

Package ‘tipmap’

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Type Package

Title Tipping Point Analysis for Bayesian Dynamic Borrowing

Version 0.5.2

Description Tipping point analysis for clinical trials that employ Bayesian dynamic borrowing via robust meta-analytic predictive (MAP) priors. Further functions facilitate expert elicitation of a primary weight of the informative component of the robust MAP prior and computation of operating characteristics. Intended use is the planning, analysis and interpretation of extrapolation studies in pediatric drug development, but applicability is generally wider.

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URL <https://github.com/Boehringer-Ingelheim/tipmap>

BugReports <https://github.com/Boehringer-Ingelheim/tipmap/issues>

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create_new_trial_data	<i>Data on new trial in target population</i>
-----------------------	---

Description

Creates a vector containing data on the new trial in the target population. This may be hypothetical data in the planning stage.

Usage

```
create_new_trial_data(n_total, est, se)
```

Arguments

n_total	The total sample size.
est	Treatment effect estimate.
se	Standard error of the treatment effect estimate.

Value

A numeric vector with data on the new trial, incl. quantiles of an assumed normal data likelihood.

See Also

[create_posterior_data](#), [create_tipmap_data](#)

Examples

```
new_trial_data <- create_new_trial_data(
  n_total = 30, est = 1.27, se = 0.95
)
```

`create_posterior_data` *Creates posterior distributions for a range of weights on the informative component of the robust MAP prior*

Description

Returns a data frame containing the default quantiles of posterior mixture distributions generated with varying weights on the informative component of the MAP prior.

Usage

```
create_posterior_data(map_prior, new_trial_data, sigma, null_effect = 0)
```

Arguments

<code>map_prior</code>	A MAP prior containing information about the trial(s) in the source population, created using RBest.
<code>new_trial_data</code>	A vector containing information about the new trial. See <code>create_new_trial_data()</code> .
<code>sigma</code>	Standard deviation to be used for the weakly informative component of the MAP prior, recommended to be the unit-information standard deviation.
<code>null_effect</code>	The mean of the robust component of the MAP prior. Defaults to 0.

Value

A data frame containing posterior distributions for varying weights

References

Best, N., Price, R. G., Pouliquen, I. J., & Keene, O. N. (2021). Assessing efficacy in important subgroups in confirmatory trials: An example using Bayesian dynamic borrowing. *Pharm Stat*, 20(3), 551–562. <https://doi.org/10.1002/pst.2093>

See Also

[create_new_trial_data](#), [create_prior_data](#)

Examples

```
# create vector containing data on new trial
new_trial_data <- create_new_trial_data(
  n_total = 30,
  est = 1.27,
  se = 0.95
)

# read MAP prior created by RBest
map_prior <- load_tipmap_data("tipmapPrior.rds")

# create posterior data
## Not run:
posterior_data <- create_posterior_data(
  map_prior = map_prior,
  new_trial_data = new_trial_data,
  sigma = 12
)

## End(Not run)
```

create_prior_data	<i>Creates input data frame for construction of MAP prior</i>
-------------------	---

Description

Assembling information from trials in the source population in a structured way (required as a pre-processing step for MAP prior creation).

Usage

```
create_prior_data(study_label = NULL, n_total, est, se)
```

Arguments

study_label	An optional vector containing trial labels.
n_total	A vector containing total sample sizes.
est	A vector containing treatment effect estimates.
se	A vector containing standard errors of the effect estimates.

Value

A data frame containing data on the trials in the source population.

See Also

[create_new_trial_data](#), [create_posterior_data](#)

Examples

```
prior_data <- create_prior_data(
  n_total = c(160, 240, 320),
  est = c(1.23, 1.40, 1.51),
  se = c(0.4, 0.36, 0.31)
)
```

create_tipmap_data	<i>Create data frame ready to use for tipping point analysis</i>
--------------------	--

Description

Combines new trial data created by `createTargetData()`, a posterior distribution created by `create_posterior_data()` and a robust MAP prior using `RBesT::automixfit()` and an optional meta-analysis, e.g. created using the meta package, into a data frame needed for the functions `tipmap_plot()` and `get_tipping_point()`.

