

Package: SATS (via r-universe)

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Title Signature Analyzer for Targeted Sequencing

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Description SATS stands for Signature Analyzer for Targeted Sequencing and performs mutational signature analysis for targeted sequenced tumors. Unlike the canonical analysis of mutational signatures, SATS factorizes the mutation counts matrix into a panel context matrix (measuring the size of the targeted sequenced genome for each tumor in the unit of million base pairs (Mb)), a signature profile matrix, and a signature activity matrix. SATS also calculates the expected number of mutations attributed by a signature, namely signature burden, for each targeted sequenced tumor. For more details see Lee et al. (2024) <[doi:10.1101/2023.05.18.23290188](https://doi.org/10.1101/2023.05.18.23290188)>.

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BSgenome.Hsapiens.UCSC.hg38

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SATS-package	<i>SATS (Signature Analyzer for Targeted Sequencing)</i>
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Description

This package is created to perform mutational signature analysis for targeted sequenced tumors. Unlike the canonical analysis of mutational signatures, SATS factorizes the mutation counts matrix into a panel context matrix (measuring the size of the targeted sequenced genome for each tumor in the unit of million base pairs (Mb)), a signature profile matrix, and a signature activity matrix. SATS also calculates the expected number of mutations attributed by a signature, namely signature burden, for each targeted sequenced tumor.

Details

This package includes a novel algorithm, SATS, to perform mutational signature analysis for targeted sequenced tumors. The algorithm first applies the `signeR` algorithm to extract profiles of de novo mutational signatures by appropriately adjusting for various panel sizes. Next, the profiles of identified de novo mutational signatures are mapped to the profiles of catalog signatures of tumor mutation burden (TMB), in the unit of the number of mutations per million base pairs, using penalized non-negative least squares. Then, given the panel sizes and profiles of mapped TMB catalog signatures, signature activities are estimated for all samples simultaneously through the Expectation-Maximization (EM) algorithm. Finally, the expected number of mutations attributed by a signature, namely signature burden, is calculated for each targeted sequenced tumor.

The main functions in this package are [GenerateLMatrix](#), [EstimateSigActivity](#), [CalculateSignatureBurdens](#), and [MappingSignature](#).

Author(s)

Donghyuk Lee <dhyuklee@pusan.ac.kr> and Bin Zhu <bin.zhu@nih.gov>

References

Lee, D., Hua, M., Wang, D., Song, L., Yu, K., Yang, X., Shi, J., Landi, M., Zhu, B. The mutational signatures of 100,477 targeted sequenced tumors. Submitted.

`CalculateSignatureBurdens`*Calculate signature burdens*

Description

Estimation of the expected number of mutations attributed by TMB-based catalog signatures (signature burden) given the panel size matrix, the catalog signature profile matrix and the signature activities matrix.

Usage

```
CalculateSignatureBurdens(L, W, H)
```

Arguments

L	Panel size matrix or data frame with samples in columns, see GenerateLMatrix
W	Catalog signature profiles matrix or data frame with signatures in columns
H	Activity matrix or data frame with samples in columns, see EstimateSigActivity

Details

The panel size matrix L is of size P (the mutation context) by N (the sample size). The catalog signature profile matrix has dimension of P by K (the number of signatures) and the activity matrix H is of size K by N. For single base substitutions (SBS), P is 96. If K is the number of signatures and N is the number of samples, then H must be of dimension K X N, `ncol(L) = N`, and `ncol(W) = K`. For the catalog signature profile matrix W, reference SBS TMB signature profiles in `data(SimData)` can be used.

Value

A matrix of dimension K X N, where K is the number of signatures and N is the number of samples.

Author(s)

Donghyuk Lee <dhyuklee@pusan.ac.kr> and Bin Zhu <bin.zhu@nih.gov>

See Also

[EstimateSigActivity](#)

Examples

```
data(SimData, package="SATS")
```

```
CalculateSignatureBurdens(SimData$L, SimData$TrueW_TMB, SimData$TrueH)
# For more detailed usage, please refer to README and the user manual
# in https://github.com/binzhulab/SATS/tree/main.
```

EstimateSigActivity *Estimate signature activity*

Description

Estimation of signature activities given the original mutation type matrix, the panel size matrix, and the catalog signature profile matrix.

Usage

```
EstimateSigActivity(V, L, W, n.start=50, iter.max=5000, eps=1e-5)
```

Arguments

V	Mutation type matrix or data frame with samples in columns
L	Panel size matrix or data frame with samples in columns, see GenerateLMatrix
W	Catalog signature profiles matrix or data frame with signatures in columns
n.start	Number of initializations. The default is 50.
iter.max	Maximum number iterations in the EM algorithm. The default is 5000.
eps	Stopping tolerance in the EM algorithm. The default is 1e-5.

