# Package 'RHclust'

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Type Package

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Title Vector in Partition

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age contains functions designed to cluster subjects based on gene features including single n cleotide polymorphisms (SNPs), DNA methylation (CPG), gene expression (GE), and covar ate data. The novel concept follows the general K-means (Hartigan and Wong (1979) <doi:10.2307 2346830=""> framework but uses weighted Euclidean distances across the gene features to cluster subjects. This approach is unique in that it attempts to capture all pairwise interactions in an effort to cluster based on their complex biological interactions.</doi:10.2307>	u- i-
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2 BinaryClass

BinaryClass	Binary Classification
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# **Description**

A confusion matrix but allows for analysis of non-equal level data classifications.

# Usage

```
BinaryClass(x)
```

# **Arguments**

Х

Can be a data frame dimensions at least 2 rows and 2 columns meant to represent observed and predicted values where the observed (true) values are in the first column and predicted columns in the second column.

## **Details**

BinaryClass() is similar to a confusion matrix with binary classification outputs. The true positive values per column are identified based on the maximum number of assignments per category.

#### Value

Table the results of 'table()' on 'x'

Accuracy overall accuracy of classification

CI confidence interval of overall accuracy using Clopper-Pearson Interval

Group Measures the sensitivity, specificity, positive predictive value, negative predictive value,

prevelance detection rate, detection prevalence, and balanced accuracy for each

class

#### Author(s)

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# **Examples**

```
# Basic example
true = c(rep(1,5), rep(2,5), rep(3,5), rep(4,5))
pred = c(rep(1,4),4,rep(2,5),2,rep(3,4),1,rep(4,4))
df = cbind(true,pred)
BinaryClass(df)

true = c(rep(1,5), rep(2,5), rep(3,5), rep(4,5))
pred = c(rep(1,5),rep(2,5),rep(3,10))
df = cbind(true,pred)
```

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```
BinaryClass(df)

sd = SimData(k = c(10,40,50))
out = VIP(sd, v = 3, optimize = 'elbow', nstart = 5)
df = out$`BC Test`
BinaryClass(df)

## Looping through different clusters

sd = SimData(seed = 1, gene = 1)
acc = NULL
for (i in 1:5){
  out = VIP(sd, v = i, optimize = 'off', nstart = 5)
  acc[i] = BinaryClass(out$`BC Test`)$Accuracy
}

plot(acc, type = 'b', main = 'Accuracy Comparison', xlab = 'Clusters', ylab = 'Acc')
```

SimData

GE, CPG, SNP, and Covariate Simulated Data

# **Description**

Simulated data generator containing continuous variables representing gene expression (GE) data and DNA methylation data as M-values (GPG), and categorical variable representing single nucleotide polymorphisms (SNP). GE and CPG data are simulated from a normal distribution and SNP data is simulated from a multinomial distribution. Covariate data can have uniformly distributed data or normally distributed. Cluster separation can also be distinct or non-distinct.

#### **Usage**