Usage

```
create_tipmap_data(new_trial_data, posterior, map_prior, meta_analysis = NULL)
```

Arguments

<code>new_trial_data</code>	A data frame containing data on the new trial in the target population. See <code>create_new_trial_data()</code> .
<code>posterior</code>	A mixture combining MAP prior and target population. See <code>create_posterior_data()</code> .
<code>map_prior</code>	A robust MAP prior created by <code>RBesT::automixfit()</code> .
<code>meta_analysis</code>	A data frame containing a meta-analysis of trial(s) to be borrowed from. See <code>createPriorData()</code> .

Value

A data frame ready to be used for `tipmap_plot()` and `get_tipping_point()`

See Also

[create_new_trial_data](#), [create_posterior_data](#), [tipmap_plot](#), [get_tipping_points](#)

Examples

```
# specify new trial data
new_trial_data <- create_new_trial_data(n_total = 30, est = 1.5, se = 2.1)

# read MAP prior data
map_prior <- load_tipmap_data("tipmapPrior.rds")

# read posterior data
```

```
posterior <- load_tipmap_data("tipPost.rds")

tip_dat <- create_tipmap_data(
  new_trial_data = new_trial_data,
  posterior = posterior,
  map_prior = map_prior
)
```

default_quantiles	<i>Default quantiles</i>
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Description

Default quantiles

Usage

default_quantiles

Format

An object of class `numeric` of length 13.

default_weights	<i>Default weights</i>
-----------------	------------------------

Description

Default weights

Usage

default_weights

Format

An object of class `numeric` of length 201.

draw_beta_mixture_nsamples

Draw samples from a mixture of beta distributions

Description

Draws samples from a mixture of beta distributions, representing pooled weights on the informative component of a robust MAP prior, as elicited from experts via the roulette method.

Usage

```
draw_beta_mixture_nsamples(n, chips_mult, expert_weight = NULL)
```

Arguments

n	Numeric value, the number of samples to be drawn.
chips_mult	Numeric matrix, containing expert weighting (distributions of chips). Rows should represent experts, columns should represent bins / weight intervals.
expert_weight	An optional numeric vector, containing the weight assigned to each expert (defaults to equal weights).

Value

A numeric vector containing samples from a pooled distribution of expert opinions.

See Also

[fit_beta_mult_exp](#) and [get_summary_mult_exp](#).

Examples

```
rweights <- draw_beta_mixture_nsamples(
  n = 50,
  chips_mult = rbind(
    c(0, 0, 0, 0, 2, 3, 3, 2, 0, 0),
    c(0, 0, 0, 1, 2, 4, 2, 1, 0, 0),
    c(0, 0, 0, 2, 2, 2, 2, 2, 0, 0)
  ),
  expert_weight = rep(1/3, 3)
)
print(rweights)
## Not run:
hist(rweights)

## End(Not run)
```

fit_beta_1exp	<i>Fit beta distribution for one expert</i>
---------------	---

Description

Fit beta distribution to data elicited from one expert via the roulette method.

Usage

```
fit_beta_1exp(df)
```

Arguments

df A dataframe generated by [get_model_input_1exp](#).

Details

This function is based on `SHELF::fitdist` and yields identical results.

Value

Parameters (alpha and beta) of a beta fit.

See Also

[get_model_input_1exp](#) and [fit_beta_mult_exp](#).

Examples

```
chips <- c(0, 2, 3, 2, 1, 1, 1, 0, 0, 0)
x <- get_cum_probs_1exp(chips)
y <- get_model_input_1exp(x)
fit_beta_1exp(df = y)[“par”]
```

fit_beta_mult_exp	<i>Fit beta distributions for multiple experts</i>
-------------------	--

Description

Fit beta distributions to data elicited from multiple experts via the roulette method.

Usage

```
fit_beta_mult_exp(chips_mult)
```

Arguments

`chips_mult` A dataframe or matrix containing weights. It should contain one row per expert and 10 columns, one for each bin, representing weights from 0 to 1.

Value

A dataframe containing the parameters of the individual beta distributions.

See Also

[fit_beta_1exp](#).

Examples

```
beta_fits <- fit_beta_mult_exp(
  chips_mult = rbind(
    c(0, 0, 0, 0, 2, 3, 3, 2, 0, 0),
    c(0, 0, 0, 1, 2, 4, 2, 1, 0, 0),
    c(0, 0, 0, 2, 2, 2, 2, 2, 0, 0)
  )
)
print(beta_fits)
```

<code>get_cum_probs_1exp</code>	<i>Get cumulative probabilities from distribution of chips of one expert</i>
---------------------------------	--

Description

Get cumulative probabilities from distribution of chips of one expert

Usage

```
get_cum_probs_1exp(chips)
```

Arguments

`chips` Vector of integers, representing the distribution of chips assigned by one expert, as elicited through the roulette method. Each element of the vector represents one bin in the grid.

