

Package ‘ivtools’

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Description Contains tools for instrumental variables estimation. Currently, non-parametric bounds, two-stage estimation and G-estimation are implemented. Balke, A. and Pearl, J. (1997) <doi:10.2307/2965583>, Vansteelandt S., Bowden J., Babanezhad M., Goetghebeur E. (2011) <doi:10.1214/11-STS360>.

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ah	<i>Fitting semiparametric additive hazards regression models.</i>
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Description

ah is a wrapper around the ahaz function in the **ahaz** package, with a more user-friendly and standard interface. Refer to the manual for ahaz for details.

Usage

```
ah(formula, data, weights, robust=FALSE)
```

Arguments

formula	an object of class "formula": a symbolic description of the model to be fitted.
data	a data frame containing the variables in the model.
weights	an optional vector of prior weights to be used in the fitting process.
robust	robust calculation of variance; see manual for ahaz.

Details

See manual for ahaz.

Value

An object of class "ah" is a list containing the same elements as an object of class "ahaz", plus

call	the matched call.
formula	the formula argument.
coefficients	a named vector of estimated coefficients.
vcov	the variance-covariance matrix for the estimated coefficients.
incl	the ahaz function does not allow for missing data. Thus, if data contains rows with missing data on any of the variables in the model, then these rows are excluded before calling ahaz. incl is a vector containing the rownames of those rows that are included in the analysis, that is, the rows with no missing data on any of the variables in the model.

Note

The ahaz function does not allow for ties. Thus, before calling ah any ties have to be manually broken.

Author(s)

Arvid Sjolander.

References

Lin D.Y., Ying Z. (1994). Semiparametric analysis of the additive risk model. *Biometrika* **81**(1), 61-71.

Examples

```
require(ahaz)

##This example is adapted from the example given for the ahaz function
##in the ahaz package

data(sorlie)

# Break ties
set.seed(10101)
sorlie$time <- sorlie$time+runif(nrow(sorlie))*1e-2

# Fit additive hazards model
fit <- ah(formula=Surv(time, status)~X13+X14+X15+X16+X17+X18+X19+X20+X21+X22,
  data=sorlie)
summary(fit)
```

confint.ivmod

Confidence interval

Description

This is a confint method for class "ivmod".

Usage

```
## S3 method for class 'ivmod'
confint(object, parm, level=0.95, ...)
```

Arguments

object	an object of class "ivmod".
parm	not used.
level	the coverage probability of the confidence intervals.
...	not used.

Author(s)

Arvid Sjolander.

estfun	<i>Computes the estimating function sum for "ivmod" objects, fitted with estmethod="g".</i>
--------	---

Description

estfun computes the estimating function $H(\psi)$ for a "ivmod" object, fitted with estmethod="g", for a range of values of ψ . The estfun is not implemented for "ivah" objects, since G-estimation in additive hazards models is based on a recursive estimation technique, and not standard estimating equations.

Usage

```
estfun(object, lower, upper, step)
```

Arguments

object	an object of class "ivmod", fitted with estmethod="g".
lower	an optional vector of lower values for ψ . Defaults to $\psi - 0.5$.
upper	an optional vector of upper values for ψ . Defaults to $\psi + 0.5$.
step	an optional vector of steps between lower and upper. Defaults to 0.01 for each element of ψ .

Details

estfun may be useful for visual inspection of the estimating function, to make sure that a solution to the estimating equation

$$H(\psi) = 0$$

was found, see 'Examples'. For the i :th element of ψ , the estimating function sum is computed for a range of values within (lower[i], upper[i]), at the G-estimate of the remaining elements of ψ .

Value

An object of class "estfun" is a list containing

f	a named list of matrices; one matrix for each element of ψ . The first column of the i :th matrix contains the values for the i :th element of ψ at which the estimating function sum is computed, the second column contains the values of the estimating function sum.
est	the G-estimate of ψ .

Author(s)

Arvid Sjolander.

References

Burgess S, Granel R, Palmer TM, Sterne JA, Didelez V. (2014). Lack of identification in semi-parametric instrumental variable models with binary outcomes. *American Journal of Epidemiology* **180**(1), 111-119.

Vansteelandt S., Bowden J., Babanezhad M., Goetghebeur E. (2011). On instrumental variables estimation of causal odds ratios. *Statistical Science* **26**(3), 403-422.

Examples

```

set.seed(9)

##Note: the parameter values in the examples below are chosen to make
##Y0 independent of Z, which is necessary for Z to be a valid instrument.

n <- 1000
psi0 <- 0.5
psi1 <- 0.2

##---Example 1: linear model and interaction between X and L---

L <- rnorm(n)
Z <- rnorm(n, mean=L)
X <- rnorm(n, mean=Z)
m0 <- X-Z+L
Y <- rnorm(n, mean=psi0*X+psi1*X*L+m0)
data <- data.frame(L, Z, X, Y)

#G-estimation
fitZ.L <- glm(formula=Z~L, data=data)
fitIV <- ivglm(estmethod="g", X="X", Y="Y", fitZ.L=fitZ.L, data=data,
  formula=~L, link="identity")
summary(fitIV)
H <- estfun(fitIV)
plot(H)

##---Example 2: logistic model and no covariates---

Z <- rbinom(n, 1, 0.5)
X <- rbinom(n, 1, 0.7*Z+0.2*(1-Z))
m0 <- plogis(1+0.8*X-0.39*Z)
Y <- rbinom(n, 1, plogis(psi0*X+log(m0/(1-m0))))
data <- data.frame(Z, X, Y)

#G-estimation
fitZ.L <- glm(formula=Z~1, data=data)
fitY.LZX <- glm(formula=Y~X+Z+X*Z, family="binomial", data=data)
fitIV <- ivglm(estmethod="g", X="X", fitZ.L=fitZ.L, fitY.LZX=fitY.LZX,
  data=data, link="logit")
summary(fitIV)
H <- estfun(fitIV)

```

plot(H)

ivah *Instrumental variable estimation of the causal exposure effect in additive hazards (AH) models*

Description

ivah performs instrumental variable estimation of the causal exposure effect in AH models with individual-level data. Below, Z , X , and T are the instrument, the exposure, and the outcome, respectively. L is a vector of covariates that we wish to control for in the analysis; these would typically be confounders for the instrument and the outcome.

