Package 'simFastBOIN'

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Description Design and evaluate phase I dose-finding trials that use the Bayesian optimal interval (BOIN) design of Liu and Yuan (2015) <doi:10.1111/rssc.12089>. Functions are provided to tabulate the decision boundaries, to simulate trials, to estimate the dose-toxicity curve under a monotonicity constraint and to select the maximum tolerated dose. The simulation engine is written in C++ and draws one random variate per patient in enrollment order, which reproduces the reference implementation in the 'BOIN' package trial by trial for a given seed. The traditional 3+3 design is provided as a comparator, with operating characteristics obtained in closed form rather than by simulation.

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`as.data.frame.boin_boundary` *Coerce BOIN Decision Boundaries to a Data Frame*

Description

Return the integer decision boundaries produced by `boin_boundary` as one row per sample size.

Usage

```
## S3 method for class 'boin_boundary'
as.data.frame(x, row.names = NULL, optional = FALSE, ...)
```

Arguments

x	An object of class boin_boundary.
row.names	Passed on for compatibility with the generic, normally unused.
optional	Passed on for compatibility with the generic, normally unused.
...	Further arguments, currently ignored.

Value

A data frame with columns n_pts, escalate_if_dlt_leq, deescalate_if_dlt_geq and eliminate_if_dlt_geq, plus stop_if_dlt_geq when the boundaries were built with extrasafe = TRUE.

Examples

```
bd <- boin_boundary(target = 0.30, max_n = 18)
as.data.frame(bd)[seq(3, 18, by = 3), ]
```

---

boin_boundary *Integer Decision Boundaries for the BOIN Design*

Description

Tabulate, for every attainable number of patients treated at a dose, the number of DLTs that triggers escalation, de-escalation, elimination and, when requested, the stricter safety stopping rule at the lowest dose.

Usage

```
boin_boundary(
  target,
  max_n,
  p_saf = NULL,
  p_tox = NULL,
  cutoff_eli = 0.95,
  extrasafe = FALSE,
  offset = 0.05,
  stay_on_1_of_3 = FALSE
)
```

Arguments

target	Numeric scalar. Target DLT probability, for example 0.30.
max_n	Integer scalar. Largest number of patients that can be treated at a single dose, which is the number of columns of the resulting table. For a trial with n_cohort cohorts of size cohort_size this is n_cohort * cohort_size.

p_saf	Numeric scalar. Highest DLT probability deemed subtherapeutic. Defaults to 0.6 * target.
p_tox	Numeric scalar. Lowest DLT probability deemed overly toxic. Defaults to 1.4 * target.
cutoff_eli	Numeric scalar. Posterior probability cutoff above which a dose is eliminated for toxicity. Defaults to 0.95.
extrasafe	Logical scalar. When TRUE, also tabulate the safety stopping boundary applied at the lowest dose. Defaults to FALSE.
offset	Numeric scalar between 0 and 0.5. Amount by which cutoff_eli is relaxed for the safety stopping rule. Defaults to 0.05.
stay_on_1_of_3	Logical scalar. When TRUE, one DLT out of three patients leads to staying at the current dose rather than de-escalating. Defaults to FALSE. See the details.

Details

The escalation boundary is floor(lambda_e * n) and the de-escalation boundary is ceiling(lambda_d * n), with the convention that when lambda_d * n is a whole number de-escalation requires one more DLT. The elimination boundary is the smallest positive number of DLTs for which Pr(p > target | data) exceeds cutoff_eli under a uniform Beta(1, 1) prior, and is not evaluated before three patients have been treated. The de-escalation boundary is capped at the elimination boundary.

With the default thresholds these definitions reproduce BOIN::get.boundary() exactly.

Value

An object of class boin_boundary, which is a list with components

lambda_e	Escalation interval boundary.
lambda_d	De-escalation interval boundary.
n	Number of patients, 1 to max_n.
b_esc	Escalate when the number of DLTs is at most this value.
b_deesc	De-escalate when the number of DLTs reaches this value.
b_elim	Eliminate the dose when the number of DLTs reaches this value, NA when no elimination is possible at that sample size.
b_stop	Safety stopping boundary at the lowest dose, all NA unless extrasafe is TRUE.
stay_on_1_of_3	Whether the modification was requested.
stay_on_1_of_3_applied	Whether it changed the boundaries.

together with the design parameters used.

Staying on one DLT out of three

For some target rates the optimal BOIN decision after one DLT in three patients is to de-escalate, because the likelihood of overdosing then exceeds the likelihood of proper dosing. Long practice with the 3+3 design has nonetheless made staying at the dose the widely accepted choice, and

`stay_on_1_of_3 = TRUE` aligns the design with that practice by raising the de-escalation boundary at three patients from one DLT to two. Nothing else in the table changes.

The modification is applied only where it is meaningful, that is when one DLT out of three currently triggers de-escalation. It never overrides an escalation, and it never overrides an elimination, which is a safety rule. Whether it took effect is reported in `stay_on_1_of_3_applied`. With the default thresholds it takes effect for target rates from about 0.098 to 0.279; below that range one DLT out of three already eliminates the dose, and above it the design already stays.

References

Liu S. and Yuan, Y. (2015). Bayesian Optimal Interval Designs for Phase I Clinical Trials. Journal of the Royal Statistical Society: Series C, 64, 507-523.

See Also

`boin_lambda`, `boin_decision_table`

Examples

```
bd <- boin_boundary(target = 0.30, max_n = 18)
bd

# At a target of 0.25 one DLT out of three de-escalates by default
boin_boundary(target = 0.25, max_n = 18)$b_deesc[3]

# and stays once the modification is switched on
modified <- boin_boundary(target = 0.25, max_n = 18, stay_on_1_of_3 = TRUE)
modified$b_deesc[3]
modified$stay_on_1_of_3_applied

# At a target of 0.30 the design already stays, so nothing changes
boin_boundary(target = 0.30, max_n = 18, stay_on_1_of_3 = TRUE)$stay_on_1_of_3_applied
```

---

boin_decision_table *Decision Table for the BOIN Design*

Description

Build the lookup table that maps a pair of DLT and patient counts at the current dose to the dose assignment decision.

