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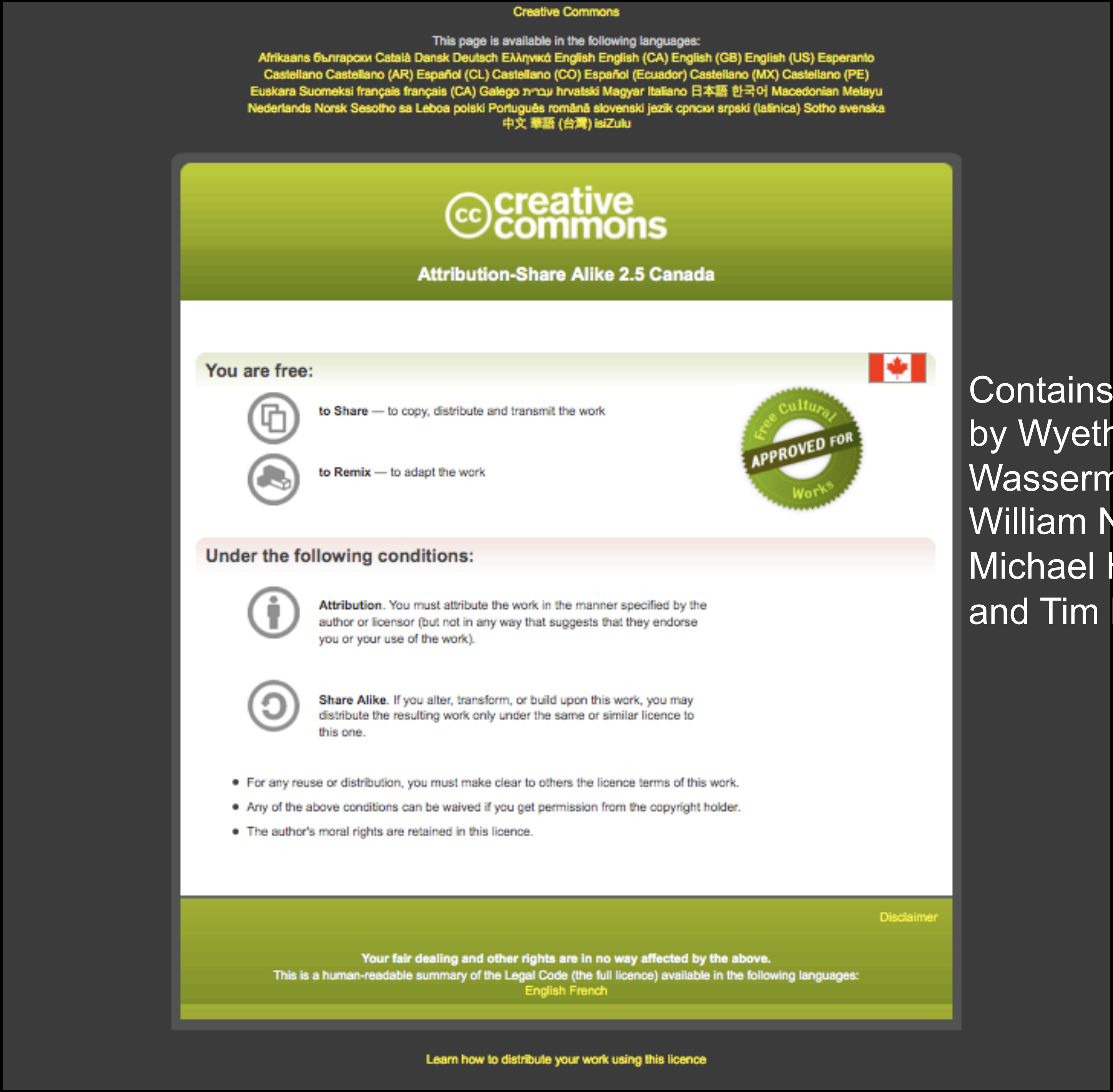

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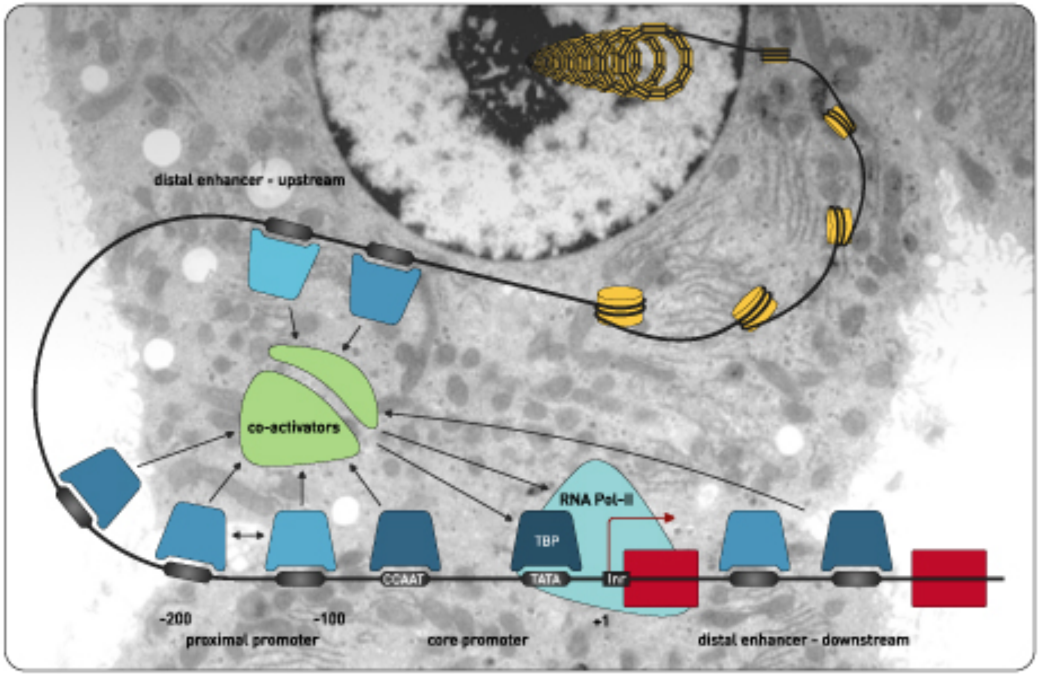
Contains material by Wyeth Wasserman, William Noble, Michael Hoffman, and Tim Bailey

Gene regulation and motif analysis

Michael M. Hoffman (@michaelhoffman)

Pathway and Network Analysis of –omics Data

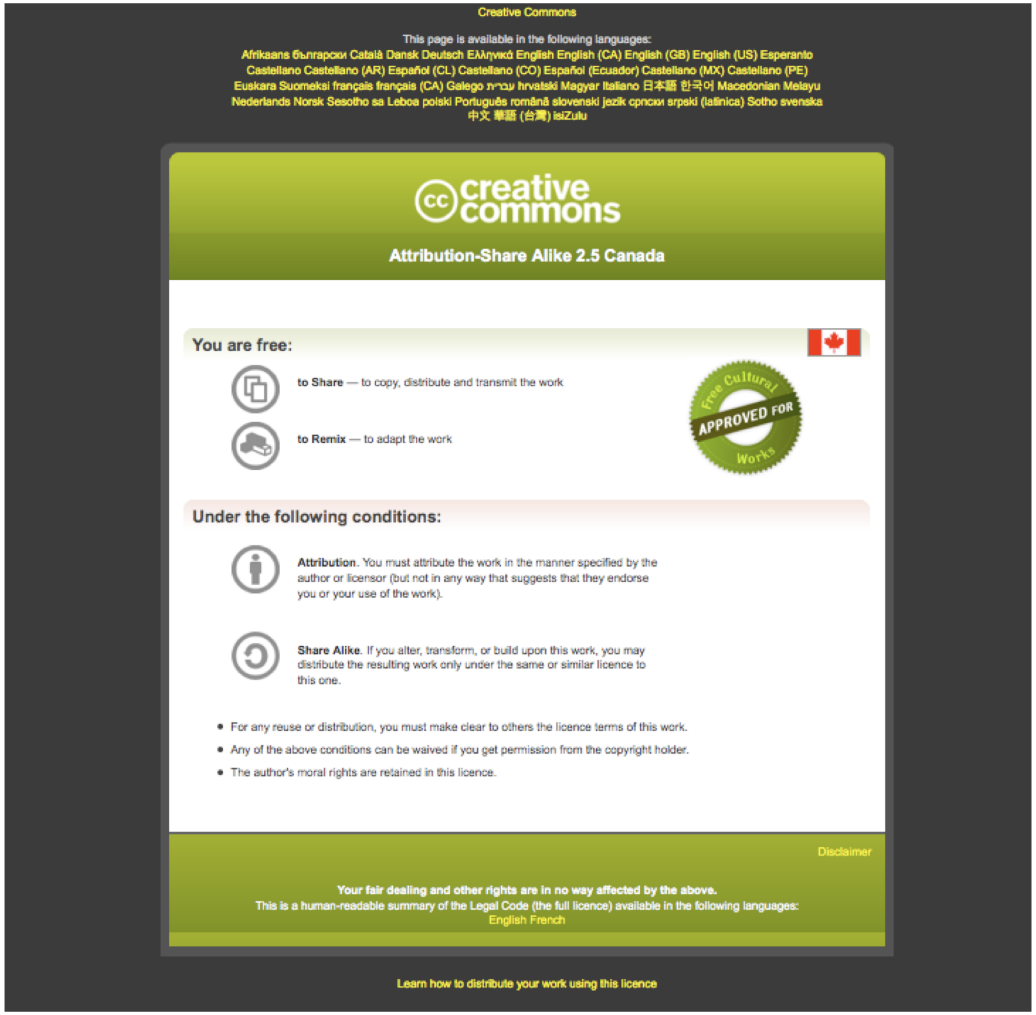
May 10-12, 2021



https://hoffmanlab.org/

Learning Objectives

- By the end of this lecture, you will:
  - Understand challenges in predicting transcription factor (TF) binding
  - Be able to identify binding sites for known TFs
  - Be able to discover TF binding motifs in genomic regions like ChIP-seq peaks or promoters using iRegulon and Cytoscape



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Overview

Part 1: Introduction to eukaryotic transcription

Part 2: Prediction of transcription factor binding sites

Part 3: Discovering novel motifs enriched in regulatory regions

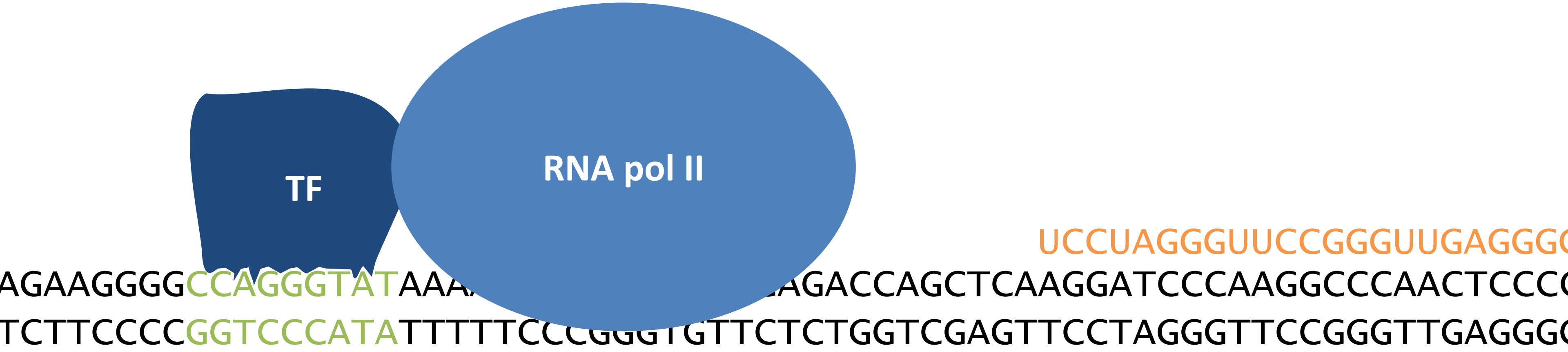
Part 4: Effectiveness of position weight matrix models

Part 5: Incorporating information about the biochemistry of gene regulation

Part 1
Introduction to eukaryotic transcription

Transcription over-simplified

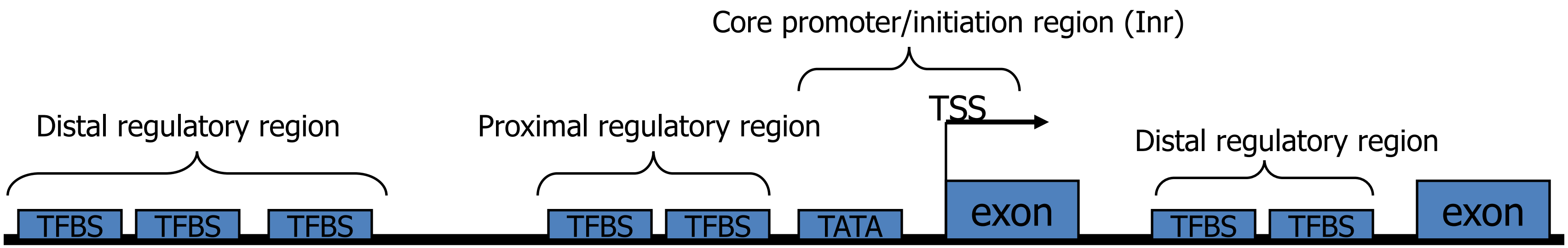
1. **TF** binds to DNA at **TF binding site**
2. **TF** recruits **RNA polymerase II**
3. **RNA polymerase II** produces **RNA**



TF
RNA pol II
UCCUAGGGUUCCGGGUUGAGGG
AGAAGGGGCCAGGGTATAAA
AGACCAGCTCAAGGATCCCAAGGCCAACTCCC
TCTTCCCCGGTCCCATATTTTTCCCGGGTGTTCTCTGGTCGAGTTCCTAGGGTTCCGGGTTGAGGG

