Package 'HiCDCPlus'

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Type Package

Title Hi-C Direct Caller Plus

Version 0.99.4
Description Systematic 3D interaction calls and differential analysis for Hi-C and HiChIP. The HiC-DC+ (Hi-C/HiChIP direct caller plus) package enables principled statistical analysis of Hi-C and HiChIP data sets – including calling significant interactions within a single experiment and performing differential analysis between conditions given replicate experiments – to facilitate global integrative studies. HiC-DC+ estimates significant interactions in a Hi-C or HiChIP experiment directly from the raw contact matrix for each chromosome up to a specified genomic distance, binned by uniform genomic intervals or restriction enzyme fragments, by training a background model to account for random polymer ligation and systematic sources of read count variation.
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add_1D_features

add_1D_features

Description

Adds 1D features to the gi_list instance. If any bin on gi_list overlaps with multiple feature records, feature values are aggregated for the bin according to the vector valued function agg (e.g., sum, mean)

Usage

```
add_1D_features(gi_list, df, chrs = NULL, features = NULL, agg = mean)
```

Arguments

gi_list	List of GenomicInteractions objects where each object named with chromosomes contains intrachromosomal interaction information (see ?gi_list_validate for a detailed explanation of valid gi_list instances).
df	DataFrame with columns named 'chr', and 'start' and features to be added with their respective names.
chrs	a subset of chromosomes' e.g., c('chr21','chr22'). Defaults to all chromosomes specified in the data frame df.

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features	features to be added. Needs to be a subset of colnames(df). Defaults to all
	columns in df other than 'chr', 'start', and 'end'.
agg	any vector valued function with one data argument: defaults to mean.

Value

a gi_list instance with 1D features stored in regions metadata handle of each list element (e.g., gi_list[[1]]@regions@elementMetadata) in the instance

Examples

```
df<-data.frame(chr='chr9',start=seq(1e6,10e6,1e6),end=seq(2e6,11e6,1e6))
gi_list<-generate_df_gi_list(df)
feats<-data.frame(chr='chr9',start=seq(1e6,10e6,1e6),gc=runif(10))
gi_list<-add_1D_features(gi_list,feats)</pre>
```

add_2D_features add_2D_features

Description

Adds 2D features to a gi_list instance. If any bin on gi_list overlaps with multiple feature records, features are aggregated among matches according to the univariate vector valued function agg (e.g., sum, mean). For efficient use of memory, using add/expand 1D features (see ?add_1D_features and expand_1D_features) in sequence is recommended instead of using add_2D_features directly for each chromosome.

Usage

```
add_2D_features(gi, df, features = NULL, agg = sum)
```

Arguments

gi	Element of a valid gi_list instance (restricted to a single chromosome e.g., gi_list[['chr9']]—see ?gi_list_validate for a detailed explanation of valid gi_list instances).
df	data frame for a single chromosome containing columns named chr, startI and startJ and features to be added with their respective names (if df contains multiple chromosomes, you can convert it into a list of smaller data.frames for each chromosome and apply this function with sapply).
features	features to be added. Needs to be subset of colnames(df). Defaults to all columns in df other than 'chr', 'start', and 'end'.
agg	any vector valued function with one data argument: defaults to mean.

Value

```
a gi_list element with 2D features stored in metadata handle (i.e., mcols(gi)).
```

Examples

```
df<-data.frame(chr='chr9',start=seq(1e6,10e6,1e6))
gi_list<-generate_df_gi_list(df,Dthreshold=500e3)
feats<-data.frame(chr='chr9',
startI=seq(1e6,10e6,1e6),startJ=seq(1e6,10e6,1e6),counts=rpois(10,lambda=5))
gi_list[['chr9']]<-add_2D_features(gi_list[['chr9']],feats)</pre>
```

```
add\_hicpro\_allvalidpairs\_counts \\ add\_hicpro\_allvalidpairs\_counts
```

Description

This function converts HiC-Pro outputs in all ValidPairs format into a gi_list instance.

Usage

```
add_hicpro_allvalidpairs_counts(
    gi_list,
    allvalidpairs_path,
    chrs = NULL,
    binned = TRUE,
    add_inter = FALSE
)
```

Arguments

gi_list valid gi_list instance. See ?gi_list_validate for details. You can also detect

whether a gi_list instance is uniformly binned, along with its bin size using

gi_list_binsize_detect.

allvalidpairs_path

allValidPairsfile obtained from HiC-Pro (e.g., 'GSM2572593_con_rep1.allvalidPairs.txt')

chrs a subset of chromosomes' e.g., c('chr21','chr22'). Defaults to all chromosomes

in the gi_list instance.

binned TRUE if the gi_list instance is uniformly binned (helps faster execution). De-

faults to TRUE.

add_inter Interchromosomal interaction counts added as a 1D feature named 'inter' on re-

gions metadata handle of each gi_list element (e.g., gi_list[[1]]@regions@elementMetadata

or not; default FALSE

Value

gi_list instance with counts on the metadata (e.g., mcols(gi_list[[1]]) handle on each list element, and 'inter' on regions metadata handle of each element if add_inter=TRUE.

Description

This function converts HiC-Pro matrix and bed outputs into a gi_list instance.

Usage

```
add_hicpro_matrix_counts(
   gi_list,
   absfile_path,
   matrixfile_path,
   chrs = NULL,
   add_inter = FALSE
)
```

Arguments

gi_list valid, uniformly binned gi_list instance. See ?gi_list_validate and gi_list_binsize_detect

for details.

absfile_path absfile BED out of HiC-Pro (e.g., 'rawdata_10000_abs.bed')

 $matrixfile_path$

matrix count file out of HiC-Pro (e.g., 'rawdata_10000.matrix')

chrs a subset of chromosomes' e.g., c('chr21','chr22'). Defaults to all chromosomes

in the gi_list instance.

add_inter Interchromosomal interaction counts added as a 1D feature named 'inter' on re-

gions metadata handle of each gi_list element (e.g., gi_list[[1]]@regions@elementMetadata

or not; default FALSE

Value

gi_list instance with counts on the metadata (e.g., mcols(gi_list[[1]]) handle on each list element, and 'inter' on regions metadata handle of each element if add_inter=TRUE.

add_hic_counts add_hic_counts

Description

This function adds counts from a .hic file into a valid, binned, gi_list instance.

```
add_hic_counts(gi_list, hic_path, chrs = NULL, add_inter = FALSE)
```

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Arguments

gi_list valid, uniformly binned gi_list instance. See ?gi_list_validate and gi_list_binsize_detect

for details.

hic_path path to the .hic file

chrs a subset of chromosomes' e.g., c('chr21','chr22'). Defaults to all chromosomes

in the gi_list instance.

add_inter Interchromosomal interaction counts added as a 1D feature named 'inter' on re-

gions metadata handle of each gi_list element (e.g., gi_list[[1]]@regions@elementMetadata

or not; default FALSE

Value

gi_list instance with counts on the metadata (e.g., mcols(gi_list[[1]]) handle on each list element, and 'inter' on regions metadata handle of each element if add_inter=TRUE.

