

Package ‘DTR’

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Description Estimation and comparison of survival distributions of dynamic treatment regimes (DTRs) from sequentially randomized clinical trials

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DTR-package	<i>Estimation and comparison of dynamic treatment regimes (DTRs) from sequentially randomized clinical trials</i>
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Description

This is a package for the estimation and comparison of survival distributions of dynamic treatment regimes (DTRs) from sequentially randomized clinical trials. In a sequentially randomized design, patients are initially randomized to one of the first-stage therapies. Based on their responses to the first-stage therapy, they are then randomized to one of the second-stage therapies. The second-stage therapy could be a rescue therapy if the response is not favorable, or maintenance therapy if favorable response is achieved. There are treatment sequences resulted from such designs: first-stage therapy -> response -> second-stage therapy. The treatment sequences are also referred to as dynamic treatment regimes (DTRs) or adaptive treatment strategies or treatment policies in the literature.

The estimation functions include [LDTestimate](#), [WRSEestimate](#), and [CHRestimate](#).

The comparisons functions include [contrast_wald](#), [contrast_chr](#), [PHfit](#), [contrast_ph](#), and [contrast_logrank](#).

The functions for data simulation include [simLDTdata](#), [simWRSEdata](#), [simPHdata](#), [simCHRdata](#), and [simLRdata](#).

Details

In sequentially randomized designs, there could be more than two therapies available at each stage. For simplicity, and to maintain similarity to the most common sequentially randomized clinical trials, a simple two-stage randomization design allowing two treatment options at each stage is used in the current version of the package. In detail, patients are initially randomized to either A1 or A2 at the first stage. Based on their response status, they are then randomized to either B1 or B2 at the

second stage. Therefore, there are a total of four DTRs: A1B1, A1B2, A2B1, and A2B2.

The function `simLDTdata` generates data sets from sequentially randomized clinical trials as described in the simulation study of Lunceford, Davidian and Tsiatis (2002).

The function `LDTestimate` computes the estimates of the survival function and their estimated standard errors for DTRs at observed event times as proposed in Lunceford, Davidian and Tsiatis (2002) Equation (3) and Equation (10).

The function `simWRSEdata` generates data sets from sequentially randomized clinical trials as described in the simulation study of Guo and Tsiatis (2005).

The function `WRSEestimate` computes the weighted risk set estimator (WRSE) of the survival function and their estimated standard errors for DTRs at observed event times as proposed in Guo and Tsiatis (2002) Equation (3) and Equation (16).

The function `contrast_wald` compares the survival distributions of dynamic treatment regimes (DTRs) from sequentially randomized clinical trials based on the LDT estimator proposed in Lunceford, Davidian and Tsiatis (2002) or the WRSE estimator proposed in Guo and Tsiatis (2005) using the Wald-type tests.

The function `simPHdata` generates a data set from sequentially randomized clinical trials as described in the simulation study of Tang and Wahed (2011).

The function `PHfit` fits a generalized Cox model as proposed in Tang and Wahed (2011).

The function `contrast_ph` compares the survival distributions (i.e. hazard functions) of dynamic treatment regimes (DTRs) from sequentially randomized clinical trials after adjustment for covariates as proposed in Tang and Wahed (2011).

The function `simCHRdata` generates a data set from sequentially randomized clinical trials as described in the simulation study of Tang and Wahed (2013) [Epub ahead of print].

The function `CHRestimate` computes the estimates for the cumulative hazard ratios (CHRs) between two different dynamic treatment regimes (DTRs) and their variance estimates at given time points as proposed in Tang and Wahed (2013) [Epub ahead of print].

The function `contrast_chr` compares the cumulative hazard functions of dynamic treatment regimes (DTRs) from sequentially randomized clinical trials by calculating the natural logarithms of cumulative hazard ratios (CHRs) and performing the Wald-type tests based on natural logarithms of CHRs as proposed in Tang and Wahed (2013) [Epub ahead of print].

The function `simLRdata` generates a data set from sequentially randomized clinical trials as described in the simulation study of Kidwell and Wahed (2013).

The function `contrast_logrank` compares the survival distributions of dynamic treatment regimes (DTRs) from sequentially randomized clinical trials using the weighted logrank tests as proposed in Kidwell and Wahed (2013).

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References

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- Feng W, Wahed AS: Supremum weighted log-rank test and sample size for comparing two-stage adaptive treatment strategies. *Biometrika* 95:695-707, 2008
- Tang X, Wahed AS: Comparison of treatment regimes with adjustment for auxiliary variables. *Journal of Applied Statistics* 38(12):2925-2938, 2011
- Kidwell KM, Wahed AS: Weighted log-rank statistic to compare shared-path adaptive treatment strategies. *Biostatistics*, 14(2):299-312, 2013
- Tang X, Wahed AS: Cumulative hazard ratio estimation for treatment regimes in sequentially randomized clinical trials. *Statistics in Biosciences*, 2013 [Epub ahead of print]

See Also

[simLDTdata](#), [LDTestimate](#), [simWRSEdata](#), [WRSEestimate](#), [contrast_wald](#), [simPHdata](#), [PHfit](#), [contrast_ph](#), [simCHRdata](#), [CHRestimate](#), [contrast_chr](#), [simLRdata](#), [contrast_logrank](#)

CHR.object

Cumulative hazard ratio object

Description

This class of objects is returned by the CHR class of functions to represent a list of cumulative hazard ratio estimates and estimated standard errors for dynamic treatment regimes (DTRs). Objects of this class have methods for the functions `print`, `summary`, and `plot`.

Arguments

coefficients	coefficient estimate(s) for the covariate(s)
comparison	comparisons between DTRs (i.e. A1B2 vs. A1B1, A2B1 vs. A1B1, A2B2 vs. A1B1, A2B1 vs. A1B2, A2B2 vs. A1B2, and A2B2 vs. A2B1)
time75P	75th percentile of the observed times
time	event times
n.risk	number of patients at risk at each event time
n.event	number of events at each event time
CHR1211	the cumulative hazard ratio estimate for comparing A1B2 to A1B1 at each event time
CHR2111	the cumulative hazard ratio estimate for comparing A2B1 to A1B1 at each event time
CHR2211	the cumulative hazard ratio estimate for comparing A2B2 to A1B1 at each event time
CHR2112	the cumulative hazard ratio estimate for comparing A2B1 to A1B2 at each event time
CHR2212	the cumulative hazard ratio estimate for comparing A2B2 to A1B2 at each event time
CHR2221	the cumulative hazard ratio estimate for comparing A2B2 to A2B1 at each event time
SE1211	the estimated standard error for CHR1211 at each event time
SE2111	the estimated standard error for CHR2111 at each event time
SE2211	the estimated standard error for CHR2211 at each event time
SE2112	the estimated standard error for CHR2112 at each event time
SE2212	the estimated standard error for CHR2212 at each event time
SE2221	the estimated standard error for CHR2221 at each event time
COV1211_2111	the estimated covariance between CHR1211 and CHR2111 at each event time
COV1211_2211	the estimated covariance between CHR1211 and CHR2211 at each event time
COV1211_2112	the estimated covariance between CHR1211 and CHR2112 at each event time
COV1211_2212	the estimated covariance between CHR1211 and CHR2212 at each event time
COV1211_2221	the estimated covariance between CHR1211 and CHR2221 at each event time
COV2111_2211	the estimated covariance between CHR2111 and CHR2211 at each event time
COV2111_2112	the estimated covariance between CHR2111 and CHR2112 at each event time
COV2111_2212	the estimated covariance between CHR2111 and CHR2212 at each event time
COV2111_2221	the estimated covariance between CHR2111 and CHR2221 at each event time
COV2211_2112	the estimated covariance between CHR2211 and CHR2112 at each event time
COV2211_2212	the estimated covariance between CHR2211 and CHR2212 at each event time
COV2211_2221	the estimated covariance between CHR2211 and CHR2221 at each event time
COV2112_2212	the estimated covariance between CHR2112 and CHR2212 at each event time

