

## ShinyArchR.UiO: User-friendly, integrative and open-source tool for visualisation of single-cell ATAC-seq data using ArchR

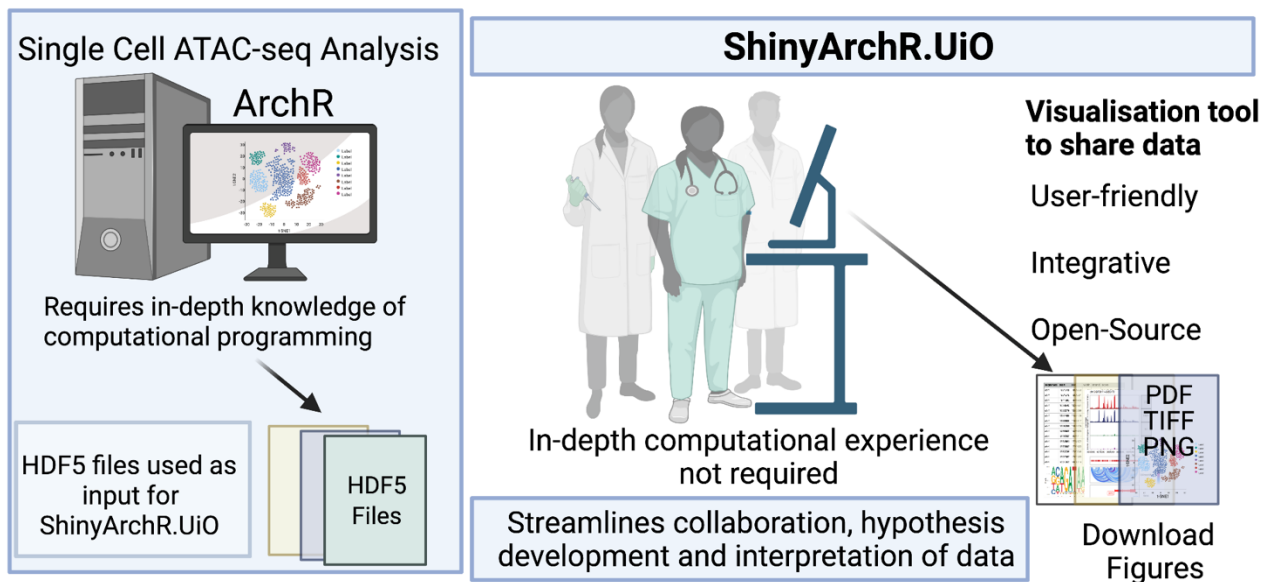
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## Supplementary Information

### Graphical abstract



**Fig. S1. An overview of the ShinyArchR.UiO application.** Illustration is generated in Biorender.com.

## SI (1)

The Analysis of Regulatory Chromatin in R (ArchR) package is used for analysis of single-cell chromatin accessibility data and requires high-performance computing environments (Granja *et al.*, 2021). ArchR software toolkit can be utilized for single cell assay for transposase-accessible chromatin with high throughput sequencing (scATAC-seq) data obtained from multiple scATAC-seq implementations, including the 10x Genomics Chromium system. The ArchR software stores all data (i.e., metadata, data matrices, and accessible fragments) associated with each sample in Arrow files. ShinyArchR.UiO requires HDF5 file formatted Arrow files stored on a disk or server, which greatly reduces the memory footprint for obtaining different plots from massive-scale single-cell chromatin accessibility data.

### Input Data for ArchR processing

ArchR compatible with a wide range of input formats, including fragment files or BAM files, is also capable of reading scATAC-seq data. scATAC-seq fragment files contain the corresponding cell ID for each scATAC-seq fragment, sorted into tabix files. BAM files contain information about each scATAC-seq fragment, raw sequence, cellular barcode ID, and other information in tabularized format. The preprocessing pipeline defines what input format is used. The 10x Genomics Cell Ranger software, for example, returns fragment files, while sci-ATAC-seq applications use BAM files. To read fragment files, ArchR uses “scanTabix” and it uses “scanBam” to read BAM files. To support the input process, input data chunks are converted to a compressed table-based representation of fragments, which includes the fragment chromosome, offset-adjusted start and end positions, as well as the cellular barcode ID. To preserve memory consumption while maintaining quick access to chunks, chunks are stored in a temporary HDF5-formatted file. The final step involves reading, organizing, and rewriting all portions of each chromosome to an Arrow file within a single HDF5 group referred to as a “fragment”. In this way, ArchR is able to handle extremely large input files efficiently and with very low memory usage, allowing it to fully utilize parallel processing.

Down sampled demo data for ShinyArchR.UiO: We utilized the tutorial data downloaded using the `getTutorialData()` function. The down sampled tutorial data of hematopoietic cells approximately 0.5 GB in size is used for the analysis with the steps described in full manual of ArchR (<https://www.archrproject.com/bookdown/index.html>).

The rmarkdown Rscript used for the down sampled tutorial data is available at:  
[https://github.com/EskelandLab/ShinyArchRUiO/blob/main/example\\_data/archR-example.Rmd](https://github.com/EskelandLab/ShinyArchRUiO/blob/main/example_data/archR-example.Rmd)

### Description of ShinyArchR.UiO

The ShinyArchR.UiO application has six tabs as shown in Figure S2.

In **scClusters**, we present with five different options for comparison of multi-dimensional reduction plot UMAPs:

- I. Sample based on original identities of the cells
- II. Clusters showing identified cell “communities” or scATAC-seq identified populations of cells using the `addClusters` function of ArchR.
- III. Unconstrained UMAP shows scATAC-seq with scRNA-seq integration using a complete agnostic approach that takes all of the cells of the scATAC-seq experiment and attempts to align them to any of the cells in the scRNA-seq experiment.
- IV. Constrained integration shows integration by overlaying the scRNA-seq cell types on scATAC-seq data modality.

- V. Remapped UMAP shows new reclassified cluster labels/communities on scATAC-seq data after constrained integration with scRNA-seq.

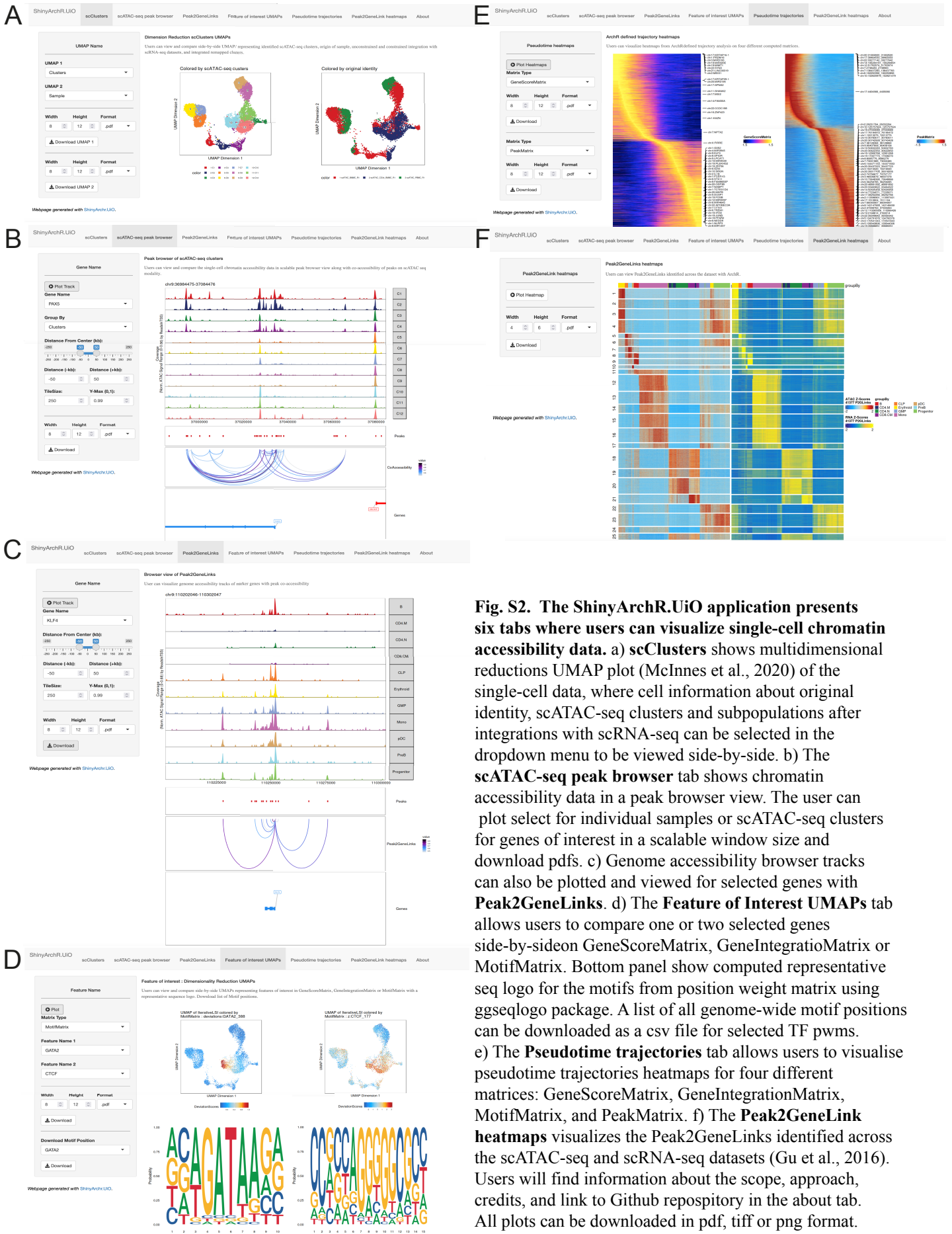
In the **scATAC-seq peak browser**, the user can view unique scATAC-seq accessibility tracks in a selected gene locus for individual scATAC-seq clusters or input samples. The user can visualize peak regions overlaid on browser tracks to the feature's parameter in the *plotBrowserTrack()* function along with co-accessibility of scATAC-seq peaks.

