Package 'FHtest'

September 23, 2020

Title Tests for Right and Interval-Censored Survival Data Based on the

Type Package

Treming-trainington Class
Version 1.5
Date 2020-9-23
Author Ramon Oller, Klaus Langohr
Maintainer Ramon Oller < ramon.oller@uvic.cat>
Description Functions to compare two or more survival curves with: a) The Fleming-Harrington test for right- censored data based on permutations and on counting processes. b) An extension of the Fleming-Harrington test for interval- censored data based on a permutation distribution and on a score vector distribution.
License GPL (>= 2)
Encoding latin1
Depends interval, KMsurv
Imports survival, perm, MASS
NeedsCompilation no
Repository CRAN
Date/Publication 2020-09-23 19:40:02 UTC
R topics documented:
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FHtest-package	Tests for Right and Interval-Censored Survival Data Based on the Fleming-Harrington Class

Description

This package offers several tests for the comparison of two or more survival curves:

- a) The Fleming-Harrington test for right-censored data based on permutations and on counting processes.
- b) An extension of the Fleming-Harrington test for interval-censored data based on a permutation distribution and on a score vector distribution.

Details

Package: FHtest
Type: Package
Version: 1.5
Date: 2020-9-23
License: GPL (>= 2)

Author(s)

Ramon Oller and Klaus Langohr
Ramon Oller ramon.oller@uvic.cat>

References

Oller, R. and Gómez, G. (2012). A generalized Fleming and Harrington's class of tests for intervalcensored data. The Canadian Journal of Statistics **40**, 501–516.

Oller, R. and Langohr, K. (2017). FHtest: An R Package for the Comparison of Survival Curves with Censored Data. Journal of Statistical Software **81**, 1–25.

duser Data set of drug users in Badalona (Spain)

Description

Data set of 940 drug users in Badalona (Spain). The data come from the detoxification unit of *Hospital Universitari Germans Trias i Pujol* in Badalona, Spain

Usage

```
data(duser)
```

Format

A data frame with 940 observations on the following 5 variables.

```
left Left endpoint of time to HIV-infection
right Right endpoint of time to HIV-infection
zper Calendar period
zgen Gender (0: male; 1: female)
age Age
```

Source

Detoxification unit, Hospital Universitari Germans Trias i Pujol, Badalona, Spain.

References

Gómez, G., Calle, M. L., Egea, J. M. and Muga, R. (2000). Risk of HIV infection as a function of the duration of intravenous drug use: A non-parametric Bayesian approach. Statistics in Medicine 19, 2641–2656.

Oller, R. and Gómez, G. (2012). A generalized Fleming and Harrington's class of tests for intervalcensored data. The Canadian Journal of Statistics **40**, 501–516.

FHtesticp

The Fleming-Harrington test for interval-censored data based on a permutation distribution

Description

The FHtesticp function performs a test for interval-censored data based on a permutation distribution. It uses the G- ρ , λ family of statistics for testing the differences of two or more survival curves.

Usage

Arguments

L Numeric vector of the left endpoints of the censoring intervals (equivalent to the

first element of Surv when type = "interval2").

R Numeric vector of the right endpoints of the censoring intervals (equivalent to

the second element of Surv when type = "interval2").

group A vector denoting the group variable for which the test is desired. If group is a

factor or character, then a k-sample test is performed, where k is the number of unique values of group. If group is numeric, then a trend ("correlation" type) test is performed. If there are only two groups, both methods give the same

results.

rho A scalar parameter that controls the type of test (see details).

lambda A scalar parameter that controls the type of test (see details).

alternative Character giving the type of alternative hypothesis for two-sample and trend

tests: "different", "increasing" or "decreasing" survival functions. For

the k-sample case, "different" should be chosen.

icFIT A precalculated icfit object for increased computation speed. This should be

the icfit from the pooled data. Normally initfit should be used instead (see

Warning below).

initfit An object of class icfit or icsurv or a character vector giving a function name,

used for the initial estimate (see Warning below). Ignored if icFIT is not NULL.

permcontrol List of arguments for controlling permutation tests. Default value is permControl.

icontrol List of arguments for controling the NPMLE algorithm in call to icfit. Default

value is icfitControl.

exact A logical value, where TRUE denotes exact test. Ignored if method is not NULL.

method A character value, one of "pclt", "exact.network", "exact.ce", "exact.mc".

If no value is specified, function methodRule chooses the value.

methodRule A function used to choose the method. Default value is methodRuleIC1 (see

details in perm).