Usage

```
ivah(estmethod, X, T, fitZ.L=NULL, fitX.LZ=NULL, fitT.LX=NULL, data,
     ctrl=FALSE, clusterid=NULL, event, max.time, max.time.psi, n.sim=100,
     vcov.fit=TRUE, ...)
```

Arguments

estmethod	a string specifying the desired estimation method; either "ts" for two-stage estimation, or "g" for G-estimation.
X	a string specifying the name of the exposure X in data. This is not needed if fitX.LZ is specified.
T	a string specifying the name of the follow-up time T in data. This is not needed if fitT.LZ is specified.
fitZ.L	an object of class "glm", as returned by the glm function in the stats package. This is a fitted GLM for $E(Z L)$. If there are no covariates, then fitZ.L may be specified as a model with an intercept only. This argument is not used when estmethod="ts".
fitX.LZ	an object of class "glm", as returned by the glm function in the stats package. This is a fitted GLM for $E(X L, Z)$. This argument is not used when estmethod="g".
fitT.LX	If estmethod="ts", then this is an object of class "ah", as returned by the ah function in the ivtools package. In this case it is a fitted AH model for $\lambda(t L, X)$. This argument is not used when estmethod="g".
data	a data frame containing the variables in the model. The covariates, instrument, exposure and outcome can have arbitrary names, e.g. they don't need to be called L, Z, X and T.
ctrl	logical. Should the control function $R = X - \hat{X}$ be used when re-fitting fitY? This argument is not used when estmethod="g".

<code>clusterid</code>	an optional string containing the name of a cluster identification variable when data are clustered. Specifying <code>clusterid</code> corrects the standard errors but does not affect the estimates. This argument is not used when <code>estmethod="g"</code> , since correction for clustered data is currently not implemented for G-estimation.
<code>event</code>	a string specifying the name of the status indicator, 0="no event", 1="event". This argument is not used when <code>estmethod="ts"</code> .
<code>max.time</code>	optional follow-up for estimating $B(t)$ with G-estimation. Defaults to maximal observed follow-up time in data. This argument is not used when <code>estmethod="ts"</code> .
<code>max.time.psi</code>	optional follow-up for estimating ψ with G-estimation. Defaults to maximal observed follow-up time in data. This argument is not used when <code>estmethod="ts"</code> .
<code>n.sim</code>	optional number of resamplings for testing goodness-of-fit of constant effects model for G-estimation. Defaults to 100. This argument is not used when <code>estmethod="ts"</code> .
<code>vcov.fit</code>	logical. Should the variance-covariance matrix be computed?
<code>...</code>	optional arguments passed on to the <code>nleqslv</code> function, which is used to solve the estimating equations when <code>estmethod="g"</code> . See the help pages for <code>nleqslv</code> . This argument is not used when <code>estmethod="ts"</code> .

Details

The `ivah` estimates different parameters, depending on whether `estmethod="ts"` or `estmethod="g"`. If `estmethod="ts"`, then `ivah` uses two-stage estimation to estimate the parameter ψ in the causal AH model

$$\lambda(t|L, Z, X) - \lambda_0(t|L, Z, X) = m^T(L)X\psi.$$

Here, $\lambda_0(t|L, Z, X)$ is counterfactual hazard function, had the exposure been set to 0. The vector function $m(L)$ contains interaction terms between L and X . These are specified implicitly through the model `fitY`. The model `fitX.LZ` is used to construct predictions $\hat{X} = \hat{E}(X|L, Z)$. These predictions are subsequently used to re-fit the model `fitY`, with X replaced with \hat{X} . The obtained coefficient(s) for X is the two-stage estimator of ψ .

If `estmethod="g"`, then `ivah` uses G-estimation to estimate the function $B(t)$ in the causal AH model

$$\lambda(t|L, Z, X) - \lambda_0(t|L, Z, X) = XdB(t).$$

It also delivers an estimate of $dB(t)$ assuming that this function is constant across time ($=\psi$).

