Working example of MOSS' application on pan-cancer multi-omic data.

Contents

Introduction.

In this document we show an application of MOSS on a large data set consisting of 33 cancer types across 5008 samples and and 60112 features (expression of 20319 genes **-GE-**, methylation at 28241 CpG islands **-METH-**, and copy number variant intensity for 11552 genes **-CNV-**), from The Cancer Genome Atlas (TCGA) data set (Network 2012). For a description of the data edition and quality controls, please refer to (González-Reymúndez and Vázquez 2020). The whole example takes ~53 minutes on a Dell desktop computer (XPS 8900, x64, 06B8, Intel i7-67000 CPU), running under Windows 10 (see session info at the end of the document). To obtain the visual results in the following sections, packages *ggplot2* (Wickham 2009) and *ComplexHeatmaps* (Gu, Eils, and Schlesner 2016) must be installeld.

Retrieving and loading pan-cancer data from repository.

The following lines load MOSS and additional packages for visualizing results and handling FBM matrices.

```
require(bigstatsr)
require(ggplot2)
require(ggpmisc)
library(MOSS)
```

The following code assumes that you have downloaded the following files from here

- GE.RData
- METH.RData
- CNV.RData

and saved them in your current folder.

```
#Loading omic data.
load(file = "GE.RData")
load(file = "METH.RData")
load(file = "CNV.RData")

#Creating a list with omic blocks.
omic_blocks <- list("GE" = GE,
                    "METH" = METH,
                    "CNV"= CNV)
```

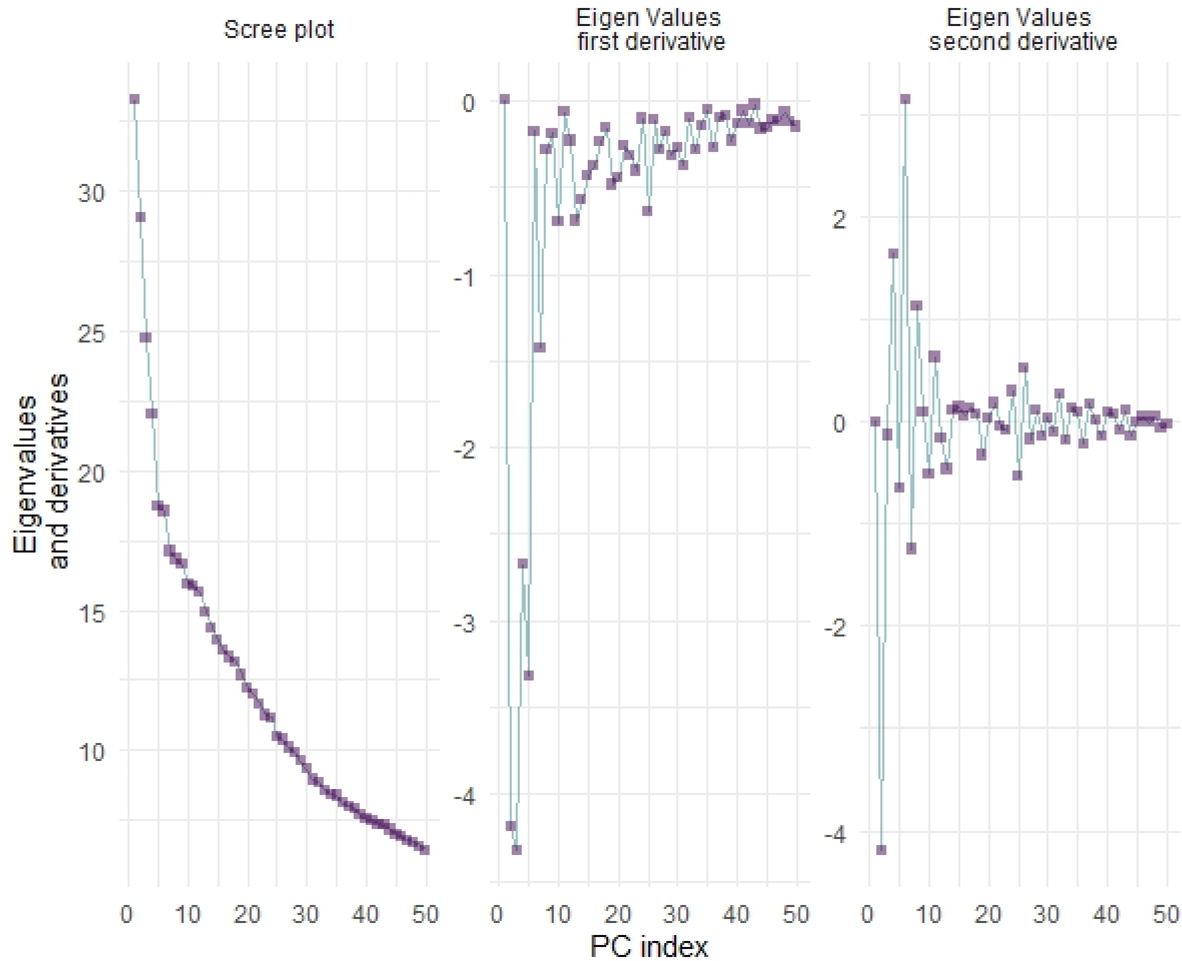
Omic integration of pan-cancer omic data via sparse principal components.