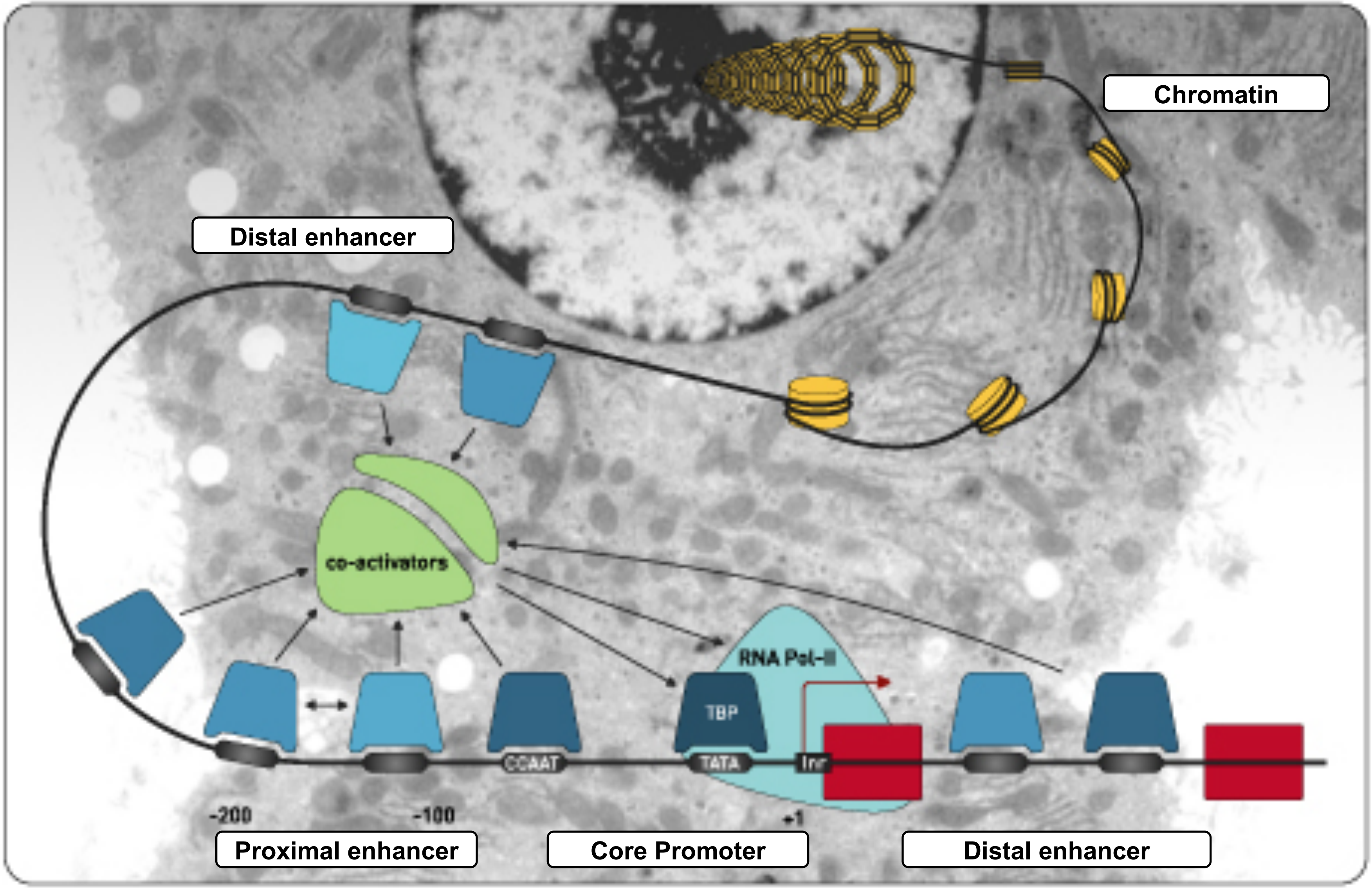
Anatomy of transcriptional regulation

WARNING: Terms vary widely in meaning between scientists

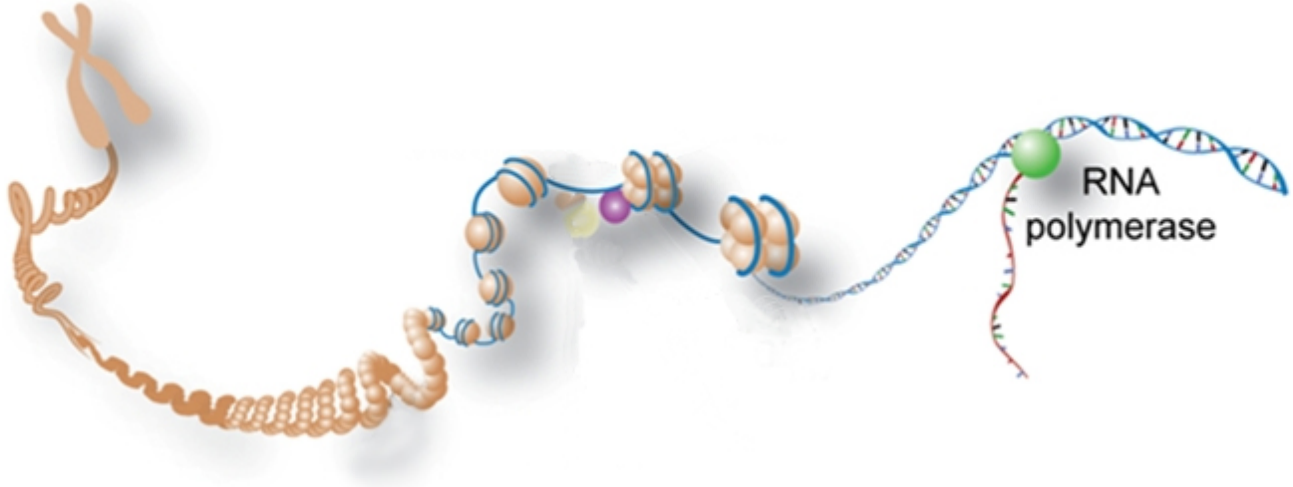


- Core promoter – Sufficient for initiation of transcription; orientation dependent
    - TSS – transcription start site
        - Often really a transcription start *region*
- TFBS – single transcription factor binding site
- Regulatory regions
    - Proximal/distal – vague reference to distance from TSS
    - May be positive (enhancing) or negative (repressing)
    - Orientation independent (generally)
    - Modules – Sets of TFBS within a region that function together
- Transcriptional unit
    - DNA sequence transcribed as a single polycistronic mRNA

Complexity in transcription

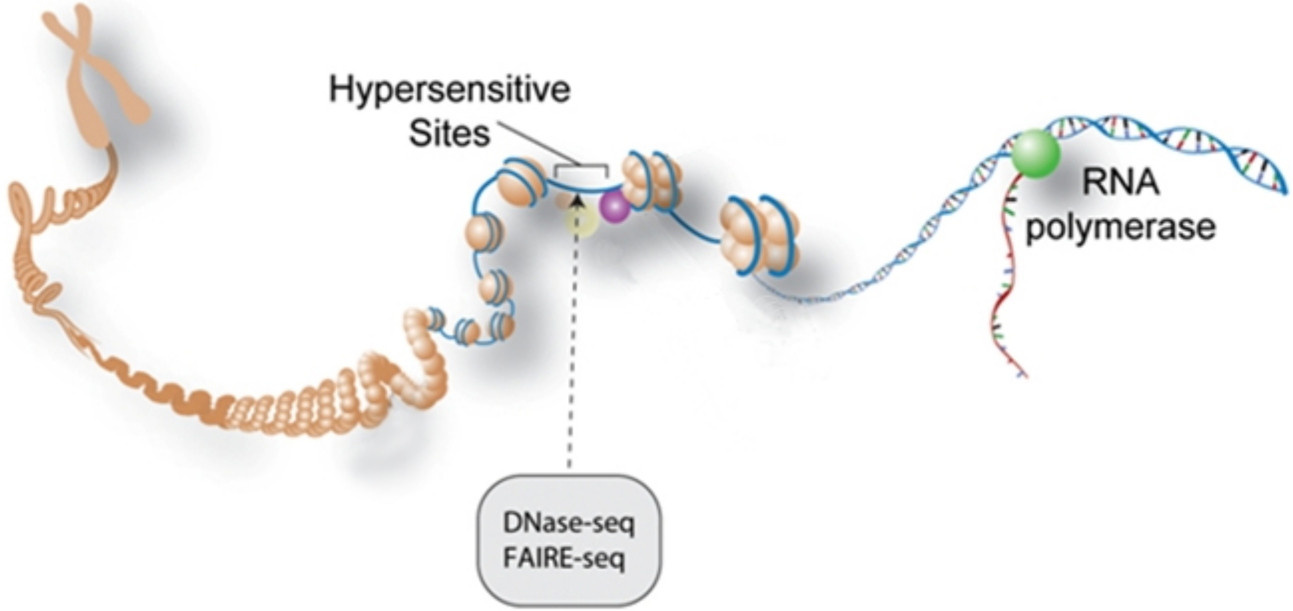


Functional genomics



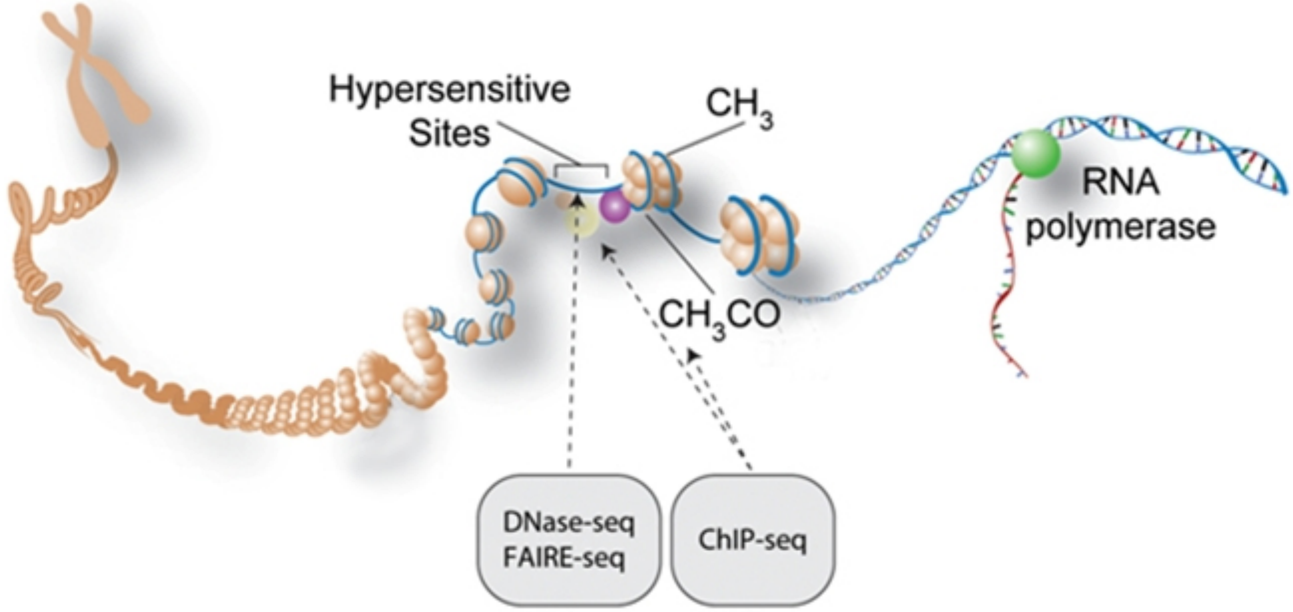
ENCODE Project Consortium 2011. *PLoS Biol* 9:e1001046.

Functional genomics



ENCODE Project Consortium 2011. *PLoS Biol* 9:e1001046.

Functional genomics



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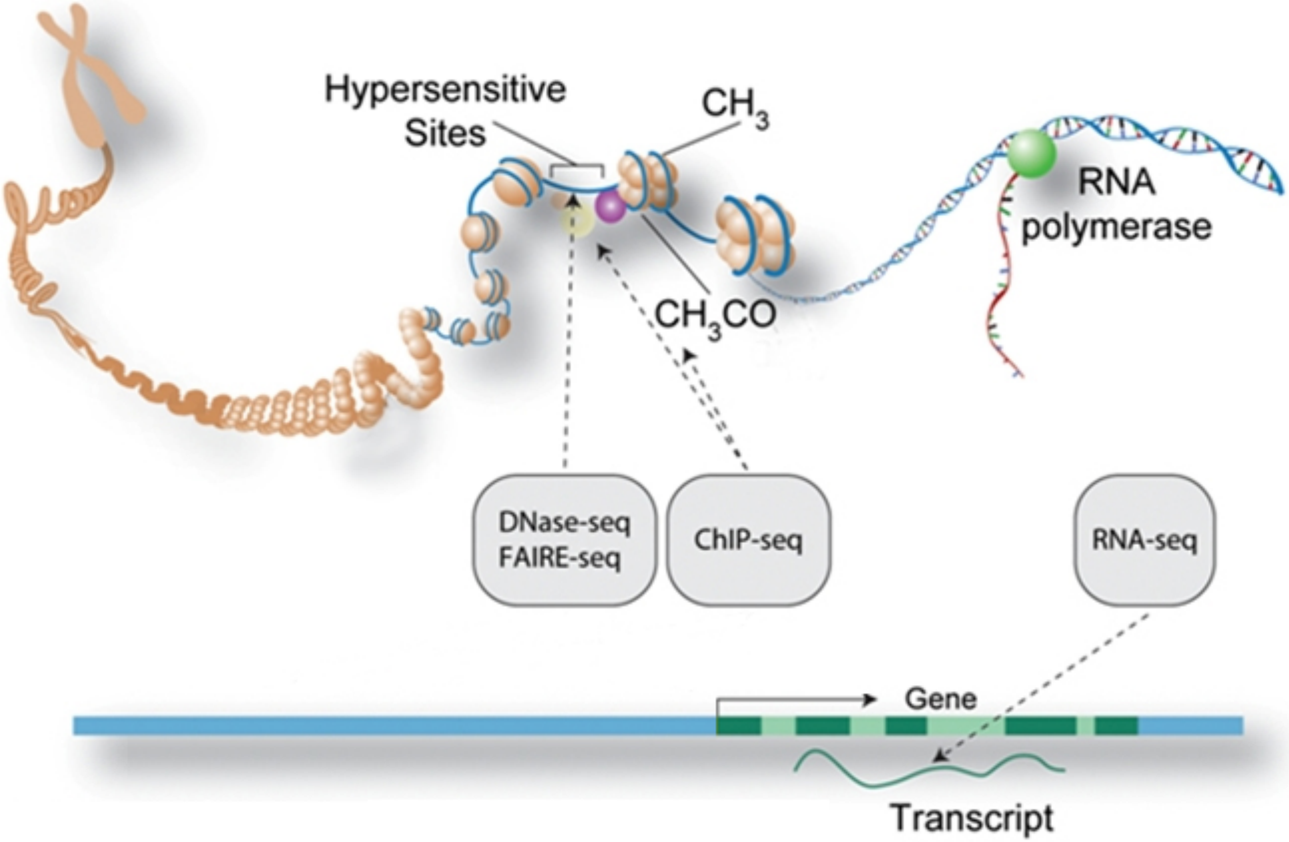
Functional genomics



