Package ‘ewoc’

June 7, 2020

Type Package
Title Escalation with Overdose Control
Version 0.3.0
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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 and performs simulations to obtain operating characteristics.
License GPL (>= 2)
LazyData TRUE
URL https://github.com/dnzmarcio/ewoc/
BugReports https://github.com/dnzmarcio/ewoc/issues
Imports Formula(>= 1.2-1), rjags(>= 4-6), coda(>= 0.18-1), ggplot2(>= 2.2.0), graphics(>= 3.3.1), stats(>= 3.3.1), foreach(>= 1.4.3), doParallel(>= 1.0.11), parallel (>= 3.4.0), doRNG (>= 1.7.1)
RoxygenNote 7.1.0
NeedsCompilation no
Repository CRAN
Date/Publication 2020-06-07 07:20:02 UTC

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## accuracy_index

**Description**

Calculate the Accuracy Index.

**Usage**

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

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


average_toxicity

Average Toxicity Number

Description

Calculate the Average Toxicity Number.

Usage

```r
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

**dlt_curve_d1classical**  
*Plot the DLT curve based on the EWOC classical model*

**Description**

Plot the DLT curve based on the EWOC classical model

**Usage**

```r
 dlt_curve_d1classical(mtd, rho, theta, min_dose, max_dose, dose_set = NULL)
```

**Arguments**

- `mtd`: a numerical value indicating the true value of the parameter mtd.
- `rho`: a numerical value indicating the true value of the parameter rho.
- `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.
- `dose_set`: a numerical vector of doses that probability of DLT will be calculated.

---

**dlt_curve_d1extended**  
*Plot the DLT curve based on the EWOC extended model*

**Description**

Plot the DLT curve based on the EWOC extended model

**Usage**

```r
 dlt_curve_d1extended(rho, theta, min_dose, max_dose, dose_set = NULL)
```

**Arguments**

- `rho`: a numerical vector indicating the true value of the parameters rho_0 and rho_1.
- `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.
- `dose_set`: a numerical vector of doses that probability of DLT will be calculated.
dlt_curve_d1ph

Plot the DLT curve based on the EWOC proportional hazards model

Description

Plot the DLT curve based on the EWOC proportional hazards model

Usage

\texttt{dlt\_curve\_d1ph(mtd, rho, theta, min\_dose, max\_dose, shape, tau, distribution = "exponential", dose\_set = NULL)}

Arguments

- \texttt{mtd}: a numerical value indicating the true value of the parameter mtd.
- \texttt{rho}: a numerical value indicating the true value of the parameter rho.
- \texttt{theta}: a numerical value defining the proportion of expected patients to experience a medically unacceptable, dose-limiting toxicity (DLT) if administered the MTD.
- \texttt{min\_dose}: a numerical value defining the lower bound of the support of the MTD.
- \texttt{max\_dose}: a numerical value defining the upper bound of the support of the MTD.
- \texttt{shape}: a numerical value indicating the true value of the parameter shape. It is only necessary if ‘distribution’ = "weibull".
- \texttt{tau}: a numerical value defining the period of time for a possible toxicity be observed.
- \texttt{distribution}: a character establishing the distribution for the time of events. It can be defined as ‘exponential’ or ‘weibull’.
- \texttt{dose\_set}: a numerical vector of doses that probability of DLT will be calculated.
Evaluation of the DLT rate

dlt_rate

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

```r
## Not run:
DLT <- 0
dose <- 20
step_zero <- ewoc_d1classical(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_d1classical(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 <- 20
step_zero <- ewoc_d1classical(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_d1classical(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_d1classical**  
**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 classical parametrization for binary responses and single agent.

