Package 'wintime'

June 30, 2025

Type Package

Title Win Time Methods for Time-to-Event Data in Clinical Trials

Version 0.4.0

Description
Performs an analysis of time-to-event clinical trial data using various ``win time" methods, including 'ewt', 'ewtr', 'rmt', 'ewtp', 'rewtp', 'ewtpr', 'rewtpr', 'max', 'wtr', 'rwtr', 'pwt', and 'rpwt'. These methods are used to calculate and compare
treatment effects on ordered composite endpoints. The package handles event times, event indicators, and treatment
arm indicators and supports calculations on observed and resampled data. Detailed explanations of each method and
usage examples are provided in ``Use of win time for ordered composite endpoints in clinical trials," by Troendle et al.
(2024)<https://pubmed.ncbi.nlm.nih.gov/38417455/>. For more information, see the package documentation or the vignette titled ``Introduction to wintime."

URL https://pubmed.ncbi.nlm.nih.gov/38417455/

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Contents

`bootstrap` *Resample using bootstraps*

Description

This function reruns the desired wintime package method on a given number of bootstrap samples. This resampling method is recommended for all pairwise wintime methods including Win time ratio (WTR), Restricted win time ratio (RWTR), Pairwise win time (PWT), and Restricted Pairwise win time (RPWT). This function is also recommended for the EWTR_composite max test (MAX).

Usage

```
bootstrap(
  type,
  time_restriction,
  model,
  n,
  m,
  Time,
  Delta,
  trt,
  cov,
```

```
  z_ewtr,
  z_comp,
  resample_num,
  seed,
  nimp
)
```

Arguments

type	A string value indicating the wintime package method that will run with resampling.
time_restriction	The time cutoff value (days).
model	A string value indicating the model used on observed data ('markov' or 'km').
n	The total number of trial participants.
m	The number of events in the hierarchy.
Time	A m x n matrix of event times (days). Rows should represent events and columns should represent participants. Event rows should be in increasing order of clinical severity.
Delta	A m x n matrix of event indicators. Rows should represent events and columns should represent participants. Event rows should be in increasing order of clinical severity.
trt	A numeric vector of treatment arm indicators (1 for treatment, 0 for control).
cov	A n x p matrix of covariate values, where p is the number of covariates. Rows should represent participants and columns should represent covariate values.
z_ewtr	The Z-statistic of EWTR.
z_comp	The Z-statistic of the composite event approach.
resample_num	The number of desired bootstraps.
seed	The seed used for random number generation.
nimp	The number of random imputations for Redistribution-to-the-right.

Value

A list of a vector of length resample_num containing the calculated treatment effect estimates (for type='max' these are z-statistics) for each bootstrap, a m x resample_num matrix of the components of the treatment effect.

COMP *Run composite analysis*

Description

This function fits a Cox Model to time-to-event data and calculates the z statistic. In the wintime package, this function is used for the EWTR-composite max test (MAX) method.

Usage

```
COMP(n, Time, Delta, cov, trt)
```

Arguments

n	The total number of trial participants.
Time	A m x n matrix of event times (days), where m is the number of events in the hierarchy. Rows should represent events and columns should represent participants. Event rows should be in increasing order of clinical severity.
Delta	A m x n matrix of event indicators, where m is the number of events in the hierarchy. Rows should represent events and columns should represent participants. Event rows should be in increasing order of clinical severity.
cov	A n x p matrix of covariate values, where p is the number of covariates. Rows should represent participants and columns should represent covariate values.
trt	A vector of length n containing treatment arm indicators (1 for treatment, 0 for control).

Value

A list containing: The z-statistic of the treatment effect from the Cox Model fit, the treatment effect estimate, the variance of the treatment effect estimate, the p-value for treatment effect.

EWT *Expected win time*

Description

Calculates the state space probabilities using a Kaplan-Meier model (recommended) or a Markov model. This function uses these probabilities to compare both arms and calculate the expected win time of the treatment arm.

Usage

```
EWT(
  m,
  dist_state0,
  dist_state1,
  unique_event_times0,
  unique_event_times1,
  nunique_event_times0,
  nunique_event_times1
)
```

Arguments

m	The number of events in the hierarchy.
dist_state0	A matrix of control arm state probabilities (returned from wintime::km() or wintime::markov()).
dist_state1	A matrix of treatment arm state probabilities (returned from wintime::km() or wintime::markov()).
unique_event_times0	A vector of unique control arm event times (days) (returned from wintime::km() or wintime::markov()).
unique_event_times1	A vector of unique treatment arm event times (days) (returned from wintime::km() or wintime::markov()).
nunique_event_times0	The number of unique control arm event times (returned from wintime::km() or wintime::markov()).
nunique_event_times1	The number of unique treatment arm event times (returned from wintime::km() or wintime::markov()).