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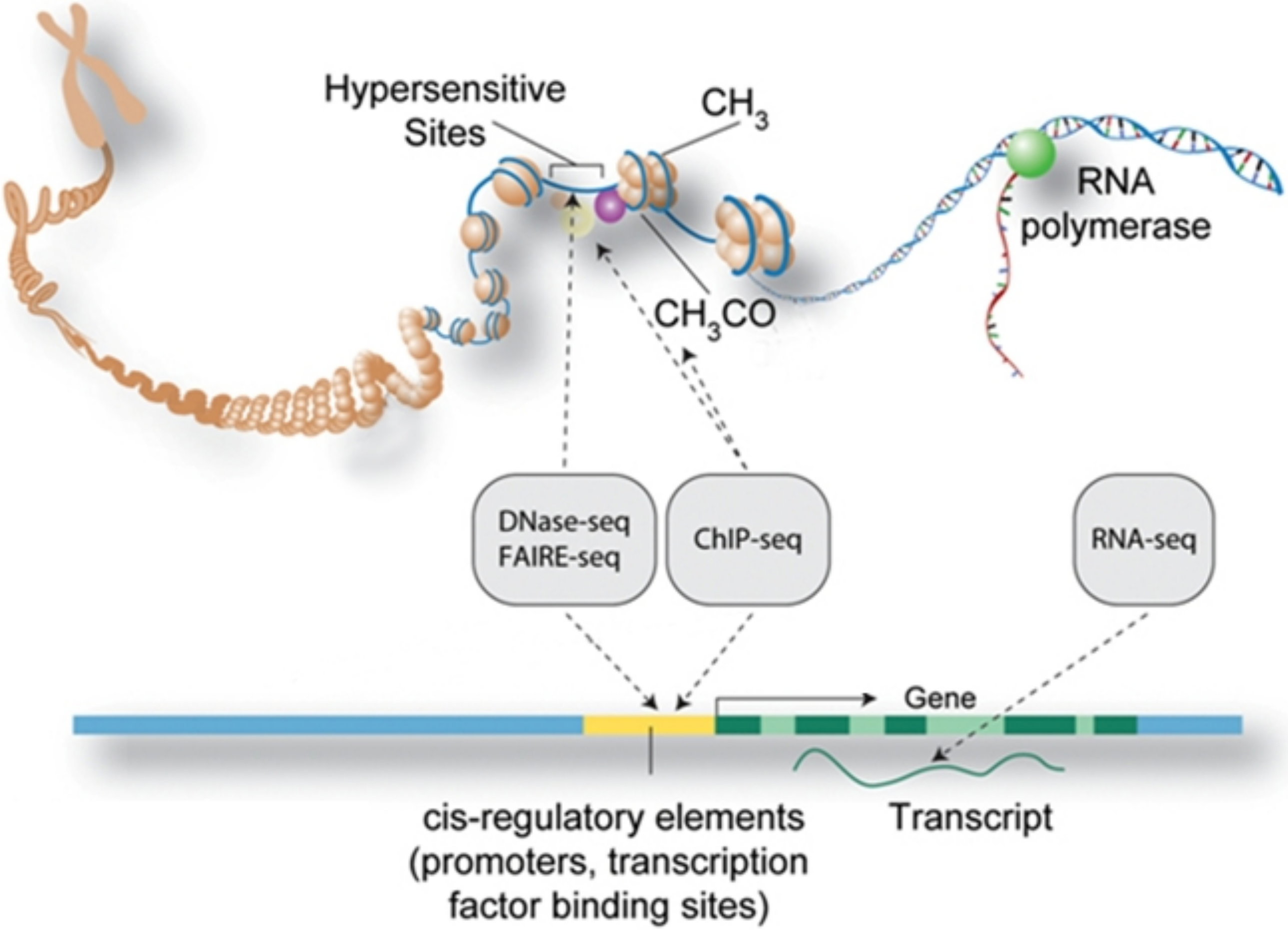
Functional genomics



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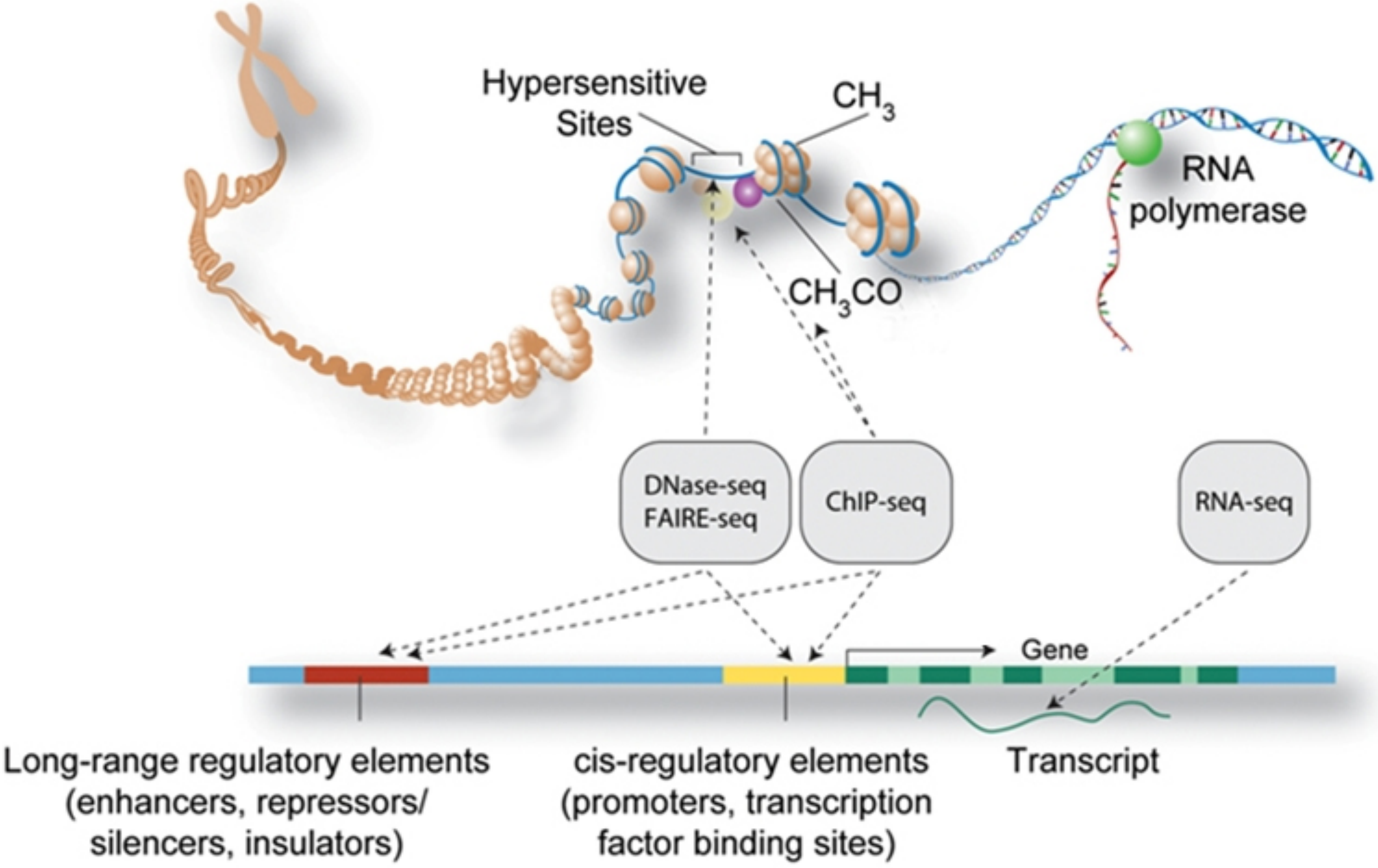
Functional genomics


Hypersensitive Sites
CH_3
RNA polymerase
CH_3CO
DNase-seq
FAIRE-seq
ChIP-seq
RNA-seq
Gene
Transcript
Long-range regulatory elements (enhancers, repressors/ silencers, insulators)
cis-regulatory elements (promoters, transcription factor binding sites)

ENCODE Project Consortium 2011. *PLoS Biol* 9:e1001046.

ENCODE
The Encyclopedia of DNA Elements

Accessing regulatory data

- ENCODE Project
  - http://encodeproject.org/
- UCSC Genome Browser
  - http://genome.ucsc.edu/
- Ensembl
  - http://ensembl.org/
- Gene Expression Omnibus (GEO)
  - http://www.ncbi.nlm.nih.gov/geo/

Part 2
Prediction of
TF binding sites

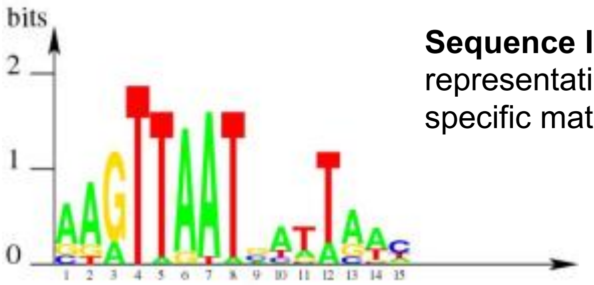
Teaching a computer
to find transcription factor
binding sites

Representing binding sites for a TF

- Single site
  - AAGTTAATGATTAAC
- Set of sites, represented as a consensus
  - VDRTWRWWSHDWVDH (IUPAC degenerate DNA)
- Set of sites, represented as a position frequency matrix (PFM)

A	14	16	4	0	1	19	20	1	4	13	4	4	13	12	3
C	3	0	0	0	0	0	0	0	7	3	1	0	3	1	12
G	4	3	17	0	0	2	0	0	9	1	3	0	5	2	2
T	0	2	0	21	20	0	1	20	1	4	13	17	0	6	4

Information content



Sequence logo: graphical representation of position-specific matrix.

Set of binding sites

```
AAGTTAATGATTAAC
CAGTTAATAAATAAC
GAGTTAAACACTAAA
CAGTTAATTAGTAAC
GAGTTAATAAATAAC
CAGTTATTCAGTAAC
GAGTTAATAAATCAT
CAGTTAATCAGTAAT
AGATTAAAGAATAAT
AAGTTAACGATTAAC
AGGTTAACGATACAC
ATGTTGATGATAAAC
AAGTTAATGATAAAT
AAGTTAACGATAAAC
AAATTAATGATTCAC
GAGTTAATGATTAAA
AAGTTAATCATTGAC
AAGTTGATGATTAAG
AAATTAATGATTGAC
ATGTTAATGATTAAC
AAGTAAATGATTAAA
AAGTTAATGATTGCC
AAGTTAATGATTGAC
AAATTAATGATTGAC
AAGTTAATGATTAGG
AAGTTAATGATTAAT
AAGTTAATGATTAGC
AAGTTAATGATTAAT
```

Position frequency matrix (PFM) → position weight matrix (PWM)

PFM f → $f(b,i)$

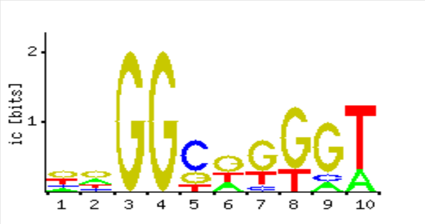
$$\text{base } b \quad \begin{array}{c|ccccc|}
\hline
\mathrm{A} & 5 & 0 & 1 & 0 & 0 \\
\mathrm{C} & 0 & 2 & 2 & 4 & 0 \\
\mathrm{G} & 0 & 3 & 1 & 0 & 4 \\
\mathrm{T} & 0 & 0 & 1 & 1 & 1 \\
\hline
\end{array}$$

column i

Detecting binding sites in a single sequence

Raw scores

Sp1



ACCCTCCCCAGGGGCGGGGGGCGGTGGCCAGGACGGTAGCTCC

```
A  [-0.2284  0.4368    -1.5    -1.5    -1.5  0.4368    -1.5    -1.5 -0.2284  0.4368 ]
C  [-0.2284 -0.2284    -1.5    -1.5  1.5128    -1.5 -0.2284    -1.5 -0.2284    -1.5 ]
G  [ 1.2348  1.2348  2.1222  2.1222  0.4368  1.2348  1.5128  1.7457  1.7457    -1.5 ]
T  [ 0.4368 -0.2284    -1.5    -1.5 -0.2284  0.4368  0.4368  0.4368    -1.5  1.7457 ]
```

Abs_score = 13.4 (sum of column scores)

Relative scores

```
A  [-0.2284  0.4368    -1.5    -1.5    -1.5  0.4368    -1.5    -1.5 -0.2284  0.4368 ]
C  [-0.2284 -0.2284    -1.5    -1.5  1.5128    -1.5 -0.2284    -1.5 -0.2284    -1.5 ]
G  [ 1.2348  1.2348  2.1222  2.1222  0.4368  1.2348  1.5128  1.7457  1.7457    -1.5 ]
T  [ 0.4368 -0.2284    -1.5    -1.5 -0.2284  0.4368  0.4368  0.4368    -1.5  1.7457 ]
```

Max_score = 15.2 (sum of highest column scores)

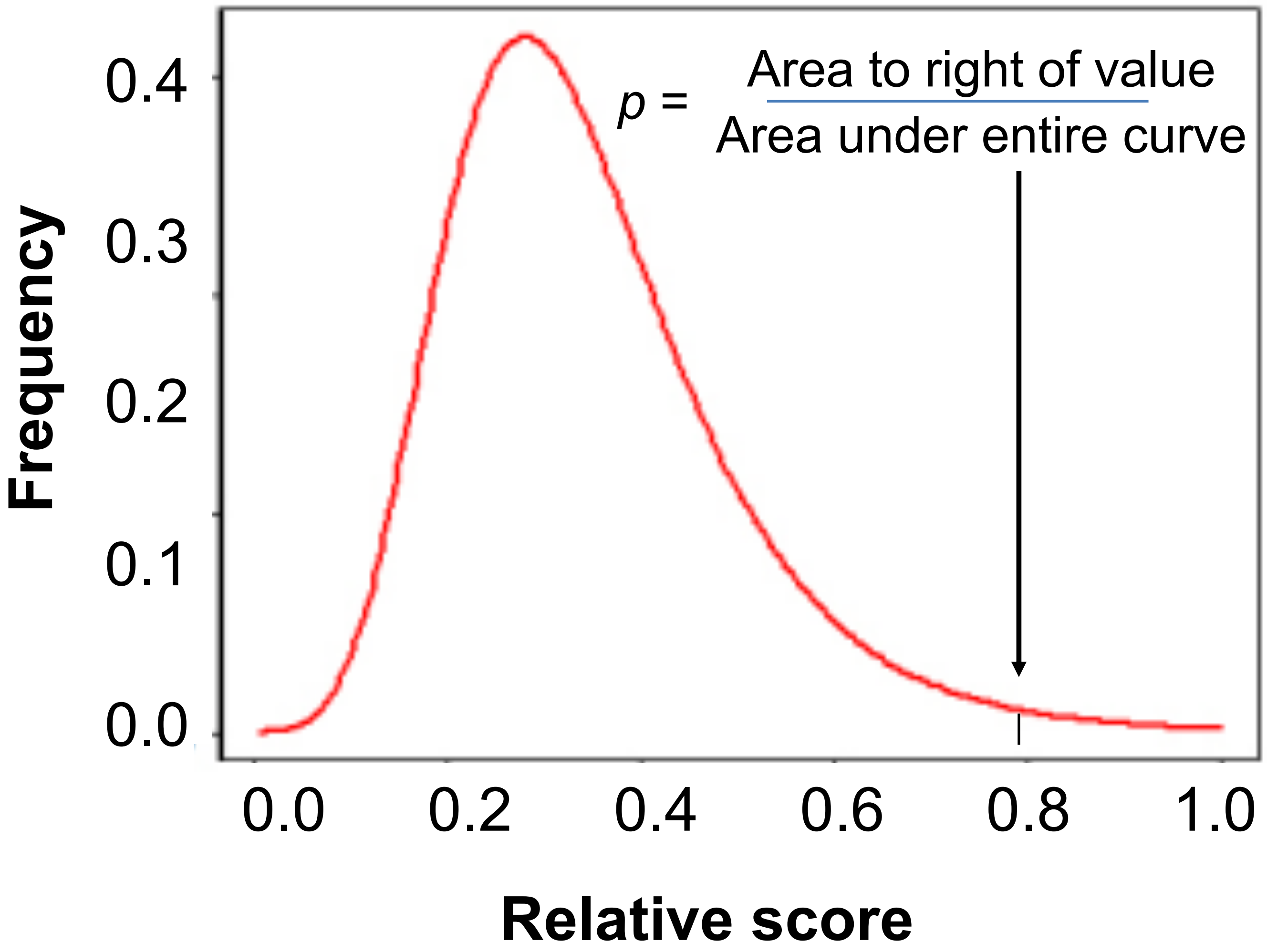
```
A  [-0.2284  0.4368    -1.5    -1.5    -1.5  0.4368    -1.5    -1.5 -0.2284  0.4368 ]
C  [-0.2284 -0.2284    -1.5    -1.5  1.5128    -1.5 -0.2284    -1.5 -0.2284    -1.5 ]
G  [ 1.2348  1.2348  2.1222  2.1222  0.4368  1.2348  1.5128  1.7457  1.7457    -1.5 ]
T  [ 0.4368 -0.2284    -1.5    -1.5 -0.2284  0.4368  0.4368  0.4368    -1.5  1.7457 ]
```

