Package ‘dtpcrm’

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Type Package

Title Dose Transition Pathways for Continual Reassessment Method

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Description Provides the dose transition pathways (DTP) to project in advance the doses recommended by a model-based design for subsequent patients (stay, escalate, deescalate or stop early) using all the accumulated toxicity information; See Yap et al (2017) <doi: 10.1158/1078-0432.CCR-17-0582>. DTP can be used as a design and an operational tool and can be displayed as a table or flow diagram. The 'dtpcrm' package also provides the modified continual reassessment method (CRM) and time-to-event CRM (TITE-CRM) with added practical considerations to allow stopping early when there is sufficient evidence that the lowest dose is too toxic and/or there is a sufficient number of patients dosed at the maximum tolerated dose.

License GPL (>= 2)

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LazyData true

Imports diagram, dfcrm

Suggests knitr, rmarkdown, testthat

VignetteBuilder knitr

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applied_crm

Description

applied_crm is used to execute the continual reassessment method with specified design options to determine the dose for the next subject.

Usage

applied_crm(prior, target, tox, level, no_skip_esc = TRUE, no_skip_deesc = TRUE, global_coherent_esc = TRUE, stop_func = NULL, ...)

Arguments

- **prior**: A vector of prior estimates of toxicity probabilities for the dose levels.
- **target**: The target DLT rate.
- **tox**: A vector of subject outcomes; 1 indicates toxicity, 0 otherwise.
- **level**: A vector of dose levels assigned to subjects. The length of level must be equal to that of tox.
- **no_skip_esc**: If FALSE, the method will not enforce skipping of doses in escalation. Default is TRUE.
- **no_skip_deesc**: If FALSE, the method will not enforce no skipping of doses in de-escalation. Default is TRUE.
- **global_coherent_esc**: If FALSE, the method will not enforce global coherent escalation, that is, escalation if the overall rate of toxicity seen at the current dose level is above the target rate. Default is TRUE.
stop_func

An optional argument to provide a function which will utilised alongside the CRM to determine if the trial should be stopped.

... Any other arguments detailed in dfcrm::crm.

Details

For maximum likelihood estimation, the variance of the estimate of beta (post.var) is approximated by the posterior variance of beta with a dispersed normal prior.

The empiric model is specified as $F(d, beta) = d^{\exp(beta)}$. The logistic model is specified as logit$(F(d,beta)) = \text{intcpt} + \exp(beta) \ast d$. For method="bayes", the prior on beta is normal with mean 0. Exponentiation of beta ensures an increasing dose-toxicity function.

This function is largely a wrapper for the dfcrm function crm. It provides functionality for additional design choices for the CRM including global coherency and stopping for excess toxicity and stopping when sufficient number of subjects are dosed at MTD.

Value

An object of class "mtd" is returned as per package "dfcrm", additional information is provided if a stopping function is used.

prior
Initial guesses of toxicity rates.
target
The target probability of toxicity at the MTD.
ptox
Updated estimates of toxicity rates.
ptoxL
Lower confidence/probability limits of toxicity rates.
ptoxU
Upper confidence/probability limits of toxicity rates.
mtd
The updated estimate of the MTD.
prior.var
The variance of the normal prior.
post.var
The posterior variance of the model parameter.
estimate
Estimate of the model parameter.
method
The method of estimation.
model
The working model.
dosescaled
The scaled doses obtained via backward substitution.
tox
Patients’ toxicity indications.
level
Dose levels assigned to patients.
stop
A logical variable detailing if the trial should be stopped; TRUE to stop, FALSE otherwise.
stop_reason
A detailed reason for why the trial should be stopped. Only provided if stop is TRUE.

References


Examples

```
prior <- c(0.1, 0.3, 0.5)
target <- 0.2
tox <- c(0, 0, 1, 0, 1, 1)
level <- c(1, 1, 1, 2, 2, 2)
applied_crm(prior, target, tox, level, no_skip_esc = TRUE, no_skip_deesc = TRUE,
global_coherent_esc = TRUE, stop_func = NULL)
```

---

`applied_crm_sim`  
*Simulate CRM trials using specified design options*

Description

`applied_crm_sim` is used to simulate trials using the continual reassessment method with specified design options to determine the operating characteristics.