Value

A list of the expected win time of the treatment arm, the components of the treatment effect.

EWTP *Expected win time against trial population*

Description

Calculates the combined arm state space probabilities using a Markov model or a Kaplan-Meier model (recommended). This function uses these probabilities to compare each participant's clinical state to a distribution of combined arm states.

Usage

```
EWTP(
  n,
  m,
  nunique,
  maxfollow,
  untimes,
  Time,
  Delta,
  dist,
  markov_ind,
  cov,
  trt
)
```

Arguments

n	The total number of trial participants.
m	The number of events in the hierarchy.
nunique	The number of unique combined arm event times (returned from wintime::markov() or wintime::km()).
maxfollow	The max combined arm follow up time (days) (returned from wintime::markov() or wintime::km()).
untimes	A vector containing unique combined arm event times (days) (returned from wintime::markov() or wintime::km()).
Time	A m x n matrix of event times (days). Rows should represent events and columns should represent participants. Rows should be in increasing order of clinical severity.
Delta	A m x n matrix of event indicators Rows should represent events and columns should represent participants. Rows should be in increasing order of clinical severity.
dist	A matrix of combined arm state probabilities (returned from wintime::markov() or wintime::km()).
markov_ind	An indicator of the model type used (1 for Markov, 0 for Kaplan-Meier).
cov	A n x p matrix of covariate values, where p is the number of covariates.
trt	A vector of length n containing treatment arm indicators (1 for treatment, 0 for control).

Value

A list containing: The estimated treatment effect from the linear regression model, the variance, the Z-statistic, the components of the treatment effect, and the variance of the components.

EWTPR *Expected win time against trial population With redistribution to the right*

Description

Calculates the combined arm state space probabilities using a Markov model or a Kaplan-Meier model (recommended). This function uses these probabilities to compare each participant's clinical state to a distribution of combined arm states. Calculation is extended by redistribution-to-the-right principles

Usage

```
EWTPR(
  n,
  m,
  nunique2,
  maxfollow2,
  untimes2,
  Time,
  Delta,
  dist2,
  markov_ind,
  cov,
  trt,
  comkm,
  trans_prob2,
  nunique1,
  maxfollow1,
  untimes1,
  dist1,
  trtkm,
  trans_prob1,
  nunique0,
  maxfollow0,
  untimes0,
  dist0,
  conkm,
  trans_prob0,
  nimp
)
```

Arguments

n	The total number of trial participants.
m	The number of events in the hierarchy.

nunique2	The number of unique combined arm event times (returned from wintime::markov() or wintime::km()).
maxfollow2	The max combined arm follow up time (days) (returned from wintime::markov() or wintime::km()).
untimes2	A vector containing unique combined arm event times (days) (returned from wintime::markov() or wintime::km()).
Time	A m x n matrix of event times (days). Rows should represent events and columns should represent participants. Rows should be in increasing order of clinical severity.
Delta	A m x n matrix of event indicators Rows should represent events and columns should represent participants. Rows should be in increasing order of clinical severity.
dist2	A matrix of combined arm state probabilities (returned from wintime::markov() or wintime::km()).
markov_ind	An indicator of the model type used (1 for Markov, 0 for Kaplan-Meier).
cov	A n x p matrix of covariate values, where p is the number of covariates.
trt	A vector of length n containing treatment arm indicators (1 for treatment, 0 for control).
comkm	A m x nunique matrix of combined arm survival probabilities (returned from wintime::markov() or wintime::km()).
trans_prob2	A (m x m x number of combined arm event times) matrix where (i,j,k)'th value is transition probability from state i to state j at k'th combined arm event time. (returned from wintime::markov() or wintime::km()).
nunique1	The number of unique trt arm event times (returned from wintime::markov() or wintime::km()).
maxfollow1	The max trt arm follow up time (days) (returned from wintime::markov() or wintime::km()).
untimes1	A vector containing unique trt arm event times (days) (returned from wintime::markov() or wintime::km()).
dist1	A matrix of trt arm state probabilities (returned from wintime::markov() or wintime::km()).
trtkm	A m x nunique matrix of trt arm survival probabilities (returned from wintime::markov() or wintime::km()).
trans_prob1	A (m x m x number of trt arm event times) matrix where (i,j,k)'th value is transition probability from state i to state j at k'th trt arm event time. (returned from wintime::markov() or wintime::km()).
nunique0	The number of unique control arm event times (returned from wintime::markov() or wintime::km()).
maxfollow0	The max control arm follow up time (days) (returned from wintime::markov() or wintime::km()).
untimes0	A vector containing unique control arm event times (days) (returned from wintime::markov() or wintime::km()).

