Package 'RPEXE.RPEXT'

May 7, 2026

Title Reduced Piecewise Exponential Estimate/Test Software

Version 0.0.2

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URL https://github.com/hangangtrue/RPEXE.RPEXT

BugReports https://github.com/hangangtrue/RPEXE.RPEXT/issues

Description This reduced piecewise exponential survival software implements the likelihood ratio test and backward elimination procedure in Han, Schell, and Kim (2012 <doi:10.1080/19466315.2012.698945>, 2014 <doi:10.1002/sim.5915>), and Han et al. (puts to the program can be either times when events/censoring occur or the vectors of total time on test and the number of events. Outputs of the programs are times and the corresponding p-values in the backward elimination. Details about the model and implementation are given in Han et al. 2014. This program can run in R version 3.2.2 and above.

Depends R (>= 3.2.2)

License GPL-3

Imports stats, graphics

Encoding UTF-8

LazyData true

RoxygenNote 7.1.0

Suggests knitr, rmarkdown

VignetteBuilder knitr

NeedsCompilation no

Repository CRAN

Date/Publication 2020-05-21 06:30:03 UTC

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`bisec` *Bisection algorithm in Beta distribution*

Description

Running bisection algorithm to search for a2, the minimizer of (log((a2)^dea1*(1-a2)^dea2-delta))^2

Usage

```
bisec(delta, dea1, dea2, upbd, lowbd)
```

Arguments

delta	Test statistic in Han et al. (2012), delta = (ttot1/(ttot1+ttot2))^dea1*(ttot2/(ttot1+ttot2))^dea2;
dea1	first parameter in Beta distribution (number of events from the first arm)
dea2	second parameter in Beta distribution (number of events from the second arm)
upbd	upper bound of a2
lowbd	lower bound of a2

Value

a2

Examples

```
bisec(-74.4824, 33, 98, 1, 0.252)
```

---

data2 *RPEXE_fitting*

Description

A breast cancer clinical trial dataset in Adelson et al. (2016).

Usage

```
data(data2)
```

Details

- first column - times : time to event
- second column - censor : censoring status; 0=censored, 1=event.
- third column - group : labels the single agent arm and combination arm

References

[1] Adelson, K. B., Ramaswamy, B., Sparano, J. A., Christos, P. J., Wright, J. J., Raptis, G., Han, G., Villalona-Calero, M., Ma, C., Hershman, D., Baar, J., Klein, P., Cigler, T., Budd, T., Novik, Y., Tan, A.R., Tannenbaum, S., Goel, A., Levine, E., Shapiro, C. L., Andreopoulou, E., Naughton, M., Kalinsky, K., Waxman, S., Germain, D. (2016) "Randomized Phase II Trial of Fulvestrant Alone or in Combination with Bortezomib in Hormone Receptor-Positive Metastatic Breast Cancer Resistant to Aromatase Inhibitors: A New York Cancer Consortium Trial," Nature Partner Journals Breast Cancer, Volume 2, Article ID 16037, DOI: 10.1038/npjbcancer.2016.37.

df *JAMA Breast cancer*

Description

A dataset containing predictions for chemo-censitivity and pathological response from Hatzis (2011)

Usage

```
data(df)
```

Details

- validate: Validation status
- drfs: Censoring status; 0=censored, 1=event.
- drfs.time: Time to event or censoring
- er.status: ER status, P=positive, N=negative
- chemo.pred: Prediction for chemo sensitivity from the ACES predictor, sensitive or insensitive
- pre.N: Prediction of nodal status
- pCR.RD: pathological complete response (pCR) or residual disease (RD)
- pre.grade: prediction of tumor grade
- pre.T: T stage prediction
- dlda30: DLDA30 prediction for the pathological response.