The **Peak2GeneLinks** tab shows tracks for scRNA-seq data integrated with scATAC-seq using constrained remap clusters/communities correlating peak accessibility with gene expression at a selected gene locus. The co-accessibility arcs connects the peaks with a single base of TSS for the gene.

**Feature of interest** present UMAP plots for GeneScoreMatrix, GeneIntegrationMatrix or MotifMatrix. Gene score is a measure of how highly expressed a gene will be based on the accessibility of regulatory elements in the vicinity of the gene (100kb up or downstream of the selected gene). GeneIntegrationMatrix align scATAC-seq cells with scRNA-seq cells by correlating GeneScoreMatrix with gene expression matrix. The users can also view representative seqlogo of motifs present in MotifMatrix that are identified in the dataset and download genome-wide list of motif positions in a csv file.

**Pseudotime trajectory heatmaps** are shown for Motif, GeneScore, GeneIntegration, and peak accessibility by passing the corresponding matrix. ArchR plots changes in TF deviations, gene scores, or integrated gene expression across pseudo-time to identify regulators or regulatory elements that are dynamic throughout the trajectories.

**Peak2GeneLinks heatmaps** shows correspondence of all peak-to-gene links with two side-by-side two heatmaps: scATAC-seq data and scRNA-seq data.



**Fig. S2. The ShinyArchR.UiO application presents six tabs where users can visualize single-cell chromatin accessibility data.** a) **scClusters** shows multidimensional reductions UMAP plot (McInnes et al., 2020) of the single-cell data, where cell information about original identity, scATAC-seq clusters and subpopulations after integrations with scRNA-seq can be selected in the dropdown menu to be viewed side-by-side. b) The **scATAC-seq peak browser** tab shows chromatin accessibility data in a peak browser view. The user can plot select for individual samples or scATAC-seq clusters for genes of interest in a scalable window size and download pdfs. c) Genome accessibility browser tracks can also be plotted and viewed for selected genes with **Peak2GeneLinks**. d) The **Feature of Interest UMAPs** tab allows users to compare one or two selected genes side-by-side on GeneScoreMatrix, GeneIntegrationMatrix or MotifMatrix. Bottom panel show computed representative seq logo for the motifs from position weight matrix using ggseqlogo package. A list of all genome-wide motif positions can be downloaded as a csv file for selected TF pwms. e) The **Pseudotime trajectories** tab allows users to visualise pseudotime trajectories heatmaps for four different matrices: GeneScoreMatrix, GeneIntegrationMatrix, MotifMatrix, and PeakMatrix. f) The **Peak2GeneLink heatmaps** visualizes the Peak2GeneLinks identified across the scATAC-seq and scRNA-seq datasets (Gu et al., 2016). Users will find information about the scope, approach, credits, and link to Github repository in the about tab. All plots can be downloaded in pdf, tiff or png format.

## SI (2)

### A detailed tutorial for setup

Single-cell chromatin accessibility data can be processed and analysed using ArchR (Granja *et al.*, 2021). The analysis can be performed using standard ArchR settings on a test dataset of hematopoietic cells or can be applied on user's own datasets. The project folders saved can be used as input for visualization of data by ShinyArchR.UiO: 1) Project-folder1: Cross-platform linkage of scATAC-seq with scRNA-seq analysis of ArchR analysis., 2) Project-folder2: Labelling scATAC-seq clusters with scRNA-seq information and 3) Project-folder3: Pseudotime trajectory analysis. Genome-wide maps of open chromatin regions of multiple pre-processed scATAC-seq datasets can result in a large amount of data, therefore, we highly recommend evaluating the storage capacity for hosting purposes.

## SI (3)

### Please follow the steps for ShinyArchR.UiO setup on the local system

1. Download ShinyArchR.UiO or git clone at <https://Github.com/EskelandLab/ShinyArchRUiO>.
2. Provide the path to the saved folders in global.R file

```
savedArchRProject1 <- loadArchRProject("path to project-folder1/")
savedArchRProject2 <- loadArchRProject("path to project-folder2/")
savedArchRProject3 <- loadArchRProject("path to project-folder3/")
```
3. Provide trajectory name as given in your analysis in getTrajectory function in chunk "Add Metadata of Trajectory" in global.R
4. Open app.R in RStudio or on R graphical User Interface, press RunApp to run ShinyArchR.UiO.
5. Setting ShinyArchR.UiO from the terminal.

Run the command

```
R -e "shiny::runApp('~/.ShinyArchR.UiO', launch.browser = TRUE)"
```

The global.R script will install required packages for the first time automatically.

Alternatively, the user can install packages manually using these command.

```
#Installing required packages
install.packages(c("devtools", "shiny", "Seurat",
"magick", "hexbin", "shinybusy", "gridExtra", "grid", "shinycssloaders")

#Install ArchR

devtools::install_github("GreenleafLab/ArchR", ref="master", repos=BiocManager::re
positories())

#Install ArchR dependencies
library(ArchR)
ArchR::installExtraPackages()

## Now load or install&load all
package.check <- lapply(
  packages,
  FUN <- function(x) {
    if (!require(x, character.only = TRUE)) {
      install.packages(x, dependencies = TRUE),
      library(x, character.only = TRUE)
    }
  }
)
options(repos = BiocManager::repositories())
```

## Reference Genomes

ShinyArchR.UiO supports visualization of additional genome annotations and custom annotations. In our demo version, we utilized data aligned using hg19 genome version. User can select “hg19”, “hg38”, “mm9”, and “mm10” genomes by using `addArchRGenome()` function for these genomes.

Alternatively, the user can analyze data for any species by custom genome and gene annotations using the `createGeneAnnotation()` and `createGenomeAnnotation()` functions of ArchR. The project folder saved after the analysis can then be visualized after ShinyArchR.UiO setup. The reference genome annotations used should be consistent with the scATAC-seq analysis as well as ShinyArchR.UiO.

## SI (4)

### System requirements

ArchR provides higher performance and lower memory consumption than any other available scATAC-seq tool due to its optimized data structures and parallelization methods (Granja *et al.*, 2021). The ArchR package is designed to be used on Unix-based laptop computers and allows the user to do ad hoc analysis and visualize results for moderate-size experiments (less than 100,000 cells). ArchR enables analysis of more than 1.2 million cells in under 8 hours on small scale server infrastructure utilizing local resources (8 cores, 32 GB RAM, and a personal MacBook Pro; 8 cores, 32 GB RAM laptop, with an external USB hard drive). The ability to export plots and projects to a flexible format that can be downloaded and used after generation on a server for higher cell counts or users who prefer server-based analysis (Granja *et al.*, 2021). The data generated during ArchR analysis can efficiently be visualized using ShinyArchR.UiO for hundreds of thousands of cells without large amounts of memory or computing power, meeting experimental needs that are as fast as commercial platforms, such as the 10x Genomics Chromium system.

The datasets with higher cell counts require more memory footprint and can be easily hosted on local server as for our demo instance of <https://cancell.medisin.uio.no/shinyarchr.UiO>. We have tested a down sampled tutorial data of ArchR constituted of 10250 cells and our inhouse data ranging from 20k cells, 30k cells to 70k cells on a MacOS 2 GHz Quad-Core Intel Core i5 processor, 16 GB RAM and intel Iris Plus Graphics 1536 MB graphics card and on ubuntu-20.04.2.0-desktop-amd64.iso. 11 GB on VirtualBox 5.2.28. The ShinyArchR.UiO setup takes about 5, 8, 12, and 20 minutes for 10k , 20k, 30k and 70k cells, respectively after installation of the packages. Using MacOS 2.4 GHz 8-Core Intel Core i9, 32 GB RAM this takes 2, 4, 5, and 10 minutes respectively for initial setup. ShinyArchR.UiO have the same memory footprint as ArchR and scales well with the larger datasets.

