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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applied.crm  Execute the 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 no skipping of doses in escalation. De-
  fault is TRUE.
no_skip_deesc  If FALSE, the method will not enforce no skipping of doses in de-escalation. De-
  fault is TRUE.
global_coherent_esc  If FALSE, the method will not enforce global coherent escalation, that is, esca-
  lation 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 utilise 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 empirical model is specified as $F(d, \beta) = d^{\exp(\beta)}$. The logistic model is specified as $\logit(F(d,\beta)) = \text{intcpt} + \exp(\beta) \cdot d$. 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

```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)
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**

```r
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 characterististics 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
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)

applied_titecrm  
Execute the TITE-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

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 utilise 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)
```

---

**applied_titecrmts_sim**  _Simulate TITE-CRM trials using specified design options_

**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, recreate, 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.
- `recreate` 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

```r
# It may take quite long for large num_sims
prior <- c(0.1, 0.3, 0.5)
target <- 0.2
ture_tox <- c(0.05, 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,
  recrate = 3, initdes = c(rep(1, 3), rep(2, 3), rep(3, 15)),
  dose_func = applied_titecrm)
```

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

```r
applied_titecrm_sim(true_tox, prior, target, max_sample_size,
  first_dose, num_sims, cohort_size = 1, obswin, minfu, recrate, 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.
- `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.

cohort_size  The size of the subject 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.
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_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,
doanse_func = applied_titecrm)
Usage

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

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'))
```
**plot.crm**

Plot of posterior estimates from the CRM

**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**

```r
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.
**stop_for_consensus_reached**

**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
cr = 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 <- 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.
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)
```

**stop_for_excess_toxicity_empiric**

*Stopping for excess toxicity - Empiric 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_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

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)

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

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)
}

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)
}
Summary

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.

Examples

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

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