Package 'GFDrmst'

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Type Package

Title Multiple RMST-Based Tests in General Factorial Designs

Version 0.1.0

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Description

We implemented multiple tests based on the restricted mean survival time (RMST) for general factorial designs as described in Munko et al. (2024) <doi:10.1002/sim.10017>. Therefore, an asymptotic test, a groupwise bootstrap test, and a permutation test are incorporated with a Wald-type test statistic. The asymptotic and groupwise bootstrap test take the asymptotic exact dependence structure of the test statistics into account to gain more power. Furthermore, confidence intervals for RMST contrasts can be calculated and plotted and a stepwise extension that can improve the power of the multiple tests is available.

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Encoding UTF-8

Suggests condSURV

Imports GFDmcv, lpSolve, shinyWidgets, shinyMatrix, shiny (>= 1.5.0), tippy (>= 0.1.0), mvtnorm, MASS (>= 7.3-53), plyr (>= 1.8.6), shinyjs (>= 2.0.0), shinythemes (>= 1.1.2)

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GFDrmstGUI	*A Shiny app for multiple RMST-based tests*

Description

This function provides a shiny app for performing multiple RMST-based tests. Here, the asymptotic, groupwise bootstrap or permutation test can be applied.

Usage

```
GFDrmstGUI()
```

Details

Note that the calculations for the groupwise bootstrap and the permutation test may take a while, especially with stepwise extension.

Value

No return value, called for side effects.

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plot.GFDrmst	*Plot simultaneous confidence intervals for a* GFDrmst *object*

Description

Simultaneous confidence intervals for the linear combinations of restricted mean survival times are plotted.

Usage

```
## S3 method for class 'GFDrmst'
plot(x, ...)
```

Arguments

x   An object of class "GFDrmst", usually a result of a call to RMST.test.

...   Further arguments are ignored.

Details

The displayed vectors on the y-axis are the coefficients $\mathbf{H}_\ell$ for the linear combinations of the RMSTs.

Value

No return value, called for side effects.

See Also

[RMST.test](#)

Examples

```
data(colonCS, package = "condSURV")

out <- RMST.test(formula = "Stime ~ rx",
                 event = "event",
                 data = colonCS,
                 hyp_mat = "Tukey",
                 tau = 3000,
                 method = "asymptotic")
plot(out)
```

RMST.test   *Function to perform multiple RMST-based tests*

Description

Linear hypotheses of the restricted mean survival times (RMSTs) of k different groups can be tested simultaneously. Therefore, the multivariate distribution of local Wald-type test statistics is approximated by (1) estimating the covariance between the test statistics (method = "asymptotic"), (2) a groupwise bootstrap procedure (method = "groupwise") or (3) a permutation approach (method = "permutation"), respectively. Hence, adjusted p-values can be obtained.

Usage

```
RMST.test(
  time = NULL,
  status = NULL,
  group = NULL,
  formula = NULL,
  event = NULL,
  data = NULL,
  hyp_mat,
  hyp_vec = NULL,
  tau,
  method = c("groupwise", "permutation", "asymptotic"),
  stepwise = FALSE,
  alpha = 0.05,
  Nres = 4999,
  seed = 1
)
```

Arguments

time	A vector containing the observed event times. Default option is NULL. Either time, status, group or formula, event, data needs to be specified.
status	A vector of the same length as time containing the corresponding censoring status indicator with values 0 = censored and 1 = uncensored. Default option is NULL. Either time, status, group or formula, event, data needs to be specified.
group	A vector of the same length as time containing the corresponding group labels. Default option is NULL. Either time, status, group or formula, event, data needs to be specified.
formula	A model formula object. The left hand side contains the time variable and the right hand side contains the factor variables of interest. Default option is NULL. Either time, status, group or formula, event, data needs to be specified.
event	The name of censoring status indicator with values 0 = censored and 1 = uncensored. Default option is NULL. Either time, status, group or formula, event, data needs to be specified.
data	A data.frame or list containing the variables in formula and the censoring status indicator. Default option is NULL. Either time, status, group or formula, event, data needs to be specified.
hyp_mat	A list containing all the hypothesis matrices H for the multiple tests or one of the options "Tukey", "Dunnett" and "center" for Tukey's or Dunnett's contrasts or the centering matrix, respectively, or a matrix if only one hypothesis is of interest. For the permutation test, all matrices need to be contrast matrices.
hyp_vec	A list containing all the hypothesis vectors c for the multiple tests or a vector if only one hypothesis is of interest. By default (NULL), all hypothesis vectors are set to zero vectors of suitable length.
tau	A numeric value specifying the end of the relevant time window for the analysis. Default option is NULL.
method	One of the methods "groupwise", "permutation" and "asymptotic" that should be used for calculating the critical values. Default option is "groupwise".
stepwise	A logical vector indicating whether a stepwise extension of the test should be performed. If TRUE, no confidence intervals can be computed for the linear combinations but it may be that more tests can reject. Default option is FALSE.
alpha	A numeric value specifying the global level of significance. Default option is 0.05.
Nres	The number of random variables to approximate the limiting distribution. This is only used if at least one hypothesis matrix is not a row vector. The default option is 4999.
seed	A single value, interpreted as an integer, for providing reproducibility of the results or NULL if reproducibility is not wanted. Default option is 1.

