

Package ‘PureCN’

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Type Package

Title Copy number calling and SNV classification using targeted short read sequencing

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Description This package estimates tumor purity, copy number, and loss of heterozygosity (LOH), and classifies single nucleotide variants (SNVs) by somatic status and clonality. PureCN is designed for targeted short read sequencing data, integrates well with standard somatic variant detection and copy number pipelines, and has support for tumor samples without matching normal samples.

Depends R (>= 3.5.0), DNACopy, VariantAnnotation (>= 1.14.1)

Imports GenomicRanges (>= 1.20.3), IRanges (>= 2.2.1), RColorBrewer, S4Vectors, data.table, grDevices, graphics, stats, utils, SummarizedExperiment, Seqinfo, GenomeInfoDb, GenomicFeatures, Rsamtools, Biobase, Biostrings, BiocGenerics, rtracklayer, ggplot2, gridExtra, futile.logger, VGAM, tools, methods, mclust, rhdf5, Matrix

Suggests BiocParallel, BiocStyle, PSCBS, R.utils, TxDb.Hsapiens.UCSC.hg19.knownGene, covr, knitr, optparse, org.Hs.eg.db, jsonlite, markdown, rmarkdown, testthat

Enhances genomicsdb (>= 0.0.3)

VignetteBuilder knitr

License Artistic-2.0

BugReports <https://github.com/lima1/PureCN/issues>

URL <https://github.com/lima1/PureCN>

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<i>adjustLogRatio</i>	<i>Adjust tumor vs. normal coverage log ratio for tumor purity and ploidy</i>
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Description

This function can be used to adjust the log ratio for tumor purity and ploidy for downstream tools that expect a log2 ratio (for example GISTIC).

Usage

```
adjustLogRatio(ratio, purity, ploidy, is.log2 = TRUE, min.ratio = 2^-8)
```

Arguments

<code>ratio</code>	Vector of log2 tumor vs normal coverage ratios.
<code>purity</code>	Purity of sample.
<code>ploidy</code>	Ploidy of sample.
<code>is.log2</code>	log.ratio is log2 transformed.
<code>min.ratio</code>	Minimum (non-log2-transformed) ratio. Set to approx -8 log2 adjusted.

Value

numeric(length(log.ratio)), log.ratio adjusted for purity and ploidy

Author(s)

Markus Riester

References

Nature Biotechnology. * Toal (2018), <https://github.com/lima1/PureCN/issues/40>

Examples

```

normal.coverage.file <- system.file("extdata", "example_normal.txt.gz",
  package = "PureCN")
tumor.coverage.file <- system.file("extdata", "example_tumor.txt.gz",
  package = "PureCN")
normal <- readCoverageFile(normal.coverage.file)
tumor <- readCoverageFile(tumor.coverage.file)
log.ratio <- calculateLogRatio(normal, tumor)
log.ratio.adjusted <- adjustLogRatio(log.ratio, 0.65, 1.73)

```

 annotateTargets

Annotate targets with gene symbols

Description

This function can be used to add a ‘Gene’ meta column containing gene symbols to a GRanges object. It applies heuristics to find the protein coding genes that were likely meant to target in the assay design in case transcripts overlap.

Usage

```
annotateTargets(x, txdb, org)
```

Arguments

x	A GRanges object with intervals to annotate
txdb	A TxDb database, e.g. TxDb.Hsapiens.UCSC.hg19.knownGene
org	A OrgDb object, e.g. org.Hs.eg.db.

Value

A GRanges object.

Author(s)

Markus Riester

Examples

```

library(TxDb.Hsapiens.UCSC.hg19.knownGene)
library(org.Hs.eg.db)

normal.coverage.file <- system.file("extdata", "example_normal.txt.gz",
  package = "PureCN")
x <- head(readCoverageFile(normal.coverage.file), 100)
x <- annotateTargets(x, TxDb.Hsapiens.UCSC.hg19.knownGene, org.Hs.eg.db)

```

bootstrapResults	<i>Bootstrapping variant fits</i>
------------------	-----------------------------------

Description

This function bootstraps variants, then optionally re-ranks solutions by using the bootstrap estimate of the likelihood score, and then optionally removes solutions that never ranked high in any bootstrap replicate.

Usage

```
bootstrapResults(res, n = 500, top = NULL, reorder = FALSE)
```

Arguments

res	Return object of the runAbsoluteCN function.
n	Number of bootstrap replicates.
top	Include solution if it appears in the top n solutions of any bootstrap replicate. If NULL, do not filter solutions.
reorder	Reorder results by bootstrap value.

Value

Returns a [runAbsoluteCN](#) object with added bootstrap value to each solution. This value is the fraction of bootstrap replicates in which the solution ranked first.

Author(s)

Markus Riester

See Also

[runAbsoluteCN](#)

Examples

```
data(purecn.example.output)
ret.boot <- bootstrapResults(purecn.example.output, n=100)
plotAbs(ret.boot, type="overview")
```

calculateBamCoverageByInterval

Function to calculate coverage from BAM file

Description

Takes a BAM file and an interval file as input and returns coverage for each interval. Coverage should be then GC-normalized using the [correctCoverageBias](#) function before determining purity and ploidy with [runAbsoluteCN](#). Uses the scanBam function and applies low quality, duplicate reads as well as secondary alignment filters.

Usage

```
calculateBamCoverageByInterval(
  bam.file,
  interval.file,
  output.file = NULL,
  index.file = bam.file,
  keep.duplicates = FALSE,
  chunks = 20,
  ...
)
```

Arguments

bam.file	Filename of a BAM file.
interval.file	File specifying the intervals. Interval is expected in first column in format CHR:START-END.
output.file	Optionally, write minimal coverage file. Can be read with the readCoverageFile function.
index.file	The bai index. This is expected without the .bai file suffix, see ?scanBam.
keep.duplicates	Keep or remove duplicated reads.
chunks	Split interval.file into specified number of chunks to reduce memory usage.
...	Additional parameters passed to ScanBamParam.

Value

Returns total and average coverage by intervals.

Author(s)

Markus Riester

See Also

[preprocessIntervals](#) [correctCoverageBias](#) [runAbsoluteCN](#)

Examples

```

bam.file <- system.file("extdata", "ex1.bam", package = "PureCN",
  mustWork = TRUE)
interval.file <- system.file("extdata", "ex1_intervals.txt",
  package = "PureCN", mustWork = TRUE)

# Calculate raw coverage from BAM file. These need to be corrected for
# GC-bias using the correctCoverageBias function before determining purity
# and ploidy.
coverage <- calculateBamCoverageByInterval(bam.file = bam.file,
  interval.file = interval.file)

```

calculateLogRatio	<i>Calculate coverage log-ratio of tumor vs. normal</i>
-------------------	---

Description

This function is automatically called by [runAbsoluteCN](#) when normal and tumor coverage are provided (and not a segmentation file or target-level log-ratios). This function is therefore normally not called by the user.

Usage

```
calculateLogRatio(normal, tumor)
```

Arguments

normal	Normal coverage read in by the readCoverageFile function.
tumor	Tumor coverage read in by the readCoverageFile function.

Value

numeric(length(tumor)), tumor vs. normal copy number log-ratios for all targets.

Author(s)

Markus Riester

Examples

```

normal.coverage.file <- system.file("extdata", "example_normal.txt.gz",
  package = "PureCN")
tumor.coverage.file <- system.file("extdata", "example_tumor.txt.gz",
  package = "PureCN")
normal <- readCoverageFile(normal.coverage.file)
tumor <- readCoverageFile(tumor.coverage.file)
log.ratio <- calculateLogRatio(normal, tumor)

```

calculateMappingBiasGatk4

Calculate Mapping Bias from GATK4 GenomicsDB

Description

Function calculate mapping bias for each variant in the provided panel of normals GenomicsDB.

Usage

```
calculateMappingBiasGatk4(
  workspace,
  reference.genome,
  min.normals = 1,
  min.normals.betafit = 7,
  min.normals.assign.betafit = 3,
  min.normals.position.specific.fit = 10,
  min.median.coverage.betafit = 5,
  num.betafit.clusters = 9,
  min.betafit.rho = 1e-04,
  max.betafit.rho = 0.2,
  AF.info.field = "AF"
)
```

Arguments

workspace	Path to the GenomicsDB created by GenomicsDBImport
reference.genome	Reference FASTA file.
min.normals	Minimum number of normals with heterozygous SNP for calculating position-specific mapping bias.
min.normals.betafit	Minimum number of normals with heterozygous SNP fitting a beta distribution
min.normals.assign.betafit	Minimum number of normals with heterozygous SNPs to assign to a beta binomial fit cluster
min.normals.position.specific.fit	Minimum normals to use position-specific beta-binomial fits. Otherwise only clustered fits are used.
min.median.coverage.betafit	Minimum median coverage of normals with heterozygous SNP for fitting a beta distribution
num.betafit.clusters	Maximum number of beta binomial fit clusters
min.betafit.rho	Minimum dispersion factor rho
max.betafit.rho	Maximum dispersion factor rho
AF.info.field	Field in the workspace that stores the allelic fraction

Value

A GRanges object with mapping bias and number of normal samples with this variant.

Author(s)

Markus Riester

Examples

```
## Not run:
resources_file <- system.file("extdata", "gatk4_pon_db.tgz",
  package = "PureCN")
tmp_dir <- tempdir()
untar(resources_file, exdir = tmp_dir)
workspace <- file.path(tmp_dir, "gatk4_pon_db")
bias <- calculateMappingBiasGatk4(workspace, "hg19")
saveRDS(bias, "mapping_bias.rds")
unlink(tmp_dir, recursive=TRUE)

## End(Not run)
```

`calculateMappingBiasVcf`*Calculate Mapping Bias*

Description

Function calculate mapping bias for each variant in the provided panel of normals VCF.

Usage

```
calculateMappingBiasVcf(
  normal.panel.vcf.file,
  min.normals = 1,
  min.normals.betafit = 7,
  min.normals.assign.betafit = 3,
  min.normals.position.specific.fit = 10,
  min.median.coverage.betafit = 5,
  num.betafit.clusters = 9,
  min.betafit.rho = 1e-04,
  max.betafit.rho = 0.2,
  yieldSize = 50000,
  genome
)
```

Arguments

`normal.panel.vcf.file`

character(1) Combined VCF file of a panel of normals, reference and alt counts as AD genotype field. Needs to be compressed and indexed with bgzip and tabix, respectively.

min.normals	Minimum number of normals with heterozygous SNP for calculating position-specific mapping bias.
min.normals.betafit	Minimum number of normals with heterozygous SNP fitting a beta binomial distribution
min.normals.assign.betafit	Minimum number of normals with heterozygous SNPs to assign to a beta binomial fit cluster
min.normals.position.specific.fit	Minimum normals to use position-specific beta-binomial fits. Otherwise only clustered fits are used.
min.median.coverage.betafit	Minimum median coverage of normals with heterozygous SNP for fitting a beta binomial distribution
num.betafit.clusters	Maximum number of beta binomial fit clusters
min.betafit.rho	Minimum dispersion factor rho
max.betafit.rho	Maximum dispersion factor rho
yieldSize	See TabixFile
genome	See readVcf

Value

A GRanges object with mapping bias and number of normal samples with this variant.

Author(s)

Markus Riester

Examples

```
normal.panel.vcf <- system.file("extdata", "normalpanel.vcf.gz",
  package = "PureCN")
bias <- calculateMappingBiasVcf(normal.panel.vcf, genome = "h19")
saveRDS(bias, "mapping_bias.rds")
```

calculatePowerDetectSomatic

Power calculation for detecting somatic mutations

Description

This function calculates the probability of correctly rejecting the null hypothesis that an alt allele is a sequencing error rather than a true (mono-)clonal mutation.

Usage

```
calculatePowerDetectSomatic(
  coverage,
  f = NULL,
  purity = NULL,
  ploidy = NULL,
  cell.fraction = 1,
  error = 0.001,
  fpr = 5e-07,
  verbose = TRUE
)
```

Arguments

coverage	Mean sequencing coverage.
f	Mean expected allelic fraction. If NULL, requires purity and ploidy and then calculates the expected fraction.
purity	Purity of sample. Only required when f is NULL.
ploidy	Ploidy of sample. Only required when f is NULL.
cell.fraction	Fraction of cells harboring mutation. Ignored if f is not NULL.
error	Estimated sequencing error rate.
fpr	Required false positive rate for mutation vs. sequencing error.
verbose	Verbose output.

Value

A list with elements

power	Power to detect somatic mutations.
k	Minimum number of supporting reads.
f	Expected allelic fraction.

