# Store and query genome data with database back-end

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## Contents

# 1 Abstract

Bioinformatics has become an important part of many areas of biology, and the methodology of extracting useful results from large amounts of raw data effectively and efficiently plays an essential role in analyzing and understanding bioinformatics data. Bioconductor contains plenty of resources of annotation data and experiment data, but it is not always easy and fast to query them.

Two R packages: Organism.dplyr and MultiExperimentDb are developed for easier use of genome wide annotation packages and comparison between multiple experiments. Organism.dplyr provides an integrated presentation of mapping between organism level information and genomic coordinates information, while MultiExperimentDb provides functionality for storing and comparing multiple bioinformatics experiments which contains large matrix data.

# 2 Introduction

This project aims to resolve two problems: easy use of annotation resource about organism level information and genomic coordinates information, and storing and manipulating multiple experiments in *SummarizedExperiment* format in one object.

R packages `Organism.dplyr` and `MultiExperimentDb` are developed to solve the problems and the details are described below. For each package, developing background, methodology, result display and discussion are illustrated.

# 3 Representing and accessing SQL-based bioinformatics resources

## 3.1 Background

Annotation packages in *Bioconductor* which hold organism level and genomic coordinates information are being used more and more by users who analyze of high-throughput genomic data.

OrgDb packages are used for mapping between a central gene identifier and other identifiers while the TxDb packages contain information for connecting a set of genomic coordinates to various transcript oriented features. However, since organism level information and genomic coordinates information are stored in different packages/databases, mapping between gene identifiers and genomic ranges is not easy. For example, finding the transcript ranges according to accession number.

Organism.dplyr provides an alternative interface to these data by integrating the gene identifier mapping functionality of the OrgDb packages (e.g.,org.Hs.eg.db) and the genome coordinate functionality of the TxDb packages (e.g., TxDb.Hsapiens.UCSC.hg38.knownGene).

## 3.2 Methods

### 3.2.1 Approach

#### 3.2.1.1 Data representation

The Organism.dplyr package stores data in an on disk sqlite database file combining data from a given 'TxDb' package and the corresponding 'org' package, thus one database contains information of gene identifiers and genomic coordinates. Once the database is created and stored at given directory, it can be accessed another time.

Data from the OrgDb and TxDb packages are reconstructed and new tables are created in sqlite file. SQL code for creating the database, including both schema and data, are stored in sql files, one file for each organism, separating from the rest of R code. This strategy makes the SQL code clean and easy to maintain.

A *src_organism* object is created by this package to point to the database. Methods from the R Package `dplyr` (a grammar of data manipulation) can be applied to the object created by this package.

#### 3.2.1.2 Software development

Best practices are applied to the software development:

- Unit tests are created to make sure each module of the code works properly.
- R Package `roxygen2` is used for documentation of namespace and help pages.
- Object oriented programming is used for developing this package, and repeated code are extracted to separate functions for reuse.

FIXME: Add a bit about compatibility / interoperability, e.g., you've supported - the select() interface that worked on OrgDbs - extraction methods from GenomicFeatures that worked on TxDbs - methods from dplyr

### 3.2.2 Features

This package provides an interface to map between gene identifiers (entrez id, gene symbol, ensembl id, accession number, ipi number, go id, etc.) as well as between identifiers and range coordinates (including different levels: gene, transcription, exon and cds).

Filters can be applied to genomic coordinates extractor functions, and all columns in the database can be possible filters. The filter functions give users flexibility of extracting genomic coordinates using combination of different conditions.

The data are stored in a sqlite file on disk and accessed by invoking methods on a *src_organism* object. The *src_organism* points to the database file and only reads in the subset of data required to perform the `R command` instead of the whole database.

## 3.3 Results

### 3.3.1 Constructing a *src_organism* object

A *src_organism* object can be created by supplying the name of a 'TxDb' package or an organism name. In both cases, the underlying database is constructed from data in both the 'TxDb' and corresponding 'org' package. Supported organisms and mapping releationships can be seen with 'supportedOrganims()'.

```
    library(Organism.dplyr)
    library(ggplot2)
    supportedOrganisms()
```

#### 3.3.1.1 Make sqlite database by specifying a 'TxDb'

The `src_organism()` constructor creates an on disk sqlite database file with data from a 'TxDb' package and corresponding 'org' package. When the dbpath is specified the file is created at the given path, otherwise a temporary file is created.

Running `src_organism()` without a given path will save the sqlite file to a tempdir():

```
src <- src_organism("TxDb.Hsapiens.UCSC.hg38.knownGene")
```

Alternatively you can provide explicit path to where the sqlite file should be saved.

```
src <- src_organism("TxDb.Hsapiens.UCSC.hg38.knownGene", "path/to/save/sqlite")
```

#### 3.3.1.2 Make sqlite database by specifying organism name

The `src_ucsc()` constructor creates a *src_organism* object from an organism name, genome and identifer. If the genome and identifier are not provided the most recent 'TxDb' pacakge is used.

```
src <- src_ucsc("human", "path/to/save/sqlite")
```

#### 3.3.1.3 Access existing sqlite file

An existing on disk sqlite file can be accessed without recreating the database.

```
path <- system.file("extdata", package = "Organism.dplyr")
src <- src_organism(dbpath = paste0(path, "/example.sqlite"))
src
## src:  sqlite 3.11.1 [C:\Program Files\R\R-devel\library\Organism.dplyr\extdata\example.sqlite]
## tbls: id, id_accession, id_go, id_go_all, id_omim_pm, id_protein,
##   id_transcript, ranges_cds, ranges_exon, ranges_gene, ranges_tx
```

### 3.3.2 Common operations

#### 3.3.2.1 Basic operations

All methods from package [dplyr][] can be used on a *src_organism* object.

Look at all available tables.

```
src_tbls(src)
##  [1] "id"            "id_accession"  "id_go"         "id_go_all"
##  [5] "id_omim_pm"    "id_protein"    "id_transcript" "ranges_cds"
##  [9] "ranges_exon"   "ranges_gene"   "ranges_tx"
```

Look at data from one specific table.

```
tbl(src, "id")
## Source:   query [?? x 6]
## Database: sqlite 3.11.1 [C:\Program Files\R\R-devel\library\Organism.dplyr\extdata\example.sqlite]
##
##       entrez     map         ensembl   symbol
##        <chr>   <chr>           <chr>    <chr>
## 1  100506674    5p12            <NA>  BRCAT54
## 2  102723839    <NA>            <NA> BRCAT107
## 3     394269   17q21            <NA>  BRCA1P1
## 4     394269   17q21            <NA>  BRCA1P1
## 5     394269   17q21            <NA>  BRCA1P1
## 6     394269   17q21            <NA>  BRCA1P1
## 7       5728 10q23.3 ENSG00000171862     PTEN
## 8       5728 10q23.3 ENSG00000171862     PTEN
## 9       5728 10q23.3 ENSG00000171862     PTEN
## 10      5728 10q23.3 ENSG00000171862     PTEN
## # ... with more rows, and 2 more variables: genename <chr>, alias <chr>
```

Look at fields of one table.

```
colnames(tbl(src, "id"))
## [1] "entrez"   "map"      "ensembl"  "symbol"   "genename" "alias"
```

Below are some examples of querying tables using dplyr.