dist0	A matrix of control arm state probabilities (returned from wintime::markov() or wintime::km()).
conkm	A m x nunique matrix of control arm survival probabilities (returned from wintime::markov() or wintime::km()).
trans_prob0	A (m x m x number of control arm event times) matrix where (i,j,k)'th value is transition probability from state i to state j at k'th control arm event time. (returned from wintime::markov() or wintime::km()).
nimp	The number of random imputations.

Value

A list containing: The estimated treatment effect from the linear regression model, the variance, the Z-statistic, the components of the treatment effect, and the variance of the components.

EWTR *Expected win time against reference*

Description

Calculates the control group state space probabilities using a Markov model (recommended) or a Kaplan-Meier model. This function uses these probabilities to compare each participant's clinical state to a distribution of control group states.

Usage

```
EWTR(
  n,
  m,
  nunique,
  maxfollow,
  untimes,
  Time,
  Delta,
  dist,
  markov_ind,
  cov,
  trt
)
```

Arguments

n	The total number of trial participants.
m	The number of events in the hierarchy.
nunique	The number of unique control group event times (returned from wintime::markov() or wintime::km()).

maxfollow	The max control group follow up time (days) (returned from wintime::markov() or wintime::km()).
untimes	A vector containing unique control group event times (days) (returned from wintime::markov() or wintime::km()).
Time	A m x n matrix of event times (days). Rows should represent events and columns should represent participants. Rows should be in increasing order of clinical severity.
Delta	A m x n matrix of event indicators Rows should represent events and columns should represent participants. Rows should be in increasing order of clinical severity.
dist	A matrix of control group state probabilities (returned from wintime::markov() or wintime::km()).
markov_ind	An indicator of the model type used (1 for Markov, 0 for Kaplan-Meier).
cov	A n x p matrix of covariate values, where p is the number of covariates.
trt	A vector of length n containing treatment arm indicators (1 for treatment, 0 for control).

Value

A list containing: The estimated treatment effect from the linear regression model, the variance, the Z-statistic, the components of the treatment effect, and the variance of the components.

---

getWintimeIntegral *Helper functions for package functions*

Description

Win time difference

Usage

```
getWintimeIntegral(m, etimes, time0, time1, delta0, delta1)
```

Arguments

m	The number of events in the hierarchy.
etimes	A sorted vector of event times (days) (returned from wintime::setEventTimes()).
time0	A vector containing the control person's event times (days).
time1	A vector containing the treatment person's event times (days).
delta0	A vector containing the control person's event indicators.
delta1	A vector containing the treatment person's event indicators.

Details

This function calculates the win time difference integral for a single pair. This function is used in all pairwise win time methods.

Value

A list of the win time difference integral and its components.

`getWintimeIntegral_rest` *Win time difference with time restriction*

Description

This function calculates the win time difference integral for a single pair with truncation at time_restriction. This function is used in all pairwise win time methods.

Usage

```
getWintimeIntegral_rest(
  m,
  etimes,
  time0,
  time1,
  delta0,
  delta1,
  time_restriction
)
```

Arguments

`m`	The number of events in the hierarchy.
`etimes`	A sorted vector of event times (days) (returned from wintime::setEventTimes()).
`time0`	A vector containing the control person's event times (days).
`time1`	A vector containing the treatment person's event times (days).
`delta0`	A vector containing the control person's event indicators.
`delta1`	A vector containing the treatment person's event indicators.
`time_restriction`	The time restriction (days) for calculation.

Value

A list of the win time difference integral and its components.

km *Fit a Kaplan-Meier model*

Description

This function fits Kaplan-Meier models to calculate the state probabilities for each arm. In the win-time package, the returned state probability distributions are used in all non-pairwise methods. The Kaplan-Meier model is recommended for the Expected win time (EWT) method and the Restricted mean survival in favor of treatment (RMT) method.

Usage

```
km(n0, n1, m, Time, Delta)
```

Arguments

n0	The number of participants in the control arm.
n1	The number of participants in the treatment arm.
m	The number of events in the hierarchy.
Time	A m x (n0 + n1) matrix of event times (days). Rows should represent events and columns should represent participants. Event rows should be in increasing order of clinical severity.
Delta	A m x (n0 + n1) matrix of event indicators. Rows should represent events and columns should represent participants. Event rows should be in increasing order of clinical severity.