Usage

```
boin_decision_table(
  target,
  max_n,
  p_saf = NULL,
```

```
  p_tox = NULL,
  cutoff_eli = 0.95,
  stay_on_1_of_3 = FALSE
)
```

Arguments

target	Numeric scalar. Target DLT probability.
max_n	Integer scalar. Largest number of patients treated at a single dose.
p_saf	Numeric scalar. Highest DLT probability deemed subtherapeutic. Defaults to 0.6 * target.
p_tox	Numeric scalar. Lowest DLT probability deemed overly toxic. Defaults to 1.4 * target.
cutoff_eli	Numeric scalar. Posterior probability cutoff for dose elimination. Defaults to 0.95.
stay_on_1_of_3	Logical scalar. When TRUE, one DLT out of three patients leads to staying at the current dose rather than de-escalating. Defaults to FALSE. See boin_boundary for what the modification does.

Details

The table is derived from boin_boundary and therefore agrees with the decisions taken by the simulation engine. Elimination takes precedence over the other rules, then escalation, then de-escalation.

Value

An object of class boin_decision_table, which is a character matrix with max_n + 1 rows, labeled by the number of DLTs from 0 to max_n, and max_n columns, labeled by the number of patients from 1 to max_n. Entries are "E" to escalate, "S" to stay, "D" to de-escalate and "DE" to de-escalate and eliminate the dose together with all higher doses. Combinations with more DLTs than patients are NA. The object has print and plot methods; subsetting it returns a plain matrix.

See Also

boin_boundary, plot.boin_decision_table

Examples

```
decisions <- boin_decision_table(target = 0.30, max_n = 12)
decisions

# Only the sample sizes reached at the end of a cohort of three
print(decisions, cohort_size = 3)

# One DLT out of three de-escalates at a target of 0.25
boin_decision_table(target = 0.25, max_n = 9)["1", "3"]

# and stays once the modification is switched on
```

```
boin_decision_table(target = 0.25, max_n = 9, stay_on_1_of_3 = TRUE)["1", "3"]
```

`boin_isotonic` *Isotonic Estimates of the DLT Probability*

Description

Estimate the DLT probability at each dose under the constraint that toxicity does not decrease with dose, using the pool adjacent violators algorithm.

Usage

```
boin_isotonic(n_pts, n_tox, admissible = NULL)
```

Arguments

`n_pts`	Integer matrix with one row per trial and one column per dose, or a vector for a single trial, giving the number of patients treated.
`n_tox`	Integer matrix or vector of the same shape as `n_pts`, giving the number of DLTs observed.
`admissible`	Logical matrix of the same shape as `n_pts`, or `NULL`. Doses that are `FALSE` are left out of the estimation and returned as `NA`. Defaults to all doses that have treated at least one patient.

Details

Pseudo-counts of 0.05 DLTs and 0.1 patients are added before the fit, and doses are pooled with inverse variance weights. Doses left out through `admissible` do not influence the estimates of the remaining doses, which matters when eliminated doses must be excluded before selecting the MTD.

Value

A numeric matrix with one row per trial and one column per dose. Doses that did not enter the estimation are `NA`.

References

Liu S. and Yuan, Y. (2015). Bayesian Optimal Interval Designs for Phase I Clinical Trials. Journal of the Royal Statistical Society: Series C, 64, 507-523.

See Also

`boin_select_mtd`

Examples

```
# A single trial
boin_isotonic(n_pts = c(3, 6, 9, 12), n_tox = c(0, 1, 3, 4))

# Several trials at once
n_pts <- matrix(c(3, 6, 9, 12,
                  3, 6, 9, 12,
                  3, 6, 9, 12), nrow = 3, byrow = TRUE)
n_tox <- matrix(c(0, 1, 3, 4,
                  0, 0, 2, 3,
                  1, 2, 4, 6), nrow = 3, byrow = TRUE)
boin_isotonic(n_pts, n_tox)
```

---

boin_lambda *Escalation and De-escalation Interval Boundaries*

Description

Compute the two boundaries that define the BOIN decision interval. A dose is escalated when the observed DLT rate falls at or below `lambda_e` and de-escalated when it reaches `lambda_d`.

Usage

```
boin_lambda(target, p_saf = NULL, p_tox = NULL)
```

Arguments

`target`	Numeric scalar. Target DLT probability, for example 0.30.
`p_saf`	Numeric scalar. Highest DLT probability deemed subtherapeutic, so that dose escalation should be undertaken. Defaults to `0.6 * target`.
`p_tox`	Numeric scalar. Lowest DLT probability deemed overly toxic, so that dose de-escalation is required. Defaults to `1.4 * target`.

Details

The boundaries minimize the probability of incorrect dose assignment under a three-point hypothesis on the DLT probability at the current dose. Values of `p_saf` and `p_tox` close to `target` should be avoided, because the sample sizes of phase I trials cannot distinguish the target rate from rates close to it.

Value

A list with components `lambda_e` and `lambda_d`.

References

Liu S. and Yuan, Y. (2015). Bayesian Optimal Interval Designs for Phase I Clinical Trials. Journal of the Royal Statistical Society: Series C, 64, 507-523.

Examples

```
boin_lambda(target = 0.30)

boin_lambda(target = 0.25, p_saf = 0.12, p_tox = 0.40)
```

`boin_p_tox` *Toxic Threshold Giving a Required De-escalation Boundary*

Description

Find the value of `p_tox` for which the BOIN de-escalation boundary `lambda_d` equals a required value. This inverts `boin_lambda`, which maps `p_tox` to `lambda_d`.