Author(s)

Markus Riester

References

Carter et al. (2012), Absolute quantification of somatic DNA alterations in human cancer. Nature Biotechnology.

Examples

```
purity <- c(0.1, 0.15, 0.2, 0.25, 0.4, 0.6, 1)
coverage <- seq(5, 35, 1)
power <- lapply(purity, function(p) sapply(coverage, function(cv)
  calculatePowerDetectSomatic(coverage = cv, purity = p, ploidy = 2,
    verbose = FALSE)$power))

# Figure S7b in Carter et al.
plot(coverage, power[[1]], col = 1, xlab = "Sequence coverage",
```

```

      ylab = "Detection power", ylim = c(0, 1), type = "l")

  for (i in 2:length(power)) lines(coverage, power[[i]], col = i)
  abline(h = 0.8, lty = 2, col = "grey")
  legend("bottomright", legend = paste("Purity", purity),
        fill = seq_along(purity))

  # Figure S7c in Carter et al.
  coverage <- seq(5, 350, 1)
  power <- lapply(purity, function(p) sapply(coverage, function(cv)
    calculatePowerDetectSomatic(coverage = cv, purity = p, ploidy = 2,
      cell.fraction = 0.2, verbose = FALSE)$power))
  plot(coverage, power[[1]], col = 1, xlab = "Sequence coverage",
      ylab = "Detection power", ylim = c(0, 1), type = "l")

  for (i in 2:length(power)) lines(coverage, power[[i]], col = i)
  abline(h = 0.8, lty = 2, col = "grey")
  legend("bottomright", legend = paste("Purity", purity),
        fill = seq_along(purity))

```

calculateTangentNormal

Calculate tangent normal

Description

Reimplementation of GATK4 denoising. Please cite the relevant GATK publication if you use this in a publication.

Usage

```

calculateTangentNormal(
  tumor.coverage.file,
  normalDB,
  num.eigen = 20,
  ignore.sex = FALSE,
  sex = NULL
)

```

Arguments

tumor.coverage.file	Coverage file or data of a tumor sample.
normalDB	Database of normal samples, created with createNormalDatabase .
num.eigen	Number of eigen vectors used.
ignore.sex	If FALSE, detects sex of sample and returns best normals with matching sex.
sex	Sex of sample. If NULL, determine with getSexFromCoverage and default parameters. Valid values are F for female, M for male. If all chromosomes are diploid, specify diploid.

Author(s)

Markus Riester

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

```
tumor.coverage.file <- system.file('extdata', 'example_tumor.txt.gz',
  package = 'PureCN')
normal.coverage.file <- system.file("extdata", "example_normal.txt.gz",
  package = "PureCN")
normal2.coverage.file <- system.file("extdata", "example_normal2.txt.gz",
  package = "PureCN")
normal.coverage.files <- c(normal.coverage.file, normal2.coverage.file)
normalDB <- createNormalDatabase(normal.coverage.files)
pool <- calculateTangentNormal(tumor.coverage.file, normalDB)
```

callAlterations

*Calling of amplifications and deletions***Description**

Function to extract major copy number alterations from a [runAbsoluteCN](#) return object.

Usage

```
callAlterations(
  res,
  id = 1,
  cutoffs = c(0.5, 6, 7),
  log.ratio.cutoffs = c(-0.9, 0.9),
  failed = NULL,
  all.genes = FALSE
)
```

Arguments

res	Return object of the runAbsoluteCN function.
id	Candidate solutions to be used. id=1 will use the maximum likelihood (or curated) solution.
cutoffs	Copy numbers cutoffs to call losses, focal amplifications and broad amplifications.
log.ratio.cutoffs	Copy numbers log-ratio cutoffs to call losses and amplifications in failed samples.
failed	Indicates whether sample was failed. If NULL, use available annotation, which can be set in the curation file.
all.genes	If FALSE, then only return amplifications and deletions passing the thresholds.

Value

A data.frame with gene-level amplification and deletion calls.

Author(s)

Markus Riester

See Also

[runAbsoluteCN](#)

Examples

```
data(purecn.example.output)
callAlterations(purecn.example.output)
callAlterations(purecn.example.output, all.genes=TRUE)["ESR2",]
```

callAlterationsFromSegmentation

Calling of amplifications and deletions from segmentations

Description

This function can be used to obtain gene-level copy number calls from segmentations. This is useful for comparing PureCN's segmentations with segmentations obtained by different tools on the gene-level. Segmentation file can contain multiple samples.

Usage

```
callAlterationsFromSegmentation(
  sampleid,
  chr,
  start,
  end,
  num.mark = NA,
  seg.mean,
  C,
  interval.file,
  fun.focal = findFocal,
  args.focal = list(),
  ...
)
```

Arguments

sampleid	The sampleid column in the segmentation file.
chr	The chromosome column.
start	The start positions of the segments.
end	The end positions of the segments.

num.mark	Optionally, the number of probes or markers in each segment.
seg.mean	The segment mean.
C	The segment integer copy number.
interval.file	A mapping file that assigns GC content and gene symbols to each exon in the coverage files. Used for generating gene-level calls. First column in format CHR:START-END. Second column GC content (0 to 1). Third column gene symbol. This file is generated with the preprocessIntervals function.
fun.focal	Function for identifying focal amplifications. Defaults to findFocal .
args.focal	Arguments for focal amplification function.
...	Arguments passed to callAlterations .

Value

A list of [callAlterations](#) data.frame objects, one for each sample.

Author(s)

Markus Riester

Examples

```
data(purecn.example.output)
seg <- purecn.example.output$results[[1]]$seg
interval.file <- system.file("extdata", "example_intervals.txt",
                             package = "PureCN")

calls <- callAlterationsFromSegmentation(sampleid = seg$ID, chr = seg$chrom,
                                         start = seg$loc.start, end = seg$loc.end, num.mark = seg$num.mark,
                                         seg.mean = seg$seg.mean, C = seg$C, interval.file = interval.file)
```

callAmplificationsInLowPurity

Calling of amplifications in low purity samples

Description

Function to extract amplification from a [runAbsoluteCN](#) return object in samples of too low purity for the standard [callAlterations](#).

Usage

```
callAmplificationsInLowPurity(
  res,
  normalDB,
  pvalue.cutoff = 0.001,
  percentile.cutoff = 90,
  min.width = 3,
  all.genes = FALSE,
  purity = NULL,
  BPPARAM = NULL
)
```

Arguments

<code>res</code>	Return object of the runAbsoluteCN function.
<code>normalDB</code>	Normal database, created with createNormalDatabase .
<code>pvalue.cutoff</code>	Copy numbers log-ratio cutoffs to call amplifications as calculating using the log-ratios observed in <code>normalDB</code>
<code>percentile.cutoff</code>	Only report genes with log2-ratio mean exceeding this sample-wise cutoff.
<code>min.width</code>	Minimum number of targets
<code>all.genes</code>	If FALSE, then only return amplifications passing the thresholds.
<code>purity</code>	If not NULL, then scale log2-ratios to the corresponding integer copy number. Useful when accurate ctDNA fractions (between 4-10 percent) are available.
<code>BPPARAM</code>	BiocParallelParam object. If NULL, does not use parallelization for fitting local optima.

Value

A data.frame with gene-level amplification calls.

Author(s)

Markus Riester

See Also

[runAbsoluteCN](#) [callAlterations](#)

Examples

```
data(purecn.example.output)
normal.coverage.file <- system.file("extdata", "example_normal.txt.gz",
  package = "PureCN")
normal2.coverage.file <- system.file("extdata", "example_normal2.txt.gz",
  package = "PureCN")
normal.coverage.files <- c(normal.coverage.file, normal2.coverage.file)
normalDB <- createNormalDatabase(normal.coverage.files)
callAmplificationsInLowPurity(purecn.example.output, normalDB)["EIF2A", ]
```

callCIN

Call Chromosomal Instability

Description

This function provides detailed CIN information.

Usage

```
callCIN(
  res,
  id = 1,
  allele.specific = TRUE,
  reference.state = c("dominant", "normal")
)
```

Arguments

<code>res</code>	Return object of the runAbsoluteCN function.
<code>id</code>	Candidate solution to extract CIN from. <code>id=1</code> will use the maximum likelihood solution.
<code>allele.specific</code>	Use allele-specific or only total copy number for detecting abnormal regions. Copy-number neutral LOH would be ignored when this parameter is set to FALSE.
<code>reference.state</code>	Copy number regions different from the reference state are counted as abnormal. Default is dominant means the most common state. The other option is normal, which defines normal heterozygous, diploid as reference. The default is robust to errors in ploidy.

Value

Returns `double(1)` with CIN value.

Author(s)

Markus Riester

See Also

[runAbsoluteCN](#)

Examples

```
data(purecn.example.output)
head(callCIN(purecn.example.output))
```

callLOH

Get regions of LOH

Description

This function provides detailed LOH information by region.

Usage

```
callLOH(res, id = 1, arm.cutoff = 0.9, keep.no.snp.segments = TRUE)
```

Arguments

res	Return object of the runAbsoluteCN function.
id	Candidate solution to extract LOH from. id=1 will use the maximum likelihood solution.
arm.cutoff	Min fraction LOH on a chromosome arm to call whole arm events.
keep.no.snp.segments	Segments without heterozygous SNPs have no LOH information. This defines whether these segments should be reported anyways.

Value

Returns `data.frame` with LOH regions.

Author(s)

Markus Riester

See Also

[runAbsoluteCN](#)

Examples

```
data(purecn.example.output)
head(callLOH(purecn.example.output))
```

callMutationBurden	<i>Call mutation burden</i>
--------------------	-----------------------------

Description

This function provides detailed mutation burden information.

Usage

```
callMutationBurden(
  res,
  id = 1,
  remove.flagged = TRUE,
  min.prior.somatic = 0.1,
  max.prior.somatic = 1,
  min.cellfraction = 0,
  fun.countMutation = function(vcf) width(vcf) == 1,
  callable = NULL,
  exclude = NULL
)
```

Arguments

<code>res</code>	Return object of the runAbsoluteCN function.
<code>id</code>	Candidate solution to extract mutation burden from. <code>id=1</code> will use the maximum likelihood solution.
<code>remove.flagged</code>	Remove variants flagged by predictSomatic .
<code>min.prior.somatic</code>	Exclude variants with somatic prior probability lower than this cutoff.
<code>max.prior.somatic</code>	Exclude variants with somatic prior probability higher than this cutoff. This is useful for removing hotspot mutations in small panels that might inflate the mutation burden.
<code>min.cellfraction</code>	Exclude variants with cellular fraction lower than this cutoff. These are sub-clonal mutations or artifacts with very low allelic fraction.
<code>fun.countMutation</code>	Function that can be used to filter the input VCF further for filtering, for example to only keep missense mutations. Expects a logical vector indicating whether variant should be counted (TRUE) or not (FALSE). Default is to keep only single nucleotide variants.
<code>callable</code>	GRanges object with callable genomic regions, for example obtained by 'GATK CallableLoci' BED file, imported with <code>rtracklayer</code> .
<code>exclude</code>	GRanges object with genomic regions that should be excluded from the callable regions, for example intronic regions. Requires <code>callable</code> .

Value

Returns `data.frame` with mutation counts and sizes of callable regions.

Author(s)

Markus Riester

See Also

[runAbsoluteCN](#) [predictSomatic](#)

Examples

```
data(purecn.example.output)
callMutationBurden(purecn.example.output)

# To calculate exact mutations per megabase, we can provide a BED
# file containing all callable regions
callableBed <- import(system.file("extdata", "example_callable.bed.gz",
  package = "PureCN"))

# We can exclude some regions for mutation burden calculation,
# for example intronic regions.
exclude <- GRanges(seqnames = "chr1", IRanges(start = 1,
  end = max(end(callableBed))))

# We can also exclude specific mutations by filtering the input VCF
```

```
myVcfFilter <- function(vcf) seqnames(vcf)!="chr2"

callsCallable <- callMutationBurden(purecn.example.output,
  callable = callableBed, exclude = exclude,
  fun.countMutation = myVcfFilter)
```

centromeres	<i>A list of data.frames containing centromere positions.</i>
-------------	---

Description

A list of data.frames containing centromere positions for hg18, hg19 and hg38. Downloaded from the UCSC genome browser.

Usage

```
data(centromeres)
```

Value

A list with three data frames, "hg18", "hg19", and "hg38". Each contains three columns

chrom a factor with levels chr1 chr10 chr11 chr12 chr13 chr14 chr15 chr16 chr17 chr18 chr19
chr2 chr20 chr21 chr22 chr3 chr4 chr5 chr6 chr7 chr8 chr9 chrX chrY

chromStart a numeric vector

chromEnd a numeric vector

References

The script downloadCentromeres.R in the extdata directory was used to generate the data.frames.

