

# Package ‘BuyseTest’

March 3, 2020

**Type** Package

**Title** Generalized Pairwise Comparisons

**Version** 1.8.5

**Date** 2020-03-03

**Description** Implementation of the Generalized Pairwise Comparisons (GPC) as defined in Buyse (2010) <doi:10.1002/sim.3923> for complete observations, and extended in Peron (2018) <doi:10.1177/0962280216658320> to deal with right-censoring. GPC compare two groups of observations (intervention vs. control group) regarding several prioritized endpoints to estimate the probability that a random observation drawn from one group performs better than a random observation drawn from the other group. The net benefit and win ratio statistics, i.e. the difference and ratio between the probabilities relative to the intervention and control groups, can then be estimated. Confidence intervals and p-values are obtained using permutations, a non-parametric bootstrap, or the asymptotic theory. The software enables the use of thresholds of minimal importance difference, stratification, non-prioritized endpoints (O'Brien test), and corrections to deal with missing values.

**License** GPL-3

**Encoding** UTF-8

**URL** <https://github.com/bozenne/BuyseTest>

**BugReports** <https://github.com/bozenne/BuyseTest/issues>

**Depends** R (>= 2.10), Rcpp

**Imports** data.table, doParallel, foreach, methods, lava, parallel, prodlim, stats, stats4, utils

**Suggests** cvAUC, pbapply, pROC, R.rsp, riskRegression, survival, testthat

**LinkingTo** Rcpp, RcppArmadillo

**SystemRequirements** C++11

**VignetteBuilder** R.rsp

**NeedsCompilation** yes

**RoxygenNote** 6.1.1

**Collate** '0-onLoad.R' '1-setGeneric.R' 'BuyseRes-object.R'  
 'BuyseRes-coef.R' 'BuyseRes-confint.R' 'BuyseRes-iid.R'  
 'BuyseRes-summary.R' 'BuyseRes\_get.R' 'BuyseRes\_show.R'  
 'BuyseSim-object.R' 'BuyseSim-summary.R' 'BuyseSim\_show.R'  
 'BuyseTest-check.R' 'BuyseTest-inference.R'  
 'BuyseTest-initialization.R' 'BuyseTest-package.R'  
 'BuyseTest-print.R' 'BuyseTest.R' 'BuyseTest.options-object.R'  
 'BuyseTest.options.R' 'PairScore.R' 'RcppExports.R' 'auc.R'  
 'constStrata.R' 'discreteRoot.R' 'powerBuyseTest.R'  
 'prodlim-iid.R' 'simBuyseTest.R' 'simCompetingRisks.R'  
 'valid.R'

**Author** Brice Ozenne [aut, cre] (<<https://orcid.org/0000-0001-9694-2956>>),  
 Julien Peron [ctb],  
 Eva Cantagallo [aut]

**Maintainer** Brice Ozenne <[brice.mh.ozenne@gmail.com](mailto:brice.mh.ozenne@gmail.com)>

**Repository** CRAN

**Date/Publication** 2020-03-03 12:20:06 UTC

**R topics documented:**

BuyseTest-package . . . . .	3
auc . . . . .	4
boot2pvalue . . . . .	5
BuyseRes-class . . . . .	7
BuyseRes-coef . . . . .	7
BuyseRes-confint . . . . .	8
BuyseRes-show . . . . .	10
BuyseRes-summary . . . . .	10
BuyseSim-class . . . . .	13
BuyseSim-show . . . . .	13
BuyseSim-summary . . . . .	14
BuyseTest . . . . .	15
BuyseTest.options . . . . .	21
BuyseTest.options-class . . . . .	22
BuyseTest.options-methods . . . . .	23
coef.BuyseTestAuc . . . . .	23
confint.BuyseTestAuc . . . . .	24
constStrata . . . . .	24
discreteRoot . . . . .	25
getCount . . . . .	26
getPairScore . . . . .	27
getSurvival . . . . .	29
GPC_cpp . . . . .	30
iid . . . . .	32
iidProdlim . . . . .	33

<i>BuyseTest</i> -package	3
powerBuyseTest . . . . .	34
simCompetingRisks . . . . .	35
Simulation function . . . . .	37
<b>Index</b>	<b>40</b>

---

BuyseTest-package	<i>BuyseTest</i> package: <i>Generalized Pairwise Comparisons</i>
-------------------	---

---

## Description

Implementation of the Generalized Pairwise Comparisons. `BuyseTest` is the main function of the package. See the vignette of an overview of the functionalities of the package. Run `citation("BuyseTest")` in R for how to cite this package in scientific publications. See the section reference below for examples of application in clinical studies.

## Details

The Generalized Pairwise Comparisons form all possible pairs of observations, one observation being taken from the intervention group and the other is taken from the control group, and compare the value of their endpoints.

If the difference in endpoint value between the two observations of the pair is greater than the threshold of clinical relevance, the pair is classified as favorable (i.e. win). If the difference is lower than minus the threshold of clinical relevance the pair is classified as unfavorable (i.e. loss). Otherwise the pair is classified as neutral. In presence of censoring, it might not be possible to compare the difference to the threshold. In such cases the pair is classified as uninformative.

Simultaneously analysis of several endpoints is performed by prioritizing the endpoints, assigning the highest priority to the endpoint considered the most clinically relevant. The endpoint with highest priority is analyzed first, and neutral and uninformative pair are analyzed regarding endpoint of lower priority.

## References

Examples of application in clinical studies:

J. Peron, P. Roy, K. Ding, W. R. Parulekar, L. Roche, M. Buyse (2015). **Assessing the benefit-risk of new treatments using generalized pairwise comparisons: the case of erlotinib in pancreatic cancer.** *British journal of cancer* 112:(6)971-976.

J. Peron, P. Roy, T. Conroy, F. Desseigne, M. Ychou, S. Gourgou-Bourgade, T. Stanbury, L. Roche, B. Ozenne, M. Buyse (2016). **An assessment of the benefit-risk balance of FOLFIRINOX in metastatic pancreatic adenocarcinoma.** *Oncotarget* 7:82953-60, 2016.

Comparison between the net benefit and alternative measures of treatment effect:

J. Peron, P. Roy, B. Ozenne, L. Roche, M. Buyse (2016). **The net chance of a longer survival as a patient-oriented measure of benefit in randomized clinical trials.** *JAMA Oncology* 2:901-5.

E. D. Saad , J. R. Zalberg, J. Peron, E. Coart, T. Burzykowski, M. Buyse (2018). **Understanding and communicating measures of treatment effect on survival: can we do better?.** *J Natl Cancer Inst.*

---

 auc

*Estimation of the Area Under the ROC Curve*


---

### Description

Estimation of the Area Under the ROC curve, possibly after cross validation, to assess the discriminant ability of a biomarker regarding a disease status.

### Usage

```
auc(labels, predictions, fold = NULL, observation = NULL,
     direction = ">", null = 0.5, conf.level = 0.95,
     transformation = FALSE)
```

### Arguments

labels	[integer/character vector] the disease status (should only take two different values).
predictions	[numeric vector] A vector with the same length as labels containing the biomarker values.
fold	[character/integer vector] If using cross validation, the index of the fold. Should have the same length as labels.
observation	[integer vector] If using cross validation, the index of the corresponding observation in the original dataset. Necessary to compute the standard error when using cross validation.
direction	[character] ">" lead to estimate $P[Y>X]$ , "<" to estimate $P[Y<X]$ , and "auto" to estimate $\max(P[Y>X], P[Y<X])$ .
null	[numeric, 0-1] the value against which the AUC should be compared when computing the p-value.
conf.level	[numeric, 0-1] the confidence level of the confidence intervals.
transformation	[logical] should a log-log transformation be used when computing the confidence intervals and the p-value.

### Details

Compared to other functions computing the AUC (e.g. the auc function of the ROCR package), the AUC is defined here as  $P[Y>X]$  with a strict inequality sign (i.e. not  $P[Y\geq X]$ ).

### Value

A *data.frame* containing for each fold the AUC value with its standard error (when computed). The last line of the data.frame contains the global AUC value with its standard error.

## References

Erin LeDell, Maya Petersen, and Mark van der Laan (2015). **Computationally efficient confidence intervals for cross-validated area under the ROC curve estimates.** *Electron J Stat.* 9(1):1583–1607.

## Examples

```
library(data.table)

n <- 200
set.seed(10)
X <- rnorm(n)
dt <- data.table(Y = as.factor(rbinom(n, size = 1, prob = 1/(1+exp(1/2-X)))),
                 X = X,
                 fold = unlist(lapply(1:10,function(iL){rep(iL,n/10)})))

## compute auc
auc(labels = dt$Y, predictions = dt$X, direction = ">")

## compute auc after 10-fold cross-validation
auc(labels = dt$Y, prediction = dt$X, fold = dt$fold, observation = 1:NROW(dt))
```

---

boot2pvalue

---

*Compute the p.value from the distribution under H1*


---

## Description

Compute the p.value associated with the estimated statistic using a bootstrap sample of its distribution under H1.

