Package: submax (via r-universe)

August 24, 2024

Type Package

Title Effect Modification in Observational Studies Using the Submax Method

Version 1.1.1

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Description Effect modification occurs if a treatment effect is larger or more stable in certain subgroups defined by observed covariates. The submax or subgroup-maximum method of Lee et al. (2017) <arXiv:1702.00525> does an overall test and separate tests in subgroups, correcting for multiple testing using the joint distribution.

Imports stats, mvtnorm, sensitivityfull

License GPL-2

Encoding UTF-8

LazyData true

NeedsCompilation no

Repository CRAN

Date/Publication 2017-12-14 12:41:36 UTC

Contents

submax-package *Effect Modification in Observational Studies Using the Submax Method*

Description

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Details

The DESCRIPTION file:

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Index of help topics:

The main function is submax(). Also helpful is score(). See their documentation.

Author(s)

Paul R. Rosenbaum

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References

Lee, K., Small, D. S., & Rosenbaum, P. R. (2017). A new, powerful approach to the study of effect modification in observational studies. arXiv preprint arXiv:1702.00525.

Examples

```
#Reproduces parts of Table 2 of Lee et al. (2017)
data(Active)
submax(Active$delta,Active[,1:7],gamma=1.70,alternative="less")
```

`Active` *Physical Activity and Survival in NHANES*

Description

Physical activity and survival in the NHANES I Epidemiologic Follow-up Study or NHEFS. This is the example in Lee et al. (2017). It is patterned after a study by Davis et al. (1994). The NHEFS combined the NHANES I study with follow-up for survival. There are 470 matched pairs consisting of a treated group who were quite inactive at the time of NHANES I and a matched control group who were very active.

Usage

```
data("Active")
```

Format

A data frame with 470 observations on the following 12 variables.

`All` 470 ones, one for each pair

`male` 1 for male, 0 for female

`female` 1 for female, 0 for male

`poor` 1 for income less than 2x poverty level, 0 otherwise

`notpoor` 1 for income greater than 2x poverty level, 0 otherwise

`smoker` 1 for current smoker, 0 otherwise

`nonsmoker` 1 for current nonsmoker, 0 otherwise

`delta` O Brien and Fleming scores for censored matched pairs. See details.

`treated.followup.time` Death or censoring time for inactive individual

`treated.censored.time` Equals Inf if the inactive individual was censored

`control.followup.time` Death or censoring time for active individual

`control.censored.time` Equals Inf if the active individual was censored

Details

Pairs were exactly matched for male/female, poor/notpoor and smoker/nonsmoker. Additionally, pairs were matched for age, white/nonwhite, years of education, employed or not during the previous 3 months, marital status, alcohol consumption and dietary quality. The covariates that were not exactly matched were matched by minimizing the total Mahalanobis distance within matched pairs. Table 1 of Lee et al. (2017) shows covariate balance before and after matching. These matching techniques are described in Chapter 8 and Section 9.2 of Rosenbaum (2010). The matching is the usual kind in epidemiology and biostatistics, that is, so-called without-replacement matching, in which no person appears twice.

The example reproduces a row from Table 2 of Lee et al. (2017).

The values in delta in Active are the Prentice-Wilcoxon scores for censored paired data proposed by O Brien and Fleming (1987). Specifically, delta is the Δ in section 2 of of O Brien and Fleming (1987). Following their suggestion at the end of their section 2, data are considered censored at the earlier censoring time in a matched pair. These deltas are computed separately in 8 = 2x2x2 subgroups defined by male/female x poor/notpoor x smoker/nonsmoker. Separate computation of Δ in subgroups is not needed for the global test of no treatment effect at all in section 3.2 of Lee et al. (2017), but it is an aspect of the simultaneous inference by closed testing in section 4 of Lee et al. (2017).

The NHEFS was, essentially, the NHANES I snapshot survey combined with follow-up for survival. Data on mortality and time of death were collected in four follow-up surveys in 1982-1984, 1986, 1987 and 1992. Tracing of subjects which enable determination of whether the subject was alive or had died was high. Ninety six percent of the study population had been successfully traced at some point through the 1992 follow-up. Tracing rates for each follow-up ranged from 90 to 94 percent. See Cox et al. (1997).

Source

The data set was constructed by Kwonsang Lee from the NHEFS; see Lee et al. (2017). The original NHEFS data are publicly available at the NHANES web-page at CDC.