COV2112_2221	the estimated covariance between CHR2112 and CHR2221 at each event time
COV2212_2221	the estimated covariance between CHR2212 and CHR2221 at each event time
CHR1211.LOG	the log cumulative hazard ratio estimate for comparing A1B2 to A1B1 at each event time
CHR2111.LOG	the log cumulative hazard ratio estimate for comparing A2B1 to A1B1 at each event time
CHR2211.LOG	the log cumulative hazard ratio estimate for comparing A2B2 to A1B1 at each event time
CHR2112.LOG	the log cumulative hazard ratio estimate for comparing A2B1 to A1B2 at each event time
CHR2212.LOG	the log cumulative hazard ratio estimate for comparing A2B2 to A1B2 at each event time
CHR2221.LOG	the log cumulative hazard ratio estimate for comparing A2B2 to A2B1 at each event time
SE1211.LOG	the estimated standard error for CHR1211.LOG at each event time
SE2111.LOG	the estimated standard error for CHR2111.LOG at each event time
SE2211.LOG	the estimated standard error for CHR2211.LOG at each event time
SE2112.LOG	the estimated standard error for CHR2112.LOG at each event time
SE2212.LOG	the estimated standard error for CHR2212.LOG at each event time
SE2221.LOG	the estimated standard error for CHR2221.LOG at each event time
COV1211_2111.LOG	the estimated covariance between CHR1211.LOG and CHR2111.LOG at each event time
COV1211_2211.LOG	the estimated covariance between CHR1211.LOG and CHR2211.LOG at each event time
COV1211_2112.LOG	the estimated covariance between CHR1211.LOG and CHR2112.LOG at each event time
COV1211_2212.LOG	the estimated covariance between CHR1211.LOG and CHR2212.LOG at each event time
COV1211_2221.LOG	the estimated covariance between CHR1211.LOG and CHR2221.LOG at each event time
COV2111_2211.LOG	the estimated covariance between CHR2111.LOG and CHR2211.LOG at each event time
COV2111_2112.LOG	the estimated covariance between CHR2111.LOG and CHR2112.LOG at each event time
COV2111_2212.LOG	the estimated covariance between CHR2111.LOG and CHR2212.LOG at each event time

COV2111_2221.LOG
the estimated covariance between CHR2111.LOG and CHR2221.LOG at each event time

COV2211_2112.LOG
the estimated covariance between CHR2211.LOG and CHR2112.LOG at each event time

COV2211_2212.LOG
the estimated covariance between CHR2211.LOG and CHR2212.LOG at each event time

COV2211_2221.LOG
the estimated covariance between CHR2211.LOG and CHR2221.LOG at each event time

COV2112_2212.LOG
the estimated covariance between CHR2112.LOG and CHR2212.LOG at each event time

COV2112_2221.LOG
the estimated covariance between CHR2112.LOG and CHR2221.LOG at each event time

COV2212_2221.LOG
the estimated covariance between CHR2212.LOG and CHR2221.LOG at each event time

See Also

[CHRestimate](#), [print.CHR](#), [summary.CHR](#), [print.summary.CHR](#), [plot.CHR](#)

CHRdata

CHR data set

Description

This data set was generated from sequentially randomized clinical trials as described in the simulation study of Tang and Wahed (2013) [Epub ahead of print]. It contains the following variables: "X" is the first-stage indicator, X=0 if assigned to A1, and X=1 if assigned to A2; "R" is the response status, R=1 for responders, and R=0 for non-responders; "Z" is the second-stage indicator among responders (R=1), Z=0 if assigned to B1, and Z=1 if assigned to B2; "U" is the observed survival time, U is death time if delta=1, and U is censoring time if delta=0; "delta" is the censoring indicator, delta=1 for event, and delta=0 for censored; and "V1" and "V2" are covariates.

Usage

CHRdata

Format

A data frame with rows corresponding to patients.

Source

Generated by Xinyu Tang in R

References

Tang X, Wahed AS: Cumulative hazard ratio estimation for treatment regimes in sequentially randomized clinical trials. *Statistics in Biosciences*, 2013 [Epub ahead of print]

Examples

```
## Not run:
data("CHRdata")
## End(Not run)
```

CHRestimate

Function for calculating cumulative hazard ratio (CHR) estimates

Description

This function computes the estimates for the cumulative hazard ratios (CHRs) between two different dynamic treatment regimes (DTRs) and their variance estimates at observed event times as proposed in Tang and Wahed (2013) [Epub ahead of print].

Usage

```
CHRestimate(data, covar=names(data)[!names(data)
%in% c("X", "R", "Z", "U", "delta")])
```

Arguments

data	a data frame (X, R, Z, U, delta, ...) representing the data from a two-stage randomization design with therapies A1 and A2 available at the first stage, and B1 and B2 available at the second stage. X: first-stage indicator, X=0 if assigned to A1, and X=1 if assigned to A2 R: response status, R=1 for responders, and R=0 for non-responders Z: second-stage indicator, Z=0 if assigned to B1, and Z=1 if assigned to B2 U: observed survival time, U is death time if delta=1, and U is censoring time if delta=0 delta: censoring indicator, delta=1 for died, and delta=0 for censored ...: other variables
covar	covariate(s) to be adjusted. The default uses all the variables in the data other than X, R, Z, U and delta

Details

In sequentially randomized designs, there could be more than two therapies available at each stage. For simplicity, and to maintain similarity to the most common sequentially randomized clinical trials, a simple two-stage randomization design allowing two treatment options at each stage is used in the current version of the package. In detail, patients are initially randomized to either A1 or A2 at the first stage. Based on their response status, they are then randomized to either B1 or B2 at the second stage. Therefore, there are a total of four DTRs: A1B1, A1B2, A2B1, and A2B2. Based on four DTRs, six different cumulative hazard ratios (CHRs) are computed: $\text{CHR}(A1B2 \text{ vs. } A1B1)$, $\text{CHR}(A2B1 \text{ vs. } A1B1)$, $\text{CHR}(A2B2 \text{ vs. } A1B1)$, $\text{CHR}(A2B1 \text{ vs. } A1B2)$, $\text{CHR}(A2B2 \text{ vs. } A2B1)$, and $\text{CHR}(A2B2 \text{ vs. } A2B1)$. The natural logarithms of the CHRs are also computed.

Value

The function returns an object of class CHR. See `CHR.object` for details.

Note

The data frame generated from `simCHRdata` is the same as the input data frame for `CHRestimate`. The function allows one covariate or more than one covariates, but does not allow no adjustment for covariates.

References

Tang X, Wahed AS: Cumulative hazard ratio estimation for treatment regimes in sequentially randomized clinical trials. *Statistics in Biosciences*, 2013 [Epub ahead of print]

See Also

[simCHRdata](#), [CHR.object](#), [print.CHR](#), [summary.CHR](#), [print.summary.CHR](#), [plot.CHR](#)

Examples

```
## Not run:  
data("CHRdata")  
est <- CHRestimate(data=CHRdata, covar="V1")  
est  
## End(Not run)
```

contrast_chr

Function to compare dynamic treatment regimes (DTRs) based on cumulative hazard ratios (CHRs)

Description

This function compares the cumulative hazard functions of dynamic treatment regimes (DTRs) from sequentially randomized clinical trials by calculating the natural logarithms of cumulative hazard ratios (CHRs) and performing the Wald-type tests based on natural logarithms of CHRs as proposed in Tang and Wahed (2013) [Epub ahead of print].

Usage

```
contrast_chr(est, t = quantile(est$time, 0.75))
```

Arguments

est	the result of a call to the CHRestimate function
t	a time point of interest. For example, t=5 for the comparisons of survival estimates at 5 years among DTRs. Default t is set to be the 75th percentile of the observed time (i.e. 75th percentile of U).

