class18

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Mutational Signatures in Human Cancer

Data for Skin Cutaneous Melanoma >Q1. How many cancer samples are included in the dataset? 448

Q2. Which is the most mutated gene? TTN

Q3. Which is the most common treatment undergone by patients? Radiation 1

Generating mutational matrices and visualizing mutational profiles

Lets read the file

```
library(maftools)
mela = read.maf("data_mutations.txt")
```

```
-Reading
-Validating
--Removed 27563 duplicated variants
-Silent variants: 209854
-Summarizing
--Possible FLAGS among top ten genes:
  TTN
  MUC16
-Processing clinical data
--Missing clinical data
-Finished in 22.1s elapsed (19.7s cpu)
```

Next make a mutational matrix

```
mm_mela = trinucleotideMatrix(maf = mela, prefix = 'chr', add = TRUE,
                              ref_genome = "BSgenome.Hsapiens.UCSC.hg19")
```

```
Attaching package: 'BiocGenerics'

The following objects are masked from 'package:stats':

    IQR, mad, sd, var, xtabs

The following objects are masked from 'package:base':

    anyDuplicated, aperm, append, as.data.frame, basename, cbind,
    colnames, dirname, do.call, duplicated, eval, evalq, Filter, Find,
    get, grep, grepl, intersect, is.unsorted, lapply, Map, mapply,
    match, mget, order, paste, pmax, pmax.int, pmin, pmin.int,
    Position, rank, rbind, Reduce, rownames, sapply, setdiff, sort,
    table, tapply, union, unique, unsplit, which.max, which.min


Attaching package: 'S4Vectors'

The following objects are masked from 'package:base':

    expand.grid, I, unname


Attaching package: 'IRanges'

The following object is masked from 'package:grDevices':

    windows


Attaching package: 'Biostrings'

The following object is masked from 'package:base':

    strsplit
```

```
-Extracting 5' and 3' adjacent bases
-Extracting +/- 20bp around mutated bases for background C>T estimation
-Estimating APOBEC enrichment scores
--Performing one-way Fisher's test for APOBEC enrichment
---APOBEC related mutations are enriched in  1.818 % of samples (APOBEC enrichment score > 2
-Creating mutation matrix
--matrix of dimension 440x96
```

```
mm_mela = t(mm_mela$nmf_matrix)
```

Next we generate mutational profiles

```
library(MutationalPatterns)
```

```
Loading required package: NMF
```

```
Loading required package: registry
```

```
Loading required package: rngtools
```

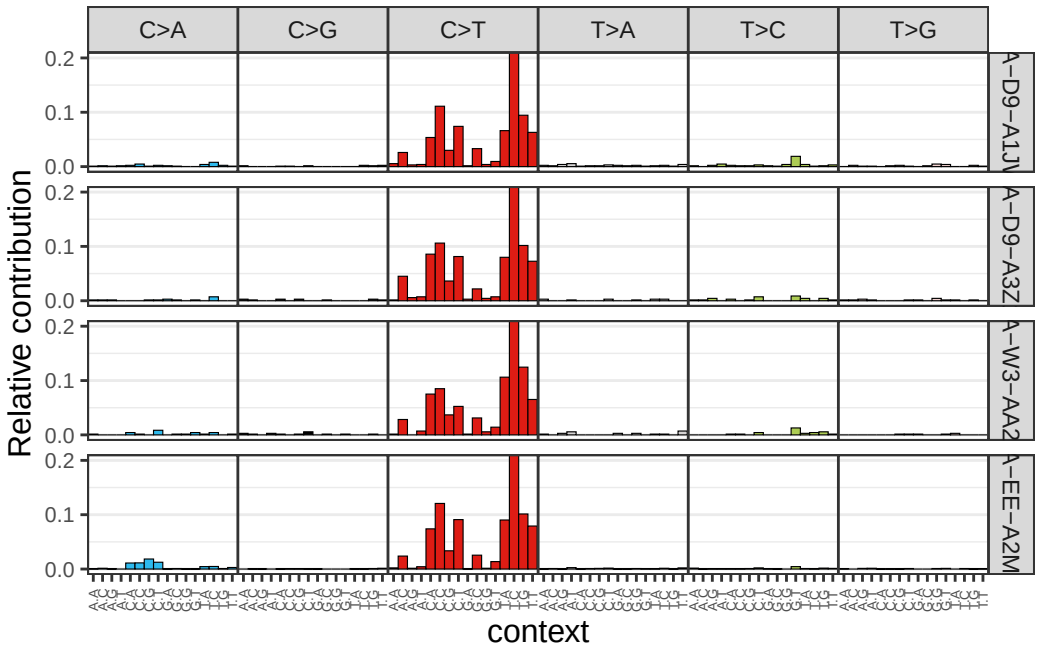
```
Loading required package: cluster
```

```
NMF - BioConductor layer [OK] | Shared memory capabilities [NO: windows] | Cores 3/4
```