References

Cox, C. S., Mussolino, M. E., Rothwell, S. T., Lane, M. A., Golden, C. D., Madans, J. H., and Feldman, J. J. (1997). Plan and operation of the NHANES I Epidemiologic Followup Study, 1992. Vital and health statistics. Ser. 1, Programs and collection procedures, (35), 1-231.

Davis, M. A., Neuhaus, J. M., Moritz, D. J., Lein, D., Barclay, J. D., and Murphy, S. P. (1994). Health behaviors and survival among middle aged and older men and women in the NHANES I Epidemiologic Follow-Up Study. Preventive Medicine, 23, 369-376.

Lee, K., Small, D. S., & Rosenbaum, P. R. (2017). A new, powerful approach to the study of effect modification in observational studies. <arXiv:1702.00525>.

O Brien, P. C. and Fleming, T. R. (1987). A paired Prentice-Wilcoxon test for censored paired data. Biometrics, 43, 169-180. The variable delta in Active is the delta in section 2 of this paper. Following their suggestion at the end of their section 2, data are considered censored at the earlier censoring time in a matched pair.

Rosenbaum, P. R. (2010). Design of Observational Studies. New York: Springer.

Examples

```
# The example is from Lee et al. (2017).
data(Active)
submax(Active$delta,Active[,1:7],gamma=1,alternative="less")
```

`amplify` *Amplification of sensitivity analysis in observational studies.*

Description

Uses the method in Rosenbaum and Silber (2009) to interpret a value of the sensitivity parameter gamma. Each value of gamma amplifies to a curve (lambda,delta) in a two-dimensional sensitivity analysis, the inference being the same for all points on the curve. That is, a one-dimensional sensitivity analysis in terms of gamma has a two-dimensional interpretation in terms of (lambda,delta).

Usage

```
amplify(gamma, lambda)
```

Arguments

`gamma`	gamma > 1 is the value of the sensitivity parameter, for instance the parameter in senmv. length(gamma)>1 will generate an error.
`lambda`	lambda is a vector of values > gamma. An error will result unless lambda[i] > gamma > 1 for every i.

Details

A single value of gamma, say gamma = 2.2 in the example, corresponds to a curve of values of (lambda, delta), including (3, 7), (4, 4.33), (5, 3.57), and (7, 3) in the example. An unobserved covariate that is associated with a lambda = 3 fold increase in the odds of treatment and a delta = 7 fold increase in the odds of a positive pair difference is equivalent to gamma = 2.2.

The curve is gamma = (lambda*delta + 1)/(lambda+delta). Amplify is given one gamma and a vector of lambdas and solves for the vector of deltas. The calculation is elementary.

This interpretation of gamma is developed in detail in Rosenbaum and Silber (2009), and it makes use of Wolfe's (1974) family of semiparametric deformations of an arbitrary symmetric distribuiton.

Strictly speaking, the amplification describes matched pairs, not matched sets. For matched sets, it is natural to think of the amplification as describing any one of the k matched pair differences in a k-to-1 matched set.

The curve has asymptotes that the function amplify does not compute: gamma corresponds with (lambda,delta) = (gamma, Inf) and (Inf, gamma).

A related though distict idea is developed in Gastwirth et al (1998). The two approaches agree when the outcome is binary, that is, for McNemar's test.

Value

Returns a vector of values of delta of length(lambda) with names lambda.

Note

The amplify function is also in the sensitivitymv and the sensitivitymult packages. The calculations are elementary.

Author(s)

Paul R. Rosenbaum

References

Gastwirth, J. L., Krieger, A. M., Rosenbaum, P. R. (1998) Dual and simultaneous sensitivity analysis for matched pairs. Biometrika, 85, 907-920.

Lee, K., Small, D. S., & Rosenbaum, P. R. (2017). A new, powerful approach to the study of effect modification in observational studies. arXiv:1702.00525.

Rosenbaum, P. R. and Silber, J. H. (2009) Amplification of sensitivity analysis in observational studies. Journal of the American Statistical Association, 104, 1398-1405. <doi:10.1198/jasa.2009.tm08470>

Rosenbaum, P. R. (2015). Two R packages for sensitivity analysis in observational studies. Observational Studies, v. 1. (Free on-line.)

Wolfe, D. A. (1974) A charaterization of population weighted symmetry and related results. Journal of the American Statistical Association, 69, 819-822.

