MotifDb

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Abstract

Many kinds of biological activity are regulated by the binding of proteins to their cognate substrates. Of particular interest is the sequence-specific binding of transcription factors to DNA, often in regulatory regions just upstream of the transcription start site of a gene. These binding events play a pivotal role in regulating gene expression. Sequence specificity among closely related binding sites is nearly always incomplete: some variety in the DNA sequence is routinely observed. For this reason, these inexact binding sequence patterns are commonly described as *motifs* represented numerically as frequency matrices, and visualized as sequence logos. Despite their importance in current research, there has been until now no single, annotated, comprehensive collection of publicly available motifs. The current package provides such a collection, offering more than two thousand annotated matrices from multiple organisms, within the context of the Bioconductor project. The matrices can be filtered and selected on the basis of their metadata, used with other Bioconductor packages (MotIV for motif comparison, seqLogo for visualization) or easily exported for use with standard software and websites such as those provided by the MEME Suite[1].

Contents

1 Introduction and Basic Operations

The first step is to load the necessary packages:

```
> library (MotifDb)
> library (MotIV)
> library (seqLogo)
```

There are more than two thousand matrices, from five sources:

```
> length (MotifDb)
```

```
[1] 8369
```

```
> sort (table (values (MotifDb)$dataSource), decreasing=TRUE)
```

[1] http://meme.sdsc.edu/meme/doc/meme.html

```
    jaspar2016     HOCOMOCOv10      cispb_1.02       jolma2013    SwissRegulon
          1209            1066             874             843             684
       stamlab FlyFactorSurvey     JASPAR_2014     JASPAR_CORE           hPDI
           683             614             592             459             437
     UniPROBE           HOMER          ScerTF
           380             332             196
```

And 22 organisms (though the majority of the matrices come from just four):

```
> sort (table (values (MotifDb)$organism), decreasing=TRUE)
```

```
    Hsapiens     Mmusculus Dmelanogaster   Scerevisiae     Athaliana
        4094          1251          1147           876           351
    Celegans   Pfalciparum   Rnorvegicus        Zmays    Vertebrata
          67            28            28            19            17
     Ncrassa      Psativum        Amajus   Ddiscoideum     Anidulans
          15            10             9             9             8
     Ppatens       Osativa       Xlaevis       Ggallus        Drerio
           7             5             5             4             3
      Gallus      Hroretzi      Hvulgare    Ocuniculus      Phybrida
           3             3             3             3             3
     Rrattus     Taestivam   Bdistachyon       Cparvum       Csativa
           3             3             2             2             2
  Nsylvestris        Otauri Acarolinensis        Apisum      Aterreus
           2             2             1             1             1
   Gaculeatus   Hcapsulatum    Mdomestica    Mgallopavo      Mmurinus
           1             1             1             1             1
  Mtruncatula      Ngruberi Nhaematococca          Nsp.    Nvectensis
           1             1             1             1             1
    Pcapensis     Ppygmaeus  Ptetraurelia  Tthermophila     Vvinifera
           1             1             1             1             1
  Xtropicalis
           1
```

With these categories of metadata

```
> colnames (values (MotifDb))
```

```
 [1] "providerName"    "providerId"      "dataSource"      "geneSymbol"
 [5] "geneId"          "geneIdType"      "proteinId"       "proteinIdType"
 [9] "organism"        "sequenceCount"   "bindingSequence" "bindingDomain"
[13] "tfFamily"        "experimentType"  "pubmedID"
```

2 Selection

There are three ways to extract subsets of interest from the MotifDb collection. All three operate upon the MotifDb metadata, matching values in one or more of those fifteen attributes (listed just above), and returning the subset of MotifDb which meet the specified criteria. The three techniques: *query*, *subset* and *grep*

2.1 query

This is the simplest technique to use, and will suffice in many circumstances. For example, if you want all of the human matrices:

```
> query (MotifDb, 'hsapiens')
```

```
MotifDb object of length 4094
| Created from downloaded public sources: 2013-Aug-30
| 4094 position frequency matrices from 10 sources:
|        HOCOMOCOv10:  640
|        JASPAR_2014:  117
|        JASPAR_CORE:   66
|       SwissRegulon:  684
|           UniPROBE:    2
|         cispb_1.02:  313
|               hPDI:  437
|         jaspar2016:  442
|          jolma2013:  710
|            stamlab:  683
| 1 organism/s
|           Hsapiens: 4094
```

```
Hsapiens-jolma2013-BCL6B
Hsapiens-jolma2013-CTCF
Hsapiens-jolma2013-EGR1
Hsapiens-jolma2013-EGR1-2
Hsapiens-jolma2013-EGR2
...
Hsapiens-stamlab-UW.Motif.0681
Hsapiens-stamlab-UW.Motif.0682
Hsapiens-stamlab-UW.Motif.0683
Hsapiens-UniPROBE-Sox4.UP00401
Hsapiens-UniPROBE-Oct_1.UP00399
```

If you want all matrices associated with ***Sox*** transcription factors, regardless of dataSource or organism:

```
> query (MotifDb, 'sox')
```

```
MotifDb object of length 157
| Created from downloaded public sources: 2013-Aug-30
| 157 position frequency matrices from 10 sources:
|    FlyFactorSurvey:    2
|        HOCOMOCOv10:   25
|              HOMER:    9
|        JASPAR_2014:    8
|        JASPAR_CORE:    5
|       SwissRegulon:   19
|           UniPROBE:   15
|               hPDI:    2
|         jaspar2016:   16
|          jolma2013:   56
| 6 organism/s
|           Hsapiens:   87
|          Mmusculus:   57
|      Dmelanogaster:    2
|        Rnorvegicus:    1
|         Vertebrata:    1
|              other:    9
Hsapiens-SwissRegulon-SOX10.SwissRegulon
Hsapiens-SwissRegulon-SOX11.SwissRegulon
Hsapiens-SwissRegulon-SOX12.SwissRegulon
Hsapiens-SwissRegulon-SOX13.SwissRegulon
Hsapiens-SwissRegulon-SOX14.SwissRegulon
...
Hsapiens-jaspar2016-SOX4-MA0867.1
Hsapiens-jaspar2016-SOX8-MA0868.1
Mmusculus-jaspar2016-Sox11-MA0869.1
Mmusculus-jaspar2016-Sox1-MA0870.1
Hsapiens-jaspar2016-SRY-MA0084.1
```