## Usage

```
boot2pvalue(x, null, estimate = NULL, alternative = "two.sided",
            FUN.ci = quantileCI, checkSign = TRUE,
            tol = .Machine$double.eps^0.5)
```

## Arguments

x	[numeric vector] a vector of bootstrap estimates of the statistic.
null	[numeric] value of the statistic under the null hypothesis.
estimate	[numeric] the estimated statistic.
alternative	[character] a character string specifying the alternative hypothesis, must be one of "two.sided" (default), "greater" or "less".
FUN.ci	[function] the function used to compute the confidence interval. Must take x, alternative, conf.level and sign.estimate as arguments and only return the relevant limit (either upper or lower) of the confidence interval.

checkSign	[logical] should a warning be output if the sign of the estimate differs from the sign of the mean bootstrap value?
tol	[numeric] the absolute convergence tolerance.

## Details

For test statistic close to 0, this function returns 1.

For positive test statistic, this function search the quantile alpha such that:

- $\text{quantile}(x, \text{probs} = \alpha) = 0$  when the argument alternative is set to "greater".
- $\text{quantile}(x, \text{probs} = 0.5 * \alpha) = 0$  when the argument alternative is set to "two.sided".

If the argument alternative is set to "less", it returns 1.

For negative test statistic, this function search the quantile alpha such that:

- $\text{quantile}(x, \text{probs} = 1 - \alpha) = 0$  when the argument alternative is set to "less".
- $\text{quantile}(x, \text{probs} = 1 - 0.5 * \alpha) = 0$  when the argument alternative is set to "two.sided".

If the argument alternative is set to "greater", it returns 1.

## Examples

```
set.seed(10)

#### no effect ####
x <- rnorm(1e3)
boot2pvalue(x, null = 0, estimate = mean(x), alternative = "two.sided")
## expected value of 1
boot2pvalue(x, null = 0, estimate = mean(x), alternative = "greater")
## expected value of 0.5
boot2pvalue(x, null = 0, estimate = mean(x), alternative = "less")
## expected value of 0.5

#### positive effect ####
x <- rnorm(1e3, mean = 1)
boot2pvalue(x, null = 0, estimate = 1, alternative = "two.sided")
## expected value of 0.32 = 2*pnorm(q = 0, mean = -1) = 2*mean(x<=0)
boot2pvalue(x, null = 0, estimate = 1, alternative = "greater")
## expected value of 0.16 = pnorm(q = 0, mean = 1) = mean(x<=0)
boot2pvalue(x, null = 0, estimate = 1, alternative = "less")
## expected value of 0.84 = 1-pnorm(q = 0, mean = 1) = mean(x>=0)

#### negative effect ####
x <- rnorm(1e3, mean = -1)
boot2pvalue(x, null = 0, estimate = -1, alternative = "two.sided")
## expected value of 0.32 = 2*(1-pnorm(q = 0, mean = -1)) = 2*mean(x>=0)
boot2pvalue(x, null = 0, estimate = -1, alternative = "greater")
```

```
## expected value of 0.84 = pnorm(q = 0, mean = -1) = mean(x<=0)
boot2pvalue(x, null = 0, estimate = -1, alternative = "less") # pnorm(q = 0, mean = -1)
## expected value of 0.16 = 1-pnorm(q = 0, mean = -1) = mean(x>=0)
```

---

BuyseRes-class	<i>Class "BuyseRes" (output of BuyseTest)</i>
----------------	---

---

### Description

A [BuyseTest](#) output is reported in a BuyseRes object.

### Author(s)

Brice Ozenne

### See Also

[BuyseTest](#) for the function computing generalized pairwise comparisons.  
[BuyseRes-summary](#) for the summary of the BuyseTest function results

---

BuyseRes-coef	<i>Coef Method for Class "BuyseRes"</i>
---------------	---

---

### Description

Extract summary statistics from the result of a [BuyseTest](#) function.

### Usage

```
## S4 method for signature 'BuyseRes'
coef(object, statistic = NULL, stratified = FALSE,
      cumulative = TRUE, ...)
```

### Arguments

object	output of <a href="#">BuyseTest</a>
statistic	[character] the type of summary statistic. See the detail section.
stratified	[logical] should the summary statistic be strata-specific? Otherwise a summary statistic over all strata is returned.
cumulative	[logical] should the score be cumulated over endpoints? Otherwise display the contribution of each endpoint.
...	ignored.

## Details

One of the following statistic can be specified:

- "netBenefit": returns the net benefit.
- "winRatio": returns the win ratio.
- "count.favorable": returns the number of pairs in favor of the treatment.
- "count.unfavorable": returns the number of pairs in favor of the control.
- "count.neutral": returns the number of neutral pairs.
- "count.uninf": returns the number of uninformative pairs.
- "pc.favorable": returns the percentage of pairs in favor of the treatment, i.e.  $P[X \geq Y + \tau]$ .
- "pc.unfavorable": returns the percentage of pairs in favor of the control, i.e.  $P[Y \geq X + \tau]$ .
- "pc.neutral": returns the percentage of neutral pairs.
- "pc.uninf": returns the percentage of uninformative pairs.

## Author(s)

Brice Ozenne

---

BuyseRes-confint

*Confidence Intervals for Model Parameters*

---

## Description

Computes confidence intervals for net benefit statistic or the win ratio statistic.

## Usage

```
## S4 method for signature 'BuyseRes'
confint(object, statistic = NULL,
        conf.level = NULL, alternative = NULL, method.ci.resampling = NULL,
        order.Hprojection = NULL, transformation = NULL, cluster = NULL)
```

## Arguments

object	an R object of class <code>BuyseRes</code> , i.e., output of <code>BuyseTest</code>
statistic	[character] the statistic summarizing the pairwise comparison: "netBenefit" displays the net benefit, as described in Buyse (2010) and Peron et al. (2016)), whereas "winRatio" displays the win ratio, as described in Wang et al. (2016). Default value read from <code>BuyseTest.options()</code> .
conf.level	[numeric] confidence level for the confidence intervals. Default value read from <code>BuyseTest.options()</code> .
alternative	[character] the type of alternative hypothesis: "two.sided", "greater", or "less". Default value read from <code>BuyseTest.options()</code> .



<code>method.ci.resampling</code>	[character] the method used to compute the confidence intervals and p-values when using bootstrap or permutation. "percentile" uses the quantiles of the empirical distribution, "gaussian" uses the quantiles of a Gaussian distribution, and "student" uses the quantiles of a Student's t-distribution (only available for bootstrap).
<code>order.Hprojection</code>	[integer, 1-2] order of the H-decomposition used to compute the variance.
<code>transformation</code>	[logical] should the CI be computed on the logit scale / log scale for the net benefit / win ratio and backtransformed. Otherwise they are computed without any transformation. Default value read from <code>BuyseTest.options()</code> . Not relevant when using permutations or percentile bootstrap.
<code>cluster</code>	[numeric vector] Group of observations for which the iid assumption holds .

### Details

When using a permutation test, the uncertainty associated with the estimator is computed under the null hypothesis. Thus the confidence interval may not be valid if the null hypothesis is false. More precisely, the quantiles of the distribution of the statistic are computed under the null hypothesis and then shifted by the point estimate of the statistic.

### Value

A matrix containing a column for the estimated statistic (over all strata), the lower bound and upper bound of the confidence intervals, and the associated p-values. When using resampling methods:

- an attribute `n.resampling` specified how many samples have been used to compute the confidence intervals and the p-values.
- an attribute `method.ci.resampling` method used to compute the confidence intervals and p-values.

### Author(s)

Brice Ozenne

### See Also

[BuyseTest](#) for performing a generalized pairwise comparison.  
[BuyseRes-summary](#) for a more detailed presentation of the `BuyseRes` object.

BuyseRes-show

*Show Method for Class "BuyseRes"*

---

**Description**

Display the main results stored in a [BuyseRes](#) object.

**Usage**

```
## S4 method for signature 'BuyseRes'  
show(object)
```

**Arguments**

object            an R object of class [BuyseRes](#), i.e., output of [BuyseTest](#)

**Author(s)**

Brice Ozenne

**See Also**

[BuyseTest](#) for performing a generalized pairwise comparison.  
[BuyseRes-summary](#) for a more detailed presentation of the [BuyseRes](#) object.

---

BuyseRes-summary*Summary Method for Class "BuyseRes"*

---

**Description**

Summarize the results from the [BuyseTest](#) function.