Examples

```
# The following is the calculation in Section 3.1 of Lee et al. (2017).
amplify(1.77,c(2,3,4))
```

---

mercury *NHANES Mercury/Fish Data*

Description

Data from NHANES 2009-2010. 397 treated people who ate at least 15 servings of fish or shellfish during the previous month are matched to two controls who ate at most one serving of fish or shellfish. The values in methylmercury record the level of methylmercury in blood in mu-g/dl.

Usage

```
data("mercury")
```

Format

A data frame with 1191 observations on the following 6 variables.

`SEQN` NHANES 2009-2010 id number

`methylmercury` Methylmercury in blood in mu-g/dl

`fish` 1 if ate >= 15 servings of fish or shellfish, 0 if <=1 serving

`mset` Matched set indicator, 1,...,397.

`female` 1 if female, 0 if male

`black` 1 if black, 0 otherwise

Details

Sets were matched 2-to-1 for for age, sex, ratio of household income to the poverty level, education, ethnic group (black, Hispanic, or other), and cigarette smoking. A table showing covariate balance after matching is in Rosenbaum (2014, Table 1).

Source

From NHANES 2009-2010, publicly available at the NHANES web page at CDC.

References

Rosenbaum, P. R. (2014) Weighted M-statistics with superior design sensitivity in matched observational studies with multiple controls. Journal of the American Statistical Association, 2014. <doi:10.1080/01621459.2013.879261>

Examples

```
data(mercury)
boxplot(mercury$methylmercury~mercury$fish)
```

`mscorev` *Computes M-scores for Permuational M-tests.*

Description

Of limited interest to most users, function mscorev() computes M-scores. A similar function function is in the package sensitivitymv.

Usage

```
mscorev(ymat, inner = 0, trim = 3, lambda = 0.5)
```

Arguments

ymat	If there are I matched sets and the largest matched set contains J individuals, then y is an I by J matrix with one row for each matched set. If matched set i contains one treated individual and k controls, where k is at least 1 and at most J-1, then y[i,1] is the treated individual's response, y[i,2],...,y[i,k+1] are the responses of the k controls, and y[i,k+2],...,y[i,J] are equal to NA. Although y can contain NA's, y[i,1] and y[i,2] must not be NA for every i. That is, every matched set must have at least one treated subject and one control.
inner	inner and trim together define the ψ-function for the M-statistic. The default values yield a version of Huber's ψ-function, while setting inner = 0 and trim = Inf uses the mean within each matched set. The ψ-function is an odd function, so $\psi(w) = -\psi(-w)$. For $w \geq 0$, the ψ-function is $\psi(w) = 0$ for $0 \leq w \leq$ inner, is $\psi(w) =$ trim for $w \geq$ trim, and rises linearly from 0 to trim for inner < w < trim. If uncertain about inner, trim and lambda, then use the defaults. An error will result unless $0 \leq$ inner $\leq$ trim. Taking trim < Inf limits the influence of outliers; see Huber (1981). Taking trim < Inf and inner = 0 uses Huber's psi function. Taking trim = Inf does no trimming and is similar to a weighted mean; see TonT. Taking inner > 0 often increases design sensitivity; see Rosenbaum (2013).
trim	inner and trim together define the ψ-function for the M-statistic. See inner.
lambda	Before applying the ψ-function to treated-minus-control differences, the differences are scaled by dividing by the lambda quantile of all within set absolute differences. Typically, lambda = 1/2 for the median. The value of lambda has no effect if trim=Inf and inner=0. See Maritz (1979) for the paired case and Rosenbaum (2007) for matched sets. An error will result unless 0 < lambda < 1.

Value

Generally, a matrix with the same dimensions as ymat containing the M-scores.

Note

The example reproduces Table 3 in Rosenbaum (2007).

Matched sets of unequal size are weighted using weights that would be efficient in a randomization test under a simple model with additive set and treatment effects and errors with constant variance; see Rosenbaum (2007). Specifically, the total score in set (row) i is divided by the number ni of individuals in row i, as in expression (8) in Rosenbaum (2007).

Author(s)

Paul R. Rosenbaum

References

Huber, P. (1981) Robust Statistics. New York: John Wiley. (M-estimates based on M-statistics.)

Maritz, J. S. (1979). A note on exact robust confidence intervals for location. Biometrika 66 163–166. (Introduces exact permutation tests based on M-statistics by redefining the scaling parameter.)

