6.874, 6.802, 20.390, 20.490, HST.506
Computational Systems Biology
Deep Learning in the Life Sciences

Lecture 8: TF binding

Gene regulation, DNA regulatory code, 3D conformation folding

Prof. Manolis Kellis
Guest lecture: David Kelley

Massachusetts Institute of Technology

http://mit6874.github.io

Slides credit: 6.047, Anshul Kundaje, David Gifford

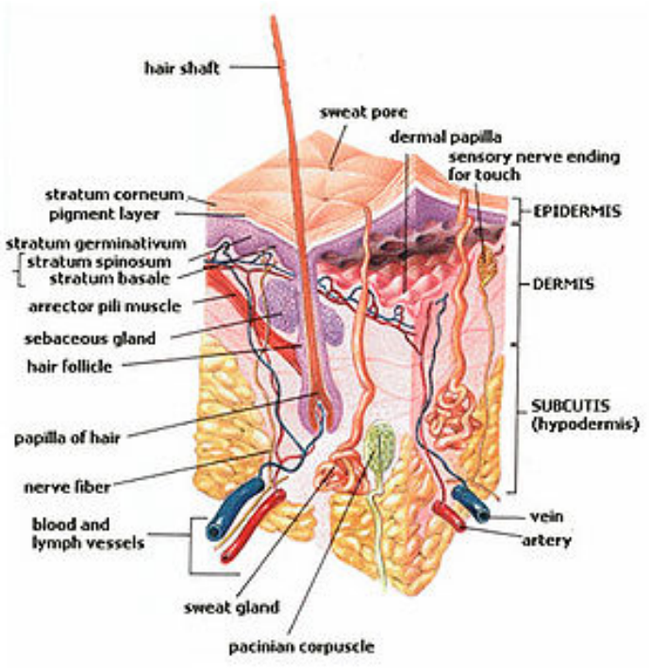
Deep Learning for Regulatory Genomics

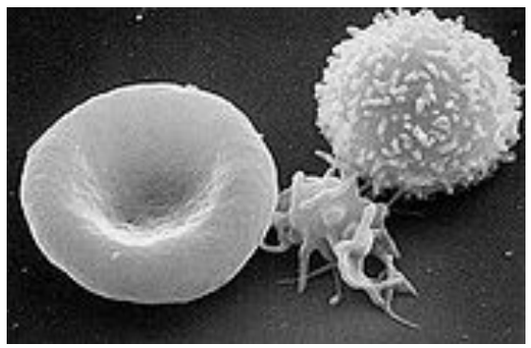
1. **Biological foundations: Building blocks of Gene Regulation**
   - Gene regulation: Cell diversity, Epigenomics, Regulators (TFs), Motifs, Disease role
   - Probing gene regulation: TFs/histones: ChIP-seq, Accessibility: DNase/ATAC-seq
   - Three-dimensional chromatin structure, Hi-C, ChIA-PET, TADs, Loop Extrusion
2. **Classical methods for Regulatory Genomics and Motif Discovery**
   - Enrichment-based motif discovery: Expectation Maximization, Gibbs Sampling
   - Experimental: PBMs, SELEX. Comparative genomics: Evolutionary conservation.
3. **Regulatory Genomics CNNs (Convolutional Neural Networks): Foundations**
   - Key idea: pixels ⇔ DNA letters. Patches/filters ⇔ Motifs. Higher ⇔ combinations
   - Learning convolutional filters ⇔ Motif discovery. Applying them ⇔ Motif matches
4. **Regulatory Genomics CNNs/RNNs in Practice: Diverse Architectures**
   - DeepBind: Learn motifs, use in (shallow) fully-connected layer, mutation impact
   - DeepSea: Train model directly on mutational impact prediction
   - Basset: Multi-task DNase prediction in 164 cell types, reuse/learn motifs
   - ChromPuter: Multi-task prediction of different TFs, reuse partner motifs
   - DeepLIFT: Model interpretation based on neuron activation properties
   - DanQ: Recurrent Neural Network for sequential data analysis
5. **Guest Lecture: David Kelley on Basset and Deep Learning for Hi-C looping**

1a. Basics of gene regulation

One Genome – Many Cell Types

ACCAGTTACGACGGTCA
GGGTACTGATACCCCAA
ACCGTTGACCGCATTTA
CAGACGGGGTTTGGGTT
TTGCCCCACACAGGTAC
GTTAGCTACTGGTTTAG
CAATTTACCGTTACAAC
GTTTACAGGGTTACGGT
TGGGATTTGAAAAAAAG
TTTGAGTTGGTTTTTTC
ACGGTAGAACGTACCGT
TACCAGTA





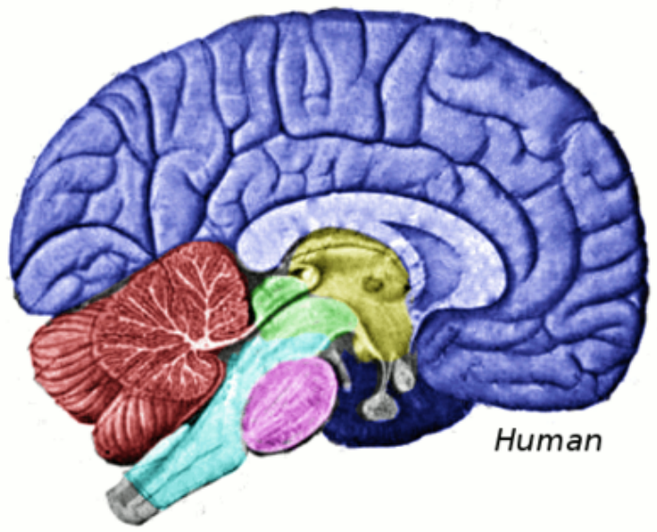
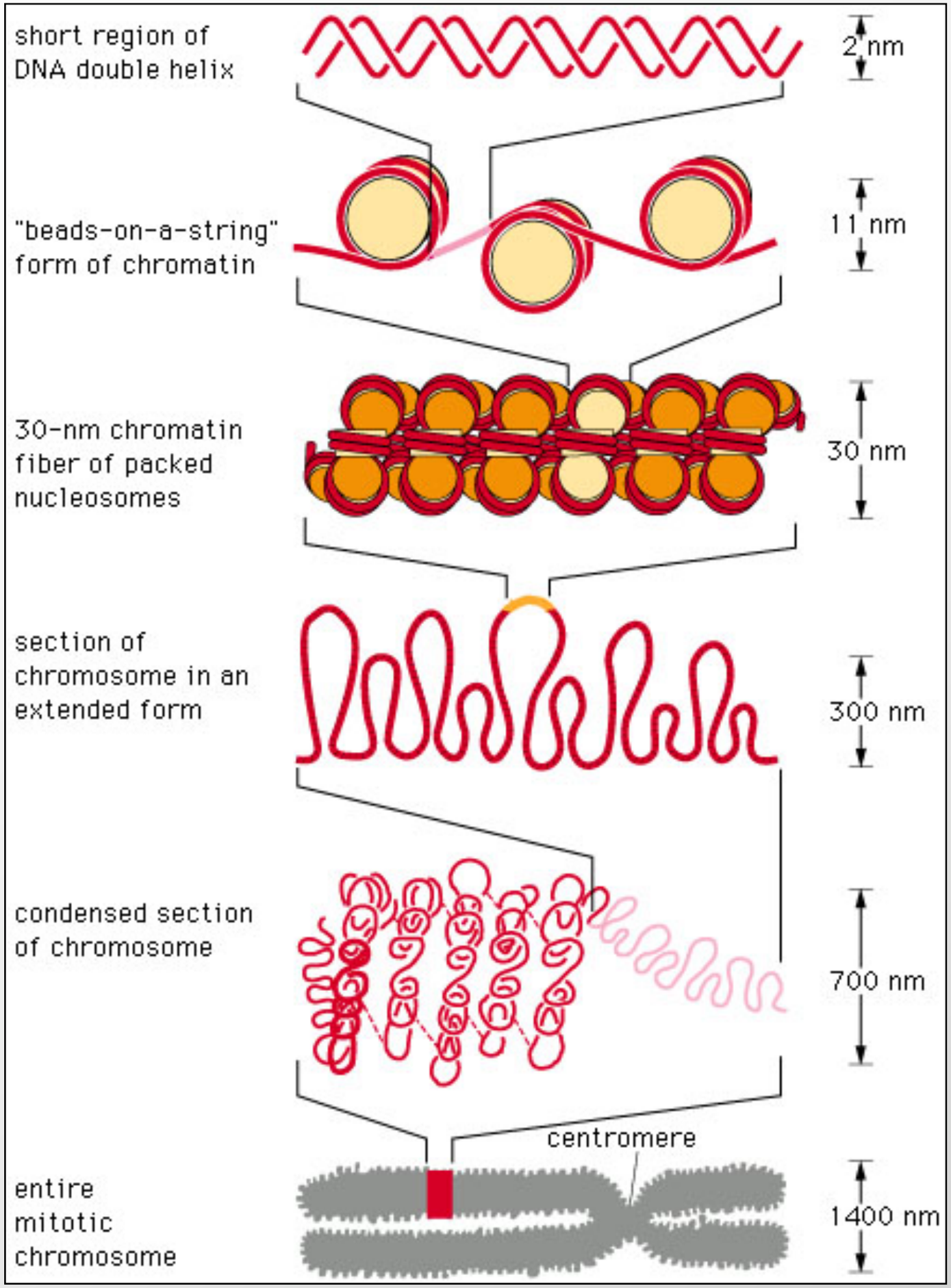


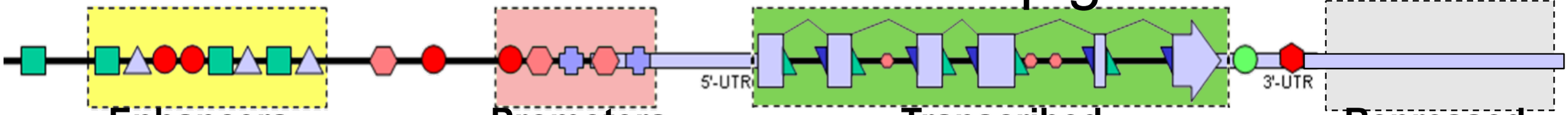
Image Source wikipedia

DNA packaging

- Why packaging
  - DNA is very long
  - Cell is very small
- Compression
  - Chromosome is 50,000 times shorter than extended DNA
- Using the DNA
  - Before a piece of DNA is used for anything, this compact structure must open locally
- Now emerging:
  - Role of accessibility
  - State in chromatin itself
  - Role of 3D interactions



