Package 'TxEffectsSurvival'

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Type Package

Title Treatment Effect Inference for Terminal and Non-Terminal Events under Competing Risks

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Description Provides several confidence interval and testing procedures, based on either semiparametric (using event-specific win ratios) or nonparametric measures, including the ratio of integrated cumulative hazard (RICH) and the ratio of integrated transformed cumulative hazard (RITCH), for treatment effect inference with terminal and non-terminal events under competing risks. The semiparametric results were developed in Yang et al. (2022 <doi:10.1002/sim.9266>), and the nonparametric results were developed in Yang (2025 <doi:10.1002/sim.70205>). For comparison, results for the win ratio (Finkelstein and Schoenfeld 1999 <doi:10.1002/(SICI)1097-0258(19990615)18:11%3C1341::AID-SIM129%3E3.0.CO;2-7>), Pocock et al. 2012 <doi:10.1093/eurheartj/ehr352>, and Bebu and Lachin 2016 <doi:10.1093/biostatistics/kxv032>) are included. The package also supports univariate survival analysis with a single event. In this package, effect size estimates and confidence intervals are obtained for each event type, and several testing procedures are implemented for the global null hypothesis of no treatment effect on either terminal or non-terminal events. Furthermore, a test of proportional hazards assumptions, under which the event-specific win ratios converge to hazard ratios, and a test of equal hazard ratios, are provided. For summarizing the treatment effect across all events, confidence intervals for linear combinations of the event-specific win ratios, RICH, or RITCH are available using pre-determined or data-driven weights. Asymptotic properties of these inference procedures are discussed in Yang et al. (2022 <doi:10.1002/sim.9266>) and Yang (2025 <doi:10.1002/sim.70205>).

License GPL (>= 3)

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`TxEffectsSurvival-package`

Inference for Treatment Effects on Terminal and Non-Terminal Events under Competing Risks

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Description

This package implements procedures for treatment effect inference on a terminal event and a non-terminal event. It estimates the effect size using either event-specific win ratios, RICH or RITCH, and the corresponding confidence intervals are provided. For easy comparison, results for the win ratio (Finkelstein and Schoenfeld 1999, Pocock et al. 2012; Bebu and Lachin 2016) are also included. Moreover, testing procedures are provided for the global null hypothesis of no treatment effect on either event. Additionally, it offers confidence intervals for linear combinations of the effect size estimates using fixed or data-driven weights. Finite-sample correction and transformations are used to improve type I error control in moderate samples. For further details, see Yang and Troendle (2021), Yang et al. (2022), and Yang (2025).

Details

Package:	TxEffectsSurvival
Type:	Package
Version:	0.0.1
License:	GPL (>= 3)

Value

No return value, called for side effects.

Author(s)

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References

Yang, S. (2025). Testing and Estimation of Treatment Effects in Clinical Trials for Terminal and Non-Terminal Events Subject to Competing Risks. *Statistics in Medicine*. doi:10.1002/sim.70205

Yang, S., Troendle, J., Pak, D., & Leifer, E. (2022). Event-specific win ratios for inference with terminal and non-terminal events. *Statistics in Medicine*, 41(7), 1225–1241. doi:10.1002/sim.9266

Yang, S., & Troendle, J. (2021). Event-specific win ratios and testing with terminal and non-terminal events. *Clinical Trials*, 18(2), 180–187. doi:10.1177/1740774520972408

Bebu, I., & Lachin, J. M. (2016). Large sample inference for a win ratio analysis of a composite outcome based on prioritized components. *Biostatistics*, 17(1), 178–187. doi:10.1093/biostatistics/kxv032

Pocock, S. J., Ariti, C. A., Collier, T. J., & Wang, D. (2012). The win ratio: a new approach to the analysis of composite endpoints in clinical trials based on clinical priorities. *European Heart Journal*, 33(2), 176–182. doi:10.1093/eurheartj/ehr352

Finkelstein, D. M., & Schoenfeld, D. A. (1999). Combining mortality and longitudinal measures in clinical trials. *Statistics in Medicine*, 18(11), 1341–1354. doi:10.1002/(SICI)10970258(19990615)18:11<1341::AID-SIM129>3.0.CO;27

See Also

`tnt.analysis`

Examples

```
# Example: Treatment effect analysis using colon cancer trial data
data("colon_wr")

yh   <- colon_wr$yh     # non-terminal event time
hcen <- colon_wr$hcen   # censoring indicator for non-terminal event
yd   <- colon_wr$yd     # terminal event time
dcen <- colon_wr$dcen   # censoring indicator for terminal event
z    <- colon_wr$z      # treatment group (0 = control, 1 = treatment)

# Run the analysis
# The output includes test statistics and confidence intervals
# for RICH and RITCH measures (among others)
res <- tnt.analysis(
  yh, hcen, yd, dcen, z,
  lin   = c(0.5, 0.5),
  alpha = 0.05
)

# Display results
print(res)
```

`colon_wr` *Colon cancer trial example data (Obs vs Lev+5FU) for semi-competing risks analyses*

Description

A derived dataset from `survival::colon`, restricted to subjects in the `Obs` and `Lev+5FU` arms (excluding `Lev`). It is organized for semi-competing risks analyses with a non-terminal event (recurrence) and a terminal event (death). Each row corresponds to one subject.

