Package 'tehtuner'

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Title Fit and Tune Models to Detect Treatment Effect Heterogeneity

Version 0.3.0

Description Implements methods to fit Virtual Twins models (Foster et al. (2011) <doi:10.1002/sim.4322>) for identifying subgroups with differential effects in the context of clinical trials while controlling the probability of falsely detecting a differential effect when the conditional average treatment effect is uniform across the study population using parameter selection methods proposed in Wolf et al. (2022) <doi:10.1177/17407745221095855>.

License GPL (>= 3)

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Suggests knitr, rmarkdown, spelling, testthat (>= 3.0.0)

Language en-US

URL https://github.com/jackmwolf/tehtuner

BugReports https://github.com/jackmwolf/tehtuner/issues

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Author Jack Wolf [aut, cre] (ORCID: <https://orcid.org/0000-0002-8919-8740>)

Maintainer Jack Wolf <jackwolf910@gmail.com>

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Contents

`get_mnpp` *Get the MNPP for the Step 2 model*

Description

Find the lowest penalty parameter so that the Step 2 model fit for the estimated CATE from Step 1 is constant for all subjects.

Usage

```
get_mnpp(z, data, step2, Trt, Y, threshold)
```

Arguments

z	a numeric vector of estimated CATEs from Step 1
data	a data frame containing a response, binary treatment indicators, and covariates.
step2	a character string specifying the Step 2 model. Supports "lasso", "rtree", "classtree", or "ctree".
Trt	a string specifying the name of the column of data contains the treatment indicators.
Y	a string specifying the name of the column of data contains the response.
threshold	for "step2 = 'classtree'" only. The value against which to test if the estimated individual treatment effect from Step 1 is higher (TRUE) or lower (FALSE).

---

get_mnpp.classtree *Get the MNPP for a Classification Tree*

Description

Finds the lowest complexity parameter for a null regression tree fit

Usage

```
get_mnpp.classtree(z, data, Trt, Y, threshold)
```

Arguments

z	a numeric vector of estimated CATEs from Step 1
data	a data frame containing a response, binary treatment indicators, and covariates.
Trt	a string specifying the name of the column of data contains the treatment indicators.
Y	a string specifying the name of the column of data contains the response.
threshold	for "step2 = 'classtree'" only. The value against which to test if the estimated individual treatment effect from Step 1 is higher (TRUE) or lower (FALSE).

Value

the MNPP

get_mnpp.ctree *Get the MNPP for a Conditional Inference Tree*

Description

Finds the lowest test statistic for a null conditional inference tree

Usage

```
get_mnpp.ctree(z, data, Trt, Y)
```

Arguments

z	a numeric vector of estimated CATEs from Step 1
data	a data frame containing a response, binary treatment indicators, and covariates.
Trt	a string specifying the name of the column of data contains the treatment indicators.
Y	a string specifying the name of the column of data contains the response.

Value

the MNPP

get_mnpp.lasso *Get the MNPP for a Model fit via Lasso*

Description

Finds the lowest penalty parameter for a null lasso model.

Usage

```
get_mnpp.lasso(z, data, Trt, Y)
```

Arguments

z	a numeric vector of estimated CATEs from Step 1
data	a data frame containing a response, binary treatment indicators, and covariates.
Trt	a string specifying the name of the column of data contains the treatment indicators.
Y	a string specifying the name of the column of data contains the response.

get_mnpp.rtree *Get the MNPP for a Regression Tree*

Description

Finds the lowest complexity parameter for a null regression tree fit

Usage

```
get_mnpp.rtree(z, data, Trt, Y)
```

Arguments

z	a numeric vector of estimated CATEs from Step 1
data	a data frame containing a response, binary treatment indicators, and covariates.
Trt	a string specifying the name of the column of data contains the treatment indicators.
Y	a string specifying the name of the column of data contains the response.