Combinations of marks encode epigenomic state

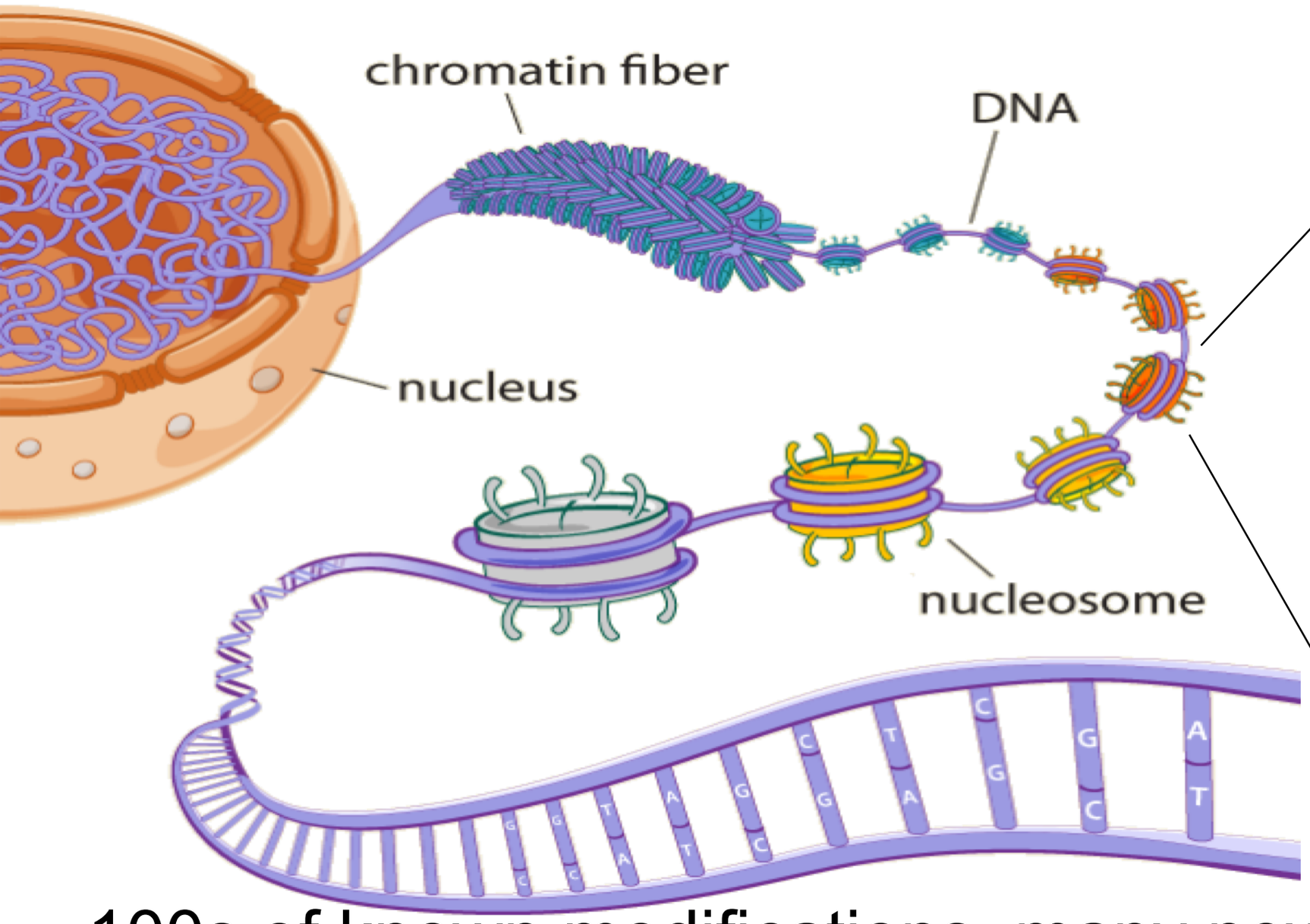


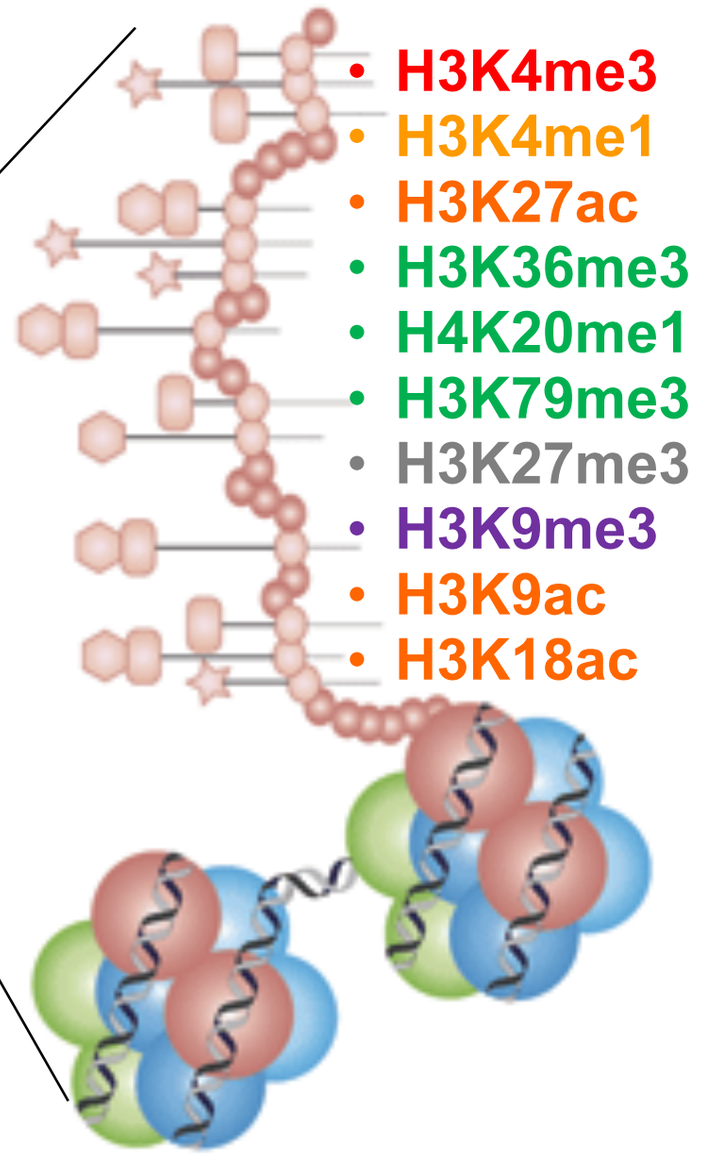
Enhancers
- H3K4me1
- H3K27ac
- DNase

Promoters
- H3K4me3
- H3K9ac
- DNase

Transcribed
- H3K36me3
- H3K79me2
- H4K20me1

Repressed
- H3K9me3
- H3K27me3
- DNAmethyl

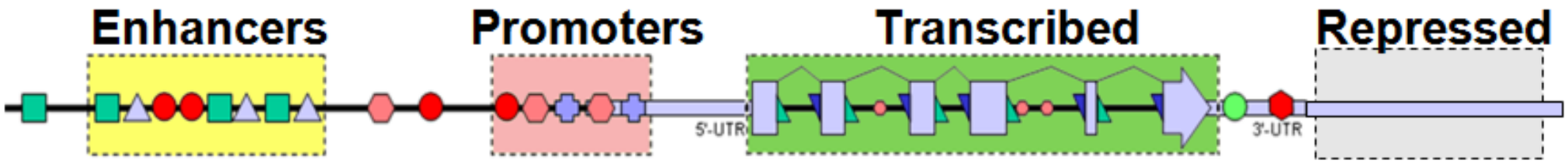




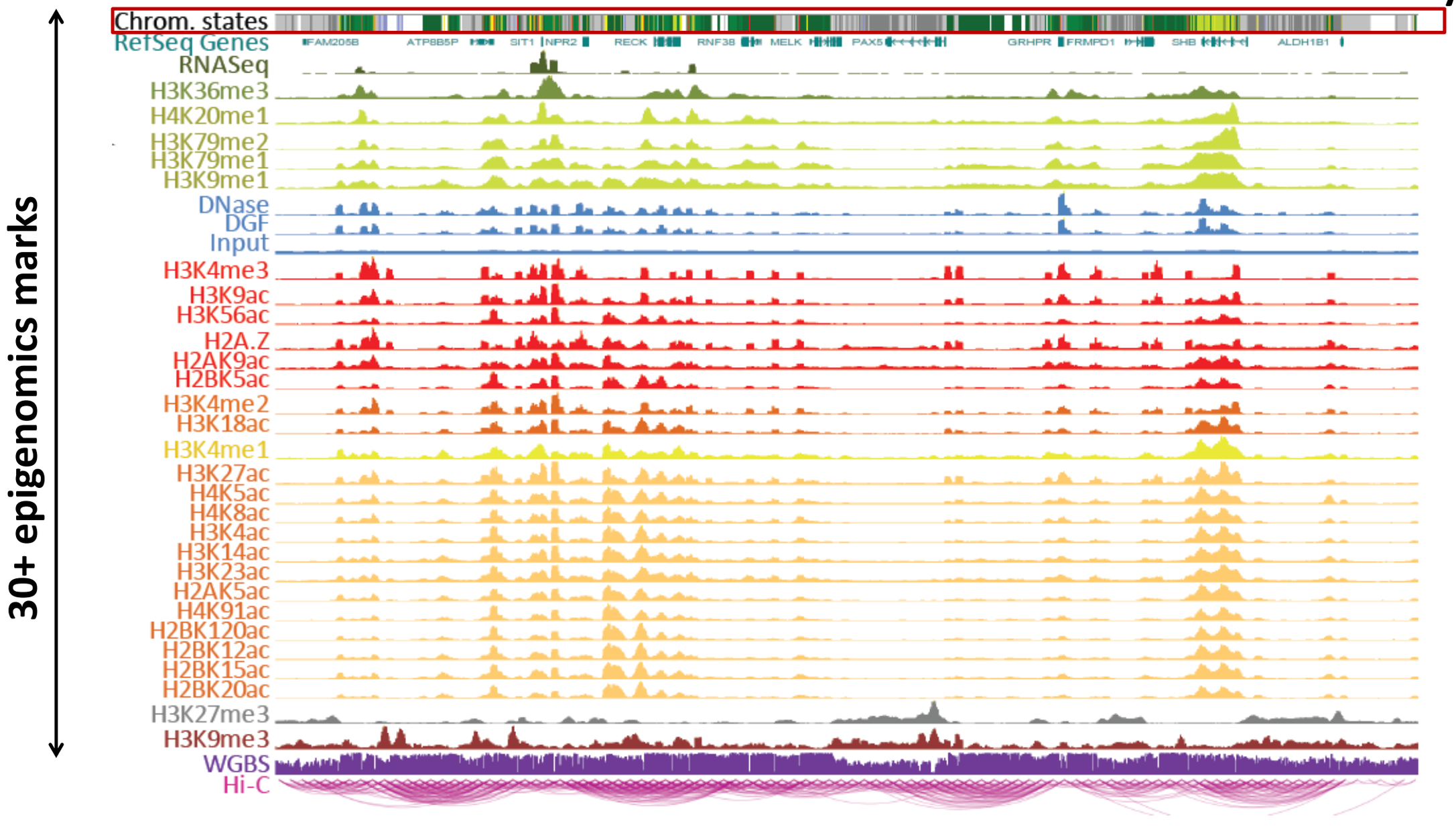
- H3K4me3
- H3K4me1
- H3K27ac
- H3K36me3
- H4K20me1
- H3K79me3
- H3K27me3
- H3K9me3
- H3K9ac
- H3K18ac

- 100s of known modifications, many new still emerging
- Systematic mapping using ChIP-, Bisulfite-, DNase-Seq

Summarize multiple marks into chromatin states



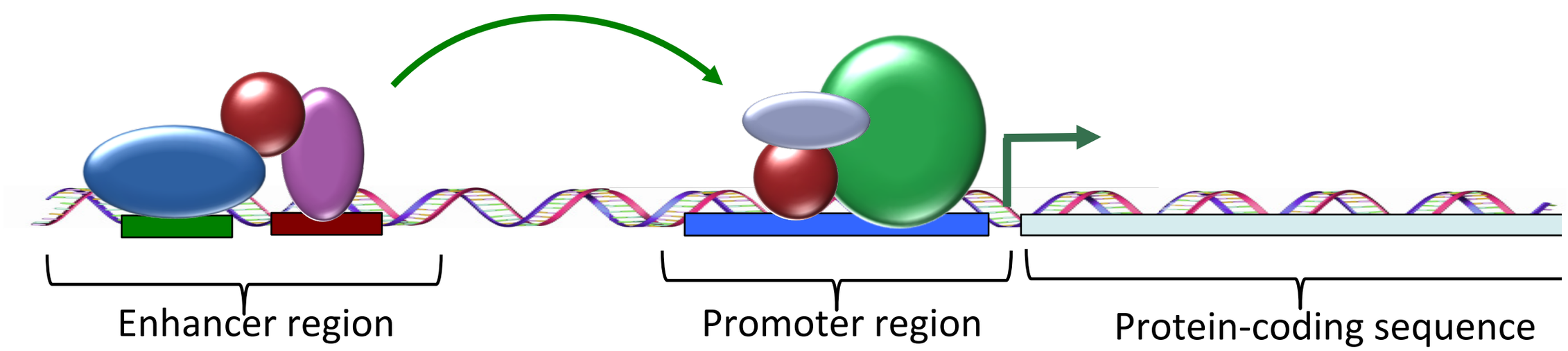
Chromatin state track summary



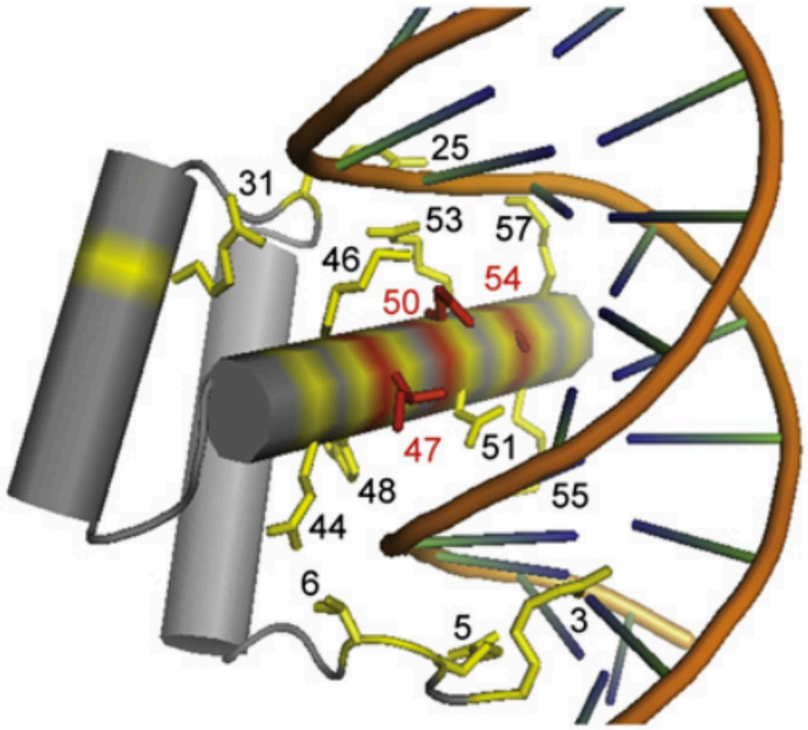
WashU Epigenome Browser

ChromHMM: multi-variate hidden Markov model

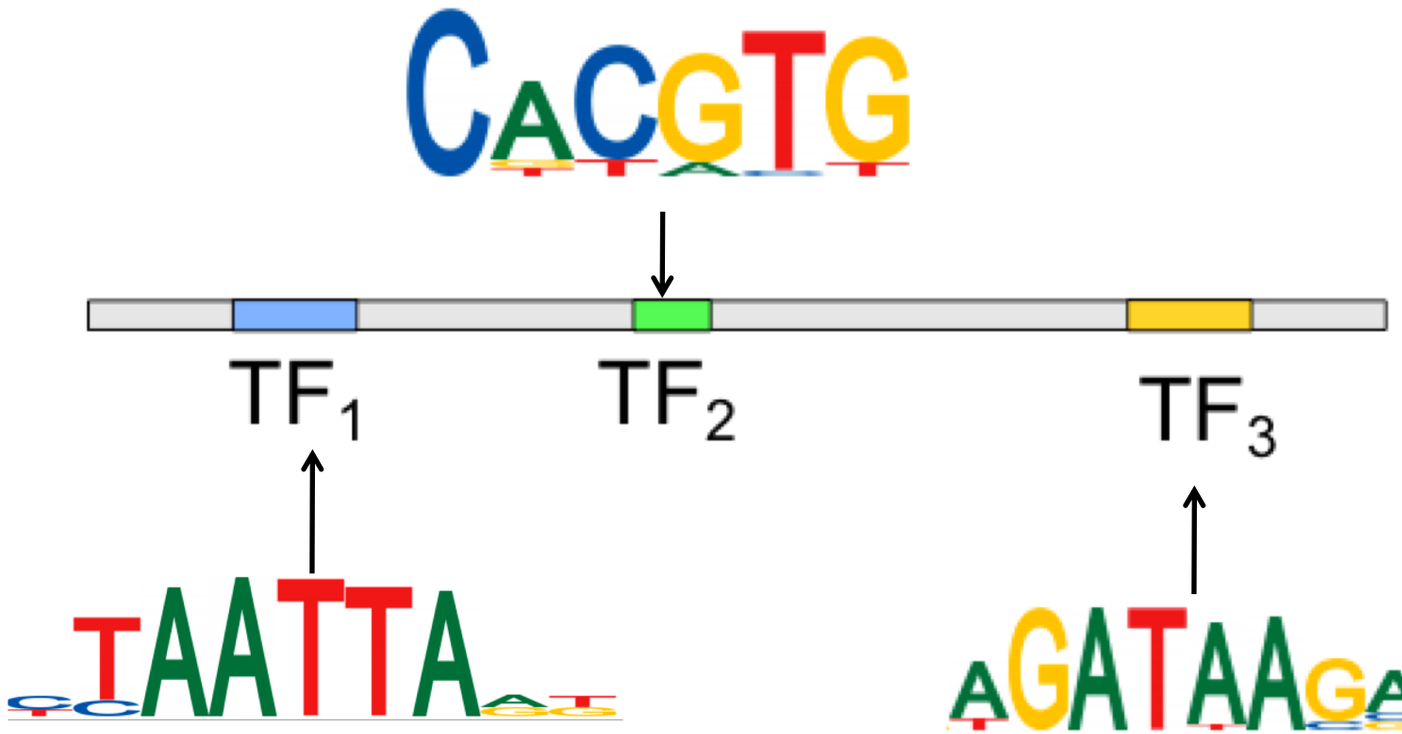
Transcription factors control activation of cell-type-specific promoters and enhancers



