

Package ‘LACHESIS’

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Title Functions used to analyze early tumor evolution from whole genome sequencing data

Version 0.99.4

Description This package provides modalities to analyze tumor evolution from whole genome sequencing data. In particular, it provides estimates of mutation densities at genomic segments and uses these to time the origin of the tumor.

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Author Verena Körber [aut, cre] (ORCID:
 <<https://orcid.org/0009-0005-3888-2648>>),
 Anand Mayakonda [aut],
 Maximilia Eggle [aut]
Maintainer Verena Körber <verena.korber@endcls.ox.ac.uk>

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classifyLACHESIS	<i>Classify a tumor’s start of clonal outgrowth during tumorigenesis as "early" or "late" (favorable/ unfavorable prognosis) depending on the mutation density at its MRCA</i>
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Description

Takes SNV density timing as computed by LACHESIS as input and classifies the tumors in the cohort.

Usage

```
classifyLACHESIS(  
  lachesis,  
  mrca.cutpoint = NULL,  
  output.dir = NULL,  
  infer.cutpoint = FALSE,  
  entity = "neuroblastoma",  
  surv.time = "OS.time",  
  surv.event = "OS"  
)
```

Arguments

lachesis	output generated from LACHESIS .
mrca.cutpoint	optional; value based on SNV_densities_cohort.pdf observation, will be used as inferred from a test data set if not specified by user.
output.dir	link to directory in which output is to be stored.
infer.cutpoint	logical; should the MRCA cutpoint be inferred from the data?
entity	optional; the tumor entity if classifying according to a pre-defined threshold. Currently, only "neuroblastoma" is supported.
surv.time	column name containing survival time; defaults to OS.time.
surv.event	column name containing event; defaults to OS.

Value

data.table with binary assignment early/ late

Examples

```
# An example file with sample annotations and meta data
input.files <- system.file("extdata", "Sample_template.txt",
  package = "LACHESIS"
)
input.files <- data.table::fread(input.files)

# cnv and snv files for example tumors
nbe11 <- list.files(system.file("extdata/NBE11/", package = "LACHESIS"),
  full.names = TRUE
)
nbe15 <- list.files(system.file("extdata/NBE15/", package = "LACHESIS"),
  full.names = TRUE
)
nbe26 <- list.files(system.file("extdata/NBE26/", package = "LACHESIS"),
  full.names = TRUE
)

cnv.file <- c(nbe11[1], nbe15[1], nbe26[1])
snv.file <- c(nbe11[2], nbe15[2], nbe26[2])

input.files$cnv.file <- cnv.file
input.files$snv.file <- snv.file

# Make an example input file with paths to cnv and snv file along with other
# meta data
lachesis_input <- tempfile(
  pattern = "lachesis", tmpdir = tempdir(),
  fileext = ".tsv"
)
data.table::fwrite(x = input.files, file = lachesis_input, sep = "\t")

# Example with template file with paths to multiple cnv/snv files as an input
```

```
lachesis <- LACHESIS(input.files = lachesis_input)
classifyLACHESIS(lachesis)
```

clonalMutationCounter *Count clonal mutations on one or several chromosomal copies*

Description

This function counts the number of clonal mutations residing on a single or multiple copies per genomic segment. Segments of equal copy number and B-allele count are merged per chromosome.

Usage

```
clonalMutationCounter(
  nbObj = NULL,
  min.cn = 1,
  max.cn = 4,
  chromosomes = seq_len(22)
)
```

Arguments

<code>nbObj</code>	combined SNV and CNV information as generated by nbImport .
<code>min.cn</code>	minimal copy number.
<code>max.cn</code>	maximal copy number.
<code>chromosomes</code>	the chromosomes to be evaluated.

Value

a data table reporting the length of each segment, the number of clonal mutations on all A-allele copies, the number of clonal mutations on all B-allele copies and the total number of clonal mutations (including clonal mutations on a single copy only).

Examples

```
snvs <- system.file("extdata", "NBE15",
  "snvs_NBE15_somatic_snvs_conf_8_to_10.vcf",
  package = "LACHESIS"
)
s_data <- readVCF(vcf = snvs, vcf.source = "dkfz")
aceseq_cn <- system.file("extdata", "NBE15",
  "NBE15_comb_pro_extra2.51_1.txt",
  package = "LACHESIS"
)
c_data <- readCNV(aceseq_cn)
nb <- nbImport(cnv = c_data, snv = s_data, purity = 1, ploidy = 2.51)
cl_muts <- clonalMutationCounter(nb)
```

estimateClonality	<i>Assigning clonality status to every SNV</i>
-------------------	--

Description

Assigns clonality status to every SNV based on the variant allele frequency distribution. The function uses maximum a posteriori assignment of single variants to either "subclonal", "clonal", "early clonal" or "late clonal" (if distinguishable). The likelihood is computed according to a binomial distribution; prior probabilities are empirically determined based on the relative SNV burden per clonal state.

Usage

```
estimateClonality(  
  nbObj = NULL,  
  mrcaObj = NULL,  
  ID = NULL,  
  purity = NULL,  
  driver.file = NULL,  
  ref.build = "hg19"  
)
```

Arguments

nbObj	combined SNV and CNV information as generated by nbImport .
mrcaObj	clonal SNV counts stratified by copy number as generated by MRCA .
ID	sample name.
purity	tumor cell content.
driver.file	optional, path to file with "chrom", "snv_start", "ref", "alt", "gene" column containing known driver SNVs.
ref.build	Reference genome. Default hg19. Can be hg18, hg19 or hg38.

