Package 'tteICE'

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Type Package

Title Treatment Effect Estimation for Time-to-Event Data with Intercurrent Events

Version 1.1.1

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Description Analysis of treatment effects in clinical trials with time-to-event outcomes is complicated by intercurrent events. This package implements methods for estimating and inferring the cumulative incidence functions for time-to-event (TTE) outcomes with intercurrent events (ICE) under the five strategies outlined in the ICH E9 (R1) addendum, see Deng (2025) <doi:10.1002/sim.70091>. This package can be used for analyzing data from both randomized controlled trials and observational studies. In general, the data involve a primary outcome event and, potentially, an intercurrent event. Two data structures are allowed: competing risks, where only the time to the first event is recorded, and semicompeting risks, where the times to both the primary outcome event and intercurrent event (or censoring) are recorded. For estimation methods, users can choose nonparametric estimation (which does not use covariates) and semiparametrically efficient estimation.

URL https://github.com/mephas/tteICE, https://mephas.github.io/tteICE/

BugReports https://github.com/mephas/tteICE/issues

License GPL-3

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RoxygenNote 7.3.3

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Contents

`tteICE-package` *tteICE: Treatment Effect Estimation for Time-to-Event Data with Intercurrent Events*

Description

This package aims to analyze treatment effects in clinical trials with time-to-event outcomes is complicated by intercurrent events. This package implements methods for estimating and inferring the cumulative incidence functions for time-to-event (TTE) outcomes with intercurrent events (ICE) under the five strategies outlined in the ICH E9 (R1) addendum, see Deng (2025) doi:10.1002/sim.70091. This package can be used for analyzing data from both randomized controlled trials and observational studies. In general, the data involve a primary outcome event and, potentially, an intercurrent event. Two data structures are allowed: competing risks, where only the time to the first event is recorded, and semicompeting risks, where the times to both the primary outcome event and intercurrent event (or censoring) are recorded. For estimation methods, nonparametric estimation (which does not use covariates) and semiparametrically efficient estimation are presented.

Details

Main functions:

- `tteICE` Using formula to fit cumulative incidence functions (CIFs) for competing/semicompeting risk time-to-event data with intercurrent events.
- `scr.tteICE` Fit CIFs for semicompeting risk time-to-event data with intercurrent events.
- `surv.tteICE` Fit CIFs for competing risk time-to-event with intercurrent events.
- `plot.tteICE` Plot results from 'tteICE' objects.
- `print.tteICE` Print a short summary of results from 'tteICE' objects
- `summary.tteICE` Summarize results from 'tteICE' objects
- `predict.tteICE` Predict risks for 'tteICE' objects at specific time points
- `tteICEShiny` Interactive Shiny app for the 'tteICE' package

Example data:

- `bmt` Data from Section 1.3 of Klein and Moeschberger (1997)

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See Also

Useful links:

- https://github.com/mephas/tteICE
- https://mephas.github.io/tteICE/
- Report bugs at https://github.com/mephas/tteICE/issues

`bmt` *Data from Section 1.3 of Klein and Moeschberger (1997)*

Description

The `bmt` data frame has 137 rows and 22 columns.

Usage

```
bmt
```

Format

This data frame contains the following columns:

group Disease Group 1-ALL, 2-AML Low Risk, 3-AML High Risk

t1 Time To Death Or On Study Time

t2 Disease Free Survival Time (Time To Relapse, Death Or End Of Study)

d1 Death Indicator 1-Dead 0-Alive

d2 Relapse Indicator 1-Relapsed, 0-Disease Free

d3 Disease Free Survival Indicator 1-Dead Or Relapsed, 0-Alive Disease Free)

ta Time To Acute Graft-Versus-Host Disease

da Acute GVHD Indicator 1-Developed Acute GVHD 0-Never Developed Acute GVHD)

tc Time To Chronic Graft-Versus-Host Disease

dc Chronic GVHD Indicator 1-Developed Chronic GVHD 0-Never Developed Chronic GVHD

tp Time To Platelet Recovery

dp Platelet Recovery Indicator 1-Platelets Returned To Normal, 0-Platelets Never Returned to Normal

z1 Patient Age In Years

z2 Donor Age In Years

z3 Patient Sex: 1-Male, 0-Female

z4 Donor Sex: 1-Male, 0-Female

z5 Patient CMV Status: 1-CMV Positive, 0-CMV Negative

z6 Donor CMVStatus: 1-CMV Positive, 0-CMV Negative

z7 Waiting Time to Transplant In Days

z8 FAB: 1-FAB Grade 4 Or 5 and AML, 0-Otherwise

z9 Hospital: 1-The Ohio State University, 2-Alferd, 3-St. Vincent, 4-Hahnemann

z10 MTX used as a Graft-Versus-Host-Prophylactic: 1-Yes 0-No

Source

Klein and Moeschberger (1997) Survival Analysis Techniques for Censored and Truncated Data, Springer.

Examples

```
data(bmt)
```

`plot.tteICE` *Plot method for 'tteICE' objects*

Description

This function plots the estimated potential cumulative incidence functions or treatment effect curve with pointwise confidence intervals.

Usage

```
## S3 method for class 'tteICE'
plot(
  x,
  type = c("ate", "inc")[1],
  decrease = FALSE,
  conf.int = 0.95,
  xlab = "Time",
  xlim = NULL,
  ylim = NULL,
  plot.configs = list(),
  ...
)
```

Arguments

`x`	A fitted object returned by the function `tteICE`, `surv.tteICE`, or `scr.tteICE`.
`type`	Which plot to create: `type="ate"` indicates to plot the estimated treatment effects; `type="inc"` indicates to plot the estimated cumulative incidence functions (CIFs).
`decrease`	Corresponds to the argument in `plot_ate` and `plot_inc`.
`conf.int`	#' Confidence level for the pointwise confidence intervals If `conf.int = NULL`, no confidence intervals are provided.
`xlab`	Label for the x-axis.
`xlim`	A numeric vector of length 2 specifying the limits of the x-axis. If `xlim=NULL` (default), the range is determined automatically from the data.

ylim	A numeric vector of length 2 giving the limits of the y-axis. If ylim=NULL (default), the range is determined automatically by the type of plot, corresponding to the argument in plot_ate and plot_inc.
plot.configs	A named list of additional plot configurations. See details in plot_ate and plot_inc
...	Other arguments in function plot.default or function curve

Value

Plot the results from a tteICE object

See Also

plot_ate, plot_inc, surv.tteICE, scr.tteICE, tteICE

Examples

```
## load data
data(bmt)
bmt = transform(bmt, d4=d2+d3)
A = as.numeric(bmt$group>1)
bmt$A = A

## simple model fitting and plotting
library(survival)
fit1 = tteICE(Surv(t2,d4,type = "mstate")~A, data=bmt)
plot(fit1, type="ate")
plot(fit1, type="inc")


## plot cumulative incidence functions with p-values
fit2 = surv.tteICE(A, bmt$t2, bmt$d4, "composite")
plot(fit2, type="inc", decrease=TRUE, ylim=c(0,1),
     plot.configs=list(show.p.value=TRUE))

## plot treatment effects for semicompeting risk data
fit3 = scr.tteICE(A, bmt$t1, bmt$d1, bmt$t2, bmt$d2, "composite")
plot(fit3, type="ate", ylim=c(-1,1), xlab="time",
     plot.configs=list(col="red"))
```

---

plot_ate *Plot estimated treatment effects*

Description

This function plots the estimated treatment effect, defined as the difference in potential cumulative incidences under treated and control groups, along with pointwise confidence intervals.

Usage

```
plot_ate(
  fit,
  decrease = FALSE,
  conf.int = 0.95,
  xlab = "Time",
  ylim = c(-1, 1),
  xlim = NULL,
  plot.configs = list(ylab = NULL, main = NULL, lty = 1, lwd = 2, col = "black",
    add.null.line = TRUE, null.line.lty = 2, ci.lty = 5, ci.lwd = 1.5, ci.col =
    "darkgrey"),
  ...
)
```

Arguments

`fit`	A fitted object returned by the function `tteICE`, `surv.tteICE`, or `scr.tteICE`.
`decrease`	A logical value indicating the type of curve difference to display. If `decrease = FALSE` (default), the difference in cumulative incidence functions (CIFs) is plotted. If `decrease = TRUE`, the difference in survival functions is plotted instead.
`conf.int`	Confidence level for the pointwise confidence intervals If `conf.int = NULL`, no confidence intervals are provided.
`xlab`	Label for the x-axis.
`ylim`	A numeric vector of length 2 specifying the limits of the y-axis. Defaults to `ylim = c(-1, 1)`.
`xlim`	A numeric vector of length 2 specifying the limits of the x-axis. If `xlim = NULL` (default), the limits are determined automatically from the data.
`plot.configs`	A named `list` of additional plot configurations. Common entries include: • `ylab`: character, label for the y-axis (default: `ylab=NULL`, use the default label). • `main`: character, title for the plot (default: `main=NULL`, use the default label). • `lty`: line type for effect curve (default: `lty=1`). • `lwd`: line width for effect curve (default: `lwd=2`). • `col`: line color for effect curve (default: `col="black"`). • `add.null.line`: logical, whether to draw a horizontal line at 0 (default: `add.null.line=TRUE`, add the null line). • `null.line.lty`: line type for horizontal line at 0 (default: `null.line.lty=2`. • `ci.lty`: line type for confidence interval curves (default: `ci.lty=5`). • `ci.lwd`: line width for confidence interval curves (default: `ci.lwd=1.5`). • `ci.col`: line color for confidence interval curves (default: `ci.col="darkgrey"`).
`...`	Additional graphical arguments passed to function `plot.default` or function `curve`

Value

Plot the average treatment effect (ATE) results from a tteICE object

See Also

plot.default, points, curve, plot.tteICE

Examples

```
## Load data
data(bmt)
bmt = transform(bmt, d4=d2+d3)
A = as.numeric(bmt$group>1)
bmt$A = A

## simple model fitting and plotting
library(survival)
fit = tteICE(Surv(t2,d4,type = "mstate")~A, data=bmt)
plot_ate(fit)

## model fitting using competing risk data
fit1 = surv.tteICE(A, bmt$t2, bmt$d4, 'composite')

## Plot asymptotic confidence intervals based on explicit formulas
plot_ate(fit1, ylim=c(-0.4,0.4))

## Plot bootstrap confidence intervals
fit2 = surv.tteICE(A, bmt$t2, bmt$d4, 'natural', nboot=50) ## SE=0??
plot_ate(fit2, ylim=c(-0.4,0.4))

## Model with semicompeting risk data
fit3 = scr.tteICE(A, bmt$t1, bmt$d1, bmt$t2, bmt$d2, "composite")

## Plot asymptotic confidence intervals based on explicit formulas
plot_ate(fit3, ylim=c(-0.4,0.4),
         plot.configs=list(add.null.line=FALSE))

## Plot bootstrap confidence intervals
fit4 = scr.tteICE(A, bmt$t1, bmt$d1, bmt$t2, bmt$d2,
                  "composite", nboot=50)           ## SE=0??

plot_ate(fit4, ylim=c(-0.4,0.4),
         plot.configs=list(add.null.line=FALSE, lty=2, main=""))
```

---

plot_inc *Plot estimated cumulative incidence functions (CIFs)*

Description

This function plots the estimated potential cumulative incidence function, along with pointwise confidence intervals.

