specific dose, based on the model parameters and additional prior settings (see the details above)

See Also

LogisticNormal, LogisticLogNormal, LogisticLogNormalSub, LogisticKadane, DualEndpoint, ComboLogistic

---

nextBest *Find the next best dose*

Description

Compute the recommended next best dose.

Usage

```
nextBest(nextBest, doselimit, samples, model, data, ...)

## S4 method for signature 'NextBestMTD,numeric,Samples,Model,Data'
nextBest(nextBest, doselimit,
  samples, model, data, ...)

## S4 method for signature 'NextBestNCRM,numeric,Samples,Model,Data'
nextBest(nextBest,
  doselimit, samples, model, data, ...)
```

```
## S4 method for signature 'NextBestNCRM,numeric,Samples,Model,DataParts'
nextBest(nextBest,
  doselimit, samples, model, data, ...)


  ## S4 method for signature
## 'NextBestThreePlusThree,missing,missing,missing,Data'
nextBest(nextBest,
  doselimit, samples, model, data, ...)


  ## S4 method for signature
## 'NextBestDualEndpoint,numeric,Samples,DualEndpoint,Data'
nextBest(nextBest,
  doselimit, samples, model, data, ...)
```

Arguments

nextBest	The rule, an object of class NextBest
doselimit	The maximum allowed next dose. If this is an empty (length 0) vector, then no dose limit will be applied in the course of dose recommendation calculation, and a corresponding warning is given.
samples	the Samples object
model	The model input, an object of class Model
data	The data input, an object of class Data
...	possible additional arguments without method dispatch

Details

This function outputs the next best dose recommendation based on the corresponding rule nextBest, the posterior samples from the model and the underlying data.

Value

a list with the next best dose (element value) on the grid defined in data, and a plot depicting this recommendation (element plot)

Methods (by class)

- nextBest = NextBestMTD,doselimit = numeric,samples = Samples,model = Model,data = Data: Find the next best dose based on the MTD rule
- nextBest = NextBestNCRM,doselimit = numeric,samples = Samples,model = Model,data = Data: Find the next best dose based on the NCRM method
- nextBest = NextBestNCRM,doselimit = numeric,samples = Samples,model = Model,data = DataParts: Find the next best dose based on the NCRM method when two parts trial is used
- nextBest = NextBestThreePlusThree,doselimit = missing,samples = missing,model = missing,data = Find the next best dose based on the 3+3 method
- nextBest = NextBestDualEndpoint,doselimit = numeric,samples = Samples,model = DualEndpoint,da Find the next best dose based on the dual endpoint model

NextBest-class *The virtual class for finding next best dose*

Description

The virtual class for finding next best dose

See Also

NextBestMTD, NextBestNCRM, NextBestDualEndpoint, NextBestThreePlusThree

NextBestDualEndpoint *Initialization function for "NextBestDualEndpoint"*

Description

Initialization function for "NextBestDualEndpoint"

Usage

```
NextBestDualEndpoint(target, overdose, maxOverdoseProb)
```

Arguments

target	see NextBestDualEndpoint
overdose	see NextBestDualEndpoint
maxOverdoseProb	see NextBestDualEndpoint

Value

the NextBestDualEndpoint object

NextBestDualEndpoint-class *The class with the input for finding the next dose based on the dual endpoint model*

Description

This rule first excludes all doses that exceed the probability maxOverdoseProb of having an overdose toxicity, as specified by the overdose interval overdose. Then, it picks under the remaining admissible doses the one that maximizes the probability to be in the target biomarker range, relative to the maximum biomarker level across the dose grid or relative to the Emax parameter in case a parametric model was selected (e.g. DualEndpointBeta, DualEndpointEmax))

Slots

`target` the biomarker target range, relative to the maximum, that needs to be reached. For example, (0.8, 1.0) means we target a dose with at least 80 (0.5, 0.8) would mean that we target a dose between 50 the maximum biomarker level.

`overdose` the overdose toxicity interval (lower limit excluded, upper limit included)

`maxOverdoseProb` maximum overdose probability that is allowed

`NextBestMTD` *Initialization function for class "NextBestMTD"*

Description

Initialization function for class "NextBestMTD"

Usage

```
NextBestMTD(target, derive)
```

Arguments

`target`	see `NextBestMTD`
`derive`	see `NextBestMTD`

Value

the `NextBestMTD` object

`NextBestMTD-class` *The class with the input for finding the next best MTD estimate*

Description

The class with the input for finding the next best MTD estimate

Slots

`target` the target toxicity probability

`derive` the function which derives from the input, a vector of posterior MTD samples called `mtdSamples`, the final next best MTD estimate.

NextBestNCRM *Initialization function for "NextBestNCRM"*

Description

Initialization function for "NextBestNCRM"

Usage

```
NextBestNCRM(target, overdose, maxOverdoseProb)
```

Arguments

target	see NextBestNCRM
overdose	see NextBestNCRM
maxOverdoseProb	see NextBestNCRM

Value

the NextBestNCRM object

NextBestNCRM-class *The class with the input for finding the next dose in target interval*

Description

Note that to avoid numerical problems, the dose selection algorithm has been implemented as follows: First admissible doses are found, which are those with probability to fall in overdose category being below maxOverdoseProb. Next, within the admissible doses, the maximum probability to fall in the target category is calculated. If that is above 5% (i.e., it is not just numerical error), then the corresponding dose is the next recommended dose. Otherwise, the highest admissible dose is the next recommended dose.