Usage

```
applied_crm_sim(true_tox, prior, target, max_sample_size, first_dose,
                   num_sims, cohort_size = 1, dose_func = applied_crm, ...)
```

Arguments

- `true_tox` A vector of ‘true’ underlying rates of toxicity for each of the dose levels.
- `prior` A vector of prior estimates of toxicity probabilities for the dose levels.
- `target` The target DLT rate.
- `max_sample_size` The maximum number of subjects to be recruited in any simulation.
- `first_dose` The first dose level to tested.
- `num_sims` The total number of simulations to be run.
- `cohort_size` The size of the cohorts. Default is 1.
- `dose_func` The function to be employed in executing the CRM. Default is `applied_crm`.
- `...` Any other arguments detailed in `dtpcrm::applied_crm`.

Value

A list containing two further lists. The first of these lists contains the operating characteristics of the design, the second contains the underlying data for each of the simulation iterations.

References


Examples

```r
# It may take quite long for large num_sims
prior <- c(0.1, 0.3, 0.5)
target <- 0.2
ture_tox <- c(0.15, 0.25, 0.45)
first_dose <- 1
num_sims <- 5 # recommend doing 5000 simulations for the final design

applied_crm_sim(true_tox, prior, target, max_sample_size = 30, first_dose,
    num_sims, cohort_size = 1, dose_func = applied_crm)
```

---

**Description**

`applied_titecrm` is used to execute the time-to-event continual reassessment method with specified design options to determine the dose for the next subject.

**Usage**

```r
applied_titecrm(prior, target, tox, level, followup, obswin,
    no_skip_esc = TRUE, no_skip_deesc = TRUE, global_coherent_esc = TRUE,
    stop_func = NULL, ...)
```

**Arguments**

- `prior`: A vector of prior estimates of toxicity probabilities for the dose levels.
- `target`: The target DLT rate.
- `tox`: A vector of subject outcomes; 1 indicates toxicity, 0 otherwise.
- `level`: A vector of dose levels assigned to subjects. The length of level must be equal to that of tox.
- `followup`: A vector of follow up times of subjects. The length must be equal to that of tox.
- `obswin`: The observation period with respect to which DLT is assessed.
- `no_skip_esc`: If FALSE, the method will not enforce no skipping of doses in escalation. Default is TRUE.
- `no_skip_deesc`: If FALSE, the method will not enforce no skipping of doses in de-escalation. Default is TRUE.
- `global_coherent_esc`: If FALSE, the method will not enforce global coherent escalation, that is, escalation if the overall rate of toxicity seen at the current dose level is above the target rate. Default is TRUE.
- `stop_func`: An optional argument to provide a function which will utilised alongside the TITE-CRM to determine if the trial should be stopped.
- `...`: Any other arguments detailed in dfcrm::titecrm.
Details

The adaptive weighting scheme is given in Cheung and Chappell (2000) given in the reference list.

Value

An object of class "mtd" is returned as per package "dfcrm", additional information is provided if a stopping function is used.

- **prior**: Initial guesses of toxicity rates.
- **target**: The target probability of toxicity at the MTD.
- **ptox**: Updated estimates of toxicity rates.
- **ptoxL**: Lower confidence/probability limits of toxicity rates.
- **ptoxU**: Upper confidence/probability limits of toxicity rates.
- **mtd**: The updated estimate of the MTD.
- **prior.var**: The variance of the normal prior.
- **post.var**: The posterior variance of the model parameter.
- **estimate**: Estimate of the model parameter.
- **method**: The method of estimation.
- **model**: The working model.
- **dosescaled**: The scaled doses obtained via backward substitution.
- **tox**: subjects' toxicity indications.
- **level**: Dose levels assigned to subjects.
- **followup**: Follow-up times of subjects.
- **obswin**: Observation window with respect to which DLT is assessed.
- **weights**: Weights assigned to subjects.
- **entry**: Entry times of subjects.
- **exit**: Exit times of subjects.
- **scheme**: Weighting scheme.
- **stop**: A logical variable detailing if the trial should be stopped; TRUE to stop, FALSE otherwise.
- **stop_reason**: A detailed reason for why the trial should be stopped. Only provided if stop is TRUE.

