Package 'bigtcr'

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Title Nonparametric Analysis of Bivariate Gap Time with Competing Risks

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Description For studying recurrent disease and death with competing risks, comparisons based on the well-known cumulative incidence function can be confounded by different prevalence rates of the competing events. Alternatively, comparisons of the conditional distribution of the survival time given the failure event type are more relevant for investigating the prognosis of different patterns of recurrence disease. This package implements a nonparametric estimator for the conditional cumulative incidence function and a nonparametric conditional bivariate cumulative incidence function for the bivariate gap times proposed in Huang et al. (2016) <doi:10.1111/biom.12494>.

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Contents

`bigtcr-package` *Bivariate Gap Time with Competing Risks*

Description

This package implements the non-parametric estimator for the conditional cumulative incidence function and the non-parametric conditional bivariate cumulative incidence function for the bivariate gap times proposed in Huang et al. (2016).

Conditional Cumulative Incidence Functions

Denote by T the time to a failure event of interest. Suppose the study participants can potentially experience any of several, say J, different types of failure events. Let $\epsilon = 1, \ldots, J$ indicate the failure event type.

The cumulative incidence function (CIF) for the jth competing event is defined as

$$F_j(t) = \text{pr}(T \leq t, \epsilon = j), \quad j = 1, \ldots, J.$$

Huang et al. (2016) proposed a non-parametric estimator for the conditional cumulative incidence function (CCIF)

$$G_j(t) = \text{pr}(T \leq t \mid T \leq \eta, \epsilon = j), \quad t \in [0, \eta], \quad j = 1, \ldots, J,$$

where the constant η is determined from the knowledge that survival times could potentially be observed up to time η.

To compare the CCIF of different failure types $j \neq k$, we consider the following class of stochastic processes

$$Q(t) = K(t)\{\widehat{G}_j(t) - \widehat{G}_k(t)\},$$

where $K(t)$ is a weight function. For a formal test, we propose to use the supremum test statistic

$$\sup_{t \in [0,\eta]} \mid Q(t) \mid,$$

an omnibus test that is consistent against any alternatives under which $G_j(t) \neq G_k(t)$ for some $t \in [0, \eta]$.

An approximate p-value corresponding to the supremum test statistic is obtained by applying the technique of permutation test.

Bivariate Gap Time Distribution With Competing Risks

For bivariate gap times (e.g. time to disease recurrence and the residual lifetime after recurrence), let V and W denote the two gap times so that $V + W$ gives the total survival time T. Note that, given the first gap time V being uncensored, the observable region of the second gap time W is restricted to $C - V$. Because the two gap times W and V are usually correlated, the second gap time W is subject to induced informative censoring $C - V$. As a result, conventional statistical methods can not be applied directly to estimate the marginal distribution of W.

Huang et al. (2016) proposed non-parametric estimators for the cumulative incidence function for the bivariate gap time (V, W)

$$F_j(v, w) = \text{pr}(V \leq v, W \leq w, \epsilon = j)$$

and the conditional bivariate cumulative incidence function

$$H_j(v, w) = \text{pr}(V \leq v, W \leq w \mid T \leq \eta, \epsilon = j).$$

To compare the joint distribution functions $H_j(v, w)$ and $H_k(v, w)$ of different failure types $j \neq k$, we consider the supremum test $\sup_{v+w\leq\eta} \mid Q^*(v, w) \mid$ based on the following class of processes

$$Q^*(v, w) = K^*(v, w)\{\widehat{H}_j(v, w) - \widehat{H}_k(v, w)\},$$

where $K^*(v, w)$ is a prespecified weight function.

The approximate p-value can be obtained through simulation by applying the technique of permutation tests.

Nonparametric Association Measure for the Bivariate Gap Time With Competing Risks

To evaluate the association between the bivariate gap times, Huang et al. (2016) proposed a modified Kendall's tau measure that was estimable with observed data

$$\tau_j^* = 4 \times \text{pr}(V_1 > V_2, W_1 > W_2 \mid V_1 + W_1 \leq \eta, V_2 + W_2 < \eta, \epsilon_1 = j, \epsilon_2 = j) - 1.$$

References

Huang CY, Wang C, Wang MC (2016). Nonparametric analysis of bivariate gap time with competing risks. Biometrics. 72(3):780-90. doi: 10.1111/biom.12494

`get.ccif` *Conditional Cumulative Incidence Function (CCIF) Estimation*

Description

Estimate the conditional cumulative incidence function. See `bigtcr-package`.

Usage

```
get.ccif(obs.y, event, tau = Inf)
```

Arguments

obs.y	Y: time to failure events or censoring
event	0: censored; $1, \ldots J$: type of failure events
tau	Conditioning time τ under which the CCIF is defined

Value

A matrix with class ccif that has J columns. Columns 1 to J correspond to $G_1(t)$ to $G_J(t)$. Each row represents a distinct observed time point t and the row name contains the value of t.