## ShinyArchR.UiO Instance specifications

```
RHEL system and SELinux, nginx and SSL
Model name:      Intel(R) Xeon(R) Platinum 8168 CPU @ 2.70GHz
Architecture:    x86_64
CPU op-mode(s):  32-bit, 64-bit
CPU(s):          4
CPU family:      6
RAM: 31Gi
Icon name: computer-vm
Virtualization: vmware
Operating System: Red Hat Enterprise Linux 8.4 (Ootpa)
CPE OS Name: cpe:/o:redhat:enterprise_linux:8.4:GA
Kernel: Linux 4.18.0-305.el8.x86_64
```

R version 4.0.0 and over is recommended.

Please ensure ArchR (Granja *et al.*, 2021), Seurat (Stuart *et al.*, 2019; Satija *et al.*, 2015), Magic (Dijk *et al.*, 2018), ggplot2 (Wickham, 2009), rtracklayer (Lawrence *et al.*, 2009) and other dependencies required are installed and loaded properly in the R environment. More details about required packages and their dependencies (Table S1) can be found in the session information at our Github repository (<https://Github.com/EskelandLab/ShinyArchRUiO>).

Users can raise an Github issue on the ShinyArchR.UiO GitHub repository if they face any errors or issues related to set up.

## SI (5)

### Frequently Asked Questions

- Q: How much memory/storage space does ShinyArchR.UiO and the shiny app consume?
  - a. The shiny app itself is not memory intensive and is meant to be a heavy-duty app where multiple users can access the app at the same time. The memory required is dependent on the size of saved project files from ArchR.
  - b. Simultaneously, ArchR employs Arrow files, in an HDF5 file format, to store massive single-cell chromatin accessibility data on disk.
  - c. Initial setup of ShinyArchR.UiO is computation intensive. This includes steps for computing marker genes for Peak2GeneLinks analysis and other plots. A typical laptop with 4GB RAM can handle datasets from estimated 10-20k cells while 16GB RAM machines can handle around 30k-100k cells.
- Q: Does ShinyArchR.UiO support performance gain across different operating systems?
  - a. ShinyArchR.UiO is a tool to visualize scATAC-seq data analysed by the ArchR software, which is predominantly optimized for Unix-based systems such as Linux and MacOS. ShinyArchR.UiO is tested and should work on Windows. However, users cannot take advantage of parallelization on Windows.

**Table S1** Packages and other dependencies used in ShinyArchR.UiO

Package	Version	Reference
<b>abind</b>	1.4.5	Tony Plate and Richard Heiberger (2016). abind: Combine Multidimensional Arrays. R package version 1.4-5. <a href="https://CRAN.R-project.org/package=abind">https://CRAN.R-project.org/package=abind</a>
<b>annotate</b>	1.68.0	R. Gentleman (2020). annotate: Annotation for microarrays. R package version 1.68.0.
<b>AnnotationDbi</b>	1.52.0	H Pagès, Marc Carlson, Seth Falcon and Nianhua Li (2020). AnnotationDbi: Manipulation of SQLite-based annotations in Bioconductor. R package version 1.52.0. <a href="https://bioconductor.org/packages/AnnotationDbi">https://bioconductor.org/packages/AnnotationDbi</a>
<b>ArchR</b>	1.0.1	Jeffrey Granja and Ryan Corces (2020). ArchR: Analyzing single-cell regulatory chromatin in R.. R package version 1.0.1.
<b>assertthat</b>	0.2.1	Hadley Wickham (2019). assertthat: Easy Pre and Post Assertions. R package version 0.2.1. <a href="https://CRAN.R-project.org/package=assertthat">https://CRAN.R-project.org/package=assertthat</a>
<b>Biobase</b>	2.50.0	Orchestrating high-throughput genomic analysis with Bioconductor. W. Huber, V.J. Carey, R. Gentleman, ..., M. Morgan Nature Methods, 2015:12, 115.
<b>BiocGenerics</b>	0.36.0	Orchestrating high-throughput genomic analysis with Bioconductor. W. Huber, V.J. Carey, R. Gentleman, ..., M. Morgan Nature Methods, 2015:12, 115.
<b>BiocParallel</b>	1.24.1	Martin Morgan, Valerie Obenchain, Michel Lang, Ryan Thompson and Nitesh Turaga (2020). BiocParallel: Bioconductor facilities for parallel evaluation. R package version 1.24.1. <a href="https://github.com/Bioconductor/BiocParallel">https://github.com/Bioconductor/BiocParallel</a>
<b>Biostrings</b>	2.58.0	H. Pagès, P. Aboyoun, R. Gentleman and S. DebRoy (2020). Biostrings: Efficient manipulation of biological strings. R package version 2.58.0. <a href="https://bioconductor.org/packages/Biostrings">https://bioconductor.org/packages/Biostrings</a>
<b>bit</b>	4.0.4	Jens Oehlschlägel and Brian Ripley (2020). bit: Classes and Methods for Fast Memory-Efficient Boolean Selections. R package version 4.0.4. <a href="https://CRAN.R-project.org/package=bit">https://CRAN.R-project.org/package=bit</a>
<b>bit64</b>	4.0.5	Jens Oehlschlägel and Leonardo Silvestri (2020). bit64: A S3 Class for Vectors of 64bit Integers. R package version 4.0.5. <a href="https://CRAN.R-project.org/package=bit64">https://CRAN.R-project.org/package=bit64</a>
<b>bitops</b>	1.0.7	S original by Steve Dutky initial R port, extensions by Martin Maechler
<b>blob</b>	1.2.1	Hadley Wickham (2020). blob: A Simple S3 Class for Representing Vectors of Binary Data
<b>BSSgenome</b>	1.58.0	H Pagès (2020). BSSgenome: Software infrastructure for efficient representation of full
<b>cachem</b>	1.0.5	Winston Chang (2021). cachem: Cache R Objects with Automatic Pruning. R package version 1.0.5. <a href="https://CRAN.R-project.org/package=cachem">https://CRAN.R-project.org/package=cachem</a>
<b>Cairo</b>	1.5.12.2	Simon Urbanek and Jeffrey Horner (2020). Cairo: R Graphics Device using Cairo Graphics Library for Creating
<b>caTools</b>	1.18.2	Jarek Tuszynski (2021). caTools: Tools: Moving Window Statistics, GIF, Base64, ROC AUC, etc. R package version 1.18.2. <a href="https://CRAN.R-project.org/package=caTools">https://CRAN.R-project.org/package=caTools</a>
<b>circlize</b>	0.4.13	Gu, Z. (2014) circlize implements and enhances circular visualization in R. Bioinformatics.
<b>clue</b>	0.3.59	Hornik K (2005). "A CLUE for CLUster Ensembles." <i>Journal of Statistical Software</i> , <b>14</b> (12). doi: 10.18637/jss.v014.i12.
<b>cluster</b>	2.1.1	Maechler, M., Rousseeuw, P., Struyf, A., Hubert, M., Hornik, K.(2021). cluster: Cluster Analysis Basics and Extensions. R package version 2.1.1.
<b>CNEr</b>	1.26.0	Ge Tan, Dimitris Polychronopoulos, Boris Lenhard (2019). CNEr: A toolkit for exploring extreme noncoding conservation PLoS Comput. Biol. 15, e1006940.
<b>codetools</b>	0.2.18	Luke Tierney (2020). codetools: Code Analysis Tools for R. R package version 0.2-18. <a href="https://CRAN.R-project.org/package=codetools">https://CRAN.R-project.org/package=codetools</a>
<b>colorspace</b>	2.0.2	Zeileis A, Fisher JC, Hornik K, Ihaka R, McWhite CD, Murrell P, Stauffer R, Wilke CO (2020). "colorspace: A Toolbox for Manipulating and Assessing Colors and Palettes." <i>Journal of Statistical Software</i> , <b>96</b> (1), 1–49. doi: 10.18637/jss.v096.i01.
<b>compiler</b>	4.0.5	R Core Team (2021). R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. URL <a href="https://www.R-project.org/">https://www.R-project.org/</a> .



