

Package ‘TitanCNA’

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Type Package

Title Subclonal copy number and LOH prediction from whole genome sequencing of tumours

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Description Hidden Markov model to segment and predict regions of subclonal copy number alterations (CNA) and loss of heterozygosity (LOH), and estimate cellular prevalence of clonal clusters in tumour whole genome sequencing data.

License GPL-3

biocViews Sequencing, WholeGenome, DNaseq, ExomeSeq, StatisticalMethod, CopyNumberVariation, HiddenMarkovModel, Genetics, GenomicVariation

URL <https://github.com/gavinha/TitanCNA>

NeedsCompilation yes

R topics documented:

TitanCNA-package	2
computeSdbwIndex	3
correctReadDepth	5
extractAlleleReadCounts	7
filterData	8
Formatting and output of Titan results	10
getPositionOverlap	13
loadAlleleCounts	14
loadDefaultParameters	15
Plotting TITAN results	17
removeEmptyClusters	19
runEMclonalCN	21
TitanCNA trained dataset	24

viterbiClonalCN	25
WIG Import Functions	26

Index	28
--------------	-----------

TitanCNA-package	<i>TITAN: Subclonal copy number and LOH prediction whole genome sequencing of tumours</i>
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Description

TITAN is a software tool for inferring subclonal copy number alterations (CNA) and loss of heterozygosity (LOH). The algorithm also infers clonal group cluster membership for each event and the tumour proportion, or cellular prevalence, for each event.

Details

Package: TitanCNA
 Type: Package
 Version: 1.9.0
 Date: 2016-02-17
 License: see LICENSE

example("TitanCNA-package") for quick tour of functionality and visualization
 vignette("TitanCNA") for detailed example

Author(s)

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References

Ha, G., Roth, A., Khattra, J., Ho, J., Yap, D., Prentice, L. M., Melnyk, N., McPherson, A., Bashashati, A., Laks, E., Biele, J., Ding, J., Le, A., Rosner, J., Shumansky, K., Marra, M. A., Huntsman, D. G., McAlpine, J. N., Aparicio, S. A. J. R., and Shah, S. P. (2014). TITAN: Inference of copy number architectures in clonal cell populations from tumour whole genome sequence data. *Genome Research*, 24: 1881-1893. (PMID: 25060187)

Examples

```
message('Running TITAN ...')
#### LOAD DATA ####
infile <- system.file("extdata", "test_alleleCounts_chr2.txt", package = "TitanCNA")
data <- loadAlleleCounts(infile)

#### LOAD PARAMETERS ####
message('titan: Loading default parameters')
numClusters <- 2
params <- loadDefaultParameters(copyNumber = 5,
                                numberClonalClusters = numClusters, skew = 0.1)
```

```

#### READ COPY NUMBER FROM HMMCOPY FILE ####
message('titan: Correcting GC content and mappability biases...')
tumWig <- system.file("extdata", "test_tum_chr2.wig", package = "TitanCNA")
normWig <- system.file("extdata", "test_norm_chr2.wig", package = "TitanCNA")
gc <- system.file("extdata", "gc_chr2.wig", package = "TitanCNA")
map <- system.file("extdata", "map_chr2.wig", package = "TitanCNA")
cnData <- correctReadDepth(tumWig, normWig, gc, map)
logR <- getPositionOverlap(data$chr, data$posn, cnData)
data$logR <- log(2^logR) #transform to natural log

#### FILTER DATA FOR DEPTH, MAPPABILITY, NA, etc ####
data <- filterData(data, c(1:22,"X"), minDepth = 10, maxDepth = 200, map = NULL)

#### EM (FWD-BACK) TO TRAIN PARAMETERS ####
#### Can use parallelization packages ####
K <- length(params$genotypeParams$alphaKHyper)
params$genotypeParams$alphaKHyper <- rep(500, K)
params$ploidyParams$phi_0 <- 1.5
convergeParams <- runEMclonalCN(data, gParams = params$genotypeParams,
                               nParams = params$normalParams,
                               pParams = params$ploidyParams,
                               sParams = params$cellPrevParams,
                               maxiter = 3, maxiterUpdate = 500,
                               txnExpLen = 1e9, txnZstrength = 1e9,
                               useOutlierState = FALSE,
                               normalEstimateMethod = "map",
                               estimates = TRUE, estimatePloidy = TRUE)

#### COMPUTE OPTIMAL STATE PATH USING VITERBI ####
optimalPath <- viterbiClonalCN(data, convergeParams)

#### FORMAT RESULTS ####
results <- outputTitanResults(data, convergeParams, optimalPath,
                              filename = NULL, posteriorProbs = FALSE,
                              subcloneProfiles = TRUE)

#### REMOVE EMPTY CLUSTERS ####
corrResults <- removeEmptyClusters(convergeParams, results, proportionThreshold = 0.001,
                                   proportionThresholdClonal = 0.3)
convergeParams <- corrResults$convergeParams
results <- corrResults$results

#### PLOT RESULTS ####
norm <- tail(convergeParams$n, 1)
ploidy <- tail(convergeParams$phi, 1)

par(mfrow=c(4, 1))
plotCNlogRByChr(results, chr = 2, ploidy = ploidy, normal = norm, geneAnnot = NULL,
                ylim = c(-2, 2), cex = 0.5, xlab = "", main = "Chr 2")
plotAllelicRatio(results, chr = 2, geneAnnot = NULL, ylim = c(0, 1), cex = 0.5,
                 xlab = "", main = "Chr 2")
plotClonalFrequency(results, chr = 2, normal = norm, geneAnnot = NULL,
                    ylim = c(0, 1), cex = 0.5, xlab = "", main = "Chr 2")
plotSubcloneProfiles(results, chr = 2, cex = 2, main = "Chr 2")

```

Description

Compute the S_Dbw Validity Index internal cluster validation from the **TitanCNA** results to use for model selection.

Usage

```
computeSDBwIndex(x, centroid.method = "median",
  data.type = "LogRatio", S_Dbw.method = "Halkidi",
  symmetric = TRUE)
```

Arguments

x	Formatted TitanCNA results output from outputTitanResults . See Example.
centroid.method	median or mean method to compute cluster centroids during internal cluster validation.
data.type	Compute S_Dbw validity index based on copy number (use 'LogRatio') or allelic ratio (use 'AllelicRatio').
symmetric	TRUE if the TITAN analysis was carried out using symmetric genotypes. See loadAlleleCounts .
S_Dbw.method	Compute S_Dbw validity index using Halkidi or Tong method. See details and references.

Details

S_Dbw Validity Index is an internal clustering evaluation that is used for model selection (Halkidi et al. 2002). It attempts to choose the model that minimizes within cluster variances (scat) and maximizes density-based cluster separation (Dens). Then, $S_Dbw(lc_Tlx\ z) = Dens(lc_Tlx\ z) + scat(lc_Tlx\ z)$.

In the context of **TitanCNA**, if `data.type='LogRatio'`, then the S_Dbw internal data consists of copy number log ratios, and the resulting joint states of copy number (c_T , for all c_T in $\{0 : \max.copy.number\}$) and clonal cluster (z) make up the clusters in the internal evaluation. If `data.type='AllelicRatio'`, then the S_Dbw internal data consists of the allelic ratios. The optimal **TitanCNA** run is chosen as the run with the minimum S_Dbw. If `data.type='Both'`, then the sum of the S_Dbw for 'LogRatio' and 'AllelicRatio' are added together. This helps account for both data types when choosing the optimal solution.