**Usage**

```
## S4 method for signature 'BuyseRes'  
summary(object, print = TRUE, percentage = TRUE,  
  statistic = NULL, conf.level = NULL, strata = if  
  (length(object@level.strata) == 1) { "global" } else { NULL },  
  type.display = 1, digit = c(2, 4, 5), ...)
```

**Arguments**

object	output of <a href="#">BuyseTest</a>
print	[logical] Should the table be displayed?.
percentage	[logical] Should the percentage of pairs of each type be displayed ? Otherwise the number of pairs is displayed.
statistic	[character] the statistic summarizing the pairwise comparison: "netBenefit" displays the net benefit, as described in Buyse (2010) and Peron et al. (2016), whereas "winRatio" displays the win ratio, as described in Wang et al. (2016). Default value read from <code>BuyseTest.options()</code> .
conf.level	[numeric] confidence level for the confidence intervals. Default value read from <code>BuyseTest.options()</code> .
strata	[character vector] the name of the strata to be displayed. Can also be "global" to display the average over all strata.
type.display	[numeric or character] the results/summary statistics to be displayed. Either an integer indicating referring to a type of display in <code>BuyseTest.options()</code> or the name of the column to be output (e.g. <code>c("strata", "Delta", "p.value")</code> ).
digit	[integer vector] the number of digit to use for printing the counts and the delta.
...	arguments to be passed to <a href="#">BuyseRes-confint</a>

**Details****Content of the output**

The "results" table in the output show the result of the GPC at each endpoint, as well as its contribution to the global statistics. More precisely, the column:

- endpoint lists the endpoints, by order of priority.
- threshold lists the threshold associated to each endpoint.
- total lists the total number of pairs to be analyzed at the current priority.
- total(%) lists the total percentage of pairs to be analyzed at the current priority.
- favorable lists the number of pairs classified in favor of the treatment at the current priority.
- favorable(%) lists the number of pairs classified in favor of the treatment at the current priority.
- unfavorable lists the number of pairs classified in favor of the control at the current priority.
- unfavorable(%) lists the percentage of pairs classified in favor of the control at the current priority.
- neutral lists the number of pairs classified as neutral at the current priority.
- neutral(%) lists the percentage of pairs classified as neutral at the current priority.
- uninf lists the number of pairs that could not be classified at the current priority (due to missing values/censoring).
- uninf(%) lists the percentage of pairs that could not be classified at the current priority (due to missing values/censoring).
- delta lists the value of the statistic (i.e. net benefit or win ratio) computed on the pairs analyzed at the current priority only.

- `Delta` lists the value of the statistic (i.e. net benefit or win ratio) computed on all the pairs analyzed up to the current priority.
- `Delta(%)` lists the net benefit or win ratio fraction (i.e. statistic up to the current priority divided by the final statistic).
- `information(%)` lists the information fraction (i.e. number of favorable and unfavorable pairs up to the current priority divided by the final number of favorable and unfavorable pairs).
- `CI` Confidence interval for the value of `Delta` (performed independently at each priority, no adjustment for multiple comparison).
- `p.value` p-value for the test `Delta=0` (performed independently at each priority, no adjustment for multiple comparison).
- `resampling` number of samples used to compute the confidence intervals or p-values from permutations or bootstrap samples. Only displayed if some bootstrap samples have been discarded, for example, they did not lead to sample any case or control.

Note: when using the Peron scoring rule or a correction for uninformative pairs, the columns `total`, `favorable`, `unfavorable`, `neutral`, and `uninf` are computing by summing the contribution of the pairs. This may lead to a decimal value.

### Statistical inference

When the interest is in obtaining p-values, we recommend the use of a permutation test. However, when using a permutation test confidence intervals are not displayed in the summary. This is because there is no (to the best of our knowledge) straightforward way to obtain good confidence intervals with permutations. An easy way consist in using the quantiles of the permutation distribution and then shift by the point estimate of the statistic. This is what is output by `BuyseRes-confint`. However this approach leads to a much too high coverage when the null hypothesis is false. The limits of the confidence interval can also end up being outside of the interval of definition of the statistic (e.g. outside  $[-1,1]$  for the proportion in favor of treatment). Therefore, for obtaining confidence intervals, we recommend the bootstrap method or the u-statistic method.

### Win ratio

For the win ratio, the proposed implementation enables the use of thresholds and endpoints that are not time to events as well as the correction proposed in Peron et al. (2016) to account for censoring. These development have not been examined by Wang et al. (2016), or in other papers (to the best of our knowledge). They are only provided here by implementation convenience.

### Competing risks

In presence of competing risks, looking at the net benefit/win ratio computed with respect to the event of interest will likely not give a full picture of the difference between the two groups. For instance a treatment may decrease the risk of the event of interest (i.e. increase the net benefit for this event) by increasing the risk of the competing event. If the competing event is death, this is not desirable. It is therefore advised to taking into consideration the risk of the competing event, e.g. by re-running `BuyseTest` where cause 1 and 2 have been inverted.

### Author(s)

Brice Ozenne

**See Also**

[BuyseTest](#) for performing a generalized pairwise comparison.  
[BuyseRes-class](#) for a presentation of the BuyseRes object.  
[BuyseRes-confint](#) to output confidence interval and p-values in a matrix format.

**Examples**

```
library(data.table)

dt <- simBuyseTest(1e2, n.strata = 3)

## Not run:
BT <- BuyseTest(treatment ~ TTE(eventtime, status = status) + Bin(toxicity), data=dt)

## End(Not run)

summary(BT)
summary(BT, percentage = FALSE)
summary(BT, statistic = "winRatio")
```

---

BuyseSim-class	<i>Class "BuyseSim" (output of BuyseTest)</i>
----------------	---

---

**Description**

A [powerBuyseTest](#) output is reported in a BuyseSim object.

**Author(s)**

Brice Ozenne

**See Also**

[powerBuyseTest](#) for the function computing generalized pairwise comparisons.  
[BuyseSim-summary](#) for the summary of the BuyseTest function results

---

BuyseSim-show	<i>Show Method for Class "BuyseSim"</i>
---------------	---

---

**Description**

Display the main results stored in a [BuyseSim](#) object.

**Usage**

```
## S4 method for signature 'BuyseSim'
show(object)
```

**Arguments**

object            an R object of class [BuyseSim](#), i.e., output of [BuyseTest](#)

**Author(s)**

Brice Ozenne

**See Also**

[BuyseTest](#) for performing a generalized pairwise comparison.  
[BuyseSim-summary](#) for a more detailed presentation of the [BuyseSim](#) object.

---

BuyseSim-summary

*Summary Method for Class "BuyseSim"*


---

**Description**

Summarize the results from the [powerBuyseTest](#) function.

**Usage**

```
## S4 method for signature 'BuyseSim'
summary(object, print = TRUE, statistic = NULL,
        legend = TRUE, method.inference = NULL, col.rep = TRUE,
        digit = 4)
```

**Arguments**

object            output of [powerBuyseTest](#)

print            [logical] Should the table be displayed?

statistic        [character] the statistic summarizing the pairwise comparison: "netBenefit" displays the net benefit whereas "winRatio" displays the win ratio.

legend           [logical] should explanations about the content of each column be displayed?

method.inference [character vector] for which inference method the rejection rate should be displayed?

col.rep          [logical] should the number of successful simulations be displayed?

digit            [integer vector] the number of digit to use for printing the counts and the delta.

**Author(s)**

Brice Ozenne

**See Also**[powerBuyseTest](#) for performing a simulation study for generalized pairwise comparison.

---

`BuyseTest`*Generalized Pairwise Comparisons (GPC)*

---

**Description**

Performs Generalized Pairwise Comparisons for binary, continuous and time-to-event endpoints.