Details

Two different comparisons are performed:

- 1) An overall comparison $H_0: A1B1=A1B2=A2B1=A2B2$
- 2) Pairwise comparisons including $H_0: A1B1=A1B2$, $H_0: A1B1=A2B1$, $H_0: A1B1=A2B2$, $H_0: A1B2=A2B1$, $H_0: A1B2=A2B2$, and $H_0: A2B1=A2B2$

Value

The function returns a data frame with four columns: H0, test statistic, df, and p.

H0	the null hypotheses being tested, for example, $H_0(t=3)$ if the comparisons are made at t=3
test statistic	the calculated chi-square test statistic
df	the degree of freedom
p	the resulting p-value

References

Tang X, Wahed AS: Cumulative hazard ratio estimation for treatment regimes in sequentially randomized clinical trials. *Statistics in Biosciences*, 2013 [Epub ahead of print]

See Also

[CHRestimate](#), [CHR.object](#)

Examples

```
## Not run:
data("CHRdata")
est <- CHRestimate(data=CHRdata, covar="V1")
contrast_chr(est, t=1.5)
## End(Not run)
```

contrast_logrank	<i>Function to compare dynamic treatment regimes (DTRs) using weighted logrank tests</i>
------------------	--

Description

This function compares the survival distributions of dynamic treatment regimes (DTRs) from sequentially randomized clinical trials using the weighted logrank tests proposed in Kidwell and Wahed (2013).

Usage

```
contrast_logrank(data)
```

Arguments

data	<p>a data frame (X, TR, R, Z, U, delta) representing the data from a two-stage randomization design with therapies A1 and A2 available at the first stage, and B1 and B2 available at the second stage.</p> <p>X: first-stage indicator, X=0 if assigned to A1, and X=1 if assigned to A2</p> <p>TR: optional time to response for responders (R=1), only needed if method="WRSE"</p> <p>R: response status, R=1 for responders, and R=0 for non-responders</p> <p>Z: second-stage indicator, Z=0 if assigned to B1, and Z=1 if assigned to B2</p> <p>U: observed survival time, U is death time if delta=1, and U is censoring time if delta=0</p> <p>delta: censoring indicator, delta=1 for died, and delta=0 for censored</p>
------	---

Details

In sequentially randomized designs, there could be more than two therapies available at each stage. For simplicity, and to maintain similarity to the most common sequentially randomized clinical trials, a simple two-stage randomization design allowing two treatment options at each stage is used in the current version of the package. In detail, patients are initially randomized to either A1 or A2 at the first stage. Based on their response status, they are then randomized to either B1 or B2 at the second stage. Therefore, there are a total of four dynamic treatment regimes (DTRs): A1B1, A1B2, A2B1, and A2B2.

Two different comparisons are performed:

- 1) An overall comparison $H_0: A1B1=A1B2=A2B1=A2B2$
- 2) Pairwise comparisons including $H_0: A1B1=A1B2$, $H_0: A1B1=A2B1$, $H_0: A1B1=A2B2$, $H_0: A1B2=A2B1$, $H_0: A1B2=A2B2$, and $H_0: A2B1=A2B2$

Value

The function returns a data frame with four columns: H0, (standardized) test statistic, df, and p.

H0	the null hypotheses being tested, for example, $H_0: A1B1=A1B2=A2B1=A2B2$ for overall comparison
----	--

(standardized) test statistic	the calculated (standardized) test statistic, chi-square test statistic for overall comparison, and z test statistic for pairwise comparisons
df	the degree of freedom
p	the resulting p-value

Note

The data frame generated from [simLRdata](#) is the same as the input data frame for [contrast_logrank](#).

References

- Guo X: Statistical analysis in two-stage randomization designs in clinical trials. PhD thesis, Department of Statistics, North Carolina State University, 2005
- Feng W, Wahed AS: Supremum weighted log-rank test and sample size for comparing two-stage adaptive treatment strategies. *Biometrika* 95:695-707, 2008
- Kidwell KM, Wahed AS: Weighted log-rank statistic to compare shared-path adaptive treatment strategies. *Biostatistics*, 14(2):299-312, 2013

See Also

[simLRdata](#)

Examples

```
## Not run:
data("LRdata")
contrast_logrank(data=LRdata)
## End(Not run)
```

contrast_ph	<i>Function to compare dynamic treatment regimes (DTRs) after adjustment for covariates</i>
-------------	---

Description

This function compares the survival distributions (i.e. hazard functions) of dynamic treatment regimes (DTRs) from sequentially randomized clinical trials after adjustment for covariates as proposed in Tang and Wahed (2011).

Usage

```
contrast_ph(fit)
```

Arguments

`fit` the result of a call to the [PHfit](#) function

Details

Four different comparisons are performed:

- 1) An overall comparison $H_0: A1B1=A1B2=A2B1=A2B2$
- 2) First-stage comparison $H_0: A1=A2$
- 3) Second-stage comparison $H_0: B1=B2$
- 4) Pairwise comparisons including $H_0: A1B1=A1B2$, $H_0: A1B1=A2B1$, $H_0: A1B1=A2B2$, $H_0: A1B2=A2B1$, $H_0: A1B2=A2B2$, and $H_0: A2B1=A2B2$

Value

The function returns a data frame with four columns: H_0 , test statistic, df, and p.

H_0	the null hypotheses being tested, for example, $H_0 (t=3)$ if the comparisons are made at $t=3$
test statistic	the calculated chi-square test statistic
df	the degree of freedom
p	the resulting p-value

References

Tang X, Wahed AS: Comparison of treatment regimes with adjustment for auxiliary variables. Journal of Applied Statistics 38(12):2925-2938, 2011

See Also

[PHfit, coxph.object](#)

Examples

```
## Not run:
data("PHdata")
f <- PHfit(data=PHdata, covar="V")
contrast_ph(f)
## End(Not run)
```

contrast_wald	<i>Function to compare dynamic treatment regimes (DTRs) using Wald-type tests</i>
---------------	---

Description

This function compares the survival estimates at specific time point among dynamic treatment regimes (DTRs) using the Wald-type tests.

Usage

```
contrast_wald(est, t = quantile(est$time, 0.75))
```

Arguments

est	the result of a call to the LDTestimate function or WRSEestimate function
t	a time point of interest. For example, t=5 for the comparisons of survival estimates at 5 years among DTRs. Default t is set to be the 75th percentile of the observed time (i.e. 75th percentile of U).

Details

Two different comparisons are performed:

- 1) An overall comparison $H_0: A1B1=A1B2=A2B1=A2B2$
- 2) Pairwise comparisons including $H_0: A1B1=A1B2$, $H_0: A1B1=A2B1$, $H_0: A1B1=A2B2$, $H_0: A1B2=A2B1$, $H_0: A1B2=A2B2$, and $H_0: A2B1=A2B2$

Value

The function returns a data frame with four columns: H0, test statistic, df, and p.

H0	the null hypotheses being tested, for example, $H_0(t=3)$ if the comparisons are made at t=3
test statistic	the calculated chi-square test statistic
df	the degree of freedom
p	the resulting p-value

References

- Lunceford JK, Davidian M, Tsiatis AA: Estimation of survival distributions of treatment policies in two-stage randomization designs in clinical trials. *Biometrics* 58:48-57, 2002
- Guo X, Tsiatis AA: A weighted risk set estimator for survival distributions in two-stage randomization designs with censored survival data. *Int. J. Biostatistics* 1:1-15, 2005

See Also

[LDTestimate](#), [WRSEestimate](#), [DTR.object](#)

Examples

```
## Not run:
# LDT estimates
data("LDTdata")
est <- LDTestimate(data=LDTdata)
contrast_wald(est, t=1)

# WRSE estimates
data("WRSEdata")
est <- WRSEestimate(data=WRSEdata)
contrast_wald(est, t=300)

## End(Not run)
```

DTR.object	<i>Dynamic treatment regime object</i>
------------	--

Description

This class of objects is returned by the DTR class of functions to represent a list of survival estimates and estimated standard errors for dynamic treatment regimes (DTRs). Objects of this class have methods for the functions `print`, `summary`, and `plot`.