Note that for `S_Dbw.method`, the Tong method has an incorrect formulation of the `scat(c)` function. The function should be a weighted sum, but that is not the formulation shown in the publication. `computeSDBwIndex` uses (n_i/N) instead of $(N-n_i)/N$ in the `scat` formula, where n_i is the number of datapoints in cluster i and N is the total number of datapoints.

Value

[list](#) with components:

<code>dens.bw</code>	density component of S_Dbw index
<code>scat</code>	scatter component of S_Dbw index
<code>S_DbwIndex</code>	Sum of <code>dens.bw</code> and <code>scat</code> .

Author(s)

Gavin Ha <gavinha@gmail.com>

References

- Halkidi, M., Batistakis, Y., and Vazirgiannis, M. (2002). Clustering validity checking methods: part ii. SIGMOD Rec., 31(3):19–27.
- Tong, J. and Tan, H. Clustering validity based on the improved S_Dbw* index. (2009). Journal of Electronics (China), Volume 26, Issue 2, pp 258-264.
- Ha, G., Roth, A., Khattra, J., Ho, J., Yap, D., Prentice, L. M., Melnyk, N., McPherson, A., Bashashati, A., Laks, E., Biele, J., Ding, J., Le, A., Rosner, J., Shumansky, K., Marra, M. A., Huntsman, D. G., McAlpine, J. N., Aparicio, S. A. J. R., and Shah, S. P. (2014). TITAN: Inference of copy number architectures in clonal cell populations from tumour whole genome sequence data. Genome Research, 24: 1881-1893. (PMID: 25060187)

See Also

[outputModelParameters](#), [loadAlleleCounts](#)

Examples

```
data(EMresults)

#### COMPUTE OPTIMAL STATE PATH USING VITERBI ####
#options(cores=1)
optimalPath <- viterbiClonalCN(data, convergeParams)

#### FORMAT RESULTS ####
results <- outputTitanResults(data, convergeParams, optimalPath,
                             filename = NULL, posteriorProbs = FALSE)

#### COMPUTE S_Dbw Validity Index FOR MODEL SELECTION ####
s_dbw <- computeSdbwIndex(results, data.type = "LogRatio",
                          centroid.method = "median", S_Dbw.method = "Tong")
```

correctReadDepth	<i>Correct GC content and mappability biases in sequencing data read counts</i>
------------------	---

Description

Correct GC content and mappability biases in tumour sequence read counts using Loess curve fitting. Wrapper for function in **HMMcopy**.

Usage

```
correctReadDepth(tumWig, normWig, gcWig, mapWig, genomeStyle = "NCBI", targetedSequence = NULL)
```

Arguments

tumWig	File path to fixedStep WIG format file for the tumour sample. See wigToRangedData in the HMMcopy for more details.
normWig	File path to fixedStep WIG format file for the normal sample.
gcWig	File path to fixedStep WIG format file for the GC content based on the specific reference genome sequence used.

mapWig	File path to fixedStep WIG format file for the mappability scores computed on the specific reference genome used.
genomeStyle	The genome style to use for chromosomes by TitanCNA . Use one of 'NCBI' or 'UCSC'. It does not matter what style is found in inCounts, genomeStyle will be the style returned.
targetedSequence	data.frame with 3 columns: chr, start position, stop position. Use this argument for exome capture sequencing or targeted deep sequencing data. This is experimental and may not work as desired.

Details

Wrapper for [correctReadcount](#) in **HMMcopy** package. It uses a sampling of 50000 bins to find the Loess fit. Then, the log ratio for every bin is returned as the log base 2 of the ratio between the corrected tumour read count and the corrected normal read count.

Value

[data.frame](#) containing columns:

chr	Chromosome; uses 'X' and 'Y' for sex chromosomes
start	Start genomic coordinate for bin in which read count is corrected
end	End genomic coordinate for bin in which read count is corrected
logR	Log ratio, $\log_2(\text{tumour}:\text{normal})$, for bin in which read count is corrected

Author(s)

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References

Ha, G., Roth, A., Lai, D., Bashashati, A., Ding, J., Goya, R., Giuliany, R., Rosner, J., Oloumi, A., Shumansky, K., Chin, S.F., Turashvili, G., Hirst, M., Caldas, C., Marra, M. A., Aparicio, S., and Shah, S. P. (2012). Integrative analysis of genome wide loss of heterozygosity and monoallelic expression at nucleotide resolution reveals disrupted pathways in triple negative breast cancer. *Genome Research*, 22(10):1995,2007. (PMID: 22637570)

Ha, G., Roth, A., Khattra, J., Ho, J., Yap, D., Prentice, L. M., Melnyk, N., McPherson, A., Bashashati, A., Laks, E., Biele, J., Ding, J., Le, A., Rosner, J., Shumansky, K., Marra, M. A., Huntsman, D. G., McAlpine, J. N., Aparicio, S. A. J. R., and Shah, S. P. (2014). TITAN: Inference of copy number architectures in clonal cell populations from tumour whole genome sequence data. *Genome Research*, 24: 1881-1893. (PMID: 25060187)

See Also

[correctReadcount](#) and [wigToRangedData](#) in the **HMMcopy** package. WIG: <http://genome.ucsc.edu/goldenPath/help/wiggle.html>

Examples

```
tumWig <- system.file("extdata", "test_tum_chr2.wig", package = "TitanCNA")
normWig <- system.file("extdata", "test_norm_chr2.wig", package = "TitanCNA")
gc <- system.file("extdata", "gc_chr2.wig", package = "TitanCNA")
map <- system.file("extdata", "map_chr2.wig", package = "TitanCNA")

#### GC AND MAPPABILITY CORRECTION ####
cnData <- correctReadDepth(tumWig, normWig, gc, map)
```

```
extractAlleleReadCounts
```

Function to extract allele read counts from a sequence alignment (BAM) file

Description

Function to extract allele read counts from a sequence alignment (BAM) file at specific positions of interest. The positions are passed in as the file path to a file in variant call format (VCF).

Usage

```
extractAlleleReadCounts(bamFile, bamIndex, positions,
  outputFilename = NULL, pileupParam = PileupParam())
```

Arguments

bamFile	File path location to the sequencing alignment file (BAM format) from which to extract read counts.
bamIndex	File path location to the BAM index file (usually with extension .bai) corresponding to the sequencing alignment file bamFile.
positions	File path location to the variant call format (VCF) file containing the positions at which read counts are to be extracted.
outputFilename	If given, will specify the file path to which the result will be output as tab-delimited text. Otherwise, the no output is written to file.
pileupParam	PileupParam object from the Rsamtools . See Details.

Details

The `pileupParam` object allows users to specify the sequencing parameters to consider when generating the pileup from which read counts are extracted. This includes `'max_depth'`, `'min_base_quality'`, `'min_mapq'`, `'min_nucleotide_depth'=10` (recommended), `'min_minor_allele_depth'`, `'distinguish_strands'`, `'distinguish_nucleotides'=TRUE` (must be TRUE).