References

[1] Hatzis, C., Pusztai, L., Valero, V., Booser, D. J., Esserman, L., Lluch, A., et al. (2011). A genomic predictor of response and survival following taxane-anthracycline chemotherapy for invasive breast cancer. The Journal of the American Medical Association 305, 1873–1881.

exact_pvalue *P-value for the two exponential comparison in Han et al.(2012)*

Description

This function computes the exact p-value from the likelihood ratio test

Usage

```
exact_pvalue(ttot1,ttot2,dea1,dea2,mono)
```

Arguments

ttot1	total time on test 1
ttot2	total time on test 2
dea1	number of death 1
dea2	number of death 2
mono	0: 2-sided hypothesis: H0: lam1 is equal to lam2; H1: lam1 is not equal to lam2 1: 1-sided hypothesis: H0: lam1 is greater than or equal to lam2; H1: lam1 is less than lam2 2: 1-sided hypothesis: H0: lam1 is less than or equal to lam2; H1: lam1 is greater than lam2

Value

a2: Beta distribution quantile computed using bisec.R pval: p-value

Examples

```
exact_pvalue(1, 302.04, 2, 25, 1)
```

---

gamllik *Log likelihood from the gamma distribution*

Description

A function computing the log likelihood from the gamma distribution under an order restriction reduction

Usage

```
gamllik(structtime,structttot,structdeaths,time_die,ttot,deaths)
```

Arguments

structtime	change-point times to be used to compute the likelihood value
structttot	total time on test (ttot) between each time point and the previous time point (or 0) corresponding to structtime
structdeaths	number of deaths corresponding to structttot
time_die	all event and censoring times from small to large
ttot	total time on test corresponding to time_die
deaths	the number of deaths corresponding to "ttot"

Value

log of the likelihood

Examples

```
time_die <- c(0.05,0.08,0.38,0.41,0.64)
ttot <- c(9.2,5.8,52.1,5.8,40.0)
deaths <- c(1,1,1,1,1)
structtime <- c(0.05,0.64)
structttot <- c(9.2, 40.0)
structdeaths = c(1, 5)
gamllik(structtime,structttot,structdeaths,time_die,ttot,deaths)
```

---

km *Kaplan-Meier curve*

Description

This function plots the Kaplan-Meier curve without returning outputs

Usage

```
km(time, censor, plotcens)
```

Arguments

time	a vector of event or censoring time
censor	a vector indicating censoring: 0 = censored; 1 = uncensored
plotcens	0: don't add censored data symbol to the output curve 1: add censored data symbol to the output curve

Value

Kaplan-Meier curve only

Examples

```
t1 <- c(2,3,4,5.5,7,10,12,15)
c1 <- c(0,0,1,0,0,1,0,0)
km(t1,c1,0)
```

kmvalue *Obtain values for Kaplan-Meier plotting*

Description

Obtain values for Kaplan-Meier plotting

Usage

```
kmvalue(x)
```

Arguments

x	Nx2 data matrix,first columen represents survival time of the i-th subject, second column represents censored flag (0 if not censored, 1 if censored)

Value

Values used for Kaplan-Meier plotting

Examples

```
t1 <- c(2,3,4,5.5,7,10,12,15)
c1 <- c(0,0,1,0,0,1,0,0)
x1<-cbind(t1,c1)
kmvalue(x1)
```

km_blacksolid *Kaplan-Meier curve*

Description

This function plots the Kaplan-Meier curve without returning outputs

Usage

```
km_blacksolid(time, censor, plotcens)
```

Arguments

time	a vector of event or censoring time
censor	a vector indicating censoring: 0 = censored; 1 = uncensored
plotcens	0: don't add censored data symbol to the output curve 1: add censored data symbol to the output curve

Value

Kaplan-Meier curve only

Examples

```
t1 <- c(2,3,4,5.5,7,10,12,15)
c1 <- c(0,0,1,0,0,1,0,0)
km_blacksolid(t1,c1,0)
```

`km_combine` *Comparing two Kaplan Meier curves in one plot*

Description

The function compares two Kaplan Meier curves in one plot

Usage

```
km_combine(x1, x2, pos = 0)
```

Arguments

`x1`	Nx2 data matrix,first columen represents survival time of the i-th subject, second column represents censored flag (0 if not censored, 1 if censored)
`x2`	Nx2 data matrix,first columen represents survival time of the i-th subject, second column represents censored flag (0 if not censored, 1 if censored)
`pos`	The position of the legend. Can be 0 or 1. The legend will be on the topright if set to 0. The legend will be on the bottomleft if set to 1. Default is 0.

