

Package ‘ewoc’

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Type Package

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Author Marcio A. Diniz <marcio.diniz@cshs.org>

Maintainer Marcio A. Diniz <marcio.diniz@cshs.org>

Description An implementation of a variety of escalation with overdose control designs introduced by Babb, Rogatko and Zacks (1998) <doi:10.1002/(SICI)1097-0258(19980530)17:10%3C1103::AID-SIM793%3E3.0.CO;2-9>. It calculates the next dose as a clinical trial proceeds as well as performs simulations to obtain operating characteristics.

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LazyData TRUE

URL <https://github.com/dnzmarcio/ewoc/>

BugReports <https://github.com/dnzmarcio/ewoc/issues>

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accuracy_index	<i>Accuracy Index</i>
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Description

Calculate the Accuracy Index.

Usage

```
accuracy_index(mtd_estimate, dose_set, true_prob, theta, loss = c("squared",
  "absolute", "classification", "overdose"), alpha = NULL)
```

Arguments

mtd_estimate	a numerical vector of the MTD estimates.
dose_set	a numerical vector of allowable doses in the trial.
true_prob	a numerical vector of the true probabilities associated with 'dose_set'.
theta	a numerical value defining the proportion of expected patients to experience a medically unacceptable, dose-limiting toxicity (DLT) if administered the MTD.
loss	a loss function between the true probabilities of toxicity 'true_prob' and the target DLT rate 'theta'.
alpha	a numerical value indicating the weight of overdose for the overdose loss function.

Value

Accuracy Index for given loss function of the MTD estimates.

References

Cheung, Y. K. (2011). Dose finding by the continual reassessment method. CRC Press.

average_toxicity	<i>Average Toxicity Number</i>
------------------	--------------------------------

Description

Calculate the Average Toxicity Number.

Usage

```
average_toxicity(dose, dose_set, true_prob, theta)
```

Arguments

dose	a numerical matrix of assigned doses for each step of the trial (column) and for each trial (row).
dose_set	a numerical vector of allowable doses in the trial.
true_prob	a numerical vector of the true probabilities associated with 'dose_set'.
theta	a numerical value defining the proportion of expected patients to experience a medically unacceptable, dose-limiting toxicity (DLT) if administered the MTD.

Value

Average Toxicity Number.

References

Cheung, Y. K. (2011). Dose finding by the continual reassessment method. CRC Press.

dlt_rate	<i>Evaluation of the DLT rate</i>
----------	-----------------------------------

Description

Calculate the DLT rate for each trial, the average DLT rate, the percent of trials which have $DLT_{rate} > target_{rate} + margin$, the percent of trials which have $DLT_{rate} < target_{rate} - margin$ and the percent of trials which have $target_{rate} - margin < DLT_{rate} < target_{rate} + margin$.

Usage

```
dlt_rate(dlt_matrix, trial = FALSE, target_rate = NULL, margin = NULL,
        digits = 2)
```

Arguments

dlt_matrix	a matrix of the number of DLT for each step of the trial (column) and for each trial (row).
trial	a logical value indicating if the DLT rate for each trial should be returned.
target_rate	a numerical value of the target rate of DLT.
margin	a numerical value of the acceptable distance from the target_rate.
digits	a numerical value indicating the number of digits.

Value

trial a numerical vector of the DLT rate for each trial.

average a numerical value of the average of DLT rate considering a batch of trials.

upper the percent of trials which the DLT rate > target_rate + margin if margin != NULL and target_rate != NULL.

lower the percent of trials which the DLT rate < target_rate - margin if margin != NULL and target_rate != NULL.

interval the percent of trials which the target_rate - margin < DLT rate < target_rate + margin if margin != NULL and target_rate != NULL.