Value

`data.frame` containing columns:

chr	Chromosome; character
position	Position; numeric
ref	Reference counts; character

refCount	Reference counts; numeric
Nref	Non-reference counts; character
NrefCount	Non-reference counts; numeric

Author(s)

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References

Ha, G., Roth, A., Khattra, J., Ho, J., Yap, D., Prentice, L. M., Melnyk, N., McPherson, A., Bashashati, A., Laks, E., Biele, J., Ding, J., Le, A., Rosner, J., Shumansky, K., Marra, M. A., Huntsman, D. G., McAlpine, J. N., Aparicio, S. A. J. R., and Shah, S. P. (2014). TITAN: Inference of copy number architectures in clonal cell populations from tumour whole genome sequence data. *Genome Research*, 24: 1881-1893. (PMID: 25060187)

See Also

[PileupParam](http://samtools.sourceforge.net/); <http://samtools.sourceforge.net/>

Examples

```
## Not run:
countsDF <- extractAlleleReadCounts(bamFile, bamIndex,
  positions, outputFilename = NULL,
  pileupParam = PileupParam())
data <- loadAlleleCounts(countsDF, symmetric = TRUE,
  genomeStyle = "NCBI")

## End(Not run)
```

filterData

Filter list object based on read depth and missing data

Description

Filters all vectors in list based on specified chromosome(s) of interest, minimum and maximum read depths, missing data, mappability score threshold

Usage

```
filterData(data ,chrs = NULL, minDepth = 10, maxDepth = 200,
  positionList = NULL, map = NULL, mapThres = 0.9,
  centromeres = NULL, centromere.flankLength = 0)
```

Arguments

data [list](#) object that contains an arbitrary number of components. Should include 'chr', 'tumDepth'. All vector elements must have the same number of rows where each row corresponds to information pertaining to a chromosomal position.

chr	character or vector of character specifying the chromosomes to keep. Chromosomes not included in this array will be filtered out. Chromosome style must match the genomeStyle used when running loadAlleleCounts
minDepth	Numeric integer specifying the minimum tumour read depth to include. Positions \geq minDepth are kept.
maxDepth	Numeric integer specifying the maximum tumour read depth to include. Positions \leq maxDepth are kept.
positionList	data.frame with two columns: 'chr' and 'posn'. positionList lists the chromosomal positions to use in the analysis. All positions not overlapping this list will be excluded. Use NULL to use all current positions in data.
map	Numeric array containing map scores corresponding to each position in data. Optional for filtering positions based on mappability scores.
mapThres	Numeric float specifying the mappability score threshold. Only applies if map is specified. map scores \geq mapThres are kept.
centromeres	data.frame containing list of centromere regions. This should contain 3 columns: chr, start, and end. If this argument is used, then data at and flanking the centromeres will be removed.
centromere.flankLength	Integer indicating the length (in base pairs) to the left and to the right of the centromere designated for removal of data.

Details

All vectors in the input data list object, and map, must all have the same number of rows.

Value

The same [list](#) data containing filtered components.

Author(s)

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References

Ha, G., Roth, A., Khattra, J., Ho, J., Yap, D., Prentice, L. M., Melnyk, N., McPherson, A., Bashashati, A., Laks, E., Biele, J., Ding, J., Le, A., Rosner, J., Shumansky, K., Marra, M. A., Huntsman, D. G., McAlpine, J. N., Aparicio, S. A. J. R., and Shah, S. P. (2014). TITAN: Inference of copy number architectures in clonal cell populations from tumour whole genome sequence data. *Genome Research*, 24: 1881-1893. (PMID: 25060187)

See Also

[loadAlleleCounts](#)

Examples

```
infile <- system.file("extdata", "test_alleleCounts_chr2.txt",
                     package = "TitanCNA")
tumWig <- system.file("extdata", "test_tum_chr2.wig", package = "TitanCNA")
normWig <- system.file("extdata", "test_norm_chr2.wig", package = "TitanCNA")
gc <- system.file("extdata", "gc_chr2.wig", package = "TitanCNA")
```

```

map <- system.file("extdata", "map_chr2.wig", package = "TitanCNA")

#### LOAD DATA ####
data <- loadAlleleCounts(infile, genomeStyle = "NCBI")

#### GC AND MAPPABILITY CORRECTION ####
cnData <- correctReadDepth(tumWig, normWig, gc, map)

#### READ COPY NUMBER FROM HMMCOPY FILE ####
logR <- getPositionOverlap(data$chr, data$posn, cnData)
data$logR <- log(2^logR) #use natural logs

#### FILTER DATA FOR DEPTH, MAPPABILITY, NA, etc ####
filterData <- filterData(data, as.character(1:24), minDepth = 10,
maxDepth = 200, map = NULL, mapThres=0.9)

```

Formatting and output of Titan results

*Formatting and printing **TitanCNA** results.*

Description

Function to format **TitanCNA** results in to a data.frame and output the results to a tab-delimited file.

Usage

```

outputTitanResults(data, convergeParams, optimalPath, filename = NULL,
  posteriorProbs = FALSE, subcloneProfiles = TRUE)
outputModelParameters(convergeParams, results, filename,
  S_Dbw.scale = 1, S_Dbw.method = "Tong")

```

Arguments

data	list object that contains the components for the data to be analyzed. chr, posn, ref, and tumDepth that can be obtained using loadAlleleCounts , and logR that can be obtained using correctReadDepth and getPositionOverlap (see Example).
convergeParams	list object that is returned from the function runEMclonalCN in TitanCNA .
optimalPath	numeric array containing the optimal TitanCNA genotype and clonal cluster states for each data point in the analysis. optimalPath is obtained from running viterbiClonalCN .
results	Formatted TitanCNA results output from outputTitanResults .
filename	Path of the file to write the TitanCNA results.
posteriorProbs	Logical TRUE to include the posterior marginal probabilities in printing to filename.
subcloneProfiles	Logical TRUE to include the subclone profiles to the output data.frame. Currently, this only works for 1 or 2 clonal clusters.

<code>S_Dbw.scale</code>	The <code>S_Dbw</code> validity index can be adjusted to account for differences between datasets. <code>S_Dbw.scale</code> can be used to penalize the <code>S_Dbw.dens.bw</code> component. The default is 1.
<code>S_Dbw.method</code>	Compute <code>S_Dbw</code> validity index using Halkidi or Tong method. See computeS_DbwIndex .

Details

`outputModelParameters` outputs to a file with the estimated TITAN model parameters and model selection index. Each row contains information regarding different parameters:

- 1) Normal contamination estimate - proportion of normal content in the sample; tumour content is 1 minus this number
- 2) Average tumour ploidy estimate - average number of estimated copies in the genome; 2 represents diploid
- 3) Clonal cluster cellular prevalence - Z denotes the number of clonal clusters; each value (space-delimited) following are the cellular prevalence estimates for each cluster. Cellular prevalence here is defined as the proportion of tumour sample that does contain the aberrant genotype.
- 4) Genotype binomial means for clonal cluster Z - set of 21 binomial estimated parameters for each specified cluster
- 5) Genotype Gaussian means for clonal cluster Z - set of 21 Gaussian estimated means for each specified cluster
- 6) Genotype Gaussian variance - set of 21 Gaussian estimated variances; variances are shared for across all clusters
- 7) Number of iterations - number of EM iterations needed for convergence
- 8) Log likelihood - complete data log-likelihood for current cluster run
- 9) `S_Dbw.dens.bw` - density component of `S_Dbw` index; see [computeS_DbwIndex](#)
- 10) `S_Dbw.scats` - scatter component of `S_Dbw` index; see [computeS_DbwIndex](#)
- 11) `S_Dbw.validity` index - used for model selection where the run with optimal number of clusters based on lowest `S_Dbw` index. This value is slightly modified from that computed from [computeS_DbwIndex](#). It is computed as $S_Dbw = S_Dbw.scale * dens.bw + scats$
- 12) `S_Dbw.dens.bw`, `scats`, validity index is computed for `LogRatio` and `AllelicRatio` datatypes, as well as the combination of Both. For Both, the values are summed for both datatypes.

