Package 'escalation'

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Type Package

Title Modular Approach to Dose Finding Clinical Trials

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Description Methods for working with dose-finding clinical trials. We start by providing a common interface to various dose-finding methodologies like the continual reassessment method (CRM) by O'Quigley et al. (1990) <doi:10.2307/2531628>, the Bayesian optimal interval design (BOIN) by Liu & Yuan (2015) <doi:10.1111/rssc.12089>, and the 3+3 described by Korn et al. (1994) <doi:10.1002/sim.4780131802>. We then add optional embellishments to provide extra desirable behaviour, like avoiding skipping doses, stopping after n patients have been treated at the recommended dose, or demanding that n patients are treated before stopping is allowed. By daisy-chaining together these embellishments using the pipe operator from 'magrittr', it is simple to tailor the behaviour of dose-finding designs so that they do what you want. Furthermore, using this flexible interface for creating dose-finding designs, it is simple to run simulations or calculate dose-pathways for future cohorts of patients.

License GPL (>= 3)

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R topics documented:

`as_tibble.dose_paths` *Cast* `dose_paths` *object to* `tibble`.

Description

Cast `dose_paths` object to `tibble`.

Usage

```
## S3 method for class 'dose_paths'
as_tibble(x, ...)
```

Arguments

`x`	Object of class `dose_finding_paths`.
`...`	Extra args passed onwards.

Value

Object of class `tibble`

`calculate_probabilities`
Calculate dose-path probabilities

Description

Crystallise a set of `dose_paths` with probabilities to calculate how likely each path is. Once probabilised in this way, the probabilities of the terminal nodes in this set of paths will sum to 1. This allows users to calculate operating characteristics.

Usage

```
calculate_probabilities(dose_paths, true_prob_tox)
```

Arguments

dose_paths	Object of type dose_paths
true_prob_tox	Numeric vector, true probability of toxicity.

See Also

dose_paths

Examples

```
# Calculate dose paths for the first three cohorts in a 3+3 trial of 5 doses:
paths <- get_three_plus_three(num_doses = 5) %>%
  get_dose_paths(cohort_sizes = c(3, 3, 3))

# Set the true probabilities of toxicity
true_prob_tox <- c(0.12, 0.27, 0.44, 0.53, 0.57)
# And calculate exact operating performance
x <- paths %>% calculate_probabilities(true_prob_tox)
prob_recommend(x)
```

---

cohort *Cohort numbers of evaluated patients.*

Description

Get a vector of integers that reflect the cohorts to which the evaluated patients belong.

Usage

```
cohort(x, ...)
```

Arguments

x	Object of type selector.
...	Extra args are passed onwards.

Value

an integer vector

Examples

```
skeleton <- c(0.05, 0.1, 0.25, 0.4, 0.6)
target <- 0.25
model <- get_dfcrm(skeleton = skeleton, target = target)
fit <- model %>% fit('1NNN 2NTN')
fit %>% cohort()
```

`cohorts_of_n` *Sample times between patient arrivals using the exponential distribution.*

Description

Sample times between patient arrivals using the exponential distribution.

Usage

```
cohorts_of_n(n = 3, mean_time_delta = 1)
```

Arguments

`n`	integer, sample arrival times for this many patients.
`mean_time_delta`	the average gap between patient arrival times. I.e. the reciprocal of the rate parameter in an Exponential distribution.

Value

`data.frame` with column time_delta containing durations of time between patient arrivals.

Examples

```
cohorts_of_n()
cohorts_of_n(n = 10, mean_time_delta = 5)
```

`continue` *Should this dose-finding experiment continue?*

Description

Should this dose-finding experiment continue? Or have circumstances prevailed that dictate this trial should stop? This method is critical to the automatic calculation of statistical operating characteristics and dose-pathways. You add stopping behaviours to designs using calls like `stop_at_n` and `stop_when_too_toxic`.

Usage

```
continue(x, ...)
```

Arguments

x	Object of type selector.
...	Extra args are passed onwards.

Value

logical

Examples

```
skeleton <- c(0.05, 0.1, 0.25, 0.4, 0.6)
target <- 0.25
model1 <- get_dfcrm(skeleton = skeleton, target = target)
fit1 <- model1 %>% fit('1NNN 2NTN')
fit1 %>% continue()

model2 <- get_dfcrm(skeleton = skeleton, target = target) %>%
  stop_at_n(n = 6)
fit2 <- model2 %>% fit('1NNN 2NTN')
fit2 %>% continue()
```

---

crystallised_dose_paths

Dose-paths with probabilities attached.

Description

dose_paths reflect all possible paths a dose-finding trial may take. When the probability of those paths is calculated using an assumed set of true dose-event probabilities, in this package those paths are said to be crysallised. Once crystallised, operating charactersitics can be calculated.

Usage

```
crystallised_dose_paths(dose_paths, true_prob_tox, terminal_nodes)
```

Arguments

dose_paths	Object of type dose_paths
true_prob_tox	vector of probabilities
terminal_nodes	tibble of terminal nodes on the dose-paths

Value

An object of type crystallised_dose_paths

Examples

```
# Calculate dose paths for the first three cohorts in a 3+3 trial of 5 doses:
paths <- get_three_plus_three(num_doses = 5) %>%
  get_dose_paths(cohort_sizes = c(3, 3, 3))

# Set the true probabilities of toxicity
true_prob_tox <- c(0.12, 0.27, 0.44, 0.53, 0.57)
# Crytallise the paths with the probabilities of toxicity
x <- paths %>% calculate_probabilities(true_prob_tox)
# And then examine, for example, the probabilities of recommending each dose
# at the terminal nodes of these paths:
prob_recommend(x)
```

---

demand_n_at_dose *Demand there are n patients at a dose before condisdering stopping.*

Description

This method continues a dose-finding trial until there are n patients at a dose. Once that condition is met, it delegates stopping responsibility to its parent dose selector, whatever that might be. This class is greedy in that it meets its own needs before asking any other selectors in a chain what they want. Thus, different behaviours may be achieved by nesting dose selectors in different orders. See examples.

Usage

```
demand_n_at_dose(parent_selector_factory, n, dose)
```

Arguments

parent_selector_factory	Object of type selector_factory.
n	Continue at least until there are n at a dose.
dose	'any' to continue until there are n at any dose; 'recommended' to continue until there are n at the recommended dose; or an integer to continue until there are n at a particular dose-level.

Value

an object of type selector_factory that can fit a dose-finding model to outcomes.

Examples

```
skeleton <- c(0.05, 0.1, 0.25, 0.4, 0.6)
target <- 0.25

# This model will demand 9 at any dose before it countenances stopping.
model1 <- get_dfcrm(skeleton = skeleton, target = target) %>%
```

```
  demand_n_at_dose(n = 9, dose = 'any')

# This model will recommend continuing:
model1 %>% fit('1NNT 1NNN 2TNN 2NNN') %>% continue()
# It tells you to continue because there is no selector considering when
# you should stop - dfcrm implements no stopping rule by default.

# In contrast, we can add a stopping selector to discern the behaviour of
# demand_n_at_dose. We will demand 9 are seen at the recommended dose before
# stopping is permitted in model3:
model2 <- get_dfcrm(skeleton = skeleton, target = target) %>%
  stop_at_n(n = 12)
model3 <- get_dfcrm(skeleton = skeleton, target = target) %>%
  stop_at_n(n = 12) %>%
  demand_n_at_dose(n = 9, dose = 'recommended')

# This model advocates stopping because 12 patients are seen in total:
model2 %>% fit('1NNN 1NNN 2TNN 2NNN') %>% continue()
# But this model advocates continuing because 9 patients have not been seen
# at any dose yet:
model3 %>% fit('1NNN 1NNN 2TNN 2NNN') %>% continue()
# This shows how demand_n_at_dose overrides stopping behaviours that come
# before it in the daisychain.

# Once 9 are seen at the recommended dose, the decision to stop is made:
fit <- model3 %>% fit('1NNN 1NNN 2TNN 2NNN 2TTN')
fit %>% continue()
fit %>% recommended_dose()
```

`dont_skip_doses` *Prevent skipping of doses.*

Description

This method optionally prevents dose selectors from skipping doses when escalating and / or deescalating. The default is that skipping when escalating is prevented but skipping when deescalating is permitted, but both of these behaviours can be altered.

Usage

```
dont_skip_doses(
  parent_selector_factory,
  when_escalating = TRUE,
  when_deescalating = FALSE
)
```

Arguments

`parent_selector_factory`
: Object of type `selector_factory`.

when_escalating
: TRUE to prevent skipping when attempting to escalate.

when_deescalating
: TRUE to prevent skipping when attempting to deescalate.

Value

an object of type `selector_factory` that can fit a dose-finding model to outcomes.

