Package 'dipm'

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Title Depth Importance in Precision Medicine (DIPM) Method	
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Maintainer Cai Li <cai.li.stats@gmail.com></cai.li.stats@gmail.com>	
Description An implementation by Chen, Li, and Zhang (2022) <doi:10.1093 bioadv="" vbac041=""> of the Depth Importance in Precision Medicine (DIPM) method in Chen and Zhang (2022) <doi:10.1093 biostatistics="" kxaa021=""> and Chen and Zhang (2020) <doi:10.1007 978-3-030-46161-4_16="">. The DIPM method is a classification tree that searches for subgroups with especially poor or strong performance in a given treatment group.</doi:10.1007></doi:10.1093></doi:10.1093>	
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Author Cai Li [aut, cre], Victoria Chen [aut], Heping Zhang [aut] Date/Publication 2025-04-16 00:10:07 UTC	
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dipm

Depth Importance in Precision Medicine (DIPM)

Description

This function creates a classification tree designed to identify subgroups in which subjects perform especially well or especially poorly in a given treatment group.

Usage

```
dipm(
  formula,
  data,
  types = NULL,
  nmin = 5,
  nmin2 = 5,
  ntree = NULL,
  mtry = Inf,
  maxdepth = Inf,
  print = TRUE,
  dataframe = FALSE,
  prune = FALSE
```

Arguments

form	ula
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A description of the model to be fit with format Y \sim treatment | X1 + X2 for data with a continuous outcome variable Y and Surv(Y, delta) \sim treatment | X1 + X2 for data with a right-censored survival outcome variable Y and a status indicator delta

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data

A matrix or data frame of the data

types

A vector, data frame, or matrix of the types of each variable in the data; if left blank, the default is to assume all of the candidate split variables are ordinal; otherwise, all variables in the data must be specified, and the possible variable types are: "response", "treatment", "status", "binary", "ordinal", and "nominal" for outcome variable Y, the treatment variable, the status indicator (if applicable), binary candidate split variables, ordinal candidate split variables, and nominal candidate split variables respectively

nmin

An integer specifying the minimum node size of the overall classification tree

nmin2

An integer specifying the minimum node size of embedded trees

ntree

An integer specifying the number of embedded trees to construct at each node of the overall classification tree; if left blank, the default value of ceiling(min(max(sqrt(n),

sqrt(nc)), 1000)) will be used if mtry = Inf below and ceiling(min(max(n, nc), 1000)) otherwise; n is the total sample size of the data, and nc is the total

number of candidate split variables

mtry An integer specifying the number of candidate split variables to randomly select at each node of embedded trees; if mtry is set equal to the default value of Inf, then all possible splits of all candidate split variables are considered at the nodes of the embedded trees; otherwise, a recommended value of mtry to use is the square root of the total number of candidate split variables rounded up to the nearest integer maxdepth An integer specifying the maximum depth of the overall classification tree; this argument is optional but useful for shortening computation time; if left blank, the default is to grow the full tree until the minimum node size nmin is reached maxdepth2 An integer specifying the maximum depth of embedded trees; this argument is optional but useful for shortening computation time; if left blank, the default is to grow each full, embedded tree until the minimum node size nmin2 is reached print A boolean (TRUE/FALSE) value, where TRUE prints a more readable version of the final tree to the screen dataframe A boolean (TRUE/FALSE) value, where TRUE returns the final tree as a dataframe A boolean (TRUE/FALSE) value, where TRUE prunes the final tree using pmprune prune function

Details

This function creates a classification tree to identify subgroups relevant to the precision medicine setting. At each node of the classification tree, a random forest of so-called embedded trees are fit and used to calculate a depth variable importance score for each candidate split variable in the data. The candidate split variable with the largest variable importance score is identified as the best split variable of the node. Then, all possible splits of the selected split variable are considered, and the split with the greatest split criteria value is finally selected as the best split of the best variable.

The depth variable importance score was originally proposed by Chen et al. (2007), and the score has been adapted to the precision medicine setting here. The depth variable importance score is a relatively simple measure that takes into account two components: the depth of a split in a tree and the strength of the split. The strength of the split is captured with a G test statistic that may be modified depending on the type of analysis at hand. When the outcome variable is continuous, G is the test statistic that tests the significance of the split by treatment interaction term in a linear regression model. When the outcome variable is a right-censored survival time, G is the test statistic that tests the significance of the split by interaction term in a Cox proportional hazards model.