Slots

target the target toxicity interval (limits included)

overdose the overdose toxicity interval (lower limit excluded, upper limit included)

maxOverdoseProb maximum overdose probability that is allowed

NextBestThreePlusThree *Initialization function for "NextBestThreePlusThree"*

Description

Initialization function for "NextBestThreePlusThree"

Usage

```
NextBestThreePlusThree()
```

Value

the NextBestThreePlusThree object

NextBestThreePlusThree-class *The class with the input for finding the next dose in target interval*

Description

Implements the classical 3+3 dose recommendation. No input is required, hence this class has no slots.

or-Stopping-Stopping *The method combining two atomic stopping rules*

Description

The method combining two atomic stopping rules

Usage

```
## S4 method for signature 'Stopping,Stopping'
e1 | e2
```

Arguments

e1	First Stopping object
e2	Second Stopping object

Value

The StoppingAny object

or-Stopping-StoppingAny

The method combining a stopping list and an atomic

Description

The method combining a stopping list and an atomic

Usage

```
## S4 method for signature 'StoppingAny,Stopping'
e1 | e2
```

Arguments

e1	StoppingAny object
e2	Stopping object

Value

The modified StoppingAny object

or-StoppingAny-Stopping

The method combining an atomic and a stopping list

Description

The method combining an atomic and a stopping list

Usage

```
## S4 method for signature 'Stopping,StoppingAny'
e1 | e2
```

Arguments

e1	Stopping object
e2	StoppingAny object

Value

The modified StoppingAny object

`plot,Data,missing-method`
Plot method for the "Data" class

Description

Plot method for the "Data" class

Usage

```
## S4 method for signature 'Data,missing'
plot(x, y, ...)
```

Arguments

x	the Data object we want to plot
y	missing
...	not used

Value

the ggplot object

`plot,DataCombo,missing-method`
Plot method for the "DataCombo" class

Description

Plot method for the "DataCombo" class

Usage

```
## S4 method for signature 'DataCombo,missing'
plot(x, y, select = head(x@drugNames, 2L),
  shorten = 0.03, ...)
```

Arguments

x	the DataDual object we want to plot
y	missing
select	two drug names that we want to use for plotting. Defaults to the first two drug names.
shorten	relative amount of shortening the arrows. default: 0.05
...	not used

Value

the ggplot object

plot,DataDual,missing-method

Plot method for the "DataDual" class

Description

Plot method for the "DataDual" class

Usage

```
## S4 method for signature 'DataDual,missing'
plot(x, y, ...)
```

Arguments

x	the DataDual object we want to plot
y	missing
...	not used

Value

the ggplot object

plot,DualSimulations,missing-method

Plot dual-endpoint simulations

Description

This plot method can be applied to DualSimulations objects in order to summarize them graphically. In addition to the standard plot types, there is

sigma2W Plot a boxplot of the final biomarker variance estimates in the simulated trials

rho Plot a boxplot of the final correlation estimates in the simulated trials

Usage

```
## S4 method for signature 'DualSimulations,missing'
plot(x, y, type = c("trajectory",
  "dosesTried", "sigma2W", "rho"), ...)
```

Arguments

x	the DualSimulations object we want to plot from
y	missing
type	the type of plots you want to obtain.
...	not used

Value

A single ggplot2 object if a single plot is asked for, otherwise a gridExtra{gTree} object.

`plot,DualSimulationsSummary,missing-method`

Plot summaries of the dual-endpoint design simulations

Description

This plot method can be applied to `DualSimulationsSummary` objects in order to summarize them graphically. Possible `type` of plots at the moment are those listed in `plot,SimulationsSummary,missing-method` plus:

meanBiomarkerFit Plot showing the average fitted dose-biomarker curve across the trials, together with 95% credible intervals, and comparison with the assumed truth (as specified by the `trueBiomarker` argument to `summary,DualSimulations-method`)

You can specify any subset of these in the `type` argument.

Usage

```
## S4 method for signature 'DualSimulationsSummary,missing'
plot(x, y, type = c("nObs",
  "doseSelected", "propDLTs", "nAboveTarget", "meanFit", "meanBiomarkerFit"),
  ...)
```

Arguments

`x`	the `DualSimulationsSummary` object we want to plot from
`y`	missing
`type`	the types of plots you want to obtain.
`...`	not used

Value

A single `ggplot2` object if a single plot is asked for, otherwise a `gridExtra{gTree}` object.

`plot,GeneralSimulations,missing-method`

Plot simulations

Description

Summarize the simulations with plots

Usage

```
## S4 method for signature 'GeneralSimulations,missing'
plot(x, y, type = c("trajectory",
  "dosesTried"), ...)
```

Arguments

x	the GeneralSimulations object we want to plot from
y	missing
type	the type of plots you want to obtain.
...	not used

Details

This plot method can be applied to GeneralSimulations objects in order to summarize them graphically. Possible types of plots at the moment are:

trajectory Summary of the trajectory of the simulated trials

dosesTried Average proportions of the doses tested in patients

You can specify one or both of these in the type argument.

Value

A single ggplot2 object if a single plot is asked for, otherwise a gridExtra{gTree} object.