Examples

```
data(centromeres)
```

correctCoverageBias	<i>Correct for library-specific coverage biases</i>
---------------------	---

Description

Takes as input coverage data and a mapping file for GC content and optionally replication timing. Will then normalize coverage data for GC-bias. Plots the pre and post normalization GC profiles.

Usage

```
correctCoverageBias(  
  coverage.file,  
  interval.file,  
  output.file = NULL,  
  plot.bias = FALSE,  
  plot.max.density = 50000,  
  output.qc.file = NULL  
)
```

Arguments

coverage.file	Coverage file or coverage data parsed with the readCoverageFile function.
interval.file	File providing GC content for each exon in the coverage files. First column in format CHR:START-END. Additional optional columns provide gene symbols, mappability and replication timing. This file is generated with the preprocessIntervals function.
output.file	Optionally, write file with GC corrected coverage. Can be read with the readCoverageFile function.
plot.bias	Optionally, plot profiles of the pre-normalized and post-normalized coverage. Provides a quick visual check of coverage bias.
plot.max.density	By default, if the number of intervals in the probe-set is > 50000, uses a kernel density estimate to plot the coverage distribution. This uses the <code>stat_density</code> function from the <code>ggplot2</code> package. Using this parameter, change the threshold at which density estimation is applied. If the <code>plot.bias</code> parameter is set as <code>FALSE</code> , this will be ignored.
output.qc.file	Write miscellaneous coverage QC metrics to file.

Author(s)

Angad Singh, Markus Riester

See Also

[preprocessIntervals](#)

Examples

```
normal.coverage.file <- system.file("extdata", "example_normal.txt.gz",  
  package = "PureCN")  
interval.file <- system.file("extdata", "example_intervals.txt",  
  package = "PureCN")  
coverage <- correctCoverageBias(normal.coverage.file, interval.file)
```

createCurationFile	<i>Create file to curate PureCN results</i>
--------------------	---

Description

Function to create a CSV file that can be used to mark the correct solution in the output of a [runAbsoluteCN](#) run.

Usage

```
createCurationFile(  
  file.rds,  
  overwrite.uncurated = TRUE,  
  overwrite.curated = FALSE  
)
```

Arguments

file.rds	Output of the runAbsoluteCN function, serialized with saveRDS.
overwrite.uncurated	Overwrite existing files unless flagged as 'Curated'.
overwrite.curated	Overwrite existing files even if flagged as 'Curated'.

Value

A data.frame with the tumor purity and ploidy of the maximum likelihood solution.

Author(s)

Markus Riester

See Also

[runAbsoluteCN](#)

Examples

```
data(purecn.example.output)  
file.rds <- "Sample1_PureCN.rds"  
saveRDS(purecn.example.output, file = file.rds)  
createCurationFile(file.rds)
```

createNormalDatabase *Create database of normal samples*

Description

Function to create a database of normal samples, used to normalize tumor coverages.

Usage

```
createNormalDatabase(
  normal.coverage.files,
  sex = NULL,
  coverage.outliers = c(0.25, 4),
  min.coverage = 0.25,
  max.missing = 0.03,
  low.coverage = 15,
  optimal.off.target.counts = 120,
  plot = FALSE,
  ...
)
```

Arguments

normal.coverage.files	Vector with file names pointing to coverage files of normal samples.
sex	character(length(normal.coverage.files)) with sex for all files. F for female, M for male. If all chromosomes are diploid, specify diploid. If NULL, determine from coverage.
coverage.outliers	Exclude samples with coverages below or above the specified cutoffs (fractions of the normal sample coverages median). Only for databases with more than 5 samples.
min.coverage	Exclude intervals with coverage lower than the specified fraction of the chromosome median in the pool of normals.
max.missing	Exclude intervals with zero coverage in the specified fraction of normal samples.
low.coverage	Specifies the maximum number of total reads (NOT average coverage) to call a target low coverage.
optimal.off.target.counts	Used to suggest an optimal off-target interval width (BETA).
plot	Diagnostics plot, useful to tune parameters.
...	Arguments passed to the prcomp function.

Value

A normal database that can be used in the [calculateTangentNormal](#) function to retrieve a coverage normalization sample for a given tumor sample.

Author(s)

Markus Riester

See Also

[calculateTangentNormal](#)

Examples

```
normal.coverage.file <- system.file("extdata", "example_normal.txt.gz",
  package = "PureCN")
normal2.coverage.file <- system.file("extdata", "example_normal2.txt.gz",
  package = "PureCN")
normal.coverage.files <- c(normal.coverage.file, normal2.coverage.file)
normalDB <- createNormalDatabase(normal.coverage.files)
```

filterIntervals	<i>Remove low quality intervals</i>
-----------------	-------------------------------------

Description

This function determines which intervals in the coverage files should be included or excluded in the segmentation. It is called via the `fun.filterIntervals` argument of [runAbsoluteCN](#). The arguments are passed via `args.filterIntervals`.

Usage

```
filterIntervals(
  normal,
  tumor,
  log.ratio,
  seg.file,
  filter.lowhigh.gc = 0.001,
  min.coverage = 15,
  min.total.counts = 100,
  min.targeted.base = 5,
  min.mappability = c(0.6, 0.1),
  min.fraction.offtarget = 0.05,
  normalDB = NULL
)
```

Arguments

<code>normal</code>	Coverage data for normal sample.
<code>tumor</code>	Coverage data for tumor sample.
<code>log.ratio</code>	Copy number log-ratios, one for each interval in the coverage file.
<code>seg.file</code>	If not NULL, then do not filter intervals, because data is already segmented via the provided segmentation file.
<code>filter.lowhigh.gc</code>	Quantile q (defines lower q and upper $1-q$) for removing intervals with outlier GC profile. Assuming that GC correction might not have been worked on those. Requires <code>interval.file</code> .

<code>min.coverage</code>	Minimum coverage in both normal and tumor. Intervals with lower coverage are ignored. If a <code>normalDB</code> is provided, then this database already provides information about low quality intervals and the <code>min.coverage</code> is set to <code>min.coverage/10000</code> .
<code>min.total.counts</code>	Exclude intervals with fewer than that many reads in combined tumor and normal.
<code>min.targeted.base</code>	Exclude intervals with targeted base (size in bp) smaller than this cutoff. This is useful when the same interval file was used to calculate GC content. For such small targets, the GC content is likely very different from the true GC content of the probes.
<code>min.mappability</code>	<code>double(2)</code> specifying the minimum mappability score for on-target, off-target in that order.
<code>min.fraction.offtarget</code>	Skip off-target regions when less than the specified fraction of all intervals passes all filters
<code>normalDB</code>	Normal database, created with createNormalDatabase .

Value

`logical(length(log.ratio))` specifying which intervals should be used in segmentation.

Author(s)

Markus Riester

Examples

```
normal.coverage.file <- system.file("extdata", "example_normal.txt.gz",
  package = "PureCN")
normal2.coverage.file <- system.file("extdata", "example_normal2.txt.gz",
  package = "PureCN")
normal.coverage.files <- c(normal.coverage.file, normal2.coverage.file)
normalDB <- createNormalDatabase(normal.coverage.files)

tumor.coverage.file <- system.file("extdata", "example_tumor.txt.gz",
  package = "PureCN")
vcf.file <- system.file("extdata", "example.vcf.gz",
  package = "PureCN")
interval.file <- system.file("extdata", "example_intervals.txt",
  package = "PureCN")

# The max.candidate.solutions, max.ploidy and test.purity parameters are set to
# non-default values to speed-up this example. This is not a good idea for real
# samples.
ret <- runAbsoluteCN(normal.coverage.file = normal.coverage.file,
  tumor.coverage.file = tumor.coverage.file,
  genome = "hg19", vcf.file = vcf.file, normalDB = normalDB,
  sampleid = "Sample1", interval.file = interval.file,
  args.filterIntervals = list(min.targeted.base = 10), max.ploidy = 4,
  test.purity = seq(0.3, 0.7, by = 0.05), max.candidate.solutions = 1)
```

filterVcfBasic	<i>Basic VCF filter function</i>
----------------	----------------------------------

Description

Function to remove artifacts and low confidence/quality variant calls.

Usage

```
filterVcfBasic(
  vcf,
  tumor.id.in.vcf = NULL,
  use.somatic.status = TRUE,
  snp.blacklist = NULL,
  af.range = c(0.03, 0.97),
  contamination.range = c(0.01, 0.075),
  min.coverage = 15,
  min.base.quality = 25,
  max.base.quality = 50,
  base.quality.offset = 1,
  min.supporting.reads = NULL,
  error = 0.001,
  target.granges = NULL,
  remove.off.target.snvs = TRUE,
  model.homozygous = FALSE,
  interval.padding = 50,
  DB.info.flag = "DB"
)
```

Arguments

vcf	CollapsedVCF object, read in with the readVcf function from the VariantAnnotation package.
tumor.id.in.vcf	The tumor id in the CollapsedVCF (optional).
use.somatic.status	If somatic status and germline data is available, then use this information to remove non-heterozygous germline SNPs or germline SNPS with biased allelic fractions.
snp.blacklist	A file with blacklisted genomic regions. Must be parsable by import from rtracklayer, for a example a BED file with file extension '.bed'.
af.range	Exclude variants with allelic fraction smaller or greater than the two values, respectively. The higher value removes homozygous SNPs, which potentially have allelic fractions smaller than 1 due to artifacts or contamination. If a matched normal is available, this value is ignored, because homozygosity can be confirmed in the normal.
contamination.range	Count variants in germline databases with allelic fraction in the specified range. If the number of these putative contamination variants exceeds an expected value

and if they are found on almost all chromosomes, the sample is flagged as potentially contaminated and extra contamination estimation steps will be performed later on.

<code>min.coverage</code>	Minimum coverage in tumor. Variants with lower coverage are ignored.
<code>min.base.quality</code>	Minimum base quality in tumor. Requires a BQ genotype field in the VCF. Values below this value will be ignored.
<code>max.base.quality</code>	Maximum base quality in tumor. Requires a BQ genotype field in the VCF. Variants exceeding this value will have their BQ capped at this value.
<code>base.quality.offset</code>	Subtracts the specified value from the base quality score. Useful to add some cushion for too optimistically calibrated scores. Requires a BQ genotype field in the VCF.
<code>min.supporting.reads</code>	Minimum number of reads supporting the alt allele. If NULL, calculate based on coverage and assuming sequencing error of 10^{-3} .
<code>error</code>	Estimated sequencing error rate. Used to calculate minimum number of supporting reads using calculatePowerDetectSomatic when base quality scores are not available.
<code>target.granges</code>	GenomicRanges object specifying the target positions. Used to remove off-target reads. If NULL, do not check whether variants are on or off-target.
<code>remove.off.target.snvs</code>	If set to a true value, will remove all SNVs outside the covered regions.
<code>model.homozygous</code>	If set to TRUE, does not remove homozygous variants. Ignored in case a matched normal is provided in the VCF.
<code>interval.padding</code>	Include variants in the interval flanking regions of the specified size in bp. Requires <code>target.granges</code> .
<code>DB.info.flag</code>	Flag in INFO of VCF that marks presence in common germline databases. Defaults to DB that may contain somatic variants if it is from an unfiltered germline database.

Value

A list with elements

<code>vcf</code>	The filtered CollapsedVCF object.
<code>flag</code>	A flag (logical(1)) if problems were identified.
<code>flag_comment</code>	A comment describing the flagging.

Author(s)

Markus Riester

See Also

[calculatePowerDetectSomatic](#)

Examples

```
# This function is typically only called by runAbsolute via
# fun.filterVcf and args.filterVcf.
vcf.file <- system.file("extdata", "example.vcf.gz", package="PureCN")
vcf <- readVcf(vcf.file, "hg19")
vcf.filtered <- filterVcfBasic(vcf)
```

filterVcfMuTect

Filter VCF MuTect

Description

Function to remove artifacts and low confidence/quality calls from a MuTect generated VCF file. Also applies filters defined in filterVcfBasic. This function will only keep variants listed in the stats file and those not matching the specified failure reasons.