Lin Logical vector: should L be included in the interval?

Rin Logical vector: should R be included in the interval?

formula A formula with a numeric vector as response (which assumes no censoring) or

Surv object. The right side of the formula is the group variable. No strata()

is allowed.

data Data frame for variables in formula.

subset An optional vector specifying a subset of observations to be used.

na.action A function that indicates what should happen if the data contain NAs. Default

value is set to getOption("na.action").

... Additional arguments.

Details

The appropriate selection of the parameters rho and lambda gives emphasis to early, middle or late hazard differences. For instance, in a given clinical trial, if one would like to assess whether the effect of a treatment or therapy on the survival is stronger at the earlier phases of the therapy, we should choose lambda = 0, with increasing values of rho emphasizing stronger early differences. If there were a clinical reason to believe that the effect of the therapy would be more pronounced towards the middle or the end of the follow-up period, it would make sense to choose rho = lambda > 0 or rho = 0 respectively, with increasing values of lambda emphasizing stronger middle or late differences. The choice of the weights has to be made prior to the examination of the data and taking into account that they should provide the greatest statistical power, which in turns depends on how it is believed the null is violated.

The censoring in the default case (when Lin = Rin = NULL) assumes there are n (n = length(L)) failure times, and the *i*th one is in the interval between L[i] and R[i]. The default is not to include L[i] in the interval unless L[i] = R[i], and to include R[i] in the interval unless R[i] = Inf. When Lin and Rin are not NULL they describe whether to include L and R in the associated interval. If either Lin or Rin is length 1 then it is repeated n times, otherwise they should be logicals of length n.

Many standard statistical tests may be put into the form of the permutation test (see Graubard and Korn, 1987). There is a choice of four different methods to calculate the *p*-values (the last two are only available for the two-sample test): (1) pclt: using permutational central limit theorem (see, e.g., Sen, 1985). (2) exact.mc: exact method using Monte Carlo. (3) exact.network: exact method using a network algorithm (see, e.g., Agresti, Mehta, and Patel, 1990). Currently, the network method does not implement many of the time saving suggestions such as clubbing. (4) exact.ce: exact method using complete enumeration. This is good for very small sample sizes and when doing simulations, since the complete enumeration matrix need only be calculated once for the simulation.

There are several ways to perform the permutation test, and the function methodRuleIC1 chooses which of these ways will be used. The choice is basically between using a permutational central limit theorem (method = "pclt") or using an exact method. There are several algorithms for the exact method. Note that there are two exact two-sided methods for calculating p-values (see permControl and the tsmethod option).

Value

information	Full description of the test.
data.name	Description of data variables.
n	Number of observations in each group.
fit	Object of class icfit giving the NPMLE of all responses combined (ignoring the group variable).
diff	The weighted observed minus expected number of events in each group.
scores	Vector with the same length as L and R, containing the rank scores (see Oller and Gómez, 2012).
statistic	Either the chi-square or Z statistic.
var	The variance matrix of the test.
alt.phrase	Phrase used to describe the alternative hypothesis.

```
    p-value p-value associated with the alternative hypothesis.
    p.conf.int Confidence interval of p-value. For method = "exact.mc" only.
    The matched call.
```

Warning

Since the input of icFIT is only for saving computational time, no checks are carried out to determine if the icFIT is in fact the correct one. Thus, one may get wrong answers with no warnings if the wrong icFIT object is chosen. A safer way to save computational time is to choose for initfit either a precalculated icfit object or an icsurv object from a function in the Icens package such as EMICM. If this is done, either the correct answer or a warning will be returned even if a bad guess for initfit is chosen. Additionally, one may specify a function name for initfit. The default is NULL which uses a simple initial fit function (the weighted average of the A matrix, see the code of icfit.default (Package interval)). A fast but somewhat unstable function uses initcomputeMLE which uses function computeMLE of the 'MLEcens' package. See the help for icfit for details on the initfit option.

Author(s)

R. Oller and K. Langohr

References

Fay, M. P. (1996). Rank invariant tests for interval-censored data under the grouped continuous model. Biometrics **52**, 811–822.

Fay, M. P. (1999). Comparing several score tests for interval-censored data. Statistics in Medicine 18, 273–285.

Gómez, G., Calle, M. L., Oller, R. and Langohr, K. (2009). Tutorial on methods for interval-censored data and their implementation in R. Statistical Modelling **9**, 259–297.

Oller, R. and Gómez, G. (2012). A generalized Fleming and Harrington's class of tests for intervalcensored data. The Canadian Journal of Statistics **40**, 501–516.