`outputTitanResults` outputs a file that has the similar format described in 'Value' section.

Value

`outputTitanResults` also returns a `data.frame`, where each row corresponds to a position in the analysis, and with the following columns:

<code>Chr</code>	character denoting chromosome number. <code>ChrX</code> and <code>ChrY</code> uses 'X' and 'Y'.
<code>Position</code>	genomic coordinate
<code>RefCount</code>	number of reads matching the reference base
<code>NRefCount</code>	number of reads matching the non-reference base
<code>Depth</code>	total read depth at the position
<code>AllelicRatio</code>	<code>RefCount/Depth</code>
<code>LogRatio</code>	\log_2 ratio between normalized tumour and normal read depths
<code>CopyNumber</code>	predicted TitanCNA copy number


```
#### OUTPUT RESULTS TO FILE ####
outparam <- paste("cluster2_params.txt", sep = "")
outputModelParameters(convergeParams, results, outparam)
```

getPositionOverlap *Function to assign values to given chromosome-position that overlaps a list of chromosomal segments*

Description

Given a list of chromosomes and positions, uses a C-based function that searches a list of segments to find the overlapping segment. Then, takes the value (4th column in segment data.frame) of the overlapping segment and assigns to the given chromosome and position.

Usage

```
getPositionOverlap(chr, posn, dataVal)
```

Arguments

chr Numeric [array](#) denoting the chromosome for a list of positions. Must have the same number of elements as posn.

posn Numeric [array](#) denoting the position in the chromosome for a list of positions. Must have the same number of elements as chr.

dataVal [data.frame](#) containing a list of segments described with 4 columns: chromosome, start coordinate, end coordinate, value of interest (e.g. log ratio). Chromosome can be all numeric or chrX and chrY can use 'X' and 'Y'.

Value

Numeric [array](#) of values from the 4th column of [data.frame](#) cnData. Each element corresponds to a genomic location from chr and posn that overlapped the segment in cnData.

Author(s)

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References

Ha, G., Roth, A., Khattra, J., Ho, J., Yap, D., Prentice, L. M., Melnyk, N., McPherson, A., Bashashati, A., Laks, E., Biele, J., Ding, J., Le, A., Rosner, J., Shumansky, K., Marra, M. A., Huntsman, D. G., McAlpine, J. N., Aparicio, S. A. J. R., and Shah, S. P. (2014). TITAN: Inference of copy number architectures in clonal cell populations from tumour whole genome sequence data. *Genome Research*, 24: 1881-1893. (PMID: 25060187)

See Also

[loadAlleleCounts](#), [correctReadDepth](#)

Examples

```

infile <- system.file("extdata", "test_alleleCounts_chr2.txt",
                      package = "TitanCNA")
tumWig <- system.file("extdata", "test_tum_chr2.wig", package = "TitanCNA")
normWig <- system.file("extdata", "test_norm_chr2.wig", package = "TitanCNA")
gc <- system.file("extdata", "gc_chr2.wig", package = "TitanCNA")
map <- system.file("extdata", "map_chr2.wig", package = "TitanCNA")

#### LOAD DATA ####
data <- loadAlleleCounts(infile)

#### GC AND MAPPABILITY CORRECTION ####
cnData <- correctReadDepth(tumWig, normWig, gc, map)

#### READ COPY NUMBER FROM HMMCOPY FILE ####
logR <- getPositionOverlap(data$chr, data$posn, cnData)

```

loadAlleleCounts	<i>Function to load tumour allele counts from a text file or data.frame</i>
------------------	---

Description

Function to load in the allele counts from tumour sequencing data from a delimited text file or data.frame object.

Usage

```
loadAlleleCounts(inCounts, symmetric = TRUE, genomeStyle = "NCBI", sep = "\t", header = TRUE)
```

Arguments

inCounts	Full file path to text file or data.frame containing tumour allele count data. inCounts must be 6 columns: chromosome, position, reference base, reference read counts, non-reference base, non-reference read counts. ‘chromosome’ column can be in ‘NCBI’ or ‘UCSC’ genome style; only autosomes, sex chromosomes, and mitochondrial chromosome are included (e.g. 1-22,X,Y,MT). The reference and non-reference base columns can be any arbitrary character; it is not used by TitanCNA .
symmetric	logical; if TRUE, then the symmetric allelic counts will be used. ref will equal max(ref, nonRef). This parameter must be the same as the symmetric parameter for loadDefaultParameters .
genomeStyle	The genome style to use for chromosomes by TitanCNA . Use one of ‘NCBI’ or ‘UCSC’. It does not matter what style is found in inCounts, genomeStyle will be the style returned.
sep	Character indicating the delimiter used for the columns for infile. Default is tab-delimited, "\t".
header	logical to indicate if the input tumour counts file contains a header line.

Value

[list](#) containing components for

chr	Chromosome; character, NCBI or UCSC genome style format
posn	Position; integer
ref	Reference counts; numeric
nonRef	Non-reference counts; numeric
tumDepth	Tumour depth; numeric

Author(s)

Gavin Ha <gavinha@gmail.com>

References

Ha, G., Roth, A., Khattra, J., Ho, J., Yap, D., Prentice, L. M., Melnyk, N., McPherson, A., Bashashati, A., Laks, E., Biele, J., Ding, J., Le, A., Rosner, J., Shumansky, K., Marra, M. A., Huntsman, D. G., McAlpine, J. N., Aparicio, S. A. J. R., and Shah, S. P. (2014). TITAN: Inference of copy number architectures in clonal cell populations from tumour whole genome sequence data. *Genome Research*, 24: 1881-1893. (PMID: 25060187)

See Also

[loadDefaultParameters](#)

Examples

```
infile <- system.file("extdata", "test_alleleCounts_chr2.txt",
                     package = "TitanCNA")
#### LOAD DATA FROM TEXT FILE ####
data <- loadAlleleCounts(infile, symmetric = TRUE,
                       genomeStyle = "NCBI", header = TRUE)

## Not run:
countsDF <- extractAlleleReadCounts(tumBam, tumBamIndex,
                                   germlineHetPosns, outputFilename = NULL,
                                   pileupParam = PileupParam())
data <- loadAlleleCounts(countsDF, symmetric = TRUE,
                       genomeStyle = "NCBI")

## End(Not run)
```

loadDefaultParameters *Load TITAN parameters*

Description

Load TITAN model parameters based on maximum copy number and number of clonal clusters.

Usage

```
loadDefaultParameters(copyNumber = 5, numberClonalClusters = 1, skew = 0,
                    symmetric = TRUE, data = NULL)
```

Arguments

copyNumber	Maximum number of absolute copies to account for in the model. Default (and recommended) is 5.
numberClonalClusters	Number of clonal clusters to use in the analysis. Each cluster represents a potential clone. Using '1' treats the sample as being clonal (no subclonality). '2' or higher treats the tumour data as being subclonal.
skew	numeric float indicating the heterozygous baseline shift for the allelic ratios towards 1. This is may be required for SOLiD data, but for most cases, this argument can be omitted.
symmetric	logical; if TRUE, then treat genotypes as symmetric. See Details.
data	data is the output of function loadAlleleCounts . If provided and symmetric=TRUE, then it will compute the median allelic ratio to use as the baseline for heterozygous genotypes; otherwise, the baseline will default to 0.55 (reference/depth) if data=NULL. If symmetric=FALSE, this argument will not be used.