Examples

```
skeleton <- c(0.05, 0.1, 0.25, 0.4, 0.6)
target <- 0.25
model1 <- get_dfcrm(skeleton = skeleton, target = target) %>%
  dont_skip_doses()
fit1 <- model1 %>% fit('1NNN')

model2 <- get_dfcrm(skeleton = skeleton, target = target)
fit2 <- model2 %>% fit('1NNN')

# fit1 will not skip doses
fit1 %>% recommended_dose()
# But fit2 will:
fit2 %>% recommended_dose()

# Similar demonstration for de-escalation
model1 <- get_dfcrm(skeleton = skeleton, target = target) %>%
  dont_skip_doses(when_deescalating = TRUE)
fit1 <- model1 %>% fit('1NNN 2N 3TTT')

model2 <- get_dfcrm(skeleton = skeleton, target = target)
fit2 <- model2 %>% fit('1NNN 2N 3TTT')

# fit1 will not skip doses
fit1 %>% recommended_dose()
# But fit2 will:
fit2 %>% recommended_dose()
```

---

doses_given *Doses given to patients.*

Description

Get a vector of the dose-levels that have been administered to patients.

Usage

```
doses_given(x, ...)
```

Arguments

x	Object of type selector.
...	Extra args are passed onwards.

Value

an integer vector

Examples

```
skeleton <- c(0.05, 0.1, 0.25, 0.4, 0.6)
target <- 0.25
model <- get_dfcrm(skeleton = skeleton, target = target)
fit <- model %>% fit('1NNN 2NTN')
fit %>% doses_given()
```

---

dose_indices *Dose indices*

Description

Get the integers from 1 to the number of doses under investigation.

Usage

```
dose_indices(x, ...)
```

Arguments

x	Object of type selector.
...	Extra args are passed onwards.

Value

an integer vector

Examples

```
skeleton <- c(0.05, 0.1, 0.25, 0.4, 0.6)
target <- 0.25
model <- get_dfcrm(skeleton = skeleton, target = target)
fit <- model %>% fit('1NNN 2NTN')
fit %>% dose_indices()
```

dose_paths *Dose pathways*

Description

A dose-escalation design exists to select doses in response to observed outcomes. The entire space of possible responses can be calculated to show the behaviour of a design in response to all feasible outcomes. The `get_dose_paths` function performs that task and returns an instance of this object.

Usage

```
dose_paths()
```

See Also

`selector`

Examples

```
# Calculate dose-paths for the 3+3 design:
paths <- get_three_plus_three(num_doses = 5) %>%
  get_dose_paths(cohort_sizes = c(3, 3))
```

dose_paths_function *Get function for calculating dose pathways.*

Description

This function does not need to be called by users. It is used internally.

Usage

```
dose_paths_function(selector_factory)
```

Arguments

`selector_factory`
: Object of type `selector_factory`.

Value

A function.

empiric_tox_rate *Observed toxicity rate at each dose.*

Description

Get the empirical or observed toxicity rate seen at each dose under investigation. This is simply the number of toxicities divded by the number of patients evaluated.

Usage

```
empiric_tox_rate(x, ...)
```

Arguments

x	Object of class selector
...	arguments passed to other methods

Value

a numerical vector

Examples

```
# CRM example
skeleton <- c(0.05, 0.1, 0.25, 0.4, 0.6)
target <- 0.25
outcomes <- '1NNN 2NTN'
fit <- get_dfcrm(skeleton = skeleton, target = target) %>% fit(outcomes)
fit %>% empiric_tox_rate()
```

enforce_three_plus_three *Enforce that a trial path has followed the 3+3 method.*

Description

This function stops with en error if it detects that outcomes describing a trial path have diverged from that advocated by the 3+3 method.

Usage

```
enforce_three_plus_three(outcomes, allow_deescalate = FALSE)
```

Arguments

outcomes	Outcomes observed. See parse_phase1_outcomes.
allow_deescalate	TRUE to allow de-escalation, as described by Korn et al. Default is FALSE.

Value

Nothing. Function stops if problem detected.

Examples

```
## Not run:
enforce_three_plus_three('1NNN 2NTN 2NNN')  # OK
enforce_three_plus_three('1NNN 2NTN 2N')  # OK too, albeit in-progress cohort
enforce_three_plus_three('1NNN 1N')  # Not OK because should have escalated

## End(Not run)
```

---

fit *Fit a dose-finding model.*

Description

Fit a dose-finding model to some outcomes.

Usage

```
fit(selector_factory, outcomes, ...)
```

Arguments

selector_factory	Object of type selector_factory.
outcomes	Outcome string. See parse_phase1_outcomes.
...	Extra args are passed onwards.

Value

Object of generic type selector.

See Also

selector, selector_factory

Examples

```
skeleton <- c(0.05, 0.1, 0.25, 0.4, 0.6)
target <- 0.25
model <- get_dfcrm(skeleton = skeleton, target = target)
fit <- model %>% fit('1NNN 2NTN')
fit %>% recommended_dose()  # Etc
```

`follow_path` *Follow a pre-determined dose administration path.*

Description

This method creates a dose selector that will follow a pre-specified trial path. Whilst the trial path is matched by realised outcomes, the selector will recommend the next dose in the desired sequence. As soon as the observed outcomes diverge from the desired path, the selector stops giving dose recommendations. This makes it possible, for instance, to specify a fixed escalation plan that should be followed until the first toxicity is seen. This tactic is used by some model-based designs to get rapidly to the doses where the action is. See, for example, the dfcrm package and Cheung (2011).

Usage

```
follow_path(path)
```

Arguments

`path`	Follow this outcome path. See `parse_phase1_outcomes`.

Value

an object of type `selector_factory` that can fit a dose-finding model to outcomes.

References

Cheung. Dose Finding by the Continual Reassessment Method. 2011. Chapman and Hall/CRC. ISBN 9781420091519

Examples

```
model1 <- follow_path(path = '1NNN 2NNN 3NNN 4NNN')

fit1 <- model1 %>% fit('1NNN 2N')
fit1 %>% recommended_dose()
fit1 %>% continue()
# The model recommends continuing at dose 2 because the observed outcomes
# perfectly match the desired escalation path.

fit2 <- model1 %>% fit('1NNN 2NT')
fit2 %>% recommended_dose()
fit2 %>% continue()
# Uh oh. Toxicity has now been seen. This class recommends no dose now.
```

get_boin *Get an object to fit the BOIN model using the BOIN package.*

Description

Get an object to fit the BOIN model using the BOIN package.

Usage

```
get_boin(num_doses, target, use_stopping_rule = TRUE, ...)
```

Arguments

num_doses	Number of doses under investigation.
target	We seek a dose with this probability of toxicity.
use_stopping_rule	TRUE to use the toxicity stopping rule described in Yan et al. (2019). FALSE to suppress the authors' stopping rule, with the assumption being that you will test the necessity to stop early in some other way.
...	Extra args are passed to select.mtd.

Value

an object of type selector_factory that can fit the BOIN model to outcomes.

References

Yan, F., Pan, H., Zhang, L., Liu, S., & Yuan, Y. (2019). BOIN: An R Package for Designing Single-Agent and Drug-Combination Dose-Finding Trials Using Bayesian Optimal Interval Designs. Journal of Statistical Software, 27(November 2017), 0–35. https://doi.org/10.18637/jss.v000.i00

Liu, S., & Yuan, Y. (2015). Bayesian optimal designs for Phase I clinical trials. J. R. Stat. Soc. C, 64, 507–523. https://doi.org/10.1111/rssc.12089

Examples

```
target <- 0.25
model1 <- get_boin(num_doses = 5, target = target)

outcomes <- '1NNN 2NTN'
model1 %>% fit(outcomes) %>% recommended_dose()
```

`get_dfcrm` *Get an object to fit the CRM model using the dfcrm package.*

Description

This function returns an object that can be used to fit a CRM model using methods provided by the dfcrm package.

Dose selectors are designed to be daisy-chained together to achieve different behaviours. This class is a **resumptive** selector, meaning it carries on when the previous dose selector, where present, has elected not to continue. For example, this allows instances of this class to be preceded by a selector that follows a fixed path in an initial escalation plan, such as that provided by `follow_path`. In this example, when the observed trial outcomes deviate from that initial plan, the selector following the fixed path elects not to continue and responsibility passes to this class. See Examples.

Usage

```
get_dfcrm(parent_selector_factory = NULL, skeleton, target, ...)
```

Arguments

`parent_selector_factory`	optional object of type `selector_factory` that is in charge of dose selection before this class gets involved. Leave as NULL to just use CRM from the start.
`skeleton`	Dose-toxicity skeleton, a non-decreasing vector of probabilities.
`target`	We seek a dose with this probability of toxicity.
`...`	Extra args are passed to `crm`.

Value

an object of type `selector_factory` that can fit the CRM model to outcomes.