Value

the MNPP

get_theta_null *Permute a dataset under the null hypothesis and get the MNPP*

Description

Permute a dataset under the null hypothesis and get the MNPP

Usage

```
get_theta_null(data, Trt, Y, zbar, step1, step2, threshold, ...)
```

Arguments

data	a data frame containing a response, binary treatment indicators, and covariates.
Trt	a string specifying the name of the column of data contains the treatment indicators.
Y	a string specifying the name of the column of data contains the response.
zbar	the estimated marginal treatment effect
step1	character strings specifying the Step 1 model. Supports either "lasso", "mars", "randomforest", or "superlearner".

step2	a character string specifying the Step 2 model. Supports "lasso", "rtree", "classtree", or "ctree".
threshold	for "step2 = 'classtree'" only. The value against which to test if the estimated individual treatment effect from Step 1 is higher (TRUE) or lower (FALSE).
...	additional arguments to the Step 1 model call.

Value

the MNPP for the permuted data set

---

get_vt1 *Get the appropriate Step 1 estimation function associated with a method*

Description

Get the appropriate Step 1 estimation function associated with a method

Usage

```
get_vt1(step1)
```

Arguments

step1	character strings specifying the Step 1 model. Supports either "lasso", "mars", "randomforest", or "superlearner".

Value

a function that estimates the CATE through Step 1 of Virtual Twins

---

get_vt2 *Get the appropriate Step 2 estimation function associated with a method*

Description

Get the appropriate Step 2 estimation function associated with a method

Usage

```
get_vt2(step2)
```

Arguments

step2	a character string specifying the Step 2 model. Supports "lasso", "rtree", "classtree", or "ctree".

Value

a function that fits a model for the CATE through Step 2 of Virtual Twins

---

permute *Generate a dataset with permuted treatment indicators*

Description

Sets the marginal treatment effect to zero and then permute all treatment indicators.

Usage

```
permute(data, Trt, Y, zbar)
```

Arguments

data	a data frame containing a response, binary treatment indicators, and covariates.
Trt	a string specifying the name of the column of data contains the treatment indicators.
Y	a string specifying the name of the column of data contains the response.
zbar	the estimated marginal treatment effect

Value

a permuted dataset of the same size as data

---

print.tunevt *Print an object of class tunevt*

Description

Prints a Virtual Twins model for the conditional average treatment effect with a tuned Step 2 model.

Usage

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

Arguments

x	an object of class tunevt
digits	the number of significant digits to use when printing.
...	further arguments passed to or from other methods.

Value

An object of class "tunevt".

An object of class "tunevt" is a list containing at least the following components:

call	the matched call
vtmod	the model estimated by the given step2 procedure fit with the permuted tuning parameter for the estimated CATEs from the step1 model. See vt2_lasso, vt2_rtree, or vt2_ctree for specifics.
mnpp	the MNPP for the estimated CATEs from Step 1.
theta_null	a vector of the MNPPs from each permutation under the null hypothesis.
pvalue	the probability of observing a MNPP as or more extreme as the observed MNPP under the null hypothesis of no effect heterogeneity.
z	if keepz = TRUE, the estimated CATEs from the step1 model.

---

tehtuner_example *Simulated example data*

Description

Simulated data from a clinical trial with heterogeneous treatment effects where the CATE was a function of V1 and V9.

Usage

```
tehtuner_example
```

Format

A data frame with 1000 rows and 12 columns:

Trt Binary treatment indicator

Y Continuous response

V1,V2,V3,V4,V5,V6,V7,V8 Continuous covariates

V9,V10 Binary covariates

test_null_theta_ctree *Test if a Value Gives a Null Conditional Inference Tree*

Description

Fits a conditional inference tree with minimal test statistic `theta` and tests if the tree has more than one terminal node.

Usage

```
test_null_theta_ctree(theta, z, data, Trt, Y)
```

Arguments

`theta`	a positive double
`z`	a numeric vector of estimated CATEs from Step 1
`data`	a data frame containing a response, binary treatment indicators, and covariates.
`Trt`	a string specifying the name of the column of `data` contains the treatment indicators.
`Y`	a string specifying the name of the column of `data` contains the response.

Value

a boolean. `True` if `theta` is large enough to give a null conditional inference tree. `False` otherwise.

tunevt *Fit a tuned Virtual Twins model*

Description

`tunevt` fits a Virtual Twins model to estimate factors and subgroups associated with differential treatment effects while controlling the Type I error rate of falsely detecting at least one heterogeneous effect when the treatment effect is uniform across the study population.