For all yeast transcription factors with a homeo domain

```
> query (query (MotifDb, 'cerevisiae'), 'homeo')
```

```
MotifDb object of length 28
| Created from downloaded public sources: 2013-Aug-30
| 28 position frequency matrices from 4 sources:
|        JASPAR_2014:   10
|        JASPAR_CORE:   10
|           UniPROBE:    4
|         jaspar2016:    4
| 1 organism/s
|        Scerevisiae:   28
Scerevisiae-UniPROBE-Cup9.UP00308
Scerevisiae-UniPROBE-Matalpha2.UP00307
Scerevisiae-UniPROBE-Pho2.UP00268
Scerevisiae-UniPROBE-Yox1.UP00274
Scerevisiae-JASPAR_CORE-CUP9-MA0288.1
...
Scerevisiae-JASPAR_2014-YOX1-MA0433.1
Scerevisiae-jaspar2016-CUP9-MA0288.1
Scerevisiae-jaspar2016-HMRA2-MA0318.1
Scerevisiae-jaspar2016-MATALPHA2-MA0328.1
Scerevisiae-jaspar2016-TOS8-MA0408.1
```

The last example may inspire more confidence in the precision of the result than is justified, and for a couple of reasons. First, the assignment of protein binding domains to specific categories is, as of 2012, an ad hoc and incomplete process. Second, the query commands matches the supplied character string to *all* metadata columns. In this case, 'homeo' appears both in the *bindingDomain* column and the *tfFamily* column, and the above *query* will return matches from both. Searching and filtering should always be accompanined by close scrutiny of the data, such as these commands illustrate:

```
> unique (grep ('homeo', values(MotifDb)$bindingDomain, ignore.case=T, v=T))
```

```
 [1] "Homeobox"                          "Hox9_act;Homeobox"
 [3] "LIM;Homeobox"                      "PAX;Homeobox"
 [5] "OAR;Homeobox"                      "Pou;Homeobox"
 [7] "Distant similarity to homeodomain" "Homeo"
 [9] "Homeo, PAX"                        "Homeo, POU"
```

```
> unique (grep ('homeo', values(MotifDb)$tfFamily, ignore.case=T, v=T))
```

```
[1] "Homeo"
[2] "Homeo::Nuclear Factor I-CCAAT-binding"
[3] "Homeodomain"
[4] "Paired plus homeo domain"
[5] "TALE-type homeo domain factors"
[6] "homeodomain"
```

2.2 grep

This selection method (and the next, *subset*) require that you address metadata columns explicitly. This is a little more work, but the requisite direct engagement with the metadata is worthwhile. Repeating the 'query' examples from above, you can see how more knowedge of MotifDb metadata is required.

```
> mdb.human <- MotifDb [grep ('Hsapiens', values (MotifDb)$organism)]
> mdb.sox <- MotifDb [grep ('sox', values (MotifDb)$geneSymbol, ignore.case=TRUE)]
> yeast.indices = grepl ('scere', values (MotifDb)$organism, ignore.case=TRUE)
> homeo.indices.domain = grepl ('homeo', values (MotifDb)$bindingDomain, ignore.case=TRUE)
> homeo.indices.family = grepl ('homeo', values (MotifDb)$tfFamily, ignore.case=TRUE)
> yeast.homeo.indices = yeast.indices & (homeo.indices.domain | homeo.indices.family)
> yeast.homeoDb = MotifDb [yeast.homeo.indices]
```

An alternate and somewhat more compact approach:

```
> yeast.homeo.indices <- with(values(MotifDb),
+   grepl('scere', organism, ignore.case=TRUE) &
+     (grepl('homeo', bindingDomain, ignore.case=TRUE) |
+      grepl('homeo', tfFamily, ignore.case=TRUE)))
>
```

2.3 subset

MotifDb::subset emulates the R base data.frame *subset* command, which is not unlike an SQL select function. Unfortunately – and just like the R base subset function – this MotifDb method cannot be used reliably within a script: *It is only reliable when called interactively.* Here, with mixed success (as you will see) , we use MotifDb::subset to reproduce the *query* and *grep* selections shown above.

```
> if (interactive ())
+   subset (MotifDb, organism=='Hsapiens')
```

One can easily find all the 'sox' genes with the subset command, avoiding possible upper/lower case conflicts by passing the metadata's geneSymbol column through the function 'tolower':

```
> if (interactive ())
+   subset (MotifDb, tolower (geneSymbol) == 'sox4')
```

Similarly, subset has limited application for a permissive 'homeo' search. But for the retrieval by explicitly specified search terms, subset works very well:

```
> if (interactive ())
+   subset (MotifDb, organism=='Scerevisiae' & bindingDomain=='Homeo')
```

2.4 The Egr1 Case Study

We now do a simple geneSymbol search, followed by an examination of the sub-MotifDb the search returns. We are looking for all matrices associated with the well-known and highly conserved zinc-finger transcription factor, Egr1. There are two of these in MotifDb, both from mouse, and each from a different data source.

```
> # subset is convenient:
> if (interactive ())
+ as.list (subset (MotifDb, tolower (geneSymbol) == 'egr1'))
> # grep returns indices which allow for more flexibility
> indices = grep ('egr1', values (MotifDb)$geneSymbol, ignore.case=TRUE)
> length (indices)
```

```
[1] 13
```

