Package 'medflex'

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Title Flexible Mediation Analysis using Natural Effect Models

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Description medflex allows to run flexible mediation analyses using natural
effect models as described in Lange, Vansteelandt and Bekaert (2012),
Vansteelandt, Bekaert and Lange (2012) and Loeys, Moerkerke, De Smet,
Buysse, Steen and Vansteelandt (2013).

Depends R (>= 3.1.2), multcomp (>= 1.3-6)

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URL https://github.com/jmpsteen/medflex

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Imports boot (>= 1.3-8), Matrix (>= 1.1-4), sandwich (>= 2.3-2)

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1.9-8), rpart (>= 4.1-8), SuperLearner (>= 2.0-15), VGAM (>=
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R topics documented:

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expData   *Expanded dataset*

Description

Expanded dataset including either ratio-of-mediator probability weights or imputed nested counterfactual outcomes.

Value

A data frame, resulting from applying [neWeight](#) or [neImpute](#) on an original dataset data. This data frame has nRep * length(data) rows, containing all original variables (except the original exposure variable) and two variables reflecting observed and hypothetical values of the exposure for each observation unit.

These auxiliary variables (*x* and *x**) are named after the exposure variable and carry integers as suffixes. Suffixes 0 and 1 are used for variables whose corresponding parameters in the final natural effect model index natural direct and indirect effects, respectively.

This object also stores some additional attributes, which are used as input for [neModel](#), such as

model	the fitted imputation model object
data	original dataset
call	the matched call
terms	the neTerms (internal class) object used
weigths	ratio-of-mediator probability weights (only stored if object inherits from class weightData)

Note

If the weighting-based approach ([neWeight](#)) is applied, the original outcome values are copied for the nested counterfactual outcomes and the object stores an additional attribute, "weights", containing a vector with ratio-of-mediator probability weights.

If the imputation-based approach ([neImpute](#)) is applied, the nested counterfactual outcomes are imputed by predictions from the imputation model.

In the former case, this object inherits from classes c("data.frame", "expData", "impData"), whereas in the latter case it inherits from classes c("data.frame", "expData", "weightData").

See Also

[neImpute](#), [neWeight](#)

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neImpute   *Expand the dataset and impute nested counterfactual outcomes*

Description

This function both expands the data along hypothetical exposure values and imputes nested counterfactual outcomes.

Usage

```
neImpute(object, ...)
```

Arguments

object	an object used to select a method.
...	additional arguments.

Details

Generic function that both expands the data along hypothetical exposure values (for each observation unit *i*) and imputes nested counterfactual outcomes in this expanded dataset in a single run. Imputed counterfactual outcomes

$$\hat{E}(Y_i|X_i = x, M_i, C_i)$$

are predictions from the imputation model that can be specified either externally as a fitted model object (neImpute.default) or internally (neImpute.formula).

Value

A data frame of class c("data.frame", "expData", "impData"). See expData for its structure.

References

Vansteelandt, S., Bekaert, M., & Lange, T. (2012). Imputation Strategies for the Estimation of Natural Direct and Indirect Effects. *Epidemiologic Methods*, **1**(1), Article 7.

Loeys, T., Moerkerke, B., De Smet, O., Buysse, A., Steen, J., & Vansteelandt, S. (2013). Flexible Mediation Analysis in the Presence of Nonlinear Relations: Beyond the Mediation Formula. *Multivariate Behavioral Research*, **48**(6), 871-894.

See Also

neImpute.default, neImpute.formula, neModel, expData

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neImpute.default   *Expand the dataset and impute nested counterfactual outcomes*

Description

This function both expands the data along hypothetical exposure values and imputes nested counterfactual outcomes.

Usage

```
## Default S3 method:
neImpute(object, formula, data, nMed = 1, nRep = 5,
  xSampling = c("quantiles", "random"), xFit, percLim = c(0.05, 0.95), ...)
```

Arguments

object	fitted model object representing the imputation model.
formula	a [formula](#) object providing a symbolic description of the imputation model. Redundant if already specified in call for fitted model specified in object (see details).
data	data, as matrix or data frame, containing the exposure (and other relevant) variables. Redundant if already specified in call for fitted model specified in object (see details).
nMed	number of mediators.
nRep	number of replications or hypothetical values of the exposure to sample for each observation unit.
xSampling	character string indicating how to sample from the conditional exposure distribution. Possible values are "quantiles" or "random" (see details).
xFit	an optional fitted object (preferably glm) for the conditional exposure distribution (see details).
percLim	a numerical vector of the form c(lower, upper) indicating the extreme percentiles to sample when using "quantiles" as sampling method to sample from the conditional exposure distribution (see details).
...	additional arguments.

Details

Imputed counterfactual outcomes are predictions from the imputation model that needs to be specified as a fitted object in the object argument.

If the model-fitting function used to fit the imputation model does not require specification of a formula or data argument (when using e.g. [SuperLearner](#)), these need to be specified explicitly in order to enable neImpute.default to extract pointers to variable types relevant for mediation analysis.

Whether a [formula](#) is specified externally (in the call for the fitted imputation model object which is specified in object) or internally (via the formula argument), it always needs to be of the form Y ~ X + M1 + M2 + M3 + C1 + C2, with the same outcome as in the final natural effect model and with predictor variables entered in the following prespecified order:

1. exposure X: The first predictor is coded as exposure or treatment.

2. mediator(s) M: The second predictor is coded as mediator. In case of multiple mediators (nMed > 1), then predictors 2:(nMed + 1) are coded as mediators.

3. baseline covariates C: All remaining predictor variables are automatically coded as baseline covariates.

If multiple mediators are specified (nMed > 1), the natural indirect effect parameter in the natural effect model captures the joint mediated effect. That is, the effect of the exposure on the outcome via these mediators considered jointly. The remaining effect of the exposure on the outcome (not mediated through the specified mediators) is then captured by the natural indirect effect parameter.

In contrast to imputation models with categorical exposures, additional arguments need to be specified if the exposure is continuous. All of these additional arguments are related to the sampling procedure for the exposure.

