Package 'RNMF'

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Title An optimized Non-Negative Matrix Factorization based on R in cancer research

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Description We present an optimized non-Negative Matrix Factorization (NMF) based on R to extract the mutational signature in cancer research. A key model of cumulative contribution abundance (CCA) was designed to highlight the association between genes and mutational signatures.

Depends R (>= 3.6.0)

License GPL (>= 2)

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SigsInput Convert the mutation dataset into input datas for the mutational signature

Description

Convert the mutation dataset into input datas for the mutational signature. The format of the input dataset contains MAF and VCF. We used classifications for each type of mutation from PCAWG project. For SBSs, the primary classification comprised 96 classes (available https://cancer.sanger.ac.uk/cosmic/signatures/SBS) constituted by the 6 base substitutions C>A, C>G, C>T, T>A, T>C and T>G (in which the mutated base is represented by the pyrimidine of the base pair), plus the flanking 5' and 3' bases. In some analyses, two flanking bases 5' and 3' to the mutated base were considered (producing 1,536 classes) or mutations within transcribed genome regions were selected and classified according to whether the mutated pyrimidine fell on the transcribed or untranscribed strand (producing 192 classes). We also derived a classification for classes; **DBSs** (78 available https://cancer.sanger.ac.uk/cosmic/signatures/DBS). Indels were classified as deletions or insertions and—when of a single base—as C or T, and according to the length of the mononucleotide repeat tract in which they occurred. Longer indels were classified as occurring at repeats or with overlapping microhomology at deletion boundaries, and according to the size of indel, repeat and microhomology (83 classes; available at https://cancer.sanger.ac.uk/cosmic/signatures/ID).

Usage

```
SigsInput(file = NULL, Filetype = c('MAF','VCF'), AnalCOSMICSigType = c('SBS','DBS','ID'), genome.build = c("Ch37","Ch38"), sample.id = 'Tumor_Sample_Barcode', chr = 'Chromosome', pos = 'Start_position', ref = 'Reference_Allele', alt = 'Tumor_Seq_Allele2', ID.mc.cores = 1, ID.row83 = TRUE)
```

- file A mutation file obtained by annotation of mutation locations by Oncotator or other annotation software.
- Filetype The format of the input dataset, contains MAF and VCF.
 - 1) File with 'MAF' form was generated by Oncotator,
 - 2) and File with 'VCF' form must have at least five columns with the colnames of "CHROM POS REF ALT SAMPLENAME", for SBS as: 1 1432333 T C T1,

```
for DBS as: 1 1432333
                         TA CG T1,
for ID as: 1
              1432333
                         Т
```

- AnalCOSMICSigType Type of mutation based on PCAWG project, canbe SBS, DBS or ID.
- genome.build The version of the reference genome used in the mutation set.
- sample.id Column name in the mutation file corresponding to the Sample
- chr Column name in the mutation file corresponding to the chromosome.
- pos Column name in the mutation file corresponding to the mutation position.
- ref Column name in the mutation file corresponding to the reference base.
- alt Column name in the mutation file corresponding to the alternate base.
- ID.mc.cores The number of cores to use in ID type, i.e. at most how many child processes will be run simultaneously. Must be exactly 1 on Windows (which uses the master process).
- ID.row83 Whether to keep 83 properties for ID type.

Wen Luo (design, implementation), Zhenzhang Li (design, testing)

Examples

```
SigsInput(file = 'Oncotator.HK100.maf', Filetype = 'MAF', AnalCOSMICSigType
= 'SBS', genome.build = "Ch37", sample.id = 'Tumor Sample Barcode', chr =
'Chromosome', pos = 'Start position', ref = 'Reference Allele', alt =
'Tumor Seq Allele2')
```

denovoNMF Non-Negative Matrix Factorization in cancer research

Description

We present an optimized non-Negative Matrix Factorisation (NMF) based on R to extract the mutational signature in cancer research.