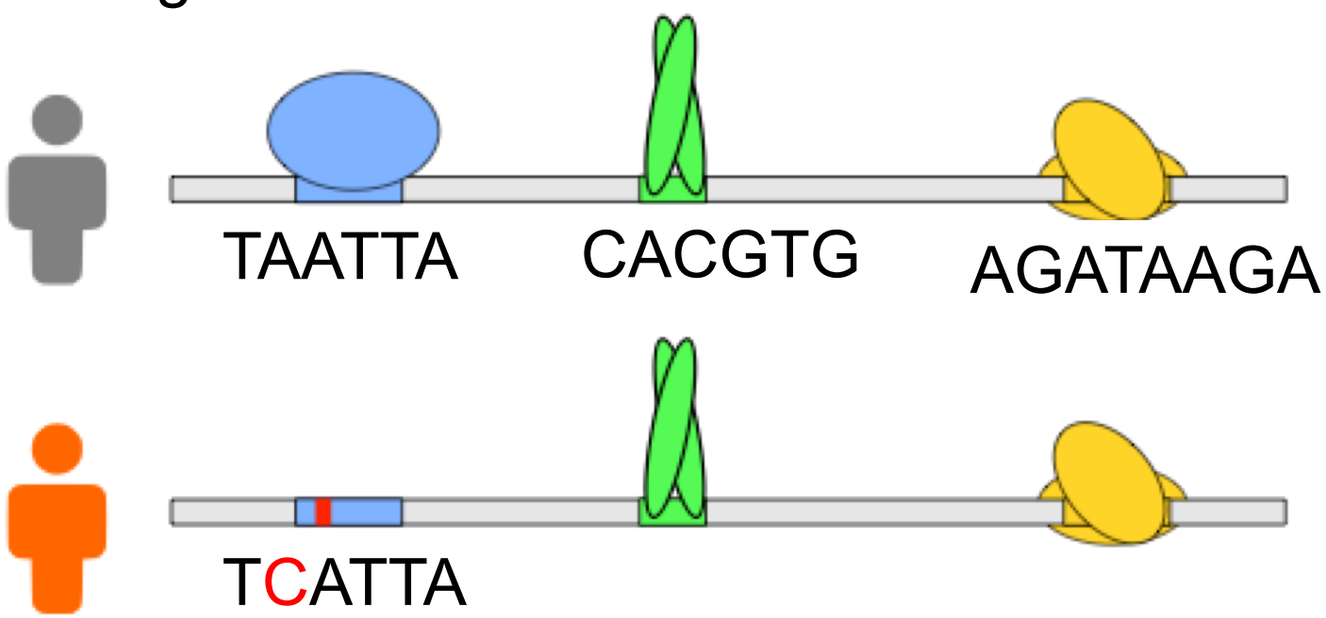
TFs use DNA-binding domains to recognize specific DNA sequences in the genome



DNA-binding domain of
Engrailed



"Logo" or "motif"

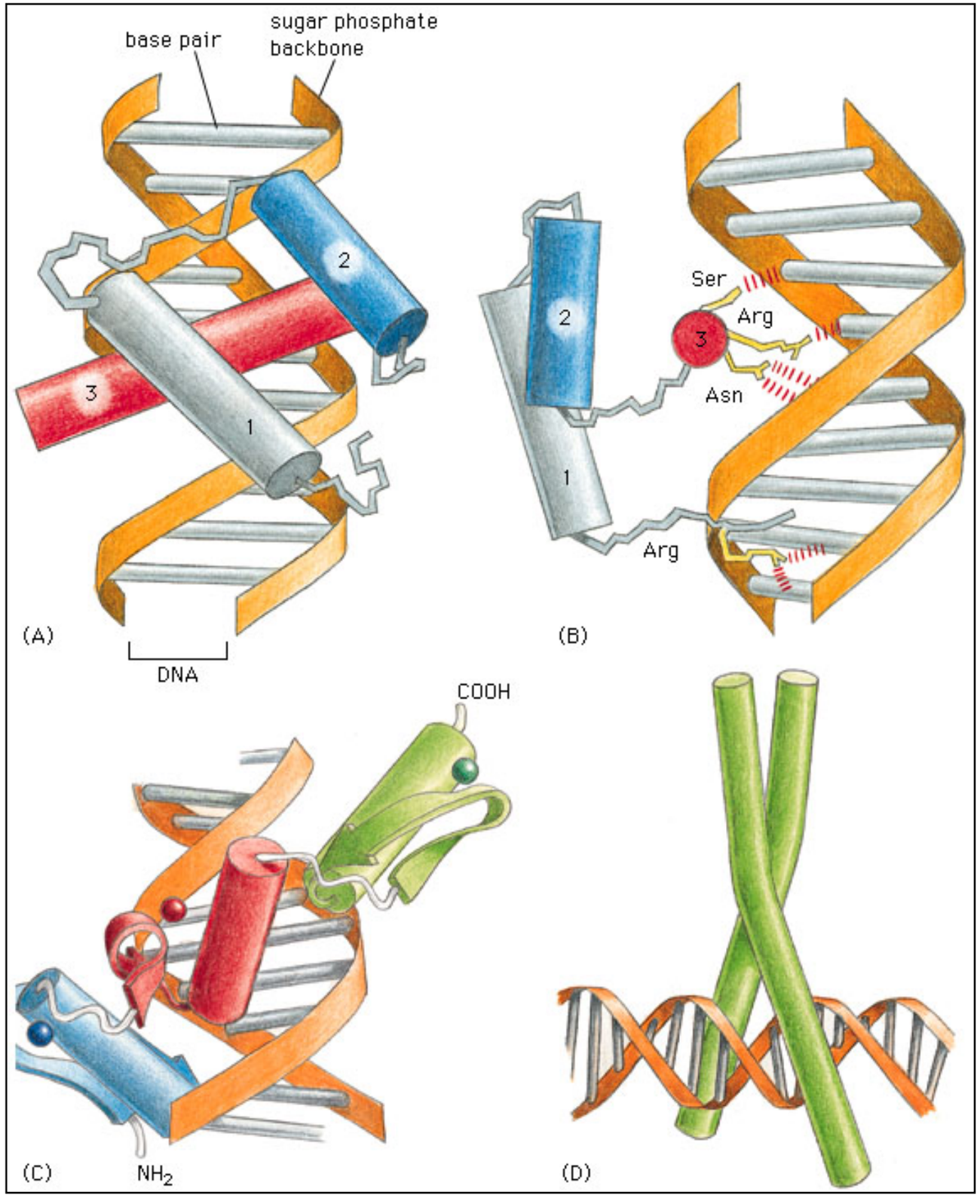


Regulator structure ⇔ recognized motifs

- Proteins 'feel' DNA
  - Read chemical properties of bases
  - Do NOT open DNA (no base complementarity)

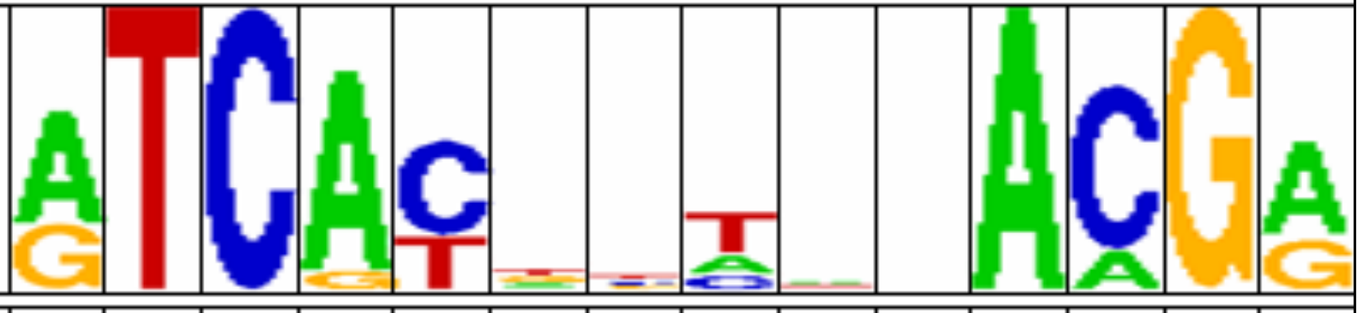
- 3D Topology dictates specificity
  - Fully constrained positions:
    ➔ every atom matters
  - "Ambiguous / degenerate" positions
    ➔ loosely contacted

- Other types of recognition
  - MicroRNAs: complementarity
  - Nucleosomes: GC content
  - RNAs: structure/seqn combination



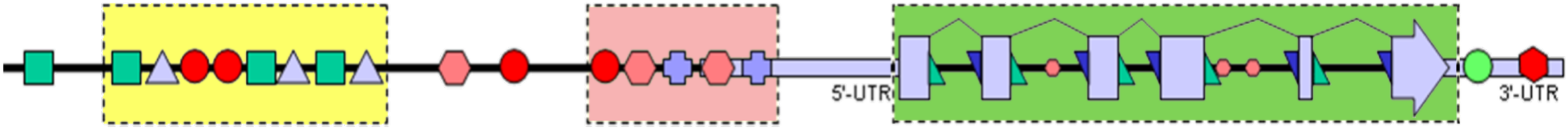
Motifs summarize TF sequence specificity

Target genes bound by ABF1 regulator		Coordinates		Genome sequence at bound site
ACS1	acetyl CoA synthetase	-491	-479	|ATCATTCTGGACG|
ACS1	acetyl CoA synthetase	-433	-421	|ATCATCTCGGACG|
ACS1	acetyl CoA synthetase	-311	-299	|ATCATTTGCCACG|
CHA1	catabolic L-serine dehydratase	-280	-254	A|ATCACCGCGAACG|GA
ENO2	Enolase	-470	-461	ggcgttat|GTCACTAACGACG|tgcacca
HMR	silencer	-256	-283	ATCAATAC|ATCATAAAATACG|AACGATC
LPD1	lipoamide dehydrogenase	-288	-300	gat|ATCAAAATTAACG|tag
LPD1	lipoamide dehydrogenase	-301	-313	gat|ATCACCGTTGACG|tca
PGK	phosphoglycerate kinase	-523	-496	CAAACAA|ATCACGAGCGACG|GTAATTTC
RPC160	RNA pol III/C 160 kDa subunit	-385	-349	|ATCACTATATACG|TGAA
RPC40	RNA pol III/C 40 kDa subunit	-137	-116	|GTCACTATAAACG|
rpL2	ribosomal protein L2	-185	-167	TAAT|aTCAcgtcACACG|AC
SPR3	CDC3/10/11/12 family homolog	-315	-303	|ATCACTAAATACG|
YPT1	TUB2	-193	-172	CCTAG|GTCACTGTACACG|TATA

Position		1	2	3	4	5	6	7	8	9	10	11	12	13	14
Position Weight Matrix (PWM)	A	**56**	4	4	**81**	4	23	15	27	31	31	**89**	23	4	**58**
	G	**32**	4	4	12	4	31	23	4	19	23	4	4	**89**	**35**
	C	4	4	**89**	4	**58**	12	23	19	19	23	4	**69**	4	4
	T	4	**89**	4	4	**35**	35	39	50	31	23	4	4	4	4
Motif Logo															
Consensus		**R**	**T**	**C**	**A**	**Y**	N	N	H	N	N	**A**	**C**	**G**	**R**

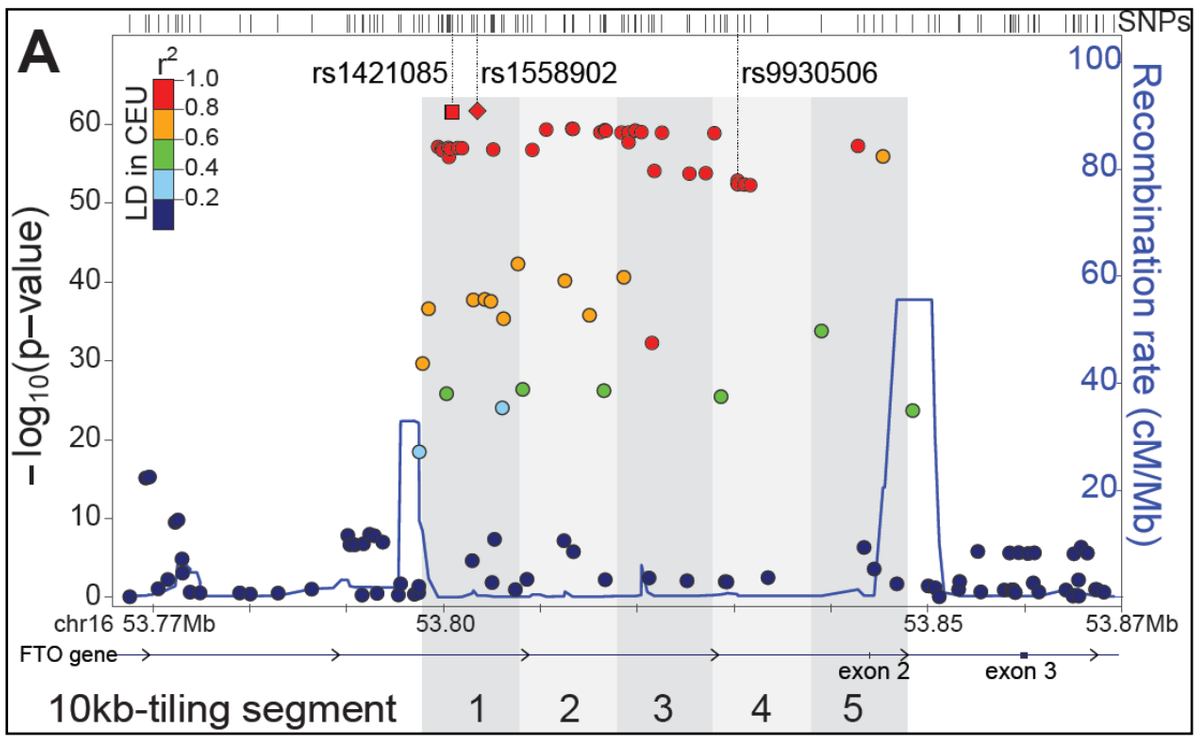
- Summarize information
- Integrate many positions
- Measure of information
- Distinguish motif vs. motif instance
- Assumptions:
  - Independence
  - Fixed spacing