Examples

```
## Not run:
DLT <- 0
dose <- 30
step_zero <- ewoc_d1classic(DLT ~ dose, type = 'discrete',
                           theta = 0.33, alpha = 0.25,
                           min_dose = 0, max_dose = 100,
                           dose_set = seq(0, 100, 20),
                           rho_prior = matrix(1, ncol = 2, nrow = 1),
                           mtd_prior = matrix(1, ncol = 2, nrow = 1),
                           rounding = "nearest")

stop_rule_sim(step_zero)
response_sim <- response_d1classic(rho = 0.05, mtd = 20, theta = 0.33,
                                 min_dose = 10, max_dose = 50)

sim <- ewoc_simulation(step_zero = step_zero,
                      n_sim = 1, sample_size = 2,
                      alpha_strategy = "increasing",
                      response_sim = response_sim,
                      stop_rule_sim = stop_rule_sim,
                      ncores = 2)

dlt_rate(sim$dlt_sim)

## End(Not run)

## Not run:
DLT <- 0
dose <- 30
step_zero <- ewoc_d1classic(DLT ~ dose, type = 'discrete',
```

```

        theta = 0.33, alpha = 0.25,
        min_dose = 0, max_dose = 100,
        dose_set = seq(0, 100, 20),
        rho_prior = matrix(1, ncol = 2, nrow = 1),
        mtd_prior = matrix(1, ncol = 2, nrow = 1),
        rounding = "nearest")
stop_rule_sim(step_zero)
response_sim <- response_d1classic(rho = 0.05, mtd = 20, theta = 0.33,
                                min_dose = 10, max_dose = 50)
sim <- ewoc_simulation(step_zero = step_zero,
                      n_sim = 2, sample_size = 30,
                      alpha_strategy = "increasing",
                      response_sim = response_sim,
                      stop_rule_sim = stop_rule_sim,
                      ncores = 2)
dlt_rate(sim$dlt_sim)

## End(Not run)

```

ewoc_d1classic

Escalation With Overdose Control

Description

Finding the next dose for a phase I clinical trial based on the Escalation with Overdose Control (EWOC) design considering the classic parametrization for binary responses and single agent.

Usage

```

ewoc_d1classic(formula, theta, alpha, mtd_prior, rho_prior, min_dose, max_dose,
               type = c("continuous", "discrete"), first_dose = NULL, last_dose = NULL,
               dose_set = NULL, max_increment = NULL, rounding = c("down", "nearest"),
               n_adapt = 5000, burn_in = 1000, n_mcmc = 1000, n_thin = 1,
               n_chains = 1)

```

Arguments

formula	an object of class Formula : a symbolic description of the model to be fitted with only one regressor term corresponding to the dose for the right side and a numeric vector a response containing number of DLT for the left side.
theta	a numerical value defining the proportion of expected patients to experience a medically unacceptable, dose-limiting toxicity (DLT) if administered the MTD.
alpha	a numerical value defining the probability that the dose selected by EWOC is higher than the MTD.
mtd_prior	a matrix 1 x 2 of hyperparameters for the Beta prior distribution associated with the parameter MTD.

rho_prior	a matrix 1 x 2 of hyperparameters for the Beta prior distribution associated with the parameter rho.
min_dose	a numerical value defining the lower bound of the support of the MTD.
max_dose	a numerical value defining the upper bound of the support of the MTD.
type	a character describing the type of the Maximum Tolerable Dose (MTD) variable.
first_dose	a numerical value for the first allowable dose in the trial. It is only necessary if type = 'continuous'.
last_dose	a numerical value for the last allowable dose in the trial. It is only necessary if type = 'continuous'.
dose_set	a numerical vector of allowable doses in the trial. It is only necessary if type = 'discrete'.
max_increment	a numerical value indicating the maximum increment from the current dose to the next dose.
rounding	a character indicating how to round a continuous dose to the one of elements of the dose set. It is only necessary if type = 'discrete'.
n_adapt	the number of iterations for adaptation. See adapt for details.
burn_in	numerical value indicating the number of iterations before to start monitoring.
n_mcmc	numerical value indicating the number of iterations to monitor.
n_thin	numerical value corresponding to the thinning interval for monitors.
n_chains	numerical value indicating the number of parallel chains for the model.

Value

next_dose the next recommend dose.
 mtd the posterior MTD distribution.
 rho the posterior rho_0 distribution.
 sample a list of the MCMC chains distribution.
 trial a list of the trial conditions.

References

Babb, J., Rogatko, A. and Zacks, S., 1998. Cancer phase I clinical trials: efficient dose escalation with overdose control. *Statistics in medicine*, 17(10), pp.1103-1120.

Examples

```
DLT <- 0
dose <- 20
test <- ewoc_d1classic(DLT ~ dose, type = 'discrete',
  theta = 0.33, alpha = 0.25,
  min_dose = 0, max_dose = 100,
  dose_set = seq(0, 100, 20),
  rho_prior = matrix(1, ncol = 2, nrow = 1),
  mtd_prior = matrix(1, ncol = 2, nrow = 1),
  rounding = "nearest")
```

```
summary(test)
plot(test)
```

ewoc_d1extended

Escalation With Overdose Control

Description

Finding the next dose for a phase I clinical trial based on the Escalation with Overdose Control (EWOC) design considering the extended parametrization for binary response and single agent.