---

plot,GeneralSimulationsSummary,missing-method

Plot summaries of the general simulations

Description

Graphical display of the general simulation summary

Usage

```
## S4 method for signature 'GeneralSimulationsSummary,missing'
plot(x, y, type = c("nObs",
  "doseSelected", "propDLTs", "nAboveTarget"), ...)
```

Arguments

x	the GeneralSimulationsSummary object we want to plot from
y	missing
type	the types of plots you want to obtain.
...	not used

Details

This plot method can be applied to GeneralSimulationsSummary objects in order to summarize them graphically. Possible types of plots at the moment are:

nObs Distribution of the number of patients in the simulated trials

doseSelected Distribution of the final selected doses in the trials. Note that this can include zero entries, meaning that the trial was stopped because all doses in the dose grid appeared too toxic.

propDLTs Distribution of the proportion of patients with DLTs in the trials

nAboveTarget Distribution of the number of patients treated at doses which are above the target toxicity interval (as specified by the `truth` and `target` arguments to `summary,GeneralSimulations-method`)

You can specify any subset of these in the `type` argument.

Value

A single `ggplot2` object if a single plot is asked for, otherwise a `gridExtra{gTree}` object.

`plot,Samples,ComboLogistic-method`

Plotting dose-toxicity combo model fits

Description

Plotting dose-toxicity combo model fits

Usage

```
## S4 method for signature 'Samples,ComboLogistic'
plot(x, y, data, focus, resolution = 20,
  ...)
```

Arguments

`x`	the `Samples` object
`y`	the `ComboLogistic` object
`data`	the `DataCombo` object
`focus`	one or two drug names of this combo for which the model fit plot should be produced
`resolution`	number of points to be used in each dimension for 2D plots (default: 20) - higher number is higher resolution
`...`	passed to the single agent plotting method if `focus` specifies only one drug name

Value

todo

plot,Samples,DualEndpoint-method

Plotting dose-toxicity and dose-biomarker model fits

Description

When we have the dual endpoint model, also the dose-biomarker fit is shown in the plot

Usage

```
## S4 method for signature 'Samples,DualEndpoint'
plot(x, y, data, extrapolate = TRUE,
  showLegend = FALSE, ...)
```

Arguments

x	the Samples object
y	the DualEndpoint object
data	the DataDual object
extrapolate	should the biomarker fit be extrapolated to the whole dose grid? (default)
showLegend	should the legend be shown? (not default)
...	additional arguments for the parent method plot,Samples,Model-method

Value

This returns the ggplot object with the dose-toxicity and dose-biomarker model fits

plot,Samples,Model-method

Plotting dose-toxicity model fits

Description

Plotting dose-toxicity model fits

Usage

```
## S4 method for signature 'Samples,Model'
plot(x, y, data, ..., xlab = "Dose level",
  ylab = "Probability of DLT [%]", showLegend = TRUE)
```

Arguments

x	the Samples object
y	the Model object
data	the Data object
xlab	the x axis label
ylab	the y axis label
showLegend	should the legend be shown? (default)
...	not used

Value

This returns the ggplot object for the dose-toxicity model fit

---

`plot,SimulationsSummary,missing-method`
Plot summaries of the model-based design simulations

Description

Graphical display of the simulation summary

Usage

```
## S4 method for signature 'SimulationsSummary,missing'
plot(x, y, type = c("nObs",
  "doseSelected", "propDLTs", "nAboveTarget", "meanFit"), ...)
```

Arguments

x	the SimulationsSummary object we want to plot from
y	missing
type	the types of plots you want to obtain.
...	not used

Details

This plot method can be applied to SimulationsSummary objects in order to summarize them graphically. Possible type of plots at the moment are those listed in plot,GeneralSimulationsSummary,missing-meth plus:

meanFit Plot showing the average fitted dose-toxicity curve across the trials, together with 95% credible intervals, and comparison with the assumed truth (as specified by the truth argument to summary,Simulations-method)

You can specify any subset of these in the type argument.

Value

A single ggplot2 object if a single plot is asked for, otherwise a gridExtra{gTree} object.

plot.arrange *Plots arrange objects*

Description

Plots arrange objects

Usage

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

Arguments

x	the arrange object
...	additional parameters for grid.draw

prob *Compute the probability for a given dose, given model and samples*

Description

Compute the probability for a given dose, given model and samples

Usage

```
prob(dose, model, samples, ...)

## S4 method for signature 'numeric,Model,Samples'
prob(dose, model, samples, ...)

## S4 method for signature 'matrix,ComboLogistic,Samples'
prob(dose, model, samples, ...)
```

Arguments

dose	the dose
model	the Model or ComboLogistic object
samples	the Samples
...	unused

Value

either the vector (for Model objects) or the matrix (for ComboLogistic objects) of probability samples.

Methods (by class)

- dose = numeric,model = Model,samples = Samples:
- dose = matrix,model = ComboLogistic,samples = Samples:

`Quantiles2LogisticNormal` *Convert prior quantiles (lower, median, upper) to logistic (log) normal model*

Description

This function uses generalised simulated annealing to optimise a `LogisticNormal` model to be as close as possible to the given prior quantiles.