References

Examples

```r
prior <- c(0.1, 0.3, 0.5)
target <- 0.2
tox <- c(0, 0, 1, 0, 1, 1)
level <- c(1, 1, 1, 2, 2, 2)
followup <- c(96, 82, 77, 60, 51, 44)
obswin <- 80

applied_titecrm(prior = prior, target = target, tox = tox, level = level,
followup = followup, obswin = obswin)
```

Description

`applied_titecrmts_sim` is used to simulate trials using the two-stage time-to-event continual re-assessment method with specified design options to determine the operating characteristics.

Usage

```r
applied_titecrmts_sim(true_tox, prior, target, max_sample_size,
num_sims, cohort_size = 1, obswin, minfu, recrate, initdes,
dose_func = applied_titecrm, ...)
```

Arguments

- `true_tox`: A vector of 'true' underlying rates of toxicity for each of the dose levels.
- `prior`: A vector of prior estimates of toxicity probabilities for the dose levels.
- `target`: The target DLT rate.
- `max_sample_size`: The maximum number of subjects to be recruited in any simulation.
- `num_sims`: The total number of simulations to be run.
- `cohort_size`: The size of the cohorts. Default is 1.
- `obswin`: The observation period for total subject follow-up.
- `minfu`: The minimum amount of follow-up required for each subject.
- `recrate`: The number of subjects recruited per obswin.
- `initdes`: A vector specifying the doses to be assigned to subjects as per the initial design.
- `dose_func`: The function to be employed in executing the CRM. Default is `applied_titecrm`.
- `...`: Any other arguments detailed in `dtp::applied_titecrm`.

Value

A list containing two further lists. The first of these lists contains the operating characteristics of the design, the second contains the underlying data for each of the simulation iterations.
References


Examples

# It may take quite long for large num_sims
prior <- c(0.1, 0.3, 0.5)
target <- 0.2
true_tox <- c(0.05, 0.2, 0.35)
first_dose <- 1
num_sims <- 5  # recommend doing 5000 simulations for the final design
obswin = 80

applied_titecrmts_sim(true_tox = true_tox, prior = prior, target = target,
max_sample_size = 21, num_sims = num_sims,
cohort_size = 3, obswin = obswin, minfu = 20,
recreate = 3, initdes = c(rep(1, 3), rep(2, 3), rep(3, 15)),
dose_func = applied_titecrm)

applied_titecrm_sim  Simulate TITE-CRM trials using specified design options

Description

applied_titecrm_sim is used to simulate trials using the time-to-event continual reassessment method with specified design options to determine the operating characteristics.

Usage

applied_titecrm_sim(true_tox, prior, target, max_sample_size,
first_dose, num_sims, cohort_size = 1, obswin, minfu, recreate, dose_func
= applied_titecrm, ...)

Arguments

ttrue_tox  A vector of 'true' underlying rates of toxicity for each of the dose levels.
prior  A vector of prior estimates of toxicity probabilities for the dose levels.
target  The target DLT rate.
max_sample_size  The maximum number of subjects to be recruited in any simulation.
first_dose  The first dose level to tested.
num_sims  The total number of simulations to be run.
calculate_dtps

DESCRIPTION

calculate_dtps is used to produce the dose transition pathways for the continual reassessment method with specified design options. These pathways present the possible model recommendations based on all permutations of trial outcomes.

Value

A list containing two further lists. The first of these lists contains the operating characteristics of the design, the second contains the underlying data for each of the simulation iterations.