Details

The restricted mean survival time (RMST) of group i is defined as

$$\mu_i := \int\limits_0^\tau S_i(t)\mathrm{d}t$$

for all $i \in \{1, ..., k\}$, where S_i denotes the survival function of group i. Let

$$\boldsymbol{\mu} := (\mu_1, ..., \mu_k)'$$

be the vector of the RMSTs and

$$\widehat{\boldsymbol{\mu}} := (\widehat{\mu}_1, ..., \widehat{\mu}_k)'$$

be the vector of their estimators. Let $\mathbf{H}_\ell \in \mathbb{R}^{r_\ell \times k}$ with $\mathrm{rank}(\mathbf{H}_\ell) > 0$ and $\mathbf{c}_\ell \in \mathbb{R}^{r_\ell}$ for all $\ell \in \{1, ..., L\}$. We are considering the multiple testing problem with null and alternative hypotheses

$$\mathcal{H}_{0,\ell} : \mathbf{H}_\ell \boldsymbol{\mu} = \mathbf{c}_\ell \quad \text{vs.} \quad \mathcal{H}_{1,\ell} : \mathbf{H}_\ell \boldsymbol{\mu} \neq \mathbf{c}_\ell, \qquad \text{for } \ell \in \{1, ..., L\}.$$

If stepwise = TRUE, the closed testing procedure is applied. In this case, no confidence intervals can be computed for the linear combinations but it may be that more tests can reject.

Note that the calculations for the groupwise bootstrap and the permutation test may take a while, especially with stepwise extension.

Value

A list of class GFDrmst containing the following components:

method	A character containing the method which has been used.
test_stat	A numeric vector containing the calculated Wald-type test statistics for the local hypotheses.
p.value	A numeric vector containing the adjusted p-values for the local hypotheses.
res	A list containing the results of the multiple tests including the hypothesis matrices, estimators of the linear combinations of RMSTs, potentially confidence intervals for the linear combinations (if all matrices are row vectors and stepwise = FALSE), Wald-type test statistics, critical values and the test decisions.
alpha	A numeric value containing the global level of significance.

References

Munko, M., Ditzhaus, M., Dobler, D., Genuneit, J. (2024). RMST-based multiple contrast tests in general factorial designs. Statistics in Medicine, 1-18. doi:10.1002/sim.10017

Examples

```
data(colonCS, package = "condSURV")

# multiple asymptotic tests
out <- RMST.test(formula = "Stime ~ rx",
```

```
                          event = "event",
                          data = colonCS,
                          hyp_mat = "Tukey",
                          tau = 3000,
                          method = "asymptotic")
summary(out)
plot(out)
## or, equivalently,
out <- RMST.test(time = colonCS$Stime,
                          status = colonCS$event,
                          group = colonCS$rx,
                          hyp_mat = "Tukey",
                          tau = 3000,
                          method = "asymptotic")
summary(out)
plot(out)


# multiple groupwise bootstrap tests
# this may take a few seconds
out_gw <- RMST.test(formula = "Stime ~ rx",
                          event = "event",
                          data = colonCS,
                          hyp_mat = "Tukey",
                          tau = 3000,
                          method = "groupwise")
summary(out_gw)
plot(out_gw)

# multiple permutation tests
# this may take a few seconds
out_perm <- RMST.test(formula = "Stime ~ rx",
                          event = "event",
                          data = colonCS,
                          hyp_mat = "Tukey",
                          tau = 3000,
                          method = "permutation")
summary(out_perm)
plot(out_perm)
```

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summary.GFDrmst   *Summarizing RMST-based multiple testing output*

Description

summary method for class "GFDrmst".

Usage

```
## S3 method for class 'GFDrmst'
summary(object, digits = 8,...)
```

Arguments

`object`	An object of class `"GFDrmst"`, usually a result of a call to [RMST.test]().
`digits`	An integer indicating the number of decimal places to be used. Default option is 8.
`...`	Further arguments are ignored.

Details

The function prints the information about the used method, significance level, hypothesis matrices, Wald-type test statistics, adjusted p-values and the overall results of the tests.

Value

No return value, called for side effects.

See Also

[RMST.test]()

Examples

```
data(colonCS, package = "condSURV")

out <- RMST.test(formula = "Stime ~ rx",
                 event = "event",
                 data = colonCS,
                 hyp_mat = "Tukey",
                 tau = 3000,
                 method = "asymptotic")
summary(out, digits = 3)
```

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