Introduction to the pageRank Package

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1 Introduction

1.1 Background

The *pageRank* package provides implementations of temporal PageRank as defined by [1], as well as multiplex PageRank as defined by [2]. As the extension of original steady-state PageRank [3,4] in temporal networks, temporal PageRank ranks nodes based on their connections that change over time. Multiplex PageRank, on the other hand, extends PageRank analysis to multiplex networks. In such networks, the same nodes might interact with one another in different layers. Multiplex PageRank is calculated

according to the topology of a predefined base network, with regular PageRank of other supplemental networks as edge weights and personalization vector.

PageRank-related approaches can be applied to prioritize key transcriptional factors (TFs) in gene regulatory networks (GRNs). Specifically, the *pageRank* package provides functions for generating temporal GRNs from corresponding static counterparts. The *pageRank* package also provides functions for converting multi-omics, e.g. gene expression, chromatin accessibility and chromosome conformation profiles to multiplex GRNs. Such temporal and multiplex GRNs can thus be used for temporal and multiplex PageRank-based TF prioritization, respectively.

1.2 Installation

pageRank requires the R version 4.0 or later, packages *BSgenome.Hsapiens.UCSC.hg19*, *TxDb.Hsapiens.UCSC.hg19.knownGene*, *org.Hs.eg.db*, *annotate*, *GenomicFeatures*, *JASPAR2018*, *TFBSTools* and *bcellViper*, to run the examples. After installing R, all required components can be obtained with:

```
if (!requireNamespace("BiocManager", quietly=TRUE)) install.packages("BiocManager")
BiocManager::install("BSgenome.Hsapiens.UCSC.hg19")
BiocManager::install("TxDb.Hsapiens.UCSC.hg19.knownGene")
BiocManager::install("org.Hs.eg.db")
BiocManager::install("annotate")
BiocManager::install("GenomicFeatures")
BiocManager::install("JASPAR2018")
BiocManager::install("TFBSTools")
BiocManager::install("bcellViper")
```

2 PageRank Analysis

2.1 Temporal PageRank

We applied `diff_graph()` to calculate temporal PageRank. This is a simplified version of temporal PageRank described by [1] by only analyzing temporally adjacent graph pairs.

```
> library(pageRank)
> set.seed(1)
> graph1 <- igraph::erdos.renyi.game(100, 0.01, directed = TRUE)
> igraph::V(graph1)$name <- 1:100
> #the 1st graph with name as vertex attributes
> set.seed(2)
> graph2 <- igraph::erdos.renyi.game(100, 0.01, directed = TRUE)
```

```
> igraph::V(graph2)$name <- 1:100
> #the 2nd graph with name as vertex attributes
> diff_graph(graph1, graph2)

IGRAPH f5c3f78 DN-- 98 190 --
+ attr: name (v/c), pagerank (v/n), moi (e/n)
+ edges from f5c3f78 (vertex names):
 [1] 1 ->60  2 ->15  2 ->57  3 ->10  3 ->16  3 ->84  4 ->43  5 ->20  5 ->66
[10] 5 ->72  5 ->81  5 ->91  6 ->25  6 ->50  7 ->37  7 ->67  7 ->73  7 ->85
[19] 8 ->80  9 ->90  10->26  11->6   11->100 12->70  12->82  12->92  13->30
[28] 13->48  13->51  13->61  15->74  15->77  16->85  17->31  17->32  17->34
[37] 17->50  17->58  19->17  19->96  20->23  20->79  20->87  21->41  21->45
[46] 22->4   22->41  23->57  24->61  25->66  26->34  26->39  26->72  27->22
[55] 27->43  28->98  29->95  30->84  32->49  33->10  34->16  34->99  35->81
[64] 36->17  36->33  36->45  36->53  36->77  37->33  37->54  38->6   38->17
+ ... omitted several edges
```

Differential graph graph1-graph2 will be outputed. The Differential graph has "moi (mode of interaction, 1 and -1 for interactions gained and losed in graph1, respectively)" as edge attribute. The Differential graph has "pagerank" and "name" as vertex attributes.