Value

A combined Kaplan Meier curve

Examples

```
t1 <- c(2,3,4,5.5,7,10,12,15)
c1 <- c(0,0,1,0,0,1,0,0)
t2 <- c(1,3,5,4,8,10,9,11)
c2 <- c(0,0,0,0,1,0,0,0)
x1<-cbind(t1,c1)
x2<-cbind(t2,c2)
km_combine(x1,x2)
km_combine(x1,x2,pos=1)
```

km_log *Plot a Kaplan Meier curve in log scale*

Description

The function plots a Kaplan Meier curve in log scale

Usage

```
km_log(time, censor, plotcens)
```

Arguments

time	time of observed event
censor	a vector indicating censored or not at the given times, 0 = censored; 1 = uncensored
plotcens	0: add censored data to the output curve 1: don't add censored data to the output curve

Value

A Kaplan Meier curve in log scale

Examples

```
t1 <- c(2,3,4,5.5,7,10,12,15)
c1 <- c(0,0,1,0,0,1,0,0)
km_log(t1,c1,0)
```

km_red *Plot a Kaplan Meier curve in red*

Description

The function plots a Kaplan Meier curve in red

Usage

```
km_red(time, censor, plotcens)
```

Arguments

time	time of observed event
censor	a vector indicating censored or not at the given times, 0 = censored; 1 = uncensored
plotcens	0: add censored data to the output curve 1: don't add censored data to the output curve

Value

A red Kaplan Meier curve

Examples

```
t1 <- c(2,3,4,5.5,7,10,12,15)
c1 <- c(0,0,1,0,0,1,0,0)
km_red(t1,c1,0)
```

`km_redsolid` *Plot a Kaplan Meier curve in red solid line*

Description

The function plots a Kaplan Meier curve in red solid line

Usage

```
km_redsolid(time, censor, plotcens)
```

Arguments

`time`	time of observed event
`censor`	a vector indicating censored or not at the given times, 0 = censored; 1 = uncensored
`plotcens`	0: add censored data to the output curve 1: don't add censored data to the output curve

Value

A red solid Kaplan Meier curve

Examples

```
t1 <- c(2,3,4,5.5,7,10,12,15)
c1 <- c(0,0,1,0,0,1,0,0)
km_redsolid(t1,c1,0)
```

loopcuts *Change-point p-values with backward elimination*

Description

A function that iterates to compute the p-values from the backward elimination procedure (Han et al. 2014)

Usage

```
loopcuts(time,censor,cuttimes,mono)
```

Arguments

time	a sequence of time
censor	a vector indicating censored or not at the given times, 0 = censored; 1 = uncensored
cuttimes	unique, sorted, possible times to make the cuts, including 0 and the ending time
mono	0: 2-sided hypothesis: H0: lam1 is equal to lam2; H1: lam1 is not equal to lam2 1: 1-sided hypothesis: H0: lam1 is greater than or equal to lam2; H1: lam1 is less than lam2 2: 1-sided hypothesis: H0: lam1 is less than or equal to lam2; H1: lam1 is greater than lam2

Value

the times in the backward elimination procedure and the corresponding p-values for each change-point in the iteration

Examples

```
data(loopcuts_t_c)
data(loopcuts_cut)
time = loopcuts_t_c[,1]
censor = loopcuts_t_c[,2]
loopcuts(time, censor, loopcuts_cut, 1)
```

loopcuts_cut *Example data for loopcuts_cuttimes*

Description

Example data for loopcuts_cuttimes

Usage

```
data(loopcuts_cut)
```

loopcuts_onestep *Change-point p-values at given time points*

Description

This function computes the p-values at the current time points in input "time"