Arguments

DTR	dynamic treatment regimes (i.e. A1B1, A1B2, A2B1, and A2B2)
records	number of observations for each regime
events	number of events for each regime
sensorDTR	dynamic treatment regimes corresponding to censoring times
ensortime	censoring times
ensorsurv	the survival estimate corresponding to each censoring time (ensortime) and dynamic treatment regime (sensorDTR)
time	event times
n.risk	number of patients at risk at each event time
n.event	number of events at each event time
SURV11	the survival estimate for A1B1 at each event time
SURV12	the survival estimate for A1B2 at each event time
SURV21	the survival estimate for A2B1 at each event time
SURV22	the survival estimate for A2B2 at each event time
SE11	the estimated standard error for SURV11 at each event time
SE12	the estimated standard error for SURV12 at each event time
COV1112	the estimated covariance between SURV11 and SURV12 at each event time
SE21	the estimated standard error for SURV21 at each event time
SE22	the estimated standard error for SURV22 at each event time
COV2122	the estimated covariance between SURV21 and SURV22 at each event time

See Also

[LDTestimate](#), [WRSEestimate](#), [print.DTR](#), [summary.DTR](#), [print.summary.DTR](#), [plot.DTR](#)

LDTdata

LDT data set

Description

This data set was generated from sequentially randomized clinical trials as described in the simulation study of Lunceford, Davidian and Tsiatis (2002). It contains the following variables: "X" is the first-stage indicator, X=0 if assigned to A1, and X=1 if assigned to A2; "R" is the response status, R=1 for responders, and R=0 for non-responders; "Z" is the second-stage indicator among responders (R=1), Z=0 if assigned to B1, and Z=1 if assigned to B2; "U" is the observed survival time, U is death time if delta=1, and U is censoring time if delta=0; "delta" is the censoring indicator, delta=1 for event, and delta=0 for censored.

Usage

```
LDTData
```

Format

A data frame with rows corresponding to patients.

Source

Generated by Xinyu Tang in R

References

Lunceford JK, Davidian M, Tsiatis AA: Estimation of survival distributions of treatment policies in two-stage randomization designs in clinical trials. *Biometrics* 58:48-57, 2002

Examples

```
## Not run:
data("LDTdata")

## End(Not run)
```

LDTestimate

Function for calculating LTD estimates

Description

The function computes the survival estimates and estimated standard errors for dynamic treatment regimes (DTRs) at the observed event times as proposed in Lunceford, Davidian and Tsiatis (2002) Equation (3) and Equation (10).

Usage

```
LDTestimate(data, L = .Machine$double.xmax)
```

Arguments

data a data frame (X, R, Z, U, delta) representing the data from a two-stage randomization design with therapies A1 and A2 available at the first stage, and B1 and B2 available at the second stage.
X: treatment arm, X=0 for A1, and X=1 for A2
R: response status, R=1 for responders, and R=0 for non-responders
Z: second-stage indicator, Z=0 if assigned to B1, and Z=1 if assigned to B2
U: observed survival time, U is event time if delta=1, and U is censoring time if delta=0
delta: censoring indicator, delta=1 for event, and delta=0 for censored

L restricted survival time. Default is .Machine\$double.xmax, which is the largest double value of R. Set L to a numeric number smaller than the maximum follow-up time if restricted follow-up time up to L is considered.

Details

In sequentially randomized designs, there could be more than two therapies available at each stage. For simplicity, and to maintain similarity to the most common sequentially randomized clinical trials, a two-stage randomization design allowing two treatment options at each stage is used in the current version of the package. In detail, patients are initially randomized to either A1 or A2 at the first stage. Based on their response status, they are then randomized to either B1 or B2 at the second stage. Therefore, there are a total of four DTRs: A1B1, A1B2, A2B1, and A2B2.

Value

The function returns an object of class DTR. See `DTR.object` for details.

References

Lunceford JK, Davidian M, Tsiatis AA: Estimation of survival distributions of treatment policies in two-stage randomization designs in clinical trials. *Biometrics* 58:48-57, 2002

See Also

[simLDTdata](#), [DTR.object](#), [print.DTR](#), [summary.DTR](#), [print.summary.DTR](#), [plot.DTR](#)

Examples

```
## Not run:  
data("LDTdata")  
est <- LDTestimate(data=LDTdata)  
est  
## End(Not run)
```

LRdata

LR data set

Description

This data set was generated from sequentially randomized clinical trials as described in the simulation study of Kidwell and Wahed (2013). It contains the following variables: "X" is the first-stage indicator, X=0 if assigned to A1, and X=1 if assigned to A2; "TR" is the time to response for responders (R=1); "R" is the response status, R=1 for responders, and R=0 for non-responders; "Z" is the second-stage indicator among responders (R=1), Z=0 if assigned to B1, and Z=1 if assigned to B2; "U" is the observed survival time, U is death time if delta=1, and U is censoring time if delta=0; and "delta" is the censoring indicator, delta=1 for event, and delta=0 for censored.

Usage

LRdata

Format

A data frame with rows corresponding to patients.

Source

Generated by Xinyu Tang in R

References

Kidwell KM, Wahed AS: Weighted log-rank statistic to compare shared-path. adaptive treatment strategies. *Biostatistics*. 14(2):299-312, 2013

Examples

```
## Not run:  
data("LRdata")  
  
## End(Not run)
```

PHdata

PH data set

Description

This data set was generated from sequentially randomized clinical trials as described in the simulation study of Tang and Wahed (2011). It contains the following variables: "X" is the first-stage indicator, X=0 if assigned to A1, and X=1 if assigned to A2; "TR" is the time to response for responders (R=1); "R" is the response status, R=1 for responders, and R=0 for non-responders; "Z" is the second-stage indicator among responders (R=1), Z=0 if assigned to B1, and Z=1 if assigned to B2; "U" is the observed survival time, U is death time if delta=1, and U is censoring time if delta=0; "delta" is the censoring indicator, delta=1 for event, and delta=0 for censored; and "V" is the covariate.

Usage

PHdata

Format

A data frame with rows corresponding to patients.

Source

Generated by Xinyu Tang in R

References

Tang X, Wahed AS: Comparison of treatment regimes with adjustment for auxiliary variables. Journal of Applied Statistics 38(12):2925-2938, 2011

Examples

```
## Not run:  
data("PHdata")  
## End(Not run)
```

PHfit

Function for fitting a generalized proportional hazards model

Description

The function fits a generalized proportional hazards model as proposed in Tang and Wahed (2011).

Usage

PHfit(data, covar=NULL)

Arguments

data	<p>a data frame (X, TR, R, Z, U, delta, ...) representing the data from a two-stage randomization design with therapies A1 and A2 available at the first stage, and B1 and B2 available at the second stage.</p> <p>X: first-stage indicator, X=0 if assigned to A1, and X=1 if assigned to A2</p> <p>TR: time to response</p> <p>R: response status, R=1 for responders, and R=0 for non-responders</p> <p>Z: second-stage indicator, Z=0 if assigned to B1, and Z=1 if assigned to B2</p> <p>U: observed survival time, U is death time if delta=1, and U is censoring time if delta=0</p> <p>delta: censoring indicator, delta=1 for died, and delta=0 for censored</p> <p>...: other variables</p>
covar	<p>covariate(s) to be adjusted in the model. The default (covar=NULL) fits a model without any covariates</p>

Details

In sequentially randomized designs, there could be more than two therapies available at each stage. For simplicity, and to maintain similarity to the most common sequentially randomized clinical trials, a two-stage randomization design allowing two treatment options at each stage is used in the current version of the package. In detail, patients are initially randomized to either A1 or A2 at the first stage. Based on their response status, they are then randomized to either B1 or B2 at the second stage. Therefore, there are a total of four DTRs: A1B1, A1B2, A2B1, and A2B2.

Value

The function returns an object of class `coxph`. See `coxph.object` for details.