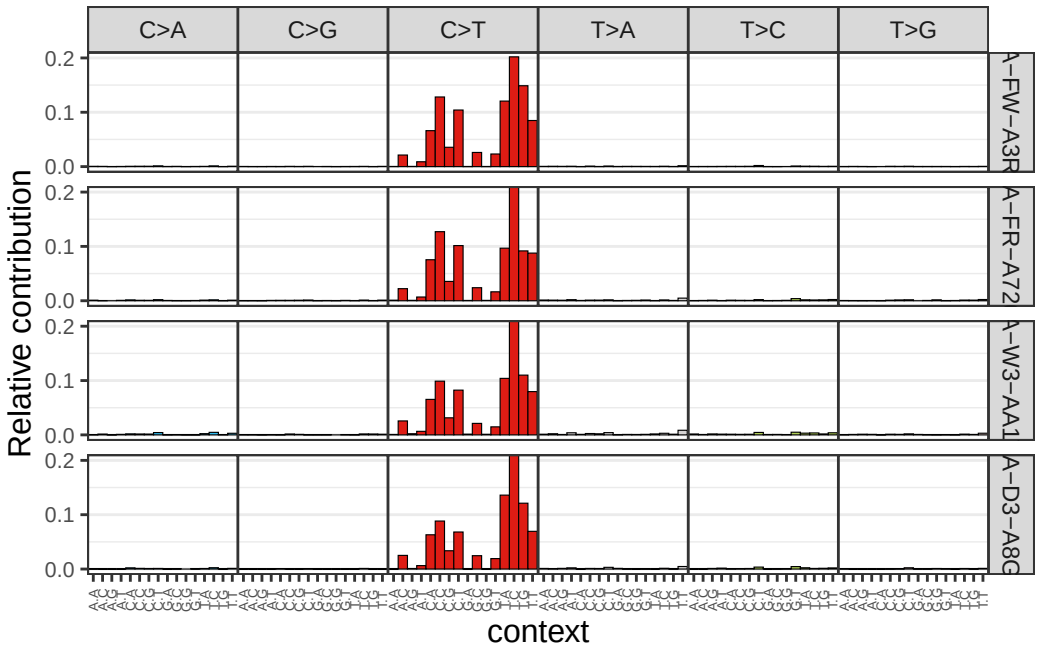
```
Attaching package: 'NMF'
```

```
The following object is masked from 'package:S4Vectors':

    nrun
```

