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)

Encoding UTF-8

LazyData true

Imports diagram, dfcrm

Suggests knitr, rmarkdown, testthat

VignetteBuilder knitr

RoxygenNote 6.1.1

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applied_crm

Execute the CRM

Description

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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 probabilties for the dose levels. The target DLT rate. target A vector of subject outcomes; 1 indicates toxicity, 0 otherwise. tox A vector of dose levels assigned to subjects. The length of level must be equal level to that of tox. If FALSE, the method will not enforce no skipping of doses in escalation. Deno_skip_esc fault is TRUE. If FALSE, the method will not enforce no skipping of doses in de-escalation. no_skip_deesc 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.

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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)) = intcpt + exp(beta) * 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

O'Quigley, J. O., Pepe, M., and Fisher, L. (1990). Continual reassessment method: A practical design for phase I clinical trials in cancer. Biometrics 46:33-48.

Cheung, Y. K. (2011). Dose Finding by the Continual Reassessment Method. New York: Chapman & Hall/CRC Press.

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Examples

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 probabilties 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 arguements 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

O'Quigley, J. O., Pepe, M., and Fisher, L. (1990). Continual reassessment method: A practical design for phase I clinical trials in cancer. Biometrics 46:33-48.

Cheung, Y. K. (2011). Dose Finding by the Continual Reassessment Method. New York: Chapman & Hall/CRC Press.

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Examples

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 probabilties 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.

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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.

i j

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

O'Quigley, J. O., Pepe, M., and Fisher, L. (1990). Continual reassessment method: A practical design for phase I clinical trials in cancer. Biometrics 46:33-48.

Cheung, Y. K. (2011). Dose Finding by the Continual Reassessment Method. New York: Chapman & Hall/CRC Press.

Cheung, Y. K. and Chappell, R. (2000). Sequential designs for phase I clinical trials with late-onset toxicities. Biometrics 56:1177-1182.

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Examples

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 reassessment method with specified design options to determine the operating characteristics.

Usage

```
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.

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 assisted to subjects as per the initial design.

The function to be employed in executing the CRM. Default is applied_titecrm.

... Any other arguements detailed in dtp::applied_titecrm.

Value

A list containg 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.

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References

O'Quigley, J. O., Pepe, M., and Fisher, L. (1990). Continual reassessment method: A practical design for phase I clinical trials in cancer. Biometrics 46:33-48.

Cheung, Y. K. (2011). Dose Finding by the Continual Reassessment Method. New York: Chapman & Hall/CRC Press.

Examples

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

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 probabilties 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.

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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 subjects.
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 arguements detailed in dtp::applied_titecrm.

Value

A list containg 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

O'Quigley, J. O., Pepe, M., and Fisher, L. (1990). Continual reassessment method: A practical design for phase I clinical trials in cancer. Biometrics 46:33-48.

Cheung, Y. K. (2011). Dose Finding by the Continual Reassessment Method. New York: Chapman & Hall/CRC Press.

Examples

calculate_dtps

Produce the Dose Transition Pathways

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 permumations of trial outcomes.

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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.

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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.

plot_crm

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

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 specifiying 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

```
stop_for_consensus_reached

Stopping for consensus
```

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

```
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' indicting whether or not the trial should stop. The package dtpcrm contains a few of these functions for possible use with applied_crm.

Examples

```
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 specifed value at a defined dose is greater than some further specified certainty value.

Usage

```
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 selcted dose is not to exceed.
prob_cert	A numeric; specifying the probability value to be used when assessing the certainty required that toxicty at the specificed 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

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 specifed 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 selcted dose is not to exceed.
prob_cert	A numeric; specifying the probability value to be used when assessing the certainty required that toxicty at the specificed 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

stop_for_sample_size Stopping for sample size reached

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

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

Arguments

```
x An object of class 'mtd'. max_sample_size
```

An integer; specifying the maxmium 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 modifiy the 'mtd' class object produced by applied_crm to include a logical value under the name 'stop' indicting whether or not the trial should stop. The package dtpcrm contains a few of these functions for possible use with applied_crm.

```
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)</pre>
```

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summary_crm

Provide a summary of applied crm output

Description

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

Usage

```
summary_crm(x)
```

Arguments

Х

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

O'Quigley, J. O., Pepe, M., and Fisher, L. (1990). Continual reassessment method: A practical design for phase I clinical trials in cancer. Biometrics 46:33-48.

Cheung, Y. K. (2011). Dose Finding by the Continual Reassessment Method. New York: Chapman & Hall/CRC Press.

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summary_crm(crm_obj)

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