Details

The panel size matrix L and mutation type matrix V are of size P (the mutation context) by N (the sample size). The catalog signature profile matrix has dimension of P by K (the number of signatures). For single base substitutions (SBS), P is 96. For the objects V, L, and W, we must have $\dim(V) = \dim(L)$ and $\text{ncol}(W) = K$, where K is the number of signatures. EstimateSigActivity() uses the EM algorithm to estimate signature n.start, iter.max and eps control EM part. Because the convergence to a local saddle point can be an issue of the EM algorithm, it would be good practice to try multiple initial values (n.start, the default is 50). For each initial value, the default value of the maximal iteration of the EM algorithm (iter.max) is 5000, and the stopping tolerance (eps) is set to 1e-5. For the catalog signature profile matrix W, reference SBS TMB signature profiles in data(SimData) can be used.

Value

A list containing the estimated activity matrix H, the log-likelihood loglike, and the logical value converged.

Author(s)

Donghyuk Lee <dhyuklee@pusan.ac.kr> and Bin Zhu <bin.zhu@nih.gov>

See Also

[CalculateSignatureBurdens](#)

Examples

```
data(SimData, package="SATS")

EstimateSigActivity(SimData$V, SimData$L, SimData$TrueW_TMB)

# For more detailed usage, please refer to README and the user manual
# in https://github.com/binzhulab/SATS/tree/main.
```

GenerateLMatrix	<i>Generate an L Matrix</i>
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Description

Generation of the L matrix.

Usage

```
GenerateLMatrix(Panel_context, Patient_Info)
```

Arguments

Panel_context A data frame returned from [GeneratePanelSize](#).
Patient_Info A data frame with columns 'PATIENT_ID' and 'SEQ_ASSAY_ID'.

Details

The `GenerateLMatrix()` function relies on the 'Patient_Info' data frame to link each patient to their specific sequencing assay, identified by 'SEQ_ASSAY_ID'. This is the same core information required by the `genomic_information` argument in the `GeneratePanelSize()` function. The values in the 'SEQ_ASSAY_ID' column will be used as the column names for the resulting L matrix, ensuring each column corresponds to a unique sample.

It is important to understand the distinction between the two functions. `GeneratePanelSize()` is a simpler utility that only calculates the total size (in base pairs) of each panel type and does not require patient-level information. However, to generate the correctly dimensioned L matrix with the proper trinucleotide contexts for each specific sample, you must call `GenerateLMatrix()`.

Value

A data frame (L matrix) of 96 by N, where N is the number of tumors.

Author(s)

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See Also

[GeneratePanelSize](#)

Examples

```

data(SimData, package="SATS")

Panel_context <- GeneratePanelSize(genomic_information=SimData$PanelEx, Class="SBS",
                                   SBS_order="COSMIC")
L_mat <- GenerateLMatrix(Panel_context, SimData$PatientInfo)
# For more detailed usage, please refer to README and the user manual
# in https://github.com/binzhulab/SATS/tree/main.

```

GeneratePanelSize *Generate Panel Size Matrix*

Description

Generation of the panel size matrix given the panel information.

Usage

```

GeneratePanelSize(genomic_information, Class = c("SBS", "DBS"),
                  SBS_order = c("COSMIC", "signeR"), ref.genome="hg19")

```

Arguments

genomic_information	Data frame of panel information (see details).
Class	A character string specifying the mutation class. Must be either "SBS" (for single base substitutions) or "DBS" (for double base substitutions). If "DBS" is selected, the SBS_order argument is ignored.
SBS_order	Mutation type order either one of "COSMIC" or "signeR" (see details).
ref.genome	The reference genome "hg19" or "hg38".

Details

The first argument 'genomic_information' should contain columns 'Chromosome', 'Start_Position', 'End_Position', 'SEQ_ASSAY_ID'. The column 'Chromosome' contains chromosome number where 'Start_Position' and 'End_Position' columns are start and end positions of the targeted panel. The last column 'SEQ_ASSAY_ID' distinguishes different panels consisting of the result. Please note that the column names of 'genomic_information' identical to 'Chromosome', 'Start_Position', 'End_Position', 'SEQ_ASSAY_ID'. The second argument specifies mutation type order as either one of "COSMIC" or "signeR" where "COSMIC" corresponds to the order from the COSMIC database v3.2 and "signeR" corresponds to the order from the signeR package. **Note:** The result of 'GeneratePanelSize()' may NOT be an 'L' matrix. The GenerateLMatrix() function can be used to construct the L matrix. The resulting augmented matrix can be used as the opportunity matrix for 'signeR()' function, 'L' matrix for 'EstimateSigActivity()' and 'CalculateSignatureBurdens()' functions. Therefore, it is important the mutation type order (row names) should be the same as input matrix (Mutation type matrix 'V'). We highly recommend to confirm that both 'V' and 'L' matrices have the same mutation type order corresponding to one of COSMIC database v3.2 or

signeR package (both have the same order but have different expression) to conduct the consistent analysis.

Value

A data frame of 96 by 'S' (the number of panels, 'SEQ_ASSAY_ID') where entries denote the number of trinucleotides per million base pairs.