References

Tang X, Wahed AS: Comparison of treatment regimes with adjustment for auxiliary variables. *Journal of Applied Statistics* 38(12):2925-2938, 2011

See Also

[simPHdata](#), [coxph.object](#)

Examples

```
## Not run:
data("PHdata")
f <- PHfit(data=PHdata, covar="V")
summary(f)

## End(Not run)
```

plot.CHR	<i>Plot method for CHR objects</i>
----------	------------------------------------

Description

Plot the cumulative hazard ratio estimates and their 95% confidence bands for the comparison between two dynamic treatment regimes

Usage

```
## S3 method for class 'CHR'
plot(x, log.CHR = FALSE, confidence.interval = FALSE,
     xlab = "Time", line.color = c("black", "grey30", "grey50",
     "grey60", "grey70", "grey80"), legend.position = "right", ...)
```

Arguments

<code>x</code>	an object of class CHR, usually returned by the <code>CHRestimate</code> function.
<code>log.CHR</code>	if <code>log.CHR=FALSE</code> (default), the cumulative hazard ratio estimates are plotted; if <code>log.CHR=TRUE</code> , the log cumulative hazard ratio estimates are plotted
<code>confidence.interval</code>	If <code>confidence.interval=FALSE</code> (default), the 95% confidence bands are not plotted. If <code>confidence.interval=TRUE</code> , the 95% confidence bands are plotted as shadows.
<code>xlab</code>	label given to the x-axis. Default is "Time".
<code>line.color</code>	colors for the lines. Default are "black", "grey30", "grey50", "grey60", "grey70", and "grey80" for A1B2 vs. A1B1, A2B1 vs. A1B1, A2B2 vs. A1B1, A2B1 vs. A1B2, A2B2 vs. A1B2, and A2B2 vs. A2B1 respectively.
<code>legend.position</code>	the position of legend: "left", "right" (default), "bottom", "top", or two-element numeric vector (e.g. <code>c(0.6,0.9)</code>)
<code>...</code>	for future methods

See Also

[CHR.object](#), [print.CHR](#), [summary.CHR](#), [print.summary.CHR](#)

Examples

```
## Not run:
data("CHRdata")
est <- CHRestimate(data=CHRdata)
plot(est, confidence.interval=TRUE)
plot(est, log.CHR=TRUE, confidence.interval=FALSE)
## End(Not run)
```

plot.DTR

*Plot method for DTR objects***Description**

Plot the survival estimates and their 95% confidence bands for each dynamic treatment regime

Usage

```
## S3 method for class 'DTR'
plot(x, confidence.interval = FALSE,
     xlab = "Time", ylab = "Survival probability",
     line.color = c("black", "grey40", "grey60", "grey80"),
     legend.position = "right", censored=FALSE, ...)
```

Arguments

x	an object of class DTR, usually returned by the LDTestimate function or WRSEestimate function.
confidence.interval	If confidence.interval=FALSE (default), the 95% confidence bands are not plotted. If confidence.interval=TRUE, the 95% confidence bands are plotted as shadows.
xlab	label given to the x-axis. Default is "Time".
ylab	label given to the y-axis. Default is "Survival probability".
line.color	colors for the lines. Default are "black", "grey40", "grey60", and "grey80" for A1B1, A1B2, A2B1, and A2B2 respectively.
legend.position	the position of legend: "left", "right" (default), "bottom", "top", or two-element numeric vector (e.g. c(0.6,0.9))
censored	If censored=FALSE (default), the censoring ticks are not plotted. If censored=TRUE, the censoring times are plotted as ticks
...	for future methods

See Also

[DTR.object](#), [print.DTR](#), [summary.DTR](#), [print.summary.DTR](#)

Examples

```
## Not run:
data("LDTdata")
est <- LDTestimate(data=LDTdata)
plot(est, confidence.interval=TRUE, censored=TRUE)

data("WRSEdata")
```

```
est <- WRSEestimate(data=WRSEdata)
plot(est)
## End(Not run)
```

print.CHR *Print a short summary of cumulative hazard ratio estimates*

Description

Print the comparison between two dynamic treatment regimes, 75th percentile of the observed times, the cumulative hazard ratio estimates with 95% confidence intervals at 75th percentile of the observed times for each comparison, and the log cumulative hazard ratio estimates with 95% confidence intervals at 75th percentile of the observed times for each comparison.

Usage

```
## S3 method for class 'CHR'
print(x, ...)
```

Arguments

x an object of class "CHR", which is the result of the CHRestimate function
... for future results

Details

The 75th percentile of the observed times is selected.

See Also

[CHR.object](#), [summary.CHR](#), [print.summary.CHR](#), [plot.CHR](#)

print.DTR *Print a short summary of survival curves*

Description

Print number of observations, number of events, and the median survival with confidence limits for the median for dynamic treatment regimes

Usage

```
## S3 method for class 'DTR'
print(x, ...)
```

Arguments

x an object of class "DTR", which is the result of the `LDTestimate` function or `WRSEestimate` function

... for future results

Details

The median and its confidence interval are defined by drawing a horizontal line at 0.5 on the plot of the survival curve and its confidence bands.

See Also

[DTR.object](#), [summary.DTR](#), [print.summary.DTR](#), [plot.DTR](#)

`print.summary.CHR` *Print a summary of cumulative hazard ratio estimates*

Description

Prints the result of `summary.CHR`.

Usage

```
## S3 method for class 'summary.CHR'  
print(x, ...)
```

Arguments

x the result of a call to the [CHRestimate](#) function

... for future results

See Also

[CHR.object](#), [print.CHR](#), [summary.CHR](#), [plot.CHR](#)

```
print.summary.DTR      Print a summary of survival curves
```

Description

Prints the results of `summary.DTR`.

Usage

```
## S3 method for class 'summary.DTR'
print(x, ...)
```

Arguments

`x` the result of a call to the [LDTestimate](#) function or [WRSEestimate](#) function
`...` for future results

See Also

[DTR.object](#), [print.DTR](#), [summary.DTR](#), [plot.DTR](#)

```
simCHRdata      Function to simulate data from sequentially randomized clinical trials  

                 (Tang and Wahed 2013 [Epub ahead of print])
```

Description

This function generates a data set from sequentially randomized clinical trials as described in the simulation study of Tang and Wahed (2013) [Epub ahead of print].

Usage

```
simCHRdata(n,max.c,pi.x,pi.r,pi.z,gamma10,
           gamma11,gamma12,gamma20,gamma21,gamma22,alpha10,
           alpha11,alpha12,alpha20,alpha21,alpha22,beta)
```

Arguments

`n` total number of subjects participating in the clinical trial
`max.c` censoring time C is generated from `uniform(max.c/2, max.c)`
`pi.x` the probability of being assigned to A2 at the first stage. The first-stage treatment indicator X is generated from `Bernoulli(pi.x)`. $X=0$ if assigned to A1 at the first stage, and $X=1$ if assigned to A2 at the first stage.
`pi.r` the probability of response. Response status R is generated from `Bernoulli(pi.r)`