**Usage**

```
BuyseTest(formula, data, scoring.rule = NULL, correction.uninf = NULL,
  model.tte = NULL, method.inference = NULL, n.resampling = NULL,
  strata.resampling = NULL, hierarchical = NULL, weight = NULL,
  neutral.as.uninf = NULL, keep.pairScore = NULL, seed = 10,
  cpus = NULL, trace = NULL, treatment = NULL, endpoint = NULL,
  type = NULL, threshold = NULL, status = NULL, operator = NULL,
  censoring = NULL, strata = NULL, keep.comparison, method.tte)
```

**Arguments**

<code>formula</code>	[formula] a symbolic description of the GPC model, typically <code>treatment ~ type1(endpoint1) + type2(endpoint2, threshold2) + strata</code> . See Details, section "Specification of the GPC model".
<code>data</code>	[data.frame] dataset.
<code>scoring.rule</code>	[character] method used to compare the observations of a pair in presence of right censoring (i.e. "timeToEvent" endpoints). Can be "Gehan" or "Peron". See Details, section "Handling missing values".
<code>correction.uninf</code>	[integer] should a correction be applied to remove the bias due to the presence of uninformative pairs? 0 indicates no correction, 1 impute the average score of the informative pairs, and 2 performs IPCW. See Details, section "Handling missing values".
<code>model.tte</code>	[list] optional survival models relative to each time to each time to event endpoint. Models must <code>prodlim</code> objects and stratified on the treatment and strata variable. When used, the uncertainty from the estimates of these survival models is ignored.

method.inference	[character] method used to compute confidence intervals and p-values. Can be "none", "u-statistic", "permutation", "bootstrap", "bootstrap", "studentized bootstrap". See Details, section "Statistical inference".
n.resampling	[integer] the number of permutations/samples used for computing the confidence intervals and the p.values. See Details, section "Statistical inference".
strata.resampling	[character] the variable on which the permutation/sampling should be stratified. See Details, section "Statistical inference".
hierarchical	[logical] should only the uninformative pairs be analyzed at the lower priority endpoints (hierarchical GPC)? Otherwise all pairs will be compared for all endpoint (full GPC).
weight	[numeric vector] weights used to cumulating the pairwise scores over the endpoints. Only used when hierarchical=FALSE. Disregarded if the argument formula is defined.
neutral.as.uninf	[logical] should paired classified as neutral be re-analyzed using endpoints of lower priority (as it is done for uninformative pairs). See Details, section "Handling missing values".
keep.pairScore	[logical] should the result of each pairwise comparison be kept?
seed	[integer, >0] the seed to consider for the permutation test. If NULL no seed is set.
cpus	[integer, >0] the number of CPU to use. Only the permutation test can use parallel computation. See Details, section "Statistical inference".
trace	[integer] should the execution of the function be traced ? 0 remains silent and 1-3 correspond to a more and more verbose output in the console.
treatment, endpoint, type, threshold, status, operator, censoring, strata	Alternative to formula for describing the GPC model. See Details, section "Specification of the GPC model".
keep.comparison	Obsolete. Alias for 'keep.pairScore'.
method.tte	Obsolete. Alias for 'scoring.rule'.

## Details

### Specification of the GPC model:

There are two way to specify the GPC model in BuyseTest. A *Formula interface* via the argument formula where the response variable should be a binary variable defining the treatment arms. The rest of the formula should indicate the endpoints by order of priority and the strata variables (if any). A *Vector interface* using the following arguments

- treatment: [character] name of the treatment variable identifying the control and the experimental group. Must have only two levels (e.g. 0 and 1).
- endpoint: [character vector] the name of the endpoint variable(s).
- threshold: [numeric vector] critical values used to compare the pairs (threshold of minimal important difference). There must be one threshold for each endpoint variable; it must be NA for binary endpoints and positive for continuous or time to event endpoints.



- **status:** [character vector] the name of the binary variable(s) indicating whether the endpoint was observed or censored. Must value NA when the endpoint is not a time to event.
- **operator:** [character vector] the sign defining a favorable endpoint. ">0" indicates that higher values are favorable while "<0" indicates the opposite. When the operator is set to "<0" the corresponding column in the dataset is internally multiplied by -1.#'
- **type:** [character vector] indicates whether it is a binary outcome ("b", "bin", or "binary"), a continuous outcome ("c", "cont", or "continuous"), or a time to event outcome ("t", "tte", "time", or "timetoevent")
- **censoring:** [character vector] is the endpoint subject to right or left censoring ("left" or "right"). The default is right-censoring.
- **strata:** [character vector] if not NULL, the GPC will be applied within each group of patient defined by the strata variable(s).

The formula interface can be more concise, especially when considering few outcomes, but may be more difficult to apprehend for new users. Note that arguments endpoint, threshold, status, operator, type, and censoring must have the same length.

### GPC procedure

The GPC procedure form all pairs of observations, one belonging to the experimental group and the other to the control group, and class them in 4 categories:

- *Favorable pair:* the endpoint is better for the observation in the experimental group.
- *Unfavorable pair:* the endpoint is better for the observation in the control group.
- *Neutral pair:* the difference between the endpoints of the two observations is (in absolute value) below the threshold. When  $\text{threshold}=0$ , neutral pairs correspond to pairs with equal endpoint. Lower-priority outcomes (if any) are then used to classified the pair into favorable/unfavorable.
- *Uninformative pair:* censoring/missingness prevents from classifying into favorable, unfavorable or neutral.

With complete data, pairs can be decidedly classified as favorable/unfavorable/neutral. In presence of missing values, the GPC procedure uses the scoring rule (argument `scoring.rule`) and the correction for uninformative pairs (argument `correction.uninf`) to classify the pairs. The classification may not be 0,1, e.g. the probability that the pair is favorable/unfavorable/neutral with the Peron's scoring rule. To export the classification of each pair set the argument `codekeep.pairScore` to TRUE and call the function `getPairScore` on the result of the `BuyseTest` function.

### Handling missing values

- `scoring.rule:` indicates how to handle right-censoring in time to event endpoints. The Gehan's scoring rule (argument `scoring.rule="Gehan"`) only scores pairs that can be decidedly classified as favorable, unfavorable, or neutral while the "Peron"'s scoring rule (argument `scoring.rule="Peron"`) uses the empirical survival curves of each group to also score the

pairs that cannot be decidedly classified. The Peron's scoring rule is the recommended scoring rule but only handles right-censoring.

- `correction.uninf`: indicates how to handle missing values that could not be classified by the scoring rule. `0` treat them as uninformative: if `neutral.as.uninf=FALSE` - this is an equivalent to complete case analysis - while for `neutral.as.uninf=TRUE` uninformative pairs are treated as neutral, i.e., analyzed at the following endpoint (if any). However both will (in general) lead to biased estimates for the proportion of favorable, unfavorable, or neutral pairs. Inverse probability of censoring weights (IPCW, `correction.uninf=2`) is only recommended when the analysis is stopped after the first endpoint with uninformative pairs. Imputing the average score of the informative pairs (`correction.uninf=1`) is the recommended approach. Note that both corrections will convert the whole proportion of uninformative pairs of a given endpoint into favorable, unfavorable, or neutral pairs.

### Statistical inference

The argument `method.inference` defines how to approximate the distribution of the GPC estimators and so how standard errors, confidence intervals, and p-values are computed. Available methods are:

- argument `method.inference="none"`: only the point estimate is computed which makes the execution of the `BuyseTest` faster than with the other methods.
- argument `method.inference="u-statistic"`: uses a Gaussian approximation to obtain the distribution of the GPC estimators. The U-statistic theory indicates that this approximation is asymptotically exact. The variance is computed using a H-projection of order 1 (default option), which is a consistent but downward biased estimator. An unbiased estimator can be obtained using a H-projection of order 2 (only available for the uncorrected Gehan's scoring rule, see `BuyseTest.options`). **WARNING**: the current implementation of the H-projection has not been validated when using corrections for uninformative pairs (`correction.uninf=1`, or `correction.uninf=2`).
- argument `method.inference="permutation"`: perform a permutation test, estimating in each sample the summary statistics (net benefit, win ratio).
- argument `method.inference="bootstrap"`: perform a non-parametric bootstrap, estimating in each sample the summary statistics (net benefit, win ratio).
- argument `method.inference="studentized bootstrap"`: perform a non-parametric bootstrap, estimating in each sample the summary statistics (net benefit, win ratio) and the variance-covariance matrix of the estimator.

Additional arguments for permutation and bootstrap resampling:

- `strata.resampling` If NA or of length 0, the permutation/non-parametric bootstrap will be performed by resampling in the whole sample. Otherwise, the permutation/non-parametric bootstrap will be performed separately for each level that the variable defined in `strata.resampling` take.
- `n.resampling` set the number of permutations/samples used. A large number of permutations (e.g. `n.resampling=10000`) are needed to obtain accurate CI and p.value. See (Buyse et al., 2010) for more details.

- `cpus` indicates whether the resampling procedure can be splitted on several cpus to save time. Can be set to "all" to use all available cpus. The detection of the number of cpus relies on the `detectCores` function from the *parallel* package.

### Default values

The default of the arguments `scoring.rule`, `correction.uninf`, `method.inference`, `n.resampling`, `hierarchical`, `neutral.as.uninf`, `keep.pairScore`, `strata.resampling`, `cpus`, `trace` is read from `BuyseTest.options()`.