Regulatory motifs at all levels of pre/post-tx regulation

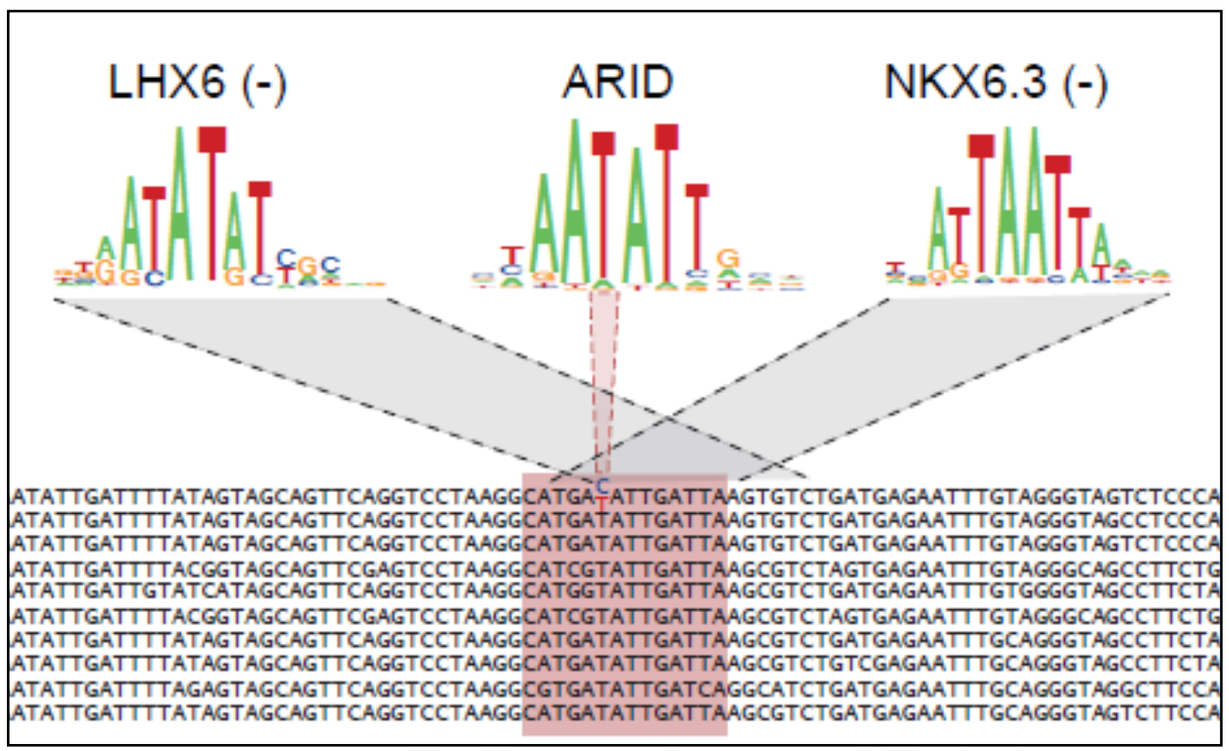


- The parts list: ~20-30k genes
  - Protein-coding genes, RNA genes (tRNA, microRNA, snRNA)
- The circuitry: constructs controlling gene usage
  - Enhancers, promoters, splicing, post-transcriptional motifs
- The regulatory code, complications:
  - Combinatorial coding of 'unique tags'
    - Data-centric encoding of addresses
  - Overlaid with 'memory' marks
    - Large-scale on/off states
  - Modulation of the large-scale coding
    - Post-transcriptional and post-translational information
- Today: discovering motifs in co-regulated promoters and *de novo* motif discovery & target identification

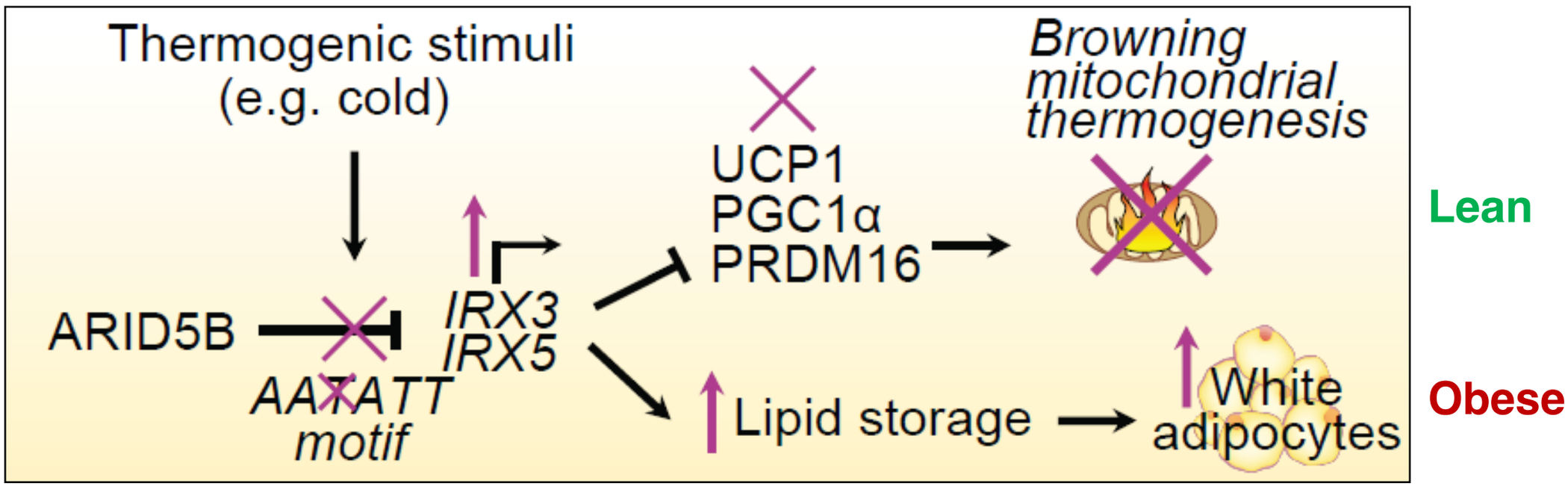
Disrupted motif at the heart of FTO obesity locus