Usage

```
Quantiles2LogisticNormal(dosegrid, refDose, lower, median, upper,
  level = 0.95, logNormal = FALSE, parstart = NULL, parlower = c(-10,
  -10, 0, 0, -0.95), parupper = c(10, 10, 10, 10, 0.95), verbose = TRUE,
  control = list(threshold.stop = 0.01, maxit = 50000, temperature = 50000,
  max.time = 600))
```

Arguments

`dosegrid`	the dose grid
`refDose`	the reference dose
`lower`	the lower quantiles
`median`	the medians
`upper`	the upper quantiles
`level`	the credible level of the (lower, upper) intervals (default: 0.95)
`logNormal`	use the log-normal prior? (not default) otherwise, the normal prior for the logistic regression coefficients is used
`parstart`	starting values for the parameters. By default, these are determined from the medians supplied.
`parlower`	lower bounds on the parameters (intercept alpha and the slope beta, the corresponding standard deviations and the correlation.)
`parupper`	upper bounds on the parameters
`verbose`	be verbose? (default)
`control`	additional options for the optimisation routine, see `GenSA` for more details

Value

a list with the best approximating `model` (`LogisticNormal` or `LogisticLogNormal`), the resulting `quantiles`, the `required` quantiles and the `distance` to the required quantiles, as well as the final `parameters` (which could be used for running the algorithm a second time)

Report — *A Reference Class to represent sequentially updated reporting objects.*

Description

A Reference Class to represent sequentially updated reporting objects.

Fields

`object` The object from which to report

`df` the data frame to which columns are sequentially added

`dfNames` the names to which strings are sequentially added

RuleDesign — *Initialization function for "RuleDesign"*

Description

Initialization function for "RuleDesign"

Usage

```
RuleDesign(nextBest, cohortSize, data, startingDose)
```

Arguments

`nextBest`	see `RuleDesign`
`cohortSize`	see `RuleDesign`
`data`	see `RuleDesign`
`startingDose`	see `RuleDesign`

Value

the `RuleDesign` object

RuleDesign-class — *Class for rule-based designs*

Description

The difference to `Design` class is that model, stopping and increments slots are missing.

Slots

`nextBest` how to find the next best dose, an object of class `NextBest`

`cohortSize` rules for the cohort sizes, an object of class `CohortSize`

`data` what is the dose grid, any previous data, etc., contained in an object of class `Data`

`startingDose` what is the starting dose? Must lie on the grid in `data`

Samples *Initialization function for "Samples"*

Description

Initialization function for "Samples"

Usage

```
Samples(data, options)
```

Arguments

data	see Samples
options	see Samples

Value

the Samples object

Samples-class *Class for the MCMC output*

Description

Class for the MCMC output

Slots

`data` a list where each entry contains the samples of a (vector-valued) parameter in a vector/matrix in the format (number of samples) x (dimension of the parameter).

`options` the McmcOptions which have been used

sampleSize *Compute the number of samples for a given MCMC options triple*

Description

Compute the number of samples for a given MCMC options triple

Usage

```
sampleSize(mcmcOptions)
```

Arguments

mcmcOptions	the McmcOptions object

Value

the resulting sample size

setSeed *Helper function to set and save the RNG seed*

Description

This is basically copied from simulate.lm

Usage

```
setSeed(seed = NULL)
```

Arguments

seed	an object specifying if and how the random number generator should be initialized ("seeded"). Either NULL (default) or an integer that will be used in a call to set.seed before simulating the response vectors. If set, the value is saved as the seed slot of the returned object. The default, NULL will not change the random generator state.

Value

The RNGstate will be returned, in order to call this function with this input to reproduce the obtained simulation results

Author(s)

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show,DualSimulationsSummary-method *Show the summary of the dual-endpoint simulations*

Description

Show the summary of the dual-endpoint simulations

Usage

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

Arguments

object	the DualSimulationsSummary object we want to print

Value

invisibly returns a data frame of the results with one row and appropriate column names

---

`show,GeneralSimulationsSummary-method`
Show the summary of the simulations

Description

Show the summary of the simulations

Usage

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

Arguments

`object`	the `GeneralSimulationsSummary` object we want to print

Value

invisibly returns a data frame of the results with one row and appropriate column names

---

`show,SimulationsSummary-method`
Show the summary of the simulations

Description

Show the summary of the simulations

Usage

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

Arguments

`object`	the `SimulationsSummary` object we want to print

Value

invisibly returns a data frame of the results with one row and appropriate column names

simulate,Design-method

Simulate outcomes from a CRM design

Description

Simulate outcomes from a CRM design

Usage

```
## S4 method for signature 'Design'
simulate(object, nsim = 1L, seed = NULL, truth,
  args = NULL, firstSeparate = FALSE, mcmcOptions = McmcOptions(),
  parallel = FALSE, ...)
```

Arguments

object	the Design object we want to simulate data from
nsim	the number of simulations (default: 1)
seed	see setSeed
truth	a function which takes as input a dose (vector) and returns the true probability (vector) for toxicity. Additional arguments can be supplied in args.
args	data frame with arguments for the truth function. The column names correspond to the argument names, the rows to the values of the arguments. The rows are appropriately recycled in the nsim simulations. In order to produce outcomes from the posterior predictive distribution, e.g, pass an object that contains the data observed so far, truth contains the prob function from the model in object, and args contains posterior samples from the model.
firstSeparate	enroll the first patient separately from the rest of the cohort? (not default) If yes, the cohort will be closed if a DLT occurs in this patient.
mcmcOptions	object of class McmcOptions, giving the MCMC options for each evaluation in the trial. By default, the standard options are used
parallel	should the simulation runs be parallelized across the clusters of the computer? (not default)
...	not used