Value

A list containing: a matrix of control arm state probabilities, a matrix of treatment arm state probabilities, a vector of unique control arm event times (days), a vector of unique treatment arm event times (days), the number of unique control arm event times, the number of unique treatment arm event times, the control arm max follow time (days), the treatment arm max follow time (days), a matrix of combined arm state probabilities, a vector of unique combined arm event times (days), the number of unique combined arm event times, the combined arm max follow time (days), a (m x number unique combined arm event times) matrix of combined arm km survival probabilities, matrix of trt arm km survival probabilities, matrix of control arm km survival probabilities.

Examples

```
# ----------------------------
# Example inputs
# ----------------------------

# Event time vectors
TIME_1 <- c(256,44,29,186,29,80,11,380,102,33)
TIME_2 <- c(128,44,95,186,69,66,153,380,117,33)
TIME_3 <- c(435,44,95,186,69,270,1063,380,117,33)
```

```
# Event time matrix
Time <- rbind(TIME_1, TIME_2, TIME_3)

# Event indicator vectors
DELTA_1 <- c(1,0,1,0,1,1,1,0,1,0)
DELTA_2 <- c(1,0,0,0,0,1,1,0,0,0)
DELTA_3 <- c(0,0,0,0,0,0,0,0,0,0)

# Event indicator matrix
Delta <- rbind(DELTA_1, DELTA_2, DELTA_3)

# Treatment arm indicator vector
trt <- c(1,1,1,1,1,0,0,0,0,0)

# Number of control arm patients
n0 <- sum(trt == 0)

# Number of treatment arm patients
n1 <- sum(trt == 1)

# Number of events in the hierarchy
m <- nrow(Time)

# ------------------------
# km Examples
# ------------------------

z <- km(n0, n1, m, Time, Delta)
print(z)
```

`markov` *Fit a Markov model*

Description

This function fits an extended Markov model to calculate the state probabilities for each arm. In the wintime package, the returned state probability distributions are used in all non-pairwise methods. The extended Markov model is recommended for the Expected win time against reference (EWTR) method and the EWTR-composite max test (MAX) method.

Usage

```
markov(n0, n1, m, Time, Delta)
```

Arguments

`n0`	The number of participants in the control arm.
`n1`	The number of participants in the active treatment arm.

m	The number of events in the hierarchy.
Time	A m x (n0 + n1) matrix of event times (days). Rows should represent events and columns should represent participants. Event rows should be in increasing order of clinical severity.
Delta	A m x (n0 + n1) matrix of event indicators. Rows should represent events and columns should represent participants. Event rows should be in increasing order of clinical severity.

Value

A list containing: a matrix of control arm state probabilities, a matrix of treatment arm state probabilities, a vector of unique control arm event times (days), a vector of unique treatment arm event times (days), the number of unique control arm event times, the number of unique treatment arm event times, the control arm max follow time (days), the treatment arm max follow time (days), a matrix of combined arm state probabilities, a vector of unique combined arm event times (days), the number of unique combined arm event times, the combined arm max follow time (days), a (m x m x number of combined arm event times) matrix where (i,j,k)'th value is transition probability from state i to state j at k'th combined arm event time, matrix where (i,j,k)'th value is transition probability from state i to state j at k'th trt arm event time, matrix where (i,j,k)'th value is transition probability from state i to state j at k'th control arm event time.

Examples

```
# ------------------------------
# Example inputs
# ------------------------------

# Event time vectors
TIME_1 <- c(256,44,29,186,29,80,11,380,102,33)
TIME_2 <- c(128,44,95,186,69,66,153,380,117,33)
TIME_3 <- c(435,44,95,186,69,270,1063,380,117,33)

# Event time matrix
Time <- rbind(TIME_1, TIME_2, TIME_3)

# Event indicator vectors
DELTA_1 <- c(1,0,1,0,1,1,1,0,1,0)
DELTA_2 <- c(1,0,0,0,0,1,1,0,0,0)
DELTA_3 <- c(0,0,0,0,0,0,0,0,0,0)

# Event indicator matrix
Delta <- rbind(DELTA_1, DELTA_2, DELTA_3)

# Treatment arm indicator vector
trt <- c(1,1,1,1,1,0,0,0,0,0)

# Number of control arm patients
n0 <- sum(trt == 0)

# Number of treatment arm patients
n1 <- sum(trt == 1)
```

```
# Number of events in the hierarchy
m <- nrow(Time)

# -------------------------
# markov Examples
# -------------------------

z <- markov(n0, n1, m, Time, Delta)
print(z)
```

---

perm *Resample using permutations*

Description

This function reruns the desired wintime package method on a given number of permutations. This resampling method is recommended for the Expected win time (EWT) and Restricted mean survival in favor of treatment (RMT) methods.