Examples

```
Gj <- get.ccif(obs.y = pancancer$obs.y, event = pancancer$min.type, tau   = 120);
```

---

get.gap.ccif *Conditional Bivariate Cumulative Incidence Function Estimation*

Description

Estimate the conditional bivariate cumulative incidence function. See bigtcr-package.

Usage

```
get.gap.ccif(obs.y, event, v, tau = Inf)
```

Arguments

obs.y	Y: time to failure events or censoring
event	0: censored; $1, \ldots J$: type of failure events
v	Time to the first failure event (e.g. disease recurrence)
tau	Conditioning time τ under which the CCIF is defined

Value

A matrix with class gap.ccif that has $J+2$ columns. Column 1 and 2 are (v, w). The rest columns correspond to $H_1(v, w)$ to $H_J(v, w)$. Each row represents a distinct observed time point and the row name contains the value of this time point.

Examples

```
Hj <- get.gap.ccif(obs.y=pancancer$obs.y, event=pancancer$min.type, v=pancancer$v, tau=120)
```

get.gap.kt *Cause-Specific Kendall's tau Estimation*

Description

Estimate the modified cause-specific Kendall's tau for the evaluation of association for bivariate gap time with competing risks. See bigtcr-package.

Usage

```
get.gap.kt(obs.y, event, v, tau = Inf, nbs = 0)
```

Arguments

obs.y	Y: time to failure events or censoring
event	0: censored; $1, \ldots J$: type of failure events
v	Time to the first failure event (e.g. disease recurrence)
tau	Conditioning time τ under which the CCIF is defined
nbs	Number of bootstrap samples for bootstrap variances. When nbs is smaller than 1, bootstrap variances are not evaluated.

Value

A list of the estimation and variances of modified casue-specific Kendall's tau

Examples

```
Kt <- get.gap.kt(obs.y=pancancer$obs.y, event=pancancer$min.type,
               v=pancancer$v, tau=120, nbs=5)
```

get.gap.pval *Comparison of Bivariate CCIF*

Description

Compare the bivariate CCIF of different failure typess by applying the technique of permutation test. See bigtcr-package.

Usage

```
get.gap.pval(obs.y, event, v, tau = Inf, comp.event = c(1, 2), np = 1000,
  Kt = function(x) {     1 })
```

Arguments

obs.y	Y: time to failure events or censoring
event	0: censored; $1, \ldots J$: type of failure events
v	Time to the first failure event (e.g. disease recurrence)
tau	Conditioning time τ under which the CCIF is defined
comp.event	Failure events for CCIF comparison
np	Number of permutations
Kt	A weight function that takes one parameter t and return the weight for t. Default weight function is constant 1

Value

P-value of the hypothesis test $H_0 : H_j = H_k = \ldots = H_l$.

Examples

```
gap.pval <- get.gap.pval(pancancer$obs.y, pancancer$min.type, pancancer$v,
                         tau=120, comp.event=c(1,2), np=20);
```

---

get.kendalltau *Kendall's tau Estimation*

Description

Estimate Kendall's tau association between two random variables

Usage

```
get.kendalltau(v, w)
```

Arguments

v	Vector of numeric values. Missing values will be ignored.
w	vector of numeric values. Missing values will be ignored.

Examples

```
kt <- get.kendalltau(pancancer$v, pancancer$w);
```

get.pval *Comparison of CCIF*

Description

Compare the CCIF of different failure typess by applying the technique of permutation test. See bigtcr-package.

Usage

```
get.pval(obs.y, event, tau = Inf, comp.event = c(1, 2), np = 1000,
  Kt = function(x) {     1 })
```

Arguments

obs.y	Y: time to failure events or censoring
event	0: censored; $1, \ldots J$: type of failure events
tau	Conditioning time τ under which the CCIF is defined
comp.event	Failure events for CCIF comparison
np	Number of permutations
Kt	A weight function that takes one parameter t and return the weight for t. Default weight function is constant 1

Value

P-value of the hypothesis test $H_0 : G_j = G_k = \ldots = G_l$.

Examples

```
pval <- get.pval(pancancer$obs.y, pancancer$min.type,
                 tau=120, comp.event=c(1,2), np=20);
```

pancancer *Example Pancreatic Cancer Dataset*

Description

Simulated data used in **bigtcr** examples.

Format

A dataframe with 3 variables:

obs.y Observed time to failure events or censoring in months

min.type Type of failure events

- **0** Censored
- **1** death with metastasis limited to lung only
- **2** death with metastasis that involves sites other than lung (e.g. liver)
- **3** death without disease recurrence

v Time to recurrence. NA if no recurrence observed

Details

Data simulated based on the patients who had surgical resection of pancreatic adenocarcinomas and had postoperative follow-up at the Johns Hopkins Hospital between 1998 and 2007.

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