Usage

```
tunevt(
  data,
  Y = "Y",
  Trt = "Trt",
  step1 = "randomforest",
  step2 = "rtree",
  alpha0,
  p_reps,
```

```
  threshold = NA,
  keepz = FALSE,
  parallel = FALSE,
  ...
)
```

Arguments

data	a data frame containing a response, binary treatment indicators, and covariates.
Y	a string specifying the name of the column of data contains the response.
Trt	a string specifying the name of the column of data contains the treatment indicators.
step1	character strings specifying the Step 1 model. Supports either "lasso", "mars", "randomforest", or "superlearner".
step2	a character string specifying the Step 2 model. Supports "lasso", "rtree", "classtree", or "ctree".
alpha0	the nominal Type I error rate.
p_reps	the number of permutations to run.
threshold	for "step2 = 'classtree'" only. The value against which to test if the estimated individual treatment effect from Step 1 is higher (TRUE) or lower (FALSE).
keepz	logical. Should the estimated CATE from Step 1 be returned?
parallel	Should the loop over replications be parallelized? If FALSE, then no, if TRUE, then yes. Note that running in parallel requires a *parallel backend* that must be registered before performing the computation. See the foreach documentation for more details.
...	additional arguments to the Step 1 model call.

Details

Virtual Twins is a two-step approach to detecting differential treatment effects. Subjects' conditional average treatment effects (CATEs) are first estimated in Step 1 using a flexible model. Then, a simple and interpretable model is fit in Step 2 to model either (1) the expected value of these estimated CATEs if step2 is equal to "lasso", "rtree", or "ctree" or (2) the probability that the CATE is greater than a specified threshold if step2 is equal to "classtree".

The Step 2 model is dependent on some tuning parameter. This parameter is selected to control the Type I error rate by permuting the data under the null hypothesis of a constant treatment effect and identifying the minimal null penalty parameter (MNPP), which is the smallest penalty parameter that yields a Step 2 model with no covariate effects. The 1-alpha0 quantile of the distribution of is then used to fit the Step 2 model on the original data.

Value

An object of class "tunevt".

An object of class "tunevt" is a list containing at least the following components:

call	the matched call

vtmod	the model estimated by the given step2 procedure fit with the permuted tuning parameter for the estimated CATEs from the step1 model. See vt2_lasso, vt2_rtree, or vt2_ctree for specifics.
mnpp	the MNPP for the estimated CATEs from Step 1.
theta_null	a vector of the MNPPs from each permutation under the null hypothesis.
pvalue	the probability of observing a MNPP as or more extreme as the observed MNPP under the null hypothesis of no effect heterogeneity.
z	if keepz = TRUE, the estimated CATEs from the step1 model.

References

Foster JC, Taylor JM, Ruberg SJ (2011). "Subgroup identification from randomized clinical trial data." *Statistics in Medicine*, **30**(24), 2867–2880. ISSN 02776715, doi:10.1002/sim.4322.

Wolf JM, Koopmeiners JS, Vock DM (2022). "A permutation procedure to detect heterogeneous treatment effects in randomized clinical trials while controlling the type I error rate." *Clinical Trials*, **19**(5), 512-521. ISSN 1740-7745, doi:10.1177/17407745221095855, Publisher: SAGE Publications.

Deng C, Wolf JM, Vock DM, Carroll DM, Hatsukami DK, Leng N, Koopmeiners JS (2023). "Practical guidance on modeling choices for the virtual twins method." *Journal of Biopharmaceutical Statistics*. doi:10.1080/10543406.2023.2170404.

Examples

```
data(tehtuner_example)
# Low p_reps for example use only
tunevt(
  tehtuner_example, step1 = "lasso", step2 = "rtree",
  alpha0 = 0.2, p_reps = 5
)
```

---

tune_theta *Estimate the penalty parameter for Step 2 of Virtual Twins*

Description

Permutes data under the null hypothesis of a constant treatment effect and calculates the MNPP on each permuted data set. The 1 - alpha quantile of the distribution is taken.