Usage

```
boin_p_tox(target, lambda_d)
```

Arguments

`target`	Numeric scalar. Target DLT probability.
`lambda_d`	Numeric scalar. Required de-escalation boundary. Must lie strictly between `target` and 1.

Details

`lambda_d` increases strictly with `p_tox`, from `target` in the limit as `p_tox` approaches `target` to 1 in the limit as `p_tox` approaches 1, so the solution exists and is unique for any `lambda_d` strictly between those bounds. The root is found numerically.

A boundary close to the target needs a toxic threshold close to the target, and the rest of the package refuses a `p_tox` within ten percent of `target`, on the grounds that phase I sample sizes cannot tell the two rates apart. The value is still returned, since the inversion is well defined, but a warning names the smallest boundary that leaves a usable threshold. For a target of 0.30 that smallest boundary is about 0.315.

A design team that wants to tighten the de-escalation boundary usually states the boundary rather than the threshold behind it. This function turns that statement into the `p_tox` to pass to the other functions, so that the whole design follows from it.

Value

A numeric scalar, the value of `p_tox` that produces `lambda_d`.

See Also

`boin_lambda`, `boin_boundary`

Examples

```
# A target of 0.30 gives a de-escalation boundary of 0.359 by default
boin_lambda(target = 0.30)$lambda_d

# The toxic threshold that tightens it to 0.33
p_tox <- boin_p_tox(target = 0.30, lambda_d = 0.33)
p_tox

# which is what it claims to be
boin_lambda(target = 0.30, p_tox = p_tox)$lambda_d

# A boundary too close to the target leaves an unusable threshold, and says so
boin_p_tox(target = 0.30, lambda_d = 0.31)

# and shifts the de-escalation boundary down by one DLT at every cohort end
as.data.frame(boin_boundary(0.30, 18))[seq(3, 18, 3), ]
as.data.frame(boin_boundary(0.30, 18, p_tox = p_tox))[seq(3, 18, 3), ]
```

---

boin_select_mtd *Select the MTD from Completed Trials*

Description

Choose the maximum tolerated dose for each of a set of completed trials from the final patient and DLT counts.

Usage

```
boin_select_mtd(
  n_pts,
  n_tox,
  target,
  cutoff_eli = 0.95,
  extrasafe = FALSE,
  offset = 0.05,
  bound_mtd = FALSE,
  p_tox = NULL,
  mtd_max_estimate = NULL,
  min_mtd_sample = 1
)
```

Arguments

n_pts	Integer matrix with one row per trial and one column per dose, or a vector for a single trial, giving the number of patients treated.
n_tox	Integer matrix or vector of the same shape as n_pts, giving the number of DLTs observed.

target	Numeric scalar. Target DLT probability.
cutoff_eli	Numeric scalar. Posterior probability cutoff for dose elimination. Defaults to 0.95.
extrasafe	Logical scalar. Apply the stricter safety rule at the lowest dose, in which case no dose is selected when the lowest dose is judged too toxic. Defaults to FALSE.
offset	Numeric scalar between 0 and 0.5. Amount by which cutoff_eli is relaxed for the safety rule. Defaults to 0.05.
bound_mtd	Logical scalar. Require the isotonic estimate at the selected dose to be at or below the de-escalation boundary. Defaults to FALSE.
p_tox	Numeric scalar. Lowest DLT probability deemed overly toxic, used to derive the de-escalation boundary when bound_mtd is TRUE. Defaults to 1.4 * target.
mtd_max_estimate	Numeric scalar or NULL. Largest isotonic estimate a dose may have and still be selected. Supplying it bounds the selection whatever bound_mtd says, and replaces the de-escalation boundary that bound_mtd would otherwise use. Defaults to NULL.
min_mtd_sample	Integer scalar. Smallest number of patients a dose must have received to be eligible. Defaults to 1, which admits every dose that treated a patient.

Details

Dose elimination is re-derived from the final data of each trial rather than carried over from the dose-finding stage, which is what the reference implementation does and which matters when a trial ends at its maximum sample size. The isotonic fit is computed over the admissible doses only, so that eliminated doses do not influence the estimates of the doses that remain. The dose whose estimate is closest to target is selected, with ties broken by a small increasing perturbation across the admissible doses.

bound_mtd caps the estimate at the de-escalation boundary, which always lies above target. A cap at or below the target rate therefore cannot be expressed that way, and needs mtd_max_estimate. The two caps are independent of the decision table, so bounding the selection does not change how the trial was run.

Values of reason are "selected", "lowest_dose_eliminated", "no_admissible_dose" and "no_dose_below_bound".

Value

A data frame with one row per trial and columns

trial	Trial index.
mtd	Selected dose level, or NA when no dose is selected.
reason	Why the dose was or was not selected.

References

Liu S. and Yuan, Y. (2015). Bayesian Optimal Interval Designs for Phase I Clinical Trials. Journal of the Royal Statistical Society: Series C, 64, 507-523.

See Also

boin_isotonic, boin_simulate

Examples

```
n_pts <- matrix(c(3, 6, 9, 3,
                  3, 6, 9, 3), nrow = 2, byrow = TRUE)
n_tox <- matrix(c(0, 1, 3, 2,
                  0, 1, 2, 1), nrow = 2, byrow = TRUE)

boin_select_mtd(n_pts, n_tox, target = 0.30)

boin_select_mtd(n_pts, n_tox, target = 0.30, bound_mtd = TRUE)

# Require the isotonic estimate at the selected dose to be at most 0.30,
# which the de-escalation boundary cannot express
boin_select_mtd(n_pts, n_tox, target = 0.30, mtd_max_estimate = 0.30)
```

---

boin_simulate *Simulate BOIN Trials*

Description

Run the BOIN dose-finding algorithm over many simulated trials and return the patient and DLT counts at every dose. This is the simulation engine behind sim_boin, exposed for users who want the raw trial data.

