

# Extracting sparse mutational signatures via LASSO

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**Overview.** Point mutations occurring in a genome can be divided into 96 categories based on the base being mutated, the base it is mutated into and its two flanking bases. Therefore, for any patient, it is possible to represent all the point mutations occurring in that patient's tumor as a vector of length 96, where each element represents the count of mutations for a given category in the patient.

A mutational signature represents the pattern of mutations produced by a mutagen or mutagenic process inside the cell. Each signature can also be represented by a vector of length 96, where each element represents the probability that this particular mutagenic process generates a mutation of the 96 above mentioned categories. In this R package, we provide a set of functions to extract and visualize the mutational signatures that best explain the mutation counts of a large number of patients.

*In this vignette, we give an overview of the package by presenting some of its main functions.*

# Contents

1

Changelog

2

2

Algorithms and useful links

2

3

Using the SparseSignatures R package

2

4

sessionInfo()

11

## 1 Changelog

1.0.0 package released on Bioconductor in May 2018.

## 2 Algorithms and useful links

| Acronym          | Extended name  | Reference                   |
|------------------|--|-----------------------------|
| SparseSignatures | De Novo Mutational Signature Discovery in Tumor Genomes using SparseSignatures | <a href="#">Publication</a> |

## 3 Using the SparseSignatures R package

We now present the main features of the package. To start, we show how to load data and transform them to a count matrix to perform the signatures discovery; first we load some example data provided in the package.

```
library("SparseSignatures")

## Loading required package: NMF
## Loading required package: pkgmaker
## Loading required package: registry
## Loading required package: rngtools
## Loading required package: cluster

## NMF - BioConductor layer [OK] | Shared memory capabilities [NO: synchronicity]
| Cores 23/24

## To enable shared memory capabilities, try: install.extras('
## NMF
## ')

data(ssm560_reduced)
head(ssm560_reduced)
```

## Extracting sparse mutational signatures via LASSO

| ##    | sample   | chrom | pos       | ref | alt |
|-------|----------|-------|-----------|-----|-----|
| ## 1: | PD10014a | 1     | 186484577 | A   | C   |
| ## 2: | PD10014a | 7     | 141761948 | G   | A   |
| ## 3: | PD10014a | 7     | 71266228  | C   | T   |
| ## 4: | PD10014a | 8     | 82304475  | A   | T   |
| ## 5: | PD10014a | 3     | 191275626 | T   | A   |
| ## 6: | PD10014a | 4     | 135265376 | C   | T   |

These data are a reduced version with only 3 patients of the 560 breast tumors provided by Nik-Zainal, Serena, et al. (2016). We can transform such input data to a count matrix to perform the signatures discovery with the function `import.counts.data`. To do so, we also need to specify the reference genome as a `BSgenome` object and the format of the 96 nucleotides to be considered. This can be done as follows, where in the example we use `hs37d5` as our reference genome.

```
library("BSgenome.Hsapiens.1000genomes.hs37d5")

## Loading required package: BSgenome
## Loading required package: S4Vectors
## Loading required package: stats4
##
## Attaching package: 'S4Vectors'
## The following object is masked from 'package:NMF':
##
##   nrun
## The following object is masked from 'package:pkgmaker':
##
##   new2
## The following object is masked from 'package:base':
##
##   expand.grid
## Loading required package: IRanges
## Loading required package: GenomeInfoDb
## Loading required package: GenomicRanges
## Loading required package: Biostrings
## Loading required package: XVector
##
## Attaching package: 'Biostrings'
## The following object is masked from 'package:base':
##
##   strsplit
## Loading required package: rtracklayer

bsg = BSgenome.Hsapiens.1000genomes.hs37d5
data(mutation_categories)
```