1. Gene symbol start with "BRCA"

```
tbl(src, "id") %>%
    filter(symbol %like% "BRCA%") %>%
    dplyr::select(entrez, map, ensembl, symbol) %>%
    distinct() %>% arrange(symbol) %>% collect()
## # A tibble: 7 × 4
##      entrez     map         ensembl   symbol
##       <chr>   <chr>           <chr>    <chr>
## 1       672   17q21 ENSG00000012048    BRCA1
## 2    394269   17q21            <NA>  BRCA1P1
## 3       675 13q12.3 ENSG00000139618    BRCA2
## 4     60500   13q21            <NA>    BRCA3
## 5 102723839    <NA>            <NA> BRCAT107
## 6 100506674    5p12            <NA>  BRCAT54
## 7      8068   11q23            <NA>   BRCATA
```

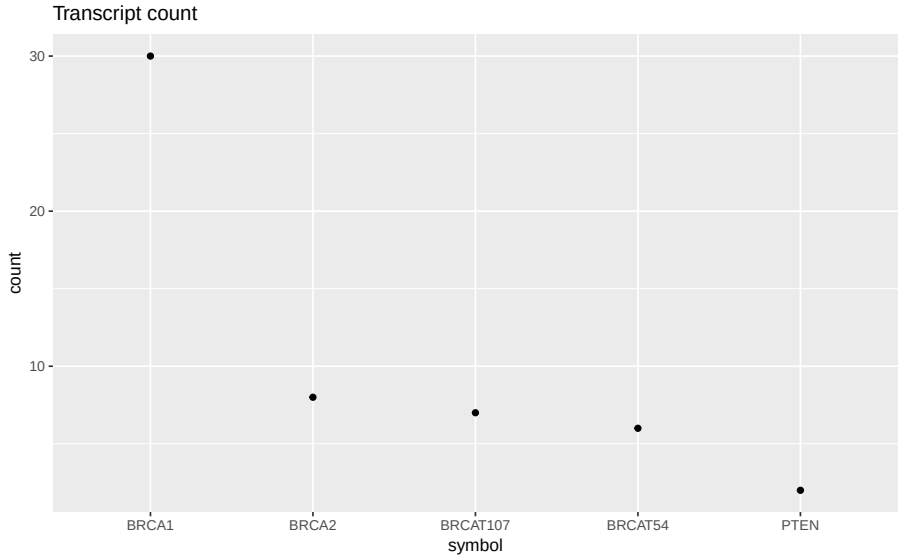
2. Go info for gene symbol "PTEN"

```
    inner_join(tbl(src, "id"), tbl(src, "id_go")) %>%
        filter(symbol == "PTEN") %>%
        dplyr::select(entrez, ensembl, symbol, go, evidence, ontology)
## Joining, by = "entrez"
## Source:   query [?? x 6]
## Database: sqlite 3.11.1 [C:\Program Files\R\R-devel\library\Organism.dplyr\extdata\example.sqlite]
##
##    entrez         ensembl symbol         go evidence ontology
##     <chr>           <chr>  <chr>      <chr>    <chr>    <chr>
## 1    5728 ENSG00000171862   PTEN GO:0000079      TAS       BP
## 2    5728 ENSG00000171862   PTEN GO:0000287      IEA       MF
## 3    5728 ENSG00000171862   PTEN GO:0001525      IEA       BP
## 4    5728 ENSG00000171862   PTEN GO:0001933      IDA       BP
## 5    5728 ENSG00000171862   PTEN GO:0001933      ISS       BP
## 6    5728 ENSG00000171862   PTEN GO:0002902      IEA       BP
## 7    5728 ENSG00000171862   PTEN GO:0004438      IDA       MF
## 8    5728 ENSG00000171862   PTEN GO:0004721      IDA       MF
## 9    5728 ENSG00000171862   PTEN GO:0004722      IDA       MF
## 10   5728 ENSG00000171862   PTEN GO:0004725      IDA       MF
## # ... with more rows
```

3. Genes transcripts count

```
txcount <- inner_join(tbl(src, "id"), tbl(src, "ranges_tx")) %>%
    dplyr::select(symbol, tx_id) %>%
    group_by(symbol) %>%
    summarise(count = count(symbol)) %>%
    dplyr::select(symbol, count) %>%
    arrange(desc(count)) %>%
    collect(n=Inf)
## Joining, by = "entrez"

txcount
## # A tibble: 5 × 2
##     symbol count
##      <chr> <int>
## 1    BRCA1    30
## 2  BRCAT54     8
## 3    BRCA2     7
## 4     PTEN     6
## 5 BRCAT107     2
```




4. Gene coordinates of symbol "PTEN" and "BRCA1" as *GRanges*

```
inner_join(tbl(src, "id"), tbl(src, "ranges_gene")) %>%
    filter(symbol %in% c("PTEN", "BRCA1")) %>%
    dplyr::select(gene_chrom, gene_start, gene_end, gene_strand,
                  symbol, map) %>%
    collect() %>% GenomicRanges::GRanges()
## Joining, by = "entrez"
## GRanges object with 2 ranges and 2 metadata columns:
##       seqnames               ranges strand |      symbol         map
##          <Rle>            <IRanges>  <Rle> | <character> <character>
##   [1]    chr10 [87863113, 87971930]      + |        PTEN     10q23.3
##   [2]    chr17 [43044295, 43170245]      - |       BRCA1       17q21
##   -------
##   seqinfo: 2 sequences from an unspecified genome; no seqlengths
```

#### 3.3.2.2 "select" interface

Methods `select()`, `keytypes()`, `keys()`, `columns()` and `mapIds` from *AnnotationDbi* are implemented for *src_organism* objects.