Usage

```
ewoc_d1extended(formula, theta, alpha, rho_prior, min_dose, max_dose,
  type = c("continuous", "discrete"), first_dose = NULL, last_dose = NULL,
  dose_set = NULL, max_increment = NULL, rounding = c("down", "nearest"),
  n_adapt = 5000, burn_in = 1000, n_mcmc = 1000, n_thin = 1,
  n_chains = 1)
```

Arguments

formula	an object of class Formula : a symbolic description of the model to be fitted with only one regressor term corresponding to the dose for the right side and a numeric vector as a response containing number of DLT for the left side.
theta	a numerical value defining the proportion of expected patients to experience a medically unacceptable, dose-limiting toxicity (DLT) if administered the MTD.
alpha	a numerical value defining the probability that the dose selected by EWOC is higher than the MTD.
rho_prior	a matrix 3 x 2 of hyperparameters for the Beta prior distribution associated with each parameter rho. Each row corresponds to a parameter.
min_dose	a numerical value defining the lower bound of the support of the MTD.
max_dose	a numerical value defining the upper bound of the support of the MTD.
type	a character describing the type of the Maximum Tolerable Dose (MTD) variable.
first_dose	a numerical value for the first allowable dose in the trial.
last_dose	a numerical value for the last allowable dose in the trial.
dose_set	a numerical vector of allowable doses in the trial. It is only necessary if type = "discrete".
max_increment	a numerical value indicating the maximum increment from the current dose to the next dose.
rounding	a character indicating how to round a continuous dose to the one of elements of the dose set. It is only necessary if type = "discrete".
n_adapt	the number of iterations for adaptation. See adapt for details.

burn_in the number of iterations before to start monitoring.
 n_mcmc the number of iterations to monitor.
 n_thin thinning interval for monitors.
 n_chains the number of parallel chains for the model.

Value

next_dose the next recommend dose.
 mtd a numerical vector for the posterior MTD distribution considering the next patient covariable.
 rho a matrix for the posterior rho_0 and rho_1 distributions.
 sample a list of the MCMC chains distribution.
 trial a list of the trial conditions.

Examples

```
DLT <- 0
dose <- 30

test <- ewoc_d1extended(DLT ~ dose, type = 'discrete',
  theta = 0.33, alpha = 0.25,
  dose_set = c(30, 40, 50),
  min_dose = 20, max_dose = 100,
  rho_prior = matrix(1, ncol = 2, nrow = 2),
  rounding = "nearest")

summary(test)
plot(test)
```

 ewoc_d1ph

Escalation With Overdose Control

Description

Finding the next dose for a phase I clinical trial based on Escalation with Overdose Control (EWOC) design considering parametrization for time to event response and single agent.

Usage

```
ewoc_d1ph(formula, theta, alpha, tau, type = c("continuous", "discrete"),
  rho_prior, mtd_prior, shape_prior = NULL, min_dose, max_dose,
  first_dose = NULL, last_dose = NULL, dose_set = NULL,
  max_increment = NULL, distribution = c("exponential", "weibull"),
  rounding = c("down", "nearest"), n_adapt = 5000, burn_in = 1000,
  n_mcmc = 1000, n_thin = 1, n_chains = 1)
```