```
SimData(seed = NULL, gene = 36,
    k = c(33,33,34),
    GEbar = 5, GEsd = 0.5,
    CPGbar = 4, CPGsd = 0.5,
    SameCPG = FALSE, SameSNP = FALSE,
    ProbDist = NULL, SameGeneDist = TRUE,
    distinct=TRUE)
```

#### **Arguments**

seed Set specified seed for reproducibility

gene Numeric input that specifies the number genes

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k Cluster pattern/distribution across subjects formatted as a vector, i.e. c(33,33,34)

representing 33 subjects in the first cluster, 33 in the second cluster, and 34 in

the third cluster.

GEbar Optional numeric input to change the mean distribution of GE data
GEsd Optional numeric input to change the standard deviation of GE data
CPGbar Optional numeric input to change the mean distribution of CPG data
CPGsd Optional numeric input to change the standard deviation of CPG data

SameCPG Logical value that if set to True sets the distribution of each CPG cluster around

the same mean

SameSNP Logical value that if set to True changes the probability distribution of SNPs to

be the same per cluster

ProbDist Optional list input that allows the change of SNP probability distributions per

cluster. Default list stops at 5 cluster distributions. Default ProbDist = list(c(0.50,0.25,0.25),

c(0.20,0.55,0.25), c(0.30,0.15,0.55), c(0.20,0.50,0.30), c(0.45,0.20,0.35))

SameGeneDist Logical that set the covariates to follow the genetic clustering scheme where the

data is uniformly distributed amongst each subgroup in each cluster. Or if set to

FALSE sets the covariates to be noisy and have no discernible groups.

distinct Logical that sets the covariate data clusters to be distinct at default, or non-

distance when set to FALSE

#### **Details**

SimData creates simulated data that aims to represent real world data for gene expression (GE), DNA methylations (CPG), and single neucleotide polymorphisms (SNP). Covariate data is used to represent other potentially useful health data to further weight the genetics data. The goal of this function is to allow the user the ability to manipulate their data for testing of the VIP() or VIPcov() functions.

## Value

Clusters Vector of cluster assignment for each subject.

Vec Numeric representation of values per cluster used for sensitivity measures.

GE Simulated continuous data for GE. Means of each cluster changes by a factor of

5 with default standard deviation of 0.5.

CPG Simulated continuous data for CPG. Means of each cluster changes by a factor

of 4 with default standard deviation of 0.5.

SNP Simulated categorical data for SNP.

GE\_Index Index names for GE.
CPG\_Index Index names for CPG.
SNP\_Index Index names for SNP.

Covariates Simulated data for covariate data. By default contains 10 columns of cateogrical

data and 10 columns of numeric data.

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# **Examples**

VIP

Vector in Partition

# **Description**

Clustering of subjects based on similar patterns of gene expression, DNA methylation, and SNPs.

# Usage

# Arguments

Simulated

set to name of simulated data built from SimData(), else set to NULL for real data.

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SNP	Data frame or data matrix containing categorical SNP data. Input must be in form of N x M, with N rows of subjects and M columns of SNPs. Rownames are permitted. Run SimData()\$SNP for examples.
CPG	Data frame or data matrix containing numeric CPG data. Input must be in form of N x M, with N rows of subjects and M columns of CPG. Rownames are permitted. Run SimData()\$CPG for examples.
GE	Data frame or data matrix containing numeric GE data. Input must be in form of N x M, with N rows of subjects and M columns of GE. Rownames are permitted. Run SimData()\$GE for examples.
SNPname	Names for SNP data. Data must be a data frame of Nx2 dimensions with SNP sites as column 1, and GE indexes in column 2. Order of SNPs must match the order of the SNP columns in the argument SNP. See SimData()\$SNP_Index for examples.