Examples

```
gi_list<-generate_binned_gi_list(50e3,chrs='chr22')
gi_list<-add_hic_counts(gi_list,
hic_path=system.file("extdata", "GSE63525_HMEC_combined_example.hic",
package = "HiCDCPlus"))</pre>
```

construct_features

construct_features

Description

This function lists all restriction enzyme cutsites of a given genome and genome version with genomic features outlined in Carty et al. (2017) https://www.nature.com/articles/ncomms15454; GC content, mappability, and effective length

Usage

```
construct_features(
  output_path,
  gen = "Hsapiens",
  gen_ver = "hg19",
  sig = "GATC",
  bin_type = "Bins-uniform",
  binsize = 5000,
  wg_file = NULL,
  chrs = NULL
)
```

Arguments

output_path the path to the folder and name prefix you want to place feature files into. The

feature file will have the suffix '_bintolen.txt.gz'.

gen name of the species: e.g., default 'Hsapiens'.
gen_ver genomic assembly version: e.g., default 'hg19'.

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sig	restriction enzyme cut pattern (or a vector of patterns; e.g., 'GATC' or c('GATC', 'GANTC')).
bin_type	'Bins-uniform' if uniformly binned by binsize in bp, or 'Bins-RE-sites' if binned by number of restriction enzyme fragments.
binsize	binsize in bp if bin_type='Bins-uniform' (or number of RE fragment cut sites if bin_type='Bins-RE-sites'), defaults to 5000.
wg_file	path to the bigWig file containing mappability values across the genome of interest.
chrs	select a subset of chromosomes' e.g., c('chr21','chr22'). Defaults to all chromosomes (except Y and M) in the genome specified.

Value

a features 'bintolen' file that contains GC, mappability and length features.

Examples

Description

This function lists all restriction enzyme cutsites of a given genome and genome version with genomic features outlined in Carty et al. (2017) for a single chromosome. https://www.nature.com/articles/ncomms15454; GC content, mappability, and effective length

Usage

```
construct_features_chr(
  chrom,
  gen = "Hsapiens",
  gen_ver = "hg19",
  sig = "GATC",
  bin_type = "Bins-uniform",
  binsize = 5000,
  wg_file = NULL
)
```

Arguments

```
chrom select a chromosome.

gen name of the species: e.g., default 'Hsapiens'.

gen_ver genomic assembly version: e.g., default 'hg19'.

sig restriction enzyme cut pattern (or a vector of patterns; e.g., 'GATC' or c('GATC','GANTC')).
```

bin_type	'Bins-uniform' if uniformly binned by binsize in bp, or 'Bins-RE-sites' if binned by number of restriction enzyme fragments.
binsize	binsize in bp if bin_type='Bins-uniform' (or number of RE fragment cut sites if bin_type='Bins-RE-sites'), defaults to 5000.
wg_file	path to the bigWig file containing mappability values across the genome of interest.

Value

a features 'bintolen' file that contains GC, mappability and length features.

Examples

```
df<-construct_features_chr(chrom='chr22',
gen='Hsapiens', gen_ver='hg19',sig=c('GATC','GANTC'),bin_type='Bins-uniform',
binsize=100000,wg_file=NULL)</pre>
```

construct_features_parallel

construct_features_parallel

Description

This function lists all restriction enzyme cutsites of a given genome and genome version with genomic features outlined in Carty et al. (2017) https://www.nature.com/articles/ncomms15454; GC content, mappability, and effective length

Usage

```
construct_features_parallel(
  output_path,
  gen = "Hsapiens",
  gen_ver = "hg19",
  sig = "GATC",
  bin_type = "Bins-uniform",
  binsize = 5000,
  wg_file = NULL,
  chrs = NULL,
  ncore = NULL
)
```

Arguments

output_path	the path to the folder and name prefix you want to place feature files into. The feature file will have the suffix '_bintolen.txt.gz'.
gen	name of the species: e.g., default 'Hsapiens'.
gen_ver	genomic assembly version: e.g., default 'hg19'.
sig	restriction enzyme cut pattern (or a vector of patterns; e.g., 'GATC' or c('GATC','GANTC')).
bin_type	'Bins-uniform' if uniformly binned by binsize in bp, or 'Bins-RE-sites' if binned by number of restriction enzyme fragments.

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bins	ize	binsize in bp if bin_type='Bins-uniform' (or number of RE fragment cut sites if bin_type='Bins-RE-sites'), defaults to 5000.
wg_f	ile	path to the bigWig file containing mappability values across the genome of interest.
chrs		select a subset of chromosomes' e.g., $c(\text{'chr21','chr22'})$. Defaults to all chromosomes (except Y and M) in the genome specified.
ncor	е	Number of cores to parallelize. Defaults to parallel::detectCores()-1.

Value

a features 'bintolen' file that contains GC, mappability and length features.

Examples

```
outdir<-paste0(tempdir(check=TRUE),'/')</pre>
construct_features_parallel(output_path=outdir,gen='Hsapiens',
gen_ver='hg19',sig=c('GATC','GANTC'),bin_type='Bins-uniform',binsize=100000,
wg_file=NULL,chrs=c('chr21'),ncore=2)
```

expand_1D_features

expand_1D_features

Description

Expands 1D features on the regions metadata handle of each list element (e.g., gi_list[[1]]@regions@elementMetada to the to 2D metadata e.g., mcols(gi_list[[1]])). Two feature values corresponding to each anchor is summarized as a score using a vector valued function agg that takes two vector valued arguments of the same size and outputs a vector of the same size as the input vectors. This defaults to the transform. vec function outlined in (Carty et al., 2017). For efficient use of memory, using add/expand 1D features (see ?add_1D_features and expand_1D_features) in sequence is recommended instead of using add_2D_features directly for each chromosome.