Arguments

formula	an object of class Formula : a symbolic description of the model to be fitted with only one regressor term corresponding to the dose for the right side and a matrix as a response containing time and status for the left side.
theta	a numerical value defining the proportion of expected patients to experience a medically unacceptable, dose-limiting toxicity (DLT) if administered the MTD.
alpha	a numerical value defining the probability that the dose selected by EWOC is higher than the MTD.
tau	a numerical value defining the period of time for a possible toxicity be observed.
type	a character describing the type of the Maximum Tolerable Dose (MTD) variable. It can be 'discrete' or 'continuous'.
rho_prior	a matrix 1x2 of hyperparameters for the Beta prior distribution associated with the parameter rho.
mtd_prior	a matrix 1x2 of hyperparameters for the Beta prior distribution associated with the parameter MTD.
shape_prior	a matrix 1x2 of hyperparameters for the Gamma prior distribution associated with the shape parameter r for the Weibull distribution. It is only necessary if distribution = 'weibull'.
min_dose	a numerical value defining the lower bound of the support of the MTD.
max_dose	a numerical value defining the upper bound of the support of the MTD.
first_dose	a numerical value for the first allowable dose in the trial. It is only necessary if type = 'continuous'.
last_dose	a numerical value for the last allowable dose in the trial. It is only necessary if type = 'continuous'.
dose_set	a numerical vector of allowable doses in the trial. It is only necessary if type = 'discrete'.
max_increment	a numerical value indicating the maximum increment from the current dose to the next dose.
distribution	a character establishing the distribution for the time of events. It can be 'exponential' or 'weibull'.
rounding	a character indicating how to round a continuous dose to the one of elements of the dose set. It can be 'nearest' or 'down'. It is only necessary if type = 'discrete'.
n_adapt	the number of iterations for adaptation. See adapt for details.
burn_in	the number of iterations before to start monitoring.
n_mcmc	the number of iterations to monitor.
n_thin	thinning interval for monitors.
n_chains	the number of parallel chains for the model.

Value

next_dose the next recommend dose.
mtd the posterior MTD distribution.
rho the posterior rho_0 distribution.
sample a list of the MCMC chains distribution.
trial a list of the trial conditions.

References

Tighiouart M, Liu Y, Rogatko A. Escalation with overdose control using time to toxicity for cancer phase I clinical trials. PloS one. 2014 Mar 24;9(3):e93070.

Examples

```
time <- 9
status <- 0
dose <- 30

test <- ewoc_d1ph(cbind(time, status) ~ dose, type = 'discrete',
  theta = 0.33, alpha = 0.25, tau = 10,
  min_dose = 30, max_dose = 50,
  dose_set = seq(30, 50, 5),
  rho_prior = matrix(1, ncol = 2, nrow = 1),
  mtd_prior = matrix(1, ncol = 2, nrow = 1),
  distribution = 'exponential',
  rounding = 'nearest')

summary(test)
plot(test)
```

ewoc_simulation

Generic EWOC simulation

Description

Generic function for simulating EWOC trials.

Usage

```
ewoc_simulation(step_zero, n_sim, sample_size, alpha_strategy = "fixed",
  alpha_rate = NULL, response_sim, stop_rule_sim = NULL, ncores = 1)
```

Arguments

<code>step_zero</code>	an object from the classes 'ewoc_d1classic', 'ewoc_d1extended', 'ewoc_d1ph' created using dummy data.
<code>n_sim</code>	a number indicating the number of phase I clinical trials to be simulated.
<code>sample_size</code>	a number indicating the number of patients enrolled for each clinical trial.
<code>alpha_strategy</code>	a character indicating the strategy to apply for the feasibility value. Default is "constant". Options are "increasing" and "conditional".
<code>alpha_rate</code>	a numerical value indicating the rate of the feasibility strategy. Only necessary if <code>alpha_strategy</code> is either 'increasing' or 'conditional'.
<code>response_sim</code>	a function which is self-contained and will be used as a generator function of the response variables in the simulation. Its only input is 'dose' and output is the indicator of DLT for classical and extended EWOC and the time until DLT for PH EWOC.
<code>stop_rule_sim</code>	a function having as an input an object containing all the information related to the trial as the returned object <code>trial</code> from either <code>ewoc_d1classic</code> , <code>ewoc_d1extended</code> , <code>ewoc_d1ph</code> and as output a logical value indicating the trial should be stopped.
<code>ncores</code>	a numeric value indicating the number of cores to be used in the simulation performed in parallel.

Value

`alpha_sim` a matrix $n_sim \times sample_size$ containing the values of feasibility used for each step in the trial and each trial in the simulation.

`dlt_sim` a matrix $n_sim \times sample_size$ containing ones and zeros indicating the occurrence of DLT (1) and the absence of DLT (0) for each step in the trial and each trial in the simulation.

`dose_sim` a matrix $n_sim \times sample_size$ containing the doses assigned for each step in the trial and each trial in the simulation.

`mtd_sim` a numeric vector $n_sim \times 1$ containing the recommended MTD for each trial in the simulation.

`rho_sim` a numeric vector $n_sim \times k$ containing the estimated rho parameter(s) for each trial in the simulation, where $k = 1$ for `ewoc_d1classic`, `ewoc_d1ph`, and $k = 2$ for `ewoc_d1extended`.