## Extracting sparse mutational signatures via LASSO

```
head(mutation_categories)

##      context alt      cat
## 1:      A:A C>A A[C>A]A
## 2:      C:A C>A C[C>A]A
## 3:      G:A C>A G[C>A]A
## 4:      T:A C>A T[C>A]A
## 5:      A:A C>G A[C>G]A
## 6:      C:A C>G C[C>G]A

imported_data = import.counts.data(input=ssm560_reduced, bsg=bsg, mutation_categories=mutation_categories)

## Warning in import.counts.data(input = ssm560_reduced, bsg = bsg, mutation_categories
## = mutation_categories): Some samples have fewer than 100 mutations:
## PD10010a, PD10011a, PD10014a

head(imported_data)

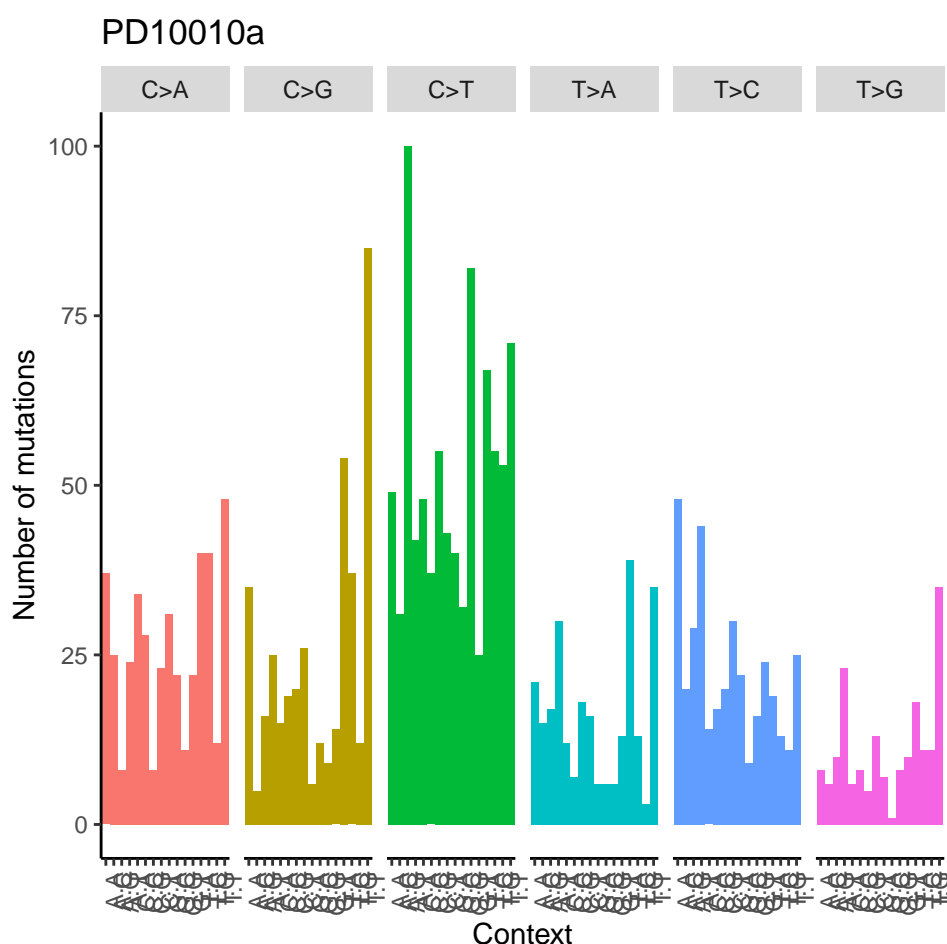
##      A[C>A]A A[C>A]C A[C>A]G A[C>A]T A[C>G]A A[C>G]C A[C>G]G A[C>G]T A[C>T]A
## PD10010a      37      25       8       24       35       5       16       25       49
## PD10011a     103      59      16       73      113      54      31     102     116
## PD10014a     235     241      37      234     158      71      26     180     229
##      A[C>T]C A[C>T]G A[C>T]T A[T>A]A A[T>A]C A[T>A]G A[T>A]T A[T>C]A A[T>C]C
## PD10010a      31     100      42       21       15       17       30       48       20
## PD10011a      73     228     109       61       70       56     165     184     116
## PD10014a      89     178     186      105      90     126     174     261     122
##      A[T>C]G A[T>C]T A[T>G]A A[T>G]C A[T>G]G A[T>G]T C[C>A]A C[C>A]C C[C>A]G
## PD10010a      29      44       8        6      10      23      34      28       8
## PD10011a     113     169      77      41      73     105     105      75      30
## PD10014a     167     211      76      27      84      59     244     238      35
##      C[C>A]T C[C>G]A C[C>G]C C[C>G]G C[C>G]T C[C>T]A C[C>T]C C[C>T]G C[C>T]T
## PD10010a      23      15      19      20      26      48      37      55      43
## PD10011a     102      60      37      22      65      71      52     108     103
## PD10014a     243     107     105      40     144     136     124     144     197
##      C[T>A]A C[T>A]C C[T>A]G C[T>A]T C[T>C]A C[T>C]C C[T>C]G C[T>C]T C[T>G]A
## PD10010a      12       7      18      16      14      17      20      30       6
## PD10011a     116      80      89     103     103      78     102     158      40
## PD10014a     116     139     145     217     103     144     112     129      47
##      C[T>G]C C[T>G]G C[T>G]T G[C>A]A G[C>A]C G[C>A]G G[C>A]T G[C>G]A G[C>G]C
## PD10010a       8       5      13      31      22      11      22       6      12
## PD10011a      65      55     188      78      50      14      55      55      66
## PD10014a      54      70     107     146     126      24     160      63      70
##      G[C>G]G G[C>G]T G[C>T]A G[C>T]C G[C>T]G G[C>T]T G[T>A]A G[T>A]C G[T>A]G
## PD10010a       9      14      40      32      82      25       6       6       6
## PD10011a      13      87      76      63     118      81      69      41      56
## PD10014a      25     120     141      99     180     163      62      66      83
##      G[T>A]T G[T>C]A G[T>C]C G[T>C]G G[T>C]T G[T>G]A G[T>G]C G[T>G]G G[T>G]T
## PD10010a      13      22       9      16      24       7       1       8      10
## PD10011a      86      96      62      82      93      56      46      35      99
## PD10014a     126     110      81     102     135      32      18      61      78
##      T[C>A]A T[C>A]C T[C>A]G T[C>A]T T[C>G]A T[C>G]C T[C>G]G T[C>G]T T[C>T]A
## PD10010a      40      40      12      48      54      37      12      85      67
## PD10011a      78      80      12      83     116     104      29     194     119
```