Value

a data.table with per-SNV clonality assignment

Examples

```
# Example using variants associated with specific SBS mutational signatures  
# from vcf file  
snvs <- system.file("extdata", "NBE15",  
  "snvs_NBE15_somatic_snvs_conf_8_to_10.vcf",  
  package = "LACHESIS"  
)  
s_data <- readVCF(vcf = snvs, vcf.source = "dkfz")  
aceseq_cn <- system.file("extdata", "NBE15",
```

```

    "NBE15_comb_pro_extra2.51_1.txt",
    package = "LACHESIS"
)
c_data <- readCNV(aceseq_cn)
sig.filepath <- system.file("extdata",
    "NBE15-Decomposed_MutationType_Probabilities.txt",
    package = "LACHESIS"
)
nb <- nbImport(
    cnv = c_data, snv = s_data, purity = 1, ploidy = 2.51,
    sig.assign = TRUE, ID = "NBE15", sig.file = sig.filepath
)
cl_muts <- clonalMutationCounter(nb)
norm_muts <- normalizeCounts(cl_muts)
mrca <- MRCA(norm_muts)
estimateClonality(nbObj = nb, mrcaObj = mrca, ID = "NBE15", purity = 1)

```

LACHESIS

Run MRCA density estimation for a set of tumors

Description

Takes a set of SNV and CNV files as input and outputs per-tumor SNV densities. Input can either be a tab-delimited file containing the sample specifications or vectors giving direct paths to the sample files. CNV file requires columns for the chromosome number, start and end of the segment, and either the total copy number or the number of A- and B-alleles

Usage

```

LACHESIS(
  input.files = NULL,
  ids = NULL,
  vcf.tumor.ids = NULL,
  cnv.files = NULL,
  snv.files = NULL,
  vcf.source = NULL,
  purity = NULL,
  ploidy = NULL,
  cnv.chr.col = NULL,
  cnv.start.col = NULL,
  cnv.end.col = NULL,
  cnv.A.col = NULL,
  cnv.B.col = NULL,
  cnv.tcn.col = NULL,
  age = NULL,
  OS.time = NULL,
  OS = NULL,

```

```

EFS.time = NULL,
EFS = NULL,
output.dir = NULL,
ignore.XY = TRUE,
min.cn = 1,
max.cn = 4,
merge.tolerance = 10^5,
min.vaf = 0.01,
min.depth = 30,
vcf.info.af = "AF",
vcf.info.dp = "DP",
min.seg.size = 10^7,
fp.mean = 0,
fp.sd = 0,
excl.chr = NULL,
ref.build = "hg19",
filter.value = "PASS",
sig.assign = FALSE,
sig.file = NULL,
assign.method = "sample",
sig.select = NULL,
min.p = NULL,
driver.file = NULL,
...
)

```

Arguments

<code>input.files</code>	a tab-delimited sample-specification file, it must contain the sample name, the path to the SNV file, path to CNV file, and optionally purity, ploidy, <code>cnv.chr.col</code> , <code>cnv.start.col</code> , <code>cnv.end.col</code> , <code>cnv.A.col</code> , <code>cnv.B.col</code> , <code>cnv.tcn.col</code> . A template for this spreadsheet can be downloaded from ...
<code>ids</code>	vector of sample names, will be ignored if <code>input.files</code> is specified.
<code>vcf.tumor.ids</code>	vector of sample names as given in the vcf file; will be ignored if <code>input.files</code> is specified.
<code>cnv.files</code>	vector of cnv files in same order as <code>ids</code> ; should be in tab-delimited format, will be ignored if <code>input.files</code> is specified.
<code>snv.files</code>	vector of snv files in same order as <code>ids</code> ; should be in vcf format, will be ignored if <code>input.files</code> is specified.
<code>vcf.source</code>	Tool used for generating VCF file. Can be <code>strelka</code> or <code>mutect</code> or <code>dkfz</code> or <code>sentieon</code> .
<code>purity</code>	vector tumor cell content in same order as <code>ids</code> ; will be ignored if <code>input.files</code> is specified.
<code>ploidy</code>	average copy number in the tumor sample in same order as <code>ids</code> ; will be ignored if <code>input.files</code> is specified.
<code>cnv.chr.col</code>	column index of chromosome number in <code>cnv.files</code> .

<code>cnv.start.col</code>	column index of first position of the segment.
<code>cnv.end.col</code>	column index of last position of the segment.
<code>cnv.A.col</code>	column index of the number of A alleles. If A and B are not provided, allele configuration are assumed as 1:1 for disomic, 2:1 for trisomic and 3:1 for tetrasomic regions.
<code>cnv.B.col</code>	column index of the number of B alleles. If A and B are not provided, allele configuration are assumed as 1:1 for disomic, 2:1 for trisomic and 3:1 for tetrasomic regions.
<code>cnv.tcn.col</code>	column index of the total copy number. Is computed to A + B if not provided.
<code>age</code>	optional, the age at diagnosis.
<code>OS.time</code>	optional, overall survival time.
<code>OS</code>	optional, overall survival indicator variable.
<code>EFS.time</code>	optional, event-free survival time.
<code>EFS</code>	optional, event-free survival indicator variable.
<code>output.dir</code>	link to directory in which output is to be stored.
<code>ignore.XY</code>	Ignore allosomes. Default TRUE.
<code>min.cn</code>	minimum copy number to be included in the analysis. Default 2.
<code>max.cn</code>	maximum copy number to be included in the analysis. Default 4.
<code>merge.tolerance</code>	the maximum distance below which adjacent segments with equal copy number are merged. Defaults to 10^5 bp.
<code>min.vaf</code>	Remove variants with vcf below threshold. Default 0.01.
<code>min.depth</code>	Minimum required depth for a variant to be considered. Default 30.
<code>vcf.info.af</code>	The string encoding the allele frequency field in the FORMAT column of the .vcf file. Defaults to AF and will be ignored if <code>vcf.source != sentieon</code> .
<code>vcf.info.dp</code>	The string encoding the read depth field in the FORMAT column of the .vcf file. Defaults to DP and will be ignored if <code>vcf.source != sentieon</code> .
<code>min.seg.size</code>	the minimal segment length to be included in the quantification.
<code>fp.mean</code>	optional, the average false positive rate of clonal mutations (e.g., due to incomplete tissue sampling). Defaults to 0.
<code>fp.sd</code>	optional, the standard deviation of the false positive rate of clonal mutations (e.g., due to incomplete tissue sampling). Defaults to 0.
<code>excl.chr</code>	a vector of chromosomes that should be excluded from the quantification. e.g., due to reporter constructs in animal models.
<code>ref.build</code>	Reference genome. Default hg19. Can be hg18, hg19 or hg38.
<code>filter.value</code>	The FILTER column value for variants that passed the filtering, defaults to PASS.
<code>sig.assign</code>	Logical. If TRUE, each variant will be assigned to the most likely mutational signature.
<code>sig.file</code>	The path to the output file from SigProfilerAssignment, typically named "Decomposed_MutationType_Probabilities.txt". If NULL and <code>sig.assign = TRUE</code> , signatures will be assigned using functions from MutationalPatterns.