Usage

```
plot_inc(
  fit,
  decrease = FALSE,
  conf.int = 0.95,
  xlab = "Time",
  xlim = NULL,
  ylim = c(0, 1),
 plot.configs = list(ylab = NULL, main = NULL, lty = 1, lwd = 2, ci.lty = 5, ci.lwd =
  1.5, legend = c("Treated", "Control"), col = c("brown", "darkcyan"), legend.cex =
    0.9, show.p.value = TRUE),
  ...
)
```

Arguments

`fit`	A fitted object returned by the function `tteICE`, `surv.tteICE`, or `scr.tteICE`.
`decrease`	A logical variable indicating the type of curve to display. If `decrease = FALSE` (default), cumulative incidence functions (CIFs) are plotted. If `decrease = TRUE`, survival functions are plotted instead.
`conf.int`	Confidence level for the pointwise confidence intervals If `conf.int = NULL`, no confidence intervals are provided.
`xlab`	Label for the x-axis.
`xlim`	A numeric vector of length 2 specifying the limits of the x-axis. If `xlim = NULL` (default), the limits are determined automatically from the data.
`ylim`	A numeric vector of length 2 specifying the limits of the y-axis. Defaults to `ylim = c(0, 1)`.
`plot.configs`	A named `list` of additional plot configurations. Common entries include: • `ylab`: character, label for the y-axis (default: `ylab=NULL`, use the default label). • `main`: character, title for the plot (default: `main=NULL`, use the default label). • `lty`: line type for the curve (default: `lty=1`). • `lwd`: line width for the curve (default: `lwd=2`). • `ci.lty`: line type for confidence interval curves (default: `ci.lty=5`, `ci.lwd=1.5`). • `ci.lwd`: line width for confidence interval curves (default: `ci.lwd=1.5`). • `legend`: legend for the two group (default: `legend=c('Treated','Control')`). • `col`: color of the curve for the two group (default: `col=c('brown','darkcyan')`). • `legend.cex`: font size for the legend (default: `legend.cex=0.9`). • `show.p.value`: whether to show the p-value between two groups (default: `show.p.value=TRUE`, show the p-value)
`...`	Additional graphical arguments passed to function `plot.default` or function `curve`

Value

Plot the cumulative incidence function results from a tteICE object

See Also

plot.default, points, curve, plot.tteICE

Examples

```
## load data
data(bmt)
bmt = transform(bmt, d4=d2+d3)
A = as.numeric(bmt$group>1)
bmt$A = A

## simple model fitting and plotting
library(survival)
fit = tteICE(Surv(t2,d4,type = "mstate")~A, data=bmt)
plot_inc(fit)

## model fitting using competing risk data
fit1 = surv.tteICE(A, bmt$t2, bmt$d4, 'treatment')

## plot asymptotic confidence intervals based on explicit formulas
plot_inc(fit1, ylim=c(0,1),
         plot.configs=list(legend=c('AML','ALL'), show.p.value=FALSE) )

## plot bootstrap confidence intervals
fit2 = surv.tteICE(A, bmt$t2, bmt$d4, 'treatment', nboot=50)
plot_inc(fit2, ylim=c(0,1),
         plot.configs=list(legend=c('AML','ALL')))

## model fitting using semicompeting risk data
fit3 = scr.tteICE(A, bmt$t1, bmt$d1, bmt$t2, bmt$d2, "composite")

## plot asymptotic confidence intervals based on explicit formulas
plot_inc(fit3, ylim=c(0,1), plot.configs=list(add.null.line=FALSE))

## plot bootstrap confidence intervals
fit4 = scr.tteICE(A, bmt$t1, bmt$d1, bmt$t2, bmt$d2,
                  "composite", nboot=50) ##??
plot_inc(fit4, ylim=c(0,1),
         plot.configs=list(lty=2, lwd=3, main="My title"))
```

---

predict.tteICE *Predict method for 'tteICE' objects at specific time points*

Description

This function predicts the potential cumulative incidence function and treatment effect at specific time points.

Usage

```
## S3 method for class 'tteICE'
predict(object, timeset = NULL, ...)
```

Arguments

object	A fitted object returned by the function tteICE, surv.tteICE, or scr.tteICE.
timeset	Time at which to predict the risk. If timeset=NULL, risks will be predict at the quartiles of the maximum follow-up time.
...	Other arguments in function predict

Value

A matrix with each row being time points, potential cumulative incidences (under treated and under control), treatment effects, standard errors, and P-values.

predict a tteICE object. The meanings of each row are: time points, potential cumulative incidences (under treated and under control), treatment effects, standard errors, and P-values.

See Also

scr.tteICE, surv.tteICE, tteICE surv.boot

surv.tteICE, scr.tteICE, tteICE

Examples

```
## load data
data(bmt)
bmt = transform(bmt, d4=d2+d3)
A = as.numeric(bmt$group>1)
bmt$A = A
X = as.matrix(bmt[,c('z1','z3','z5')])

## predict results at specified time points
## model fitting using semicompeting risk data
fit1 = scr.tteICE(A, bmt$t1, bmt$d1, bmt$t2, bmt$d2, "composite")
predict(fit1, timeset=c(670,2000))

## predict results without specifying any time points
## model fitting using competing risk data
fit2 = surv.tteICE(A, bmt$t2, bmt$d4, "composite")
predict(fit2)

## a simpler way
library(survival)
fit3 = tteICE(Surv(t2, d4, type = "mstate")~A|z1+z3+z5,
              data=bmt, strategy="composite", method='eff')
predict(fit3, timeset=c(670,2000))
predict(fit3)
```

print.tteICE *Print method for 'tteICE' objects*

Description

This function summarizes the results

Usage

```
## S3 method for class 'tteICE'
print(x, digits = 4, ...)
```

Arguments

x	A fitted object returned by the function tteICE, surv.tteICE, or scr.tteICE.
digits	The digits of the results
...	Other arguments in function print.default

Value

Print the summary of a tteICE object

See Also

surv.tteICE, scr.tteICE, tteICE

Examples

```
## load data
data(bmt)
bmt = transform(bmt, d4=d2+d3)
A = as.numeric(bmt$group>1)
bmt$A = A

## print the results
fit1 = surv.tteICE(A, bmt$t2, bmt$d4, "composite")
print(fit1)

fit2 = scr.tteICE(A, bmt$t1, bmt$d1, bmt$t2, bmt$d2, "composite")
print(fit2, digits=2)

library(survival)
fit3 = tteICE(Surv(t2, d4, type = "mstate")~A,
              data=bmt, strategy="composite", method='eff')
print(fit3, digits=3)
```

`scr.composite` *Fit CIFs using composite variable strategy for semicompeting risks data*

Description

This function nonparametrically estimates the potential cumulative incidence function using composite variable strategy (semicompeting risks data structure). This strategy adopts the first occurrence of either the intermediate or primary event as the event of interest.

Usage

```
scr.composite(
  A,
  Time,
  status,
  Time_int,
  status_int,
  weights = rep(1, length(A))
)
```

Arguments

`A`	Treatment indicator, 1 for treatment and 0 for control.
`Time`	Time to the primary (terminal) event.
`status`	Indicator of the primary (terminal) event, 1 for event and 0 for censoring.
`Time_int`	Time to the intercurrent event.
`status_int`	Indicator of the intercurrent event, 1 for event and 0 for censoring.
`weights`	Weight for each subject.

Details

The composite variable strategy addresses the problem of intercurrent events by expanding the outcome variables. It aggregates the intercurrent event and the primary outcome event into a single composite outcome variable. The idea is not new in the context of progression-free survival, where the composite outcome variable is defined as the occurrence of either a non-terminal event (e.g., cancer progression) or a terminal event (e.g., death). One widely used composite outcome variable has the form $Q(w) = \min\{T(w), R(w)\}$ for $w = 1, 0$. When this simple form is adopted, the difference in counterfactual cumulative incidences is $\tau(t) = P(Q(1) < t) - P(Q(0) < t)$, representing the difference in probabilities of experiencing either intercurrent events or primary outcome events during $(0, t)$ under active treatment and placebo.

Value

A list including

time1 Time points in the treated group.

time0 Time points in the control group.

cif1 Estimated cumulative incidence function in the treated group.

cif0 Estimated cumulative incidence function in the control group.

se1 Standard error of the estimated cumulative incidence function in the treated group.

se0 Standard error of the estimated cumulative incidence function in the control group.

time Time points in both groups.

ate Estimated treatment effect (difference in cumulative incidence functions).

se Standard error of the estimated treatment effect.

p.val P value of testing the treatment effect based on logrank test.

See Also

`scr.composite.eff`, `scr.tteICE`

`scr.composite.eff` *Fit CIFs using composite variable strategy for semicompeting risks data, based on efficient influence functions*

Description

This function estimates the potential cumulative incidence function based on efficient influence functions using composite variable strategy (semicompeting risks data structure). Cox models are employed for survival models. This strategy adopts the first occurrence of either the intermediate or primary event as the event of interest.

Usage

```
scr.composite.eff(A, Time, status, Time_int, status_int, X = NULL)
```

Arguments

`A`	Treatment indicator, 1 for treatment and 0 for control.
`Time`	Time to the primary (terminal) event.
`status`	Indicator of the primary (terminal) event, 1 for event and 0 for censoring.
`Time_int`	Time to the intercurrent event.
`status_int`	Indicator of the intercurrent event, 1 for event and 0 for censoring.
`X`	Baseline covariates.

Details

The composite variable strategy addresses the problem of intercurrent events by expanding the outcome variables. It aggregates the intercurrent event and the primary outcome event into a single composite outcome variable. The idea is not new in the context of progression-free survival, where the composite outcome variable is defined as the occurrence of either a non-terminal event (e.g., cancer progression) or a terminal event (e.g., death). One widely used composite outcome variable has the form $Q(w) = \min\{T(w), R(w)\}$ for $w = 1, 0$. When this simple form is adopted, the difference in counterfactual cumulative incidences is $\tau(t) = P(Q(1) < t) - P(Q(0) < t)$, representing the difference in probabilities of experiencing either intercurrent events or primary outcome events during $(0, t)$ under active treatment and placebo.

Value

A list including

time1 Time points in the treated group.

time0 Time points in the control group.

cif1 Estimated cumulative incidence function in the treated group.

cif0 Estimated cumulative incidence function in the control group.

se1 Standard error of the estimated cumulative incidence function in the treated group.

se0 Standard error of the estimated cumulative incidence function in the control group.

time Time points in both groups.

ate Estimated treatment effect (difference in cumulative incidence functions).

se Standard error of the estimated treatment effect.

p.val P value of testing the treatment effect based on the efficient influence function of the restricted mean survival time lost by the end of study.

See Also

`scr.composite`, `scr.tteICE`

---

scr.natural *Fit CIFs using hypothetical strategy (I) for semicompeting risks data*

Description

This function nonparametrically estimates the potential cumulative incidence function using hypothetical strategy (semicompeting risks data structure). The intercurrent event is only permitted under treated if it would occur under control.

Usage

```
scr.natural(A, Time, status, Time_int, status_int, weights = rep(1, length(A)))
```

Arguments

A	Treatment indicator, 1 for treatment and 0 for control.
Time	Time to the primary (terminal) event.
status	Indicator of the primary (terminal) event, 1 for event and 0 for censoring.
Time_int	Time to the intercurrent event.
status_int	Indicator of the intercurrent event, 1 for event and 0 for censoring.
weights	Weight for each subject.

Details

The hypothetical strategy envisions a hypothetical clinical trial condition where the occurrence of intercurrent events is restricted in certain ways. By doing so, the distribution of potential outcomes under the hypothetical scenario can capture the impact of intercurrent events explicitly through a pre-specified criterion. We use $T'(w), w = 1, 0$ to denote the time to the primary outcome event in the hypothetical scenario. The time-dependent treatment effect specific to this hypothetical scenario is written as $\tau(t) = P(T'(1) < t) - P(T'(0) < t)$, representing the difference in probabilities of experiencing primary outcome events during $(0, t)$ in the pre-specified hypothetical scenario under active treatment and placebo.

The key question is how to envision $T'(w)$. We manipulate the hazard specific to intercurrent event $\lambda_2(t; w)$ while assuming the hazard specific to the primary outcome event $\lambda_1(t; w)$ remains unchanged. Specifically, we envision that the intercurrent events that occurred when individuals were assigned to test drugs were only permitted if these intercurrent events would have also occurred if these individuals had been assigned to the placebo. In this hypothetical scenario, when assigned to placebo, individuals would be equally likely to experience intercurrent events as they are assigned to placebo in the real-world trial in terms of the hazards; when assigned to test drug, the hazard of intercurrent events would be identical to that if assigned to placebo in the real-world trial. That is, $\lambda_2'(t; 0) = \lambda_2'(t; 1) = \lambda_2(t; 0)$. The treatment effect corresponds to the natural direct effect, with the hazard of intercurrent events set at the level under control. Markovness is assumed in estimation.

