

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 Suite¹.

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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] 9933

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

¹<http://meme.sdsc.edu/meme/doc/meme.html>

jaspar2018	jaspar2016	HOCOMOCOv10	cisbp_1.02	jolma2013
1564	1209	1066	874	843
SwissRegulon	stamlab	FlyFactorSurvey	JASPAR_2014	JASPAR_CORE
684	683	614	592	459
hPDI	UniPROBE	HOMER	ScerTF	
437	380	332	196	

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

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

Hsapiens	4616
Mmusculus	1411
Dmelanogaster	1287
Scerevisiae	1051
Athaliana	803
Celegans	90
NA	40
Rnorvegicus	35
Pfalciparum	28
Zmays	27
Vertebrata	18
Ncrassa	15
Psativum	13
Amajus	12
Ddiscoideum	9
Anidulans	8
Ggallus	8
Ppatens	7
Xlaevis	7
Mmusculus;Rnorvegicus;Hsapiens	6
Osativa	5
Hroretzi	4
Hvulgare	4
Ocuniculus	4
Phybrida	4
Rrattus	4
Taestivam	4
Drerio	3
Gallus	3
Mmusculus;Hsapiens	3
Bdistachyon	2
Cparvum	2
Csativa	2
Mmusculus;Rnorvegicus	2
Mmusculus;Rnorvegicus;Xlaevis;Stropicalis;Ggallus;Hsapiens;Btaurus;Ocuniculus	2
Nsp.	2
Nsylvestris	2

```

2
Otauri
2
Acarolinensis
1
Apisum
1
Aterreus
1
Gaculeatus
1
Hcapsulatum
1
Mdomestica
1
Mgallopavo
1
Mmurinus
1
Mmusculus;Rnorvegicus;Hsapiens;Ocuniculus
1
Mmusculus;Rnorvegicus;Omykiss;Ggallus;Hsapiens
1
Mmusculus;Rrattus;Hsapiens;Ocuniculus
1
Mtruncatula
1
Ngruberi
1
Nhaematococca
1
Nvectensis
1
Pcapensis
1
Ppygmaeus
1
Ptetraurelia
1
Rnorvegicus;Hsapiens
1
Tthermophila
1
Vvinifera
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 4631
| Created from downloaded public sources: 2013-Aug-30
| 4631 position frequency matrices from 11 sources:
|   HOCOMOCOv10: 640

```

```

|       JASPAR_2014: 117
|       JASPAR_CORE: 66
|       SwissRegulon: 684
|       UniPROBE: 2
|       cisbp_1.02: 313
|       hPDI: 437
|       jaspar2016: 442
|       jaspar2018: 537
|       jolma2013: 710
|       stamlab: 683
| 8 organism/s
|       Hsapiens: 4616
| Mmusculus;Rnorvegicus;Hsapiens: 6
| Mmusculus;Hsapiens: 3
| Mmusculus;Rnorvegicus;Xlaevis;Stropicalis;Ggallus;Hsapiens;Btaurus;Ocuniculus: 2
| Mmusculus;Rnorvegicus;Hsapiens;Ocuniculus: 1
| Mmusculus;Rnorvegicus;Omykiss;Ggallus;Hsapiens: 1
|       other: 2
Hsapiens-SwissRegulon-AHR.SwissRegulon
Hsapiens-SwissRegulon-AIRE.SwissRegulon
Hsapiens-SwissRegulon-ALX1.SwissRegulon
Hsapiens-SwissRegulon-ALX3.SwissRegulon
Hsapiens-SwissRegulon-ALX4.SwissRegulon
...
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 176
| Created from downloaded public sources: 2013-Aug-30
| 176 position frequency matrices from 11 sources:
|   FlyFactorSurvey: 2
|   HOCOMOCOv10: 25
|   HOMER: 9
|   JASPAR_2014: 8
|   JASPAR_CORE: 5
|   SwissRegulon: 19
|   UniPROBE: 15
|   hPDI: 2
|   jaspar2016: 16
|   jaspar2018: 19
|   jolma2013: 56
| 7 organism/s
|   Hsapiens: 95
|   Mmusculus: 67
|   Dmelanogaster: 2
| Mmusculus;Rnorvegicus;Hsapiens: 1
|   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
...
Mmusculus-UniPROBE-Sox30.UP00023
Mmusculus-UniPROBE-Sox4.UP00062
Mmusculus-UniPROBE-Sox5.UP00091
Mmusculus-UniPROBE-Sox7.UP00034
Mmusculus-UniPROBE-Sox8.UP00051