There are a variety of ways to examine and extract data from this object, a MotifList of length 2.

```
> MotifDb [indices]
```

```
MotifDb object of length 13
| Created from downloaded public sources: 2013-Aug-30
| 13 position frequency matrices from 8 sources:
|        HOCOMOCOv10:    3
|              HOMER:    1
|        JASPAR_2014:    1
|        JASPAR_CORE:    1
|       SwissRegulon:    1
|           UniPROBE:    1
|         jaspar2016:    2
|          jolma2013:    3
| 3 organism/s
|           Hsapiens:    7
|          Mmusculus:    5
|              other:    1
Hsapiens-SwissRegulon-EGR1.SwissRegulon
Hsapiens-HOCOMOCOv10-EGR1_HUMAN.H10MO.A
Hsapiens-HOCOMOCOv10-EGR1_HUMAN.H10MO.S
Mmusculus-HOCOMOCOv10-EGR1_MOUSE.H10MO.A
NA-HOMER-Egr1(Zf)/K562-Egr1-ChIP-Seq(GSE32465)/Homer
...
Hsapiens-jaspar2016-EGR1-MA0162.2
Hsapiens-jolma2013-EGR1
Hsapiens-jolma2013-EGR1-2
Mmusculus-jolma2013-Egr1
Mmusculus-UniPROBE-Egr1.UP00007
```