Value

`ivah` returns an object of class "ivah", which inherits from class "ivmod". An object of class "ivah" is a list containing

<code>call</code>	the matched call.
<code>input</code>	input is a list containing all input arguments
<code>est</code>	a vector containing the estimate of ψ .
<code>vcov</code>	the variance-covariance matrix for the estimate of ψ , obtained with the sandwich formula.

estfunall	a matrix of all subject-specific contributions to the estimating functions used in the estimation process. One row for each subject, one column for each parameter. If estmethod="ts", then the first columns correspond to the parameters estimated by fitX.LZ, and the last columns correspond to the parameters estimated by the re-fitted model fitY. If estmethod="g", then estfunall is NULL.
d.estfun	the jacobian matrix of colMeans(estfun). If estmethod="g", then d.estfun is NULL.
converged	logical. Was a solution found to the estimating equations?
fitY	the re-fitted model fitY used in the estimation process when estmethod="ts". This element is NULL when estmethod="g".
stime	the ordered event times within (0,max.time). This element is NULL when estmethod="ts".
B	the estimate of $B(t)$. This element is NULL when estmethod="ts".
se_B	the standard error of the estimate of $B(t)$. This element is NULL when estmethod="ts".
pval_0	p-value corresponding to supremum test of the null $B(t) = 0$. This element is NULL when estmethod="ts".
eps_B	the iid-decomposition of $\sqrt{n}(\hat{B}(t) - B(t))$. This element is NULL when estmethod="ts".
pval_psi	p-value corresponding to the null $\psi = 0$. This element is NULL when estmethod="ts".
pval_GOF_sup	p-value corresponding to supremum test of the null $B(t) = \psi$. This element is NULL when estmethod="ts".
pval_GOF_CvM	as pval_GOF_sup but now based on the Cramer Von Mises test statistic. This element is NULL when estmethod="ts".
GOF.resamp	a matrix with first row the ordered jump times in (0,max.time.bet), second row the observed test process, and the remaining rows are 50 processes sampled under the null. This element is NULL when estmethod="ts".

Note

ivah allows for weights. However, these are defined implicitly through the input models. Thus, when models are used as input to ivah, these models have to be fitted with the same weights.

Left-truncation and correction of standard errors for clustered data are currently not implemented when estmethod="g".

Author(s)

Arvid Sjolander and Torben Martinussen.

References

- Martinussen T., Vansteelandt S., Tchetgen Tchetgen E.J., Zucker D.M. (2017). Instrumental variables estimation of exposure effects on a time-to-event endpoint using structural cumulative survival models. *Epidemiology* **73**(4): 1140-1149.
- Sjolander A., Martinussen T. (2019). Instrumental variable estimation with the R package ivtools. *Epidemiologic Methods* **8**(1), 1-20.

Tchetgen Tchetgen E.J., Walter S., Vansteelandt S., Martinussen T., Glymour M. (2015). Instrumental variable estimation in a survival context. *Epidemiology* **26**(3): 402-410.

Examples

```
require(ahaz)

set.seed(9)

n <- 1000
psi0 <- 0.2
psi1 <- 0.0

U <- runif(n)
L <- runif(n)
Z <- rbinom(n, 1, plogis(-0.5+L))
X <- runif(n, min=Z+U, max=2+Z+U)
T <- rexp(n, rate=psi0*X+psi1*X*L+0.2*U+0.2*L)
C <- 5 #administrative censoring at t=5
d <- as.numeric(T<C)
T <- pmin(T, C)
data <- data.frame(L, Z, X, T, d)
#break ties
data$T <- data$T+rnorm(n=nrow(data), sd=0.001)

#two-stage estimation
fitX.LZ <- glm(formula=X~Z+L, data=data)
fitT.LX <- ah(formula=Surv(T, d)~X+L+X*L, data=data)
fitIV <- ivah(estmethod="ts", fitX.LZ=fitX.LZ, fitT.LX=fitT.LX, data=data,
  ctrl=TRUE)
summary(fitIV)

#G-estimation
fitZ.L <- glm(formula=Z~L, family="binomial", data=data)
fitIV <- ivah(estmethod="g", X="X", T="T", fitZ.L=fitZ.L, data=data,
  event="d", max.time=4, max.time.psi=4, n.sim=100)
summary(fitIV)
plot(fitIV)
```

 ivbounds

Bounds for counterfactual outcome probabilities in instrumental variables scenarios

Description

ivbounds computes non-parametric bounds for counterfactual outcome probabilities in instrumental variables scenarios. Let Y , X , and Z be the outcome, exposure, and instrument, respectively. Y

and X must be binary, whereas Z can be either binary or ternary. Ternary instruments are common in, for instance, Mendelian randomization. Let $p(Y_x = 1)$ be the counterfactual probability of the outcome, had all subjects been exposed to level x . `ivbounds` computes bounds for the counterfactual probabilities $p(Y_1 = 1)$ and $p(Y_0 = 1)$. Below, we define $p_{yx.z} = p(Y = y, X = x | Z = z)$.

Usage

```
ivbounds(data, Z, X, Y, monotonicity=FALSE, weights)
```

Arguments

<code>data</code>	either a data frame containing the variables in the model, or a named vector (<code>p00.0, ..., p11.1</code>) when Z is binary, or a named vector (<code>p00.0, ..., p11.2</code>) when Z is ternary.
<code>Z</code>	a string containing the name of the instrument Z in <code>data</code> if <code>data</code> is a data frame. In this case Z has to be coded as (0,1) when binary, and coded as (0,1,2) when ternary. Z is not specified if <code>data</code> is a vector of probabilities.
<code>X</code>	a string containing the name of the exposure X in <code>data</code> if <code>data</code> is a data frame. In this case X has to be coded as (0,1). X is not specified if <code>data</code> is a vector of probabilities.
<code>Y</code>	a string containing the name of the outcome Y in <code>data</code> if <code>data</code> is a data frame. In this case Y has to be coded as (0,1). Y is not specified if <code>data</code> is a vector of probabilities.
<code>monotonicity</code>	logical. It is sometimes realistic to make the monotonicity assumption $z \geq z' \Rightarrow X_z \geq X_{z'}$. Should the bounds be computed under this assumption?
<code>weights</code>	an optional vector of ‘prior weights’ to be used in the fitting process. Should be <code>NULL</code> or a numeric vector. Only applicable if <code>data</code> is a data frame.