REFERENCES


EXAMPLES

# It may take quite long for large num_sims
prior <- c(0.1, 0.3, 0.5)
target <- 0.2
true_tox <- c(0.05, 0.2, 0.35)
first_dose <- 1
num_sims <- 5 # recommend doing 5000 simulations for the final design
obswin = 80

applied_titecrm_sim(true_tox = true_tox, prior = prior, target = target,
max_sample_size = 21, first_dose = first_dose,
num_sims = num_sims, cohort_size = 3,
obswin = obswin, minfu = 20, recreate = 3,
dose_func = applied_titecrm)
Usage

```r
calculate_dtps(next_dose, cohort_sizes, prev_tox = c(), prev_dose = c(), dose_func = applied_crm, ...)
```

Arguments

- **next_dose**: An integer value representing the dose to be assigned to the first cohort of subjects in the pathways.
- **cohort_sizes**: A vector of cohort sizes representing the size of the cohorts to be treated with the recommended dose at each decision point.
- **prev_tox**: A vector of previous subject outcomes; 1 indicates toxicity, 0 otherwise.
- **prev_dose**: A vector of previous subject doses; The length of prev_dose must be equal to that of prev_tox.
- **dose_func**: A function such as applied_crm which produces an object of class 'mtd'. To be used for calculation of the next recommended dose for each pathway permutation.
- **...**: Any other arguments to be passed to dose_func; for specific arguments related to applied_crm see.

Value

Produces a dataframe containing all possible permutations of outcomes for each cohort based on cohort_sizes and the recommended doses for such permutations.

Examples

```r
prior <- c(0.1, 0.2, 0.5)
target <- 0.15
prev_tox <- c(0, 0, 0)
prev_dose <- c(2, 2, 2)
cohort_sizes <- c(2, 3)

next_dose = applied_crm(prior = prior, target = target,
                        tox = prev_tox, level = prev_dose)$mtd

dose_func <- applied_crm

DTP = calculate_dtps(next_dose, cohort_sizes, prev_tox = prev_tox, 
                      prev_dose = prev_dose, dose_func = applied_crm, 
                      prior = prior, target = target)
```
dtpflow

Produce DTP flow diagram

Description

dtpflow will produce a flow diagram of the possible paths for the next three cohorts of subjects.

Usage

dtpflow(dtptable, cohort.labels = c('C1', 'C2', 'C3'))

Arguments

dtptable a dataframe produced by calculate_dtps where cohort_sizes was of length 3.
cohort.labels A vector of length 3, containing character strings for the cohort labels.

Details

The function will produce a visual flow diagram for the first three cohorts of the provided dataframe.

Examples

```r
prior <- c(0.1, 0.2, 0.5)
target <- 0.15
prev_tox <- c(0, 0, 0)
prev_dose <- c(2, 2, 2)
cohort_sizes <- c(2, 3, 3)

next_dose = applied_crm(prior = prior, target = target,
    tox = prev_tox, level = prev_dose)$mtd
dose_func <- applied_crm

DTP = calculate_dtps(next_dose, cohort_sizes, prev_tox = prev_tox,
    prev_dose = prev_dose, dose_func = applied_crm,
    prior = prior, target = target)
dtpflow(dtptable = DTP, cohort.labels = c('C1', 'C2', 'C3'))
```
Description

Provides functionality for plotting the posterior estimates of probabilities of toxicity at each dose level for both the most recent update and for past cohort updates if specified.

Usage

plot_crm(crm, dose_labels, cohort_sizes = NULL, file = NULL, height = 600, width = 750, dose_func = NULL, 
...,
ylim = c(0, 1), lwd = 1, cex.axis = 1, cex.lab = 1,
cex = 1, cohort.last = F)

Arguments

crm
  An object of class 'mtd' produced by applied_crm to be plotted.
dose_labels
  A vector of character strings detailing the labels to be used for each dose level in the plot.
cohort_sizes
  An optional vector of cohort sizes; if provided the previous estimates for each cohort will be plotted in addition.
file
  An optional string for the file name; if provided the plot will be saved as a .PNG to the current working directory under the provided file name.
height
  A numeric value specifying the vertical pixel count of the plot. Default is 600.
width
  A numeric value specifying the horizontal pixel count of the plot. Default is 750.
dose_func
  Must be provided if cohort_sizes is provided. The function to be used to when implementing the CRM for previous cohorts.
... 
  Arguments to be provided to dose_func detailing CRM specification. See applied_crm.
ylim
  The y-axis range. Default is c(0, 1)
lwd
  line width relative to the default (default=1). 2 is twice as wide. Default is 1.
cex.axis
  The magnification to be used for axis annotation relative to the current setting of cex. Default is 1.
cex.lab
  The magnification to be used for x and y labels relative to the current setting of cex. Default is 1.
cex
  A numerical value giving the amount by which plotting text and symbols should be magnified relative to the default. Default is 1.
cohort.last
  If TRUE, the last cohort will have lwd = 6 for emphasis. Default is FALSE.
Details