Usage

ewoc_d1classical(
  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,
  no_skip_dose = TRUE,
  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'.
ewoc_d1classical

\begin{description}
\item[	exttt{last\_dose}] a numerical value for the last allowable dose in the trial. It is only necessary if type = \texttt{"continuous"}.
\item[	exttt{dose\_set}] a numerical vector of allowable doses in the trial. It is only necessary if type = \texttt{"discrete"}.
\item[	exttt{max\_increment}] a numerical value indicating the maximum increment from the current dose to the next dose. It is only applied if type = \texttt{"continuous"}.
\item[	exttt{no\_skip\_dose}] a logical value indicating if it is allowed to skip doses. It is only necessary if type = \texttt{"discrete"}. The default is TRUE.
\item[	exttt{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 = \texttt{"discrete"}.
\item[	exttt{n\_adapt}] the number of iterations for adaptation. See \texttt{adapt} for details.
\item[	exttt{burn\_in}] numerical value indicating the number of iterations before to start monitoring.
\item[	exttt{n\_mcmc}] numerical value indicating the number of iterations to monitor.
\item[	exttt{n\_thin}] numerical value corresponding to the thinning interval for monitors.
\item[	exttt{n\_chains}] numerical value indicating the number of parallel chains for the model.
\end{description}

Value

\begin{description}
\item[	exttt{next\_dose}] the next recommend dose.
\item[	exttt{mtd}] the posterior MTD distribution.
\item[	exttt{rho}] the posterior rho_0 distribution.
\item[	exttt{sample}] a list of the MCMC chains distribution.
\item[	exttt{trial}] a list of the trial conditions.
\end{description}

References


Examples

\begin{Sinput}
DLT <- 0
dose <- 20
test <- ewoc_d1classical(DLT ~ dose, type = \texttt{"discrete"},
                          theta = 0.33, alpha = 0.25,
                          min_dose = 20, max_dose = 100,
                          dose_set = seq(20, 100, 20),
                          rho_prior = matrix(1, ncol = 2, nrow = 1),
                          mtd_prior = matrix(1, ncol = 2, nrow = 1),
                          rounding = \texttt{"nearest"})

summary(test)
plot(test)
\end{Sinput}
**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**

```r
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, no_skip_dose = TRUE, 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. It is only applied if type = 'continuous'.
no_skip_dose a logical value indicating if it is allowed to skip doses. It is only necessary if type = 'discrete'. The default is TRUE.
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.

References


Examples

```r
DLT <- 0
dose <- 20
test <- ewoc_d1extended(DLT ~ dose, type = 'discrete',
  theta = 0.33, alpha = 0.25,
  dose_set = seq(20, 100, 20),
  min_dose = 20, max_dose = 100,
  rho_prior = matrix(1, ncol = 2, nrow = 2),
  rounding = "nearest")
summary(test)
plot(test)
```
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,
  no_skip_dose = TRUE,
  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. It is only applied if type = 'continuous'.

no_skip_dose a logical value indicating if it is allowed to skip doses. It is only necessary if type = 'discrete'. The default is TRUE.

distribution a character establishing the distribution for the time of events. It can be defined as '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

ewoc_simulation

Examples

time <- 9
status <- 0
dose <- 20

test <- ewoc_d1ph(cbind(time, status) ~ dose, type = 'discrete',
theta = 0.33, alpha = 0.25, tau = 10,
min_dose = 20, max_dose = 100,
dose_set = seq(20, 100, 20),
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              EWOC simulation

Description

Generic function for simulating EWOC trials.

Usage

ewoc_simulation(
  step_zero,
  n_sim,
  sample_size,
  response_sim,
  fixed_first_cohort = TRUE,
  n_cohort = 1,
  alpha_strategy = "conditional",
  alpha_rate = 0.05,
  stop_rule_sim = NULL,
  ncores = 1,
  seed = 1234,
  ...
)

Arguments

step_zero      an object from the classes either 'ewoc_d1classical' or 'ewoc_d1extended' or 'ewoc_d1ph' created using the first cohort data.
n_sim         a number indicating the number of phase I clinical trials to be simulated.
sample_size   a number indicating the number of patients enrolled for each clinical trial.
response_sim 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 proportional hazards EWOC.

fixed_first_cohort a logical value indicating if the first cohort should be randomly generated or be fixed as the input in 'step_zero'.

n_cohort a number indicating the number of patients enrolled at each cohort. It is only used for 'ewoc_d1classical' and 'ewoc_d1extended'.

alpha_strategy a character indicating the strategy to apply for the feasibility value. Default is "constant". Options are "increasing" and "conditional".

alpha_rate a numerical value indicating the rate of the feasibility strategy. Only necessary if alpha_strategy is either 'increasing' or 'conditional'.

stop_rule_sim a function having as an input an object containing all the information related to the trial as the returned object trial from either ewoc_d1classical, ewoc_d1extended, ewoc_d1ph and as output a logical value indicating the trial should be stopped.

ncores a numeric value indicating the number of cores to be used in the simulation performed in parallel. Use parallel::detectCores() to check the number of cores available.

seed is an integer value, containing the random number generator (RNG) state for random number generation.

Value

alpha_sim a matrix n_sim x 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 x 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 x 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 x 1 containing the recommended MTD for each trial in the simulation.

rho_sim a numeric vector n_sim x k containing the estimated rho parameter(s) for each trial in the simulation, where k = 1 for ewoc_d1classical, ewoc_d1ph, and k = 2 for ewoc_d1extended.

Examples