Value

A numeric vector with the cumulative distribution of chips.

See Also

[get_model_input_1exp](#) and [fit_beta_1exp](#).

Examples

```
chips <- c(0, 2, 3, 2, 1, 1, 1, 0, 0, 0)
x <- get_cum_probs_1exp(chips)
print(x)
```

get_model_input_1exp *Transform cumulative probabilities to fit beta distributions*

Description

Transform cumulative probabilities to fit beta distributions

Usage

```
get_model_input_1exp(cum_probs, w = NULL)
```

Arguments

cum_probs	Numeric vector, containing cumulative probabilities of weights for one expert, as elicited through the roulette method. Each element of the vector represents one bin in the grid.
w	Numeric vector, upper interval limit of bin (defaults to 1:length(cum_probs) / length(cum_probs)).

Value

Dataframe to be used as input to fit beta distributions by [fit_beta_1exp](#).

See Also

[get_cum_probs_1exp](#) and [fit_beta_1exp](#).

Examples

```
chips <- c(0, 2, 3, 2, 1, 1, 1, 0, 0, 0)
x <- get_cum_probs_1exp(chips)
print(x)
y <- get_model_input_1exp(x)
print(y)
```

`get_posterior_by_weight`*Filter posterior by given weights*

Description

Returns quantiles of the posterior distribution of the treatment effect for one or more specified weights.

Usage

```
get_posterior_by_weight(posterior, weight)
```

Arguments

<code>posterior</code>	The posterior data to be filtered (see <code>create_posterior_data()</code>).
<code>weight</code>	The weight(s) to be filtered by.

Value

The filtered posterior values

See Also

[create_posterior_data](#)

Examples

```
get_posterior_by_weight(  
  posterior = load_tipmap_data("tipPost.rds"),  
  weight = c(0.05, 0.1)  
)
```

`get_summary_mult_exp` *Summarize expert weights*

Description

Computes minimum, maximum, mean and quartiles for expert weights.

Usage

```
get_summary_mult_exp(chips_mult, n = 500, expert_weight = NULL)
```

Arguments

- `chips_mult` Numeric matrix, containing expert weights.
- `n` Number of samples to be drawn to obtain summary statistics (defaults to 500).
- `expert_weight` Weights assigned to each expert (defaults to equal weights).

Value

A vector containing summary statistics.

Examples

```
get_summary_mult_exp(
  chips_mult = rbind(
    c(0, 0, 0, 0, 2, 3, 3, 2, 0, 0),
    c(0, 0, 0, 1, 2, 4, 2, 1, 0, 0),
    c(0, 0, 0, 2, 2, 2, 2, 2, 0, 0)
  ),
  n = 50
)
```

`get_tipping_points` *Identify tipping point for a specific quantile.*

Description

Identifies the weights closest to tipping points for specified quantiles.

Usage

```
get_tipping_points(tipmap_data, quantile, null_effect = 0)
```

Arguments

- `tipmap_data` A data frame created by `create_tipmap_data()`.
- `quantile` The quantile(s) of the tipping point. Possible values are 0.025, 0.05, 0.1, 0.2, 0.8, 0.9, 0.95 and 0.975.
- `null_effect` The null treatment effect. Defaults to 0.

Value

The weight closest to the tipping point for the specified quantile

See Also

[create_tipmap_data](#)

Examples

```
tip_dat <- load_tipmap_data("tipdat.rds")#'
get_tipping_points(tip_dat, quantile = 0.025)
get_tipping_points(tip_dat, quantile = c(0.025, 0.05, 0.1, 0.2), null_effect = 0.1)
```

load_tipmap_data	<i>Load exemplary datasets</i>
------------------	--------------------------------

Description

Loads one of three exemplary datasets in the package.

Usage

```
load_tipmap_data(file)
```

Arguments

file	The dataset to be loaded.
------	---------------------------

Value

A pre-saved dataset.

Examples

```
load_tipmap_data(file = "tipdat.rds")
load_tipmap_data(file = "tipmapPrior.rds")
load_tipmap_data(file = "tipPost.rds")
```

oc_bias	<i>Assessing bias</i>
---------	-----------------------

Description

Assessment of absolute bias in posterior means and medians for a given weight and evidence level, using simulated data as input.

