Package ‘basket’

October 17, 2021

Title Basket Trial Analysis

Version 0.10.11


Depends R (>= 3.5.0)

License LGPL-2

Maintainer Michael J. Kane <michael.kane@yale.edu>

Imports GenSA, foreach, ggplot2, stats, tibble, tidyr, dplyr, igraph, gridExtra, iterators, crayon, cli, RColorBrewer, tidygraph, ggraph,

LazyData true

Encoding UTF-8

RoxygenNote 7.1.2

URL https://github.com/kaneplusplus/basket

BugReports https://github.com/kaneplusplus/basket/issues

Suggests knitr, rmarkdown, testthat (>= 3.0.0), doParallel

VignetteBuilder knitr
basket-package

Config/testthat/edition 3

NeedsCompilation no

Author Nan Chen [aut],
Ryan Hafen [ctb],
Brian Hobbs [aut],
Alex Kaizer [aut],
Michael J. Kane [aut, cre] (<https://orcid.org/0000-0003-1899-6662>)

Repository CRAN

Date/Publication 2021-10-16 23:30:22 UTC

R topics documented:

- basket-package .......................................................... 2
- basket ................................................................. 3
- basket_map ............................................................ 5
- basket_name ......................................................... 6
- basket_pep ........................................................... 7
- cluster_baskets ..................................................... 7
- cluster_map ......................................................... 8
- cluster_membership ................................................. 9
- cluster_pep .......................................................... 10
- get_seed ............................................................... 10
- mem_exact .......................................................... 11
- mem_mcmc ........................................................... 12
- plot_density ......................................................... 14
- plot_map ............................................................. 15
- plot_mem ............................................................ 16
- plot_pep .............................................................. 16
- plot_pep_graph ..................................................... 17
- sample_posterior .................................................. 18
- update_p0 ............................................................ 19
- vemu ................................................................. 20

Index 21

Basket Trial Analysis

Description

The R basket package provides for the designs and analysis of basket trials for multi-source exchangeability models (MEM) <https://doi.org/10.1093/biostatistics/kxx031> allowing arms to "share" power with similar arms in a trial. The package is intended to perform the exact or MCMC computation of the operating characteristics of different scenarios. Calculations derived from these analyses include the posterior probabilities, HPD boundaries, effective sample sizes (ESS), mean and median estimations can be calculated with this package using the MEM method. Along with providing
"basketwise" analyses, the package includes similar calculations for "clusterwise" analyses where a cluster is a set of similar baskets. In addition, plotting tools are provided to visualize basket and cluster density as well as their exchangeability. The package includes the following main functions:

- `[basket_name()]` Get the basket names in an analysis
- `[basket_pep()]` Get the Posterior Exchangeability Probability (PEP) matrix for the arms in the trial.
- `[basket_map()]` Get the Maximum A Posteriori (MAP) matrix for the arms in the trial.
- `[cluster_pep()]` Get the Posterior Exchangeability Probability (PEP) matrix for the arms in the trial.
- `[cluster_map()]` Get the Maximum A Posteriori (MAP) matrix for the arms in the trial.
- `[sample_posterior()]` Sample from the posterior distribution of the arms in the trial.
- `[mem_exact()]` Create a basket analysis using the exact method.
- `[mem_mcmc()]` Create a basket analysis using the exact method.
- `[summary()]` Summarize the results of an analysis.
- `[update_p0()]` Update the null that a basket response rate is above a specified value.
- `[plot_density()]` Plot the estimated densities of arms or clusters.
- `[plot_pep()]` Show the exchangeogram of the PEP matrix.
- `[plot_mem()]` Plot the arm prior, MAP, and PEP of a basket trial.