Usage

```
expand_1D_features(gi_list, chrs = NULL, features = NULL, agg = transform.vec)
```

Arguments

gi_list	List of GenomicInteractions objects where each object named with chromosomes contains intra-chromosomal interaction information (see ?gi_list_validate for a detailed explanation of valid gi_list instances).
chrs	a subset of chromosomes' e.g., c('chr21','chr22'). Defaults to all chromosomes in the gi_list instance.
features	$features \ to \ be \ added. \ Defaults \ to \ all \ 1D \ features \ in \ elements \ of \ gi_list[[1]] @ regions@elementMether \ added. \\$
agg	any vector valued function with two data arguments: defaults to transform.vec

Value

a gi_list element with 2D features stored in metadata handle (i.e., mcols(gi)).

described in HiC-DC (Carty et al., 2017).

Examples

```
df<-data.frame(chr='chr9',start=seq(1e6,10e6,1e6),end=seq(2e6,11e6,1e6))
gi_list<-generate_df_gi_list(df)
feats<-data.frame(chr='chr9',start=seq(1e6,10e6,1e6),gc=runif(10))
gi_list<-add_1D_features(gi_list,feats)
gi_list<-expand_1D_features(gi_list)</pre>
```

```
extract_hic_eigenvectors
```

extract_hic_eigenvectors

Description

This function uses Juicer command line tools to extract first eigenvectors across chromosomes from counts data in a .hic file and outputs them to text file of the structure chr start end score where the score column contains the eigenvector elements.

Usage

```
extract_hic_eigenvectors(
  hicfile,
  mode = "KR",
  binsize = 1e+05,
  chrs = NULL,
  gen = "Hsapiens",
  gen_ver = "hg19"
)
```

Arguments

hicfile	path to the input .hic file.
mode	Normalization mode to extract first eigenvectors from Allowable options are: 'NONE' for raw (normalized counts if .hic file is written using hicdc2hic or hic2icenorm_gi_list), 'KR' for Knight-Ruiz normalization, 'VC' for Vanilla-Coverage normalization and 'VC_SQRT' for square root vanilla coverage. Defaults to 'KR'.
binsize	the uniform binning size for compartment scores in bp. Defaults to 100e3.
chrs	a subset of chromosomes' e.g., c('chr21','chr22'). Defaults to all chromosomes except "Y", and "M" for the specified gen and gen_ver.
gen	name of the species: e.g., default 'Hsapiens'.
gen_ver	genomic assembly version: e.g., default 'hg19'.

Value

path to the eigenvector text files for each chromosome containing chromosome, start, end and compartment score values that may need to be flipped signs for each chromosome. File paths follow gsub('.hic','_<chromosome>_eigenvectors.txt',hicfile)

Examples

```
eigenvector_filepaths<-extract_hic_eigenvectors(
hicfile=system.file("extdata", "GSE63525_HMEC_combined_example.hic",
package = "HiCDCPlus"),
chrs=c("chr22"),binsize=50e3)</pre>
```

Description

Generates a valid uniformly binned gi_list instance.

Usage

```
generate_binned_gi_list(
  binsize,
  chrs = NULL,
  Dthreshold = 2e+06,
  gen = "Hsapiens",
  gen_ver = "hg19"
)
```

Arguments

Dthreshold

binsize Desired binsize in bp, e.g., 5000, 25000.

chrs a subset of chromosomes' e.g., c('chr21','chr22'). Defaults to all chromosomes except "Y", and "M" for the specified gen and gen_ver.

maximum distance (included) to check for significant interactions, defaults to

except 1, and wi for the specified gen and gen_ver.

2e6 or maximum in the data; whichever is smaller.

gen name of the species: e.g., default 'Hsapiens'.
gen_ver genomic assembly version: e.g., default 'hg19'.

Value

a valid, uniformly binned gi_list instance.

```
gi_list<-generate_binned_gi_list(1e6,chrs='chr22')</pre>
```

Description

Generates a gi_list instance from a bintolen file generated by generate. features (see ?generate. features) for details).

Usage

```
generate_bintolen_gi_list(
  bintolen_path,
  chrs = NULL,
  Dthreshold = 2e+06,
  binned = TRUE,
  binsize = NULL,
  gen = "Hsapiens",
  gen_ver = "hg19"
)
```

Arguments

bintolen_path path to the flat file containing columns named bins and features

chrs select a subset of chromosomes' e.g., c('chr21','chr22'). Defaults to all chro-

mosomes specified in the bintolen file.

Dthreshold maximum distance (included) to check for significant interactions, defaults to

2e6 or maximum in the data; whichever is smaller.

binned TRUE if the bintolen file is uniformly binned. Defaults to TRUE.

bin size in bp to be generated for the object. Defaults to the binsize in the

bintolen file, if exists.

gen name of the species: e.g., default 'Hsapiens'
gen_ver genomic assembly version: e.g., default 'hg19'

Value

a valid gi_list instance with genomic features derived from specified restriction enzyme cut patterns when generating the bintolen file using construct_features (see ?construct_features for help). Genomic 1D features are stored in the regions metadata handle of each list element (e.g., gi_list[[1]]@regions@elementMetadata).

```
chrs<-'chr22'
bintolen_path<-system.file("extdata", "test_bintolen.txt.gz",
package = "HiCDCPlus")
gi_list<-generate_bintolen_gi_list(bintolen_path,chrs)</pre>
```

generate_df_gi_list 13

```
generate_df_gi_list
generate_df_gi_list
```

Description

Generates a gi_list instance from a data frame object describing the regions.