## Extracting sparse mutational signatures via LASSO

|             |         |         |         |         |         |         |         |         |         |
|-------------|---------|---------|---------|---------|---------|---------|---------|---------|---------|
| ## PD10014a | 202     | 191     | 17      | 253     | 198     | 159     | 33      | 325     | 188     |
| ##          | T[C>T]C | T[C>T]G | T[C>T]T | T[T>A]A | T[T>A]C | T[T>A]G | T[T>A]T | T[T>C]A | T[T>C]C |
| ## PD10010a | 55      | 53      | 71      | 39      | 13      | 3       | 35      | 19      | 13      |
| ## PD10011a | 94      | 78      | 126     | 121     | 43      | 64      | 91      | 125     | 79      |
| ## PD10014a | 153     | 93      | 184     | 124     | 89      | 73      | 221     | 143     | 118     |
| ##          | T[T>C]G | T[T>C]T | T[T>G]A | T[T>G]C | T[T>G]G | T[T>G]T |         |         |         |
| ## PD10010a | 11      | 25      | 18      | 11      | 11      | 35      |         |         |         |
| ## PD10011a | 83      | 113     | 68      | 90      | 140     | 251     |         |         |         |
| ## PD10014a | 75      | 148     | 71      | 54      | 76      | 160     |         |         |         |

The function `import.counts.data` can also take a text file as input with the same format as the one shown above. Now, we show an example of a visualization feature provided by the package, and we show the counts for the first patient PD10010a in the following plot.

```
patient.plot(countMatrix=imported_data,patientName="PD10010a")
```



**Figure 1:** Visualization of the counts from patient PD10010a from the dataset published in Nik-Zainal, Serena, et al

After the data are loaded, signatures can be discovered. To do so, we need to define a set of parameters on which to perform the estimation.

## Extracting sparse mutational signatures via LASSO

First of all, we need to specify the ranges for the number of signatures (variable K) and the LASSO penalty value (variable lambda rate) to be considered. The latter is more complicated to estimate, as it requires that the values in the range not to be too small in order to avoid dense signatures, but also should not be too high in order to still perform a good fit of the observed counts.