Rosenbaum, P. R. (2007) Sensitivity analysis for m-estimates, tests and confidence intervals in matched observational studies. Biometrics, 2007, 63, 456-464. <doi:10.1111/j.1541-0420.2006.00717.x>

Rosenbaum, P. R. (2013). Impact of multiple matched controls on design sensitivity in observational studies. Biometrics 69 118-127. (Introduces inner trimming.) <doi:10.1111/j.1541-0420.2012.01821.x>

Rosenbaum, P. R. (2015). Two R packages for sensitivity analysis in observational studies. Observational Studies, v. 1. (Free on-line.)

Examples

```
# The example reproduces Table 3 in Rosenbaum (2007).
data(tbmetaphase)
mscorev(tbmetaphase,trim=1)
```

---

score *Creates M-scores for Use by submax().*

Description

The score() function is an optional aid in using the submax() function. The submax() function may be used on its own, but the user must then create the y matrix and the cmat matrix. The score() function can be used to create the y matrix and cmat matrix for use in the submax() function. It creates Huber-Maritz M-scores.

Usage

```
score(y, z, mset, x, expandx = FALSE, scale = "closed", inner = 0, trim = 3,
lambda = 1/2, xnames=NULL)
```

Arguments

y	A vector of responses with no missing data.
z	Treatment indicator, z=1 for treated, z=0 for control with length(z)==length(y).
mset	Matched set indicator, 1, 2, ..., sum(z) with length(mset)==length(y). Matched set indicators should be either integers or a factor.
x	A matrix of binary covariates. These are the potential effect modifiers. If x is a binary vector for one covariate, it will be reshaped into a matrix. An error will result if x does not have 1 or 0 coordinates. The matrix x should length(y) rows.
expandx	If expandx=FALSE, then x is used as is. If expandx=TRUE, then a column of 1's is added to x, as well as 1-x[,j] for each column j. For example, if x is a single column, 1 for female, 0 for male, then with expandx=TRUE, x will be replaced by 3 columns, all 1's, female, and 1-female=male.

`scale` scale determines how the observations are scaled in computing M-scores. scale must equal "closed"" or "global" or "interaction". If you use the mean (or equivalently the total) as your test statistic (by setting inner=0 and trim=Inf), then scaling is not needed and the scale parameter is ignored. If scale=global, then all observations are used in computing a single scale factor. This is appropriate when testing Fisher's global hypothesis of no treatment effect at all. If scale=interaction, then the scale is determined separately in each of the unique groups formed from the interaction of all of the columns of x. This can be reasonable if the interaction groups are not too small. If x had a column for men, a column for women, a column for people over 50, a column for people under 50, then there would be 4 interaction groups, such as men under 50. If scale=closed, then a single scale factor is computed using every y[i] such that x[i,j]=1 for at least one j. With scale=closed, the score() function will return matrices y and cmat that only contain the rows i such that x[i,j]=1 for at least one j. For instance, if your hypotheses are confined to women, then the men will be excluded. score=closed is useful in closed testing, as described in Lee et al. (2017). If x contains a column of 1's, then scale=closed and scale=global are equivalent. Of course, x will contain a column of 1's if you set expandx=TRUE. You can use scale=interaction only if sets are exactly matched for all effect modifiers in x, but this is not required for scale=global or scale=closed. If you set scale=interaction when sets are not exactly matched, you will receive a warning and scale will be reset to the default of closed.

`inner` inner and trim together define the ψ-function for the M-statistic. The default values yield a version of Huber's ψ-function, while setting inner = 0 and trim = Inf uses the mean or total within each matched set. The ψ-function is an odd function, so $\psi(w) = -\psi(-w)$. For $w \geq 0$, the ψ-function is $\psi(w) = 0$ for $0 \leq w \leq$ inner, is $\psi(w) =$ trim for $w \geq$ trim, and rises linearly from 0 to trim for inner < w < trim.

If uncertain about inner, trim and lambda, then use the defaults.

An error will result unless $0 \leq$ inner $\leq$ trim.

`trim` inner and trim together define the ψ-function for the M-statistic. See inner.

`lambda` Before applying the ψ-function to treated-minus-control differences, the differences are scaled by dividing by the lambda quantile of all within set absolute differences. Typically, lambda = 1/2 for the median. The value of lambda has no effect if trim=Inf and inner=0. See Maritz (1979) for the paired case and Rosenbaum (2007) for matched sets.

An error will result unless 0 < lambda < 1.

`xnames` If xnames=NULL and x is a matrix or data.frame with column names, then those names are used to label output. If xnames is not null, and x is a matrix, then xnames must be a vector of dim(x)[2] names, and these names are used to label output. If x is a vector, not a matrix, then the output will be easier to read if you give it a name, xnames="a.name". This is particularly true if x is a vector and expandx=TRUE.