Usage

```
filterVcfMuTect(
  vcf,
  tumor.id.in.vcf = NULL,
  stats.file = NULL,
  ignore = c("clustered_read_position", "fstar_tumor_lod", "nearby_gap_events",
    "poor_mapping_region_alternate_allele_mapq", "poor_mapping_region_mapq0",
    "possible_contamination", "strand_artifact", "seen_in_panel_of_normals"),
  ...
)
```

Arguments

vcf	CollapsedVCF object, read in with the readVcf function from the VariantAnnotation package.
tumor.id.in.vcf	The tumor id in the VCF file, optional.
stats.file	MuTect stats file. If NULL, will check if VCF was generated by MuTect2 and if yes will call filterVcfMuTect2 instead.
ignore	MuTect flags that mark variants for exclusion.
...	Additional arguments passed to filterVcfBasic .

Value

A list with elements vcf, flag and flag_comment. vcf contains the filtered CollapsedVCF, flag a logical(1) flag if problems were identified, further described in flag_comment.

Author(s)

Markus Riester

See Also

[filterVcfBasic](#)

Examples

```
### This function is typically only called by runAbsolute via the
### fun.filterVcf and args.filterVcf comments.
library(VariantAnnotation)
vcf.file <- system.file("extdata", "example.vcf.gz", package="PureCN")
vcf <- readVcf(vcf.file, "hg19")
vcf.filtered <- filterVcfMuTect(vcf)
```

filterVcfMuTect2	<i>Filter VCF MuTect2</i>
------------------	---------------------------

Description

Function to remove artifacts and low confidence/quality calls from a GATK4/MuTect2 generated VCF file. Also applies filters defined in filterVcfBasic.

Usage

```
filterVcfMuTect2(
  vcf,
  tumor.id.in.vcf = NULL,
  ignore = c("clustered_events", "t_lod", "str_contraction", "read_position", "position",
    "fragment_length", "multiallelic", "clipping", "strand_artifact", "strand_bias",
    "slippage", "weak_evidence", "orientation", "haplotype"),
  ...
)
```

Arguments

vcf	CollapsedVCF object, read in with the readVcf function from the VariantAnnotation package.
tumor.id.in.vcf	The tumor id in the VCF file, optional.
ignore	MuTect2 flags that mark variants for exclusion.
...	Additional arguments passed to filterVcfBasic .

Value

A list with elements vcf, flag and flag_comment. vcf contains the filtered CollapsedVCF, flag a logical(1) flag if problems were identified, further described in flag_comment.

Author(s)

Markus Riester

See Also

[filterVcfBasic](#)

Examples

```
### This function is typically only called by runAbsolute via the
### fun.filterVcf and args.filterVcf comments.
library(VariantAnnotation)
vcf.file <- system.file("extdata", "example.vcf.gz", package="PureCN")
vcf <- readVcf(vcf.file, "hg19")
vcf.filtered <- filterVcfMuTect(vcf)
```

findFocal

Find focal amplifications

Description

Function to find focal amplifications in segmented data. This is automatically called in [runAbsoluteCN](#).

Usage

```
findFocal(seg, max.size = 3e+06, cn.diff = 2, min.amp.cn = 5)
```

Arguments

seg	Segmentation data.
max.size	Cutoff for focal in base pairs.
cn.diff	Minimum copy number delta between neighboring segments.
min.amp.cn	Minimum amplification integer copy number. Segments with lower copy number are not tested.

Value

logical(n), indicating for all n segments whether they are focally amplified or not.

Author(s)

Markus Riester

See Also

[runAbsoluteCN](#)

Examples

```
normal.coverage.file <- system.file("extdata", "example_normal_tiny.txt",
  package = "PureCN")
tumor.coverage.file <- system.file("extdata", "example_tumor_tiny.txt",
  package = "PureCN")
vcf.file <- system.file("extdata", "example.vcf.gz",
  package = "PureCN")
interval.file <- system.file("extdata", "example_intervals_tiny.txt",
  package = "PureCN")

# The max.candidate.solutions, max.ploidy and test.purity parameters are set to
```

```
# non-default values to speed-up this example. This is not a good idea for real
# samples.
ret <-runAbsoluteCN(normal.coverage.file = normal.coverage.file,
  tumor.coverage.file = tumor.coverage.file, vcf.file = vcf.file,
  genome="hg19", sampleid = "Sample1", interval.file = interval.file,
  max.candidate.solutions = 1, max.ploidy = 4,
  test.purity = seq(0.3, 0.7, by = 0.05),
  args.focal=list(max.size = 2e+06), fun.focal = findFocal)
```

findHighQualitySNPs	<i>Find High Quality SNPs</i>
---------------------	-------------------------------

Description

Function to extract high quality SNPs from the mapping bias database. Useful for generating fingerprinting panels etc.

Usage

```
findHighQualitySNPs(
  mapping.bias.file,
  max.bias = 0.2,
  min.pon = 2,
  triallelc = FALSE,
  vcf.file = NULL,
  genome
)
```

Arguments

mapping.bias.file	Generated by calculateMappingBiasVcf .
max.bias	Maximum mapping bias
min.pon	Minimum number of normal samples, useful to get reliable mapping bias.
triallelic	By default, ignore positions with multiple alt alleles.
vcf.file	Optional VCF file (for example dbSNP). Needs to be bgzip and tabix processed.
genome	See readVcf

Value

A GRanges object with mapping bias passing filters. If `vcf.file` is provided, it will be the variants in the corresponding file overlapping with the passed variants.

Author(s)

Markus Riester

Examples

```
normal.panel.vcf <- system.file("extdata", "normalpanel.vcf.gz",
  package = "PureCN")
bias <- calculateMappingBiasVcf(normal.panel.vcf, genome = "h19")
```

getSexFromCoverage	<i>Get sample sex from coverage</i>
--------------------	-------------------------------------

Description

This function determines the sex of a sample by the coverage ratio of chrX and chrY. Loss of chromosome Y (LOY) can result in a wrong female call. For small targeted panels, this will only work when sufficient sex marker genes such as AMELY are covered. For optimal results, parameters might need to be tuned for the assay.

Usage

```
getSexFromCoverage(
  coverage.file,
  min.ratio = 25,
  min.ratio.na = 20,
  remove.outliers = TRUE
)
```

Arguments

coverage.file	Coverage file or data read with readCoverageFile .
min.ratio	Min chrX/chrY coverage ratio to call sample as female.
min.ratio.na	Min chrX/chrY coverage ratio to call sample as NA. This ratio defines a grey zone from min.ratio.na to min.ratio in which samples are not called. The default is set to a copy number ratio that would be rare in male samples, but lower than expected in female samples. Contamination can be a source of ambiguous calls. Mappability issues on chromosome Y resulting in low coverage need to be considered when setting cutoffs.
remove.outliers	Removes coverage outliers before calculating mean chromosome coverages.

Value

Returns a character(1) with M for male, F for female, or NA if unknown.

Author(s)

Markus Riester

See Also

[getSexFromVcf](#)

Examples

```
tumor.coverage.file <- system.file("extdata", "example_tumor.txt.gz",
  package = "PureCN")
sex <- getSexFromCoverage(tumor.coverage.file)
```

getSexFromVcf

*Get sample sex from a VCF file***Description**

This function detects non-random distribution of homozygous variants on chromosome X compared to all other chromosomes. A non-significant Fisher's exact p-value indicates more than one chromosome X copy. This function is called in runAbsoluteCN as sanity check when a VCF is provided. It is also useful for determining sex when no sex marker genes on chrY (e.g. AMELY) are available.

Usage

```
getSexFromVcf(
  vcf,
  tumor.id.in.vcf = NULL,
  min.or = 4,
  min.or.na = 2.5,
  max.pv = 0.001,
  homozygous.cutoff = 0.95,
  af.cutoff = 0.2,
  min.coverage = 15,
  use.somatic.status = TRUE
)
```

Arguments

vcf	CollapsedVCF object, read in with the readVcf function from the VariantAnnotation package.
tumor.id.in.vcf	The tumor id in the CollapsedVCF (optional).
min.or	Minimum odds-ratio to call sample as male. If p-value is not significant due to a small number of SNPs on chromosome X, sample will be called as NA even when odds-ratio exceeds this cutoff.
min.or.na	Minimum odds-ratio to not call a sample. Odds-ratios in the range min.or.na to min.or define a grey area in which samples are not called. Contamination can be a source of ambiguous calls.
max.pv	Maximum Fisher's exact p-value to call sample as male.
homozygous.cutoff	Minimum allelic fraction to call position homozygous.
af.cutoff	Remove all SNVs with allelic fraction lower than the specified value.
min.coverage	Minimum coverage in tumor. Variants with lower coverage are ignored.
use.somatic.status	If somatic status and germline data is available, then exclude somatic variants.

Value

Returns a character (1) with M for male, F for female, or NA if unknown.

Author(s)

Markus Riester

See Also

[getSexFromCoverage](#)

Examples

```
vcf.file <- system.file("extdata", "example.vcf.gz", package = "PureCN")
vcf <- readVcf(vcf.file, "hg19")
# This example vcf is filtered and contains no homozygous calls,
# which are necessary for determining sex from chromosome X.
getSexFromVcf(vcf)
```

plotAbs

Plots for analyzing PureCN solutions

Description

This function provides various plots for finding correct purity and ploidy combinations in the results of a [runAbsoluteCN](#) call.

Usage

```
plotAbs(
  res,
  id = 1,
  type = c("hist", "overview", "BAF", "AF", "all"),
  chr = NULL,
  germline.only = TRUE,
  show.contour = FALSE,
  purity = NULL,
  ploidy = NULL,
  alpha = TRUE,
  show.segment.means = c("SNV", "segments", "both"),
  max.mapping.bias = 0.8,
  palette.name = "Paired",
  col.snps = "#2b6391",
  col.chr.shading = "#f0f0f0",
  ...
)
```

Arguments

res	Return object of the runAbsoluteCN function.
id	Candidate solutions to be plotted. id=1 will draw the plot for the maximum likelihood solution.
type	Different types of plots. hist will plot a histogram, assigning log-ratio peaks to integer values. overview will plot all local optima, sorted by likelihood. BAF plots something like a B-allele frequency plot known from SNP arrays: it plots allele frequencies of germline variants (or most likely germline when status is not available) against copy number. AF plots observed allelic fractions against expected (purity), maximum likelihood (optimal multiplicity) allelic fractions. all plots types BAF and AF for all local optima, and is useful for generating a PDF for manual inspection.
chr	If NULL, show all chromosomes, otherwise only the ones specified (type="BAF" only).
germline.only	If TRUE, show only variants most likely being germline in BAF plot. Useful to set to FALSE (in combination with chr) to study potential artifacts.
show.contour	For type="overview", display contour plot.
purity	Display expected integer copy numbers for purity, defaults to purity of the solution (type="hist" and "AF" only).
ploidy	Display expected integer copy numbers for ploidy, defaults to ploidy of the solution (type="hist" and "AF" only).
alpha	Add transparency to the plot if VCF contains many variants (>2000, type="AF" and type="BAF" only).
show.segment.means	Show segment means in germline allele frequency plot? If both, show SNVs and segment means. If SNV show all SNVs. Only for type="AF".
max.mapping.bias	Exclude variants with high mapping bias from plotting. Note that bias is reported on an inverse scale; a variant with mapping bias of 1 has no bias. (type="AF" and type="BAF" only).
palette.name	The default RColorBrewer palette.
col.snps	The color used for germline SNPs.
col.chr.shading	The color used for shading alternate chromosomes.
...	Additional parameters passed to the plot function.

Value

Returns NULL.

Author(s)

Markus Riester

See Also

[runAbsoluteCN](#)

Examples

```
data(purecn.example.output)
plotAbs(purecn.example.output, type="overview")
# plot details for the maximum likelihood solution (rank 1)
plotAbs(purecn.example.output, 1, type="hist")
plotAbs(purecn.example.output, 1, type="BAF")
plotAbs(purecn.example.output, 1, type = "BAF", chr="chr2")
```

poolCoverage

Pool coverage from multiple samples

Description

Averages the coverage of a list of samples.

Usage

```
poolCoverage(all.data, remove.chrs = c(), w = NULL)
```

Arguments

<code>all.data</code>	List of normals, read with readCoverageFile .
<code>remove.chrs</code>	Remove these chromosomes from the pool.
<code>w</code>	numeric(length(all.data)) vector of weights. If NULL, weight all samples equally.

Value

A data.frame with the averaged coverage over all normals.

Author(s)

Markus Riester

See Also

[readCoverageFile](#)

Examples

```
normal.coverage.file <- system.file("extdata", "example_normal.txt.gz",
  package = "PureCN")
normal2.coverage.file <- system.file("extdata", "example_normal2.txt.gz",
  package = "PureCN")
normal.coverage.files <- c(normal.coverage.file, normal2.coverage.file)
pool <- poolCoverage(lapply(normal.coverage.files, readCoverageFile),
  remove.chrs = c("chrX", "chrY"))
```

predictSomatic	<i>Predict germline vs. somatic status</i>
----------------	--

Description

This function takes as input the output of a [runAbsoluteCN](#) run and provides SNV posterior probabilities for all possible states.