1. `keytypes()`

Use `keytypes()` to discover which keytypes can be passed to keytype argument of methods `select()` or `keys()`.

```
keytypes(src)
##  [1] "accnum"       "alias"        "cds_chrom"    "cds_end"
##  [5] "cds_id"       "cds_name"     "cds_start"    "cds_strand"
##  [9] "ensembl"      "ensemblprot"  "ensembltrans" "entrez"
## [13] "enzyme"       "evidence"     "evidenceall"  "exon_chrom"
## [17] "exon_end"     "exon_id"      "exon_name"    "exon_rank"
## [21] "exon_start"   "exon_strand"  "gene_chrom"   "gene_end"
## [25] "gene_start"   "gene_strand"  "genename"     "go"
```

```
## [29] "goall"        "ipi"          "map"          "omim"
## [33] "ontology"     "ontologyall"  "pfam"         "pmid"
## [37] "prosite"      "refseq"       "symbol"       "tx_chrom"
## [41] "tx_end"       "tx_id"        "tx_name"      "tx_start"
## [45] "tx_strand"    "tx_type"      "unigene"      "uniprot"
```

2. `columns()`

Use `columns()` to discover which kinds of data can be returned for the *src_organism* object.

```
columns(src)
##  [1] "accnum"       "alias"        "cds_chrom"    "cds_end"
##  [5] "cds_id"       "cds_name"     "cds_start"    "cds_strand"
##  [9] "ensembl"      "ensemblprot"  "ensembltrans" "entrez"
## [13] "enzyme"       "evidence"     "evidenceall"  "exon_chrom"
## [17] "exon_end"     "exon_id"      "exon_name"    "exon_rank"
## [21] "exon_start"   "exon_strand"  "gene_chrom"   "gene_end"
## [25] "gene_start"   "gene_strand"  "genename"     "go"
## [29] "goall"        "ipi"          "map"          "omim"
## [33] "ontology"     "ontologyall"  "pfam"         "pmid"
## [37] "prosite"      "refseq"       "symbol"       "tx_chrom"
## [41] "tx_end"       "tx_id"        "tx_name"      "tx_start"
## [45] "tx_strand"    "tx_type"      "unigene"      "uniprot"
```

3. `keys()`

`keys()` returns keys for the *src_organism* object. By default it returns the primary keys for the database, and returns the keys from that keytype when the keytype argument is used.

Keys of entrez

```
head(keys(src))
## [1] "100506674" "102723839" "394269"    "5728"      "60500"     "672"
```

Keys of symbol

```
head(keys(src, "symbol"))
## [1] "BRCA1"    "BRCA1P1"  "BRCA2"    "BRCA3"    "BRCAT107" "BRCAT54"
```

4. `select()`

`select()` retrieves the data as a *tibble* based on parameters for selected keys columns and keytype arguments. If requested columns that have multiple matches for the keys, `select_tbl()` will return a *tibble* with one row for each possible match, and `select()` will return a data frame.

```
keytype <- "symbol"
keys <- c("PTEN", "BRCA1")
columns <- c("entrez", "tx_id", "tx_name","exon_id")
select_tbl(src, keys, columns, keytype)
## Joining, by = "entrez"
## Source:   query [?? x 5]
## Database: sqlite 3.11.1 [C:\Program Files\R\R-devel\library\Organism.dplyr\extdata\example.sqlite]
##
```

```
##    symbol entrez  tx_id    tx_name exon_id
##     <chr>  <chr>  <int>      <chr>   <int>
## 1   BRCA1    672 147976 uc002icq.4  439447
## 2   BRCA1    672 147976 uc002icq.4  439452
## 3   BRCA1    672 147976 uc002icq.4  439453
## 4   BRCA1    672 147976 uc002icq.4  439455
## 5   BRCA1    672 147976 uc002icq.4  439456
## 6   BRCA1    672 147976 uc002icq.4  439457
## 7   BRCA1    672 147976 uc002icq.4  439460
## 8   BRCA1    672 147976 uc002icq.4  439462
## 9   BRCA1    672 147976 uc002icq.4  439464
## 10  BRCA1    672 147976 uc002icq.4  439465
## # ... with more rows
```

5. `mapIds()`

`mapIds()` gets the mapped ids (column) for a set of keys that are of a particular keytype. Usually returned as a named character vector.

```
mapIds(src, keys, column = "tx_name", keytype)
## Joining, by = "entrez"
##         PTEN        BRCA1
## "uc001kfb.4" "uc002icq.4"
```

#### 3.3.2.3 Genomic coordinates extractors

Eleven genomic coordinates extractor methods are available in this package: `transcripts()`, `exons()`, `cds()`, `genes()`, `promoters()`, `transcriptsBy()`, `exonsBy()`, `cdsBy()`, `intronsByTranscript()`, `fiveUTRsByTranscript()`, `threeUTRsByTranscript()`.

These extractors are similar to those in the `GenomicFeatures` package with a couple of notable differences. The first is that all extractors have a '_tbl' counterpart function, e.g., `exons_tbl()`, which return a *tibble* object from the `dplyr` package instead of the usual *GRanges* or *GRangesList*.

The second difference is the enhanced functionality of the 'filter' argument. In Organism.dplyr methods, the 'filter' argument can be a list of filters defined by any variable in the database. Use `possibleFilters()` to see all options.

```
possibleFilters()
##  [1] "AccnumFilter"       "AliasFilter"        "Cds_chromFilter"
##  [4] "Cds_idFilter"       "Cds_nameFilter"     "Cds_strandFilter"
##  [7] "EnsemblFilter"      "EnsemblprotFilter"  "EnsembltransFilter"
## [10] "EntrezFilter"       "EnzymeFilter"       "EvidenceFilter"
## [13] "EvidenceallFilter"  "Exon_chromFilter"   "Exon_idFilter"
## [16] "Exon_nameFilter"    "Exon_rankFilter"    "Exon_strandFilter"
## [19] "FlybaseFilter"      "Flybase_cgFilter"   "Flybase_protFilter"
## [22] "Gene_chromFilter"   "Gene_strandFilter"  "GenenameFilter"
## [25] "GoFilter"           "GoallFilter"        "IpiFilter"
## [28] "MapFilter"          "MgiFilter"          "OmimFilter"
## [31] "OntologyFilter"     "OntologyallFilter"  "PfamFilter"
## [34] "PmidFilter"         "PrositeFilter"      "RefseqFilter"
```

```
## [37] "SymbolFilter"       "Tx_chromFilter"     "Tx_idFilter"
## [40] "Tx_nameFilter"      "Tx_strandFilter"    "Tx_typeFilter"
## [43] "UnigeneFilter"      "UniprotFilter"      "WormbaseFilter"
## [46] "ZfinFilter"         "Cds_startFilter"    "Cds_endFilter"
## [49] "Exon_startFilter"   "Exon_endFilter"     "Gene_startFilter"
## [52] "Gene_endFilter"     "Tx_startFilter"     "Tx_endFilter"
```

