# Package 'DTR'

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**Title** Estimation and Comparison of Dynamic Treatment Regimes

**Depends** R (>= 3.2.3)

**Imports** survival, ggplot2, aod

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

**License** GPL (>= 2)

**URL** http://CRAN.R-project.org/package=DTR

**NeedsCompilation** no

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## R topics documented:

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`DTR-package` *Estimation and comparison of dynamic treatment regimes (DTRs) from sequentially randomized clinical trials*

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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

Tang X, Melguizo M: DTR: An R Package for Estimation and Comparison of Survival Outcomes of Dynamic Treatment Regimes. Journal of Statistical Software 65(7):1-28 2005 http://www.jstatsoft.org/v65/i07/
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: Statistical analysis in two-stage randomization designs in clinical trials. PhD thesis, Department of Statistics, North Carolina State University, 2005
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
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

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`CHR.object` *Cumulative hazard ratio object*

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## 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`

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`CHRdata` *CHR data set*

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## Description

This data set was generates 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.<br>X: first-stage indicator, X=0 if assigned to A1, and X=1 if assigned to A2<br>R: response status, R=1 for responders, and R=0 for non-responders<br>Z: second-stage indicator, Z=0 if assigned to B1, and Z=1 if assigned to B2<br>U: observed survival time, U is death time if delta=1, and U is censoring time if delta=0<br>delta: censoring indicator, delta=1 for died, and delta=0 for censored<br>...: 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: CHR(A1B2 vs. A1B1), CHR(A2B1 vs. A1B1), CHR(A2B2 vs. A1B1), CHR(A2B1 vs. A1B2), CHR(A2B2 vs. A2B1), and CHR(A2B2 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 H0: A1B1=A1B2=A2B1=A2B2
2) Pairwise comparisons including H0: A1B1=A1B2, H0: A1B1=A2B1, H0: A1B1=A2B2, H0: A1B2=A2B1, H0: A1B2=A2B2, and H0: 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, H0 (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` *Function to compare dynamic treatment regimes (DTRs) using weighted logrank tests*

## 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` | 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.<br>X: first-stage indicator, X=0 if assigned to A1, and X=1 if assigned to A2<br>TR: optional time to response for responders (R=1), only needed if method="WRSE"<br>R: response status, R=1 for responders, and R=0 for non-responders<br>Z: second-stage indicator, Z=0 if assigned to B1, and Z=1 if assigned to B2<br>U: observed survival time, U is death time if delta=1, and U is censoring time if delta=0<br>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 dynamic treatment regimes (DTRs): A1B1, A1B2, A2B1, and A2B2.
Two different comparisons are performed:
1) An overall comparison H0: A1B1=A1B2=A2B1=A2B2
2) Pairwise comparisons including H0: A1B1=A1B2, H0: A1B1=A2B1, H0: A1B1=A2B2, H0: A1B2=A2B1, H0: A1B2=A2B2, and H0: 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, H0: 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 *Function to compare dynamic treatment regimes (DTRs) after adjustment for covariates*

---

## 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 H0: A1B1=A1B2=A2B1=A2B2
2) First-stage comparison H0: A1=A2
3) Second-stage comparison H0: B1=B2
4) Pairwise comparisons including H0: A1B1=A1B2, H0: A1B1=A2B1, H0: A1B1=A2B2, H0: A1B2=A2B1, H0: A1B2=A2B2, and H0: 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, H0 (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` *Function to compare dynamic treatment regimes (DTRs) using Wald-type tests*

---

## 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 H0: A1B1=A1B2=A2B1=A2B2
2) Pairwise comparisons including H0: A1B1=A1B2, H0: A1B1=A2B1, H0: A1B1=A2B2, H0: A1B2=A2B1, H0: A1B2=A2B2, and H0: 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, H0 (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 *Dynamic treatment regime object*

## 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 |
| censorDTR | dynamic treatment regimes corresponding to censoring times |
| censortime | censoring times |
| censorsurv | the survival estimate corresponding to each censoring time (censortime) and dynamic treatment regime (censorDTR) |
| 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 generates 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.<br>X: treatment arm, X=0 for A1, and X=1 for A2<br>R: response status, R=1 for responders, and R=0 for non-responders<br>Z: second-stage indicator, Z=0 if assigned to B1, and Z=1 if assigned to B2<br>U: observed survival time, U is event time if delta=1, and U is censoring time if delta=0<br>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 generates 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 generates 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 | 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.<br>X: first-stage indicator, X=0 if assigned to A1, and X=1 if assigned to A2<br>TR: time to response<br>R: response status, R=1 for responders, and R=0 for non-responders<br>Z: second-stage indicator, Z=0 if assigned to B1, and Z=1 if assigned to B2<br>U: observed survival time, U is death time if delta=1, and U is censoring time if delta=0<br>delta: censoring indicator, delta=1 for died, and delta=0 for censored<br>. . . : other variables |
| covar | covariate(s) to be adjusted in the model. The default (covar=NULL) fits a model without any covariates |

## 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 *Plot method for* CHR *objects*

## 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

| | |
|---|---|
| x | an object of class CHR, usually returned by the CHRestimate function. |
| log.CHR | if log.CHR=FALSE (default), the cumulative hazard ratio estimates are plotted; if log.CHR=TRUE, the log cumulative hazard ratio estimates are plotted |
| 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". |
| line.color | 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. |
| legend.position | the position of legend: "left", "right" (default), "bottom", "top", or two-element numeric vector (e.g. c(0.6,0.9)) |
| ... | 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` *Function to simulate data from sequentially randomized clinical trials (Lunceford, Davidian and Tsiatis 2002)*

---

## 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*_alpha is drawn from exponential(alpha) with mean 1/alpha |
| beta1 | post-response survival time under B1, T*_11 is drawn from exponential(e^beta1) |
| beta2 | post-response survival time under B2, T*_12 is drawn from exponential(e^(beta1+beta2*T*_11)) |
| 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 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` *Function to simulate data from sequentially randomized clinical trials (Kidwell and Wahed 2013)*

---

## 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 exponential(1/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 exponential(1/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 exponential(1/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 exponential(1/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 exponential(1/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 exponential(1/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 exponential(1/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 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 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)*

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## 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)
```

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

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## 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
```

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# 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

| | |
|---|---|
| object | the result of a call to the CHRestimate function |
| log.CHR | if log.CHR=FALSE (default), the summary of cumulative hazard ratio estimates is returned; if log.CHR=TRUE, the summary of log cumulative hazard ratio estimates is returned |
| ... | 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)
```

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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 generates 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.<br>X: treatment arm, X=0 for A1, and X=1 for A2<br>TR: the time to response for responders (R=1)<br>R: response status, R=1 for responders, and R=0 for non-responders<br>Z: second-stage indicator, Z=0 if assigned to B1, and Z=1 if assigned to B2<br>U: observed survival time, U is death time if delta=1, and U is censoring time if delta=0<br>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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