Strongest association with obesity



C-to-T disruption of AT-rich regulatory motif

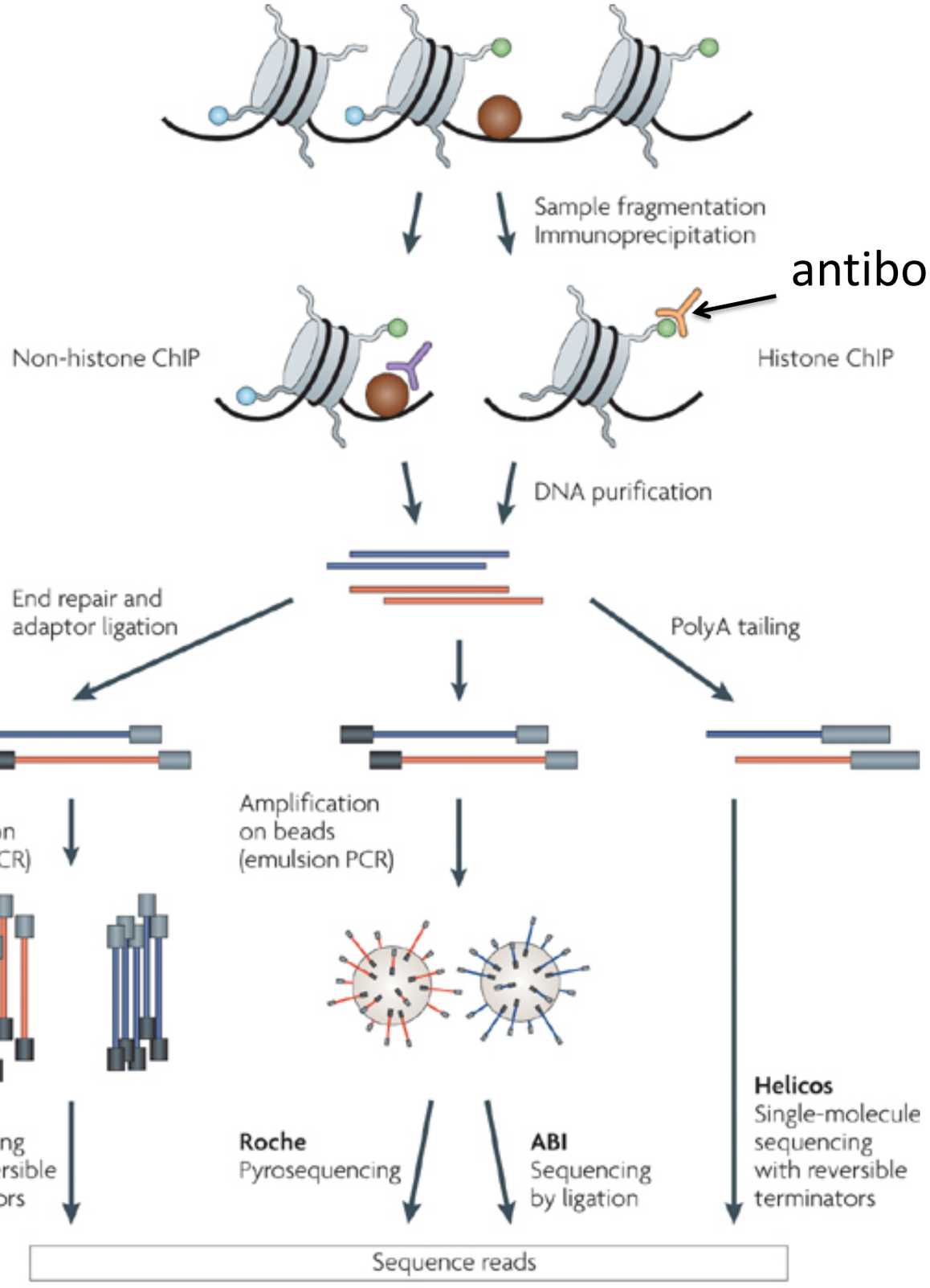


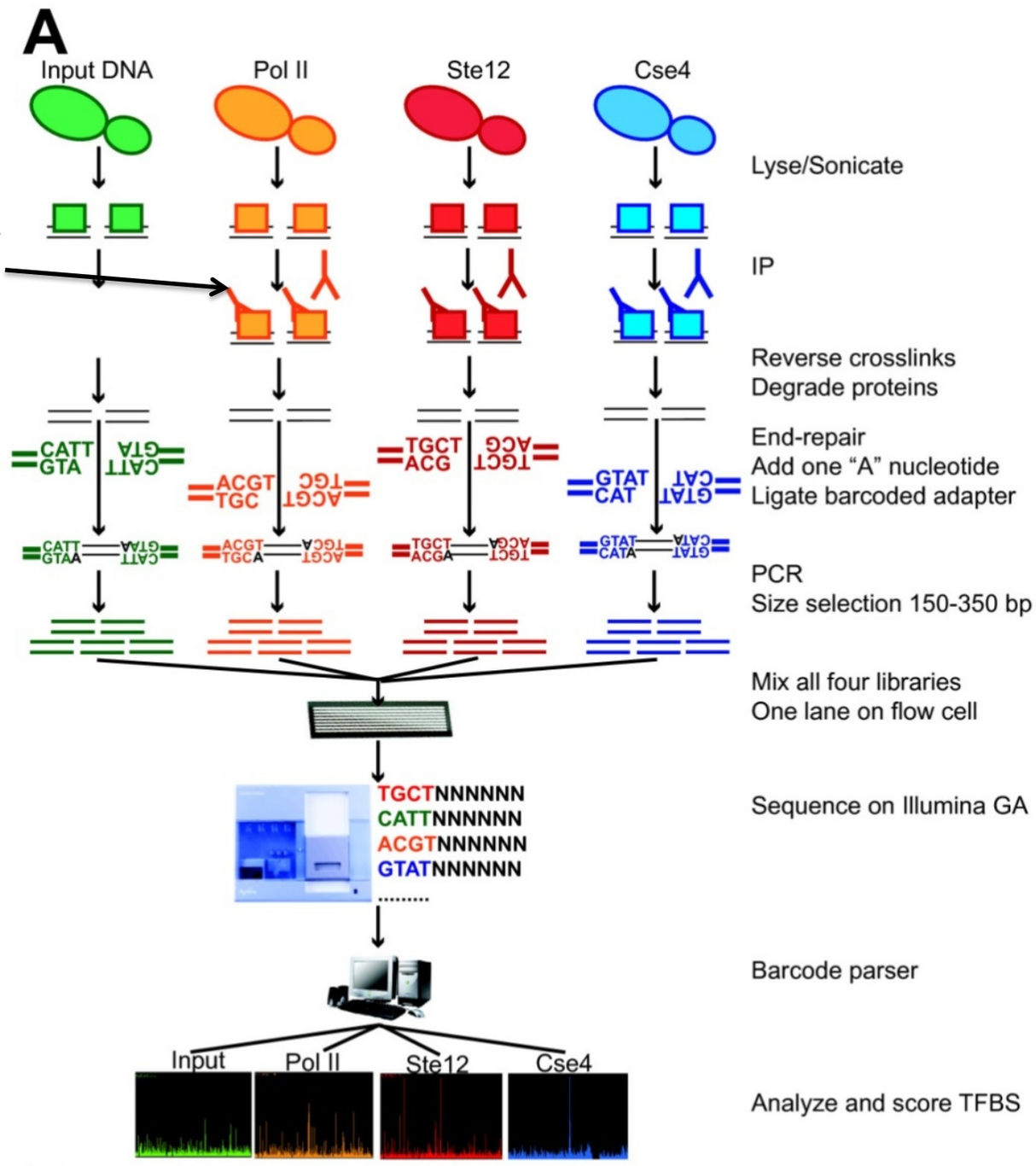
Restoring motif restores thermogenesis

1b. Technologies for probing gene regulation

Mapping regulator binding: ChIP-seq

(Chromatin immunoprecipitation followed by sequencing) TF=transcription factor





Bar-coded multiplexed sequencing

ChIP-chip and ChIP-Seq technology overview

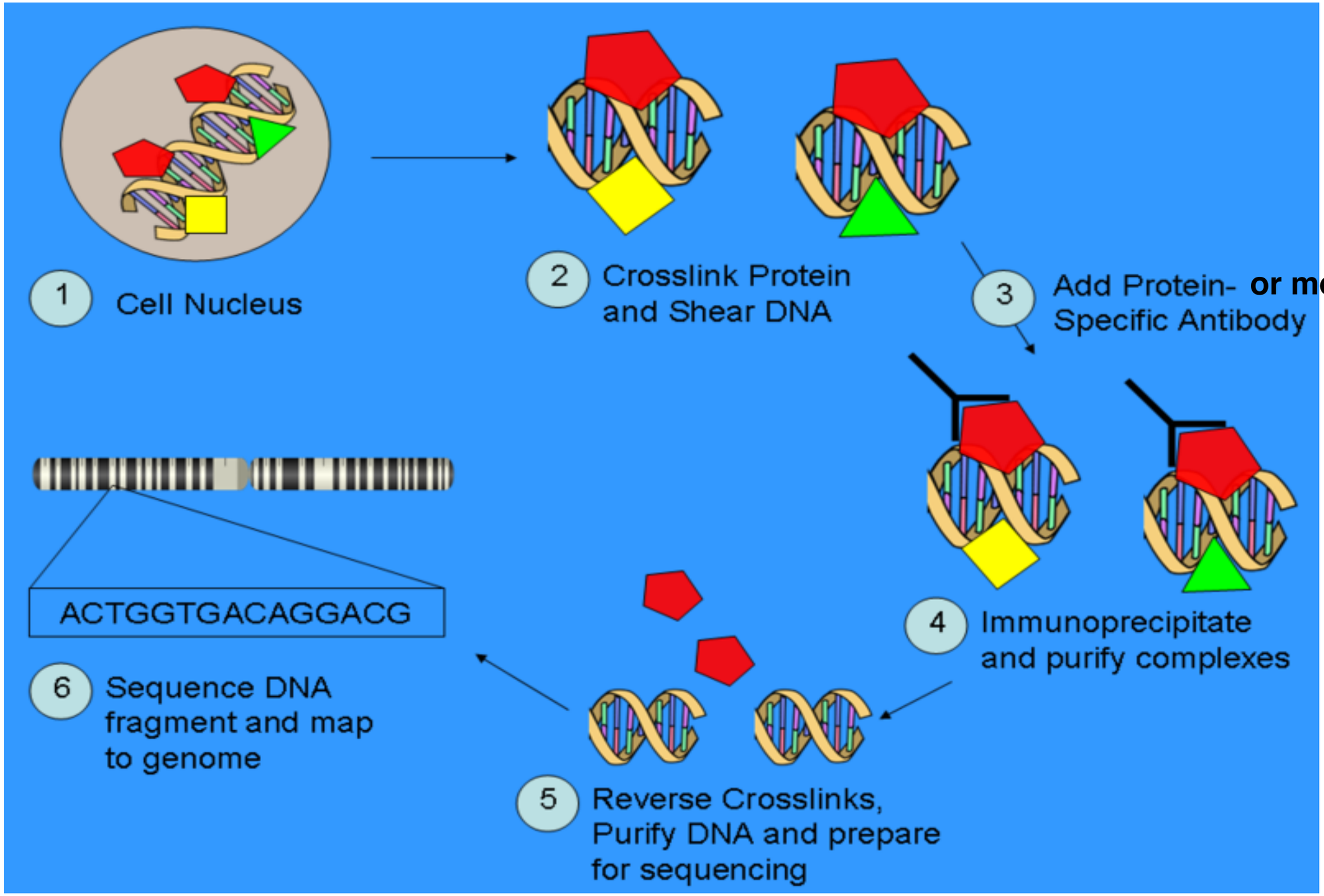


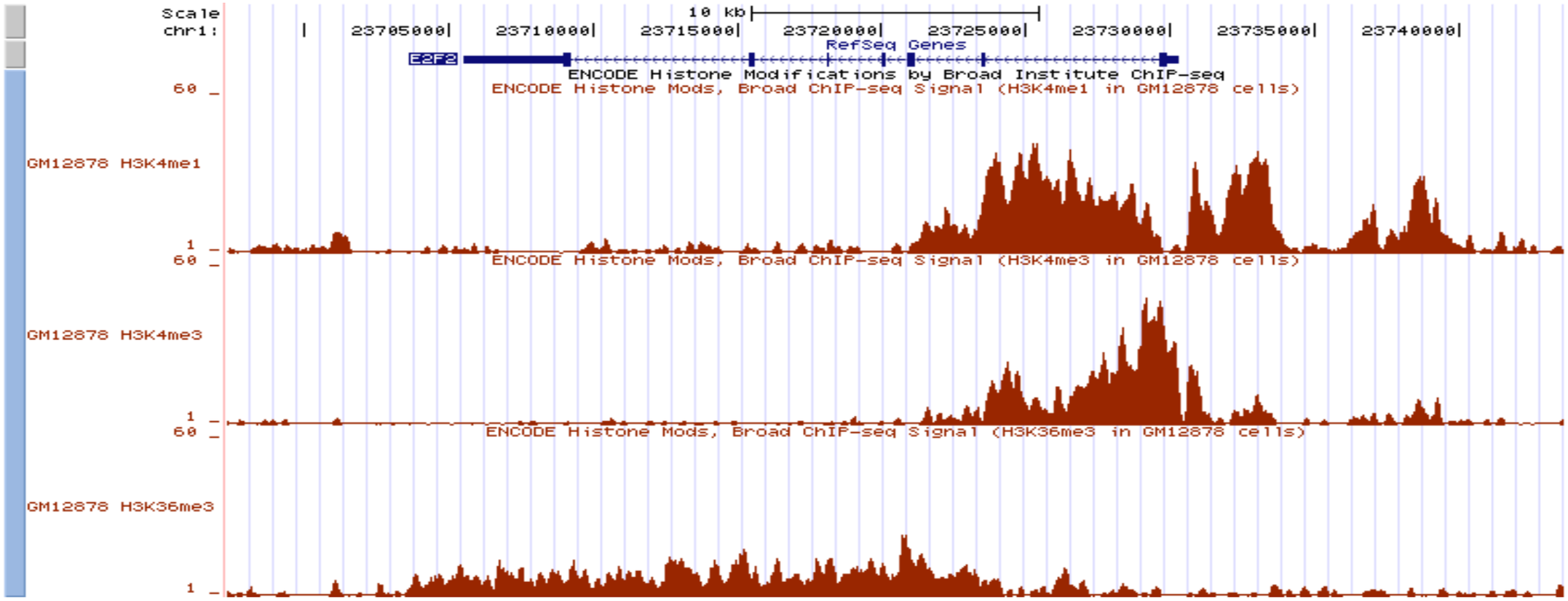
Image adapted from Wikipedia

Modification-specific antibodies → Chromatin Immuno-Precipitation

followed by: ChIP-chip: array hybridization

ChIP-Seq: Massively Parallel Next-gen Sequencing

ChIP-Seq Histone Modifications: What the raw data looks like

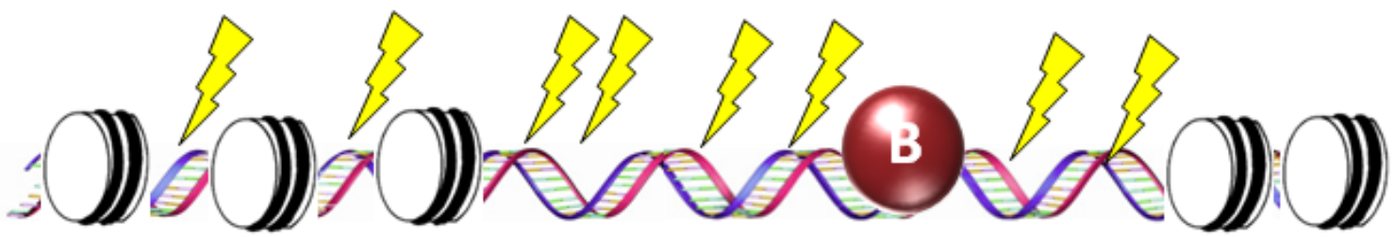


- Each sequence tag is 30 base pairs long
- Tags are mapped to unique positions in the ~3 billion base reference genome
- Number of reads depends on sequencing depth. Typically on the order of 10 million mapped reads.

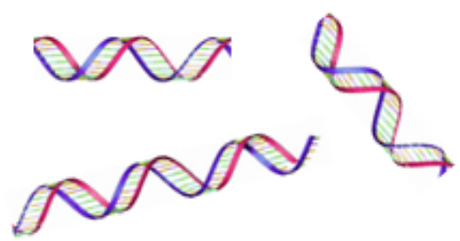
Chromatin accessibility can reveal TF binding

Sherwood, RI, et al. "**Discovery of directional and nondirectional pioneer transcription factors by modeling DNase profile magnitude and shape"** *Nat. Biotech 2014.*

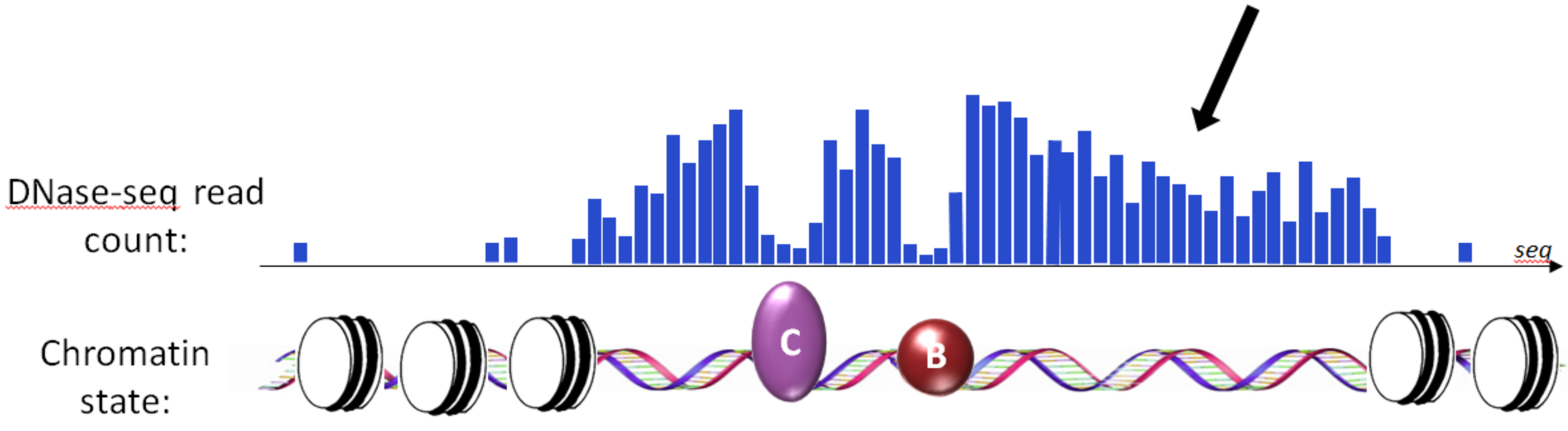
DNase-seq reveals genome protection profiles



Digest nuclei with DNase-I
(concentration/exposure specific)

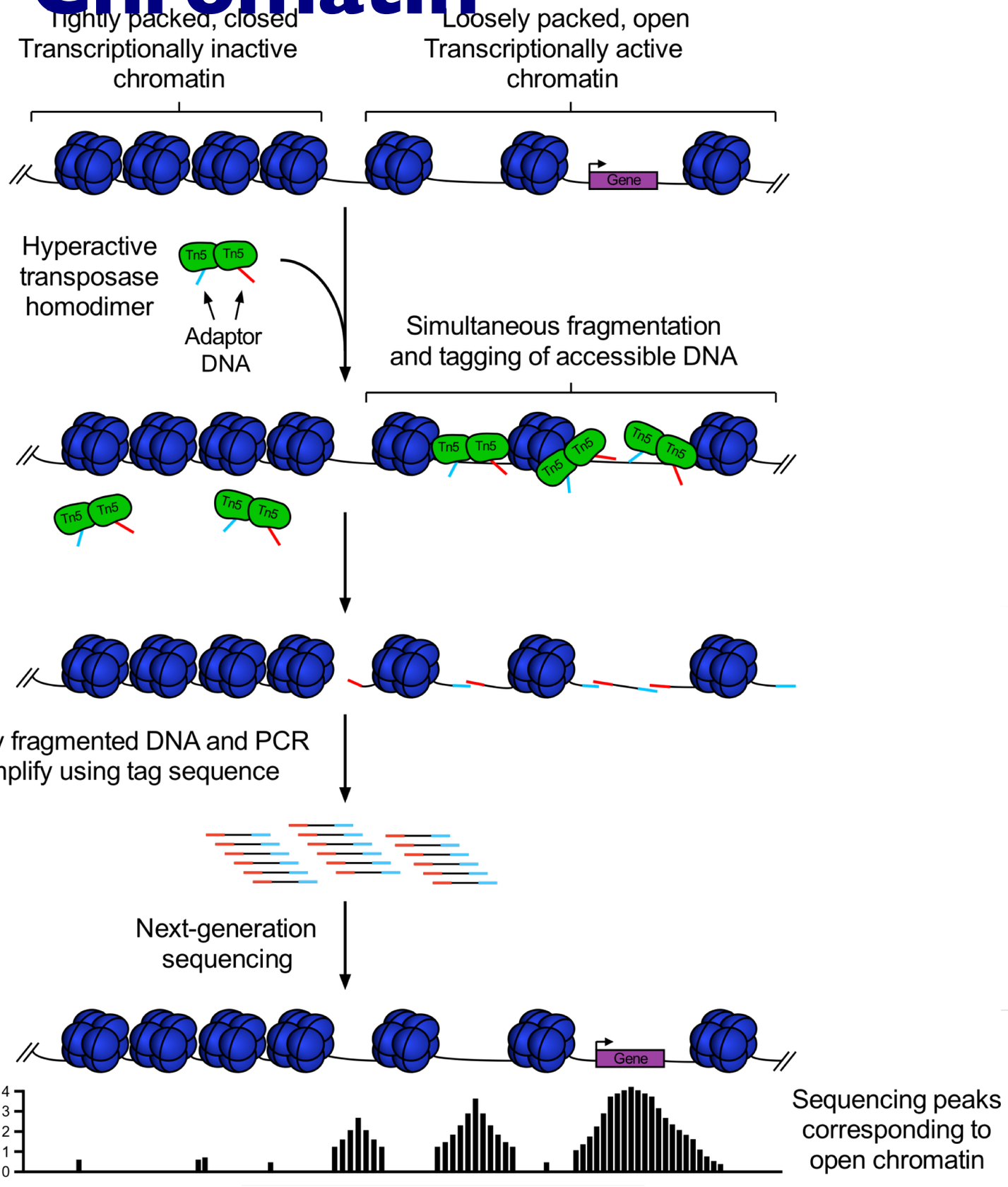


Collect DNA, size separate(100-300bp)