CPGname	Names for CPG data. Data must be a data frame of Nx2 dimensions with CPG sites as column 1, and GE indexes in column 2. Order of CPGs must match the order of the CPG columns in the argument GE. See SimData()\$CPG_Index for examples.
GEname	Names for GE data. Data must be a data frame of Nx2 dimensions with GE sites as column 1, and GE indexes in column 2. Order of GEs must match the order of the GE columns in the argument GE. See SimData()\$GE_Index for examples.
V	Numeric scalar or vector of number for clusters, or a range of clusters with format $c(l,u)$ for cluster $l:u$
optimize	Returned the optimal number of clusters. Input 'min' returns cluster assignment with lowest WSS for clusters in v. Input 'slope' indicates whether the algorithm should pick the lowest WSS value based on the first increasing slope. Input 'elbow' fits a line between the first and last fitted WSS and finds the corresponding cluster with the maximum distance to that line. All but 'slope' return plots.
iter_max	Maximum number of iterations allowed.
nstart	If nstart > 1, repetitive computations with random initializations are computed and the result with minimum tot_dist is returned.
fit	Penalizing factor for WSS of clusters. Can be set to either 'aic' or 'bic'.
seed	Optional input to sample the same initial cluster centers.
type	Optional input for special cases for data without CPGs or SNP inputs. Options include "Default", "NoSNP", or "NoCPG"
ct	Central tendency option for cluster assignment. Options include 'mean' or 'median'.
verbose	Logical whether information about the cluster procedure should be given.

# **Details**

Similar to k-means and k-proto clustering, this algorithm computes clusters based on weighted factors of mixed data relative to genetic/epigenetic data. Clusters are assigned using sumed euclidean distance of numerics (GE and CPG) weighted by matching categorical (SNP) data. Central tendancy of numeric data can be set to either mean or median with input ct.

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Data must be ordered such that rows in each data set correspond to the same subject and order of the indexes match the order of the columns in the data. The current algorithm does not allow for any missing data. The aim is for GE, CPG, and SNP data to be clustered into v groups such that within sum of squares is minimized. If groups of clusters are close, the algorithm may not converge correctly and signals a warning if cluster size is reduced.

Optimization functionality was used for simulated data analysis, but is allowed for user exploratory analysis as well. 'min' simply returns the lowest fitted WSS fit parameter. 'slope' loops through clusters in  $\nu$  and returns the cluster based on the first increasing slope of fitted WSS. For example, if AIC output is c(100,80,35,50), cluster 3 would be returned since the slope increases from 3 to 4. If there is no increasing slope, the 'min' optimizer will be returned. 'elbow' seeks to find the elbow of the plot based on saturation point. This worked the best for simulation studies but requires more clusters to make proper predictions, in our case it required a range of at least 5 clusters c(1,5) to search to correctly identify the 3 simulated clusters. For ease of exploratory analysis,  $\nu$ =1 is allowed.

## Value

size Number of subjects assigned to each cluster.

cluster Vector of cluster assignment.

GECenters Matrix of cluster centers for GE.

CPGCenters Matrix of cluster centers for CPG.

SNPCenters Matrix of cluster centers for SNP.

within Vector of within cluster sum of squares with one component per cluster.

tot\_within Sumed total of within-cluster sum of squares.

Moved Number of iterations before convergence.

AIC Value of tot\_within with aic penalizer.

BIC Value of tot\_within with bic penalizer.

outputPlot Returns the tot\_within, aic, bic, and v values for ploting.

# Author(s)

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#### References

Hartigan, J. A. and Wong, M. A. (1979). Algorithm AS 136: A K-means clustering algorithm. Applied Statistics, 28, 100–108. 10.2307/2346830.

#### **Examples**