Usage

```
denovoNMF(originalGenomes, sampleNames, subtypes, kmin = 1, kmax = 10,
AnalCOSMICSigType = 'SBS', steptol = 10^-9, totalIterations = 20, spacetime =
100, \text{ mc.cores} = 1)
```

Arguments

originalGenomes - a file, data matrix for NMF, [m x n, m stands for feature counts and n stands for sample counts].

- sampleNames a list file of sample names, data matrix for NMF, [n x 1, n stands for sample counts].
- subtypes a list of types of mutation, data matrix for NMF, [m x 1, m stands for feature counts].
- kmin Minimum classification of mutational signatures.
- kmax Maximum classification of mutational signatures.
- AnalCOSMICSigType Type of mutation based on PCAWG project, can be SBS, DBS or ID.
- steptol A positive scalar providing the minimum allowable relative step length.
- totalIterations The iterations number, must be at least 5.
- spacetime The length of definite solution space of NMF, must be at least 20.
- mc.cores The number of cores to use, i.e. at most how many child processes will be running simultaneously. Must be exactly 1 on Windows (which uses the master process).

Wen Luo (design, implementation), Zhenzhang Li (implementation, testing)

References

Alexandrov L B, Nik-Zainal S, Wedge D C, et al. Deciphering signatures of mutational processes operative in human cancer[J]. Cell reports, 2013, 3(1): 246-259.

Alexandrov L B, Kim J, Haradhvala N J, et al. The repertoire of mutational signatures in human cancer[J]. Nature, 2020, 578(7793): 94-101.

Examples

denovoNMF('originalGenomes', 'sampleNames', 'subtypes', kmin = 1, kmax = 10, AnalCOSMICSigType = 'SBS', steptol = 10^-9, totalIterations = 20, spacetime = 100, mc.cores = 20)

InverseNMF Determine the contribution of known mutational processes

Description

We present an optimized tool based on R to determine the weights of each mutational signature contributing to an individual tumor sample.

Usage

InverseNMF(originalGenomes, sampleNames, subtypes, AnalCOSMICSigType =

```
c('SBS','DBS','ID'), genome.build = c("Ch37","Ch38"), cutoff = 0.06,
SBS.version = c("V2","V3"), Pmatrix = NULL, steptol = 10^-10, plot = TRUE)
```

Arguments

- originalGenomes a file, data matrix for NMF, [m x n, m stands for feature counts and n stands for sample counts].
- sampleNames a list file of sample names, data matrix for NMF, [n x 1, n stands for sample counts].
- subtypes a list of types of mutation, data matrix for NMF, [m x 1, m stands for feature counts].
- AnalCOSMICSigType Type of mutation based on PCAWG project, canbe SBS, DBS or ID.
- genome.build The version of the reference genome used in the mutation set.
- cutoff A threshold between 0 and 1, and was chosen to correct the weight that are most likely caused by errors.
- SBS.version Mutational signatures version 3 and version 2 signatures in COSMIC.
- Pmatrix A mutational signature matrix file P with a format like the output result of RNMF software.
- steptol A positive scalar providing the minimum allowable relative step length.
- plot Whether to plot the image.

Author(s)

Wen Luo (design, implementation), Zhenzhang Li (implementation, testing)

Examples

```
InverseNMF('originalGenomes',
                                      'sampleNames',
                                                               'subtypes',
AnalCOSMICSigType = 'SBS', genome.build = "Ch37", cutoff = 0.06,
SBS.version = "V2", Pmatrix = NULL, steptol = 10^-10, plot = TRUE)
```

Description

We present a tool to calculate the cumulative contribution abundance of genes in cancer research.

Usage

cumulativeCA(file = NULL, Filetype = c('MAF', 'VCF'), Pfile = NULL, Sfile =

cumulativeCA *Cumulative contribution abundance of genes*

NULL, sample.id = 'Tumor_Sample_Barcode', chr = 'Chromosome', pos = 'Start_position', ref = 'Reference_Allele', alt = 'Tumor_Seq_Allele2', Hugo = 'Hugo_Symbol', AnalCOSMICSigType = c('SBS','DBS','ID'), genome.build = c("Ch37","Ch38"), groupFile = NULL, geneListSortFile = NULL, ID.mc.cores = 2, ID.row83 = TRUE, plot = TRUE)