Produces a plot of current dose-toxicity estimates including the priors and outputs a .png of plot to current directory if 'file' is provided. Potential for history of estimates by cohort if cohort.sizes is provided; dose_func is required to do this.

Examples

```r
prior <- c(0.1, 0.3, 0.5)
target <- 0.2
tox <- c(0, 0, 1, 0, 1, 1)
level <- c(1, 1, 1, 2, 2, 2)

crm <- applied_crm(prior, target, tox, level, no_skip_esc = TRUE, no_skip_deesc = TRUE,
global_coherent_esc = TRUE, stop_func = NULL)

plot_crm(crm, dose_labels = c("1", "2", "3"))
```

Description

This is a function for use with applied_crm for the stop_func argument. The rule will suggest stopping in the scenario that a particular number of patients has already been treated at the current recommended MTD.

Usage

```r
stop_for_consensus_reached(x, req_at_mtd)
```

Arguments

- `x`: An object of class 'mtd'.
- `req_at_mtd`: An integer; the number of patients required at current estimate of MTD to suggest stopping for consensus.

Details

This function is an example of a possible stopping function to be used with applied_crm, it will modify the 'mtd' class object produced by applied_crm to include a logical value under the name 'stop' indicating whether or not the trial should stop. The package dtpcrm contains a few of these functions for possible use with applied_crm.
stop_for_excess_toxicity_empiric

Examples

```r
prior <- c(0.1, 0.3, 0.5)
target <- 0.2
tox <- c(0, 0, 1, 0, 1, 1)
level <- c(1, 1, 1, 2, 2, 2)

stop_rule <- function(x){
  x <- stop_for_consensus_reached(x, req_at_mtd = 6)
}

crm <- applied_crm(prior, target, tox, level, no_skip_esc = TRUE, no_skip_deesc = TRUE,
                     global_coherent_esc = TRUE, stop_func = stop_rule)
```

Description

This is a function for use with applied_crm for the stop_func argument. The rule will suggest stopping in the scenario that the probability of toxicity being greater than a specified value at a defined dose is greater than some further specified certainty value.

Usage

```r
stop_for_excess_toxicity_empiric(x, tox_lim, prob_cert, dose = 1,
                                 nsamps = 10^6, suppress_dose = TRUE)
```

Arguments

- `x`: An object of class 'mtd'.
- `tox_lim`: A numeric; specifying the value for which the estimated toxicity at the selected dose is not to exceed.
- `prob_cert`: A numeric; specifying the probability value to be used when assessing the certainty required that toxicity at the specified dose exceeds tox_lim.
- `dose`: An integer; the dose to be assessed.
- `nsamps`: number of samples used for beta in the underlying normal sampling of beta.
- `suppress_dose`: A logical value indicating if the MTD should be set to NA if trial should stop.

Details

This function is an example of a possible stopping function to be used with applied_crm, it will modify the 'mtd' class object produced by applied_crm to include a logical value under the name 'stop' indicating whether or not the trial should stop. The package dtpcrm contains a few of these functions for possible use with applied_crm.
Examples

```r
prior <- c(0.1, 0.3, 0.5)
target <- 0.2
tox <- c(0, 0, 1, 0, 1, 1)
level <- c(1, 1, 1, 2, 2, 2)

stop_rule <- function(x){
  x <- stop_for_excess_toxicity_empiric(x, tox_lim = 0.25, prob_cert = 0.85)
}

crm <- applied_crm(prior, target, tox, level, no_skip_esc = TRUE, no_skip_deesc = TRUE,
global_coherent_esc = TRUE, stop_func = stop_rule)
```

```r

stop_for_excess_toxicity_logistic

Stopping for excess toxicity - Logistic method
```

Description

This is a function for use with applied_crm for the stop_func argument. The rule will suggest stopping in the scenario that the probability of toxicity being greater than a specified value at a defined dose is greater than some further specified certainty value.