Details

`ivbounds` uses linear programming techniques to bound the counterfactual probabilities $p(Y_1 = 1)$ and $p(Y_0 = 1)$. Bounds for a causal effect, defined as a contrast between these, are obtained by plugging in the bounds for $p(Y_1 = 1)$ and $p(Y_0 = 1)$ into the contrast. For instance, bounds for the causal risk difference $p(Y_1 = 1) - p(Y_0 = 1)$ are obtained as $[\min\{p(Y_1 = 1)\} - \max\{p(Y_0 = 1)\}, \max\{p(Y_1 = 1)\} - \min\{p(Y_0 = 1)\}]$. In addition to the bounds, `ivbounds` evaluates the IV inequality

$$\max_x \sum_y \max_z p_{yx.z} \leq 1.$$

Value

An object of class “`ivbounds`” is a list containing

<code>call</code>	the matched call.
<code>p0</code>	a named vector with elements “ <code>min</code> ” and “ <code>max</code> ”, containing the evaluated lower and upper bounds for $p(Y_0 = 1)$, respectively.
<code>p1</code>	a named vector with elements “ <code>min</code> ” and “ <code>max</code> ”, containing the evaluated lower and upper bounds for $p(Y_1 = 1)$, respectively.

<code>p0.symbolic</code>	a named vector with elements "min" and "max", containing the lower and upper bounds for $p(Y_0 = 1)$, respectively, on a symbolic form (i.e. as strings).
<code>p1.symbolic</code>	a named vector with elements "min" and "max", containing the lower and upper bounds for $p(Y_1 = 1)$, respectively, on a symbolic form (i.e. as strings).
<code>IVinequality</code>	logical. Does the IV inequality hold?
<code>conditions</code>	a character vector containing the violated conditions, if <code>IVinequality=FALSE</code> .

Author(s)

Arvid Sjolander.

References

Balke, A. and Pearl, J. (1997). *Bounds on treatment effects from studies with imperfect compliance*. *Journal of the American Statistical Association* **92**(439), 1171-1176.

Sjolander A., Martinussen T. (2019). Instrumental variable estimation with the R package ivtools. *Epidemiologic Methods* **8**(1), 1-20.

Examples

```
##Vitamin A example from Balke and Pearl (1997).
n000 <- 74
n001 <- 34
n010 <- 0
n011 <- 12
n100 <- 11514
n101 <- 2385
n110 <- 0
n111 <- 9663
n0 <- n000+n010+n100+n110
n1 <- n001+n011+n101+n111

#with data frame...
data <- data.frame(Y=c(0,0,0,0,1,1,1,1), X=c(0,0,1,1,0,0,1,1),
  Z=c(0,1,0,1,0,1,0,1))
n <- c(n000, n001, n010, n011, n100, n101, n110, n111)
b <- ivbounds(data=data, Z="Z", X="X", Y="Y", weights=n)
summary(b)

#...or with vector of probabilities
p <- n/rep(c(n0, n1), 4)
names(p) <- c("p00.0", "p00.1", "p01.0", "p01.1",
  "p10.0", "p10.1", "p11.0", "p11.1")
b <- ivbounds(data=p)
summary(b)
```

ivcoxph	<i>Instrumental variable estimation of the causal exposure effect in Cox proportional hazards (PH) models</i>
---------	---

Description

ivcoxph performs instrumental variable estimation of the causal exposure effect in Cox PH models with individual-level data. Below, Z , X , and T are the instrument, the exposure, and the outcome, respectively. L is a vector of covariates that we wish to control for in the analysis; these would typically be confounders for the instrument and the outcome.

Usage

```
ivcoxph(estmethod, X, fitZ.L=NULL, fitX.LZ=NULL, fitX.L=NULL, fitT.LX=NULL,
        fitT.LZX=NULL, data, formula=~1, ctrl=FALSE, clusterid=NULL, t=NULL,
        vcov.fit=TRUE, ...)
```

Arguments

estmethod	a string specifying the desired estimation method; either "ts" for two-stage estimation, or "g" for G-estimation.
X	a string specifying the name of the exposure X in data. This is not needed if fitX.LZ is specified.
fitZ.L	an object of class "glm", as returned by the glm function in the stats package. This is a fitted GLM for $E(Z L)$. If there are no covariates, then fitZ.L may be specified as a model with an intercept only. This argument is not used when estmethod="ts".
fitX.LZ	an object of class "glm", as returned by the glm function in the stats package. This is a fitted GLM for $E(X L, Z)$.
fitX.L	an object of class "glm", as returned by the glm function in the stats package. This is a fitted GLM for $E(X L)$. If there are no covariates, then fitX.L may be specified as a model with an intercept only. This argument is not used when estmethod="ts".
fitT.LX	an object of class "coxph", as returned by the coxph function in the survival package. This is a fitted Cox PH model for $\lambda(t L, X)$. This argument is not used when estmethod="g".
fitT.LZX	either an object of class "coxph" or an object of class "survfit", as returned by the coxph function in the survival package. This is a fitted Cox PH model for $\lambda(t L, Z, X)$ or a non-parametric model for $S(t L, Z, X)$, respectively. This argument is not used when estmethod="ts".
data	a data frame containing the variables in the model. The covariates, instrument, exposure and outcome can have arbitrary names, e.g. they don't need to be called L, Z, X and T.