Details

Taking trim < Inf limits the influence of outliers; see Huber (1981).

Taking trim < Inf and inner = 0 uses Huber's psi function.

Taking trim = Inf and inner = 0 does no trimming and is similar to a mean or a weighted mean.

Taking inner > 0 often increases design sensitivity; see Rosenbaum (2013). This is most evident with matched pairs, where inner=0.5 may be a good choice.

An M-statistic similar to a trimmed mean is obtained by setting inner=0, trim=1, and 1-lambda to the total amount to be trimmed from both tails. For example, inner=0, trim=1, lambda=0.9 trims 10 percent, perhaps 5 percent from each tail. Arguably, inner=0, trim=1, and lambda=0.99 is very much like a mean, but also safer than a mean.

In general, each call to submax() tests a global null hypothesis of no treatment effect, but does this by looking in several subgroups defined by pretreatment covariates, that is, by potential effect modifiers. We often want to say something about the subgroups themselves, not the global null hypothesis. This is possible by using closed testing (Marcus et al. 1976), which may entail several calls to submax(). Before using closed testing, it is suggested that you read the section in Lee et al. (2017) discussing closed testing.

Matched sets of unequal size are weighted with a view to efficiency. See the documentation for mscorev() and the references mentioned there.

Value

`y`	A matrix of M-scores suitable for use as the y matrix in the submax() function.
`cmat`	A matrix of comparisons suitable for use as the cmat matrix in the submax function.
`detail`	A data.frame reminding you of the settings that produced the M-scores. It contains inner, trim, lambda, scale, permutational.t, and anyinexact, where permutational.t=TRUE if you set inner=0 and trim=Inf, and anyinexact=TRUE if some of the potential effect modifiers are not exactly matched.

Note

Several other packages use M-scores, so their examples and documentation may be helpful. These include sensitivitymv, sensitivitymw, sensitivitymult, sensitivityfull, and senstrat. In particular, sensitivitymw and sensitivitymult compute sensitivity analyses for confidence intervals.

If you have inexactly matched sets, but you want to use scale=interaction, then you must discard the inexactly matched sets before using score().

Author(s)

Paul R. Rosenbaum.

References

Huber, P. (1981) Robust Statistics. New York: John Wiley. (M-estimates based on M-statistics.)

Lee, K., Small, D. S., & Rosenbaum, P. R. (2017). A new, powerful approach to the study of effect modification in observational studies. arXiv:1702.00525.

Marcus, R., Eric, P., & Gabriel, K. R. (1976). On closed testing procedures with special reference to ordered analysis of variance. Biometrika, 63, 655-660.

Maritz, J. S. (1979). A note on exact robust confidence intervals for location. Biometrika 66 163–166. (Introduces exact permutation tests based on M-statistics by redefining the scaling parameter.)

Rosenbaum, P. R. (2007). Sensitivity analysis for m-estimates, tests and confidence intervals in matched observational studies. Biometrics 63 456-64. (R package sensitivitymv) <doi:10.1111/j.1541-0420.2006.00717.x>

Rosenbaum, P. R. (2013). Impact of multiple matched controls on design sensitivity in observational studies. Biometrics 69 118-127. (Introduces inner trimming.) <doi:10.1111/j.1541-0420.2012.01821.x>

Rosenbaum, P. R. (2014). Weighted M-statistics with superior design sensitivity in matched observational studies with multiple controls. J. Am. Statist. Assoc. 109 1145-1158. (R package sensitivitymw) <doi:10.1080/01621459.2013.879261>

Rosenbaum, P. R. (2015). Two R packages for sensitivity analysis in observational studies. Observational Studies, v. 1. (Free on-line.)