Usage

```
perm(
  type,
  time_restriction,
  model,
  n,
  m,
  Time,
  Delta,
  trt,
  cov,
  z_ewtr,
  z_comp,
  resample_num,
  seed,
  nimp
)
```

Arguments

type	A string value indicating the wintime package method that will run with resampling.
time_restriction	The time cutoff value (days).
model	A string value indicating the model used on observed data ('markov' or 'km').

n	The total number of trial participants.
m	The number of events in the hierarchy.
Time	A m x n matrix of event times (days). Rows should represent events and columns should represent participants. Event rows should be in increasing order of clinical severity.
Delta	A m x n matrix of event indicators. Rows should represent events and columns should represent participants. Event rows should be in increasing order of clinical severity.
trt	A numeric vector of treatment arm indicators (1 for treatment, 0 for control).
cov	A n x p matrix of covariate values, where p is the number of covariates. Rows should represent participants and columns should represent covariate values.
z_ewtr	The Z-statistic of EWTR.
z_comp	The Z-statistic of the composite event approach.
resample_num	The number of desired permutations.
seed	The seed used for random number generation.
nimp	The number of random imputations for Redistribution-to-the-right.

Value

A list of a vector of length resample_num containing the treatment effect estimates (for type='max' these are z-statistics) for each permutation, a m x resample_num matrix of the components of the treatment effect..

PWT *Pairwise win time*

Description

This function calculates the sum of each pair's win time difference divided by the total number of pairs.

Usage

```
PWT(n, n0, n1, m, Time, Delta, tg, tau)
```

Arguments

n	The total number of trial participants.
n0	The number of control arm patients.
n1	The number of treatment arm patients.
m	The number of events in the hierarchy.
Time	A m x n matrix of event time (days). Rows should represent events and columns should represent participants. Event rows should be in increasing order of clinical severity.

Delta	A m x n matrix of event indicators. Rows should represent events and columns should represent participants. Event rows should be in increasing order of clinical severity.
tg	A numeric vector containing treatment arm indicators (1 for treatment, 0 for control).
tau	The maximum follow up time (days).

Value

The pairwise win time, and the components of the pairwise win time.

REWTP *Expected win time against trial population*

Description

Calculates the combined arm state space probabilities using a Markov model or a Kaplan-Meier model (recommended). This function uses these probabilities to compare each participant's clinical state to a distribution of combined arm states.

Usage

```
REWTP(
  n,
  m,
  nunique,
  maxfollow,
  untimes,
  Time,
  Delta,
  dist,
  markov_ind,
  cov,
  trt,
  time_restriction
)
```

Arguments

n	The total number of trial participants.
m	The number of events in the hierarchy.
nunique	The number of unique combined arm event times (returned from wintime::markov() or wintime::km()).
maxfollow	The max combined arm follow up time (days) (returned from wintime::markov() or wintime::km()).

untimes	A vector containing unique combined arm event times (days) (returned from wintime::markov() or wintime::km()).
Time	A m x n matrix of event times (days). Rows should represent events and columns should represent participants. Rows should be in increasing order of clinical severity.
Delta	A m x n matrix of event indicators Rows should represent events and columns should represent participants. Rows should be in increasing order of clinical severity.
dist	A matrix of combined arm state probabilities (returned from wintime::markov() or wintime::km()).
markov_ind	An indicator of the model type used (1 for Markov, 0 for Kaplan-Meier).
cov	A n x p matrix of covariate values, where p is the number of covariates.
trt	A vector of length n containing treatment arm indicators (1 for treatment, 0 for control).
time_restriction	The time restriction (days) for calculation.

Value

A list containing: The estimated treatment effect from the linear regression model, the variance, the Z-statistic, the components of the treatment effect, and the variance of the components.

REWTPR *Time Restricted Expected win time against trial population With redistribution to the right*

Description

Calculates the combined arm state space probabilities using a Markov model or a Kaplan-Meier model (recommended). This function uses these probabilities to compare each participant's clinical state to a distribution of combined arm states. Calculation is extended by redistribution-to-the-right principles and truncated at the user-specified time_restriction (days).