Oller, R. and Langohr, K. (2017). FHtest: An R Package for the Comparison of Survival Curves with Censored Data. Journal of Statistical Software **81**, 1–25.

See Also

FHtestics, icfit (Package interval), icsurv (Package Icens).

Examples

```
## Two-sample tests
data(bcos)
FHtesticp(Surv(left, right, type = "interval2") ~ treatment, data = bcos)
FHtesticp(Surv(left, right, type = "interval2") ~ treatment, data = bcos, exact = TRUE)
FHtesticp(Surv(left, right, type = "interval2") ~ treatment, data = bcos, rho = 1)

data(duser)
FHtesticp(Surv(left, right, type = "interval2") ~ as.factor(age > 21), data = duser,
```

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FHtestics

The Fleming-Harrington test for interval-censored data based on a score vector distribution

Description

The FHtestics function performs a test for interval-censored data based on a score vector distribution. It uses the G- ρ family of statistics (being $\lambda=0$) for testing the differences of two or more survival curves.

Usage

Arguments

L	Numeric vector of the left endpoints of the censoring intervals (equivalent to the first element of Surv when type = "interval2").
R	Numeric vector of the right endpoints of the censoring intervals (equivalent to the second element of Surv when type = "interval2").
group	A vector denoting the group variable for which the test is desired. If group is a factor or character, then a k-sample test is performed, where k is the number of unique values of group. If group is numeric, then a trend ("correlation" type) test is performed. If there are only two groups, both methods give the same results.
rho	A scalar parameter that controls the type of test (see details).
lambda	A scalar parameter that controls the type of test. With this method, lambda has

to be zero.

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alternative	Character giving the type of alternative hypothesis for two-sample and trend tests: "different", "increasing" or "decreasing" survival functions. For the k-sample case, "different" should be chosen.
tol	Tolerance for the calculation of the g-inverse. Values less than tol are set to zero.
icFIT	A precalculated icfit object for increased computation speed. This should be the icfit from the pooled data. Normally initfit should be used instead (see Warning below).
initfit	An object of class icfit or icsurv or a character vector giving a function name, used for the initial estimate (see Warning below). Ignored if icFIT is not NULL.
icontrol	List of arguments for controling the NPMLE algorithm in call to icfit. Default value is icfitControl.
Lin	Logical vector: should L be included in the interval?
Rin	Logical vector: should R be included in the interval?
formula	A formula with a numeric vector as response (which assumes no censoring) or Surv object. The right side of the formula is the group variable. No strata() is allowed.
data	Data frame for variables in formula.
subset	An optional vector specifying a subset of observations to be used.
na.action	A function that indicates what should happen if the data contain NAs. Default value is set to getOption("na.action").
	Additional arguments.

Details

The appropriate selection of the parameter rho gives emphasis to early hazard differences. For instance, in a given clinical trial, if one would like to assess whether the effect of a treatment or therapy on the survival is stronger at the earlier phases of the therapy, we should choose rho>0 emphasizing stronger early differences.

The censoring in the default case (when Lin = Rin = NULL) assumes there are n (n = length(L)) failure times, and the *i*th one is in the interval between L[i] and R[i]. The default is not to include L[i] in the interval unless L[i] = R[i], and to include R[i] in the interval unless R[i] = Inf. When Lin and Rin are not NULL they describe whether to include L and R in the associated interval. If either Lin or Rin is length 1 then it is repeated n times, otherwise they should be logicals of length n.

It is difficult to prove the asymptotic validity of the standard score tests for this likelihood, because the number of nuisance parameters typically grows with the sample size and often many of the parameters are equal at the nonparametric MLE, i.e., they are on the boundary of the parameter space (Fay, 1996). Specifically, when the score test is performed, an adjustment is made so that the nuisance parameters are defined based on the data and do not approach the boundary of the parameter space (see Fay, 1996). Theoretically, the score test should perform well when there are many individuals but few observation times, and its advantage in this situation is that it retains validity even when the censoring mechanism may depend on the treatment.