Besides these parameters, we also need to estimate the initial values of beta to be used during the estimation. We now show how to do this on the set of counts from 560 tumors provided in Nik-Zainal, Serena, et al. (2016).

```
data(patients)
head(patients)
```

| ##         | A[C>A]A | A[C>A]C | A[C>A]G | A[C>A]T | A[C>G]A | A[C>G]C | A[C>G]G | A[C>G]T | A[C>T]A |
|------------|---------|---------|---------|---------|---------|---------|---------|---------|---------|
| ## PD8623a | 24      | 23      | 4       | 20      | 10      | 19      | 2       | 11      | 43      |
| ## PD8618a | 29      | 19      | 2       | 15      | 11      | 12      | 2       | 8       | 31      |
| ## PD6418a | 23      | 29      | 4       | 26      | 12      | 9       | 1       | 12      | 39      |
| ## PD7214a | 19      | 20      | 5       | 18      | 11      | 5       | 4       | 7       | 30      |
| ## PD4968a | 59      | 64      | 5       | 34      | 25      | 16      | 1       | 18      | 81      |
| ## PD4954a | 102     | 87      | 19      | 82      | 80      | 48      | 13      | 88      | 117     |

| ##         | A[C>T]C | A[C>T]G | A[C>T]T | A[T>A]A | A[T>A]C | A[T>A]G | A[T>A]T | A[T>C]A | A[T>C]C |
|------------|---------|---------|---------|---------|---------|---------|---------|---------|---------|
| ## PD8623a | 25      | 77      | 28      | 16      | 12      | 23      | 37      | 57      | 7       |
| ## PD8618a | 17      | 91      | 24      | 10      | 10      | 8       | 18      | 50      | 23      |
| ## PD6418a | 36      | 104     | 36      | 13      | 19      | 26      | 22      | 53      | 19      |
| ## PD7214a | 22      | 65      | 21      | 12      | 18      | 17      | 18      | 41      | 12      |
| ## PD4968a | 57      | 246     | 70      | 26      | 46      | 53      | 66      | 93      | 39      |
| ## PD4954a | 53      | 125     | 79      | 64      | 48      | 37      | 52      | 97      | 41      |

| ##         | A[T>C]G | A[T>C]T | A[T>G]A | A[T>G]C | A[T>G]G | A[T>G]T | C[C>A]A | C[C>A]C | C[C>A]G |
|------------|---------|---------|---------|---------|---------|---------|---------|---------|---------|
| ## PD8623a | 30      | 42      | 12      | 6       | 8       | 16      | 32      | 21      | 6       |
| ## PD8618a | 31      | 59      | 1       | 3       | 6       | 7       | 18      | 15      | 3       |
| ## PD6418a | 32      | 57      | 7       | 4       | 6       | 8       | 24      | 19      | 2       |
| ## PD7214a | 23      | 43      | 4       | 5       | 3       | 9       | 15      | 13      | 1       |
| ## PD4968a | 47      | 85      | 17      | 6       | 7       | 16      | 45      | 27      | 10      |
| ## PD4954a | 64      | 97      | 26      | 11      | 38      | 41      | 100     | 90      | 18      |

| ##         | C[C>A]T | C[C>G]A | C[C>G]C | C[C>G]G | C[C>G]T | C[C>T]A | C[C>T]C | C[C>T]G | C[C>T]T |
|------------|---------|---------|---------|---------|---------|---------|---------|---------|---------|
| ## PD8623a | 26      | 13      | 13      | 4       | 19      | 32      | 40      | 73      | 31      |
| ## PD8618a | 14      | 4       | 9       | 4       | 3       | 21      | 33      | 61      | 30      |
| ## PD6418a | 23      | 15      | 15      | 4       | 8       | 42      | 36      | 71      | 51      |
| ## PD7214a | 10      | 7       | 5       | 2       | 12      | 31      | 32      | 48      | 40      |
| ## PD4968a | 53      | 13      | 15      | 14      | 27      | 82      | 88      | 145     | 79      |
| ## PD4954a | 83      | 77      | 48      | 22      | 65      | 90      | 64      | 84      | 99      |

| ##         | C[T>A]A | C[T>A]C | C[T>A]G | C[T>A]T | C[T>C]A | C[T>C]C | C[T>C]G | C[T>C]T | C[T>G]A |
|------------|---------|---------|---------|---------|---------|---------|---------|---------|---------|
| ## PD8623a | 10      | 10      | 10      | 11      | 14      | 15      | 15      | 23      | 3       |
| ## PD8618a | 6       | 4       | 7       | 5       | 11      | 17      | 10      | 13      | 4       |
| ## PD6418a | 6       | 13      | 9       | 14      | 19      | 8       | 13      | 14      | 6       |
| ## PD7214a | 9       | 4       | 3       | 6       | 8       | 9       | 9       | 8       | 0       |
| ## PD4968a | 13      | 25      | 20      | 36      | 22      | 24      | 29      | 37      | 7       |
| ## PD4954a | 41      | 48      | 55      | 57      | 46      | 53      | 40      | 74      | 17      |