References


Bayesian basket trial design with exchangeability monitoring BP Hobbs, R Landin Statistics in medicine 37 (25), 3557-357. <https://doi.org/10.1002/sim.7893>


Create a Basket Trial Analysis

Description

This function creates an analysis modeling the exchangeability and distribution characteristics of cohorts in a basket trial, where a single therapy is given to multiple cohorts. The model is based on the multi-source exchangeability model. This is a generalization of the Bayesian hierarchical model and it accommodates multiple sets of latent factors shared combinations of cohorts.
Usage

```
basket(
  responses,
  size,
  name,
  p0 = 0.15,
  shape1 = 0.5,
  shape2 = 0.5,
  prior = diag(length(responses))/2 + matrix(0.5, nrow = length(responses), ncol = length(responses)),
  hpd_alpha = 0.05,
  alternative = "greater",
  call = NULL,
  cluster_function = cluster_membership,
  method = c("mcmc", "lmem", "exact"),
  mcmc_iter = 2e+05,
  mcmc_burnin = 50000,
  initial_mem = round(prior - 0.001),
  cluster_analysis = FALSE,
  seed = get_seed()
)
```

Arguments

- **responses**: the number of responses in each basket.
- **size**: the size of each basket.
- **name**: the name of each basket.
- **p0**: the null response rate for the poster probability calculation. (default 0.15)
- **shape1**: the first shape parameter(s) for the prior of each basket. (default 0.5)
- **shape2**: the second shape parameter(s) for the prior of each basket. (default 0.5)
- **prior**: the matrix giving the prior inclusion probability for each pair of baskets. The default is on on the main diagonal and 0.5 elsewhere.
- **hpd_alpha**: the highest posterior density trial significance. (default 0.05)
- **alternative**: the alternative case definition (default "greater").
- **call**: the call of the function. (default NULL)
- **cluster_function**: a function to cluster baskets.
- **method**: "mcmc", "lmem" (local MEM), or "exact". See details for an explanation. (default "mcmc")
- **mcmc_iter**: if the method is "mcmc" then this specifies the number of mcmc iterations. Otherwise, it is ignored. (default 200000)
- **mcmc_burnin**: if the method is "mcmc" then this specifies the number of burn-in iterations. (default 50000)
- **initial_mem**: if the method is "mcmc" then this specifies the initial MEM matrix. Otherwise, it is ignored.
basket_map

cluster_analysis
    if the cluster analysis is conducted.
seed
    the random seed for the mcmc calculations. By default this is .Random.seed. If this value
    is not initialized, then it is first initialized with Sys.time() and then returned.

Details

The model may be fit using an exact calculation via mcmc, or a local version of MEM. The first
conducts posterior inference through the entire set of exchangeability relationships in the sample
domain. This approach is computationally feasible only when the number of cohorts is relatively
small. As a rule of thumb this option should be used with a maximum of 20 cohorts. By default, the
second(mcmc) is used and it is based on the Metropolis algorithm and it extends the model’s imple-
mentation to larger collections of subpopulations. The algorithm initiates with a burn-in period (see
mcmc_burnin), which are discarded from the analysis. The third is based on a recent paper by Wei
et al. The calculation is computationally efficient and tends to borrow to a lesser extent than other
implemented methods.

Examples

# 3 baskets, each with enrollment size 5
trial_sizes <- rep(5, 3)

# The response rates for the baskets.
resp_rate <- 0.15

# The trials: a column of the number of responses and a column of the
# the size of each trial.
trials <- data.frame(
    responses = rbinom(trial_sizes, trial_sizes, resp_rate),
    size = trial_sizes,
    name = letters[1:3]
)

summary(basket(trials$responses, trials$size, trials$name))

basket_map

Get the Basketwise Maximum A Posteriori Probability Matrix

Description

MEM analyses include the maximum a posterior exchangeability probability (MAP) of included
arms indicating whether two arms in the trial are exchangeable. This function returns the matrix of
those relationships.

Usage

basket_map(x)
Arguments

x either an exchangeability model or basket object.