Usage

```
boin_simulate(
  target,
  p_true,
  n_cohort,
  cohort_size,
  n_trials = 10000,
  start_dose = 1,
  n_earlystop = 18,
  p_saf = NULL,
  p_tox = NULL,
  cutoff_eli = 0.95,
  extrasafe = FALSE,
  offset = 0.05,
  titration = FALSE,
  stay_on_1_of_3 = FALSE,
  n_earlystop_rule = c("with_stay", "simple"),
  seed = 123
)
```

Arguments

target	Numeric scalar. Target DLT probability, for example 0.30.
p_true	Numeric vector. True DLT probability at each dose level, in increasing dose order.
n_cohort	Integer scalar. Number of cohorts in a trial.
cohort_size	Integer scalar or vector. Number of patients per cohort. A scalar is used for every cohort. A vector shorter than n_cohort is padded with its last element and a longer one is truncated.
n_trials	Integer scalar. Number of trials to simulate. Defaults to 10000.
start_dose	Integer scalar. Dose level for the first cohort. Defaults to 1. It is ignored when titration is TRUE, because the titration phase always begins at the lowest dose.
n_earlystop	Integer scalar. The trial stops once this many patients have been treated at the current dose and the design would stay there. Defaults to 18.
p_saf	Numeric scalar. Highest DLT probability deemed subtherapeutic. Defaults to 0.6 * target.
p_tox	Numeric scalar. Lowest DLT probability deemed overly toxic. Defaults to 1.4 * target.
cutoff_eli	Numeric scalar. Posterior probability cutoff for dose elimination. Defaults to 0.95.
extrasafe	Logical scalar. Apply the stricter safety stopping rule at the lowest dose. Defaults to FALSE.
offset	Numeric scalar between 0 and 0.5. Amount by which cutoff_eli is relaxed for the safety stopping rule. Defaults to 0.05.
titration	Logical scalar. Start with single patient cohorts until the first DLT is seen. Ignored when the first cohort size is one. Defaults to FALSE.
stay_on_1_of_3	Logical scalar. When TRUE, one DLT out of three patients leads to staying at the current dose rather than de-escalating. Defaults to FALSE. See boin_boundary.
n_earlystop_rule	Character scalar, either "with_stay" or "simple". Under "with_stay" the trial stops at n_earlystop only when the design would remain at the current dose, which is the rule used by the reference implementation. Under "simple" it stops as soon as the threshold is reached.
seed	Integer scalar or NULL. Random seed. When NULL the current state of the random number generator is used. The state of the calling session is restored on exit. Defaults to 123.

Details

One uniform variate is drawn per patient, in enrollment order. Two details matter for reproducibility: the titration phase draws one variate per dose level whether or not it is used, and a cohort cut short by the maximum sample size still draws a full cohort's worth. This is the random number consumption of BOIN::get.oc(), so with the same seed and matching arguments a run reproduces the reference implementation trial by trial.

Possible values of stop_reason are "lowest_dose_eliminated", "lowest_dose_too_toxic", "n_earlystop", "max_sample_size" and "max_cohorts".

Value

An object of class `boin_trials`, which is a list with components

`n_pts`	Integer matrix, `n_trials` by number of doses, of patients treated.
`n_tox`	Integer matrix of the same shape, of DLTs observed.
`eliminated`	Logical matrix of the same shape, marking doses eliminated during the trial.
`cohorts_used`	Integer vector of cohorts completed in each trial.
`stop_reason`	Character vector giving why each trial ended.
`boundary`	The `boin_boundary` object used.
`settings`	List of the design parameters.

References

Liu S. and Yuan, Y. (2015). Bayesian Optimal Interval Designs for Phase I Clinical Trials. Journal of the Royal Statistical Society: Series C, 64, 507-523.

See Also

`sim_boin`, `boin_select_mtd`

Examples

```
trials <- boin_simulate(
  target = 0.30,
  p_true = c(0.05, 0.15, 0.30, 0.45, 0.60),
  n_cohort = 10,
  cohort_size = 3,
  n_trials = 200,
  seed = 123
)
trials

head(trials$n_pts)
table(trials$stop_reason)
```

`boin_stopping_table` *Safety Stopping Boundary as a Two-Row Table*

Description

Present the safety stopping boundary at the lowest dose as a compact table with one column per sample size, which is the shape usually wanted in a protocol or a report.

Usage

```
boin_stopping_table(x, cohort_size = NULL)
```

Arguments

x	An object of class boin_boundary, built with extrasafe = TRUE.
cohort_size	Integer scalar or NULL. When supplied, only the sample sizes that are multiples of cohort_size are kept.

Details

The same numbers are available one row per sample size from as.data.frame() on the boundary object. This function transposes them and labels the rows, which suits a table pasted into a document or rendered with knitr::kable() or DT::datatable().

Value

A data frame with two rows, labeled by the quantity they hold, and one column per sample size. Sample sizes at which no number of DLTs triggers the rule are dropped.

See Also

boin_boundary

Examples

```
bd <- boin_boundary(target = 0.30, max_n = 18, extrasafe = TRUE)

boin_stopping_table(bd)

# Only the sample sizes reached at the end of a cohort of three
boin_stopping_table(bd, cohort_size = 3)
```

---

oc_3p3 *Exact Operating Characteristics of the 3+3 Design*

Description

Compute the operating characteristics of the traditional 3+3 dose-finding design exactly. The probability of every path the design can take is evaluated in closed form, so the result carries no Monte Carlo error and no seed is involved. Use it as a comparator for the BOIN results returned by sim_boin.

Usage

```
oc_3p3(
  p_true,
  mtd_rule = c("previous", "expand"),
  start_dose = 1,
  overdose_cutoff = NULL
)
```

Arguments

p_true	Numeric vector. True DLT probability at each dose level, in increasing dose order.
mtd_rule	Character scalar, either "previous" or "expand". The two definitions of the MTD in common use. See Details. Defaults to "previous".
start_dose	Integer scalar. Dose level for the first cohort. Defaults to 1.
overdose_cutoff	Numeric scalar or NULL. Doses whose true DLT probability exceeds this value count as overdoses in the overdose component of the result. Defaults to NULL, which uses one third.