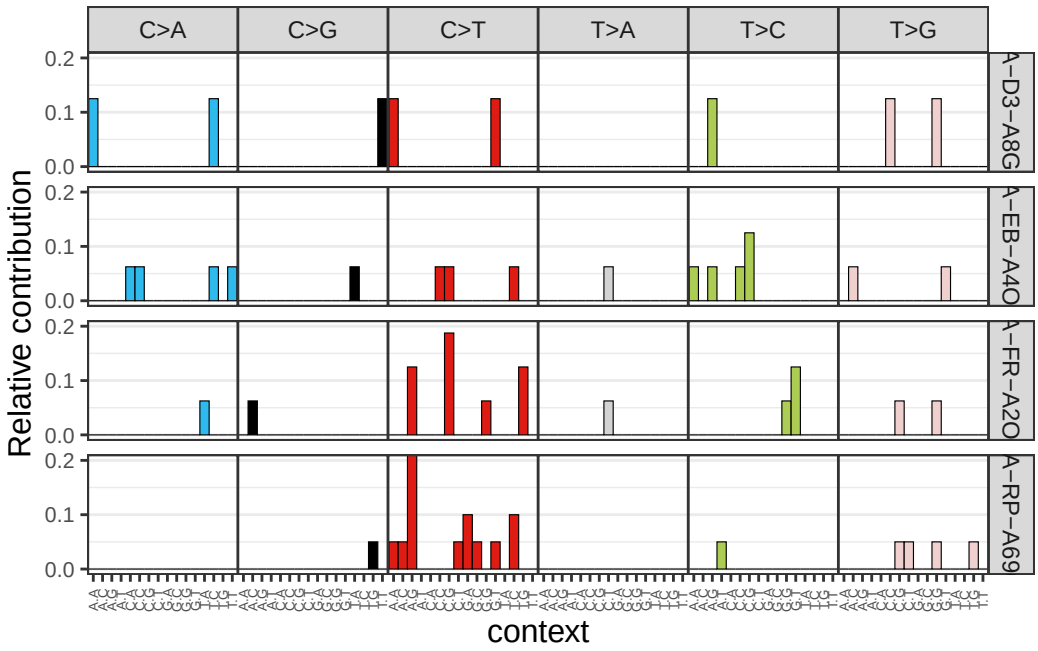
```
set.seed(11111)

samples_to_plot = sample(1:ncol(mm_mela),4)
plot_96_profile(mm_mela[,samples_to_plot], condensed = T)
```



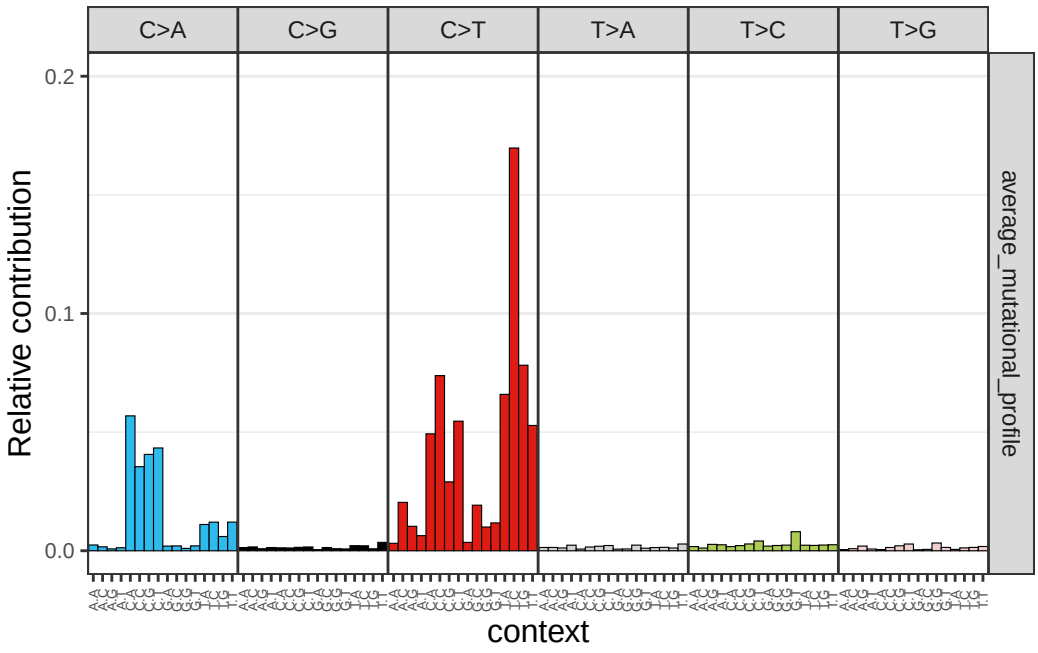

```
# Generate mutational profiles (top 4 mutated samples and top 4 less mutated)
mutations_in_samples = colSums(mm_mela)
mutations_in_samples = sort(mutations_in_samples, decreasing = T)
samples_to_plot = names(mutations_in_samples)[1:4]
plot_96_profile(mm_mela[,samples_to_plot], condensed = T)
```




```
mutations_in_samples = sort(mutations_in_samples, decreasing = F)
samples_to_plot = names(mutations_in_samples)[1:4]
plot_96_profile(mm_mela[,samples_to_plot], condensed = T)
```




```
# Generate average mutational profiles
relative_mutational_profile = apply(mm_mela, 2, prop.table) # obtained relative
                                                            # mutational matrix
average_mutational_profile = rowMeans(relative_mutational_profile)
average_mutational_profile = data.frame(average_mutational_profile)
plot_96_profile(average_mutational_profile, condensed = T)
```