Whereas the number of replications nRep for categorical variables equals the number of levels for the exposure coded as a factor (i.e. the number of hypothetical exposure values), the number of desired replications needs to be specified explicitly for continuous exposures. Its default is 5.

If xFit is left unspecified, the hypothetical exposure levels are automatically sampled from a linear model for the exposure, conditional on a linear combination of all covariates. If one wishes to use another model for the exposure, this default model specification can be overruled by referring to a fitted model object in the xFit argument. Misspecification of this sampling model does not induce bias in the estimated coefficients and standard errors of the natural effect model.

The xSampling argument allows to specify how the hypothetical exposure levels should be sampled from the conditional exposure distribution (which is either entered explicitly using the xFit argument or fitted automatically as described in the previous paragraph). The "random" option randomly samples nRep draws from the exposure distribution, whereas the "quantiles" option (default) samples nRep quantiles at equal-sized probability intervals. Only the latter hence yields fixed exposure levels given nRep and xFit.

In order to guarantee that the entire support of the distribution is being sampled (which might be a concern if nRep is chosen to be small), the default lower and upper sampled quantiles are the 5th and 95th percentiles. The intermittent quantiles correspond to equal-sized probability intervals. So, for instance, if nRep = 4, then the sampled quantiles will correspond to probabilities 0.05, 0.35, 0.65 and 0.95. These default 'outer' quantiles can be changed by specifying the percLim argument accordingly. By specifying percLim = NULL, the standard quantiles will be sampled (e.g., 0.2, 0.4, 0.6 and 0.8 if nRep = 4).

Value

A data frame of class c("data.frame", "expData", "impData"). See expData for its structure.

See Also

neImpute, neImpute.formula, neModel, expData

Examples

```
data(UPBdata)

## example using glm imputation model with binary exposure
fit.glm <- glm(UPB ~ attbin + negaff + gender + educ + age,
               family = binomial, data = UPBdata)
impData <- neImpute(fit.glm)
```

```
head(impData)

## example using glm imputation model with continuous exposure
fit.glm <- glm(UPB ~ att + negaff + gender + educ + age,
                family = binomial, data = UPBdata)
impData <- neImpute(fit.glm, nRep = 2)
head(impData)

## example using vglm (yielding identical results as with glm)
library(VGAM)
fit.vglm <- vglm(UPB ~ att + negaff + gender + educ + age,
                  family = binomialff, data = UPBdata)
impData2 <- neImpute(fit.vglm, nRep = 2)
head(impData2)

## example using SuperLearner
library(Matrix)
library(SuperLearner)
SL.library <- c("SL.glm", "SL.glm.interaction", "SL.rpart",
                "SL.step", "SL.stepAIC", "SL.step.interaction",
                "SL.bayesglm", "SL.glmnet")
pred <- c("att", "negaff", "gender", "educ", "age")
fit.SL <- SuperLearner(Y = UPBdata$UPB, X = subset(UPBdata, select = pred),
                        SL.library = SL.library, family = binomial())
impSL <- neImpute(fit.SL,
                  formula = UPB ~ att + negaff + gender + educ + age,
                  data = UPBdata)
head(impSL)
```

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neImpute.formula   *Expand the dataset and impute nested counterfactual outcomes*

Description

This function both expands the data along hypothetical exposure values and imputes nested counterfactual outcomes.

Usage

```
## S3 method for class 'formula'
neImpute(object, family, data, FUN = glm, nMed = 1,
  nRep = 5, xSampling = c("quantiles", "random"), xFit, percLim = c(0.05,
  0.95), ...)
```

Arguments

object	a [formula](#) object providing a symbolic description of the imputation model (see details).
family	a description of the error distribution and link function to be used in the model. Consult the help files of the model-fitting function specified in FUN for more details on appropriate argument specification.

data	data, as matrix or data frame, containing the exposure (and other relevant) variables. Redundant if already specified in call for fitted model specified in `object` (see details).
FUN	function used to fit model specified in `formula`.
nMed	number of mediators.
nRep	number of replications or hypothetical values of the exposure to sample for each observation unit.
xSampling	character string indicating how to sample from the conditional exposure distribution. Possible values are `"quantiles"` or `"random"` (see details).
xFit	an optional fitted object (preferably `glm`) for the conditional exposure distribution (see details).
percLim	a numerical vector of the form `c(lower, upper)` indicating the extreme percentiles to sample when using `"quantiles"` as sampling method to sample from the conditional exposure distribution (see details).
...	additional arguments (passed to FUN).

Details

Imputed counterfactual outcomes are predictions from the imputation model that is fitted internally by extracting information from the arguments `object`, `family`, `data`, `FUN` and `...`.

For imputation model specification via the `object` argument, use a [formula](#) of the form

`Y ~ X + M1 + M2 + M3 + C1 + C2,`

with the same outcome as in the final natural effect model and with predictor variables entered in the following prespecified order:

1. exposure X: The first predictor is coded as exposure or treatment.
2. mediator(s) M: The second predictor is coded as mediator. In case of multiple mediators (`nMed > 1`), then predictors `2:(nMed + 1)` are coded as mediators.
3. baseline covariates C: All remaining predictor variables are automatically coded as baseline covariates.

If multiple mediators are specified (`nMed > 1`), the natural indirect effect parameter in the natural effect model captures the joint mediated effect. That is, the effect of the exposure on the outcome via these mediators considered jointly. The remaining effect of the exposure on the outcome (not mediated through the specified mediators) is then captured by the natural indirect effect parameter.

The type of imputation model can be defined by specifying an appropriate model-fitting function via the `FUN` argument (its default is [glm](#)). This method can only be used with model-fitting functions that require a `formula` argument (so not when using e.g. [SuperLearner](#)).

In contrast to imputation models with categorical exposures, additional arguments need to be specified if the exposure is continuous. All of these additional arguments are related to the sampling procedure for the exposure.

Whereas the number of replications `nRep` for categorical variables equals the number of levels for the exposure coded as a factor (i.e. the number of hypothetical exposure values), the number of desired replications needs to be specified explicitly for continuous exposures. Its default is 5.