Arguments

- file A mutation file obtained by annotation of mutation locations by Oncotator or other annotation software.
- Filetype The format of the input dataset, contains MAF and VCF.
 - 1) File with 'MAF' form was generated by Oncotator,
 - 2) and File with 'VCF' form must have at least five columns with the colnames of "CHROM POS REF ALT SAMPLENAME",

```
for SBS as: 1 1432333 T C T1,
for DBS as: 1 1432333 TA CG T1,
for ID as: 1 1432333 T - T1.
```

- Pfile A mutational signature matrix file P with a format like the output result of RNMF software.
- Sfile A abundance fractions matrix S with a format like the output result of RNMF software.
- sample.id Column name in the mutation file corresponding to the Sample ID.
- chr Column name in the mutation file corresponding to the chromosome.
- pos Column name in the mutation file corresponding to the mutation position.
- ref Column name in the mutation file corresponding to the reference base.
- alt Column name in the mutation file corresponding to the alternate base.
- Hugo Column name in the mutation file corresponding to the gene.
- AnalCOSMICSigType Type of mutation based on PCAWG project, canbe SBS, DBS or ID.
- genome.build The version of the reference genome used in the mutation set.
- groupFile Group files with two columns: 'SampleID', 'Group'.
- geneListSortFile Sorted gene list with two columns: 'Hugo_Symbol', 'Chromosome'.
- ID.mc.cores The number of cores to use in ID type, i.e. at most how many child processes will be run simultaneously. Must be exactly 1 on Windows (which uses the master process).
- ID.row83 Whether to keep 83 properties for ID type.
- plot Whether to plot the image.

Author(s)

Wen Luo (design), Zhenzhang Li (implementation, testing)

Examples

```
cumulativeCA(file = 'Inputtest.maf', Pfile = 'SignatureComposition.12.Normalized.txt', Sfile = 'SampleContribution.12.Normalized.txt', sample.id = 'Tumor_Sample_Barcode', chr = 'Chromosome', pos = 'Start_position', ref = 'Reference_Allele', alt = 'Tumor_Seq_Allele2', Hugo = 'Hugo_Symbol', AnalCOSMICSigType = 'SBS')
```

eachMutationCA Contribution abundance of each mutation

Description

We present a tool to calculate the contribution abundance of each mutation in cancer research.

Usage

```
eachMutationCA(file = NULL, Pfile = NULL, Sfile = NULL, sample.id = 'Tumor_Sample_Barcode', chr = 'Chromosome', pos = 'Start_position', ref = 'Reference_Allele', alt = 'Tumor_Seq_Allele2', Hugo = 'Hugo_Symbol', Subtype = 'tricontext', AnalCOSMICSigType = c('SBS','DBS','ID'), genome.build = c("Ch37","Ch38"), significantGenesList = NULL, ID.mc.cores = 2, ID.row83 = TRUE)
```

Arguments

• file - A file with non-silent mutations obtained by annotation of mutation locations by Oncotator or other annotation software. And then can be generated through the SigsInput function. The format of the input dataset, contains MAF and VCF. File must have at least seven columns with the colnames of "Hugo_Symbol CHROM POS REF ALT

```
SAMPLENAME SUBTYPE",
for SBS as: 1 1432333 T C T1 C[C>T]T,
for DBS as: 1 1432333 GC AA T1 GC>AA,
for ID as: 1 1432333 T - T1 1:Del:T:3.
```

- Pfile A mutational signature matrix file P with a format like the output result of RNMF software.
- Sfile A abundance fractions matrix S with a format like the output result of RNMF software.
- sample.id Column name in the mutation file corresponding to the Sample ID.
- chr Column name in the mutation file corresponding to the chromosome.
- pos Column name in the mutation file corresponding to the mutation position.
- ref Column name in the mutation file corresponding to the reference base.