Examples

# Create an MEM analysis of the Vemurafenib trial data.
data(vemu_wide)

mem_analysis <- mem_exact(
  vemu_wide$responders,
  vemu_wide$evaluable,
  vemu_wide$baskets
)

# Get basket MAPs.
basket_map(mem_analysis)

<table>
<thead>
<tr>
<th>basket.name</th>
<th>The Names of the Baskets</th>
</tr>
</thead>
</table>

Description

Retrieve the basket names in an exchangeability model.

Usage

basket_name(model)

Arguments

model the model to retrieve the basket names of

Examples

# 3 baskets, each with enrollement size 5
trial_sizes <- rep(5, 3)

# The response rates for the baskets.
resp_rate <- 0.15

# The trials: a column of the number of responses and a column of the # the size of each trial.
trials <- data.frame(
  responses = rbinom(trial_sizes, trial_sizes, resp_rate),
  size = trial_sizes,
  name = paste("Basket", seq_len(3)))
basket_pep

)  
basket_name(mem_mcmc(trials$responses, trials$size, trials$basket))

basket_pep  The Basketwise Posterior Exchangeability Probability Matrix

Description
MEM analyses include the posterior exchangeability probability (PEP) of included arms giving the probability that any two arms are exchangeable. This function returns the matrix of those probabilities.

Usage
basket_pep(x)

Arguments
x  either an exchangeability model or basket object.

Examples
# Create an MEM analysis of the Vemurafenib trial data.
data(vemu_wide)

mem_analysis <- mem_exact(
  vemu_wide$response,
  vemu_wide$evaluable,
  vemu_wide$baskets
)

# Get the PEP for baskets.
basket_pep(mem_analysis)

cluster_baskets  Get the Cluster Members of MEM Models

Description
Object returned by the ‘mem_mcmc()’ and ‘mem_exact()’ include information about the arms in the trials and the cluster composed of sets of similar arms. This function returns the name of each arm in a cluster.
Usage

cluster_baskets(x)

Arguments

x either an exchangeability model or basket object.

Value

A named list is returned where the name is the cluster name and each element of the list is comprise do a character vector of the baskets in each cluster.

Examples

# Create an MEM analysis of the Vemurafenib trial data.
data(vemu_wide)

mem_analysis <- mem_exact(
  vemu_wide$responders,
  vemu_wide$evaluable,
  vemu_wide$baskets,
  cluster_analysis = TRUE
)

# Get the baskets in the clusters.
cluster_baskets(mem_analysis)

cluster_map

Get the Clusterwise Maximum A Posteriori Probability Matrix

Description

MEM analyses include the maximum a posterior exchangeability probability (MAP) of included arms indicating whether two arms in the trial are exchangeable. This function returns the matrix of those relationships.

Usage

cluster_map(x)

Arguments

x either an exchangeability model or basket object.
### Examples

```r
# Create an MEM analysis of the Vemurafenib trial data.
data(vemu_wide)
mem_analysis <- mem_exact(
  vemu_wide$responders,
  vemu_wide$evaluable,
  vemu_wide$baskets
)

# Get the cluster MAPs.
cluster_map(mem_analysis)
```

### Description

This is the default function used to cluster cohorts in the `basket`, `mem_mcmc`, and `mem_exact` functions. The approach creates a graph where each vertex is a cohort and the weight between two cohorts is determined by their posterior exchangeability probability. The graph is then clustered using `igraph`'s `louvain` function, which determines the number of clusters and the cluster memberships, and has been shown to perform well with real clinical data.

### Usage

```r
cluster_membership(m)
```

### Arguments

- `m` the adjacency matrix.

### Value

A factor variable with cluster memberships for each cohort in the study.

### See Also

- `basket`
- `mem_mcmc`
- `mem_exact`
cluster_pep  

Get the Clusterwise Posterior Exchangeability Matrix

Description

MEM analyses include the posterior exchangeability probability (PEP) of clusters of arms giving the probability that any two arms are exchangeable. This function returns the matrix of those probabilities.

Usage

cluster_pep(x)

Arguments

x  either an exchangeability model or basket object.