Value

A list including

time1 Time points in the treated group.

time0 Time points in the control group.

cif1 Estimated cumulative incidence function in the treated group.

cif0 Estimated cumulative incidence function in the control group.

se1 Standard error of the estimated cumulative incidence function in the treated group.

se0 Standard error of the estimated cumulative incidence function in the control group.

time Time points in both groups.

ate Estimated treatment effect (difference in cumulative incidence functions).

se Standard error of the estimated treatment effect.

p.val P value of testing the treatment effect based on logrank test.

See Also

scr.natural.eff, scr.tteICE

---

scr.natural.eff *Fit CIFs using hypothetical strategy (I) for semicompeting risks data, based on efficient influence functions*

Description

This function estimates the potential cumulative incidence function based on efficient influence functions using hypothetical strategy (semicompeting risks data structure). Cox models are employed for survival models. The intercurrent event is only permitted under treated if it would occur under control.

Usage

```
scr.natural.eff(A, Time, status, Time_int, status_int, X = NULL)
```

Arguments

A	Treatment indicator, 1 for treatment and 0 for control.
Time	Time to the primary (terminal) event.
status	Indicator of the primary (terminal) event, 1 for event and 0 for censoring.
Time_int	Time to the intercurrent event.
status_int	Indicator of the intercurrent event, 1 for event and 0 for censoring.
X	Baseline covariates.

Details

The hypothetical strategy envisions a hypothetical clinical trial condition where the occurrence of intercurrent events is restricted in certain ways. By doing so, the distribution of potential outcomes under the hypothetical scenario can capture the impact of intercurrent events explicitly through a pre-specified criterion. We use $T'(w), w = 1, 0$ to denote the time to the primary outcome event in the hypothetical scenario. The time-dependent treatment effect specific to this hypothetical scenario is written as $\tau(t) = P(T'(1) < t) - P(T'(0) < t)$, representing the difference in probabilities of experiencing primary outcome events during $(0, t)$ in the pre-specified hypothetical scenario under active treatment and placebo.

The key question is how to envision $T'(w)$. We manipulate the hazard specific to intercurrent event $\lambda_2(t; w)$ while assuming the hazard specific to the primary outcome event $\lambda_1(t; w)$ remains unchanged. Specifically, we envision that the intercurrent events that occurred when individuals were assigned to test drugs were only permitted if these intercurrent events would have also occurred if these individuals had been assigned to the placebo. In this hypothetical scenario, when assigned to placebo, individuals would be equally likely to experience intercurrent events as they are assigned to placebo in the real-world trial in terms of the hazards; when assigned to test drug, the hazard of intercurrent events would be identical to that if assigned to placebo in the real-world trial. That is, $\lambda_2'(t; 0) = \lambda_2'(t; 1) = \lambda_2(t; 0)$. The treatment effect corresponds to the natural direct effect, with the hazard of intercurrent events set at the level under control. Markovness is assumed in estimation.

Value

A list including

time1 Time points in the treated group.

time0 Time points in the control group.

cif1 Estimated cumulative incidence function in the treated group.

cif0 Estimated cumulative incidence function in the control group.

se1 Standard error of the estimated cumulative incidence function in the treated group.

se0 Standard error of the estimated cumulative incidence function in the control group.

time Time points in both groups.

ate Estimated treatment effect (difference in cumulative incidence functions).

se Standard error of the estimated treatment effect.

p.val P value of testing the treatment effect based on the efficient influence function of the restricted mean survival time lost by the end of study.

See Also

`scr.natural`, `scr.tteICE`

`scr.principal` *Fit CIFs using principal stratum strategy for semicompeting risks data*

Description

This function nonparametrically estimates the potential cumulative incidence function using principal stratum strategy (semicompeting risks data structure). The estimand is defined in a subpopulation where intercurrent events would never occur regardless of treatment conditions.

Usage

```
scr.principal(
  A,
  Time,
  status,
  Time_int,
  status_int,
  weights = rep(1, length(A))
)
```

Arguments

A	Treatment indicator, 1 for treatment and 0 for control.
Time	Time to the primary (terminal) event.
status	Indicator of the primary (terminal) event, 1 for event and 0 for censoring.
Time_int	Time to the intercurrent event.
status_int	Indicator of the intercurrent event, 1 for event and 0 for censoring.
weights	Weight for each subject.

Details

The principal stratum strategy aims to stratify the population into subpopulations based on the joint potential occurrences of intercurrent events under the two treatment assignments $(R(1), R(0))$. Suppose we are interested in a principal stratum comprised of individuals who would never experience intercurrent events, regardless of which treatment they receive. This principal stratum can be indicated by $\{R(1) = R(0) = \infty\}$. The treatment effect is now defined within this subpopulation, $\tau(t) = P(T(1) < t \mid R(1) = R(0) = \infty) - P(T(0) < t \mid R(1) = R(0) = \infty)$, representing the difference in probabilities of experiencing primary outcome events during $(0, t)$ under active treatment and placebo in the subpopulation that will not experience intercurrent events regardless of treatment during $(0, t)$. A principal ignorability assumption is made for identification. If the size of the target principal stratum is small, the results could be highly variable.

Value

A list including

time1 Time points in the treated group.

time0 Time points in the control group.

cif1 Estimated cumulative incidence function in the treated group.

cif0 Estimated cumulative incidence function in the control group.

se1 Standard error of the estimated cumulative incidence function in the treated group.

se0 Standard error of the estimated cumulative incidence function in the control group.

time Time points in both groups.

ate Estimated treatment effect (difference in cumulative incidence functions).

se Standard error of the estimated treatment effect.

p.val P value of testing the treatment effect, which is not available under this strategy.

See Also

scr.principal.eff, scr.tteICE

`scr.principal.eff` *Fit CIFs using principal stratum strategy for semicompeting risks data, based on efficient influence functions*

Description

This function estimates the potential cumulative incidence function based on efficient influence functions using principal stratum strategy (semicompeting risks data structure). Cox models are employed for survival models. The estimand is defined in a subpopulation where intercurrent events would never occur regardless of treatment conditions.

Usage

```
scr.principal.eff(A, Time, status, Time_int, status_int, X = NULL)
```

Arguments

`A`	Treatment indicator, 1 for treatment and 0 for control.
`Time`	Time to the primary (terminal) event.
`status`	Indicator of the primary (terminal) event, 1 for event and 0 for censoring.
`Time_int`	Time to the intercurrent event.
`status_int`	Indicator of the intercurrent event, 1 for event and 0 for censoring.
`X`	Baseline covariates.

Details

The principal stratum strategy aims to stratify the population into subpopulations based on the joint potential occurrences of intercurrent events under the two treatment assignments $(R(1), R(0))$. Suppose we are interested in a principal stratum comprised of individuals who would never experience intercurrent events, regardless of which treatment they receive. This principal stratum can be indicated by $\{R(1) = R(0) = \infty\}$. The treatment effect is now defined within this subpopulation, $\tau(t) = P(T(1) < t \mid R(1) = R(0) = \infty) - P(T(0) < t \mid R(1) = R(0) = \infty)$, representing the difference in probabilities of experiencing primary outcome events during $(0, t)$ under active treatment and placebo in the subpopulation that will not experience intercurrent events regardless of treatment during $(0, t)$. A principal ignorability assumption is made for identification. If the size of the target principal stratum is small, the results could be highly variable.

Value

A list including

time1 Time points in the treated group.

time0 Time points in the control group.

cif1 Estimated cumulative incidence function in the treated group.

cif0 Estimated cumulative incidence function in the control group.

se1 Standard error of the estimated cumulative incidence function in the treated group.

se0 Standard error of the estimated cumulative incidence function in the control group.

time Time points in both groups.

ate Estimated treatment effect (difference in cumulative incidence functions).

se Standard error of the estimated treatment effect.

p.val P value of testing the treatment effect based on the efficient influence function of the restricted mean survival time lost by the end of study.

See Also

scr.principal, scr.tteICE

`scr.removed` *Fit CIFs using hypothetical strategy (II) for semicompeting risks data*

Description

This function nonparametrically estimates the potential cumulative incidence function using hypothetical strategy (semicompeting risks data structure). The intercurrent event is assumed to be absent in the hypothetical scenario.

Usage

```
scr.removed(A, Time, status, Time_int, status_int, weights = rep(1, length(A)))
```

Arguments

`A`	Treatment indicator, 1 for treatment and 0 for control.
`Time`	Time to the primary (terminal) event.
`status`	Indicator of the primary (terminal) event, 1 for event and 0 for censoring.
`Time_int`	Time to the intercurrent event.
`status_int`	Indicator of the intercurrent event, 1 for event and 0 for censoring.
`weights`	Weight for each subject.

Details

The hypothetical strategy envisions a hypothetical clinical trial condition where the occurrence of intercurrent events is restricted in certain ways. By doing so, the distribution of potential outcomes under the hypothetical scenario can capture the impact of intercurrent events explicitly through a pre-specified criterion. We use $T'(w), w = 1, 0$ to denote the time to the primary outcome event in the hypothetical scenario. The time-dependent treatment effect specific to this hypothetical scenario is written as $\tau(t) = P(T'(1) < t) - P(T'(0) < t)$, representing the difference in probabilities of experiencing primary outcome events during $(0, t)$ in the pre-specified hypothetical scenario under active treatment and placebo.

The key question is how to envision $T'(w)$. We manipulate the hazard specific to intercurrent event $\lambda_2(t;w)$ while assuming the hazard specific to the primary outcome event $\lambda_1(t;w)$ remains unchanged. Specifically, we envision that intercurrent events are absent in the hypothetical scenario for all individuals, so $\lambda_2'(t;0) = \Lambda_2'(t;1) = 0$. This hypothetical scenario leads to an estimand called the marginal cumulative incidence. The treatment effect corresponds to the controlled direct effect with the intercurrent events removed.

Value

A list including

time1 Time points in the treated group.

time0 Time points in the control group.

cif1 Estimated cumulative incidence function in the treated group.

cif0 Estimated cumulative incidence function in the control group.

se1 Standard error of the estimated cumulative incidence function in the treated group.

se0 Standard error of the estimated cumulative incidence function in the control group.

time Time points in both groups.

ate Estimated treatment effect (difference in cumulative incidence functions).

se Standard error of the estimated treatment effect.

p.val P value of testing the treatment effect based on logrank test.

See Also

`scr.removed.eff`, `scr.tteICE`

---

scr.removed.eff *Fit CIFs using hypothetical strategy (II) for semicompeting risks data, based on efficient influence functions*

Description

This function estimates the potential cumulative incidence function based on efficient influence functions using hypothetical strategy (semicompeting risks data structure). Cox models are employed for survival models. The intercurrent event is assumed to be absent in the hypothetical scenario.

Usage

```
scr.removed.eff(A, Time, status, Time_int, status_int, X = NULL)
```

Arguments

A	Treatment indicator, 1 for treatment and 0 for control.
Time	Time to the primary (terminal) event.
status	Indicator of the primary (terminal) event, 1 for event and 0 for censoring.
Time_int	Time to the intercurrent event.
status_int	Indicator of the intercurrent event, 1 for event and 0 for censoring.
X	Baseline covariates.

Details

The hypothetical strategy envisions a hypothetical clinical trial condition where the occurrence of intercurrent events is restricted in certain ways. By doing so, the distribution of potential outcomes under the hypothetical scenario can capture the impact of intercurrent events explicitly through a pre-specified criterion. We use $T'(w), w = 1, 0$ to denote the time to the primary outcome event in the hypothetical scenario. The time-dependent treatment effect specific to this hypothetical scenario is written as $\tau(t) = P(T'(1) < t) - P(T'(0) < t)$, representing the difference in probabilities of experiencing primary outcome events during $(0, t)$ in the pre-specified hypothetical scenario under active treatment and placebo.
The key question is how to envision $T'(w)$. We manipulate the hazard specific to intercurrent event $\lambda_2(t; w)$ while assuming the cause-specific hazard specific to the primary outcome event under no intercurrent events $\lambda_1(t; w)$ remains unchanged. Specifically, we envision that intercurrent events are absent in the hypothetical scenario for all individuals, so $\lambda_2'(t; 0) = \Lambda_2'(t; 1) = 0$. This hypothetical scenario leads to an estimand called the marginal cumulative incidence. The treatment effect corresponds to the controlled direct effect with the intercurrent events removed.