formula	an object of class "formula", with no left-hand side. This specifies the causal interaction terms $m(L)$; see 'Details'. Defaults to ~ 1 , i.e. main effect only. This argument is not used when <code>estmethod="ts"</code> .
ctrl	logical. Should the control function $R = X - \hat{X}$ be used when re-fitting <code>fitT.LX</code> ? This argument is not used when <code>estmethod="g"</code> .
clusterid	an optional string containing the name of a cluster identification variable when data are clustered. Specifying <code>clusterid</code> corrects the standard errors but does not affect the estimates.
t	a numeric scalar specifying the time point at which to solve the estimating equation when <code>estmethod="g"</code> ; see 'Details'. If not specified, then the estimating equation is solved at the optimal value of <code>t</code> , defined as the value that minimizes $trace\{var(\hat{\psi})\}$; see Martinussen et al (2017). This argument is not used when <code>estmethod="ts"</code> .
vcov.fit	logical. Should the variance-covariance matrix be computed?
...	optional arguments passed on to the <code>nleqslv</code> function, which is used to solve the estimating equations when <code>estmethod="g"</code> . See the help pages for <code>nleqslv</code> . This argument is not used when <code>estmethod="ts"</code> .

Details

`ivcoxph` estimates the parameter ψ in the causal Cox PH model

$$\log\{\lambda(t|L, Z, X)\} - \log\{\lambda_0(t|L, Z, X)\} = m^T(L)X\psi.$$

Here, $\lambda_0(t|L, Z, X)$ is counterfactual hazard function, had the exposure been set to 0. The vector function $m(L)$ contains interaction terms between L and X . If `estmethod="ts"`, then these are specified implicitly through the model `fitT.LX`. If `estmethod="g"`, then these are specified explicitly through the `formula` argument.

If `estmethod="ts"`, then two-stage estimation of ψ is performed. In this case, the model `fitX.LZ` is used to construct predictions $\hat{X} = \hat{E}(X|L, Z)$. These predictions are subsequently used to re-fit the model `fitT.LX`, with X replaced with \hat{X} . The obtained coefficient(s) for \hat{X} in the re-fitted model is the two-stage estimator of ψ .

If `estmethod="g"`, then G-estimation of ψ is performed. In this case, the estimator is obtained as the solution to the estimating equation

$$H(\psi) = \sum_{i=1}^n \hat{d}(L_i, Z_i) h_i(\psi; t) = 0,$$

where

$$h_i(\psi; t) = \hat{S}(t|L_i, Z_i, X_i) \exp\{-m^T(L_i)\psi X_i\}.$$

The estimated function $\hat{d}(L, Z)$ is chosen so that the true function has conditional mean 0, given L ; $E\{d(L, Z)|L\} = 0$. The specific form of $\hat{d}(L, Z)$ is determined by the user-specified models. If `fitX.LZ` and `fitX.L` are specified, then $\hat{d}(L, Z) = m(L)\{\hat{E}(X|L, Z) - \hat{E}(X|L)\}$, where $\hat{E}(X|L, Z)$ and $\hat{E}(X|L)$ are obtained from `fitX.LZ` and `fitX.L`, respectively. If these are not specified, then $\hat{d}(L, Z) = m(L)\{Z - \hat{E}(Z|L)\}$, where $\hat{E}(Z|L)$ is obtained from `fitZ.L`, which then must be specified. The estimating equation is solved at the value of t specified by the argument `t`. $\hat{S}(t|L_i, Z_i, X_i)$ is an estimate of $S(t|L_i, Z_i, X_i)$ obtained from the model `fitT.LZX`.

Value

ivcoxph returns an object of class "ivcoxph", which inherits from class "ivmod". An object of class "ivcoxph" is a list containing

call	the matched call.
input	input is a list containing all input arguments
est	a vector containing the estimate of ψ .
vcov	the variance-covariance matrix for the estimate of ψ , obtained with the sandwich formula.
estfunall	a matrix of all subject-specific contributions to the estimating functions used in the estimation process. One row for each subject, one column for each parameter. If estmethod="ts", then the first columns correspond to the parameters estimated by fitX.LZ, and the last columns correspond to the parameters estimated by the re-fitted model fitT.LX. If estmethod="g", then the first columns correspond to ψ , and the remaining columns correspond to the parameters estimated by fitZ.L, fitX.LZ, fitX.L and fitT.LZX, whichever were used in the estimation process.
d.estfun	the jacobian matrix of colMeans(estfunall).
converged	logical. Was a solution found to the estimating equations?
fitT.LX	the re-fitted model fitT.LX used in the estimation process when estmethod="ts". This element is NULL when estmethod="g".
t	the value of t used in the estimation process. This element is NULL when estmethod="ts".

Note

ivcoxph allows for weights. However, these are defined implicitly through the input models. Thus, when models are used as input to ivcoxph, these models have to be fitted with the same weights. When estmethod="g" the weights are taken from fitX.LZ, if specified by the user. If fitX.LZ is not specified then the weights are taken from fitZ.L. Hence, if weights are used, then either fitX.LZ or fitZ.L must be specified.

Author(s)

Arvid Sjolander.

References

- Martinussen T., Sorensen D.D., Vansteelandt S. (2019). Instrumental variables estimation under a structural Cox model. *Biostatistics* **20**(1), 65-79.
- Sjolander A., Martinussen T. (2019). Instrumental variable estimation with the R package ivtools. *Epidemiologic Methods* **8**(1), 1-20.
- Tchetgen Tchetgen E.J., Walter S., Vansteelandt S., Martinussen T., Glymour M. (2015). Instrumental variable estimation in a survival context. *Epidemiology* **26**(3), 402-410.

