Package 'perfectphyloR'

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Title Reconstruct Perfect Phylogenies from DNA Sequence Data

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Description Reconstructs perfect phylogeny at a user-given focal point and to depict and test association in a genomic region based on the reconstructed partitions. Charith B Karunarathna and Jinko Graham (2019) <bioarXiv:10.1101/674523>.

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R topics documented:

`perfectphyloR-package`

Reconstruct perfect phylogenies from DNA sequence data

Description

Functions to reconstruct perfect phylogeny underlying a sample of DNA sequences, at a focal single-nucleotide variant (SNV) and to depict and test association in a genomic region based on the reconstructed partitions.

Author(s)

Charith Karunarathna and Jinko Graham

`createHapMat` *Create an object of class* `hapMat`

Description

This function creates a `hapMat` data object, a required input for `reconstructPP`.

Usage

```
createHapMat(hapmat, snvNames, hapNames, posns)
```

Arguments

`hapmat`	A matrix of 0's and 1's, with rows representing haplotypes and columns representing single-nucleotide variants (SNVs).
`snvNames`	A vector of names of SNVs for the columns of `hapmat`.
`hapNames`	A vector of names of haplotypes for the rows of `hapmat`.
`posns`	A numeric vector specifying the genomic positions (e.g. in base pairs) of SNVs in the columns of `hapmat`.

Value

An object of class `hapMat`.

Examples

```
hapmat = matrix(c(1,1,1,0,
                  0,0,0,0,
                  1,1,1,1,
                  1,0,0,0,
                  1,1,0,0,
                  1,0,0,1,
                  1,0,0,1), byrow = TRUE, ncol = 4)
snvnames = c(paste("SNV", 1:4, sep = ""))
allhaps = c("h1", "h2", "h3", "h4", "h5", "h6", "h7")
# Physical positions
posns = c(1000, 2000, 3000, 4000)

# Create hapMat data object
ex_hapMat <- createHapMat(hapmat = hapmat,
                                snvNames = snvnames,
                                hapNames = allhaps,
                                posns = posns)
```

---

dCorTest *dCor test for similarity of two matrices*

Description

This function performs dCor test for association between two distance matrices and computes permutation P value. Permutation P value is computed by randomly permuting rows and columns of the second distance matrix.

Usage

```
dCorTest(Dx, Dy, nperm)
```

Arguments

`Dx`	A numeric matrix of pairwise distances.
`Dy`	A second numeric matrix of pairwise distances.
`nperm`	The number of times to permute the rows and columns of `Dy`.

Value

A list contains RV coefficient and permutation P value.

References

G. J. Szekely, M. L. Rizzo, and N. K. Bakirov. (2007). Measuring and testing dependence by correlation of distances. The Annals of Statistics, 35(6):2769 - 2794.

Examples

```
x <- runif(8)
y <- runif(8)
# Distance matrices
distX = as.matrix(dist(x, upper = TRUE, diag = TRUE))
distY = as.matrix(dist(y, upper = TRUE, diag = TRUE))

dCorTest(Dx = distX, Dy = distY, nperm = 1000)
```

---

ex_hapMatSmall_data

Example small dataset

Description

A subset of `ex_hapMat_data`, containing 10 sequences (haplotypes) with 20 SNVs.

Usage

```
data(ex_hapMatSmall_data)
```

Format

A list of ten haplotypes with the physical positions of each SNV.

hapmat A matrix of 0's and 1's, with rows representing haplotypes and columns representing SNVs.

snvNames A vector of names of SNVs for the columns of `hapmat`.

hapNames A vector of names of haplotypes for the rows of `hapmat`.

posns a numeric vector specifying the genomic positions (e.g. in base pairs) of SNVs in the columns of `hapmat`.

ex_hapMat_data *Example dataset*

Description

A `hapMat` data object containing 200 sequences (haplotypes) with 2747 SNVs.