<b>ComplexHeatmap</b>	2.7.10.9002	Gu, Z. (2016) Complex heatmaps reveal patterns and correlations in multidimensional genomic data. <i>Bioinformatics</i> .
<b>cowplot</b>	1.1.1	Claus O. Wilke (2020). cowplot: Streamlined Plot Theme and Plot Annotations for 'ggplot2'. R package version 1.1.1. <a href="https://CRAN.R-project.org/package=cowplot">https://CRAN.R-project.org/package=cowplot</a>
<b>crayon</b>	1.4.1	Gábor Csárdi (2021). crayon: Colored Terminal Output. R package version 1.4.1. <a href="https://CRAN.R-project.org/package=crayon">https://CRAN.R-project.org/package=crayon</a>
<b>data.table</b>	1.14.0	Matt Dowle and Arun Srinivasan (2021). data.table: Extension of `data.frame`. R package version 1.14.0. <a href="https://CRAN.R-project.org/package=data.table">https://CRAN.R-project.org/package=data.table</a>
<b>DBI</b>	1.1.1	R Special Interest Group on Databases (R-SIG-DB), Hadley Wickham and Kirill Müller (2021). DBI: R Database Interface. R package version 1.1.1. <a href="https://CRAN.R-project.org/package=DBI">https://CRAN.R-project.org/package=DBI</a>
<b>DelayedArray</b>	0.16.3	Hervé Pagès, Peter Hickey and Aaron Lun (2021). DelayedArray: A unified framework for working transparently with on-disk and
<b>deldir</b>	0.2.10	Rolf Turner (2021). deldir: Delaunay Triangulation and Dirichlet (Voronoi) Tessellation. R package version 0.2-10. <a href="https://CRAN.R-project.org/package=deldir">https://CRAN.R-project.org/package=deldir</a>
<b>digest</b>	0.6.27	Dirk Eddelbuettel with contributions by Antoine Lucas, Jarek Tuszynski, Henrik Bengtsson, Simon Urbanek, Mario Frasca, Bryan Lewis, Murray Stokely, Hannes Muehleisen, Duncan Murdoch, Jim Hester, Wush Wu, Qiang Kou, Thierry Onkelinx, Michel Lang, Viliam Simko, Kurt Hornik, Radford Neal, Kendon Bell, Matthew de Queljoe, Ion Suruceanu, Bill Denney, Dirk Schumacher and Winston Chang. (2020). digest: Create Compact Hash Digests of R Objects. R package version 0.6.27. <a href="https://CRAN.R-project.org/package=digest">https://CRAN.R-project.org/package=digest</a>
<b>DirichletMultinomial</b>	1.32.0	Martin Morgan (2020). DirichletMultinomial: Dirichlet-Multinomial Mixture Model Machine Learning for
<b>doParallel</b>	1.0.16	Microsoft Corporation and Steve Weston (2020). doParallel: Foreach Parallel Adaptor for the 'parallel' Package. R package version 1.0.16. <a href="https://CRAN.R-project.org/package=doParallel">https://CRAN.R-project.org/package=doParallel</a>
<b>dplyr</b>	1.0.7	Hadley Wickham, Romain François, Lionel Henry, Kirill Müller (2021). dplyr: A Grammar of Data Manipulation. R package version 1.0.7. <a href="https://CRAN.R-project.org/package=dplyr">https://CRAN.R-project.org/package=dplyr</a>
<b>ellipsis</b>	0.3.2	Hadley Wickham (2021). ellipsis: Tools for Working with .... R package version 0.3.2. <a href="https://CRAN.R-project.org/package=ellipsis">https://CRAN.R-project.org/package=ellipsis</a>
<b>fansi</b>	0.5.0	Brodie Gaslam (2021). fansi: ANSI Control Sequence Aware String Functions. R package version 0.5.0. <a href="https://CRAN.R-project.org/package=fansi">https://CRAN.R-project.org/package=fansi</a>
<b>fastmap</b>	1.1.0	Winston Chang (2021). fastmap: Fast Data Structures. R package version 1.1.0. <a href="https://CRAN.R-project.org/package=fastmap">https://CRAN.R-project.org/package=fastmap</a>
<b>fitdistrplus</b>	1.1.5	Marie Laure Delignette-Muller, Christophe Dutang (2015). fitdistrplus: An R Package for Fitting Distributions. <i>Journal of Statistical Software</i> , 64(4), 1-34. URL <a href="http://www.jstatsoft.org/v64/i04/">http://www.jstatsoft.org/v64/i04/</a> .
<b>foreach</b>	1.5.1	Microsoft and Steve Weston (2020). foreach: Provides Foreach Looping Construct. R package version 1.5.1. <a href="https://CRAN.R-project.org/package=foreach">https://CRAN.R-project.org/package=foreach</a>
<b>future</b>	1.21.0	H. Bengtsson, A Unifying Framework for Parallel and Distributed Processing in R using Futures, arXiv:2008.00553, 2020
<b>future.apply</b>	1.7.0	H. Bengtsson, A Unifying Framework for Parallel and Distributed Processing in R using Futures, arXiv:2008.00553, 2020
<b>generics</b>	0.1.0	Hadley Wickham, Max Kuhn and Davis Vaughan (2020). generics: Common S3 Generics not Provided by Base R Methods Related to
<b>GenomeInfoDb</b>	1.26.7	Sonali Arora, Martin Morgan, Marc Carlson, H. Pagès (2021). GenomeInfoDb: Utilities for manipulating chromosome names, including modifying
<b>GenomeInfoDbData</b>	1.2.4	Bioconductor Core Team (2020). GenomeInfoDbData: Species and taxonomy ID look up tables used by GenomeInfoDb. R package version 1.2.4.
<b>GenomicAlignments</b>	1.26.0	Lawrence M, Huber W, Pagès H, Aboyoun P, Carlson M, et al. (2013) Software for Computing and Annotating Genomic Ranges. <i>PLoS Comput Biol</i> 9(8): e1003118. doi:10.1371/journal.pcbi.1003118
<b>GenomicRanges</b>	1.42.0	Lawrence M, Huber W, Pagès H, Aboyoun P, Carlson M, et al. (2013) Software for Computing and Annotating Genomic Ranges. <i>PLoS Comput Biol</i> 9(8): e1003118. doi:10.1371/journal.pcbi.1003118

<b>GetoptLong</b>	1.0.5	Zuguang Gu (2020). GetoptLong: Parsing Command-Line Arguments and Simple Variable Interpolation. R package version 1.0.5. <a href="https://CRAN.R-project.org/package=GetoptLong">https://CRAN.R-project.org/package=GetoptLong</a>
<b>ggplot2</b>	3.3.5	H. Wickham. ggplot2: Elegant Graphics for Data Analysis. Springer-Verlag New York, 2016.
<b>ggrepel</b>	0.9.1	Kamil Slowikowski (2021). ggrepel: Automatically Position Non-Overlapping Text Labels with
<b>ggridges</b>	0.5.3	Claus O. Wilke (2021). ggridges: Ridgeline Plots in 'ggplot2'. R package version 0.5.3. <a href="https://CRAN.R-project.org/package=ggridges">https://CRAN.R-project.org/package=ggridges</a>
<b>ggseqlogo</b>	0.1	Omar Wagih (2017). ggseqlogo: A 'ggplot2' Extension for Drawing Publication-Ready Sequence
<b>GlobalOptions</b>	0.1.2	Zuguang Gu (2020). GlobalOptions: Generate Functions to Get or Set Global Options. R package version 0.1.2. <a href="https://CRAN.R-project.org/package=GlobalOptions">https://CRAN.R-project.org/package=GlobalOptions</a>
<b>globals</b>	0.14.0	Henrik Bengtsson (2020). globals: Identify Global Objects in R Expressions. R package version 0.14.0. <a href="https://CRAN.R-project.org/package=globals">https://CRAN.R-project.org/package=globals</a>
<b>glue</b>	1.4.2	Jim Hester (2020). glue: Interpreted String Literals. R package version 1.4.2. <a href="https://CRAN.R-project.org/package=glue">https://CRAN.R-project.org/package=glue</a>
<b>GO.db</b>	3.12.1	Marc Carlson (2020). GO.db: A set of annotation maps describing the entire Gene Ontology. R package version 3.12.1.
<b>goftest</b>	1.2.2	Julian Faraway, George Marsaglia, John Marsaglia and Adrian Baddeley (2019). goftest: Classical Goodness-of-Fit Tests for Univariate Distributions. R package version 1.2-2. <a href="https://CRAN.R-project.org/package=goftest">https://CRAN.R-project.org/package=goftest</a>
<b>gridExtra</b>	2.3	Baptiste Auguie (2017). gridExtra: Miscellaneous Functions for "Grid" Graphics. R package version 2.3. <a href="https://CRAN.R-project.org/package=gridExtra">https://CRAN.R-project.org/package=gridExtra</a>
<b>gtable</b>	0.3.0	Hadley Wickham and Thomas Lin Pedersen (2019). gtable: Arrange 'Grobs' in Tables. R package version 0.3.0. <a href="https://CRAN.R-project.org/package=gtable">https://CRAN.R-project.org/package=gtable</a>
<b>gtools</b>	3.9.2	Gregory R. Warnes, Ben Bolker and Thomas Lumley (2021). gtools: Various R Programming Tools. R package version 3.9.2. <a href="https://CRAN.R-project.org/package=gtools">https://CRAN.R-project.org/package=gtools</a>
<b>hexbin</b>	1.28.2	Dan Carr, ported by Nicholas Lewin-Koh, Martin Maechler and contains copies of lattice functions written by Deepayan Sarkar (2021). hexbin: Hexagonal Binning Routines. R package version 1.28.2. <a href="https://CRAN.R-project.org/package=hexbin">https://CRAN.R-project.org/package=hexbin</a>
<b>hms</b>	1.1.0	Kirill Müller (2021). hms: Pretty Time of Day. R package version 1.1.0. <a href="https://CRAN.R-project.org/package=hms">https://CRAN.R-project.org/package=hms</a>
<b>htmltools</b>	0.5.1.1	Joe Cheng, Carson Sievert, Winston Chang, Yihui Xie and Jeff Allen (2021). htmltools: Tools for HTML. R package version 0.5.1.1. <a href="https://CRAN.R-project.org/package=htmltools">https://CRAN.R-project.org/package=htmltools</a>
<b>htmlwidgets</b>	1.5.3	Ramnath Vaidyanathan, Yihui Xie, JJ Allaire, Joe Cheng, Carson Sievert and Kenton Russell (2020). htmlwidgets: HTML Widgets for R. R package version 1.5.3. <a href="https://CRAN.R-project.org/package=htmlwidgets">https://CRAN.R-project.org/package=htmlwidgets</a>
<b>httpuv</b>	1.6.1	Joe Cheng and Winston Chang (2021). httpuv: HTTP and WebSocket Server Library. R package version 1.6.1. <a href="https://CRAN.R-project.org/package=httpuv">https://CRAN.R-project.org/package=httpuv</a>
<b>httr</b>	1.4.2	Hadley Wickham (2020). httr: Tools for Working with URLs and HTTP. R package version 1.4.2. <a href="https://CRAN.R-project.org/package=httr">https://CRAN.R-project.org/package=httr</a>
<b>ica</b>	1.0.2	Nathaniel E. Helwig (2018). ica: Independent Component Analysis. R package version 1.0-2. <a href="https://CRAN.R-project.org/package=ica">https://CRAN.R-project.org/package=ica</a>
<b>igraph</b>	1.2.6	Csardi G, Nepusz T: The igraph software package for complex network research, InterJournal, Complex Systems 1695. 2006. <a href="https://igraph.org">https://igraph.org</a>
<b>IRanges</b>	2.24.1	Lawrence M, Huber W, Pag`es H, Aboyoun P, Carlson M, et al. (2013) Software for Computing and Annotating Genomic Ranges. PLoS Comput Biol 9(8): e1003118. doi:10.1371/journal.pcbi.1003118
<b>irlba</b>	2.3.3	Jim Baglama, Lothar Reichel and B. W. Lewis (2019). irlba: Fast Truncated Singular Value Decomposition and Principal
<b>iterators</b>	1.0.13	Revolution Analytics and Steve Weston (2020). iterators: Provides Iterator Construct. R package version 1.0.13. <a href="https://CRAN.R-project.org/package=iterators">https://CRAN.R-project.org/package=iterators</a>
<b>jsonlite</b>	1.7.2	Jeroen Ooms (2014). The jsonlite Package: A Practical and Consistent Mapping Between JSON Data and R Objects. arXiv:1403.2805 [stat.CO] URL <a href="https://arxiv.org/abs/1403.2805">https://arxiv.org/abs/1403.2805</a> .