Examples

# Create an MEM analysis of the Vemurafenib trial data.
data(vemu_wide)

mem_analysis <- mem_exact(
  vemu_wide$response,
  vemu_wide$evaluable,
  vemu_wide$baskets
)

# Get cluster PEPs.
basket_pep(mem_analysis)

get_seed  

Get the Current Random Seed

Description

Get the value of the current random seed. If one has not been initialized, then initialize it and return the new seed value.

Usage

get_seed()
**mem_exact**

*Fit the Exact MEM Model*

**Description**

Fit the MEM model using full Bayesian inference.

**Usage**

```r
mem_exact(
  responses,
  size,
  name,
  p0 = 0.15,
  shape1 = 0.5,
  shape2 = 0.5,
  prior = diag(length(responses))/2 + matrix(0.5, nrow = length(responses), ncol =
    length(responses)),
  hpd_alpha = 0.05,
  alternative = "greater",
  seed = 1000,
  cluster_analysis = FALSE,
  call = NULL,
  cluster_function = cluster_membership
)
```

**Arguments**

- **responses**
  the number of responses in each basket.

- **size**
  the size of each basket.

- **name**
  the name of each basket.

- **p0**
  the null response rate for the posterior probability calculation (default 0.15).

- **shape1**
  the first shape parameter(s) for the prior of each basket (default 0.5).

- **shape2**
  the second shape parameter(s) for the prior of each basket (default 0.5).

- **prior**
  the matrix giving the prior inclusion probability for each pair of baskets. The
  default is on on the main diagonal and 0.5 elsewhere.

- **hpd_alpha**
  the highest posterior density trial significance.

- **alternative**
  the alternative case definition (default greater)

- **seed**
  the random number seed.

- **cluster_analysis**
  if the cluster analysis is conducted.

- **call**
  the call of the function (default NULL).

- **cluster_function**
  a function to cluster baskets
See Also

cluster_membership

Examples

# 3 baskets, each with enrollement size 5
trial_sizes <- rep(5, 3)

# The response rates for the baskets.
resp_rate <- 0.15

# The trials: a column of the number of responses and a column of the
# the size of each trial.
trials <- data.frame(
  responses = rbinom(trial_sizes, trial_sizes, resp_rate),
  size = trial_sizes,
  name = letters[1:3]
)

summary(mem_exact(trials$responses, trials$size, trials$name))
call = NULL,
cluster_function = cluster_membership
)

Arguments

responses  the number of responses in each basket.
size      the size of each basket.
name      the name of each basket.
p0        the null response rate for the posterior probability calculation (default 0.15).
shape1    the first shape parameter(s) for the prior of each basket (default 0.5).
shape2    the second shape parameter(s) for the prior of each basket (default 0.5).
prior     the matrix giving the prior inclusion probability for each pair of baskets. The default is on the main diagonal and 0.5 elsewhere.
hpd_alpha the highest posterior density trial significance.
alternative the alternative case definition (default greater)
mcmc_iter the number of MCMC iterations.
mcmc_burnin the number of MCMC Burn_in iterations.
initial_mem the initial MEM matrix.
seed      the random number seed.
cluster_analysis
           if the cluster analysis is conducted.
call      the call of the function.
cluster_function
           a function to cluster baskets

Examples

# 3 baskets, each with enrollment size 5
trial_sizes <- rep(5, 3)

# The response rates for the baskets.
resp_rate <- 0.15

# The trials: a column of the number of responses and a column of the # the size of each trial.
trials <- data.frame(
    responses = rbinom(trial_sizes, trial_sizes, resp_rate),
    size = trial_sizes,
    name = letters[1:3]
)
res <- mem_mcmc(trials$response, trials$size)
plot_density

Plot the Response Densities in Basket Trials

Description
The MEM analysis calculates the probability of exchangeability of baskets and clusters in a basket trial. This function creates density plots of the response rates of each basket or each cluster under the MEM design taking into account the extent to which power can be borrowed from similar trials.