When using dipm, note the following requirements for the supplied data. First, the dataset must contain an outcome variable Y and a treatment variable. If Y is a right-censored survival time outcome, then there must also be a status indicator delta, where values of 1 denote the occurrence of the (harmful) event of interest, and values of 0 denote censoring. If there are only two treatment groups, then the two possible values must be 0 or 1. If there are more than two treatment groups, then the possible values must be integers starting from 1 to the total number of treatment assignments. In regard to the candidate split variables, if a variable is binary, then the variable must take values of 0 or 1. If a variable is nominal, then the values must be integers starting from 1 to the total number of categories. There cannot be any missing values in the dataset. For candidate split variables with missing values, the missings together (MT) method proposed by Zhang et al. (1996) is helpful.

Value

dipm returns the final classification tree as a party object by default or a data frame. See Hothorn and Zeileis (2015) for details. The data frame contains the following columns of information:

node Unique integer values that identify each node in the tree, where all of the nodes

are indexed starting from 1

splitvar Integers that represent the candidate split variable used to split each node, where

all of the variables are indexed starting from 1; for terminal nodes, i.e., nodes

without child nodes, the value is set equal to NA

splitvar_name The names of the candidate split variables used to split each node obtained from

the column names of the supplied data; for terminal nodes, the value is set equal

to NA

type Characters that denote the type of each candidate split variable; "bin" is for

binary variables, "ord" for ordinal, and "nom" for nominal; for terminal nodes,

the value is set equal to NA

splitval Values of the left child node of the current split/node; for binary variables, a

value of 0 is printed, and subjects with values of 0 for the current splitvar are in the left child node, while subjects with values of 1 are in the right child node; for ordinal variables, splitval is numeric and implies that subjects with values of the current splitvar less than or equal to splitval are in the left child node, while the remaining subjects with values greater than splitval are in the right child node; for nominal variables, the splitval is a set of integers separated by commas, and subjects in that set of categories are in the left child node, while the remaining subjects are in the right child node; for terminal nodes, the value

is set equal to NA

1child Integers that represent the index (i.e., node value) of each node's left child node;

for terminal nodes, the value is set equal to NA

rchild Integers that represent the index (i.e., node value) of each node's right child

node; for terminal nodes, the value is set equal to NA

depth Integers that specify the depth of each node; the root node has depth 1, its chil-

dren have depth 2, etc.

nsubj Integers that count the total number of subjects within each node

besttrt Integers that denote the identified best treatment assignment of each node

References

Chen, V., Li, C., and Zhang, H. (2022). dipm: an R package implementing the Depth Importance in Precision Medicine (DIPM) tree and Forest-based method. *Bioinformatics Advances*, **2**(1), vbac041.

Chen, V. and Zhang, H. (2022). Depth importance in precision medicine (DIPM): A tree-and forest-based method for right-censored survival outcomes. *Biostatistics* **23**(1), 157-172.

Chen, V. and Zhang, H. (2020). Depth importance in precision medicine (DIPM): a tree and forest based method. In *Contemporary Experimental Design, Multivariate Analysis and Data Mining*, 243-259.

Chen, X., Liu, C.-T., Zhang, M., and Zhang, H. (2007). A forest-based approach to identifying gene and gene-gene interactions. *Proceedings of the National Academy of Sciences of the United States of America* **204**, 19199-19203.

Zhang, H., Holford, T., and Bracken, M.B. (1996). A tree-based method of analysis for prospective studies. *Statistics in Medicine* **15**, 37-49.

Hothorn, T. and Zeileis, A. (2015). partykit: a modular toolkit for recursive partytioning in R. *The Journal of Machine Learning Research* **16**(1), 3905-3909.