Details

Generally, **TitanCNA** should be run once for each number of clonal clusters in the range of 1 to 5. Then, use model selection to choose the run with the optimal number of clusters.

If the allelic ratio data is skewed towards one allele, then use skew to help define the baseline. For example, if the data is skewed towards the reference, then use 0.1 so that the heterozygous baseline is at 0.6. The allelic ratio baseline is normally at 0.5.

sParams, which represents the parameters for estimation of subclonality, always contains values for one cluster that represents the clonally dominant cluster (events present in nearly all tumour cells) with an initial value of `sParams$s_0[1] = 0.001`.

Setting symmetric to TRUE will treat reference and non-reference alleles the same. For example, genotypes AA (homozygous for reference allele) and BB (homozygous for non-reference allele) as being equivalent. This will reduce the state space substantially.

Value

[list](#) containing 4 sets of parameters, each as a component:

genotypeParams	Parameters for copy number and allelic ratios genotype states
normalParams	Parameters for normal contamination
ploidyParams	Parameters for average tumour ploidy
sParams	Parameters for modeling subclonality: clonal clusters and cellular prevalence

Author(s)

Gavin Ha <gavinha@gmail.com>

References

Ha, G., Roth, A., Khattra, J., Ho, J., Yap, D., Prentice, L. M., Melnyk, N., McPherson, A., Bashashati, A., Laks, E., Biele, J., Ding, J., Le, A., Rosner, J., Shumansky, K., Marra, M. A., Huntsman, D. G., McAlpine, J. N., Aparicio, S. A. J. R., and Shah, S. P. (2014). TITAN: Inference of copy number architectures in clonal cell populations from tumour whole genome sequence data. *Genome Research*, 24: 1881-1893. (PMID: 25060187)

See Also[loadAlleleCounts](#)**Examples**

```
#### LOAD PARAMETERS ####
numClusters <- 2
params <- loadDefaultParameters(copyNumber = 5,
                                numberClonalClusters = numClusters)
```

 Plotting TITAN results

*Plotting functions for **TitanCNA** results.*

Description

Three plotting functions for **TitanCNA** results. `plotCNlogRByChr` plots the copy number results from log ratio data. `plotAllelicRatio` plots the allelic imbalance and loss of heterozygosity (LOH) from allelic ratio data. `plotClonalFrequency` plots the clonal cluster and cellular prevalence results for each data point.

Usage

```
plotAllelicRatio(dataIn, chr = NULL, geneAnnot = NULL, spacing = 4,
                 xlim = NULL, ...)
plotClonalFrequency(dataIn, chr = NULL, normal = NULL, geneAnnot = NULL,
                    spacing = 4, xlim = NULL, ...)
plotCNlogRByChr(dataIn, chr = NULL, segs = NULL, geneAnnot = NULL, ploidy = NULL,
                 normal = NULL, spacing = 4, alphaVal = 1, xlim = NULL, ...)
plotSubcloneProfiles(dataIn, chr = NULL, geneAnnot = NULL,
                     spacing = 4, xlim = NULL, ...)
```

Arguments

<code>dataIn</code>	Formatted TitanCNA results output from outputTitanResults . See Example.
<code>chr</code>	Plot results for specified chr. If chr is NULL, then results for the entire genome is plot.
<code>segs</code>	data.frame containing named columns: Chromosome, Median_logR, Start_Position.bp., End_Position.bp.. This data can be read in from the segments generated by the TITANRunner pipeline. These segments will be overlaid in the plots as lines at the median log ratio for each segment.
<code>geneAnnot</code>	data.frame specifying the genes to annotate in the plot. Gene boundaries are indicated using vertical dotted grey lines and gene symbols are shown at the top of the plot. <code>geneAnnot</code> must have four columns: gene symbol, chr, start coordinate, stop coordinate.
<code>normal</code>	numeric scalar indicating the normal contamination. This can be obtained from converge parameters output using runEMclonalCN . See Example.
<code>ploidy</code>	numeric scalar indicating the tumour ploidy used to adjust the copy number plot plotCNlogRByChr . This can be obtained from converge parameters output using runEMclonalCN . See Example. If NULL is used, then ploidy adjustment is not used in the plot.

spacing	Number of lines of spacing for the margin spacing at the bottom of the plot. Useful if an idiogram/karogram is plot underneath.
alphaVal	Set an alpha value between 0 and 1 to allow transparency in the points being plot.
xlim	Two element vector to specify the xlim for the plot. If NULL, then entire chromosome is plot.
...	Additional arguments used in the plot function.

Details

[plotCNlogRByChr](#) plots the copy number alterations from log ratio data. The Y-axis is based on log ratios. Log ratios are computed ratios between normalized tumour and normal read depths. Data points close to 0 represent diploid, above 0 are copy gains, below 0 are deletions. `ploidy` argument adjusts the baseline of the data points. Colours represent the copy number state. Bright Green - Homozygous deletion (HOMD) Green - Hemizygous deletion (DLOH) Blue - Diploid heterozygous (HET), Copy-neutral LOH (NLOH) Dark Red - GAIN Red - Allele-specific CNA (ASCNA), Unbalanced CNA (UBCNA), Balanced CNA (BCNA)

[plotAllelicRatio](#) plots the allelic imbalance and loss of heterozygosity from allelic ratio data. The Y-axis is based on allelic ratios. Allelic ratios are computed as RefCount/Depth . Data points close to 1 represent homozygous reference base, close to 0 represent homozygous non-reference base, and close to 0.5 represent heterozygous. Normal contamination influences the divergence away from 0.5 for LOH events. No adjustments are made to the plot as the original data from `dataIn` are shown. Colours represent the allelic imbalance and LOH state. Grey - HET, BCNA Bright Green - HOMD Green - DLOH, ALOH Blue - NLOH Dark Red - GAIN Red - ASCNA, UBCNA

[plotClonalFrequency](#) plots the cellular prevalence and clonal clusters from the results. The Y-axis is the cellular prevalence that includes the normal proportion. Therefore, the cellular prevalence here refers to the proportion in the sample (including normal). Lines are drawn for each data point indicating the cellular prevalence. Heterozygous diploid are not shown because it is a normal genotype and is not categorized as being subclonal (this means 100% of cells are normal). The black horizontal line represents the tumour content labeled as 'T'. Each horizontal grey line represents the cellular prevalence of the clonal clusters labeled as Z1, Z2, etc. Colours are the same for allelic ratio plots.

[plotSubcloneProfiles](#) plots the predicted copy number profile for individual subclones inferred by TITAN. Currently, this only works for solutions having 1 or 2 clonal clusters. The colours are the same as for [plotAllelicRatio](#).