All filters take two parameters: value and condition, condition could be one of "==", "!=", "startsWith", "endsWith", ">", "<", ">=" and "<=", default condition is "==".

```
EnsemblFilter("ENSG00000171862")
## class: EnsemblFilter
## condition: ==
## value: ENSG00000171862
SymbolFilter("BRCA", "startsWith")
## class: SymbolFilter
## condition: startsWith
## value: BRCA
```

Besides, `GRangesFilter()` could also be used as filter for the methods with result displaying as *GRanges* or *GRangesList*.

```
filters <- list(SymbolFilter(c("PTEN", "BRCA1")),
                EntrezFilter(5728),
                GRangesFilter(as("chr10:87869000-87876000", "GRanges")))
transcripts_tbl(src, filter=filters)
## filter by 'granges' only supported by methods returning GRanges or GRangesList
## Joining, by = "entrez"
## Source:   query [?? x 8]
## Database: sqlite 3.11.1 [C:\Program Files\R\R-devel\library\Organism.dplyr\extdata\example.sqlite]
##
##   tx_chrom tx_start   tx_end tx_strand tx_id    tx_name symbol entrez
##      <chr>    <int>    <int>     <chr> <int>      <chr>  <chr>  <chr>
## 1    chr10 87863113 87971930         + 87010 uc001kfb.4   PTEN   5728
## 2    chr10 87863438 87942691         + 87011 uc057ush.1   PTEN   5728
## 3    chr10 87864449 87867049         + 87012 uc057usi.1   PTEN   5728
## 4    chr10 87864468 87894326         + 87013 uc057usj.1   PTEN   5728
## 5    chr10 87925523 87933487         + 87016 uc057usm.1   PTEN   5728
## 6    chr10 87952199 87961309         + 87017 uc057usn.1   PTEN   5728
transcripts(src, filter=filters)
## Joining, by = "entrez"
## GRanges object with 3 ranges and 4 metadata columns:
##       seqnames               ranges strand |     tx_id     tx_name
##          <Rle>            <IRanges>  <Rle> | <integer> <character>
##   [1]    chr10 [87863113, 87971930]      + |     87010  uc001kfb.4
##   [2]    chr10 [87863438, 87942691]      + |     87011  uc057ush.1
##   [3]    chr10 [87864468, 87894326]      + |     87013  uc057usj.1
##            symbol      entrez
##       <character> <character>
##   [1]        PTEN        5728
##   [2]        PTEN        5728
##   [3]        PTEN        5728
```

```
##   -------
##   seqinfo: 455 sequences (1 circular) from hg38 genome
```

Transcript coordinates of gene symbol equal to "PTEN" or "BRCA1", and transcript start position between 87863438 and 87933487.

```
transcripts_tbl(src, filter = list(
    SymbolFilter(c("PTEN", "BRCA1")),
    Tx_startFilter(87863438,">="),
    Tx_startFilter(87933487, "<=")
))
## Joining, by = "entrez"
## Source:   query [?? x 7]
## Database: sqlite 3.11.1 [C:\Program Files\R\R-devel\library\Organism.dplyr\extdata\example.sqlite]
##
##   tx_chrom tx_start   tx_end tx_strand tx_id    tx_name symbol
##      <chr>    <int>    <int>     <chr> <int>      <chr>  <chr>
## 1    chr10 87863438 87942691         + 87011 uc057ush.1   PTEN
## 2    chr10 87864449 87867049         + 87012 uc057usi.1   PTEN
## 3    chr10 87864468 87894326         + 87013 uc057usj.1   PTEN
## 4    chr10 87925523 87933487         + 87016 uc057usm.1   PTEN
```

## 3.4 Discussion

### 3.4.1 Assessment of Organism.dplyr

#### 3.4.1.1 Strengths

- Combine data of gene identifiers and genomic coordinates into one sqlite file
- Provide flexibility of filters for genomic coordinates extractor functions
- sqlite file can be stored on disk and it is easy to access multiple times

#### 3.4.1.2 Weakness

- It takes longer time to create sqlite file the first time
- The sqlite file could be big in size

### 3.4.2 Future development

- Make filter functions more flexible by adding conditions (and, or) between filters
- Support more organisms

# 4 Coordinated on-disk representation of multiple bioinformatic experiments

## 4.1 Background

Package MultiExperimentDb provides functionality for storing and comparing multiple *SummarizedExperiment* objects, the data can be added to one object and stored on disk for reuse.

This package is designed for comparing data between different experiments, the experiments added to a *MultiExperimentDb* object should have some similarity such as common features or samples. This overlap allows features or samples to be extracted and viewed together across experiments by combining by row or column.

## 4.2 Methods

Package MultiExperimentDb creates a *MultiExperimentDb* object to store all data on disk, with assays data in matrix format stored in HDF5 file, and annotation data like rowData, colDate, rowRanges stored in sqlite database.

This design reduces the overall memory footprint and can provide faster random asses to subsets of data because we are indexing into data on disk vs making copies of in-memory objects. By storing large matrices on disk in HDF5 file and displaying in R using *DelayedMatrix* object, minimal data needs to be brought into R. This design fastens matrix data manipulation, including subset, binding, etc.

Data of *MultiExperimentDb* object with multiple SummarizedExperiments is stored in one sqlite file and one HDF5 file. Assay data in large matrix format is stored in HDF5 file, when one experiment is added, assay data of that experiment is added to the HDF5 file as one dataset with experiment name as dataset name. Rownames, colnames, rowdata, coldata, rowranges are stored in one sqlite database file and each experiment represented by one unique index and one unique experiment name.

## 4.3 Results

### 4.3.1 Constructing a *MultiExperimentDb*

The `MultiExperimentDb()` constructor creates an empty *MultiExperimentDb* instance. When hdf5path and sqlitepath are given, files are created at the given path(s), otherwise temporary files are created. An empty *MultiExperimentDb* object needs to be created as first step before adding any experiments.

Creating a *MultiExperimentDb* instance without given paths will save the hdf5 and sqlite files in a tempfile():

```
library(MultiExperimentDb)
medb <- MultiExperimentDb()
```

Alternatively you can provide explicit paths to where the files should be saved.

```
medb <- MultiExperimentDb(hdf5path = "path/to/save/hdf5/",
                          sqlitepath = "path/to/save/sqlite")
```

The class supports common operations such as `length()`, `dim()`, `dimnames()` etc.