Assigning reference mutational signatures

Leveraging the COSMIC mutational signatures, we will perform a mutational signature assignment analysis to quantify the number of mutations contributed by each signature to a given cancer sample and, therefore, decipher which mutational processes have been active in each individual tumor.

```
# Mutational signature assignment
cosmic_signatures = get_known_signatures(source = 'COSMIC_v3.2')
fit_res = fit_to_signatures(mm_mela, cosmic_signatures)

# Top contributing signatures
contributions = fit_res$contribution

top_contributing_signatures_abs = rowMeans(contributions)
top_contributing_signatures_abs = sort(top_contributing_signatures_abs,
                                       decreasing = T)[1:4]

## Top 4 contributing signatures (absolute values)
top_contributing_signatures_abs
```

```
  SBS7a      SBS7b      SBS38       SBS4
```

```
366.97614 340.91011 204.44450  99.49106
```

```
relative_contributions = apply(contributions,2,prop.table)
top_contributing_signatures_rel = rowMeans(relative_contributions)
top_contributing_signatures_rel = sort(top_contributing_signatures_rel,
                                       decreasing = T)[1:4]

## Top 4 contributing signatures (relative values)
top_contributing_signatures_rel
```

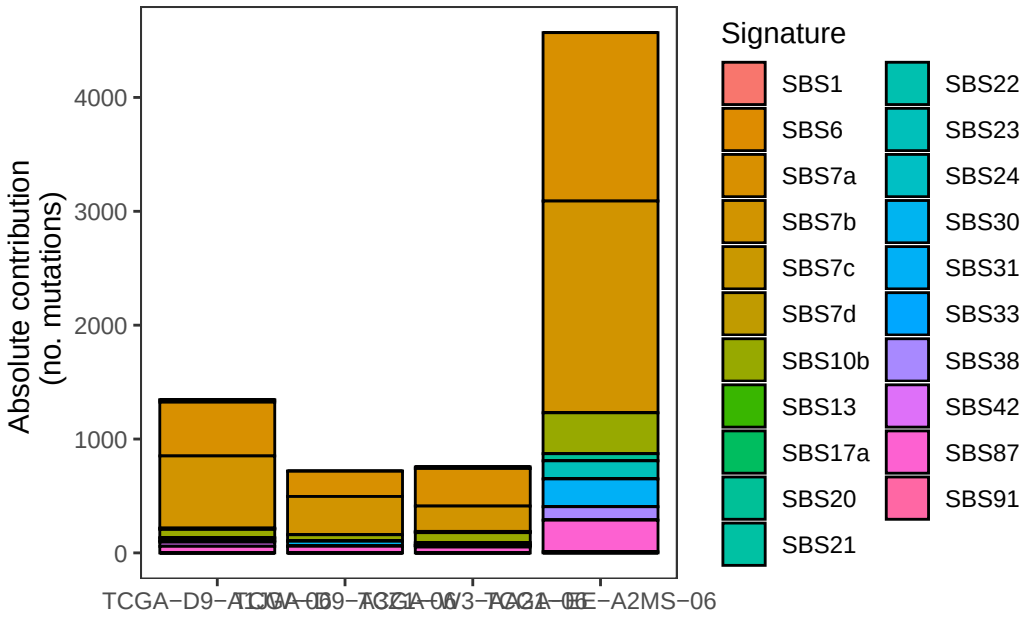
```
     SBS7b      SBS7a      SBS38       SBS4
0.26336351 0.26019455 0.10885595 0.07240978
```

```
# Mutational signature assignment strict
fit_res_strict = fit_to_signatures_strict(mm_mela, cosmic_signatures)
fit_res_strict = fit_res_strict$fit_res
contributions_strict = fit_res_strict$contribution
```