Min_score = -10.3 (sum of lowest column scores)

$$\text{Rel\_score} = \frac{\text{Abs\_score} - \text{Min\_score}}{\text{Max\_score} - \text{Min\_score}} \cdot 100\ \%$$

$$= \frac{13.4 - (-10.3)}{15.2 - (-10.3)} \cdot 100\% = \mathbf{93\%}$$

Empirical p-value score



$$p = \frac{\text{Area to right of value}}{\text{Area under entire curve}}$$

JASPAR:

An open-access database of TF binding profiles

http://jaspar.genereg.net

New Release Coming for 2018

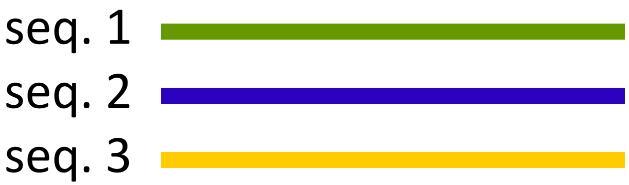
with Entirely New Interface

Part 3:

De novo discovery of transcription factor binding sites

Motif discovery problem

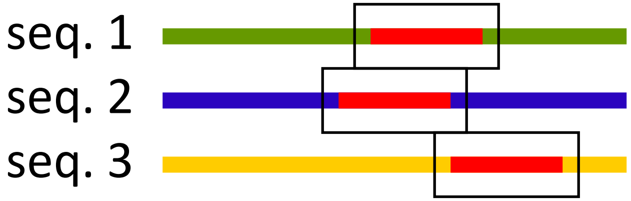
- Given sequences



seq. 1
seq. 2
seq. 3

- Find motif

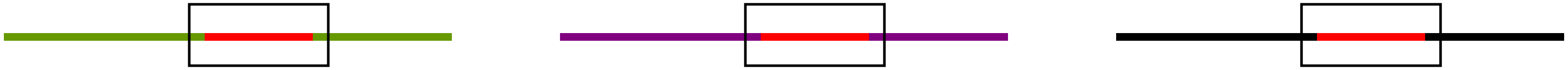
IGRGGFGEVY at position 515
LGEGCFGQVV at position 430
VGSGGFGQVY at position 682



seq. 1
seq. 2
seq. 3

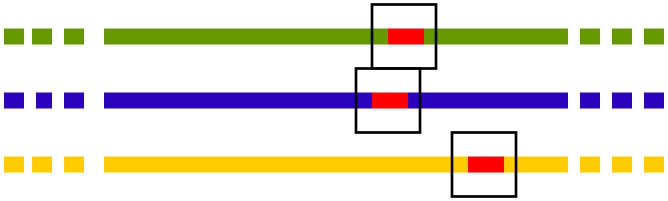
Motif discovery problem

- Given:
  - a sequence or family of sequences.
- Find:
  - the number of motifs
  - the width of each motif
  - the locations of motif occurrences

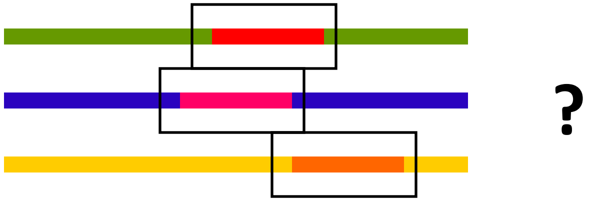


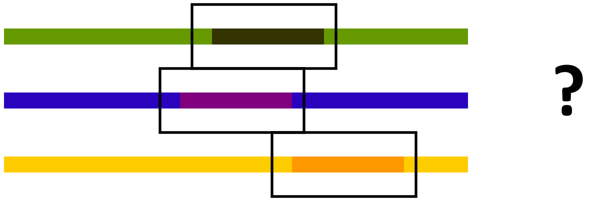
Why is this hard?

- Input sequences are long (thousands or millions of residues).



- Motif may be *subtle*
  - Instances are short.
  - Instances are only slightly similar.





TFBS motif discovery example

We are given a set of promoters from co-regulated genes.

TCTCTCTCCACGGCTAATTAGGTGATCATGAAAAAATGAAAAATTCATGAGAAAAGAGTCAGACATCGAAACATACAT …*HIS7*

ATGGCAGAATCACTTTAAAACGTGGCCCCACCCGCTGCACCCTGTGCATTTTGTACGTTACTGCGAAATGACTCAACG …*ARO4*

CACATCCAACGAATCACCTCACCGTTATCGTGACTCACTTTCTTTCGCATCGCCGAAGTGCCATAAAAAATATTTTTT …*ILV6*

TGCGAACAAAAGAGTCATTACAACGAGGAAATAGAAGAAAATGAAAAATTTTCGACAAAATGTATAGTCATTTCTATC …*THR4*

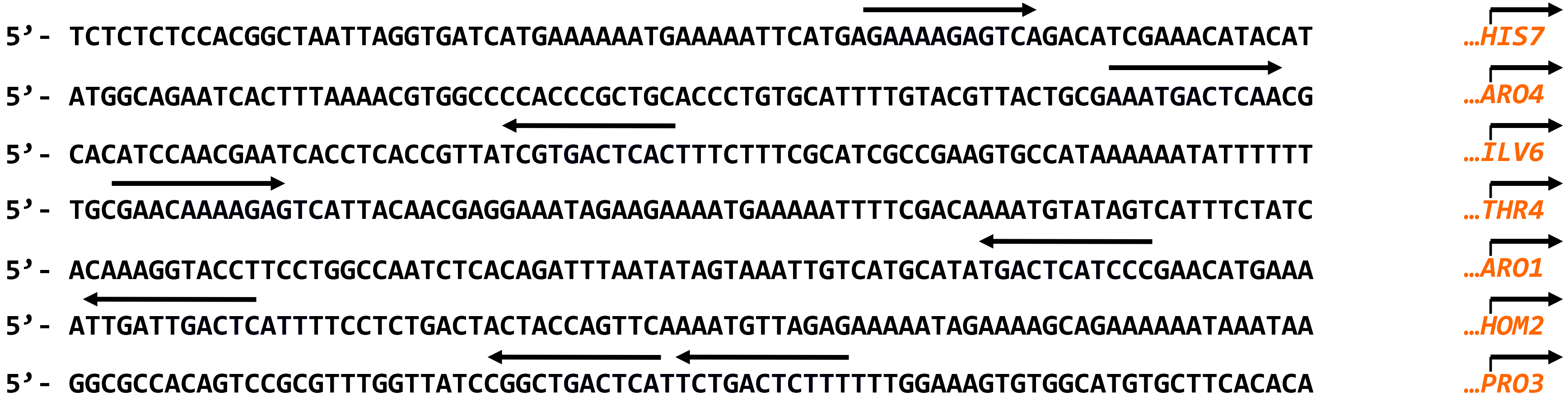
ACAAAGGTACCTTCCTGGCCAATCTCACAGATTTAATATAGTAAATTGTCATGCATATGACTCATCCCGAACATGAAA …*ARO1*

ATTGATTGACTCATTTTCCTCTGACTACTACCAGTTCAAAATGTTAGAGAAAAATAGAAAAGCAGAAAAAATAAATAA …*HOM2*

GGCGCCACAGTCCGCGTTTGGTTATCCGGCTGACTCATTCTGACTCTTTTTTGGAAAGTGTGGCATGTGCTTCACACA …*PRO3*

TFBS motif discovery example

An unknown transcription factor binds to positions unknown to us, on either DNA strand.



5’- TCTCTCTCCACGGCTAATTAGGTGATCATGAAAAAATGAAAAATTCATGAGAAAAGAGTCAGACATCGAAACATACAT …HIS7

5’- ATGGCAGAATCACTTTAAAACGTGGCCCCACCCGCTGCACCCTGTGCATTTTGTACGTTACTGCGAAATGACTCAACG …ARO4

5’- CACATCCAACGAATCACCTCACCGTTATCGTGACTCACTTTCTTTCGCATCGCCGAAGTGCCATAAAAAATATTTTTT …ILV6

5’- TGCGAACAAAAGAGTCATTACAACGAGGAAATAGAAGAAAATGAAAAATTTTCGACAAAATGTATAGTCATTTCTATC …THR4

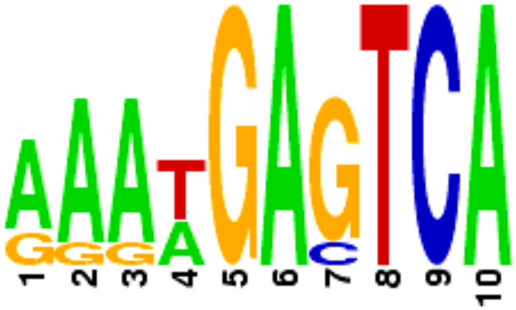
5’- ACAAAGGTACCTTCCTGGCCAATCTCACAGATTTAATATAGTAAATTGTCATGCATATGACTCATCCCGAACATGAAA …ARO1

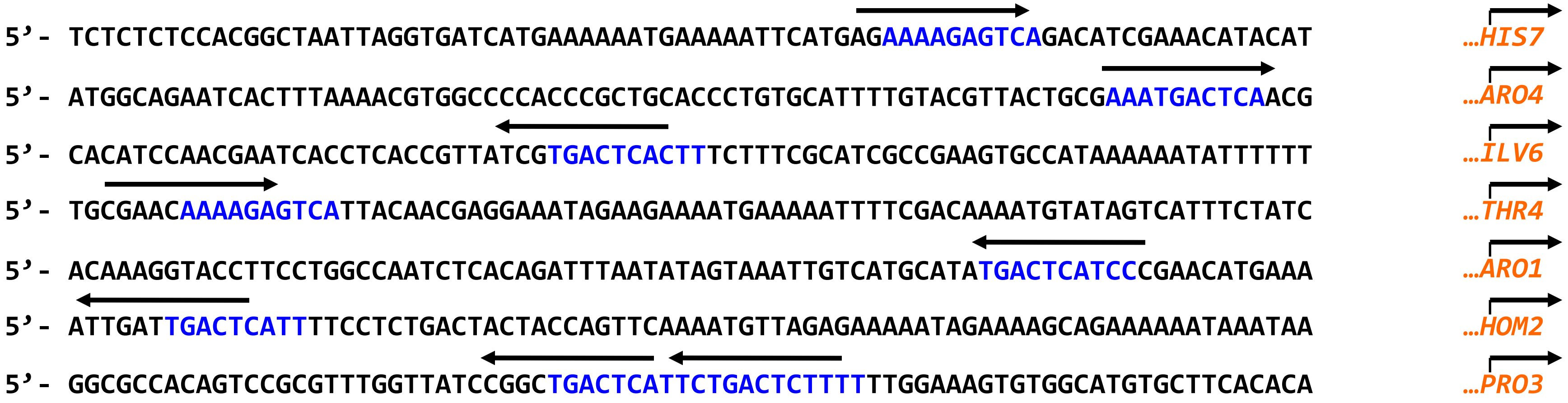
5’- ATTGATTGACTCATTTTCCTCTGACTACTACCAGTTCAAAATGTTAGAGAAAAATAGAAAAGCAGAAAAAATAAATAA …HOM2

5’- GGCGCCACAGTCCGCGTTTGGTTATCCGGCTGACTCATTCTGACTCTTTTTTGGAAAGTGTGGCATGTGCTTCACACA …PRO3

TFBS motif discovery example

DNA binding motif of the transcription factor can be described by a position weight matrix (PWM).





5’- TCTCTCTCCACGGCTAATTAGGTGATCATGAAAAAATGAAAAATTCATGAGAAAAGAGTCAGACATCGAAACATACAT ...*HIS7*

5’- ATGGCAGAATCACTTTAAAACGTGGCCCCACCCGCTGCACCCTGTGCATTTTGTACGTTACTGCGAAATGACTCAACG ...*ARO4*

5’- CACATCCAACGAATCACCTCACCGTTATCGTGACTCACTTTCTTTCGCATCGCCGAAGTGCCATAAAAAATATTTTTT ...*ILV6*

5’- TGCGAACAAAAGAGTCATTACAACGAGGAAATAGAAGAAAATGAAAAATTTTCGACAAAATGTATAGTCATTTCTATC ...*THR4*

5’- ACAAAGGTACCTTCCTGGCCAATCTCACAGATTTAATATAGTAAATTGTCATGCATATGACTCATCCCGAACATGAAA ...*ARO1*

5’- ATTGATTGACTCATTTTCCTCTGACTACTACCAGTTCAAAATGTTAGAGAAAAATAGAAAAGCAGAAAAAATAAATAA ...*HOM2*

5’- GGCGCCACAGTCCGCGTTTGGTTATCCGGCTGACTCATTCTGACTCTTTTTTGGAAAGTGTGGCATGTGCTTCACACA ...*PRO3*

TFBS motif discovery example

Sequence motif discovery problem is to discover the sites (or the motif) given just the sequences.