If `xFit` is left unspecified, the hypothetical exposure levels are automatically sampled from a linear model for the exposure, conditional on a linear combination of all covariates. If one wishes to use another model for the exposure, this default model specification can be overruled by referring to a fitted model object in the `xFit` argument. Misspecification of this sampling model does not induce bias in the estimated coefficients and standard errors of the natural effect model.

The xSampling argument allows to specify how the hypothetical exposure levels should be sampled from the conditional exposure distribution (which is either entered explicitly using the xFit argument or fitted automatically as described in the previous paragraph). The "random" option randomly samples nRep draws from the exposure distribution, whereas the "quantiles" option (default) samples nRep quantiles at equal-sized probability intervals. Only the latter hence yields fixed exposure levels given nRep and xFit.

In order to guarantee that the entire support of the distribution is being sampled (which might be a concern if nRep is chosen to be small), the default lower and upper sampled quantiles are the 5th and 95th percentiles. The intermittent quantiles correspond to equal-sized probability intervals. So, for instance, if nRep = 4, then the sampled quantiles will correspond to probabilities 0.05, 0.35, 0.65 and 0.95. These default 'outer' quantiles can be changed by specifying the percLim argument accordingly. By specifying percLim = NULL, the standard quantiles will be sampled (e.g., 0.2, 0.4, 0.6 and 0.8 if nRep = 4).

Value

A data frame of class c("data.frame", "expData", "impData"). See expData for its structure.

See Also

neImpute, neImpute.default, neModel, expData

Examples

```
data(UPBdata)

## example using glm imputation model with binary exposure
impData <- neImpute(UPB ~ attbin + negaff + gender + educ + age,
                    family = binomial, data = UPBdata)
head(impData)

## example using glm imputation model with continuous exposure
impData <- neImpute(UPB ~ att + negaff + gender + educ + age,
                    family = binomial, data = UPBdata, nRep = 2)
head(impData)

## example using vglm (yielding identical results as with glm)
library(VGAM)
impData2 <- neImpute(UPB ~ att + negaff + gender + educ + age,
                     family = binomialff, data = UPBdata,
                     nRep = 2, FUN = vglm)
head(impData2)
```

---

neLht | *Linear hypotheses for natural effect models*

Description

neLht allows to calculate linear combinations of natural effect model parameter estimates.
neEffdecomp automatically extracts relevant causal parameter estimates from a natural effect model.

Usage

```
neEffdecomp(model, xRef, covLev, ...)

## S3 method for class 'neModel'
neEffdecomp(model, xRef, covLev, ...)

neLht(model, ...)

## S3 method for class 'neModel'
neLht(model, ...)
```

Arguments

model	a fitted natural effect model object.
xRef	a vector including reference levels for the exposure, $x*$ and x, at which natural effect components need to be evaluated (see details).
covLev	a vector including covariate levels at which natural effect components need to be evaluated (see details).
...	additional arguments (passed to glht).

Details

neLht is a wrapper of glht and offers the same functionality (see 'Details' section of glht for details on argument specification). It returns objects that inherit from the class "neLht" in order to make output of their corresponding methods (see neLht-methods) more compatible for natural effect models containing bootstrap variance-covariance matrices and standard errors.

neEffdecomp is a convenience function that automatically extracts causal parameter estimates from a natural effect model and derives natural effect components. That is, natural direct, natural indirect and total causal effect estimates are returned if no exposure-mediator interaction is modelled (i.e. two-way decomposition). If mediated interaction is allowed for in the natural effect model, there are two ways of decomposing the total effect into (natural) direct and indirect effects components: either as the sum of the pure direct and the total indirect effect or as the sum of the pure indirect and the total direct effect (i.e. three-way decomposition). In total, five causal effect estimates are returned in this case.

For continuous exposures, default exposure levels at which natural effect components are evaluated are $x* = 0$ and $x = 1$. For multicategorical exposures, default levels are the reference level of the factor that encodes the exposure variable and the level corresponding to its first dummy variable for $x*$ and x, respectively. If one wishes to evaluate natural effect components at different reference levels (e.g. if the natural effect model includes mediated interaction, quadratic or polynomial terms for the exposure; see examples), these can be specified as a vector of the form c(x*,x) via the xRef argument.

For natural effect models encoding effect modification by baseline covariates (i.e. moderated mediation), covariate levels at which natural effect components are evaluated can also be specified. By default, these levels are set to 0 for continuous covariates and to the reference level for categorical covariates coded as factors. These covariate levels can be changed via the covLev argument, which requires a vector including valid covariate levels for each of the covariates that are specified in the natural effect model (also those for which no effect modification is postulated). If corresponding covariate levels are specified in the same order as covariates are specified in the natural effect model, the names of the covariates do not need to be included in the vector. If covariate names are specified in the vector, the order of covariate (levels) is of no importance (see example).

Value

An object of class c("neLhtBoot", "neLht", "glht") (see glht). neEffdecomp returns an
object that additionally inherits from class "neEffdecomp".

See neLht-methods for methods for neLht objects (and glht-methods for additional methods for
glht objects).

Note

neEffdecomp is internally called by plot.neModel to create confidence interval plots for neModel
objects.