```
## simple output of 3 clusters assignments sd = SimData(1, g = 36, c(33,33,34)) VIPout = VIP(sd, v = 3) # loop through clusters 1-10 and outputs plot of WSS, AIC, and BIC
```

VIPcov

VIPcov

Vector in Partition with covariates

# **Description**

Clustering of subjects based on similar patterns of gene expression, DNA methylation, and SNPs weighted by covariates.

## Usage

## **Arguments**

Simulated	set to name of simulated data built from $SimData(\tt),$ else set to NULL for real data.
SNP	Data frame or data matrix containing categorical SNP data. Input must be in form of N x M, with N rows of subjects and M columns of SNPs. Rownames are permitted. Run SimData() $$SNP$$ for examples.
CPG	Data frame or data matrix containing numeric CPG data. Input must be in form of N x M, with N rows of subjects and M columns of CPG. Rownames are permitted. Run $SimData()$ CPG for examples.

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GΕ Data frame or data matrix containing numeric GE data. Input must be in form of N x M, with N rows of subjects and M columns of GE. Rownames are permitted. Run SimData()\$GE for examples. **SNPname** Names for SNP data. Data must be a data frame of Nx2 dimensions with SNP sites as column 1, and GE indexes in column 2. Order of SNPs must match the order of the SNP columns in the argument SNP. See SimData()\$SNP\_Index for examples. **CPGname** Names for CPG data. Data must be a data frame of Nx2 dimensions with CPG sites as column 1, and GE indexes in column 2. Order of CPGs must match the order of the CPG columns in the argument GE. See SimData()\$CPG\_Index for examples. GEname Names for GE data. Data must be a data frame of Nx2 dimensions with GE sites as column 1, and GE indexes in column 2. Order of GEs must match the order of the GE columns in the argument GE. See SimData()\$GE\_Index for examples. covariates Data frame or matrix containing numeric and or categorical variables used for weighting the distance matrix of the genetics data. Numeric scalar or vector of number for clusters, or a range of clusters with format c(l,u) for cluster l:u lambda Weighting factor for the covariate data. The default value is calculated by taking the average variance of the numeric variables divided by the average concentraion of the factors for the categorical variables. When non-mixed type data are used, the value is set to 1 unless specified otherwise. Weighting factor for the genetics distance measure. Default is set to 1 gamma optimize Returned the optimal number of clusters. Input 'min' returns cluster assignment with lowest WSS for clusters in v. Input 'slope' indicates whether the algorithm should pick the lowest WSS value based on the first increasing slope. Input 'elbow' fits a line between the first and last fitted WSS and finds the corresponding cluster with the maximum distance to that line. All but 'slope' return plots. Maximum number of iterations allowed. iter\_max If nstart > 1, repetitive computations with random initializations are computed nstart and the result with minimum tot dist is returned. fit Penalizing factor for WSS of clusters. Can be set to either 'aic' or 'bic'. Optional input to sample the same initial cluster centers. seed Optional input for special cases for data without CPGs or SNP inputs. Options type include "Default", "NoSNP", or "NoCPG" ct Central tendency option for cluster assignment. Options include 'mean' or 'median'.

#### **Details**

verbose

This method is an extension of the VIP() function and allows for the clustering method to be further weighted by the covarite distance. The covariate distance measure is similar to that seen in *kproto()* where the euclidian measure of the numerics data is weighted by matching categorical variables and

Logical whether information about the cluster procedure should be given.

VIPcov

a weighting factor. Clsuters are assigned based on these two distance measures where the Central tendancy of numeric data can be set to either mean or median with input ct.

Data must be ordered such that rows in each data set correspond to the same subject and order of the indexes match the order of the columns in the data. The current algorithm does not allow for any missing data. The aim is for GE, CPG, and SNP data to be clustered into v groups after being weighted by covariates such that within sum of squares is minimized. If groups of clusters are close, the algorithm may not converge correctly and signals a warning if cluster size is reduced.

Optimization functionality was used for simulated data analysis, but is allowed for user exploratory analysis as well. 'min' simply returns the lowest fitted WSS fit parameter. 'slope' loops through clusters in v and returns the cluster based on the first increasing slope of fitted WSS. For example, if AIC output is c(100,80,35,50), cluster 3 would be returned since the slope increases from 3 to 4. If there is no increasing slope, the 'min' optimizer will be returned. 'elbow' seeks to find the elbow of the plot based on saturation point. This worked the best for simulation studies but requires more clusters to make proper predictions, in our case it required a range of at least 5 clusters c(1,5) to search to correctly identify the 3 simulated clusters. For ease of exploratory analysis, v=1 is allowed. 'lambda' is used as a weighting factor for the covariate distance measure, while 'gamma' is the weighting factor for the genetics distance.

#### Value

size Number of subjects assigned to each cluster.

cluster Vector of cluster assignment.

GECenters Matrix of cluster centers for GE.

CPGCenters Matrix of cluster centers for CPG.

SNPCenters Matrix of cluster centers for SNP.

Adjusted Logical if the genetics distance measure is weighted by covariates.

Lambda Lambda value used to weight the covariate distance measure.

within Vector of within cluster sum of squares with one component per cluster.

tot\_within Sumed total of within-cluster sum of squares.

Moved Number of iterations before convergence.

AIC Value of tot\_within with aic penalizer.

BIC Value of tot\_within with bic penalizer.

outputPlot Returns the tot\_within, aic, bic, and v values for ploting.

#### Author(s)

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#### References

Hartigan, J. A. and Wong, M. A. (1979). Algorithm AS 136: A K-means clustering algorithm. Applied Statistics, 28, 100–108. 10.2307/2346830.

Z. Huang. (1998) Extensions to the k-means algorithm for clustering large data sets with categorical variables. Data Mining and Knowledge Discovery, 2:283–304, doi: 10.1023/A:1009769707641.

Szepannek G (2018). "clustMixType: User-Friendly Clustering of Mixed-Type Data in R." The R Journal, 200-208. doi:10.32614/RJ-2018-048, https://doi.org/10.32614/RJ-2018-048.

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## **Examples**