Additional (hidden) arguments are

- `alternative` [character] the alternative hypothesis. Must be one of "two.sided", "greater" or "less" (used by `confint`).
- `conf.level` [numeric] level for the confidence intervals (used by `confint`).
- `keep.survival` [logical] export the survival values used by the Peron's scoring rule.
- `order.Hprojection` [1 or 2] the order of the H-projection used to compute the variance when `method.inference="u-statistic"`.

### Value

An R object of class [BuyseRes](#).

### Author(s)

Brice Ozenne

### References

- On the GPC procedure: Marc Buyse (2010). **Generalized pairwise comparisons of prioritized endpoints in the two-sample problem**. *Statistics in Medicine* 29:3245-3257
- On the win ratio: D. Wang, S. Pocock (2016). **A win ratio approach to comparing continuous non-normal outcomes in clinical trials**. *Pharmaceutical Statistics* 15:238-245
- On the Peron's scoring rule: J. Peron, M. Buyse, B. Ozenne, L. Roche and P. Roy (2018). **An extension of generalized pairwise comparisons for prioritized outcomes in the presence of censoring**. *Statistical Methods in Medical Research* 27: 1230-1239
- On the Gehan's scoring rule: Gehan EA (1965). **A generalized two-sample Wilcoxon test for doubly censored data**. *Biometrika* 52(3):650-653
- On inference in GPC using the U-statistic theory: I. Bebu, J. M. Lachin (2015). **Large sample inference for a win ratio analysis of a composite outcome based on prioritized components**. *Biostatistics* 17(1):178-187

### See Also

- [BuyseRes-summary](#) for a summary of the results of generalized pairwise comparison.
- [BuyseRes-class](#) for a presentation of the `BuyseRes` object.
- [constStrata](#) to create a strata variable from several clinical variables.

**Examples**

```

library(data.table)

# reset the default value of the number of permutation sample
BuyseTest.options(method.inference = "none") # no permutation test

#### simulate some data ####
set.seed(10)
df.data <- simBuyseTest(1e2, n.strata = 2)

# display
if(require(prodlim)){
  resKM_tempo <- prodlim(Hist(eventtime,status)~treatment, data = df.data)
  plot(resKM_tempo)
}

#### one time to event endpoint ####
BT <- BuyseTest(treatment ~ TTE(eventtime, status = status), data= df.data)

summary(BT) # net benefit
summary(BT, percentage = FALSE)
summary(BT, statistic = "winRatio") # win Ratio

## bootstrap to compute the CI
## Not run:
  BT <- BuyseTest(treatment ~ TTE(eventtime, status = status), data=df.data,
                  method.inference = "permutation", n.resampling = 1e3)

## End(Not run)

summary(BT, statistic = "netBenefit") ## default
summary(BT, statistic = "winRatio")

## parallel bootstrap
## Not run:
  BT <- BuyseTest(treatment ~ TTE(eventtime, status = status), data=df.data,
                  method.inference = "permutation", n.resampling = 1e3, cpus = 2)
  summary(BT)

## End(Not run)

## method Gehan is much faster but does not optimally handle censored observations
BT <- BuyseTest(treatment ~ TTE(eventtime, status = status), data=df.data,
                scoring.rule = "Gehan", trace = 0)
summary(BT)

#### one time to event endpoint: only differences in survival over 1 unit ####
BT <- BuyseTest(treatment ~ TTE(eventtime, threshold = 1, status = status), data=df.data)
summary(BT)

#### one time to event endpoint with a strata variable
BT <- BuyseTest(treatment ~ strata + TTE(eventtime, status = status), data=df.data)

```

```

summary(BT)

#### several endpoints with a strata variable
f <- treatment ~ strata + T(eventtime, status, 1) + B(toxicity)
f <- update(f,
            ~. + T(eventtime, status, 0.5) + C(score, 1) + T(eventtime, status, 0.25))

BT <- BuyseTest(f, data=df.data)
summary(BT)

#### real example : Veteran dataset of the survival package ####
#### Only one endpoint. Type = Time-to-event. Thresold = 0. Stratfication by histological subtype
#### scoring.rule = "Gehan"

if(require(survival)){
## Not run:
  data(veteran,package="survival")

  ## scoring.rule = "Gehan"
  BT_Gehan <- BuyseTest(trt ~ celltype + TTE(time,threshold=0,status=status),
                       data=veteran, scoring.rule="Gehan",
                       method.inference = "permutation", n.resampling = 1e3)

  summary_Gehan <- summary(BT_Gehan)
  summary_Gehan <- summary(BT_Gehan, statistic = "winRatio")

  ## scoring.rule = "Peron"
  BT_Peron <- BuyseTest(trt ~ celltype + TTE(time,threshold=0,status=status),
                       data=veteran, scoring.rule="Peron",
                       method.inference = "permutation", n.resampling = 1e3)

  class(BT_Peron)
  summary(BT_Peron)

## End(Not run)
}

```

---

BuyseTest.options

*Global options for BuyseTest package*


---

## Description

Update or select global options for the BuyseTest package.

## Usage

```
BuyseTest.options(..., reinitialise = FALSE)
```

## Arguments

... options to be selected or updated  
reinitialise should all the global parameters be set to their default value

## Details

It only affects the [BuyseTest](#) function

## Examples

```
library(data.table)

## see all global parameters
BuyseTest.options()

## see some of the global parameters
BuyseTest.options("n.resampling", "trace")

## update some of the global parameters
BuyseTest.options(n.resampling = 10, trace = 1)
BuyseTest.options("n.resampling", "trace")

## reinitialise all global parameters
BuyseTest.options(reinitialise = TRUE)
```

---

BuyseTest.options-class

*Class "BuyseTest.options" (global setting for the BuyseTest package)*

---

## Description

Class defining the global settings for the BuyseTest package.

## Author(s)

Brice Ozenne

## See Also

[BuyseTest.options](#) to select or update global settings.

---

 BuyseTest.options-methods

*Methods for the class "BuyseTest.options"*


---

### Description

Methods to update or select global settings

### Usage

```
## S4 method for signature 'BuyseTest.options'
alloc(object, field)
```

```
## S4 method for signature 'BuyseTest.options'
select(object, name.field)
```

### Arguments

object	an object of class BuyseTest.options.
field	a list named with the name of the fields to update and containing the values to assign to these fields
name.field	a character vector containing the names of the field to be selected.

---

 coef.BuyseTestAuc

*Extract the AUC Value*


---

### Description

Extract the AUC value.

### Usage

```
## S3 method for class 'BuyseTestAuc'
coef(object, ...)
```

### Arguments

object	object of class BuyseTestAUC (output of the auc function).
...	not used. For compatibility with the generic function.

### Value

Estimated value for the AUC (numeric).

---

`confint.BuyseTestAuc` *Extract the AUC value with its Confidence Interval*

---

### Description

Extract the AUC value with its Confidence Interval and p-value testing whether the AUC equals 0.5.

### Usage

```
## S3 method for class 'BuyseTestAuc'
confint(object, ...)
```

### Arguments

`object` object of class `BuyseTestAUC` (output of the `auc` function).  
`...` not used. For compatibility with the generic function.

### Value

Estimated value for the AUC, its standard error, the lower and upper bound of the confidence interval and the p-value.

---

`constStrata` *Strata creation*

---

### Description

Create strata from several variables.

### Usage

```
constStrata(data, strata, sep = ".", lex.order = FALSE, trace = TRUE,
  as.numeric = FALSE)
```

### Arguments

`data` [data.frame] dataset.  
`strata` [character vector] A vector of the variables capturing the stratification factors.  
`sep` [character] string to construct the new level labels by joining the constituent ones.  
`lex.order` [logical] Should the order of factor concatenation be lexically ordered ?  
`trace` [logical] Should the execution of the function be traced ?  
`as.numeric` [logical] Should the strata be converted from factors to numeric?



**Details**

This function uses the interaction function from the *base* package to form the strata.

**Value**

A *factor vector* or a *numeric vector*.

**Author(s)**

Brice Ozenne

**Examples**

```
library(data.table)

data(veteran,package="survival")

# strata with two variables : celltype and karno
veteran$strata1 <- constStrata(veteran,c("celltype","karno"))
table(veteran$strata1)

# strata with three variables : celltype, karno and age dichotomized at 60 years
veteran$age60 <- veteran$age>60
veteran$age60 <- factor(veteran$age60,labels=c("<=60",">60")) # convert to factor with labels
veteran$strata2 <- constStrata(veteran,c("celltype","karno","age60"))
table(veteran$strata2) # factor strata variable

veteran$strata2 <- constStrata(veteran,c("celltype","karno","age60"), as.numeric=TRUE)
table(veteran$strata2) # numeric strata variable
```

---

discreteRoot

*Dichotomic search for monotone function*

---

**Description**

Find the root of a monotone function on a discrete grid of value using dichotomic search

**Usage**

```
discreteRoot(fn, grid, increasing = TRUE, check = TRUE,
  tol = .Machine$double.eps^0.5)
```

**Arguments**

fn	[function] objective function to minimize in absolute value.
grid	[vector] possible minimizers.
increasing	[logical] is the function fn increasing?
check	[logical] should the program check that fn takes a different sign for the first vs. the last value of the grid?
tol	[numeric] the absolute convergence tolerance.

