Package 'BioPETsurv'

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Type Package

Title Biomarker Prognostic Enrichment Tool for Time-to-Event Trial

Version 0.1.0

Description Prognostic Enrichment is a strategy of enriching a clinical trial for testing an intervention intended to prevent or delay an unwanted clinical event. A prognostically enriched trial enrolls only patients who are more likely to experience the unwanted clinical event than the broader patient population (R. Temple (2010) <doi:10.1038/clpt.2010.233>). By testing the intervention in an enriched study population, the trial may be adequately powered with a smaller sample size, which can have both practical and ethical advantages.
This package provides tools to evaluate biomarkers for prognostic enrichment of clinical trials with survival/time-to-event outcomes.

Depends R (>= 3.1.0)

License GPL (>= 2)

Encoding UTF-8

LazyData true

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Imports survival, ggplot2, gridExtra

NeedsCompilation no

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R topics documented:

sim_data *Simulating Biomarker and Survival Observations*

Description

This function simulates biomarkers and generates survival observations depending on biomarker values. The simulated data can be used to explore prognostic enrichment using `surv_enrichment`.

Usage

```
sim_data(n = 500, biomarker = "normal", effect.size = 1.25,
         baseline.hazard = "constant", end.time = 10,
         end.survival = 0.5, shape = NULL, seed = 2333)
```

Arguments

`n`	The number of observations to simulate.
`biomarker`	Character specifying the shape of the biomarker distribution. Choices are `normal` for a symmetric distribution and `lognormal` for a right-skewed distribution.
`effect.size`	The hazard ratio corresponding to one standard deviation increment in the biomarker.
`baseline.hazard`	Character ("constant"/"increasing"/"decreasing") specifying whether the overall hazard in the population is constant, increasing or decreasing over time.
`end.time`	The length of observation in the simulated dataset. In the data simulation, any events after this time will be censored at this time.
`end.survival`	The survival rate in the population at the end of observation.
`shape`	(Optional) the Weibull shape parameter for the baseline hazard. Values smaller and larger than 1 correspond to decreasing and increasing respectively.
`seed`	(Optional) specify the random seed used for simulation.

Details

The biomarker will be simulated from a standardized normal or lognormal distribution. It is important that `effect.size` should correspond to a 1 SD increment in the biomarker. Conditioning on the biomarker values and assuming proportional hazards, survival times are simulated from a Weibull distribution with user-specified shape parameter, and the scale parameter is determined by the specified event rate and effect size.

Value

Returns a list of the following items:

`data`	A data frame with 4 columns: the value of biomarker, observed event time, event indicator and the true event time.
`km.plot`	The Kaplan-Meier survival curves of the simulated dataset at enrichment levels 0, 25%, 50% and 75%.

Examples

```
## Simulate a dataset with 500 observations,
## where the biomarker is Normally distributed (with SD=1).
## The hazard ratio corresponding to every one unit of increament in the biomarker is 1.25.
## The observation period is 10 months,
## and the survival probability of the population at the end of observation is 0.5.
## Hazards are constant over time.
sim_obj <- sim_data(n = 500, biomarker = "normal", effect.size = 1.25,
                    baseline.hazard = "constant", end.time = 10, end.survival = 0.5)
dat <- sim_obj$data
```

SurvMarkers *Example dataset for package 'BioPETsurv'*

Description

A dataset containing values of two biomarkers and survival outcomes of 1533 individuals.

Usage

```
data(SurvMarkers)
```

Format

A data frame with 1533 rows and 4 variables:

time observed times of event or censoring

event indicator of event; 0 means censored and 1 means event

x1 A modestly prognostic biomarker (concordance index=0.64)

x2 A strongly prognostic biomarker (concordance index=0.82)

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surv_enrichment *Prognostic Enrichment for Clinical Trials with Survival Outcomes*

Description

This function evaluates biomarkers for prognostic enrichment of clinical trials with survival outcomes, using data with biomarker values and survival observations. A more detailed tutorial is available here.