Author(s)

Gavin Ha <gavinha@gmail.com>

References

Ha, G., Roth, A., Khattra, J., Ho, J., Yap, D., Prentice, L. M., Melnyk, N., McPherson, A., Bashashati, A., Laks, E., Biele, J., Ding, J., Le, A., Rosner, J., Shumansky, K., Marra, M. A., Huntsman, D. G., McAlpine, J. N., Aparicio, S. A. J. R., and Shah, S. P. (2014). TITAN: Inference of copy number architectures in clonal cell populations from tumour whole genome sequence data. *Genome Research*, 24: 1881-1893. (PMID: 25060187)

See Also

[outputTitanResults](#), [runEMclonalCN](#), [computeSdbwIndex](#)

Examples

```

data(EMresults)

#### COMPUTE OPTIMAL STATE PATH USING VITERBI ####
optimalPath <- viterbiClonalCN(data, convergeParams)

#### FORMAT RESULTS ####
results <- outputTitanResults(data, convergeParams, optimalPath,
                              filename = NULL, posteriorProbs = FALSE)

#### PLOT RESULTS ####
norm <- tail(convergeParams$n, 1)
ploidy <- tail(convergeParams$phi, 1)

par(mfrow=c(4, 1))
plotCNlogRByChr(results, chr = 2, segs = NULL, ploidy = ploidy, normal = norm,
geneAnnot = NULL, ylim = c(-2, 2), cex = 0.5, xlab = "",
main = "Chr 2")
plotAllelicRatio(results, chr = 2, geneAnnot = NULL, ylim = c(0, 1), cex = 0.5,
xlab = "", main = "Chr 2")
plotClonalFrequency(results, chr = 2, normal = norm, geneAnnot = NULL,
ylim = c(0, 1), cex = 0.5, xlab = "", main = "Chr 2")
plotSubcloneProfiles(results, chr = 2, cex = 2, main = "Chr 2")

```

removeEmptyClusters	<i>Post-process TitanCNA results by removing clusters with proportion of data points altered lower than a threshold. The number of clonal clusters, cellular prevalence, and normal contamination will be adjusted to reflect the remaining clonal clusters.</i>
---------------------	--

Description

Filters all vectors in list based on specified chromosome(s) of interest, minimum and maximum read depths, missing data, mappability score threshold

Usage

```
removeEmptyClusters(convergeParams, results, proportionThreshold = 0.001, proportionThresholdClonal)
```

Arguments

convergeParams **list** object that is returned from the function `runEMclonalCN` in **TitanCNA**.

results **data.frame** returned by `outputTitanResults`. Each row corresponds to a genomic SNP position in the analysis.

proportionThreshold
Minimum proportion of the genome altered (by SNPs) for a cluster to be retained. Clonal clusters having lower proportion of alteration are removed.

proportionThresholdClonal
Minimum proportion of genome altered by clonal events (by SNPs) for the highest cellular prevalence cluster.

Details

All vectors in the input data list object, and map, must all have the same number of rows.

Value

`list` with components:

`convergeParams` The same data structure and format as the input `convergeParams` with removed clusters and adjusted parameters.

`results` The same data structure and format as the input `results` with removed clusters and adjusted clonal cluster and cellular prevalence values.

Author(s)

Gavin Ha <gavinha@gmail.com>

References

Ha, G., Roth, A., Khattra, J., Ho, J., Yap, D., Prentice, L. M., Melnyk, N., McPherson, A., Bashashati, A., Laks, E., Biele, J., Ding, J., Le, A., Rosner, J., Shumansky, K., Marra, M. A., Huntsman, D. G., McAlpine, J. N., Aparicio, S. A. J. R., and Shah, S. P. (2014). TITAN: Inference of copy number architectures in clonal cell populations from tumour whole genome sequence data. *Genome Research*, 24: 1881-1893. (PMID: 25060187)

See Also

[outputTitanResults](#)

Examples

```
data(EMresults)

#### COMPUTE OPTIMAL STATE PATH USING VITERBI ####
optimalPath <- viterbiClonalCN(data, convergeParams)

#### FORMAT RESULTS ####
results <- outputTitanResults(data, convergeParams, optimalPath,
                             filename = NULL, posteriorProbs = FALSE,
                             subcloneProfiles = TRUE)

#### REMOVE EMPTY CLONAL CLUSTERS ####
corrResults <- removeEmptyClusters(convergeParams, results, proportionThreshold = 0.001,
proportionThresholdClonal = 0.3)
convergeParams <- corrResults$convergeParams
results <- corrResults$results
```

runEMclonalCN	<i>Function to run the Expectation Maximization Algorithm in TitanCNA.</i>
---------------	--

Description

Function to run the Expectation Maximization Algorithm for inference of model parameters: cellular prevalence, normal proportion, tumour ploidy. This is a key function in the **TitanCNA** package and is the most computationally intense. This function makes calls to a C subroutine that allows the algorithm to be run more efficiently.

Usage

```
runEMclonalCN(data, gParams, nParams, pParams, sParams,
              txnExpLen = 1e15, txnZstrength = 5e05, maxiter = 15,
              maxiterUpdate = 1500, pseudoCounts = 1e-300,
              normalEstimateMethod = "map", estimateS = TRUE,
              estimatePloidy = TRUE, useOutlierState = FALSE, verbose = TRUE)
```

Arguments

data	list object that contains the components for the data to be analyzed. chr, posn, ref, and tumDepth that can be obtained using loadAlleleCounts , and logR that can be obtained using correctReadDepth and getPositionOverlap (see Example).
gParams	list object that contains the copy number and allelic ratio genotype parameters. Can be obtained from loadDefaultParameters .
nParams	list object that contains the normal contamination parameters. Can be obtained from loadDefaultParameters .
pParams	list object that contains the tumour ploidy parameters. Can be obtained from loadDefaultParameters .
sParams	list object that contains the subclonality (cellular prevalence and clonal cluster) parameters. Can be obtained from loadDefaultParameters .
txnExpLen	Influences prior probability of genotype transitions in the HMM. Smaller value have lower tendency to change state; however, too small and it produces underflow problems. 1e-9 works well for up to 3 million total positions.
txnZstrength	Influences prior probability of clonal cluster transitions in the HMM. Smaller value have lower tendency to change clonal cluster state. 1e-9 works well for up to 3 million total positions.
pseudoCounts	Small, machine precision values to add to probabilities to avoid underflow. For example, <code>.Machine\$double.eps</code> .
maxiter	Maximum number of expectation-maximization iterations allowed. In practice, for TitanCNA , it will usually not exceed 20.
maxiterUpdate	Maximum number of coordinate descent iterations during the M-step (of EM algorithm) when parameters are estimated.
normalEstimateMethod	Specifies how to handle normal proportion estimation. Using <code>map</code> will use the maximum a posteriori estimation. Using <code>fixed</code> will not estimate the normal proportion; the normal proportion will be fixed to whatever is specified in <code>params\$normalParams\$n_0</code> . See Details.

estimateS	Logical indicating whether to account for clonality and estimate subclonal events. See Details.
estimatePloidy	Logical indicating whether to estimate and account for tumour ploidy.
useOutlierState	Logical indicating whether an additional outlier state should be used. In practice, this is usually not necessary.
verbose	Set to FALSE to suppress program messages.

Details

This function is implemented with the `"foreach"` package and therefore supports parallelization. See `"doMC"` or `"doMPI"` for some parallelization packages.

The forwards-backwards algorithm is used for the E-step in the EM algorithm. This is done using a call to a C subroutine for each chromosome. The maximization step uses maximum a posteriori (MAP) for estimation of parameters.