Value

an object of class Simulations

simulate,DualDesign-method
Simulate outcomes from a dual-endpoint design

Description

Simulate outcomes from a dual-endpoint design

Usage

```
## S4 method for signature 'DualDesign'
simulate(object, nsim = 1L, seed = NULL, trueTox,
  trueBiomarker, args = NULL, sigma2W, rho = 0, firstSeparate = FALSE,
  mcmcOptions = McmcOptions(), parallel = FALSE, ...)
```

Arguments

object	the DualDesign object we want to simulate data from
nsim	the number of simulations (default: 1)
seed	see setSeed
trueTox	a function which takes as input a dose (vector) and returns the true probability (vector) for toxicity. Additional arguments can be supplied in args.
trueBiomarker	a function which takes as input a dose (vector) and returns the true biomarker level (vector). Additional arguments can be supplied in args.
args	data frame with arguments for the trueTox and trueBiomarker function. The column names correspond to the argument names, the rows to the values of the arguments. The rows are appropriately recycled in the nsim simulations.
sigma2W	variance for the biomarker measurements
rho	correlation between toxicity and biomarker measurements (default: 0)
firstSeparate	enroll the first patient separately from the rest of the cohort? (not default) If yes, the cohort will be closed if a DLT occurs in this patient.
mcmcOptions	object of class McmcOptions, giving the MCMC options for each evaluation in the trial. By default, the standard options are used
parallel	should the simulation runs be parallelized across the clusters of the computer? (not default)
...	not used

Value

an object of class DualSimulations

simulate,RuleDesign-method

Simulate outcomes from a rule-based design

Description

Simulate outcomes from a rule-based design

Usage

```
## S4 method for signature 'RuleDesign'
simulate(object, nsim = 1L, seed = NULL, truth,
  args = NULL, parallel = FALSE, ...)
```

Arguments

object	the RuleDesign object we want to simulate data from
nsim	the number of simulations (default: 1)
seed	see setSeed
truth	a function which takes as input a dose (vector) and returns the true probability (vector) for toxicity. Additional arguments can be supplied in args.
args	data frame with arguments for the truth function. The column names correspond to the argument names, the rows to the values of the arguments. The rows are appropriately recycled in the nsim simulations.
parallel	should the simulation runs be parallelized across the clusters of the computer? (not default)
...	not used

Value

an object of class GeneralSimulations

Simulations

Initialization function for the "Simulations" class

Description

Initialization function for the "Simulations" class

Usage

```
Simulations(fit, stopReasons, ...)
```

Arguments

fit	see Simulations
stopReasons	see Simulations
...	additional parameters from GeneralSimulations

Value

the Simulations object

Simulations-class *Class for the simulations output from model based designs*

Description

This class captures the trial simulations from model based designs. Additional slots fit and stopReasons compared to the general class GeneralSimulations.

Slots

`fit` list with the final fits

`stopReasons` list of stopping reasons for each simulation run

SimulationsSummary-class *Class for the summary of model-based simulations output*

Description

In addition to the slots in the parent class GeneralSimulationsSummary, it contains two slots with model fit information.

Details

Note that objects should not be created by users, therefore no initialization function is provided for this class.

Slots

`fitAtDoseMostSelected` fitted toxicity rate at dose most often selected

`meanFit` list with the average, lower (2.5 quantiles of the mean fitted toxicity at each dose level

size *Determine the size of the next cohort*

Description

This function determines the size of the next cohort.

Usage

```
size(cohortSize, dose, data, ...)

## S4 method for signature 'CohortSizeRange,ANY,Data'
size(cohortSize, dose, data, ...)

## S4 method for signature 'CohortSizeDLT,ANY,Data'
size(cohortSize, dose, data, ...)

## S4 method for signature 'CohortSizeMax,ANY,Data'
size(cohortSize, dose, data, ...)

## S4 method for signature 'CohortSizeMin,ANY,Data'
size(cohortSize, dose, data, ...)

## S4 method for signature 'CohortSizeConst,ANY,Data'
size(cohortSize, dose, data, ...)

## S4 method for signature 'CohortSizeParts,ANY,DataParts'
size(cohortSize, dose, data, ...)
```

Arguments

cohortSize	The rule, an object of class CohortSize
dose	the next dose
data	The data input, an object of class Data
...	additional arguments

Value

the size as integer value

Methods (by class)

- cohortSize = CohortSizeRange,dose = ANY,data = Data: Determine the cohort size based on the range into which the next dose falls into
- cohortSize = CohortSizeDLT,dose = ANY,data = Data: Determine the cohort size based on the number of DLTs so far
- cohortSize = CohortSizeMax,dose = ANY,data = Data: Size based on maximum of multiple cohort size rules
- cohortSize = CohortSizeMin,dose = ANY,data = Data: Size based on minimum of multiple cohort size rules

- `cohortSize = CohortSizeConst,dose = ANY,data = Data`: Constant cohort size
- `cohortSize = CohortSizeParts,dose = ANY,data = DataParts`: Cohort size based on the parts

`Stopping-class` *The virtual class for stopping rules*

Description

The virtual class for stopping rules

See Also

`StoppingList`, `StoppingCohortsNearDose`, `StoppingPatientsNearDose`, `StoppingMinCohorts`, `StoppingMinPatients`, `StoppingTargetProb` `StoppingMTDdistribution`, `StoppingTargetBiomarker`

`StoppingAll` *Initialization function for "StoppingAll"*

Description

Initialization function for "StoppingAll"

Usage

```
StoppingAll(stopList)
```

Arguments

`stopList`	see `StoppingAll`

Value

the `StoppingAll` object

`StoppingAll-class` *Stop based on fullfillment of all multiple stopping rules*

Description

This class can be used to combine multiple stopping rules with an AND operator.