```r
## Not run:
### Classical EWOC
DLT <- 0
dose <- 20
```
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```r
step_zero <- ewoc_d1classical(DLT ~ dose, type = 'discrete',
    theta = 0.33, alpha = 0.25,
    min_dose = 20, max_dose = 100,
    dose_set = seq(20, 100, 20),
    rho_prior = matrix(1, ncol = 2, nrow = 1),
    mtd_prior = matrix(1, ncol = 2, nrow = 1),
    rounding = 'nearest')
response_sim <- response_d1classical(rho = 0.05, mtd = 60, theta = 0.33,
    min_dose = 20, max_dose = 100)
sim <- ewoc_simulation(step_zero = step_zero,
    n_sim = 2, sample_size = 30, n_cohort = 1,
    alpha_strategy = "conditional",
    response_sim = response_sim,
    ncores = 1)

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

### PH EWOC
time <- 0
status <- 0
step_zero <- ewoc_d1ph(cbind(time, status) ~ dose, type = 'discrete',
    theta = 0.33, alpha = 0.25, tau = 10,
    min_dose = 20, max_dose = 100,
    dose_set = seq(20, 100, 20),
    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 = 60, theta = 0.33,
    min_dose = 20, max_dose = 100,
    tau = 10, distribution = "exponential")
sim <- ewoc_simulation(step_zero = step_zero,
    n_sim = 2, sample_size = 30, n_cohort = 1,
    alpha_strategy = "conditional",
    response_sim = response_sim,
    ncores = 1)
```
inv_standard_dose

## End(Not run)

### Description

Unstandardizing a dose between minimum and maximum doses.

### Usage

```r
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

**Logit**

### Description

Calculating the logit of a probability

### Usage

```r
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**

```r
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**

```r
## Not run:
DLT <- 0
doze <- 20
step_zero <- ewoc_d1classical(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_d1classical(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

Mean Square Error of the MTD estimates

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 <- 20
step_zero <- ewoc_d1classical(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_d1classical(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)
mtd_rho_d1extended  \hspace{1em} Convert mtd to rho_1 and vice-versa

Description

Converting mtd to rho_1 given rho_0 for EWOC design using extended parametrization and vice-versa.

Usage

mtd_rho_d1extended(mtd = NULL, rho_1 = NULL, rho_0, theta, min_dose, max_dose)

Arguments

- mtd: a numerical value defining the mtd value to be converted into rho_1 value.
- rho_1: a numerical value defining the probability of DLT at the max_dose.
- rho_0: a numerical value defining the probability of DLT at the min_dose.
- 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

- mtd: a numerical value for the maximum tolerable dose.
- rho_1: a numerical value for the probability of DLT at the max_dose.

opc  \hspace{1em} Operating characteristics for EWOC simulations

Description

Generic operating characteristics for one or more scenarios in EWOC simulations.