Usage

```
oc_bias(
  m,
  se,
  true_effect,
  weights = seq(0, 1, by = 0.01),
  map_prior,
  sigma,
  n_cores = 1,
  eval_strategy = "sequential"
)
```

Arguments

<code>m</code>	Numerical vector of simulated effect estimates.
<code>se</code>	Numerical vector of simulated standard errors (<code>m</code> and <code>se</code> need to have the same length).
<code>true_effect</code>	Numerical value, representing the true treatment effect (usually the mean of the simulated <code>m</code>).
<code>weights</code>	Vector of weights of the informative component of the MAP prior (defaults to <code>seq(0, 1, by = 0.01)</code>).
<code>map_prior</code>	A MAP prior containing information about the trials in the source population, created using <code>RBest</code> ; a mixture of normal distributions is required.
<code>sigma</code>	Standard deviation of the weakly informative component of the MAP prior, recommended to be the unit-information standard deviation.
<code>n_cores</code>	Integer value, representing the number of cores to be used (defaults to 1); only applies if <code>eval_strategy</code> is not "sequential".
<code>eval_strategy</code>	Character variable, representing the evaluation strategy, either "sequential", "multisession", or "multicore" (see documentation of <code>future::plan</code> , defaults to "sequential").

Value

A 2-dimensional array containing results on bias.

See Also

[oc_pos](#) and [oc_coverage](#).

Examples

```
set.seed(123)
n_sims <- 5 # small number for exemplary application
sim_dat <- list(
  "m" = rnorm(n = n_sims, mean = 1.15, sd = 0.1),
  "se" = rnorm(n = n_sims, mean = 1.8, sd = 0.3)
)
```

```

results <- oc_bias(
  m = sim_dat[["m"]],
  se = sim_dat[["se"]],
  true_effect = 1.15,
  weights = seq(0, 1, by = 0.01),
  map_prior = load_tipmap_data("tipmapPrior.rds"),
  sigma = 16.23,
  eval_strategy = "sequential",
  n_cores = 1
)
print(results)

```

oc_coverage

Assessing coverage

Description

Assessment of coverage of posterior intervals for a given weight and evidence level, using simulated data as input.

Usage

```

oc_coverage(
  m,
  se,
  true_effect,
  weights = seq(0, 1, by = 0.01),
  map_prior,
  sigma,
  n_cores = 1,
  eval_strategy = "sequential"
)

```

Arguments

m	Numerical vector of simulated effect estimates.
se	Numerical vector of simulated standard errors (m and se need to have the same length).
true_effect	Numerical value, representing the true treatment effect (usually the mean of the simulated m).
weights	Vector of weights of the informative component of the MAP prior (defaults to seq(0, 1, by = 0.01)).
map_prior	A MAP prior containing information about the trials in the source population, created using RBest; a mixture of normal distributions is required.
sigma	Standard deviation of the weakly informative component of the MAP prior, recommended to be the unit-information standard deviation.

n_cores	Integer value, representing the number of cores to be used (defaults to 1); only applies if eval_strategy is not "sequential".
eval_strategy	Character variable, representing the evaluation strategy, either "sequential", "multisession", or "multicore" (see documentation of <code>future::plan</code> , defaults to "sequential").

Value

A 2-dimensional array containing results on coverage.

See Also

[oc_pos](#) and [oc_bias](#).

Examples

```
set.seed(123)
n_sims <- 5 # small number for exemplary application
sim_dat <- list(
  "m" = rnorm(n = n_sims, mean = 1.15, sd = 0.1),
  "se" = rnorm(n = n_sims, mean = 1.8, sd = 0.3)
)
results <- oc_coverage(
  m = sim_dat[["m"]],
  se = sim_dat[["se"]],
  true_effect = 1.15,
  weights = seq(0, 1, by = 0.01),
  map_prior = load_tipmap_data("tipmapPrior.rds"),
  sigma = 16.23
)
print(results)
```

oc_pos

Assessing probability of success

Description

Assessment of the probability of truly or falsely (depending on simulated scenario) rejecting the null hypothesis of interest for a given weight and evidence level, using simulated data as input.