| ##         | C[T>G]C | C[T>G]G | C[T>G]T | G[C>A]A | G[C>A]C | G[C>A]G | G[C>A]T | G[C>G]A | G[C>G]C |
|------------|---------|---------|---------|---------|---------|---------|---------|---------|---------|
| ## PD8623a | 7       | 14      | 15      | 13      | 20      | 3       | 13      | 9       | 2       |
| ## PD8618a | 4       | 6       | 5       | 17      | 13      | 9       | 14      | 2       | 10      |
| ## PD6418a | 8       | 8       | 14      | 20      | 20      | 9       | 16      | 5       | 6       |
| ## PD7214a | 7       | 8       | 12      | 24      | 7       | 2       | 8       | 6       | 6       |

## Extracting sparse mutational signatures via LASSO

```
## PD4968a      10      7      24      35      25      12      30      9      13
## PD4954a      19     37     42     53     67     13     42     40     28
##           G[C>G]G G[C>G]T G[C>T]A G[C>T]C G[C>T]G G[C>T]T G[T>A]A G[T>A]C G[T>A]G
## PD8623a       1      6     33     24     61     29      3     11      6
## PD8618a       0      5     23     33     67     29      3     12      4
## PD6418a       3      5     35     39     94     34      7     12      9
## PD7214a       3      4     31     47     50     24      1      8      6
## PD4968a       1     11     68     62    190     65      8     21     14
## PD4954a       1     63     72     69     85     67     19     29     22
##           G[T>A]T G[T>C]A G[T>C]C G[T>C]G G[T>C]T G[T>G]A G[T>G]C G[T>G]G G[T>G]T
## PD8623a       6     15     10      6     23      1      3      5      4
## PD8618a       5     17     10      8     23      0      1      1      0
## PD6418a       8     36     11     22     22      1      3      3      6
## PD7214a       8     26     12      8     18      1      3      2      2
## PD4968a      18     43     19     29     35      6      3      3     11
## PD4954a      49     61     37     34     54     12      7     32     36
##           T[C>A]A T[C>A]C T[C>A]G T[C>A]T T[C>G]A T[C>G]C T[C>G]G T[C>G]T T[C>T]A
## PD8623a      34     24      8     31     22     20      1     32    119
## PD8618a      22     17     10     25     15     14      1     30     47
## PD6418a      34     23      5     35      9     12      2     24     43
## PD7214a      14     22      6     24      9      7      2     24     52
## PD4968a      79     57      9     87     64     27      8    120    464
## PD4954a     92    109     11    106    158     89     17    279    166
##           T[C>T]C T[C>T]G T[C>T]T T[T>A]A T[T>A]C T[T>A]G T[T>A]T T[T>C]A T[T>C]C
## PD8623a      59     52     98     29     15      6     18     25     17
## PD8618a      26     37     37     20      4      3     13     21     12
## PD6418a      56     52     65     31      9      9     15     25     17
## PD7214a      38     41     62     14      8      7     16     19     14
## PD4968a     177    157    337    127     20     19     42     41     42
## PD4954a     114     48    150     62     44     27     71     58     38
##           T[T>C]G T[T>C]T T[T>G]A T[T>G]C T[T>G]G T[T>G]T
## PD8623a      11     26      9     11     10     27
## PD8618a      12     16      4      3      6     11
## PD6418a       9     36      9      6      9     20
## PD7214a      13     22      4     10      8     19
## PD4968a      23     44     15      8     15     38
## PD4954a      30     57     40     29     37     62
```

First, we can estimate the initial values of beta as follows.

```
starting_betas = starting.betas. estimation(x=patients,K=3:12,background_signature=background)
```

Then, we also need to explore the search space of values for the LASSO penalty in order to make a good choice. To do so, we can use the function `evaluate.lambda.range` to test different values as follows.

```
lambda_range = evaluate.lambda.range(x=patients,K=10,beta=starting_betas[[8,1]],
                                     lambda_values=c(0.05,0.10))
```

As the executions of these functions can be very time-consuming, we also provide as examples together with the package a set of pre-computed results by the two functions `starting.betas. estimation` and `evaluate.lambda.range` obtained with the commands above.