pi.z	the probability of being assigned to B2 among responders. The second-stage treatment indicator Z is generated from Bernoulli(pi.z) among responders ($R=1$). $Z=0$ if assigned to B1 at the second stage, and $Z=1$ if assigned to B2 at the second stage. For non-responders ($R=0$), $Z=0$
gamma10	for individuals who are assigned to A1 at first-stage, and do not respond, survival times are drawn from Weibull distribution with parameters alpha10 and gamma10
gamma11	for individuals who are assigned to A1 at first-stage, respond to A1, and are assigned to B1 at second-stage, survival times are drawn from Weibull distribution with parameters alpha11 and gamma11
gamma12	for individuals who are assigned to A1 at first-stage, respond to A1, and are assigned to B2 at second-stage, survival times are drawn from Weibull distribution with parameters alpha12 and gamma12
gamma20	for individuals who are assigned to A2 at first-stage, and do not respond, survival times are drawn from Weibull distribution with parameters alpha20 and gamma20
gamma21	for individuals who are assigned to A2 at first-stage, respond to A2, and are assigned to B1 at second-stage, survival times are drawn from Weibull distribution with parameters alpha21 and gamma21
gamma22	for individuals who are assigned to A2 at first-stage, respond to A2, and are assigned to B2 at second-stage, survival times are drawn from Weibull distribution with parameters alpha22 and gamma22
alpha10	for individuals who are assigned to A1 at first-stage, and do not respond, survival times are drawn from Weibull distribution with parameters alpha10 and gamma10
alpha11	for individuals who are assigned to A1 at first-stage, respond to A1, and are assigned to B1 at second-stage, survival times are drawn from Weibull distribution with parameters alpha11 and gamma11
alpha12	for individuals who are assigned to A1 at first-stage, respond to A1, and are assigned to B2 at second-stage, survival times are drawn from Weibull distribution with parameters alpha12 and gamma12
alpha20	for individuals who are assigned to A2 at first-stage, and do not respond, survival times are drawn from Weibull distribution with parameters alpha20 and gamma20
alpha21	for individuals who are assigned to A2 at first-stage, respond to A2, and are assigned to B1 at second-stage, survival times are drawn from Weibull distribution with parameters alpha21 and gamma21
alpha22	for individuals who are assigned to A2 at first-stage, respond to A2, and are assigned to B2 at second-stage, survival times are drawn from Weibull distribution with parameters alpha22 and gamma22
beta	the coefficient vector for two covariates $V1$ and $V2$, for example, $\beta=c(0.5,0.5)$. Both covariates $V1$ and $V2$ are generated from Bernoulli(0.5)

Details

In sequentially randomized designs, there could be more than two therapies available at each stage. For simplicity, and to maintain similarity to the most common sequentially randomized clinical trials, a simple two-stage randomization design allowing two treatment options at each stage is used in the current version of the package. In detail, patients are initially randomized to either A1 or A2 at the first stage. Based on their response status, they are then randomized to either B1 or B2 at the second stage. Therefore, there are a total of four dynamic treatment regimes (DTRs): A1B1, A1B2, A2B1, and A2B2.

Value

The function returns a data set with columns: X, R, Z, U, delta, V1 and V2.

X	first-stage indicator, X=0 if assigned to A1, and X=1 if assigned to A2
R	response status, R=1 for responders, and R=0 for non-responders
Z	second-stage indicator among responders (R=1), Z=0 if assigned to B1, and Z=1 if assigned to B2
U	observed survival time, U is event time if delta=1, and U is censoring time if delta=0
delta	censoring indicator, delta=1 for event, and delta=0 for censored
V1	a binary covariate following Bernoulli(0.5)
V2	a binary covariate following Bernoulli(0.5)

Note

Set a seed right before `simCHRdata` will help reproduce the same data.

References

Tang X, Wahed AS: Cumulative hazard ratio estimation for treatment regimes in sequentially randomized clinical trials. *Statistics in Biosciences*, 2013 [Epub ahead of print]

See Also

[CHRestimate](#)

Examples

```
#-----Example function usage-----  
n <- 200  
max.c <- 5  
pi.x <- 0.5  
pi.r <- 0.6  
pi.z <- 0.5  
gamma10 <- 1  
gamma11 <- 1.5
```

```

gamma12 <- 1.2
gamma20 <- 1
gamma21 <- 1.5
gamma22 <- 1.3
alpha10 <- 0.5
alpha11 <- 0.2
alpha12 <- 0.1
alpha20 <- 0.5
alpha21 <- 0.2
alpha22 <- 0.05
beta <- c(0.5, 0.5)

set.seed(123)
CHRdata <- simCHRdata(n,max.c,pi.x,pi.r,
pi.z,gamma10,gamma11,gamma12,gamma20,gamma21,
gamma22,alpha10,alpha11,alpha12,alpha20,alpha21,
alpha22,beta)

```

simLDTdata	<i>Function to simulate data from sequentially randomized clinical trials (Lunceford, Davidian and Tsiatis 2002)</i>
------------	--

Description

This function generates a data set from sequentially randomized clinical trials as described in the simulation study of Lunceford, Davidian and Tsiatis (2002). Because different assignments at the first stage are independent to each other, the function only generates data for one of the assignments at the first stage. For example, if there are two first-stage therapies A1 and A2 available, the function only simulates the data for one of the two arms (e.g. A1).

Usage

```

simLDTdata(n, max.c, pi.r, pi.z, lambda, alpha,
beta1, beta2, L=.Machine$double.xmax)

```

Arguments

n	number of subjects assigned to A1
max.c	censoring time C is generated from uniform(0, max.c)
pi.r	the probability of response. Response status R is generated from Bernoulli(pi.r)
pi.z	the probability of being assigned to B2 among responders. The second-stage treatment indicator Z is generated from Bernoulli(pi.z) among responders (R=1). Z=0 if assigned to B1 at the second stage, and Z=1 if assigned to B2 at the second stage. For non-responders (R=0), Z=0
lambda	for nonresponders (R=0), a survival time T*_lambda is drawn from exponential(lambda) with mean 1/lambda

alpha	for responders, a response time T^*_α is drawn from $\text{exponential}(\alpha)$ with mean $1/\alpha$
beta1	post-response survival time under B1, T^*_{11} is drawn from $\text{exponential}(e^{\beta_1})$
beta2	post-response survival time under B2, T^*_{12} is drawn from $\text{exponential}(e^{(\beta_1 + \beta_2 T^*_{11})})$
L	restricted survival time. Default is <code>.Machine\$double.xmax</code> , which is the largest double value of R. Set L to a numeric number smaller than the maximum follow-up time if restricted follow-up time up to L is considered.

Details

In sequentially randomized designs, there could be more than two therapies available at each stage. For simplicity, and to maintain similarity to the most common sequentially randomized clinical trials, a simple two-stage randomization design allowing two treatment options at each stage is used in the current version of the package. In detail, patients are initially randomized to either A1 or A2 at the first stage. Based on their response status, they are then randomized to either B1 or B2 at the second stage. Therefore, there are a total of four dynamic treatment regimes (DTRs): A1B1, A1B2, A2B1, and A2B2.

Value

The function returns a data set with columns: R, Z, U, and delta.

R	response status, R=1 for responders, and R=0 for non-responders
Z	second-stage indicator, Z=0 if assigned to B1, and Z=1 if assigned to B2
U	observed survival time, U is event time if delta=1, and U is censoring time if delta=0
delta	censoring indicator, delta=1 for event, and delta=0 for censored

Note

Set a seed right before `simLDTdata` will help reproduce the same data.

References

Lunceford JK, Davidian M, Tsiatis AA: Estimation of survival distributions of treatment policies in two-stage randomization designs in clinical trials. *Biometrics* 58:48-57, 2002

See Also

[LDTestimate](#)

Examples

```
#-----Example function usage-----
n <- 100
L <- 1.5
max.c <- 2.5
```

```

pi.r <- 0.5
pi.z <- 0.5
lambda <- 1.33
alpha <- 6.67
beta1 <- 0.29
beta2 <- -0.67

# Generate data from SRD
set.seed(123)
data.A1 <- simLDTdata(n,max.c,pi.r,pi.z,
lambda,alpha,beta1,beta2,L)
data.A2 <- simLDTdata(n,max.c,pi.r,pi.z,
lambda,alpha,beta1,beta2,L)
LDTdata <- cbind(X=c(rep(0,n), rep(1,n)),
rbind(data.A1, data.A2)) # X=0 for A1; X=1 for A2

```

simLRdata	<i>Function to simulate data from sequentially randomized clinical trials (Kidwell and Wahed 2013)</i>
-----------	--

Description

This function generates a data set from sequentially randomized clinical trials as described in the simulation study of Kidwell and Wahed (2013).