Usage

```
generate_df_gi_list(
   df,
   chrs = NULL,
   Dthreshold = 2e+06,
   gen = "Hsapiens",
   gen_ver = "hg19"
)
```

Arguments

df	DataFrame with columns named 'chr', 'start', (and optionally 'end', if the regions have gaps) and 1D features with their respective column names.
chrs	select a subset of chromosomes' e.g., c('chr21','chr22'). Defaults to all chromosomes specified in df.
Dthreshold	maximum distance (included) to check for significant interactions, defaults to 2e6 or maximum in the data, whichever is smaller.
gen	name of the species: e.g., default 'Hsapiens'
gen_ver	genomic assembly version: e.g., default 'hg19'

Value

a valid gi_list instance with genomic features supplied from df. Genomic 1D features are stored in the regions metadata handle of each list element (e.g., gi_list[[1]]@regions@elementMetadata).

Examples

```
df<-data.frame(chr='chr9',start=seq(1e6,10e6,1e6))
gi_list<-generate_df_gi_list(df)</pre>
```

```
get_chrs get_chrs
```

Description

This function finds all chromosomes of a given genome and genome version except for Y and M.

```
get_chrs(gen = "Hsapiens", gen_ver = "hg19")
```

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Arguments

gen name of the species: e.g., default 'Hsapiens'
gen_ver genomic assembly version: e.g., default 'hg19'

Value

string vector of chromosomes.

Examples

```
get_chrs('Hsapiens','hg19')
```

get_chr_sizes

get_chr_sizes

Description

This function finds all chromosome sizes of a given genome, genome version and set of chromosomes.

Usage

```
get_chr_sizes(gen = "Hsapiens", gen_ver = "hg19", chrs = NULL)
```

Arguments

gen name of the species: e.g., default 'Hsapiens'

gen_ver genomic assembly version: e.g., default 'hg19'

chrs select a subset of chromosomes' e.g., c('chr21','chr22'). Defaults to all chro-

mosomes (except Y and M) in the genome specified.

Value

named vector containing names as chromosomes and values as chromosome sizes.

```
get_chr_sizes('Hsapiens','hg19',c('chr21','chr22'))
```

get_enzyme_cutsites 15

```
get_enzyme_cutsites get_enzyme_cutsites
```

Description

This function finds all restriction enzyme cutsites of a given genome, genome version, and set of cut patterns

Usage

```
get_enzyme_cutsites(sig, gen = "Hsapiens", gen_ver = "hg19", chrs = NULL)
```

Arguments

sig a set of restriction enzyme cut patterns (e.g., 'GATC' or c('GATC', 'GANTC'))

gen name of the species: e.g., default 'Hsapiens'
gen_ver genomic assembly version: e.g., default 'hg19'

chrs a subset of chromosomes' e.g., c('chr21','chr22'). Defaults to all chromosomes

(except Y and M) in the genome specified by gen and gen_ver.

Value

list of chromosomes.

Examples

```
get_enzyme_cutsites(gen='Hsapiens',gen_ver='hg19',
sig=c('GATC','GANTC'),chrs=c('chr22'))
```

gi_list2HTClist gi_list2HTClist

Description

This function converts a gi_list instance into a HTClist instance compatible for use with the R Bioconductor package HiTC https://bioconductor.org/packages/HiTC/

Usage

```
gi_list2HTClist(gi_list, chrs = NULL)
```

Arguments

gi_list List of GenomicInteractions objects with a counts column where each object

named with chromosomes contains intra-chromosomal interaction information (minimally containing counts and genomic distance in mcols(gi_list)— see ?gi_list_validate for a detailed explanation of valid gi_list instances).

chrs select a subset of chromosomes' e.g., c('chr21','chr22'). Defaults to chromo-

somes in gi_list.

gi_list_binsize_detect

Value

a HTClist instance compatible for use with HiTC

Examples

```
gi_list<-generate_binned_gi_list(50e3,chrs=c('chr22'))
gi_list<-add_hic_counts(gi_list,
hic_path<-system.file("extdata", "GSE63525_HMEC_combined_example.hic",
package = "HiCDCPlus"))
htc_list<-gi_list2HTClist(gi_list)</pre>
```

Description

This function finds the bin size of a uniformly binned valid gi_list instance in bp. It raises an error if the gi_list instance is not uniformly binned.

Usage

```
gi_list_binsize_detect(gi_list)
```

Arguments

gi_list

gi_list object to be verified. In order to pass without errors, a gi_list object (1) has to be a list of InteractionSet::GInteractions objects,(2) each list element has to be named as chromosomes and only contain intra-chromosomal interaction information, (3) mcols(.) for each list element should at least contain pairwise genomic distances in a column named 'D' and (4) each list element needs to be uniformly binned

Value

uniform binsize in base pairs or an error if the gi_list instance is not uniformly binned.

```
gi_list<-generate_binned_gi_list(1e6,chrs='chr22')
gi_list_binsize_detect(gi_list)</pre>
```

```
\label{eq:gi_list_Dthreshold_detect} gi\_list\_Dthreshold\_detect
```

Description

This function finds the maximum genomic distance in a valid gi_list object.

Usage

```
gi_list_Dthreshold.detect(gi_list)
```

Arguments

gi_list

A valid gi_list instance. See ?gi_list_validate for more details about the attributes of a valid gi_list instance.

Value

maximum genomic distance in the object

Examples

```
gi_list<-generate_binned_gi_list(1e6,chrs='chr22')
gi_list_Dthreshold.detect(gi_list)</pre>
```

gi_list_read

gi_list_read

Description

Reads a written gi_list instance using gi_list_write into a valid gi_list instance.

```
gi_list_read(
   fname,
   chrs = NULL,
   Dthreshold = NULL,
   features = NULL,
   gen = "Hsapiens",
   gen_ver = "hg19"
)
```

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Arguments

fname path to the file to read from (can end with .txt, .rds, or .txt.gz).

chrs select a subset of chromosomes' e.g., c('chr21','chr22'). Defaults to all chromosomes contained in the fname.

Dthreshold maximum distance (included) to check for significant interactions, defaults to the maximum in the data.

Select the subset of features (1-D or 2-D) to be added to the gi_list instance (without the trailing I or J), defaults to all features (score column gets ingested as 'score').

gen name of the species: e.g., default 'Hsapiens'

gen_ver genomic assembly version: e.g., default 'hg19'

Value

A valid gi_list instance with 1D features stored in regions metadata handle of each list element (e.g., gi_list[[1]]@regions@elementMetadata) in the instance and with 2D features stored in metadata handle (i.e., mcols(gi)).