Usage

```
predictSomatic(res, id = 1, return.vcf = FALSE)
```

Arguments

res	Return object of the runAbsoluteCN function.
id	Candidate solutions to be analyzed. id=1 will analyze the maximum likelihood solution.
return.vcf	Returns an annotated CollapsedVCF object. Note that this VCF will only contain variants not filtered out by the filterVcf functions. Variants outside segments or intervals might be included or not depending on runAbsoluteCN arguments.

Value

A data.frame or CollapsedVCF with SNV state posterior probabilities.

Author(s)

Markus Riester

See Also

[runAbsoluteCN](#)

Examples

```
data(purecn.example.output)
# the output data was created using a matched normal sample, but in case
# no matched normal is available, this will help predicting somatic vs.
# germline status
purecnSnvs <- predictSomatic(purecn.example.output)

# Prefer GRanges?
purecnSnvs <- GRanges(predictSomatic(purecn.example.output))

# write a VCF file
purecnVcf <- predictSomatic(purecn.example.output, return.vcf=TRUE)
writeVcf(purecnVcf, file = "Sample1_PureCN.vcf")
```

```
preprocessIntervals  Preprocess intervals
```

Description

Optimize intervals for copy number calling by tiling long intervals and by including off-target regions. Uses scanFa from the Rsamtools package to retrieve GC content of intervals in a reference FASTA file. If provided, will annotate intervals with mappability and replication timing scores.

Usage

```
preprocessIntervals(
  interval.file,
  reference.file,
  output.file = NULL,
  off.target = FALSE,
  average.target.width = 400,
  min.target.width = 100,
  min.off.target.width = 20000,
  average.off.target.width = 2e+05,
  off.target.padding = -500,
  mappability = NULL,
  min.mappability = c(0.6, 0.1, 0.7),
  reptiming = NULL,
  average.reptiming.width = 1e+05,
  exclude = NULL,
  off.target.seqlevels = c("targeted", "all"),
  small.targets = c("resize", "drop")
)
```

Arguments

<code>interval.file</code>	File specifying the intervals. Interval is expected in first column in format CHR:START-END. Instead of a file, a GRanges object can be provided. This allows the use of BED files for example. Note that GATK interval files are 1-based (first position of the genome is 1). Other formats like BED files are often 0-based. The import function will automatically convert to 1-based GRanges.
<code>reference.file</code>	Reference FASTA file.
<code>output.file</code>	Optionally, write GC content file.
<code>off.target</code>	Include off-target regions.
<code>average.target.width</code>	Split large targets to approximately this size.
<code>min.target.width</code>	Make sure that target regions are of at least this specified width. See <code>small.targets</code> .
<code>min.off.target.width</code>	Only include off-target regions of that size
<code>average.off.target.width</code>	Split off-target regions to that

<code>off.target.padding</code>	Pad off-target regions.
<code>mappability</code>	Annotate intervals with mappability score. Assumed on a scale from 0 to 1, with score being 1/(number alignments). Expected as GRanges object with first meta column being the score. Regions outside these ranges are ignored, assuming that mappability covers the whole accessible genome.
<code>min.mappability</code>	<code>double(3)</code> specifying the minimum mappability score for on-target, off-target, and chrY regions in that order. The chrY regions are only used for sex determination in 'PureCN' and are therefore treated differently. Requires mappability.
<code>reptiming</code>	Annotate intervals with replication timing score. Expected as GRanges object with first meta column being the score.
<code>average.reptiming.width</code>	Tile reptiming into bins of specified width.
<code>exclude</code>	Any target that overlaps with this GRanges object will be excluded.
<code>off.target.seqlevels</code>	Controls how to deal with chromosomes/contigs found in the <code>reference.file</code> but not in the <code>interval.file</code> .
<code>small.targets</code>	Strategy to deal with targets smaller than <code>min.target.width</code> .

Value

Returns GC content by interval as GRanges object.

Author(s)

Markus Riester

References

Talevich et al. (2016). CNVkit: Genome-Wide Copy Number Detection and Visualization from Targeted DNA Sequencing. PLoS Comput Biol.

Examples

```
reference.file <- system.file("extdata", "ex2_reference.fa",
  package = "PureCN", mustWork = TRUE)
interval.file <- system.file("extdata", "ex2_intervals.txt",
  package = "PureCN", mustWork = TRUE)
bed.file <- system.file("extdata", "ex2_intervals.bed",
  package = "PureCN", mustWork = TRUE)
preprocessIntervals(interval.file, reference.file,
  output.file = "gc_file.txt")

intervals <- import(bed.file)
preprocessIntervals(intervals, reference.file,
  output.file = "gc_file.txt")
```

processMultipleSamples

Multi sample normalization and segmentation

Description

This function performs normalization and segmentation when multiple for the same patient are available.

Usage

```
processMultipleSamples(
  tumor.coverage.files,
  sampleids,
  normalDB,
  num.eigen = 20,
  genome,
  plot.cnv = TRUE,
  w = NULL,
  min.interval.weight = 1/3,
  max.segments = NULL,
  chr.hash = NULL,
  centromeres = NULL,
  ...
)
```

Arguments

tumor.coverage.files	Coverage data for tumor samples.
sampleids	Sample ids, used in output files.
normalDB	Database of normal samples, created with createNormalDatabase .
num.eigen	Number of eigen vectors used.
genome	Genome version, for example hg19. Needed to get centromere positions.
plot.cnv	Segmentation plots.
w	Weight of samples. Can be used to downweight poor quality samples. If NULL, sets to inverse of median on-target duplication rate if available, otherwise does not do any weighting.
min.interval.weight	Can be used to ignore intervals with low weights.
max.segments	If not NULL, try a higher undo. SD parameter if number of segments exceeds the threshold.
chr.hash	Mapping of non-numerical chromosome names to numerical names (e.g. chr1 to 1, chr2 to 2, etc.). If NULL, assume chromosomes are properly ordered.
centromeres	A GRanges object with centromere positions.
...	Arguments passed to the segmentation function.

Details

CURRENTLY DEFUNCT BECAUSE IT DEPENDS ON THE DEFUNCT COPYNUMBER PACKAGE. We are working on a replacement.

Value

data.frame containing the segmentation.

Author(s)

Markus Riester

References

Nilsen G., Liestol K., Van Loo P., Vollen H., Eide M., Rueda O., Chin S., Russell R., Baumbusch L., Caldas C., Borresen-Dale A., Lingjaerde O. (2012). "Copynumber: Efficient algorithms for single- and multi-track copy number segmentation." BMC Genomics, 13(1), 591.

See Also

[runAbsoluteCN](#)

Examples

```
normal1.coverage.file <- system.file("extdata", "example_normal.txt.gz",
  package = "PureCN")
normal2.coverage.file <- system.file("extdata", "example_normal2.txt.gz",
  package = "PureCN")
tumor1.coverage.file <- system.file("extdata", "example_tumor.txt.gz",
  package = "PureCN")
tumor2.coverage.file <- system.file("extdata", "example_tumor2.txt.gz",
  package = "PureCN")

normal.coverage.files <- c(normal1.coverage.file, normal2.coverage.file)
tumor.coverage.files <- c(tumor1.coverage.file, tumor2.coverage.file)

normalDB <- createNormalDatabase(normal.coverage.files)

# seg <- processMultipleSamples(tumor.coverage.files,
#   sampleids = c("Sample1", "Sample2"),
#   normalDB = normalDB,
#   genome = "hg19")
```

PureCN-defunct

Defunct functions in package ‘PureCN’

Description

These functions are defunct and no longer available.

Details

The following functions are defunct; use the replacement indicated below:

- autoCurateResults: no replacement
- calculateGCCContentByInterval: [preprocessIntervals](#)
- calculateIntervalWeights: [createNormalDatabase](#)
- createExonWeightFile: [createNormalDatabase](#)
- createSNPBlacklist: [setMappingBiasVcf](#)
- createTargetWeights: [createNormalDatabase](#)
- filterTargets: [filterIntervals](#)
- findBestNormal: [calculateTangentNormal](#)
- getDiploid: no replacement
- plotBestNormal: no replacement
- readCoverageGatk: [readCoverageFile](#)

PureCN-deprecated	<i>Deprecated functions in package ‘PureCN’</i>
-------------------	---

Description

These functions are provided for compatibility with older versions of ‘PureCN’ only, and will be defunct at the next release.

Details

The following functions are deprecated and will be made defunct; use the replacement indicated below:

purecn.DNAcopy.bdry	<i>DNAcopy boundary data</i>
---------------------	------------------------------

Description

This provides the output of the DNAcopy::getbdry call using [segmentationCBS](#) default parameters.

Usage

```
data(purecn.DNAcopy.bdry)
```

Value

Output of the DNAcopy::getbdry call.

`purecn.example.output` *Example output*

Description

This provides the output of the `runAbsoluteCN` call used in the vignette and examples.

Usage

```
data(purecn.example.output)
```

Value

Output of the `runAbsoluteCN` call used in the vignette.

`readAllelicCountsFile` *Read allelic counts file*

Description

Read file containing counts of ref and alt alleles of common Toolkit 4.

Usage

```
readAllelicCountsFile(file, format, zero = NULL)
```

Arguments

<code>file</code>	Input file containing counts of ref and alt alleles
<code>format</code>	File format. If missing, derived from the file extension. Currently only GATK4 CollectAllelicCounts (tsv) format supported.
<code>zero</code>	Start position is 0-based. Default is FALSE for GATK, TRUE for BED file based intervals.

Value

A CollapsedVCF with the parsed allelic counts.

Author(s)

Markus Riester

Examples

```
ac.file <- system.file("extdata", "example_allelic_counts.tsv",
  package="PureCN")
vcf_ac <- readAllelicCountsFile(ac.file)
```

readCoverageFile	<i>Read coverage file</i>
------------------	---------------------------

Description

Read coverage file produced by external tools like The Genome Analysis Toolkit or by [calculateBamCoverageByInterval](#)

Usage

```
readCoverageFile(file, format, zero = NULL, read.length = 100)
```

Arguments

file	Target coverage file.
format	File format. If missing, derived from the file extension. Currently GATK3 DepthofCoverage, GATK4 CollectFragmentCounts (hdf5), and CNVkit formats supported.
zero	Start position is 0-based. Default is FALSE for GATK, TRUE for BED file based intervals.
read.length	For output formats which do not provide both counts and total coverages, approximate them using the specified read length.

Value

A data.frame with the parsed coverage information.

Author(s)

Markus Riester

See Also

[calculateBamCoverageByInterval](#)

Examples

```
tumor.coverage.file <- system.file("extdata", "example_tumor.txt.gz",  
  package = "PureCN")  
coverage <- readCoverageFile(tumor.coverage.file)
```

readCurationFile	<i>Read curation file</i>
------------------	---------------------------

Description

Function that can be used to read the curated output of the [runAbsoluteCN](#) function.

Usage

```
readCurationFile(  
  file.rds,  
  file.curation = gsub(".rds$", ".csv", file.rds),  
  remove.failed = FALSE,  
  report.best.only = FALSE,  
  min.ploidy = NULL,  
  max.ploidy = NULL  
)
```

Arguments

<code>file.rds</code>	Output of the runAbsoluteCN function, serialized with <code>saveRDS</code> .
<code>file.curation</code>	Filename of a curation file that points to the correct tumor purity and ploidy solution.
<code>remove.failed</code>	Do not return solutions that failed.
<code>report.best.only</code>	Only return correct/best solution (useful on low memory machines when lots of samples are loaded).
<code>min.ploidy</code>	Minimum ploidy to be considered. If <code>NULL</code> , all. Can be used to automatically ignore unlikely solutions.
<code>max.ploidy</code>	Maximum ploidy to be considered. If <code>NULL</code> , all. Can be used to automatically ignore unlikely solutions.

Value

The return value of the corresponding [runAbsoluteCN](#) call, but with the results array manipulated according the curation CSV file and arguments of this function.

Author(s)

Markus Riester

See Also

[runAbsoluteCN](#) [createCurationFile](#)

Examples

```
data(purecn.example.output)
file.rds <- "Sample1_PureCN.rds"
createCurationFile(file.rds)
# User can change the maximum likelihood solution manually in the generated
# CSV file. The correct solution is then loaded with readCurationFile.
purecn.curated.example.output <- readCurationFile(file.rds)
```

readIntervalFile	<i>Read interval file</i>
------------------	---------------------------

Description

Read file containing coordinates of on- and off-target intervals generated by [preprocessIntervals](#).