See Also

spmtree

```
# ... an example with a continuous outcome variable
      and two treatment groups
N = 100
set.seed(123)
if (!identical(tolower(Sys.getenv("NOT_CRAN")), "true")){
Sys.setenv(OMP_THREAD_LIMIT = "2")
# generate binary treatments
treatment = rbinom(N, 1, 0.5)
# generate candidate split variables
X1 = rnorm(n = N, mean = 0, sd = 1)
X2 = rnorm(n = N, mean = 0, sd = 1)
X3 = rnorm(n = N, mean = 0, sd = 1)
X4 = rnorm(n = N, mean = 0, sd = 1)
X5 = rnorm(n = N, mean = 0, sd = 1)
X = cbind(X1, X2, X3, X4, X5)
colnames(X) = paste0("X", 1:5)
# generate continuous outcome variable
calculateLink = function(X, treatment){
    ((X[, 1] \le 0) & (X[, 2] \le 0)) *
        (25 * (1 - treatment) + 8 * treatment) +
    ((X[, 1] \le 0) & (X[, 2] > 0)) *
        (18 * (1 - treatment) + 20 * treatment) +
    ((X[, 1] > 0) & (X[, 3] \le 0)) *
        (20 * (1 - treatment) + 18 * treatment) +
    ((X[, 1] > 0) & (X[, 3] > 0)) *
```

```
(8 * (1 - treatment) + 25 * treatment)
}
Link = calculateLink(X, treatment)
Y = rnorm(N, mean = Link, sd = 1)
# combine variables in a data frame
data = data.frame(X, Y, treatment)
# fit a dipm classification tree
tree1 = dipm(Y ~ treatment | ., data, mtry = 1, maxdepth = 3)
# predict optimal treatment for new subjects
predict(tree1, newdata = head(data),
FUN = function(n) as.numeric(n$info$opt_trt))
#
# ... an example with a continuous outcome variable
     and three treatment groups
N = 600
set.seed(123)
# generate treatments
treatment = sample(1:3, N, replace = TRUE)
# generate candidate split variables
X1 = round(rnorm(n = N, mean = 0, sd = 1), 4)
X2 = round(rnorm(n = N, mean = 0, sd = 1), 4)
X3 = sample(1:4, N, replace = TRUE)
X4 = sample(1:5, N, replace = TRUE)
X5 = rbinom(N, 1, 0.5)
X6 = rbinom(N, 1, 0.5)
X7 = rbinom(N, 1, 0.5)
X = cbind(X1, X2, X3, X4, X5, X6, X7)
colnames(X) = paste0("X", 1:7)
# generate continuous outcome variable
calculateLink = function(X,treatment){
    10.2 - 0.3 * (treatment == 1) - 0.1 * X[, 1] +
    2.1 * (treatment == 1) * X[, 1] +
   1.2 * X[, 2]
}
Link = calculateLink(X, treatment)
Y = rnorm(N, mean = Link, sd = 1)
# combine variables in a data frame
data = data.frame(X, Y, treatment)
# create vector of variable types
```

```
types = c(rep("ordinal", 2), rep("nominal", 2), rep("binary", 3),
        "response", "treatment")
# fit a dipm classification tree
tree2 = dipm(Y ~ treatment | ., data, types = types, maxdepth = 2)
# ... an example with a survival outcome variable
      and two treatment groups
N = 300
set.seed(321)
# generate binary treatments
treatment = rbinom(N, 1, 0.5)
# generate candidate split variables
X1 = rnorm(n = N, mean = 0, sd = 1)
X2 = rnorm(n = N, mean = 0, sd = 1)
X3 = rnorm(n = N, mean = 0, sd = 1)
X4 = rnorm(n = N, mean = 0, sd = 1)
X5 = rnorm(n = N, mean = 0, sd = 1)
X = cbind(X1, X2, X3, X4, X5)
colnames(X) = paste0("X", 1:5)
# generate survival outcome variable
calculateLink = function(X, treatment){
   X[, 1] + 0.5 * X[, 3] + (3 * treatment - 1.5) * (abs(X[, 5]) - 0.67)
}
Link = calculateLink(X, treatment)
T = rexp(N, exp(-Link))
C0 = rexp(N, 0.1 * exp(X[, 5] + X[, 2]))
Y = pmin(T, C0)
delta = (T \le C0)
# combine variables in a data frame
data = data.frame(X, Y, delta, treatment)
# fit a dipm classification tree
tree3 = dipm(Surv(Y, delta) ~ treatment | .,data, ntree = 1, maxdepth = 2,
           maxdepth2 = 6)
#
# ... an example with a survival outcome variable
     and four treatment groups
N = 800
set.seed(321)
```