Examples

```
## Not run:
### Classic EWOC
DLT <- 0
dose <- 30
step_zero <- ewoc_d1classic(DLT ~ dose, type = 'discrete',
                           theta = 0.33, alpha = 0.25,
                           min_dose = 0, max_dose = 100,
                           dose_set = seq(0, 100, 20),
                           rho_prior = matrix(1, ncol = 2, nrow = 1),
                           mtd_prior = matrix(1, ncol = 2, nrow = 1),
```

```

        rounding = "nearest")
response_sim <- response_d1classic(rho = 0.05, mtd = 20, theta = 0.33,
                                min_dose = 10, max_dose = 50)
sim <- ewoc_simulation(step_zero = step_zero,
                      n_sim = 2, sample_size = 30,
                      alpha_strategy = "increasing",
                      response_sim = response_sim,
                      ncores = 2)

### Extended EWOC
DLT <- 0
dose <- 30
step_zero <- ewoc_d1extended(DLT ~ dose, type = 'discrete',
                             theta = 0.33, alpha = 0.25,
                             min_dose = 0, max_dose = 100,
                             dose_set = seq(0, 100, 20),
                             rho_prior = matrix(1, ncol = 2, nrow = 2),
                             rounding = "nearest")
response_sim <- response_d1extended(rho = c(0.05, 0.5),
                                   min_dose = 10, max_dose = 50)
sim <- ewoc_simulation(step_zero = step_zero,
                      n_sim = 2, sample_size = 30,
                      alpha_strategy = "increasing",
                      response_sim = response_sim,
                      ncores = 2)

### PH EWOC
time <- 0
status <- 0
dose <- 30

step_zero <- ewoc_d1ph(cbind(time, status) ~ dose, type = 'discrete',
                       theta = 0.33, alpha = 0.25, tau = 10,
                       min_dose = 30, max_dose = 50,
                       dose_set = seq(30, 50, 5),
                       rho_prior = matrix(1, ncol = 2, nrow = 1),
                       mtd_prior = matrix(1, ncol = 2, nrow = 1),
                       distribution = 'exponential',
                       rounding = 'nearest')
response_sim <- response_d1ph(rho = 0.05, mtd = 40, theta = 0.33,
                              min_dose = 30, max_dose = 50,
                              tau = 10, distribution = "exponential")
sim <- ewoc_simulation(step_zero = step_zero,
                      n_sim = 2, sample_size = 30,
                      alpha_strategy = "increasing",
                      response_sim = response_sim,
                      ncores = 2)

## End(Not run)

```

inv_standard_dose	<i>Inverse standardization of the dose</i>
-------------------	--

Description

Unstandardizing a dose between minimum and maximum doses.

Usage

```
inv_standard_dose(dose, min_dose, max_dose)
```

Arguments

dose	a numerical value defining the standardized dose to be unstandardized.
min_dose	a numerical value defining the lower bound of the support of the MTD.
max_dose	a numerical value defining the upper bound of the support of the MTD.

Value

dose a numerical value between min_dose and max_dose.

logit	<i>Logit</i>
-------	--------------

Description

Calculating the logit of a probability

Usage

```
logit(p)
```

Arguments

p	a numerical value defining the probability to be transformed into logit scale.
---	--

Value

logit a numerical value in logit scale.

`mtd_bias`*Bias of the MTD estimates*

Description

Calculate the bias.

Usage

```
mtd_bias(mtd_estimate, true_mtd)
```

Arguments

`mtd_estimate` a numerical vector of the MTD estimates.
`true_mtd` a numerical value of the true Maximum Tolerable Dose.

Value

Bias of the MTD estimates.

Examples

```
## Not run:  
DLT <- 0  
dose <- 30  
step_zero <- ewoc_d1classic(DLT ~ dose, type = 'discrete',  
                           theta = 0.33, alpha = 0.25,  
                           min_dose = 0, max_dose = 100,  
                           dose_set = seq(0, 100, 20),  
                           rho_prior = matrix(1, ncol = 2, nrow = 1),  
                           mtd_prior = matrix(1, ncol = 2, nrow = 1),  
                           rounding = "nearest")  
response_sim <- response_d1classic(rho = 0.05, mtd = 20, theta = 0.33,  
                                  min_dose = 10, max_dose = 50)  
sim <- ewoc_simulation(step_zero = step_zero,  
                      n_sim = 2, sample_size = 30,  
                      alpha_strategy = "increasing",  
                      response_sim = response_sim,  
                      ncores = 2)  
mtd_bias(sim$mtd_sim, true_mtd = 20)  
  
## End(Not run)
```

mtd_mse	<i>Mean Square Error of the MTD estimates</i>
---------	---

Description

Calculate the Mean Square Error (MSE).