Usage
plot_density(x, ...)

Arguments
x the exchangeability model.
...
other options. See Details for more information.

Details
The ... options can be used to specify the colors of the response density plot or, when plotting an object of class `exchangeability_model` the type can be specified. In this case, the default is `type = c("both", "basket", "cluster")`.

Examples
# Create an MEM analysis of the Vemurafenib trial data.
data(vemu_wide)

mem_analysis <- mem_exact(
  vemu_wide$responders,
  vemu_wide$evaluable,
  vemu_wide$baskets
)

plot_density(mem_analysis)
Description

The Maximum A Posteriori Probability (MAP) of an MEM is the estimate of the exchangeability structure of a basket trial. This function visualizes this matrix as an exchangeogram.

Usage

```
plot_map(x, ...)
```

Arguments

- `x` basket element of the exchangeability model.
- `...` other options passed to ggplot2 to alter the visual

Details

The `plot_map` function attempts to place the basket names to the left of the main diagonal in a way that makes it easy to read. However, for especially long basket names options are provided. Here is a list of all options available to “fine tune” the visualizations. These auxiliary options include:

- `[palette]` A color palette consisting of 3 colors: the first corresponds to a low degree of exchangeability, the second to 50 exchangeability, and the third to a high degree of exchangeability. Interpolation between these colors is performed for intermediary degrees of exchangeability.
- `[text_color]` A text string setting the color of the exchangeability values printed on the plot. (Default "white")
- `[tile_color]` A text string setting the color of the edges of the tiles. (Default "white")
- `[expand]` The proportion to expand the viewport (Default `expand = c(0.3, 0.3)`)
- `[text_size]` The text size. (Default 4)
- `[legend_position]` The legend position. (Default `legend_position = c(0.25, 0.8)`)
- `[draw_legend]` Should the legend be drawn? (Default TRUE)
- `[basket_name_hoffset]` The horizontal offset of the basket names. (Default 0)
- `[basket_name_hjust]` The basket name justification. (Default 1 - right justified)

Examples

```r
# Create an MEM analysis of the Vemurafenib trial data.
data(vemu_wide)
mem_analysis <- mem_exact(
vemu_wide$responders,
```

```r
plot_map(mem_analysis)
```
plot_mem

Plot the Prior, MAP, and PEP of a Basket Trial

Description

: Plot the Prior, MAP, and PEP Matrices

Usage

plot_mem(x, type = c("prior", "map", "pep"), ...)

Arguments

x the exchangeability model.

Arguments

plot_pep

Plot the Posterior Exchangeability of a Basket Trial

Description

The posterior exchangeability of the baskets in a MEM analysis can be visualized via an exchangeogram using this function.

Usage

plot_pep(x, ...)

Arguments

x basket element of the exchangeability model.

... other options passed to ggplot2 to alter the visual characteristics of the plot. See Details for more information.
Details

The `plot_pep` function attempts to place the basket names to the left of the main diagonal in a way that makes it easy to read. However, for especially long basket names options are provided. Here is a list of all options available to “fine tune” the visualizations. These auxiliary options include:

- `[palette]` A color palette consisting of 3 colors: the first corresponds to a low degree of exchangeability, the second to 50 exchangeability, and the third to a high degree of exchangeability. Interpolation between these colors is performed for intermediary degrees of exchangeability. 
- `[text_color]` A text string setting the color of the exchangeability values printed on the plot. (Default “white”) 
- `[tile_color]` A text string setting the color of the edges of the tiles. (Default `RColorBrewer::brewer.pal(3,"BuGn")`) 
- `[expand]` The proportion to expand the viewport (Default `expand = c(0.3, 0.3)`) 
- `[text_size]` The text size. (Default `4`) 
- `[legend_position]` The legend position. (Default `legend_position = c(0.25, 0.8)`) 
- `[draw_legend]` Should the legend be drawn? (Default `TRUE`) 
- `[basket_name_hoffset]` The horizontal offset of the basket names. (Default `0`) 
- `[basket_name_hjust]` The basket name justification. (Default `1 - right justified`) 