Usage

```
readIntervalFile(interval.file, strict = TRUE, verbose = TRUE)
```

Arguments

interval.file	A mapping file that assigns GC content and gene symbols to each exon in the coverage files. Used for generating gene-level calls. First column in format CHR:START-END. Second column GC content (0 to 1). Third column gene symbol. This file is generated with the preprocessIntervals function.
strict	Error out with missing columns
verbose	Verbose output

Value

A GRanges object with the parsed intervals.

Author(s)

Markus Riester

Examples

```
interval.file <- system.file("extdata", "example_intervals.txt",
  package = "PureCN")
x <- readIntervalFile(interval.file)
```

readLogRatioFile	<i>Read file containing interval-level log2 tumor/normal ratios</i>
------------------	---

Description

Read log2 ratio file produced by external tools like The Genome Analysis Toolkit version 4.

Usage

```
readLogRatioFile(file, format, zero = NULL)
```

Arguments

file	Log2 coverage file.
format	File format. If missing, derived from the file extension. Currently GATK4 DenoiseReadCounts format supported. A simple GATK3-style format, two columns with coordinates as string in format chr:start-stop in first and log2-ratio in second is also supported.
zero	Start position is 0-based. Default is FALSE for GATK, TRUE for BED file based intervals.

Value

A GRange with the log2 ratio.

Author(s)

Markus Riester

Examples

```
logratio.file <- system.file("extdata", "example_gatk4_denoised_cr.tsv.gz",  
  package = "PureCN")  
logratio <- readLogRatioFile(logratio.file)
```

readSegmentationFile	<i>Read file containing segmentations</i>
----------------------	---

Description

Read segmentation files produced by DNACopy, CNVkit or GATK4.

Usage

```
readSegmentationFile(
  seg.file,
  sampleid,
  model.homozygous = FALSE,
  format,
  zero = FALSE,
  verbose = TRUE
)
```

Arguments

seg.file	File with segmentation
sampleid	Sampleid, for segmentation files containing multiple samples
model.homozygous	Unless TRUE, checks for very small log2-ratios that cannot happen in samples with normal contamination
format	File format. If missing, derived from the file extension. Currently DNACopy, and GATK4 (ModelSegments) format supported. CNVkit uses DNACopy format.
zero	Start position is 0-based. Default is FALSE.
verbose	Verbose output.

Value

A data.frame.

Author(s)

Markus Riester

Examples

```
seg.file <- system.file("extdata", "example_seg.txt",
  package = "PureCN")
seg <- readSegmentationFile(seg.file, "Sample1")
```

runAbsoluteCN

Run PureCN implementation of ABSOLUTE

Description

This function takes as input tumor and normal control coverage data and a VCF containing allelic fractions of germline variants and somatic mutations. Normal control does not need to be from the same patient. In case VCF does not contain somatic status, it should contain either dbSNP or population allele frequencies, and optionally COSMIC annotation. Returns purity and ploidy combinations, sorted by likelihood score. Provides copy number and LOH data, by both gene and genomic region.

Usage

```
runAbsoluteCN(  
  normal.coverage.file = NULL,  
  tumor.coverage.file = NULL,  
  log.ratio = NULL,  
  seg.file = NULL,  
  seg.file.sdev = 0.4,  
  vcf.file = NULL,  
  normalDB = NULL,  
  genome,  
  centromeres = NULL,  
  sex = c("?", "F", "M", "diploid"),  
  fun.filterVcf = filterVcfMuTect,  
  args.filterVcf = list(),  
  fun.setPriorVcf = setPriorVcf,  
  args.setPriorVcf = list(),  
  fun.setMappingBiasVcf = setMappingBiasVcf,  
  args.setMappingBiasVcf = list(),  
  fun.filterIntervals = filterIntervals,  
  args.filterIntervals = list(),  
  fun.segmentation = segmentationCBS,  
  args.segmentation = list(),  
  fun.focal = findFocal,  
  args.focal = list(),  
  sampleid = NULL,  
  min.ploidy = 1.4,  
  max.ploidy = 6,  
  test.num.copy = 0:7,  
  test.purity = seq(0.15, 0.95, by = 0.01),  
  prior.purity = NULL,  
  prior.K = 0.999,  
  prior.contamination = 0.01,  
  max.candidate.solutions = 20,  
  candidates = NULL,  
  min.coverage = 15,  
  max.coverage.vcf = 300,  
  max.non.clonal = 0.2,  
  max.homozygous.loss = c(0.05, 1e+07),  
  non.clonal.M = 1/3,  
  max.mapping.bias = 0.8,  
  max.pon = 3,  
  iterations = 30,  
  min.variants.segment = 5,  
  log.ratio.calibration = 0.1,  
  smooth.log.ratio = TRUE,  
  model.homozygous = FALSE,  
  error = 0.001,  
  interval.file = NULL,  
  max.dropout = c(0.95, 1.1),  
  min.logr.sdev = 0.15,  
  max.logr.sdev = 0.6,  
  max.segments = 300,  
)
```

```

min.gof = 0.8,
min.variants = 20,
plot.cnv = TRUE,
vcf.field.prefix = "",
cosmic.vcf.file = NULL,
DB.info.flag = "DB",
POPAF.info.field = "POP_AF",
Cosmic.CNT.info.field = "Cosmic.CNT",
min.pop.af = 0.001,
model = c("beta", "betabin"),
post.optimize = FALSE,
speedup.heuristics = 2,
BPPARAM = NULL,
log.file = NULL,
verbose = TRUE
)

```

Arguments

<code>normal.coverage.file</code>	Coverage file of normal control (optional if <code>log.ratio</code> is provided - then it will be only used to filter low coverage exons). Should be already GC-normalized with correctCoverageBias . Needs to be either a file name or data read with the readCoverageFile function.
<code>tumor.coverage.file</code>	Coverage file of tumor. If NULL, requires <code>seg.file</code> and an interval file via <code>interval.file</code> . Should be already GC-normalized with correctCoverageBias . Needs to be either a file name or data read with the readCoverageFile function.
<code>log.ratio</code>	Copy number log-ratios for all exons in the coverage files. If NULL, calculated based on coverage files.
<code>seg.file</code>	Segmented data. Optional, to support third-party segmentation tools. If NULL, use coverage files or <code>log.ratio</code> to segment the data.
<code>seg.file.sdev</code>	If <code>seg.file</code> provided, the log-ratio standard deviation, used to model likelihood of sub-clonal copy number events.
<code>vcf.file</code>	VCF file. Optional, but typically needed to select between local optima of similar likelihood. Can also be a CollapsedVCF, read with the <code>readVcf</code> function. Requires a DB info flag for likely germline status. The default <code>fun.setPriorVcf</code> function will also look for a <code>Cosmic.CNT</code> slot (see <code>cosmic.vcf.file</code>), containing the hits in the COSMIC database. Again, do not expect very useful results without a VCF file.
<code>normalDB</code>	Normal database, created with createNormalDatabase . If provided, used to calculate gene-level p-values (requires <code>Gene</code> column in <code>interval.file</code>) and to filter targets with low coverage in the pool of normal samples.
<code>genome</code>	Genome version, for example hg19. See <code>readVcf</code> .
<code>centromeres</code>	A <code>GRanges</code> object with centromere positions. If NULL, use pre-stored positions for genome versions hg18, hg19 and hg38.
<code>sex</code>	Sex of sample. If <code>?</code> , detect using getSexFromCoverage function and default parameters. Default parameters might not work well with every assay and might need to be tuned. If set to diploid, then PureCN will assume all chromosomes are diploid and will not try to detect sex.

<code>fun.filterVcf</code>	Function for filtering variants. Expected output is a list with elements <code>vcf</code> (<code>CollapsedVCF</code>), <code>flag</code> (<code>logical(1)</code>) and <code>flag_comment</code> (<code>character(1)</code>). The flags will be added to the output data and can be used to warn users, for example when samples look too noisy. Default filter will remove variants flagged by MuTect, but will keep germline variants. If ran in matched normal mode, it will by default use somatic status of variants and filter non-somatic calls with allelic fraction significantly different from 0.5 in normal. Defaults to filterVcfMuTect , which in turn also calls filterVcfBasic .
<code>args.filterVcf</code>	Arguments for variant filtering function. Arguments <code>vcf</code> , <code>tumor.id.in.vcf</code> , <code>min.coverage</code> , <code>model.homozygous</code> and <code>error</code> are required in the filter function and are automatically set.
<code>fun.setPriorVcf</code>	Function to set prior for somatic status for each variant in the VCF. Defaults to setPriorVcf .
<code>args.setPriorVcf</code>	Arguments for somatic prior function.
<code>fun.setMappingBiasVcf</code>	Function to set mapping bias for each variant in the VCF. Defaults to setMappingBiasVcf .
<code>args.setMappingBiasVcf</code>	Arguments for mapping bias function.
<code>fun.filterIntervals</code>	Function for filtering low-quality intervals in the coverage files. Needs to return a logical vector whether an interval should be used for segmentation. Defaults to filterIntervals .
<code>args.filterIntervals</code>	Arguments for target filtering function. Arguments <code>normal</code> , <code>tumor</code> , <code>log.ratio</code> , <code>min.coverageseg.file</code> and <code>normalDB</code> are required and automatically set.
<code>fun.segmentation</code>	Function for segmenting the copy number log-ratios. Expected return value is a <code>data.frame</code> representation of the segmentation. Defaults to segmentationCBS .
<code>args.segmentation</code>	Arguments for segmentation function. Arguments <code>normal</code> , <code>tumor</code> , <code>log.ratio</code> , <code>plot.cnv</code> , <code>sampleid</code> , <code>vcf</code> , <code>tumor.id.in.vcf</code> , <code>centromeres</code> are required in the segmentation function and automatically set.
<code>fun.focal</code>	Function for identifying focal amplifications. Defaults to findFocal .
<code>args.focal</code>	Arguments for focal amplification function.
<code>sampleid</code>	Sample id, provided in output files etc.
<code>min.ploidy</code>	Minimum ploidy to be considered.
<code>max.ploidy</code>	Maximum ploidy to be considered.
<code>test.num.copy</code>	Copy numbers tested in the grid search. Note that focal amplifications can have much higher copy numbers, but they will be labeled as subclonal (because they do not fit the integer copy numbers).
<code>test.purity</code>	Considered tumor purity values.
<code>prior.purity</code>	<code>numeric(length(test.purity))</code> with priors for tested purity values. If <code>NULL</code> , use flat priors.
<code>prior.K</code>	This defines the prior probability that the multiplicity of a SNV corresponds to either the maternal or the paternal copy number (for somatic variants additionally to a multiplicity of 1). For perfect segmentations, this value would be 1; values smaller than 1 thus may provide some robustness against segmentation errors.

prior.contamination	The prior probability that a known SNP is from a different individual.
max.candidate.solutions	Number of local optima considered in optimization and variant fitting steps. If there are too many local optima, it will use specified number of top candidate solutions, but will also include all optima close to diploid, because silent genomes have often lots of local optima.
candidates	Candidates to optimize from a previous run (return.object\$candidates). If NULL, do 2D grid search and find local optima.
min.coverage	Minimum coverage in both normal and tumor. Intervals and variants with lower coverage are ignored. This value is provided to the args.filterIntervals and args.filterVcf lists, but can be overwritten in these lists if different cutoffs for the coverage and variant filters are wanted. To increase the sensitivity of homozygous deletions in high purity samples, the coverage cutoff in tumor is automatically lowered by 50 percent if the normal coverage is high.
max.coverage.vcf	This will set the maximum number of reads in the SNV fitting. This is to avoid that small non-reference biases that come apparent only at high coverages have a dramatic influence on likelihood scores. Only relevant for model = "beta".
max.non.clonal	Maximum genomic fraction assigned to a subclonal copy number state.
max.homozygous.loss	double(2) with maximum chromosome fraction assigned to homozygous loss and maximum size of a homozygous loss segment.
non.clonal.M	Average expected cellular fraction of sub-clonal somatic mutations. This is to calculate expected allelic fractions of a single sub-clonal bin for variants. For all somatic variants, more accurate cellular fractions are calculated.
max.mapping.bias	Exclude variants with high mapping bias from the likelihood score calculation. Note that bias is reported on an inverse scale; a variant with mapping bias of 1 has no bias.
max.pon	Exclude variants found more than max.pon times in pool of normals and not in germline databases. Requires mapping.bias.file in setMappingBiasVcf . Should be set to a value high enough to be much more likely an artifact and not a true germline variant not present in germline databases.
iterations	Maximum number of iterations in the Simulated Annealing copy number fit optimization. Note that this is an integer optimization problem that should converge quickly. Allowed range is 10 to 250.
min.variants.segment	Flag segments with fewer variants. The minor copy number estimation is not reliable with insufficient variants.
log.ratio.calibration	Re-calibrate log-ratios in the window purity*log.ratio.calibration.
smooth.log.ratio	Smooth log.ratio using the DNACopy package.
model.homozygous	Homozygous germline SNPs are uninformative and by default removed. In 100 percent pure samples such as cell lines, however, heterozygous germline SNPs appear homozygous in case of LOH. Setting this parameter to TRUE will keep homozygous SNPs and include a homozygous SNP state in the likelihood model. Not necessary when matched normal samples are available.