Details

The escalation rule is the traditional one. Three patients are treated at the current dose. No DLT leads to the next dose up. One DLT out of three leads to three more patients at the same dose, and then to the next dose up if no further DLT is seen and to stopping otherwise. Two or more DLTs out of three stop the trial at once. A trial that escalates past the highest dose ends there.

The two MTD rules differ only in what happens once escalation has stopped. "previous" names the dose below the one declared too toxic, and the highest dose when escalation ran out of doses. "expand" instead takes the MTD to be the highest dose at which at most one of six patients had a DLT: starting from the highest dose still eligible, a dose that has only three patients is expanded to six and assessed, and the search moves down a level whenever the expanded dose fails. Neither rule is universally the standard, so the comparator being matched should be checked before a rule is chosen. The two agree on which doses are visited during escalation, and so on the probability that a patient is exposed to an overly toxic dose; they differ in the sample size and in the selection percentages.

The 3+3 design has no fixed maximum sample size, so the within-trial exposure percentage and the 60 percent and 80 percent thresholds reported for BOIN in sim_boin have no counterpart here.

Value

An object of class oc_3p3, which is a list with components

sel_percent	Percentage of trials selecting each dose as the MTD.
percent_no_mtd	Percentage of trials ending without an MTD.
n_pts_dose	Average number of patients treated at each dose.
n_tox_dose	Average number of DLTs observed at each dose.
total_n_pts	Average total number of patients per trial.
total_n_tox	Average total number of DLTs per trial.
overdose	List describing the design's relationship with doses above overdose_cutoff: pct_patients (the percentage of all patients treated at such a dose, that is the probability that a patient is dosed above the cutoff), avg_n_patients, pct_trials_any (the percentage of trials treating at least one patient there), pct_trials_mtd_above (the percentage of all trials whose selected MTD is above the cutoff) and pct_mtd_above_when_selected (the same among the trials that selected an MTD). The cutoff and the dose levels doses that exceed it are also returned.

together with p_true, n_doses, mtd_rule, start_dose, method and the call.

See Also

sim_3p3, sim_boin

Examples

```
oc_3p3(p_true = c(0.30, 0.48, 0.67))

# The other definition of the MTD
oc_3p3(p_true = c(0.30, 0.48, 0.67), mtd_rule = "expand")

# Exposure to doses above a stated DLT rate
oc_3p3(p_true = c(0.20, 0.40, 0.60), overdose_cutoff = 1 / 3)$overdose
```

---

plot.boin_decision_table

Plot a BOIN Decision Table

Description

Draw the decision table produced by boin_decision_table as a grid of colored cells, one per pair of DLT and patient counts, with the decision letter in each cell.

Usage

```
## S3 method for class 'boin_decision_table'
plot(x, text_size = 1, colors = NULL, ...)
```

Arguments

x	An object of class boin_decision_table.
text_size	Numeric scalar. Multiplier applied to every text size in the figure. Use a larger value when the figure is exported at high resolution, for example into a report. Defaults to 1.
colors	Named character vector of four colors, with names "E", "S", "D" and "DE". Defaults to a palette whose adjacent categories remain distinguishable under the common forms of color vision deficiency.
...	Further arguments, currently ignored.

Details

Every cell carries its decision letter, so the figure does not rely on color alone to convey the decision and remains readable in grayscale.

Requires the **ggplot2** package, which is only suggested by **simFastBOIN** rather than required.

Value

A **ggplot2** object, which can be printed, saved with `ggplot2::ggsave()` or extended with further layers.

See Also

`boin_decision_table`, `print.boin_decision_table`

Examples

```
decisions <- boin_decision_table(target = 0.30, max_n = 12)

plot(decisions)

# Larger text for a high resolution export
plot(decisions, text_size = 2)

# A palette of your own
plot(decisions, colors = c(E = "#4DAF4A", S = "#377EB8",
                           D = "#FF7F00", DE = "#E41A1C"))
```

---

print.boin_boundary *Print BOIN Decision Boundaries*

Description

Display the interval boundaries and the integer decision boundaries produced by `boin_boundary`.

Usage

```
## S3 method for class 'boin_boundary'
print(x, cohort_size = NULL, ...)
```

Arguments

`x`	An object of class `boin_boundary`.
`cohort_size`	Integer scalar or `NULL`. When supplied, only the sample sizes that are multiples of `cohort_size` are shown, which is how the boundaries are consulted during a trial with equally sized cohorts.
`...`	Further arguments, currently ignored.

Value

The object `x`, invisibly.

Examples

```
bd <- boin_boundary(target = 0.30, max_n = 18, extrasafe = TRUE)
print(bd, cohort_size = 3)
```

`print.boin_decision_table` *Print a BOIN Decision Table*

Description

Display the decision table produced by `boin_decision_table`, optionally restricted to the sample sizes reached at the end of a cohort.

Usage

```
## S3 method for class 'boin_decision_table'
print(x, cohort_size = NULL, ...)
```

Arguments

`x`	An object of class `boin_decision_table`.
`cohort_size`	Integer scalar or `NULL`. When supplied, only the sample sizes that are multiples of `cohort_size` are shown, which is how the table is consulted during a trial with equally sized cohorts.
`...`	Further arguments, currently ignored.

Value

The object `x`, invisibly.

See Also

`boin_decision_table`, `plot.boin_decision_table`

Examples

```
decisions <- boin_decision_table(target = 0.30, max_n = 18)

print(decisions, cohort_size = 3)
```

print.boin_oc *Print Operating Characteristics of a BOIN Design*

Description

Display the summary table produced by sim_boin.