The following code shows how to run a sparse principal components analysis. By setting argument "exact.dg=FALSE", we can explore different degrees of sparsity without a direct correspondence to number of features. This allows Elastic Net to select a potentially larger number of non_zero elements, larger than the specified degree of sparsity. In this way, we can use a less dense grid to tune the degree of sparsity. In this example, however, we will work with a small grid of values ranging from 1 to 100.

```
set.seed(347)
out <- MOSS::moss(data.blocks = omic_blocks,
            method = 'pca',
            scale.arg  = TRUE,
            norm.arg  = TRUE,
            K.X = 50,
            tSNE = list(perp=100,
                        n.iter=1e3,
                        n.samples=1),
            clus.lab = MOSS::metdat(x = rownames(GE),
                                    i = 1),
            nu.v = 1:100,
            exact.dg = FALSE,
            use.fbm = TRUE,
            alpha.v = 0.5,
            plot = TRUE)
```

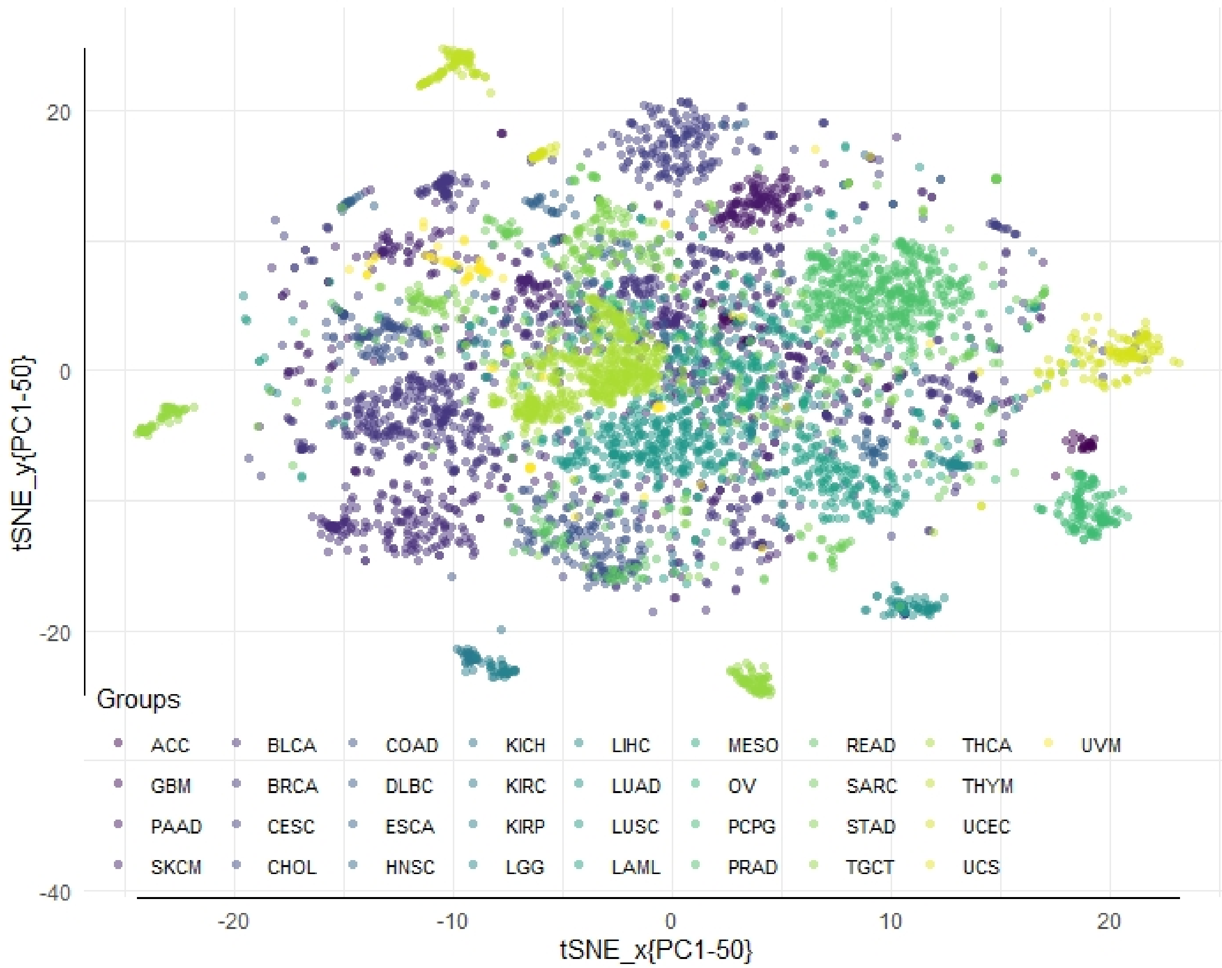
The following code returns a plot of eigenvalues, together with their first and second derivative across PC index:

```
#Showing scree plot.
out$scree_plot
```