References

Cheung, K. 2019. dfcrm: Dose-Finding by the Continual Reassessment Method. R package version 0.2-2.1. https://CRAN.R-project.org/package=dfcrm

Cheung, K. 2011. Dose Finding by the Continual Reassessment Method. Chapman and Hall/CRC. ISBN 9781420091519

O'Quigley J, Pepe M, Fisher L. Continual reassessment method: a practical design for phase 1 clinical trials in cancer. Biometrics. 1990;46(1):33-48. doi:10.2307/2531628

Examples

```
skeleton <- c(0.05, 0.1, 0.25, 0.4, 0.6)
target <- 0.25
model1 <- get_dfcrm(skeleton = skeleton, target = target)
```

```
# By default, dfcrm fits the empiric model:
outcomes <- '1NNN 2NTN'
model1 %>% fit(outcomes) %>% recommended_dose()

# But we can provide extra args to get_dfcrm that are than passed onwards to
# the call to dfcrm::crm to override the defaults. For example, if we want
# the one-parameter logistic model:
model2 <- get_dfcrm(skeleton = skeleton, target = target, model = 'logistic')
model2 %>% fit(outcomes) %>% recommended_dose()
# dfcrm does not offer a two-parameter logistic model but other classes do.

# We can use an initial dose-escalation plan, a pre-specified path that
# should be followed until trial outcomes deviate, at which point the CRM
# model takes over. For instance, if we want to use two patients at each of
# the first three doses in the absence of toxicity, irrespective the model's
# advice, we would run:
model1 <- follow_path('1NN 2NN 3NN') %>%
  get_dfcrm(skeleton = skeleton, target = target)

# If outcomes match the desired path, the path is followed further:
model1 %>% fit('1NN 2N') %>% recommended_dose()

# But when the outcomes diverge:
model1 %>% fit('1NN 2T') %>% recommended_dose()

# Or the pre-specified path comes to an end:
model1 %>% fit('1NN 2NN 3NN') %>% recommended_dose()
# The CRM model takes over.
```

`get_dose_paths` *Calculate future dose paths.*

Description

A dose-escalation design exists to select doses in response to observed outcomes. The entire space of possible responses can be calculated to show the behaviour of a design in response to all feasible outcomes. This function performs that task.

Usage

```
get_dose_paths(selector_factory, cohort_sizes, ...)
```

Arguments

`selector_factory`	Object of type `selector_factory`.
`cohort_sizes`	Integer vector representing sizes of
`...`	Extra args are passed onwards.

Value

Object of type dose_paths.

Examples

```
# Calculate paths for a 3+3 design for the next two cohorts of three patients
paths <- get_three_plus_three(num_doses = 5) %>%
  get_dose_paths(cohort_sizes = c(3, 3))
```

---

get_three_plus_three *Get an object to fit the 3+3 model.*

Description

Get an object to fit the 3+3 model.

Usage

```
get_three_plus_three(num_doses, allow_deescalate = FALSE, ...)
```

Arguments

num_doses	Number of doses under investigation.
allow_deescalate	TRUE to allow de-escalation, as described by Korn et al. Default is FALSE.
...	Extra args are not currently used.

Value

an object of type selector_factory that can fit the 3+3 model to outcomes.

References

Storer BE. Design and Analysis of Phase I Clinical Trials. Biometrics. 1989;45(3):925-937. doi:10.2307/2531693

Korn EL, Midthune D, Chen TT, Rubinstein LV, Christian MC, Simon RM. A comparison of two phase I trial designs. Statistics in Medicine. 1994;13(18):1799-1806. doi:10.1002/sim.4780131802

Examples

```
model <- get_three_plus_three(num_doses = 5)

fit1 <- model %>% fit('1NNN 2NTN')
fit1 %>% recommended_dose()
fit1 %>% continue()

fit2 <- model %>% fit('1NNN 2NTN 2NNT')
fit2 %>% recommended_dose()
```

```
fit2 %>% continue()
```

---

graph_paths *Visualise dose-paths as a graph*

Description

Visualise dose-paths as a graph

Usage

```
graph_paths(paths, viridis_palette = "viridis", RColorBrewer_palette = NULL)
```

Arguments

paths	Object of type dose_paths
viridis_palette	optional name of a colour palette in the viridis package.
RColorBrewer_palette	optional name of a colour palette in the RColorBrewer package.

Details

The viridis package supports palettes: viridis, magma, plasma, inferno, and cividis. The RColorBrewer package supports many palettes. Refer to those packages on CRAN for more details.

Examples

```
paths <- get_three_plus_three(num_doses = 5) %>%
  get_dose_paths(cohort_sizes = c(3, 3, 3))

graph_paths(paths)
graph_paths(paths, viridis_palette = 'plasma')
graph_paths(paths, RColorBrewer_palette = 'YlOrRd')
```

mean_prob_tox *Mean toxicity rate at each dose.*

Description

Get the estimated mean toxicity rate at each dose under investigation. This is a set of modelled statistics. The underlying models estimate toxicity probabilities in different ways. If no model-based estimate of the mean is available, this function will return a vector of NAs.

Usage

```
mean_prob_tox(x, ...)
```

Arguments

x	Object of class selector
...	arguments passed to other methods

Value

a numerical vector

Examples

```
# CRM example
skeleton <- c(0.05, 0.1, 0.25, 0.4, 0.6)
target <- 0.25
outcomes <- '1NNN 2NTN'
fit <- get_dfcrm(skeleton = skeleton, target = target) %>% fit(outcomes)
fit %>% mean_prob_tox()
```

median_prob_tox *Median toxicity rate at each dose.*

Description

Get the estimated median toxicity rate at each dose under investigation. This is a set of modelled statistics. The underlying models estimate toxicity probabilities in different ways. If no model-based estimate of the median is available, this function will return a vector of NAs.

Usage

```
median_prob_tox(x, ...)
```

Arguments

x	Object of class selector
...	arguments passed to other methods

Value

a numerical vector

Examples

```
# CRM example
skeleton <- c(0.05, 0.1, 0.25, 0.4, 0.6)
target <- 0.25
outcomes <- '1NNN 2NTN'
fit <- get_dfcrm(skeleton = skeleton, target = target) %>% fit(outcomes)
fit %>% median_prob_tox()
```

---

model_frame *Model data-frame.*

Description

Get the model data-frame for a dose-finding analysis, inlcuding columns for patient id, cohort id, dose administered, and toxicity outcome. In some scenarios, further columns are provided.

Usage

```
model_frame(x, ...)
```

Arguments

x	Object of type selector.
...	Extra args are passed onwards.

Value

tibble, which acts like a data.frame.

Examples

```
skeleton <- c(0.05, 0.1, 0.25, 0.4, 0.6)
target <- 0.25
model <- get_dfcrm(skeleton = skeleton, target = target)
fit <- model %>% fit('1NNN 2NTN')
fit %>% model_frame()
```

num_cohort_outcomes *Number of different possible outcomes for a cohort of patients*

Description

Number of different possible outcomes for a cohort of patients, each of which will experience one of a number of discrete outcomes. For instance, in a typical phase I dose-finding trial, each patient will experience: no-toxicity (N); or toxicity (T). The number of possible outcomes per patient is two. For a cohort of three patients, the number of cohort outcomes is four: NNN, NNT, NTT, TTT. Consider a more complex example: in a seamless phase I/II trial with efficacy and toxicity outcomes, an individual patient will experience one of four distinct outcomes: efficacy only (E); toxicity only (T); both efficacy and toxicity (B) or neither. How many different outcomes are there for a cohort of three patients? The answer is 20 but it is non-trivial to see why. This convenience function calculates that number using the formula for the number of combinations with replacement,

Usage

```
num_cohort_outcomes(num_patient_outcomes, cohort_size)
```

Arguments

num_patient_outcomes	integer, number of distinct possible outcomes for each single patient
cohort_size	integer, number of patients in the cohort

Value

integer, number of distinct possible cohort outcomes

Examples

```
# As described in example, N or T in a cohort of three:
num_cohort_outcomes(num_patient_outcomes = 2, cohort_size = 3)
# Also described in example, E, T, B or N in a cohort of three:
num_cohort_outcomes(num_patient_outcomes = 4, cohort_size = 3)
```

num_doses *Number of doses.*

Description

Get the number of doses under investigation in a dose-finding trial.

Usage

```
num_doses(x, ...)
```

Arguments

x	Object of type selector.
...	Extra args are passed onwards.

Value

integer

Examples

```
skeleton <- c(0.05, 0.1, 0.25, 0.4, 0.6)
target <- 0.25
model <- get_dfcrm(skeleton = skeleton, target = target)
fit <- model %>% fit('1NNN 2NTN')
fit %>% num_doses()
```

---

num_dose_path_nodes *Number of nodes in dose-paths analysis*

Description

Number of possible nodes in an exhaustive analysis of dose-paths in a dose-finding trial. The number of nodes at depth i is the the number of nodes at depth i-1 multiplied by the number of possible cohort outcomes at depth i. For instance, if there were 16 nodes at the previous depth and four possible cohort outcomes at the current depth, then there are 64 possible nodes at the current depth. Knowing the number of nodes in a dose-paths analysis helps the analyst decide whether simulation or dose-paths are a better tool for assessing operating characteristics of a dose-finding design.

Usage

```
num_dose_path_nodes(num_patient_outcomes, cohort_sizes)
```

Arguments

num_patient_outcomes	integer, number of distinct possible outcomes for each single patient
cohort_sizes	integer vector of cohort sizes

Value

integer vector, number of nodes at increasing depths. The total number of nodes is the sum of this vector.

Examples

```
# In a 3+3 design, there are two possible outcomes for each patient and
# patients are evaluated in cohorts of three. In an analysis of dose-paths in
# the first two cohorts of three, how many nodes are there?
num_dose_path_nodes(num_patient_outcomes = 2, cohort_sizes = rep(3, 2))
# In contrast, using an EffTox design there are four possible outcomes for
# each patient. In a similar analysis of dose-paths in the first two cohorts
# of three, how many nodes are there now?
num_dose_path_nodes(num_patient_outcomes = 4, cohort_sizes = rep(3, 2))
```

---

num_patients *Number of patients evaluated.*

Description

Get the number of patients evaluated in a dose-finding trial.