Examples

```
data(mercury)
attach(mercury)
# The mercury data has two binary covariates, black and female,
# that will be considered as potential effect modifiers.
# Both black and female are not exactly matched.  Of 397
# matched sets, 72 contain three blacks, 319 contain no
# blacks, 3 contain one black, and 3 contain 2 blacks.
table(table(mset,black)[,2])
# A similar situation arises with females.
table(table(mset,female)[,2])
# When considering females as an effect modifier, only
# sets exactly matched for female are used, etc.  A
# set that is inexact for black may be used when looking
# at females, providing that set is exactly matched for female.


male<-1-female
nonblack<-1-black
everyone<-rep(1,dim(mercury)[1])
x<-cbind(everyone,female,male,black,nonblack)
sc<-score(methylmercury,fish,mset,x)

# At gamma=4, the global null of no effect is
# rejected at alpha=0.05 by every subgroup test
submax(sc$y,sc$cmat,gamma=4,fast=TRUE)

# What does expandx do?
sc<-score(methylmercury,fish,mset,cbind(female,black))
head(sc$cmat)
sc<-score(methylmercury,fish,mset,cbind(female,black),expandx=TRUE)
head(sc$cmat)

# Using exandx with a vector: remember to give it a name.
sc<-score(methylmercury,fish,mset,female,xnames="Female",expandx=TRUE)
head(sc$cmat)
```

```
 ## Not run:
# For closed testing, the process is repeated with fewer columns.
# In general, if cmat has L columns, closed testing may require
# up to (2^L)-1 tests.  Here are two of those tests.
  sc<-score(methylmercury,fish,mset,cbind(female,black))
  submax(sc$y,sc$cmat,gamma=4)
# Note that the critical.constant has become smaller, making it
# easier to reject a component hypothesis when fewer hypotheses
# are tested.
  sc<-score(methylmercury,fish,mset,female,xnames="Female")
  submax(sc$y,sc$cmat,gamma=4,fast=TRUE)
# Use of closed testing is discussed in Lee et al. (2017).

# For a two-sided test, change alpha and do 2 tests.
  submax(sc$y,sc$cmat,gamma=4,alpha=0.025,alternative = "greater")
  submax(sc$y,sc$cmat,gamma=4,alpha=0.025,alternative = "less")
# So we reject in the positive direction in all 5 component tests.

## End(Not run)
detach(mercury)
```

`separable1fc` *Computes the Separable Approximation.*

Description

Of limited interest to most users, separable1fc() is called by the main function, submax().

Usage

```
separable1fc(ymat, gamma = 1)
```

Arguments

`ymat`	A matrix of scores produced by mscoref.
`gamma`	The sensitivity parameter $\Gamma \geq 1$.

Details

See Gastwirth, Krieger and Rosenbaum (2000) and Rosenbaum (2007, section 4) for discussion of the separable approximation.

Value

`tstat`	Vector of length I = dim(ymat)[1] giving the values of the test statistic in the I matched sets.
`expect`	Vector of length I giving the maximum expectations in the I matched sets.
`vari`	Vector of length I giving the maximum variances at the maximum expectations in the I matched sets.

Note

This function is similar to the separable1f() function in the sensitivityfull package. Unlike that function, separable1fc() returns the I components for the I matched sets, rather than computing a summary statistic from them.

Author(s)

Paul R. Rosenbaum

References

Gastwirth, J. L., Krieger, A. M. and Rosenbaum, P. R. (2000). Asymptotic separability in sensitivity analysis. J. Roy. Statist. Soc. B. 62 545-555. <doi:10.1111/1467-9868.00249>

Rosenbaum, P. R. (2007). Sensitivity analysis for m-estimates, tests and confidence intervals in matched observational studies. Biometrics 63 456-64. (See section 4.) <doi:10.1111/j.1541-0420.2006.00717.x>

Examples

```
# The following artificial example computes mscores for a
# full matching, then applies separable1fc() to
# perform a sensitivity analysis.  Compare with
# the example below from the sensitivityfull package.

# The artificial example that follows has I=9
# matched sets.  The first 3 sets have one treated
# individual and two controls with treated subjects
# in column 1.  The next 3 sets are
# matched pairs, with treated subjects in column 1.
# The next 3 sets have one control and two treated
# subjects, with the control in column 1.  Simulated
# from a Normal distribution with an additive effect
# of tau=1.

y<-c(2.2, 1.4, 1.6, 2.4, 0.7, 1.3, 1.2, 0.6, 0.3,
0.5, -0.1, -1.3, -0.3, 0.1, 0.4, 3.0, 1.1, 1.4, -0.8,
0.1, 0.8, NA, NA, NA, 1.1, 0.5, 1.8)
y<-matrix(y,9,3)
treated1<-c(rep(TRUE,6),rep(FALSE,3))

s<-separable1fc(sensitivityfull::mscoref(y,treated1),gamma=2)
1-pnorm((sum(s$tstat)-sum(s$expect))/sqrt(sum(s$vari)))
sensitivityfull::senfm(y,treated1,gamma=2)
s
```

submax *Effect Modification Using the Submax Method in Observational Studies*

Description

Effect modification means that the magnitude or stability of a treatment effect varies with observed covariates. When there is effect modification, causal conclusions may be less sensitive to unmeasured biases in a subgroup in which the treatment effect is larger or more stable. The submax or subgroup maximum method looks at an overall test and subgroup tests, correcting for multiple testing using the joint distribution of the tests. The submax method was proposed by Lee et al. (2017).