See Also

confint, plot.neLht, neLht-methods, glht, glht-methods, neModel, plot.neModel, summary

Examples

```
data(UPBdata)

impData <- neImpute(UPB ~ att * negaff + gender + educ + age,
                    family = binomial, data = UPBdata)
neMod <- neModel(UPB ~ att0 * att1 + gender + educ + age,
                 family = binomial, expData = impData)

lht <- neLht(neMod, linfct = c("att0 = 0", "att0 + att0:att1 = 0",
                               "att1 = 0", "att1 + att0:att1 = 0",
                               "att0 + att1 + att0:att1 = 0"))
summary(lht)

## or obtain directly via neEffdecomp
eff <- neEffdecomp(neMod)
summary(eff)

## changing reference levels for multicategorical exposures
UPBdata$attcat <- factor(cut(UPBdata$att, 3), labels = c("L", "M", "H"))
impData <- neImpute(UPB ~ attcat * negaff + gender + educ + age,
                    family = binomial, data = UPBdata)
neMod <- neModel(UPB ~ attcat0 * attcat1 + gender + educ + age,
                 family = binomial, expData = impData)
neEffdecomp(neMod)
neEffdecomp(neMod, xRef = c("L", "H"))
neEffdecomp(neMod, xRef = c("M", "H"))


## changing reference levels for continuous exposures
impData <- neImpute(UPB ~ poly(att, 2, raw = TRUE) * negaff + gender + educ + age,
                    family = binomial, data = UPBdata)
neMod <- neModel(UPB ~ poly(att0, 2, raw = TRUE) * poly(att1, 2, raw = TRUE) + gender + educ + age,
                 family = binomial, expData = impData)
neEffdecomp(neMod)
neEffdecomp(neMod, xRef = c(2, 1))

## changing covariate levels when allowing for modification
## of the indirect effect by baseline covariates
impData <- neImpute(UPB ~ (att + negaff + gender + educ + age)^2,
```

```
                            family = binomial, data = UPBdata)
neMod <- neModel(UPB ~ att0 * att1 + gender + educ + age + att1:gender + att1:educ + att1:age,
                    family = binomial, expData = impData)
neEffdecomp(neMod)
neEffdecomp(neMod, covLev = c("F", "L", 0)) # default covariate levels
neEffdecomp(neMod, covLev = c("F", "M", mean(UPBdata$age)))
neEffdecomp(neMod, covLev = c(age = mean(UPBdata$age), educ = "M", gender = "F"))
# yields identical results
```

---

neLht-methods   *Methods for linear hypotheses in natural effect models*

Description

Obtain confidence intervals and statistical tests for linear hypotheses in natural effect models.

Usage

```
## S3 method for class 'neLhtBoot'
confint(object, parm, level = 0.95, type = "norm", ...)

## S3 method for class 'neLht'
confint(object, parm, level = 0.95,
  calpha = univariate_calpha(), ...)

## S3 method for class 'neLht'
summary(object, test = univariate(), ...)
```

Arguments

object	an object of class neLht.
parm	a specification of which parameters are to be given confidence intervals, either a vector of numbers or a vector of names. If missing, all parameters are considered.
level	the confidence level required.
type	the type of bootstrap intervals required. The default ″norm″ returns normal approximation bootstrap confidence intervals. Currently, only ″norm″, ″basic″ and ″perc″ are supported (see [boot.ci]).
...	additional arguments.
calpha	a function computing the critical value. The default univariate_calpha() returns unadjusted confidence intervals, whereas adjusted_calpha() returns adjusted confidence intervals.
test	a function for computing p-values. The default univariate() does not apply a multiple testing correction. The function adjusted() allows to correct for multiple testing (see [summary.glht] and [adjusted]) and Chisquare() allows to test global linear hypotheses.

Details

confint yields bootstrap confidence intervals. These confidence intervals are internally called via the boot.ci function from the **boot** package (and not via the corresponding confint.glht function from the **multcomp** package!). The default confidence level specified in level (which corresponds to the conf argument in boot.ci) is 0.95 and the default type of bootstrap confidence interval, "norm", is based on the normal approximation (for more details see boot.ci).

A summary table with large sample tests, similar to that for glht, can be obtained using summary.

In contrast to summary.glht, which by default returns *p*-values that are adjusted for multiple testing, the summary function returns unadjusted *p*-values. Adjusted *p*-values can also be obtained by specifying the test argument (see adjusted for more details).

Global Wald tests considering all linear hypotheses simultaneously (i.e. testing the global null hypothesis) can be requested by specifying test = Chisqtest().

See glht-methods for additional methods for glht objects.

Note

Z-values in the summary table are simply calculated by dividing the parameter estimate by its corresponding bootstrap standard error. Corresponding *p*-values in the summary table are only indicative, since the null distribution for each statistic is assumed to be approximately standard normal. Therefore, where possible, it is recommended to focus mainly on bootstrap confidence intervals for inference, rather than the provided *p*-values.

See Also

neLht, plot.neLht, glht, glht-methods

Examples

```
data(UPBdata)

impData <- neImpute(UPB ~ att * negaff + gender + educ + age,
                    family = binomial, data = UPBdata)
neMod <- neModel(UPB ~ att0 * att1 + gender + educ + age,
                 family = binomial, expData = impData)

lht <- neLht(neMod, linfct = c("att0 = 0", "att0 + att0:att1 = 0",
                               "att1 = 0", "att1 + att0:att1 = 0",
                               "att0 + att1 + att0:att1 = 0"))

## obtain bootstrap confidence intervals
confint(lht)
confint(lht, parm = c("att0", "att0 + att0:att1"))
confint(lht, parm = 1:2)
confint(lht, type = "perc", level = 0.90)

## summary table
summary(lht)

## summary table with omnibus Chisquare test
summary(lht, test = Chisqtest())
```

---

neModel   *Fit a natural effect model*

Description

neModel is used to fit a natural effect model on the expanded dataset.

Usage

```
neModel(formula, family = gaussian, expData, xFit, se = c("bootstrap",
  "robust"), nBoot = 1000, parallel = c("no", "multicore", "snow"),
  ncpus = getOption("boot.ncpus", 1L), progress = TRUE, ...)
```

Arguments

formula	a [formula](#) object providing a symbolic description of the natural effect model.
family	a description of the error distribution and link function to be used in the model. This can be a character string naming a family function, a family function or the result of a call to a family function. (See [family](#) for details of family functions.)
expData	the expanded dataset (of class ["expData"](#)).
xFit	fitted model object representing a model for the exposure (used for inverse treatment (exposure) probability weighting).
se	character string indicating the type of standard errors to be calculated. The default type is based on the bootstrap (see details).
nBoot	number of bootstrap replicates (see R argument of [boot](#)).
parallel	The type of parallel operation to be used (if any). If missing, the default is taken from the option "boot.parallel" (and if that is not set, "no").
ncpus	integer: number of processes to be used in parallel operation: typically one would chose this to the number of available CPUs (see details).
progress	logical value indicating whether or not a progress bar should be displayed. Progress bars are automatically disabled for multicore processing.
...	additional arguments (passed to [glm](#)).