`loadMultiExperimentDb(hdf5path, sqlitepath)` can be used to create a *MultiExperimentDb* object from existing hdf5 and sqlite files stored on disk. It can be used when experiments are added to *MultiExperimentDb* object and saved on disk, then need to be accessed another time.

```
path <- system.file("extdata", package = "MultiExperimentDb")
medb <- loadMultiExperimentDb(paste0(path, "/medb.h5"),
                              paste0(path, "/medb.sqlite"))
medb
## class: MultiExperimentDb
## hdf5path: C:/Program Files/R/R-devel/library/MultiExperimentDb/extdata/medb.h5
## sqlitepath: C:/Program Files/R/R-devel/library/MultiExperimentDb/extdata/medb.sqlite
## dim: 1300 8
## experiments:
##   geuFPKM1 (1000 x 6)
##     rownames: ENSG00000152931.6, ENSG00000183696.9,
##       ENSG00000139269.2, ..., ENSG00000161016.10, ENSG00000150787.3
##     colnames: HG00096, HG00097, HG00099, HG00100, HG00101, HG00102
##   geuFPKM2 (1001 x 6)
##     rownames: ENSG00000115211.10, ENSG00000231419.2,
##       ENSG00000196233.6, ..., ENSG00000167460.9, ENSG00000171208.5
##     colnames: HG00099, HG00100, HG00101, HG00102, HG00103, HG00104
```

Get sqlite database path and HDF5 file path of a *MultiExperimentDb* object with the `hdf5path()` and `sqlitepath()` accessors.

```
hdf5path(medb)
## [1] "C:/Program Files/R/R-devel/library/MultiExperimentDb/extdata/medb.h5"
sqlitepath(medb)
## [1] "C:/Program Files/R/R-devel/library/MultiExperimentDb/extdata/medb.sqlite"
```

## 4.3.2 Common operations on a *MultiExperimentDb*

### 4.3.2.1 Adding data

An experiment (i.e., *SummarizedExperiment* object) can be added to a *MultiExperimentDb* instance with `addExperiment()`. Experiment names must be unique.

Add data to the *MultiExperimentDb*.

```
medb <- MultiExperimentDb()
library(geuvPack)
data(geuFPKM)
medb <- addExperiment(medb, geuFPKM[1:1000, 1:6], "geuFPKM1")
medb <- addExperiment(medb, geuFPKM[300:1300, 3:8], "geuFPKM2")
experimentNames(medb)
## [1] "geuFPKM1" "geuFPKM2"
```

```
medb
## class: MultiExperimentDb
## hdf5path: C:\Users\YU19864\AppData\Local\Temp\RtmpqIXrJA\file133853261acc.h5
## sqlitepath: C:\Users\YU19864\AppData\Local\Temp\RtmpqIXrJA\file13383d22bc5.sqlite
## dim: 1300 8
## experiments:
##   geuFPKM1 (1000 x 6)
##     rownames: ENSG00000152931.6, ENSG00000183696.9,
##       ENSG00000139269.2, ..., ENSG00000161016.10, ENSG00000150787.3
##     colnames: HG00096, HG00097, HG00099, HG00100, HG00101, HG00102
##   geuFPKM2 (1001 x 6)
##     rownames: ENSG00000115211.10, ENSG00000231419.2,
##       ENSG00000196233.6, ..., ENSG00000167460.9, ENSG00000171208.5
##     colnames: HG00099, HG00100, HG00101, HG00102, HG00103, HG00104
```

#### 4.3.2.2 Extract experiment and assay data

The `experiment()` function extracts a single experiment from a *MultiExperimentDb* as a *SummarizedExperiment* object, all methods of *SummarizedExperiment* can be applied, such as `colData()`, `rowRanges()`, etc.

```
se <- experiment(medb, "geuFPKM1")
colData(se)[, 1:3]
## DataFrame with 6 rows and 3 columns
##         Source.Name Comment.ENA_SAMPLE. Characteristics.Organism.
##         <character>           <factor>                 <factor>
## HG00096     HG00096           ERS185276              Homo sapiens
## HG00097     HG00097           ERS185206              Homo sapiens
## HG00099     HG00099           ERS185128              Homo sapiens
## HG00100     HG00100           ERS185086              Homo sapiens
## HG00101     HG00101           ERS185085              Homo sapiens
## HG00102     HG00102           ERS185453              Homo sapiens
rowRanges(se)[, 1:3]
## GRanges object with 1000 ranges and 3 metadata columns:
##                       seqnames                ranges strand |   source
##                          <Rle>             <IRanges>  <Rle> | <factor>
##    ENSG00000152931.6     chr5 [ 59783540,  59843484]      + |   HAVANA
##    ENSG00000183696.9     chr7 [ 48128225,  48148330]      + |   HAVANA
##    ENSG00000139269.2    chr12 [ 57846106,  57853063]      + |   HAVANA
##    ENSG00000169129.8    chr10 [116054583, 116164515]      - |   HAVANA
##   ENSG00000134602.11     chrX [131157293, 131209971]      + |   HAVANA
##                  ...      ...                   ...    ... .      ...
##    ENSG00000169231.8     chr1 [155165379, 155178842]      - |   HAVANA
##    ENSG00000250937.2    chr12 [  8404007,   8450140]      + |   HAVANA
##    ENSG00000123595.5     chrX [ 13707244,  13728625]      + |   HAVANA
##   ENSG00000161016.10     chr8 [146015150, 146017972]      - |   HAVANA
##    ENSG00000150787.3    chr11 [112097088, 112140678]      + |   HAVANA
##                         type     score
##                       <factor> <numeric>
##    ENSG00000152931.6     gene      <NA>
```

```
##    ENSG00000183696.9     gene      <NA>
##    ENSG00000139269.2     gene      <NA>
##    ENSG00000169129.8     gene      <NA>
##   ENSG00000134602.11     gene      <NA>
##                  ...      ...       ...
##    ENSG00000169231.8     gene      <NA>
##    ENSG00000250937.2     gene      <NA>
##    ENSG00000123595.5     gene      <NA>
##   ENSG00000161016.10     gene      <NA>
##    ENSG00000150787.3     gene      <NA>
##   -------
##   seqinfo: 25 sequences from an unspecified genome; no seqlengths
```