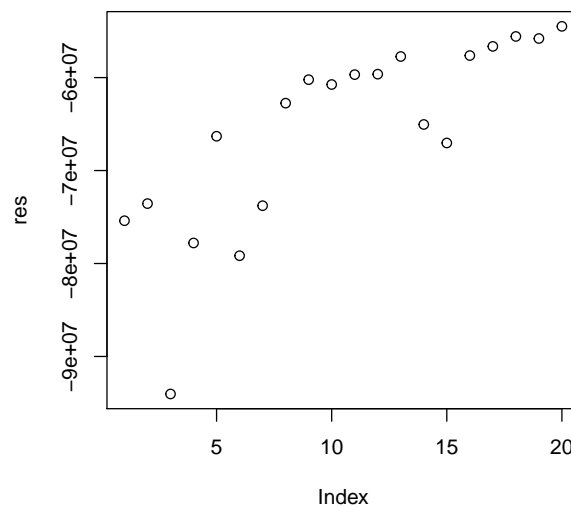
## Extracting sparse mutational signatures via LASSO

```
data(starting_betas_example)
data(lambda_range_example)
```

To evaluate the best lambda range, we need to carefully consider the log-likelihood of the solutions at each iteration of our method. This can be done by exploiting the `as.` functions that we provide. Here are some examples.

```
# example of using too small a value of lambda
# the log-likelihood is very unstable across the iterations
res = as.loglik.progression.in.range(lambda.range.result=lambda_range_example, lambda_value=0.01)
```

```
plot(res)
```



**Figure 2:** Example of using too small a value of lambda: the log-likelihood is very unstable across the iterations

```
# example of using too high a value of lambda
# the log-likelihood drops after the first iteration
res = as.loglik.progression.in.range(lambda.range.result=lambda_range_example, lambda_value=0.30)
```

```
plot(res)
```

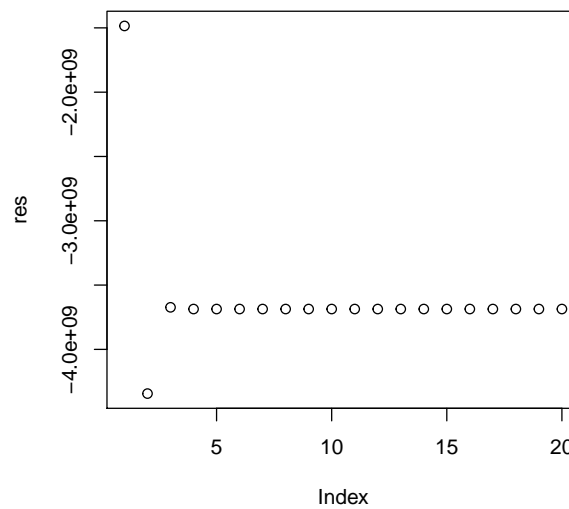
```
# example of using a good value of lambda
# the log-likelihood is increasing across the iterations
res = as.loglik.progression.in.range(lambda.range.result=lambda_range_example, lambda_value=0.15)
```

```
plot(res)
```

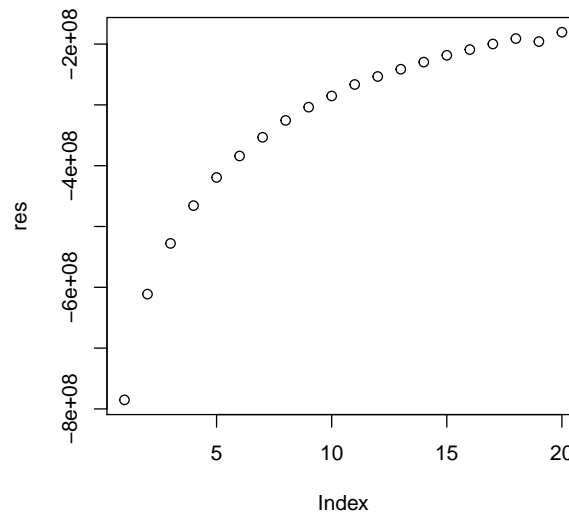
Now that we have evaluated all the required parameters, we need to decide which configuration of number of signatures and lambda value is the best. To do so, we rely on cross-validation.

```
cv = nmf.LassoCV(x=patients, K=3:10)
```

