Motifs and Position Weight Matrices

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June 23 – 28, 2013

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Position weight matrix (PWM)

- A probabilistic description of (short) sequences
- Useful for describing, e.g., transcription factor binding sites
- Easy to construct and use, e.g., scanning genomic sequences for occurence of binding motifs
- A quick case study

Position weight matrix

- HNF4alpha transcription factor binding sites

```
  A DNAStringSet instance of length 71
     width seq
 [1]    13 AGTTCAAGGATCA
 [2]    13 GGGGTCAAGGGTT
 ...   ... ...
[71]    13 AAACCAAAGTTCA
```

- Consensus matrix / position frequency matrix (first 7 columns)

	[,1]	[,2]	[,3]	[,4]	[,5]	[,6]	[,7]
A	29	2	13	5	3	63	56
C	7	2	5	23	53	1	2
G	30	60	35	20	4	3	11
T	5	7	18	23	11	4	2

Position weight matrix

- Approximately: log probability p_{ij} of symbol i at position j, given background (prior) probability b_i, $log_2(p_{ij}/b_i)$
- Scaled so possible score ranges from 0 to 1

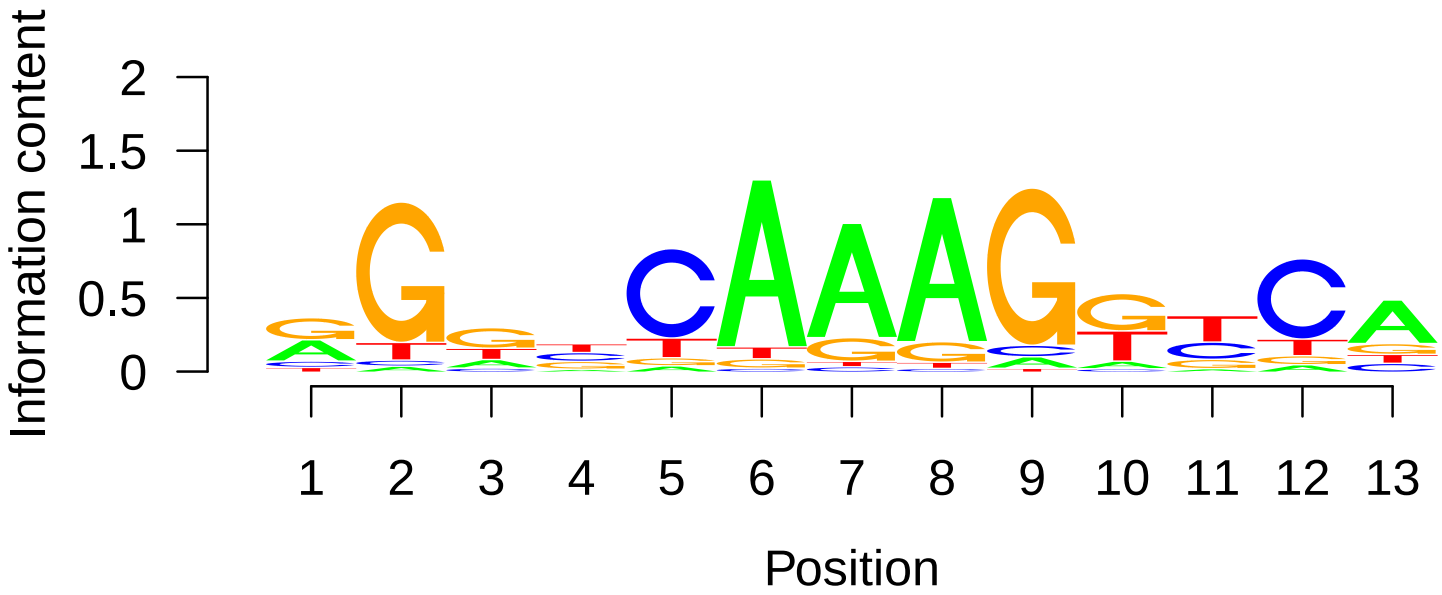
```
   [,1]   [,2]  [,3]  [,4]  [,5]   [,6]   [,7]
A 0.065 -0.007 0.042 0.016 0.003  0.087  0.083
C 0.025 -0.007 0.016 0.058 0.082 -0.024 -0.007
G 0.066  0.085 0.070 0.054 0.010  0.003  0.038
T 0.016  0.025 0.051 0.058 0.038  0.010 -0.007
```