Usage

```
surv_enrichment(formula, data, hr = 0.8, end.of.trial=NULL, a=NULL, f=NULL,
     method = "KM", lambda = 0.05,
     cost.screening = NULL, cost.keeping = NULL, cost.unit.keeping = NULL,
     power = 0.9, alpha = 0.05, one.sided = FALSE,
     selected.biomarker.quantiles = seq(from = 0, to = 0.95, by = 0.05),
     do.bootstrap = FALSE, n.bootstrap = 1000, seed = 2333,
     print.summary.tables = FALSE)
```

Arguments

formula	Object of class formula, in the form outcome ~ predictors, where the outcome is a survival object as returned by function Surv(). The predictor(s) include the biomarker(s) of interest and/or other covariates. If multiple predictors are inputed, this function will consider a composite biomarker based on a Cox model with all predictors.
data	Data frame containing the survival outcome (as returned by Surv()) and predictors specified in the formula argument. Observations with missing value(s) will be dropped.
hr	The hazard ratio (comparing the treatment versus control group) that the trial seeks to detect. Should be a number between 0 and 1.
end.of.trial	A scalar or a vector that gives the duration(s) of fixed-length trial(s) that are being considered. The unit of time should be the same as the survival times in the data. Either end.of.trial or a combination of a and f must be specified.
a	A scalar specifying the accrual period of the trial. It is assumed that patients are recruited at a uniform rate during this period.
f	A scalar specifying the follow-up period of the trial, that is, all patients are followed during this period right after the accrual period.
method	Character specifying which method would be used to estimate event probabilities. Choices are KM for the Kaplan-Meier estimator and NNE for the nearest neighbor estimator described in Heagerty et al (2000). Algorithm of NNE was adapted from the code in the survivalROC R package. If method = "NNE" is specified, only fixed-length trials (instead of accrual and follow-up) and cost.keeping (instead of cost.unit.keeping) can be specified, and no standard errors will be estimated. Default is KM.
lambda	The smoothing parameter used by method NNE (see documentation of package survivalROC). Default is 0.05.
cost.screening	(Optional) the cost of measuring the biomarker for each patient to determine eligibility for the trial.
cost.keeping	(Optional) the cost of enrolling and retaining a patient in a trial. If specified for a trial with accrual and follow-up periods, it is treated as the "average" cost for one patient under such design, and is used for all patients in the trial.
cost.unit.keeping	(Optional) the cost of enrolling and retaining a patient per unit time in the trial. Can be specified as an alternative to cost.keeping, assuming that patients who experienced a clinical event no longer cost in the trial.

power — The power (probability of rejecting the null hypothesis given that it is false) for sample size calculation.

alpha — The type I error rate (probability of falsely rejecting the null given that it is true) for sample size calculation.

one.sided — Logical indicating whether the alternative hypothesis is one-sided (instead of two-sided). Default is FALSE.

selected.biomarker.quantiles — Numeric vector specifying the quantiles of the biomarker measured in controls that will be used to screen trial participants. Default is 0, 0.05, ..., 0.95. All entries must be between at least 0 and less than 1.

do.bootstrap — Logical specifying whether bootstrap standard errors should be calculated for a trial with accrual and follow-up periods. Default is FALSE. (Standard errors will always be calculated for fixed-length trials.)

n.bootstrap — Number of bootstrap samples for standard error estimation.

seed — Specify the random seed used to generate bootstrap samples.

print.summary.tables — Logical specifying whether a table of clinical trial metrics should be printed.

Value

Returns a list of the following items:

summary.table — A matrix containing all clinical trial metrics that were calculated (listed below) at each enrichment level.

event.prob — Vector(s) of estimated event probabilities at each enrichment level. If more than one vector was presented, each column corresponds to a specified length of trial.

event.prob.se — Estimated standard errors of event probabilities at each enrichment level for each trial length.

n.patients — Vector(s) of clinical trial sample size required.

n.patients.se — Estimated standard errors of the sample sizes.

n.screened — The number of patients that need to be screened to enroll the trial.

n.screened.se — Estimated standard errors of n.screened.

cost — The estimated total cost of the trial, combining screening costs and the total cost of patients in the trial.

cost.se — Estimated standard errors of cost.

cost.reduction — The reduction in total cost comparing an enriched trial to an unenriched trial. A positive number indicates that an enriched trial would cost less than an unenriched one.

cost.reduction.se — Estimated standard errors of cost.reduction from bootstrap.

response — The response (a Survival object) specified in argument formula.

biomarker — The biomarker, or the composite biomarker calculated via Cox regression.