Usage

```
data(ex_hapMat_data)
```

Format

A list of 200 haplotypes with the physical positions of each SNV.

hapmat A matrix of 0's and 1's, with rows representing haplotypes and columns representing SNVs.

snvNames A vector of names of SNVs for the columns of `hapmat`.

hapNames A vector of names of haplotypes for the rows of `hapmat`.

posns A numeric vector specifying the genomic positions (e.g. in base pairs) of SNVs in the columns of `hapmat`.

HHGtest *HHG test for association of two distance matrices*

Description

This function performs HHG test to find the association between two distance matrices. It permutes rows and columns of the second matrix randomly to calculate P value.

Usage

```
HHGtest(Dx, Dy, nperm)
```

Arguments

`Dx`	A numeric matrix of pairwise distances.
`Dy`	A second numeric matrix of pairwise distances.
`nperm`	The number of times to permute the rows and columns of `Dy`.

Value

A list contains HHG coefficient and permutation P value.

References

Barak, B., and Shachar, K., based in part on an earlier implementation by Ruth Heller and Yair Heller. (2017). HHG: Heller-Heller-Gorfine Tests of Independence and Equality of Distributions. R package version 2.2. https://CRAN.R-project.org/package=HHG

Examples

```
x <- runif(8)
y <- runif(8)
# Distance matrices
distX = as.matrix(dist(x, upper = TRUE, diag = TRUE))
distY = as.matrix(dist(y, upper = TRUE, diag = TRUE))

HHGtest(Dx = distX, Dy = distY, nperm = 1000)
```

`MantelTest` *Mantel test for association of two distance matirces*

Description

This function performs Mantel test for correlation between two distance matrices. It computes P value by randomly permuting rows and columns of the second matrix.

Usage

```
MantelTest(Dx, Dy, nperm)
```

Arguments

`Dx`	A numeric matrix of pairwise distances.
`Dy`	A second numeric matrix of pairwise distances.
`nperm`	The number of times to permute the rows and columns of `Dy`.

Value

A list contains Mantel statistic and permutation P value.

References

Mantel, N. (1967) The detection of disease clustering and a generalized regression approach. Cancer Research, 27, 209 - 220.

Examples

```
x <- runif(8)
y <- runif(8)
# Distance matrices
distX = as.matrix(dist(x, upper = TRUE, diag = TRUE))
distY = as.matrix(dist(y, upper = TRUE, diag = TRUE))

MantelTest(Dx = distX, Dy = distY, nperm = 1000)
```

---

phenoDist *Phenotypic distances*

Description

This is the pairwise phenotypic distances described in Karunarathna and Graham (2018).

Usage

```
data(phenoDist)
```

Format

An object of class `matrix`.

References

Karunarathna, C. B., and Graham, J. (2018) Using gene genealogies to localize rare variants associated with complex traits in diploid populations. Human heredity, 83(1), 30-39.

---

plotDend *Plot reconstructed dendrogram*

Description

This function plots reconstructed dendrogram in a genomic region.

Usage

```
plotDend(dend, direction = "downwards")
```

Arguments

dend	An object of class phylo or of class multiPhylo returned from reconstructPP or reconsPPregion.
direction	A character string specifying the direction of the dendrogram. Four values are possible: "downwards" (the default), "upwards", "leftwards" and "rightwards".

Examples

```
data(ex_hapMat_data)

ex_dend <- reconstructPP(hapMat = ex_hapMat_data,
                         focalSNV = 3,
                         minWindow = 1,
                         sep = "-")

plotDend(dend = ex_dend, direction = "downwards")
```

RandIndexTest *Rand Index Test*

Description

This function performs Rand index test for association between two phylo objects.

Usage

```
RandIndexTest(dend1, dend2, k = 2, nperm)
```

Arguments

dend1	An object of type phylo.
dend2	A second object of type phylo.
k	An integer that specifies the number of clusters that the dendrogram should be cut into. The default is k = 2. Clusters are defined by starting from the root of the dendrogram and cutting across.
nperm	The number of times to permute tips of the dend2.