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Value

information	Full description of the test.
data.name	Description of data variables.
n	Number of observations in each group.
fit	Object of class icfit giving the NPMLE of all responses combined (ignoring the group variable).
diff	The weighted observed minus expected number of events in each group.
scores	Vector with the same length as L and R, containing the rank scores (see Oller and Gómez, 2012).
statistic	Either the chi-square or Z statistic.
var	The variance matrix of the test.
d2L.dB2	Second derivative of the log-likelihood with respect to β .
d2L.dgam2	Second derivative of the log-likelihood with respect to γ .
d2L.dBdgam	Derivative of the log-likelihood with respect to β and γ .
alt.phrase	Phrase used to describe the alternative hypothesis.
pvalue	<i>p</i> -value associated with the alternative hypothesis.
p.conf.int	Confidence interval of p -value. For method = "exact.mc" only.
call	The matched call.

Warning

Since the input of icFIT is only for saving computational time, no checks are carried out to determine if the icFIT is in fact the correct one. Thus, one may get wrong answers with no warnings if the wrong icFIT object is chosen. A safer way to save computational time is to choose for initfit either a precalculated icfit object or an icsurv object from a function in the Icens package such as EMICM. If this is done, either the correct answer or a warning will be returned even if a bad guess for initfit is chosen. Additionally, one may specify a function name for initfit. The default is NULL which uses a simple initial fit function (the weighted average of the A matrix, see the code of icfit.default (Package interval)). A fast but somewhat unstable function uses initcomputeMLE which uses function computeMLE of the 'MLEcens' package. See the help for icfit for details on the initfit option.

Author(s)

R. Oller and K. Langohr

References

Fay, M. P. (1996). Rank invariant tests for interval-censored data under the grouped continuous model. Biometrics **52**, 811–822.

Fay, M. P. (1999). Comparing several score tests for interval-censored data. Statistics in Medicine 18, 273–285.

Gómez, G., Calle, M. L., Oller, R. and Langohr, K. (2009). Tutorial on methods for interval-censored data and their implementation in R. Statistical Modelling **9**, 259–297.

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Oller, R. and Gómez, G. (2012). A generalized Fleming and Harrington's class of tests for intervalcensored data. The Canadian Journal of Statistics **40**, 501–516.

Oller, R. and Langohr, K. (2017). FHtest: An R Package for the Comparison of Survival Curves with Censored Data. Journal of Statistical Software **81**, 1–25.

See Also

FHtesticp, icfit (Package interval), icsurv (Package Icens).

Examples

```
## Two-sample tests
data(bcos)
FHtestics(Surv(left, right, type = "interval2") ~ treatment, data = bcos)
FHtestics(Surv(left, right, type = "interval2") ~ treatment, data = bcos, rho = 1)
data(duser)
FHtestics(Surv(left, right, type = "interval2") ~ as.numeric(age > 21), data = duser,
          rho = 1, Lin = TRUE, Rin = TRUE, subset = (zper == 3),
          icontrol = icfitControl(maxit = 100000))
## Trend test
data(illust3)
FHtestics(Surv(left, right, type = "interval2") ~ group, data = illust3,
          subset = c(1:100, 601:700, 1201:1300), rho = 2, Lin = TRUE, Rin = TRUE,
          alternative = "increasing")
## K-sample test
FHtestics(Surv(left, right, type = "interval2") ~ as.factor(group), data = illust3,
          subset = c(1:100, 601:700, 1201:1300), rho = 3, Lin = TRUE, Rin = TRUE)
```

FHtestrcc

The Fleming-Harrington test for right-censored data based on counting processes

Description

The FHtestrcc function performs a test for right-censored data based on counting processes. It uses the $G-\rho$, λ family of statistics for testing the differences of two or more survival curves.

Usage

```
## Default S3 method:
FHtestrcc(L, R, group, rho = 0, lambda = 0, alternative, ...)
## S3 method for class 'formula'
FHtestrcc(formula, data, subset, na.action, ...)
```

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Arguments

L Numeric vector of the left endpoints of the censoring intervals (exact and right-

censored data are represented as intervals of [a,a] and (a, infinity) respectively).

R Numeric vector of the right endpoints of the censoring intervals (exact and right-

censored data are represented as intervals of [a,a] and (a, infinity) respectively).

group A vector denoting the group variable for which the test is desired. If group is a

factor or character, then a k-sample test is performed, where k is the number of unique values of group. If group is numeric, then a trend ("correlation" type) test is performed. If there are only two groups, both methods give the same

results.

rho A scalar parameter that controls the type of test (see details).

lambda A scalar parameter that controls the type of test (see details).

alternative Character giving the type of alternative hypothesis for two-sample and trend

tests: "different", "increasing" or "decreasing" survival functions. For

the k-sample case, "different" should be chosen.

formula A formula with a numeric vector as response (which assumes no censoring) or

Surv object. The right side of the formula is the group variable. No strata()

is allowed.

data Data frame for variables in formula.

subset An optional vector specifying a subset of observations to be used.

na.action A function that indicates what should happen if the data contain NAs. Default

value is set to getOption("na.action").