Usage

```

simLRdata(n,max.c,pi.x,pi.r,pi.z,
mean.NR.1,mean.NR.2,mean.R.1,mean.R.2,
mean.RE.11,mean.RE.12,mean.RE.21,mean.RE.22)

```

Arguments

n	total number of subjects participating in the clinical trial
max.c	censoring time C is generated from uniform(0, max.c)
pi.x	the probability of being assigned to A2 at the first stage. The first-stage treatment indicator X is generated from Bernoulli(pi.x). X=0 if assigned to A1 at the first stage, and X=1 if assigned to A2 at the first stage.
pi.r	the probability of response. Response status R is generated from Bernoulli(pi.r)
pi.z	the probability of being assigned to B2 among responders. The second-stage treatment indicator Z is generated from Bernoulli(pi.z) among responders (R=1). Z=0 if assigned to B1 at the second stage, and Z=1 if assigned to B2 at the second stage. For non-responders (R=0), Z=0
mean.NR.1	for patients who are assigned to A1 (X=0) and do not respond (R=0), a survival time T.NR.1 is drawn from exponential(1/mean.NR.1) with mean equal to mean.NR.1

mean.NR.2	for patients who are assigned to A2 ($X=1$) and do not respond ($R=0$), a survival time $T.NR.2$ is drawn from $\text{exponential}(1/\text{mean.NR.2})$ with mean equal to mean.NR.2
mean.R.1	for patients who are assigned to A1 ($X=0$) and respond ($R=1$), time to response $T.R.1$ is drawn from $\text{exponential}(1/\text{mean.R.1})$ with mean equal to mean.R.1
mean.R.2	for patients who are assigned to A2 ($X=1$) and respond ($R=1$), time to response $T.R.2$ is drawn from $\text{exponential}(1/\text{mean.R.2})$ with mean equal to mean.R.2
mean.RE.11	for patients who are assigned to A1 ($X=0$), respond ($R=1$), and then assigned to B1 ($Z=0$), a time from response to event is generated from $\text{exponential}(1/\text{mean.RE.11})$ with mean equal to mean.RE.11
mean.RE.12	for patients who are assigned to A1 ($X=0$), respond ($R=1$), and then assigned to B2 ($Z=1$), a time from response to event is generated from $\text{exponential}(1/\text{mean.RE.12})$ with mean equal to mean.RE.12
mean.RE.21	for patients who are assigned to A2 ($X=1$), respond ($R=1$), and then assigned to B1 ($Z=0$), a time from response to event is generated from $\text{exponential}(1/\text{mean.RE.21})$ with mean equal to mean.RE.21
mean.RE.22	for patients who are assigned to A2 ($X=1$), respond ($R=1$), and then assigned to B2 ($Z=1$), a time from response to event is generated from $\text{exponential}(1/\text{mean.RE.22})$ with mean equal to mean.RE.22

Details

In sequentially randomized designs, there could be more than two therapies available at each stage. For simplicity, and to maintain similarity to the most common sequentially randomized clinical trials, a simple two-stage randomization design allowing two treatment options at each stage is used in the current version of the package. In detail, patients are initially randomized to either A1 or A2 at the first stage. Based on their response status, they are then randomized to either B1 or B2 at the second stage. Therefore, there are a total of four dynamic treatment regimes (DTRs): A1B1, A1B2, A2B1, and A2B2.

Value

The function returns a data set with columns: X, TR, R, Z, U, and delta.

X	first-stage indicator, $X=0$ if assigned to A1, and $X=1$ if assigned to A2
TR	time to response for responders ($R=1$)
R	response status, $R=1$ for responders, and $R=0$ for non-responders
Z	second-stage indicator, $Z=0$ if assigned to B1, and $Z=1$ if assigned to B2
U	observed survival time, U is event time if $\text{delta}=1$, and U is censoring time if $\text{delta}=0$
delta	censoring indicator, $\text{delta}=1$ for event, and $\text{delta}=0$ for censored

Note

Set a seed right before `simLRdata` will help reproduce the same data.

References

Kidwell KM, Wahed AS: Weighted log-rank statistic to compare shared-path. adaptive treatment strategies. *Biostatistics*. 14(2):299-312, 2013

See Also

[contrast_logrank](#)

Examples

```
#-----Example function usage-----
n <- 100
max.c <- 12 # 30% censoring
pi.x <- 0.5
pi.r <- 0.6 # 60% response rate
pi.z <- 0.5
mean.NR.1 <- 1
mean.NR.2 <- 1
mean.R.1 <- 1
mean.R.2 <- 1
mean.RE.11 <- 5
mean.RE.12 <- 5
mean.RE.21 <- 5
mean.RE.22 <- 5

set.seed(123)
LRdata <- simLRdata(n,max.c,pi.x,pi.r,
pi.z,mean.NR.1,mean.NR.2,mean.R.1,mean.R.2,
mean.RE.11,mean.RE.12,mean.RE.21,mean.RE.22)
```

simPHdata

*Function to simulate data from sequentially randomized clinical trials
(Tang and Wahed 2011)*

Description

This function generates a data set from sequentially randomized clinical trials as described in the simulation study of Tang and Wahed (2011).

Usage

```
simPHdata(n, max.c, pi.x, pi.z, lambda, alpha,
beta1, beta2, beta3, beta4, beta5, gamma)
```


Arguments

n	total number of subjects participating in the clinical trial
max.c	censoring time C is generated from uniform(0, max.c)
pi.x	the probability of being assigned to A2 at the first stage. The first-stage treatment indicator X is generated from Bernoulli(pi.x). X=0 if assigned to A1 at the first stage, and X=1 if assigned to A2 at the first stage.
pi.z	the probability of being assigned to B2 among responders. The second-stage treatment indicator Z is generated from Bernoulli(pi.z) among responders (R=1). Z=0 if assigned to B1 at the second stage, and Z=1 if assigned to B2 at the second stage. For non-responders (R=0), Z=0
lambda	baseline hazard
alpha	a response time TR is drawn from exponential(alpha) with mean equal to 1/alpha
beta1	coefficient for first-stage indicator X
beta2	coefficient for time-varying response indicator $R(t)=R*I(TR<t)$
beta3	coefficient for the interaction between X and R(t)
beta4	coefficient for the interaction between R(t) and second-stage indicator Z
beta5	coefficient for the three-way interaction among X, R(t), and Z
gamma	coefficient for the covariate V. Covariate V is drawn from normal distribution with mean 1 and standard deviation 0.5

Details

In sequentially randomized designs, there could be more than two therapies available at each stage. For simplicity, and to maintain similarity to the most common sequentially randomized clinical trials, a simple two-stage randomization design allowing two treatment options at each stage is used in the current version of the package. In detail, patients are initially randomized to either A1 or A2 at the first stage. Based on their response status, they are then randomized to either B1 or B2 at the second stage. Therefore, there are a total of four dynamic treatment regimes (DTRs): A1B1, A1B2, A2B1, and A2B2.

Value

The function returns a data set with columns: X, TR, R, Z, U, delta, and V.

X	first-stage indicator, X=0 if assigned to A1, and X=1 if assigned to A2
TR	time to response
R	response status, R=1 for responders, and R=0 for non-responders
Z	second-stage indicator among responders (R=1), Z=0 if assigned to B1, and Z=1 if assigned to B2
U	observed survival time, U is event time if delta=1, and U is censoring time if delta=0
delta	censoring indicator, delta=1 for event, and delta=0 for censored
V	a continuous covariate following normal distribution with mean 1 and standard deviation 0.5

Note

Set a seed right before `simPHdata` will help reproduce the same data.

References

Tang X, Wahed AS: Comparison of treatment regimes with adjustment for auxiliary variables. *Journal of Applied Statistics* 38(12):2925-2938, 2011

See Also

[PHfit](#), [contrast_ph](#)

Examples

```
#-----Example function usage-----
n <- 400
pi.x <- 0.5
pi.z <- 0.5
lambda <- 1/4
alpha <- 1/6
beta1 <- -0.5
beta2 <- -0.8
beta3 <- 0.5
beta4 <- 1
beta5 <- -1
gamma <- -0.5
max.c <- 14

set.seed(123)
PHdata <- simPHdata(n,max.c,pi.x,pi.z,lambda,alpha,
beta1,beta2,beta3,beta4,beta5,gamma)
```

simWRSEdata

*Function to simulate data from sequentially randomized clinical trials
(Guo and Tsiatis 2005)*

Description

This function generates a data set from sequentially randomized clinical trials as described in the simulation study of Guo and Tsiatis (2005). Because different assignments at the first stage are independent to each other, the function only generates data for one of the assignments at the first stage. For example, if there are two first-stage therapies A1 and A2 available, the function only simulates the data for one of the two arms (e.g. A1).