Usage

```
data("colon_wr")
```

Format

A data frame with one row per subject and the following variables:

yh Time to *non-terminal* event (recurrence).

hcen Status for the non-terminal event: `1` = recurrence observed, `0` = censored.

yd Time to *terminal* event (death).

dcen Status for the terminal event: `1` = death observed, `0` = censored.

z Treatment indicator: `0` = `Obs`, `1` = `Lev+5FU`.

Details

The source data are `survival::colon`. We first restrict to `rx != "Lev"` and then, per subject, extract event time/status for recurrence (`etype = 1`) and death (`etype = 2`). The original treatment factor is recoded to a binary indicator $z \in \{0, 1\}$.

Source

survival package, dataset `colon`.

Examples

```
# Load example dataset
data("colon_wr")

# Contents of colon_wr:
#   yh    : Time to non-terminal event (recurrence)
#   hcen  : Event indicator for recurrence (1 = recurrence, 0 = censored)
#   yd    : Time to terminal event (death)
#   dcen  : Event indicator for death (1 = death, 0 = censored)
#   z     : Treatment group (0 = Obs, 1 = Lev+5FU)
```

`tnt.analysis` *Inference for Treatment Effects on Terminal and Non-Terminal Events under Competing Risks*

Description

`tnt.analysis` provides several procedures for evaluating treatment effects on terminal and non-terminal events in the presence of competing risks. Based on the methodologies proposed in Yang et al. (2022) and Yang (2025), the function implements a variety of robust and flexible semiparametric and nonparametric estimation and hypothesis testing procedures that accommodate complex event-time structures with semi-competing risks.

Specifically, the function primarily provides the following inferential procedures for estimation and hypothesis testing:

- **Event-Specific Win Ratios (ESWR)**: Event-specific win ratios obtained separately for terminal and non-terminal events, enabling powerful and interpretable global tests (linear combination, maximum, and χ^2), as proposed by Yang and Troendle (2021).
- **Log-Rank Generalized Rank Estimator (LRGRE)**: A generalized rank-based estimator extending the log-rank test to semi-competing risks settings, providing robust group comparisons for non-terminal and terminal events.
- **Integrated Cumulative Hazard (ICH)**: A nonparametric estimator calculated as the ratio of integrated cause-specific hazard in the treatment group over that in the control group. Values less than 1 indicate a beneficial effect. Robust to violations of proportional hazards.
- **Integrated Transformed Cumulative Hazard (ITCH)**: A stabilized version of ICH using a monotone transformation $\Phi(t) = 1-\exp(-t)$ to improve performance under heavy censoring or non-PH conditions.
- **Linear Combination Tests**: Global tests that combine event-specific estimates using either user-specified or data-adaptive weights. The default weight is $l = (0.5, 0.5)$. Applicable to ESWR, LRGRE, ICH, and ITCH.
- **Maximum Test**: A global test based on the maximum of event-specific test statistics, which rejects the global null if and only if at least one event-specific estimate is significant. It ensures coherency and tends to offer greater power when treatment effects differ across event types.
- **Test of Proportional Hazards**: A diagnostic test for assessing whether the proportional hazards assumption holds for the terminal event and the non-terminal event.
- **Test of Equal Hazard Ratios**: A diagnostic test for evaluating whether the hazard ratios for the terminal and non-terminal events are equal, assuming proportional hazards hold for both.

Usage

```
## Default S3 method:
tnt.analysis(nonterm_time, nonterm_event, term_time, term_event, z,
lin = c(0.5, 0.5), alpha = 0.05, repnum = 1e6, tau_r = 0.9, ...)
```

Arguments

`nonterm_time`	A numeric vector indicating the time to the non-terminal event or censoring.
`nonterm_event`	A binary indicator for the non-terminal event (1 = event, 0 = censored).
`term_time`	A numeric vector indicating the time to the terminal event or censoring.
`term_event`	A binary indicator for the terminal event (1 = event, 0 = censored).
`z`	A numeric vector for the treatment group indicator (1 = treatment, 0 = control).
`lin`	A numeric vector of length 2 specifying the weights for the linear combination of event-specific estimates. The first element corresponds to the non-terminal event and the second to the terminal event. The weights must be non-negative and sum to one. Default is `lin=c(0.5, 0.5)`.
`alpha`	The significance level used for confidence intervals and hypothesis testing. Default is `alpha=0.05`.
`repnum`	The number of Monte Carlo replications used to simulate bivariate normal distributions for critical value and p-value estimation. Default is `repnum=1e6`.
`tau_r`	A numeric value between 0 and 1 specifying the truncation proportion for the integration range $[0, \tau]$ used in computing ICH and ITCH, where $\tau =$ `tau_r` $\times$ (total trial duration). Default is `tau_r=0.9`. For trials with very long follow-up, a smaller value (e.g., 0.8) may improve numerical stability. See `details` for the definition of total trial duration.
`...`	Additional arguments (currently ignored). Included for future extensibility.