<b>KEGGREST</b>	1.30.1	Dan Tenenbaum and Bioconductor Package Maintainer (2020). KEGGREST: Client-side REST access to the Kyoto Encyclopedia of Genes and
<b>KernSmooth</b>	2.23.18	Matt Wand (2020). KernSmooth: Functions for Kernel Smoothing Supporting Wand & Jones (1995). R package version 2.23-18. <a href="https://CRAN.R-project.org/package=KernSmooth">https://CRAN.R-project.org/package=KernSmooth</a>
<b>later</b>	1.2.0	Winston Chang and Joe Cheng (2021). later: Utilities for Scheduling Functions to Execute Later with Event
<b>lattice</b>	0.20.41	Sarkar, Deepayan (2008) Lattice: Multivariate Data Visualization with R. Springer, New York. ISBN 978-0-387-75968-5
<b>lazyeval</b>	0.2.2	Hadley Wickham (2019). lazyeval: Lazy (Non-Standard) Evaluation. R package version 0.2.2. <a href="https://CRAN.R-project.org/package=lazyeval">https://CRAN.R-project.org/package=lazyeval</a>
<b>leiden</b>	0.3.8	S. Thomas Kelly (2021). leiden: R implementation of the Leiden algorithm. R package version 0.3.8 <a href="https://github.com/TomKellyGenetics/leiden">https://github.com/TomKellyGenetics/leiden</a>
<b>lifecycle</b>	1.0.0	Lionel Henry and Hadley Wickham (2021). lifecycle: Manage the Life Cycle of your Package Functions. R package version 1.0.0. <a href="https://CRAN.R-project.org/package=lifecycle">https://CRAN.R-project.org/package=lifecycle</a>
<b>listenv</b>	0.8.0	Henrik Bengtsson (2019). listenv: Environments Behaving (Almost) as Lists. R package version 0.8.0. <a href="https://CRAN.R-project.org/package=listenv">https://CRAN.R-project.org/package=listenv</a>
<b>lmtest</b>	0.9.38	Achim Zeileis, Torsten Hothorn (2002). Diagnostic Checking in Regression Relationships. R News 2(3), 7-10. URL <a href="https://CRAN.R-project.org/doc/Rnews/">https://CRAN.R-project.org/doc/Rnews/</a>
<b>magick</b>	2.7.2	Jeroen Ooms (2021). magick: Advanced Graphics and Image-Processing in R. R package version 2.7.2. <a href="https://CRAN.R-project.org/package=magick">https://CRAN.R-project.org/package=magick</a>
<b>magrittr</b>	2.0.1	Stefan Milton Bache and Hadley Wickham (2020). magrittr: A Forward-Pipe Operator for R. R package version 2.0.1. <a href="https://CRAN.R-project.org/package=magrittr">https://CRAN.R-project.org/package=magrittr</a>
<b>MASS</b>	7.3.53.1	Venables, W. N. & Ripley, B. D. (2002) Modern Applied Statistics with S. Fourth Edition. Springer, New York. ISBN 0-387-95457-0
<b>Matrix</b>	1.3.4	Douglas Bates and Martin Maechler (2021). Matrix: Sparse and Dense Matrix Classes and Methods. R package version 1.3-4. <a href="https://CRAN.R-project.org/package=Matrix">https://CRAN.R-project.org/package=Matrix</a>
<b>MatrixGenerics</b>	1.2.1	Constantin Ahlmann-Eltze, Peter Hickey and H Pagès (2021). MatrixGenerics: S4 Generic Summary Statistic Functions that Operate on
<b>matrixStats</b>	0.59.0	Henrik Bengtsson (2021). matrixStats: Functions that Apply to Rows and Columns of Matrices (and to
<b>memoise</b>	2.0.0	Hadley Wickham, Jim Hester, Winston Chang, Kirill Müller and Daniel Cook (2021). memoise: Memoisation of Functions. R package version 2.0.0. <a href="https://CRAN.R-project.org/package=memoise">https://CRAN.R-project.org/package=memoise</a>
<b>mgcv</b>	1.8.34	Wood, S.N. (2011) Fast stable restricted maximum likelihood
<b>mime</b>	0.11	Yihui Xie (2021). mime: Map Filenames to MIME Types. R package version 0.11. <a href="https://CRAN.R-project.org/package=mime">https://CRAN.R-project.org/package=mime</a>
<b>miniUI</b>	0.1.1.1	Joe Cheng (2018). miniUI: Shiny UI Widgets for Small Screens. R package version 0.1.1.1. <a href="https://CRAN.R-project.org/package=miniUI">https://CRAN.R-project.org/package=miniUI</a>
<b>munsell</b>	0.5.0	Charlotte Wickham (2018). munsell: Utilities for Using Munsell Colours. R package version 0.5.0. <a href="https://CRAN.R-project.org/package=munsell">https://CRAN.R-project.org/package=munsell</a>
<b>nlme</b>	3.1.152	Jose Pinheiro and Douglas Bates and Saikat DebRoy and Deepayan Sarkar and {R Core Team} (2021). <i>nlme: Linear and Nonlinear Mixed Effects Models</i> . R package version 3.1-152, <a href="https://CRAN.R-project.org/package=nlme">https://CRAN.R-project.org/package=nlme</a> .
<b>parallely</b>	1.26.1	Henrik Bengtsson (2021). parallely: Enhancing the 'parallel' Package. R package version 1.26.1. <a href="https://CRAN.R-project.org/package=parallely">https://CRAN.R-project.org/package=parallely</a>
<b>patchwork</b>	1.1.1	Thomas Lin Pedersen (2020). patchwork: The Composer of Plots. R package version 1.1.1. <a href="https://CRAN.R-project.org/package=patchwork">https://CRAN.R-project.org/package=patchwork</a>
<b>pbapply</b>	1.4.3	Peter Solymos and Zygmunt Zawadzki (2020). pbapply: Adding Progress Bar to '*apply' Functions. R package version 1.4-3. <a href="https://CRAN.R-project.org/package=pbapply">https://CRAN.R-project.org/package=pbapply</a>
<b>pillar</b>	1.6.1	Kirill Müller and Hadley Wickham (2021). pillar: Coloured Formatting for Columns. R package version 1.6.1. <a href="https://CRAN.R-project.org/package=pillar">https://CRAN.R-project.org/package=pillar</a>
<b>pkgconfig</b>	2.0.3	Gábor Csárdi (2019). pkgconfig: Private Configuration for 'R' Packages. R package version 2.0.3. <a href="https://CRAN.R-project.org/package=pkgconfig">https://CRAN.R-project.org/package=pkgconfig</a>
<b>plotly</b>	4.9.4.1	C. Sievert. Interactive Web-Based Data Visualization with R, plotly, and shiny. Chapman and Hall/CRC Florida, 2020.