Usage

```
num_patients(x, ...)
```

Arguments

x	Object of type selector.
...	Extra args are passed onwards.

Value

integer

Examples

```
skeleton <- c(0.05, 0.1, 0.25, 0.4, 0.6)
target <- 0.25
model <- get_dfcrm(skeleton = skeleton, target = target)
fit <- model %>% fit('1NNN 2NTN')
fit %>% num_patients()
```

num_tox *Total number of toxicities seen.*

Description

Get the number of toxicities seen in a dose-finding trial.

Usage

```
num_tox(x, ...)
```

Arguments

x	Object of type selector.
...	Extra args are passed onwards.

Value

integer

Examples

```
skeleton <- c(0.05, 0.1, 0.25, 0.4, 0.6)
target <- 0.25
model <- get_dfcrm(skeleton = skeleton, target = target)
fit <- model %>% fit('1NNN 2NTN')
fit %>% num_tox()
```

n_at_dose *Number of patients treated at each dose.*

Description

Get the number of patients evaluated at each dose under investigation.

Usage

```
n_at_dose(x, ...)
```

Arguments

x	Object of class selector
...	arguments passed to other methods

Value

an integer vector

Examples

```
# CRM example
skeleton <- c(0.05, 0.1, 0.25, 0.4, 0.6)
target <- 0.25
outcomes <- '1NNN 2NTN'
fit <- get_dfcrm(skeleton = skeleton, target = target) %>% fit(outcomes)
fit %>% n_at_dose()
```

---

n_at_recommended_dose *Number of patients treated at the recommended dose.*

Description

Get the number of patients evaluated at the recommended dose.

Usage

```
n_at_recommended_dose(x, ...)
```

Arguments

x	Object of class selector
...	arguments passed to other methods

Value

an integer

Examples

```
# CRM example
skeleton <- c(0.05, 0.1, 0.25, 0.4, 0.6)
target <- 0.25
outcomes <- '1NNN 2NTN'
fit <- get_dfcrm(skeleton = skeleton, target = target) %>% fit(outcomes)
fit %>% n_at_recommended_dose()
```

`parse_phase1_outcomes` *Parse a string of phase I dose-finding outcomes to vector notation.*

Description

Parse a string of phase I dose-finding outcomes to a binary vector notation necessary for model invocation.

The outcome string describes the doses given, outcomes observed and groups patients into cohorts. The format of the string is described in Brock (2019), and that itself is the phase I analogue of the similar idea described in Brock et al. (2017). See Examples.

The letters T and N are used to represents patients that experienced (T)oxicity and (N)o toxicity. These letters are concatenated after numerical dose-levels to convey the outcomes of cohorts of patients. For instance, `2NNT` represents a cohort of three patients that were treated at dose-level 2, one of whom experienced toxicity, and two that did not. The results of cohorts are separated by spaces. Thus, `2NNT 1NN` extends our previous example, where the next cohort of two were treated at dose-level 1 and neither experienced toxicity. See examples.

Usage

```
parse_phase1_outcomes(outcomes, as_list = TRUE)
```

Arguments

`outcomes`	character string, conveying doses given and outcomes observed.
`as_list`	TRUE (the default) to return a `list`; FALSE to return a `data.frame`

Value

If `as_list == TRUE`, a list with elements `tox`, `doses` and `num_patients`. These elements are congruent with those of the same name in `crm_params`, for example. If `as_list == FALSE`, a data.frame with columns `tox` and `doses`.

References

Brock, K. (2019). trialr: Bayesian Clinical Trial Designs in R and Stan. arXiv:1907.00161 [stat.CO]

Brock, K., Billingham, L., Copland, M., Siddique, S., Sirovica, M., & Yap, C. (2017). Implementing the EffTox dose-finding design in the Matchpoint trial. BMC Medical Research Methodology, 17(1), 112. https://doi.org/10.1186/s12874-017-0381-x

Examples

```
x = parse_phase1_outcomes('1NNN 2NTN 3TTT')
# Three cohorts of three patients. The first cohort was treated at dose 1 and
# non had toxicity. The seond cohort was treated at dose 2 and one of the
# three had toxicity. Finally, cohort three was treated at dose 3 and all
# patients had toxicity. See:
x$num_patients  # 9
```

```
x$doses         # c(1, 1, 1, 2, 2, 2, 3, 3, 3)
x$tox           # c(0, 0, 0, 0, 1, 0, 1, 1, 1)
sum(x$tox)      # 4

# The same information can be parsed to a data-frame:
y = parse_phase1_outcomes('1NNN 2NTN 3TTT', as_list = FALSE)
y
```

`phase1_outcomes_to_cohorts` *Break a phase I outcome string into a list of cohort parts.*

Description

Break a phase I outcome string into a list of cohort parts.

Break a phase I outcome string into a list of cohort parts.

The outcome string describes the doses given, outcomes observed and the timing of analyses that recommend a dose. The format of the string is described in Brock (2019), and that itself is the phase I analogue of the similar idea described in Brock _et al_. (2017).

The letters T and N are used to represents patients that experienced (T)oxicity and (N)o toxicity. These letters are concatenated after numerical dose-levels to convey the outcomes of cohorts of patients. For instance, `2NNT` represents a cohort of three patients that were treated at dose-level 2, one of whom experienced toxicity, and two that did not. The results of cohorts are separated by spaces and it is assumed that a dose-finding decision takes place at the end of a cohort. Thus, `2NNT 1NN` builds on our previous example, where the next cohort of two were treated at dose-level 1 and neither of these patients experienced toxicity. See examples.

Usage

```
phase1_outcomes_to_cohorts(outcomes)
```

Arguments

`outcomes`	character string representing the doses given, outcomes observed, and timing of analyses. See Description.

Value

a list with a slot for each cohort. Each cohort slot is itself a list, containing elements: * `dose`, the integer dose delivered to the cohort; * `outcomes`, a character string representing the `T` or `N` outcomes for the patients in this cohort.

References

Brock, K. (2019). trialr: Bayesian Clinical Trial Designs in R and Stan. arXiv:1907.00161 [stat.CO]

Brock, K., Billingham, L., Copland, M., Siddique, S., Sirovica, M., & Yap, C. (2017). Implementing the EffTox dose-finding design in the Matchpoint trial. BMC Medical Research Methodology, 17(1), 112. https://doi.org/10.1186/s12874-017-0381-x

Examples

```
x = phase1_outcomes_to_cohorts('1NNN 2NNT 3TT')
length(x)
x[[1]]$dose
x[[1]]$outcomes
x[[2]]$dose
x[[2]]$outcomes
x[[3]]$dose
x[[3]]$outcomes
```

`prob_administer` *Percentage of patients treated at each dose.*

Description

Get the percentage of patients evaluated at each dose under investigation.

Usage

```
prob_administer(x, ...)
```

Arguments

`x`	Object of class `selector`
`...`	arguments passed to other methods

Value

a numerical vector

Examples

```
# CRM example
skeleton <- c(0.05, 0.1, 0.25, 0.4, 0.6)
target <- 0.25
outcomes <- '1NNN 2NTN'
fit <- get_dfcrm(skeleton = skeleton, target = target) %>% fit(outcomes)
fit %>% prob_administer()
```

prob_recommend *Probability of recommendation*

Description

Get the probabilities that each of the doses under investigation is recommended.

Usage

```
prob_recommend(x, ...)
```

Arguments

x	Object of type simulations.
...	arguments passed to other methods

Value

vector of probabilities

Examples

```
true_prob_tox <- c(0.12, 0.27, 0.44, 0.53, 0.57)
sims <- get_three_plus_three(num_doses = 5) %>%
  simulate_trials(num_sims = 50, true_prob_tox = true_prob_tox)
sims %>% prob_recommend
```

prob_tox_exceeds *Probability that the toxicity rate exceeds some threshold.*

Description

Get the probability that the toxicity rate at each dose exceeds some threshold.

Usage

```
prob_tox_exceeds(x, threshold, ...)
```

Arguments

x	Object of type selector
threshold	Probability that toxicity rate exceeds what?
...	arguments passed to other methods

Value

numerical vector of probabilities

Examples

```
# CRM example
skeleton <- c(0.05, 0.1, 0.25, 0.4, 0.6)
target <- 0.25
outcomes <- '1NNN 2NTN'
fit <- get_dfcrm(skeleton = skeleton, target = target) %>% fit(outcomes)
# What is probability that tox rate at each dose exceeds target by >= 10%?
fit %>% prob_tox_exceeds(threshold = target + 0.1)
```

---

prob_tox_quantile *Quantile of the toxicity rate at each dose.*

Description

Get the estimated quantile of the toxicity rate at each dose under investigation. This is a set of modelled statistics. The underlying models estimate toxicity probabilities in different ways. If no model-based estimate of the median is available, this function will return a vector of NAs.

Usage

```
prob_tox_quantile(x, p, ...)
```

Arguments

x	Object of class selector
p	quantile probability, decimal value between 0 and 1
...	arguments passed to other methods

Value

a numerical vector

Examples

```
# CRM example
skeleton <- c(0.05, 0.1, 0.25, 0.4, 0.6)
target <- 0.25
outcomes <- '1NNN 2NTN'
fit <- get_dfcrm(skeleton = skeleton, target = target) %>% fit(outcomes)
fit %>% prob_tox_quantile(p = 0.9)
```

prob_tox_samples *Get samples of the probability of toxicity.*

Description

Get samples of the probability of toxicity. For instance, a Bayesian approach that supports sampling would be expected to return posterior samples of the probability of toxicity. If this class does not support sampling, this function will raise an error. You can check whether this class supports sampling by calling supports_sampling.