Details

`stopList` contains all stopping rules, which are again objects of class `Stopping`. All stopping rules must be fulfilled in order that the result of this rule is to stop.

Slots

`stopList` list of stopping rules

StoppingAny *Initialization function for "StoppingAny"*

Description

Initialization function for "StoppingAny"

Usage

```
StoppingAny(stopList)
```

Arguments

stopList	see StoppingAny

Value

the StoppingAny object

StoppingAny-class *Stop based on fullfillment of any stopping rule*

Description

This class can be used to combine multiple stopping rules with an OR operator.

Details

stopList contains all stopping rules, which are again objects of class Stopping. Any of these rules must be fulfilled in order that the result of this rule is to stop.

Slots

stopList	list of stopping rules

StoppingCohortsNearDose *Initialization function for "StoppingCohortsNearDose"*

Description

Initialization function for "StoppingCohortsNearDose"

Usage

```
StoppingCohortsNearDose(nCohorts, percentage)
```

Arguments

nCohorts	see StoppingCohortsNearDose
percentage	see StoppingCohortsNearDose

Value

the StoppingCohortsNearDose object

StoppingCohortsNearDose-class *Stop based on number of cohorts near to next best dose*

Description

Stop based on number of cohorts near to next best dose

Slots

nCohorts	number of required cohorts
percentage	percentage (between 0 and 100) within the next best dose the cohorts must lie

StoppingList *Initialization function for "StoppingList"*

Description

Initialization function for "StoppingList"

Usage

```
StoppingList(stopList, summary)
```

Arguments

stopList	see StoppingList
summary	see StoppingList

Value

the StoppingList object

StoppingList-class *Stop based on multiple stopping rules*

Description

This class can be used to combine multiple stopping rules.

Details

stopList contains all stopping rules, which are again objects of class Stopping, and the summary is a function taking a logical vector of the size of stopList and returning a single logical value. For example, if the function all is given as summary function, then this means that all stopping rules must be fulfilled in order that the result of this rule is to stop.

Slots

stopList list of stopping rules

summary the summary function to combine the results of the stopping rules into a single result

---

StoppingMinCohorts *Initialization function for "StoppingMinCohorts"*

Description

Initialization function for "StoppingMinCohorts"

Usage

```
StoppingMinCohorts(nCohorts)
```

Arguments

nCohorts	see StoppingMinCohorts

Value

the StoppingMinCohorts object

StoppingMinCohorts-class

Stop based on minimum number of cohorts

Description

Stop based on minimum number of cohorts

Slots

`nCohorts` minimum required number of cohorts

StoppingMinPatients

Initialization function for "StoppingMinPatients"

Description

Initialization function for "StoppingMinPatients"

Usage

```
StoppingMinPatients(nPatients)
```

Arguments

`nPatients`	see `StoppingMinPatients`

Value

the `StoppingMinPatients` object

StoppingMinPatients-class

Stop based on minimum number of patients

Description

Stop based on minimum number of patients

Slots

`nPatients` minimum allowed number of patients

StoppingMTDdistribution *Initialization function for "StoppingMTDdistribution"*

Description

Initialization function for "StoppingMTDdistribution"

Usage

```
StoppingMTDdistribution(target, thresh, prob)
```

Arguments

target	see StoppingMTDdistribution
thresh	see StoppingMTDdistribution
prob	see StoppingMTDdistribution

Value

the StoppingMTDdistribution object

StoppingMTDdistribution-class *Stop based on MTD distribution*

Description

Has 90% probability above a threshold of 50% of the current MTD been reached? This class is used for this question.

Slots

target the target toxicity probability (e.g. 0.33) defining the MTD

thresh the threshold relative to the MTD (e.g. 0.5)

prob required probability (e.g. 0.9)

StoppingPatientsNearDose *Initialization function for "StoppingPatientsNearDose"*

Description

Initialization function for "StoppingPatientsNearDose"

Usage

```
StoppingPatientsNearDose(nPatients, percentage)
```

Arguments

nPatients	see StoppingPatientsNearDose
percentage	see StoppingPatientsNearDose

Value

the StoppingPatientsNearDose object

StoppingPatientsNearDose-class *Stop based on number of patients near to next best dose*

Description

Stop based on number of patients near to next best dose

Slots

nPatients	number of required patients
percentage	percentage (between 0 and 100) within the next best dose the patients must lie

StoppingTargetBiomarker *Initialization function for "StoppingTargetBiomarker"*

Description

Initialization function for "StoppingTargetBiomarker"

Usage

```
StoppingTargetBiomarker(target, prob)
```

Arguments

target	see StoppingTargetBiomarker
prob	see StoppingTargetBiomarker

Value

the StoppingTargetBiomarker object

StoppingTargetBiomarker-class *Stop based on probability of target biomarker*

Description

Stop based on probability of target biomarker

Slots

target the biomarker target range, relative to the maximum, that needs to be reached. So this must be a probability range (1 is allowed here)

prob required target probability for reaching sufficient precision

---

StoppingTargetProb *Initialization function for "StoppingTargetProb"*

Description

Initialization function for "StoppingTargetProb"

Usage

```
StoppingTargetProb(target, prob)
```

Arguments

target	see StoppingTargetProb
prob	see StoppingTargetProb

Value

the StoppingTargetProb object

StoppingTargetProb-class *Stop based on probability of target tox interval*

Description

Stop based on probability of target tox interval

Slots

`target` the target toxicity interval, e.g. `c(0.2, 0.35)`

`prob` required target toxicity probability (e.g. `0.4`) for reaching sufficient precision

stopTrial *Stop the trial?*

Description

This function returns whether to stop the trial.