```
## simple output of 3 clusters assignments
sd = SimData(1, g = 36, c(33,33,34))
VIPout = VIPcov(sd, v = 3, covariates = sd$Covariates)
# loop through clusters 1-10 and outputs plot of WSS, AIC, and BIC
VIPout = VIPcov(sd, v = c(1,10), covariates = sd$Covariates)
# loop through clusters 1-10 but picks first instance of increasing slope
VIPout = VIPcov(sd, v = c(1,10), optimize = 'slope', covariates = sd$Covariates)
# Individual inputs
sd = SimData(1, g = 36, k = c(33,33,34))
VIPout = VIPcov(SNP = sd$SNP, CPG = sd$CPG, GE = sd$GE,
            SNPname = sd$SNP_Index, CPGname = sd$CPG_Index,
            GEname = sd$GE_Index,
            v = c(1,5), optimize = 'off', nstart = 5, covariates = sd$Covariates)
## Varying clusters
sd = SimData(k = c(10, 40, 50))
out = VIPcov(sd, v = c(1,6), optimize = 'elbow', nstart = 30, covariates = sd$Covariates)
```

**VIPnoCPG** 

Vector in Partition without CPG data

# **Description**

Clustering of subjects based on similar patterns of gene expression and SNPs.

#### **Usage**

#### **Arguments**

Simulated

set to name of simulated data built from SimData(), else set to NULL for real data.

**SNP** 

Data frame or data matrix containing categorical SNP data. Input must be in form of N x M, with N rows of subjects and M columns of SNPs. Rownames are permitted. Run SimData()\$SNP for examples.

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GE Data frame or data matrix containing numeric GE data. Input must be in form of

N x M, with N rows of subjects and M columns of GE. Rownames are permitted.

Run SimData()\$GE for examples.

SNPname Names for SNP data. Data must be a data frame of Nx2 dimensions with SNP

sites as column 1, and GE indexes in column 2. Order of SNPs must match the order of the SNP columns in the argument SNP. See SimData()\$SNP\_Index for

examples.

GEname Names for GE data. Data must be a data frame of Nx2 dimensions with GE sites

as column 1, and GE indexes in column 2. Order of GEs must match the order of the GE columns in the argument GE. See SimData()\$GE\_Index for examples.

v Numeric scalar or vector of number for clusters, or a range of clusters with

format c(l,u) for cluster l:u

optimize Returned the optimal number of clusters. Input 'min' returns cluster assignment

with lowest WSS for clusters in v. Input 'slope' indicates whether the algorithm should pick the lowest WSS value based on the first increasing slope. Input 'elbow' fits a line between the first and last fitted WSS and finds the corresponding cluster with the maximum distance to that line. All but 'slope' return plots.

iter\_max Maximum number of iterations allowed.

nstart If nstart > 1, repetitive computations with random initializations are computed

and the result with minimum tot dist is returned.

fit Penalizing factor for WSS of clusters. Can be set to either 'aic' or 'bic'.

seed Optional input to sample the same initial cluster centers.

ct Central tendency option for cluster assignment. Options include 'mean' or 'me-

dian'.

verbose Logical whether information about the cluster procedure should be given.

#### **Details**

The details are outlined in the main VIP() function. The only difference in this function is the absence of CPG data.

#### Value

size Number of subjects assigned to each cluster.

cluster Vector of cluster assignment.

GECenters Matrix of cluster centers for GE.

SNPCenters Matrix of cluster centers for SNP.

within Vector of within cluster sum of squares with one component per cluster.

tot\_within Sumed total of within-cluster sum of squares.

Moved Number of iterations before convergence.

AIC Value of tot\_within with aic penalizer.

BIC Value of tot\_within with bic penalizer.

outputPlot Returns the tot\_within, aic, bic, and v values for ploting.

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#### References

Hartigan, J. A. and Wong, M. A. (1979). Algorithm AS 136: A K-means clustering algorithm. Applied Statistics, 28, 100–108. 10.2307/2346830.

## **Examples**