Author(s)

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Examples

```
## Not run:
data(SimData, package="SATS")

# Package BSgenome.Hsapiens.UCSC.hg19 is needed for this example
library(BSgenome.Hsapiens.UCSC.hg19)

## For the single base substitution (SBS) case:
Panel_context1 <- GeneratePanelSize(genomic_information = SimData$PanelEx, Class = "SBS",
                                   SBS_order = "COSMIC", ref.genome="hg19")
L_mat1 <- GenerateLMatrix(Panel_context1, SimData$PatientInfo)
Panel_context2 <- GeneratePanelSize(genomic_information = SimData$PanelEx, Class = "SBS",
                                   SBS_order = "signeR", ref.genome="hg19")
L_mat2 <- GenerateLMatrix(Panel_context2, SimData$PatientInfo)

## For the double base substitution (DBS) case:
Panel_context_DBS <- GeneratePanelSize(genomic_information = SimData$PanelEx, Class = "DBS",
                                       ref.genome = "hg19")
L_mat_DBS <- GenerateLMatrix(Panel_context_DBS, SimData$PatientInfo)

# For more detailed usage, please refer to README and the user manual
# in https://github.com/binzhulab/SATS/tree/main

## End(Not run)
```

MappingSignature

Find a subset of TMB-based catalog SBS signatures

Description

This function finds a subset of TMB-based catalog SBS signatures whose linear combination approximate de novo SBS signatures detected by signeR.

Usage

```
MappingSignature(W_hat, W_ref=NULL, niter=100, cutoff.I2=0.1, min.repeats=80,
                COSMICv="v3.4")
```

Arguments

<code>W_hat</code>	Matrix or data frame of de novo signatures from <code>signeR</code>
<code>W_ref</code>	NULL or a matrix or data frame of TMB-based catalog signatures. If NULL, then it will default to <code>RefTMB\$TMB_SBS_v3.2</code> or <code>RefTMB\$TMB_SBS_v3.4</code> depending on the value of <code>COSMICv</code> below (see RefTMB).
<code>niter</code>	Number of iterations. The default is 100.
<code>cutoff.I2</code>	Cutoff value to select signatures. The default is 0.1.
<code>min.repeats</code>	Minimum number of iterations to select signatures with $I^2 > \text{cutoff.I2}$. The default is 80.
<code>COSMICv</code>	Version of the TMB-based COSMIC signatures ("v3.2" or "v3.4"). This option is ignored if <code>W_ref</code> is not NULL. The default is "v3.4".

Details

`MappingSignature()` applies penalized non-negative least squares (pNNLS) for selecting the TMB-based catalog signatures. Specifically, it repeats pNNLS 100 times (`niter`) to reduce the randomness of cross-validation involved in pNNLS. Then TMB-based catalog signatures are selected with a coefficient greater than 0.1 (`cutoff.I2`) in more than 80 repeats (`min.repeats`).

Value

A data frame with column names of `W_ref` (it returns COSMIC SBS names if COSMIC catalog based reference signatures are used) and `freq` (the number of repetitions greater than cutoff coefficient values out of `niter` iterations).

Author(s)

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RefTMB

Example Data

Description

The pan-cancer repertoire of reference signatures and the reference TMB (Tumor mutation burden) signature profiles of SBS (Single base substitutions) and DBS (Double base substitutions).

Details

This file consists of the list `RefTMB` with the following objects:

- `TMB_SBS_v3.2` : The version 3.2 reference SBS TMB signature profiles of size 96 by 76.
- `TMB_DBS_v3.2` : The version 3.2 reference DBS TMB signature profiles of size 78 by 11.
- `TMB_SBS_v3.4` : The version 3.4 reference SBS TMB signature profiles of size 96 by 85.
- `TMB_DBS_v3.4` : The version 3.4 reference DBS TMB signature profiles of size 78 by 20.
- `SBS_refSigs` : The list of cancer specific SBS signature names.
- `DBS_refSigs` : The list of cancer specific DBS signature names.

SimData

Data for examples

Description

Simulated data as an example

Details

This file consists of the list SimData with the following objects:

- **V** : Simulated mutation catalog matrix of size 96 by 10027 generated from the Poisson distribution with the mean corresponding to each element of $L*(WH)$, where $*$ is elementwise multiplication, **L** is the panel size matrix below, **W** is the profile matrix of the tumor mutation burden (TrueW_TMB below), and **H** is the signature activity matrix (TrueH below).
- **L** : Panel size matrix of size 96 by 10027.
- **TrueH** : Simulated signature activity matrix of size 6 by 10027 used to generate **V**.
- **TrueW_TMB** : Tumor mutation burden based signatures size 96 by 6 for 6 SBS signatures (SBS1, SBS2/13, SBS4, SBS5, SBS40, SBS89) used to generate **V**.
- **SingleTumorEx** : A single simulated tumor (column singleV) and its sequencing context (column singleL).
- **PanelEx**: An example sequencing panel information with Chromosome, Start_Position, End_Position, SEQ_ASSAY_ID.
- **PatientInfo**: An example patient data containing patients ID associated with SEQ_ASSAY_ID.

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