- Score a 'subject' sequence by adding elements of corresponding entries in PWM

Use

```
> library(Biostrings)
> data(HNF4alpha)
> pfm <- consensusMatrix(HNF4alpha)
> pwm <- PWM(consensusMatrix(HNF4alpha))
```

seqLogo:



Use

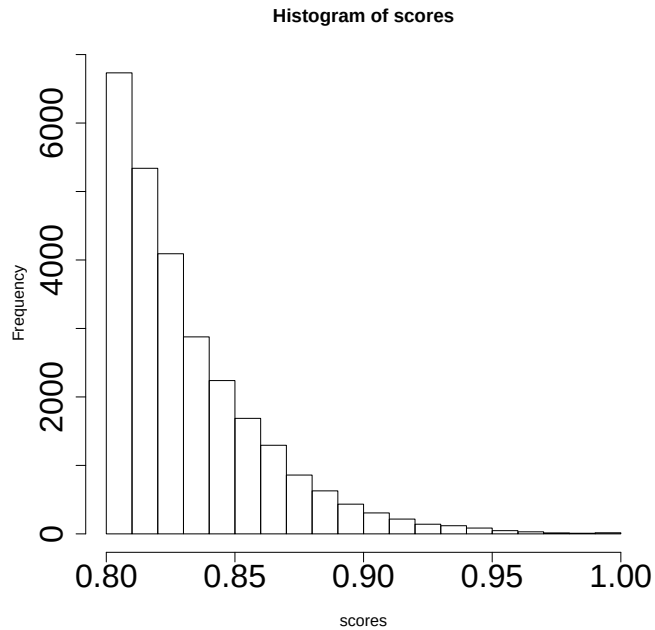
```
> library(BSgenome.Dmelanogaster.UCSC.dm3)
> hits <- matchPWM(pwm, Dmelanogaster$chr3R)
> length(hits)
[1] 27164
> head(hits)
  Views on a 27905053-letter DNAString subject
subject: GAATTCTCTCTTGTTGTAG...GTTCGCATTCTAGGAATTC
views:
    start   end width
[1]   485   497    13 [GGGGTAAAGAGCT]
[2]  1415  1427    13 [GAACCAAAGTTCC]
[3]  6264  6276    13 [GGGTCATAGTTCC]
[4]  7573  7585    13 [TGGCCAACGTTCA]
[5]  7655  7667    13 [GTATCAAAGTGCC]
[6]  8086  8098    13 [CGGCCAAAGCCCG]
```

Use

- Scores

```
> scores <-
+   PWMscoreStartingAt(
+     pwm, subject(hits),
+     start(hits))
> hist(scores)
```

- Minus strand – take the `reverseComplement` of the PWM!



Software

- *Biostrings* for PWM matching
- *MotifDb* for a catalog of known motifs
- *seqLogo* for visualization

Case study

- Huang et al., 2013, Highly Recurrent TERT Promoter Mutations in Human Melanoma, Science 339:957
- Prior whole-genome sequencing of malignant melanomas; two somatic telomerase reverse transcriptase (TERT) promoter mutations in 17 of 19 cases: C228T and C250T
- Validate & extend to additional tumor cell lines
- C228T and C250T introduce E-twenty-six (ETS) transcription factor binding sites
- Suggests plausible MAP kinase pathway; recurrent somatic mutations in regulatory regions as driver events in cancer

Case study

Lab workflow:

- (Call variants in TERT promoter region)
- Score catalog of known PWMs for match to reference versus variant sequence

Acknowledgments

- Paul Shannon (*MotifDb*; lab workflow)
- Hervé Pagès (*Biostrings*)
- Patrick Aboyoun (`PWM` & friends)
- Valerie Obenchain (lab workflow)