Details

This function is a wrapper for [glm](#), providing unbiased bootstrap standard errors for the parameter estimates.

The formula argument requires to be specified in function of the variables from the expanded dataset (specified in expData) whose corresponding parameters index the direct and indirect effect. Stratum-specific natural effects can be estimated by additionally modeling the relation between the outcome and baseline covariates. If the set of baseline covariates adjusted for in the formula argument is not sufficient to control for confounding (e.g. when fitting a population-average natural effect model), an adequate model for the exposure (conditioning on a sufficient set of baseline covariates) should be specified in the xFit argument. In this case, such a model for the exposure distribution is needed to weight by the reciprocal of the probability (density) of the exposure (i.e. inverse probability weighting) in order to adjust for confounding. Just as for ratio-of-mediator probability weighting (see paragraph below), this kind of weighting is done internally.

In contrast to [glm](), the expData argument (rather than data argument) requires specification of a data frame that inherits from the class ["expData"](), which contains additional information about e.g. the fitted working model, the variable types or terms of this working model and possibly ratio-of-mediator probability weights. The latter are automatically extracted from the [expData]() object and weighting is done internally.

As the default [glm]() standard errors fail to reflect the uncertainty inherent to the working model(s) (i.e. either a model for the mediator or an imputation model for the outcome and possibly a model for the exposure), bootstrap standard errors (using the [boot]() function from the **boot** package) or robust standard errors are calculated. The default type of standard errors is bootstrap standard errors. Robust standard errors (based on the sandwich estimator) can be requested to be calculated instead by specifying se = "robust".

The bootstrap procedure entails refitting these working models on each bootstrap sample, reconstructing the expanded dataset and subsequently refitting the specified natural effect model on this dataset. In order to obtain stable standard errors, the number of bootstrap samples (specified via the nBoot argument) should be chosen relatively high (default is 1000).

To speed up the bootstrap procedure, parallel processing can be used by specifying the desired type of parallel operation via the parallel argument (for more details, see [boot]()). The number of parallel processes (ncpus) is suggested to be specified explicitly (its default is 1, unless the global option options("boot.cpus") is specified). The function [detectCores]() from the **parallel** package can be helpful at determining the number of available cores (although this may not always correspond to the number of *allowed* cores).

Value

An object of class ["neModel"]() consisting of a list of 2 objects:

neModelFit	the fitted natural model object (of class ["glm"]()) with downwardly biased standard errors
bootRes, vcov	the bootstrap results (of class ["boot"](); if se = "bootstrap") or the sandwich estimator variance-covariance matrix (if se = "robust")

See [neModel-methods]() for methods for neModel objects.

Note

It is important to note that the original mediator(s) should not be specified in the formula argument, as the natural indirect effect in natural effect models should be captured solely by parameter(s) corresponding to the auxiliary hypothetical variable $x*$ in the expanded dataset (see [expData]()).

References

Lange, T., Vansteelandt, S., & Bekaert, M. (2012). A Simple Unified Approach for Estimating Natural Direct and Indirect Effects. *American Journal of Epidemiology*, **176**(3), 190-195.

Vansteelandt, S., Bekaert, M., & Lange, T. (2012). Imputation Strategies for the Estimation of Natural Direct and Indirect Effects. *Epidemiologic Methods*, **1**(1), Article 7.

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See Also

[neModel-methods](), [plot.neModel](), [neImpute](), [neWeight](), [neLht](), [neEffdecomp]()

Examples

```
data(UPBdata)

###############################
## weighting-based approach ##
###############################
weightData <- neWeight(negaff ~ att + gender + educ + age,
                          data = UPBdata)

## stratum-specific natural effects
# bootstrap SE
weightFit1b <- neModel(UPB ~ att0 * att1 + gender + educ + age,
                          family = binomial, expData = weightData)
summary(weightFit1b)
# robust SE
weightFit1r <- neModel(UPB ~ att0 * att1 + gender + educ + age,
                          family = binomial, expData = weightData, se = "robust")
summary(weightFit1r)

## population-average natural effects
expFit <- glm(att ~ gender + educ + age, data = UPBdata)
# bootstrap SE
weightFit2b <- neModel(UPB ~ att0 * att1, family = binomial,
                          expData = weightData, xFit = expFit)
summary(weightFit2b)
# robust SE
weightFit2r <- neModel(UPB ~ att0 * att1, family = binomial,
                          expData = weightData, xFit = expFit, se = "robust")
summary(weightFit2r)

###############################
## imputation-based approach ##
###############################
impData <- neImpute(UPB ~ att * negaff + gender + educ + age,
                      family = binomial, data = UPBdata)

## stratum-specific natural effects
# bootstrap SE
impFit1b <- neModel(UPB ~ att0 * att1 + gender + educ + age,
                      family = binomial, expData = impData)
summary(impFit1b)
# robust SE
impFit1r <- neModel(UPB ~ att0 * att1 + gender + educ + age,
                      family = binomial, expData = impData, se = "robust")
summary(impFit1r)

## population-average natural effects
# bootstrap SE
impFit2b <- neModel(UPB ~ att0 * att1, family = binomial,
                      expData = impData, xFit = expFit)
summary(impFit2b)
# robust SE
impFit2r <- neModel(UPB ~ att0 * att1, family = binomial,
                      expData = impData, xFit = expFit, se = "robust")
summary(impFit2r)
```

---

neModel-methods   *Methods for natural effect models*

Description

Extractor functions, confidence intervals and statistical tests for natural effect models.