**Author(s)**

Brice Ozenne

---

getCount	<i>Extract the Number of Favorable, Unfavorable, Neutral, Uninformative pairs</i>
----------	---

---

**Description**

Extract the number of favorable, unfavorable, neutral, uninformative pairs.

**Usage**

```
getCount(object, type)

## S4 method for signature 'BuyseRes'
getCount(object, type)
```

**Arguments**

object	an R object of class <a href="#">BuyseRes</a> , i.e., output of <a href="#">BuyseTest</a>
type	the type of pairs to be counted. Can be "favorable", "unfavorable", neutral, or uninf. Can also be "all" to select all of them.

**Value**

A "vector" containing the number of pairs

**Author(s)**

Brice Ozenne

---

getPairScore	<i>Extract the Score of Each Pair</i>
--------------	---------------------------------------

---

## Description

Extract the score of each pair.

## Usage

```
getPairScore(object, endpoint = NULL, strata = NULL, sum = FALSE,
  rm.withinStrata = TRUE, rm.strata = is.na(object@strata),
  rm.indexPair = TRUE, rm.weight = FALSE,
  rm.corrected = (object@correction.uninf == 0), unlist = TRUE,
  trace = 1)
```

```
## S4 method for signature 'BuyseRes'
getPairScore(object, endpoint = NULL,
  strata = NULL, sum = FALSE, rm.withinStrata = TRUE,
  rm.strata = is.na(object@strata), rm.indexPair = TRUE,
  rm.weight = FALSE, rm.corrected = (object@correction.uninf == 0),
  unlist = TRUE, trace = 1)
```

## Arguments

object	an R object of class <a href="#">BuyseRes</a> , i.e., output of <a href="#">BuyseTest</a>
endpoint	[integer/character vector] the endpoint for which the scores should be output.
strata	[integer/character vector] the strata for which the scores should be output.
sum	[logical] should the scores be cumulated over endpoints?
rm.withinStrata	[logical] should the columns indicating the position of each member of the pair within each treatment group be removed?
rm.strata	[logical] should the column containing the level of the strata variable be removed from the output?
rm.indexPair	[logical] should the column containing the number associated to each pair be removed from the output?
rm.weight	[logical] should the column weight be removed from the output?
rm.corrected	[logical] should the columns corresponding to the scores after weighting be removed from the output?
unlist	[logical] should the structure of the output be simplified when possible?
trace	[logical] should a message be printed to explain what happened when the function returned NULL?



```

## Extract scores
pScore <- getPairScore(BT.keep, endpoint = 1)

## look at one pair
pScore[91]

## retrieve pair in the original dataset
pVeteran <- veteran[pScore[91,c(index.1,index.2)],]
pVeteran

## the observation from the control group is censored at 97
## the observation from the treatment group has an event at 112
## since the threshold is 20, and (112-20)<97
## we know that the pair is not in favor of the treatment

## the formula for probability in favor of the control is
##  $Sc(97)/Sc(112+20)$ 
## where  $Sc(t)$  is the survival at time  $t$  in the control arm.

## we first estimate the survival in each arm
e.KM <- prodlim(Hist(time,status)~trt, data = veteran)

## and compute the survival
iSurv <- predict(e.KM, times = c(97,112+20),
                 newdata = data.frame(trt = 1, stringsAsFactors = FALSE))[[1]]

## the probability in favor of the control is then
pUF <- iSurv[2]/iSurv[1]
pUF
## and the complement to one of that is the probability of being neutral
pN <- 1 - pUF
pN

if(require(testthat)){
  testthat::expect_equal(pUF, pScore[91, unfavorable])
  testthat::expect_equal(pN, pScore[91, neutral])
}

```

---

getSurvival

*Extract the Survival and Survival Jumps*


---

## Description

Extract the survival and survival jumps.

## Usage

```

getSurvival(object, type = NULL, endpoint = NULL, strata = NULL,
            unlist = TRUE, trace = TRUE)

```

```
## S4 method for signature 'BuyseRes'
getSurvival(object, type = NULL, endpoint = NULL,
            strata = NULL, unlist = TRUE, trace = TRUE)
```

### Arguments

object	an R object of class <code>BuyseRes</code> , i.e., output of <code>BuyseTest</code>
type	[character vector] the type of survival to be output. See details.
endpoint	[integer/character vector] the endpoint for which the survival should be output.
strata	[integer/character vector] the strata for which the survival should be output.
unlist	[logical] should the structure of the output be simplified when possible.
trace	[logical] should a message be printed to explain what happened when the function returned NULL.

### Details

The argument `type` can take any of the following values:

- "survTimeC": survival at the event times for the observations of the control arm.
- "survTimeT": survival at the event times for the observations of the treatment arm.
- "survJumpC": survival at the jump times for the survival model in the control arm.
- "survJumpT": survival at the time times for the survival model in the treatment arm.
- "lastSurv": survival at the last event time.

### Author(s)

Brice Ozenne

---

GPC_cpp	<i>C++ function performing the pairwise comparison over several endpoints.</i>
---------	--

---

### Description

GPC\_cpp call for each endpoint and each strata the pairwise comparison function suited to the type of endpoint and store the results.

### Usage

```
GPC_cpp(endpoint, status, indexC, posC, indexT, posT, threshold, weight,
        method, D, D_UTTE, n_strata, nUTTE_analyzedPeron_M1, index_endpoint,
        index_status, index_UTTE, list_survTimeC, list_survTimeT, list_survJumpC,
        list_survJumpT, list_lastSurv, p_C, p_T, iid_survJumpC, iid_survJumpT,
        zeroPlus, correctionUninf, hierarchical, hprojection, neutralAsUninf,
        keepScore, returnIID, debug)
```

**Arguments**

endpoint	A matrix containing the values of each endpoint (in columns) for each observation (in rows).
status	A matrix containing the values of the status variables relative to each endpoint (in columns) for each observation (in rows).
indexC	A list containing, for each strata, which rows of the endpoint and status matrices corresponds to the control observations. Not unique when bootstrapping.
posC	A list containing, for each strata, the unique identifier of each control observations.
indexT	A list containing, for each strata, which rows of the endpoint and status matrices corresponds to the treatment observations. Not unique when bootstrapping.
posT	A list containing, for each strata, the unique identifier of each treatment observations.
threshold	Store the thresholds associated to each endpoint. Must have length D. The threshold is ignored for binary endpoints.
weight	Store the weight associated to each endpoint. Must have length D.
method	The index of the method used to score the pairs. Must have length D. 1 for continuous, 2 for Gehan, and 3 for Peron.
D	The number of endpoints.
D_UTTE	The number of distinct time to event endpoints.
n_strata	The number of strata.
nUTTE_analyzedPeron_M1	The number of unique time-to-event endpoints that have been analyzed the Peron scoring rule before the current endpoint. Must have length D.
index_endpoint	The position of the endpoint at each priority in the argument endpoint. Must have length D.
index_status	The position of the status at each priority in the argument status. Must have length D.
index_UTTE	The position, among all the unique tte endpoints, of the TTE endpoints. Equals -1 for non tte endpoints. Must have length n_TTE.
list_survTimeC	A list of matrix containing the survival estimates (-threshold, 0, +threshold ...) for each event of the control group (in rows).
list_survTimeT	A list of matrix containing the survival estimates (-threshold, 0, +threshold ...) for each event of the treatment group (in rows).
list_survJumpC	A list of matrix containing the survival estimates and survival jumps when the survival for the control arm jumps.
list_survJumpT	A list of matrix containing the survival estimates and survival jumps when the survival for the treatment arm jumps.
list_lastSurv	A list of matrix containing the last survival estimate in each strata (rows) and treatment group (columns).
p_C	Number of nuisance parameter in the survival model for the control group, for each endpoint and strata

p_T	Number of nuisance parameter in the survival model for the treatment group, for each endpoint and strata
iid_survJumpC	A list of matrix containing the iid of the survival estimates in the control group.
iid_survJumpT	A list of matrix containing the iid of the survival estimates in the treatment group.
zeroPlus	Value under which doubles are considered 0?
correctionUninf	Should the uninformative weight be re-distributed to favorable and unfavorable?
hierarchical	Should only the uninformative pairs be analyzed at the lower priority endpoints (hierarchical GPC)? Otherwise all pairs will be compared for all endpoint (full GPC).
hprojection	Order of the H-projection used to compute the variance.
neutralAsUninf	Should paired classified as neutral be re-analyzed using endpoints of lower priority?
keepScore	Should the result of each pairwise comparison be kept?
returnIID	Should the iid be computed?
debug	Print messages tracing the execution of the function to help debugging. The amount of messages increase with the value of debug (0-5).