Details

These methods follow the statistical inference framework proposed by Yang (2025), without relying on parametric assumptions or restrictive model specifications. They are well-suited for semi-competing risks settings, where non-terminal events (e.g., hospitalizations) may be censored by terminal events (e.g., death), and both types are clinically important.

Global tests—including the linear combination, maximum, and χ^2 tests—offer flexible approaches to detecting treatment effects on either or both event types. Inference remains valid regardless of whether the proportional hazards assumption holds, with ICH and ITCH estimators providing additional robustness under non-proportional hazards.

In the implementation, the total trial duration is defined as $\tau = \max(\{yh, yd\}) + 0.001$. This upper bound is applied in the estimation of both ESWR and LRGRE. For ICH and ITCH, the analysis window is further truncated to $\tau_0 = \tau \times$ `tau_r`, where `tau_r` is a user-defined proportion (default = 0.9). Log transformations are used for the data-driven test, while log-log transformations are used for confidence intervals for non-terminal and terminal events. To improve finite-sample performance, a small-sample correction factor (cn) is applied to standard errors and test statistics. Specifically, $cn = 1 + 15/\max(n, 100)$ is used for the chi-square test and the maximum test, while $cn = 1 + 10/\max(n, 100)$ is used for the data-driven test and the corresponding confidence intervals.

To apply the package for univariate survival data analysis, see Example 2 in the Examples section below.

Value

An object of class "tnt.analysis", which is a named list containing the following elements:

sum_table	A contingency table summarizing the observed event patterns.
wrlin	Estimated win ratio from a linear combination of event-specific win ratios using user-specified weights lin.
rho	Estimated correlation between the event-specific test statistics (non-terminal and terminal).
pvalinall	Two-sided p-value for the linear combination test.
lin_ar	Data-driven linear combination weights.
wrlin_ar	Estimated win ratio from the data-adaptive linear combination lin_ar.
lincileswr	Confidence interval for the data-adaptive win ratio estimate, constructed on the log-transformed scale.
peswrlog	Two-sided p-value for the global test based on the log-transformed ESWR and data-adaptive weights.
chi, pvachi	Chi-square test statistic and its corresponding p-value.
mx, pvalmx	Maximum-type test statistic and corresponding Monte Carlo-based p-values.
logrank	Standard log-rank test result.
wrtest0	Unadjusted win ratio test result based on time to first event.
zvaephl, pvaephl	Z-statistic and p-value for testing the equality of hazard ratios between terminal and non-terminal events.
pvalph	P-value for testing the proportional hazards assumptions for both event types.
ci1, ci2	Pointwise confidence intervals for the event-specific win ratios for the non-terminal and terminal events, respectively.
cil	Confidence interval for the linear combination of win ratios using user-defined weights lin.

References

Yang, S. (2025). Testing and Estimation of Treatment Effects in Clinical Trials for Terminal and Non-Terminal Events Subject to Competing Risks. *Statistics in Medicine*. doi:10.1002/sim.70205

Yang, S., Troendle, J., Pak, D., & Leifer, E. (2022). Event-specific win ratios for inference with terminal and non-terminal events. *Statistics in Medicine*, 41(7), 1225–1241. doi:10.1002/sim.9266

Examples

```
# Example 1: joint analysis of non-terminal and terminal events
data("colon_wr")

yh   <- colon_wr$yh     # non-terminal event time
hcen <- colon_wr$hcen   # censoring indicator for non-terminal event
yd   <- colon_wr$yd     # terminal event time
dcen <- colon_wr$dcen   # censoring indicator for terminal event
```

```
z    <- colon_wr$z      # treatment group (0 = control, 1 = treatment)

# Run the analysis
# The output includes test statistics and confidence intervals
# for RICH and RITCH measures (among others)
res <- tnt.analysis(
  yh, hcen, yd, dcen, z,
  lin   = c(0.5, 0.5),
  alpha = 0.05
)

# Display results
print(res)

# Example 2: univariate analysis (workaround)
# tnt.analysis is primarily designed for joint analysis of non-terminal and terminal events,
# but univariate analysis can be conducted by assigning identical inputs to both.

res <- tnt.analysis(yh, hcen, yh, hcen, z)
res$global.tests$lincomb
res$ci.results$lincomb
```

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