Now view the matrices as a named list:

```
> as.list (MotifDb [indices])
```

```
$`Hsapiens-SwissRegulon-EGR1.SwissRegulon`
          1          2         3 4   5   6          7 8         9 10
A 0.20000000 0.13333333 0.0000000 0 0.0 0.2 0.06666667 0 0.1333333  0
C 0.26666667 0.06666667 0.8666667 0 0.0 0.0 0.00000000 0 0.6666667  0
G 0.06666667 0.80000000 0.0000000 1 0.2 0.8 0.93333333 1 0.0000000  1
T 0.46666667 0.00000000 0.1333333 0 0.8 0.0 0.00000000 0 0.2000000  0
         11
A 0.06666667
C 0.00000000
G 0.46666667
T 0.46666667

$`Hsapiens-HOCOMOCOv10-EGR1_HUMAN.H10MO.A`
      1     2     3     4     5     6     7     8     9    10    11    12    13
A 0.190 0.208 0.212 0.270 0.222 0.116 0.168 0.042 0.034 0.160 0.008 0.032 0.262
C 0.192 0.206 0.144 0.140 0.074 0.082 0.484 0.042 0.008 0.006 0.000 0.038 0.452
G 0.438 0.446 0.452 0.468 0.380 0.756 0.050 0.808 0.452 0.804 0.976 0.914 0.006
T 0.180 0.140 0.192 0.122 0.324 0.046 0.298 0.108 0.506 0.030 0.016 0.016 0.280
     14    15    16    17    18
A 0.180 0.072 0.236 0.278 0.218
C 0.012 0.012 0.092 0.098 0.184
G 0.750 0.774 0.534 0.458 0.490
T 0.058 0.142 0.138 0.166 0.108

$`Hsapiens-HOCOMOCOv10-EGR1_HUMAN.H10MO.S`
          1          2          3          4          5          6
```

```
A 0.1515633 0.04398516 0.05988341 0.003709592 0.009538951 0.07578166
C 0.1886592 0.06041335 0.82829889 0.001059883 0.013248543 0.01907790
G 0.3184950 0.88288288 0.01854796 0.993640700 0.490726020 0.90196078
T 0.3412825 0.01271860 0.09326974 0.001589825 0.486486486 0.00317965
           7          8           9          10         11
A 0.025437202 0.01218866 0.089030207 0.021727610 0.09062003
C 0.065712772 0.01006889 0.748277689 0.007419184 0.06518283
G 0.900900901 0.97774245 0.007419184 0.955484897 0.60943296
T 0.007949126 0.00000000 0.155272920 0.015368309 0.23476418

$`Mmusculus-HOCOMOCOv10-EGR1_MOUSE.H10MO.A`
           1          2           3          4           5          6
A 0.1515633 0.04398516 0.05988341 0.003709592 0.009538951 0.07578166
C 0.1886592 0.06041335 0.82829889 0.001059883 0.013248543 0.01907790
G 0.3184950 0.88288288 0.01854796 0.993640700 0.490726020 0.90196078
T 0.3412825 0.01271860 0.09326974 0.001589825 0.486486486 0.00317965
           7          8           9          10         11
A 0.025437202 0.01218866 0.089030207 0.021727610 0.09062003
C 0.065712772 0.01006889 0.748277689 0.007419184 0.06518283
G 0.900900901 0.97774245 0.007419184 0.955484897 0.60943296
T 0.007949126 0.00000000 0.155272920 0.015368309 0.23476418

$`NA-HOMER-Egr1(Zf)/K562-Egr1-ChIP-Seq(GSE32465)/Homer`
      1     2     3     4     5     6     7     8     9    10
A 0.128 0.078 0.154 0.001 0.001 0.027 0.001 0.001 0.153 0.034
C 0.072 0.036 0.523 0.001 0.001 0.001 0.002 0.001 0.415 0.002
G 0.142 0.882 0.023 0.997 0.282 0.971 0.973 0.997 0.010 0.940
T 0.658 0.004 0.300 0.001 0.716 0.001 0.024 0.001 0.422 0.024

$`Mmusculus-JASPAR_CORE-Egr1-MA0162.1`
           1           2           3 4   5   6           7 8         9 10
A 0.20000000 0.13333333 0.0000000 0 0.0 0.2 0.06666667 0 0.1333333  0
C 0.26666667 0.06666667 0.8666667 0 0.0 0.0 0.00000000 0 0.6666667  0
G 0.06666667 0.80000000 0.0000000 1 0.2 0.8 0.93333333 1 0.0000000  1
T 0.46666667 0.00000000 0.1333333 0 0.8 0.0 0.00000000 0 0.2000000  0
          11
A 0.06666667
C 0.00000000
G 0.46666667
T 0.46666667

$`Hsapiens-JASPAR_2014-EGR1-MA0162.2`
           1          2          3          4          5         6 7          8
A 0.08958877 0.1228786 0.09464752 0.10892624 0.01901110 0.2375163 0 0.00000000
C 0.46736292 0.5586651 0.49355418 0.85109334 0.94435379 0.0000000 1 0.96703655
G 0.25155026 0.1108845 0.18358355 0.00000000 0.00000000 0.5580940 0 0.00000000
T 0.19149804 0.2075718 0.22821475 0.03998042 0.03663512 0.2043897 0 0.03296345
           9         10         11         12         13         14
A 0.00000000 0.29797650 0.00000000 0.1932115 0.00000000 0.2468995
C 0.82849217 0.68219648 0.97519582 0.0000000 0.80360640 0.4565111
G 0.04985313 0.00000000 0.00000000 0.5384302 0.11586162 0.1560868
T 0.12165470 0.01982702 0.02480418 0.2683584 0.08053198 0.1405026

$`Mmusculus-jaspar2016-Egr1-MA0162.1`
           1           2         3 4   5   6           7 8         9 10
A 0.20000000 0.13333333 0.0000000 0 0.0 0.2 0.06666667 0 0.1333333  0
C 0.26666667 0.06666667 0.8666667 0 0.0 0.0 0.00000000 0 0.6666667  0
G 0.06666667 0.80000000 0.0000000 1 0.2 0.8 0.93333333 1 0.0000000  1
T 0.46666667 0.00000000 0.1333333 0 0.8 0.0 0.00000000 0 0.2000000  0
          11
A 0.06666667
C 0.00000000
G 0.46666667
T 0.46666667

$`Hsapiens-jaspar2016-EGR1-MA0162.2`
           1          2          3          4          5         6 7          8
A 0.08958877 0.1228786 0.09464752 0.10892624 0.01901110 0.2375163 0 0.00000000
C 0.46736292 0.5586651 0.49355418 0.85109334 0.94435379 0.0000000 1 0.96703655
G 0.25155026 0.1108845 0.18358355 0.00000000 0.00000000 0.5580940 0 0.00000000
T 0.19149804 0.2075718 0.22821475 0.03998042 0.03663512 0.2043897 0 0.03296345
           9         10         11         12         13         14
A 0.00000000 0.29797650 0.00000000 0.1932115 0.00000000 0.2468995
C 0.82849217 0.68219648 0.97519582 0.0000000 0.80360640 0.4565111
G 0.04985313 0.00000000 0.00000000 0.5384302 0.11586162 0.1560868
T 0.12165470 0.01982702 0.02480418 0.2683584 0.08053198 0.1405026

$`Hsapiens-jolma2013-EGR1`
           1          2           3          4           5          6
A 0.2494781 0.51390568 0.003223727 0.105202754 0.000000000 0.002604167
C 0.2411273 0.39540508 0.969696970 0.005355777 0.980025773 0.992838542
G 0.1539666 0.03627570 0.007736944 0.854246366 0.007731959 0.000000000
T 0.3554280 0.05441354 0.019342360 0.035195103 0.012242268 0.004557292
           7          8           9         10         11         12         13
A 0.000000000 0.652638191 0.003253090 0.01906158 0.010000 0.68089431 0.2790573
C 0.928214732 0.343592965 0.995445673 0.01136364 0.938125 0.06910569 0.2485270
G 0.009363296 0.000000000 0.000000000 0.93181818 0.011875 0.14227642 0.1253348
```

```
T 0.062421973 0.003768844 0.001301236 0.03775660 0.040000 0.10772358 0.3470809
         14
A 0.2673936
C 0.1905504
G 0.1396677
T 0.4023884

$`Hsapiens-jolma2013-EGR1-2`
          1           2           3          4 5           6         7
A 0.2722977 0.737507906 0.006723716 0.01834431 0 0.000000000 0.0000000
C 0.2309510 0.249209361 0.987775061 0.00000000 1 0.992159228 0.9797136
G 0.1139988 0.001897533 0.001833741 0.98165569 0 0.000000000 0.0000000
T 0.3827525 0.011385199 0.003667482 0.00000000 0 0.007840772 0.0202864
          8           9          10         11         12         13
A 0.795439739 0.0000000000 0.0000000000 0.00000000 0.86166008 0.29390244
C 0.200000000 0.9993943065 0.0000000000 0.99220156 0.01317523 0.27926829
G 0.004560261 0.0000000000 0.9990732159 0.00000000 0.10540184 0.06341463
T 0.000000000 0.0006056935 0.0009267841 0.00779844 0.01976285 0.36341463
         14
A 0.3035714
C 0.1255952
G 0.1077381
T 0.4630952

$`Mmusculus-jolma2013-Egr1`
          1          2           3            4           5            6
A 0.3231418 0.32278481 0.618181818 0.0000000000 0.075444498 0.0000000000
C 0.3241961 0.30907173 0.366753247 0.9968454259 0.004324844 0.9994728519
G 0.1133368 0.03691983 0.003636364 0.0005257624 0.911100432 0.0005271481
T 0.2393253 0.33122363 0.011428571 0.0026288118 0.009130226 0.0000000000
          7 8           9          10         11          12         13
A 0.001578117 0 0.517114271 0.003149606 0.00422833 0.001579779 0.89181562
C 0.997369805 1 0.481305951 0.995275591 0.16732105 0.998420221 0.05738476
G 0.001052078 0 0.001579779 0.000000000 0.25581395 0.000000000 0.03621825
T 0.000000000 0 0.000000000 0.001574803 0.57263667 0.000000000 0.01458137
          14         15         16
A 0.44251055 0.31170886 0.26213080
C 0.32278481 0.19778481 0.31012658
G 0.04957806 0.04272152 0.09651899
T 0.18512658 0.44778481 0.33122363

$`Mmusculus-UniPROBE-Egr1.UP00007`
          1          2           3          4           5           6
A 0.2115466 0.14198757 0.03260499 0.11512588 0.003516173 0.004715059
C 0.2827083 0.72243721 0.87717185 0.07060553 0.990021152 0.982482238
G 0.2034722 0.05485440 0.01243161 0.78128969 0.002264928 0.009896878
T 0.3022730 0.08072082 0.07779155 0.03297890 0.004197748 0.002905824
           7           8           9          10          11          12
A 0.001626612 0.262351637 0.005889514 0.02289301 0.02303758 0.56763334
C 0.975937323 0.731731673 0.985755764 0.09046006 0.85994854 0.05739392
G 0.001661635 0.002729558 0.002081402 0.64932246 0.03791264 0.16679165
T 0.020774430 0.003187133 0.006273319 0.23732447 0.07910124 0.20818108
         13        14
A 0.1765973 0.1830489
C 0.3312648 0.1837744
G 0.1253083 0.2267928
T 0.3668295 0.4063840
```