```
# No CPG data
sd = SimData()
noCPGout = VIP(sd, v = c(1,5), optimize = 'off', nstart = 30, type = 'NoCPG')
noCPGout = VIPnoCPG(sd, v = c(1,5), optimize = 'off', nstart = 30)
```

**VIPnoSNP** 

Vector in Partition without SNP data

# **Description**

Clustering of subjects based on similar patterns of gene expression and DNA methylation.

# Usage

# Arguments

Simulated	set to name of simulated data built from SimData(), else set to NULL for real data.
CPG	Data frame or data matrix containing numeric CPG data. Input must be in form of N x M, with N rows of subjects and M columns of CPG. Rownames are permitted. Run SimData()\$CPG for examples.
GE	Data frame or data matrix containing numeric GE data. Input must be in form of N x M, with N rows of subjects and M columns of GE. Rownames are permitted. Run SimData()\$GE for examples.
CPGname	Names for CPG data. Data must be a data frame of Nx2 dimensions with CPG sites as column 1, and GE indexes in column 2. Order of CPGs must match the

examples.

order of the CPG columns in the argument GE. See SimData()\$CPG\_Index for

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GEname Names for GE data. Data must be a data frame of Nx2 dimensions with GE sites

as column 1, and GE indexes in column 2. Order of GEs must match the order of the GE columns in the argument GE. See SimData()\$GE\_Index for examples.

v Numeric scalar or vector of number for clusters, or a range of clusters with

format c(l,u) for cluster l:u

optimize Returned the optimal number of clusters. Input 'min' returns cluster assignment

with lowest WSS for clusters in v. Input 'slope' indicates whether the algorithm should pick the lowest WSS value based on the first increasing slope. Input 'elbow' fits a line between the first and last fitted WSS and finds the corresponding cluster with the maximum distance to that line. All but 'slope' return plots.

Maximum number of iterations allowed.

nstart If nstart > 1, repetitive computations with random initializations are computed

and the result with minimum tot\_dist is returned.

fit Penalizing factor for WSS of clusters. Can be set to either 'aic' or 'bic'.

seed Optional input to sample the same initial cluster centers.

ct Central tendency option for cluster assignment. Options include 'mean' or 'me-

dian'.

verbose Logical whether information about the cluster procedure should be given.

#### **Details**

iter\_max

The details are outlined in the main VIP() function. The only difference in this function is the absence of SNP data.

## Value

size Number of subjects assigned to each cluster.

cluster Vector of cluster assignment.

GECenters Matrix of cluster centers for GE.

CPGCenters Matrix of cluster centers for CPG.

within Vector of within cluster sum of squares with one component per cluster.

tot\_withinSumed total of within-cluster sum of squares.MovedNumber of iterations before convergence.AICValue of tot\_within with aic penalizer.BICValue of tot\_within with bic penalizer.

outputPlot Returns the tot\_within, aic, bic, and v values for ploting.

# Author(s)

jkhndwrk@memphis.edu

# References

Hartigan, J. A. and Wong, M. A. (1979). Algorithm AS 136: A K-means clustering algorithm. Applied Statistics, 28, 100–108. 10.2307/2346830.

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# Examples

```
# No SNP data
sd = SimData()
noSNPout = VIP(sd, v = c(1,5), optimize = 'off', nstart = 30, type = 'NoSNP')
noSNPout = VIPnoSNP(sd, v = c(1,5), optimize = 'off', nstart = 30)
```

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