5’- TCTCTCTCCACGGCTAATTAGGTGATCATGAAAAAATGAAAAATTCATGAGAAAAGAGTCAGACATCGAAACATACAT …*HIS7*

5’- ATGGCAGAATCACTTTAAAACGTGGCCCCACCCGCTGCACCCTGTGCATTTTGTACGTTACTGCGAAATGACTCAACG …*ARO4*

5’- CACATCCAACGAATCACCTCACCGTTATCGTGACTCACTTTCTTTCGCATCGCCGAAGTGCCATAAAAAATATTTTTT …*ILV6*

5’- TGCGAACAAAAGAGTCATTACAACGAGGAAATAGAAGAAAATGAAAAATTTTCGACAAAATGTATAGTCATTTCTATC …*THR4*

5’- ACAAAGGTACCTTCCTGGCCAATCTCACAGATTTAATATAGTAAATTGTCATGCATATGACTCATCCCGAACATGAAA …*ARO1*

5’- ATTGATTGACTCATTTTCCTCTGACTACTACCAGTTCAAAATGTTAGAGAAAAATAGAAAAGCAGAAAAAATAAATAA …*HOM2*

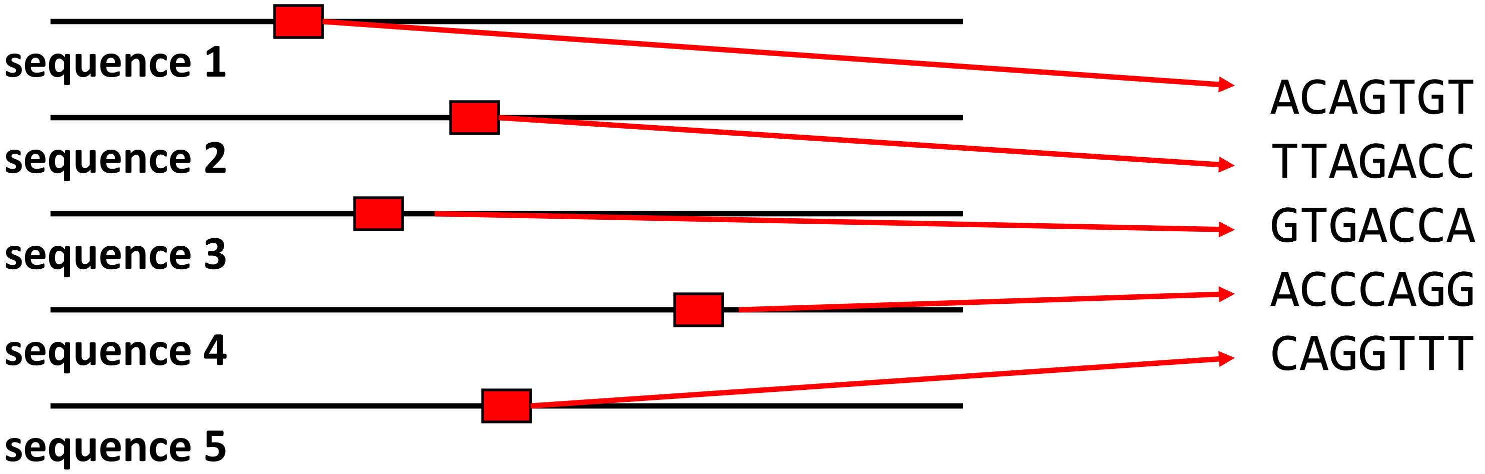
5’- GGCGCCACAGTCCGCGTTTGGTTATCCGGCTGACTCATTCTGACTCTTTTTTGGAAAGTGTGGCATGTGCTTCACACA …*PRO3*

Alternating approach

1. Guess an initial weight matrix
2. Use weight matrix to predict instances in the input sequences
3. Use instances to predict a weight matrix
4. Repeat 2 & 3 until satisfied.

Gibbs Sampler: 1. Initialization

- Randomly guess an instance s_i from each of t input sequences $\{S_1, \ldots, S_t\}$.



Gibbs Sampler: 2a. Define PWM

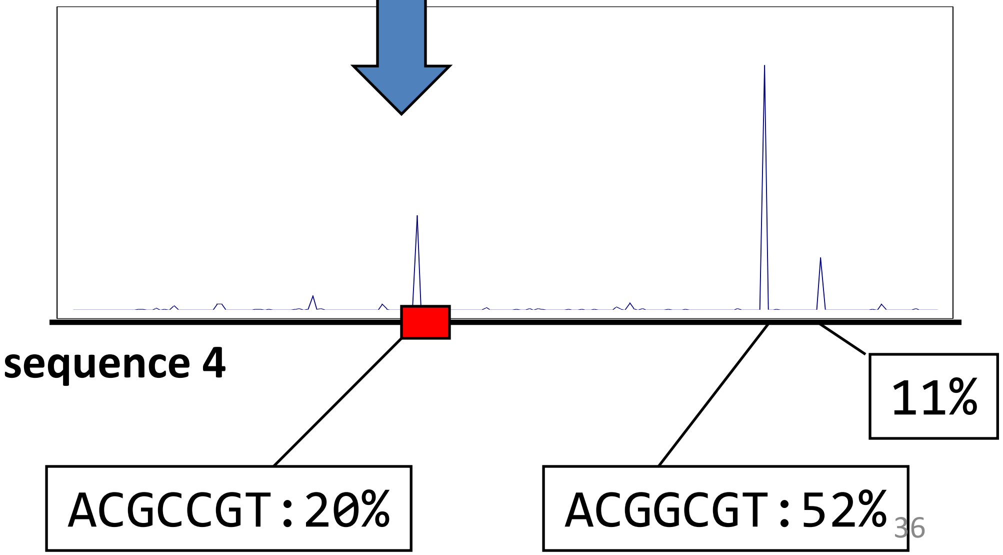
ACAGTGT
TAGGCGT
ACACCGT
???????
CAGGTTT

A	.45	.45	.45	.05	.05	.05	.05
C	.25	.45	.05	.25	.45	.05	.05
G	.05	.05	.45	.65	.05	.65	.05
T	.25	.05	.05	.05	.45	.25	.85

Gibbs Sampler: 2b. Predict instances

ACAGTGT
TAGGCGT
ACACCGT
???????
CAGGTTT

A	.45	.45	.45	.05	.05	.05	.05
C	.25	.45	.05	.25	.45	.05	.05
G	.05	.05	.45	.65	.05	.65	.05
T	.25	.05	.05	.05	.45	.25	.85



sequence 4

11%

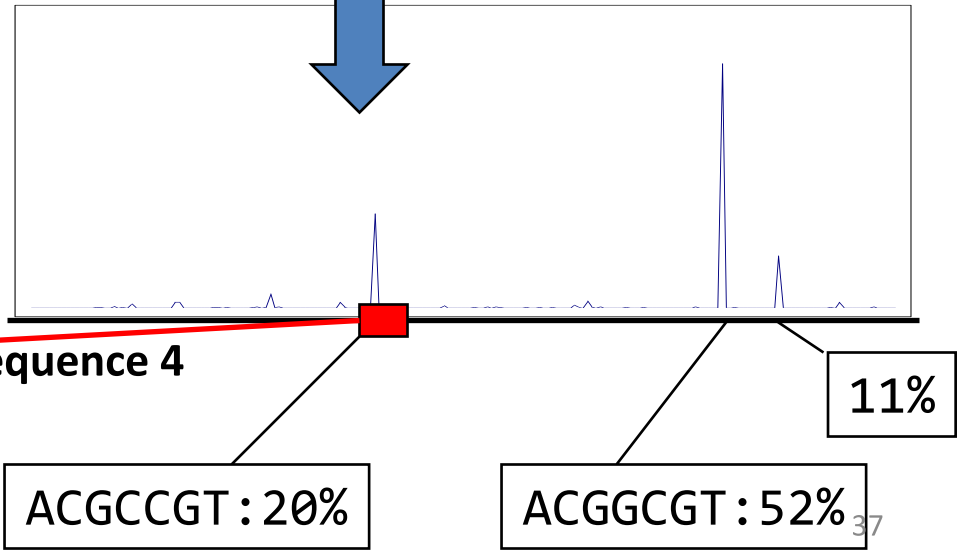
ACGCCGT:20%

ACGGCGT:52%

Gibbs Sampler: 3. Pick new instance

ACAGTGT
TAGGCGT
ACACCGT
???????
CAGGTTT

A	.45	.45	.45	.05	.05	.05	.05
C	.25	.45	.05	.25	.45	.05	.05
G	.05	.05	.45	.65	.05	.65	.05
T	.25	.05	.05	.05	.45	.25	.85



sequence 4

ACGCCGT:20%

ACGGCGT:52%

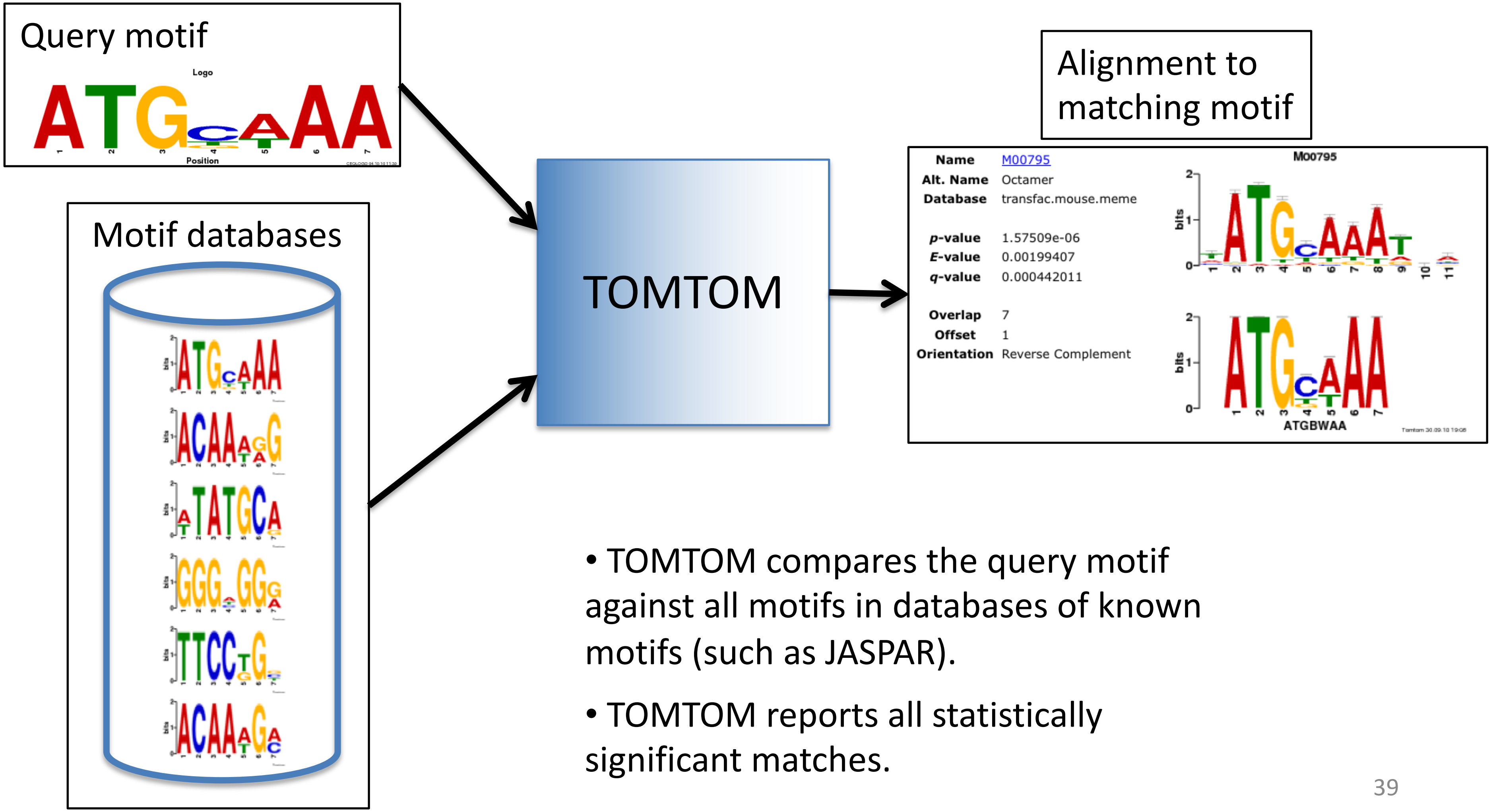
11%

ACAGTGT
TAGGCGT
ACACCGT
ACGCCGT
CAGGTTT

Gibbs sampler

- Initially: randomly guess an instance s_i from each of t input sequences $\{S_1, ..., S_t\}$.
- Steps 2 & 3 (search):
  - Throw away an instance s_i: remaining (t - *1*) instances define weight matrix.
  - Weight matrix defines instance probability at each position of input string S_i
  - Pick new s_i according to probability distribution
- Return highest-scoring motif seen

TOMTOM:
predict which proteins may bind a DNA motif



Name	M00795
Alt. Name	Octamer
Database	transfac.mouse.meme
***p*-value**	1.57509e-06
***E*-value**	0.00199407
***q*-value**	0.000442011
Overlap	7
Offset	1
Orientation	Reverse Complement

- TOMTOM compares the query motif against all motifs in databases of known motifs (such as JASPAR).
- TOMTOM reports all statistically significant matches.

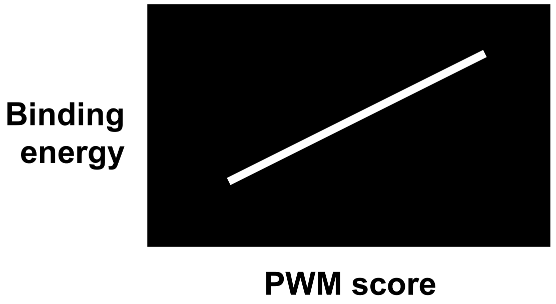
Part 4

Effectiveness of the position weight matrix model

The Good…

- Tronche (1997) tested 50 predicted HNF1 TFBS using an in vitro binding test and found that 96% of the predicted sites were bound!

- Stormo and Fields (1998) found in detailed biochemical studies that the best weight matrices produce scores highly correlated with in vitro binding energy



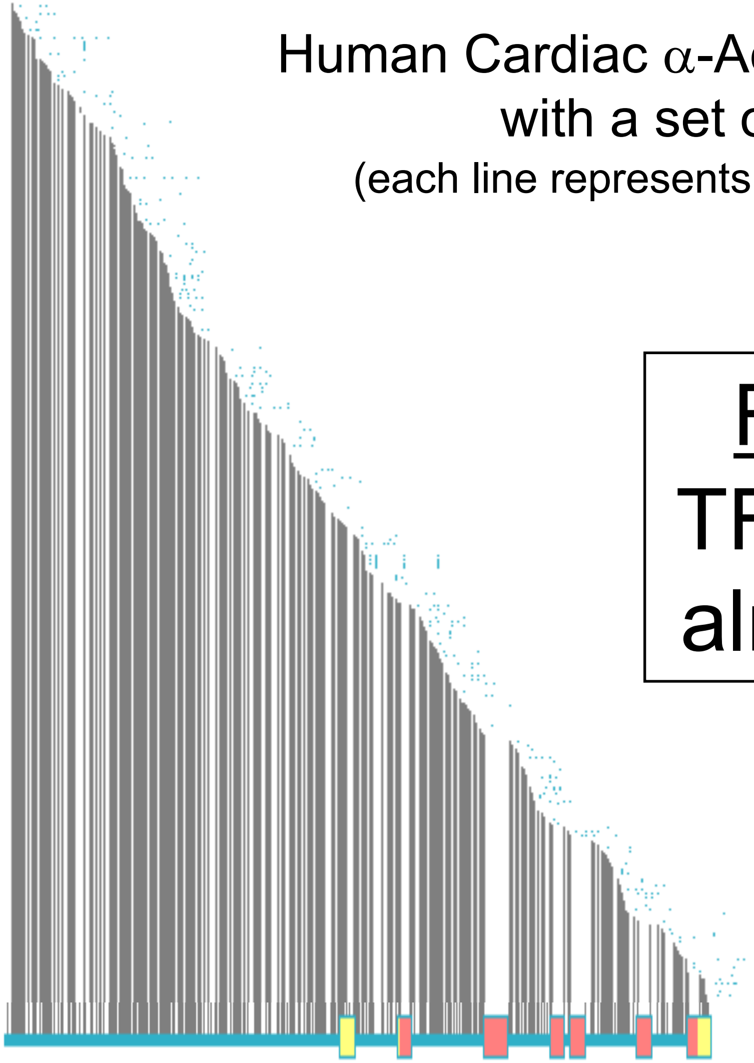
…the Bad…

- Fickett (1995) found that a profile for the MyoD TF made predictions at a rate of 1 per ~500 bp of human DNA sequence

    - This corresponds to an average of 20 sites / gene (assuming 10,000 bp as average gene size)

…and the Ugly!