All other quantities are the same as the input by user.

References

Heagerty, Patrick J., Thomas Lumley, and Margaret S. Pepe (2000) <doi:10.1111/j.0006-341x.2000.00337.x> "Time-dependent ROC curves for censored survival data and a diagnostic marker"

Heagerty, Patrick J., Paramita Saha-Chaudhuri, and Maintainer Paramita Saha-Chaudhuri (2013) <https://cran.r-project.org/web/packages/survivalROC/survivalROC.pdf> "Package 'survivalROC'."

Examples

```
require(survival)
data(SurvMarkers)

SurvMarkers$surv <- Surv(SurvMarkers$time, SurvMarkers$event)

## Using a composite biomarker (combining x1 and x2) to plan a trial
## with an accrual period of 12 months and a follow-up period of 36 months.
## The cost for keeping a patient in the trial is $300/month.
## We wish to detect a hazard ratio of 0.8 with a two-sided test,
## with type I error 0.05 and power 0.9.
## The Kaplan-Meier method is used to calculate event probabilities.
rslt <- surv_enrichment(formula = surv~x1+x2, data = SurvMarkers, hr = 0.8, a=12, f=36,
                      cost.screening = 300, cost.keeping = NULL, cost.unit.keeping = 300,
                         method = "KM", power = 0.9, alpha = 0.05, one.sided = FALSE,
                        selected.biomarker.quantiles = seq(from = 0, to = 0.9, by = 0.1),
                         do.bootstrap = FALSE, print.summary.tables = FALSE)
```

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surv_plot_enrichment *Plotting Clinical Trial Metrics for Prognostic Enrichment*

Description

This function plots summaries of prognostic enrichment of clinical trials with survival outcomes, based on clinical trial metrics estimated by `surv_enrichment`.

Usage

```
surv_plot_enrichment(x, km.quantiles = c(0,0.25,0.5,0.75),
                     km.range = NULL, alt.color = NULL)
```

Arguments

`x`	Object returned by `surv_enrichment`.
`km.quantiles`	Enrichment levels on which Kaplan-Meier survival estimates (Plot 1) are plotted. Defaults to four quartiles.
`km.range`	(Optional) a scalar specifying the range of time for which Kaplan-Meier survival estimates (Plot 1) are plotted. Defaults to the last time point of observation.
`alt.color`	(Optional) allows the user to specify the color of curves for clinical trial metrics (Plots 2-6). The length should match the number of trial lengths considered. Defaults to `ggplot2` color palette.

Value

A grid containing either the first 4 or 6 plots described below.

km.plot	The Kaplan-Meier survival curves for specified enrichment levels. The vertical reference line(s) correspond to end.of.trial or a,f. This will be presented even if method = "NNE" was specified.
prob.plot	The estimated event probability (and 95% confidence intervals) at each enrichment level.
ss.plot	The estimated sample size (and confidence intervals) at each enrichment level.
screen.plot	The estimated number of patients that need to be screened (and confidence intervals) to enroll the trial.
cost.plot	The estimated total cost of the trial (and confidence intervals).
reduction.cost.plot	The percentage of reduction in total cost comparing an enriched versus unenriched trial.
summary	A grid of the first 4 or all 6 plots combined together.

Examples

```
## Following the example of 'surv_enrichment':
data(SurvMarkers)
library(survival)

SurvMarkers$surv <- Surv(SurvMarkers$time, SurvMarkers$event)
rslt <- surv_enrichment(formula = surv~x1+x2, data = SurvMarkers, hr = 0.8, a=12, f=36,
                     cost.screening = 300, cost.keeping = NULL, cost.unit.keeping = 300,
                        method = "KM", power = 0.9, alpha = 0.05, one.sided = FALSE,
                       selected.biomarker.quantiles = seq(from = 0, to = 0.9, by = 0.1),
                        do.bootstrap = FALSE, print.summary.tables = FALSE)

plots <- surv_plot_enrichment(rslt, km.quantiles = c(0,0.25,0.5,0.75))
```

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