**Author(s)**

Brice Ozenne

---

iid

*Extract the H-decomposition of the Estimator*

---

**Description**

Extract the H-decomposition of the GPC estimator.

**Usage**

```
iid(object, endpoint = NULL, normalize = TRUE, type = "all",
     cluster = NULL)

## S4 method for signature 'BuyseRes'
iid(object, endpoint = NULL, normalize = TRUE,
     type = "all", cluster = NULL)
```



**Arguments**

object	an R object of class <a href="#">BuyseRes</a> , i.e., output of <a href="#">BuyseTest</a>
endpoint	[character] for which endpoint(s) the H-decomposition should be output? If NULL returns the sum of the H-decomposition over all endpoints.
normalize	[logical] if TRUE the iid is centered and multiplied by the sample size. Otherwise not.
type	[character] type of iid to be output. Can be only for the nuisance parameters ("nuisance"), or for the u-statistic given the nuisance parameters ("u-statistic"), or both.
cluster	[numeric vector] return the H-decomposition aggregated by cluster.

**Author(s)**

Brice Ozenne

**See Also**

[BuyseTest](#) for performing a generalized pairwise comparison.  
[BuyseRes-summary](#) for a more detailed presentation of the BuyseRes object.

---

 iidProdlim

---

*Extract i.i.d. decomposition from a prodlim model*


---

**Description**

Compute the influence function for each observation used to estimate the model

**Usage**

```
iidProdlim(object, add0 = FALSE)
```

**Arguments**

object	A prodlim object.
add0	[logical] add the 0 to vector of relevant times.

**Details**

This function is a simplified version of the iidCox function of the riskRegression package. Formula for the influence function can be found in (Ozenne et al., 2017).

**Author(s)**

Brice Ozenne

## References

Brice Ozenne, Anne Lyngholm Sorensen, Thomas Scheike, Christian Torp-Pedersen and Thomas Alexander Gerds. riskRegression: Predicting the Risk of an Event using Cox Regression Models. The R Journal (2017) 9:2, pages 440-460.

## Examples

```
library(data.table)
library(prodlim)

set.seed(10)
dt <- simBuyseTest(10)
setkeyv(dt, "treatment")

e.KM <- prodlim(Hist(eventtime,status)~treatment, data = dt)
iidProdlim(e.KM)
```

---

powerBuyseTest

*Performing simulation studies with BuyseTest*

---

## Description

Performs a simulation studies for several sample sizes. Returns estimates, standard errors, confidence intervals and p.values.

## Usage

```
powerBuyseTest(sim, sample.size, sample.sizeC = NULL,
  sample.sizeT = NULL, n.rep, null = c(0, 1), cpus = 1, seed = 10,
  conf.level = NULL, order.Hprojection = NULL, transformation = NULL,
  trace = 1, ...)
```

## Arguments

sim	[function] take two arguments: the sample size in the control group (n.C) and the sample size in the treatment group (n.C) and generate datasets. The datasets must be data.table objects.
sample.size	[integer vector, >0] the various sample sizes at which the simulation should be perform. Disregarded if any of the arguments sample.sizeC or sample.sizeT are specified.
sample.sizeC	[integer vector, >0] the various sample sizes in the control group.
sample.sizeT	[integer vector, >0] the various sample sizes in the treatment group.
n.rep	[integer, >0] the number of simulations.
null	[numeric vector] the null hypothesis to be tested for the net benefit (first element) and the win ratio (second element).

cpus [integer, >0] the number of CPU to use. Only the permutation test can use parallel computation. Default value read from `BuyseTest.options()`.  
 seed [integer, >0] the seed to consider for the simulation study.  
 conf.level [numeric] confidence level for the confidence intervals. Default value read from `BuyseTest.options()`.  
 order.Hprojection [integer 1,2] the order of the H-project to be used to compute the variance of the net benefit/win ratio.  
 transformation [logical] should the CI be computed on the logit scale / log scale for the net benefit / win ratio and backtransformed. Otherwise they are computed without any transformation. Default value read from `BuyseTest.options()`.  
 trace [integer] should the execution of the function be traced?  
 ... parameters from `BuyseTest`.

**Author(s)**

Brice Ozenne

**Examples**

```

library(data.table)

## using simBuyseTest
powerBuyseTest(sim = simBuyseTest, sample.size = c(100), n.rep = 2,
               formula = treatment ~ bin(toxicity),
               method.inference = "u-statistic", trace = 4)

## using user defined simulation function
simFCT <- function(n.C, n.T){
  out <- data.table(Y=rnorm(n.C+n.T),
                   T=c(rep(1,n.C),rep(0,n.T))
                  )
  return(out)
}

powerBuyseTest(sim = simFCT, sample.size = c(100), n.rep = 2,
               formula = T ~ cont(Y), method.inference = "u-statistic", trace = 4)

```

---

 simCompetingRisks

*Simulation of Gompertz competing risks data for the BuyseTest*


---

**Description**

Simulate Gompertz competing risks data with proportional (via prespecified sub-distribution hazard ratio) or non-proportional sub-distribution hazards. A treatment variable with two groups (treatment and control) is created.

**Usage**

```
simCompetingRisks(n.T, n.C, p.1C = NULL, v.1C, v.1T, v.2C, v.2T,
  SHR = NULL, b.1T = NULL, b.1C = NULL, b.2T = NULL, b.2C = NULL,
  cens.distrib = NULL, param.cens = NULL, latent = NULL)
```

**Arguments**

n.T	[integer, >0] number of patients in the treatment arm
n.C	[integer, >0] number of patients in the control arm
p.1C	[integer, >0] proportion of events of interest in the control group. Can be NULL if and only if (b.1T, b.1C, b.2T, b.2C) are provided.
v.1C, v.1T, v.2C, v.2T	[double, <0] shape parameters for Gompertz distribution of time to event of interest in control/treatment (C/T) group and of time to competing event in control/treatment (C/T) group respectively
SHR	[double, >0] pre-specified sub-distribution hazard ratio for event of interest. Can be NULL if and only if (b.1T, b.1C, b.2T, b.2C) are provided.
b.1C, b.1T, b.2C, b.2T	[double, >0] rate parameters for Gompertz distribution of time to event of interest in control/treatment (C/T) group and of time to competing event in control/treatment (C/T) group respectively. Can be NULL if and only if (p.1C, SHR) are provided.
cens.distrib	[character] censoring distribution. Can be "exponential" for exponential censoring or "uniform" for uniform censoring. NULL means no censoring.
param.cens	[>0] parameter for censoring distribution. Should be a double for rate parameter of exponential censoring distribution or a vector of doubles for lower and upper bounds of uniform censoring distribution. NULL means no censoring
latent	[logical] If TRUE, also export the latent variables (e.g. true event times, true event types and censoring times). NULL sets this parameter to FALSE.

**Details**

The times to the event of interest and to the competing event in each group follow an improper Gompertz distribution (see Jeong and Fine, 2006), whose cumulative distribution function is

$$F(t; b, v) = 1 - \exp(b(1 - \exp(vt)) / v)$$

and hazard functions is

$$h(t; b, v) = b \exp(vt)$$

The shape parameters must be negative to have improper distributions for the times to the two events in each group. Note however that in each group, the overall cumulative incidence function must be proper (i.e. the maximum values of the cumulative incidence of each event type sum up to 1 in each group). When only providing the shape parameters, the rate parameters are computed to fulfill this condition. In case you wish to provide the rate parameters too, make sure that the condition is met.