Examples

```
outputdir<-paste0(tempdir(check=TRUE),'/')
gi_list<-generate_binned_gi_list(1e6,chrs='chr22')
gi_list_write(gi_list,paste0(outputdir,'testgiread.txt'))
gi_list2<-gi_list_read(paste0(outputdir,'testgiread.txt'))</pre>
```

 gi_list_topdom gi_list_topdom

Description

This function converts a gi_list instance with ICE normalized counts into TAD annotations through an implementation of TopDom v0.0.2 (https://github.com/HenrikBengtsson/TopDom) adapted as TopDom at this package. If you're using this function, please cite TopDom according to the documentation at https://github.com/HenrikBengtsson/TopDom/blob/0.0.2/docs/

```
gi_list_topdom(
  gi_list,
  chrs = NULL,
  file_out = FALSE,
  fpath = NULL,
  window.size = 5
)
```

gi_list_validate 19

Arguments

gi_list	List of GenomicInteractions objects where each object named with chromosomes contains intrachromosomal interaction information (see ?gi_list_validate for a detailed explanation of valid gi_list instances).
chrs	select a subset of chromosomes' e.g., c('chr21','chr22'). Defaults to chromosomes in gi_list.
file_out	If true, outputs TAD annotations into files with paths beginning with fpath. Defaults to FALSE

Outputs TAD annotations into files with paths beginning in fpath.

window.size integer, number of bins to extend. Defaults to 5.

Value

fpath

a list instance with TAD annotation reporting for each chromosome

Examples

```
hic_path<-system.file("extdata", "GSE63525_HMEC_combined_example.hic",
package = "HiCDCPlus")
gi_list<-hic2icenorm_gi_list(hic_path,binsize=50e3,chrs='chr22')
tads<-gi_list_topdom(gi_list)</pre>
```

gi_list_validate gi_list_validate

Description

This function validates a gi_list instance.

Usage

```
gi_list_validate(gi_list)
```

Arguments

gi_list object to be verified. In order to pass without errors, a gi_list object (1)

has to be a list of InteractionSet::GInteractions objects, (2) each list element has to be named as chromosomes and only contain intra-chromosomal interaction information, (3) mcols(.) for each list element should at least contain pairwise

genomic distances in a column named 'D'.

Value

invisible value if the gi_list instance is valid. Otherwise, an error is raised.

```
gi_list<-generate_binned_gi_list(1e6,chrs='chr22')
gi_list_validate(gi_list)</pre>
```

20 gi_list_write

gi_list_write gi_list_write

Description

Writes a valid gi_list instance into a file.

Usage

```
gi_list_write(
  gi_list,
  fname,
  chrs = NULL,
  columns = "minimal",
  rows = "all",
  significance_threshold = 0.05,
  score = NULL
)
```

Arguments

gi_list List of GenomicInteractions objects where each object named with chromo-

somes contains intra-chromosomal interaction information (see ?gi_list_validate

for a detailed explanation of valid gi_list instances).

fname path to the file to write to (can end with .txt, or .txt.gz).

chrs select a subset of chromosomes' e.g., c('chr21','chr22'). Defaults to all chro-

mosomes in the gi_list.

columns Can be 'minimal', which is just distance and counts (and HiCDCPlus result

columns 'qvalue', 'pvalue', 'mu', and 'sdev', if exists; see ?HiCDCPlus) information, 'minimal_plus_features', which is distance, counts, and other calculated 2D features, 'minimal_plus_score', which generates a .hic pre compatible text file, or 'all', which is distance, counts, calculated 2D features, as well as all 1D

features. Defaults to 'minimal'.

rows Can be 'all' or 'significant', which filters rows according to FDR adjusted pyalue

column 'qvalue' (this has to exist in mcols(.)) at significance_threshold.

Defaults to 'all'.

significance_threshold

Row filtering threshold on 'qualue'. Defaults to 0.05.

score Score column to extract to .hic pre compatible file. See mode options in ?hicdc2hic

for more details.

Value

a tab separated flat file concatenating all intra-chromosomal interaction information.

```
outputdir<-paste0(tempdir(check=TRUE),'/')
gi_list<-generate_binned_gi_list(1e6,chrs='chr22')
gi_list_write(gi_list,paste0(outputdir,'test.txt'))</pre>
```

hic2icenorm_gi_list 21

Description

This function converts a .hic file into a gi_list instance with ICE normalized counts on the counts column for TAD annotation using a copy of TopDom (see ?TopDom_0.0.2) as well as an (optional) .hic file with ICE normalized counts for visualization with Juicebox. This function requires installing the Bioconductor package HiTC.

Usage

```
hic2icenorm_gi_list(
  hic_path,
  binsize = 50000,
  chrs = NULL,
  hic_output = FALSE,
  gen = "Hsapiens",
  gen_ver = "hg19",
  Dthreshold = Inf
)
```

Arguments

hic_path	Path to the .hic file.
binsize	Desired bin size in bp (default 50000).
chrs	select a subset of chromosomes' e.g., c('chr21','chr22'). Defaults to chromosomes in gen and gen_ver except 'chrY' and 'chrM'.
hic_output	If TRUE, a .hic file with the name gsub("\.hic\$","_icenorm.hic",hic_path) is generated containing the ICE normalized counts under 'NONE' normalization.
gen	name of the species: e.g., default 'Hsapiens'
gen_ver	genomic assembly version: e.g., default 'hg19'
Dthreshold	maximum distance (included) to check for significant interactions, defaults to

Value

a thresholded gi_list instance with ICE normalized intra-chromosomal counts for further use with this package, HiCDCPlus.

Examples

```
hic_path<-system.file("extdata", "GSE63525_HMEC_combined_example.hic",
package = "HiCDCPlus")
gi_list=hic2icenorm_gi_list(hic_path,binsize=50e3,chrs=c('chr22'))</pre>
```

maximum in the data.

22 hicdc2hic

hicdc2hic

hicdc2hic

Description

This function converts various modes from HiCDCPlus gi_list (uniformly binned) instance back into a .hic file with the mode passed as counts that can be retrieved using Juicer Dump (https://github.com/aidenlab/juicer/vExtraction) with 'NONE' normalization.