Usage

```
simWRSEdata(n, max.c, pi.r, pi.z, mean.T0,
            mean.TR, mean.T1, mean.T2)
```

Arguments

n	number of subjects assigned to A1
max.c	censoring time C is generated from uniform(0, max.c)
pi.r	the probability of response. Response status R is generated from Bernoulli(pi.r)
pi.z	the probability of being assigned to B2 among responders. The second-stage treatment indicator Z is generated from Bernoulli(pi.z) among responders (R=1). Z=0 if assigned to B1 at the second stage, and Z=1 if assigned to B2 at the second stage. For non-responders (R=0), Z=0
mean.T0	for nonresponders (R=0), a survival time T0 is drawn from exponential(1/mean.T0) with mean equal to mean.T0
mean.TR	for responders (R=1), a response time TR is drawn from exponential(1/mean.TR) with mean equal to mean.TR
mean.T1	the survival time from the response/consent to event time if assigned to B1, T1* is generated from exponential(1/mean.T1) with mean equal to mean.T1
mean.T2	the survival time from the response/consent to event time if assigned to B2, T2* is generated from exponential(1/mean.T2) with mean equal to mean.T2

Details

In sequentially randomized designs, there could be more than two therapies available at each stage. For simplicity, and to maintain similarity to the most common sequentially randomized clinical trials, a simple two-stage randomization design allowing two treatment options at each stage is used in the current version of the package. In detail, patients are initially randomized to either A1 or A2 at the first stage. Based on their response status, they are then randomized to either B1 or B2 at the second stage. Therefore, there are a total of four dynamic treatment regimes (DTRs): A1B1, A1B2, A2B1, and A2B2.

Value

The function returns a data set with columns: TR, R, Z, U, and delta.

TR	a time to response for responders (R=1)
R	response status, R=1 for responders, and R=0 for non-responders
Z	second-stage indicator, Z=0 if assigned to B1, and Z=1 if assigned to B2
U	observed survival time, U is event time if delta=1, and U is censoring time if delta=0
delta	censoring indicator, delta=1 for event, and delta=0 for censored

Note

Set a seed right before `simWRSEdata` will help reproduce the same data.

References

Guo X, Tsiatis AA: A weighted risk set estimator for survival distributions in two-stage randomization designs with censored survival data. *Int. J. Biostatistics* 1:1-15, 2005

See Also

[WRSEestimate](#)

Examples

```
#-----Example function usage-----
n <- 100
max.c <- 3.5*365
pi.r <- 0.5
pi.z <- 0.5
mean.T0 <- 182.5
mean.TR <- 365
mean.T1 <- 365
mean.T2 <- 547.5

# Generate full data from SRD
set.seed(123)
data.A1 <- simWRSEdata(n,max.c,pi.r,pi.z,
  mean.T0,mean.TR,mean.T1,mean.T2)
data.A2 <- simWRSEdata(n,max.c,pi.r,pi.z,
  mean.T0,mean.TR,mean.T1,mean.T2)
WRSEdata <- cbind(X=c(rep(0,n), rep(1,n)),
  rbind(data.A1, data.A2)) # X=0 for A1; X=1 for A2
```

summary.CHR

Summary of cumulative hazard ratio estimates

Description

Returns an object of class `summary.CHR`. See `CHR` object for details.

Usage

```
## S3 method for class 'CHR'
summary(object, log.CHR=FALSE, ...)
```

Arguments

<code>object</code>	the result of a call to the CHRestimate function
<code>log.CHR</code>	if <code>log.CHR=FALSE</code> (default), the summary of cumulative hazard ratio estimates is returned; if <code>log.CHR=TRUE</code> , the summary of log cumulative hazard ratio estimates is returned
<code>...</code>	for future methods

Value

The function returns an object of class `summary.CHR`.

See Also

[CHR.object](#), [print.CHR](#), [print.summary.CHR](#), [plot.CHR](#)

Examples

```
## Not run:
data("CHRdata")
est <- CHRestimate(data=CHRdata, covar="V1")
summary(est, log.CHR=TRUE)
## End(Not run)
```

summary.DTR

Summary of survival curves

Description

Returns an object of class `summary.DTR`. See `DTR.object` for details.

Usage

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

Arguments

`object` the result of a call to the [LDTestimate](#) function or [WRSEestimate](#) function
`...` for future methods

Value

The function returns an object of class `summary.DTR`.

See Also

[DTR.object](#), [print.DTR](#), [print.summary.DTR](#), [plot.DTR](#)

Examples

```
## Not run:
data("LDTdata")
est <- LDTestimate(data=LDTdata)
summary(est)
## End(Not run)
```

 WRSEdata

WRSE data set

Description

This data set was generated from sequentially randomized clinical trials as described in the simulation study of Guo and Tsiatis (2005). It contains the following variables: "X" is the first-stage indicator, X=0 if assigned to A1, and X=1 if assigned to A2; "TR" is the time to response for responders (R=1); "R" is the response status, R=1 for responders, and R=0 for non-responders; "Z" is the second-stage indicator among responders (R=1), Z=0 if assigned to B1, and Z=1 if assigned to B2; "U" is the observed survival time, U is death time if delta=1, and U is censoring time if delta=0; and "delta" is the censoring indicator, delta=1 for event, and delta=0 for censored.

Usage

```
WRSEdata
```

Format

A data frame with rows corresponding to patients.

Source

Generated by Xinyu Tang in R

References

Guo X, Tsiatis AA: A weighted risk set estimator for survival distributions in two-stage randomization designs with censored survival data. *Int. J. Biostatistics* 1:1-15, 2005

Examples

```
## Not run:
data("WRSEdata")
## End(Not run)
```

 WRSEestimate

Function for calculating WRSE estimates

Description

The function computes the weighted risk set estimates (WRSE) of the survival functions and their estimated standard errors for dynamic treatment regimes (DTRs) at observed event times as proposed in Guo and Tsiatis (2005) Equation (3) and Equation (16).

Usage

```
WRSEestimate(data)
```

Arguments

data a data frame (X, TR, R, Z, U, delta) representing the data from a two-stage randomized designs with therapies A1 and A2 available at the first stage, and B1 and B2 available at the second stage.
 X: treatment arm, X=0 for A1, and X=1 for A2
 TR: the time to response for responders (R=1)
 R: response status, R=1 for responders, and R=0 for non-responders
 Z: second-stage indicator, Z=0 if assigned to B1, and Z=1 if assigned to B2
 U: observed survival time, U is death time if delta=1, and U is censoring time if delta=0
 delta: censoring indicator, delta=1 for died, and delta=0 for censored

Details

In sequentially randomized designs, there could be more than two therapies available at each stage. For simplicity, and to maintain similarity to the most common sequentially randomized clinical trials, a simple two-stage randomization design allowing two treatment options at each stage is used in the current version of the package. In detail, patients are initially randomized to either A1 or A2 at the first stage. Based on their response status, they are then randomized to either B1 or B2 at the second stage. Therefore, there are a total of four DTRs: A1B1, A1B2, A2B1, and A2B2.

Value

The function returns an object of class DTR. See `DTR.object` for details.

References

Guo X, Tsiatis AA: A weighted risk set estimator for survival distributions in two-stage randomization designs with censored survival data. *Int. J. Biostatistics* 1:1-15, 2005

See Also

[simWRSEdata](#), [DTR.object](#), [print.DTR](#), [summary.DTR](#), [print.summary.DTR](#), [plot.DTR](#)

Examples

```
## Not run:
data("WRSEdata")
est <- WRSEestimate(data=WRSEdata)
est
## End(Not run)
```

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