Usage

```
## S3 method for class 'neModel'
coef(object, ...)

## S3 method for class 'neModelBoot'
confint(object, parm, level = 0.95, type = "norm",
  ...)

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

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

## S3 method for class 'neModel'
vcov(object, ...)

## S3 method for class 'neModel'
weights(object, ...)
```

Arguments

object	a fitted natural effect model object.
...	additional arguments (see `boot.ci` for confint or `summary.glm` for summary).
parm	a specification of which parameters are to be given confidence intervals, either a vector of numbers or a vector of names. If missing, all parameters are considered.
level	the confidence level required.
type	the type of bootstrap intervals required. The default "norm" returns normal approximation bootstrap confidence intervals. Currently, only "norm", "basic" and "perc" are supported (see `boot.ci`).

Details

`confint` yields bootstrap confidence intervals. These confidence intervals are internally called via the `boot.ci` function from the **boot** package. The default confidence level specified in `level` (which corresponds to the `conf` argument in `boot.ci`) is 0.95 and the default type of bootstrap confidence interval, "norm", is based on the normal approximation (for more details see `boot.ci`).

A summary table with large sample tests, similar to that for `glm` output, can be obtained using summary.

vcov returns the variance covariance matrix calculated from the bootstrap samples stored in object$bootRes (see neModel).

weights returns a vector containing the regression weights used to fit the natural effect model. These weights can be based on

1. ratio-of-mediator probability (density) weights (only if the weighting-based approach is used)
2. inverse probability of treatment (exposure) weights (only if xFit was specified in neModel)

Note

Z-values in the summary table are simply calculated by dividing the parameter estimate by its corresponding bootstrap standard error. Corresponding *p*-values in the summary table are only indicative, since the null distribution for each statistic is assumed to be approximately standard normal. Therefore, where possible, it is recommended to focus mainly on bootstrap confidence intervals for inference, rather than the provided *p*-values.

See Also

neModel, plot.neModel, weights

Examples

```
data(UPBdata)

weightData <- neWeight(negaff ~ att + educ + gender + age,
                       data = UPBdata)
neMod <- neModel(UPB ~ att0 * att1 + educ + gender + age,
                 family = binomial, expData = weightData)

## extract coefficients
coef(neMod)

## extract variance-covariance matrix
vcov(neMod)

## extract regression weights
w <- weights(neMod)
head(w)

## obtain bootstrap confidence intervals
confint(neMod)
confint(neMod, parm = c("att0"))
confint(neMod, type = "perc", level = 0.90)

## summary table
summary(neMod)
```

neWeight	*Expand the dataset and calculate ratio-of-mediator probability weights*

Description

This function both expands the data along hypothetical exposure values and calculates ratio-of-mediator probability weights.

Usage

```
neWeight(object, ...)
```

Arguments

object   an object used to select a method.

...   additional arguments.

Details

Generic function that both expands the data along hypothetical exposure values and calculates ratio-of-mediator probability weights

$$\frac{\hat{P}(M_i|X_i = x^*, C_i)}{\hat{P}(M_i|X_i = x, C_i)}$$

for each observation unit i in this expanded dataset in a single run. These weights are ratios of probabilities or probability densities from the mediator model distribution, which can be specified either externally as a fitted model object (neWeight.default) or internally (neWeight.formula).

Value

A data frame of class c("data.frame", "expData", "weightData"). See expData for its structure.

References

Lange, T., Vansteelandt, S., & Bekaert, M. (2012). A Simple Unified Approach for Estimating Natural Direct and Indirect Effects. *American Journal of Epidemiology*, **176**(3), 190-195.

See Also

neWeight.default, neWeight.formula, expData

---

neWeight.default   *Expand the dataset and calculate ratio-of-mediator probability weights*

Description

This function both expands the data along hypothetical exposure values and calculates ratio-of-mediator probability weights.

Usage

```
## Default S3 method:
neWeight(object, formula, data, nRep = 5,
  xSampling = c("quantiles", "random"), xFit, percLim = c(0.05, 0.95), ...)
```

Arguments

object	fitted model object representing the mediator model.
formula	a [formula](#) object providing a symbolic description of the mediator model. Redundant if already specified in call for fitted model specified in object (see details).
data	data, as matrix or data frame, containing the exposure (and other relevant) variables. Redundant if already specified in call for fitted model specified in object (see details).
nRep	number of replications or hypothetical values of the exposure to sample for each observation unit.
xSampling	character string indicating how to sample from the conditional exposure distribution. Possible values are "quantiles" or "random" (see details).
xFit	an optional fitted object (preferably glm) for the conditional exposure distribution (see details).
percLim	a numerical vector of the form c(lower, upper) indicating the extreme percentiles to sample when using "quantiles" as sampling method to sample from the conditional exposure distribution (see details).
...	additional arguments.

Details

The calculated weights are ratios of fitted probabilities or probability densities from the distribution of the mediator model. This model needs to be specified as a fitted object in the object argument.

If the model-fitting function used to fit the mediator model does not require specification of a formula or data argument, these need to be specified explicitly in order to enable neWeight.default to extract pointers to variable types relevant for mediation analysis.

Whether a [formula](#) is specified externally (in the call for the fitted mediator model object which is specified in object) or internally (via the formula argument), it always needs to be of the form M ~ X + C1 + C2, with predictor variables entered in the following prespecified order:

1. exposure X: The first predictor is coded as exposure or treatment.

2. baseline covariates C: All remaining predictor variables are automatically coded as baseline covariates.

In contrast to imputation models with categorical exposures, additional arguments need to be specified if the exposure is continuous. All of these additional arguments are related to the sampling procedure for the exposure.

Whereas the number of replications nRep for categorical variables equals the number of levels for the exposure coded as a factor (i.e. the number of hypothetical exposure values), the number of desired replications needs to be specified explicitly for continuous exposures. Its default is 5.

If xFit is left unspecified, the hypothetical exposure levels are automatically sampled from a linear model for the exposure, conditional on a linear combination of all covariates. If one wishes to use another model for the exposure, this default model specification can be overruled by referring to a

fitted model object in the `xFit` argument. Misspecification of this sampling model does not induce bias in the estimated coefficients and standard errors of the natural effect model.