... Additional arguments.

Details

The appropriate selection of the parameters rho and lambda gives emphasis to early, middle or late hazard differences. For instance, in a given clinical trial, if one would like to assess whether the effect of a treatment or therapy on the survival is stronger at the earlier phases of the therapy, we should choose lambda = 0, with increasing values of rho emphasizing stronger early differences. If there were a clinical reason to believe that the effect of the therapy would be more pronounced towards the middle or the end of the follow-up period, it would make sense to choose rho = lambda > 0 or rho = 0 respectively, with increasing values of lambda emphasizing stronger middle or late differences. The choice of the weights has to be made prior to the examination of the data and taking into account that they should provide the greatest statistical power, which in turns depends on how it is believed the null is violated.

Value

information Full description of the test.

data.name Description of data variables.

n Number of observations in each group.

obs The weighted observed number of events in each group.

exp The weighted expected number of events in each group.

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 $\mbox{statistic} \qquad \mbox{Either the chi-square or } Z \mbox{ statistic}.$

var The variance matrix of the test.

alt.phrase Phrase used to describe the alternative hypothesis.

pvalue p-value associated with the alternative hypothesis.

call The matched call.

Author(s)

R. Oller and K. Langohr

References

Fleming, T. R. and Harrington, D. P. (2005). *Counting Processes and Survival Analysis* New York: Wiley.

Harrington, D. P. and Fleming, T. R. (1982). A class of rank test procedures for censored survival data. Biometrika **69**, 553–566.

Kalbfleisch, J. D. and Prentice, R. L. (2002). *The Statistical Analysis of Failure Time Data*. New York: Wiley, 2nd Edition.

Lawless, J. F. (2003). Statistical Models and Methods for Lifetime Data. New York: Wiley, 2nd Edition.

Oller, R. and Langohr, K. (2017). FHtest: An R Package for the Comparison of Survival Curves with Censored Data. Journal of Statistical Software **81**, 1–25.

See Also

FHtestrcp

Examples

```
## Two-sample tests
FHtestrcc(Surv(futime, fustat) ~ rx, data = ovarian)
FHtestrcc(Surv(futime, fustat) ~ rx, data = ovarian, rho = 1)
## Trend test
library(KMsurv)
data(bmt)
FHtestrcc(Surv(t2, d3) ~ group, data = bmt, rho = 1, alternative = "decreasing")
## K-sample test
FHtestrcc(Surv(t2, d3) ~ as.character(group), data = bmt, rho = 1, lambda = 1)
```

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FHtestrcp	The Fleming-Harrington test for right-censored data based on permutations
-----------	---

Description

The FHtestrcp function performs a test for right-censored data based on a permutation distribution. It uses the $G-\rho$, λ family of statistics for testing the differences of two or more survival curves.

Usage

Arguments

_	
L	Numeric vector of the left endpoints of the censoring intervals (exact and right-censored data are represented as intervals of [a,a] and (a, infinity) respectively).
R	Numeric vector of the right endpoints of the censoring intervals (exact and right-censored data are represented as intervals of [a,a] and (a, infinity) respectively).
group	A vector denoting the group variable for which the test is desired. If group is a factor or character, then a k-sample test is performed, where k is the number of unique values of group. If group is numeric, then a trend ("correlation" type) test is performed. If there are only two groups, both methods give the same results.
rho	A scalar parameter that controls the type of test (see details).
lambda	A scalar parameter that controls the type of test (see details).
alternative	Character giving the type of alternative hypothesis for two-sample and trend tests: "different", "increasing" or "decreasing" survival functions. For the k-sample case, "different" should be chosen.
method	A character value, one of "pclt", "exact.network", "exact.ce", "exact.mc". If no value is specified, function methodRule chooses the value.
methodRule	A function used to choose the method. Default value is methodRuleIC1 (see details in perm).
exact	A logical value, where TRUE denotes exact test. Ignored if method is not NULL.
permcontrol	List of arguments for controlling permutation tests. Default value is ${\tt permControl}.$
formula	A formula with a numeric vector as response (which assumes no censoring) or Surv object. The right side of the formula is the group variable. No strata() is allowed.
data	Data frame for variables in formula.

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subset An optional vector specifying a subset of observations to be used.

na.action A function that indicates what should happen if the data contain NAs. Default

value is set to getOption("na.action").