and finally, the metadata associated with these two matrices, transposed, for easy reading and comparison:

```
> noquote (t (as.data.frame (values (MotifDb [indices]))))
```

```
               [,1]
providerName   EGR1.SwissRegulon
providerId     EGR1.SwissRegulon
dataSource     SwissRegulon
geneSymbol     EGR1
geneId         <NA>
geneIdType     <NA>
proteinId      <NA>
proteinIdType  UNIPROT
organism       Hsapiens
sequenceCount  15
bindingSequence <NA>
bindingDomain  <NA>
tfFamily       <NA>
experimentType low- and high-throughput methods
pubmedID       19377474
               [,2]
providerName   EGR1_HUMAN.H10MO.A
providerId     EGR1_HUMAN.H10MO.A
dataSource     HOCOMOCOv10
geneSymbol     EGR1
geneId         <NA>
```

```
geneIdType      <NA>
proteinId       P18146
proteinIdType   UNIPROT
organism        Hsapiens
sequenceCount   500
bindingSequence <NA>
bindingDomain   <NA>
tfFamily        <NA>
experimentType  low- and high-throughput methods
pubmedID        26586801
                [,3]
providerName    EGR1_HUMAN.H10MO.S
providerId      EGR1_HUMAN.H10MO.S
dataSource      HOCOMOCOv10
geneSymbol      EGR1
geneId          <NA>
geneIdType      <NA>
proteinId       P18146
proteinIdType   UNIPROT
organism        Hsapiens
sequenceCount   1887
bindingSequence <NA>
bindingDomain   <NA>
tfFamily        <NA>
experimentType  low- and high-throughput methods
pubmedID        26586801
                [,4]
providerName    EGR1_MOUSE.H10MO.A
providerId      EGR1_MOUSE.H10MO.A
dataSource      HOCOMOCOv10
geneSymbol      EGR1
geneId          <NA>
geneIdType      <NA>
proteinId       P08046
proteinIdType   UNIPROT
organism        Mmusculus
sequenceCount   1887
bindingSequence <NA>
bindingDomain   <NA>
tfFamily        <NA>
experimentType  low- and high-throughput methods
pubmedID        26586801
                [,5]
providerName    Egr1(Zf)/K562-Egr1-ChIP-Seq(GSE32465)/Homer
providerId      Egr1(Zf)/K562-Egr1-ChIP-Seq(GSE32465)/Homer
dataSource      HOMER
geneSymbol      Egr1
geneId          <NA>
geneIdType      <NA>
proteinId       ?query=Egr1(Zf)_K562-Egr1-ChIP-Seq(GSE32465)
proteinIdType   UNIPROT
organism        <NA>
sequenceCount   1
bindingSequence <NA>
bindingDomain   <NA>
tfFamily        <NA>
experimentType  low- and high-throughput methods
pubmedID        26586801
                [,6]                        [,7]
providerName    Egr1                        EGR1
providerId      MA0162.1                    MA0162.2
dataSource      JASPAR_CORE                 JASPAR_2014
geneSymbol      Egr1                        EGR1
geneId          13653                       1958
geneIdType      ENTREZ                      ENTREZ
proteinId       P08046                      P18146
proteinIdType   UNIPROT                     UNIPROT
organism        Mmusculus                   Hsapiens
sequenceCount   15                          12256
bindingSequence <NA>                        <NA>
bindingDomain   Zinc-coordinating           Zinc-coordinating
tfFamily        BetaBetaAlpha-zinc finger   BetaBetaAlpha-zinc finger
experimentType  bacterial 1-hybrid          ChIP-seq
pubmedID        16041365                    16041365
                [,8]
providerName    MA0162.1
providerId      MA0162.1
dataSource      jaspar2016
geneSymbol      Egr1
geneId          <NA>
geneIdType      <NA>
proteinId       P08046
proteinIdType   UNIPROT
organism        Mmusculus
sequenceCount   15
bindingSequence <NA>
bindingDomain   <NA>
```

```
tfFamily        BetaBetaAlpha-zinc finger
experimentType  bacterial 1-hybrid
pubmedID        24194598
                [,9]
providerName    MA0162.2
providerId      MA0162.2
dataSource      jaspar2016
geneSymbol      EGR1
geneId          <NA>
geneIdType      <NA>
proteinId       P18146
proteinIdType   UNIPROT
organism        Hsapiens
sequenceCount   12256
bindingSequence <NA>
bindingDomain   <NA>
tfFamily        Three-zinc finger Krppel-related factors
experimentType  ChIP-seq
pubmedID        24194598
                [,10]                   [,11]
providerName    Hsapiens-jolma2013-EGR1 Hsapiens-jolma2013-EGR1-2
providerId      EGR1                    EGR1
dataSource      jolma2013               jolma2013
geneSymbol      EGR1                    EGR1
geneId          1958                    1958
geneIdType      ENTREZ                  ENTREZ
proteinId       <NA>                    <NA>
proteinIdType   <NA>                    <NA>
organism        Hsapiens                Hsapiens
sequenceCount   1831                    1703
bindingSequence NMCGCCCMCGCANN          NACGCCCACGCANN
bindingDomain   <NA>                    <NA>
tfFamily        C2H2                    C2H2
experimentType  SELEX                   SELEX
pubmedID        23332764                23332764
                [,12]                    [,13]
providerName    Mmusculus-jolma2013-Egr1 SCI09/Egr1_pwm_primary.txt
providerId      Egr1                     UP00007
dataSource      jolma2013                UniPROBE
geneSymbol      Egr1                     Egr1
geneId          1958                     13653
geneIdType      ENTREZ                   ENTREZ
proteinId       <NA>                     P08046
proteinIdType   <NA>                     UNIPROT
organism        Mmusculus                Mmusculus
sequenceCount   2013                     <NA>
bindingSequence NNMCGCCCMCTCANNN         <NA>
bindingDomain   <NA>                     ZnF_C2H2
tfFamily        C2H2                     <NA>
experimentType  SELEX                    protein binding microarray
pubmedID        23332764                 19443739
```