Usage

```
loopcuts_onestep(time,censor,cuttimes,mono)
```

Arguments

time	a sequence of time
censor	a vector indicating censored or not at the given times, 0 = censored; 1 = uncensored
cuttimes	unique, sorted, possible times to make the cuts, including 0 and the ending time
mono	0: 2-sided hypothesis: H0: lam1 is equal to lam2; H1: lam1 is not equal to lam2 1: 1-sided hypothesis: H0: lam1 is greater than or equal to lam2; H1: lam1 is less than lam2 2: 1-sided hypothesis: H0: lam1 is less than or equal to lam2; H1: lam1 is greater than lam2

Value

P-values at for all time points in "time"

Examples

```
data(loopcuts_t_c)
time = loopcuts_t_c[,1]
censor = loopcuts_t_c[,2]
loopcuts_onestep(time, censor, 28.03013699, 1)
```

loopcuts_t_c *Example data for loopcut_times_censoring*

Description

Example data for loopcut_times_censoring

Usage

```
data(loopcuts_t_c)
```

`loopcuts_umbrella` *Change-point p-values with backward elimination under umbrella alternative order restriction*

Description

A function that iterates to compute the p-values from the backward elimination procedure (Han et al. 2014) with umbrella alternative order restriction.

Usage

```
loopcuts_umbrella(time,censor,cuttimes,mono)
```

Arguments

`time`	a sequence of time
`censor`	a vector indicating censored or not at the given times, 0 = censored; 1 = uncensored
`cuttimes`	unique, sorted, possible times to make the cuts, including 0 and the ending time
`mono`	0: 2-sided hypothesis: H0: lam1 is equal to lam2; H1: lam1 is not equal to lam2 1: 1-sided hypothesis: H0: lam1 is greater than or equal to lam2; H1: lam1 is less than lam2 2: 1-sided hypothesis: H0: lam1 is less than or equal to lam2; H1: lam1 is greater than lam2

Value

the times in the backward elimination procedure and the corresponding p-values for each change-point in the iteration

Examples

```
data(loopcuts_t_c)
data(loopcuts_umbrella_cuttimes_mono)
time = loopcuts_t_c[,1]
censor = loopcuts_t_c[,2]
cuttimes = loopcuts_umbrella_cuttimes_mono[,1]
mono = loopcuts_umbrella_cuttimes_mono[,2]
loopcuts_umbrella(time, censor, cuttimes, mono)
```

loopcuts_umbrella_cuttimes_mono *Example data for loopcut_umbrella*

Description

Example data for loopcut_umbrella

Usage

```
data(loopcuts_umbrella_cuttimes_mono)
```

loopcut_onestep_data *Example data for loopcut_onestep*

Description

Example data for loopcut_onestep

Usage

```
data(loopcut_onestep_data)
```

pava_dfr *PAVA order restriction under decreasing failure rate (DFR)*

Description

This function imposes the PAVA DFR order restriction by eliminating change-points violating the restriction

Usage

```
pava_dfr(time_die,ttot,deaths)
```

Arguments

time_die	event times
ttot	the total time on test (ttot) corresponding to the event times
deaths	the number of deaths at each event time

Value

time2: the event times after PAVA ttot2: the corresponding ttot deaths2 the corresponding number of deaths

Examples

```
data(pava_dfrd)
t_d = pava_dfrd[,1]
t = pava_dfrd[,2]
d = pava_dfrd[,3]
pava_dfr(t_d, t, d)
```

---

pava_dfrd *Example data for pava*

Description

Example data for pava

Usage

```
data(pava_dfrd)
```

---

pava_ifr *PAVA order restriction under increasing failure rate (IFR)*

Description

This function imposes the PAVA IFR order restriction by eliminating change-points violating the restriction

Usage

```
pava_ifr(time_die,ttot,deaths)
```

Arguments

time_die	event times
ttot	the total time on test (ttot) corresponding to the event times
deaths	the number of deaths at each event time

Value

time2 the event times after PAVA ttot2 the corresponding ttot after PAVA deaths2 the corresponding number of deaths after PAVA

Examples

```
data(pava_dfrd)
t_d = pava_dfrd[,1]
t = pava_dfrd[,2]
d = pava_dfrd[,3]
pava_ifr(t_d, t, d)
```