Usage

```
stopTrial(stopping, dose, samples, model, data, ...)

## S4 method for signature 'StoppingList,ANY,ANY,ANY,ANY'
stopTrial(stopping, dose, samples,
  model, data, ...)

## S4 method for signature 'StoppingAll,ANY,ANY,ANY,ANY'
stopTrial(stopping, dose, samples,
  model, data, ...)

## S4 method for signature 'StoppingAny,ANY,ANY,ANY,ANY'
stopTrial(stopping, dose, samples,
  model, data, ...)

## S4 method for signature 'StoppingCohortsNearDose,numeric,ANY,ANY,Data'
stopTrial(stopping,
  dose, samples, model, data, ...)

## S4 method for signature 'StoppingPatientsNearDose,numeric,ANY,ANY,Data'
stopTrial(stopping,
  dose, samples, model, data, ...)

## S4 method for signature 'StoppingMinCohorts,ANY,ANY,ANY,Data'
stopTrial(stopping, dose,
  samples, model, data, ...)

## S4 method for signature 'StoppingMinPatients,ANY,ANY,ANY,Data'
```

```
stopTrial(stopping, dose,
  samples, model, data, ...)

## S4 method for signature 'StoppingTargetProb,numeric,Samples,Model,ANY'
stopTrial(stopping,
  dose, samples, model, data, ...)


  ## S4 method for signature 'StoppingMTDdistribution,numeric,Samples,Model,ANY'
stopTrial(stopping,
  dose, samples, model, data, ...)


  ## S4 method for signature
## 'StoppingTargetBiomarker,numeric,Samples,DualEndpoint,ANY'
stopTrial(stopping,
  dose, samples, model, data, ...)
```

Arguments

stopping	The rule, an object of class Stopping
dose	the recommended next best dose
samples	the Samples object
model	The model input, an object of class Model
data	The data input, an object of class Data
...	additional arguments

Value

logical value: TRUE if the trial can be stopped, FALSE otherwise. It should have an attribute message which gives the reason for the decision.

Methods (by class)

- stopping = StoppingList,dose = ANY,samples = ANY,model = ANY,data = ANY: Stop based on multiple stopping rules
- stopping = StoppingAll,dose = ANY,samples = ANY,model = ANY,data = ANY: Stop based on fulfillment of all multiple stopping rules
- stopping = StoppingAny,dose = ANY,samples = ANY,model = ANY,data = ANY: Stop based on fulfillment of any stopping rule
- stopping = StoppingCohortsNearDose,dose = numeric,samples = ANY,model = ANY,data = Data: Stop based on number of cohorts near to next best dose
- stopping = StoppingPatientsNearDose,dose = numeric,samples = ANY,model = ANY,data = Data: Stop based on number of patients near to next best dose
- stopping = StoppingMinCohorts,dose = ANY,samples = ANY,model = ANY,data = Data: Stop based on minimum number of cohorts
- stopping = StoppingMinPatients,dose = ANY,samples = ANY,model = ANY,data = Data: Stop based on minimum number of patients
- stopping = StoppingTargetProb,dose = numeric,samples = Samples,model = Model,data = ANY: Stop based on probability of target tox interval

- `stopping = StoppingMTDdistribution,dose = numeric,samples = Samples,model = Model,data = ANY:` Stop based on MTD distribution
- `stopping = StoppingTargetBiomarker,dose = numeric,samples = Samples,model = DualEndpoint,data` Stop based on probability of targeting biomarker

`summary,DualSimulations-method`

Summarize the dual-endpoint design simulations, relative to given true dose-toxicity and dose-biomarker curves

---

Description

Summarize the dual-endpoint design simulations, relative to given true dose-toxicity and dose-biomarker curves

Usage

```
## S4 method for signature 'DualSimulations'
summary(object, trueTox, trueBiomarker,
  target = c(0.2, 0.35), ...)
```

Arguments

`object`	the `DualSimulations` object we want to summarize
`trueTox`	a function which takes as input a dose (vector) and returns the true probability (vector) for toxicity.
`trueBiomarker`	a function which takes as input a dose (vector) and returns the true biomarker level (vector).
`target`	the target toxicity interval (default: 20-35%) used for the computations
`...`	Additional arguments can be supplied here for `trueTox` and `trueBiomarker`

Value

an object of class `DualSimulationsSummary`

`summary,GeneralSimulations-method`

Summarize the simulations, relative to a given truth

Description

Summarize the simulations, relative to a given truth

Usage

```
## S4 method for signature 'GeneralSimulations'
summary(object, truth, target = c(0.2, 0.35),
  ...)
```

Arguments

object	the GeneralSimulations object we want to summarize
truth	a function which takes as input a dose (vector) and returns the true probability (vector) for toxicity
target	the target toxicity interval (default: 20-35%) used for the computations
...	Additional arguments can be supplied here for truth