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```
# generate treatments
treatment = sample(1:4, N, replace = TRUE)
# generate candidate split variables
X1 = round(rnorm(n = N, mean = 0, sd = 1), 4)
X2 = round(rnorm(n = N, mean = 0, sd = 1), 4)
X3 = sample(1:4, N, replace = TRUE)
X4 = sample(1:5, N, replace = TRUE)
X5 = rbinom(N, 1, 0.5)
X6 = rbinom(N, 1, 0.5)
X7 = rbinom(N, 1, 0.5)
X = cbind(X1, X2, X3, X4, X5, X6, X7)
colnames(X) = paste0("X", 1:7)
# generate survival outcome variable
calculateLink = function(X, treatment, noise){
   -0.2 * (treatment == 1) +
   -1.1 * X[, 1] +
   1.2 * (treatment == 1) * X[, 1] +
    1.2 * X[, 2]
}
Link = calculateLink(X, treatment)
T = rweibull(N, shape=2, scale = exp(Link))
Cnoise = runif(n = N) + runif(n = N)
C0 = rexp(N, exp(0.3 * -Cnoise))
Y = pmin(T, C0)
delta = (T \le C0)
# combine variables in a data frame
data = data.frame(X, Y, delta, treatment)
# create vector of variable types
types = c(rep("ordinal", 2), rep("nominal", 2), rep("binary", 3),
        "response", "status", "treatment")
# fit two dipm classification trees
tree4 = dipm(Surv(Y, delta) ~ treatment | ., data, types = types, ntree = 1,
           maxdepth = 2, maxdepth2 = 6)
tree5 = dipm(Surv(Y, delta) ~ treatment | X3 + X4, data, types = types, ntree = 1,
           maxdepth = 2, maxdepth2 = 6)
```

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Description

This function provides a new plot method for dipm and spmtree. It visualizes stratified treatment groups through boxplots for a continuous outcome and survival plots for a survival outcome, respectively.

Usage

```
node_dipm(obj, ...)
```

Arguments

obj A party tree object returned from either the dipm() or spmtree() function
... Arguments passed on to plotfun

Details

This function visualizes the precision medicine trees proposed in Chen and Zhang (2020a, b).

Value

No return value, called for plot

References

Chen, V., Li, C., and Zhang, H. (2022). dipm: an R package implementing the Depth Importance in Precision Medicine (DIPM) tree and Forest-based method. *Bioinformatics Advances*, **2**(1), vbac041.

Chen, V. and Zhang, H. (2020). Depth importance in precision medicine (DIPM): a tree and forest based method. In *Contemporary Experimental Design, Multivariate Analysis and Data Mining*, 243-259.

Chen, V. and Zhang, H. (2022). Depth importance in precision medicine (DIPM): A tree-and forest-based method for right-censored survival outcomes. *Biostatistics* **23**(1), 157-172.

Seibold, H., Zeileis, A., and Hothorn, T. (2019). model4you: An R package for personalised treatment effect estimation. *Journal of Open Research Software* 7(1).

Hothorn, T. and Zeileis, A. (2015). partykit: a modular toolkit for recursive partytioning in R. *The Journal of Machine Learning Research* **16**(1), 3905-3909.

See Also