Usage

```
tune_theta(
  data,
  Trt,
  Y,
  zbar,
```

```
  step1,
  step2,
  threshold,
  alpha0,
  p_reps,
  parallel,
  ...
)
```

Arguments

data	a data frame containing a response, binary treatment indicators, and covariates.
Trt	a string specifying the name of the column of data contains the treatment indicators.
Y	a string specifying the name of the column of data contains the response.
zbar	the estimated marginal treatment effect
step1	character strings specifying the Step 1 model. Supports either "lasso", "mars", "randomforest", or "superlearner".
step2	a character string specifying the Step 2 model. Supports "lasso", "rtree", "classtree", or "ctree".
threshold	for "step2 = 'classtree'" only. The value against which to test if the estimated individual treatment effect from Step 1 is higher (TRUE) or lower (FALSE).
alpha0	the nominal Type I error rate.
p_reps	the number of permutations to run.
parallel	Should the loop over replications be parallelized? If FALSE, then no, if TRUE, then yes. Note that running in parallel requires a *parallel backend* that must be registered before performing the computation. See the foreach documentation for more details.
...	additional arguments to the Step 1 model call.

Value

the estimated penalty parameter

---

validate_alpha0 *Check if alpha0 is a valid input to tunevt*

Description

Check if alpha0 is a valid input to tunevt

Usage

```
validate_alpha0(data, alpha0)
```

Arguments

`data`	a data frame containing a response, binary treatment indicators, and covariates.
`alpha0`	the nominal Type I error rate.

Value

TRUE if `alpha0` is a valid input. Errors otherwise.

`validate_p_reps` *Check if p_reps is a valid input to tunevt*

Description

Check if p_reps is a valid input to tunevt

Usage

```
validate_p_reps(data, p_reps)
```

Arguments

`data`	a data frame containing a response, binary treatment indicators, and covariates.
`p_reps`	the number of permutations to run.

Value

TRUE if `p_reps` is a valid input. Errors otherwise.

`validate_Trt` *Check if Trt is a valid input to tunevt*

Description

Check if Trt is a valid input to tunevt

Usage

```
validate_Trt(data, Trt)
```

Arguments

`data`	a data frame containing a response, binary treatment indicators, and covariates.
`Trt`	a string specifying the name of the column of `data` contains the treatment indicators.

Value

TRUE if `Trt` is a valid input. Errors otherwise.

validate_Y *Check if Y is a valid input to tunevt*

Description

Check if Y is a valid input to tunevt

Usage

```
validate_Y(data, Y)
```

Arguments

data	a data frame containing a response, binary treatment indicators, and covariates.
Y	a string specifying the name of the column of data contains the response.

Value

TRUE if Y is a valid input. Errors otherwise.

vt1_lasso *Estimate the CATE Using the Lasso for Step 1 of Virtual Twins*

Description

Estimate the CATE Using the Lasso for Step 1 of Virtual Twins

Usage

```
vt1_lasso(data, Trt, Y, ...)
```

Arguments

data	a data frame containing a response, binary treatment indicators, and covariates.
Trt	a string specifying the name of the column of data contains the treatment indicators.
Y	a string specifying the name of the column of data contains the response.
...	additional arguments to cv.glmnet

Value

Estimated CATEs for each subject in data.

See Also

Other VT Step 1 functions: vt1_mars(), vt1_rf(), vt1_super()

vt1_mars *Estimate the CATE Using MARS for Step 1 of Virtual Twins*

Description

Estimate the CATE Using MARS for Step 1 of Virtual Twins

Usage

```
vt1_mars(data, Trt, Y, ...)
```

Arguments

data	a data frame containing a response, binary treatment indicators, and covariates.
Trt	a string specifying the name of the column of data contains the treatment indicators.
Y	a string specifying the name of the column of data contains the response.
...	additional arguments to earth

Value

Estimated CATEs for each subject in data.

See Also

Other VT Step 1 functions: vt1_lasso(), vt1_rf(), vt1_super()

vt1_rf *Estimate the CATE Using a Random Forest for Step 1 of Virtual Twins*

Description

Estimate the CATE Using a Random Forest for Step 1 of Virtual Twins

Usage

```
vt1_rf(data, Trt, Y, ...)
```

Arguments

data	a data frame containing a response, binary treatment indicators, and covariates.
Trt	a string specifying the name of the column of data contains the treatment indicators.
Y	a string specifying the name of the column of data contains the response.
...	additional arguments to rfsrc

Value

Estimated CATEs for each subject in data.