. . . Additional arguments.

Details

The appropriate selection of the parameters rho and lambda gives emphasis to early, middle or late hazard differences. For instance, in a given clinical trial, if one would like to assess whether the effect of a treatment or therapy on the survival is stronger at the earlier phases of the therapy, we should choose lambda = 0, with increasing values of rho emphasizing stronger early differences. If there were a clinical reason to believe that the effect of the therapy would be more pronounced towards the middle or the end of the follow-up period, it would make sense to choose rho = lambda > 0 or rho = 0 respectively, with increasing values of lambda emphasizing stronger middle or late differences. The choice of the weights has to be made prior to the examination of the data and taking into account that they should provide the greatest statistical power, which in turns depends on how it is believed the null is violated.

Many standard statistical tests may be put into the form of the permutation test (see Graubard and Korn, 1987). There is a choice of four different methods to calculate the *p*-values (the last two are only available for the two-sample test): (1) pclt: using permutational central limit theorem (see, e.g., Sen, 1985). (2) exact.mc: exact method using Monte Carlo. (3) exact.network: exact method using a network algorithm (see, e.g., Agresti, Mehta, and Patel, 1990). Currently, the network method does not implement many of the time saving suggestions such as clubbing. (4) exact.ce: exact method using complete enumeration. This is good for very small sample sizes and when doing simulations, since the complete enumeration matrix need only be calculated once for the simulation.

There are several ways to perform the permutation test, and the function methodRuleIC1 chooses which of these ways will be used. The choice is basically between using a permutational central limit theorem (method = "pclt") or using an exact method. There are several algorithms for the exact method. Note that there are two exact two-sided methods for calculating p-values (see permControl and the tsmethod option).

Value

information Full description of the test.
data.name Description of data variables.

n Number of observations in each group.

diff The weighted observed minus expected number of events in each group.

scores Vector with the same length as L and R, containing the rank scores (see Kalbfleisch

and Prentice, 2003).

statistic Either the chi-square or Z statistic.

var The variance matrix of the test.

alt.phrase Phrase used to describe the alternative hypothesis. p-value associated with the alternative hypothesis.

p.conf.int Confidence interval of p-value. For method = "exact.mc" only.

call The matched call.

illust3

Author(s)

R. Oller and K. Langohr

References

Abd-Elfattah, E. F. and Butler, R. W. (2007). The weighted log-rank class of permutation tests: P-values and confidence intervals using saddlepoint methods. Biometrika **94**, 543–551.

Fleming, T. R. and Harrington, D. P. (2005). *Counting Processes and Survival Analysis* New York: Wiley.

Harrington, D. P. and Fleming, T. R. (1982). A class of rank test procedures for censored survival data. Biometrika **69**, 553–566.

Kalbfleisch, J. D. and Prentice, R. L. (2002). *The Statistical Analysis of Failure Time Data*. New York: Wiley, 2nd Edition.

Lawless, J. F. (2003). Statistical Models and Methods for Lifetime Data. New York: Wiley, 2nd Edition.

Oller, R. and Langohr, K. (2017). FHtest: An R Package for the Comparison of Survival Curves with Censored Data. Journal of Statistical Software **81**, 1–25.

See Also

FHtestrcc

Examples

illust3

Data set of an AIDS clinical trial

Description

Data set from an AIDS clinical trial designed to study the benefits of Zidovudine therapy in patients in the early stage of HIV infection. It contains interval-censored data of 1607 individuals.

illust3

Usage

```
data(illust3)
```

Format

A data frame with 1607 observations on the following 3 variables.

left Left endpoint of censoring interval.

right Right endpoint of censoring interval.

group Treatment group (1 = deferred therapy; 2 = 500 mg/day dosage; 3 = 1500 mg/day dosage).

References

Calle, M. L. and Gómez, G. (2001). Nonparametric Bayesian estimation from interval-censored data using Monte Carlo methods. Journal of Statistical Planning and Inference **98**, 73–87.

Gómez, G., Calle, M. L. and Oller, R. (2004). Frequentist and Bayesian approaches for intervalcensored data and their implementation in R. Statistical Papers 45, 139–173.

Volberding, P. A., Lagakos, S. W., Grimes, J. M., Stein, D. S., *et al.* (1995). A Comparison of Immediate with Deferred Zidovudine Therapy for Asymptomatic HIV-Infected Adults with CD4 Cell Counts of 500 or More per Cubic Millimeter. The New England Journal of Medicine **333**, 401–407.

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