Get a single assay as *DelayedMatrix* by calling the `assay()` function with the *MultiExperimentDb* and experiment name. It returns the HDF5Array assay data corresponding to the current *MultiExperimentDb* row and column selections, example is given in subsetting section.

```
assay(medb, "geuFPKM1")[, 1:3]
## DelayedMatrix object of 1000 x 3 doubles:
##                          HG00096       HG00097       HG00099
##  ENSG00000152931.6    0.10185777    0.07810952    0.04898067
##  ENSG00000183696.9    8.18380495    5.68691051    2.43465333
##  ENSG00000139269.2    1.19991029    1.57357170    0.52161578
##  ENSG00000169129.8    0.83193983    0.06977775    0.93108575
## ENSG00000134602.11   27.64642237   24.39557150   16.44537352
##                ...             .             .             .
##  ENSG00000169231.8  1.415487e+00  1.250576e+00  1.244898e+00
##  ENSG00000250937.2 -3.594809e-03 -1.205084e-02  1.081309e-02
##  ENSG00000123595.5  2.934674e+01  2.854369e+01  2.315665e+01
## ENSG00000161016.10  1.457868e+03  1.359101e+03  8.191642e+02
##  ENSG00000150787.3  4.776680e+00  4.479469e+00  1.990667e+00
```

#### 4.3.2.3 Subsetting

A *MultiExperimentDb* object can be subset by overlapping rows or columns using standard numeric indices or feature/column names.

Subset all experiments by common rownames.

```
medb[c("ENSG00000171603.11","ENSG00000230216.1"),,]
## class: MultiExperimentDb
## hdf5path: C:\Users\YU19864\AppData\Local\Temp\RtmpqIXrJA\file133853261acc.h5
## sqlitepath: C:\Users\YU19864\AppData\Local\Temp\RtmpqIXrJA\file13383d22bc5.sqlite
## dim: 2 8
## experiments:
##   geuFPKM1 (2 x 6)
##     rownames: ENSG00000171603.11, ENSG00000230216.1
##     colnames: HG00096, HG00097, HG00099, HG00100, HG00101, HG00102
##   geuFPKM2 (2 x 6)
##     rownames: ENSG00000171603.11, ENSG00000230216.1
##     colnames: HG00099, HG00100, HG00101, HG00102, HG00103, HG00104
```

Return a subset of the "geuFPKM1" experiment with specific rows and column names.

```
medb[1:6,c("HG00099","HG00101"),"geuFPKM1"]
## class: MultiExperimentDb
## hdf5path: C:\Users\YU19864\AppData\Local\Temp\RtmpqIXrJA\file133853261acc.h5
## sqlitepath: C:\Users\YU19864\AppData\Local\Temp\RtmpqIXrJA\file13383d22bc5.sqlite
## dim: 6 2
## experiments:
##   geuFPKM1 (6 x 2)
##     rownames: ENSG00000152931.6, ENSG00000183696.9,
##       ENSG00000139269.2, ENSG00000169129.8, ENSG00000134602.11,
##       ENSG00000136237.12
##     colnames: HG00099, HG00101
```

A *MultiExperimentDb* object can also be subset by a *GRanges* object. The `grangesFromIdentifiers()` helper creates a *GRanges* from and OrgDb, TxDb and specified 'keys' and 'keytypes'. This function uses `select()` with a specified OrgDb and TxDb package to convert given gene symbols or names to genomic positions. See ?grangesFromIdentifiers man page for details.

Convert gene symbols PTEN and BRCA1 to genomic position:

```
granges <- grangesFromIdentifiers(org = "org.Hs.eg.db",
           keys = c("BRCA1", "CLSTN1","WDR45"), keytype = "SYMBOL",
           txdb = "TxDb.Hsapiens.UCSC.hg38.knownGene")
## 'select()' returned 1:1 mapping between keys and columns
granges
## GRanges object with 3 ranges and 1 metadata column:
##         seqnames              ranges strand |     gene_id
##            <Rle>           <IRanges>  <Rle> | <character>
##   11152     chrX [49074429, 49101170]      - |       11152
##   22883     chr1 [ 9729026,  9824526]      - |       22883
##     672    chr17 [43044295, 43170245]      - |         672
##   -------
##   seqinfo: 455 sequences (1 circular) from hg38 genome
```

Search all experiments by gene symbol BRCA1, CLSTN1 and WDR45:

```
medb <- medb[granges,,]
medb
## class: MultiExperimentDb
## hdf5path: C:\Users\YU19864\AppData\Local\Temp\RtmpqIXrJA\file133853261acc.h5
## sqlitepath: C:\Users\YU19864\AppData\Local\Temp\RtmpqIXrJA\file13383d22bc5.sqlite
## dim: 3 8
## experiments:
##   geuFPKM1 (2 x 6)
##     rownames: ENSG00000171603.11, ENSG00000230216.1
##     colnames: HG00096, HG00097, HG00099, HG00100, HG00101, HG00102
##   geuFPKM2 (3 x 6)
##     rownames: ENSG00000171603.11, ENSG00000230216.1,
##       ENSG00000172992.6
##     colnames: HG00099, HG00100, HG00101, HG00102, HG00103, HG00104
assay(medb, "geuFPKM1")
```

```
## DelayedMatrix object of 2 x 6 doubles:
##                      HG00096   HG00097   HG00099   HG00100   HG00101
## ENSG00000171603.11 21.474466 23.357203 13.218601 21.748905 22.694890
## ENSG00000230216.1   3.136087  5.162155  3.223215  5.606075  5.466393
##                      HG00102
## ENSG00000171603.11 27.397227
## ENSG00000230216.1   5.279783
```

A *MultiExperimentDb* can be subset on all common rows across experiments:

```
intersectRownames(medb, rownames=NULL)
## class: MultiExperimentDb
## hdf5path: C:\Users\YU19864\AppData\Local\Temp\RtmpqIXrJA\file133853261acc.h5
## sqlitepath: C:\Users\YU19864\AppData\Local\Temp\RtmpqIXrJA\file13383d22bc5.sqlite
## dim: 2 8
## experiments:
##   geuFPKM1 (2 x 6)
##     rownames: ENSG00000171603.11, ENSG00000230216.1
##     colnames: HG00096, HG00097, HG00099, HG00100, HG00101, HG00102
##   geuFPKM2 (2 x 6)
##     rownames: ENSG00000171603.11, ENSG00000230216.1
##     colnames: HG00099, HG00100, HG00101, HG00102, HG00103, HG00104
```

or all common columns across experiments:

```
intersectColnames(medb, colnames=NULL)
## class: MultiExperimentDb
## hdf5path: C:\Users\YU19864\AppData\Local\Temp\RtmpqIXrJA\file133853261acc.h5
## sqlitepath: C:\Users\YU19864\AppData\Local\Temp\RtmpqIXrJA\file13383d22bc5.sqlite
## dim: 3 4
## experiments:
##   geuFPKM1 (2 x 4)
##     rownames: ENSG00000171603.11, ENSG00000230216.1
##     colnames: HG00099, HG00100, HG00101, HG00102
##   geuFPKM2 (3 x 4)
##     rownames: ENSG00000171603.11, ENSG00000230216.1,
##       ENSG00000172992.6
##     colnames: HG00099, HG00100, HG00101, HG00102
```