---

pexeest *RPEXE estimate given change-points*

Description

This function estimates the survival probability at tx when a piecewise exponential distribution is fitted to (times,cens) cens = 0 for censored, cens = 1 for uncensored. the change point is tchange and lamest is the estimated parameters

Usage

```
pexeest(times, cens, tchange, tx)
```

Arguments

times	All the event/censoring times used to fit the model
cens	censoring status used to fit the model
tchange	Change-points
tx	Time points to estimate the survival probability

Value

quan survival probability lamest Lambda estimates for time periods divided by the change-points

Examples

```
data(pexeest_times_censoring)
data(t100)
times = pexeest_times_censoring[,1]
cens = pexeest_times_censoring[,2]
pexeest(times, cens, 28.03014, t100)
```

pexeest_times_censoring *Example data for pexeest_times_censoring*

Description

Example data for pexeest_times_censoring

Usage

```
data(pexeest_times_censoring)
```

RPEXE.RPEXT *Reduced Piecewise Exponential Estimate/Test Software*

Description

This reduced piecewise exponential survival software implements the likelihood ratio test and backward elimination procedure in Han, Schell, and Kim (2012, 2014), and Han et al. (2016). Inputs to the program can be either times when events/censoring occur or the vectors of total time on test and the number of events. Outputs of the programs are times and the corresponding p-values in the backward elimination. Details about the model and implementation are given in Han et al. 2014. This program can run in R version 3.2.2 and above.

References

[1] Han, G., Schell, M. J., and Kim, J. (2012) "Comparing Two Exponential Distributions Using the Exact Likelihood Ratio Test," Statistics in Biopharmaceutical Research, 4(4), 348-356.

[2] Han, G., Schell, M. J., and Kim, J. (2014) "Improved Survival Modeling in Cancer Research Using a Reduced Piecewise Exponential Approach," Statistics in Medicine, 33(1), 59-73.

[3] Han, G., Schell, M., Zhang, H., Zelterman, D., Pusztai, L., Adelson, K., and Hatzis, C. (2016) "Testing Violations of the Exponential Assumption in Cancer Clinical Trials with Survival Endpoints," Biometrics, DOI: 10.1111/biom.12590; PMID: 27669414.

[4] Adelson, K. B., Ramaswamy, B., Sparano, J. A., Christos, P. J., Wright, J. J., Raptis, G., Han, G., Villalona-Calero, M., Ma, C., Hershman, D., Baar, J., Klein, P., Cigler, T., Budd, T., Novik, Y., Tan, A.R., Tannenbaum, S., Goel, A., Levine, E., Shapiro, C. L., Andreopoulou, E., Naughton, M., Kalinsky, K., Waxman, S., Germain, D. (2016) "Randomized Phase II Trial of Fulvestrant Alone or in Combination with Bortezomib in Hormone Receptor-Positive Metastatic Breast Cancer Resistant to Aromatase Inhibitors: A New York Cancer Consortium Trial," Nature Partner Journals Breast Cancer, Volume 2, Article ID 16037, DOI: 10.1038/npjbcancer.2016.37.

[5] Simon GR, Extermann M, Chiappori A, Williams C, Begum M, Haura RKE, Ismail-Khan R, Schell M, Antonia SJ, Bepler G. Phase 2 trial of docetaxel and gefitinib in the first-line treatment of patients with advanced stage non-small cell lung cancer (NSCLC) who are 70 years of age or older. Cancer 2008; 112:2021–2029.

[6] Hatzis, C., Pusztai, L., Valero, V., Booser, D. J., Esserman, L., Lluch, A., et al. (2011). A genomic predictor of response and survival following taxane-anthracycline chemotherapy for invasive breast cancer. The Journal of the American Medical Association 305, 1873–1881.

`RPEXEv1_2` *RPEXE main function*

Description

This is the RPEXE main function taking inputs including time, censoring, change-point candidates, order restriction, criticl value, and display position. This function produces the RPEXE estimate. The prediction of the survival probability will be made on 100 equally spaced time points within the range of the event times based on the piecewise exponential estimate determined by all the changepoints.