<code>assign.method</code>	Method to assign signatures: "max" to assign the signature with the highest probability, "sample" to randomly assign based on signature probabilities.
<code>sig.select</code>	A character vector of specific signatures to include in the analysis (e.g., <code>c("SBS1", "SBS5", "SBS40")</code>) to focus on clock-like mutational processes).
<code>min.p</code>	Numeric. The minimum probability threshold from the SigAssignment output that a variant must meet to be considered as matching a specific signature.
<code>driver.file</code>	optional, path to file with "chrom", "snv_start", "ref", "alt", "gene" column containing known driver SNVs.
<code>...</code>	further arguments and parameters passed to LACHESIS functions.

Value

a data.table

See Also

[MRCA clonalMutationCounter normalizeCounts](#)

Examples

```
# An example file with sample annotations and meta data
input.files <- system.file("extdata", "Sample_template.txt",
  package = "LACHESIS"
)
input.files <- data.table::fread(input.files)

# cnv and snv files for example tumors
nbe11 <- list.files(system.file("extdata/NBE11/", package = "LACHESIS"),
  full.names = TRUE
)
nbe15 <- list.files(system.file("extdata/NBE15/", package = "LACHESIS"),
  full.names = TRUE
)
nbe26 <- list.files(system.file("extdata/NBE26/", package = "LACHESIS"),
  full.names = TRUE
)

cnv.file <- c(nbe11[1], nbe15[1], nbe26[1])
snv.file <- c(nbe11[2], nbe15[2], nbe26[2])

input.files$cnv.file <- cnv.file
input.files$snv.file <- snv.file

# Make an example input file with paths to cnv and snv file along with other
# meta data
lachesis_input <- tempfile(
  pattern = "lachesis", tmpdir = tempdir(),
  fileext = ".tsv"
)
data.table::fwrite(x = input.files, file = lachesis_input, sep = "\t")
```

```

# Example with template file with paths to multiple cnv/snv files as an input
lachesis <- LACHESIS(input.files = lachesis_input)

# Example with a single sample input
strelka_vcf <- system.file("extdata", "strelka2.somatic.snvs.vcf.gz",
  package = "LACHESIS"
)
aceseq_cn <- system.file("extdata",
  "ACESeq/NBE11_comb_pro_extra2.59_0.83.txt",
  package = "LACHESIS"
)
lachesis <- LACHESIS(
  ids = "NBE11", cnv.files = aceseq_cn,
  snv.files = strelka_vcf, vcf.source = "strelka", purity = 0.83,
  ploidy = 2.59
)

# Example with multiple sample and data frame input
nbe11_vcf <- system.file("extdata",
  "NBE11/snvs_NBE11_somatic_snvs_conf_8_to_10.vcf",
  package = "LACHESIS"
)
nbe11_cn <- read.delim(
  system.file("extdata",
    "NBE11/NBE11_comb_pro_extra2.59_0.83.txt",
    package = "LACHESIS"
  ),
  sep = "\t",
  header = TRUE
)
nbe15_vcf <- system.file("extdata",
  "NBE15/snvs_NBE15_somatic_snvs_conf_8_to_10.vcf",
  package = "LACHESIS"
)
nbe15_cn <- read.delim(
  system.file("extdata",
    "NBE15/NBE15_comb_pro_extra2.51_1.txt",
    package = "LACHESIS"
  ),
  sep = "\t",
  header = TRUE
)
lachesis <- LACHESIS(
  ids = c("NBE11", "NBE15"), cnv.files =
    list(nbe11_cn, nbe15_cn), snv.files = c(nbe11_vcf, nbe15_vcf),
  vcf.source = c("dkfz", "dkfz"), purity = c(0.83, 1), ploidy = c(2.59, 2.51),
  cnv.chr.col = c(1, 1), cnv.start.col = c(2, 2), cnv.end.col = c(3, 3),
  cnv.A.col = c(34, 34), cnv.B.col = c(35, 35), cnv.tcn.col = c(37, 37)
)

```

MRCA

*Compute mutation densities at ECA and MRCA***Description**

This function takes the normalized clonal mutation counts obtained with [normalizeCounts](#) to estimate mutation densities at MRCA and an earlier common ancestor, ECA.

Usage

```
MRCA(
  normObj = NULL,
  min.seg.size = 10^7,
  fp.mean = 0,
  fp.sd = 0,
  excl.chr = NULL
)
```

Arguments

<code>normObj</code>	normalized clonal SNV counts stratified by copy number as generated by normalizeCounts .
<code>min.seg.size</code>	the minimal segment length to be included in the quantification
<code>fp.mean</code>	optional, the average false positive rate of clonal mutations (e.g., due to incomplete tissue sampling). Defaults to 0.
<code>fp.sd</code>	optional, the standard deviation of the false positive rate of clonal mutations (e.g., due to incomplete tissue sampling). Defaults to 0.
<code>excl.chr</code>	a vector of chromosomes that should be excluded from the quantification. e.g., due to reporter constructs in animal models.

Value

a data table reporting the assignment of individual segments to ECA or MRCA. Mutation densities at ECA and MRCA, and the bootstrapped 95% CIs are stored as attributes. The columns in the data table report the following information:

<code>chrom</code>	Chromosome
<code>TCN</code>	Total copy number
<code>A</code>	Number of A alleles
<code>B</code>	Number of B alleles
<code>Seglength</code>	Number of bps with the given copy number configuration on this chromosome
<code>n_mut_A</code>	Normalized number of mutations present on all A alleles
<code>n_mut_B</code>	Normalized number of mutations present on all B alleles
<code>n_mut_total_clonal</code>	Normalized number of mutations per single copy of the segment

density_A_mean	Normalized mean density of mutations present on all A alleles (1/Mb)
density_B_mean	Normalized mean density of mutations present on all B alleles (1/Mb)
density_total_mean	Normalized mean density of mutations per single copy of the segment (1/Mb)
density_total_lower	Lower bound (95% CI) of normalized density of mutations per single copy of the segment (1/Mb)
density_total_upper	Upper bound (95% CI) of normalized density of mutations per single copy of the segment (1/Mb)
density_A_lower	Lower bound (95% CI) of normalized density of mutations on all A alleles of the segment (1/Mb)
density_A_upper	Upper bound (95% CI) of normalized density of mutations on all A alleles of the segment (1/Mb)
density_B_lower	Lower bound (95% CI) of normalized density of mutations on all B alleles of the segment (1/Mb)
density_B_upper	Upper bound (95% CI) of normalized density of mutations on all B alleles of the segment (1/Mb)
p_total_to_mrca	Probability that the density of mutations per single copy of the segment agrees with the mutation density at MRCA.
p_A_to_to_mrca	Probability that the density of mutations on all A alleles of the segment agrees with the mutation density at MRCA.
p_B_to_to_mrca	Probability that the density of mutations on all B alleles of the segment agrees with the mutation density at MRCA.
p_adj_total_to_mrca	Probability that the density of mutations on all alleles of the segment agrees with the mutation density at MRCA, adjusted for multiple sampling (Holm correction).
p_adj_A_to_mrca	Probability that the density of mutations on all A alleles of the segment agrees with the mutation density at MRCA, adjusted for multiple sampling (Holm correction).
p_adj_B_to_mrca	Probability that the density of mutations on all B alleles of the segment agrees with the mutation density at MRCA, adjusted for multiple sampling (Holm correction).
MRCA_qual	Quality control. PASS, if the density of mutations on single copies agrees with the density at the MRCA.
p_total_to_eca	Probability that the density of mutations per single copy of the segment agrees with the mutation density at ECA.

p_A_to_to_eca	Probability that the density of mutations on all A alleles of the segment agrees with the mutation density at ECA.
p_B_to_to_eca	Probability that the density of mutations on all B alleles of the segment agrees with the mutation density at ECA.
p_adj_total_to_eca	Probability that the density of mutations on all alleles of the segment agrees with the mutation density at ECA, adjusted for multiple sampling (Holm correction).
p_adj_A_to_eca	Probability that the density of mutations on all A alleles of the segment agrees with the mutation density at ECA, adjusted for multiple sampling (Holm correction).
p_adj_B_to_eca	Probability that the density of mutations on all B alleles of the segment agrees with the mutation density at ECA, adjusted for multiple sampling (Holm correction).
A_time	Time of A allele gain (can be "ECA", "MRCA", "ECA/MRCA" if assignment is unclear, or "not mapped to ECA or MRCA" if density does not agree with either ECA or MRCA).
B_time	Time of B allele gain (can be "ECA", "MRCA", "ECA/MRCA" if assignment is unclear, or "not mapped to ECA or MRCA" if density does not agree with either ECA or MRCA).

Examples

```
snvs <- system.file("extdata", "NBE15",
  "snvs_NBE15_somatic_snvs_conf_8_to_10.vcf",
  package = "LACHESIS"
)
s_data <- readVCF(vcf = snvs, vcf.source = "dkfz")
aceseq_cn <- system.file("extdata", "NBE15",
  "NBE15_comb_pro_extra2.51_1.txt",
  package = "LACHESIS"
)
c_data <- readCNV(aceseq_cn)
nb <- nbImport(cnv = c_data, snv = s_data, purity = 1, ploidy = 2.51)
cl_muts <- clonalMutationCounter(nb)
norm_muts <- normalizeCounts(cl_muts)
mrca <- MRCA(norm_muts)
```

nbImport

Combine CNVs and SNVs

Description

Merges CNVs and SNVs into a single data.table. Each variant is assigned to its corresponding copy number segment and status.

Usage

```
nbImport(
  cnv = NULL,
  snv = NULL,
  purity = NULL,
  ploidy = NULL,
  sig.assign = FALSE,
  assign.method = "sample",
  ID = NULL,
  sig.file = NULL,
  sig.select = NULL,
  min.p = NULL,
  ref.build = "hg19",
  cosmic.version = "COSMIC_v3.2",
  ...
)
```

Arguments

cnv	CNV data from readCNV .
snv	SNV data from readVCF .
purity	tumor cell content.
ploidy	average copy number in the tumor sample.
sig.assign	Logical. If TRUE, each variant will be assigned to a mutational signature.
assign.method	Method to assign signatures: max to assign the signature with the highest probability, sample to randomly assign based on signature probabilities.
ID	sample name.
sig.file	The path to the output file from SigProfilerAssignment, typically named "Decomposed_MutationType_Probabilities.txt". If NULL and sig.assign = TRUE, signatures will be assigned using functions from MutationalPatterns.
sig.select	A character vector of specific signatures to include in the analysis (e.g., c("SBS1", "SBS5", "SBS40") to focus on clock-like mutational processes).
min.p	Numeric. The minimum probability threshold from the SigAssignment output that a variant must meet to be considered as matching a specific signature.
ref.build	Reference genome. Default hg19. Can be hg18, hg19 or hg38.
cosmic.version	COSMIC mutational signature reference. Can be "COSMIC", "COSMIC_v3.1", "COSMIC_v3.2"
...	further arguments and parameters passed to other LACHESIS functions.

Value

a data.table

See Also

[plotNB](#)

Examples

```
# Example using all variants from vcf file
snvs <- system.file("extdata", "NBE15",
  "snvs_NBE15_somatic_snvs_conf_8_to_10.vcf",
  package = "LACHESIS"
)
s_data <- readVCF(vcf = snvs, vcf.source = "dkfz")
aceseq_cn <- system.file("extdata", "NBE15",
  "NBE15_comb_pro_extra2.51_1.txt",
  package = "LACHESIS"
)
c_data <- readCNV(aceseq_cn)
nb <- nbImport(cnv = c_data, snv = s_data, purity = 1, ploidy = 2.51)

# Example using variants associated with specific SBS mutational
# signatures from vcf file
snvs <- system.file("extdata", "NBE15",
  "snvs_NBE15_somatic_snvs_conf_8_to_10.vcf",
  package = "LACHESIS"
)
s_data <- readVCF(vcf = snvs, vcf.source = "dkfz")
aceseq_cn <- system.file("extdata", "NBE15",
  "NBE15_comb_pro_extra2.51_1.txt",
  package = "LACHESIS"
)
c_data <- readCNV(aceseq_cn)
sig.filepath <- system.file("extdata",
  "NBE15-Decomposed_MutationType_Probabilities.txt",
  package = "LACHESIS"
)
nb <- nbImport(
  cnv = c_data, snv = s_data, purity = 1, ploidy = 2.51,
  sig.assign = TRUE, ID = "NBE15", sig.file = sig.filepath,
  sig.select = c("SBS1", "SBS5", "SBS40a", "SBS18")
)
nb.2 <- nbImport(
  cnv = c_data, snv = s_data, purity = 1, ploidy = 2.51,
  sig.assign = TRUE, ID = "NBE15",
  sig.select = c("SBS1", "SBS5", "SBS40", "SBS18")
)
```