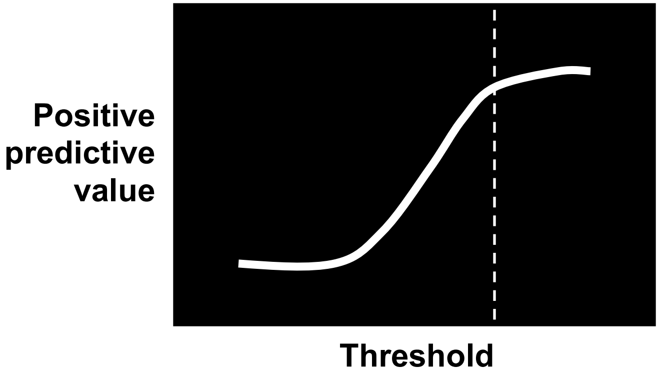
Human Cardiac α-Actin gene analyzed
with a set of profiles
(each line represents a TFBS prediction)



Futility conjecture:
TFBS predictions are
almost always wrong

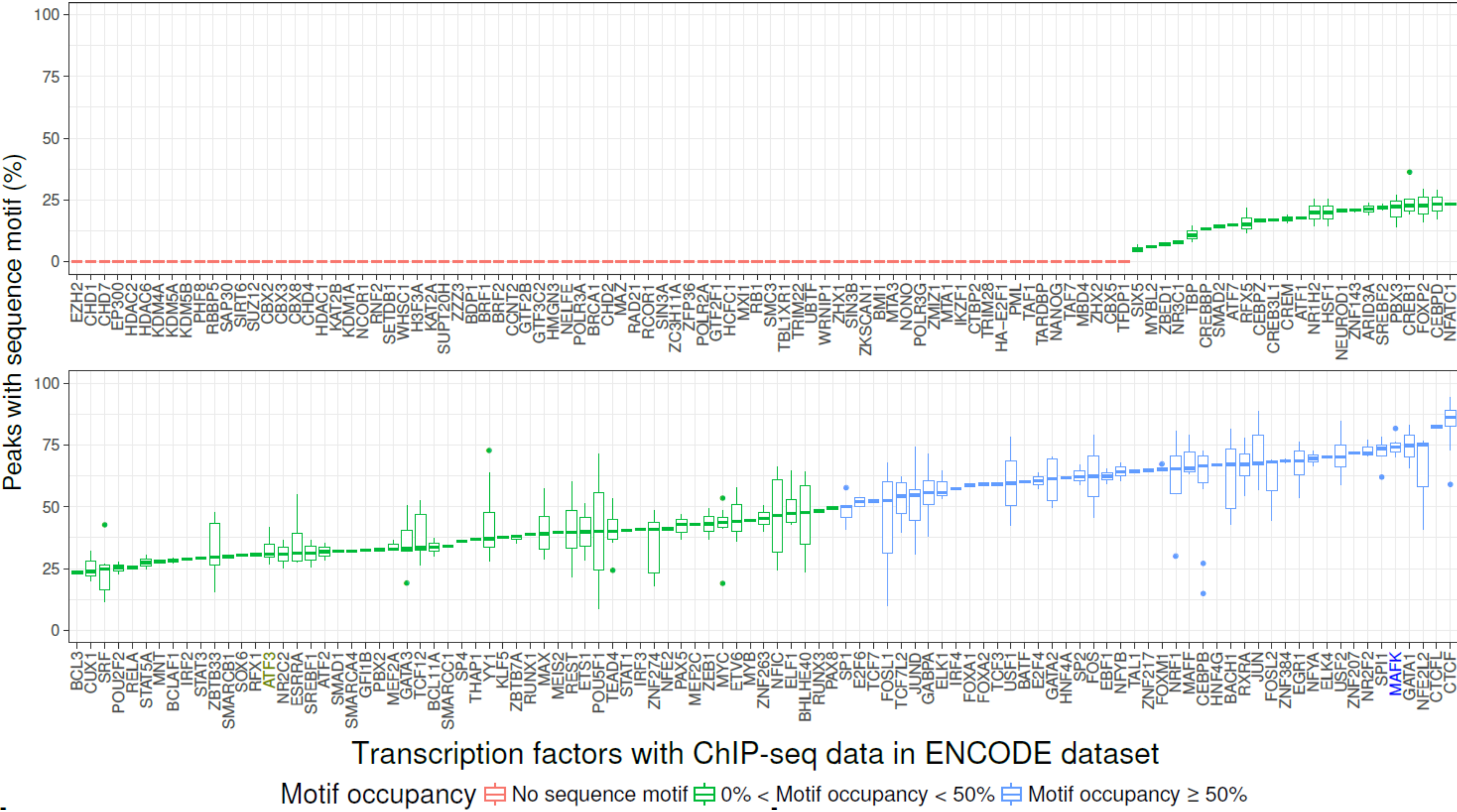
Red boxes are protein coding exons -
TFBS predictions excluded in this analysis

More stringency doesn't help

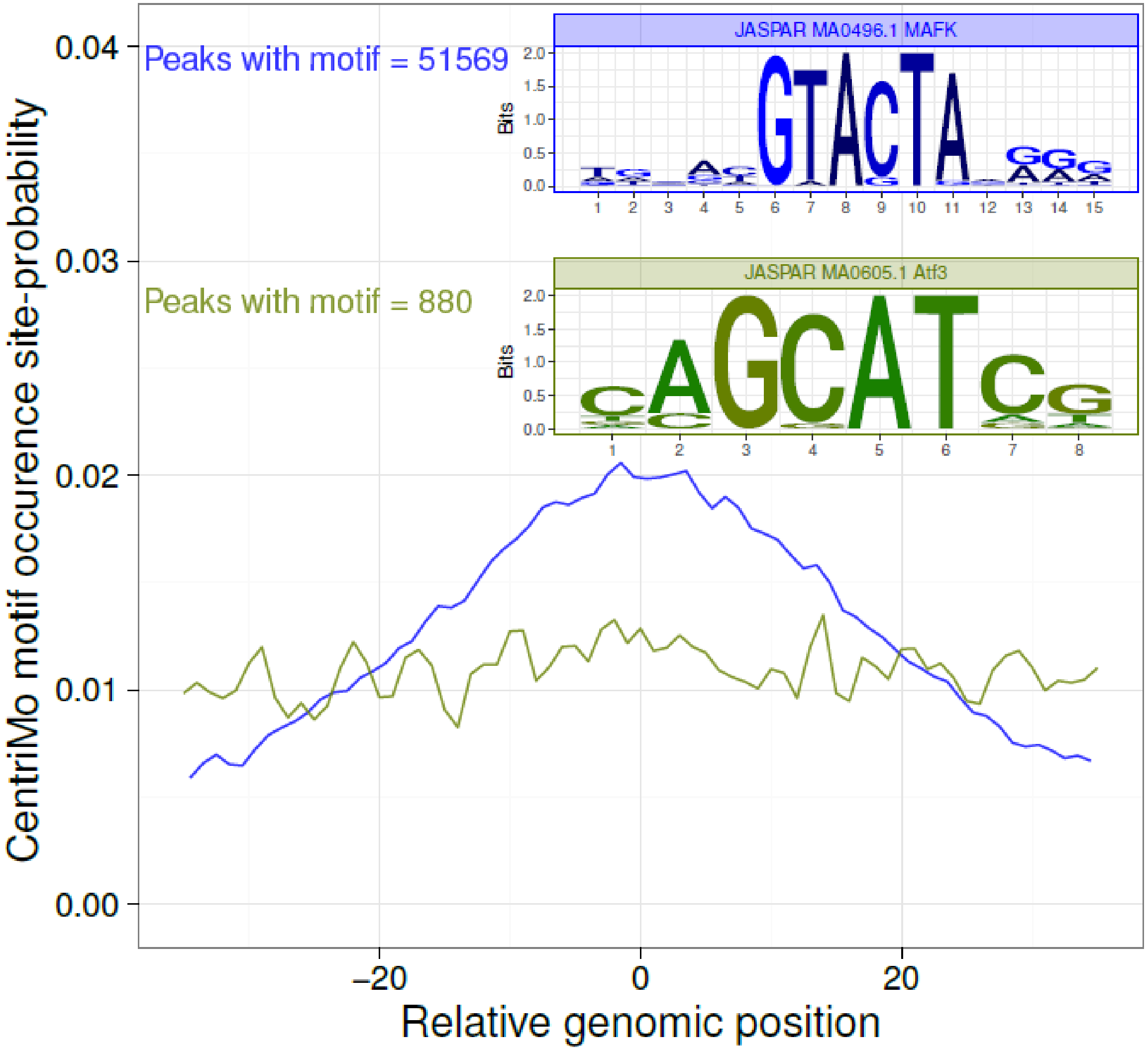


- Counter to intuition, the ratio of true positives to predictions fails to improve for "stringent" thresholds
    - For most predictive models this ratio would increase
- Why?
    - True binding sites are defined by properties not incorporated into the profile scores - above some threshold all sites *could* be bound if present in the right setting

It’s even worse than we imagined



Please make it stop



Part 4

What have we learned?

- PWMs can accurately reflect *in vitro* binding properties of DNA-binding proteins

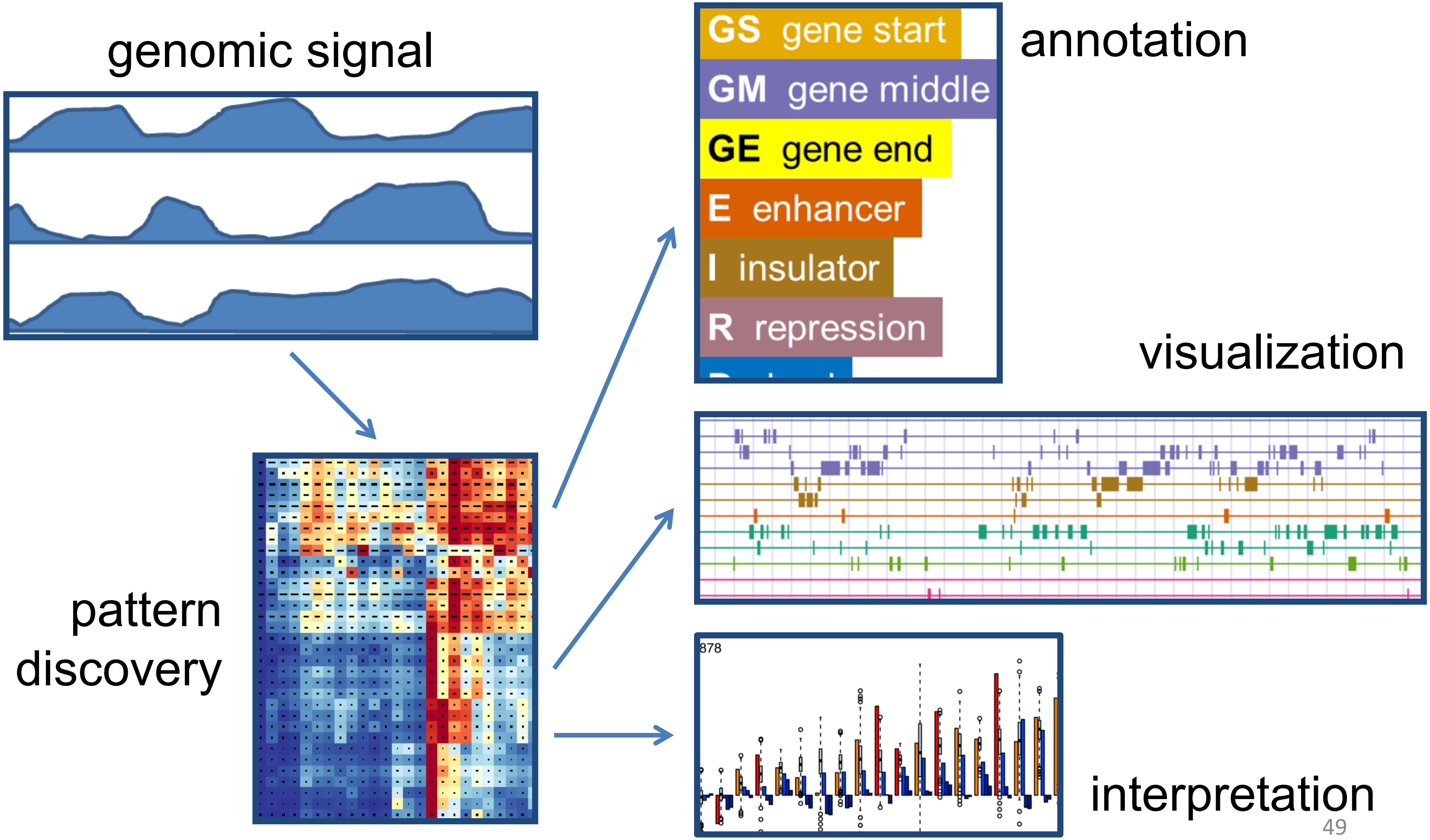
- Suitable binding sites occur at a rate far too frequent to reflect *in vivo* function

- *In vivo* presence of a DNA-binding protein often occurs without a strong motif

- Bioinformatics methods that use PWMs for binding site studies must incorporate additional information to enhance specificity
  - Unfiltered predictions are too noisy for most applications
  - Organisms with short regulatory sequences are less problematic (such as yeast and *E. coli*)