Usage

```
prob_tox_samples(x, tall = FALSE, ...)
```

Arguments

x	Object of type selector
tall	logical, if FALSE, a wide data-frame is returned with columns pertaining to the doses and column names the dose indices. If TRUE, a tall data-frame is returned with data for all doses stacked vertically. In this mode, column names will include dose and prob_tox.
...	arguments passed to other methods

Value

data-frame like object

Examples

```
# CRM example
skeleton <- c(0.05, 0.1, 0.25, 0.4, 0.6)
target <- 0.25
outcomes <- '1NNN 2NTN'
fit <- get_dfcrm(skeleton = skeleton, target = target) %>% fit(outcomes)
fit %>% prob_tox_samples()
fit %>% prob_tox_samples(tall = TRUE)
```

recommended_dose *Recommended dose for next patient or cohort.*

Description

Get the dose recommended for the next patient or cohort in a dose-finding trial.

Usage

```
recommended_dose(x, ...)
```

Arguments

x	Object of type selector.
...	Extra args are passed onwards.

Value

integer

Examples

```
skeleton <- c(0.05, 0.1, 0.25, 0.4, 0.6)
target <- 0.25
model <- get_dfcrm(skeleton = skeleton, target = target)
fit <- model %>% fit('1NNN 2NTN')
fit %>% recommended_dose()
```

---

selector *Dose selector.*

Description

This is a core class in this package. It encapsulates that an object (e.g. a CRM model, a 3+3 model) is able to recommend doses, keep track of how many patients have been treated at what doses, what toxicity outcomes have been seen, and whether a trial should continue. It offers a consistent interface to dose-finding methods from several packages, including dfcrm and BOIN. bcrm and trialr will be added.

Once you have a standardised interface, modularisation offers a powerful way to adorn dose-finding methods with extra desirable behaviour. selector objects can be daisy-chained togther using magrittr's pipe operator. For instance, the CRM fitting method in dfcrm is fantastic because it runs quickly and is simple to call. However, it does not recommend that a trial stops if a dose is too toxic or if n patients have already been treated at the recommended dose. Each of these behaviours can be bolted on via additional selectors. Furthermore, those behaviours and more can be bolted on to any dose selector because of the modular approach implemented in escalation. See Examples.

selector objects are obtained by calling the fit function on a selector_factory object. A selector_factory object is obtained by initially calling a function like get_dfcrm, get_three_plus_three or get_boin. Users may then add desired extra behaviour with subsequent calls to functions like stop_when_n_at_dose or stop_when_too_toxic.

The selector class also supports that an object will be able to perform inferential calculations on the rates of toxicity via functions like mean_prob_tox, median_prob_tox, and prob_tox_exceeds. However, naturally the sophistication of those calculations will vary by model implementation. For example, a full MCMC method will be able to quantify any probability you like by working with posterior samples. In contrast, a method like the crm function in dfcrm that uses the plug-in method to estimate posterior dose-toxicity curves cannot natively estimate the median probability of tox.

Usage

```
selector()
```

Details

Every `selector` object implements the following functions:

- tox_target
- num_patients
- cohort
- doses_given
- tox
- num_tox
- model_frame
- num_doses
- recommended_dose
- continue
- n_at_dose
- n_at_recommended_dose
- dose_indices
- prob_administer
- tox_at_dose
- empiric_tox_rate
- mean_prob_tox
- median_prob_tox
- prob_tox_quantile
- prob_tox_exceeds

See Also

selector_factory

Examples

```
# Start with a simple CRM model
skeleton <- c(0.05, 0.1, 0.25, 0.4, 0.6)
target <- 0.25
model1 <- get_dfcrm(skeleton = skeleton, target = target)

# Add a rule to stop when 9 patients are treated at the recommended dose
model2 <- get_dfcrm(skeleton = skeleton, target = target) %>%
  stop_when_n_at_dose(n = 9, dose = 'recommended')
```

```
# Add a rule to stop if toxicity rate at lowest dose likely exceeds target
model3 <- get_dfcrm(skeleton = skeleton, target = target) %>%
  stop_when_n_at_dose(n = 9, dose = 'recommended') %>%
  stop_when_too_toxic(dose = 1, tox_threshold = target, confidence = 0.5)

# We now have three CRM models that differ in their stopping behaviour.
# Let's fit each to some outcomes to see those differences:

outcomes <- '1NNN 2NTT 1NNT'
fit1 <- model1 %>% fit(outcomes)
fit2 <- model2 %>% fit(outcomes)
fit3 <- model3 %>% fit(outcomes)

fit1 %>% recommended_dose()
fit1 %>% continue()

fit2 %>% recommended_dose()
fit2 %>% continue()

fit3 %>% recommended_dose()
fit3 %>% continue()
# Already model3 wants to stop because of excessive toxicity.

# Let's carry on with models 1 and 2 by adding another cohort:

outcomes <- '1NNN 2NTT 1NNT 1NNN'
fit1 <- model1 %>% fit(outcomes)
fit2 <- model2 %>% fit(outcomes)

fit1 %>% recommended_dose()
fit1 %>% continue()

fit2 %>% recommended_dose()
fit2 %>% continue()

# Model1 wants to continue - in fact it will never stop.
# In contrast, model2 has seen 9 at dose 1 so, rather than suggest dose 1
# again, it suggests the trial should stop.

# For contrast, let us consider a BOIN model on the same outcomes
boin_fitter <- get_boin(num_doses = length(skeleton), target = target)
fit4 <- boin_fitter %>% fit(outcomes)
fit4 %>% recommended_dose()
fit4 %>% continue()

# Full selector interface:
fit <- fit2
fit %>% tox_target()
fit %>% num_patients()
fit %>% cohort()
fit %>% doses_given()
fit %>% tox()
fit %>% num_tox()
```

```
fit %>% model_frame()
fit %>% num_doses()
fit %>% dose_indices()
fit %>% recommended_dose()
fit %>% continue()
fit %>% n_at_dose()
fit %>% n_at_recommended_dose()
fit %>% prob_administer()
fit %>% tox_at_dose()
fit %>% empiric_tox_rate()
fit %>% mean_prob_tox()
fit %>% median_prob_tox()
fit %>% prob_tox_quantile(0.9)
fit %>% prob_tox_exceeds(0.5)
```

`selector_factory` *Dose selector factory.*

Description

Along with `selector`, this is the second core class in the `escalation` package. It exists to do one thing: fit outcomes from dose-finding trials to the models we use to select doses.

A `selector_factory` object is obtained by initially calling a function like `get_dfcrm`, `get_three_plus_three` or `get_boin`. Users may then add desired extra behaviour with subsequent calls to functions like `stop_when_n_at_dose` or `stop_when_too_toxic`. `selector` objects are obtained by calling the `fit` function on a `selector_factory` object. Refer to examples to see how this works.

Usage

```
selector_factory()
```

See Also

`selector`

Examples

```
# Start with a simple CRM model
skeleton <- c(0.05, 0.1, 0.25, 0.4, 0.6)
target <- 0.25
model1 <- get_dfcrm(skeleton = skeleton, target = target)

# Add a rule to stop when 9 patients are treated at the recommended dose
model2 <- get_dfcrm(skeleton = skeleton, target = target) %>%
  stop_when_n_at_dose(n = 9, dose = 'recommended')

# Add a rule to stop if toxicity rate at lowest dose likely exceeds target
model3 <- get_dfcrm(skeleton = skeleton, target = target) %>%
```

```
  stop_when_n_at_dose(n = 9, dose = 'recommended') %>%
  stop_when_too_toxic(dose = 1, tox_threshold = target, confidence = 0.5)

# We now have three CRM models that differ in their stopping behaviour.
# Let's fit each to some outcomes to see those differences:

outcomes <- '1NNN 2NTT 1NNT'
fit1 <- model1 %>% fit(outcomes)
fit2 <- model2 %>% fit(outcomes)
fit3 <- model3 %>% fit(outcomes)

fit1 %>% recommended_dose()
fit1 %>% continue()

fit2 %>% recommended_dose()
fit2 %>% continue()

fit3 %>% recommended_dose()
fit3 %>% continue()
# Already model3 wants to stop because of excessive toxicity.

# Let's carry on with models 1 and 2 by adding another cohort:

outcomes <- '1NNN 2NTT 1NNT 1NNN'
fit1 <- model1 %>% fit(outcomes)
fit2 <- model2 %>% fit(outcomes)

fit1 %>% recommended_dose()
fit1 %>% continue()

fit2 %>% recommended_dose()
fit2 %>% continue()

# Model1 wants to continue - in fact it will never stop.
# In contrast, model2 has seen 9 at dose 1 so, rather than suggest dose 1
# again, it suggests the trial should stop.

# For contrast, let us consider a BOIN model on the same outcomes
boin_fitter <- get_boin(num_doses = length(skeleton), target = target)
fit4 <- boin_fitter %>% fit(outcomes)
fit4 %>% recommended_dose()
fit4 %>% continue()
```

`select_dose_by_cibp` *Select dose by the CIBP selection criterion.*

Description

This method selects dose by the convex infinite bounds penalisation (CIBP) criterion of Mozgunov & Jaki. Their method is mindful of the uncertainty in the estimates of the probability of toxicity and uses an asymmetry parameter to penalise escalation to risky doses.