## Extracting sparse mutational signatures via LASSO



**Figure 3:** Example of using too high a value of lambda: the log-likelihood drops after the first iteration



**Figure 4:** Example of using a good value of lambda: the log-likelihood is increasing across the iterations

We notice that the computations for this task can be very time consuming, especially when many iterations of cross validations are specified (see manual) and a large set of configurations of the parameters are tested. To speed up the execution, we suggest using the parallel execution options. Also, to reduce the memory requirements, we advise splitting the cross validation in different runs, e.g., if one wants to perform 100 iterations, we would suggest making 10 independent runs of 10 iterations each. Also in this case, we provide as examples together with the package a set of pre-computed results obtained with the above command and the following settings:  $K = 3:10$ , cross validation entries = 0.10, lambda values = `c(0.05,0.10,0.15)`, number of iterations of cross-validation = 2.

```
data(cv_example)
```

We can now estimate the best configuration of the parameters in terms of median mean squared error by cross validation, where the best configuration is the one with lowest error.

## Extracting sparse mutational signatures via LASSO

```
res = as.mean.squared.error(cv_example)$median
res_best = which(res==res[which.min(res)],arr.ind=TRUE)
best_K = rownames(res)[res_best[1]]
best_lambda = colnames(res)[res_best[2]]
best_K

## [1] "5_signatures"

best_lambda

## [1] "0.1_lambda"
```

Finally, we can compute the signatures for the best configuration, i.e.,  $K = 5$  and  $\lambda = 0.10$ .

```
beta = starting_betas_example[["5_signatures", "Value"]]
res = nmf.LassoK(x=patients, K=5, beta=beta, background=background, lambda_rate=0.10,
                iterations=5, num_processes=NA)

## Performing the discovery of the signatures by NMF with Lasso...
## Performing a total of 5 iterations...
## Progress 20%...
## Progress 40%...
## Progress 60%...
## Progress 80%...
## Progress 100%...
```

We conclude this vignette by plotting the discovered signatures.

```
signatures = as.beta(res)
signatures.plot(beta=signatures, xlabels=FALSE)

## Warning in melt(beta, varnames = c("signature", "cat")): The melt generic in
data.table has been passed a matrix and will attempt to redirect to the relevant
reshape2 method; please note that reshape2 is deprecated, and this redirection is
now deprecated as well. To continue using melt methods from reshape2 while both
libraries are attached, e.g. melt.list, you can prepend the namespace like reshape2::melt(beta).
In the next version, this warning will become an error.
```