Usage

opc(sim_list, pdlt_list, mtd_list, toxicity_margin = NULL, mtd_margin = NULL)
Arguments

- **sim_list**: a list of `ewoc_simulation` objects for different scenarios created using the `ewoc_simulation` function.
- **pdlt_list**: a list of functions to calculate the probability of toxicity with a numeric vector of doses as input and a numeric vector of probabilities as output.
- **mtd_list**: a list of numerical values indicating the true MTD for each scenario.
- **toxicity_margin**: a numerical value of the acceptable margin of distance from the `target_rate`.
- **mtd_margin**: a numerical value of the acceptable margin of distance from the `mtd_list`.

Value

- **dlt_rate**: See `dlt_rate`.
- **dose_toxicity**: See `optimal_toxicity`.
- **mtd_toxicity**: See `optimal_toxicity`.
- **statistics**: See `mtd_bias` and `mtd_mse`.
- **dose_efficiency**: See `optimal_mtd`.
- **mtd_efficiency**: See `optimal_mtd`.
- **stop**: See `stop_rule`.

References


Examples

```r
## Not run:
### Only one simulation
DLT <- 0
dose <- 20
step_zero <- ewoc_d1classical(DLT ~ dose, type = 'discrete',
  theta = 0.33, alpha = 0.25,
  min_dose = 20, max_dose = 100,
  dose_set = seq(20, 100, 20),
  rho_prior = matrix(1, ncol = 2, nrow = 1),
  mtd_prior = matrix(1, ncol = 2, nrow = 1),
  rounding = "nearest")
response_sim <- response_d1classical(rho = 0.05, mtd = 60, theta = 0.33,
  min_dose = 20, max_dose = 100)
sim <- ewoc_simulation(step_zero = step_zero,
  n_sim = 1, sample_size = 30, n_cohort = 1,
  alpha_strategy = "conditional",
  response_sim = response_sim,
```
fixed_first_cohort = TRUE,
ncores = 1)

pdlt <- pdlt_d1classical(rho = 0.05, mtd = 60, theta = 0.33,
min_dose = 20, max_dose = 100)

opc(sim_list = list(sim), pdlt_list = list(pdlt),
mtd_list = list(60), toxicity_margin = 0.05, mtd_margin = 6)

### Two or more simulations

sim_list <- list()
mtd_list <- list()
pdlt_list <- list()

DLT <- 0
dose <- 20
step_zero <- ewoc_d1classical(DLT ~ dose, type = 'discrete',
theta = 0.33, alpha = 0.25,
min_dose = 20, max_dose = 100,
dose_set = seq(20, 100, 20),
rho_prior = matrix(1, ncol = 2, nrow = 1),
mtd_prior = matrix(1, ncol = 2, nrow = 1),
rounding = "nearest")
mtd_list[[1]] <- 60
response_sim <- response_d1classical(rho = 0.05, mtd = mtd_list[[1]],
theta = 0.33,
min_dose = 20, max_dose = 100)
sim_list[[1]] <- ewoc_simulation(step_zero = step_zero,
n_sim = 1, sample_size = 30, n_cohort = 1,
alpha_strategy = "conditional",
response_sim = response_sim,
fixed_first_cohort = TRUE,
ncores = 1)
pdlt_list[[1]] <- pdlt_d1classical(rho = 0.05, mtd = mtd_list[[1]],
theta = 0.33,
min_dose = 20, max_dose = 100)