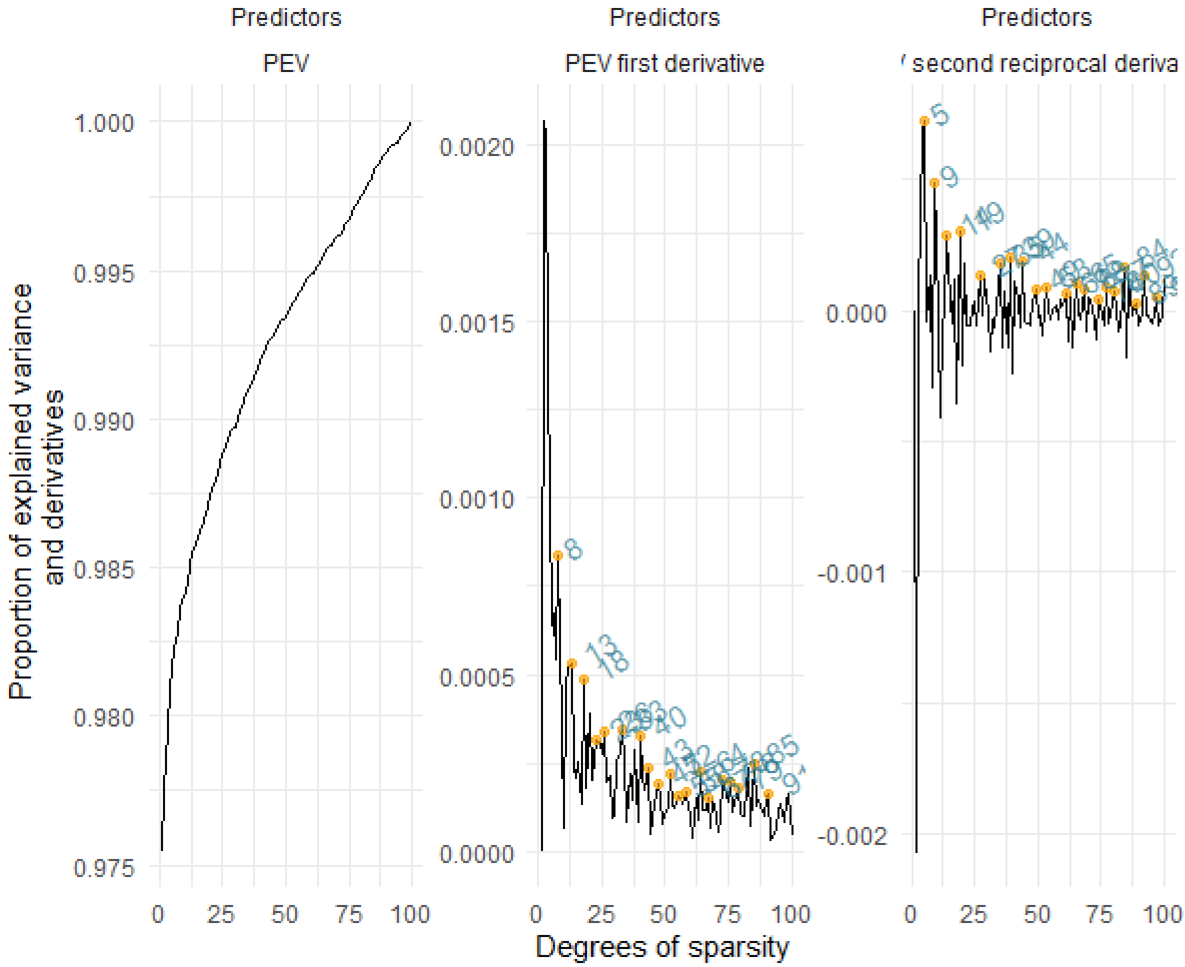
A tSNE map:

```
out$tSNE_plot
```



A plot with the marginal variation in *PEV* across degrees of sparsity at features levels is presented bellow. The numbers in the peaks of first and second-reciprocal derivatives show the point of rapid and/or accelerated changes. The minimum between the global maximum in the trajectory of first and second derivative, respectively, is automatically chosen as 'optimal':

```
out$tun_dgSpar_plot
```



Assessing pan-cancer associations between gene expression and copy number variants.