Value

A list including

time1 Time points in the treated group.

time0 Time points in the control group.

cif1 Estimated cumulative incidence function in the treated group.

cif0 Estimated cumulative incidence function in the control group.

se1 Standard error of the estimated cumulative incidence function in the treated group.

se0 Standard error of the estimated cumulative incidence function in the control group.

time Time points in both groups.

ate Estimated treatment effect (difference in cumulative incidence functions).

se Standard error of the estimated treatment effect.

p.val P value of testing the treatment effect based on the efficient influence function of the restricted mean survival time lost by the end of study.

See Also

scr.removed, scr.tteICE

`scr.treatment` *Fit CIFs using treatment policy strategy for semicompeting risks data*

Description

This function nonparametrically estimates the potential cumulative incidence function using treatment policy strategy (semicompeting risks data structure). This strategy ignores the intercurrent event and uses the time to the primary event as it was recorded.

Usage

```
scr.treatment(
  A,
  Time,
  status,
  Time_int,
  status_int,
  weights = rep(1, length(A))
)
```

Arguments

`A`	Treatment indicator, 1 for treatment and 0 for control.
`Time`	Time to the primary (terminal) event.
`status`	Indicator of the primary (terminal) event, 1 for event and 0 for censoring.
`Time_int`	Time to the intercurrent event.
`status_int`	Indicator of the intercurrent event, 1 for event and 0 for censoring.
`weights`	Weight for each subject.

Details

The treatment policy strategy addresses the problem of intercurrent events by expanding the initial treatment conditions to a treatment policy. This strategy is applicable only if intercurrent events do not hinder primary outcome events. The treatments under comparison are now two treatment policies: $(w, R(w))$, where $w = 1, 0$. One policy $(1, R(1))$ involves administering the test drug, along with any naturally occurring intercurrents, whereas the other policy $(0, R(0))$ involves administering a placebo, along with any naturally occurring intercurrents. Thus, the potential outcomes are $T(1, R(1))$ and $T(0, R(0))$. Instead of comparing the test drug and placebo themselves, the contrast of interest is made between the two treatment policies. The difference in cumulative incidences under the two treatment policies is then $\tau(t) = P(T(1, R(1)) < t) - P(T(0, R(0)) < t)$, representing the difference in probabilities of experiencing primary outcome events during $(0, t)$ under active treatment and placebo.
The average treatment effect $\tau^{\text{tp}}(t)$ has a meaningful causal interpretation only when $T(1, R(1))$ and $T(0, R(0))$ are well defined. Because the treatment policy includes the occurrence of the intercurrent event as natural, the entire treatment policy is determined by manipulating the initial treatment condition w only. Therefore, we can simplify the notations $T(w, R(w)) =$

$T(w)$ in defining estimands. As such, $\tau(t) = P(T(1)) < t) - P(T(0) < t)$ as the intention-to-treat analysis.

Value

A list including

time1 Time points in the treated group.

time0 Time points in the control group.

cif1 Estimated cumulative incidence function in the treated group.

cif0 Estimated cumulative incidence function in the control group.

se1 Standard error of the estimated cumulative incidence function in the treated group.

se0 Standard error of the estimated cumulative incidence function in the control group.

time Time points in both groups.

ate Estimated treatment effect (difference in cumulative incidence functions).

se Standard error of the estimated treatment effect.

p.val P value of testing the treatment effect based on logrank test.

See Also

`scr.treatment.eff`, `scr.tteICE`

---

scr.treatment.eff *Fit CIFs using treatment policy strategy for semicompeting risks data, based on efficient influence functions*

Description

This function estimates the potential cumulative incidence function based on efficient influence functions using treatment policy strategy (semicompeting risks data structure). Cox models are employed for the survival model. This strategy ignores the intercurrent event and uses the time to the primary event as it was recorded.

Usage

```
scr.treatment.eff(A, Time, status, Time_int, status_int, X = NULL)
```

Arguments

`A`	Treatment indicator, 1 for treatment and 0 for control.
`Time`	Time to the primary (terminal) event.
`status`	Indicator of the primary (terminal) event, 1 for event and 0 for censoring.
`Time_int`	Time to the intercurrent event.
`status_int`	Indicator of the intercurrent event, 1 for event and 0 for censoring.
`X`	Baseline covariates.

Details

The treatment policy strategy addresses the problem of intercurrent events by expanding the initial treatment conditions to a treatment policy. This strategy is applicable only if intercurrent events do not hinder primary outcome events. The treatments under comparison are now two treatment policies: $(w, R(w))$, where $w = 1, 0$. One policy $(1, R(1))$ involves administering the test drug, along with any naturally occurring intercurrents, whereas the other policy $(0, R(0))$ involves administering a placebo, along with any naturally occurring intercurrents. Thus, the potential outcomes are $T(1, R(1))$ and $T(0, R(0))$. Instead of comparing the test drug and placebo themselves, the contrast of interest is made between the two treatment policies. The difference in cumulative incidences under the two treatment policies is then $\tau(t) = P(T(1, R(1)) < t) - P(T(0, R(0)) < t)$, representing the difference in probabilities of experiencing primary outcome events during $(0, t)$ under active treatment and placebo.
The average treatment effect $\tau^{\text{tp}}(t)$ has a meaningful causal interpretation only when $T(1, R(1))$ and $T(0, R(0))$ are well defined. Because the treatment policy includes the occurrence of the intercurrent event as natural, the entire treatment policy is determined by manipulating the initial treatment condition w only. Therefore, we can simplify the notations $T(w, R(w)) = T(w)$ in defining estimands. As such, $\tau(t) = P(T(1)) < t) - P(T(0) < t)$ as the intention-to-treat analysis.

Value

A list including

time1 Time points in the treated group.

time0 Time points in the control group.

cif1 Estimated cumulative incidence function in the treated group.

cif0 Estimated cumulative incidence function in the control group.

se1 Standard error of the estimated cumulative incidence function in the treated group.

se0 Standard error of the estimated cumulative incidence function in the control group.

time Time points in both groups.

ate Estimated treatment effect (difference in cumulative incidence functions).

se Standard error of the estimated treatment effect.

p.val P value of testing the treatment effect based on the efficient influence function of the restricted mean survival time lost by the end of study.

See Also

`scr.treatment`, `scr.tteICE`

`scr.tteICE` *Fit CIFs for semicompeting risks time-to-event data with intercurrent events.*

Description

This function estimates the potential cumulative incidence function for time-to event data under ICH E9 (R1) to address intercurrent events. The input data should be of a semicompeting risks structure.

Usage

```
scr.tteICE(
  A,
  Time,
  status,
  Time_int,
  status_int,
  strategy = "composite",
  cov1 = NULL,
  method = "np",
  weights = NULL,
  subset = NULL,
  na.rm = FALSE,
  nboot = 0,
  seed = 0
)
```

Arguments

`A`	Treatment indicator, 1 for treatment and 0 for control.
`Time`	Time to the primary (terminal) event.
`status`	Indicator of the primary (terminal) event, 1 for event and 0 for censoring.
`Time_int`	Time to the intercurrent event.
`status_int`	Indicator of the intercurrent event, 1 for event and 0 for censoring.
`strategy`	Strategy to address intercurrent events, `"treatment"` indicating treatment policy strategy, `"composite"` indicating composite variable strategy, `"natural"` indicating hypothetical strategy (Scenario I, controlling the hazard of intercurrent events), `"removed"` indicating hypothetical strategy (Scenario II, removing intercurrent events), `"whileon"` indicating while on treatment strategy, and `"principal"` indicating principal stratum strategy.
`cov1`	Baseline covariates.
`method`	Estimation method, `"np"` indicating nonparametric estimation, `"ipw"` indicating invserse treatment probability weighting, `"eff"` indicating semiparametrically efficient estimation based on efficient influence functions.

weights	Weight for each subject.
subset	Subset, either numerical or logical.
na.rm	Whether to remove missing values.
nboot	Number of resamplings in the boostrapping method. If nboot is 0 or 1, then asymptotic standard error based on the explicit form is calculated instead of bootstrapping.
seed	Seed for bootstrapping.

Details

Background Intercurrent events refer to the events occurring after treatment initiation of clinical trials that affect either the interpretation of or the existence of the measurements associated with the clinical question of interest. The International Conference on Harmonization (ICH) E9 (R1) addendum proposed five strategies to address intercurrent events, namely, treatment policy strategy, composite variable strategy, while on treatment strategy, hypothetical strategy, and principal stratum strategy. To answer a specific scientific question, a strategy with a particular estimand is chosen before the study design.

Model We adopt the potential outcomes framework that defines a causal estimand as the contrast between functionals of potential outcomes. Consider a randomized controlled trial with n individuals randomly assigned to one of two treatment conditions, denoted by w, where $w = 1$ represents the active treatment (a test drug) and $w = 0$ represents the control (placebo). Assume that all patients adhere to their treatment assignments and do not discontinue treatment. Associated with individual $i = 1, ..., n$ are two potential time-to-event primary outcomes $T_i(1)$ and $T_i(0)$, if any, which represent the time durations from treatment initiation to the primary outcome event under two treatment assignments respectively. Let $R_i(1)$ and $R_i(0)$ denote the occurrence time of potential intercurrent events, if any, under the two treatment assignments, respectively. Intercurrent events are considered as absent if no post-treatment intercurrent events occur until the end of study.

Estimand We adopt the potential cumulative incidences under both treatment assignments as the target estimands. Potential cumulative incidences describe the probability of time-to-event outcomes occurring at each time point. We define the treatment effect as the contrast of two potential cumulative incidences. Cumulative incidences are model-free and collapsible, enjoying causal interpretations.

Value

A list including the fitted object and input variables.

References

Deng, Y., Han, S., & Zhou, X. H. (2025). Inference for Cumulative Incidences and Treatment Effects in Randomized Controlled Trials With Time-to-Event Outcomes Under ICH E9 (R1). *Statistics in Medicine*. doi:10.1002/sim.70091

See Also

surv.boot, surv.tteICE

Examples

```
## load data
data(bmt)
bmt = transform(bmt, d4=d2+d3)
A = as.numeric(bmt$group>1)
X = as.matrix(bmt[,c('z1','z3','z5')])

## Composite variable strategy,
## nonparametric estimation without covariates
fit1 = scr.tteICE(A, bmt$t1, bmt$d1, bmt$t2, bmt$d2, "composite")

fit10 = scr.tteICE(A, bmt$t1, bmt$d1, bmt$t2, bmt$d2, "aa") ## warning message


## Hypothetical strategy (natural effects),
## nonparametric estimation with inverse probability weighting
fit2 = scr.tteICE(A, bmt$t1, bmt$d1, bmt$t2, bmt$d2, "natural", X, method='ipw')

## nonparametric estimation with weights as non-standardized inverse probability score
ps = predict(glm(A ~ X, family='binomial'), type='response')
w = A/ps + (1-A)/(1-ps)
fit2 = scr.tteICE(A, bmt$t1, bmt$d1, bmt$t2, bmt$d2, "natural", weights=w)

## Hypothetical strategy (removing intercurrent events),
## semiparametrically efficient estimation with covariates
fit3 = scr.tteICE(A, bmt$t1, bmt$d1, bmt$t2, bmt$d2, "removed", X, method='eff')
```

`scr.whileon` *Fit CIFs using while on treatment strategy for semicompeting risks data*

Description

This function nonparametrically estimates the potential cumulative incidence function using while on treatment strategy (semicompeting risks data structure). This strategy can be understood as the competing risks model, which gives the subdistribution of the primary event.