<b>plyr</b>	1.8.6	Hadley Wickham (2011). The Split-Apply-Combine Strategy for Data Analysis. <i>Journal of Statistical Software</i> , 40(1), 1-29. URL <a href="http://www.jstatsoft.org/v40/i01/">http://www.jstatsoft.org/v40/i01/</a> .
<b>png</b>	0.1.7	Simon Urbanek (2013). png: Read and write PNG images. R package version 0.1-7. <a href="https://CRAN.R-project.org/package=png">https://CRAN.R-project.org/package=png</a>
<b>polyclip</b>	1.10.0	Angus Johnson and Adrian Baddeley (2019). polyclip: Polygon Clipping. R package version 1.10-0. <a href="https://CRAN.R-project.org/package=polyclip">https://CRAN.R-project.org/package=polyclip</a>
<b>powerLaw</b>	0.70.6	Colin S. Gillespie (2015). Fitting Heavy Tailed Distributions: The powerLaw Package. <i>Journal of Statistical Software</i> , 64(2), 1-16. URL <a href="http://www.jstatsoft.org/v64/i02/">http://www.jstatsoft.org/v64/i02/</a> .
<b>pracma</b>	2.3.3	Hans W. Borchers (2021). pracma: Practical Numerical Math Functions. R package version 2.3.3. <a href="https://CRAN.R-project.org/package=pracma">https://CRAN.R-project.org/package=pracma</a>
<b>promises</b>	1.2.0.1	Joe Cheng (2021). promises: Abstractions for Promise-Based Asynchronous Programming. R package version 1.2.0.1. <a href="https://CRAN.R-project.org/package=promises">https://CRAN.R-project.org/package=promises</a>
<b>purrr</b>	0.3.4	Lionel Henry and Hadley Wickham (2020). purrr: Functional Programming Tools. R package version 0.3.4. <a href="https://CRAN.R-project.org/package=purrr">https://CRAN.R-project.org/package=purrr</a>
<b>R.methodsS3</b>	1.8.1	Bengtsson, H. The R.oo package - Object-Oriented Programming with References Using Standard R Code, Proceedings of the 3rd International Workshop on Distributed Statistical Computing (DSC 2003), ISSN 1609-395X, Hornik, K.
<b>R.oo</b>	1.24.0	Bengtsson, H. The R.oo package - Object-Oriented Programming with References Using Standard R Code, Proceedings of the 3rd International Workshop on Distributed Statistical Computing (DSC 2003), ISSN 1609-395X, Hornik, K.
<b>R.utils</b>	2.10.1	Henrik Bengtsson (2020). R.utils: Various Programming Utilities. R package version 2.10.1. <a href="https://CRAN.R-project.org/package=R.utils">https://CRAN.R-project.org/package=R.utils</a>
<b>R6</b>	2.5.0	Winston Chang (2020). R6: Encapsulated Classes with Reference Semantics. R package version 2.5.0. <a href="https://CRAN.R-project.org/package=R6">https://CRAN.R-project.org/package=R6</a>
<b>RANN</b>	2.6.1	Sunil Arya, David Mount, Samuel E. Kemp and Gregory Jefferis (2019). RANN: Fast Nearest Neighbour Search (Wraps ANN Library) Using L2
<b>RColorBrewer</b>	1.1.2	Erich Neuwirth (2014). RColorBrewer: ColorBrewer Palettes. R package version 1.1-2. <a href="https://CRAN.R-project.org/package=RColorBrewer">https://CRAN.R-project.org/package=RColorBrewer</a>
<b>Rcpp</b>	1.0.7	Dirk Eddelbuettel and Romain Francois (2011). Rcpp: Seamless R and C++ Integration. <i>Journal of Statistical Software</i> , 40(8), 1-18. URL <a href="https://www.jstatsoft.org/v40/i08/">https://www.jstatsoft.org/v40/i08/</a> .
<b>RcppAnnoy</b>	0.0.18	Dirk Eddelbuettel (2020). RcppAnnoy: 'Rcpp' Bindings for 'Annoy', a Library for Approximate Nearest
<b>RCurl</b>	1.98.1.3	Duncan Temple Lang (2021). RCurl: General Network (HTTP/FTP/...) Client Interface for R. R package version 1.98-1.3. <a href="https://CRAN.R-project.org/package=RCurl">https://CRAN.R-project.org/package=RCurl</a>
<b>readr</b>	1.4.0	Hadley Wickham and Jim Hester (2020). readr: Read Rectangular Text Data. R package version 1.4.0. <a href="https://CRAN.R-project.org/package=readr">https://CRAN.R-project.org/package=readr</a>
<b>reshape2</b>	1.4.4	Hadley Wickham (2007). Reshaping Data with the reshape Package. <i>Journal of Statistical Software</i> , 21(12), 1-20. URL <a href="http://www.jstatsoft.org/v21/i12/">http://www.jstatsoft.org/v21/i12/</a> .
<b>reticulate</b>	1.20	Kevin Ushey, JJ Allaire and Yuan Tang (2021). reticulate: Interface to 'Python'. R package version 1.20. <a href="https://CRAN.R-project.org/package=reticulate">https://CRAN.R-project.org/package=reticulate</a>
<b>rhdf5</b>	2.34.0	Bernd Fischer, Mike Smith and Gregoire Pau (2020). rhdf5: R Interface to HDF5. R package version 2.34.0. <a href="https://github.com/grimbough/rhdf5">https://github.com/grimbough/rhdf5</a>
<b>rhdf5filters</b>	1.2.0	Mike Smith (2020). rhdf5filters: HDF5 Compression Filters. R package version 1.2.0. <a href="https://github.com/grimbough/rhdf5filters">https://github.com/grimbough/rhdf5filters</a>
<b>Rhdf5lib</b>	1.12.1	Mike Smith (2021). Rhdf5lib: hdf5 library as an R package. R package version 1.12.1. <a href="https://github.com/grimbough/Rhdf5lib">https://github.com/grimbough/Rhdf5lib</a>
<b>rjson</b>	0.2.20	Alex Couture-Beil (2018). rjson: JSON for R. R package version 0.2.20. <a href="https://CRAN.R-project.org/package=rjson">https://CRAN.R-project.org/package=rjson</a>
<b>rlang</b>	0.4.11	Lionel Henry and Hadley Wickham (2021). rlang: Functions for Base Types and Core R and 'Tidyverse' Features. R package version 0.4.11. <a href="https://CRAN.R-project.org/package=rlang">https://CRAN.R-project.org/package=rlang</a>
<b>ROCR</b>	1.0.11	Sing T, Sander O, Beerenwinkel N, Lengauer T (2005). "ROCR: visualizing classifier performance in R." <i>Bioinformatics</i> , 21(20), 7881. <a href="http://rocr.bioinf.mpi-sb.mpg.de">http://rocr.bioinf.mpi-sb.mpg.de</a> .
<b>rpart</b>	4.1.15	Terry Therneau and Beth Atkinson (2019). rpart: Recursive Partitioning and Regression Trees. R package version 4.1-15. <a href="https://CRAN.R-project.org/package=rpart">https://CRAN.R-project.org/package=rpart</a>