We used the *grep* function above to find rows in the metadata table whose *geneSymbol* column includes the string 'Egr1'. If you wish to identify matrices (and/or their attendant metadata) based upon a richer combination of criteria, for instance:

1. organism (*Mmusculus*)
2. gene symbol (*Egr1*)
3. data source (*JASPAR_CORE*)

the grep solution, while serviceable, becomes a little awkward:

```
> geneSymbol.rows = grep ('Egr1', values (MotifDb)$geneSymbol, ignore.case=TRUE)
> organism.rows = grep ('Mmusculus', values (MotifDb)$organism, ignore.case=TRUE)
> source.rows = grep ('JASPAR', values (MotifDb)$dataSource, ignore.case=TRUE)
> egr1.mouse.jaspar.rows = intersect (geneSymbol.rows,
+                             intersect (organism.rows, source.rows))
> print (egr1.mouse.jaspar.rows)
```

```
[1] 4358 5512
```

```
> egr1.motif <- MotifDb [egr1.mouse.jaspar.rows]
```

Far more concise, and fully reliable as an interactive command (though *not* if used in a script[2]):

[2]See the help page of the base R command subset for detail), is the *subset* command

```
> if (interactive ()) {
+   egr1.motif <- subset (MotifDb, organism=='Mmusculus' &
+                           dataSource=='JASPAR_CORE' &
+                           geneSymbol=='Egr1')
+   }
```

Whichever method you use, this next chunk of code displays the matrix, and then the metadata for mouse JASPAR Egr1, the latter textually-transformed for easy reading within the size constraints of this page.

```
> egr1.motif
```

```
MotifDb object of length 2
| Created from downloaded public sources: 2013-Aug-30
| 2 position frequency matrices from 2 sources:
|        JASPAR_CORE:    1
|         jaspar2016:    1
| 1 organism/s
|          Mmusculus:    2
Mmusculus-JASPAR_CORE-Egr1-MA0162.1
Mmusculus-jaspar2016-Egr1-MA0162.1
```

```
> as.list (egr1.motif)
```

```
$`Mmusculus-JASPAR_CORE-Egr1-MA0162.1`
           1          2         3 4   5   6          7 8         9 10
A 0.20000000 0.13333333 0.0000000 0 0.0 0.2 0.06666667 0 0.1333333  0
C 0.26666667 0.06666667 0.8666667 0 0.0 0.0 0.00000000 0 0.6666667  0
G 0.06666667 0.80000000 0.0000000 1 0.2 0.8 0.93333333 1 0.0000000  1
T 0.46666667 0.00000000 0.1333333 0 0.8 0.0 0.00000000 0 0.2000000  0
          11
A 0.06666667
C 0.00000000
G 0.46666667
T 0.46666667

$`Mmusculus-jaspar2016-Egr1-MA0162.1`
           1          2         3 4   5   6          7 8         9 10
A 0.20000000 0.13333333 0.0000000 0 0.0 0.2 0.06666667 0 0.1333333  0
C 0.26666667 0.06666667 0.8666667 0 0.0 0.0 0.00000000 0 0.6666667  0
G 0.06666667 0.80000000 0.0000000 1 0.2 0.8 0.93333333 1 0.0000000  1
T 0.46666667 0.00000000 0.1333333 0 0.8 0.0 0.00000000 0 0.2000000  0
          11
A 0.06666667
C 0.00000000
G 0.46666667
T 0.46666667
```

```
> noquote (t (as.data.frame (values (egr1.motif))))
```

```
                [,1]                        [,2]
providerName    Egr1                        MA0162.1
providerId      MA0162.1                    MA0162.1
dataSource      JASPAR_CORE                 jaspar2016
geneSymbol      Egr1                        Egr1
geneId          13653                       <NA>
geneIdType      ENTREZ                      <NA>
proteinId       P08046                      P08046
proteinIdType   UNIPROT                     UNIPROT
organism        Mmusculus                   Mmusculus
sequenceCount   15                          15
bindingSequence <NA>                        <NA>
bindingDomain   Zinc-coordinating           <NA>
tfFamily        BetaBetaAlpha-zinc finger   BetaBetaAlpha-zinc finger
experimentType  bacterial 1-hybrid          bacterial 1-hybrid
pubmedID        16041365                    24194598
```

Next we use the bioconductor *seqLogo* package to display this motif.

```
> seqLogo (as.list (egr1.motif)[[1]])
```