2.2 Multiplex PageRank

We applied `multiplex_page_rank()` to calculate multiplex PageRank following defination by [2].

```
> set.seed(1)
> graph1 <- igraph::erdos.renyi.game(100, 0.01, directed = TRUE)
> igraph::V(graph1)$name <- 1:100
> igraph::V(graph1)$pagerank <- igraph::page_rank(graph1)$vector
> #the base graph with pagerank and name as vertex attributes.
> set.seed(2)
> graph2 <- igraph::erdos.renyi.game(100, 0.01, directed = TRUE)
> igraph::V(graph2)$name <- 1:100
> igraph::V(graph2)$pagerank <- igraph::page_rank(graph2)$vector
> #the supplemental graph with pagerank and name as vertex attributes.
> multiplex_page_rank(graph1, graph2)

          1           2           3           4           5           6
0.022431793 0.004376548 0.005101288 0.021806420 0.004038261 0.014009056
          7           8           9          10          11          12
0.017033776 0.004038261 0.010897818 0.022024129 0.004376548 0.004038261
         13          14          15          16          17          18
```

```
0.004038261 0.004038261 0.011984174 0.010662594 0.012861595 0.004038261
         19          20          21          22          23          24
0.004038261 0.006973192 0.007883792 0.018708510 0.009449760 0.008580800
         25          26          27          28          29          30
0.009992110 0.023175991 0.016861132 0.007081820 0.004038261 0.007696307
         31          32          33          34          35          36
0.017884438 0.004465826 0.019332930 0.005497036 0.026386118 0.014886821
         37          38          39          40          41          42
0.004473382 0.012774746 0.008259414 0.008244753 0.010494265 0.015930714
         43          44          45          46          47          48
0.017448552 0.007901711 0.008117970 0.007680122 0.004038261 0.004263786
         49          50          51          52          53          54
0.011679744 0.020924465 0.008291128 0.009090471 0.008316500 0.008569083
         55          56          57          58          59          60
0.004038261 0.011492897 0.013013291 0.006154228 0.009112068 0.005053121
         61          62          63          64          65          66
0.011557465 0.008125871 0.004038261 0.009595523 0.004038261 0.013377737
         67          68          69          70          71          72
0.004473382 0.005786216 0.006188052 0.011348562 0.004807863 0.021639449
         73          74          75          76          77          78
0.005681911 0.011938368 0.004664091 0.028329952 0.005204011 0.008601557
         79          80          81          82          83          84
0.007514945 0.004714834 0.037833945 0.005251514 0.004376548 0.007672082
         85          86          87          88          89          90
0.017889151 0.004376548 0.013828925 0.005346400 0.004038261 0.010681597
         91          92          93          94          95          96
0.011139970 0.009048308 0.015566866 0.009116546 0.006681434 0.004714834
         97          98          99         100
0.012194456 0.008225016 0.005368584 0.004931364
```

Multiplex PageRank values corresponded to nodes in graph1 (base network) will be outputed.

2.3 Adjusting PageRank Calculations

The `clean_graph()` can remove nodes by residing subgraph sizes, vertex names and PageRank values. We thus can adjust graphs for PageRank calculation.

```
> set.seed(1)
> graph <- igraph::erdos.renyi.game(100, 0.01, directed = TRUE)
> igraph::V(graph)$name <- 1:100
> igraph::V(graph)$pagerank <- igraph::page_rank(graph)$vector
```

```
> #the graph to be cleaned, with pagerank and name as vertex attributes.
> clean_graph(graph, size=5)

IGRAPH 9c6abc9 DN-- 82 96 -- Erdos renyi (gnp) graph
+ attr: name (g/c), type (g/c), loops (g/l), p (g/n), name (v/n),
| pagerank (v/n)
+ edges from 9c6abc9 (vertex names):
 [1]  72->  1  88->  3  22->  4  11->  6  65->  6  87->  6  60->  7  85->  7
 [9]  84->  9  33-> 10 100-> 10  11->100   2-> 15  40-> 15   3-> 16  34-> 16
[17]  19-> 17  46-> 17   5-> 20  69-> 20 100-> 20  92-> 21  27-> 22  83-> 23
[25]  42-> 24   6-> 25  10-> 26  74-> 27  94-> 27  43-> 31  36-> 33  38-> 35
[33]  59-> 35  90-> 35  60-> 36  70-> 36  53-> 38  26-> 39  46-> 40  88-> 40
[41]  21-> 41  71-> 41  49-> 42  65-> 42  77-> 42  87-> 43 100-> 43  52-> 44
[49]  21-> 45  54-> 46  32-> 49  92-> 49   6-> 50  17-> 50  43-> 52  54-> 52
+ ... omitted several edges
```