Part 5
Incorporating information about the biochemistry of gene regulation

Segway: semi-automated genome annotation



genomic signal

pattern discovery

annotation

GS gene start

GM gene middle

GE gene end

E enhancer

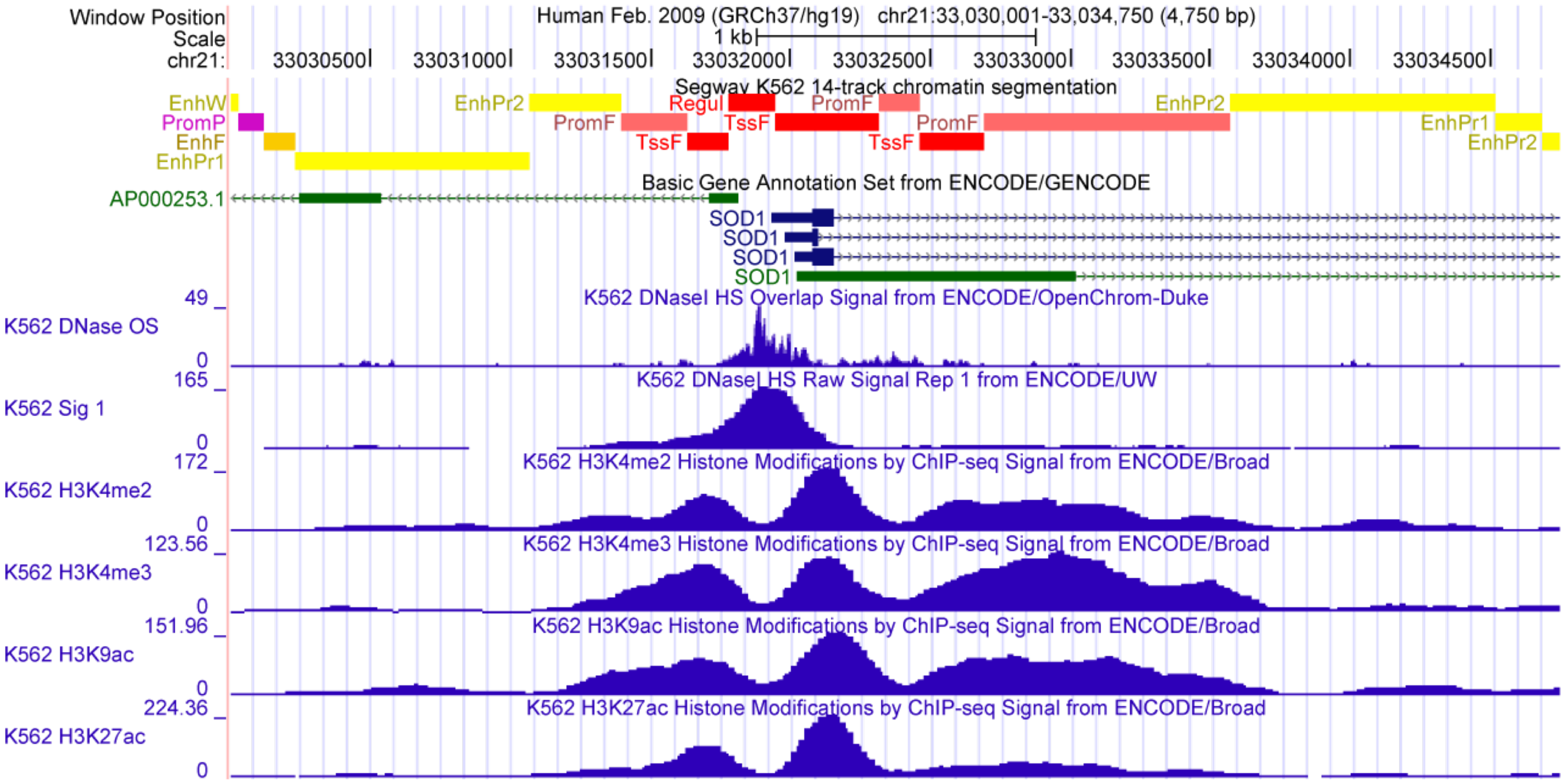
I insulator

R repression

visualization

interpretation

Transcription start site (TSS)


Window Position
Scale
chr21:
Human Feb. 2009 (GRCh37/hg19) chr21:33,030,001-33,034,750 (4,750 bp)
1 kb
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33031000
33031500
33032000
33032500
33033000
33033500
33034000
33034500
Segway K562 14-track chromatin segmentation
EnhW
PromP
EnhF
EnhPr1
EnhPr2
PromF
Regul
TssF
TssF
PromF
TssF
PromF
EnhPr2
EnhPr1
EnhPr2
Basic Gene Annotation Set from ENCODE/GENCODE
AP000253.1
SOD1
SOD1
SOD1
SOD1
49
K562 DNase OS
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K562 DNaseI HS Overlap Signal from ENCODE/OpenChrom-Duke
165
K562 Sig 1
0
K562 DNaseI HS Raw Signal Rep 1 from ENCODE/UW
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K562 H3K4me2
0
K562 H3K4me2 Histone Modifications by ChIP-seq Signal from ENCODE/Broad
123.56
K562 H3K4me3
0
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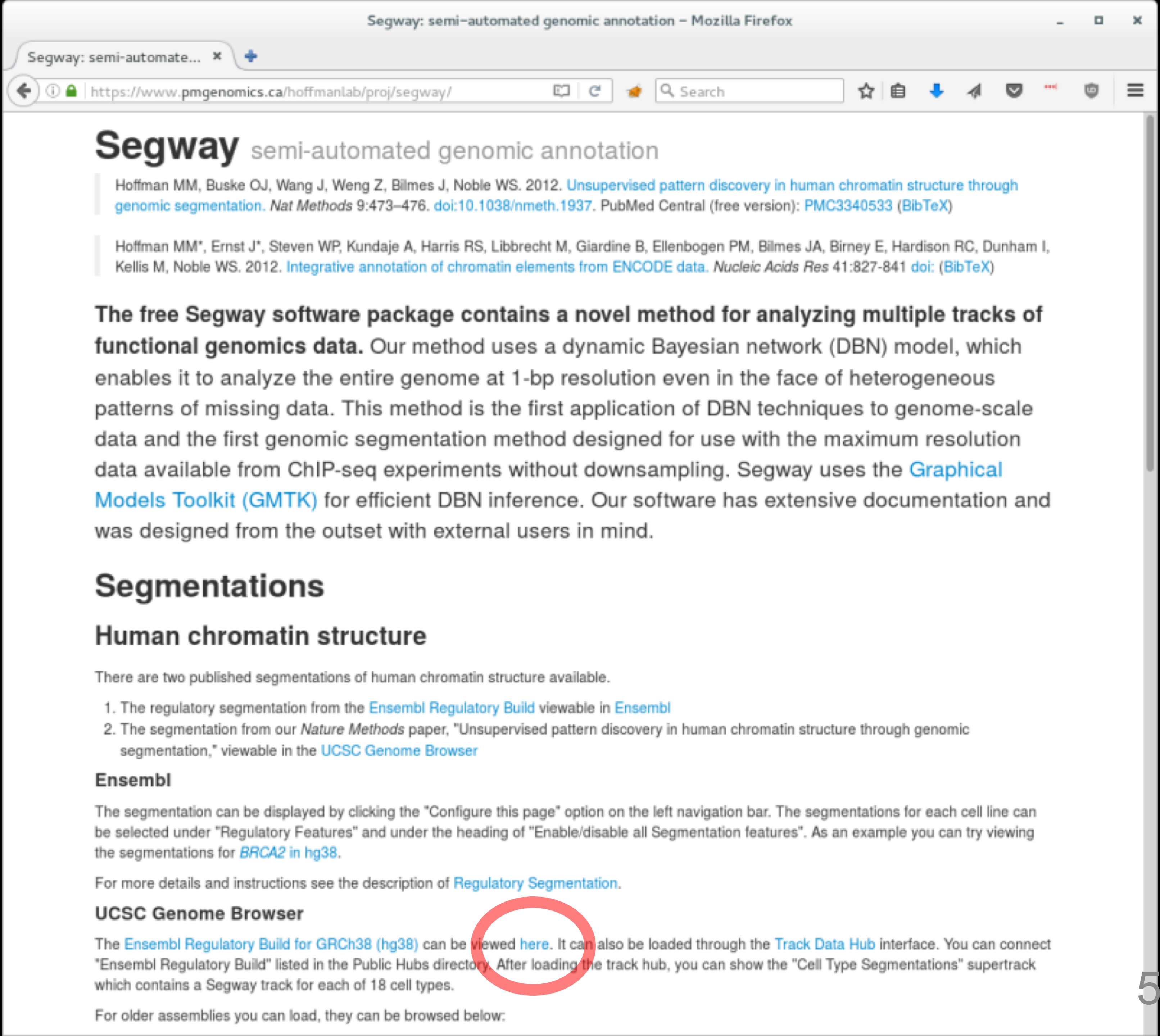
151.96
K562 H3K9ac
0
K562 H3K9ac Histone Modifications by ChIP-seq Signal from ENCODE/Broad
224.36
K562 H3K27ac
0
K562 H3K27ac Histone Modifications by ChIP-seq Signal from ENCODE/Broad

Hoffman MM *et al*. 2013. *Nucleic Acids Res* 41:827.

http://segway.hoffmanlab.org/


Segway: semi-automated genomic annotation – Mozilla Firefox
Segway: semi-automate...
https://www.pmgenomics.ca/hoffmanlab/proj/segway/
Search

Segway semi-automated genomic annotation

> Hoffman MM, Buske OJ, Wang J, Weng Z, Bilmes J, Noble WS. 2012. Unsupervised pattern discovery in human chromatin structure through genomic segmentation. *Nat Methods* 9:473–476. doi:10.1038/nmeth.1937. PubMed Central (free version): PMC3340533 (BibTeX)

> Hoffman MM*, Ernst J*, Steven WP, Kundaje A, Harris RS, Libbrecht M, Giardine B, Ellenbogen PM, Bilmes JA, Birney E, Hardison RC, Dunham I, Kellis M, Noble WS. 2012. Integrative annotation of chromatin elements from ENCODE data. *Nucleic Acids Res* 41:827-841 doi: (BibTeX)

The free Segway software package contains a novel method for analyzing multiple tracks of functional genomics data. Our method uses a dynamic Bayesian network (DBN) model, which enables it to analyze the entire genome at 1-bp resolution even in the face of heterogeneous patterns of missing data. This method is the first application of DBN techniques to genome-scale data and the first genomic segmentation method designed for use with the maximum resolution data available from ChIP-seq experiments without downsampling. Segway uses the Graphical Models Toolkit (GMTK) for efficient DBN inference. Our software has extensive documentation and was designed from the outset with external users in mind.

Segmentations

Human chromatin structure

There are two published segmentations of human chromatin structure available.

1. The regulatory segmentation from the Ensembl Regulatory Build viewable in Ensembl
2. The segmentation from our *Nature Methods* paper, "Unsupervised pattern discovery in human chromatin structure through genomic segmentation," viewable in the UCSC Genome Browser

Ensembl

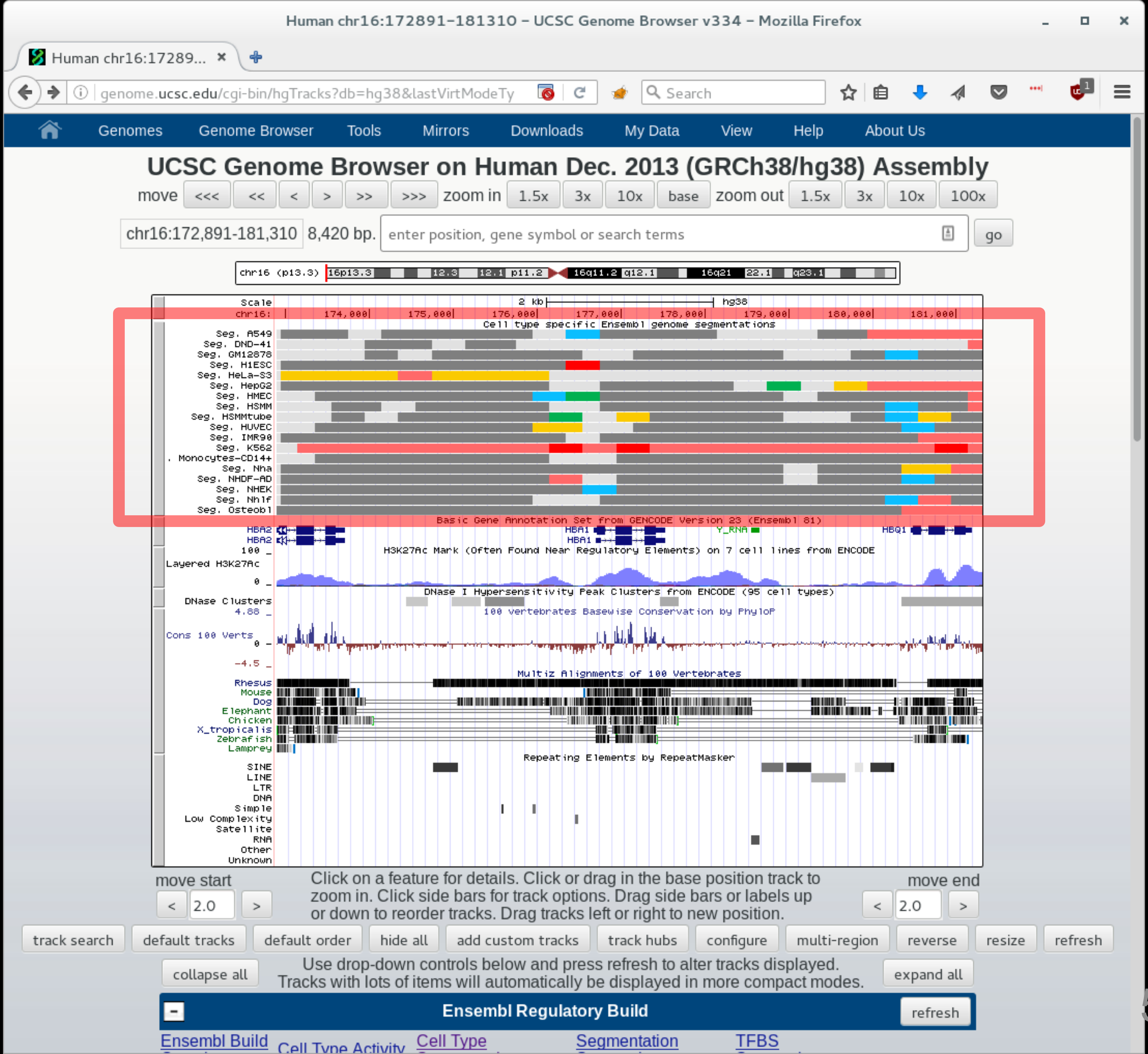
The segmentation can be displayed by clicking the "Configure this page" option on the left navigation bar. The segmentations for each cell line can be selected under "Regulatory Features" and under the heading of "Enable/disable all Segmentation features". As an example you can try viewing the segmentations for *BRCA2* in hg38.

For more details and instructions see the description of Regulatory Segmentation.

UCSC Genome Browser

The Ensembl Regulatory Build for GRCh38 (hg38) can be viewed here. It can also be loaded through the Track Data Hub interface. You can connect "Ensembl Regulatory Build" listed in the Public Hubs directory. After loading the track hub, you can show the "Cell Type Segmentations" supertrack which contains a Segway track for each of 18 cell types.

