Package: tteICE (via r-universe)

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Type Package

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

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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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`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.
- `tteICEShiny` Interactive Shiny app for the 'tteICE' package

Results output functions:

- `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
- `coef.tteICE` Show the coefficient for 'tteICE' objects
- `bshaz.tteICE` Extract the baseline hazards for 'tteICE' objects
- `zph.tteICE` Perform a test for the proportional hazards assumption for the Cox models in 'tteICE' objects

Example data:

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

Author(s)

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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)
```

`bshaz.tteICE` *Baseline hazards of 'tteICE' objects*

Description

This function extracts the baseline cumulative hazards in the survival models

Usage

```
## S3 method for class 'tteICE'
bshaz(x)
```

Arguments

`x`	A fitted object returned by the function `tteICE`, `surv.tteICE`, or `scr.tteICE`.

Value

A data frame of baseline cumulative hazards in the working Kaplan-Meier or Cox models, stratified by treatment groups. The first column is time, the following columns are baseline cumulative hazards.

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)
fit = tteICE(Surv(t2, factor(d4))~A|z1+z3+z5,
 data=bmt, strategy="whileon", method='eff')
bshaz(fit)
```

coef.tteICE *Coefficients of 'tteICE' objects*

Description

This function extracts the coefficients in the Cox models

Usage

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

Arguments

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

Value

A list of coefficients of covariates in the working Cox models, stratified by treatment groups. For the treatment policy strategy and composite variable strategy, only one Cox model is fit (for the primary outcome event or the composite event). In these two strategies, coef1 is the coefficients in the treated group, coef0 is the coefficients in the control group. For other strategies, Cox models are fitted for each event (primary outcome event and intercurrent event). In these strategies, coef11 is the coefficients for the primary outcome event in the treatment group, coef10 is the coefficients for the primary outcome event in the control group, coef21 is the coefficients for the intercurrent event in the treated group, coef20 is the coefficients for the intercurrent in the control group. If the nonparametric method is used, the return is NULL.

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)
fit = tteICE(Surv(t2, factor(d4))~A|z1+z3+z5,
 data=bmt, strategy="whileon", method='eff')
coef(fit)
```

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, factor(d4))~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"))
```

---

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, factor(d4))~A|z1+z3+z5,
              data=bmt, strategy="composite", method='eff')
predict(fit3, timeset=c(670,2000))
predict(fit3)
```

---

print.summary.tteICE *Print the summary of 'tteICE'*

Description

Print the summary of 'tteICE'

Usage

```
## S3 method for class 'summary.tteICE'
print(x, digits = 3, ...)
```

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

---

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

Description

This function summarizes the results

Usage

```
## S3 method for class 'tteICE'
print(x, digits = 3, ...)
```

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)

## library(survival)
fit3 = tteICE(Surv(t2, factor(d4))~A|z1+z3+z5,
              data=bmt, strategy="composite", method='eff')
print(fit3, digits=4)
```

`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 bootstrapping 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")

## 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')
```

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

Description

This function summarizes the results

Usage

```
## S3 method for class 'tteICE'
summary(object, digits = 3, ...)
```

Arguments

object	A fitted object returned by the function tteICE, surv.tteICE, or scr.tteICE.
digits	The digits of the results
...	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, factor(d4))~A|z1+z3+z5,
              data=bmt, strategy="composite", method='eff')
```

```
summary(fit3)
```

---

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.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 bootstrapping 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 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')
```

`tteICE` *Use 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)~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 in the following two ways.

When data take format of competing 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 is a factor variable with levels 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, factor(d4)) ~ A,
 data=bmt, strategy="composite", method='np')
print(fit1)

## model fitting for competing risk data without covariates
## with bootstrap confidence intervals
fit.bt1 = tteICE(Surv(t2, factor(d4)) ~ 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, factor(d4)) ~ 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='np')
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() && requireNamespace("shiny", quietly = TRUE)){
  tteICEShiny()
}
```

`zph.tteICE` *Checking proportional hazards of 'tteICE' objects*

Description

This function checks the proportional hazards assumption in the Cox model using Schoenfeld residuals. This function only return results for strategies based on efficient influence functions.

Usage

```
## S3 method for class 'tteICE'
zph(x)
```

Arguments

x	A fitted object returned by the function tteICE, surv.tteICE, or scr.tteICE.

Value

A list of P-values of testing the proportional hazards (PH) assumption in the working Cox models, for each covariate and a global test, stratified by treatment groups. For the treatment policy strategy and composite variable strategy, only one Cox model is fit (for the primary outcome event or the composite event). In these two strategies, ph1 is the P-values in the treated group, ph0 is the P-values in the control group. For other strategies, Cox models are fitted for each event (primary outcome event and intercurrent event). In these strategies, ph11 is the P-values for the primary outcome event in the treatment group, ph10 is the P-values for the primary outcome event in the control group, ph21 is the P-values for the intercurrent event in the treated group, ph20 is the P-values for the intercurrent in the control group. If the nonparametric method is used, the return is NULL.

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)
fit = tteICE(Surv(t2, factor(d4))~A|z1+z3+z5,
 data=bmt, strategy="whileon", method='eff')
print(fit$ph)
zph(fit)
```

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