error	Estimated sequencing error rate. Used to calculate minimum number of supporting reads for variants using <code>calculatePowerDetectSomatic</code> . Also used to calculate the probability of homozygous SNP allelic fractions (assuming reference reads are sequencing errors).
interval.file	A mapping file that assigns GC content and gene symbols to each exon in the coverage files. Used for generating gene-level calls. First column in format CHR:START-END. Second column GC content (0 to 1). Third column gene symbol. This file is generated with the <code>preprocessIntervals</code> function.
max.dropout	Measures GC bias as ratio of coverage in AT-rich (GC < 0.5) versus GC-rich on-target regions (GC >= 0.5). High coverage drop-out might indicate that data was not GC-normalized (optional with larger pool of normal samples). A warning pointing to a normalized log-ratio drop-out likely indicates that the sample quality is insufficient. For log-ratio drop-out, a warning is thrown when half the max.dropout is reached since it is calculated using both tumor and normal. Requires interval.file.
min.logr.sdev	Minimum log-ratio standard deviation used in the model. Useful to make fitting more robust to outliers in very clean data.
max.logr.sdev	Flag noisy samples with segment log-ratio standard deviation larger than this. Assay specific and needs to be calibrated.
max.segments	Flag noisy samples with a large number of segments. Assay specific and needs to be calibrated.
min.gof	Flag purity/ploidy solutions with poor fit.
min.variants	Do not attempt to fit allelic fractions for samples with fewer variants passing all filters.
plot.cnv	Generate segmentation plots.
vcf.field.prefix	Prefix all newly created VCF field names with this string.
cosmic.vcf.file	Add a Cosmic.CNT info field to the provided vcf.file using a VCF file containing the COSMIC database. The default <code>fun.setPriorVcf</code> function will give variants found in the COSMIC database a higher prior probability of being somatic. Not used in likelihood model when matched normal is available in vcf.file. Should be compressed and indexed with bgzip and tabix, respectively.
DB.info.flag	Flag in INFO of VCF that marks presence in common germline databases. Defaults to DB that may contain somatic variants if it is from an unfiltered germline database.
POPAF.info.field	As alternative to a flag, use an info field that contains population allele frequencies. The DB info flag has priority over this field when both exist.
Cosmic.CNT.info.field	Info field containing hits in the Cosmic database
min.pop.af	Minimum population allele frequency in POPAF.info.field to set a high germline prior probability.
model	Use either a beta or a beta-binomial distribution for fitting observed to expected allelic fractions of alterations in vcf.file. The latter can be useful to account for significant overdispersion, for example due to mapping biases when no pool of normals is available or due to other unmodeled biases, e.g. amplification biases. The beta-binomial model is only recommended with a sufficiently sized pool of normal samples (more than 10 normals)

post.optimize	Optimize purity using final SCNA-fit and variants. This might take a long time when lots of variants need to be fitted, but will typically result in a slightly more accurate purity, especially for rather silent genomes or very low purities. Otherwise, it will just use the purity determined via the SCNA-fit.
speedup.heuristics	Tries to avoid spending computation time on local optima that are unlikely correct. Set to 0 to turn this off, to 1 to only apply heuristics that in worst case will decrease accuracy slightly or to 2 to turn on all heuristics.
BPPARAM	BiocParallelParam object. If NULL, does not use parallelization for fitting local optima.
log.file	If not NULL, store verbose output to file.
verbose	Verbose output.

Value

A list with elements

candidates	Results of the grid search.
results	All local optima, sorted by final rank.
input	The input data.

Author(s)

Markus Riester

References

- Riester et al. (2016). PureCN: Copy number calling and SNV classification using targeted short read sequencing. *Source Code for Biology and Medicine*, 11, pp. 13.
- Carter et al. (2012), Absolute quantification of somatic DNA alterations in human cancer. *Nature Biotechnology*.

See Also

[correctCoverageBias](#) [segmentationCBS](#) [calculatePowerDetectSomatic](#)

Examples

```
normal.coverage.file <- system.file('extdata', 'example_normal_tiny.txt',
  package = 'PureCN')
tumor.coverage.file <- system.file('extdata', 'example_tumor_tiny.txt',
  package = 'PureCN')
vcf.file <- system.file('extdata', 'example.vcf.gz',
  package = 'PureCN')
interval.file <- system.file('extdata', 'example_intervals_tiny.txt',
  package = 'PureCN')

# The max.candidate.solutions, max.ploidy and test.purity parameters are set to
# non-default values to speed-up this example. This is not a good idea for real
# samples.
ret <- runAbsoluteCN(normal.coverage.file = normal.coverage.file,
  tumor.coverage.file = tumor.coverage.file, genome = 'hg19',
  vcf.file = vcf.file, sampleid = 'Sample1',
```

```

interval.file = interval.file, max.ploidy = 4,
test.purity = seq(0.3, 0.7, by = 0.05), max.candidate.solutions = 1)

# If a high-quality segmentation was obtained with third-party tools:
seg.file <- system.file('extdata', 'example_seg.txt',
  package = 'PureCN')

# By default, PureCN will re-segment the data, for example to identify
# regions of copy number neutral LOH. If this is not wanted, we can provide
# a minimal segmentation function which just returns the provided one:
funSeg <- function(seg, ...) return(seg)

res <- runAbsoluteCN(seg.file = seg.file, fun.segmentation = funSeg,
  max.ploidy = 4, test.purity = seq(0.3, 0.7, by = 0.05),
  max.candidate.solutions = 1,
  genome='hg19', interval.file = interval.file)

```

segmentationCBS

CBS segmentation

Description

The default segmentation function. This function is called via the `fun.segmentation` argument of [runAbsoluteCN](#). The arguments are passed via `args.segmentation`.

Usage

```

segmentationCBS(
  normal,
  tumor,
  log.ratio,
  seg,
  plot.cnv,
  sampleid,
  weight.flag.pvalue = 0.01,
  alpha = 0.005,
  undo.SD = NULL,
  vcf = NULL,
  tumor.id.in.vcf = 1,
  normal.id.in.vcf = NULL,
  max.segments = NULL,
  min.logr.sdev = 0.15,
  prune.hclust.h = NULL,
  prune.hclust.method = "ward.D",
  chr.hash = NULL,
  additional.cmd.args = "",
  centromeres = NULL
)

```

Arguments

<code>normal</code>	Coverage data for normal sample.
<code>tumor</code>	Coverage data for tumor sample.
<code>log.ratio</code>	Copy number log-ratios, one for each target in the coverage files.
<code>seg</code>	If segmentation was provided by the user, this data structure will contain this segmentation. Useful for minimal segmentation functions. Otherwise PureCN will re-segment the data. This segmentation function ignores this user provided segmentation.
<code>plot.cnv</code>	Segmentation plots.
<code>sampleid</code>	Sample id, used in output files.
<code>weight.flag.pvalue</code>	Flag values with one-sided p-value smaller than this cutoff.
<code>alpha</code>	Alpha value for CBS, see documentation for the segment function.
<code>undo.SD</code>	undo.SD for CBS, see documentation of the segment function. If NULL, try to find a sensible default.
<code>vcf</code>	Optional CollapsedVCF object with germline allelic ratios.
<code>tumor.id.in.vcf</code>	Id of tumor in case multiple samples are stored in VCF.
<code>normal.id.in.vcf</code>	
<code>max.segments</code>	If not NULL, try a higher undo.SD parameter if number of segments exceeds the threshold.
<code>min.logr.sdev</code>	Minimum log-ratio standard deviation used in the model. Useful to make fitting more robust to outliers in very clean data.
<code>prune.hclust.h</code>	Height in the hclust pruning step. Increasing this value will merge segments more aggressively. If NULL, try to find a sensible default.
<code>prune.hclust.method</code>	Cluster method used in the hclust pruning step. See documentation for the hclust function.
<code>chr.hash</code>	Mapping of non-numerical chromosome names to numerical names (e.g. chr1 to 1, chr2 to 2, etc.). If NULL, assume chromosomes are properly ordered.
<code>additional.cmd.args</code>	<code>character(1)</code> . Ignored.
<code>centromeres</code>	A GRanges object with centromere positions. Currently not supported in this function.

Value

`data.frame` containing the segmentation.

Author(s)

Markus Riester

References

- Olshen, A. B., Venkatraman, E. S., Lucito, R., Wigler, M. (2004). Circular binary segmentation for the analysis of array-based DNA copy number data. *Biostatistics* 5: 557-572.
- Venkatraman, E. S., Olshen, A. B. (2007). A faster circular binary segmentation algorithm for the analysis of array CGH data. *Bioinformatics* 23: 657-63.

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

```

normal.coverage.file <- system.file("extdata", "example_normal_tiny.txt",
  package = "PureCN")
tumor.coverage.file <- system.file("extdata", "example_tumor_tiny.txt",
  package = "PureCN")
vcf.file <- system.file("extdata", "example.vcf.gz",
  package = "PureCN")
interval.file <- system.file("extdata", "example_intervals_tiny.txt",
  package = "PureCN")

# The max.candidate.solutions, max.ploidy and test.purity parameters are set to
# non-default values to speed-up this example. This is not a good idea for real
# samples.
ret <-runAbsoluteCN(normal.coverage.file = normal.coverage.file,
  tumor.coverage.file = tumor.coverage.file, vcf.file = vcf.file,
  genome = "hg19", sampleid = "Sample1", interval.file = interval.file,
  max.candidate.solutions = 1, max.ploidy = 4,
  test.purity = seq(0.3, 0.7, by = 0.05),
  fun.segmentation = segmentationCBS,
  args.segmentation = list(alpha = 0.001))

```

segmentationGATK4

*GATK4 ModelSegments segmentation function***Description**

A wrapper for GATK4s ModelSegmentation function, useful when normalization is performed with other tools than GATK4, for example PureCN. This function is called via the fun.segmentation argument of [runAbsoluteCN](#). The arguments are passed via args.segmentation.

Usage

```

segmentationGATK4(
  normal,
  tumor,
  log.ratio,
  seg,
  vcf = NULL,
  tumor.id.in.vcf = 1,
  normal.id.in.vcf = NULL,
  min.logr.sdev = 0.15,
  prune.hclust.h = NULL,
  prune.hclust.method = NULL,
  changepoints.penality = NULL,
  additional.cmd.args = "",
  chr.hash = NULL,
  ...
)

```

Arguments

<code>normal</code>	Coverage data for normal sample. Ignored in this function.
<code>tumor</code>	Coverage data for tumor sample.
<code>log.ratio</code>	Copy number log-ratios, one for each exon in coverage file.
<code>seg</code>	If segmentation was provided by the user, this data structure will contain this segmentation. Useful for minimal segmentation functions. Otherwise PureCN will re-segment the data. This segmentation function ignores this user provided segmentation.
<code>vcf</code>	Optional CollapsedVCF object with germline allelic ratios.
<code>tumor.id.in.vcf</code>	Id of tumor in case multiple samples are stored in VCF.
<code>normal.id.in.vcf</code>	Id of normal in in VCF. Currently not used.
<code>min.logr.sdev</code>	Minimum log-ratio standard deviation used in the model. Useful to make fitting more robust to outliers in very clean data.
<code>prune.hclust.h</code>	Ignored in this function.
<code>prune.hclust.method</code>	Ignored in this function.
<code>changepoints.penalty</code>	The --number-of-changepoints-penalty-factor. If NULL, find a sensible default. Ignored when provided in <code>additional.cmd.args</code> .
<code>additional.cmd.args</code>	<code>character(1)</code> . By default, <code>ModelSegments</code> is called with default parameters. Provide additional arguments here.
<code>chr.hash</code>	Not needed here since <code>ModelSegments</code> does not require numbered chromosome names.
<code>...</code>	Currently unused arguments provided to other segmentation functions.