normalizeCounts

Normalize clonal mutation counts

Description

This function normalizes the clonal mutation counts obtained with [clonalMutationCounter](#). The normalized counts correspond to the number of mutations accumulated between conception/gastrulation and MRCA/copy number gain. They can hence be interpreted as "molecular time".

Usage

```
normalizeCounts(countObj = NULL)
```

Arguments

countObj clonal SNV counts stratified by copy number as generated by [clonalMutationCounter](#).

Value

a data table reporting the normalized mutation counts and densities per segment, stratified by copy number

Examples

```
snvs <- system.file("extdata", "NBE15",
  "snvs_NBE15_somatic_snvs_conf_8_to_10.vcf",
  package = "LACHESIS"
)
s_data <- readVCF(vcf = snvs, vcf.source = "dkfz")
aceseq_cn <- system.file("extdata", "NBE15",
  "NBE15_comb_pro_extra2.51_1.txt",
  package = "LACHESIS"
)
c_data <- readCNV(aceseq_cn)
nb <- nbImport(cnv = c_data, snv = s_data, purity = 1, ploidy = 2.51)
cl_muts <- clonalMutationCounter(nb)
norm_muts <- normalizeCounts(cl_muts)
```

```
plotClinicalCorrelations
```

Correlate SNV density at ECA/MRCA with clinical parameters such as age, OS, etc.

Description

Takes SNV densities as computed by LACHESIS as input and correlates them with clinical data such as age at diagnosis, survival data etc.

Usage

```
plotClinicalCorrelations(
  lachesis = NULL,
  clin.par = "Age",
  clin.suppress.outliers = FALSE,
  clin.log.densities = FALSE,
  output.file = NULL
)
```


Arguments

lachesis output generated from [LACHESIS](#).
 clin.par the clinical parameter used for correlation. Default Age.
 clin.suppress.outliers shall outliers (defined as the 2.5% tumors with lowest and highest densities) be plotted? Default TRUE.
 clin.log.densities plot logarithmic densities. Default FALSE.
 output.file optional; the file to which the plot will be stored.

Value

graph with SNV density at ECA/ MRCA copared to clinical parameters

Examples

```
# An example file with sample annotations and meta data
input.files <- system.file("extdata", "Sample_template.txt",
  package = "LACHESIS"
)
input.files <- data.table::fread(input.files)

# cnv and snv files for example tumors
nbe11 <- list.files(system.file("extdata/NBE11/", package = "LACHESIS"),
  full.names = TRUE
)
nbe15 <- list.files(system.file("extdata/NBE15/", package = "LACHESIS"),
  full.names = TRUE
)
nbe26 <- list.files(system.file("extdata/NBE26/", package = "LACHESIS"),
  full.names = TRUE
)

cnv.file <- c(nbe11[1], nbe15[1], nbe26[1])
snv.file <- c(nbe11[2], nbe15[2], nbe26[2])

input.files$cnv.file <- cnv.file
input.files$snv.file <- snv.file

# Make an example input file with paths to cnv and snv file along with other
# meta data
lachesis_input <- tempfile(
  pattern = "lachesis", tmpdir = tempdir(),
  fileext = ".tsv"
)
data.table::fwrite(x = input.files, file = lachesis_input, sep = "\t")

# Example with template file with paths to multiple cnv/snv files as an input
lachesis <- LACHESIS(input.files = lachesis_input)
plotClinicalCorrelations(lachesis)
```

plotClonality

Plotting assigned clonality status for every SNV by chromosome

Description

Visualizes results from [estimateClonality](#).

Usage

```
plotClonality(
  snvClonality = snvClonality,
  nbObj = NULL,
  sig.assign = FALSE,
  output.file = NULL,
  ...
)
```

Arguments

snvClonality	output generated from estimateClonality .
nbObj	output generated from nbImport .
sig.assign	Logical. If TRUE, clonality status distribution will be plotted for each SBS signature.
output.file	optional, will save the mutational signatures stratified by Clonality.
...	further arguments and parameters passed to other LACHESIS functions.

Value

graphs with clonality status of SNVs per chromosome and if specified, stratified by signature

Examples

```
# Example using variants associated with specific SBS mutational signatures
# from vcf file
snvs <- system.file("extdata", "NBE15",
  "snvs_NBE15_somatic_snvs_conf_8_to_10.vcf",
  package = "LACHESIS"
)
s_data <- readVCF(vcf = snvs, vcf.source = "dkfz")
aceseq_cn <- system.file("extdata", "NBE15",
  "NBE15_comb_pro_extra2.51_1.txt",
  package = "LACHESIS"
)
c_data <- readCNV(aceseq_cn)
sig.filepath <- system.file("extdata",
  "NBE15-Decomposed_MutationType_Probabilities.txt",
  package = "LACHESIS"
```

```

)
nb <- nbImport(
  cnv = c_data, snv = s_data, purity = 1, ploidy = 2.51,
  sig.assign = TRUE, ID = "NBE15", sig.file = sig.filepath
)
cl_muts <- clonalMutationCounter(nb)
norm_muts <- normalizeCounts(cl_muts)
mrca <- MRCA(norm_muts)
snvClonality <- estimateClonality(
  nbObj = nb, mrcaObj = mrca,
  ID = "NBE15", purity = 1
)
plotClonality(snvClonality, nbObj = nb, sig.assign = TRUE)

```

plotLachesis

Plot SNV densities at ECA and MRCA

Description

Visualizes results from [LACHESIS](#). Top plot, histograms of mean mutation densities; bottom plots, cumulative distribution of mean mutation densities with 95% confidence intervals.