Usage

```
scr.whileon(A, Time, status, Time_int, status_int, weights = rep(1, length(A)))
```

Arguments

`A`	Treatment indicator, 1 for treatment and 0 for control.
`Time`	Time to the primary (terminal) event.
`status`	Indicator of the primary (terminal) event, 1 for event and 0 for censoring.
`Time_int`	Time to the intercurrent event.

`status_int`	Indicator of the intercurrent event, 1 for event and 0 for censoring.
`weights`	Weight for each subject.

Details

The while on treatment strategy considers the measure of outcome variables taken only up to the occurrence of intercurrent events. The failures of primary outcome events should not be counted in the cumulative incidences if intercurrent events occurred. The difference in counterfactual cumulative incidences under this strategy is $\tau(t) = P(T(1) < t, R(1) \geq t) - P(T(0) < t, R(0) \geq t)$, representing the difference in probabilities of experiencing primary outcome events without intercurrent events during $(0, t)$ under active treatment and placebo. The cumulative incidence function is also known as the cause-specific cumulative incidence or subdistribution function.

The while on treatment strategy is closely related to the competing risks model. However, for causal interpretations, it is worth emphasizing that the hazard of $R(1)$ may differ from that of $R(0)$, leading to vast difference in the underlying features of individuals who have not experienced the primary outcome event between treatment conditions at any time $t \in (0, t^*)$, where t^* is the end of study. When the scientific question of interest is the impact of treatment on the primary outcome event, the estimand $\tau(t)$ is hard to interpret if a systematic difference in the risks of intercurrent events between two treatment conditions under comparison is anticipated.

Value

A list including

time1 Time points in the treated group.

time0 Time points in the control group.

cif1 Estimated cumulative incidence function in the treated group.

cif0 Estimated cumulative incidence function in the control group.

se1 Standard error of the estimated cumulative incidence function in the treated group.

se0 Standard error of the estimated cumulative incidence function in the control group.

time Time points in both groups.

ate Estimated treatment effect (difference in cumulative incidence functions).

se Standard error of the estimated treatment effect.

p.val P value of testing the treatment effect based on Gray test.

See Also

`scr.whileon.eff`, `scr.tteICE`

`scr.whileon.eff` *Fit CIFs using while on treatment strategy for semicompeting risks data, based on efficient influence functions*

Description

This function estimates the potential cumulative incidence function based on efficient influence functions using while on treatment strategy (semicompeting risks data structure). Cox models are employed for survival models. This strategy can be understood as the competing risks model, which gives the subdistribution of the primary event.

Usage

```
scr.whileon.eff(A, Time, status, Time_int, status_int, X = NULL)
```

Arguments

`A`	Treatment indicator, 1 for treatment and 0 for control.
`Time`	Time to the primary (terminal) event.
`status`	Indicator of the primary (terminal) event, 1 for event and 0 for censoring.
`Time_int`	Time to the intercurrent event.
`status_int`	Indicator of the intercurrent event, 1 for event and 0 for censoring.
`X`	Baseline covariates.

Details

The while on treatment strategy considers the measure of outcome variables taken only up to the occurrence of intercurrent events. The failures of primary outcome events should not be counted in the cumulative incidences if intercurrent events occurred. The difference in counterfactual cumulative incidences under this strategy is $\tau(t) = P(T(1) < t, R(1) \geq t) - P(T(0) < t, R(0) \geq t)$, representing the difference in probabilities of experiencing primary outcome events without intercurrent events during $(0, t)$ under active treatment and placebo. The cumulative incidence function is also known as the cause-specific cumulative incidence or subdistribution function.

The while on treatment strategy is closely related to the competing risks model. However, for causal interpretations, it is worth emphasizing that the hazard of $R(1)$ may differ from that of $R(0)$, leading to vast difference in the underlying features of individuals who have not experienced the primary outcome event between treatment conditions at any time $t \in (0, t^*)$, where t^* is the end of study. When the scientific question of interest is the impact of treatment on the primary outcome event, the estimand $\tau(t)$ is hard to interpret if a systematic difference in the risks of intercurrent events between two treatment conditions under comparison is anticipated.

Value

A list including

time1 Time points in the treated group.

time0 Time points in the control group.

cif1 Estimated cumulative incidence function in the treated group.

cif0 Estimated cumulative incidence function in the control group.

se1 Standard error of the estimated cumulative incidence function in the treated group.

se0 Standard error of the estimated cumulative incidence function in the control group.

time Time points in both groups.

ate Estimated treatment effect (difference in cumulative incidence functions).

se Standard error of the estimated treatment effect.

p.val P value of testing the treatment effect based on the efficient influence function of the restricted mean survival time lost by the end of study.

See Also

scr.whileon, scr.tteICE

---

summary.tteICE *Summary method for 'tteICE' objects*

Description

This function summarizes the results

Usage

```
## S3 method for class 'tteICE'
summary(object, ...)
```

Arguments

object	A fitted object returned by the function tteICE, surv.tteICE, or scr.tteICE.
...	Other arguments in function summary

Value

A list that consists of summaries of a tteICE object: data type, strategy, estimation method, maximum follow-up time, sample size, treated sample size, controlled sample size, p-value, and predicted risks at quartiles

See Also

surv.tteICE, scr.tteICE, tteICE, print.tteICE

Examples

```
## load data
data(bmt)
bmt = transform(bmt, d4=d2+d3)
A = as.numeric(bmt$group>1)
bmt$A = A
X = as.matrix(bmt[,c('z1','z3','z5')])

## Composite variable strategy,
## nonparametric estimation without covariates
fit1 = scr.tteICE(A, bmt$t1, bmt$d1, bmt$t2, bmt$d2, "composite")
summary(fit1)

fit2 = surv.tteICE(A, bmt$t2, bmt$d4, "composite")
predict(fit2)

library(survival)
fit3 = tteICE(Surv(t2, d4, type = "mstate")~A|z1+z3+z5,
              data=bmt, strategy="composite", method='eff')
summary(fit3)
```

`surv.boot` *Calculate standard errors for estimated CIFs and treatment effects*

Description

This function calculates the standard error for the estimated potential cumulative incidence function and treatment effect. Two methods to calculate the standard error are considered: the asymptotic standard error based on the explicit formula and bootstrapping.

Usage

```
surv.boot(fit, nboot = 0, seed = NULL)
```

Arguments

`fit`	A fitted object returned by the function `tteICE`, `surv.tteICE`, or `scr.tteICE`.
`nboot`	Number of resamplings in the boostrapping method. If `nboot` is 0 or 1, then asymptotic standard error based on the explicit form is calculated instead of bootstrapping.
`seed`	Seed for bootstrapping.

Value

A list including

time Time points in both groups.

cif1 Estimated cumulative incidence function in the treated group.

cif0 Estimated cumulative incidence function in the control group.

se1 Standard error of the estimated cumulative incidence function in the treated group.

se0 Standard error of the estimated cumulative incidence function in the control group.

ate Estimated treatment effect (difference in cumulative incidence functions).

se Standard error of the estimated treatment effect.

strategy Strategy used.

method Estimation method used.

See Also

surv.tteICE, scr.tteICE, tteICE

`surv.composite` *Fit CIFs using composite variable strategy for competing risks data*

Description

This function nonparametrically estimates the potential cumulative incidence function using composite variable strategy (competing risks data structure). This strategy adopts the first occurrence of either the intermediate or primary event as the event of interest.

Usage

```
surv.composite(A, Time, cstatus, weights = rep(1, length(A)))
```

Arguments

`A`	Treatment indicator, 1 for treatment and 0 for control.
`Time`	Time to event.
`cstatus`	Indicator of event, 1 for the primary event, 2 for the intercurrent event, 0 for censoring.
`weights`	Weight for each subject.

Details

The composite variable strategy addresses the problem of intercurrent events by expanding the outcome variables. It aggregates the intercurrent event and the primary outcome event into a single composite outcome variable. The idea is not new in the context of progression-free survival, where the composite outcome variable is defined as the occurrence of either a non-terminal event (e.g., cancer progression) or a terminal event (e.g., death). One widely used composite outcome variable has the form $Q(w) = \min\{T(w), R(w)\}$ for $w = 1, 0$. When this simple form is adopted, the difference in counterfactual cumulative incidences is $\tau(t) = P(Q(1) < t) - P(Q(0) < t)$, representing the difference in probabilities of experiencing either intercurrent events or primary outcome events during $(0, t)$ under active treatment and placebo.

Value

A list including

time1 Time points in the treated group.

time0 Time points in the control group.

cif1 Estimated cumulative incidence function in the treated group.

cif0 Estimated cumulative incidence function in the control group.

se1 Standard error of the estimated cumulative incidence function in the treated group.

se0 Standard error of the estimated cumulative incidence function in the control group.

time Time points in both groups.

ate Estimated treatment effect (difference in cumulative incidence functions).

se Standard error of the estimated treatment effect.

p.val P value of testing the treatment effect based on logrank test.

See Also

`surv.composite.eff`, `surv.tteICE`

---

surv.composite.eff *Fit CIFs using composite variable strategy for competing risks data, based on efficient influence functions*

Description

This function estimates the potential cumulative incidence function based on efficient influence functions using composite variable strategy (competing risks data structure). Cox models are employed for survival models. This strategy adopts the first occurrence of either the intermediate or primary event as the event of interest.

Usage

```
surv.composite.eff(A, Time, cstatus, X = NULL)
```

Arguments

`A`	Treatment indicator, 1 for treatment and 0 for control.
`Time`	Time to event.
`cstatus`	Indicator of event, 1 for the primary event, 2 for the intercurrent event, 0 for censoring.
`X`	Baseline covariates.

Details

The composite variable strategy addresses the problem of intercurrent events by expanding the outcome variables. It aggregates the intercurrent event and the primary outcome event into a single composite outcome variable. The idea is not new in the context of progression-free survival, where the composite outcome variable is defined as the occurrence of either a non-terminal event (e.g., cancer progression) or a terminal event (e.g., death). One widely used composite outcome variable has the form $Q(w) = \min\{T(w), R(w)\}$ for $w = 1, 0$. When this simple form is adopted, the difference in counterfactual cumulative incidences is $\tau(t) = P(Q(1) < t) - P(Q(0) < t)$, representing the difference in probabilities of experiencing either intercurrent events or primary outcome events during $(0, t)$ under active treatment and placebo.

Value

A list including

time1 Time points in the treated group.

time0 Time points in the control group.

cif1 Estimated cumulative incidence function in the treated group.

cif0 Estimated cumulative incidence function in the control group.

se1 Standard error of the estimated cumulative incidence function in the treated group.

se0 Standard error of the estimated cumulative incidence function in the control group.

time Time points in both groups.

ate Estimated treatment effect (difference in cumulative incidence functions).

se Standard error of the estimated treatment effect.

p.val P value of testing the treatment effect based on the efficient influence function of the restricted mean survival time lost by the end of study.

See Also

`surv.composite`, `surv.tteICE`

`surv.HR` *Estimate hazard ratios*

Description

This function estimates the hazard ratio for time-to event data under ICH E9 (R1) to address intercurrent events. Multiple strategies except the principal stratum strategy are allowed.

Usage

```
surv.HR(
  A,
  Time,
  cstatus,
  strategy = "composite",
  cov1 = NULL,
  conf.int = 0.95,
  weights = NULL,
  subset = NULL
)
```

Arguments

A	Treatment indicator, 1 for treatment and 0 for control.
Time	Time to event.
cstatus	Indicator of event, 1 for the primary event, 2 for the intercurrent event, 0 for censoring.
strategy	Strategy to address intercurrent events, "treatment" indicating treatment policy strategy, "composite" indicating composite variable strategy, "natural" indicating hypothetical strategy (Scenario I, controlling the hazard of intercurrent events), "removed" indicating hypothetical strategy (Scenario II, removing intercurrent events), and "whileon" indicating while on treatment strategy.
cov1	Baseline covariates.
conf.int	Level of the confidence interval.
weights	Weight for each subject (not applied to the while on treatment strategy).
subset	Subset, either numerical or logical.