Examples

```

require(survival)

set.seed(9)

##Note: the parameter values in the examples below are chosen to make
##Y0 independent of Z, which is necessary for Z to be a valid instrument.

n <- 10000
psi0 <- 0.5
Z <- rbinom(n, 1, 0.5)
X <- rbinom(n, 1, 0.7*Z+0.2*(1-Z))
m0 <- exp(0.8*X-0.41*Z) #T0 independent of Z at t=1
T <- rexp(n, rate=exp(psi0*X+log(m0)))
C <- rexp(n, rate=exp(psi0*X+log(m0))) #50% censoring
d <- as.numeric(T<C)
T <- pmin(T, C)
data <- data.frame(Z, X, T, d)

#two-stage estimation
fitX.LZ <- glm(formula=X~Z, data=data)
fitT.LX <- coxph(formula=Surv(T, d)~X, data=data)
fitIV <- ivcoxph(estmethod="ts", fitX.LZ=fitX.LZ, fitT.LX=fitT.LX, data=data,
  ctrl=TRUE)
summary(fitIV)

#G-estimation with non-parametric model for S(t|L,Z,X) and model for Z
fitZ.L <- glm(formula=Z~1, data=data)
fitT.LZX <- survfit(formula=Surv(T, d)~X+Z, data=data)
fitIV <- ivcoxph(estmethod="g", X="X", fitZ.L=fitZ.L, fitT.LZX=fitT.LZX,
  data=data, t=1)
summary(fitIV)

#G-estimation with Cox model for \lambda(t|L,Z,X) and model for Z
fitZ.L <- glm(formula=Z~1, data=data)
fitT.LZX <- coxph(formula=Surv(T, d)~X+X*X*Z, data=data)
fitIV <- ivcoxph(estmethod="g", X="X", fitZ.L=fitZ.L, fitT.LZX=fitT.LZX,
  data=data, t=1)
summary(fitIV)

```

ivglm

Instrumental variable estimation of the causal exposure effect in generalized linear models

Description

ivglm performs instrumental variable estimation of the causal exposure effect in generalized linear models with individual-level data. Below, Z , X , and Y are the instrument, the exposure, and the

outcome, respectively. L is a vector of covariates that we wish to control for in the analysis; these would typically be confounders for the instrument and the outcome.

Usage

```
ivglm(estmethod, X, Y, fitZ.L=NULL, fitX.LZ=NULL, fitX.L=NULL, fitY.LX=NULL,
      fitY.LZX=NULL, data, formula=~1, ctrl=FALSE, clusterid=NULL, link, vcov.fit=TRUE,
      ...)
```

Arguments

estmethod	a string specifying the desired estimation method; either "ts" for two-stage estimation, or "g" for G-estimation.
X	a string specifying the name of the exposure X in data. This is not needed if fitX.LZ is specified.
Y	a string specifying the name of the outcome Y in data. This is not needed if fitY.LX or fitY.LZX is specified.
fitZ.L	an object of class "glm", as returned by the glm function in the stats package. This is a fitted GLM for $E(Z L)$. If there are no covariates, then fitZ.L may be specified as a model with an intercept only. This argument is not used when estmethod="ts".
fitX.LZ	an object of class "glm", as returned by the glm function in the stats package. This is a fitted GLM for $E(X L, Z)$.
fitX.L	an object of class "glm", as returned by the glm function in the stats package. This is a fitted GLM for $E(X L)$. If there are no covariates, then fitX.L may be specified as a model with an intercept only. This argument is not used when estmethod="ts".
fitY.LX	an object of class "glm", as returned by the glm function in the stats package. This is a fitted GLM for $E(Y L, X)$. This argument is not used when estmethod="g".
fitY.LZX	an object of class "glm", as returned by the glm function in the stats package. This is a fitted GLM for $E(Y L, Z, X)$. This argument is not used when estmethod="ts". It is also not used when estmethod="g" and link="identity" or link="log".
data	a data frame containing the variables in the model. The covariates, instrument, exposure and outcome can have arbitrary names, e.g. they don't need to be called L, Z, X and Y.
formula	an object of class "formula", with no left-hand side. This specifies the causal interaction terms $m(L)$; see 'Details'. Defaults to ~1, i.e. main effect only. This argument is not used when estmethod="ts".
ctrl	logical. Should the control function $R = X - \hat{X}$ be used when re-fitting fitY.LX? This argument is not used when estmethod="g".
clusterid	an optional string containing the name of a cluster identification variable when data are clustered. Specifying clusterid corrects the standard errors but does not affect the estimates.

link	a string specifying the link function for the causal generalized linear model; see ‘Details’. Either "identity", "log", or "logit". This argument is not used when <code>estmethod="ts"</code> .
vcov.fit	logical. Should the variance-covariance matrix be computed?
...	optional arguments passed on to the <code>nleqslv</code> function, which is used to solve the estimating equations when <code>estmethod="g"</code> . See the help pages for <code>nleqslv</code> . This argument is not used when <code>estmethod="ts"</code> .

Details

`ivglm` estimates the parameter ψ in the causal generalized linear model

$$\eta\{E(Y|L, Z, X)\} - \eta\{E(Y_0|L, Z, X)\} = m^T(L)X\psi.$$

Here, $E(Y_0|L, Z, X)$ is counterfactual mean of the outcome, had the exposure been set to 0. The link function η is either the identity, log or logit link, as specified by the `link` argument. The vector function $m(L)$ contains interaction terms between L and X . If `estmethod="ts"`, then these are specified implicitly through the model `fitY.LX`. If `estmethod="g"`, then these are specified explicitly through the `formula` argument.