Usage

```

plotLachesis(
  lachesis = NULL,
  lach.suppress.outliers = FALSE,
  lach.log.densities = FALSE,
  lach.col.multi = "#176A02",
  lach.border = NULL,
  binwidth = NULL,
  lach.col.zero = "#4FB12B",
  output.file = NULL,
  ...
)

```

Arguments

lachesis output generated from [LACHESIS](#)

lach.suppress.outliers whether outliers (defined as the 2.5% tumors with lowest and highest densities) are to be plot. Default TRUE.

lach.log.densities plot logarithmic densities. Default FALSE.

lach.col.multi optional, bar color for multi-copy SSNV densities.

lach.border optional, border color for the bars.

binwidth optional, the binwidth in the histogram.

lach.col.zero optional, bar color for single-copy SSNV densities.

output.file optional, the file to which the plot will be stored.

... further arguments and parameters passed to other LACHESIS functions.

Value

graph with cohort overview of SNV densities at ECA/ MRCA

Examples

```
# An example file with sample annotations and meta data
input.files <- system.file("extdata", "Sample_template.txt",
  package = "LACHESIS"
)
input.files <- data.table::fread(input.files)

# cnv and snv files for example tumors
nbe11 <- list.files(system.file("extdata/NBE11/", package = "LACHESIS"),
  full.names = TRUE
)
nbe15 <- list.files(system.file("extdata/NBE15/", package = "LACHESIS"),
  full.names = TRUE
)
nbe26 <- list.files(system.file("extdata/NBE26/", package = "LACHESIS"),
  full.names = TRUE
)

cnv.file <- c(nbe11[1], nbe15[1], nbe26[1])
snv.file <- c(nbe11[2], nbe15[2], nbe26[2])

input.files$cnv.file <- cnv.file
input.files$snv.file <- snv.file

# Make an example input file with paths to cnv and snv file along with other
# meta data
lachesis_input <- tempfile(
  pattern = "lachesis", tmpdir = tempdir(),
  fileext = ".tsv"
)
data.table::fwrite(x = input.files, file = lachesis_input, sep = "\t")

# Example with template file with paths to multiple cnv/snv files as an input
lachesis <- LACHESIS(input.files = lachesis_input)
plotLachesis(lachesis)
```

`plotMutationDensities` *Plot normalized mutation density at copy number gain and MRCA per segment*

Description

Visualizes results from [MRCA](#). Top plot, histograms of mean mutation densities; bottom plots, timeline of early tumor evolution, showing mutation densities (mean and 95% CI) of individual chromosomal gains and mutation densities at ECA and MRCA.

Usage

```
plotMutationDensities(
  mrcaObj = NULL,
  samp.name = NULL,
  min.seg.size = 10^7,
  ref.build = "hg19",
  mut.col.zero = "#4FB12B",
  mut.col.multi = "#176A02",
  mut.border = NULL,
  mut.show.density = TRUE,
  mut.breaks = NULL,
  mut.xaxis = NULL,
  mut.show.realtime = FALSE,
  mut.snv.rate = 3.2,
  output.file = NULL,
  ...
)
```

Arguments

<code>mrcaObj</code>	output generated from MRCA
<code>samp.name</code>	sample name, optional
<code>min.seg.size</code>	minimal segment size to plot
<code>ref.build</code>	Reference genome. Default hg19. Can be hg18, hg19 or hg38.
<code>mut.col.zero</code>	optional, the bar color for densities of mutations present on single copies.
<code>mut.col.multi</code>	optional, the bar color for densities of mutations present on multiple copies.
<code>mut.border</code>	optional, the line color
<code>mut.show.density</code>	optional; if TRUE, the density distribution of mutation densities on single copies will be shown in the histogram of mutation densities on multiple copies.
<code>mut.breaks</code>	optional; the number of bins in the histogram.
<code>mut.xaxis</code>	optional; cutoff value for x-axis in evolutionary timeline plot in SNVs/Mb

mut.show.realtime logical; if TRUE, displays weeks post-conception on the evolutionary timeline.

mut.snv.rate optional; rate of accumulated SNVs per day in a diploid genome (i.e. 3.2 SNVs/day in neuroblastoma)

output.file optional; will save the plot.

... further arguments and parameters passed to other LACHESIS functions.

Value

graphs with mutation density at ECA and MRCA as well as evolutionary timeline plot

Examples

```
snvs <- system.file("extdata", "NBE15",
  "snvs_NBE15_somatic_snvs_conf_8_to_10.vcf",
  package = "LACHESIS"
)
s_data <- readVCF(vcf = snvs, vcf.source = "dkfz")
aceseq_cn <- system.file("extdata", "NBE15",
  "NBE15_comb_pro_extra2.51_1.txt",
  package = "LACHESIS"
)
c_data <- readCNV(aceseq_cn)
nb <- nbImport(cnv = c_data, snv = s_data, purity = 1, ploidy = 2.51)
cl_muts <- clonalMutationCounter(nb)
norm_muts <- normalizeCounts(cl_muts)
mrca <- MRCA(norm_muts)
plotMutationDensities(mrca)
```

plotNB

Plot VAF distribution per copy number

Description

Visualizes results from [nbImport](#). Top plot, measured copy numbers along the genome; bottom plots, VAF histograms of SNVs stratified by copy number and minor/major allele count.

Usage

```
plotNB(
  nb = NULL,
  snvClonality = NULL,
  ref.build = "hg19",
  min.cn = 2,
  max.cn = 4,
  nb.col.abline = "gray70",
  nb.col.cn.2 = "#7f8c8d",
  nb.col.cn = "#16a085",
```

```

    nb.col.hist = "#34495e",
    nb.border = NA,
    nb.breaks = 100,
    samp.name = NULL,
    output.file = NULL,
    sig.show = FALSE,
    ...
)

```

Arguments

nb	output generated from nbImport .
snvClonality	output generated from estimateClonality .
ref.build	Reference genome. Default hg19. Can be hg18, hg19 or hg38.
min.cn	maximum copy number to be included in the plotting. Defaults to 2.
max.cn	maximum copy number to be included in the plotting. Defaults to 4.
nb.col.abline	optional, the color code for the lines depicting clonality in the VAF histograms.
nb.col.cn.2	optional, the color code for tcn = 2 in the CNV plot.
nb.col.cn	optional, the color code for other copy numbers in the CNV plot.
nb.col.hist	optional, the color code for bars in the VAF histograms.
nb.border	optional, the line color in the VAF histograms.
nb.breaks	optional, the number of bins in the histograms.
samp.name	Sample name. Optional. Default NULL
output.file	optional, will save the plot.
sig.show	plot stratified VAF histogram with assigned mutational signatures.
...	further arguments and parameters passed to other LACHESIS functions.