Usage

```
mtd_mse(mtd_estimate, true_mtd)
```

Arguments

mtd_estimate a numerical vector of the MTD estimates.
true_mtd a numerical value of the true Maximum Tolerable Dose.

Value

MSE of the MTD estimates.

Examples

```
## Not run:  
DLT <- 0  
dose <- 30  
step_zero <- ewoc_d1classic(DLT ~ dose, type = 'discrete',  
                          theta = 0.33, alpha = 0.25,  
                          min_dose = 0, max_dose = 100,  
                          dose_set = seq(0, 100, 20),  
                          rho_prior = matrix(1, ncol = 2, nrow = 1),  
                          mtd_prior = matrix(1, ncol = 2, nrow = 1),  
                          rounding = "nearest")  
response_sim <- response_d1classic(rho = 0.05, mtd = 20, theta = 0.33,  
                                  min_dose = 10, max_dose = 50)  
sim <- ewoc_simulation(step_zero = step_zero,  
                      n_sim = 2, sample_size = 30,  
                      alpha_strategy = "increasing",  
                      response_sim = response_sim,  
                      ncores = 2)  
mtd_mse(sim$mtd_sim, true_mtd = 20)  
  
## End(Not run)
```

optimal_mtd	<i>Percent of doses in relation the optimal MTD interval</i>
-------------	--

Description

Calculate the percent of dose which are inside the optimal MTD interval [$\text{true_MTD} - \text{margin}$; $\text{true_MTD} + \text{margin}$].

Usage

```
optimal_mtd(dose_matrix, true_mtd, margin, digits = 2)
```

Arguments

dose_matrix	a numerical matrix of assigned doses for each step of the trial (column) and for each trial (row).
true_mtd	a numerical value of the true Maximum Tolerable Dose.
margin	a numerical value of the acceptable margin of distance from the true_MTD.
digits	a numerical value indicating the number of digits.

Value

interval the average percent of doses which are inside the optimal MTD interval.

underdose the average percent of doses which are smaller than the lower limit of the optimal MTD interval.

overdose the average percent of doses which are greater than the upper limit of the optimal MTD interval.

Examples

```
## Not run:
DLT <- 0
dose <- 30
step_zero <- ewoc_d1classic(DLT ~ dose, type = 'discrete',
  theta = 0.33, alpha = 0.25,
  min_dose = 0, max_dose = 100,
  dose_set = seq(0, 100, 20),
  rho_prior = matrix(1, ncol = 2, nrow = 1),
  mtd_prior = matrix(1, ncol = 2, nrow = 1),
  rounding = "nearest")
response_sim <- response_d1classic(rho = 0.05, mtd = 20, theta = 0.33,
  min_dose = 10, max_dose = 50)
sim <- ewoc_simulation(step_zero = step_zero,
  n_sim = 2, sample_size = 30,
  alpha_strategy = "increasing",
  response_sim = response_sim,
```



```

        rho_prior = matrix(1, ncol = 2, nrow = 1),
        mtd_prior = matrix(1, ncol = 2, nrow = 1),
        rounding = "nearest")
response_sim <- response_d1classic(rho = 0.05, mtd = 20, theta = 0.33,
                                min_dose = 10, max_dose = 50)
pdl_t_sim <- pdl_t_d1classic(rho = 0.05, mtd = 20, theta = 0.33,
                            min_dose = 10, max_dose = 50)
sim <- ewoc_simulation(step_zero = step_zero,
                      n_sim = 2, sample_size = 30,
                      alpha_strategy = "increasing",
                      response_sim = response_sim,
                      ncores = 2)
optimal_toxicity(sim$mtd_sim, theta = 0.33, margin = 0.05, pdl_t = pdl_t_sim)
optimal_toxicity(sim$dose_sim, theta = 0.33, margin = 0.05, pdl_t = pdl_t_sim)

## End(Not run)

```

pdl_t_d1classic	<i>Generating a probability of DLT function based on the EWOC classic model</i>
-----------------	---

Description

Generating a probability of DLT function based on the EWOC classic model

Usage

```
pdl_t_d1classic(rho, mtd, theta, min_dose, max_dose)
```

Arguments

rho	a numerical value indicating the true value of the parameter rho.
mtd	a numerical value indicating the true value of the parameter mtd.
theta	a numerical value defining the proportion of expected patients to experience a medically unacceptable, dose-limiting toxicity (DLT) if administered the MTD.
min_dose	a numerical value defining the lower bound of the support of the MTD.
max_dose	a numerical value defining the upper bound of the support of the MTD.