Value

an object of class GeneralSimulationsSummary

---

summary,Simulations-method

Summarize the model-based design simulations, relative to a given truth

---

Description

Summarize the model-based design simulations, relative to a given truth

Usage

```
## S4 method for signature 'Simulations'
summary(object, truth, target = c(0.2, 0.35), ...)
```

Arguments

object	the Simulations object we want to summarize
truth	a function which takes as input a dose (vector) and returns the true probability (vector) for toxicity
target	the target toxicity interval (default: 20-35%) used for the computations
...	Additional arguments can be supplied here for truth

Value

an object of class SimulationsSummary

ThreePlusThreeDesign *Creates a new 3+3 design object from a dose grid*

Description

Creates a new 3+3 design object from a dose grid

Usage

```
ThreePlusThreeDesign(doseGrid)
```

Arguments

doseGrid	the dose grid to be used

Value

the object of class RuleDesign with the 3+3 design

Author(s)

Daniel Sabanes Bove <sabanesd@roche.com>

update,Data-method *Update method for the "Data" class*

Description

Add new data to the Data object

Usage

```
## S4 method for signature 'Data'
update(object, x, y, ID = (if (length(object@ID))
  max(object@ID) else 0L) + seq_along(y), ...)
```

Arguments

object	the old Data object
x	the dose level (one level only!)
y	the DLT vector (0/1 vector), for all patients in this cohort
ID	the patient IDs
...	not used

Value

the new Data object

update,DataCombo-method

Update method for the "DataCombo" class

Description

Add new data to the DataCombo object

Usage

```
## S4 method for signature 'DataCombo'
update(object, x, y, ID = (if (length(object@ID))
  max(object@ID) else 0L) + seq_along(y), ...)
```

Arguments

object	the old DataCombo object
x	the dose levels vector (one dose level combination only!)
y	the DLT vector (0/1 vector), for all patients in this cohort
ID	the patient IDs
...	not used

Value

the new DataCombo object

update,DataDual-method

Update method for the "DataDual" class

Description

Add new data to the DataDual object

Usage

```
## S4 method for signature 'DataDual'
update(object, x, y, w, ID = (if (length(object@ID))
  max(object@ID) else 0L) + seq_along(y), ...)
```

Arguments

object	the old DataDual object
x	the dose level (one level only!)
y	the DLT vector (0/1 vector), for all patients in this cohort
w	the biomarker vector, for all patients in this cohort
ID	the patient IDs
...	not used

Value

the new DataDual object

`update,DataParts-method` *Update method for the "DataParts" class*

Description

Add new data to the DataParts object

Usage

```
## S4 method for signature 'DataParts'
update(object, x, y, ID = (if (length(object@ID))
  max(object@ID) else 0L) + seq_along(y), ...)
```

Arguments

object	the old DataParts object
x	the dose level (one level only!)
y	the DLT vector (0/1 vector), for all patients in this cohort
ID	the patient IDs
...	not used

Value

the new DataParts object

`Validate` *A Reference Class to help programming validation for new S4 classes*

Description

Starting from an empty msg vector, with each check that is returning FALSE the vector gets a new element - the string explaining the failure of the validation

Fields

msg the message character vector

`writeModel` *Creating a WinBUGS model file*

Description

Convert R function to a **WinBUGS** model file. BUGS models follow closely S syntax. It is therefore possible to write most BUGS models as R functions. As a difference, BUGS syntax allows truncation specification like this: `dnorm(...) I(...)` but this is illegal in R. To overcome this incompatibility, use dummy operator `%_%` before `I(...)`: `dnorm(...) %_% I(...)`. The dummy operator `%_%` will be removed before the BUGS code is saved. In S-PLUS, a warning is generated when the model function is defined if the last statement in the model is an assignment. To avoid this warning, add the line `invisible()` to the end of the model definition. This line will be removed before the BUGS code is saved.

Usage

```
writeModel(model, con = "model.bug", digits = 5)
```

Arguments

`model`	R function containing the BUGS model in the BUGS model language, for minor differences see Section Details.
`con`	passed to `writeLines` which actually writes the model file
`digits`	number of significant digits used for **WinBUGS** input, see `formatC`

Value

Nothing, but as a side effect, the model file is written

Author(s)

original idea by Jouni Kerman, modified by Uwe Ligges, DSB removed S Plus part

---

`&,Stopping,Stopping-method`
The method combining two atomic stopping rules

Description

The method combining two atomic stopping rules

Usage

```
## S4 method for signature 'Stopping,Stopping'
e1 & e2
```

Arguments

`e1`	First `Stopping` object
`e2`	Second `Stopping` object

Value

The StoppingAll object

`&,Stopping,StoppingAll-method`

The method combining an atomic and a stopping list

Description

The method combining an atomic and a stopping list

Usage

```
## S4 method for signature 'Stopping,StoppingAll'
e1 & e2
```

Arguments

e1	Stopping object
e2	StoppingAll object

Value

The modified StoppingAll object

`&,StoppingAll,Stopping-method`

The method combining a stopping list and an atomic

Description

The method combining a stopping list and an atomic

Usage

```
## S4 method for signature 'StoppingAll,Stopping'
e1 & e2
```

Arguments

e1	StoppingAll object
e2	Stopping object

Value

The modified StoppingAll object

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