The `xSampling` argument allows to specify how the hypothetical exposure levels should be sampled from the conditional exposure distribution (which is either entered explicitly using the `xFit` argument or fitted automatically as described in the previous paragraph). The `"random"` option randomly samples nRep draws from the exposure distribution, whereas the `"quantiles"` option (default) samples nRep quantiles at equal-sized probability intervals. Only the latter hence yields fixed exposure levels given nRep and `xFit`.

In order to guarantee that the entire support of the distribution is being sampled (which might be a concern if nRep is chosen to be small), the default lower and upper sampled quantiles are the 5th and 95th percentiles. The intermittent quantiles correspond to equal-sized probability intervals. So, for instance, if nRep = 4, then the sampled quantiles will correspond to probabilities 0.05, 0.35, 0.65 and 0.95. These default 'outer' quantiles can be changed by specifying the percLim argument accordingly. By specifying percLim = NULL, the standard quantiles will be sampled (e.g., 0.2, 0.4, 0.6 and 0.8 if nRep = 4).

Value

A data frame of class c("data.frame", "expData", "weightData"). See [expData](#) for its structure.

See Also

[neWeight](#), [neWeight.formula](#), [expData](#)

Examples

```
data(UPBdata)

## example using glm
fit.glm <- glm(negaff ~ att + gender + educ + age, data = UPBdata)
weightData <- neWeight(fit.glm, nRep = 2)

## example using vglm (yielding identical results as with glm)
library(VGAM)
fit.vglm <- vglm(negaff ~ att + gender + educ + age,
                 family = gaussianff, data = UPBdata)
weightData2 <- neWeight(fit.vglm, nRep = 2)
```

---

neWeight.formula   *Expand the dataset and calculate ratio-of-mediator probability weights*

Description

This function both expands the data along hypothetical exposure values and calculates ratio-of-mediator probability weights.

Usage

```
## S3 method for class 'formula'
neWeight(object, family, data, FUN = glm, nRep = 5,
  xSampling = c("quantiles", "random"), xFit, percLim = c(0.05, 0.95), ...)
```

Arguments

object	a [formula](#) object providing a symbolic description of the mediator model (see details).
family	a description of the error distribution and link function to be used in the model. Consult the help files of the model-fitting function specified in FUN for more details on appropriate argument specification.
data	data, as matrix or data frame, containing the exposure (and other relevant) variables. Redundant if already specified in call for fitted model specified in object (see details).
FUN	function used to fit model specified in formula.
nRep	number of replications or hypothetical values of the exposure to sample for each observation unit.
xSampling	character string indicating how to sample from the conditional exposure distribution. Possible values are "quantiles" or "random" (see details).
xFit	an optional fitted object (preferably glm) for the conditional exposure distribution (see details).
percLim	a numerical vector of the form c(lower, upper) indicating the extreme percentiles to sample when using "quantiles" as sampling method to sample from the conditional exposure distribution (see details).
...	additional arguments (passed to FUN).

Details

The calculated weights are ratios of fitted probabilities or probability densities from the distribution of the mediator model. This model is fitted internally by extracting information from the arguments object, family, data, FUN and ....

For mediation model specification via the object argument, use a [formula](#) of the form M ~ X + C1 + C2, with predictor variables entered in the following prespecified order:

1. exposure X: The first predictor is coded as exposure or treatment.
2. baseline covariates C: All remaining predictor variables are automatically coded as baseline covariates.

The type of mediator model can be defined by specifying an appropriate model-fitting function via the FUN argument (its default is [glm](#)). This method can only be used with model-fitting functions that require a formula argument.

In contrast to imputation models with categorical exposures, additional arguments need to be specified if the exposure is continuous. All of these additional arguments are related to the sampling procedure for the exposure.

Whereas the number of replications nRep for categorical variables equals the number of levels for the exposure coded as a factor (i.e. the number of hypothetical exposure values), the number of desired replications needs to be specified explicitly for continuous exposures. Its default is 5.

If xFit is left unspecified, the hypothetical exposure levels are automatically sampled from a linear model for the exposure, conditional on a linear combination of all covariates. If one wishes to use another model for the exposure, this default model specification can be overruled by referring to a fitted model object in the xFit argument. Misspecification of this sampling model does not induce bias in the estimated coefficients and standard errors of the natural effect model.

The xSampling argument allows to specify how the hypothetical exposure levels should be sampled from the conditional exposure distribution (which is either entered explicitly using the xFit argument or fitted automatically as described in the previous paragraph). The "random" option randomly samples nRep draws from the exposure distribution, whereas the "quantiles" option (default) samples nRep quantiles at equal-sized probability intervals. Only the latter hence yields fixed exposure levels given nRep and xFit.

In order to guarantee that the entire support of the distribution is being sampled (which might be a concern if nRep is chosen to be small), the default lower and upper sampled quantiles are the 5th and 95th percentiles. The intermittent quantiles correspond to equal-sized probability intervals. So, for instance, if nRep = 4, then the sampled quantiles will correspond to probabilities 0.05, 0.35, 0.65 and 0.95. These default 'outer' quantiles can be changed by specifying the percLim argument accordingly. By specifying percLim = NULL, the standard quantiles will be sampled (e.g., 0.2, 0.4, 0.6 and 0.8 if nRep = 4).

Value

A data frame of class c("data.frame", "expData", "weightData")). See expData for its structure.

See Also

neWeight.default, expData

Examples

```
data(UPBdata)

## example using glm
weightData <- neWeight(negaff ~ att + gender + educ + age,
                       data = UPBdata, nRep = 2)

## example using vglm (yielding identical results as with glm)
library(VGAM)
weightData2 <- neWeight(negaff ~ att + gender + educ + age,
                        family = gaussianff, data = UPBdata, nRep = 2, FUN = vglm)
```

---

plot.neLht   *Confidence interval plots for linear hypotheses in natural effect models*

Description

Confidence interval plots for linear hypotheses in natural effect models.