See Also

Other VT Step 1 functions: vt1_lasso(), vt1_mars(), vt1_super()

---

vt1_super *Estimate the CATE Using Super Learner for Step 1 of Virtual Twins*

Description

Estimate the CATE Using Super Learner for Step 1 of Virtual Twins

Usage

```
vt1_super(data, Trt, Y, SL.library, ...)
```

Arguments

data	a data frame containing a response, binary treatment indicators, and covariates.
Trt	a string specifying the name of the column of data contains the treatment indicators.
Y	a string specifying the name of the column of data contains the response.
SL.library	Either a character vector of prediction algorithms or a list containing character vector. See SuperLearner for more details.
...	additional arguments to SuperLearner

Value

Estimated CATEs for each subject in data.

See Also

Other VT Step 1 functions: vt1_lasso(), vt1_mars(), vt1_rf()

vt2_classtree *Estimate the CATE using a classification tree for Step 2*

Description

Estimate the CATE using a classification tree for Step 2

Usage

```
vt2_classtree(z, data, Trt, Y, theta, threshold)
```

Arguments

z	a numeric vector of estimated CATEs from Step 1
data	a data frame containing a response, binary treatment indicators, and covariates.
Trt	a string specifying the name of the column of data contains the treatment indicators.
Y	a string specifying the name of the column of data contains the response.
theta	tree complexity parameter (cp)
threshold	for "step2 = 'classtree'" only. The value against which to test if the estimated individual treatment effect from Step 1 is higher (TRUE) or lower (FALSE).

Value

an object of class rpart. See rpart.object.

See Also

Other VT Step 2 functions: vt2_ctree(), vt2_lasso(), vt2_rtree()

vt2_ctree *Estimate the CATE using a conditional inference tree for Step 2*

Description

Estimate the CATE using a conditional inference tree for Step 2

Usage

```
vt2_ctree(z, data, Trt, Y, theta)
```

Arguments

z	a numeric vector of estimated CATEs from Step 1
data	a data frame containing a response, binary treatment indicators, and covariates.
Trt	a string specifying the name of the column of data contains the treatment indicators.
Y	a string specifying the name of the column of data contains the response.
theta	the value of the test statistic that must be exceeded in order to implement a split (mincriterion)

Value

An object of class BinaryTree-class. See BinaryTree-class.

See Also

Other VT Step 2 functions: vt2_classtree(), vt2_lasso(), vt2_rtree()

---

vt2_lasso *Estimate the CATE using the Lasso for Step 2*

Description

Estimate the CATE using the Lasso for Step 2

Usage

```
vt2_lasso(z, data, Trt, Y, theta)
```

Arguments

z	a numeric vector of estimated CATEs from Step 1
data	a data frame containing a response, binary treatment indicators, and covariates.
Trt	a string specifying the name of the column of data contains the treatment indicators.
Y	a string specifying the name of the column of data contains the response.
theta	lasso penalty parameter (lambda)

Value

a list of length 3 containing the following elements:

mod	an object of class glmnet. See glmnet.
coefficients	coefficients associated with the penalty parameter theta.
fitted.values	predicted values associated with the penalty parameter theta.

See Also

Other VT Step 2 functions: vt2_classtree(), vt2_ctree(), vt2_rtree()

---

vt2_rtree *Estimate the CATE using a regression tree for Step 2*

Description

Estimate the CATE using a regression tree for Step 2

Usage

```
vt2_rtree(z, data, Trt, Y, theta)
```

Arguments

z	a numeric vector of estimated CATEs from Step 1
data	a data frame containing a response, binary treatment indicators, and covariates.
Trt	a string specifying the name of the column of data contains the treatment indicators.
Y	a string specifying the name of the column of data contains the response.
theta	tree complexity parameter (cp)

Value

an object of class rpart. See rpart.object.

See Also

Other VT Step 2 functions: vt2_classtree(), vt2_ctree(), vt2_lasso()

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