Details

For the treatment policy and hypothetical strategies, the hazard ratio (HR) is given by the Cox regression regarding intercurrent events as censoring. For the composite variable strategy, the hazard ratio is given by the Cox regression regarding the first occurrence of either intercurrent event or primary event as the event of interest. For the while on treatment strategy, the hazard ratio is given by the Fine-Gray subdistribution model. There is no existing method to estimate the hazard ratio using principal stratum strategy.

The weakness of using hazard ratio to infer treatment effects is critical. First, the hazard ratio relies on model specification. Second, the hazard ratio is not collapsible. Therefore, the hazard ratio should only be treated as a descriptive or exploratory measure of the treatment effect.

Value

A list including

logHR Estimated log hazard ratio (logHR) of the treatment effect on the primary event.

se Standard error of the estimated log hazard ratio (logHR).

CI Confidence interval of the hazard ratio (HR).

p.val P value of the hazard ratio.

Examples

```
data(bmt)
bmt = transform(bmt, d4=d2+d3)
A = as.numeric(bmt$group>1)

## composite variable strategy
fit = surv.HR(A, bmt$t2, bmt$d4, "composite")

## while on treatment strategy
X = bmt[,c('z1','z3','z5')]
fit = surv.HR(A, bmt$t2, bmt$d4, "whileon", cov1=X)
```

`surv.natural` *Fit CIFs using hypothetical strategy (I) for competing risks data*

Description

This function nonparametrically estimates the potential cumulative incidence function using hypothetical strategy (competing risks data structure). The intercurrent event is only permitted under treated if it would occur under control.

Usage

```
surv.natural(A, Time, cstatus, weights = rep(1, length(A)))
```

Arguments

`A`	Treatment indicator, 1 for treatment and 0 for control.
`Time`	Time to event.
`cstatus`	Indicator of event, 1 for the primary event, 2 for the intercurrent event, 0 for censoring.
`weights`	Weight for each subject.

Details

The hypothetical strategy envisions a hypothetical clinical trial condition where the occurrence of intercurrent events is restricted in certain ways. By doing so, the distribution of potential outcomes under the hypothetical scenario can capture the impact of intercurrent events explicitly through a pre-specified criterion. We use $T'(w), w = 1, 0$ to denote the time to the primary outcome event in the hypothetical scenario. The time-dependent treatment effect specific to this hypothetical scenario is written as $\tau(t) = P(T'(1) < t) - P(T'(0) < t)$, representing the difference in probabilities of experiencing primary outcome events during $(0, t)$ in the pre-specified hypothetical scenario under active treatment and placebo.

The key question is how to envision $T'(w)$. We manipulate the hazard specific to intercurrent event $\lambda_2(t; w)$ while assuming the hazard specific to the primary outcome event $\lambda_1(t; w)$

remains unchanged. Specifically, we envision that the intercurrent events that occurred when individuals were assigned to test drugs were only permitted if these intercurrent events would have also occurred if these individuals had been assigned to the placebo. In this hypothetical scenario, when assigned to placebo, individuals would be equally likely to experience intercurrent events as they are assigned to placebo in the real-world trial in terms of the hazards; when assigned to test drug, the hazard of intercurrent events would be identical to that if assigned to placebo in the real-world trial. That is, $\lambda_2'(t;0) = \lambda_2'(t;1) = \lambda_2(t;0)$. The treatment effect corresponds to the natural direct effect with the hazard of intercurrent events set at the level under control.

Value

A list including

time1 Time points in the treated group.

time0 Time points in the control group.

cif1 Estimated cumulative incidence function in the treated group.

cif0 Estimated cumulative incidence function in the control group.

se1 Standard error of the estimated cumulative incidence function in the treated group.

se0 Standard error of the estimated cumulative incidence function in the control group.

time Time points in both groups.

ate Estimated treatment effect (difference in cumulative incidence functions).

se Standard error of the estimated treatment effect.

p.val P value of testing the treatment effect based on logrank test.

See Also

`surv.natural.eff`, `surv.tteICE`

`surv.natural.eff` *Fit CIFs using hypothetical strategy (I) for competing risks data, based on efficient influence functions*

Description

This function estimates the potential cumulative incidence function based on efficient influence functions using hypothetical strategy (competing risks data structure). Cox models are employed for survival models. The intercurrent event is only permitted under treated if it would occur under control.

Usage

```
surv.natural.eff(A, Time, cstatus, X = NULL)
```

Arguments

A	Treatment indicator, 1 for treatment and 0 for control.
Time	Time to event.
cstatus	Indicator of event, 1 for the primary event, 2 for the intercurrent event, 0 for censoring.
X	Baseline covariates.

Details

The hypothetical strategy envisions a hypothetical clinical trial condition where the occurrence of intercurrent events is restricted in certain ways. By doing so, the distribution of potential outcomes under the hypothetical scenario can capture the impact of intercurrent events explicitly through a pre-specified criterion. We use $T'(w), w = 1, 0$ to denote the time to the primary outcome event in the hypothetical scenario. The time-dependent treatment effect specific to this hypothetical scenario is written as $\tau(t) = P(T'(1) < t) - P(T'(0) < t)$, representing the difference in probabilities of experiencing primary outcome events during $(0, t)$ in the pre-specified hypothetical scenario under active treatment and placebo.
The key question is how to envision $T'(w)$. We manipulate the hazard specific to intercurrent event $\lambda_2(t; w)$ while assuming the hazard specific to the primary outcome event $\lambda_1(t; w)$ remains unchanged. Specifically, we envision that the intercurrent events that occurred when individuals were assigned to test drugs were only permitted if these intercurrent events would have also occurred if these individuals had been assigned to the placebo. In this hypothetical scenario, when assigned to placebo, individuals would be equally likely to experience intercurrent events as they are assigned to placebo in the real-world trial in terms of the hazards; when assigned to test drug, the hazard of intercurrent events would be identical to that if assigned to placebo in the real-world trial. That is, $\lambda_2'(t; 0) = \lambda_2'(t; 1) = \lambda_2(t; 0)$. The treatment effect corresponds to the natural direct effect with the hazard of intercurrent events set at the level under control.

Value

A list including

time1 Time points in the treated group.

time0 Time points in the control group.

cif1 Estimated cumulative incidence function in the treated group.

cif0 Estimated cumulative incidence function in the control group.

se1 Standard error of the estimated cumulative incidence function in the treated group.

se0 Standard error of the estimated cumulative incidence function in the control group.

time Time points in both groups.

ate Estimated treatment effect (difference in cumulative incidence functions).

se Standard error of the estimated treatment effect.

p.val P value of testing the treatment effect based on the efficient influence function of the restricted mean survival time lost by the end of study.

See Also

surv.natural, surv.tteICE

---

surv.principal *Fit CIFs using principal stratum strategy for competing risks data*

Description

This function nonparametrically estimates the potential cumulative incidence function using principal stratum strategy (competing risks data structure). The estimand is defined in a subpopulation where intercurrent events would never occur regardless of treatment conditions.

Usage

```
surv.principal(A, Time, cstatus, weights = rep(1, length(A)))
```

Arguments

A	Treatment indicator, 1 for treatment and 0 for control.
Time	Time to event.
cstatus	Indicator of event, 1 for the primary event, 2 for the intercurrent event, 0 for censoring.
weights	Weight for each subject.

Details

The principal stratum strategy aims to stratify the population into subpopulations based on the joint potential occurrences of intercurrent events under the two treatment assignments $(R(1), R(0))$. Suppose we are interested in a principal stratum comprised of individuals who would never experience intercurrent events, regardless of which treatment they receive. This principal stratum can be indicated by $\{R(1) = R(0) = \infty\}$. The treatment effect is now defined within this subpopulation, $\tau(t) = P(T(1) < t \mid R(1) = R(0) = \infty) - P(T(0) < t \mid R(1) = R(0) = \infty)$, representing the difference in probabilities of experiencing primary outcome events during $(0, t)$ under active treatment and placebo in the subpopulation that will not experience intercurrent events regardless of treatment during $(0, t)$. A principal ignorability assumption is made for identification. If the size of the target principal stratum is small, the results could be highly variable.

Value

A list including

time1 Time points in the treated group.

time0 Time points in the control group.

cif1 Estimated cumulative incidence function in the treated group.

cif0 Estimated cumulative incidence function in the control group.

se1 Standard error of the estimated cumulative incidence function in the treated group.

se0 Standard error of the estimated cumulative incidence function in the control group.

time Time points in both groups.

ate Estimated treatment effect (difference in cumulative incidence functions).

se Standard error of the estimated treatment effect.

p.val P value of testing the treatment effect, which is not available under this strategy.

See Also

surv.principal.eff, surv.tteICE

`surv.principal.eff` *Fit CIFs using principal stratum strategy for competing risks data, based on efficient influence functions*

Description

This function estimates the potential cumulative incidence function based on efficient influence functions using principal stratum strategy (competing risks data structure). Cox models are employed for survival models. The estimand is defined in a subpopulation where intercurrent events would never occur regardless of treatment conditions.

Usage

```
surv.principal.eff(A, Time, cstatus, X = NULL)
```

Arguments

A	Treatment indicator, 1 for treatment and 0 for control.
Time	Time to event.
cstatus	Indicator of event, 1 for the primary event, 2 for the intercurrent event, 0 for censoring.
X	Baseline covariates.

Details

The principal stratum strategy aims to stratify the population into subpopulations based on the joint potential occurrences of intercurrent events under the two treatment assignments $(R(1), R(0))$. Suppose we are interested in a principal stratum comprised of individuals who would never experience intercurrent events, regardless of which treatment they receive. This principal stratum can be indicated by $\{R(1) = R(0) = \infty\}$. The treatment effect is now defined within this subpopulation, $\tau(t) = P(T(1) < t \mid R(1) = R(0) = \infty) - P(T(0) < t \mid R(1) = R(0) = \infty)$, representing the difference in probabilities of experiencing primary outcome events during $(0, t)$ under active treatment and placebo in the subpopulation that will not experience intercurrent events regardless of treatment during $(0, t)$. A principal ignorability assumption is made for identification. If the size of the target principal stratum is small, the results could be highly variable.

Value

A list including

time1 Time points in the treated group.

time0 Time points in the control group.

cif1 Estimated cumulative incidence function in the treated group.

cif0 Estimated cumulative incidence function in the control group.

se1 Standard error of the estimated cumulative incidence function in the treated group.

se0 Standard error of the estimated cumulative incidence function in the control group.

time Time points in both groups.

ate Estimated treatment effect (difference in cumulative incidence functions).

se Standard error of the estimated treatment effect.

p.val P value of testing the treatment effect based on the efficient influence function of the restricted mean survival time lost by the end of study.

See Also

`surv.principal`, `surv.tteICE`

`surv.removed` *Fit CIFs using hypothetical strategy (II) for competing risks data*

Description

This function nonparametrically estimates the potential cumulative incidence function using hypothetical strategy (competing risks data structure). The intercurrent event is assumed to be absent in the hypothetical scenario.

Usage

```
surv.removed(A, Time, cstatus, weights = rep(1, length(A)))
```

Arguments

`A`	Treatment indicator, 1 for treatment and 0 for control.
`Time`	Time to event.
`cstatus`	Indicator of event, 1 for the primary event, 2 for the intercurrent event, 0 for censoring.
`weights`	Weight for each subject.

Details

The hypothetical strategy envisions a hypothetical clinical trial condition where the occurrence of intercurrent events is restricted in certain ways. By doing so, the distribution of potential outcomes under the hypothetical scenario can capture the impact of intercurrent events explicitly through a pre-specified criterion. We use $T'(w), w = 1, 0$ to denote the time to the primary outcome event in the hypothetical scenario. The time-dependent treatment effect specific to this hypothetical scenario is written as $\tau(t) = P(T'(1) < t) - P(T'(0) < t)$, representing the difference in probabilities of experiencing primary outcome events during $(0, t)$ in the pre-specified hypothetical scenario under active treatment and placebo.
The key question is how to envision $T'(w)$. We manipulate the hazard specific to intercurrent event $\lambda_2(t; w)$ while assuming the hazard specific to the primary outcome event $\lambda_1(t; w)$ remains unchanged. Specifically, we envision that intercurrent events are absent in the hypothetical scenario for all individuals, so $\lambda_2'(t; 0) = \Lambda_2'(t; 1) = 0$. This hypothetical scenario leads to an estimand called the marginal cumulative incidence. The treatment effect corresponds to the controlled direct effect with the intercurrent events removed.