```

For all yeast transcription factors with a homeo domain

```

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

MotifDb object of length 32
| Created from downloaded public sources: 2013-Aug-30
| 32 position frequency matrices from 5 sources:
|   JASPAR_2014: 10
|   JASPAR_CORE: 10
|   UniPROBE: 4
|   jaspar2016: 4
|   jaspar2018: 4
| 1 organism/s

```

```

| Scerevisiae: 32
Scerevisiae-JASPAR_CORE-CUP9-MA0288.1
Scerevisiae-JASPAR_CORE-HMRA2-MA0318.1
Scerevisiae-JASPAR_CORE-MATA1-MA0327.1
Scerevisiae-JASPAR_CORE-MATALPHA2-MA0328.1
Scerevisiae-JASPAR_CORE-PHO2-MA0356.1
...
Scerevisiae-jaspar2018-TOS8-MA0408.1
Scerevisiae-UniPROBE-Cup9.UP00308
Scerevisiae-UniPROBE-Matalpha2.UP00307
Scerevisiae-UniPROBE-Pho2.UP00268
Scerevisiae-UniPROBE-Yox1.UP00274

```

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 accompanied 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 knowledge 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] 16

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 16
| Created from downloaded public sources: 2013-Aug-30
| 16 position frequency matrices from 9 sources:
|   HOCOMOCOv10: 3
|   HOMER: 1
|   JASPAR_2014: 1
|   JASPAR_CORE: 1
|   SwissRegulon: 1
|   UniPROBE: 1
|   jaspar2016: 2
|   jaspar2018: 3
|   jolma2013: 3
| 3 organism/s
|   Hsapiens: 9
|   Mmusculus: 6
|   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-jaspar2018-EGR1-MA0162.3
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 0.00000000 0 0.0 0.2 0.06666667 0 0.13333333 0
C 0.26666667 0.06666667 0.86666667 0 0.0 0.0 0.00000000 0 0.66666667 0
G 0.06666667 0.80000000 0.00000000 1 0.2 0.8 0.93333333 1 0.00000000 1
T 0.46666667 0.00000000 0.13333333 0 0.8 0.0 0.00000000 0 0.20000000 0
      11
A 0.06666667
C 0.00000000
G 0.46666667
T 0.46666667

$`Hsapiens-HOCOMOCOv10-EGR1_HUMAN.H10M0.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.H10M0.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.H10M0.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 0.00000000 0 0.0 0.2 0.06666667 0 0.13333333 0
C 0.26666667 0.06666667 0.86666667 0 0.0 0.0 0.00000000 0 0.66666667 0
G 0.06666667 0.80000000 0.00000000 1 0.2 0.8 0.93333333 1 0.00000000 1
T 0.46666667 0.00000000 0.13333333 0 0.8 0.0 0.00000000 0 0.20000000 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 0.00000000 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 0.00000000 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 0.00000000 0 0.0 0.2 0.06666667 0 0.13333333 0
C 0.26666667 0.06666667 0.86666667 0 0.0 0.0 0.00000000 0 0.66666667 0
G 0.06666667 0.80000000 0.00000000 1 0.2 0.8 0.93333333 1 0.00000000 1
T 0.46666667 0.00000000 0.13333333 0 0.8 0.0 0.00000000 0 0.20000000 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		

\$`Mmusculus-jaspar2018-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-jaspar2018-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-jaspar2018-EGR1-MA0162.3`

	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	0.000000000	0.000000000	0.00000000	0.86166008	0.29390244	
C	0.200000000	0.9993943065	0.000000000	0.99220156	0.01317523	0.27926829	
G	0.004560261	0.000000000	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						

\$`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	0.000000000	0.000000000	0.00000000	0.86166008	0.29390244	
C	0.200000000	0.9993943065	0.000000000	0.99220156	0.01317523	0.27926829	
G	0.004560261	0.000000000	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 0.61818181 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]))))