If the sample has absolutely no normal contamination, then assign `nParams$n_0 <- 0` and use argument `normalEstimateMethod="fixed"`.

`estimateS` should always be set to TRUE. If no subclonality is expected, then use `loadDefaultParameters(numberClonalClusters=0)`. Using `estimateS=FALSE` and `loadDefaultParameters(numberClonalClusters=0)` gives more or less the same results.

Value

`list` with components for results returned from the EM algorithm, including converged parameters, posterior marginal responsibilities, log likelihood, and original parameter settings.

n	Converged estimate for normal contamination parameter. <code>numeric</code> array containing estimates at each EM iteration.
s	Converged estimate(s) for cellular prevalence parameter(s). This value is defined as the proportion of tumour sample that does <i>not</i> contain the aberrant genotype. This will contrast what is output in <code>outputTitanResults</code> . <code>numeric</code> array containing estimates at each EM iteration. If more than one cluster is specified, then <code>s</code> is a <code>numeric</code> matrix.
var	Converged estimates for variance parameter of the Gaussian mixtures used to model the log ratio data. <code>numeric</code> matrix containing estimates at each EM iteration.
phi	Converged estimate for tumour ploidy parameter. <code>numeric</code> array containing estimates at each EM iteration.
piG	Converged estimate for initial genotype state distribution. <code>numeric</code> matrix containing estimates at each EM iteration.
piZ	Converged estimate for initial clonal cluster state distribution. <code>numeric</code> matrix containing estimates at each EM iteration.
muR	Mean of binomial mixtures computed as a function of <code>s</code> and <code>n</code> . <code>numeric</code> matrix containing estimates at each EM iteration. See References for mathematical details.
muC	Mean of Gaussian mixtures computed as a function of <code>s</code> , <code>n</code> , and <code>phi</code> . <code>numeric</code> matrix containing estimates at each EM iteration. See References for mathematical details.

loglik	Posterior Log-likelihood that includes data likelihood and the priors. numeric array containing estimates at each EM iteration.
rhoG	Posterior marginal probabilities for the genotype states computed during the E-step. Only the final iteration is returned as a numeric matrix.
rhoZ	Posterior marginal probabilities for the clonal cluster states computed during the E-step. Only the final iteration is returned as a numeric matrix.
genotypeParams	Original genotype parameters. See loadDefaultParameters .
ploidyParams	Original tumour ploidy parameters. See loadDefaultParameters .
normalParams	Original normal contamination parameters. See loadDefaultParameters .
clonalParams	Original subclonal parameters. See loadDefaultParameters .
txnExpLen	Original genotype transition expected length. See loadDefaultParameters .
txnZstrength	Original clonal cluster transition expected length. See loadDefaultParameters .
useOutlierState	Original setting indicating usage of outlier state. See loadDefaultParameters .

Author(s)

Gavin Ha <gavinha@gmail.com>

References

Ha, G., Roth, A., Khattra, J., Ho, J., Yap, D., Prentice, L. M., Melnyk, N., McPherson, A., Bashashati, A., Laks, E., Biele, J., Ding, J., Le, A., Rosner, J., Shumansky, K., Marra, M. A., Huntsman, D. G., McAlpine, J. N., Aparicio, S. A. J. R., and Shah, S. P. (2014). TITAN: Inference of copy number architectures in clonal cell populations from tumour whole genome sequence data. *Genome Research*, 24: 1881-1893. (PMID: 25060187)

See Also

["foreach"](#), ["doMC"](#), ["doMPI"](#), [loadAlleleCounts](#), [loadDefaultParameters](#), [viterbiClonalCN](#)

Examples

```
message('Running TITAN ...')
#### LOAD DATA ####
infile <- system.file("extdata", "test_alleleCounts_chr2.txt",
                      package = "TitanCNA")
data <- loadAlleleCounts(infile)

#### LOAD PARAMETERS ####
message('titan: Loading default parameters')
numClusters <- 2
params <- loadDefaultParameters(copyNumber = 5,
                                numberClonalClusters = numClusters, skew = 0.1)

#### READ COPY NUMBER FROM HMMCOPY FILE ####
message('titan: Correcting GC content and mappability biases...')
tumWig <- system.file("extdata", "test_tum_chr2.wig", package = "TitanCNA")
normWig <- system.file("extdata", "test_norm_chr2.wig", package = "TitanCNA")
gc <- system.file("extdata", "gc_chr2.wig", package = "TitanCNA")
map <- system.file("extdata", "map_chr2.wig", package = "TitanCNA")
cnData <- correctReadDepth(tumWig, normWig, gc, map)
```

```

logR <- getPositionOverlap(data$chr, data$posn, cnData)
data$logR <- log(2^logR) #transform to natural log

#### FILTER DATA FOR DEPTH, MAPPABILITY, NA, etc ####
data <- filterData(data, 1:24, minDepth = 10, maxDepth = 200, map = NULL)

#### EM (FWD-BACK) TO TRAIN PARAMETERS ####
#### Can use parallelization packages ####
K <- length(params$genotypeParams$alphaKHyper)
params$genotypeParams$alphaKHyper <- rep(500, K)
params$ploidyParams$phi_0 <- 1.5
convergeParams <- runEMclonalCN(data, gParams = params$genotypeParams,
                               nParams = params$normalParams,
                               pParams = params$ploidyParams,
                               sParams = params$cellPrevParams,
                               maxiter = 3, maxiterUpdate = 500,
                               txnExpLen = 1e15, txnZstrength = 5e5,
                               useOutlierState = FALSE,
                               normalEstimateMethod = "map",
                               estimateS = TRUE, estimatePloidy = TRUE)

```

TitanCNA trained dataset

TITAN EM trained results for an example dataset

Description

Data for chromosome 2 for a triple-negative breast cancer dataset and the expectation-maximization (EM) trained results. Only 20,000 datapoints are included and the data has been scrambled to anonymize patient SNPs.

data Processed input data that is first generated by [loadAlleleCounts](#), and includes log ratios that have been GC content and mappability corrected using [correctReadDepth](#).

convergeParams EM results that are generated by [runEMclonalCN](#)

Usage

```
data(EMresults)
```

Format

‘data’ is a list. ‘convergeParams’ is a list.

References

Shah SP et al. (2012). The clonal and mutational evolution spectrum of primary triple-negative breast cancers. *Nature*, 486(7403): 395-399. (PMID: 22495314)

Ha, G., Roth, A., Lai, D., Bashashati, A., Ding, J., Goya, R., Giuliany, R., Rosner, J., Oloumi, A., Shumansky, K., Chin, S.F., Turashvili, G., Hirst, M., Caldas, C., Marra, M. A., Aparicio, S., and Shah, S. P. (2012). Integrative analysis of genome wide loss of heterozygosity and monoallelic expression at nucleotide resolution reveals disrupted pathways in triple negative breast cancer. *Genome Research*, 22(10):1995,2007. (PMID: 22637570)

Ha, G., Roth, A., Khattra, J., Ho, J., Yap, D., Prentice, L. M., Melnyk, N., McPherson, A., Bashashati, A., Laks, E., Biele, J., Ding, J., Le, A., Rosner, J., Shumansky, K., Marra, M. A., Huntsman, D. G., McAlpine, J. N., Aparicio, S. A. J. R., and Shah, S. P. (2014). TITAN: Inference of copy number architectures in clonal cell populations from tumour whole genome sequence data. *Genome Research*, 24: 1881-1893. (PMID: 25060187)

viterbiClonalCN *Function to run the Viterbi algorithm for **TitanCNA**.*

Description

Function to run the Viterbi algorithm to find the optimal state path in the **TitanCNA** hidden Markov model (HMM). The states returned will indicate the optimal copy number and LOH state as well as the most likely clonal cluster for each data point. After running EM, use the converge parameters and the input data to infer the optimal state for each position. This function makes calls to a C subroutine that allows the algorithm to be run more efficiently.