- alt Column name in the mutation file corresponding to the alternate base.
- Hugo Column name in the mutation file corresponding to the gene.
- Subtype Column name in the mutation file corresponding to the Subtype.
- AnalCOSMICSigType Type of mutation based on PCAWG project, canbe SBS, DBS or ID.
- genome.build The version of the reference genome used in the mutation set.
- significantGenesList Sorted gene list with two columns: 'Hugo_Symbol', 'Chromosome'.
- ID.mc.cores The number of cores to use in ID type, i.e. at most how many child processes will be run simultaneously. Must be exactly 1 on Windows (which uses the master process).
- ID.row83 Whether to keep 83 properties for ID type.

Wen Luo (design), Zhenzhang Li (implementation, testing)

Examples

```
eachMutationCA(file = 'MutationInputSigsTypes.txt', Pfile = 'SignatureComposition.12.Normalized.txt', Sfile = 'SampleContribution.12.Normalized.txt', sample.id = 'Tumor_Sample_Barcode', chr = 'Chromosome', pos = 'Start_position', ref = 'Reference_Allele', alt = 'Tumor_Seq_Allele2', Hugo = 'Hugo_Symbol', Subtype = 'tricontext', AnalCOSMICSigType = 'SBS')
```

genePerMutSigs

Mutation enrichment analysis

Description

We present a method based on R for association analysis of genes and mutational signatures. Mutation enrichment analysis identifies an association between somatic mutations and activity of signature in a discovery cohort.

Usage

```
genePerMutSigs(Sfile = NULL, choose.Sigs = 'SBS1', Gfile = NULL, file = NULL, sample.id = 'Tumor_Sample_Barcode', Hugo = 'Hugo_Symbol', Mutfreq = 0.04, threshold = 0.06, Qvalue = 0.1, plot = TRUE)
```

- Sfile A abundance fractions matrix S with a format like the output result of RNMF software.
- choose.Sigs Select a feature for subsequent analysis, and the feature name

should match the feature header name in Sfile.

- Gfile A abundance fractions matrix of genes for all samples with a format like the output result of RNMF software.
- file A a non-silent mutation dataset, such as the annotation result file in MAF format.
- sample.id Column name in the mutation file corresponding to the Sample
 ID.
- Hugo Column name in the mutation file corresponding to the gene.
- Mutfreq A minimum sample mutation rate threshold is used to determine the genes for subsequent analysis.
- threshold A threshold is used to define the minimum contribution abundance of genes that can be displayed.
- Qvalue A FDR threshold of genes are used to highlight in red.
- plot Whether to plot the image.

Author(s)

Wen Luo (design, implementation, testing), Zhenzhang Li (design)

Examples

```
genePerMutSigs(Sfile = 'SampleContribution.12.Normalized.txt', choose.Sigs = 'SBS1', Gfile = 'SBS1.SBS.geneCumulativeContributionAbundance.txt', file = 'Non-silent.mutation.snv.txt', sample.id = 'Tumor_Sample_Barcode', Hugo = 'Hugo_Symbol', Mutfreq = 0.04, threshold = 0.2, Qvalue = 0.1, plot = TRUE)
```

samFisherSigs Mutation enrichment analysis

Description

We present a method based on R for association analysis of genes and mutational signatures. Mutation enrichment analysis identifies an association between somatic mutations and activity of signature in a discovery cohort.

Usage

```
samFisherSigs(Sfile = NULL, choose.Sigs = 'SBS1', file = NULL, sample.id = 'Tumor_Sample_Barcode', Hugo = 'Hugo_Symbol', Mutfreq = 0.04, threshold = 0.06, Qvalue = 0.1, plot = TRUE)
```

- Sfile An abundance fractions matrix S with a format like the output result from RNMF software.
- choose. Sigs Select a feature for subsequent analysis, and the feature name

should match the feature header name in Sfile.

- file A a non-silent mutation dataset, such as the annotation result file in MAF format.
- sample.id Column name in the mutation file corresponding to the Sample ID.
- Hugo Column name in the mutation file corresponding to the gene.
- Mutfreq A minimum sample mutation rate threshold is used to determine the genes for subsequent analysis.
- threshold A threshold is used to define the minimum mutational exposure to samples that can be displayed.
- Ovalue A FDR threshold of genes are used to highlight in red.
- plot Whether to plot the image.