Usage

```r
stop_for_excess_toxicity_logistic(x, tox_lim, prob_cert, dose = 1,
  nsamps = 10^6, suppress_dose = TRUE)
```

Arguments

- **x**: An object of class `mtd`.
- **tox_lim**: A numeric; specifying the value for which the estimated toxicity at the selected dose is not to exceed.
- **prob_cert**: A numeric; specifying the probability value to be used when assessing the certainty required that toxicity at the specified dose exceeds tox_lim.
- **dose**: An integer; the dose to be assessed.
- **nsamps**: Number of samples used for beta in the underlying normal sampling of beta.
- **suppress_dose**: A logical value indicating if the MTD should be set to NA if trial should stop.

Details

This function is an example of a possible stopping function to be used with applied_crm, it will modify the `mtd` class object produced by applied_crm to include a logical value under the name `stop` indicating whether or not the trial should stop. The package dtpcrm contains a few of these functions for possible use with applied_crm.
Examples

```r
prior <- c(0.1, 0.3, 0.5)
target <- 0.2
tox <- c(0, 0, 1, 0, 1, 1)
level <- c(1, 1, 1, 2, 2, 2)

stop_rule <- function(x){
  x <- stop_for_sample_size(x, max_sample_size = 20)
  x <- stop_for_excess_toxicity_logistic(x, tox_lim = 0.25, prob_cert = 0.85)
}

crm <- applied_crm(prior, target, tox, level, no_skip_esc = TRUE, no_skip_deesc = TRUE,
global_coherent_esc = TRUE, stop_func = stop_rule)
```

Description

This is a function for use with `applied_crm` for the `stop_func` argument. The rule will suggest stopping in the scenario that a maximum number of subjects has been recruited.

Usage

```r
stop_for_sample_size(x, max_sample_size)
```

Arguments

- `x`: An object of class `mtd`.
- `max_sample_size`: An integer; specifying the maximum number of subjects to be recruited.

Details

This function is an example of a possible stopping function to be used with `applied_crm`, it will modify the `mtd` class object produced by `applied_crm` to include a logical value under the name 'stop' indicating whether or not the trial should stop. The package dtpcrm contains a few of these functions for possible use with `applied_crm`.

Examples

```r
prior <- c(0.1, 0.3, 0.5)
target <- 0.2
tox <- c(0, 0, 1, 0, 1, 1)
level <- c(1, 1, 1, 2, 2, 2)

stop_rule <- function(x){
  x <- stop_for_sample_size(x, max_sample_size = 20)
  x <- stop_for_excess_toxicity_logistic(x, tox_lim = 0.25, prob_cert = 0.85)
}

crm <- applied_crm(prior, target, tox, level, no_skip_esc = TRUE, no_skip_deesc = TRUE,
global_coherent_esc = TRUE, stop_func = stop_rule)
```
summary_crm <- applied_crm(prior, target, tox, level, no_skip_esc = TRUE, no_skip_deesc = TRUE, 
global_coherent_esc = TRUE, stop_func = stop_rule)

Description

summary_crm is used to return a dataframe of the summary of the output from applied_crm.

Usage

summary_crm(x)

Arguments

x 
An object assigned to be the output from applied_crm.

Details

This function takes an object of class "mtd" and produces a dataframe containing a summary of information within the object. Specifically it shows the dose levels, prior probabilities, number of evaluable patients, number of DLTs and the posterior probability estimates along with confidence/probability intervals if estimated in the underlying object.

Value

Dataframe of the summary of the output from applied_crm.

References


Examples

prior <- c(0.1, 0.3, 0.5)
target <- 0.2
tox <- c(0, 0, 1, 0, 1, 1)
level <- c(1, 1, 2, 2, 2)

crm_obj <- applied_crm(prior, target, tox, level, no_skip_esc = TRUE, no_skip_deesc = TRUE, 
global_coherent_esc = TRUE, stop_func = NULL)
summary.crm(crm_obj)
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