providerName      Hsapiens-SwissRegulon-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
providerName      Hsapiens-HOCOMOCOv10-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
providerName      Hsapiens-HOCOMOCOv10-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
                    Mmusculus-HOCOMOCOv10-EGR1_MOUSE.H10M0.A
providerName       EGR1_MOUSE.H10M0.A
providerId         EGR1_MOUSE.H10M0.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
                    NA-HOMER-Egr1(Zf)/K562-Egr1-ChIP-Seq(GSE32465)/Homer
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
                    Mmusculus-JASPAR_CORE-Egr1-MA0162.1
providerName       Egr1
providerId         MA0162.1
dataSource         JASPAR_CORE
geneSymbol         Egr1
geneId             13653
geneIdType         ENTREZ
proteinId          P08046
proteinIdType      UNIPROT
organism           Mmusculus
sequenceCount      15
bindingSequence    <NA>
bindingDomain      Zinc-coordinating
tfFamily           BetaBetaAlpha-zinc finger
experimentType     bacterial 1-hybrid
pubmedID           16041365
                    Hsapiens-JASPAR_2014-EGR1-MA0162.2
providerName       EGR1
providerId         MA0162.2
dataSource         JASPAR_2014
geneSymbol         EGR1
geneId             1958
geneIdType         ENTREZ
proteinId          P18146
proteinIdType      UNIPROT
organism           Hsapiens
sequenceCount      12256
bindingSequence    <NA>
bindingDomain      Zinc-coordinating
tfFamily           BetaBetaAlpha-zinc finger
experimentType     ChIP-seq
pubmedID           16041365
                    Mmusculus-jaspar2016-Egr1-MA0162.1
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
                    Hsapiens-jaspar2016-EGR1-MA0162.2

```

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
 Mmusculus-jaspar2018-Egr1-MA0162.1

providerName MA0162.1
 providerId MA0162.1
 dataSource jaspar2018
 geneSymbol Egr1
 geneId <NA>
 geneIdType <NA>
 proteinId P08046
 proteinIdType UNIPROT
 organism Mmusculus
 sequenceCount 15
 bindingSequence <NA>
 bindingDomain <NA>
 tfFamily Three-zinc finger Kruppel-related factors
 experimentType bacterial 1-hybrid
 pubmedID 16041365
 Hsapiens-jaspar2018-EGR1-MA0162.2

providerName MA0162.2
 providerId MA0162.2
 dataSource jaspar2018
 geneSymbol EGR1
 geneId <NA>
 geneIdType <NA>
 proteinId P18146
 proteinIdType UNIPROT
 organism Hsapiens
 sequenceCount 12256
 bindingSequence <NA>
 bindingDomain <NA>
 tfFamily Three-zinc finger Kruppel-related factors
 experimentType ChIP-seq
 pubmedID 16041365
 Hsapiens-jaspar2018-EGR1-MA0162.3

providerName MA0162.3
 providerId MA0162.3
 dataSource jaspar2018
 geneSymbol EGR1
 geneId <NA>
 geneIdType <NA>
 proteinId P18146
 proteinIdType UNIPROT
 organism Hsapiens
 sequenceCount 2158
 bindingSequence <NA>
 bindingDomain <NA>
 tfFamily Three-zinc finger Kruppel-related factors
 experimentType HT-SELEX
 pubmedID 16041365
 Hsapiens-jolma2013-EGR1 Hsapiens-jolma2013-EGR1-2
 Hsapiens-jolma2013-EGR1 Hsapiens-jolma2013-EGR1-2

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	NACGCCACGCANN
bindingDomain	<NA>	<NA>
tfFamily	C2H2	C2H2
experimentType	SELEX	SELEX
pubmedID	23332764	23332764
	Mmusculus-jolma2013-Egr1	Mmusculus-UniPROBE-Egr1.UP00007
providerName	Mmusculus-jolma2013-Egr1	SCI09/Egr1_pwm_primary.txt
providerId	Egr1	UP000007
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	NNMCGCCCMCTCANN	<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 6633
```

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

Far more concise, and fully reliable as an interactive command (though *not* if used in a script²):

```
> 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 3
| Created from downloaded public sources: 2013-Aug-30
| 3 position frequency matrices from 3 sources:
|   JASPAR_CORE: 1
|   jaspar2016: 1
|   jaspar2018: 1
| 1 organism/s
|   Mmusculus: 3
Mmusculus-JASPAR_CORE-Egr1-MA0162.1
Mmusculus-jaspar2016-Egr1-MA0162.1
Mmusculus-jaspar2018-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
```

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

```

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 0.00000000 0 0.0 0.2 0.06666667 0 0.13333333 0
C 0.26666667 0.06666667 0.86666667 0 0.0 0.0 0.00000000 0 0.66666667 0
G 0.06666667 0.80000000 0.00000000 1 0.2 0.8 0.93333333 1 0.00000000 1
T 0.46666667 0.00000000 0.13333333 0 0.8 0.0 0.00000000 0 0.20000000 0
  11
A 0.06666667
C 0.00000000
G 0.46666667
T 0.46666667

$`Mmusculus-jaspar2018-Egr1-MA0162.1`
  1      2      3 4      5      6      7 8      9 10
A 0.20000000 0.13333333 0.00000000 0 0.0 0.2 0.06666667 0 0.13333333 0
C 0.26666667 0.06666667 0.86666667 0 0.0 0.0 0.00000000 0 0.66666667 0
G 0.06666667 0.80000000 0.00000000 1 0.2 0.8 0.93333333 1 0.00000000 1
T 0.46666667 0.00000000 0.13333333 0 0.8 0.0 0.00000000 0 0.20000000 0
  11
A 0.06666667
C 0.00000000
G 0.46666667
T 0.46666667