mtd_list[[2]] <- 40
response_sim <- response_d1classical(rho = 0.05, mtd = mtd_list[[2]],
theta = 0.33,
min_dose = 20, max_dose = 100)
sim_list[[2]] <- ewoc_simulation(step_zero = step_zero,
n_sim = 1, sample_size = 30, n_cohort = 1,
alpha_strategy = "conditional",
response_sim = response_sim,
fixed_first_cohort = TRUE,
ncores = 1)
pdlt_list[[2]] <- pdlt_d1classical(rho = 0.05, mtd = mtd_list[[2]],
theta = 0.33,
min_dose = 20, max_dose = 100)
optimal_mtd

opc(sim_list = sim_list, pdlt_list = pdlt_list,
    mtd_list = mtd_list, toxicity_margin = 0.05, mtd_margin = 6)

## End(Not run)

---

**optimal_mtd**  
Percent of doses in relation the optimal MTD interval

**Description**

Calculate the percent of doses which are inside the optimal MTD interval \([\text{true}_\text{MTD} - \text{margin} ; \text{true}_\text{MTD} + \text{margin}]\).

**Usage**

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

**Arguments**

- `dose_matrix`  
a numerical matrix or vector 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 <- 20
step_zero <- ewoc_d1classical(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),
```
```r
response_sim <- response_d1classical(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_mtd(sim$mtd_sim, true_mtd = 20, margin = 0.1*20)
optimal_mtd(sim$dose_sim, true_mtd = 20, margin = 0.1*20)

## End(Not run)
```

### `optimal_toxicity`

Percent of doses in relation the optimal toxicity interval

<table>
<thead>
<tr>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Calculate the percent of doses which are inside the optimal toxicity interval [ \text{target rate} - \text{margin} ; \text{target rate} + \text{margin} ].</td>
</tr>
</tbody>
</table>

#### Usage

`optimal_toxicity(dose_matrix, target_rate, margin, pdlt, digits = 2)`

#### Arguments

- **dose_matrix**: a numerical matrix of assigned doses for each step of the trial (column) and for each trial (row).
- **target_rate**: a numerical value of the target DLT rate.
- **margin**: a numerical value of the acceptable margin of distance from the `target_rate`.
- **pdlt**: a function to calculate the probability of toxicity with a numeric vector of doses as input and a numeric vector of probabilities as output.
- **digits**: a numerical value indicating the number of digits.

#### Value

- **interval**: the average percent of doses which are inside the optimal toxicity interval.
- **underdose**: the average percent of doses which are smaller than the lower limit of the optimal toxicity interval.
- **overdose**: the average percent of doses which are greater than the upper limit of the optimal toxicity interval.
Examples

```r
## Not run:
DLT <- 0
dose <- 20
step_zero <- ewoc_d1classical(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_d1classical(rho = 0.05, mtd = 20, theta = 0.33,
   min_dose = 10, max_dose = 50)
pdlt_sim <- pdlt_d1classical(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$mtd_sim, target_rate = 0.33, margin = 0.05, pdlt = pdlt_sim)
optimal_toxicity(sim$dose_sim, target_rate = 0.33, margin = 0.05, pdlt = pdlt_sim)
## End(Not run)
```

### pdlt_d1classical

**Generating a probability of DLT function based on the EWOC classical model**

#### Description

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

#### Usage

```r
pdlt_d1classical(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

```r
pdlt <- pdlt_d1classical(rho = 0.05, mtd = 60, theta = 0.33,
                         min_dose = 20, max_dose = 100)

pdlt(20)
```

---

**pdlt_d1extended**

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

Description

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

Usage

```r
pdlt_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

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

pdlt(20)
```
Generating a probability of DLT function based on the EWOC Proportional Hazards model

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. It can be defined as 'exponential' or 'weibull'.