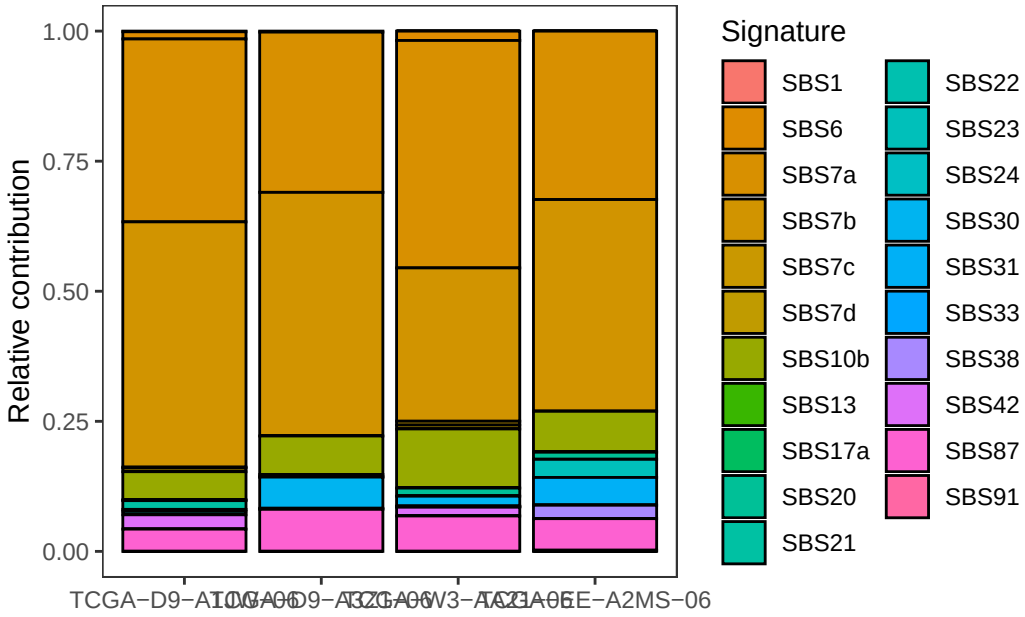
Visualizing mutational signature assignment results

To visualize the mutational signature assignment results, we will use the default visualizations available in the MutationalPatterns package. However, other visualizations are also present as part of maftools (please check the appropriate section in their vignette) or can be created using ggplot2 and the contributions output matrix from the mutational signature assignment analysis (contributions or contributions_strict).

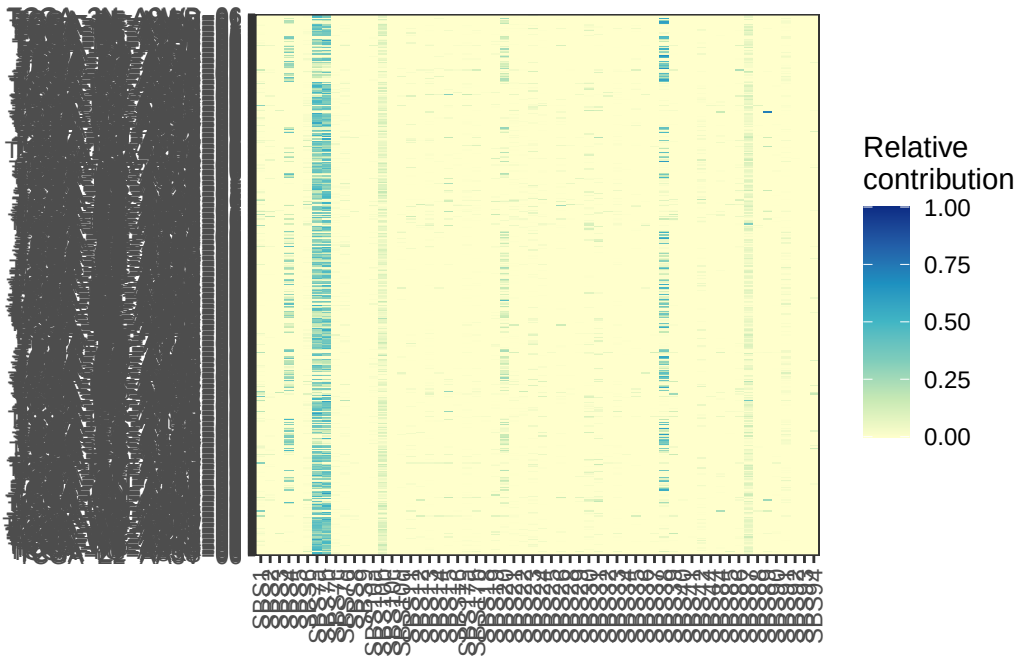
```
# Visualization of signature assignment results (fit_to_signatures)
set.seed(11111)
samples_to_plot = sample(1:ncol(mm_mela),4)

plot_contribution(contributions[,samples_to_plot], mode = "absolute")
```