Adjusted graph will be outputed, with "pagerank" and "name" as vertex attributes.
The `adjust_graph()` can re-calculate PageRank with updated damping factor, personalized vector and edge weights.

```
> set.seed(1)
> graph <- igraph::erdos.renyi.game(100, 0.01, directed = TRUE)
> igraph::V(graph)$name <- 1:100
> igraph::V(graph)$pagerank <- igraph::page_rank(graph, damping=0.85)$vector
> #the graph to be adjusted, with pagerank and name as vertex attributes.
> adjust_graph(graph, damping=0.1)

IGRAPH d159696 DN-- 100 98 -- Erdos renyi (gnp) graph
+ attr: name (g/c), type (g/c), loops (g/l), p (g/n), name (v/n),
| pagerank (v/n)
+ edges from d159696 (vertex names):
 [1]  72->  1  88->  3  22->  4  11->  6  65->  6  87->  6  60->  7  85->  7
 [9]  84->  9  33-> 10 100-> 10  11->100   2-> 15  40-> 15   3-> 16  34-> 16
[17]  19-> 17  46-> 17   5-> 20  69-> 20 100-> 20  92-> 21  27-> 22  83-> 23
[25]  42-> 24   6-> 25  10-> 26  74-> 27  94-> 27  63-> 30  43-> 31  36-> 33
[33]  38-> 35  59-> 35  90-> 35  60-> 36  70-> 36  53-> 38  26-> 39  46-> 40
[41]  88-> 40  21-> 41  71-> 41  49-> 42  65-> 42  77-> 42  87-> 43 100-> 43
[49]  52-> 44  21-> 45  54-> 46  32-> 49  92-> 49   6-> 50  17-> 50  13-> 51
+ ... omitted several edges
```

Adjusted graph will be outputed, with updated "pagerank" and "name" as vertex attributes.
Please note `diff_graph()`, `multiplex_page_rank()`, `clean_graph()` and `adjust_graph()` can be used in combination for customized PageRank analysis tasks.

3 Prioritizing TFs in GRNs

3.1 Generating GRNs from Multi-Omics Profiles

The `aracne_network()` can re-format ARACNe network in regulon object for PageRank analysis. It can also handle GRNs reverse engineered using other algorithms, as long as such GRNs are written in regulon object.

```
> library(bcellViper)
> data(bcellViper)
> head(aracne_network(regulon[1:10]))

   reg   target direction
1 AATF   SAMM50         1
2 AATF     DRG1         1
3 AATF     ATIC         1
4 AATF  SMARCC1         1
5 AATF     AHCY         1
6 AATF HSD17B10         1
```

The `accessibility_network()` can build network from accessibility, e.g. ATAC-Seq peaks.

```
> table <- data.frame(Chr=c("chr1", "chr1"), Start=c(713689, 856337), End=c(714685, 8
+                     row.names=c("A", "B"), stringsAsFactors=FALSE)
> regulators=c("FOXF2", "MZF1")
> #peaks and regulators to be analyzed
>
> library(GenomicRanges)
> library(GenomicFeatures)
> library(TxDb.Hsapiens.UCSC.hg19.knownGene)
> library(org.Hs.eg.db)
> library(annotate)
> promoter <- promoters(genes(TxDb.Hsapiens.UCSC.hg19.knownGene))
> names(promoter) <- getSYMBOL(names(promoter), data="org.Hs.eg")
> promoter <- promoter[!is.na(names(promoter))]
> #get promoter regions
>
> library(JASPAR2018)
> library(TFBSTools)
> library(motifmatchr)
> pfm <- getMatrixSet(JASPAR2018, list(species="Homo sapiens"))
> pfm <- pfm[unlist(lapply(pfm, function(x) name(x))) %in% regulators]
```

```
> #get regulator position frequency matrix (PFM) list
>
> library(BSgenome.Hsapiens.UCSC.hg19)
> accessibility_network(table, promoter, pfm, "BSgenome.Hsapiens.UCSC.hg19")

       target   reg
1 LOC100288069 FOXF2
2 LOC100288069  MZF1
3    LINC02593 FOXF2
4       SAMD11 FOXF2
5    LINC02593  MZF1
6       SAMD11  MZF1
```