**Author(s)**

Eva Cantagallo

**References**

Jeong J-H. and Fine J. (2006) **Direct parametric inference for the cumulative incidence function.** *Journal of the Royal Statistical Society* 55: 187-200

**Examples**

```
#### Providing p.1C and sHR ####
d <- simCompetingRisks(n.T = 100, n.C = 100, p.1C = 0.55, v.1C = -0.30,
v.1T = -0.30, v.2C = -0.30, v.2T = -0.30, sHR = 0.5, b.1T = NULL,
b.1C = NULL, b.2T = NULL, b.2C = NULL)
```

```
#### Providing the rate parameters ####
d <- simCompetingRisks(n.T = 100, n.C = 100, p.1C = NULL, v.1C = -0.30,
v.1T = -0.30, v.2C = -0.30, v.2T = -0.30, sHR = NULL, b.1T = 0.12,
b.1C = 0.24, b.2T = 0.33, b.2C = 0.18)
```

```
#### With exponential censoring ####
d <- simCompetingRisks(n.T = 100, n.C = 100, p.1C = 0.55, v.1C = -0.30,
v.1T = -0.30, v.2C = -0.30, v.2T = -0.30, sHR = 0.5, b.1T = NULL,
b.1C = NULL, b.2T = NULL, b.2C = NULL, cens.distrib = "exponential",
param.cens = 0.8, latent = TRUE)
```

```
### With uniform censoring ###
d <- simCompetingRisks(n.T = 100, n.C = 100, p.1C = 0.55, v.1C = -0.30,
v.1T = -0.30, v.2C = -0.30, v.2T = -0.30, sHR = 0.5, b.1T = NULL,
b.1C = NULL, b.2T = NULL, b.2C = NULL, cens.distrib = "uniform",
param.cens = c(0, 7), latent=TRUE)
```

---

Simulation function     *Simulation of data for the BuyseTest*

---

**Description**

Simulate binary, continuous or time to event data, possibly with strata. Outcomes are simulated independently of each other and independently of the strata variable.

**Usage**

```
simBuyseTest(n.T, n.C = NULL, argsBin = list(), argsCont = list(),
argsTTE = list(), n.strata = NULL, names.strata = NULL,
format = "data.table", latent = FALSE)
```

**Arguments**

<code>n.T</code>	[integer, >0] number of patients in the treatment arm
<code>n.C</code>	[integer, >0] number of patients in the control arm
<code>argsBin</code>	[list] arguments to be passed to <code>simBuyseTest_bin</code> . They specify the distribution parameters of the binary endpoints.
<code>argsCont</code>	[list] arguments to be passed to <code>simBuyseTest_continuous</code> . They specify the distribution parameters of the continuous endpoints.
<code>argsTTE</code>	[list] arguments to be passed to <code>simBuyseTest_TTE</code> . They specify the distribution parameters of the time to event endpoints.
<code>n.strata</code>	[integer, >0] number of strata. NULL indicates no strata.
<code>names.strata</code>	[character vector] name of the strata variables. Must have same length as <code>n.strata</code> .
<code>format</code>	[character] the format of the output. Can be "data.table", "data.frame" or "matrix".
<code>latent</code>	[logical] If TRUE also export the latent variables (e.g. censoring times or event times).

**Details**

This function is built upon the `lvm` and `sim` functions from the `lava` package.

Arguments in the list `argsBin`:

- `p.T` probability of event of each endpoint (binary endpoint, treatment group).
- `p.C` same as `p.T` but for the control group.
- `name` names of the binary variables.

Arguments in the list `argsCont`:

- `mu.T` expected value of each endpoint (continuous endpoint, treatment group).
- `mu.C` same as `mu.C` but for the control group.
- `sigma.T` standard deviation of the values of each endpoint (continuous endpoint, treatment group).
- `sigma.C` same as `sigma.T` but for the control group.
- `name` names of the continuous variables.

Arguments in the list `argsTTE`:

- CR should competing risks be simulated?

- rates.T hazard corresponding to each endpoint (time to event endpoint, treatment group).
- rates.C same as rates.T but for the control group.
- rates.CR same as rates.T but for the competing event (same in both groups).
- rates.Censoring.T Censoring same as rates.T but for the censoring.
- rates.Censoring.C Censoring same as rates.C but for the censoring.
- name names of the time to event variables.
- nameCensoring names of the event type indicators.

### Author(s)

Brice Ozenne

### Examples

```
library(data.table)

n <- 1e2

#### default option ####
simBuyseTest(n)

## with a strata variable having 5 levels
simBuyseTest(n, n.strata = 5)
## with a strata variable named grade
simBuyseTest(n, n.strata = 5, names.strata = "grade")
## several strata variables
simBuyseTest(1e3, n.strata = c(2,4), names.strata = c("Gender","AgeCategory"))

#### only binary endpoints ####
args <- list(p.T = c(3:5/10))
simBuyseTest(n, argsBin = args, argsCont = NULL, argsTTE = NULL)

#### only continuous endpoints ####
args <- list(mu.T = c(3:5/10), sigma.T = rep(1,3))
simBuyseTest(n, argsBin = NULL, argsCont = args, argsTTE = NULL)

#### only TTE endpoints ####
args <- list(rates.T = c(3:5/10), rates.Censoring.T = rep(1,3))
simBuyseTest(n, argsBin = NULL, argsCont = NULL, argsTTE = args)
```

# Index

- \*Topic **BuyseRes-class**
  - BuyseRes-class, 7
- \*Topic **BuyseRes-method**
  - BuyseRes-coef, 7
  - BuyseRes-confint, 8
  - BuyseRes-show, 10
  - BuyseRes-summary, 10
  - getCount, 26
  - getPairScore, 27
  - getSurvival, 29
  - iid, 32
- \*Topic **BuyseSim-class**
  - BuyseSim-class, 13
- \*Topic **BuyseSim-method**
  - BuyseSim-show, 13
  - BuyseSim-summary, 14
- \*Topic **BuyseTest.options-class**
  - BuyseTest.options-class, 22
- \*Topic **BuyseTest**
  - GPC\_cpp, 30
- \*Topic **BuyseTes**
  - BuyseTest, 15
- \*Topic **Cpp**
  - GPC\_cpp, 30
- \*Topic **classes**
  - BuyseRes-class, 7
  - BuyseSim-class, 13
  - BuyseTest.options-class, 22
- \*Topic **coef**
  - BuyseRes-coef, 7
- \*Topic **confint**
  - BuyseRes-confint, 8
- \*Topic **function**
  - BuyseTest, 15
  - constStrata, 24
  - GPC\_cpp, 30
  - simCompetingRisks, 35
  - Simulation function, 37
- \*Topic **get**
  - getCount, 26
  - getPairScore, 27
  - getSurvival, 29
- \*Topic **iid**
  - iid, 32
- \*Topic **options**
  - BuyseTest.options-class, 22
- \*Topic **simulations**
  - simCompetingRisks, 35
  - Simulation function, 37
- \*Topic **summary**
  - BuyseRes-show, 10
  - BuyseRes-summary, 10
  - BuyseSim-show, 13
  - BuyseSim-summary, 14
- alloc, BuyseTest.options-method  
(BuyseTest.options-methods), 23
- auc, 4
- boot2pvalue, 5
- BuyseRes, 8, 10, 19, 26, 27, 30, 33
- BuyseRes (BuyseRes-class), 7
- BuyseRes-class, 7
- BuyseRes-coef, 7
- BuyseRes-confint, 8
- BuyseRes-getCount (getCount), 26
- BuyseRes-getPairScore (getPairScore), 27
- BuyseRes-getSurvival (getSurvival), 29
- BuyseRes-iid (iid), 32
- BuyseRes-show, 10
- BuyseRes-summary, 10
- BuyseSim, 13, 14
- BuyseSim (BuyseSim-class), 13
- BuyseSim-class, 13
- BuyseSim-show, 13
- BuyseSim-summary, 14
- BuyseTest, 3, 7–11, 13, 14, 15, 22, 26, 27, 30, 33
- BuyseTest-package, 3



BuyseTest.options, [21](#), [22](#)  
BuyseTest.options-class, [22](#)  
BuyseTest.options-methods, [23](#)

coef, BuyseRes-method (BuyseRes-coef), [7](#)  
coef.BuyseTestAuc, [23](#)  
confint (BuyseRes-confint), [8](#)  
confint, BuyseRes-method  
    (BuyseRes-confint), [8](#)  
confint.BuyseTestAuc, [24](#)  
constStrata, [19](#), [24](#)

discreteRoot, [25](#)

getCount, [26](#)  
getCount, BuyseRes-method (getCount), [26](#)  
getPairScore, [27](#)  
getPairScore, BuyseRes-method  
    (getPairScore), [27](#)  
getSurvival, [29](#)  
getSurvival, BuyseRes-method  
    (getSurvival), [29](#)  
GPC\_cpp, [30](#)

iid, [32](#)  
iid, BuyseRes-method (iid), [32](#)  
iidProdlim, [33](#)

powerBuyseTest, [13–15](#), [34](#)

select, BuyseTest.options-method  
    (BuyseTest.options-methods), [23](#)  
show, BuyseRes-method (BuyseRes-show), [10](#)  
show, BuyseSim-method (BuyseSim-show), [13](#)  
simBuyseTest (Simulation function), [37](#)  
simCompetingRisks, [35](#)  
Simulation function, [37](#)  
summary, BuyseRes-method  
    (BuyseRes-summary), [10](#)  
summary, BuyseSim-method  
    (BuyseSim-summary), [14](#)