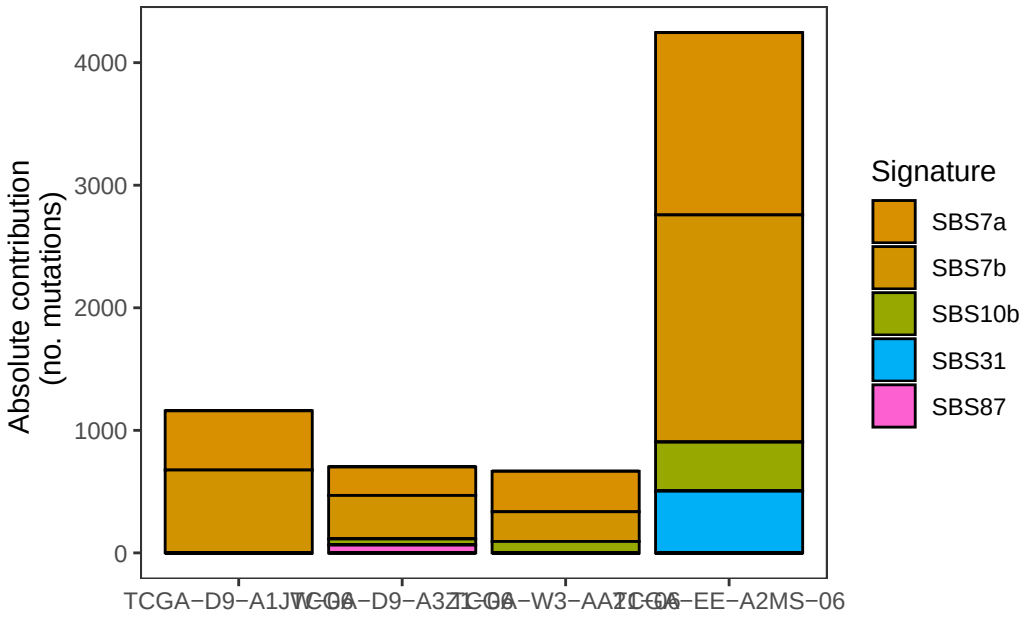

```
plot_contribution(contributions[,samples_to_plot], mode = "relative")
```



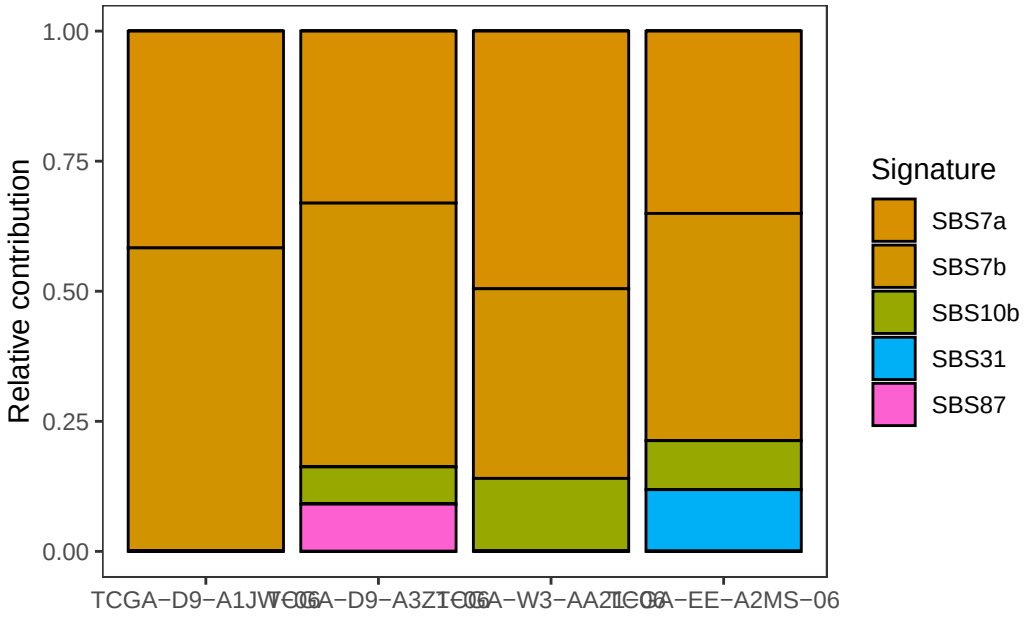
```
plot_contribution_heatmap(contributions, cluster_samples = F)
```