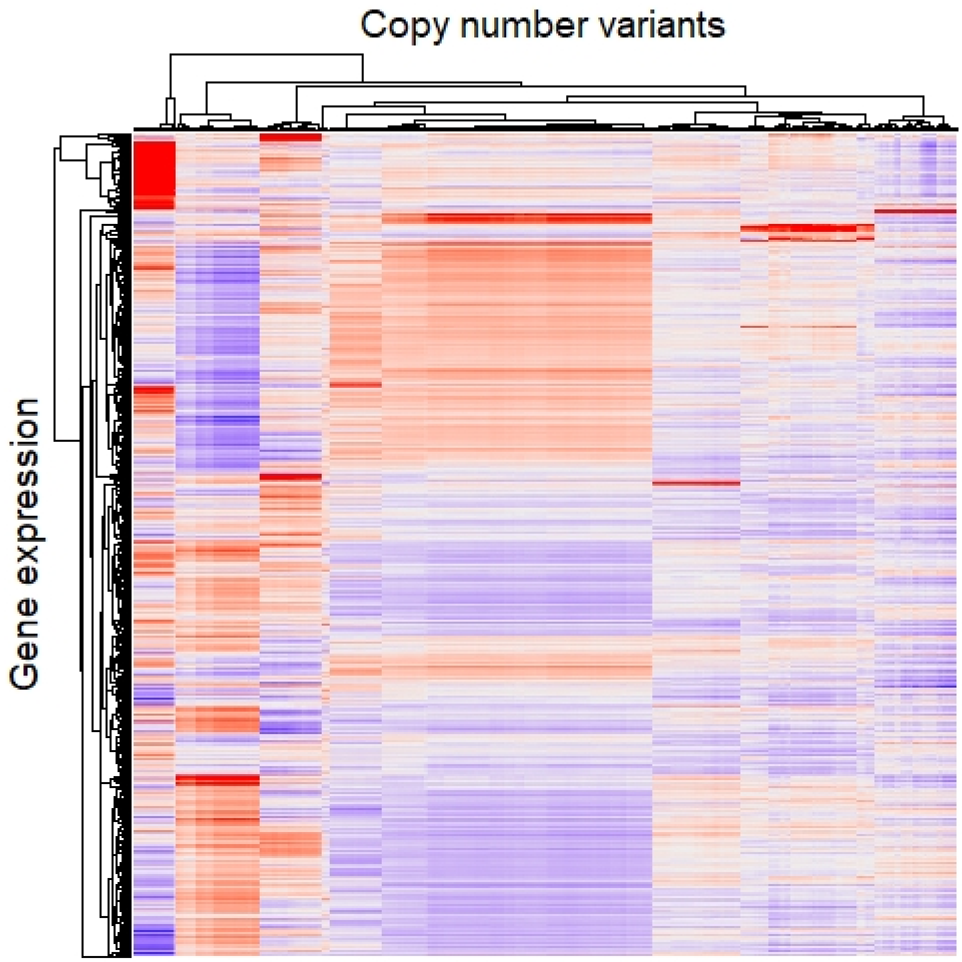
The code bellow shows how to fit a sparse low rank regression model between **GE** and **CNV**. Notice that, in this case, the number of latent factors $K.X$ will be used to approximate the **CNV** data so it is easy to compute the inverses needed to obtain B. Ideally, the user would want a higher value to assure the approximation is good enough. The value of $K.Y$, on the other hand, will control how many eigenvectors will be used to approximate **B**. In this case, the left eigenvectors represent **CNV**, and the right ones, **GE**. Sparsity in these vectors can then be used to select what combination of genes and CNVs have effects different from zero.

```
set.seed(seed = 347)
out2 <- moss(data.blocks = omic_blocks[-2],
```

```
            resp.block = 1,
            method = 'lrr',
            scale.arg = TRUE,
            norm.arg = TRUE,
            K.X = 50,
            K.Y = 2,
            nu.v = 100,
            nu.u = 100,
            exact.dg=TRUE,
            alpha.v = 0.5,
            alpha.u = 0.5,
            use.fbm = TRUE,
            plot = TRUE)

B.sub <- t(x = out$B[which(x = rowMeans(x = out2$sparse$u != 0) > 0),
which(rowMeans(out2$sparse$v != 0) > 0)])

h <- ComplexHeatmap::Heatmap(matrix = B.sub,
                        column_title = "Copy number variants",
                        row_title = "Gene expression",
                        show_column_names = FALSE,
                        show_row_names = FALSE,
                        show_heatmap_legend = FALSE)
```