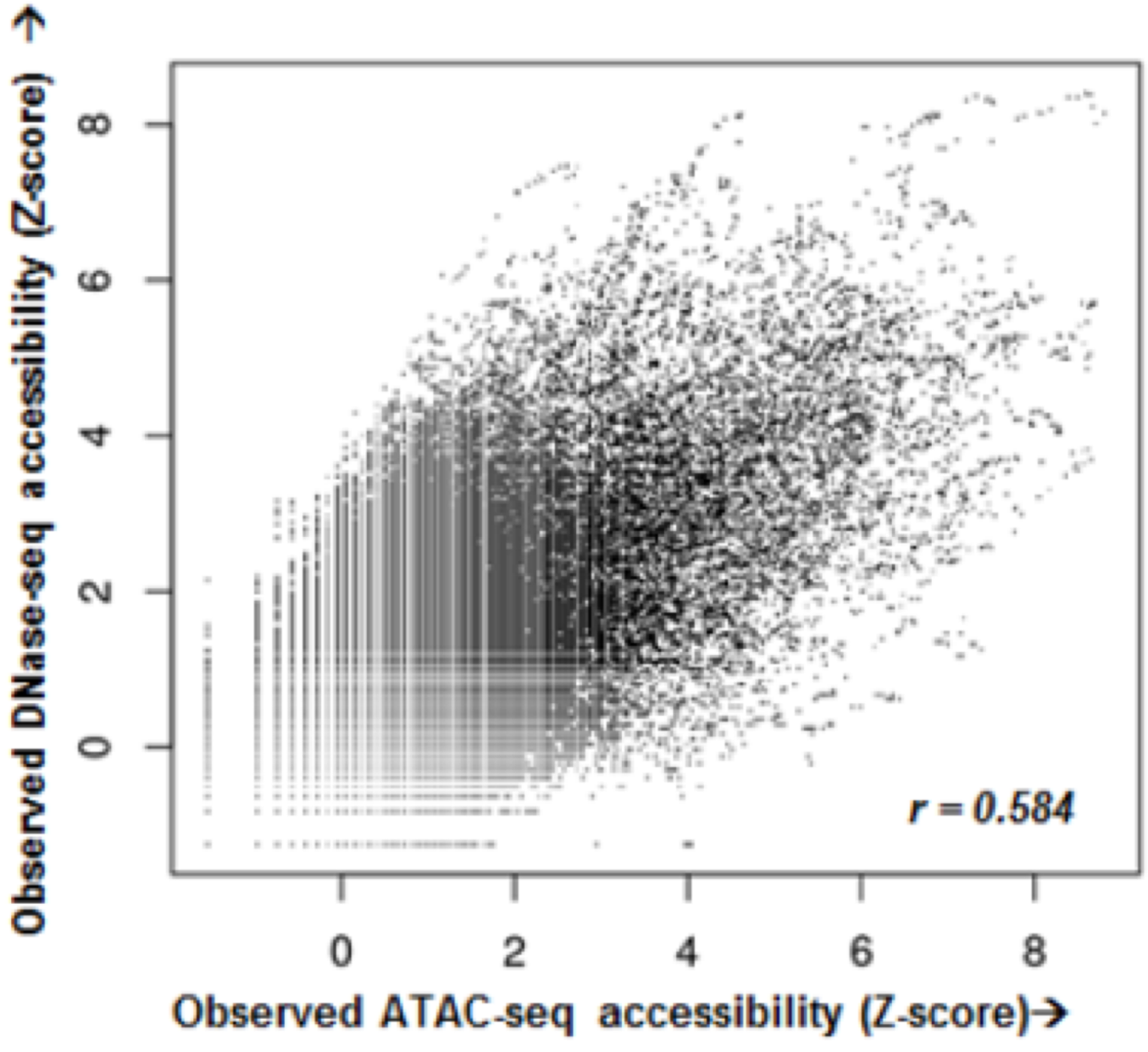
Sequence (60-100M reads)

Assay for Transposase-Accessible Chromatin (ATAC-seq)



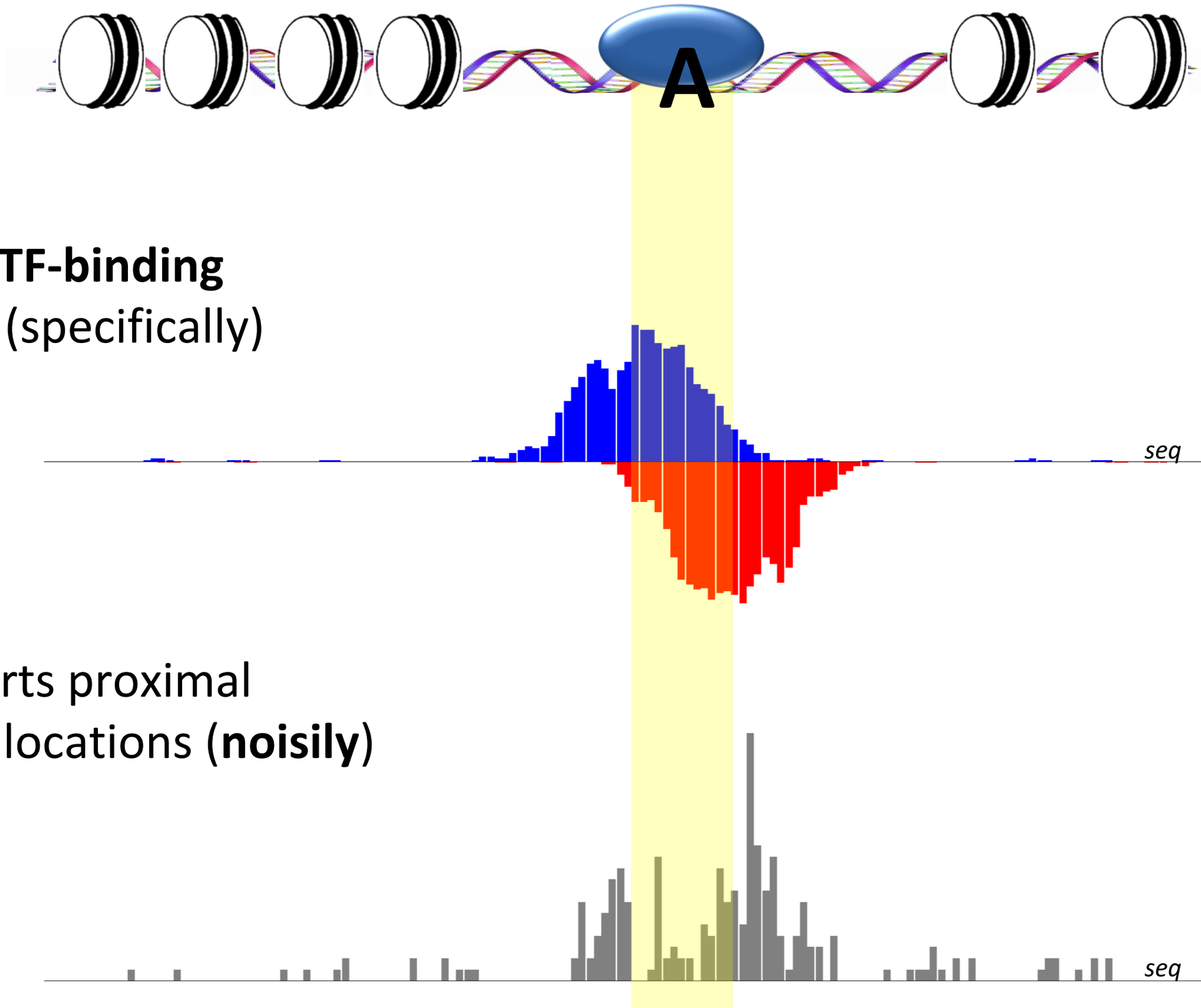
ATAC-seq and DNase-seq are not identical

GM12878, Chr. 14,
Each point is accessibility in a 2 kb window



Hashimoto TB, et al. "**A Synergistic DNA Logic Predicts Genome-wide Chromatin Accessibility"** *Genome Research* 2016

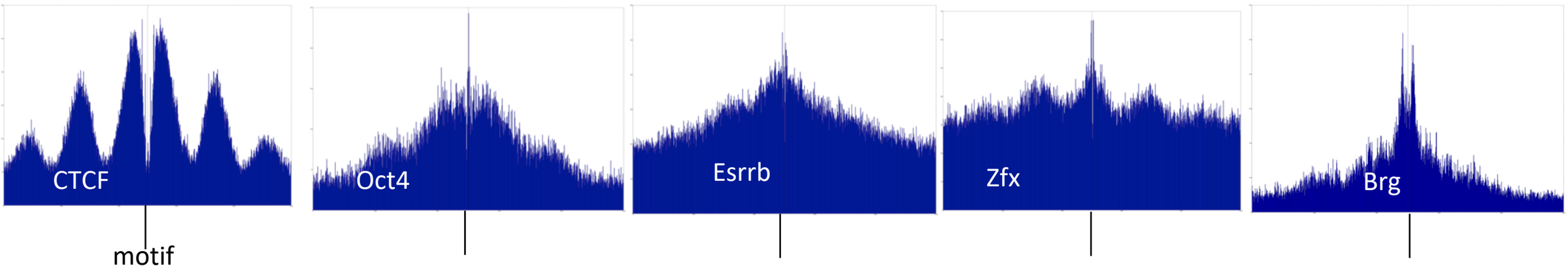
DNase-seq is less defined evidence than ChIP-seq



ChIP-seq reports **TF-binding** locations regions (specifically)

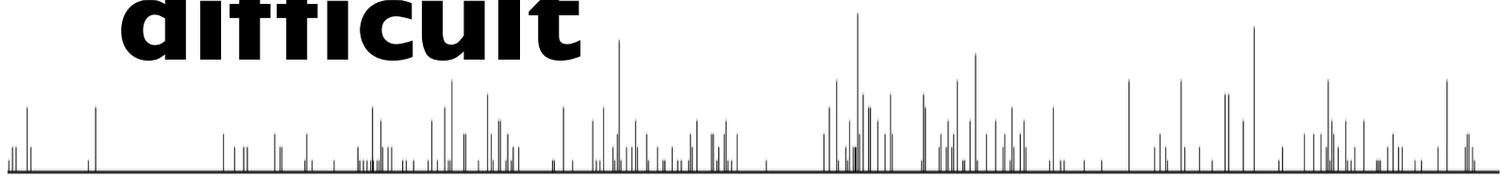
DNase-seq reports proximal **TF-non-binding** locations (**noisily**)

Bound factors leave distinct DNase-seq profiles

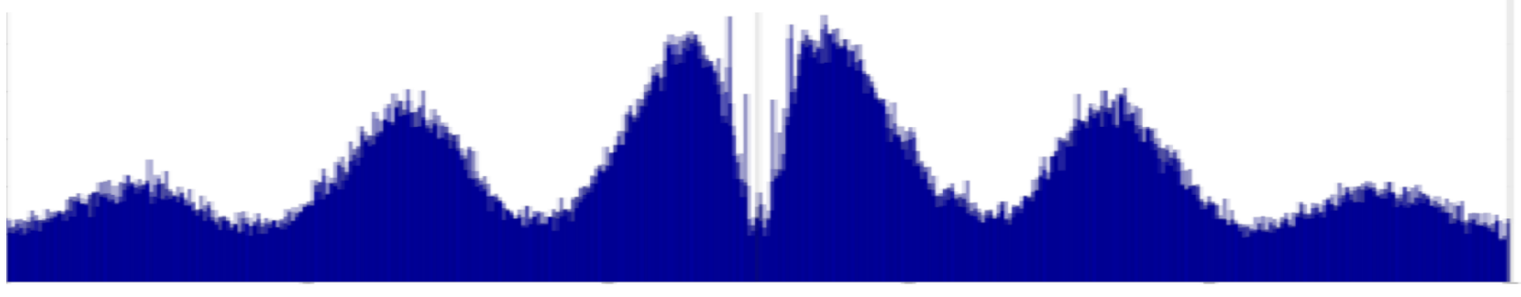


Individual binding site prediction is difficult

Individual CTCF:

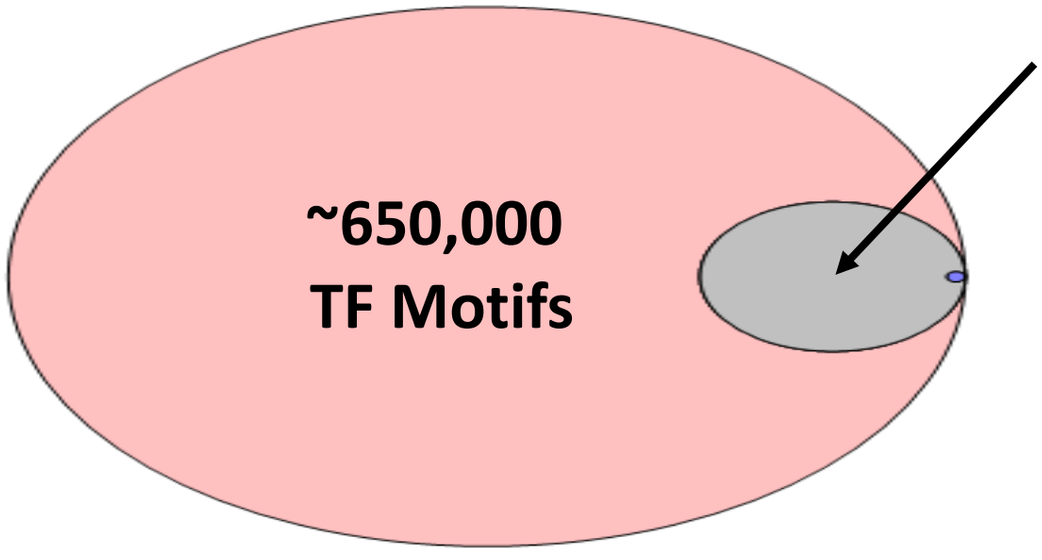


Aggregate CTCF:

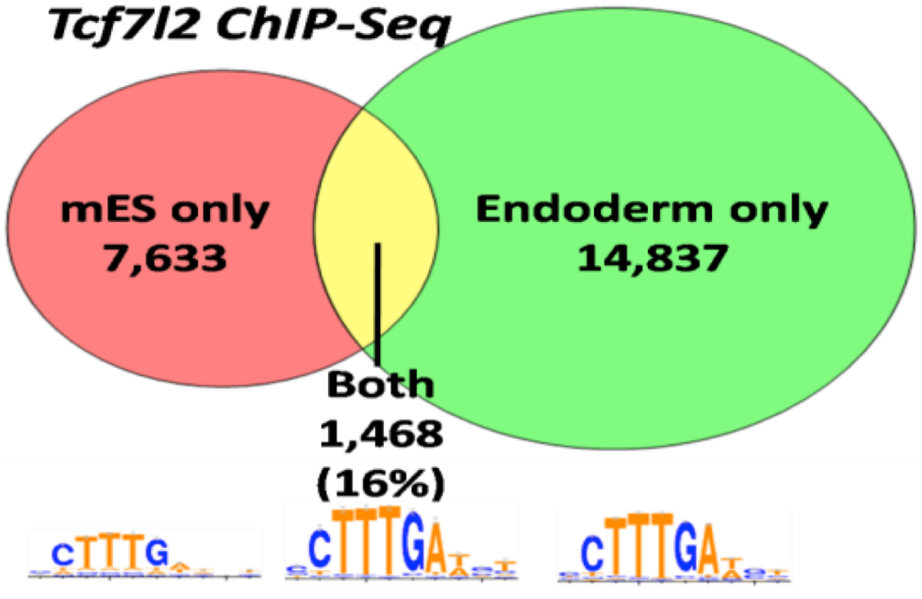


Motifs can predict TF binding

~50,000 binding sites
for a typical TF



Binding sites change
across time



Chromatin accessibly influences transcription factor binding

- Modeling accessibility profiles yields binding predictions and pioneer factor discovery
- Asymmetric accessibility is induced by *directional pioneers*
- The binding of *settler factors* can be enabled by proximal pioneer factor binding

Sherwood, RI, et al. "**Discovery of directional and nondirectional pioneer transcription factors by modeling DNase profile magnitude and shape"** *Nat. Biotech 2014.*

Deep Learning for Regulatory Genomics

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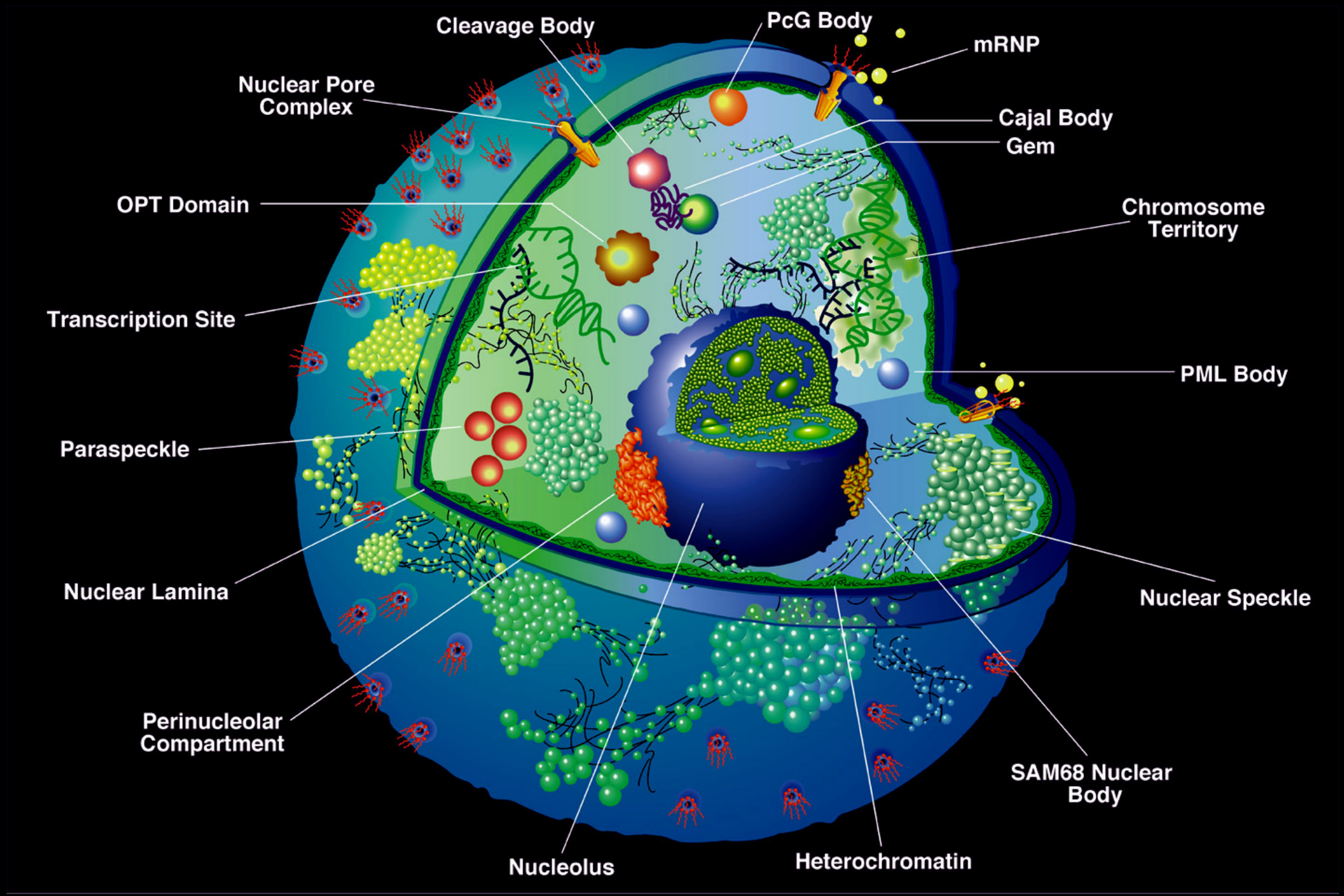
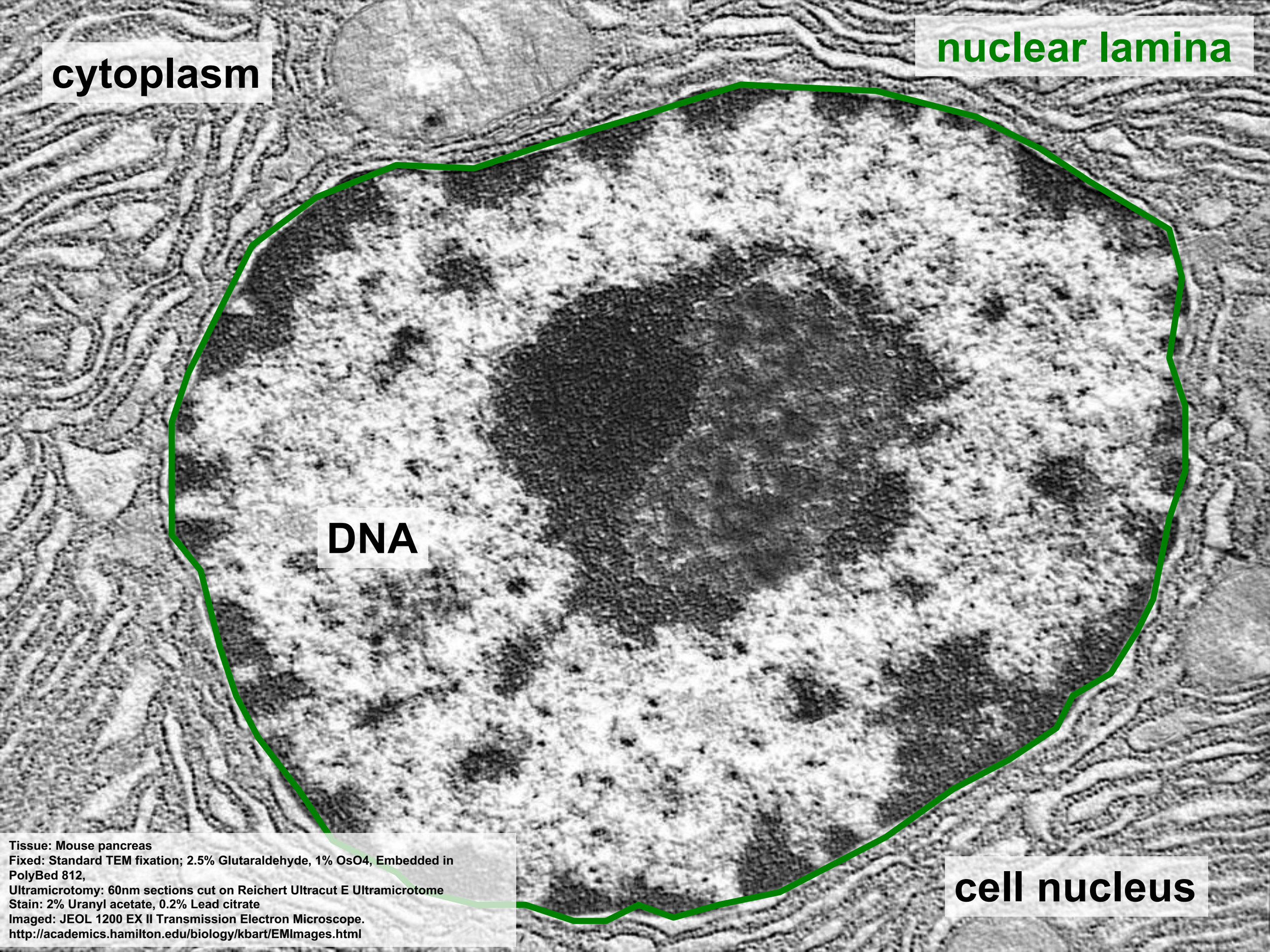
1c. 3D chromatin structure

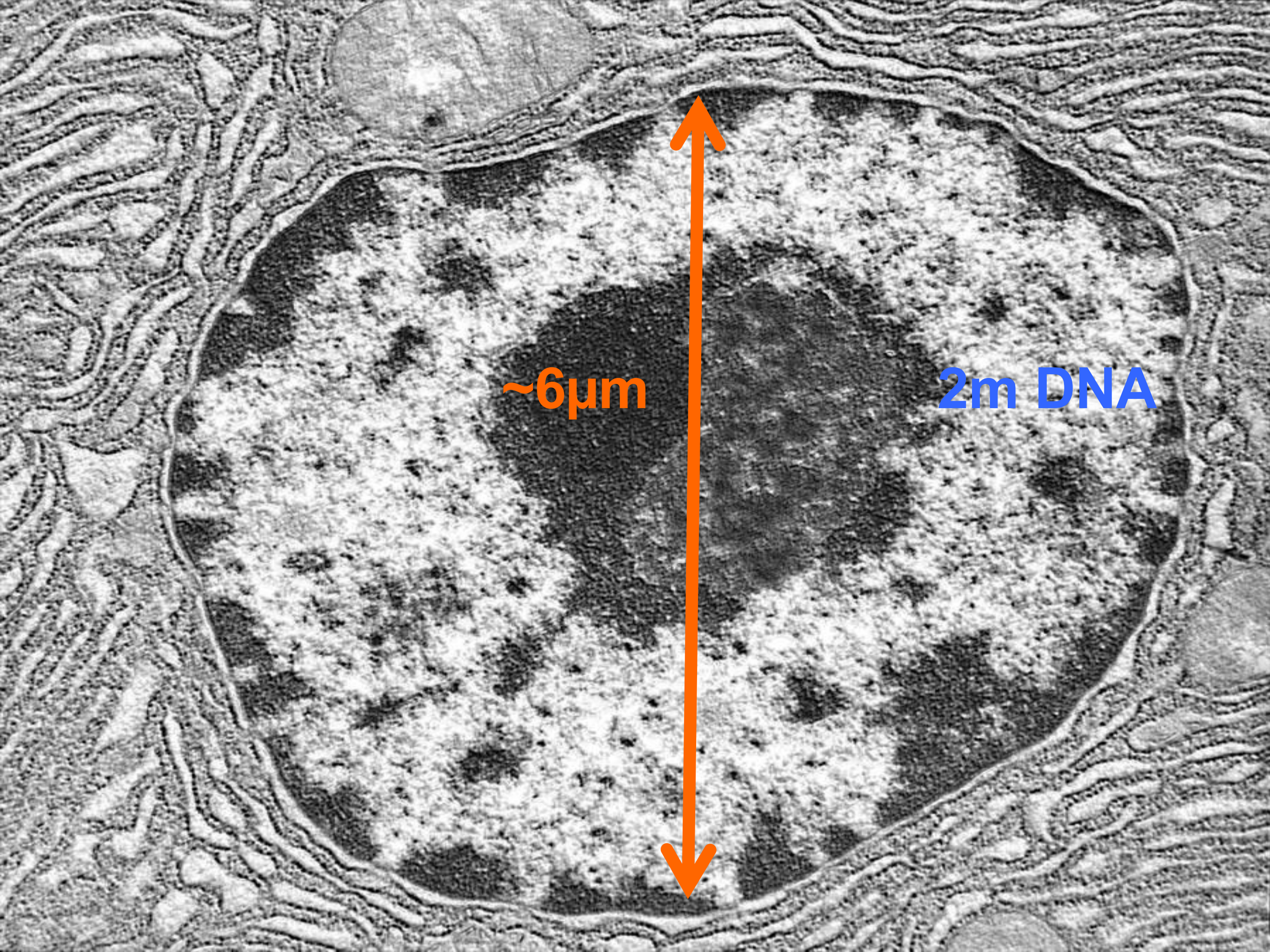
A model of the (mammalian) nucleus



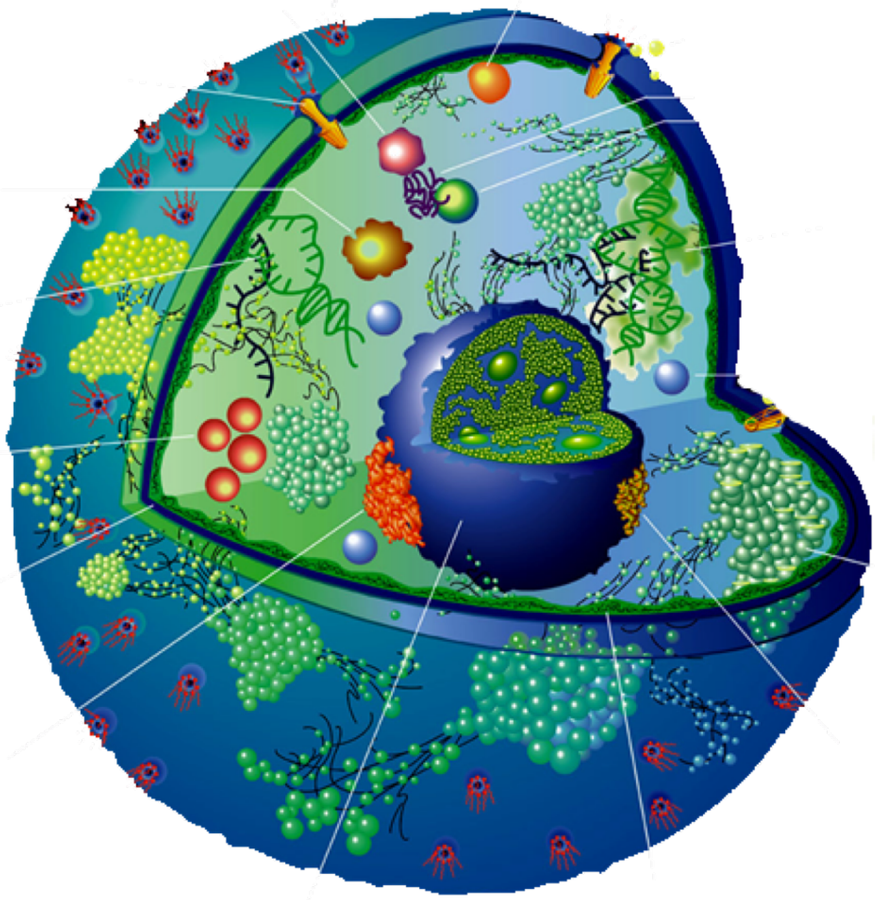
Spector, D.L. 2001. Nuclear domains. J. Cell Science 114, 2891-2893.