Usage

```
RPEXEv1_2(times,censoring,cuttimes=NULL, monotone=0, criticalp=-1, pos = 0)
```

Arguments

`times`	A sequence of times where the events occur
`censoring`	A sequence of dichotomous values indicating censored or not (0=censored and 1=not censored)
`cuttimes`	A vector of unique, sorted, possible times to make the cuts. When it's set to NULL, it's the Default value, which is sorted event times from small to large.
`monotone`	An input having indicating the monotonicity assumption – 0: no monotonic assumption (default) – 1: failure rate is decreasing over time – 2: failure rate is increasing over time – 3: monotonic failure rate – 4: failure rate is increasing and then decreasing – 5: failure rate is decreasing and then increasing – 6: failure rate is increasing and then decreasing with the peak removed first – 7: failure rate is decreasing and then increasing with the peak removed first
`criticalp`	The critical (naive) p-value cutoff where all p-values in the backward elimination that are lower than this will be regarded as being significant. For example, at type I error rate 0.05, the critical p-value was 0.004 in the real example of Han et al. (2014). Default == -1 (equivalent to NA).
`pos`	The position of the legend. Can be 0 or 1. The legend will be on the topright if set to 0. The legend will be on the bottomleft if set to 1. Default is 0.

Value

times: event/censoring times taking out from the backward elimination pvalues: p-values corresponding to "times" times_c: significant change-points pvalues_c: critical p-values that are smaller than the critical p-value trend: trend information struct: structure information for multiple order restrictions changet: change-point time of trend for umbrella alternatives.

Examples

```
t1 <- c(2,3,4,5.5,7,10,12,15)
c1 <- c(0,0,1,0,0,1,0,0)
RPEXEv1_2(t1, c1, monotone = 1,criticalp=0.05, pos = 0)
```

`simple` *None Small Cell Lung cancer data*

Description

A dataset non-small-cell lung cancer trial data from Simon et al. (2011)

Usage

```
data(simple)
```

Details

- first column - censor : censoring status; 0=censored, 1=event.
- second column - times : time to event

References

[1] Simon GR, Extermann M, Chiappori A, Williams C, Begum M, Haura RKE, Ismail-Khan R, Schell M, Antonia SJ, Bepler G. Phase 2 trial of docetaxel and gefitinib in the first-line treatment of patients with advanced stage non-small cell lung cancer (NSCLC) who are 70 years of age or older. Cancer 2008; 112:2021–2029.

`t100` *Example data for pexeest_tx*

Description

Example data for pexeest_tx

Usage

```
data(t100)
```

totaltest *total time on test*

Description

Function 'totaltest' computes total-time-on-test.

Usage

```
totaltest(time,censor)
```

Arguments

time	event/censoring times
censor	censoring status

Value

time_die time points where events occur (in ascending order) ttot total time on test corresponding to each time point in "time_die" deaths number of death corresponding to each time point in "time_die"

Examples

```
t1 <- c(2,3,4,5.5,7,10,12,15)
c1 <- c(0,0,1,0,0,1,0,0)
totaltest(t1,c1)
```

umbrella *Umbrella alternative.*

Description

Using the umbrella alternative to merge certain entries to make the sequence of ttot/deaths to increase then decrease or to decrease then increase. Note that the pava function imposes non-decreasing or non-increasing order. This function directly uses function pava().

Usage

```
umbrella(time_die,ttot,deaths,indi)
```

Arguments

time_die	a sequence of times where deaths happened.
ttot	the total time on test between each time point and the previous time point (or 0).
deaths	the number of deaths at each time point.
indi	an indicator indi == 0: monotonic failure rate (either decrease or increase) indi == 1: denoting the failure rate increase then decrease indi == 2: denoting the failure rate decrease then increase

Value

time2 == the merged time_die after the umbrealla alternative order restriction; struct == a structure saves the partition information; label == a note about how the failure rate varies; indx == the position where the change point value is.

Examples

```
data(pava_dfrd)
t_d = pava_dfrd[,1]
t = pava_dfrd[,2]
d = pava_dfrd[,3]
umbrella(t_d, t, d, 2)
```

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