Usage

```
select_dose_by_cibp(parent_selector_factory, a, target = NULL)
```

Arguments

parent_selector_factory	Object of type selector_factory.
a	Number between 0 and 2, the asymmetry parameter. See References.
target	We seek a dose with this probability of toxicity. If not provided, the value will be sought from the parent dose-selector.

Value

an object of type selector_factory that can fit a dose-finding model to outcomes.

References

Mozgunov P, Jaki T. Improving safety of the continual reassessment method via a modified allocation rule. Statistics in Medicine.1-17. doi:10.1002/sim.8450

Examples

```
skeleton <- c(0.05, 0.1, 0.25, 0.4, 0.6)
target <- 0.33

# Let's compare escalation behaviour of a CRM model without CIBP criterion:
model1 <- get_dfcrm(skeleton = skeleton, target = target)
# To one with the CIBP criterion:
model2 <- get_dfcrm(skeleton = skeleton, target = target) %>%
  select_dose_by_cibp(a = 0.3)

# Despite one-in-three tox at first dose, regular model is ready to escalate:
model1 %>% fit('1NTN') %>% recommended_dose()
# But the model using CIBP is more risk averse:
model2 %>% fit('1NTN') %>% recommended_dose()
```

---

simulate_trials *Simulate clinical trials.*

Description

This function takes a selector_factory, such as that returned by get_dfcrm, get_boin or get_three_plus_three, and conducts many notional clinical trials. We conduct simulations to learn about the operating characteristics of adaptive trial designs.

Usage

```
simulate_trials(selector_factory, num_sims, true_prob_tox, ...)
```

Arguments

selector_factory	Object of type selector_factory.
num_sims	integer, number of trial iterations to simulate.
true_prob_tox	numeric vector of true but unknown toxicity probabilities
...	Extra args are passed onwards.

Details

By default, dose decisions in simulated trials are made after each cohort of 3 patients. This can be changed by providing a function that simulates the arrival of new patients. The new patients will be added to the existing patients and the model will be fit to the set of all patients. The function that simulates patient arrivals should take as a single parameter a data-frame with one row for each existing patient and columns including cohort, patient, dose, tox, time (and possibly also eff and weight, if a phase I/II or time-to-event method is used). The provision of data on the existing patients allows the patient sampling function to be adaptive. The function should return a data-frame with a row for each new patient and a column for time_delta, the time between the arrival of this patient and the previous, as in cohorts_of_n. See Examples.

This method can simulate the culmination of trials that are partly completed. We just have to specify the outcomes already observed via the previous_outcomes parameter. Each simulated trial will commence from those outcomes seen thus far. See Examples.

We can specify the immediate next dose by specifying next_dose. If omitted, the next dose is calculated by invoking the model on the outcomes seen thus far.

Designs must eventually choose to stop the trial. However, some selectors like those derived from get_dfcrm offer no default stopping method. You may need to append stopping behaviour to your selector via something like stop_at_n or stop_when_n_at_dose, etc. To safeguard against simulating runaway trials that never end, the function will halt a simulated trial after 30 invocations of the dose-selection decision. To breach this limit, specify i_like_big_trials = TRUE in the function call. However, when you forego the safety net, the onus is on you to write selectors that will eventually stop the trial! See Examples.

The model is fit to the prevailing data at each dose selection point. By default, only the final model fit for each simulated trial is retained. This is done to conserve memory. With a high number of simulated trials, storing many model fits per trial may cause the executing machine to run out of memory. However, you can force this method to retain all model fits by specifying return_all_fits = TRUE. See Examples.

Value

Object of type simulations.

See Also

simulations

selector_factory

get_dfcrm

get_boin

get_three_plus_three

cohorts_of_n

Examples

```
true_prob_tox <- c(0.12, 0.27, 0.44, 0.53, 0.57)

# Regular usage examples, for 3+3:
sims <- get_three_plus_three(num_doses = 5) %>%
  simulate_trials(num_sims = 10, true_prob_tox = true_prob_tox)
# and continual reassessment method:
skeleton <- c(0.05, 0.1, 0.25, 0.4, 0.6)
target <- 0.25
sims <- get_dfcrm(skeleton = skeleton, target = target) %>%
  stop_at_n(n = 12) %>%
  simulate_trials(num_sims = 10, true_prob_tox = true_prob_tox)

# Lots of useful information is contained in the returned object:
sims %>% num_patients()
sims %>% num_doses()
sims %>% dose_indices()
sims %>% n_at_dose()
sims %>% n_at_recommended_dose()
sims %>% tox_at_dose()
sims %>% num_tox()
sims %>% recommended_dose()
sims %>% prob_administer()
sims %>% prob_recommend()
sims %>% trial_duration()

# By default, dose decisions are made after each cohort of 3 patients. See
# Details. To override, specify an alternative function via the
# sample_patient_arrivals parameter. E.g. to use cohorts of 2, we run:
patient_arrivals_func <- function(current_data) cohorts_of_n(n = 2)
sims <- get_dfcrm(skeleton = skeleton, target = target) %>%
  stop_at_n(n = 12) %>%
  simulate_trials(num_sims = 10, true_prob_tox = true_prob_tox,
    sample_patient_arrivals = patient_arrivals_func)

# To simulate the culmination of trials that are partly completed, specify
# the outcomes already observed via the previous_outcomes parameter:
sims <- get_dfcrm(skeleton = skeleton, target = target) %>%
stop_at_n(n = 12) %>%
simulate_trials(num_sims = 10, true_prob_tox = true_prob_tox,
                previous_outcomes = '1NTN')
# Outcomes can be described by above outcome string method or data-frame:
  previous_outcomes <- data.frame(
    patient = 1:3,
    cohort = c(1, 1, 1),
    tox = c(0, 1, 0),
    dose = c(1, 1, 1)
  )
```

```
sims <- get_dfcrm(skeleton = skeleton, target = target) %>%
  stop_at_n(n = 12) %>%
  simulate_trials(num_sims = 10, true_prob_tox = true_prob_tox,
                  previous_outcomes = previous_outcomes)

# We can specify the immediate next dose:
sims <- get_dfcrm(skeleton = skeleton, target = target) %>%
  stop_at_n(n = 12) %>%
  simulate_trials(num_sims = 10, true_prob_tox = true_prob_tox,
                  next_dose = 5)

# By default, the method will stop simulated trials after 30 dose selections.
# To suppress this, specify i_like_big_trials = TRUE. However, please take
# care to specify selectors that will eventually stop!
sims <- get_dfcrm(skeleton = skeleton, target = target) %>%
  stop_at_n(n = 99) %>%
  simulate_trials(num_sims = 1, true_prob_tox = true_prob_tox,
                  i_like_big_trials = TRUE)

# By default, only the final model fit is retained for each simulated trial.
# To retain all interim model fits, specify return_all_fits = TRUE.
sims <- get_three_plus_three(num_doses = 5) %>%
  simulate_trials(num_sims = 10, true_prob_tox = true_prob_tox,
                  return_all_fits = TRUE)
# Verify that there are now many analyses per trial with:
sapply(sims$fits, length)
```

`simulations` *Simulated trials.*

Description

This class encapsulates that many notional or virtual trials can be simulated. Each recommends a dose (or doses), keeps track of how many patients have been treated at what doses, what toxicity outcomes have been seen, and whether a trial advocates continuing, etc. We run simulations to learn about the operating characteristics of a trial design.

Computationally, the `simulations` class supports much of the same interface as `selector`, and a little more. Thus, many of the same generic functions are supported - see Examples. However, compared to `selector`s, the returned objects reflect that there are many trials instead of one, e.g. `num_patients(sims)`, returns as an integer vector the number of patients used in the simulated trials.

Usage

```
simulations(fits, true_prob_tox, ...)
```

Arguments

fits	Simulated model fits, arranged as list of lists.
true_prob_tox	vector of true toxicity probabilities
...	Extra args

Details

The simulations object implements the following functions:

- num_patients
- num_doses
- dose_indices
- n_at_dose
- tox_at_dose
- num_tox
- recommended_dose
- prob_administer
- prob_recommend
- trial_duration

Value

list with slots: fits containing model fits; and true_prob_tox, contianing the assumed true probability of toxicity.

See Also

selector

simulate_trials

Examples

```
# Simulate performance of the 3+3 design:
true_prob_tox <- c(0.12, 0.27, 0.44, 0.53, 0.57)
sims <- get_three_plus_three(num_doses = 5) %>%
  simulate_trials(num_sims = 10, true_prob_tox = true_prob_tox)
# The returned object has type 'simulations'. The supported interface is:
sims %>% num_patients()
sims %>% num_doses()
sims %>% dose_indices()
sims %>% n_at_dose()
sims %>% tox_at_dose()
sims %>% num_tox()
sims %>% recommended_dose()
sims %>% prob_administer()
sims %>% prob_recommend()
```

```
sims %>% trial_duration()

# Access the list of model fits for the ith simulated trial using:
i <- 1
sims$fits[[i]]
# and the jth model fit for the ith simulated trial using:
j <- 1
sims$fits[[i]][[j]]
# and so on.
```

`simulation_function` *Get function for simulating trials.*

Description

This function does not need to be called by users. It is used internally.