Session information.

```
sessionInfo()

R version 3.6.2 (2019-12-12)
Platform: x86_64-w64-mingw32/x64 (64-bit)
Running under: Windows >= 8 x64 (build 9200)

Matrix products: default

locale:
[1] LC_COLLATE=English_United States.1252  LC_CTYPE=English_United States.1252
[3] LC_MONETARY=English_United States.1252 LC_NUMERIC=C
[5] LC_TIME=English_United States.1252

attached base packages:
[1] stats     graphics  grDevices utils     datasets  methods   base
```

```
other attached packages:
[1] ggpubr_0.2.4    magrittr_1.5    MOSS_0.1.0      ggplot2_3.2.1   bigstatsr_1.1.4

testthat_2.3.1

loaded via a namespace (and not attached):
 [1] fs_1.3.1            flock_0.7           usethis_1.5.1       devtools_2.2.1
 [5] doParallel_1.0.15   RColorBrewer_1.1-2  rprojroot_1.3-2     tools_3.6.2
 [9] backports_1.1.5     R6_2.4.1            lazyeval_0.2.2      colorspace_1.4-1
[13] GetoptLong_0.1.8    withr_2.1.2         tidyselect_0.2.5    gridExtra_2.3
[17] prettyunits_1.1.1   processx_3.4.1      compiler_3.6.2      bigparallelr_0.2.3
[21] cli_2.0.1           xml2_1.2.2          desc_1.2.0          labeling_0.3
[25] scales_1.1.0        callr_3.4.1         stringr_1.4.0       digest_0.6.23
[29] dbscan_1.1-5        rmarkdown_2.1       htmltools_0.4.0     pkgconfig_2.0.3
[33] sessioninfo_1.1.1   rlang_0.4.3         GlobalOptions_0.1.1 ggthemes_4.2.0
[37] rstudioapi_0.10     shape_1.4.4         farver_2.0.3        dplyr_0.8.3
[41] Matrix_1.2-18       Rcpp_1.0.3          munsell_0.5.0       fansi_0.4.1
[45] viridis_0.5.1       lifecycle_0.1.0     stringi_1.4.3       yaml_2.2.1
[49] ggpmisc_0.3.3       pkgbuild_1.0.6      Rtsne_0.15          plyr_1.8.5
[53] grid_3.6.2          parallel_3.6.2      crayon_1.3.4        lattice_0.20-38
[57] cowplot_1.0.0       circlize_0.4.8      knitr_1.27          ComplexHeatmap_2.2.0
[61] ps_1.3.0            pillar_1.4.3        rjson_0.2.20        ggsignif_0.6.0
[65] reshape2_1.4.3      codetools_0.2-16    pkgload_1.0.2       bigassertr_0.1.2
[69] glue_1.3.1          evaluate_0.14       remotes_2.1.0       splus2R_1.2-2
[73] png_0.1-7           foreach_1.4.7       gtable_0.3.0        purrr_0.3.3
[77] clue_0.3-57         assertthat_0.2.1    xfun_0.12           RSpectra_0.16-0
[81] roxygen2_7.0.2      viridisLite_0.3.0   tibble_2.1.3        iterators_1.0.12
[85] memoise_1.1.0       cluster_2.1.0       ellipsis_0.3.0
```

References

González-Reymúndez, Agustín, and Ana I. Vázquez. 2020. "Multi-omic signatures identify pan-cancer classes of tumors beyond tissue of origin." *Scientific Reports* 10 (1). Nature Publishing Group: 8341. doi:10.1038/s41598-020-65119-5.

Gu, Zuguang, Roland Eils, and Matthias Schlesner. 2016. "Complex heatmaps reveal patterns and correlations in multidimensional genomic data." *Bioinformatics* 32 (18). Oxford University Press: 2847–9. doi:10.1093/bioinformatics/btw313.

Network, The Cancer Genome Atlas Research. 2012. "Comprehensive genomic characterization of squamous cell lung cancers." *Nature* 489 (7417). Nature Publishing Group: 519–25. doi:10.1038/nature11404.

Wickham, Hadley. 2009. *Ggplot2 : elegant graphics for data analysis*. Springer.