```

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

```

providerName      Mmusculus-JASPAR_CORE-Egr1-MA0162.1
providerId        MA0162.1
dataSource         JASPAR_CORE
geneSymbol        Egr1
geneId            13653
geneIdType        ENTREZ
proteinId         P08046
proteinIdType     UNIPROT
organism           Mmusculus
sequenceCount     15
bindingSequence   <NA>
bindingDomain     Zinc-coordinating
tfFamily          BetaBetaAlpha-zinc finger
experimentType    bacterial 1-hybrid
pubmedID          16041365
providerName      Mmusculus-jaspar2016-Egr1-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
providerName      Mmusculus-jaspar2018-Egr1-MA0162.1
providerId        MA0162.1
dataSource         jaspar2018
geneSymbol        Egr1
geneId            <NA>
geneIdType        <NA>
proteinId         P08046
proteinIdType     UNIPROT
organism           Mmusculus
sequenceCount     15
bindingSequence   <NA>
bindingDomain     <NA>
tfFamily          Three-zinc finger Kruppel-related factors
experimentType    bacterial 1-hybrid
pubmedID          16041365

```

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

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

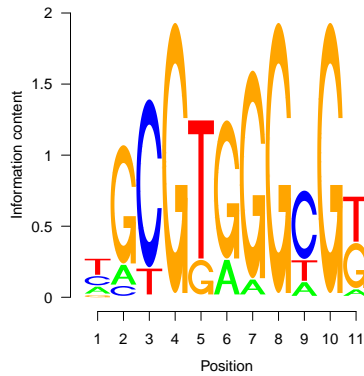


Figure 1: Mmusculus-JASPAR_CORE-Egr1-MA0162.1

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	Mmusculus-jaspar2018-Egr1-MA0162.1	1.110223e-16
5	Hsapiens-jaspar2016-EGR2-MA0472.2	3.330669e-16
6	Hsapiens-jaspar2018-EGR2-MA0472.2	3.330669e-16
7	Hsapiens-jolma2013-EGR2	3.330669e-16
8	Hsapiens-SwissRegulon-EGR2.SwissRegulon	5.218048e-15
9	NA-HOMER-Egr2(Zf)/Thymocytes-Egr2-ChIP-Seq(GSE34254)/Homer	5.218048e-15
10	Hsapiens-HOCOMOCOv10-EGR2_HUMAN.H10MO.C	9.880985e-15
11	Mmusculus-HOCOMOCOv10-EGR2_MOUSE.H10MO.C	9.880985e-15

	sequence	match	strand
1	NGCGTGGGCGK	NGCGTGGGCGK	+
2	NGCGTGGGCGK	NGCGTGGGCGK	+
3	NGCGTGGGCGK	NGCGTGGGCGK	+
4	NGCGTGGGCGK	NGCGTGGGCGK	+
5	NGCGTGGGCGK	TGCGTGGGCGK	-
6	NGCGTGGGCGK	TGCGTGGGCGK	-
7	NGCGTGGGCGK	TGCGTGGGCGK	-
8	NGCGTGGGCGK	NGYGTGGGYGKN	+
9	NGCGTGGGCGK	NGYGTGGGYGKN	+
10	NGCGTGGGCGK	NGNGTGGGCGG	+
11	NGCGTGGGCGK	NGNGTGGGCGG	+