Usage

```
REWTPR(
  n,
  m,
  nunique2,
  maxfollow2,
  untimes2,
  Time,
  Delta,
  dist2,
  markov_ind,
```

```
  cov,
  trt,
  comkm,
  trans_prob2,
  time_restriction,
  nunique1,
  maxfollow1,
  untimes1,
  dist1,
  trtkm,
  trans_prob1,
  nunique0,
  maxfollow0,
  untimes0,
  dist0,
  conkm,
  trans_prob0,
  nimp
)
```

Arguments

n	The total number of trial participants.
m	The number of events in the hierarchy.
nunique2	The number of unique combined arm event times (returned from wintime::markov() or wintime::km()).
maxfollow2	The max combined arm follow up time (days) (returned from wintime::markov() or wintime::km()).
untimes2	A vector containing unique combined arm event times (days) (returned from wintime::markov() or wintime::km()).
Time	A m x n matrix of event times (days). Rows should represent events and columns should represent participants. Rows should be in increasing order of clinical severity.
Delta	A m x n matrix of event indicators Rows should represent events and columns should represent participants. Rows should be in increasing order of clinical severity.
dist2	A matrix of combined arm state probabilities (returned from wintime::markov() or wintime::km()).
markov_ind	An indicator of the model type used (1 for Markov, 0 for Kaplan-Meier).
cov	A n x p matrix of covariate values, where p is the number of covariates.
trt	A vector of length n containing treatment arm indicators (1 for treatment, 0 for control).
comkm	A m x nunique matrix of combined arm survival probabilities (returned from wintime::markov() or wintime::km()).

`trans_prob2` A (m x m x number of combined arm event times) matrix where (i,j,k)'th value is transition probability from state i to state j at k'th combined arm event time. (returned from wintime::markov() or wintime::km()).

`time_restriction` The time restriction (days) for calculation.

`nunique1` The number of unique trt arm event times (returned from wintime::markov() or wintime::km()).

`maxfollow1` The max trt arm follow up time (days) (returned from wintime::markov() or wintime::km()).

`untimes1` A vector containing unique trt arm event times (days) (returned from wintime::markov() or wintime::km()).

`dist1` A matrix of trt arm state probabilities (returned from wintime::markov() or wintime::km()).

`trtkm` A m x nunique matrix of trt arm survival probabilities (returned from wintime::markov() or wintime::km()).

`trans_prob1` A (m x m x number of trt arm event times) matrix where (i,j,k)'th value is transition probability from state i to state j at k'th trt arm event time. (returned from wintime::markov() or wintime::km()).

`nunique0` The number of unique control arm event times (returned from wintime::markov() or wintime::km()).

`maxfollow0` The max control arm follow up time (days) (returned from wintime::markov() or wintime::km()).

`untimes0` A vector containing unique control arm event times (days) (returned from wintime::markov() or wintime::km()).

`dist0` A matrix of control arm state probabilities (returned from wintime::markov() or wintime::km()).

`conkm` A m x nunique matrix of control arm survival probabilities (returned from wintime::markov() or wintime::km()).

`trans_prob0` A (m x m x number of control arm event times) matrix where (i,j,k)'th value is transition probability from state i to state j at k'th control arm event time. (returned from wintime::markov() or wintime::km()).

`nimp` The number of random imputations.

Value

A list containing: The estimated treatment effect from the linear regression model, the variance, the Z-statistic, the components of the treatment effect, and the variance of the components.

RMT *Restricted mean survival in favor of treatment*

Description

Calculates the state space probabilities using a Kaplan-Meier model (recommended) or a Markov model. This function uses these probabilities to compare both arms and calculate the expected win time of the treatment arm up to a given time point.

Usage

```
RMT(
  m,
  time_restriction,
  dist_state0,
  dist_state1,
  unique_event_times0,
  unique_event_times1,
  nunique_event_times0,
  nunique_event_times1
)
```

Arguments

`m`	The number of events in the hierarchy.
`time_restriction`	The cutoff time point (days) for the calculation.
`dist_state0`	A matrix of control arm state probabilities (returned from wintime::km() or wintime::markov()).
`dist_state1`	A matrix of treatment arm state probabilities (returned from wintime::km() or wintime::markov()).
`unique_event_times0`	A vector of unique control arm event times (days) (returned from wintime::km() or wintime::markov()).
`unique_event_times1`	A vector of unique treatment arm event times (days) (returned from wintime::km() or wintime::markov()).
`nunique_event_times0`	The number of unique control arm event times (returned from wintime::km() or wintime::markov()).
`nunique_event_times1`	The number of unique treatment arm event times (returned from wintime::km() or wintime::markov()).

Value

A list containing: The restricted mean survival in favor of the treatment arm, the components of the treatment effect.