Value

A list including

time1 Time points in the treated group.

time0 Time points in the control group.

cif1 Estimated cumulative incidence function in the treated group.

cif0 Estimated cumulative incidence function in the control group.

se1 Standard error of the estimated cumulative incidence function in the treated group.

se0 Standard error of the estimated cumulative incidence function in the control group.

time Time points in both groups.

ate Estimated treatment effect (difference in cumulative incidence functions).

se Standard error of the estimated treatment effect.

p.val P value of testing the treatment effect based on logrank test.

See Also

`surv.removed.eff`, `surv.tteICE`

---

surv.removed.eff *Fit CIFs using hypothetical strategy (II) for competing risks data, based on efficient influence functions*

Description

This function estimates the potential cumulative incidence function based on efficient influence functions using hypothetical strategy (competing risks data structure). Cox models are employed for survival models. The intercurrent event is assumed to be absent in the hypothetical scenario.

Usage

```
surv.removed.eff(A, Time, cstatus, X = NULL)
```

Arguments

A	Treatment indicator, 1 for treatment and 0 for control.
Time	Time to event.
cstatus	Indicator of event, 1 for the primary event, 2 for the intercurrent event, 0 for censoring.
X	Baseline covariates.

Details

The hypothetical strategy envisions a hypothetical clinical trial condition where the occurrence of intercurrent events is restricted in certain ways. By doing so, the distribution of potential outcomes under the hypothetical scenario can capture the impact of intercurrent events explicitly through a pre-specified criterion. We use $T'(w), w = 1, 0$ to denote the time to the primary outcome event in the hypothetical scenario. The time-dependent treatment effect specific to this hypothetical scenario is written as $\tau(t) = P(T'(1) < t) - P(T'(0) < t)$, representing the difference in probabilities of experiencing primary outcome events during $(0, t)$ in the pre-specified hypothetical scenario under active treatment and placebo.
The key question is how to envision $T'(w)$. We manipulate the hazard specific to intercurrent event $\lambda_2(t; w)$ while assuming the hazard specific to the primary outcome event $\lambda_1(t; w)$ remains unchanged. Specifically, we envision that intercurrent events are absent in the hypothetical scenario for all individuals, so $\lambda_2'(t; 0) = \Lambda_2'(t; 1) = 0$. This hypothetical scenario leads to an estimand called the marginal cumulative incidence. The treatment effect corresponds to the controlled direct effect with the intercurrent events removed.

Value

A list including

time1 Time points in the treated group.

time0 Time points in the control group.

cif1 Estimated cumulative incidence function in the treated group.

cif0 Estimated cumulative incidence function in the control group.

se1 Standard error of the estimated cumulative incidence function in the treated group.

se0 Standard error of the estimated cumulative incidence function in the control group.

time Time points in both groups.

ate Estimated treatment effect (difference in cumulative incidence functions).

se Standard error of the estimated treatment effect.

p.val P value of testing the treatment effect based on the efficient influence function of the restricted mean survival time lost by the end of study.

See Also

surv.removed, surv.tteICE

`surv.treatment` *Fit CIFs using treatment policy strategy for competing risks data*

Description

This function nonparametrically estimates the potential cumulative incidence function using treatment policy strategy (competing risks data structure). This strategy ignores the intercurrent event and uses the time to the primary event as it was recorded.

Usage

```
surv.treatment(A, Time, cstatus, weights = rep(1, length(A)))
```

Arguments

`A`	Treatment indicator, 1 for treatment and 0 for control.
`Time`	Time to event.
`cstatus`	Indicator of event, 1 for the primary event, 2 for the intercurrent event, 0 for censoring.
`weights`	Weight for each subject.

Details

The treatment policy strategy addresses the problem of intercurrent events by expanding the initial treatment conditions to a treatment policy. This strategy is applicable only if intercurrent events do not hinder primary outcome events. The treatments under comparison are now two treatment policies: $(w, R(w))$, where $w = 1, 0$. One policy $(1, R(1))$ involves administering the test drug, along with any naturally occurring intercurrents, whereas the other policy $(0, R(0))$ involves administering a placebo, along with any naturally occurring intercurrents. Thus, the potential outcomes are $T(1, R(1))$ and $T(0, R(0))$. Instead of comparing the test drug and placebo themselves, the contrast of interest is made between the two treatment policies. The difference in cumulative incidences under the two treatment policies is then $\tau(t) = P(T(1, R(1)) < t) - P(T(0, R(0)) < t)$, representing the difference in probabilities of experiencing primary outcome events during $(0, t)$ under active treatment and placebo.
The average treatment effect $\tau^{\text{tp}}(t)$ has a meaningful causal interpretation only when $T(1, R(1))$ and $T(0, R(0))$ are well defined. Because the treatment policy includes the occurrence of the intercurrent event as natural, the entire treatment policy is determined by manipulating the initial treatment condition w only. Therefore, we can simplify the notations $T(w, R(w)) = T(w)$ in defining estimands. As such, $\tau(t) = P(T(1)) < t) - P(T(0) < t)$ as the intention-to-treat analysis.

Value

A list including

time1 Time points in the treated group.

time0 Time points in the control group.

cif1 Estimated cumulative incidence function in the treated group.

cif0 Estimated cumulative incidence function in the control group.

se1 Standard error of the estimated cumulative incidence function in the treated group.

se0 Standard error of the estimated cumulative incidence function in the control group.

time Time points in both groups.

ate Estimated treatment effect (difference in cumulative incidence functions).

se Standard error of the estimated treatment effect.

p.val P value of testing the treatment effect based on logrank test.

See Also

surv.treatment.eff, surv.tteICE

`surv.treatment.eff` *Fit CIFs using treatment policy strategy for competing risks data, based on efficient influence functions*

Description

This function estimates the potential cumulative incidence function based on efficient influence functions using treatment policy strategy (competing risks data structure). Cox models are employed for the survival model. This strategy ignores the intercurrent event and uses the time to the primary event as it was recorded.

Usage

```
surv.treatment.eff(A, Time, cstatus, X = NULL)
```

Arguments

`A`	Treatment indicator, 1 for treatment and 0 for control.
`Time`	Time to event.
`cstatus`	Indicator of event, 1 for the primary event, 2 for the intercurrent event, 0 for censoring.
`X`	Baseline covariates.

Details

The treatment policy strategy addresses the problem of intercurrent events by expanding the initial treatment conditions to a treatment policy. This strategy is applicable only if intercurrent events do not hinder primary outcome events. The treatments under comparison are now two treatment policies: $(w, R(w))$, where $w = 1, 0$. One policy $(1, R(1))$ involves administering the test drug, along with any naturally occurring intercurrents, whereas the other policy $(0, R(0))$ involves administering a placebo, along with any naturally occurring intercurrents. Thus, the potential outcomes are $T(1, R(1))$ and $T(0, R(0))$. Instead of comparing

the test drug and placebo themselves, the contrast of interest is made between the two treatment policies. The difference in cumulative incidences under the two treatment policies is then $\tau(t) = P(T(1, R(1)) < t) - P(T(0, R(0)) < t)$, representing the difference in probabilities of experiencing primary outcome events during $(0, t)$ under active treatment and placebo. The average treatment effect $\tau^{\text{tp}}(t)$ has a meaningful causal interpretation only when $T(1, R(1))$ and $T(0, R(0))$ are well defined. Because the treatment policy includes the occurrence of the intercurrent event as natural, the entire treatment policy is determined by manipulating the initial treatment condition \$w\$ only. Therefore, we can simplify the notations $T(w, R(w)) = T(w)$ in defining estimands. As such, $\tau(t) = P(T(1)) < t) - P(T(0) < t)$ as the intention-to-treat analysis.

Value

A list including

time1 Time points in the treated group.

time0 Time points in the control group.

cif1 Estimated cumulative incidence function in the treated group.

cif0 Estimated cumulative incidence function in the control group.

se1 Standard error of the estimated cumulative incidence function in the treated group.

se0 Standard error of the estimated cumulative incidence function in the control group.

time Time points in both groups.

ate Estimated treatment effect (difference in cumulative incidence functions).

se Standard error of the estimated treatment effect.

p.val P value of testing the treatment effect based on the efficient influence function of the restricted mean survival time lost by the end of study.

See Also

surv.treatment, surv.tteICE

---

surv.tteICE *Fit CIFs for competing risks time-to-event data with intercurrent events.*

Description

This function estimates the potential cumulative incidence function for time-to event data under ICH E9 (R1) to address intercurrent events. The input data should be of a competing risks structure.

Usage

```
surv.tteICE(
  A,
  Time,
  cstatus,
  strategy = "composite",
  cov1 = NULL,
  method = "np",
  weights = NULL,
  subset = NULL,
  na.rm = FALSE,
  nboot = 0,
  seed = 0
)
```

Arguments

A	Treatment indicator, 1 for treatment and 0 for control.
Time	Time to event.
cstatus	Indicator of event, 1 for the primary event, 2 for the intercurrent event, 0 for censoring.
strategy	Strategy to address intercurrent events, "treatment" indicating treatment policy strategy, "composite" indicating composite variable strategy, "natural" indicating hypothetical strategy (Scenario I, controlling the hazard of intercurrent events), "removed" indicating hypothetical strategy (Scenario II, removing intercurrent events), "whileon" indicating while on treatment strategy, and "principal" indicating principal stratum strategy.
cov1	Baseline covariates.
method	Estimation method, "np" indicating nonparametric estimation, "np" indicating inverse treatment probability weighting, "eff" indicating semiparametrically efficient estimation based on efficient influence functions.
weights	Weight for each subject.
subset	Subset, either numerical or logical.
na.rm	Whether to remove missing values.
nboot	Number of resamplings in the boostrapping method. If nboot is 0 or 1, then asymptotic standard error based on the explicit form is calculated instead of bootstrapping.
seed	Seed for bootstrapping.

Details

Background Intercurrent events refer to the events occurring after treatment initiation of clinical trials that affect either the interpretation of or the existence of the measurements associated with the clinical question of interest. The International Conference on Harmonization (ICH) E9 (R1) addendum proposed five strategies to address intercurrent events, namely, treatment

policy strategy, composite variable strategy, while on treatment strategy, hypothetical strategy, and principal stratum strategy. To answer a specific scientific question, a strategy with a particular estimand is chosen before the study design.

Model We adopt the potential outcomes framework that defines a causal estimand as the contrast between functionals of potential outcomes. Consider a randomized controlled trial with n individuals randomly assigned to one of two treatment conditions, denoted by w, where $w = 1$ represents the active treatment (a test drug) and $w = 0$ represents the control (placebo). Assume that all patients adhere to their treatment assignments and do not discontinue treatment. Associated with individual $i = 1, ..., n$ are two potential time-to-event primary outcomes $T_i(1)$ and $T_i(0)$, if any, which represent the time durations from treatment initiation to the primary outcome event under two treatment assignments respectively. Let $R_i(1)$ and $R_i(0)$ denote the occurrence time of potential intercurrent events, if any, under the two treatment assignments, respectively. Intercurrent events are considered as absent if no post-treatment intercurrent events occur until the end of study.

Estimand We adopt the potential cumulative incidences under both treatment assignments as the target estimands. Potential cumulative incidences describe the probability of time-to-event outcomes occurring at each time point. We define the treatment effect as the contrast of two potential cumulative incidences. Cumulative incidences are model-free and collapsible, enjoying causal interpretations.

Value

A list including the fitted object and input variables.