<b>Rsamtools</b>	2.6.0	Morgan M, Pagès H, Obenchain V, Hayden N (2021). <i>Rsamtools: Binary alignment (BAM), FASTA, variant call (BCF), and tabix file import</i> . R package version 2.8.0, <a href="https://bioconductor.org/packages/Rsamtools">https://bioconductor.org/packages/Rsamtools</a> .
<b>RSQLite</b>	2.2.7	Kirill Müller, Hadley Wickham, David A. James and Seth Falcon (2021). RSQLite: 'SQLite' Interface for R. R package version 2.2.7. <a href="https://CRAN.R-project.org/package=RSQLite">https://CRAN.R-project.org/package=RSQLite</a>
<b>rstudioapi</b>	0.13	Kevin Ushey, JJ Allaire, Hadley Wickham and Gary Ritchie (2020). rstudioapi: Safely Access the RStudio API. R package version 0.13. <a href="https://CRAN.R-project.org/package=rstudioapi">https://CRAN.R-project.org/package=rstudioapi</a>
<b>rtracklayer</b>	1.50.0	M. Lawrence, R. Gentleman, V. Carey: "rtracklayer: an {R} package for interfacing with genome browsers". <i>Bioinformatics</i> 25:1841-1842.
<b>Rtsne</b>	0.15	L.J.P. van der Maaten and G.E. Hinton. Visualizing High-Dimensional Data Using t-SNE. <i>Journal of Machine Learning Research</i> 9(Nov):2579-2605, 2008.
<b>S4Vectors</b>	0.28.1	H. Pagès, M. Lawrence and P. Aboyoun (2020). S4Vectors: Foundation of vector-like and list-like containers in
<b>scales</b>	1.1.1	Hadley Wickham and Dana Seidel (2020). scales: Scale Functions for Visualization. R package version 1.1.1. <a href="https://CRAN.R-project.org/package=scales">https://CRAN.R-project.org/package=scales</a>
<b>scattermore</b>	0.7	Mirek Kratochvil (2020). scattermore: Scatterplots with More Points. R package version 0.7. <a href="https://CRAN.R-project.org/package=scattermore">https://CRAN.R-project.org/package=scattermore</a>
<b>sctransform</b>	0.3.2	Hafemeister, C. & Satija, R. Normalization and variance stabilization of single-cell RNA-seq data using regularized negative binomial regression. <i>Genome Biol</i> 20, 296 (2019).
<b>seqLogo</b>	1.56.0	Oliver Bembom and Robert Ivanek (2020). seqLogo: Sequence logos for DNA sequence alignments. R package version 1.56.0.
<b>Seurat</b>	4.0.3	Hao Y, Hao S, Andersen-Nissen E, III WMM, Zheng S, Butler A, Lee MJ, Wilk AJ, Darby C, Zagar M, Hoffman P, Stoeckius M, Papalexi E, Mimitou EP, Jain J, Srivastava A, Stuart T, Fleming LB, Yeung B, Rogers AJ, McElrath JM, Blish CA, Gottardo R, Smibert P, Satija R (2021). "Integrated analysis of multimodal single-cell data." <i>Cell</i> . doi: 10.1016/j.cell.2021.04.048, <a href="https://doi.org/10.1016/j.cell.2021.04.048">https://doi.org/10.1016/j.cell.2021.04.048</a> .
<b>SeuratObject</b>	4.0.2	Rahul Satija, Andrew Butler, Paul Hoffman and Tim Stuart (2021). SeuratObject: Data Structures for Single Cell Data. R package version 4.0.2. <a href="https://CRAN.R-project.org/package=SeuratObject">https://CRAN.R-project.org/package=SeuratObject</a>
<b>shape</b>	1.4.6	Karline Soetaert (2021). shape: Functions for Plotting Graphical Shapes, Colors. R package version 1.4.6. <a href="https://CRAN.R-project.org/package=shape">https://CRAN.R-project.org/package=shape</a>
<b>shiny</b>	1.6.0	Winston Chang, Joe Cheng, JJ Allaire, Carson Sievert, Barret Schloerke, Yihui Xie, Jeff Allen, Jonathan McPherson, Alan Dipert and Barbara Borges (2021). shiny: Web Application Framework for R. R package version 1.6.0. <a href="https://CRAN.R-project.org/package=shiny">https://CRAN.R-project.org/package=shiny</a>
<b>shinybusy</b>	0.2.2	Fanny Meyer and Victor Perrier (2020). shinybusy: Busy Indicator for 'Shiny' Applications. R package version 0.2.2. <a href="https://CRAN.R-project.org/package=shinybusy">https://CRAN.R-project.org/package=shinybusy</a>
<b>shinycssloaders</b>	1.0.0	Andras Sali and Dean Attali (2020). shinycssloaders: Add Loading Animations to a 'shiny' Output While It's
<b>spatstat.core</b>	2.2.0	Adrian Baddeley, Ege Rubak, Rolf Turner (2015). <i>Spatial Point Patterns: Methodology and Applications with R</i> . London: Chapman and Hall/CRC Press, 2015. URL <a href="https://www.routledge.com/Spatial-Point-Patterns-Methodology-and-Applications-with-R/Baddeley-Rubak-Turner/9781482210200/">https://www.routledge.com/Spatial-Point-Patterns-Methodology-and-Applications-with-R/Baddeley-Rubak-Turner/9781482210200/</a>
<b>spatstat.data</b>	2.1.0	Adrian Baddeley, Rolf Turner and Ege Rubak (2021). spatstat.data: Datasets for 'spatstat' Family. R package version 2.1-0. <a href="https://CRAN.R-project.org/package=spatstat.data">https://CRAN.R-project.org/package=spatstat.data</a>
<b>spatstat.geom</b>	2.2.2	Adrian Baddeley, Ege Rubak, Rolf Turner (2015). <i>Spatial Point Patterns: Methodology and Applications with R</i> . London: Chapman and Hall/CRC Press, 2015. URL <a href="https://www.routledge.com/Spatial-Point-Patterns-Methodology-and-Applications-with-R/Baddeley-Rubak-Turner/9781482210200/">https://www.routledge.com/Spatial-Point-Patterns-Methodology-and-Applications-with-R/Baddeley-Rubak-Turner/9781482210200/</a>
<b>spatstat.sparse</b>	2.0.0	Adrian Baddeley, Rolf Turner and Ege Rubak (2021). spatstat.sparse: Sparse Three-Dimensional Arrays and Linear Algebra Utilities. R package version 2.0-0. <a href="https://CRAN.R-project.org/package=spatstat.sparse">https://CRAN.R-project.org/package=spatstat.sparse</a>
<b>spatstat.utils</b>	2.2.0	Adrian Baddeley, Rolf Turner and Ege Rubak (2021). spatstat.utils: Utility Functions for 'spatstat'. R package version 2.2-0. <a href="https://CRAN.R-project.org/package=spatstat.utils">https://CRAN.R-project.org/package=spatstat.utils</a>

<b>splines</b>	4.0.5	R Core Team (2021). R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. URL <a href="https://www.R-project.org/">https://www.R-project.org/</a> .
<b>stringi</b>	1.7.2	M Gagolewski (2021). <i>stringi: Fast and portable character string processing in R</i> . R package version 1.7.4, <a href="https://stringi.gagolewski.com/">https://stringi.gagolewski.com/</a> .
<b>stringr</b>	1.4.0	Hadley Wickham (2019). stringr: Simple, Consistent Wrappers for Common String Operations. R package version 1.4.0. <a href="https://CRAN.R-project.org/package=stringr">https://CRAN.R-project.org/package=stringr</a>
<b>SummarizedExperiment</b>	1.20.0	M Morgan ,V Obenchain,J Hester,H Pagès (2021). <i>SummarizedExperiment: SummarizedExperiment container</i> . R package version 1.22.0, <a href="https://bioconductor.org/packages/SummarizedExperiment">https://bioconductor.org/packages/SummarizedExperiment</a> .
<b>survival</b>	3.2.10	T Therneau (2021). <i>A Package for Survival Analysis in R</i> . R package version 3.2-13, <a href="https://CRAN.R-project.org/package=survival">https://CRAN.R-project.org/package=survival</a> . Terry M. Therneau, Patricia M. Grambsch (2000). <i>Modeling Survival Data: Extending the Cox Model</i> . Springer, New York. ISBN 0-387-98784-3.
<b>tensor</b>	1.5	Jonathan Rougier (2012). tensor: Tensor product of arrays. R package version 1.5. <a href="https://CRAN.R-project.org/package=tensor">https://CRAN.R-project.org/package=tensor</a>
<b>TFBSTools</b>	1.28.0	Tan, G., and Lenhard, B. (2016). TFBSTools: an R/bioconductor package for transcription factor binding site analysis. <i>Bioinformatics</i> 32, 1555-1556.
<b>TFMPvalue</b>	0.0.8	Ge Tan (2018). TFMPvalue: Efficient and Accurate P-Value Computation for Position Weight
<b>tibble</b>	3.1.2	Kirill Müller and Hadley Wickham (2021). tibble: Simple Data Frames. R package version 3.1.2. <a href="https://CRAN.R-project.org/package=tibble">https://CRAN.R-project.org/package=tibble</a>
<b>tidyr</b>	1.1.3	Hadley Wickham (2021). tidyr: Tidy Messy Data. R package version 1.1.3. <a href="https://CRAN.R-project.org/package=tidyr">https://CRAN.R-project.org/package=tidyr</a>
<b>tidyselect</b>	1.1.1	Lionel Henry and Hadley Wickham (2021). tidyselect: Select from a Set of Strings. R package version 1.1.1. <a href="https://CRAN.R-project.org/package=tidyselect">https://CRAN.R-project.org/package=tidyselect</a>
<b>tools</b>	4.0.5	R Core Team (2021). R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. URL <a href="https://www.R-project.org/">https://www.R-project.org/</a> .
<b>utf8</b>	1.2.1	Patrick O. Perry (2021). utf8: Unicode Text Processing. R package version 1.2.1. <a href="https://CRAN.R-project.org/package=utf8">https://CRAN.R-project.org/package=utf8</a>
<b>uwot</b>	0.1.10	James Melville (2020). uwot: The Uniform Manifold Approximation and Projection (UMAP) Method
<b>vctrs</b>	0.3.8	Hadley Wickham, Lionel Henry and Davis Vaughan (2021). vctrs: Vector Helpers. R package version 0.3.8. <a href="https://CRAN.R-project.org/package=vctrs">https://CRAN.R-project.org/package=vctrs</a>
<b>viridisLite</b>	0.4.0	Garnier, Simon, Ross, Noam, Rudis, Robert, Camargo, Pedro A, Sciaini, Marco, Scherer, Cédric (2021). <i>viridis - Colorblind-Friendly Color Maps for R</i> . doi: 10.5281/zenodo.4679424, R package version 0.4.0, <a href="https://sjmgarnier.github.io/viridis/">https://sjmgarnier.github.io/viridis/</a> .
<b>Withr</b>	2.4.2	Jim Hester, Kirill Müller, Kevin Ushey, Hadley Wickham and Winston Chang (2021). withr: Run Code 'With' Temporarily Modified Global State. R package version 2.4.2. <a href="https://CRAN.R-project.org/package=withr">https://CRAN.R-project.org/package=withr</a>
<b>XML</b>	3.99.0.6	Duncan Temple Lang (2021). XML: Tools for Parsing and Generating XML Within R and S-Plus. R package version 3.99-0.6. <a href="https://CRAN.R-project.org/package=XML">https://CRAN.R-project.org/package=XML</a>
<b>Xtable</b>	1.8.4	David B. Dahl, David Scott, Charles Roosen, Arni Magnusson and Jonathan Swinton (2019). xtable: Export Tables to LaTeX or HTML. R package version 1.8-4. <a href="https://CRAN.R-project.org/package=xtable">https://CRAN.R-project.org/package=xtable</a>
<b>XVector</b>	0.30.0	H Pagès and Patrick Aboyoun (2020). XVector: Foundation of external vector representation and manipulation in
<b>zlibbioc</b>	1.36.0	Martin Morgan (2020). zlibbioc: An R packaged zlib-1.2.5. R package version 1.36.0. <a href="https://bioconductor.org/packages/zlibbioc">https://bioconductor.org/packages/zlibbioc</a>
<b>zoo</b>	1.8.9	Achim Zeileis and Gabor Grothendieck (2005). zoo: S3 Infrastructure for Regular and Irregular Time Series. <i>Journal of Statistical Software</i> , 14(6), 1-27. doi:10.18637/jss.v014.i06