For older assemblies you can load, they can be browsed below:


Human chr16:172891-181310 - UCSC Genome Browser v334 - Mozilla Firefox
Human chr16:17289...
genome.ucsc.edu/cgi-bin/hgTracks?db=hg38&lastVirtModeTy
Search
Genomes
Genome Browser
Tools
Mirrors
Downloads
My Data
View
Help
About Us
move <<< << < > >> >>> zoom in 1.5x 3x 10x base zoom out 1.5x 3x 10x 100x
chr16:172,891-181,310 8,420 bp.
enter position, gene symbol or search terms
go
chr16 (p13.3) 16p13.3 12.3 12.1 p11.2 16q11.2 q12.1 16q21 22.1 q23.1
Scale 2 kb hg38
chr16: 174,000 175,000 176,000 177,000 178,000 179,000 180,000 181,000
Cell type specific Ensembl genome segmentations
Seg. A549
Seg. DND-41
Seg. GM12878
Seg. H1ESC
Seg. HeLa-S3
Seg. HepG2
Seg. HMEC
Seg. HSMM
Seg. HSMMtube
Seg. HUVEC
Seg. IMR90
Seg. K562
. Monocytes-CD14+
Seg. Nha
Seg. NHDF-AD
Seg. NHEK
Seg. Nhlf
Seg. Osteobl
Basic Gene Annotation Set from GENCODE Version 23 (Ensembl 81)
HBA2
HBA2
HBA1
HBA1
Y_RNA
HBQ1
100 _
H3K27Ac Mark (Often Found Near Regulatory Elements) on 7 cell lines from ENCODE
Layered H3K27Ac
0 _
DNase I Hypersensitivity Peak Clusters from ENCODE (95 cell types)
DNase Clusters
4.88 _
100 vertebrates Basewise Conservation by PhyloP
Cons 100 Verts
0 -
-4.5 _
Multiz Alignments of 100 Vertebrates
Rhesus
Mouse
Dog
Elephant
Chicken
X_tropicalis
Zebrafish
Lamprey
Repeating Elements by RepeatMasker
SINE
LINE
LTR
DNA
Simple
Low Complexity
Satellite
RNA
Other
Unknown
move start
< 2.0 >
move end
< 2.0 >
track search
default tracks
default order
hide all
add custom tracks
track hubs
configure
multi-region
reverse
resize
refresh
collapse all
expand all
Ensembl Regulatory Build
refresh
Ensembl Build
Cell Type Activity
Cell Type
Segmentation
TFBS

UCSC Genome Browser on Human Dec. 2013 (GRCh38/hg38) Assembly

Click on a feature for details. Click or drag in the base position track to zoom in. Click side bars for track options. Drag side bars or labels up or down to reorder tracks. Drag tracks left or right to new position.

Use drop-down controls below and press refresh to alter tracks displayed. Tracks with lots of items will automatically be displayed in more compact modes.

Zerbino DR *et al*. 2015. *Genome Biol* 16:56.

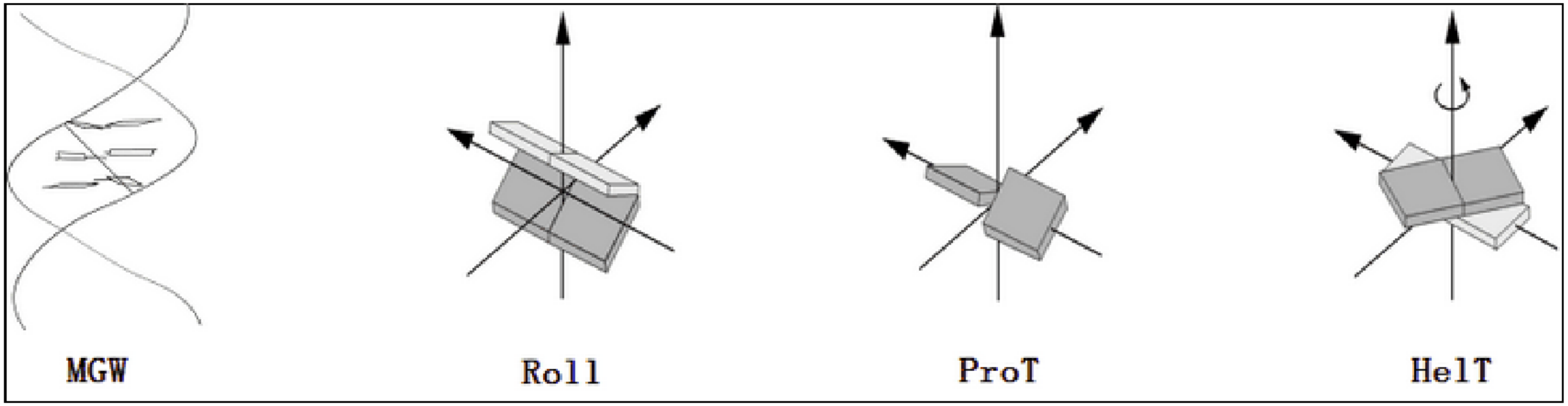
GCATACAGCATCATCAGATACGACTACAGCA
TACATAGATATCAGCATACAGCAGACTCATG
ACATCAGACAGCAGCGACGCAGACTCTCTC
ATCATACATCAGACAGCAGCATACCCCACCA
AACGATAGACONTEXTCATACTACTCATAGA
ACACACCATACTACGACTACAGACTCAGAC
CAAAGGGGTCCGCTCGACGCGCCTACTGCA
GCATCTCGGATCGCATCAMATTERSCGCAG
CTTCATCTCAGCGCAGCAGGCCCATTAGCG
AGCTACTCGAGCGATCAGCGACTCTCAGCG
ATCTACCGGGCTATTCACGAGCAGCTTACGC

DNA shape features at Transcription Factor Binding Sites

Using data from JASPAR2014, the Rohs' lab developed the TFBSshape database storing DNA shape features of TFBSs.

Considered DNA shape features are :

- Minor Groove Width (MGW)
- Roll
- Propeller Twist (ProT)
- Helix Twist (HelT)

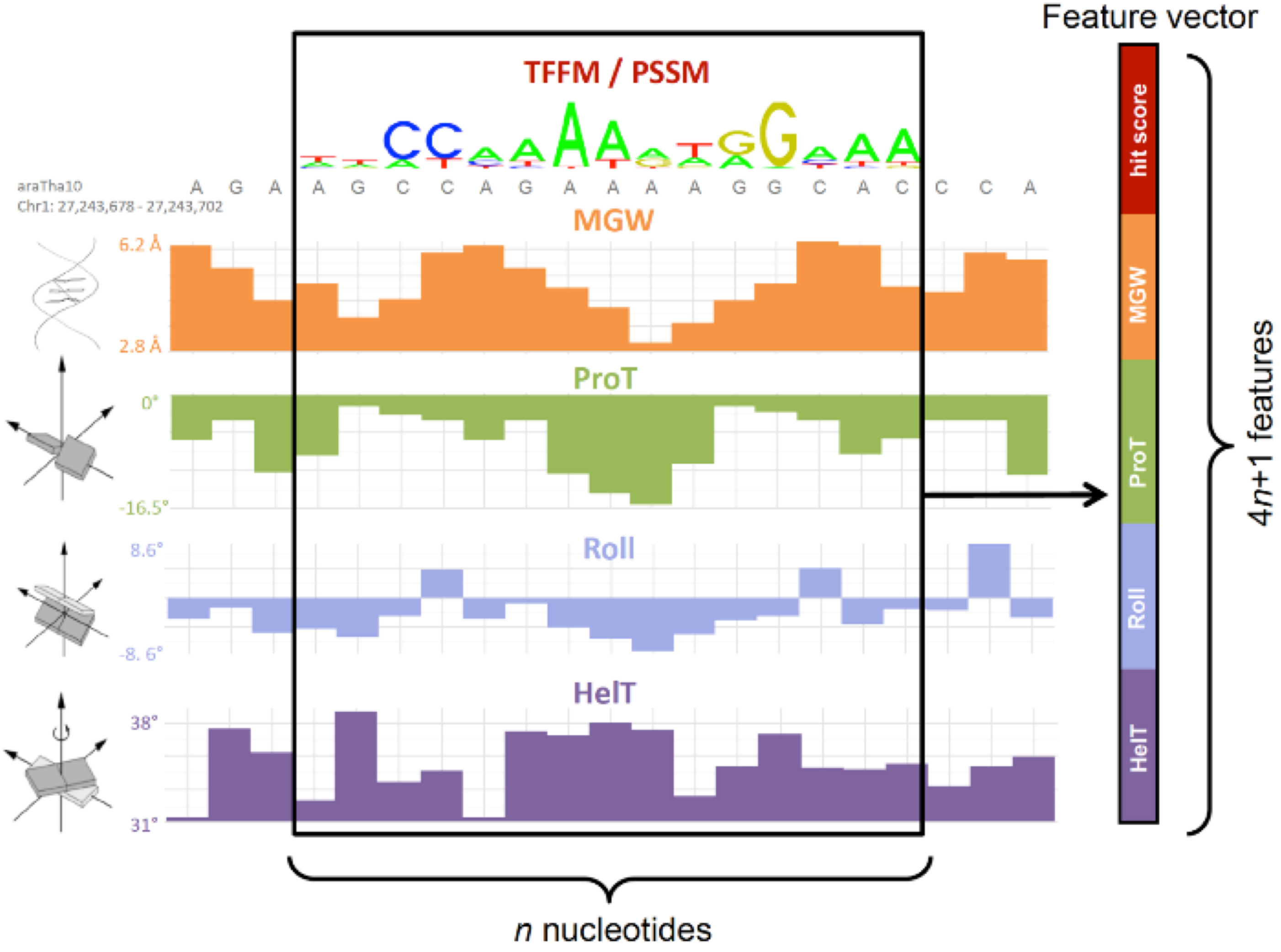


L. Yang, T. Zhou, I. Dror, A. Mathelier, W.W. Wasserman, R. Gordan, R. Rohs. *Nucl. Acids Res.*, 2014.

A. Mathelier and X. Zhao, *et al.*, B. Lenhard, A. Sandelin, W.W. Wasserman. *Nucl. Acids Res.*, 2014.

TFBSshape: http://rohslab.cmb.usc.edu/TFBSshape/

Shape Properties



Big challenges ahead

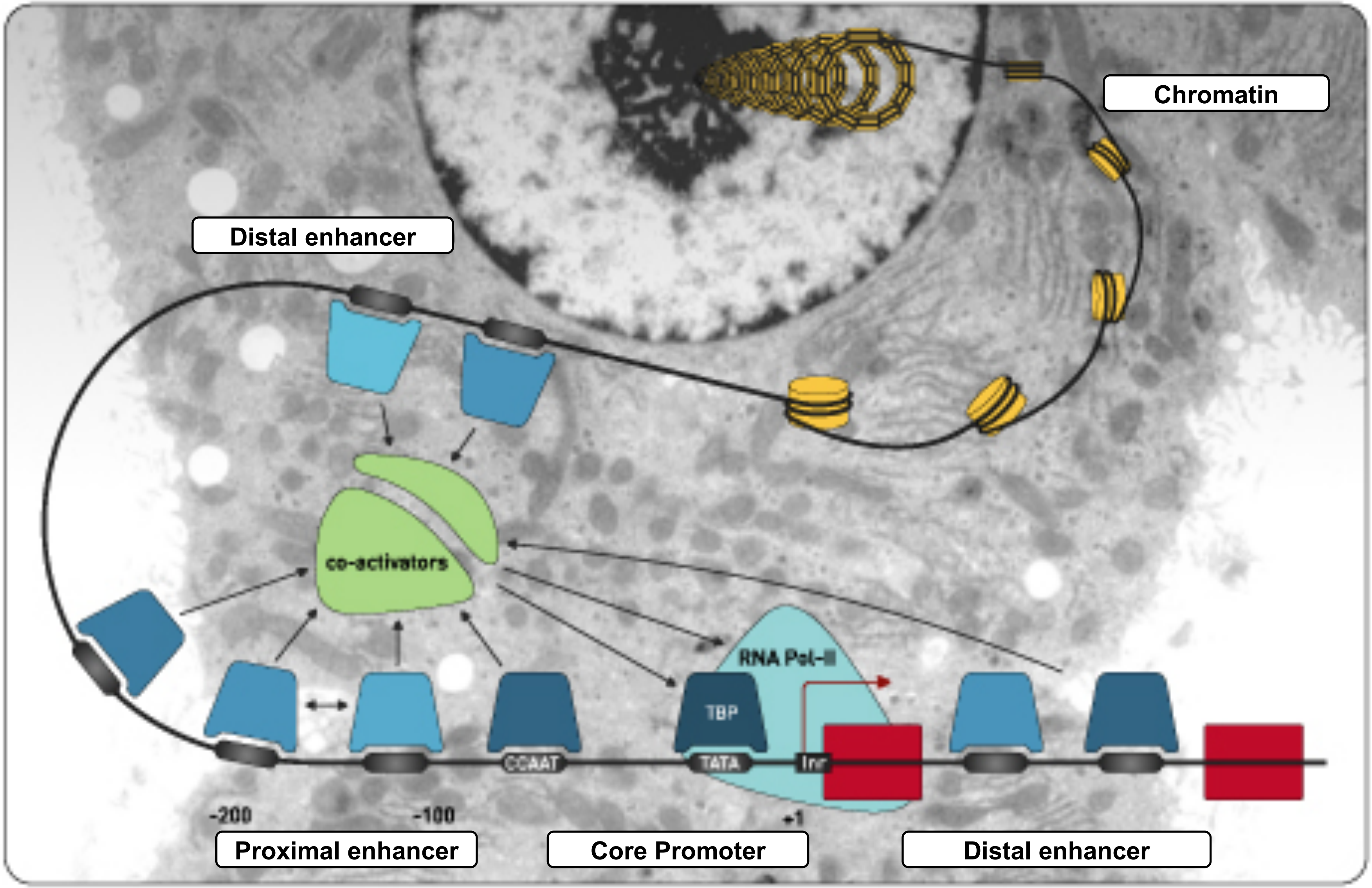
- Understanding all TFs across a developing organism

- Genetic variation in TFBS

- Integration of context and more complex predictive models

- Transition from matrices to hidden Markov models or energy models

Complexity in transcription



Reflections

- Futility conjecture – essentially predictions of individual TFBS have no relationship to an *in vivo* function
- Successful bioinformatics methods for site discrimination incorporate additional information (clusters, conservation)
- TFBS enrichment is a powerful means to identify TFs likely to contribute to observed patterns of co-expression
- Successful methods for pattern discovery will have to incorporate additional information (ChIP-seq, conservation, structural constraints on TFs, 3D genome organization)

We are on a Coffee Break & Networking Session

Workshop Sponsors:

Canadian Centre for Computational Genomics

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OICR Ontario Institute for Cancer Research

MiCM McGill initiative in Computational Medicine