## Extracting sparse mutational signatures via LASSO

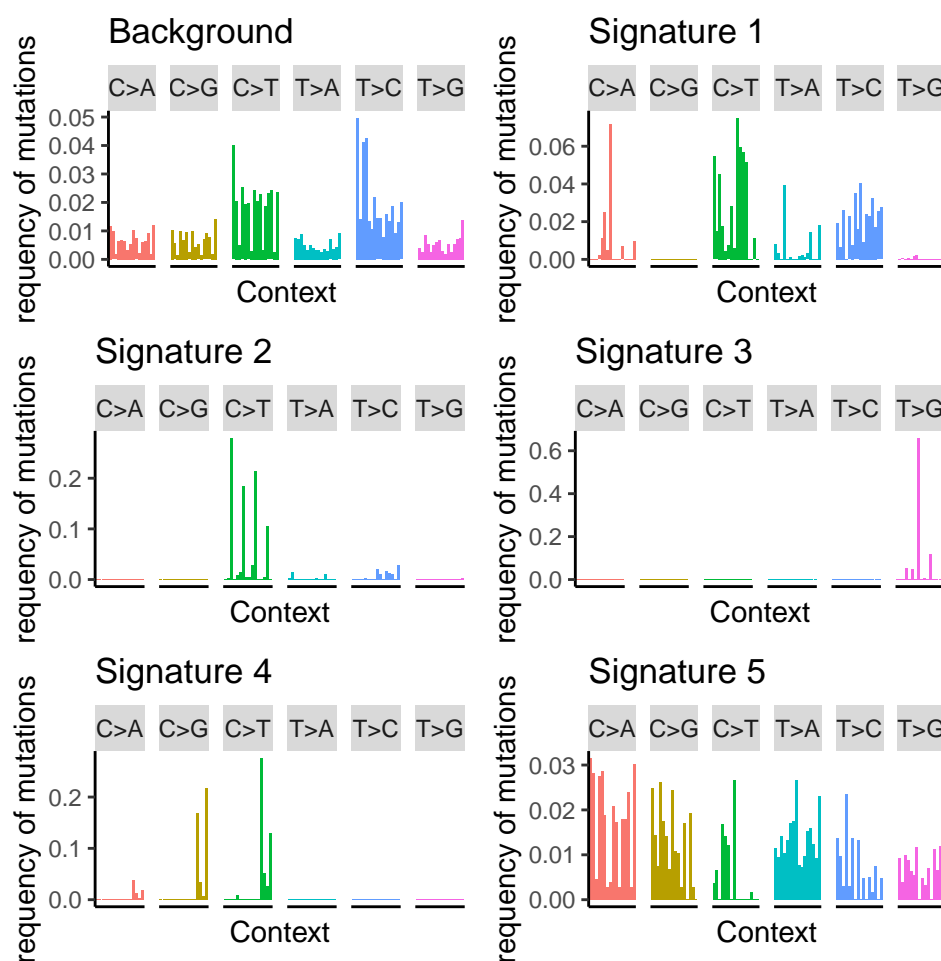


Figure 5: Visualization of the discovered signatures

## 4 sessionInfo()

- R version 4.0.0 alpha (2020-04-05 r78150), x86\_64-apple-darwin17.0
- Locale: C/en\_US.UTF-8/en\_US.UTF-8/C/en\_US.UTF-8/en\_US.UTF-8
- Running under: macOS Mojave 10.14.6
- Matrix products: default
- BLAS:  
/Library/Frameworks/R.framework/Versions/4.0/Resources/lib/libRblas.dylib
- LAPACK:  
/Library/Frameworks/R.framework/Versions/4.0/Resources/lib/libRlapack.dylib
- Base packages: base, datasets, grDevices, graphics, methods, parallel, stats, stats4, utils

## Extracting sparse mutational signatures via LASSO

- Other packages: BSgenome 1.55.4, BSgenome.Hsapiens.1000genomes.hs37d5 0.99.1, Biobase 2.47.3, BiocGenerics 0.33.3, Biostrings 2.55.7, GenomeInfoDb 1.23.17, GenomicRanges 1.39.3, IRanges 2.21.8, NMF 0.22.0, S4Vectors 0.25.15, SparseSignatures 1.7.1, XVector 0.27.2, bigmemory 4.5.36, cluster 2.1.0, knitr 1.28, pkgmaker 0.31.1, registry 0.5-1, rngtools 1.5, rtracklayer 1.47.0
- Loaded via a namespace (and not attached): BiocManager 1.30.10, BiocParallel 1.21.2, BiocStyle 2.15.6, DelayedArray 0.13.12, GenomeInfoDbData 1.2.3, GenomicAlignments 1.23.2, Matrix 1.2-18, R6 2.4.1, RColorBrewer 1.1-2, RCurl 1.98-1.1, Rcpp 1.0.4.6, Rsamtools 2.3.7, SummarizedExperiment 1.17.5, XML 3.99-0.3, assertthat 0.2.1, bibtex 0.4.2.2, bigmemory.sri 0.1.3, bitops 1.0-6, cli 2.0.2, codetools 0.2-16, colorspace 1.4-1, compiler 4.0.0, crayon 1.3.4, data.table 1.12.8, digest 0.6.25, doParallel 1.0.15, dplyr 0.8.5, ellipsis 0.3.0, evaluate 0.14, fansi 0.4.1, farver 2.0.3, foreach 1.5.0, ggplot2 3.3.0, glue 1.4.0, grid 4.0.0, gridBase 0.4-7, gridExtra 2.3, gtable 0.3.0, highr 0.8, htmltools 0.4.0, iterators 1.0.12, labeling 0.3, lattice 0.20-41, lifecycle 0.2.0, magrittr 1.5, matrixStats 0.56.0, munsell 0.5.0, nnlasso 0.3, nnls 1.4, pillar 1.4.3, pkgconfig 2.0.3, plyr 1.8.6, purrr 0.3.3, reshape2 1.4.4, rlang 0.4.5, rmarkdown 2.1.2, scales 1.1.0, stringi 1.4.6, stringr 1.4.0, tibble 3.0.0, tidyselect 1.0.0, tools 4.0.0, vctrs 0.2.4, withr 2.1.2, xfun 0.13, xtable 1.8-4, yaml 2.2.1, zlibbioc 1.33.1