RPWT *Time Restricted Pairwise win time*

Description

This function calculates the sum of each pair's win time difference (truncated at the user-specified time_restriction (days)) divided by the total number of pairs.

Usage

```
RPWT(n, n0, n1, m, Time, Delta, tg, tau, time_restriction)
```

Arguments

n	The total number of trial participants.
n0	The number of control arm patients.
n1	The number of treatment arm patients.
m	The number of events in the hierarchy.
Time	A m x n matrix of event time (days). Rows should represent events and columns should represent participants. Event rows should be in increasing order of clinical severity.
Delta	A m x n matrix of event indicators. Rows should represent events and columns should represent participants. Event rows should be in increasing order of clinical severity.
tg	A numeric vector containing treatment arm indicators (1 for treatment, 0 for control).
tau	The maximum follow up time (days).
time_restriction	The time restriction (days) for calculation.

Value

The pairwise win time, and the components of the pairwise win time.

RWTR *Restricted win time ratio*

Description

This function calculates the ratio of losses to wins on treatment. It iterates through all pairs of treatment and control patients and uses their time-to-death (or most severe clinical event) to determine a win or loss. If death is inconclusive, then a winner is determined based on wintime.

Usage

```
RWTR(n, m, tau, tg, Time, Delta)
```

Arguments

n	The total number of trial participants.
m	The number of events in the hierarchy.
tau	The maximum follow up time (days).
tg	A numeric vector containing treatment arm indicators (1 for treatment, 0 for control).
Time	A m x n matrix of event times (days), where m is the number of events in the hierarchy, and n is the total number of trial participants. Rows should represent events and columns should represent participants. Event rows should be in increasing order of clinical severity.
Delta	A m x n matrix of event indicators, where m is the number of events in the hierarchy, and n is the total number of trial participants. Rows should represent events and columns should represent participants. Event rows should be in increasing order of clinical severity.

Value

A list containing: The ratio of losses to wins on treatment, the total number of wins, and the total number of losses.

setEventTimes *Created a sorted vector of event times*

Description

This function creates a sorted vector of event times for a pair. This function is used in all pairwise functions.

Usage

```
setEventTimes(m, delta0, delta1, time0, time1, follow)
```

Arguments

m	The number of events in the hierarchy.
delta0	A vector of event indicators for the control person.
delta1	A vector of event indicators for the treatment person.
time0	A vector of event times (days) for the control person.
time1	A vector of event times (days) for the treatment person.
follow	The maximum follow up time (days).

Value

A sorted vector of event times (days) for a given pair.

---

setKM *Set event times and indicators used in the Kaplan-Meier survival curve calculation*

Description

This function creates the time_km and delta_km matrices used for wintime::km().

Usage

```
setKM(n, m, time, delta)
```

Arguments

n	The total number of trial participants.
m	The number of events in the hierarchy.
time	The row reversal of the Time matrix (days) (created inside wintime::km()).
delta	The row reversal of the Delta matrix (created inside wintime::km()).

Value

A list containing the event time matrix and the event indicator matrix used in wintime::km().

`wintime` *Run a win time calculation*

Description

This function runs one of the win time methods on observed and resampled data.

Usage

```
wintime(
  type,
  Time,
  Delta,
  trt,
  cov = NULL,
  model = NULL,
  resample = NULL,
  resample_num = 0,
  time_restriction = NA,
  seed = NA,
  nimp = 0
)
```

Arguments

`type`	A string value indicating the desired win time method. Methods include 'ewt', 'ewtr', 'rmt', 'max', 'wtr', 'rwtr', 'pwt', 'ewtp', 'rewtp', 'ewtpr','rewtpr', and 'rpwt'.
`Time`	A `m x n` matrix of event times (days), where `m` is the number of events in the hierarchy, and `n` is the total number of trial participants. Rows should represent events and columns should represent participants. Event rows should be in increasing order of clinical severity.
`Delta`	A `m x n` matrix of event indicators, where `m` is the number of events in the hierarchy, and `n` is the total number of trial participants. Rows should represent events and columns should represent participants. Event rows should be in increasing order of clinical severity.
`trt`	A numeric vector containing treatment arm indicators (1 for treatment, 0 for control).
`cov`	Optional. A `n x p` matrix of covariate values, where `n` is the total number of trial participants and `p` is the number of covariates. Rows should represent participants and columns should represent covariate values.
`model`	Optional. String value. The type of model used to calculate state distributions. Options include 'km' and 'markov'. Default depends on `type`.
`resample`	Optional. String value. The resampling method run after the observed data calculation. Options include 'boot' and 'perm'. Default depends on `type`.