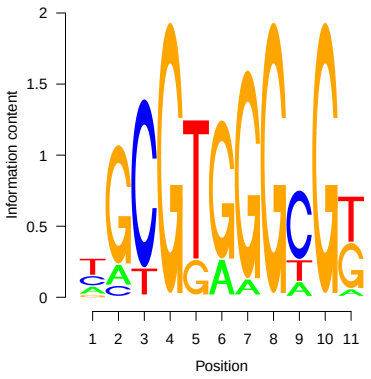


Figure 1: Mmusculus-JASPAR_CORE-Egr1-MA0162.1

3 Motif Matching

We will look for the ten position frequency matrices which are the best match to JASPAR's mouse EGR1, using the MotIV package. We actually request the top eleven hits from the entire MotifDb, since the first hit should be the target matrix itself, since that is of necessity found in the full MotifDb.

```
> egr1.hits <- motifMatch (as.list (egr1.motif) [1], as.list (MotifDb), top=11)
```

```
      Ungapped Alignment
      Scores read
      Database read
      Motif matches : 11
```

```
> # 'MotIV.toTable' -- defined above (and hidden) -- will become part of MotIV in the upcoming release
> tbl.hits <- MotIV.toTable (egr1.hits)
> print (tbl.hits)
```

```
                                                    name         eVal
1                    Hsapiens-SwissRegulon-EGR1.SwissRegulon 1.110223e-16
2                        Mmusculus-JASPAR_CORE-Egr1-MA0162.1 1.110223e-16
3                         Mmusculus-jaspar2016-Egr1-MA0162.1 1.110223e-16
4                          Hsapiens-jaspar2016-EGR2-MA0472.2 3.330669e-16
5                                    Hsapiens-jolma2013-EGR2 3.330669e-16
6                    Hsapiens-SwissRegulon-EGR2.SwissRegulon 5.218048e-15
7  NA-HOMER-Egr2(Zf)/Thymocytes-Egr2-ChIP-Seq(GSE34254)/Homer 5.218048e-15
8                    Hsapiens-HOCOMOCOv10-EGR2_HUMAN.H10MO.C 9.880985e-15
9                   Mmusculus-HOCOMOCOv10-EGR2_MOUSE.H10MO.C 9.880985e-15
10                   Hsapiens-HOCOMOCOv10-EGR1_HUMAN.H10MO.S 1.287859e-14
11                  Mmusculus-HOCOMOCOv10-EGR1_MOUSE.H10MO.A 1.287859e-14
       sequence         match strand
1   NGCGTGGGCGK  NGCGTGGGCGK      +
2   NGCGTGGGCGK  NGCGTGGGCGK      +
3   NGCGTGGGCGK  NGCGTGGGCGK      +
4   NGCGTGGGCGK  TGCGTGGGCGK      -
5   NGCGTGGGCGK  TGCGTGGGCGK      -
6  NGCGTGGGCGK- NGYGTGGGYGKN      +
7  NGCGTGGGCGK- NGYGTGGGYGKN      +
8   NGCGTGGGCGK  NGNGTGGGCGG      +
9   NGCGTGGGCGK  NGNGTGGGCGG      +
10  NGCGTGGGCGK  NGCGKGGGCGG      +
11  NGCGTGGGCGK  NGCGKGGGCGG      +
```

The *sequence* column in this table is the *consensus sequence* – with heterogeneity left out – for the matrix it describes.

Puzzling: the strand of the match reported above is opposite of what I expected, and opposite of what seqLogo displays. This is a question for the MotIV developers.

The six logos appear below, beginning with the logo of the query matrix, *Mmusculus-JASPAR_CORE-Egr1-MA0162.1*,

including two other mouse matrices, and two zinc-finger fly matrices. Examining the three mouse matrices and their metadata reveals that all three (geneSymbol differences aside) describe the same protein:

```
> if (interactive ())
+   noquote (t (as.data.frame (subset (values (MotifDb), geneId=='13653'))))
```

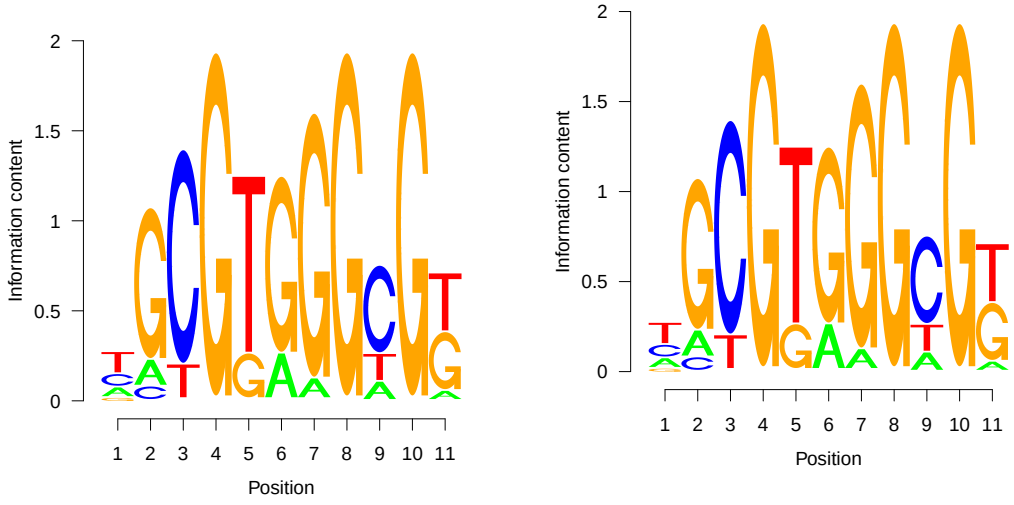
Zinc finger protein domains are classified into many *fold groups*; their respective cognate DNA sequence may classify similarly. That two fly matrices significantly match three reports of the mouse Egr1 motif suggests impressive conservation of this binding pattern, or convergent evolution.