Usage

```
## S3 method for class 'boin_oc'
print(
  x,
  digits = 1,
  percent = FALSE,
  kable = FALSE,
  kable_format = "pipe",
  ...
)
```

Arguments

x	An object of class boin_oc.
digits	Integer scalar. Number of decimal places. Defaults to 1.
percent	Logical scalar. Express the average number of patients and DLTs at each dose as a percentage of the trial total instead of a count. Defaults to FALSE.
kable	Logical scalar. Return the table through knitr::kable() rather than printing it directly, which is convenient inside a report. Requires the **knitr** package. Defaults to FALSE.
kable_format	Character scalar passed to knitr::kable(), for example "pipe", "html" or "latex". Defaults to "pipe".
...	Further arguments, currently ignored.

Value

The object x, invisibly.

Examples

```
oc <- sim_boin(
  target = 0.30,
  p_true = c(0.05, 0.15, 0.30, 0.45, 0.60),
  n_cohort = 10,
  cohort_size = 3,
  n_trials = 200,
  seed = 123
)
```

```
print(oc)
print(oc, percent = TRUE)
```

`print.boin_oc_multi` *Print Operating Characteristics Across Scenarios*

Description

Display the combined summary table produced by `sim_boin_multi`.

Usage

```
## S3 method for class 'boin_oc_multi'
print(
  x,
  digits = 1,
  percent = FALSE,
  kable = FALSE,
  kable_format = "pipe",
  ...
)
```

Arguments

`x`	An object of class `boin_oc_multi`.
`digits`	Integer scalar. Number of decimal places. Defaults to 1.
`percent`	Logical scalar. Express the average number of patients and DLTs at each dose as a percentage of the trial total instead of a count. Defaults to `FALSE`.
`kable`	Logical scalar. Return the table through `knitr::kable()` rather than printing it directly. Requires the **knitr** package. Defaults to `FALSE`.
`kable_format`	Character scalar passed to `knitr::kable()`, for example `"pipe"`, `"html"` or `"latex"`. Defaults to `"pipe"`.
`...`	Further arguments, currently ignored.

Value

The object `x`, invisibly.

Examples

```
oc <- sim_boin_multi(
  target = 0.30,
  scenarios = list(
    list(name = "MTD at dose 3", p_true = c(0.05, 0.15, 0.30, 0.45, 0.60)),
    list(name = "All toxic",     p_true = c(0.35, 0.45, 0.55, 0.65, 0.75))
  ),
  n_cohort = 10,
  cohort_size = 3,
  n_trials = 200,
  seed = 123
)

print(oc)
print(oc, percent = TRUE)
```

---

print.boin_trials *Print Simulated BOIN Trials*

Description

Show a compact summary of the object returned by `boin_simulate` instead of printing the full trial matrices.

Usage

```
## S3 method for class 'boin_trials'
print(x, ...)
```

Arguments

`x`	An object of class `boin_trials`.
`...`	Further arguments, currently ignored.

Value

The object `x`, invisibly.

Examples

```
trials <- boin_simulate(
  target = 0.30,
  p_true = c(0.05, 0.15, 0.30, 0.45, 0.60),
  n_cohort = 10,
  cohort_size = 3,
  n_trials = 100,
  seed = 1
)
```

```
print(trials)
```

`print.oc_3p3` *Print Operating Characteristics of the 3+3 Design*

Description

Display the summary table produced by `oc_3p3` or `sim_3p3`. The layout matches `print.boin_oc`, so a 3+3 table can be read beside a BOIN one.

Usage

```
## S3 method for class 'oc_3p3'
print(
  x,
  digits = 1,
  percent = FALSE,
  kable = FALSE,
  kable_format = "pipe",
  ...
)
```

Arguments

`x`	An object of class `oc_3p3`.
`digits`	Integer scalar. Number of decimal places. Defaults to 1.
`percent`	Logical scalar. Express the average number of patients and DLTs at each dose as a percentage of the trial total instead of a count. Defaults to `FALSE`.
`kable`	Logical scalar. Return the table through `knitr::kable()` rather than printing it directly, which is convenient inside a report. Requires the **knitr** package. Defaults to `FALSE`.
`kable_format`	Character scalar passed to `knitr::kable()`, for example `"pipe"`, `"html"` or `"latex"`. Defaults to `"pipe"`.
`...`	Further arguments, currently ignored.

Value

The object `x`, invisibly.

See Also

`oc_3p3`, `sim_3p3`

Examples

```
oc <- oc_3p3(p_true = c(0.30, 0.48, 0.67))

print(oc)
print(oc, percent = TRUE)
```

`sim_3p3` *Simulate the 3+3 Design*

Description

Simulate the traditional 3+3 dose-finding design and summarize the same quantities that `oc_3p3` computes exactly. The two are meant to be used together: `oc_3p3()` gives the answer without Monte Carlo error, and this function confirms it from independent trials.

Usage

```
sim_3p3(
  p_true,
  n_trials = 10000,
  mtd_rule = c("previous", "expand"),
  start_dose = 1,
  overdose_cutoff = NULL,
  seed = 123
)
```

Arguments

`p_true`	Numeric vector. True DLT probability at each dose level, in increasing dose order.
`n_trials`	Integer scalar. Number of trials to simulate. Defaults to 10000.
`mtd_rule`	Character scalar, either `"previous"` or `"expand"`. See `oc_3p3`. Defaults to `"previous"`.
`start_dose`	Integer scalar. Dose level for the first cohort. Defaults to 1.
`overdose_cutoff`	Numeric scalar or `NULL`. Doses whose true DLT probability exceeds this value count as overdoses in the `overdose` component of the result. Defaults to `NULL`, which uses one third.
`seed`	Integer scalar or `NULL`. Random seed. The state of the calling session is restored on exit. Defaults to 123.