Usage

```
submax(y, cmat, gamma = 1, alternative = "greater", alpha = 0.05, rnd = 2, fast=FALSE)
```

Arguments

y	In general, y is either a matrix with I rows for I matched sets or a vector of length I for I matched pairs. The y values are outcomes, perhaps after scoring (e.g., Huber-Maritz M-scores) or ranking (e.g., Wilcoxon) to produce a robust test. If y contains the outcomes themselves, then the outcomes are permuted in the manner of a permutational t-test. More precisely, y contains the scores $q[gij]$ discussed in section 2.1 of Lee et al. (2017). If every matched set gi is a pair, then y may be a vector of treated-minus-control pair differences, $q[gi1] - q[gi2]$. If there are I matched pairs, then y can be either a vector of length I giving the I treated-minus-control pair differences, or y can be a 2-column matrix with treated responses in the first column and control responses in the second column. If there are I matched sets and the largest matched set contains J individuals, then y is an I by J matrix with one row for each matched set. If matched set i contains one treated individual and k controls, where k is at least 1 and at most J-1, then y[i,1] is the treated individual's response, y[i,2],...,y[i,k+1] are the responses of the k controls, and y[i,k+2],...,y[i,J] are equal to NA. Although y can contain NA's, y[i,1] and y[i,2] must not be NA for every i. That is, every matched set must have at least one treated subject and one control.
cmat	A matrix with one row for each matched set in y. For each column of cmat, a statistical test is done. Typically, the first column is (1,...,1) and refers to a test that uses all of the matched sets. If the second column is 1 for matched sets of women and 0 for matched sets of men, then the second test is restricted to matched sets of women.
gamma	gamma is the sensitivity parameter Γ, where $\Gamma \geq 1$. Setting $\Gamma = 1$ is equivalent to assuming ignorable treatment assignment given the matched sets, and it performs a within-set randomization test.

`alternative` If alternative="greater", the null hypothesis of no treatment effect is tested against the alternative of a treatment effect larger than zero. If alternative="less", the null hypothesis of no treatment effect is tested against the alternative of a treatment effect smaller than 0. In particular, alternative="less" is equivalent to: (i) alternative="greater", (ii) y replaced by -y. See the note for discussion of two-sided sensitivity analyses.

`alpha` The global null hypothesis of no effect is tested at simultaneous level α in the presence of a bias of at most Γ.

`rnd` The correlation matrix of the dim(cmat)[2] test statistics is returned, rounded to rnd digits. The critical.constant is also rounded to rnd digits.

`fast` Determines the speed and accuracy of the determination of the critical.constant used in testing. fast=TRUE is faster but less precise, less stable. fast=FALSE is slower but more precise, more stable. See details.

Details

The submax procedure is developed by Lee et al. (2017), and the example reproduces analyses from that paper.

The submax() function rejects the null hypothesis at level α in the presence of a bias in treatment assignment of at most Γ if maxdeviate is greater than or equal to critical.constant.

The global null hypothesis of no effect is tested at simultaneous level α in the presence of a bias of at most Γ. If the global null is true, and the bias in treatment assignment is at most Γ, then the probability of falsely rejecting the global null hypothesis is at most α. The test looks at the largest of dim(cmat)[2] standardized test statistics and corrects for multiple testing using their joint distribution. The joint distribution is approximated by a multivariate Normal distribution, so the entire procedure is a large sample approximation.

The function score() in this package may be helpful in creating the matrics y and cmat that are arguments of the submax function.

The sensitivity bound is based on the separable approximation described in Gastwirth, Krieger and Rosenbaum (2000); see also Rosenbaum (2007).

The critical.constant is determined rather precisely by a call to the qmvnorm() function in the mvtnorm package. The qmvnorm() function uses random numbers, but this should produce negligible variability in the critical.constant. However, if you call submax() twice, there will be a tiny change in the critical.constant. There is a trade-off between precision and speed, and you can alter that trade-off – make submax faster or more precise – by editing the call to qmvnorm() in the rcode for submax(). For almost all users, there will be no need to alter the code.

Value

`maxdeviate` The submax or subgroup maximum statistic. It is the maximum standardized deviate for the several columns of cmat. In Lee et al. (2017), this is $D[\Gamma max]$

.