Value

copy number plot, VAF histograms stratified by copynumber and clonality; if specified, VAF histograms stratified by copynumber and signature

Examples

```

# Example using all variants from vcf file
snvs <- system.file("extdata", "NBE15",
  "snvs_NBE15_somatic_snvs_conf_8_to_10.vcf",
  package = "LACHESIS"
)
s_data <- readVCF(vcf = snvs, vcf.source = "dkfz")
aceseq_cn <- system.file("extdata", "NBE15",
  "NBE15_comb_pro_extra2.51_1.txt",
  package = "LACHESIS"
)
c_data <- readCNV(aceseq_cn)
nb <- nbImport(cnv = c_data, snv = s_data, purity = 1, ploidy = 2.51)

```

```

cl_muts <- clonalMutationCounter(nb)
norm_muts <- normalizeCounts(cl_muts)
mrca <- MRCA(norm_muts)
snvClonality <- estimateClonality(
  nbObj = nb, mrcaObj = mrca, ID = "NBE15",
  purity = 1
)
plotNB(nb = nb, snvClonality = snvClonality)

# Example using variants associated with specific SBS mutational
# signatures from vcf file
snvs <- system.file("extdata", "NBE15",
  "snvs_NBE15_somatic_snvs_conf_8_to_10.vcf",
  package = "LACHESIS"
)
s_data <- readVCF(vcf = snvs, vcf.source = "dkfz")
aceseq_cn <- system.file("extdata", "NBE15",
  "NBE15_comb_pro_extra2.51_1.txt",
  package = "LACHESIS"
)
c_data <- readCNV(aceseq_cn)
sig.filepath <- system.file("extdata",
  "NBE15_Decomposed_MutationType_Probabilities.txt",
  package = "LACHESIS"
)
nb <- nbImport(
  cnv = c_data, snv = s_data, purity = 1, ploidy = 2.51,
  sig.assign = TRUE, ID = "NBE15", sig.file = sig.filepath
)
cl_muts <- clonalMutationCounter(nb)
norm_muts <- normalizeCounts(cl_muts)
mrca <- MRCA(norm_muts)
snvClonality <- estimateClonality(
  nbObj = nb, mrcaObj = mrca, ID = "NBE15",
  purity = 1
)
plotNB(nb = nb, snvClonality = snvClonality, sig.show = TRUE)

```

plotSurvival

Correlate SNV density timing at MRCA with Survival

Description

Takes SNV density timing as computed by LACHESIS as input and compares survival between tumors with high and low SNV densities

Usage

```
plotSurvival(
```



```

lachesis = NULL,
mrca.cutpoint = NULL,
output.dir = NULL,
surv.time = "OS.time",
surv.event = "OS",
surv.palette = c("dodgerblue", "dodgerblue4"),
surv.time.breaks = NULL,
surv.time.scale = 1,
surv.title = "Survival probability",
surv.ylab = "Survival"
)

```

Arguments

<code>lachesis</code>	output generated from LACHESIS .
<code>mrca.cutpoint</code>	optional, MRCA density value to be used for survival stratification, will be computationally inferred to maximize survival differences if not specified by user.
<code>output.dir</code>	link to directory in which output is to be stored.
<code>surv.time</code>	column name containing survival time; defaults to <code>OS.time</code> .
<code>surv.event</code>	column name containing event; defaults to <code>OS</code> .
<code>surv.palette</code>	color palette to be used. Allowed values include "hue" for the default hue color scale; "grey" for grey color palettes; brewer palettes e.g. "RdBu", "Blues", ...; or custom color palette e.g. <code>c("blue", "red")</code> .
<code>surv.time.breaks</code>	numeric value controlling time axis breaks; defaults to <code>NULL</code> .
<code>surv.time.scale</code>	numeric value by which survival time is to be divided (e.g., 365 for converting days into years, 30 for months), defaults to 1.
<code>surv.title</code>	main title.
<code>surv.ylab</code>	y-axis label, defaults to <code>Survival</code> .

Value

survival graphs

Examples

```

# An example file with sample annotations and meta data
input.files <- system.file("extdata", "Sample_template.txt",
  package =
    "LACHESIS"
)
input.files <- data.table::fread(input.files)

# cnv and snv files for example tumors
nbe11 <- list.files(system.file("extdata/NBE11/", package = "LACHESIS"),
  full.names = TRUE

```

```

)
nbe15 <- list.files(system.file("extdata/NBE15/", package = "LACHESIS"),
  full.names = TRUE
)
nbe26 <- list.files(system.file("extdata/NBE26/", package = "LACHESIS"),
  full.names = TRUE
)

cnv.file <- c(nbe11[1], nbe15[1], nbe26[1])
snv.file <- c(nbe11[2], nbe15[2], nbe26[2])

input.files$cnv.file <- cnv.file
input.files$snv.file <- snv.file

# Make an example input file with paths to cnv and snv file along with other
# meta data
lachesis_input <- tempfile(
  pattern = "lachesis", tmpdir = tempdir(),
  fileext = ".tsv"
)
data.table::fwrite(x = input.files, file = lachesis_input, sep = "\t")

# Example with template file with paths to multiple cnv/snv files as an input
lachesis <- LACHESIS(input.files = lachesis_input)
plotSurvival(lachesis,
  surv.time = "EFS.time", surv.event = "EFS",
  mrca.cutpoint = 0.05
)

```

plotVAFdistr

Plot histogram of VAF distribution

Description

Plot frequency distribution of variant allele frequencies

Usage

```

plotVAFdistr(
  vaf = NULL,
  vaf.interval = 0.05,
  t_sample = NULL,
  vaf.show.counts = FALSE,
  vaf.show.density = TRUE,
  vaf.col = "#34495e",
  vaf.border = "#bdc3c7",
  srtcounts = 45,
  output.file = NULL,
  ...
)

```

Arguments

vaf	output produced by readVCF
vaf.interval	Interval size. Default 0.05
t_sample	Sample name for tumor. Used for plot title. Default NULL
vaf.show.counts	Show counter per break on the histogram. Default FALSE
vaf.show.density	Show additional inset plot of density. Default TRUE
vaf.col	Color to be used to fill the bars, default "#34495e"
vaf.border	Border color, default "#bdc3c7"
srtcounts	Text angle if vaf.show.counts is TRUE. Default 45
output.file	Optional, will save the plot.
...	further arguments and parameters passed to other LACHESIS functions.