Details

The design is described under `oc_3p3`. Since the operating characteristics of the 3+3 design can be written in closed form, this function is a check on that closed form rather than the way to obtain the numbers. Simulation is the only option when a quantity is wanted that the closed form does not provide, such as the distribution of the sample size rather than its mean.

Value

An object of class oc_3p3, with the components described in oc_3p3. The method component is the number of trials rather than "exact".

See Also

oc_3p3, sim_boin

Examples

```
exact <- oc_3p3(p_true = c(0.30, 0.48, 0.67))
simulated <- sim_3p3(p_true = c(0.30, 0.48, 0.67), n_trials = 2000, seed = 1)

round(exact$sel_percent, 2)
round(simulated$sel_percent, 2)
```

---

sim_boin *Operating Characteristics of a BOIN Design*

Description

Simulate a BOIN dose-finding trial many times under one dose-toxicity scenario and summarize how often each dose is selected as the MTD, how many patients are treated at each dose and how many DLTs are observed.

Usage

```
sim_boin(
  target,
  p_true,
  n_cohort,
  cohort_size,
  n_trials = 10000,
  start_dose = 1,
  n_earlystop = 18,
  p_saf = NULL,
  p_tox = NULL,
  cutoff_eli = 0.95,
  extrasafe = FALSE,
  offset = 0.05,
  titration = FALSE,
  stay_on_1_of_3 = FALSE,
  bound_mtd = FALSE,
  mtd_max_estimate = NULL,
  min_mtd_sample = 1,
  overdose_cutoff = NULL,
```

```
  n_earlystop_rule = c("with_stay", "simple"),
  keep_trials = FALSE,
  verbose = FALSE,
  seed = 123
)
```

Arguments

target	Numeric scalar. Target DLT probability, for example 0.30.
p_true	Numeric vector. True DLT probability at each dose level, in increasing dose order.
n_cohort	Integer scalar. Number of cohorts in a trial.
cohort_size	Integer scalar or vector. Number of patients per cohort. A scalar is used for every cohort. A vector shorter than `n_cohort` is padded with its last element and a longer one is truncated.
n_trials	Integer scalar. Number of trials to simulate. Defaults to 10000.
start_dose	Integer scalar. Dose level for the first cohort. Defaults to 1. It is ignored when `titration` is `TRUE`, because the titration phase always begins at the lowest dose.
n_earlystop	Integer scalar. The trial stops once this many patients have been treated at the current dose and the design would stay there. Defaults to 18. Set it to a value above the maximum sample size to switch this rule off.
p_saf	Numeric scalar. Highest DLT probability deemed subtherapeutic. Defaults to `0.6 * target`.
p_tox	Numeric scalar. Lowest DLT probability deemed overly toxic. Defaults to `1.4 * target`.
cutoff_eli	Numeric scalar. Posterior probability cutoff for dose elimination. Defaults to 0.95.
extrasafe	Logical scalar. Apply the stricter safety stopping rule at the lowest dose. Defaults to `FALSE`.
offset	Numeric scalar between 0 and 0.5. Amount by which `cutoff_eli` is relaxed for the safety stopping rule. Defaults to 0.05.
titration	Logical scalar. Start with single patient cohorts until the first DLT is seen. Ignored when the first cohort size is one. Defaults to `FALSE`.
stay_on_1_of_3	Logical scalar. When `TRUE`, one DLT out of three patients leads to staying at the current dose rather than de-escalating. Defaults to `FALSE`. See `boin_boundary`.
bound_mtd	Logical scalar. Require the isotonic estimate at the selected dose to be at or below the de-escalation boundary. Defaults to `FALSE`.
mtd_max_estimate	Numeric scalar or `NULL`. Largest isotonic estimate a dose may have and still be selected as the MTD. Supplying it bounds the selection whatever `bound_mtd` says, and unlike `bound_mtd` it can be set at or below the target rate. It changes only the selection, never the dose-finding itself. Defaults to `NULL`.
min_mtd_sample	Integer scalar. Smallest number of patients a dose must have received to be eligible as the MTD. Defaults to 1.

`overdose_cutoff`
: Numeric scalar or `NULL`. Doses whose true DLT probability exceeds this value count as overdoses in the `overdose` component of the result. Defaults to `NULL`, which uses `target`.

`n_earlystop_rule`
: Character scalar, either `"with_stay"` or `"simple"`. See `boin_simulate`.

`keep_trials`
: Logical scalar. Keep the full trial by trial data in the result. Defaults to `FALSE`.

`verbose`
: Logical scalar. Report progress while the simulation runs. Defaults to `FALSE`.

`seed`
: Integer scalar or `NULL`. Random seed. The state of the calling session is restored on exit. Defaults to 123.

Details

The engine draws one uniform variate per patient, in enrollment order, and applies the decision rules in the order used by `BOIN::get.oc()`. See `boin_simulate` for the two places where a variate is drawn but not used. With the same seed and matching arguments the two implementations agree trial by trial, not merely on average.

Note that `n_earlystop` defaults to 18 here, whereas the reference implementation defaults to 100, which in practice switches the rule off.

Value

An object of class `boin_oc`, which is a list with components

`sel_percent`
: Percentage of trials selecting each dose as the MTD.

`percent_no_mtd`
: Percentage of trials ending without an MTD.

`n_pts_dose`
: Average number of patients treated at each dose.

`n_tox_dose`
: Average number of DLTs observed at each dose.

`total_n_pts`
: Average total number of patients per trial.

`total_n_tox`
: Average total number of DLTs per trial.

`overdose`
: List describing the design's relationship with doses above `overdose_cutoff`. Two questions are answered separately. How far were patients exposed during the trial: `pct_patients` (the percentage of all simulated patients treated at such a dose, that is the probability that a patient is dosed above the cutoff), `pct_patients_by_trial` (the same percentage computed within each trial and then averaged), `avg_n_patients`, `pct_trials_any`, `pct_trials_over_60` and `pct_trials_over_80`. And how often did the design end up recommending such a dose: `pct_trials_mtd_above` (the percentage of all trials whose selected MTD is above the cutoff) and `pct_mtd_above_when_selected` (the same among the trials that selected an MTD at all). The `cutoff` and the dose levels `doses` that exceed it are also returned.