#### 4.3.2.4 Combine by columns or rows

To look at assay data of all experiments together, combine all rows of assays in a *MultiExperimentDb* object with matching columns, numbers of columns of each experiments in the *MultiExperimentDb* object don't need to be the same. When the argument `all.columns` is TRUE, the output is a matrix with columns across all assays where missing values are represented with NA. Default is FALSE, only columns that exist in all assays display.

```
rbindme(medb)
## DelayedMatrix object of 5 x 4 doubles:
##                      HG00099   HG00100   HG00101   HG00102
## ENSG00000171603.11 13.218601 21.748905 22.694890 27.397227
```

```
## ENSG00000230216.1   3.223215  5.606075  5.466393  5.279783
## ENSG00000171603.11 13.218601 21.748905 22.694890 27.397227
## ENSG00000230216.1   3.223215  5.606075  5.466393  5.279783
## ENSG00000172992.6  10.875091 13.999134 16.376246 14.116252
rbindme(medb, all.columns=TRUE)
## DelayedMatrix object of 5 x 8 doubles:
##                      HG00096   HG00097   HG00099       .   HG00103   HG00104
## ENSG00000171603.11 21.474466 23.357203 13.218601       .        NA        NA
## ENSG00000230216.1   3.136087  5.162155  3.223215       .        NA        NA
## ENSG00000171603.11        NA        NA 13.218601       . 26.124471 22.235168
## ENSG00000230216.1         NA        NA  3.223215       .  7.324214  6.869039
## ENSG00000172992.6         NA        NA 10.875091       . 17.132905 16.163483
```

Combine all columns of assays in a *MultiExperimentDb* object with matching rows, numbers of rows of each experiments in the *MultiExperimentDb* object don't need to be the same. When the argument `all.rows` is TRUE, the output is a matrix with rows across all assays where missing values are represented with NA. Default is FALSE, only rows that exist in all assays display.

```
cbindme(medb)
## DelayedMatrix object of 2 x 12 doubles:
##                      HG00096   HG00097   HG00099       .   HG00103   HG00104
## ENSG00000171603.11 21.474466 23.357203 13.218601       . 26.124471 22.235168
## ENSG00000230216.1   3.136087  5.162155  3.223215       .  7.324214  6.869039
cbindme(medb, all.rows=TRUE)
## DelayedMatrix object of 3 x 12 doubles:
##                      HG00096   HG00097   HG00099       .   HG00103   HG00104
## ENSG00000171603.11 21.474466 23.357203 13.218601       . 26.124471 22.235168
## ENSG00000230216.1   3.136087  5.162155  3.223215       .  7.324214  6.869039
## ENSG00000172992.6         NA        NA        NA       . 17.132905 16.163483
```

### 4.3.3 Comparing treated vs untreated 'airway' data

This package is designed for comparing data between different experiments with similarity (overlapping features or samples across experiments). The construction of displaying assay data with *DelayedMatrix* object reduces memory usage and optimizes performance. Below is an example of analyzing data from multiple experiments using *MultiExperimentDb*.

In the example below, a *RangedSummarizedExperiment* object of read counts in genes for an RNA-Seq experiment on human airway smooth muscle cell lines is used. Two experiments are generated from airway: airway_untrt with four untreated cell lines and airway_trt with four treated cell lines.

Create an empty *MultiExperimentDb* object.

```
medb0 <- MultiExperimentDb()
```

Add data for treated and untreated experiments to the 'medb0' object.

```
library(airway)
data(airway)
medb0 <- addExperiment(medb0,
```

```
            airway[,colData(airway)$dex == "untrt"], "airway_untrt")
medb0 <- addExperiment(medb0,
            airway[,colData(airway)$dex == "trt"], "airway_trt")

experimentNames(medb0)
## [1] "airway_untrt" "airway_trt"
length(medb0)
## [1] 2
dim(medb0)
## [1] 64102     8
dimnames(medb0)
## CharacterList of length 2
## [[1]] ENSG00000000003 ENSG00000000005 ENSG00000000419 ... LRG_98 LRG_99
## [[2]] SRR1039508 SRR1039512 SRR1039516 ... SRR1039513 SRR1039517 SRR1039521
```

Comparing object sizes of the airway data in the original *RangedSummarizedExperiment* format to the *MultiExperimentDb* format we see the *MultiExperimentDb* object is much smaller.

```
format(object.size(airway), units = "Mb")
## [1] "58.9 Mb"

format(object.size(medb0), units = "Mb")
## [1] "8.3 Mb"
```

Subset the data by the BRCA1 and BRCA2 gene symbols.

```
granges <- grangesFromIdentifiers(org = "org.Hs.eg.db",
           keys = c("BRCA1", "BRCA2"), keytype = "SYMBOL",
           txdb = "TxDb.Hsapiens.UCSC.hg19.knownGene")
## 'select()' returned 1:1 mapping between keys and columns
medb0 <- medb0[granges,,]
medb0
## class: MultiExperimentDb
## hdf5path: C:\Users\YU19864\AppData\Local\Temp\RtmpqIXrJA\file13383c24218c.h5
## sqlitepath: C:\Users\YU19864\AppData\Local\Temp\RtmpqIXrJA\file1338c7622b3.sqlite
## dim: 6 8
## experiments:
##   airway_untrt (6 x 4)
##     rownames: ENSG00000012048, ENSG00000139618, ENSG00000215515,
##       ENSG00000267002, ENSG00000267340, ENSG00000267595
##     colnames: SRR1039508, SRR1039512, SRR1039516, SRR1039520
##   airway_trt (6 x 4)
##     rownames: ENSG00000012048, ENSG00000139618, ENSG00000215515,
##       ENSG00000267002, ENSG00000267340, ENSG00000267595
##     colnames: SRR1039509, SRR1039513, SRR1039517, SRR1039521
```