Let us look at the metadata for the first fly match, whose geneId is **FBgn0003499**:

```
> noquote (t (as.data.frame (values (MotifDb)[grep ('FBgn0003499', values (MotifDb)$geneId),])))
```

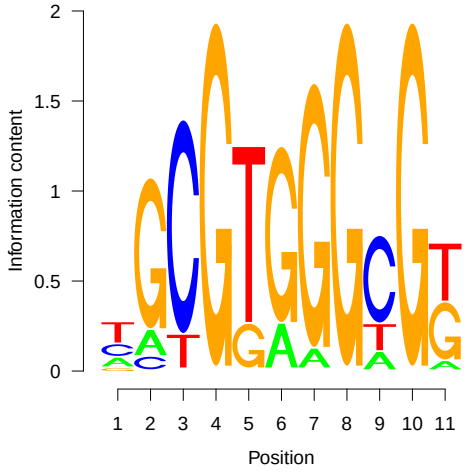
```
providerName
providerId
dataSource
geneSymbol
geneId
geneIdType
proteinId
proteinIdType
organism
sequenceCount
bindingSequence
bindingDomain
tfFamily
experimentType
pubmedID
```

that the SOLEXA motif, based upon 2316 sequences, did not (in work not shown, it appears 22nd in the an expanded motifMatch hit list, with a eval of 10e-5). It is possible that the SOLEXA motif is more accurate, and that a close examination of this case, including sequence logos, position frequency matrices, and the search parameters of motifMatch, will be instructive. Repeating the search with *tomtom* might also be illuminating – either as confirmation of MotIV and the default parameterization we used, or as a correction to it. Here we see the facilities for exploratory data analysis MotifDb provides, and the opportunities for data analysis which result.

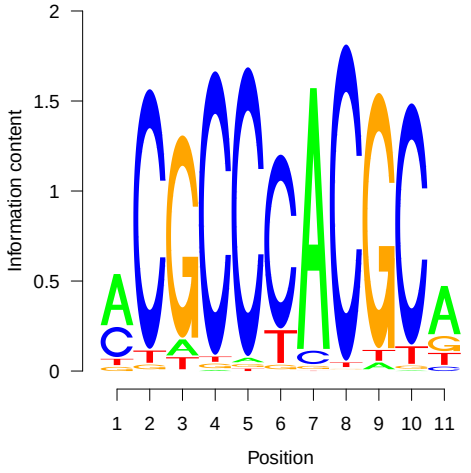


(a) Mmusculus-JASPAR_CORE-Egr1-MA0162.1

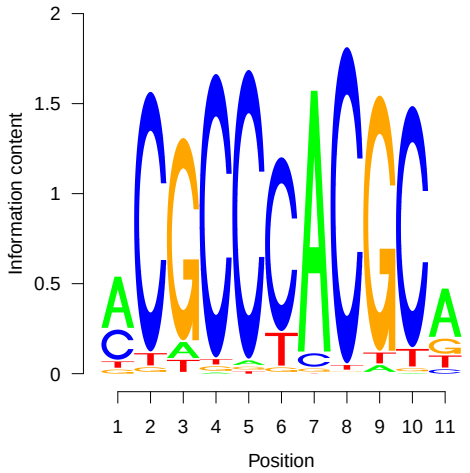
(b) Dme-FFS-sr_SANGER_5_FBgn0003499 (abbreviated)



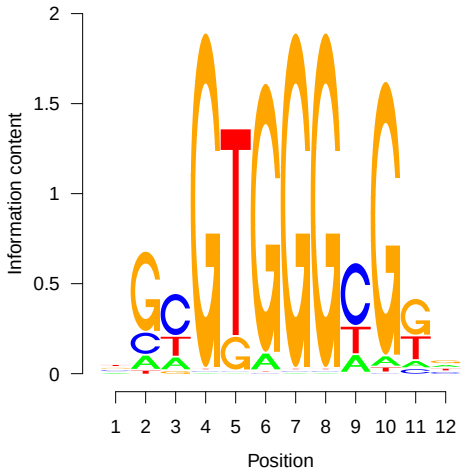
(a) Mmusculus-UniPROBE-Zif268.UP00400



(b) Dme-FFS-klu_SANGER_10_FBgn0013469



(a) Mmusculus-UniPROBE-Egr1.UP00007



(b) Dme-FFS-klu_SOLEXA_5_FBgn0013469

4 Exporting to the MEME Suite

Some users of this package may wish to export the data – both matrices and metadata – so that they may be used in other programs. The MEME suite, among others, is broadly useful, continuously improved and well-regarded throughout the bioinformatics community. The code below exports all of the MotifDb matrices as a text file in the MEME format, and all of the metadata as a tab-delimited text file.

```
> matrix.output.file = tempfile ()   # substitute your preferred filename here
> meme.text = export (MotifDb, matrix.output.file, 'meme')
> metadata.output.file = tempfile () # substitute your preferred filename here
> write.table (as.data.frame (values (MotifDb)), file=metadata.output.file, sep='\t',
+              row.names=TRUE, col.names=TRUE, quote=FALSE)
```

5 Future Work

This first version of MotifDb collects into one R package all of the best-known public domain protein-DNA binding matrices, with as much metadata as could be gleaned from the five providers. However, not all of these matrices are equally supported by data and by no means are all are accompanied by complete metadata.

With the passage of time our knowledge of protein-DNA binding sequence motifs will improve. They will be derived from more binding events, with more precision and specificity, and accompanied by more (and better understood) contextual detail. Cooperative binding, mentioned only in a few times in the current (July 2012) version of this package, will be well-represented. Metadata will improve. Better assignment of binding domains to consensus categories will be especially useful when it is available. Three-dimensional models of specific proteins binding to specific DNA may someday become commonplace.

6 References

- Portales-Casamar E, Thongjuea S, Kwon AT, Arenillas D, Zhao X, Valen E, Yusuf D, Lenhard B, Wasserman WW, Sandelin A. JASPAR 2010: the greatly expanded open-access database of transcription factor binding profiles. Nucleic Acids Res. 2010 Jan;38(Database issue):D105-10. Epub 2009 Nov 11.
- Robasky K, Bulyk ML. UniPROBE, update 2011: expanded content and search tools in the online database of protein-binding microarray data on protein-DNA interactions. Nucleic Acids Res. 2011 Jan;39(Database issue):D124-8. Epub 2010 Oct 30.
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- Zhu LJ, et al. 2011. FlyFactorSurvey: a database of Drosophila transcription factor binding specificities determined using the bacterial one-hybrid system. Nucleic Acids Res. 2011 Jan;39(Database issue):D111-7. Epub 2010 Nov 19.