Usage

```
simulation_function(selector_factory)
```

Arguments

`selector_factory`
: Object of type `selector_factory`.

Value

A function.

`spread_paths` *Spread the information in dose_finding_paths object to a wide data.frame format.*

Description

Spread the information in dose_finding_paths object to a wide data.frame format.

Usage

```
spread_paths(df = NULL, dose_finding_paths = NULL, max_depth = NULL)
```

Arguments

df	Optional data.frame like that returned by as_tibble(dose_finding_paths). Columns .depth, .node, .parent are required. All other columns are spread with a suffix reflecting depth.
dose_finding_paths	Optional instance of dose_finding_paths. Required if 'df' is null.
max_depth	integer, maximum depth of paths to traverse.

Value

A data.frame

Examples

```
## Not run:
# Calculate paths for the first two cohorts of three patients a CRM trial
skeleton <- c(0.05, 0.1, 0.25, 0.4, 0.6)
target <- 0.25
cohort_sizes <- c(3, 3)
paths <- get_dfcrm(skeleton = skeleton, target = target) %>%
  get_dose_paths(cohort_sizes = cohort_sizes)

## End(Not run)
```

---

stop_at_n *Stop when there are n patients in total.*

Description

This function adds a restriction to stop a trial when n patients have been evaluated. It does this by adding together the number of patients treated at all doses and stopping when that total exceeds n.

Dose selectors are designed to be daisy-chained together to achieve different behaviours. This class is a **greedy** selector, meaning that it prioritises its own behaviour over the behaviour of other selectors in the chain. That is, it will advocate stopping when the condition has been met, even if the selectors further up the chain would advocate to keep going. In can be interpreted as an overriding selector. This allows the decision to stop to be executed as soon as it is warranted. Be aware though, that there are other selectors that can be placed after this class that will override the stopping behaviour. See Examples.

Usage

```
stop_at_n(parent_selector_factory, n)
```

Arguments

parent_selector_factory	Object of type selector_factory.
n	Stop when there are this many patients.

Value

an object of type selector_factory that can fit a dose-finding model to outcomes.

Examples

```
skeleton <- c(0.05, 0.1, 0.25, 0.4, 0.6)
target <- 0.25

# Create CRM model that will stop when 15 patients are evaluated:
model1 <- get_dfcrm(skeleton = skeleton, target = target) %>%
  stop_at_n(n = 15)

# With 12 patients, this trial should not stop:
fit1 <- model1 %>% fit('1NNN 2NTN 2TNN 2NNN')
fit1 %>% recommended_dose()
fit1 %>% continue()

# With 15 patients, this trial should stop:
fit2 <- model1 %>% fit('1NNN 2NTN 2TNN 2NNN 2NTT')
fit2 %>% recommended_dose()
fit2 %>% continue()

# The stopping behaviour can be overruled by the order of selectors.
# In model2, demanding 9 at recommended dose will trump stopping at 12:
model2 <- get_dfcrm(skeleton = skeleton, target = target) %>%
  stop_at_n(n = 12) %>%
  demand_n_at_dose(dose = 'recommended', n = 9)

# In model3, stopping at 12 will trump demanding 9 at recommended dose:
model3 <- get_dfcrm(skeleton = skeleton, target = target) %>%
  demand_n_at_dose(dose = 'recommended', n = 9) %>%
  stop_at_n(n = 12)

# This model will continue because 9 have not been seen at recommended dose.
fit3 <- model2 %>% fit('1NNN 2NNN 2NNN 3NNN')
fit3 %>% recommended_dose()
fit3 %>% continue()

# This model will stop because 12 have been seen.
fit4 <- model3 %>% fit('1NNN 2NNN 2NNN 3NNN')
fit4 %>% recommended_dose()
fit4 %>% continue()

# With enough observations though, both models will advise stopping because
# both conditions have been met:
fit5 <- model2 %>% fit('1NNN 2NNN 2NNN 5NNN 5NNN 5NNN')
fit5 %>% recommended_dose()
fit5 %>% continue()

fit6 <- model3 %>% fit('1NNN 2NNN 2NNN 5NNN 5NNN 5NNN')
fit6 %>% recommended_dose()
fit6 %>% continue()
```

`stop_when_n_at_dose` *Stop when there are n patients at a dose.*

Description

This method stops a dose-finding trial when there are n patients at a dose. It can stop when the rule is triggered at the recommended dose, at a particular dose, or at any dose.

Usage

```
stop_when_n_at_dose(parent_selector_factory, n, dose)
```

Arguments

`parent_selector_factory`	Object of type `selector_factory`.
`n`	Stop when there are n at a dose.
`dose`	`'any'` to stop when there are n at any dose; `'recommended'` to stop when there are n at the recommended dose; or an integer to stop when there are n at a particular dose-level.

Value

an object of type `selector_factory` that can fit a dose-finding model to outcomes.

Examples

```
skeleton <- c(0.05, 0.1, 0.25, 0.4, 0.6)
target <- 0.25

# This model will stop when 12 are seen at any dose:
model1 <- get_dfcrm(skeleton = skeleton, target = target) %>%
  stop_when_n_at_dose(n = 12, dose = 'any')

# This model fit will not stop:
model1 %>% fit('1NNN 2NTN 2TNN 2NNN') %>% continue()
# But this model fit will stop:
model1 %>% fit('1NNN 2NTN 2TNN 2NNN 2NTT') %>% continue()

# This model will stop when 12 are seen at the recommended dose:
model2 <- get_dfcrm(skeleton = skeleton, target = target) %>%
  stop_when_n_at_dose(n = 12, dose = 'recommended')

# This model fit will not stop:
fit2 <- model2 %>% fit('1NNN 2NTN 2TNN 2NNN')
fit2 %>% recommended_dose()
fit2 %>% continue()
```

```
# But this model fit will stop:
fit3 <- model2 %>% fit('1NNN 2NTN 2TNN 2NNN 2NNT')
fit3 %>% recommended_dose()
fit3 %>% continue()
```

`stop_when_too_toxic` *Stop when a dose is too toxic.*

Description

This method stops a dose-finding trial when sufficient probabilistic confidence is reached that the rate of toxicity at a dose exceeds some threshold. In other words, it stops when it is likely that a dose is too toxic. It can stop when the rule is triggered at the recommended dose, at a particular dose, or at any dose. See Details.

Usage

```
stop_when_too_toxic(parent_selector_factory, dose, tox_threshold, confidence)
```

Arguments

`parent_selector_factory`	Object of type `selector_factory`.
`dose`	`'any'` to stop when any dose is too toxic; `'recommended'` to stop when the recommended dose is too toxic; or an integer to stop when a particular dose-level is too toxic.
`tox_threshold`	We are interested in toxicity probabilities greater than this threshold.
`confidence`	Stop when there is this much total probability mass supporting that the toxicity rate exceeds the threshold.

Details

The method for calculating probability mass for toxicity rates will ultimately be determined by the dose-finding model used and the attendant inferential mechanism. For instance, the `crm` function in the dfcrm package calculates the posterior expected mean and variance of the slope parameter in a CRM model. It does not use MCMC to draw samples from the posterior distribution. Thus, to perform inference on the posterior probability of toxicity, this package assumes the dfcrm slope parameter follows a normal distribution with the mean and variance calculated by dfcrm. In contrast, the `stan_crm` function in the `trialr` package needs no such assumption because it samples from the posterior parameter distribution and uses those samples to infer on the posterior probability of toxicity at each dose, dependent on the chosen model for the dose-toxicity curve.

Value

an object of type `selector_factory` that can fit a dose-finding model to outcomes.

Examples

```
skeleton <- c(0.05, 0.1, 0.25, 0.4, 0.6)
target <- 0.25

# We compare a CRM model without a toxicity stopping rule to one with it:
model1 <- get_dfcrm(skeleton = skeleton, target = target)
model2 <- get_dfcrm(skeleton = skeleton, target = target) %>%
  stop_when_too_toxic(dose = 'any', tox_threshold = 0.5, confidence = 0.7)

outcomes <- '1NNN 2NNN 3NNT 3NNN 3TNT 2NNN'
fit1 <- model1 %>% fit(outcomes)
fit2 <- model2 %>% fit(outcomes)

# Naturally the first does not advocate stopping:
fit1 %>% recommended_dose()
fit1 %>% continue()

# However, after the material toxicity at dose 3, ithe rule is fired:
fit2 %>% recommended_dose()
fit2 %>% continue()
# To verify the requirement to stop, let's calculate the probability that the
# toxicity rate exceeds 50%
fit2 %>% prob_tox_exceeds(0.5)
```

---

stop_when_tox_ci_covered

Stop when uncertainty interval of prob tox is covered.

Description

This method stops a dose-finding trial when the symmetric uncertainty interval for the probability of toxicity falls within a range. This allows trials to be stopped when sufficient precision on the pobability of toxicity has been achieved. See Details.