Usage

```
## S3 method for class 'neEffdecomp'
plot(x, level = 0.95, transf = identity, ylabels,
  yticks.at, ...)

## S3 method for class 'neLht'
plot(x, level = 0.95, transf = identity, ylabels, yticks.at,
  ...)

## S3 method for class 'neLhtBoot'
plot(x, level = 0.95, ci.type = "norm",
  transf = identity, ylabels, yticks.at, ...)
```

Arguments

x	an object of class neLht.
level	the confidence level required.
transf	transformation function to be applied internally on the (linear hypothesis) estimates and their confidence intervals (e.g. exp for logit or Poisson regression). The default is identity (i.e. no transformation).
ylabels	character vector containing the labels for the (linear hypothesis) estimates to be plotted on the y-axis.
yticks.at	numeric vector containing the y-coordinates (from 0 to 1) to draw the tick marks for the different estimates and their corresponding confidence intervals.
...	additional arguments.
ci.type	the type of bootstrap intervals required. The default "norm" returns normal approximation bootstrap confidence intervals. Currently, only "norm", "basic" and "perc" are supported (see boot.ci).

Details

This function is an adapted version of plot.glht from the **multcomp** package and yields confidence interval plots for each of the linear hypothesis parameters.

See Also

neModel, neLht, neEffdecomp

Examples

```
data(UPBdata)

impData <- neImpute(UPB ~ att * negaff + gender + educ + age,
                    family = binomial, data = UPBdata)
neMod <- neModel(UPB ~ att0 * att1 + gender + educ + age,
                 family = binomial, expData = impData)

lht <- neLht(neMod, linfct = c("att0 = 0", "att0 + att0:att1 = 0",
                               "att1 = 0", "att1 + att0:att1 = 0",
                               "att0 + att1 + att0:att1 = 0"))

## all pairs return identical output
```

```
plot(confint(lht), transf = exp)
plot(lht, transf = exp)

plot(neEffdecomp(neMod), transf = exp)
plot(neMod, transf = exp)
```

---

plot.neModel   *Confidence interval plots for natural effect estimates*

Description

Obtain effect decomposition confidence interval plots for natural effect models.

Usage

```
## S3 method for class 'neModel'
plot(x, level = 0.95, ci.type = "norm",
  transf = identity, ylabels, yticks.at, ...)
```

Arguments

x	a fitted natural effect model object.
level	the confidence level required.
ci.type	the type of bootstrap intervals required. The default "norm" returns normal approximation bootstrap confidence intervals. Currently, only "norm", "basic" and "perc" are supported (see `boot.ci`).
transf	transformation function to be applied internally on the (linear hypothesis) estimates and their confidence intervals (e.g. exp for logit or Poisson regression). The default is identity (i.e. no transformation).
ylabels	character vector containing the labels for the (linear hypothesis) estimates to be plotted on the y-axis.
yticks.at	numeric vector containing the y-coordinates (from 0 to 1) to draw the tick marks for the different estimates and their corresponding confidence intervals.
...	additional arguments.

Details

This function yields confidence interval plots for the natural effect parameters of interest. These causal parameter estimates are first internally extracted from the neModel object by applying `neEffdecomp`.

Examples

```
data(UPBdata)

impData <- neImpute(UPB ~ att * negaff + educ + gender + age,
                    family = binomial, data = UPBdata)
neMod <- neModel(UPB ~ att0 * att1 + educ + gender + age,
                 family = binomial, expData = impData)
```

```
plot(neMod)
plot(neMod, transf = exp,
     ylabels = c("PDE", "TDE", "PIE", "TIE", "TE"))
```

UPBdata   *UPB data*

Description

Data from a survey study that was part of the Interdisciplinary Project for the Optimization of Separation trajectories (IPOS). This large-scale project involved the recruitment of individuals who divorced between March 2008 and March 2009 in four major courts in Flanders. It aimed to improve the quality of life in families during and after the divorce by translating research findings into practical guidelines for separation specialists and by promoting evidence-based policy. This dataset involves a subsample of 385 individuals, namely those who responded to a battery of questionnaires related to romantic relationship and breakup characteristics (De Smet, 2012).

Format

A data frame with 385 rows and 9 variables:

att self-reported anxious attachment level (standardized)

attbin binary version of self-reported anxious attachment level: 1 = higher than sample mean, 0 = lower than sample mean

negaff level of self-reported experienced negative affectivity (standardized)

negaffcat multicategorical version of level of self-reported experienced negative affectivity: L = low, M = intermediate, H = high

initiator initiator of the divorce

gender gender: F = female, M = male

educ education level: either H = high (at least a bachelor's degree), M = intermediate (having finished secondary school) or L = low (otherwise)

age age (in years)

UPB binary variable indicating whether the individual reported having displayed unwanted pursuit behavior(s) towards the ex-partner

Source

Ghent University and Catholic University of Louvain (2010). *Interdisciplinary Project for the Optimisation of Separation trajectories - divorce and separation in Flanders.* http://www.scheidingsonderzoek.ugent.be/index-eng.html

References

De Smet, O., Loeys, T., & Buysse, A. (2012). Post-Breakup Unwanted Pursuit: A Refined Analysis of the Role of Romantic Relationship Characteristics. *Journal of Family Violence*, **27**(5), 437-452.

Loeys, T., Moerkerke, B., De Smet, O., Buysse, A., Steen, J., & Vansteelandt, S. (2013). Flexible Mediation Analysis in the Presence of Nonlinear Relations: Beyond the Mediation Formula. *Multivariate Behavioral Research*, **48**(6), 871-894.

weights.expData	*Extract regression weights from the expanded dataset*

Description

This function extracts the regression weights (to be used in the natural effect model) for each observation of an expanded dataset.

Usage

```
## S3 method for class 'expData'
weights(object, ...)
```

Arguments

object	an expanded dataset (of class "expData").
...	additional arguments.

Value

a vector of length nrow(object), containing the regression weights for the expanded dataset specified in object.

See Also

coef, confint, expData, neWeight, summary, vcov, weights

Examples

```
data(UPBdata)

weightData <- neWeight(negaff ~ att + gender + educ + age,
                       data = UPBdata, nRep = 2)
head(weights(weightData))
```

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