```
dipm, spmtree
```

```
#' #
# ... an example with a continuous outcome variable
# and two treatment groups
#
```

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```
N = 100
set.seed(123)
if (!identical(tolower(Sys.getenv("NOT_CRAN")), "true")){
Sys.setenv(OMP_THREAD_LIMIT = "2")
# generate binary treatments
treatment = rbinom(N, 1, 0.5)
# generate candidate split variables
X1 = rnorm(n = N, mean = 0, sd = 1)
X2 = rnorm(n = N, mean = 0, sd = 1)
X3 = rnorm(n = N, mean = 0, sd = 1)
X4 = rnorm(n = N, mean = 0, sd = 1)
X5 = rnorm(n = N, mean = 0, sd = 1)
X = cbind(X1, X2, X3, X4, X5)
colnames(X) = paste0("X", 1:5)
# generate continuous outcome variable
calculateLink = function(X, treatment){
    ((X[, 1] \le 0) & (X[, 2] \le 0)) *
        (25 * (1 - treatment) + 8 * treatment) +
    ((X[, 1] \le 0) & (X[, 2] > 0)) *
        (18 * (1 - treatment) + 20 * treatment) +
    ((X[,1] > 0) & (X[,3] \le 0)) *
        (20 * (1 - treatment) + 18 * treatment) +
    ((X[,1] > 0) & (X[,3] > 0)) *
        (8 * (1 - treatment) + 25 * treatment)
}
Link = calculateLink(X, treatment)
Y = rnorm(N, mean = Link, sd = 1)
# combine variables in a data frame
data = data.frame(X, Y, treatment)
# fit a dipm classification tree
tree = dipm(Y ~ treatment | ., data, mtry = 1, maxdepth = 3)
plot(tree, terminal_panel = node_dipm)
```

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Description

This function prunes classification trees designed for the precision medicine setting.

Usage

pmprune(tree)

Arguments

tree A data frame object returned from either the dipm() or spmtree() function

Details

This function implements the simple pruning strategy proposed and used in Tsai et al. (2016). Terminal sister nodes, i.e., nodes with no child nodes that share the same parent node, are removed if they have the same identified optimal treatment assignment.

Value

pmprune returns the pruned classification tree as a data frame. The data frame contains the following columns of information:

node	Unique i	integer values	that identify	each node in the	tree where all of the nodes

are indexed starting from 1

splitvar Integers that represent the candidate split variable used to split each node, where

all of the variables are indexed starting from 1; for terminal nodes, i.e., nodes

without child nodes, the value is set equal to NA

splitvar_name The names of the candidate split variables used to split each node obtained from

the column names of the supplied data; for terminal nodes, the value is set equal

to NA

type Characters that denote the type of each candidate split variable; "bin" is for

binary variables, "ord" for ordinal, and "nom" for nominal; for terminal nodes,

the value is set equal to NA

splitval Values of the left child node of the current split/node; for binary variables, a

value of 0 is printed, and subjects with values of 0 for the current splitvar are in the left child node, while subjects with values of 1 are in the right child node; for ordinal variables, splitval is numeric and implies that subjects with values of the current splitvar less than or equal to splitval are in the left child node, while the remaining subjects with values greater than splitval are in the right child node; for nominal variables, the splitval is a set of integers separated by commas, and subjects in that set of categories are in the left child node, while the remaining subjects are in the right child node; for terminal nodes, the value

is set equal to NA

1child Integers that represent the index (i.e., node value) of each node's left child node;

for terminal nodes, the value is set equal to NA

rchild Integers that represent the index (i.e., node value) of each node's right child

node; for terminal nodes, the value is set equal to NA

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depth	Integers that specify the depth of each node; the root node has depth 1, its children have depth 2, etc.
nsubj	Integers that count the total number of subjects within each node
besttrt	Integers that denote the identified best treatment assignment of each node

References

Tsai, W.-M., Zhang, H., Buta, E., O'Malley, S., Gueorguieva, R. (2016). A modified classification tree method for personalized medicine decisions. *Statistics and its Interface* **9**, 239-253.

See Also

```
dipm, spmtree
```

```
# ... an example with a continuous outcome variable
      and three treatment groups
#
N = 100
set.seed(123)
# generate treatments
treatment = sample(1:3, N, replace = TRUE)
# generate candidate split variables
X1 = round(rnorm(n = N, mean = 0, sd = 1), 4)
X2 = round(rnorm(n = N, mean = 0, sd = 1), 4)
X3 = sample(1:4, N, replace = TRUE)
X4 = sample(1:5, N, replace = TRUE)
X5 = rbinom(N, 1, 0.5)
X6 = rbinom(N, 1, 0.5)
X7 = rbinom(N, 1, 0.5)
X = cbind(X1, X2, X3, X4, X5, X6, X7)
colnames(X) = paste0("X", 1:7)
# generate continuous outcome variable
calculateLink = function(X, treatment){
    10.2 - 0.3 * (treatment == 1) - 0.1 * X[, 1] +
    2.1 * (treatment == 1) * X[, 1] +
    1.2 * X[, 2]
}
Link = calculateLink(X, treatment)
Y = rnorm(N, mean = Link, sd = 1)
# combine variables in a data frame
data = data.frame(X, Y, treatment)
```

spmtree

Simple Precision Medicine Tree

Description

This function creates a classification tree designed to identify subgroups in which subjects perform especially well or especially poorly in a given treatment group.