Usage

```
stop_when_tox_ci_covered(
  parent_selector_factory,
  dose,
  lower,
  upper,
  width = 0.9
)
```

Arguments

`parent_selector_factory`
: Object of type `selector_factory`.

dose	'any' to stop when the interval for any dose is covered; 'recommended' to stop when the interval for the recommended dose is covered ; or an integer to stop when the interval for a particular dose-level is covered.
lower	Stop when lower interval bound exceeds this value
upper	Stop when upper interval bound is less than this value
width	Width of the uncertainty interval. Default is 0.9, i.e. a range from the 5th to the 95th percentiles.

Details

The method for calculating probability mass for toxicity rates will ultimately be determined by the dose-finding model used and the attendant inferential mechanism. For instance, the crm function in the dfcrm package calculates the posterior expected mean and variance of the slope parameter in a CRM model. It does not use MCMC to draw samples from the posterior distribution. Thus, to perform inference on the posterior probability of toxicity, this package assumes the dfcrm slope parameter follows a normal distribution with the mean and variance calculated by dfcrm. In contrast, the stan_crm function in the trialr package needs no such assumption because it samples from the posterior parameter distribution and uses those samples to infer on the posterior probability of toxicity at each dose, dependent on the chosen model for the dose-toxicity curve.

Value

an object of type selector_factory that can fit a dose-finding model to outcomes.

Examples

```
skeleton <- c(0.05, 0.1, 0.25, 0.4, 0.6)
target <- 0.25

# We compare a CRM model without this stopping rule:
model1 <- get_dfcrm(skeleton = skeleton, target = target)
# To two with it, the first demanding a relatively tight CI:
model2 <- get_dfcrm(skeleton = skeleton, target = target) %>%
  stop_when_tox_ci_covered(dose = 'recommended', lower = 0.15, upper = 0.35)
# and the second demanding a relatively loose CI:
model3 <- get_dfcrm(skeleton = skeleton, target = target) %>%
  stop_when_tox_ci_covered(dose = 'recommended', lower = 0.05, upper = 0.45)

outcomes <- '1NNN 2NNN 3NNT 3NNN 3TNT 2NNN'
fit1 <- model1 %>% fit(outcomes)
fit2 <- model2 %>% fit(outcomes)
fit3 <- model3 %>% fit(outcomes)

# Naturally the first does not advocate stopping:
fit1 %>% recommended_dose()
fit1 %>% continue()

# The second does not advocate stopping either:
fit2 %>% recommended_dose()
fit2 %>% continue()
```

```
# This is because the CI is too wide:
fit2 %>% prob_tox_quantile(p = 0.05)
fit2 %>% prob_tox_quantile(p = 0.95)

# However, the third design advocates stopping because the CI at the
# recommended dose is covered:
fit3 %>% recommended_dose()
fit3 %>% continue()
# To verify the veracity, inspect the quantiles:
fit3 %>% prob_tox_quantile(p = 0.05)
fit3 %>% prob_tox_quantile(p = 0.95)
```

`supports_sampling` *Does this selector support sampling of outcomes?*

Description

Learn whether this selector supports sampling of outcomes. For instance, is it possible to get posterior samples of the probability of toxicity at each dose? If true, prob_tox_samples will return a data-frame of samples.

Usage

```
supports_sampling(x, ...)
```

Arguments

`x`	Object of type `selector`
`...`	arguments passed to other methods

Value

logical

Examples

```
# CRM example
skeleton <- c(0.05, 0.1, 0.25, 0.4, 0.6)
target <- 0.25
outcomes <- '1NNN 2NTN'
fit <- get_dfcrm(skeleton = skeleton, target = target) %>% fit(outcomes)
fit %>% supports_sampling()
```

three_plus_three *Fit the 3+3 model to some outcomes.*

Description

Fit the 3+3 model to some outcomes.

Usage

```
three_plus_three(
  outcomes,
  num_doses,
  allow_deescalate = FALSE,
  strict_mode = TRUE
)
```

Arguments

outcomes	Outcomes observed. See parse_phase1_outcomes.
num_doses	Number of doses under investigation.
allow_deescalate	TRUE to allow de-escalation, as described by Korn et al. Default is FALSE.
strict_mode	TRUE to raise errors if it is detected that the 3+3 algorithm has not been followed.

Value

lits containing recommended_dose and a logical value continue saying whether the trial should continue.

References

Storer BE. Design and Analysis of Phase I Clinical Trials. Biometrics. 1989;45(3):925-937. doi:10.2307/2531693

Korn EL, Midthune D, Chen TT, Rubinstein LV, Christian MC, Simon RM. A comparison of two phase I trial designs. Statistics in Medicine. 1994;13(18):1799-1806. doi:10.1002/sim.4780131802

Examples

```
three_plus_three('2NNN 3NNT', num_doses = 7)
```

tox *Binary toxicity outcomes.*

Description

Get a vector of the binary toxicity outcomes for evaluated patients.

Usage

```
tox(x, ...)
```

Arguments

x	Object of type selector.
...	Extra args are passed onwards.

Value

an integer vector

Examples

```
skeleton <- c(0.05, 0.1, 0.25, 0.4, 0.6)
target <- 0.25
model <- get_dfcrm(skeleton = skeleton, target = target)
fit <- model %>% fit('1NNN 2NTN')
fit %>% tox()
```

tox_at_dose *Number of toxicities seen at each dose.*

Description

Get the number of toxicities seen at each dose under investigation.

Usage

```
tox_at_dose(x, ...)
```

Arguments

x	Object of class selector
...	arguments passed to other methods

Value

an integer vector

Examples

```
# CRM example
skeleton <- c(0.05, 0.1, 0.25, 0.4, 0.6)
target <- 0.25
outcomes <- '1NNN 2NTN'
fit <- get_dfcrm(skeleton = skeleton, target = target) %>% fit(outcomes)
fit %>% tox_at_dose()
```

---

tox_target *Target toxicity rate*

Description

Get the target toxicity rate, if supported. NULL if not.

Usage

```
tox_target(x, ...)
```

Arguments

x	Object of type selector.
...	Extra args are passed onwards.

Value

numeric

Examples

```
skeleton <- c(0.05, 0.1, 0.25, 0.4, 0.6)
target <- 0.25
model <- get_dfcrm(skeleton = skeleton, target = target)
fit <- model %>% fit('1NNN 2NTN')
fit %>% tox_target()
```

trial_duration *Duration of trials.*

Description

Get the length of time that trials take to recruit all patients.

Usage

```
trial_duration(x, ...)
```

Arguments

x	Object of type simulations.
...	arguments passed to other methods

Value

vector of numerical times

Examples

```
true_prob_tox <- c(0.12, 0.27, 0.44, 0.53, 0.57)
sims <- get_three_plus_three(num_doses = 5) %>%
  simulate_trials(num_sims = 50, true_prob_tox = true_prob_tox)
sims %>% trial_duration
```

try_rescue_dose *Demand that a rescue dose is tried before stopping is permitted.*

Description

This method continues a dose-finding trial until a safety dose has been given to n patients. Once that condition is met, it delegates dose selelcting and stopping responsibility to its parent dose selector, whatever that might be. This class is greedy in that it meets its own needs before asking any other selectors higher in the chain what they want. Thus, different behaviours may be achieved by nesting dose selectors in different orders. See examples.

Usage

```
try_rescue_dose(parent_selector_factory, n, dose)
```

Arguments

parent_selector_factory	Object of type selector_factory.
n	Continue at least until there are n at a dose.
dose	an integer to identify the sought rescue dose-level.

Value

an object of type selector_factory that can fit a dose-finding model to outcomes.

Examples

```
skeleton <- c(0.05, 0.1, 0.25, 0.4, 0.6)
target <- 0.25

# This model will demand the lowest dose is tried in at least two patients
# before the trial is stopped for excess toxicity
model1 <- get_dfcrm(skeleton = skeleton, target = target) %>%
  stop_when_too_toxic(dose = 1, tox_threshold = 0.35, confidence = 0.8) %>%
  try_rescue_dose(dose = 1, n = 2)

# In contrast, this model will stop for excess toxicity without trying dose 1
model2 <- get_dfcrm(skeleton = skeleton, target = target) %>%
  stop_when_too_toxic(dose = 1, tox_threshold = 0.35, confidence = 0.8)

# For non-toxic outcomes, both designs will continue at sensible doses:
fit1 <- model1 %>% fit('2NNN')
fit1 %>% recommended_dose()
fit1 %>% continue()

fit2 <- model2 %>% fit('2NNN')
fit2 %>% recommended_dose()
fit2 %>% continue()

# For toxic outcomes, the design 1 will use dose 1 before stopping is allowed
fit1 <- model1 %>% fit('2TTT')
fit1 %>% recommended_dose()
fit1 %>% continue()

# For toxic outcomes, however, design 2 will stop despite dose 1 being
# untested:
fit2 <- model2 %>% fit('2TTT')
fit2 %>% recommended_dose()
fit2 %>% continue()

# After dose 1 is given the requisite number of times, dose recommendation
# and stopping revert to being determined by the underlying dose selector:
fit1 <- model1 %>% fit('2TTT 1T')
fit1 %>% recommended_dose()
fit1 %>% continue()
```

```
fit1 <- model1 %>% fit('2TTT 1TT')
fit1 %>% recommended_dose()
fit1 %>% continue()
```

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