Value

A numeric value between 0 and 1 and permutation P value.

References

Rand, W.M. (1971) Objective criteria for the evaluation of clustering methods. Journal of the American Statistical Association 66: 846-850.

Examples

```
data(ex_hapMat_data)
d1 <- reconstructPP(ex_hapMat_data, focalSNV = 1, minWindow = 1)
d2 <- reconstructPP(ex_hapMat_data, focalSNV = 5, minWindow = 1)
RandIndexTest(dend1 = d1,  dend2 = d2, k = 5, nperm = 100)
```

`rdistMatrix` *Rank-based distances between haplotypes in a given partition*

Description

This function computes the pairwise distances between haplotypes (tips) of the dendrogram based on the ranking of the nested partitions in the dendrogram. See the details.

Usage

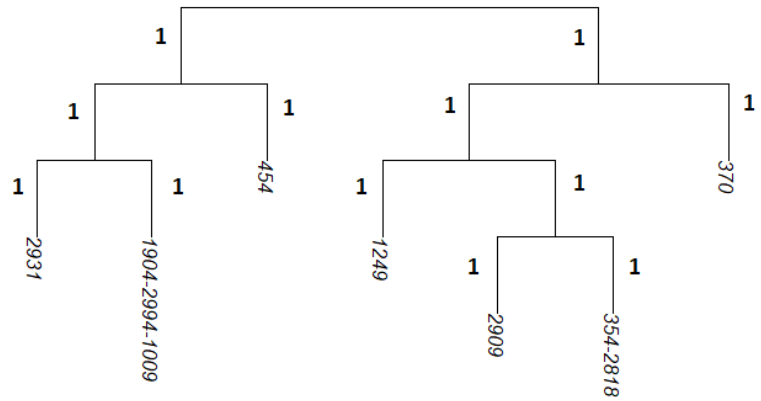
```
rdistMatrix(dend, sep = "-")
```

Arguments

`dend`	A list of nodes that represents the nested partition of haplotypes.
`sep`	A character string separator for concatenating haplotype labels in the dendrogram if they are undistingushable in the window around the focal SNV. See the arguments in `reconstructPP`.

Details

We code the distance between two haplotypes of a dendrogram as the number of inner nodes that seperate the haplotypes plus one. That is, we assign the distance between two internal neighbouring nodes as one, and the distance between an internal node and its neighbouring tip as one. To illustrate, consider the following figure of a dendrogram. In the figure, the distance between the haplotypes 2931 and 454 is 3; the distance between other haplotypes are given in the table below.



	2931	1904-2994-1009	454	1249	2909	354-2818	370
2931	0	2	3	6	7	7	5
1904-2994-1009	2	0	3	6	7	7	5
454	3	3	0	5	6	6	4
1249	6	6	5	0	3	3	3
2909	7	7	6	3	0	2	4
354-2818	7	7	6	3	2	0	4
370	5	5	4	3	4	4	0

Value

A matrix of pairwise distances between haplotypes.

Examples

```
data(ex_hapMat_data)
rdend <- reconstructPP(hapMat = ex_hapMat_data, focalSNV = 2, minWindow = 1, sep = "-" )
rdistMatrix(rdend)
```

---

reconsPPregion *Reconstruct perfect phylogeny sequencce across a region*

Description

This function reconstructs perfect phylogenies on each possible focal SNV across a genomic region.

Usage

```
reconsPPregion(hapMat, minWindow)
```

Arguments

`hapMat`	A data structure of class `hapMat`. See the arguments in `reconstructPP`.
`minWindow`	Minimum number of SNVs around the focal SNV in the window of SNVs used to reconstruct the perfect phylogeny.

Value

An object of class `multiPhylo` that contains multiple `phylo` objects.