Value

A function with dose as an input and a probability based on the logistic regression and parameters as an output.

Examples

```
pdl_t <- pdlt_d1classic(rho = 0.05, mtd = 20, theta = 0.33,  
                      min_dose = 10, max_dose = 50)  
  
pdl_t(20)
```

pdl_t_d1extended	<i>Generating a probability of DLT function based on the EWOC extended model</i>
------------------	--

Description

Generating a probability of DLT function based on the EWOC extended model

Usage

```
pdl_t_d1extended(rho, min_dose, max_dose)
```

Arguments

rho	a numerical vector indicating the true value of the parameters rho_0 and rho_1.
min_dose	a numerical value defining the lower bound of the support of the MTD.
max_dose	a numerical value defining the upper bound of the support of the MTD.

Value

A function with dose as an input and a probability based on the logistic regression and parameters as an output.

Examples

```
pdl_t <- pdlt_d1extended(rho = c(0.05, 0.5),  
                        min_dose = 10, max_dose = 50)  
  
pdl_t(20)
```

pdlt_d1ph	<i>Generating a probability of DLT function based on the EWOC Proportional Hazards model</i>
-----------	--

Description

Generating a probability of DLT function based on the EWOC Proportional Hazards model

Usage

```
pdlt_d1ph(rho, mtd, shape = NULL, theta, min_dose, max_dose, tau,  
distribution)
```

Arguments

rho	a numerical value indicating the true value of the parameter rho.
mtd	a numerical value indicating the true value of the parameter mtd.
shape	a numerical value indicating the true value of the parameter shape. It is only necessary if 'distribution' = "weibull".
theta	a numerical value defining the proportion of expected patients to experience a medically unacceptable, dose-limiting toxicity (DLT) if administered the MTD.
min_dose	a numerical value defining the lower bound of the support of the MTD.
max_dose	a numerical value defining the upper bound of the support of the MTD.
tau	a numerical value defining the period of time for a possible toxicity be observed.
distribution	a character establishing the distribution for the time of events.

Value

A function with dose as an input and a probability based on the logistic regression and parameters as an output.

Examples

```
pdlt <- pdlt_d1ph(rho = 0.05, mtd = 40, theta = 0.33,  
min_dose = 30, max_dose = 50,  
tau = 10, distribution = "exponential")  
pdlt(40)
```

response_d1classic	<i>Generating a binary response function based on the EWOC classic model</i>
--------------------	--

Description

Generating a binary response function based on the EWOC classic model

Usage

```
response_d1classic(rho, mtd, theta, min_dose, max_dose)
```

Arguments

rho	a numerical value indicating the true value of the parameter rho.
mtd	a numerical value indicating the true value of the parameter mtd.
theta	a numerical value defining the proportion of expected patients to experience a medically unacceptable, dose-limiting toxicity (DLT) if administered the MTD.
min_dose	a numerical value defining the lower bound of the support of the MTD.
max_dose	a numerical value defining the upper bound of the support of the MTD.

Value

A function with dose as an input and a Binomial variable based on the parameters as an output.

Examples

```
response_sim <- response_d1classic(rho = 0.05, mtd = 20, theta = 0.33,  
                                 min_dose = 10, max_dose = 50)  
response_sim(20)
```

response_d1extended	<i>Generating a binary response function based on the EWOC extended model</i>
---------------------	---

Description

Generating a binary response function based on the EWOC extended model

Usage

```
response_d1extended(rho, min_dose, max_dose)
```

Arguments

rho	a numerical vector indicating the true value of the parameters rho_0 and rho_1.
min_dose	a numerical value defining the lower bound of the support of the MTD.
max_dose	a numerical value defining the upper bound of the support of the MTD.

Value

A function with dose as an input and a Binomial variable based on the parameters as an output.