`resample_num` Optional. The number of desired resamples. Default is 0.

`time_restriction`
Required only for `type` = 'rmt','rewtp','rewtpr', and 'rpwt'. The cutoff time (days).

`seed` Optional. Seed used for random number generation in resampling.

`nimp` Required only for `type` = 'ewtpr','rewtpr'. The number of random imputations for Redistribution-to-the-right.

Details

The type parameter specifies the procedure you would like to run. 'ewt' is Expected Win Time. 'ewtr' is Expected Win Time Against Reference (Control Arm). 'rmt' is Restricted Mean Time in Favor of Treatment. 'max' is the MAX procedure (max(COMP,EWTR)). 'wtr' is Win Time Ratio. 'rwtr' is Restricted Win Time Ratio. 'pwt' is Pairwise Win Time. 'ewtp' is Expected Win Time Against Trial Population. 'ewtpr' is Expected Win Time Against Trial Population With Redistribution. 'rewtp' is Time Restricted Expected Win Time Against Trial Population. 'rewtpr'is Time Restricted Expected Win Time Against Trial Population With Redistribution. 'rpwt' is Time Restricted Pairwise Win Time.

Value

A list containing: the observed treatment effect, a vector of length `resample_num` containing resampled treatment effects, a message indicating the method ran and the type of resampling done, the variance, the p-value, the total wins on treatment (pairwise methods only), the total losses on treatment (pairwise methods only), a vector of length 'm' with the components of the treatment effect, a vector of length 'm' with the variance of the components. A warning message will be printed for combinations of `type` and `model`/`resample` that are not recommended.

Examples

```
# ------------------------------
# Example Inputs
# ------------------------------

# Event time vectors
TIME_1 <- c(256,44,29,186,29,80,11,380,102,33)
TIME_2 <- c(128,44,95,186,69,66,153,380,117,33)
TIME_3 <- c(435,44,95,186,69,270,1063,380,117,33)

# Event time matrix
Time <- rbind(TIME_1, TIME_2, TIME_3)

# Event indicator vectors
DELTA_1 <- c(1,0,1,0,1,1,1,0,1,0)
DELTA_2 <- c(1,0,0,0,0,1,1,0,0,0)
DELTA_3 <- c(0,0,0,0,0,0,0,0,0,0)

# Event indicator matrix
Delta <- rbind(DELTA_1, DELTA_2, DELTA_3)
```

```
# Treatment arm indicator vector
trt <- c(1,1,1,1,1,0,0,0,0,0)

# Covariate vectors
cov1 <- c(54,53,55,61,73,65,63,63,82,58,66,66)
cov2 <- c(34.4,32.1,34.7,54.1,55.7,43.6,32.1,44.8,85.2,12.5,33.4,21.4)

# Covariate vectors
cov1 <- c(66,67,54,68,77,65,55,66,77,54)
cov2 <- c(3,6,4,2,3,5,8,5,3,5)
cov3 <- c(34.6,543.6,45.8,54.7,44.3,55.6,65.9,54.7,77.9,31.2)

# Covariate matrix
cov <- cbind(cov1, cov2, cov3)

# ------------------------
# wintime Examples
# ------------------------

# Run WTR
z <- wintime("wtr", Time, Delta, trt)
print(z)

# Run EWT with default settings and 10 resamples
z <- wintime("ewt", Time, Delta, trt, resample_num = 10)
print(z)

# Run EWTR with default settings
z <- wintime("ewtr", Time, Delta, trt, cov = cov)
print(z)

# Run EWTR with KM model (This will produce a warning message)
z <- wintime("ewtr", Time, Delta, trt, cov = cov, model = "km")
print(z)
```

WTR *Win time ratio*

Description

This function calculates the ratio of losses to wins on treatment. It iterates through all pairs of treatment and control patients and uses their win time difference as the deciding factor of a win or loss.

Usage

```
WTR(n, m, tau, tg, Time, Delta)
```

Arguments

n	The total number of trial participants.
m	The number of events in the hierarchy.
tau	The maximum follow up time (days).
tg	A numeric vector containing treatment arm indicators (1 for treatment, 0 for control).
Time	A m x n matrix of event times (days). Rows should represent events and columns should represent participants. Event rows should be in increasing order of clinical severity.
Delta	A m x n matrix of event indicators. Rows should represent events and columns should represent participants. Event rows should be in increasing order of clinical severity.

Value

A list containing: The ratio of losses to wins on treatment, the total number of wins, and the total number of losses.

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