Usage

```
spmtree(
  formula,
  data,
  types = NULL,
  nmin = 5,
  maxdepth = Inf,
  print = TRUE,
  dataframe = FALSE,
  prune = FALSE
```

Arguments

formula

A description of the model to be fit with format Y \sim treatment | X1 + X2 for data with a continuous outcome variable Y and Surv(Y, delta) \sim treatment | X1 + X2 for data with a right-censored survival outcome variable Y and a status indicator delta

data

A matrix or data frame of the data

types

A vector, data frame, or matrix of the types of each variable in the data; if left blank, the default is to assume all of the candidate split variables are ordinal; otherwise, all variables in the data must be specified, and the possible variable types are: "response", "treatment", "status", "binary", "ordinal", and "nominal" for outcome variable Y, the treatment variable, the status indicator (if applicable), binary candidate split variables, ordinal candidate split variables, and nominal candidate split variables respectively

nmin An integer specifying the minimum node size of the overall classification tree

maxdepth An integer specifying the maximum depth of the overall classification tree; this

argument is optional but useful for shortening computation time; if left blank, the default is to grow the full tree until the minimum node size nmin is reached

print A boolean (TRUE/FALSE) value, where TRUE prints a more readable version

of the final tree to the screen

dataframe A boolean (TRUE/FALSE) value, where TRUE returns the final tree as a dataframe

prune A boolean (TRUE/FALSE) value, where TRUE prunes the final tree using pmprune

function

Details

To identify the best split at each node of the classification tree, all possible splits of all candidate split variables are considered. The single split with the highest split criteria score is identified as the best split of the node. For data with a continuous outcome variable, the split criteria is the DIFF value that was first proposed for usage in the relative-effectiveness based method (Zhang et al. (2010), Tsai et al. (2016)). For data with a survival outcome variable, the split criteria is the squared test statistic that tests the significance of the split by treatment interaction term in a Cox proportional hazards model.

When using spmtree, note the following requirements for the supplied data. First, the dataset must contain an outcome variable Y and a treatment variable. If Y is a right-censored survival time outcome, then there must also be a status indicator delta, where values of 1 denote the occurrence of the (harmful) event of interest, and values of 0 denote censoring. If there are only two treatment groups, then the two possible values must be 0 or 1. If there are more than two treatment groups, then the possible values must be integers starting from 1 to the total number of treatment assignments. In regard to the candidate split variables, if a variable is binary, then the variable must take values of 0 or 1. If a variable is nominal, then the values must be integers starting from 1 to the total number of categories. There cannot be any missing values in the dataset. For candidate split variables with missing values, the missings together (MT) method proposed by Zhang et al. (1996) is helpful.

Value

spmtree returns the final classification tree as a party object by default or a data frame. See Hothorn and Zeileis (2015) for details. The data frame contains the following columns of information:

node Unique integer values that identify each node in the tree, where all of the nodes

are indexed starting from 1

splitvar Integers that represent the candidate split variable used to split each node, where

all of the variables are indexed starting from 1; for terminal nodes, i.e., nodes

without child nodes, the value is set equal to NA

splitvar_name The names of the candidate split variables used to split each node obtained from

the column names of the supplied data; for terminal nodes, the value is set equal

to NA

type Characters that denote the type of each candidate split variable; "bin" is for