Usage

```
hicdc2hic(
  gi_list,
  hicfile,
  mode = "normcounts",
  chrs = NULL,
  gen_ver = "hg19",
  memory = 8
)
```

Arguments

gi_list List of GenomicInteractions objects where each object named with chromo-

somes contains intra-chromosomal interaction information (minimally containing counts and genomic distance in mcols(gi_list)—see ?gi_list_validate

for a detailed explanation of valid gi_list instances).

hicfile the path to the .hic file

mode What to put to the .hic file as score. Allowable options are: 'pvalue' for -

log10 significance p-value, 'qvalue' for -log10 FDR corrected p-value, 'norm-counts' for raw counts/expected counts, and 'zvalue' for standardized counts (raw counts-expected counts)/modeled standard deviation of expected counts

and 'raw' to pass-through 'raw counts. Defaults to 'normcounts'.

chrs select a subset of chromosomes' e.g., c('chr21','chr22'). Defaults to chromo-

 $somes \ in \ {\tt gi_list}.$

gen_ver genomic assembly version: e.g., default 'hg19'

memory Java memory to generate .hic files. Defaults to 8. Up to 64 is recommended for

higher resolutions.

Value

path of the .hic file.

```
outdir<-paste0(tempdir(check=TRUE),'/')
gi_list<-generate_binned_gi_list(50e3,chrs='chr22')
gi_list<-add_hic_counts(gi_list,
hic_path=system.file("extdata", "GSE63525_HMEC_combined_example.hic",
package = "HiCDCPlus"))
hicdc2hic(gi_list,hicfile=paste0(outdir,'out.hic'),
mode='raw')</pre>
```

hicdcdiff 23

iicdcdiff	
-----------	--

Description

This function calculates differential interactions for a set of chromosomes across conditions and replicates. You need to install DESeq2 from Bioconductor to use this function.

Usage

```
hicdcdiff(
  input_paths,
  filter_file,
  output_path,
  bin_type = "Bins-uniform",
  binsize = 5000,
  granularity = 5000,
  chrs = NULL,
  Dmin = 0,
  Dmax = 2e+06,
  diagnostics = FALSE,
  DESeq.save = FALSE,
  fitType = "local"
)
```

Arguments

Dmin

•	
input_paths	a list with names as condition names and values as paths to gi_list RDS objects (see ?gi_list_validate for a detailed explanation of valid gi_list instances) saved with saveRDS or paths to .hic files for each replicate. e.g.,list(CTCF=c('~/Downloads/GM_CTCF_rep1_MAPQ30_10kb.rds','~/Downloads/GM_CTCF_rep2_MAPQ30_10kb.rds','~/Downloads/GM_CTCF_rep2_MAPQ30_10kb.rds','~/Downloads/GM_CTCF_rep2_MAPQ30_10kb.rds','~/Downloads/GM_CTCF_rep2_MAPQ30_10kb.rds','~/Downloads/GM_CTCF_rep2_MAPQ30_10kb.rds','~/Downloads/GM_CTCF_rep2_MAPQ30_10kb.rds','~/Downloads/GM_CTCF_rep2_MAPQ30_10kb.rds','~/Downloads/GM_CTCF_rep3_MAPQ30_10kb.rds','~/
filter_file	path to the text file containing columns chr', startI, and startJ denoting the name of the chromosomes and starting coordinates of 2D interaction bins to be compared across conditions, respectively.
output_path	the path to the folder and name prefix you want to place DESeq-processed matrices (in a .txt file), plots (if diagnostics=TRUE) and DESeq2 objects (if DESeq.save=TRUE). Files will be generated for each chromosome.
bin_type	'Bins-uniform' if uniformly binned by binsize in bp, or 'Bins-RE-sites' if binned by number of restriction enzyme fragment cutsites!
binsize	binsize in bp if bin_type='Bins-uniform' (or number of RE fragments if bin_type='Bins-RE-sites'), e.g., default 5000
granularity	Desired distance granularity to base dispersion parameters on in bp. For uniformly binned analysis (i.e., bin_type=='Bins-uniform'), this defaults to the bin size. Otherwise, it is 5000.
chrs	select a subset of chromosomes' e.g., c('chr21','chr22'). Defaults to all chromosomes (except Y and M) in the filter_file.

minimum distance (included) to check for significant interactions, defaults to 0.

Put Dmin=1 to ignore D=0 bins in calculating normalization factors.

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Dmax	maximum distance (included) to check for significant interactions, defaults to 2e6 or maximum in the data; whichever is minimum.
diagnostics	if TRUE, generates diagnostic plots of the normalization factors, geometric means of such factors by distance bin, as well as MA Plots (see DESeq documentation for details about MA plots). Defaults to FALSE.
DESeq.save	if TRUE, saves the DESeq objects for each chromosome as an .rds file in the output_path. Defaults to FALSE.
fitType	follows fitType in DESeq2::estimateDispersions. Allowable options are 'parametric' (parametric regression), 'local' (local regression), and 'mean' (constant across interaction bins). Default is 'local'.

Value

paths of a list of three entities. outputpaths will have differential bins among those in filter_file. deseq2paths will have the DESeq2 object stored as an .rds file. Available if DESeq. save=TRUE plotpaths will have diagnostic plots (e.g., MA, dispersion, PCA) if diagnostics=TRUE.