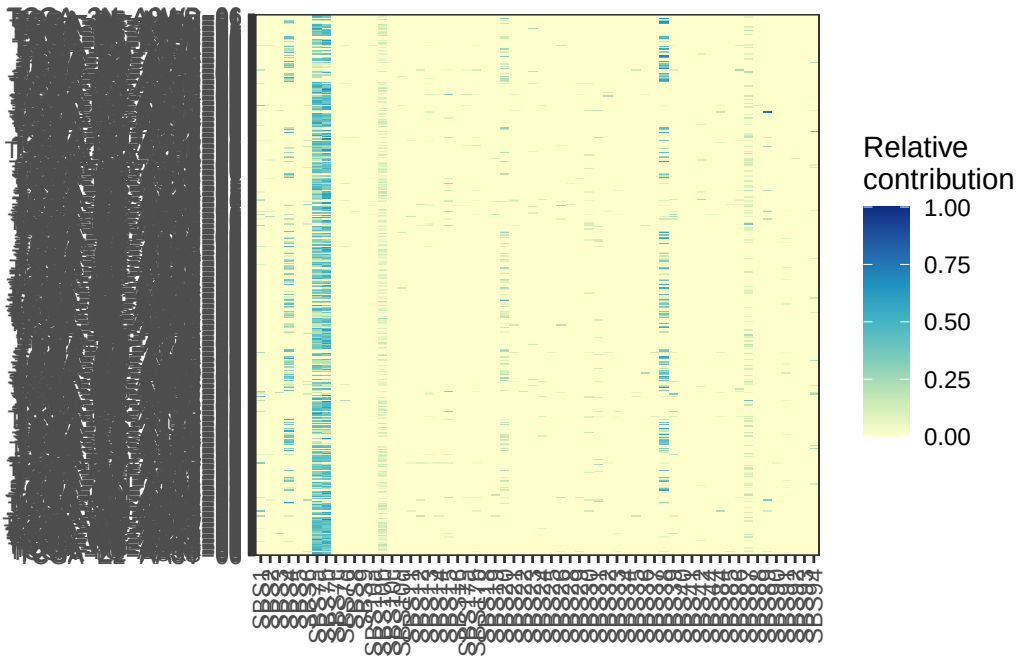

```
# Visualization of signature assignment results (strict)
plot_contribution(contributions_strict[,samples_to_plot], mode = "absolute")
```




```
plot_contribution(contributions_strict[,samples_to_plot], mode = "relative")
```

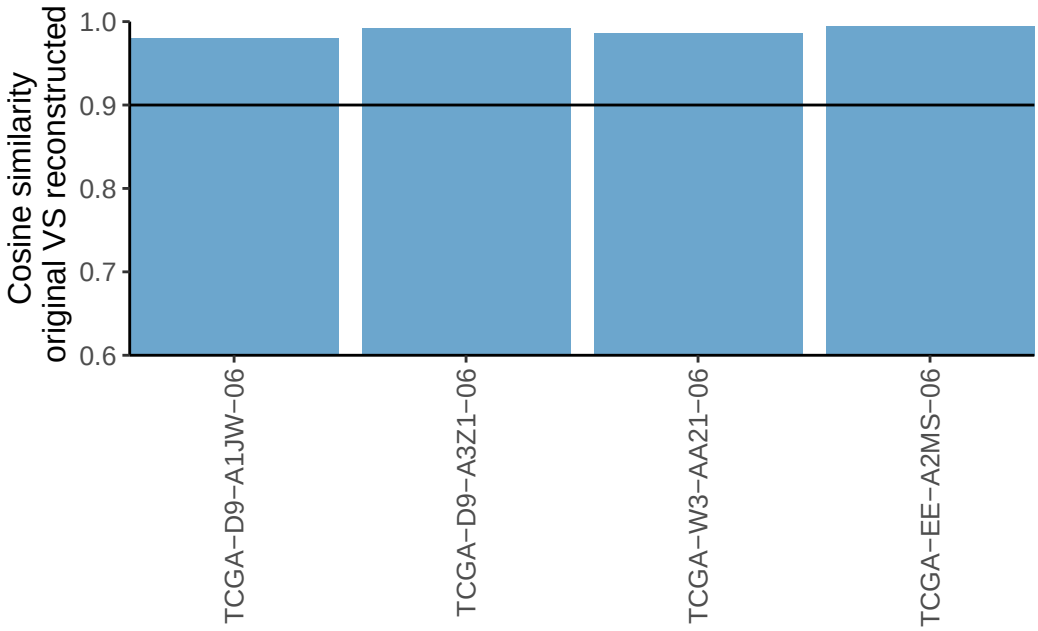


```
plot_contribution_heatmap(contributions_strict, cluster_samples = F)
```