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'))))
```

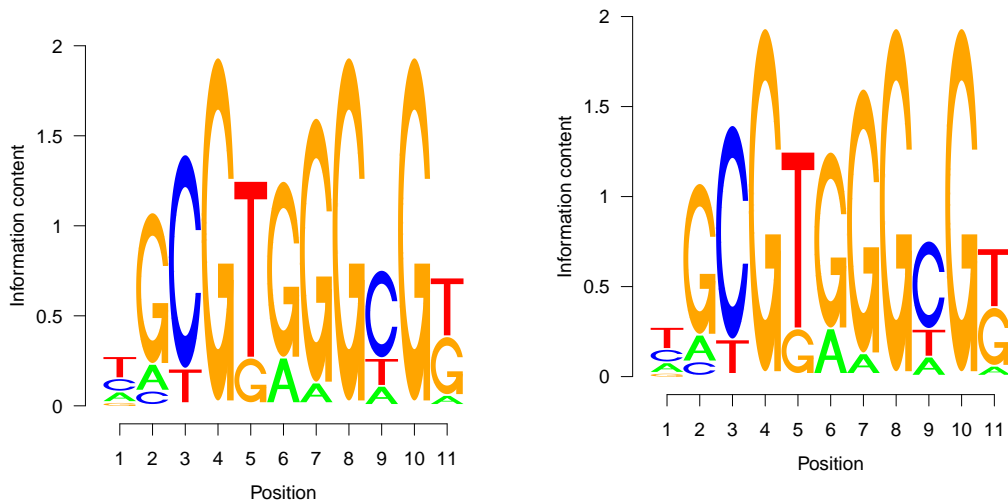
Zinc finger protein domains are classified into many *fold groups*; their respective cognate DNA sequence may classify similarly. That two fly matrices significantly match three reports of the mouse Egr1 motif suggests impressive conservation of this binding pattern, or convergent evolution.

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

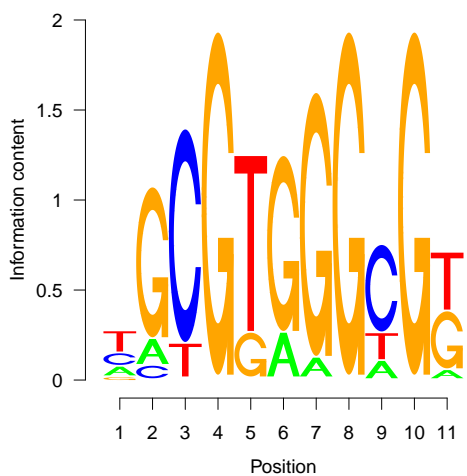
```
> noquote (t (as.data.frame (values (MotifDb)[grep ('FBgn0003499', values (MotifDb)$geneId),])))
```

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

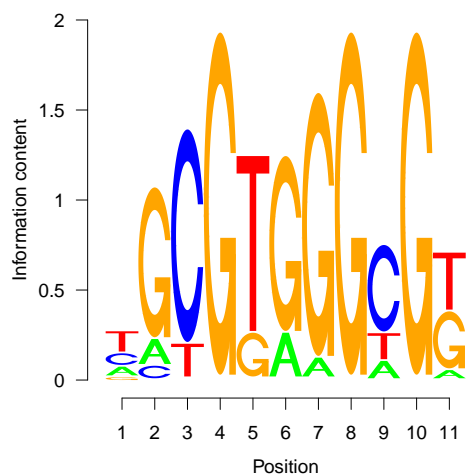
that the SOLEXA motif, based upon 2316 sequences, did not (in work not shown, it appears 22nd in the an expanded motifMatch hit list, with a eval of 10e-5). It is possible that the SOLEXA motif is more accurate, and that a close examination of this case, including sequence logos, position frequency matrices, 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.



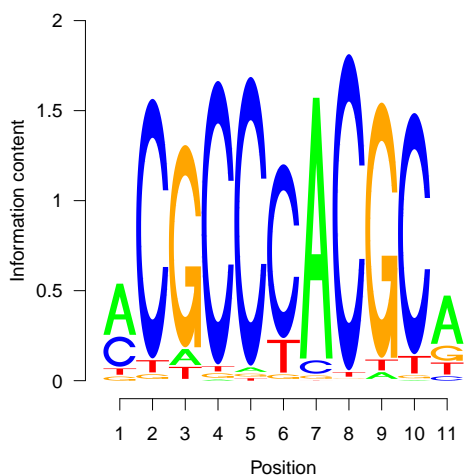
(a) Mmusculus-JASPAR_CORE-Egr1-MA0162.1 (abbreviated) (b) Dme-FFS-sr_SANGER_5_FBgn0003499



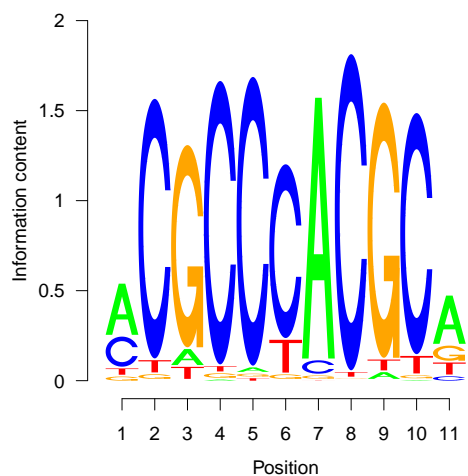
(a) Mmusculus-UniPROBE-Zif268.UP00400



(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 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.

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