`critical.constant`

If maxdeviate >= critical.constant, the global null hypothesis of no treatment effect is rejected at level α in the presence of a bias of at most Γ

deviates	There is one standardized deviate for each column of cmat, and the maximum of these is maxdeviate. If deviate[j] > critical.constant, then deviate[j] would lead to rejection of the global null hypothesis.
correlation	The correlation matrix of the deviates. By default, it is printed to two digits for easy viewing. By changing rnd=2, it can be produced with additional digits, perhaps for use in further computations.
detail	Reminds the user of the value of α and Γ.

Note

In general, each call to submax() tests a global null hypothesis of no treatment effect, but does this by looking in several subgroups defined by pretreatment covariates, that is, by potential effect modifiers. We often want to say something about the subgroups themselves, not the global null hypothesis. This is possible by using closed testing (Marcus et al. 1976), which may entail several calls to submax(). Before using closed testing, it is suggested that you read the section in Lee et al. (2017) discussing closed testing.

A 2-sided, α-level test may be obtained by performing two one-sided tests, each at level $\alpha/2$. This is a safe approach, but for $\Gamma > 1$ it is slightly conservative. Cox (1977) suggests that we view a two-sided test as two one-sided tests with a Bonferroni correction for testing two hypotheses.

Author(s)

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References

Cox, D. R. (1977). The role of signficance tests (with Discussion). Scand. J. Statist. 4, 49-70.

Gastwirth, J. L., Krieger, A. M. and Rosenbaum, P. R. (2000). Asymptotic separability in sensitivity analysis. J. Roy. Statist. Soc. B. 62 545-555. <doi:10.1111/1467-9868.00249>

Lee, K., Small, D. S. and Rosenbaum, P. R. (2017). A new, powerful approach to the study of effect modification in observational studies. <arXiv:1702.00525>.

Marcus, R., Eric, P. and Gabriel, K. R. (1976). On closed testing procedures with special reference to ordered analysis of variance. Biometrika, 63, 655-660.

Rosenbaum, P. R. (2007). Sensitivity analysis for m-estimates, tests and confidence intervals in matched observational studies. Biometrics 63 456-64. (See section 4.) <doi:10.1111/j.1541-0420.2006.00717.x>

Examples

```
# Reproduces parts of Table 2 of Lee et al. (2017).
data(Active)
submax(Active$delta,Active[,1:7],gamma=1.77,alternative="less",fast=TRUE)
amplify(1.77,c(2,3,4))

# Reproduces the closed-testing analysis in
#Section 4 of Lee et al. (2017)
submax(Active$delta,Active[,c(3,5)],gamma=1.4,alternative="less",fast=TRUE)

# See also the examples for the score() function.
```

`tbmetaphase` *Genetic damage from drugs used to treat TB*

Description

This is a matched comparison of the effects of two drug sequences, namely HRZ and H2R2Z2, for the treatment of tuberculosis. HRZ is a higher dose sequence than H2R2Z2. The outcome is a measure of genetic damage, namely the frequency of aberrant metaphases two months after treatment. Individuals were matched for the frequency of aberrant metaphases before treatment. 15 individuals treated with HRZ are matched to 1 or 2 controls treated with H2R2Z2. Each row is one matched set. If a set is a pair, the third element in a row is NA. The data are originally from Rao, Gupta and Thomas (1991) and were used as an example in Rosenbaum (2007, Table 3). Data are used to illustrate the senmv function in the sensitivitymv package.

Usage

```
data(tbmetaphase)
```

Format

A data frame with 15 observations on the following 3 variables.

`HRZ` Aberrant metaphases for individual treated with HRZ.

`H2R2Z2.1` Aberrant metaphases for first matched individual treated with H2R2Z2.

`H2R2Z2.2` Aberrant metaphases for second matched individual treated with H2R2Z2. For matched pairs, this is NA.

References

Rao, V. V. N. G., Gupta, E. V. V and Thomas, I. M. Chromosomal aberrations in tuberculosis patients before and after treatment with short-term chemotherapy. Mutation Research 1991, 259, 13-19.

Rosenbaum, P. R. Sensitivity analysis for m-estimates, tests and confidence intervals in matched observational studies. Biometrics, 2007, 63, 456-464.

Examples

```
# The example reproduces Table 3 in Rosenbaum (2007).
data(tbmetaphase)
mscorev(tbmetaphase,trim=1)
```

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