Examples

```
data(ex_hapMatSmall_data)

# Reconstruct partitions across the region of ex_hapMatSmall_data.
rdends <- reconsPPregion(hapMat = ex_hapMatSmall_data,
                         minWindow = 1)
```

`reconstructPP` *Reconstruct the perfect phylogeny at a given focal SNV*

Description

This function reconstructs the perfect phylogeny at a given focal SNV using the recursive partitioning algorithm of Gusfield (1991) on compatible SNVs, and the modification of Mailund et al. (2006) to include incompatible SNVs that are nearby.

Usage

```
reconstructPP(hapMat, focalSNV, minWindow = 1, sep = "-")
```

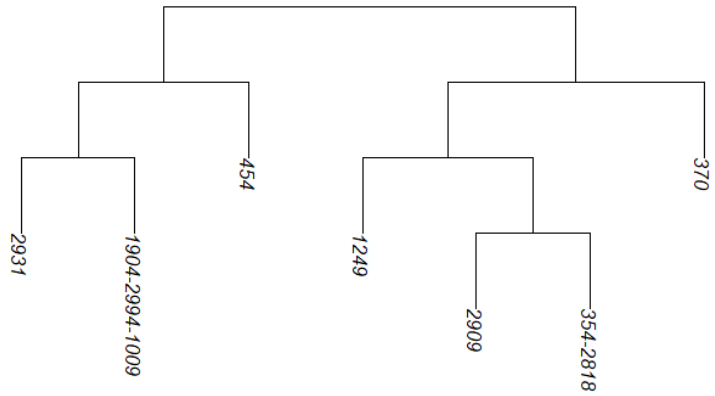
Arguments

`hapMat`	A data structure of class `hapMat`. Eg: created by the `createHapMat` function.
`focalSNV`	The column number of the focal SNV at which to reconstruct the reconstructed partitions.
`minWindow`	Minimum number of SNVs around the focal SNV in the window of SNVs used to reconstruct the partitions.
`sep`	Character string separator to separate haplotype names for haplotypes that can not be distingushed in the window around the focal point. For example, if a tip is comprised of haplotypes "h1" and "h3", and sep = "-", then the tip label will be "h1-h3". The default value is `"-"`. See details.

Details

To reconstruct the perfect phylogeny from sequence data, these two steps are followed: (1) Select a window of SNVs at a given focal SNV. (2) Build the perfect phylogey for the window of SNVs. More details can be found in the references.

The following figure shows the reconstructed partitions at the tenth SNV position of `ex_hapMatSmall_data`.



Value

An object of class `phylo` with indices of the column boundaries of the `hapMat` object that were used to reconstruct the partition in the window of SNVs.

References

Gusfield, D. (1991) Efficient algorithms for inferring evolutionary trees. Networks, 21(1), 19-28.

Mailund, T., Besenbacher, S., and Schierup, M. H. (2006) Whole genome association mapping by incompatibilities and local perfect phylogenies. BMC Bioinformatics, 7(1), 454.

Examples

```
data(ex_hapMatSmall_data)

rdend <- reconstructPP(hapMat = ex_hapMatSmall_data,
                       focalSNV = 10,
                       minWindow = 1,
                       sep = "-")

# Plot the reconstructed perfect phylogeney.

plotDend(rdend, direction = "down")

# Extract the positions of the lower and upper limits of a window of SNVs in hapMat object
# to reconstruct the partition, rdend.

ex_hapMatSmall_data$posns[rdend$snvWinIndices]
```

RVtest *RV test for association of two distance matrices*

Description

This function performs RV test for similarity of two distance matrices. It permutes rows and columns of the second matrix randomly to calculate P value.

Usage

```
RVtest(Dx, Dy, nperm)
```

Arguments

Dx	A numeric matrix of pairwise distances.
Dy	A second numeric matrix of pairwise distances.
nperm	The number of times to permute the rows and columns of Dy.

Value

A list contains RV coefficient and permutation P value.

References

Robert, P. and Escoufier, Y. (1976) A Unifying tool for linear multivariate statistical methods: the RV-coefficient. Applied Statistics, Vol.25, No.3, p. 257-265.