Examples

```
response_sim <- response_d1extended(rho = c(0.05, 0.5),
                                   min_dose = 10, max_dose = 50)
response_sim(20)
```

response_d1ph	<i>Generating a response function based on the EWOC Proportional Hazards model</i>
---------------	--

Description

Generating a response function based on the EWOC Proportional Hazards model

Usage

```
response_d1ph(rho, mtd, theta, min_dose, max_dose, tau, distribution,
              shape = NULL)
```

Arguments

rho	a numerical value indicating the true value of the parameter rho.
mtd	a numerical value indicating the true value of the parameter mtd.
theta	a numerical value defining the proportion of expected patients to experience a medically unacceptable, dose-limiting toxicity (DLT) if administered the MTD.
min_dose	a numerical value defining the lower bound of the support of the MTD.
max_dose	a numerical value defining the upper bound of the support of the MTD.
tau	a numerical value defining the period of time for a possible toxicity be observed.
distribution	a character establishing the distribution for the time of events.
shape	a numerical value indicating the true value of the parameter shape. It is only necessary if 'distribution' = "weibull".

Value

A function with dose as an input and a Binomial variable based on the parameters as an output.

Examples

```

response_sim <- response_d1ph(rho = 0.05, mtd = 40, theta = 0.33,
                             min_dose = 30, max_dose = 50,
                             tau = 10, distribution = "exponential")
response_sim(40)

```

standard_dose	<i>Standardization of the dose</i>
---------------	------------------------------------

Description

Standardizing a dose between 0 and 1.

Usage

```
standard_dose(dose, min_dose, max_dose)
```

Arguments

dose	a numerical value defining the dose to be standardized.
min_dose	a numerical value defining the lower bound of the support of the MTD.
max_dose	a numerical value defining the upper bound of the support of the MTD.

Value

standardized dose a numerical value between 0 and 1.

stop_rule	<i>Evaluation of the stop rule</i>
-----------	------------------------------------

Description

Calculate the average, minimum, maximum number of patients to stop a trial and the percent of stopped trials. Stopped trials contain NA after the last assigned dose.

Usage

```
stop_rule(dlt_matrix, sample_size, digits = 2)
```

Arguments

dlt_matrix	Matrix of the number of DLT for each step of the trial (column) and for each trial (row).
sample_size	a numerical value indicating the expected sample size.
digits	a numerical value indicating the number of digits.

Value

A list consisting of

- average: Average number of patients to stop a trial.
- min: Minimum number of patients to stop a trial.
- max: Maximum number of patients to stop a trial.
- nstop: Percent of stopped trials.

Examples

```
## Not run:
DLT <- 0
dose <- 30
step_zero <- ewoc_d1classic(DLT ~ dose, type = 'discrete',
                           theta = 0.33, alpha = 0.25,
                           min_dose = 0, max_dose = 100,
                           dose_set = seq(0, 100, 20),
                           rho_prior = matrix(1, ncol = 2, nrow = 1),
                           mtd_prior = matrix(1, ncol = 2, nrow = 1),
                           rounding = "nearest")

stop_rule_sim(step_zero)
response_sim <- response_d1classic(rho = 0.05, mtd = 20, theta = 0.33,
                                  min_dose = 10, max_dose = 50)

sim <- ewoc_simulation(step_zero = step_zero,
                      n_sim = 1, sample_size = 2,
                      alpha_strategy = "increasing",
                      response_sim = response_sim,
                      stop_rule_sim = stop_rule_sim,
                      ncores = 2)

stop_rule(sim$dlt_sim)

## End(Not run)

## Not run:
DLT <- 0
dose <- 30
step_zero <- ewoc_d1classic(DLT ~ dose, type = 'discrete',
                           theta = 0.33, alpha = 0.25,
                           min_dose = 0, max_dose = 100,
                           dose_set = seq(0, 100, 20),
                           rho_prior = matrix(1, ncol = 2, nrow = 1),
                           mtd_prior = matrix(1, ncol = 2, nrow = 1),
                           rounding = "nearest")

stop_rule_sim(step_zero)
response_sim <- response_d1classic(rho = 0.05, mtd = 20, theta = 0.33,
                                  min_dose = 10, max_dose = 50)

sim <- ewoc_simulation(step_zero = step_zero,
                      n_sim = 2, sample_size = 30,
                      alpha_strategy = "increasing",
                      response_sim = response_sim,
                      stop_rule_sim = stop_rule_sim,
```


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