Look at data of experiment "airway_trt" after subset.

```
airway_trt <- experiment(medb0, "airway_trt")
colData(airway_trt)
## DataFrame with 4 rows and 9 columns
```

```
##            SampleName     cell      dex    albut        Run avgLength
##              <factor> <factor> <factor> <factor>   <factor> <integer>
## SRR1039509 GSM1275863   N61311      trt    untrt SRR1039509       126
## SRR1039513 GSM1275867  N052611      trt    untrt SRR1039513        87
## SRR1039517 GSM1275871  N080611      trt    untrt SRR1039517       126
## SRR1039521 GSM1275875  N061011      trt    untrt SRR1039521        98
##            Experiment    Sample    BioSample
##              <factor>  <factor>     <factor>
## SRR1039509  SRX384346 SRS508567 SAMN02422675
## SRR1039513  SRX384350 SRS508572 SAMN02422670
## SRR1039517  SRX384354 SRS508576 SAMN02422673
## SRR1039521  SRX384358 SRS508580 SAMN02422677
rowRanges(airway_trt)
## GRangesList object of length 6:
## $ENSG00000012048
## GRanges object with 99 ranges and 0 metadata columns:
##        seqnames              ranges strand
##           <Rle>           <IRanges>  <Rle>
##    [1]       17 [41196312, 41197819]      -
##    [2]       17 [41196313, 41197819]      -
##    [3]       17 [41196822, 41197819]      -
##    [4]       17 [41197580, 41197819]      -
##    [5]       17 [41197646, 41197819]      -
##    ...      ...                 ...    ...
##   [95]       17 [41277294, 41277376]      -
##   [96]       17 [41277294, 41277387]      -
##   [97]       17 [41277294, 41277419]      -
##   [98]       17 [41277294, 41277467]      -
##   [99]       17 [41277294, 41277468]      -
##
## ...
## <5 more elements>
## -------
## seqinfo: 2 sequences from an unspecified genome; no seqlengths
assay(medb0, "airway_trt")
## DelayedMatrix object of 6 x 4 integers:
##                 SRR1039509 SRR1039513 SRR1039517 SRR1039521
## ENSG00000012048         98         95        168        155
## ENSG00000139618         54         30         55         40
## ENSG00000215515          0          0          0          0
## ENSG00000267002         35         24         40         45
## ENSG00000267340          1          3          9          1
## ENSG00000267595          3          5          6          6
```

Combine all columns of assays in *medb* with matching rows to look at assay data of all experiments together. First four columns come from the treated data and the last four from untreated.

```
cbindme(medb0)
## DelayedMatrix object of 6 x 8 integers:
##                 SRR1039508 SRR1039512 SRR1039516 SRR1039520 SRR1039509
```

```
## ENSG00000012048        322        418        326        265         98
## ENSG00000139618         67         79         66         96         54
## ENSG00000215515          0          0          0          0          0
## ENSG00000267002         77         84         67         60         35
## ENSG00000267340          5          7         10          8          1
## ENSG00000267595          3          2          4          5          3
##                 SRR1039513 SRR1039517 SRR1039521
## ENSG00000012048         95        168        155
## ENSG00000139618         30         55         40
## ENSG00000215515          0          0          0
## ENSG00000267002         24         40         45
## ENSG00000267340          3          9          1
## ENSG00000267595          5          6          6
```

Restore data from disk and do another subset.

```
medb1 <- loadMultiExperimentDb(hdf5path = hdf5path(medb0),
                               sqlitepath = sqlitepath(medb0))
medb1
## class: MultiExperimentDb
## hdf5path: C:\Users\YU19864\AppData\Local\Temp\RtmpqIXrJA\file13383c24218c.h5
## sqlitepath: C:\Users\YU19864\AppData\Local\Temp\RtmpqIXrJA\file1338c7622b3.sqlite
## dim: 64102 8
## experiments:
##   airway_untrt (64102 x 4)
##     rownames: ENSG00000000003, ENSG00000000005, ENSG00000000419,
##       ..., LRG_98, LRG_99
##     colnames: SRR1039508, SRR1039512, SRR1039516, SRR1039520
##   airway_trt (64102 x 4)
##     rownames: ENSG00000000003, ENSG00000000005, ENSG00000000419,
##       ..., LRG_98, LRG_99
##     colnames: SRR1039509, SRR1039513, SRR1039517, SRR1039521
```

Search across treated and untreated for given rownames.

```
medb1[c("ENSG00000213613","ENSG00000267595"),,]
## class: MultiExperimentDb
## hdf5path: C:\Users\YU19864\AppData\Local\Temp\RtmpqIXrJA\file13383c24218c.h5
## sqlitepath: C:\Users\YU19864\AppData\Local\Temp\RtmpqIXrJA\file1338c7622b3.sqlite
## dim: 2 8
## experiments:
##   airway_untrt (2 x 4)
##     rownames: ENSG00000213613, ENSG00000267595
##     colnames: SRR1039508, SRR1039512, SRR1039516, SRR1039520
##   airway_trt (2 x 4)
##     rownames: ENSG00000213613, ENSG00000267595
##     colnames: SRR1039509, SRR1039513, SRR1039517, SRR1039521
```

## 4.4 Discussion

MultiExperimentDb package is created for storing and comparing different bioinformatic experiments in *SummarizedExperiment* format within one object, so the experiments added to a *MultiExperimentDb* object should have some similarity such as common features or samples. It can be used for analyzing data from multiple similar experiments. Also it works better with experiments which contains large data matrices (for example, microarray gene expression data, read counts in genes for RNA-Seq experiments, etc.) and small annotation data (rowData, colDate and rowRanges).

The size of HDF5 file is relatively small, but sqlite file can be big if annotation data is big. However, even when sqlite file is big, it is stored on disk, and when a *MultiExperimentDb* object is created to point to the sqlite file and HDF5 file, the object size is smaller than the original *SummarizedExperiment* objects. Besides, by using *DelayedMatrix* to display assay data in R, subset and binding functions return results quickly.

# 5 Summary and Conclusions

Two R packages: `Organism.dplyr` and `MultiExperimentDb` are developed. Organism.dplyr provides an integrated presentation of mapping between organism level information and genomic coordinates information, while MultiExperimentDb provides functionality for storing and comparing multiple bioinformatics experiments which contains large matrix data.

These two packages have the following features:

- Use of back-end sqlite file and HDF5 file represents reusable on disk data storage.
- Use of dplyr and DelayedMatrix to manipulate data and bring data into R improves implementing efficiency.
- These two packages work well with other bioconductor packages, including software packages: `dplyr`, `RSQLite`, `GenomicRanges`, `GenomicFeatures`, `AnnotationDbi`, `SummarizedExperiment`, etc., AnnotationData packages: Org.* packages and TxDb. * packages, as well as ExperimentData packages in *SummarizedExperiment* format.

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# 7 Appendix

1. Organism.dplyr repository
2. MultiExperimentDb repository