Package: wintime (via r-universe)

September 3, 2024

Type Package

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

Version 0.1.0

Description Performs an analysis of time-to-event clinical trial data using various ``win time'' methods, including 'ewt', 'ewtr', 'rmt', 'max', 'wtr', 'rwtr', and 'pwt'. 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/

License MIT + file LICENSE

Encoding UTF-8

RoxygenNote 7.3.2

VignetteBuilder knitr

Imports survival

Suggests testthat (>= 3.0.0), knitr, rmarkdown (>= 2.0)

Config/testthat/edition 3

Depends R (>= 3.5.0)

NeedsCompilation no

Author James Troendle [aut, cre], Samuel Lawrence [aut]

Maintainer James Troendle <james.troendle@nih.gov>

Repository CRAN

Date/Publication 2024-09-02 12:00:02 UTC

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), and Pairwise win time (PWT). This function is also recommended for the EWTR_composite max test (MAX).

Usage

```
bootstrap(
  type,
  rmst_restriction,
  model,
  n,
  m,
  Time,
  Delta,
  trt,
  cov,
  z_ewtr,
  z_comp,
  resample_num,
  seed
)
```

Arguments

type	A string value indicating the wintime package method that will run with resampling.
rmst_restriction	The RMT 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.

Value

A vector of length resample_num containing the calculated treatment effect estimates (for type='max' these are z-statistics) for each bootstrap.

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

The z-statistic of the treatment effect from the Cox Model fit.

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

The expected win time of the treatment arm.

`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, and the Z-statistic.

`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

The win time difference integral.

`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).

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).

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,
  rmst_restriction,
  model,
  n,
  m,
  Time,
  Delta,
  trt,
  cov,
  z_ewtr,
  z_comp,
  resample_num,
  seed
)
```

Arguments

type	A string value indicating the wintime package method that will run with resampling.
rmst_restriction	The RMT 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.

Value

A vector of length resample_num containing the treatment effect estimates (for type='max' these are z-statistics) for each permutation.

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.

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,
  rmst_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.
rmst_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

The restricted mean survival in favor of the treatment arm.

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,
  rmst_restriction = NA,
  seed = NA
)
```

Arguments

`type`	A string value indicating the desired win time method. Methods include 'ewt', 'ewtr', 'rmt', 'max', 'wtr', 'rwtr', and 'pwt'.
`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.
rmst_restriction	Required only for type = 'rmt'. The RMT cutoff time (days).
seed	Optional. Seed used for random number generation in resampling.

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 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.

Index