## References

- Aboyoun,P. *et al.* (2020) GenomicRanges: Representation and manipulation of genomic intervals.
- Ahlmann-Eltze,C. *et al.* (2021) MatrixGenerics: S4 Generic Summary Statistic Functions that Operate on Matrix-Like Objects.
- Arora,S. *et al.* (2021) GenomeInfoDb: Utilities for manipulating chromosome names, including modifying them to follow a particular naming style.
- Auguie,B. (2017) gridExtra: Miscellaneous Functions for ‘Grid’ Graphics.
- Bache,S.M. and Wickham,H. (2020) magrittr: A Forward-Pipe Operator for R.
- Bates,D. and Maechler,M. (2021) Matrix: Sparse and Dense Matrix Classes and Methods.
- Bengtsson,H. (2021) matrixStats: Functions that Apply to Rows and Columns of Matrices (and to Vectors).
- Butler,A. *et al.* (2018) Integrating single-cell transcriptomic data across different conditions, technologies, and species. *Nature Biotechnology*, **36**, 411–420.
- Carr,D. *et al.* (2021) hexbin: Hexagonal Binning Routines.
- Chang,W. *et al.* (2021) shiny: Web Application Framework for R.
- Dijk,D. van *et al.* (2018) Recovering Gene Interactions from Single-Cell Data Using Data Diffusion. *Cell*, **174**, 716-729.e27.
- Dowle,M. and Srinivasan,A. (2021) data.table: Extension of `data.frame`.
- Eddelbuettel,D. *et al.* (2021) Rcpp: Seamless R and C++ Integration.
- Eddelbuettel,D. (2013) Seamless R and C++ Integration with Rcpp Springer, New York.
- Eddelbuettel,D. and Balamuta,J.J. (2018) Extending extitR with extitC++: A Brief Introduction to extitRcpp. *The American Statistician*, **72**, 28–36.
- Eddelbuettel,D. and François,R. (2011) Rcpp: Seamless R and C++ Integration. *Journal of Statistical Software*, **40**, 1–18.
- Elseberg,J. *et al.* (2012) Comparison of nearest-neighbor-search strategies and implementations for efficient shape registration. *Journal of Software Engineering for Robotics (JOSE)*, **3**, 2–12.
- Fischer,B. *et al.* (2020) rhdf5: R Interface to HDF5.
- Gentleman,R. *et al.* (2020) Biobase: Base functions for Bioconductor.
- Granja,J. and Corces,R. (2020) ArchR: Analyzing single-cell regulatory chromatin in R.
- Granja,J.M. *et al.* (2021) ArchR is a scalable software package for integrative single-cell chromatin accessibility analysis. *Nature Genetics*, **53**, 403–411.
- Gu,Z. (2021) circlize: Circular Visualization.
- Gu,Z. *et al.* (2014) circlize implements and enhances circular visualization in R. *Bioinformatics*, **30**, 2811–2812.
- Gu,Z. *et al.* (2016) Complex heatmaps reveal patterns and correlations in multidimensional genomic data. *Bioinformatics*.
- Gu,Z. (2020) ComplexHeatmap: Make Complex Heatmaps.
- Hao,Y. *et al.* (2020) Integrated analysis of multimodal single-cell data. *bioRxiv*.
- Hoffman,P. (2021) Seurat: Tools for Single Cell Genomics.
- Huber *et al.* (2015) Orchestrating high-throughput genomic analysis with Bioconductor. *Nature Methods*, **12**, 115–121.
- Huber,W. *et al.* (2015) Orchestrating high-throughput genomic analysis with Bioconductor. *Nature Methods*, **12**, 115–121.
- Korsunsky,I. *et al.* (2021) presto: Fast Functions for Differential Expression using Wilcox and AUC.
- Lawrence,M. *et al.* (2009) rtracklayer: an R package for interfacing with genome browsers. *Bioinformatics*, **25**, 1841–1842.
- Lawrence,M. *et al.* (2020) rtracklayer: R interface to genome annotation files and the UCSC genome browser.

- Lawrence, M. *et al.* (2013) Software for Computing and Annotating Genomic Ranges. *PLoS Computational Biology*, **9**.
- McInnes, L. *et al.* (2020) UMAP: Uniform Manifold Approximation and Projection for Dimension Reduction. *arXiv:1802.03426 [cs, stat]*.
- Mangenat, S. and Jefferis, G. (2018) nabor: Wraps libnabo, a Fast K Nearest Neighbour Library for Low Dimensions.
- Meyer, F. and Perrier, V. (2020) shinybusy: Busy Indicator for Shiny Applications.
- Morgan, M. *et al.* (2020) SummarizedExperiment: SummarizedExperiment container.
- Omar Wagih, ggseqlogo: a versatile R package for drawing sequence logos, *Bioinformatics*, Volume 33, Issue 22, 15 November 2017, Pages 3645–3647, <https://doi.org/10.1093/bioinformatics/btx469>
- Ooms, J. (2021) magick: Advanced Graphics and Image-Processing in R.
- Pagès, H., Abouyou, P., Gentleman, R., *et al.* (2020) Biostrings: Efficient manipulation of biological strings.
- Pagès, H. (2020) BSgenome: Software infrastructure for efficient representation of full genomes and their SNPs.
- Pagès, H., Abouyou, P., and Lawrence, M. (2020) IRanges: Foundation of integer range manipulation in Bioconductor.
- Pagès, H., Lawrence, M., *et al.* (2020) S4Vectors: Foundation of vector-like and list-like containers in Bioconductor.
- Pagès, H. and Abouyou, P. (2020) XVector: Foundation of external vector representation and manipulation in Bioconductor.
- Pedersen, T.L. (2020) patchwork: The Composer of Plots.
- R Core Team (2021) R: A Language and Environment for Statistical Computing R Foundation for Statistical Computing, Vienna, Austria.
- Sali, A. and Attali, D. (2020) shinycssloaders: Add Loading Animations to a shiny Output While It's Recalculating.
- Satija, R. *et al.* (2021) SeuratObject: Data Structures for Single Cell Data.
- Satija, R. *et al.* (2015) Spatial reconstruction of single-cell gene expression data. *Nature Biotechnology*, **33**, 495–502.
- Slowikowski, K. (2021) ggrepel: Automatically Position Non-Overlapping Text Labels with ggplot2.
- Stuart, T. *et al.* (2019) Comprehensive Integration of Single-Cell Data. *Cell*, **177**, 1888–1902.
- Team, T.B.D. (2021) BiocGenerics: S4 generic functions used in Bioconductor.
- Team, T.B.D. (2020) BSgenome.Hsapiens.UCSC.hg19: Full genome sequences for Homo sapiens (UCSC version hg19, based on GRCh37.p13).
- Wickham, H. *et al.* (2020) ggplot2: Create Elegant Data Visualisations Using the Grammar of Graphics.
- Wickham, H. (2016) ggplot2: Elegant Graphics for Data Analysis Springer-Verlag New York.
- Wickham, H. and Pedersen, T.L. (2019) gtable: Arrange Grobs in Tables.