Examples

```
outputdir<-paste0(tempdir(check=TRUE),'/')</pre>
hicdcdiff(input_paths=list(NSD2=c(
system.file("extdata", "GSE131651_NSD2_LOW_arima_example.hic",
package = "HiCDCPlus"),
system.file("extdata", "GSE131651_NSD2_HIGH_arima_example.hic",
package = "HiCDCPlus")),
TKO=c(system.file("extdata", "GSE131651_TKOCTCF_new_example.hic",
package = "HiCDCPlus"),
system.file("extdata", "GSE131651_NTKOCTCF_new_example.hic",
package = "HiCDCPlus"))),
filter_file=system.file("extdata", "GSE131651_analysis_indices.txt.gz",
package = "HiCDCPlus"),
         chrs='chr22',
         output_path=outputdir,
         fitType = 'mean',
         binsize=50000,
         diagnostics=FALSE)
```

HiCDCPlus

HiCDCPlus

Description

This function finds significant interactions in a HiC-DC readable matrix and expresses statistical significance of counts through the following: 'pvalue': significance *P*-value, 'qvalue': FDR corrected *P*-value, mu': expected counts, 'sdev': modeled standard deviation of expected counts.

```
HiCDCPlus(
  gi_list,
  covariates = NULL,
  chrs = NULL,
```

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```
distance_type = "spline",
  model_distribution = "nb",
  binned = TRUE,
  df = 6,
  Dmin = 0,
  Dmax = 2e+06,
  ssize = 0.01,
  splineknotting = "uniform",
  model_filepath = NULL
)
```

Arguments

gi_list List of GenomicInteractions objects where each object named with chromo-

somes contains intrachromosomal interaction information (minimally containing counts and genomic distance in mcols(gi_list[[1]])—see ?gi_list_validate

for a detailed explanation of valid gi_list instances).

covariates covariates to be considered in addition to genomic distance D. Defaults to all co-

variates besides 'D', 'counts', 'mu', 'sdev', pvalue', 'qvalue' in mcols(gi_list[[1]])

chrs select a subset of chromosomes' e.g., c('chr21','chr22'). Defaults to all chro-

mosomes in the gi_list.

distance_type distance covariate form: 'spline' or 'log'. Defaults to 'spline'.

model_distribution

'nb' uses a Negative Binomial model, 'nb_vardisp' uses a Negative Binomial model with a distance specific dispersion parameter inferred from the data,

'nb_hurdle' uses the legacy HiCDC model.

binned TRUE if uniformly binned or FALSE if binned by restriction enzyme fragment

cutsites

df degrees of freedom for the genomic distance spline function if distance_type='spline'.

Defaults to 6, which corresponds to a cubic spline as explained in Carty et al.

(2017)

Dmin minimum distance (included) to check for significant interactions, defaults to 0

Dmax maximum distance (included) to check for significant interactions, defaults to

2e6 or maximum in the data; whichever is minimum.

ssize Distance stratified sampling size. Can decrease for large chromosomes. Increase

recommended if model fails to converge. Defaults to 0.01.

splineknotting Spline knotting strategy. Either "uniform", uniformly spaced in distance, or

placed based on distance distribution of counts "count-based" (i.e., more closely

spaced where counts are more dense).

model_filepath Outputs fitted HiC-DC model object as an .rds file per chromosome. Defaults to

NULL (no output).

Value

A valid gi_list instance with additional mcols(.) for each chromosome: pvalue': significance *P*-value, 'qvalue': FDR corrected *P*-value, mu': expected counts, 'sdev': modeled standard deviation of expected counts.

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Examples

```
gi_list<-generate_binned_gi_list(50e3,chrs='chr22')
gi_list<-add_hic_counts(gi_list,
hic_path<-system.file("extdata", "GSE63525_HMEC_combined_example.hic",
package = "HiCDCPlus"))
gi_list<-HiCDCPlus(gi_list)</pre>
```

HiCDCPlus_chr

HiCDCPlus_chr

Description

This function finds significant interactions in a HiC-DC readable matrix restricted to a single chromosome and expresses statistical significance of counts through the following: 'pvalue': significance *P*-value, 'qvalue': FDR corrected *P*-value, mu': expected counts, 'sdev': modeled standard deviation of expected counts.

Usage

```
HiCDCPlus_chr(
   gi,
   covariates = NULL,
   distance_type = "spline",
   model_distribution = "nb",
   binned = TRUE,
   df = 6,
   Dmin = 0,
   Dmax = 2e+06,
   ssize = 0.01,
   splineknotting = "uniform",
   model_filepath = NULL
)
```

Arguments

gi Instance of a single chromosome GenomicInteractions object containing intra-

chromosomal interaction information (minimally containing counts and genomic

distance).

covariates

covariates to be considered in addition to genomic distance D. Defaults to all

covariates besides 'D', 'counts', 'mu', 'sdev', pvalue', 'qvalue' in mcols(gi)

distance_type distance covariate form: 'spline' or 'log'. Defaults to 'spline'.

model_distribution

'nb' uses a Negative Binomial model, 'nb_vardisp' uses a Negative Binomial model with a distance specific dispersion parameter inferred from the data,

'nb_hurdle' uses the legacy HiC-DC model.

binned TRUE if uniformly binned or FALSE if binned by restriction enzyme fragment

cut sites.

df degrees of freedom for the genomic distance spline function if distance_type='spline'.

Defaults to 6, which corresponds to a cubic spline as explained in Carty et al.

(2017)

HiCDCPlus_parallel 27

Dmin	minimum distance (included) to check for significant interactions, defaults to $\boldsymbol{0}$
Dmax	maximum distance (included) to check for significant interactions, defaults to 2e6 or maximum in the data; whichever is minimum.
ssize	Distance stratified sampling size. Can decrease for large chromosomes. Increase recommended if model fails to converge. Defaults to 0.01 .
splineknotting	Spline knotting strategy. Either "uniform", uniformly spaced in distance, or placed based on distance distribution of counts "count-based" (i.e., more closely spaced where counts are more dense).
model_filepath	Outputs fitted HiC-DC model object as an .rds file with chromosome name indicated on it. Defaults to NULL (no output)

Value

A valid gi instance with additional mcols(.): pvalue': significance *P*-value, 'qvalue': FDR corrected *P*-value, mu': expected counts, 'sdev': modeled standard deviation of expected counts.

Examples

```
gi_list<-generate_binned_gi_list(50e3,chrs='chr22')
gi_list<-add_hic_counts(gi_list,
hic_path<-system.file("extdata", "GSE63525_HMEC_combined_example.hic",
package = "HiCDCPlus"))
gi<-HiCDCPlus_chr(gi_list[[1]])</pre>
```

HiCDCPlus_parallel

HiCDCPlus_parallel

Description

This function finds significant interactions in a HiC-DC readable matrix and expresses statistical significance of counts through the following with a parallel implementation (using sockets; compatible with Windows): 'pvalue': significance *P*-value, 'qvalue': FDR corrected *P*-value, mu': expected counts, 'sdev': modeled standard deviation of expected counts.