Author(s)

Wen Luo (design), Zhenzhang Li (implementation, testing)

References

Xing R, Zhou Y, Yu J, et al. Whole-genome sequencing reveals novel tandem-duplication hotspots and a prognostic mutational signature in gastric cancer[J]. Nature communications, 2019, 10(1): 1-13.

Examples

```
samFisherSigs(Sfile = 'SampleContribution.12.Normalized.txt', choose.Sigs =
'SBS1', file = 'Non-silent.mutation.snv.txt', sample.id = 'Tumor Sample Barcode',
Hugo = 'Hugo Symbol', Mutfreq = 0.04, threshold = 0.2, Qvalue = 0.1, plot =
TRUE)
```

samPerMutSigs *Mutation enrichment analysis*

Description

We present a method based on R for association analysis of genes and mutational signatures. Mutation enrichment analysis identifies an association between somatic mutations and activity of signature in a discovery cohort.

Usage

```
samPerMutSigs(Sfile = NULL, choose.Sigs = 'SBS1', file = NULL, sample.id =
'Tumor Sample Barcode', Hugo = 'Hugo Symbol', Mutfreq = 0.04, threshold =
0.06, Qvalue = 0.1, plot = TRUE)
```

- Sfile A abundance fractions matrix S with a format like the output result of RNMF software.
- choose.Sigs Select a feature for subsequent analysis, and the feature name should match the feature header name in Sfile.
- file A a non-silent mutation dataset, such as the annotation result file in MAF format.
- sample.id Column name in the mutation file corresponding to the Sample ID.
- Hugo Column name in the mutation file corresponding to the gene.
- Mutfreq A minimum sample mutation rate threshold is used to determine the genes for subsequent analysis.
- threshold A threshold is used to define the minimum mutational exposure of samples that can be displayed.
- Qvalue A FDR threshold of genes are used to highlight in red.
- plot Whether to plot the image.

Wen Luo (design), Zhenzhang Li (implementation, testing)

Examples

samPerMutSigs(Sfile = 'SampleContribution.12.Normalized.txt', choose.Sigs = 'SBS1', file = 'Non-silent.mutation.snv.txt', sample.id = 'Tumor_Sample_Barcode', Hugo = 'Hugo_Symbol', Mutfreq = 0.04, threshold = 0.2, Qvalue = 0.1, plot = TRUE)

IDlego The tool is used to plot lego image for mutation spectrum

Description

The tool is used to plot lego image for mutation spectrum, and its method references ID Signatures.

Usage

```
IDlego(file='originalGenomes', subtype='subtypes', genome.build = c("Ch37","Ch38"), SequenceType = c("WGS","WES"))
```

- originalGenomes a file, data matrix for NMF, [m x n, m stands for feature counts and n stands for sample counts].
- subtypes a list of types of mutation, data matrix for NMF, [m x 1, m stands for feature counts].

- genome.build The version of the reference genome used in the mutation set.
- SequenceType Type of Sequence, canbe WGS, WES.

Wen Luo (design), Zhenzhang Li (implementation, testing)

Examples

IDlego(file='originalGenomes', subtype='subtypes', genome.build = "Ch37", SequenceType = "WGS")

DBSlego The tool is used to plot lego image for mutation spectrum

Description

The tool is used to plot lego image for mutation spectrum, and its method references DBS Signatures.

Usage

```
DBSlego(file='originalGenomes', subtype='subtypes', genome.build = c("Ch37","Ch38"), SequenceType = c("WGS","WES"))
```

Arguments

- originalGenomes a file, data matrix for NMF, [m x n, m stands for feature counts and n stands for sample counts].
- subtypes a list of types of mutation, data matrix for NMF, [m x 1, m stands for feature counts].
- genome.build The version of the reference genome used in the mutation set.
- SequenceType Type of Sequence, can be WGS, WES.

Author(s)

Wen Luo (design), Zhenzhang Li (implementation, testing)

Examples

DBSlego(file='originalGenomes', subtype='subtypes', genome.build = "Ch37", SequenceType = "WGS")

SBSlego *The tool is used to plot lego image for mutation spectrum*

Description

The tool is used to plot lego image for mutation spectrum, and its method comes from lwlegopt (https://github.com/BGI-LuoWen/lwlegopt).