Examples

```
x <- runif(8)
y <- runif(8)
# Distance matrices
distX = as.matrix(dist(x, upper = TRUE, diag = TRUE))
distY = as.matrix(dist(y, upper = TRUE, diag = TRUE))

RVtest(Dx = distX, Dy = distY, nperm = 1000)
```

tdend *True dendrogram object*

Description

A phylo object containing attributes of the comparator true dendrogram for the example data at SNV position 975 kilo base pairs.

Usage

```
data(tdend)
```

Format

A phylo object from the ape package containing four attributes:

edge A matrix containing the node labels and their child nodes.

Nnode The number of nodes.

tip.label A character vector containing the haplotype labels of the true dendrogram.

edge.length A numeric vector giving the lengths of the branches given by `edge`.

testAssoDist *Test the association between a comparator distance matrix, and the reconstructed dendrograms across a genomic region*

Description

This function calculates and tests the association between a comparator distance matrix, based on any pairwise distance measure, and the reconstructed dendrograms across a genomic region of interest usingassociation measures such as the dCor statistic, HHG statistic, Mantel statistic, and RV coefficient. See the section Applications in `vignette("perfectphyloR")` for the detailed example.

Usage

```
testAssoDist(rdend, cdmat, method, hapMat, nperm = 0, xlab = "",
  ylab = "", main = "")
```

Arguments

rdend	A multiPhylo object of reconstructed dendrograms at each focal SNV.
cdmat	A comparator matrix of pairwise distances (e.g. pairwise distances between haplotypes of a comparator dendrogram).
method	Association measures. Use "dCor" for dCor test, "HHG" for HHG test, "Mantel" for mantel test, and "RV" for RV test.
hapMat	An object of class hapMat containing SNV haplotypes.
nperm	Number of permutations for the test of any association across the genomic region of interest. The default is nperm = 0; i.e., association will not be tested.
xlab	An optional character string for the label on the x-axis in the plot that is returned (none by default).
ylab	An optional character string for the label on the y-axis in the plot that is returned (none by default).
main	An optional character string for title in the plot that is returned (none by default).

Value

A list with the following components:

Stats	A vector of observed statistics computed from the user-provided distance association method.
OmPval	A permutation-based omnibus P value for the test of any association across the genomic region using the maximum statistic over the genomic region as the test statistic.
mPval	A vector of marginal P values at each SNV position.
plt	A plot of the association profile over SNV locations in the region of interest.

See Also

HHGtest, dCorTest, RVtest, MantelTest

---

testDendAssoRI *Tests Rand Index between a comparator dendrogram and reconstructed dendrograms*

Description

This function performs the Rand Index between a user-supplied comparator dendrogram and the reconstruced dendrograms at each focal SNV position in a genomic region. See the section Applications in vignette("perfectphyloR") for the detailed example.

Usage

```
testDendAssoRI(rdend, cdend, hapMat, k = 2, nperm = 0, xlab = "",
  ylab = "", main = "")
```

Arguments

rdend	A multiPhylo object of reconstructed dendrograms at each focal SNV.
cdend	A phylo object of the comparator dendrogram.
hapMat	An object of class 'hapMat'containing SNV haplotypes.
k	An integer that specifies the number of clusters that the dendrogram should be cut into. The default is k=2. Clusters are defined by starting from the root of the dendrogram and moving towards the tips, cutting horizontally at any given point in the dendrogram.
nperm	Number of permutations for the test of any association across the genomic region of interest. The default is 'nperm = 0';i.e., association will not be tested.
xlab	An optional character string for the label on the x-axis in the plot that is returned (none by default).
ylab	An optional character string for the label on the y-axis in the plot that is returned (none by default).
main	An optional character string for title in the plot that is returned (none by default).

Value

A list with the following components:

Stats	A vector of observed Rand indices.
OmPval	A permutation-based omnibus P value for the test of any association across the genomic region using the maximum Rand index over the genomic region as the test statistics.
mPval	A vector of marginal P values at each SNV position.
plt	A plot of the association profile of Rand indices over SNV locations in the region of interest.