binary variables, "ord" for ordinal, and "nom" for nominal; for terminal nodes,

the value is set equal to NA

splitval	Values of the left child node of the current split/node; for binary variables, a value of 0 is printed, and subjects with values of 0 for the current splitvar are in the left child node, while subjects with values of 1 are in the right child node; for ordinal variables, splitval is numeric and implies that subjects with values of the current splitvar less than or equal to splitval are in the left child node, while the remaining subjects with values greater than splitval are in the right child node; for nominal variables, the splitval is a set of integers separated by commas, and subjects in that set of categories are in the left child node, while the remaining subjects are in the right child node; for terminal nodes, the value is set equal to NA
lchild	Integers that represent the index (i.e., node value) of each node's left child node; for terminal nodes, the value is set equal to NA
rchild	Integers that represent the index (i.e., node value) of each node's right child node; for terminal nodes, the value is set equal to NA
depth	Integers that specify the depth of each node; the root node has depth 1, its children have depth 2, etc.
nsubj	Integers that count the total number of subjects within each node
besttrt	Integers that denote the identified best treatment assignment of each node

References

Chen, V., Li, C., and Zhang, H. (2022). dipm: an R package implementing the Depth Importance in Precision Medicine (DIPM) tree and Forest-based method. *Bioinformatics Advances*, **2**(1), vbac041.

Chen, V. and Zhang, H. (2022). Depth importance in precision medicine (DIPM): A tree-and forest-based method for right-censored survival outcomes. *Biostatistics* **23**(1), 157-172.

Chen, V. and Zhang, H. (2020). Depth importance in precision medicine (DIPM): a tree and forest based method. In *Contemporary Experimental Design, Multivariate Analysis and Data Mining*, 243-259.

Tsai, W.-M., Zhang, H., Buta, E., O'Malley, S., Gueorguieva, R. (2016). A modified classification tree method for personalized medicine decisions. *Statistics and its Interface* **9**, 239-253.

Zhang, H., Holford, T., and Bracken, M.B. (1996). A tree-based method of analysis for prospective studies. *Statistics in Medicine* **15**, 37-49.

Zhang, H., Legro, R.S., Zhang, J., Zhang, L., Chen, X., et al. (2010). Decision trees for identifying predictors of treatment effectiveness in clinical trials and its application to ovulation in a study of women with polycystic ovary syndrome. *Human Reproduction* **25**, 2612-2621.