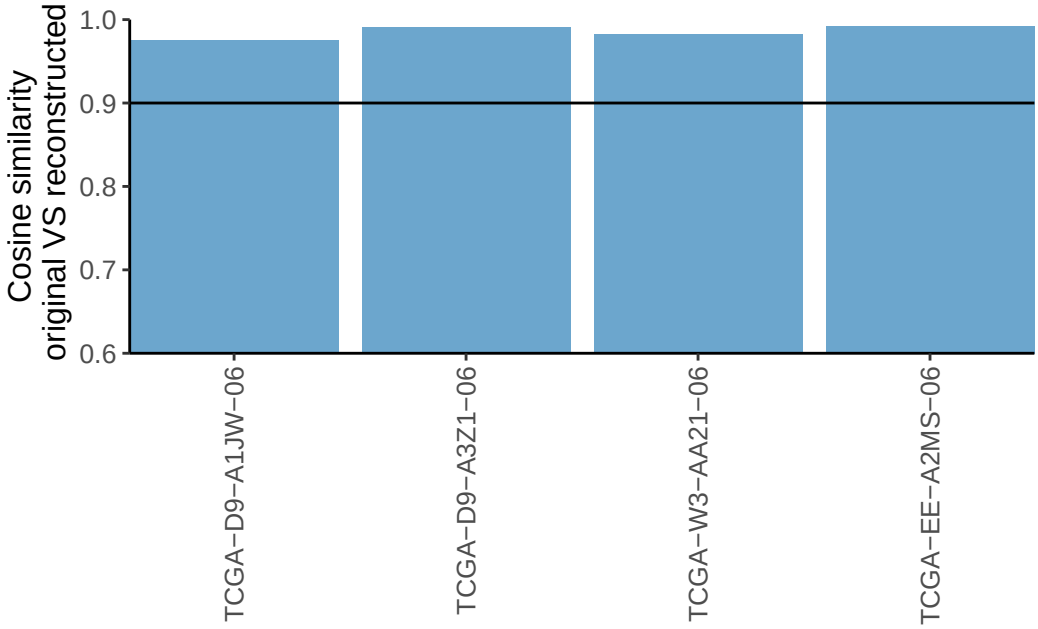


To check the cosine similarity of the reconstruction for some specific samples, we can use the following visualization from the MutationalPatterns R package.

```
# Cosine similarity reconstruction vs. original mutational profile (fit_to_signatures)
set.seed(11111)
samples_to_plot = sample(1:ncol(mm_mela),4)

plot_original_vs_reconstructed(mm_mela[,samples_to_plot],
                               fit_res$reconstructed[,samples_to_plot],
                               y_intercept = 0.90)
```




```
# Cosine similarity reconstruction vs. original mutational profile (strict)
plot_original_vs_reconstructed(mm_mela[,samples_to_plot],
                               fit_res_strict$reconstructed[,samples_to_plot],
                               y_intercept = 0.90)
```



Q. Which is the etiology of the top absolute contributing signature for liver cancer? Aristolochic acid exposure

Q. Which is the most prominent mutational context for the top contributing signature in skin cancer? C>T

Q. The etiology of the top contributing signature for lung cancer corresponds to an endogenous cellular mechanism. False

Q. SBS4 is one of the most common signatures found in lung cancer and is associated with tobacco smoking. True

Q. SBS7d is one of the most common signatures in skin cancer and is associated with UV light exposure and high numbers of C>T mutations False