`stop_reason_percent`
: Percentage of trials by reason for stopping.

`trials`
: Trial level data when `keep_trials` is `TRUE`, otherwise `NULL`.

together with the design parameters and the call.

References

Liu S. and Yuan, Y. (2015). Bayesian Optimal Interval Designs for Phase I Clinical Trials. Journal of the Royal Statistical Society: Series C, 64, 507-523.

See Also

sim_boin_multi, boin_simulate

Examples

```
oc <- sim_boin(
  target = 0.30,
  p_true = c(0.05, 0.15, 0.30, 0.45, 0.60),
  n_cohort = 10,
  cohort_size = 3,
  n_trials = 500,
  seed = 123
)
oc


# A larger run with the safety options switched on
oc_safe <- sim_boin(
  target = 0.30,
  p_true = c(0.30, 0.40, 0.50, 0.60, 0.70),
  n_cohort = 20,
  cohort_size = 3,
  n_trials = 10000,
  extrasafe = TRUE,
  bound_mtd = TRUE,
  titration = TRUE,
  seed = 123
)
oc_safe

# How often are patients dosed above a true DLT rate of 0.33?
oc_cut <- sim_boin(
  target = 0.30,
  p_true = c(0.10, 0.20, 0.30, 0.42, 0.55),
  n_cohort = 20,
  cohort_size = 3,
  n_trials = 10000,
  overdose_cutoff = 0.33,
  seed = 123
)
oc_cut$overdose$pct_patients            # patients dosed above 0.33
oc_cut$overdose$pct_trials_mtd_above     # trials recommending a dose above 0.33
```

sim_boin_multi *Operating Characteristics Across Several Scenarios*

Description

Run sim_boin under a list of dose-toxicity scenarios that share the same design, and collect the results into one table.

Usage

```
sim_boin_multi(
  target,
  scenarios,
  n_cohort,
  cohort_size,
  n_trials = 10000,
  start_dose = 1,
  n_earlystop = 18,
  p_saf = NULL,
  p_tox = NULL,
  cutoff_eli = 0.95,
  extrasafe = FALSE,
  offset = 0.05,
  titration = FALSE,
  stay_on_1_of_3 = FALSE,
  bound_mtd = FALSE,
  mtd_max_estimate = NULL,
  min_mtd_sample = 1,
  overdose_cutoff = NULL,
  n_earlystop_rule = c("with_stay", "simple"),
  keep_trials = FALSE,
  verbose = FALSE,
  seed = 123
)
```

Arguments

target	Numeric scalar. Target DLT probability.
scenarios	A list of scenarios. Each element is a list with a name and a p_true vector, or a plain numeric vector of true DLT probabilities in which case the list names are used as scenario names. Every scenario must have the same number of doses.
n_cohort	Integer scalar. Number of cohorts in a trial.
cohort_size	Integer scalar or vector. Number of patients per cohort.
n_trials	Integer scalar. Number of trials per scenario. Defaults to 10000.
start_dose	Integer scalar. Dose level for the first cohort. Defaults to 1. It is ignored when titration is TRUE.

`n_earlystop` Integer scalar. Early stopping sample size at the current dose. Defaults to 18.

`p_saf` Numeric scalar. Highest DLT probability deemed subtherapeutic. Defaults to `0.6 * target`.

`p_tox` Numeric scalar. Lowest DLT probability deemed overly toxic. Defaults to `1.4 * target`.

`cutoff_eli` Numeric scalar. Posterior probability cutoff for dose elimination. Defaults to 0.95.

`extrasafe` Logical scalar. Apply the stricter safety stopping rule at the lowest dose.

`offset` Numeric scalar between 0 and 0.5. Relaxation of `cutoff_eli` for the safety stopping rule. Defaults to 0.05.

`titration` Logical scalar. Start with single patient cohorts until the first DLT.

`stay_on_1_of_3` Logical scalar. Make one DLT out of three patients a stay rather than a de-escalation. See `boin_boundary`.

`bound_mtd` Logical scalar. Bound the isotonic estimate at the selected MTD by the de-escalation boundary.

`mtd_max_estimate` Numeric scalar or `NULL`. Largest isotonic estimate a dose may have and still be selected as the MTD. See `sim_boin`.

`min_mtd_sample` Integer scalar. Smallest number of patients for a dose to be eligible.

`overdose_cutoff` Numeric scalar or `NULL`. Doses whose true DLT probability exceeds this value count as overdoses. Defaults to `NULL`, which uses `target`.

`n_earlystop_rule` Character scalar, either `"with_stay"` or `"simple"`.

`keep_trials` Logical scalar. Keep the trial by trial data of every scenario.

`verbose` Logical scalar. Report progress while the simulations run.

`seed` Integer scalar or `NULL`. Random seed, applied to every scenario, so that a scenario simulated here matches the same scenario simulated on its own with `sim_boin`.

Value

An object of class `boin_oc_multi`, which is a list with components

`results` Named list of `boin_oc` objects, one per scenario.

`summary_table` Data frame collecting all scenarios.

`scenario_names` Character vector of scenario names.

`n_doses` Number of dose levels.

`call` The matched call.

See Also

`sim_boin`

Examples

```
scenarios <- list(
  list(name = "MTD at dose 3", p_true = c(0.05, 0.15, 0.30, 0.45, 0.60)),
  list(name = "All toxic",     p_true = c(0.35, 0.45, 0.55, 0.65, 0.75))
)

oc <- sim_boin_multi(
  target = 0.30,
  scenarios = scenarios,
  n_cohort = 10,
  cohort_size = 3,
  n_trials = 200,
  seed = 123
)
oc
```

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