Usage

```
viterbiClonalCN(data, convergeParams, genotypeParams = NULL)
```

Arguments

data [list](#) object that contains the components for the data to be analyzed. chr, posn, ref, and tumDepth that can be obtained using [loadAlleleCounts](#), and logR that can be obtained using [correctReadDepth](#) and [getPositionOverlap](#) (see Example).

convergeParams [list](#) object that is returned from the function [runEMclonalCN](#) in **TitanCNA**.

genotypeParams If convergeParams does not contain a genotypeParams element, then the user can pass this as an argument.

Details

It is difficult to interpret the output of this function directly. The user should use the function [outputTitanResults](#) after.

Value

numeric [array](#) containing the integer states corresponding to each data point in data.

Author(s)

Gavin Ha <gavinha@gmail.com>

References

Ha, G., Roth, A., Khattra, J., Ho, J., Yap, D., Prentice, L. M., Melnyk, N., McPherson, A., Bashashati, A., Laks, E., Biele, J., Ding, J., Le, A., Rosner, J., Shumansky, K., Marra, M. A., Huntsman, D. G., McAlpine, J. N., Aparicio, S. A. J. R., and Shah, S. P. (2014). TITAN: Inference of copy number architectures in clonal cell populations from tumour whole genome sequence data. *Genome Research*, 24: 1881-1893. (PMID: 25060187)

See Also

[outputTitanResults](#), [loadAlleleCounts](#)

Examples

```
data(EMresults)

#### COMPUTE OPTIMAL STATE PATH USING VITERBI ####
optimalPath <- viterbiClonalCN(data, convergeParams)
```

WIG Import Functions *WIG Import Functions*

Description

Fast fixedStep WIG file reading and parsing

Usage

```
wigToRangedData(wigfile, verbose = TRUE)
```

Arguments

wigfile	Filepath to fixedStep WIG format file
verbose	Set to FALSE to suppress messages

Details

Reads the entire file into memory, then processes the file in rapid fashion, thus performance will be limited by memory capacity.

The WIG file is expected to conform to the minimal fixedStep WIG format (see References), where each chromosome is started by a “fixedStep” declaration line. The function assumes only a single track in the WIG file, and will ignore any lines before the first line starting with “fixedStep”.

Value

[RangedData](#) for [wigToRangedData](#) with chromosome and position information, sorted in decreasing chromosomal size and increasing position.

Author(s)

Daniel Lai

References

WIG <http://genome.ucsc.edu/goldenPath/help/wiggle.html>

See Also

[wigToRangedData](#) is a wrapper around these functions for easy WIG file loading and structure formatting. It is taken from the **HMMcopy** package.

Examples

```
map <- system.file("extdata", "map_chr2.wig", package = "TitanCNA")  
mScore <- as.data.frame(wigToRangedData(map))
```

Index

- *Topic **IO**
 - correctReadDepth, [5](#)
 - extractAlleleReadCounts, [7](#)
 - Formatting and output of Titan results, [10](#)
 - loadAlleleCounts, [14](#)
 - TitanCNA-package, [2](#)
 - WIG Import Functions, [26](#)
- *Topic **aplot**
 - Plotting TITAN results, [17](#)
- *Topic **attribute**
 - loadDefaultParameters, [15](#)
- *Topic **color**
 - Plotting TITAN results, [17](#)
- *Topic **datasets**
 - TitanCNA trained dataset, [24](#)
- *Topic **htest**
 - runEMclonalCN, [21](#)
 - viterbiClonalCN, [25](#)
- *Topic **iteration**
 - runEMclonalCN, [21](#)
 - viterbiClonalCN, [25](#)
- *Topic **manip**
 - computeSdbwIndex, [4](#)
 - correctReadDepth, [5](#)
 - filterData, [8](#)
 - Formatting and output of Titan results, [10](#)
 - getPositionOverlap, [13](#)
 - removeEmptyClusters, [19](#)
 - runEMclonalCN, [21](#)
 - TitanCNA-package, [2](#)
 - viterbiClonalCN, [25](#)
- *Topic **models**
 - runEMclonalCN, [21](#)
 - viterbiClonalCN, [25](#)
- *Topic **multivariate**
 - runEMclonalCN, [21](#)
 - viterbiClonalCN, [25](#)
- *Topic **package**
 - TitanCNA-package, [2](#)
- array, [10](#), [13](#), [25](#)
- computeSdbwIndex, [3](#), [11](#), [12](#), [18](#)
- convergeParams (TitanCNA trained dataset), [24](#)
- correctReadcount, [6](#)
- correctReadDepth, [5](#), [10](#), [13](#), [21](#), [24](#), [25](#)
- data (TitanCNA trained dataset), [24](#)
- data.frame, [6](#), [7](#), [9](#), [11](#), [13](#), [17](#), [19](#)
- EMresults (TitanCNA trained dataset), [24](#)
- extractAlleleReadCounts, [7](#)
- filterData, [8](#)
- foreach, [22](#), [23](#)
- Formatting and output of Titan results, [10](#)
- getPositionOverlap, [10](#), [13](#), [21](#), [25](#)
- list, [4](#), [8–10](#), [12](#), [15](#), [16](#), [19–22](#), [25](#)
- loadAlleleCounts, [4](#), [5](#), [9](#), [10](#), [13](#), [14](#), [16](#), [17](#), [21](#), [23–26](#)
- loadDefaultParameters, [14](#), [15](#), [15](#), [21–23](#)
- outputModelParameters, [5](#), [11](#), [12](#)
- outputModelParameters (Formatting and output of Titan results), [10](#)
- outputTitanResults, [4](#), [10](#), [11](#), [17–20](#), [22](#), [25](#), [26](#)
- outputTitanResults (Formatting and output of Titan results), [10](#)
- PileupParam, [7](#), [8](#)
- plot, [18](#)
- plotAllelicRatio, [18](#)
- plotAllelicRatio (Plotting TITAN results), [17](#)
- plotClonalFrequency, [18](#)
- plotClonalFrequency (Plotting TITAN results), [17](#)
- plotCNlogRByChr, [17](#), [18](#)
- plotCNlogRByChr (Plotting TITAN results), [17](#)
- plotSubcloneProfiles, [18](#)

plotSubcloneProfiles (Plotting TITAN results), [17](#)
Plotting TITAN results, [17](#)

RangedData, [26](#)
removeEmptyClusters, [19](#)
runEMclonalCN, [10](#), [12](#), [17–19](#), [21](#), [24](#), [25](#)

TitanCNA (TitanCNA-package), [2](#)
TitanCNA trained dataset, [24](#)
TitanCNA-dataset (TitanCNA trained dataset), [24](#)
TitanCNA-package, [2](#)

viterbiClonalCN, [10](#), [12](#), [23](#), [25](#)

WIG Import Functions, [26](#)
wigToRangedData, [5](#), [6](#), [26](#)
wigToRangedData (WIG Import Functions), [26](#)