Value

`data.frame` containing the segmentation.

Author(s)

Markus Riester

See Also

[runAbsoluteCN](#)

Examples

```
normal.coverage.file <- system.file("extdata", "example_normal_tiny.txt",
  package="PureCN")
tumor.coverage.file <- system.file("extdata", "example_tumor_tiny.txt",
  package="PureCN")
vcf.file <- system.file("extdata", "example.vcf.gz",
  package="PureCN")

# The max.candidate.solutions, max.ploidy and test.purity parameters are set to
```

```
# non-default values to speed-up this example. This is not a good idea for real
# samples.
## Not run:
ret <-runAbsoluteCN(normal.coverage.file=normal.coverage.file,
  tumor.coverage.file=tumor.coverage.file, vcf.file=vcf.file,
  sampleid="Sample1", genome="hg19",
  fun.segmentation = segmentationGATK4, max.ploidy=4,
  args.segmentation = list(additional.cmd.args = "--gcs-max-retries 19"),
  test.purity=seq(0.3,0.7,by=0.05), max.candidate.solutions=1)

## End(Not run)
```

segmentationHclust	<i>Minimal segmentation function</i>
--------------------	--------------------------------------

Description

A minimal segmentation function useful when segmentation was performed by third-party tools. When a CollapsedVCF with germline SNPs is provided, it will cluster segments using hclust. Otherwise it will use the segmentation as provided. This function is called via the fun.segmentation argument of [runAbsoluteCN](#). The arguments are passed via args.segmentation.

Usage

```
segmentationHclust(
  seg,
  vcf = NULL,
  tumor.id.in.vcf = 1,
  normal.id.in.vcf = NULL,
  min.logr.sdev = 0.15,
  prune.hclust.h = NULL,
  prune.hclust.method = "ward.D",
  chr.hash = NULL,
  ...
)
```

Arguments

seg	If segmentation was provided by the user, this data structure will contain this segmentation. Useful for minimal segmentation functions. Otherwise PureCN will re-segment the data. This segmentation function ignores this user provided segmentation.
vcf	Optional CollapsedVCF object with germline allelic ratios.
tumor.id.in.vcf	Id of tumor in case multiple samples are stored in VCF.
normal.id.in.vcf	Id of normal in in VCF. Currently not used.
min.logr.sdev	Minimum log-ratio standard deviation used in the model. Useful to make fitting more robust to outliers in very clean data (currently not used in this segmentation function).

`prune.hclust.h` Height in the `hclust` pruning step. Increasing this value will merge segments more aggressively. If `NULL`, try to find a sensible default.

`prune.hclust.method` Cluster method used in the `hclust` pruning step. See documentation for the `hclust` function.

`chr.hash` Mapping of non-numerical chromosome names to numerical names (e.g. `chr1` to 1, `chr2` to 2, etc.). If `NULL`, assume chromosomes are properly ordered.

... Currently unused arguments provided to other segmentation functions.

Value

`data.frame` containing the segmentation.

Author(s)

Markus Riester

See Also

[runAbsoluteCN](#)

Examples

```
vcf.file <- system.file("extdata", "example.vcf.gz",
  package="PureCN")
interval.file <- system.file("extdata", "example_intervals_tiny.txt",
  package="PureCN")
seg.file <- system.file('extdata', 'example_seg.txt',
  package = 'PureCN')

res <- runAbsoluteCN(seg.file = seg.file,
  fun.segmentation = segmentationHclust,
  max.ploidy = 4, vcf.file = vcf.file,
  test.purity = seq(0.3, 0.7, by = 0.05),
  max.candidate.solutions = 1,
  genome = 'hg19', interval.file = interval.file)
```

segmentationPSCBS

PSCBS segmentation

Description

Alternative segmentation function using the PSCBS package. This function is called via the `fun.segmentation` argument of [runAbsoluteCN](#). The arguments are passed via `args.segmentation`.

Usage

```
segmentationPSCBS(
  normal,
  tumor,
  log.ratio,
  seg,
  plot.cnv,
  sampleid,
  weight.flag.pvalue = 0.01,
  alpha = 0.005,
  undo.SD = NULL,
  flavor = "tcn&dh",
  tauA = 0.03,
  vcf = NULL,
  tumor.id.in.vcf = 1,
  normal.id.in.vcf = NULL,
  max.segments = NULL,
  boost.on.target.max.size = 30,
  min.logr.sdev = 0.15,
  prune.hclust.h = NULL,
  prune.hclust.method = "ward.D",
  chr.hash = NULL,
  additional.cmd.args = "",
  centromeres = NULL,
  ...
)
```

Arguments

<code>normal</code>	Coverage data for normal sample. Ignored in this function.
<code>tumor</code>	Coverage data for tumor sample.
<code>log.ratio</code>	Copy number log-ratios, one for each exon in coverage file.
<code>seg</code>	If segmentation was provided by the user, this data structure will contain this segmentation. Useful for minimal segmentation functions. Otherwise PureCN will re-segment the data. This segmentation function ignores this user provided segmentation.
<code>plot.cnv</code>	Segmentation plots.
<code>sampleid</code>	Sample id, used in output files.
<code>weight.flag.pvalue</code>	Flag values with one-sided p-value smaller than this cutoff.
<code>alpha</code>	Alpha value for CBS, see documentation for the segment function.
<code>undo.SD</code>	undo.SD for CBS, see documentation of the segment function. If NULL, try to find a sensible default.
<code>flavor</code>	Flavor value for PSCBS. See <code>segmentByNonPairedPSCBS</code> .
<code>tauA</code>	tauA argument for PSCBS. See <code>segmentByNonPairedPSCBS</code> .
<code>vcf</code>	Optional VCF object with germline allelic ratios.
<code>tumor.id.in.vcf</code>	Id of tumor in case multiple samples are stored in VCF.

<code>normal.id.in.vcf</code>	Id of normal in in VCF. If NULL, use unpaired PSCBS.
<code>max.segments</code>	If not NULL, try a higher <code>undo.SD</code> parameter if number of segments exceeds the threshold.
<code>boost.on.target.max.size</code>	When off-target regions are noisy compared to on-target, try to find small segments of specified maximum size that might be missed due to the increased noise. Set to 0 to turn boosting off.
<code>min.logr.sdev</code>	Minimum log-ratio standard deviation used in the model. Useful to make fitting more robust to outliers in very clean data.
<code>prune.hclust.h</code>	Height in the <code>hclust</code> pruning step. Increasing this value will merge segments more aggressively. If NULL, try to find a sensible default.
<code>prune.hclust.method</code>	Cluster method used in the <code>hclust</code> pruning step. See documentation for the <code>hclust</code> function.
<code>chr.hash</code>	Mapping of non-numerical chromosome names to numerical names (e.g. <code>chr1</code> to 1, <code>chr2</code> to 2, etc.). If NULL, assume chromosomes are properly ordered.
<code>additional.cmd.args</code>	<code>character(1)</code> . Ignored.
<code>centromeres</code>	A <code>GRanges</code> with centromere positions. If not NULL, add breakpoints at centromeres.
<code>...</code>	Additional parameters passed to the <code>segmentByNonPairedPSCBS</code> function.

Value

`data.frame` containing the segmentation.

Author(s)

Markus Riester

References

- Olshen, A. B., Venkatraman, E. S., Lucito, R., Wigler, M. (2004). Circular binary segmentation for the analysis of array-based DNA copy number data. *Biostatistics* 5: 557-572.
- Venkatraman, E. S., Olshen, A. B. (2007). A faster circular binary segmentation algorithm for the analysis of array CGH data. *Bioinformatics* 23: 657-63.
- Olshen et al. (2011). Parent-specific copy number in paired tumor-normal studies using circular binary segmentation. *Bioinformatics*.

See Also

[runAbsoluteCN](#)

Examples

```
normal.coverage.file <- system.file("extdata", "example_normal_tiny.txt",
  package = "PureCN")
tumor.coverage.file <- system.file("extdata", "example_tumor_tiny.txt",
  package = "PureCN")
vcf.file <- system.file("extdata", "example.vcf.gz",
```

```

package = "PureCN")

# The max.candidate.solutions, max.ploidy and test.purity parameters are set to
# non-default values to speed-up this example. This is not a good idea for real
# samples.
ret <-runAbsoluteCN(normal.coverage.file = normal.coverage.file,
  tumor.coverage.file = tumor.coverage.file, vcf.file = vcf.file,
  sampleid = "Sample1", genome = "hg19",
  fun.segmentation = segmentationPSCBS, max.ploidy = 4,
  test.purity = seq(0.3, 0.7, by = 0.05), max.candidate.solutions = 1)

```

setMappingBiasVcf

Set Mapping Bias VCF

Description

Function to set mapping bias for each variant in the provided CollapsedVCF object. By default, it returns the same value for all variants, but a mapping bias file can be provided for position-specific mapping bias calculation.

Usage

```

setMappingBiasVcf(
  vcf,
  tumor.id.in.vcf = NULL,
  mapping.bias.file = NULL,
  smooth = TRUE,
  smooth.n = 5
)

```

Arguments

vcf	CollapsedVCF object, read in with the readVcf function from the VariantAnnotation package.
tumor.id.in.vcf	Id of tumor in case multiple samples are stored in VCF.
mapping.bias.file	A precomputed mapping bias database obtained by calculateMappingBiasVcf . instead. reference and alt counts as AD genotype field. Should be compressed and
smooth	Impute mapping bias of variants not found in the panel by smoothing of neighboring SNPs. Requires mapping.bias.file.
smooth.n	Number of neighboring variants used for smoothing.

Value

Adds elements to the vcf INFO field

bias	A numeric(nrow(vcf)) vector with the mapping bias of for each variant in the CollapsedVCF. Mapping bias is expected as scaling factor. Adjusted allelic fraction is (observed allelic fraction)/(mapping bias). Maximum scaling factor is 1 and means no bias.
------	--

pon.count A numeric(nrow(vcf)) vector with the number of hits in the mapping.bias.file.
 shape1, shape2 Fit of a beta distribution.

Author(s)

Markus Riester

Examples

```
# This function is typically only called by runAbsoluteCN via
# fun.setMappingBiasVcf and args.setMappingBiasVcf.
vcf.file <- system.file("extdata", "example.vcf.gz", package="PureCN")
vcf <- readVcf(vcf.file, "hg19")
vcf.bias <- setMappingBiasVcf(vcf)
```

setPriorVcf	<i>Set Somatic Prior VCF</i>
-------------	------------------------------

Description

Function to set prior for somatic mutation status for each variant in the provided CollapsedVCF object.

Usage

```
setPriorVcf(
  vcf,
  prior.somatic = c(0.5, 5e-04, 0.999, 1e-04, 0.995, 0.5),
  tumor.id.in.vcf = NULL,
  min.cosmic.cnt = 6,
  DB.info.flag = "DB",
  Cosmic.CNT.info.field = "Cosmic.CNT"
)
```

Arguments

vcf	CollapsedVCF object, read in with the readVcf function from the VariantAnnotation package.
prior.somatic	Prior probabilities for somatic mutations. First value is for the case when no matched normals are available and the variant is not in germline databases (second value). Third value is for variants with MuTect somatic call. Different from 1, because somatic mutations in segments of copy number 0 have 0 probability and artifacts can thus have dramatic influence on likelihood score. Forth value is for variants not labeled as somatic by MuTect. Last two values are optional, if vcf contains a flag Cosmic.CNT, it will set the prior probability for variants with CNT > 6 to the first of those values in case of no matched normal available (0.995 default). Final value is for the case that variant is in both germline databases and COSMIC count > 6.
tumor.id.in.vcf	Id of tumor in case multiple samples are stored in VCF.

<code>min.cosmic.cnt</code>	Minimum number of hits in the COSMIC database to call variant as likely somatic.
<code>DB.info.flag</code>	Flag in INFO of VCF that marks presence in common germline databases. Defaults to DB that may contain somatic variants if it is from an unfiltered germline database.
<code>Cosmic.CNT.info.field</code>	Info field containing hits in the Cosmic database

Value

The vcf with `numeric(nrow(vcf))` vector with the prior probability of somatic status for each variant in the CollapsedVCF added to the INFO field PR.

Author(s)

Markus Riester

Examples

```
# This function is typically only called by runAbsoluteCN via the
# fun.setPriorVcf and args.setPriorVcf comments.
vcf.file <- system.file("extdata", "example.vcf.gz", package="PureCN")
vcf <- readVcf(vcf.file, "hg19")
vcf <- setPriorVcf(vcf)
```

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