Usage

SBSlego(file='originalGenomes', subtype='subtypes', scale=10, name=NULL, title='GC', sort=NULL, top=TRUE, color=NULL, border=NULL, genome.build = c("Ch37","Ch38"), SequenceType = c("WGS","WES"), RegionLength = NULL)

Arguments

- originalGenomes a file, data matrix for NMF, [m x n, m stands for feature counts and n stands for sample counts].
- subtypes a list of types of mutation, data matrix for NMF, [m x 1, m stands for feature counts].
- scale Scale interval of Y axis.
- name Prefix_Name of output file.
- title Cancer type.
- sort Sort for trinucleotide percentage value: TRUE, FALSE and NULL.
- top Location of icon displaying: TRUE, FALSE.
- color Colours for lego figure.
- border Colours for border.
- genome.build The version of the reference genome used in the mutation set.
- SequenceType Type of Sequence, canbe WGS, WES.
- RegionLength The length of sequence region.

Author(s)

Wen Luo (design), Zhenzhang Li (implementation, testing)

Examples

SBSlego(file='originalGenomes', subtype='subtypes', scale=10, name=NULL, title='GC', sort=NULL, top=TRUE, color=NULL, border=NULL, genome.build = "Ch37", SequenceType = "WGS")

similarityCOSMIC Similarity calculation based on COSMIC Mutational

Signatures

Description

Calculate the similarities between features and draw heat maps.

Usage

```
similarityCOSMIC(Pfile, AnalCOSMICSigType = c('SBS','DBS','ID'), genome.build = c('Ch37', 'Ch38'), SBS.version = c("V2","V3"), plot = TRUE, fontsize = 6, filename = NULL)
```

Arguments

- Pfile A mutational signature matrix file P with a format like the output result of RNMF software.
- AnalCOSMICSigType Type of mutation based on PCAWG project, canbe SBS, DBS or ID.
- genome.build The version of the reference genome used in the mutation set.
- SBS.version Mutational signatures version 3 and version 2 signatures in COSMIC.
- plot Whether to plot the image.
- fontsize base fontsize for the plot.
- filename file path where to save the picture. Filetype is decided by the extension in the path. Currently following formats are supported: png, pdf, tiff, bmp, jpeg. Even if the plot does not fit into the plotting window, the file size is calculated so that the plot would fit there, unless specified otherwise.

Author(s)

Wen Luo (design), Zhenzhang Li (implementation, testing)

Examples

```
similarityCOSMIC(Pfile = 'SignatureComposition.12.Normalized.txt', AnalCOSMICSigType = 'SBS', genome.build = 'Ch37', SBS.version = "V2", plot = TRUE, fontsize = 6, filename = NULL)
```

similarityAB Similarity calculation

Description

Calculate the similarities between features and draw heat maps.

Usage

```
similarityAB(Pfile1, Pfile2, AnalCOSMICSigType = c('SBS','DBS','ID'), plot = TRUE, fontsize = 6, filename = NULL)
```

Arguments

• Pfile1 - A mutational signature matrix file A with a format like the output result from RNMF software.

- Pfile2 A mutational signature matrix file B with a format like the output result of RNMF software.
- AnalCOSMICSigType Type of mutation based on PCAWG project, canbe SBS, DBS or ID.
- plot Whether to plot the image.
- fontsize base fontsize for the plot.
- filename file path where to save the picture. Filetype is decided by the extension in the path. Currently following formats are supported: png, pdf, tiff, bmp, jpeg. Even if the plot does not fit into the plotting window, the file size is calculated so that the plot would fit there, unless specified otherwise.

Wen Luo (design, implementation), Zhenzhang Li (implementation, testing)

Examples

```
similarityAB(Pfile1 = 'A.12.Normalized.txt', Pfile2 = 'B.12.Normalized.txt', AnalCOSMICSigType = 'SBS', plot = TRUE, fontsize = 6, filename = NULL)
```

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