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See Also

dipm

```
# ... an example with a continuous outcome variable
     and two treatment groups
N = 300
set.seed(123)
if (!identical(tolower(Sys.getenv("NOT_CRAN")), "true")){
Sys.setenv(OMP_THREAD_LIMIT = "2")
}
# generate binary treatments
treatment = rbinom(N, 1, 0.5)
# generate candidate split variables
X1 = rnorm(n = N, mean = 0, sd = 1)
X2 = rnorm(n = N, mean = 0, sd = 1)
X3 = rnorm(n = N, mean = 0, sd = 1)
X4 = rnorm(n = N, mean = 0, sd = 1)
X5 = rnorm(n = N, mean = 0, sd = 1)
X = cbind(X1, X2, X3, X4, X5)
colnames(X) = paste0("X", 1:5)
# generate continuous outcome variable
calculateLink = function(X, treatment){
    ((X[, 1] \le 0) & (X[, 2] \le 0)) *
        (25 * (1 - treatment) + 8 * treatment) +
    ((X[, 1] \le 0) & (X[, 2] > 0)) *
        (18 * (1 - treatment) + 20 * treatment) +
    ((X[, 1] > 0) & (X[, 3] \le 0)) *
        (20 * (1 - treatment) + 18 * treatment) +
    ((X[, 1] > 0) & (X[, 3] > 0)) *
        (8 * (1 - treatment) + 25 * treatment)
}
Link = calculateLink(X, treatment)
Y = rnorm(N, mean = Link, sd = 1)
# combine variables in a data frame
data = data.frame(X, Y, treatment)
# fit a classification tree
tree1 = spmtree(Y ~ treatment | ., data, maxdepth = 3)
# predict optimal treatment for new subjects
predict(tree1, newdata = head(data),
FUN = function(n) as.numeric(n$info$opt_trt))
```

```
# ... an example with a continuous outcome variable
     and three treatment groups
N = 600
set.seed(123)
# generate treatments
treatment = sample(1:3, N, replace = TRUE)
# generate candidate split variables
X1 = round(rnorm(n = N, mean = 0, sd = 1), 4)
X2 = round(rnorm(n = N, mean = 0, sd = 1), 4)
X3 = sample(1:4, N, replace = TRUE)
X4 = sample(1:5, N, replace = TRUE)
X5 = rbinom(N, 1, 0.5)
X6 = rbinom(N, 1, 0.5)
X7 = rbinom(N, 1, 0.5)
X = cbind(X1, X2, X3, X4, X5, X6, X7)
colnames(X) = paste0("X", 1:7)
# generate continuous outcome variable
calculateLink = function(X, treatment){
   10.2 - 0.3 * (treatment == 1) - 0.1 * X[, 1] +
    2.1 * (treatment == 1) * X[, 1] +
   1.2 * X[, 2]
}
Link = calculateLink(X, treatment)
Y = rnorm(N, mean = Link, sd = 1)
# combine variables in a data frame
data = data.frame(X, Y, treatment)
# create vector of variable types
types = c(rep("ordinal", 2), rep("nominal", 2), rep("binary", 3),
        "response", "treatment")
# fit a classification tree
tree2 = spmtree(Y \sim treatment | ., data, types = types)
# ... an example with a survival outcome variable
     and two treatment groups
N = 300
set.seed(321)
```

```
# generate binary treatments
treatment = rbinom(N, 1, 0.5)
# generate candidate split variables
X1 = rnorm(n = N, mean = 0, sd = 1)
X2 = rnorm(n = N, mean = 0, sd = 1)
X3 = rnorm(n = N, mean = 0, sd = 1)
X4 = rnorm(n = N, mean = 0, sd = 1)
X5 = rnorm(n = N, mean = 0, sd = 1)
X = cbind(X1, X2, X3, X4, X5)
colnames(X) = paste0("X", 1:5)
# generate survival outcome variable
calculateLink = function(X, treatment){
    X[, 1] + 0.5 * X[, 3] + (3 * treatment - 1.5) * (abs(X[, 5]) - 0.67)
}
Link = calculateLink(X, treatment)
T = rexp(N, exp(-Link))
C0 = rexp(N, 0.1 * exp(X[, 5] + X[, 2]))
Y = pmin(T, C0)
delta = (T \le C0)
# combine variables in a data frame
data = data.frame(X, Y, delta, treatment)
# fit a classification tree
tree3 = spmtree(Surv(Y, delta) ~ treatment | ., data, maxdepth = 2)
# ... an example with a survival outcome variable
      and four treatment groups
N = 800
set.seed(321)
# generate treatments
treatment = sample(1:4, N, replace = TRUE)
# generate candidate split variables
X1 = round(rnorm(n = N, mean = 0, sd = 1), 4)
X2 = round(rnorm(n = N, mean = 0, sd = 1), 4)
X3 = sample(1:4, N, replace = TRUE)
X4 = sample(1:5, N, replace = TRUE)
X5 = rbinom(N, 1, 0.5)
X6 = rbinom(N, 1, 0.5)
X7 = rbinom(N, 1, 0.5)
X = cbind(X1, X2, X3, X4, X5, X6, X7)
colnames(X) = paste0("X", 1:7)
# generate survival outcome variable
```

```
calculateLink = function(X, treatment, noise){
    -0.2 * (treatment == 1) +
    -1.1 * X[, 1] +
    1.2 * (treatment == 1) * X[, 1] +
    1.2 * X[, 2]
}
Link = calculateLink(X, treatment)
T = rweibull(N, shape = 2, scale = exp(Link))
Cnoise = runif(n = N) + runif(n = N)
C0 = rexp(N, exp(0.3 * -Cnoise))
Y = pmin(T, C0)
delta = (T \le C0)
# combine variables in a data frame
data = data.frame(X, Y, delta, treatment)
# create vector of variable types
types = c(rep("ordinal", 2), rep("nominal", 2), rep("binary", 3),
        "response", "status", "treatment")
# fit two classification trees
tree4 = spmtree(Surv(Y, delta) ~ treatment | ., data, types = types, maxdepth = 2)
tree5 = spmtree(Surv(Y, delta) ~ treatment | X3 + X4, data, types = types,
             maxdepth = 2)
```

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