The `conformation_network()` can build network from conformation, e.g. HiChIP records.

```
> table <- data.frame(Chr1=c("chr1", "chr1"), Position1=c(569265, 713603), Strand1=c(
+                     Chr2=c("chr4", "chr1"), Position2=c(206628, 715110), Strand2=c(
+                     row.names=c("A", "B"), stringsAsFactors=FALSE)
> regulators=c("FOXF2", "MZF1")
> #peaks and regulators to be analyzed
>
> promoter <- promoters(genes(TxDb.Hsapiens.UCSC.hg19.knownGene))
> names(promoter) <- getSYMBOL(names(promoter), data="org.Hs.eg")
> promoter <- promoter[!is.na(names(promoter))]
> #get promoter regions
>
> pfm <- getMatrixSet(JASPAR2018, list(species="Homo sapiens"))
> pfm <- pfm[unlist(lapply(pfm, function(x) name(x))) %in% regulators]
> #get regulator position frequency matrix (PFM) list
>
> conformation_network(table, promoter, pfm, "BSgenome.Hsapiens.UCSC.hg19")

       target   reg
1      ZNF876P  MZF1
2 LOC100288069 FOXF2
3 LOC100288069  MZF1
```

3.2 Filter GRNs with Expression Profiles

The `P_graph()` can filter GRNs by quantifying joint and margin probability distributions of regulator-target pairs. Statistically significant non-random regulator-target pairs will be kept.

```
> dset <- exprs(dset)
> net <- do.call(rbind, lapply(1:10, function(i, regulon){
+   data.frame(reg=rep(names(regulon)[i], 10),
+              target=names(regulon[[i]][[1]])[1:10],
+              stringsAsFactors = FALSE)}, regulon=regulon))
> P_graph(dset, net, method="difference", null=NULL, threshold=0.05)

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+ attr: name (v/c), pagerank (v/n), pvalue (e/n)
+ edges from 73d01ac (vertex names):
[1] PPM1G ->AATF   CTBP2 ->APP    TAGLN ->APP    MTSS1 ->APP    JMJD1C->ARID4A
```