Usage

```
oc_pos(
  m,
  se,
  probs,
  weights = seq(0, 1, by = 0.01),
  map_prior,
```

```

    sigma,
    null_effect = 0,
    direction_pos = T,
    n_cores = 1,
    eval_strategy = "sequential"
  )

```

Arguments

<code>m</code>	Numerical vector of simulated effect estimates.
<code>se</code>	Numerical vector of simulated standard errors (<code>m</code> and <code>se</code> need to have the same length).
<code>probs</code>	Vector of quantiles <code>q</code> , with <code>1 minus q</code> representing an evidence level of interest (where positive effect estimate indicate a beneficial treatment).
<code>weights</code>	Vector of weights of the informative component of the MAP prior (defaults to <code>seq(0, 1, by = 0.01)</code>).
<code>map_prior</code>	A MAP prior containing information about the trials in the source population, created using <code>RBEST</code> ; a mixture of normal distributions is required.
<code>sigma</code>	Standard deviation of the weakly informative component of the MAP prior, recommended to be the unit-information standard deviation.
<code>null_effect</code>	Numerical value, representing the null effect (defaults to 0).
<code>direction_pos</code>	Logical value, <code>TRUE</code> (default) if effects greater than the <code>null_effect</code> indicate a beneficial treatment and <code>FALSE</code> otherwise.
<code>n_cores</code>	Integer value, representing the number of cores to be used (defaults to 1); only applies if <code>eval_strategy</code> is not "sequential".
<code>eval_strategy</code>	Character variable, representing the evaluation strategy, either "sequential", "multisession", or "multicore" (see documentation of <code>future::plan</code> , defaults to "sequential").

Value

A 2-dimensional array containing probabilities, either of truly (probability of success) or falsely rejecting the null hypothesis of interest for a given weight and evidence level.

See Also

[oc_bias](#) and [oc_coverage](#).

Examples

```

set.seed(123)
n_sims <- 5 # small number for exemplary application
sim_dat <- list(
  "m" = rnorm(n = n_sims, mean = 1.15, sd = 0.1),
  "se" = rnorm(n = n_sims, mean = 1.8, sd = 0.3)
)
results <- oc_pos(

```

```
m = sim_dat[["m"]],
se = sim_dat[["se"]],
probs = c(0.025, 0.05, 0.1, 0.2),
weights = seq(0, 1, by = 0.01),
map_prior = load_tipmap_data("tipmapPrior.rds"),
sigma = 16.23,
null_effect = 0,
direction_pos = TRUE,
eval_strategy = "sequential",
n_cores = 1
)
print(results)
```

tipmap_darkblue	<i>Custom dark blue</i>
-----------------	-------------------------

Description

Custom dark blue

Usage

tipmap_darkblue

Format

An object of class character of length 1.

tipmap_lightred	<i>Custom light red</i>
-----------------	-------------------------

Description

Custom light red

Usage

tipmap_lightred

Format

An object of class character of length 1.

tipmap_plot	<i>Visualize tipping point analysis</i>
-------------	---

Description

Uses a data frame created by `create_tipmap_data()` to visualize the tipping point analysis.

Usage

```
tipmap_plot(
  tipmap_data,
  target_pop_lab = "Trial in target\n population",
  y_range = NULL,
  y_breaks = NULL,
  title = NULL,
  y_lab = "Mean difference",
  x_lab = "Weight on informative component of MAP prior",
  map_prior_lab = "MAP\nprior",
  meta_analysis_lab = "MA",
  legend_title = "Posterior quantile",
  null_effect = 0
)
```

Arguments

<code>tipmap_data</code>	A data frame containing tipping point data, generated by <code>create_tipmap_data()</code> .
<code>target_pop_lab</code>	A label for the trial in the target population.
<code>y_range</code>	An optional argument specifying range of the y-axis.
<code>y_breaks</code>	An optional vector specifying breaks on the y-axis.
<code>title</code>	The plot title.
<code>y_lab</code>	The label for the y axis. Defaults to "Mean difference".
<code>x_lab</code>	The label for the x axis. Defaults to "Weight on informative component of MAP prior".
<code>map_prior_lab</code>	The label for the MAP prior. Defaults to "MAP prior"
<code>meta_analysis_lab</code>	An optional label for a meta-analysis (if included).
<code>legend_title</code>	An optional title for the plot legend. Defaults to "Posterior quantiles".
<code>null_effect</code>	The null treatment effect, determining where tipping points are calculated. Defaults to 0.

Value

A ggplot object of the tipping point plot

See Also[create_tipmap_data](#)**Examples**

```
tipmap_data <- load_tipmap_data("tipdat.rds")  
tipmap_plot(tipmap_data)
```

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