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)
Generating a binary response function based on the EWOC classical model

Description
Generating a binary response function based on the EWOC classical model

Usage
response_d1classical(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_d1classical(rho = 0.05, mtd = 20, theta = 0.33, min_dose = 10, max_dose = 50)
response_sim(20)

Generating a binary response function based on the EWOC extended model

Description
Generating a binary response function based on the EWOC extended model

Usage
response_d1extended(rho, min_dose, max_dose)
response_d1ph

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  Generating a response function based on the EWOC Proportional Hazards model

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

```r
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 Standardization of the dose

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.
Evaluation of the stopping rule

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

```r
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

```r
## Not run:
DLT <- 0
dose <- 20
step_zero <- ewoc_d1classical(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_d1classical(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,
```
## Not run:

```r
dLT <- 0
dose <- 20
step_zero <- ewoc_d1classical(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_d1classical(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)

stop_rule(sim$dlt_sim)
```

## End(Not run)
Value

A logical character indicating if the trial should be stopped or not.

Examples

```r
## Not run:
DLT <- 0
dose <- 20
step_zero <- ewoc_d1classical(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_d1classical(step_zero)
response_sim <- response_d1classical(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 = "conditional",
                       response_sim = response_sim,
                       stop_rule_sim = stop_rule_d1_classical,
                       ncores = 1)
## End(Not run)
```

Description

Generating a stop rule function for EWOC extended model

Usage

`stop_rule_d1extended(step)`

Arguments

- `step` an object from the class `ewoc_d1extended`.

Details

The stop rule function is evaluated at each step of the trial. It can be defined based on any information contained in the object `step` that is the output from one of the functions `ewoc_d1extended`. 

stop_rule_d1extended Generating a stop rule function for EWOC extended model

Description

Generating a stop rule function for EWOC extended model

Usage

`stop_rule_d1extended(step)`

Arguments

- `step` an object from the class `ewoc_d1extended`.

Details

The stop rule function is evaluated at each step of the trial. It can be defined based on any information contained in the object `step` that is the output from one of the functions `ewoc_d1extended`.
stop_rule_d1ph

Value

a logical character indicating if the trial should be stopped or not.

Examples

```r
## Not run:
DLT <- 0
dose <- 20
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")
stop_rule_d1extended(step_zero)
response_sim <- response_d1extended(rho = c(0.05, 0.95),
   min_dose = 10, max_dose = 50)
sim <- ewoc_simulation(step_zero = step_zero,
   n_sim = 2, sample_size = 30,
   alpha_strategy = "conditional",
   response_sim = response_sim,
   stop_rule_sim = stop_rule_d1extended,
   ncores = 1)
```

## End(Not run)

---

### Description

Generating a stop rule function for EWOC proportional hazards model

### Usage

```r
stop_rule_d1ph(step)
```

### Arguments

- **step**: an object from the class `ewoc_d1ph`.

### Details

The stop rule function is evaluated at each step of the trial. It can be defined based on any information contained in the object `step` that is the output from one of the functions `ewoc_d1ph`.

---

### stop_rule_d1ph

*Generating a stop rule function for EWOC proportional hazards model*
Value

a logical character indicating if the trial should be stopped or not.

Examples

```r
## Not run:
time <- 9
status <- 0
dose <- 20
step_zero <- ewoc_d1ph(cbind(time, status) ~ dose, type = 'discrete',
                        theta = 0.33, alpha = 0.25, tau = 10,
                        min_dose = 20, max_dose = 100,
                        dose_set = seq(20, 100, 20),
                        rho_prior = matrix(1, ncol = 2, nrow = 1),
                        mtd_prior = matrix(1, ncol = 2, nrow = 1),
                        distribution = 'exponential',
                        rounding = 'nearest')

stop_rule_d1ph(step_zero)
response_sim <- response_d1ph(rho = 0.05, mtd = 20, theta = 0.33,
                              min_dose = 10, max_dose = 50,
                              tau = 10, distribution = "exponential")
sim <- ewoc_simulation(step_zero = step_zero,
                        n_sim = 2, sample_size = 30,
                        alpha_strategy = "conditional",
                        response_sim = response_sim,
                        stop_rule_sim = stop_rule_d1ph,
                        ncores = 1)

## End(Not run)
```
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