If `estmethod="ts"`, then two-stage estimation of ψ is performed. In this case, the model `fitX.LZ` is used to construct predictions $\hat{X} = \hat{E}(X|L, Z)$. These predictions are subsequently used to re-fit the model `fitY.LX`, with X replaced with \hat{X} . The obtained coefficient(s) for \hat{X} in the re-fitted model is the two-stage estimator of ψ .

If `estmethod="g"`, then G-estimation of ψ is performed. In this case, the estimator is obtained as the solution to the estimating equation

$$H(\psi) = \sum_{i=1}^n \hat{d}(L_i, Z_i) h_i(\psi) = 0.$$

The function $h_i(\psi)$ is defined as

$$h_i(\psi) = Y_i - m^T(L_i)\psi X_i$$

when `link="identity"`,

$$h_i(\psi) = Y_i \exp\{-m^T(L_i)\psi X_i\}$$

when `link="log"`, and

$$h_i(\psi) = \text{expit}[\text{logit}\{\hat{E}(Y|L_i, Z_i, X_i)\} - m^T(L_i)\psi X_i]$$

when `link="logit"`. In the latter, $\hat{E}(Y|L_i, Z_i, X_i)$ is an estimate of $E(Y|L_i, Z_i, X_i)$ obtained from the model `fitY.LZX`. The estimated function $\hat{d}(L, Z)$ is chosen so that the true function has conditional mean 0, given L ; $E\{d(L, Z)|L\} = 0$. The specific form of $\hat{d}(L, Z)$ is determined by the user-specified models. If `fitX.LZ` and `fitX.L` are specified, then $\hat{d}(L, Z) = m(L)\{\hat{E}(X|L, Z) - \hat{E}(X|L)\}$, where $\hat{E}(X|L, Z)$ and $\hat{E}(X|L)$ are obtained from `fitX.LZ` and `fitX.L`, respectively. If these are not specified, then $\hat{d}(L, Z) = m(L)\{Z - \hat{E}(Z|L)\}$, where $\hat{E}(Z|L)$ is obtained from `fitZ.L`, which then must be specified.

Value

ivglm returns an object of class "ivglm", which inherits from class "ivmod". An object of class "ivglm" is a list containing

call	the matched call.
input	input is a list containing all input arguments
est	a vector containing the estimate of ψ .
vcov	the variance-covariance matrix for the estimate of ψ , obtained with the sandwich formula.
estfunall	a matrix of all subject-specific contributions to the estimating functions used in the estimation process. One row for each subject, one column for each parameter. If estmethod="ts", then the first columns correspond to the parameters estimated by fitX.LZ, and the last columns correspond to the parameters estimated by the re-fitted model fitY.LX. If estmethod="g", then the first columns correspond to ψ , and the remaining columns correspond to the parameters estimated by fitZ.L, fitX.LZ, fitX.L and fitY.LZX, whichever were used in the estimation process.
d.estfun	the jacobian matrix of colMeans(estfunall).
converged	logical. Was a solution found to the estimating equations?
fitY.LX	the re-fitted model fitY.LX used in the estimation process when estmethod="ts". This element is NULL when estmethod="g".

Note

ivglm allows for weights. However, these are defined implicitly through the input models. Thus, when models are used as input to ivglm, these models have to be fitted with the same weights. When estmethod="g" the weights are taken from fitX.LZ, if specified by the user. If fitX.LZ is not specified then the weights are taken from fitZ.L. Hence, if weights are used, then either fitX.LZ or fitZ.L must be specified.

Author(s)

Arvid Sjolander.

References

- Bowden J., Vansteelandt S. (2011). Mendelian randomization analysis of case-control data using structural mean models. *Statistics in Medicine* **30**(6), 678-694.
- Sjolander A., Martinussen T. (2019). Instrumental variable estimation with the R package ivtools. *Epidemiologic Methods* **8**(1), 1-20.
- Vansteelandt S., Bowden J., Babanezhad M., Goetghebeur E. (2011). On instrumental variables estimation of causal odds ratios. *Statistical Science* **26**(3), 403-422.

Examples

```

set.seed(9)

##Note: the parameter values in the examples below are chosen to make
##Y0 independent of Z, which is necessary for Z to be a valid instrument.

n <- 1000
psi0 <- 0.5
psi1 <- 0.2

##---Example 1: linear model and interaction between X and L---

L <- rnorm(n)
Z <- rnorm(n, mean=L)
X <- rnorm(n, mean=Z)
m0 <- X-Z+L
Y <- rnorm(n, mean=psi0*X+psi1*X*L+m0)
data <- data.frame(L, Z, X, Y)

#two-stage estimation
fitX.LZ <- glm(formula=X~Z, data=data)
fitY.LX <- glm(formula=Y~X+L+X*L, data=data)
fitIV <- ivglm(estmethod="ts", fitX.LZ=fitX.LZ, fitY.LX=fitY.LX, data=data,
  ctrl=TRUE)
summary(fitIV)

#G-estimation with model for Z
fitZ.L <- glm(formula=Z~L, data=data)
fitIV <- ivglm(estmethod="g", X="X", Y="Y", fitZ.L=fitZ.L, data=data,
  formula=~L, link="identity")
summary(fitIV)

#G-estimation with model for X
fitX.LZ <- glm(formula=X~L+Z, data=data)
fitX.L <- glm(formula=X~L, data=data)
fitIV <- ivglm(estmethod="g", Y="Y", fitX.LZ=fitX.LZ, fitX.L=fitX.L, data=data,
  formula=~L, link="identity")
summary(fitIV)

##---Example 2: logistic model and no covariates---

Z <- rbinom(n, 1, 0.5)
X <- rbinom(n, 1, 0.7*Z+0.2*(1-Z))
m0 <- plogis(1+0.8*X-0.39*Z)
Y <- rbinom(n, 1, plogis(psi0*X+log(m0/(1-m0))))
data <- data.frame(Z, X, Y)

#two-stage estimation
fitX.LZ <- glm(formula=X~Z, family="binomial", data=data)
fitY.LX <- glm(formula=Y~X, family="binomial", data=data)
fitIV <- ivglm(estmethod="ts", fitX.LZ=fitX.LZ, fitY.LX=fitY.LX, data=data,