Examples

```r
# Create an MEM analysis of the Vemurafenib trial data.
data(vemu_wide)
mem_analysis <- mem_exact(
  vemu_wide$responders,
  vemu_wide$evaluable,
  vemu_wide$baskets
)
plot_pep(mem_analysis$basket)
```

Description

Plot a Network Graph of the PEP Matrix

Usage

```r
plot_pep_graph(x,
  color_by = c("post_prob", "mean_est", "median_est"),
  layout = c("fr", "nicely", "kk", "drl"),
  pep_cutoff = 0
)
```
Sample Posterior Samples from a Basket Trial

Description
Sample Posterior Samples from a Basket Trial

Usage
sample_posterior(model, num_samples = 10000)

Arguments
model the exchangeability model
num_samples the number of samples to draw. Default 10000

Examples

# 3 baskets, each with enrollement size 5
trial_sizes <- rep(5, 3)

# The response rates for the baskets.
resp_rate <- 0.15
# The trials: a column of the number of responses and a column of the
# size of each trial.
trials <- data.frame(  
  responses = rbinom(trial_sizes, trial_sizes, resp_rate),  
  size = trial_sizes,  
  name = paste("Basket", seq_len(3))  
)

update_p0  # Update Full Bayes results with different p0 values

## Description
After running either ‘mem_mcmc’ or ‘mem_exact’, the test can be updated without rerunning the entire analysis. This function provides updating of both the null response rate along with the alternative rerunning relevant test.

## Usage
update_p0(res, p0 = 0.15, alternative = "greater")

## Arguments
- res: the result of an mem analysis.
- p0: the null response rate for the posterior probability calculation (default 0.15).
- alternative: the alternative case definition (default greater)

## Examples
```r
## Not run:  
# Create an MEM analysis of the Vemurafenib trial data.  
data(vemu_wide)

mem_analysis <- mem_exact(  
  vemu_wide$response,  
  vemu_wide$evaluable,  
  vemu_wide$baskets  
)

# Update the null from p0 = 0.15 the default, to p = 0.25.  
update_p0(mem_analysis, 0.20)

## End(Not run)
```
Summary Data from the Vemurafenib Study

Description

The ‘vemu’ and ‘vemu_wide’ data sets provides response information taken from the “Vemurafenib in multiple nonmelanoma cancers with BRAF v600 mutations” study where, in total, 18 responders were observed among the 84 patients contributing evaluable outcomes for statistical estimation. Observed response rates varied from $42\%$ and $43\%$ for baskets of NSCLC and ECD or LCH to 0 and $4\%,$ for CRC with vemurafenib mono and combination therapies, respectively. Two responders of seven patients, ATC was associated with a $29\%$ response rate, while one responder of eight patients was observed in the cholangiocarcinoma basket. Contrasting favorable results for preliminary vemurafenib activity among NSCLC and ECD or LCH patients with less favorable results for CRC patients, the authors concluded that nonmelanoma tumor types harboring $BRAF^V600$ mutations failed to respond uniformly to BRAF-targeted therapy giving credence to more conventional organ-specific nosology when compared to molecular tumor nosology.

Later, in the “Statistical challenges posed by basket trials: sensitivity analysis of the Vemurafenib study” it was shown that patient-enrollment types we likely drove the negative results for several targets, rather than Vemurafenib itself.

References

Index

basket, 3
basket-package, 2
basket_map, 5
basket_name, 6
basket_pep, 7

cluster_baskets, 7
cluster_map, 8
cluster_membership, 9
cluster_pep, 10

get_seed, 10

mem_exact, 11
mem_mcmc, 12

plot_density, 14
plot_map, 15
plot_mem, 16
plot_pep, 16
plot_pep_graph, 17

sample_posterior, 18

update_p0, 19

vemu, 20
vemu_wide (vemu), 20