```
HiCDCPlus_parallel(
   gi_list,
   covariates = NULL,
   chrs = NULL,
   distance_type = "spline",
   model_distribution = "nb",
   binned = TRUE,
   df = 6,
   Dmin = 0,
   Dmax = 2e+06,
   ssize = 0.01,
   splineknotting = "uniform",
   ncore = NULL
)
```

HiCDCPlus_parallel

Arguments

gi_list List of GenomicInteractions objects where each object named with chromo-

somes contains intrachromosomal interaction information (minimally containing counts and genomic distance in mcols(gi_list[[1]])—see ?gi_list_validate

for a detailed explanation of valid gi_list instances).

covariates covariates to be considered in addition to genomic distance D. Defaults to all

covariates besides 'D', 'counts', 'mu', 'sdev', pvalue', 'qvalue' in mcols(gi)

chrs select a subset of chromosomes' e.g., c('chr21','chr22'). Defaults to all chro-

mosomes in the gi_list.

distance_type distance covariate form: 'spline' or 'log'. Defaults to 'spline'.

model_distribution

'nb' uses a Negative Binomial model, 'nb_vardisp' uses a Negative Binomial model with a distance specific dispersion parameter inferred from the data,

'nb_hurdle' uses the legacy HiC-DC model.

binned TRUE if uniformly binned or FALSE if binned by restriction enzyme fragment

cutsites

df degrees of freedom for the genomic distance spline function if distance_type='spline'.

Defaults to 6, which corresponds to a cubic spline as explained in Carty et al.

(2017)

Dmin minimum distance (included) to check for significant interactions, defaults to 0

Dmax maximum distance (included) to check for significant interactions, defaults to

2e6 or maximum in the data; whichever is minimum.

ssize Distance stratified sampling size. Can decrease for large chromosomes. Increase

recommended if model fails to converge. Defaults to 0.01.

splineknotting Spline knotting strategy. Either "uniform", uniformly spaced in distance, or

placed based on distance distribution of counts "count-based" (i.e., more closely

spaced where counts are more dense).

ncore Number of cores to parallelize. Defaults to parallel::detectCores()-1.

Value

A valid gi_list instance with additional mcols(.) for each chromosome: pvalue': significance *P*-value, 'qvalue': FDR corrected *P*-value, mu': expected counts, 'sdev': modeled standard deviation of expected counts.

```
gi_list<-generate_binned_gi_list(50e3,chrs='chr22')
gi_list<-add_hic_counts(gi_list,
hic_path=system.file("extdata", "GSE63525_HMEC_combined_example.hic",
package = "HiCDCPlus"))
gi<-HiCDCPlus_parallel(gi_list,ncore=1)</pre>
```

HTClist2gi_list 29

HTClist2gi_list	HTClist2gi_list
11101100251_1100	111 01131251 1131

Description

This function converts a HTClist instance into a gi_list instance with counts for further use with this package, HiCDCPlus

Usage

```
HTClist2gi_list(htc_list, chrs = NULL, Dthreshold = 2e+06)
```

Arguments

htc_list A valid HTClist instance (see vignette("HiTC"))

chrs select a subset of chromosomes' e.g., c('chr21','chr22'). Defaults to chromo-

somes in htc_list.

Dthreshold maximum distance (included) to check for significant interactions, defaults to

2e6 or maximum in the data; whichever is smaller.

Value

a thresholded gi_list instance with intra-chromosomal counts for further use with HiCDCPlus

Examples

```
gi_list<-generate_binned_gi_list(50e3,chrs=c('chr22'))
gi_list<-add_hic_counts(gi_list,
hic_path=system.file("extdata", "GSE63525_HMEC_combined_example.hic",
package = "HiCDCPlus"))
htc_list<-gi_list2HTClist(gi_list)
gi_list2<-HTClist2gi_list(htc_list,Dthreshold=Inf)</pre>
```

```
straw straw
```

Description

Adapted C++ implementation of Juicer's dump. Reads the .hic file, finds the appropriate matrix and slice of data, and outputs as an R DataFrame.

```
straw(norm, fn, ch1, ch2, u, bs)
```

30 straw_dump

Arguments

norm	Normalization to apply. Must be one of NONE/VC/VC_SQRT/KR. VC is vanilla coverage, VC_SQRT is square root of vanilla coverage, and KR is Knight-Ruiz or Balanced normalization.
fn	path to the .hic file
ch1	first chromosome location (e.g., "1")
ch2	second chromosome location (e.g., "8")
u	BP (BasePair) or FRAG (restriction enzyme FRAGment)
bs	The bin size. By default, for BP, this is one of <2500000, 1000000, 500000, 250000, 100000, 50000, 25000, 100000, 50000, 25000, 10000, 5000> and for FRAG this is one of <500, 200, 100, 50, 20, 5, 2, 1>.

Details

Value

Data.frame of a sparse matrix of data from hic file. x,y,counts

straw_dump	straw_dump	

Description

Interface for Juicer's dump in case C++ straw fails (known to fail on Windows due to zlib compression not being OS agnostic and particularly not preserving null bytes, which hic files are delimited with). This function reads the hic file, finds the appropriate matrix and slice of data, writes it to a temp file, reads and modifies it, and outputs as an R DataFrame (and also deletes the temp file).

Usage

```
straw_dump(norm, fn, ch1, ch2, u, bs)
```

Arguments

norm	Normalization to apply. Must be one of NONE/VC/VC_SQRT/KR. VC is vanilla coverage, VC_SQRT is square root of vanilla coverage, and KR is Knight-Ruiz or Balanced normalization.
fn	path to the .hic file
ch1	first chromosome location (e.g., "1")
ch2	second chromosome location (e.g., "8")
u	BP (BasePair) or FRAG (restriction enzyme FRAGment)
bs	The bin size. By default, for BP, this is one of <2500000, 1000000, 500000, 250000, 100000, 50000, 100000, 50000, 100000, 50000, 50000> and for FRAG this is one of <500, 200, 100, 50, 20, 5, 2, 1>.

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Details

Value

Data.frame of a sparse matrix of data from hic file. x,y,counts

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