```

```
ctrl=TRUE)
summary(fitIV)

#G-estimation with model for Z
fitZ.L <- glm(formula=Z~1, data=data)
fitY.LZX <- glm(formula=Y~X+Z+X*Z, family="binomial", data=data)
fitIV <- ivglm(estmethod="g", X="X", fitZ.L=fitZ.L, fitY.LZX=fitY.LZX,
  data=data, link="logit")
summary(fitIV)
```

plot.estfun

Plots sums of estimating functions.

Description

This is a plot method for class "estfun".

Usage

```
## S3 method for class 'estfun'
plot(x, ...)
```

Arguments

x an object of class "estfun", fitted with method="g".
... additional arguments to plot.

Author(s)

Arvid Sjolander.

Examples

```
##See documentation for estfun.
```

plot.ivah	<i>Plots result of G-estimation in causal AH model.</i>
-----------	---

Description

This is a plot method for class "ivah". It only supports objects fitted with estmethod="g".

Usage

```
## S3 method for class 'ivah'
plot(x, gof=FALSE, CI.level=0.95, ...)
```

Arguments

x	an object of class "ivah", fitted with estmethod="g".
gof	should we plot the goodness-of-fit process? If not, then $B(t)$ is plotted together with confidence intervals.
CI.level	level for the confidence intervals.
...	not used.

Author(s)

Arvid Sjolander and Torben Martinussen.

Examples

```
##See documentation for ivah.
```

print.ivmod	<i>Prints output of instrumental variable estimation</i>
-------------	--

Description

This is a print method for class "ivmod".

Usage

```
## S3 method for class 'ivmod'
print(x, digits=max(3L, getOption("digits")-3L), ...)
```

Arguments

x	an object of class "ivmod".
digits	the number of significant digits to use.
...	not used.

Author(s)

Arvid Sjolander

Examples

```
##See documentation for ivglm, ivcoxph and ivah.
```

```
print.summary.ivbounds
```

Prints summary of instrumental variable bounds

Description

This is a print method for class "summary.ivbounds".

Usage

```
## S3 method for class 'summary.ivbounds'  
print(x, digits=max(3L, getOption("digits")-3L),  
      ...)
```

Arguments

x	an object of class "summary.ivbounds".
digits	the number of significant digits to use.
...	not used.

Author(s)

Arvid Sjolander

Examples

```
##See documentation for ivbounds.
```

print.summary.ivmod *Prints summary of instrumental variable estimation*

Description

This is a print method for class "summary.ivmod".

Usage

```
## S3 method for class 'summary.ivmod'  
print(x, digits=max(3L, getOption("digits")-3L),  
      signif.stars=getOption("show.signif.stars"), ...)
```

Arguments

x	an object of class "summary.ivmod".
digits	the number of significant digits to use.
signif.stars	logical. If TRUE, "significance stars" are printed for each coefficient.
...	not used.

Author(s)

Arvid Sjolander

Examples

```
##See documentation for ivglm, ivcoxph and ivah.
```

summary.ivbounds *Summarizes instrumental variable estimation*

Description

This is a summary method for class "ivbounds".

Usage

```
## S3 method for class 'ivbounds'  
summary(object, ...)
```

Arguments

object	an object of class "ivbounds".
...	not used.

Details

Provides the lower and upper bounds for

$$p_0 = p(Y_0 = 1)$$

$$p_1 = p(Y_1 = 1)$$

$$\text{CRD} = p_1 - p_0$$

$$\text{CRR} = p_1/p_0$$

$$\text{COR} = \frac{p_1/(1-p_1)}{p_0/(1-p_0)}$$

Author(s)

Arvid Sjolander

Examples

```
##See documentation for ivbounds.
```

```
summary.ivmod
```

Summarizes instrumental variable estimation

Description

This is a summary method for class "ivmod".

Usage

```
## S3 method for class 'ivmod'
summary(object, ...)
```

Arguments

```
object      an object of class "ivmod".
...         not used.
```

Author(s)

Arvid Sjolander

Examples

```
##See documentation for ivglm, ivcoxph and ivah.
```

VitD

Data from a cohort study on Vitamin D and mortality.

Description

This dataset originates from a real cohort study on Vitamin D and mortality, described by Martinussen et al (2017). However, to allow public availability the data were slightly mutilated before inclusion in the `ivtools` package.

Usage

```
data(VitD)
```

Format

The dataset contains the following variables:

age age at baseline.

filaggrin binary indicator of whether the subject has mutations in the filaggrin gene.

vitd vitamin D level at baseline, measured as serum 25-OH-D (nmol/L).

time follow-up time.

death indicator of whether the subject died during follow-up.

References

Martinussen T., Sorensen D.D., Vansteelandt S. (2019). Instrumental variables estimation under a structural Cox model. *Biostatistics* **20**(1), 65-79.

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