Value

VAF histogram

Examples

```
strelka_vcf <- system.file("extdata", "strelka2.somatic.snvs.vcf.gz",
  package = "LACHESIS"
)
s_data <- readVCF(
  vcf = strelka_vcf, vcf.source = "strelka",
  ignore.XY = FALSE
)
plotVAFdistr(s_data)
```

readCNV	<i>Converts a user-specified bed-file with copy number information into a standardized format that can be used as input for downstream analysis</i>
---------	---

Description

Convert a user-specified bed-file with copy number information into a standardized format. Perform various quality checks on the file input and return the clean and standardized data-frame. If column identifiers for chromosomal positions and allele-specific copy number information are not provided, the function attempts to identify these columns based on standard nomenclature. If total copy number information is provided but allele-specific information is missing, the function assumes that the number of B alleles is the rounded off of half the total copy number.

Usage

```
readCNV(
  cn.info = NULL,
  chr.col = NULL,
  start.col = NULL,
  end.col = NULL,
  A.col = NULL,
  B.col = NULL,
  tcn.col = NULL,
  merge.tolerance = 10^5,
  ignore.XY = TRUE,
  max.cn = 4,
  tumor.id = NULL
)
```

Arguments

cn.info	Path to the copy number information. Requires columns for the chromosome number, start and end of the segment, and either the total copy number or the number of A- and B-alleles
chr.col	column index of chromosome number
start.col	column index of first position of the segment
end.col	column index of last position of the segment
A.col	column index of the number of A alleles. If A and B are not provided, allele configuration are assumed as 1:1 for disomic, 2:1 for trisomic and 3:1 for tetrasomic regions.
B.col	column index of the number of B alleles. If A and B are not provided, allele configuration are assumed as 1:1 for disomic, 2:1 for trisomic and 3:1 for tetrasomic regions.
tcn.col	column index of the total copy number. Is computed to A + B if not provided.
merge.tolerance	the maximum distance below which adjacent segments with equal copy number are merged. Defaults to 10 ⁵ bp.
ignore.XY	Ignore allosomes. Default TRUE
max.cn	maximum copy number to be included in the analysis. Defaults to 4.
tumor.id	Tumor ID, optional.

Value

A standardized data frame with copy number information per segment. readCNV()

Author(s)

Verena Körber

Examples

```

aceseq_cn <- system.file("extdata",
  "ACESeq/NBE11_comb_pro_extra2.59_0.83.txt",
  package = "LACHESIS"
)
cn_data <- readCNV(aceseq_cn)
ascat_cn <- system.file("extdata",
  "ASCAT/S98.segments.txt",
  package = "LACHESIS"
)
cn_data <- readCNV(ascat_cn)
purple_cn <- system.file("extdata",
  "PURPLE/NB-S-599-T.purple.cnv.somatic.tsv",
  package = "LACHESIS"
)
cn_data <- LACHESIS::readCNV(purple_cn)

```

readVCF

*Import a VCF file and extract read count***Description**

Import a VCF file and extract read-count and variant allele frequencies. Currently VCF files generated by mutect2, strelka2 and dkfz are supported.

Usage

```

readVCF(
  vcf = NULL,
  ignore.XY = TRUE,
  vcf.source = "strelka",
  min.vaf = 0.01,
  min.depth = 30,
  t.sample = NULL,
  info.af = "AF",
  info.dp = "DP",
  filter.value = "PASS",
  filter.biallelic = TRUE,
  filter.indels = TRUE,
  ...
)

```

Arguments

vcf	Input indexed VCF file.
ignore.XY	Ignore allosomes. Default TRUE
vcf.source	Tool used for generating VCF file. Can be strelka or mutect or dkfz or sentieon

<code>min.vaf</code>	Remove variants with vcf below threshold. Default 0.01
<code>min.depth</code>	Minimum required depth for a variant to be considered. Default 30.
<code>t.sample</code>	Sample name for tumor. Must be same as in VCF. Strelka hardcodes tumor sample name to "TUMOR"
<code>info.af</code>	The string encoding the allele frequency field in the FORMAT column. Defaults to AF and will be ignored if <code>vcf.source != sentieon</code> .
<code>info.dp</code>	The string encoding the read depth field in the FORMAT column. Defaults to DP and will be ignored if <code>vcf.source != sentieon</code> .
<code>filter.value</code>	The FILTER column value for variants that passed the filtering, defaults to PASS
<code>filter.biallelic</code>	Remove biallelic variants. Default TRUE
<code>filter.indels</code>	Remove indels. Default TRUE
<code>...</code>	further arguments and parameters passed to other LACHESIS functions.

Value

a data.table with chrom, pos, ref, alt, t_ref_count, t_alt_count, t_depth, t_vaf

Examples

```
mutect_vcf <- system.file("extdata", "mutect.somatic.vcf.gz", package = "LACHESIS")
m_data <- readVCF(vcf = mutect_vcf, vcf.source = "mutect", filter.value = ".")
strelka_vcf <- system.file("extdata", "strelka2.somatic.snvs.vcf.gz", package = "LACHESIS")
s_data <- readVCF(vcf = strelka_vcf, vcf.source = "strelka")
dkfz_vcf <- system.file("extdata", "NBE15", "snvs_NBE15_somatic_snvs_conf_8_to_10.vcf", package = "LACHESIS")
d_data <- readVCF(vcf = dkfz_vcf, vcf.source = "dkfz")
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