References

Deng, Y., Han, S., & Zhou, X. H. (2025). Inference for Cumulative Incidences and Treatment Effects in Randomized Controlled Trials With Time-to-Event Outcomes Under ICH E9 (R1). *Statistics in Medicine*. doi:10.1002/sim.70091

See Also

surv.boot, scr.tteICE

Examples

```
## load data
data(bmt)
bmt = transform(bmt, d4=d2+d3)
A = as.numeric(bmt$group>1)
X = as.matrix(bmt[,c('z1','z3','z5')])

## Composite variable strategy,
## nonparametric estimation without covariates
fit1 = surv.tteICE(A, bmt$t2, bmt$d4, "composite")

## Hypothetical strategy (natural effects),
## nonparametric estimation with inverse probability weighting
fit2 = surv.tteICE(A, bmt$t2, bmt$d4, "natural", X, method='ipw')
```

```
## nonparametric estimation with weights as inverse propensity score
ps = predict(glm(A ~ X, family='binomial'), type='response')
w = A/ps + (1-A)/(1-ps)
fit2 = surv.tteICE(A, bmt$t2, bmt$d4, "natural", weights=w)

## Hypothetical strategy (removing intercurrent events),
## semiparametrically efficient estimation with covariates
fit3 = surv.tteICE(A, bmt$t2, bmt$d4, "removed", X, method='eff')
```

`surv.whileon` *Fit CIFs using while on treatment strategy for competing risks data*

Description

This function nonparametrically estimates the potential cumulative incidence function using while on treatment strategy (competing risks data structure). This strategy can be understood as the competing risks model, which gives the subdistribution of the primary event.

Usage

```
surv.whileon(A, Time, cstatus, weights = rep(1, length(A)))
```

Arguments

`A`	Treatment indicator, 1 for treatment and 0 for control.
`Time`	Time to event.
`cstatus`	Indicator of event, 1 for the primary event, 2 for the intercurrent event, 0 for censoring.
`weights`	Weight for each subject.

Details

The while on treatment strategy considers the measure of outcome variables taken only up to the occurrence of intercurrent events. The failures of primary outcome events should not be counted in the cumulative incidences if intercurrent events occurred. The difference in counterfactual cumulative incidences under this strategy is $\tau(t) = P(T(1) < t, R(1) \geq t) - P(T(0) < t, R(0) \geq t)$, representing the difference in probabilities of experiencing primary outcome events without intercurrent events during $(0, t)$ under active treatment and placebo. The cumulative incidence function is also known as the cause-specific cumulative incidence or subdistribution function.

The while on treatment strategy is closely related to the competing risks model. However, for causal interpretations, it is worth emphasizing that the hazard of $R(1)$ may differ from that of $R(0)$, leading to vast difference in the underlying features of individuals who have not experienced the primary outcome event between treatment conditions at any time $t \in (0, t^*)$, where t^* is the end of study. When the scientific question of interest is the impact of treatment on the primary outcome event, the estimand $\tau(t)$ is hard to interpret if a systematic difference in the risks of intercurrent events between two treatment conditions under comparison is anticipated.

Value

A list including

time1 Time points in the treated group.

time0 Time points in the control group.

cif1 Estimated cumulative incidence function in the treated group.

cif0 Estimated cumulative incidence function in the control group.

se1 Standard error of the estimated cumulative incidence function in the treated group.

se0 Standard error of the estimated cumulative incidence function in the control group.

time Time points in both groups.

ate Estimated treatment effect (difference in cumulative incidence functions).

se Standard error of the estimated treatment effect.

p.val P value of testing the treatment effect based on Gray test.

See Also

`surv.whileon.eff`, `surv.tteICE`

`surv.whileon.eff` *Fit CIFs using while on treatment strategy for competing risks data, based on efficient influence functions*

Description

This function estimates the potential cumulative incidence function based on efficient influence functions using while on treatment strategy (competing risks data structure). Cox models are employed for survival models. This strategy can be understood as the competing risks model, which gives the subdistribution of the primary event.

Usage

```
surv.whileon.eff(A, Time, cstatus, X = NULL)
```

Arguments

`A`	Treatment indicator, 1 for treatment and 0 for control.
`Time`	Time to event.
`cstatus`	Indicator of event, 1 for the primary event, 2 for the intercurrent event, 0 for censoring.
`X`	Baseline covariates.

Details

The while on treatment strategy considers the measure of outcome variables taken only up to the occurrence of intercurrent events. The failures of primary outcome events should not be counted in the cumulative incidences if intercurrent events occurred. The difference in counterfactual cumulative incidences under this strategy is $\tau(t) = P(T(1) < t, R(1) \geq t) - P(T(0) < t, R(0) \geq t)$, representing the difference in probabilities of experiencing primary outcome events without intercurrent events during $(0, t)$ under active treatment and placebo. The cumulative incidence function is also known as the cause-specific cumulative incidence or subdistribution function.

The while on treatment strategy is closely related to the competing risks model. However, for causal interpretations, it is worth emphasizing that the hazard of $R(1)$ may differ from that of $R(0)$, leading to vast difference in the underlying features of individuals who have not experienced the primary outcome event between treatment conditions at any time $t \in (0, t^*)$, where t^* is the end of study. When the scientific question of interest is the impact of treatment on the primary outcome event, the estimand $\tau(t)$ is hard to interpret if a systematic difference in the risks of intercurrent events between two treatment conditions under comparison is anticipated.

Value

A list including

time1 Time points in the treated group.

time0 Time points in the control group.

cif1 Estimated cumulative incidence function in the treated group.

cif0 Estimated cumulative incidence function in the control group.

se1 Standard error of the estimated cumulative incidence function in the treated group.

se0 Standard error of the estimated cumulative incidence function in the control group.

time Time points in both groups.

ate Estimated treatment effect (difference in cumulative incidence functions).

se Standard error of the estimated treatment effect.

p.val P value of testing the treatment effect based on the efficient influence function of the restricted mean survival time lost by the end of study.

See Also

`surv.whileon`, `surv.tteICE`

---

tteICE *Using formula to fit CIFs for time-to-event data with intercurrent events*

Description

This function estimates the potential cumulative incidence function for time-to event data under ICH E9 (R1) to address intercurrent events. The input data can be competing or semicompeting risks data structure.

Usage

```
tteICE(
  formula,
  add.scr = NULL,
  data,
  strategy = "composite",
  method = "np",
  weights = NULL,
  subset = NULL,
  na.rm = FALSE,
  nboot = 0,
  seed = 0
)
```

Arguments

formula	An object of class "formula" (or one that can be coerced to that class). A symbolic description of the model to be fitted. For example, `formula=Surv(time, status, type="mstate")~treatment | baseline.covariate`. The details of model specification are given under 'Details'.
add.scr	Required for semicompeting data. An object of class "Surv" (or one that can be coerced to that class). For example, `add.scr=~Surv(time.intercurrent, status.intercurrent)`. The details of model specification are given under 'Details'.
data	Data or object coercible by as.data.frame to a data frame, containing the variables in the model.
strategy	Strategy to address intercurrent events, `"treatment"` indicating treatment policy strategy, `"composite"` indicating composite variable strategy, `"natural"` indicating hypothetical strategy (Scenario I, controlling the hazard of intercurrent events), `"removed"` indicating hypothetical strategy (Scenario II, removing intercurrent events), `"whileon"` indicating while on treatment strategy, and `"principal"` indicating principal stratum strategy.
method	Estimation method, `"np"` indicating nonparametric estimation, `"np"` indicating inverse treatment probability weighting, `"eff"` indicating semiparametrically efficient estimation based on efficient influence functions.
weights	Weight for each subject.
subset	Subset, either numerical or logical.
na.rm	Whether to remove missing values.
nboot	Number of resamplings in the boostrapping method. If `nboot` is 0 or 1, then asymptotic standard error based on the explicit form is calculated instead of bootstrapping.
seed	Seed for bootstrapping.

Details

Background Intercurrent events refer to the events occurring after treatment initiation of clinical trials that affect either the interpretation of or the existence of the measurements associated

with the clinical question of interest. The International Conference on Harmonization (ICH) E9 (R1) addendum proposed five strategies to address intercurrent events, namely, treatment policy strategy, composite variable strategy, while on treatment strategy, hypothetical strategy, and principal stratum strategy. To answer a specific scientific question, a strategy with a particular estimand is chosen before the study design.

Model We adopt the potential outcomes framework that defines a causal estimand as the contrast between functionals of potential outcomes. Consider a randomized controlled trial with n individuals randomly assigned to one of two treatment conditions, denoted by w, where $w = 1$ represents the active treatment (a test drug) and $w = 0$ represents the control (placebo). Assume that all patients adhere to their treatment assignments and do not discontinue treatment. Associated with individual $i = 1, ..., n$ are two potential time-to-event primary outcomes $T_i(1)$ and $T_i(0)$, if any, which represent the time durations from treatment initiation to the primary outcome event under two treatment assignments respectively. Let $R_i(1)$ and $R_i(0)$ denote the occurrence time of potential intercurrent events, if any, under the two treatment assignments, respectively. Intercurrent events are considered as absent if no post-treatment intercurrent events occur until the end of study.

Estimand We adopt the potential cumulative incidences under both treatment assignments as the target estimands. Potential cumulative incidences describe the probability of time-to-event outcomes occurring at each time point. We define the treatment effect as the contrast of two potential cumulative incidences. Cumulative incidences are model-free and collapsible, enjoying causal interpretations.

Formula specifications The formula should be set as the following two ways.

When data take format of competing risk data, set the first argument `formula = Surv(time, status, type="mstate") ~ treatment | covariate1+covariate2` or `formula = Surv(time, status)~ A` without any baseline covariates, where `status`=0,1,2 (1 for the primary event, 2 for the intercurrent event, and 0 for censoring).

When data take the format of semicompeting risk data, set the first argument `formula = Surv(time, status) ~ treatment | covariate1+covariate2` or `formula = Surv(time, status)~ A` without any baseline covariates, where `status`=0,1 (1 for the primary event and 0 for censoring). In addition, the second argument `add.scr = ~ Surv(time.intercurrent, status.intercurrent)` is required.

Value

A list including the fitted object and input variables.

References

Deng, Y., Han, S., & Zhou, X. H. (2025). Inference for Cumulative Incidences and Treatment Effects in Randomized Controlled Trials With Time-to-Event Outcomes Under ICH E9 (R1). *Statistics in Medicine*. doi:10.1002/sim.70091

See Also

`surv.boot`, `scr.tteICE`

Examples

```
## load data
data(bmt)
bmt = transform(bmt, d4=d2+d3)
A = as.numeric(bmt$group>1)
X = as.matrix(bmt[,c('z1','z3','z5')])
bmt$A = A

library(survival)
## Composite variable strategy,
## nonparametric estimation without covariates
## Composite variable strategy,
## nonparametric estimation without covariates

## model fitting for competing risk data without covariates
fit1 = tteICE(Surv(t2, d4, type = "mstate")~A,
 data=bmt, strategy="composite", method='eff')
print(fit1)

## model fitting for competing risk data without covariates
## with bootstrap confidence intervals
fit.bt1 = tteICE(Surv(t2, d4, type = "mstate")~A,
 data=bmt, strategy="composite", method='eff', nboot=20, seed=2)
print(fit.bt1)

## model fitting for competing risk data with covariates
fit2 = tteICE(Surv(t2, d4, type = "mstate")~A|z1+z3+z5,
 data=bmt, strategy="composite", method='eff')
print(fit2)

## model fitting for semicompeting risk data without covariates
fitscr1 = tteICE(Surv(t1, d1)~A, ~Surv(t2, d2),
 data=bmt, strategy="composite", method='eff')
print(fitscr1)

## model fitting for semicompeting risk data without covariates
fitscr2 = tteICE(Surv(t1, d1)~A|z1+z3+z5, ~Surv(t2, d2),
 data=bmt, strategy="composite", method='eff')
print(fitscr2)
```

`tteICEShiny` *Shiny app for tteICE*

Description

This function opens the RShiny app for tteICE. RShiny application can be used for generating plots and basic analysis results. It provides a point-and-click interface, so users can obtain results without writing R code directly.

Usage

```
tteICEShiny()
```

Value

Rshiny interface

Examples

```
if(interactive()){
  tteICEShiny()
}
```

Index