3.3 Session Information

```
> sessionInfo()

R version 4.1.0 (2021-05-18)
Platform: x86_64-pc-linux-gnu (64-bit)
Running under: Ubuntu 20.04.2 LTS

Matrix products: default
BLAS:   /home/biocbuild/bbs-3.13-bioc/R/lib/libRblas.so
LAPACK: /home/biocbuild/bbs-3.13-bioc/R/lib/libRlapack.so

locale:
 [1] LC_CTYPE=en_US.UTF-8       LC_NUMERIC=C
 [3] LC_TIME=en_GB              LC_COLLATE=C
 [5] LC_MONETARY=en_US.UTF-8    LC_MESSAGES=en_US.UTF-8
 [7] LC_PAPER=en_US.UTF-8       LC_NAME=C
 [9] LC_ADDRESS=C               LC_TELEPHONE=C
[11] LC_MEASUREMENT=en_US.UTF-8 LC_IDENTIFICATION=C

attached base packages:
```

```
[1] stats4    parallel  stats     graphics  grDevices utils     datasets
[8] methods   base

other attached packages:
 [1] BSgenome.Hsapiens.UCSC.hg19_1.4.3
 [2] BSgenome_1.60.0
 [3] rtracklayer_1.52.0
 [4] Biostrings_2.60.0
 [5] XVector_0.32.0
 [6] motifmatchr_1.14.0
 [7] TFBSTools_1.30.0
 [8] JASPAR2018_1.1.1
 [9] annotate_1.70.0
[10] XML_3.99-0.6
[11] org.Hs.eg.db_3.13.0
[12] TxDb.Hsapiens.UCSC.hg19.knownGene_3.2.2
[13] GenomicFeatures_1.44.0
[14] AnnotationDbi_1.54.0
[15] GenomicRanges_1.44.0
[16] GenomeInfoDb_1.28.0
[17] IRanges_2.26.0
[18] S4Vectors_0.30.0
[19] bcellViper_1.27.0
[20] Biobase_2.52.0
[21] BiocGenerics_0.38.0
[22] pageRank_1.2.0

loaded via a namespace (and not attached):
 [1] bitops_1.0-7                matrixStats_0.58.0
 [3] DirichletMultinomial_1.34.0 bit64_4.0.5
 [5] filelock_1.0.2              progress_1.2.2
 [7] httr_1.4.2                  tools_4.1.0
 [9] utf8_1.2.1                  R6_2.5.0
[11] seqLogo_1.58.0              DBI_1.1.1
[13] colorspace_2.0-1            prettyunits_1.1.1
[15] tidyselect_1.1.1            curl_4.3.1
[17] bit_4.0.4                   compiler_4.1.0
[19] DelayedArray_0.18.0         caTools_1.18.2
[21] scales_1.1.1                readr_1.4.0
[23] rappdirs_0.3.3              digest_0.6.27
[25] stringr_1.4.0               Rsamtools_2.8.0
[27] R.utils_2.10.1              pkgconfig_2.0.3
```

```
[29] MatrixGenerics_1.4.0        dbplyr_2.1.1
[31] fastmap_1.1.0               rlang_0.4.11
[33] rstudioapi_0.13             RSQLite_2.2.7
[35] BiocIO_1.2.0                generics_0.1.0
[37] BiocParallel_1.26.0         gtools_3.8.2
[39] dplyr_1.0.6                 R.oo_1.24.0
[41] RCurl_1.98-1.3              magrittr_2.0.1
[43] GO.db_3.13.0                GenomeInfoDbData_1.2.6
[45] Matrix_1.3-3                Rcpp_1.0.6
[47] munsell_0.5.0               fansi_0.4.2
[49] lifecycle_1.0.0             R.methodsS3_1.8.1
[51] stringi_1.6.2               yaml_2.2.1
[53] SummarizedExperiment_1.22.0 zlibbioc_1.38.0
[55] BiocFileCache_2.0.0         plyr_1.8.6
[57] grid_4.1.0                  blob_1.2.1
[59] crayon_1.4.1                CNEr_1.28.0
[61] lattice_0.20-44             hms_1.1.0
[63] KEGGREST_1.32.0             pillar_1.6.1
[65] igraph_1.2.6                rjson_0.2.20
[67] biomaRt_2.48.0              reshape2_1.4.4
[69] TFMPvalue_0.0.8             glue_1.4.2
[71] vctrs_0.3.8                 png_0.1-7
[73] gtable_0.3.0                poweRlaw_0.70.6
[75] purrr_0.3.4                 assertthat_0.2.1
[77] cachem_1.0.5                ggplot2_3.3.3
[79] xtable_1.8-4                restfulr_0.0.13
[81] pracma_2.3.3                tibble_3.1.2
[83] GenomicAlignments_1.28.0    memoise_2.0.0
[85] ellipsis_0.3.2
```

4 References

1. Rozenshtein, Polina, and Aristides Gionis. "Temporal pagerank." Joint European Conference on Machine Learning and Knowledge Discovery in Databases. Springer, Cham, 2016.
2. Halu, Arda, et al. "Multiplex pagerank." PloS one 8.10 (2013).
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4. Page, Lawrence, et al. The pagerank citation ranking: Bringing order to the web. Stanford InfoLab, 1999.