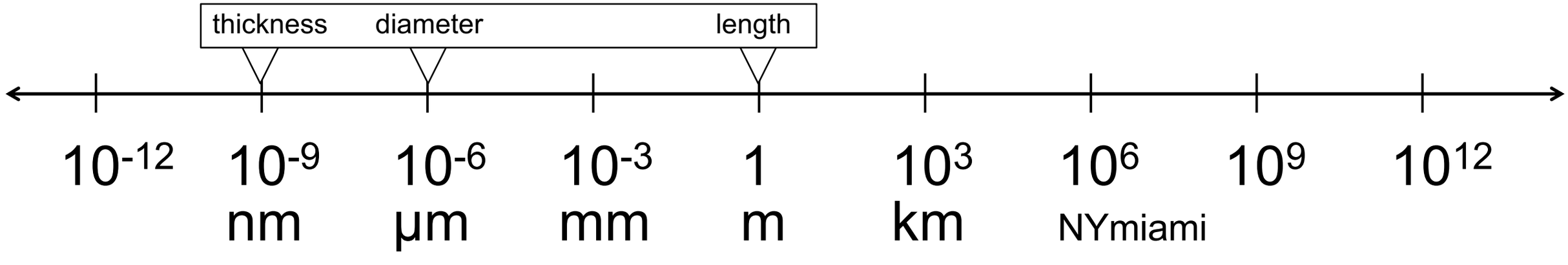
Tissue: Mouse pancreas
Fixed: Standard TEM fixation; 2.5% Glutaraldehyde, 1% OsO4, Embedded in PolyBed 812,
Ultramicrotomy: 60nm sections cut on Reichert Ultracut E Ultramicrotome
Stain: 2% Uranyl acetate, 0.2% Lead citrate
Imaged: JEOL 1200 EX II Transmission Electron Microscope.
http://academics.hamilton.edu/biology/kbart/EMImages.html

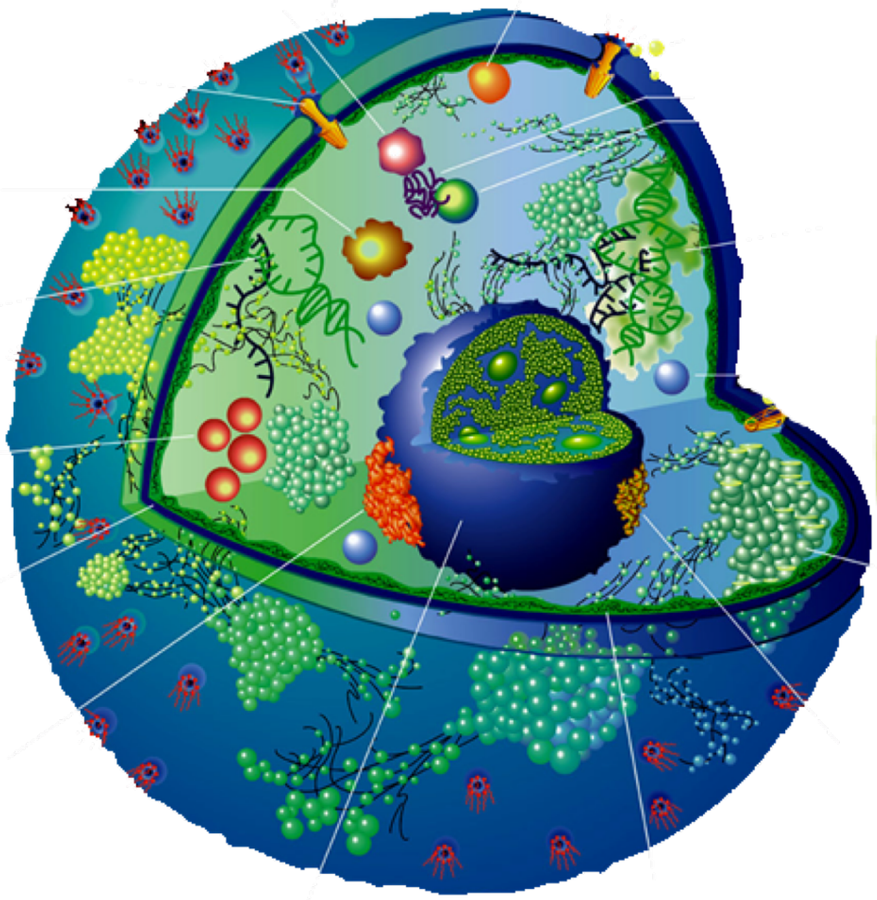

~6µm
2m DNA

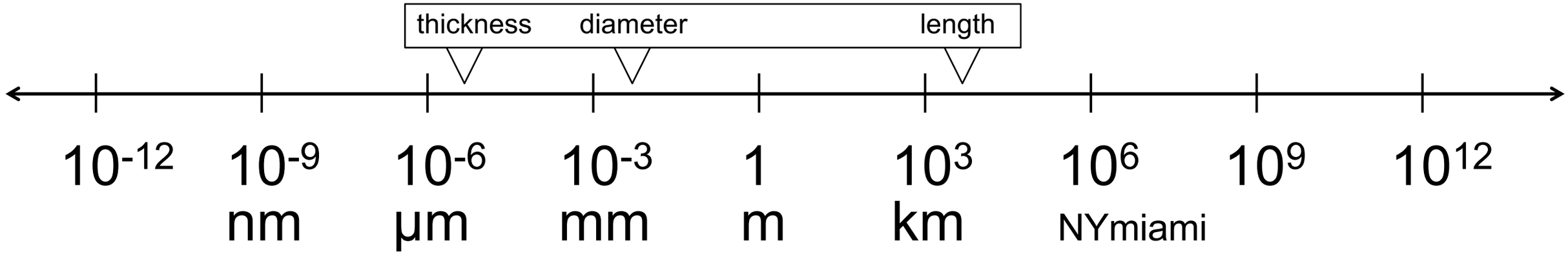
nucleus



diameter: 6µm
thread length: 2m
thread thickness: 2.5nm

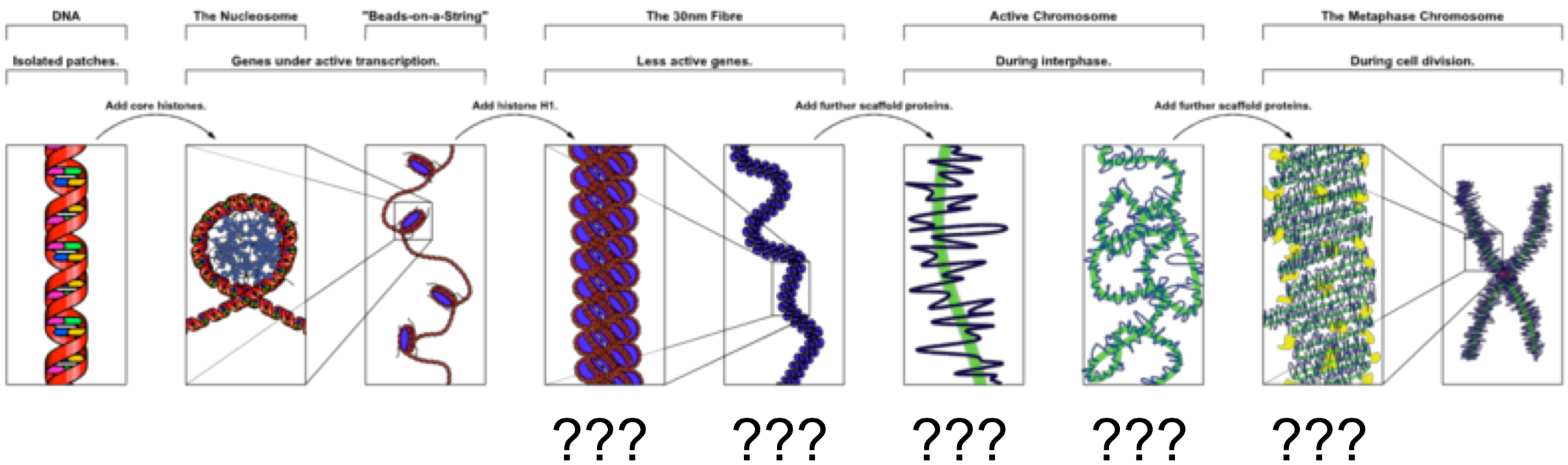


	nucleus	tennis ball
		
diameter:	6µm	6.7cm
thread length:	2m	~20km (8 x MIT - Harvard)
thread thickness:	2.5nm	~20µm

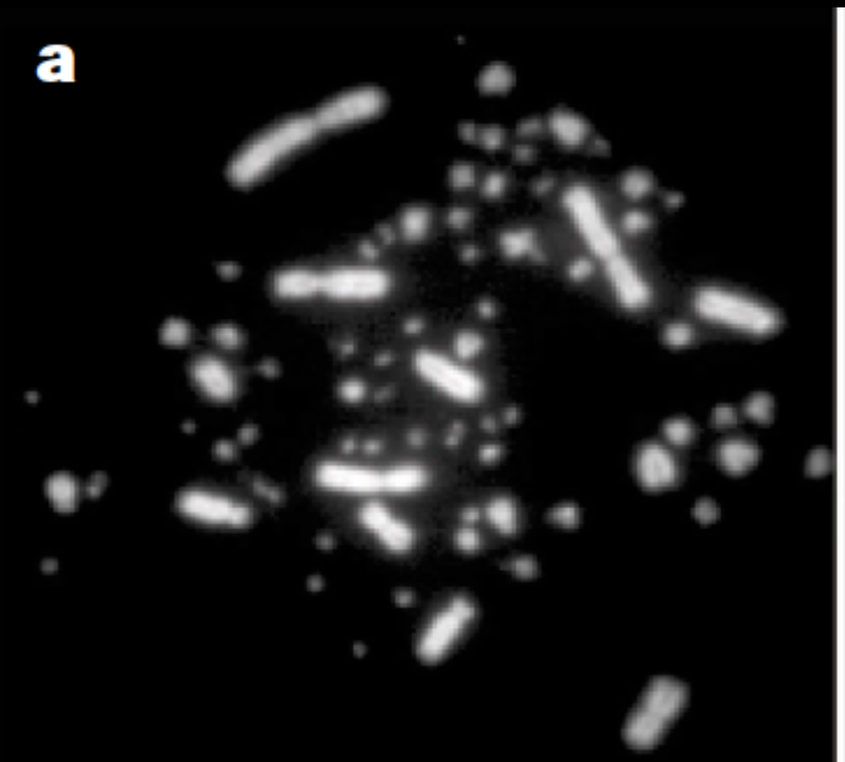


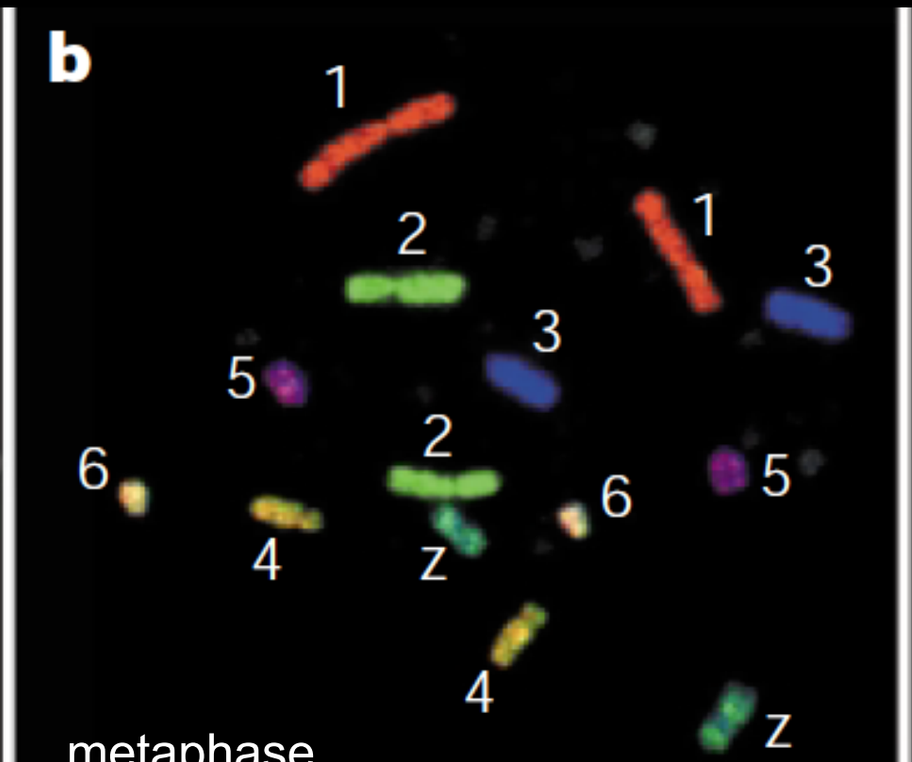
DNA compaction

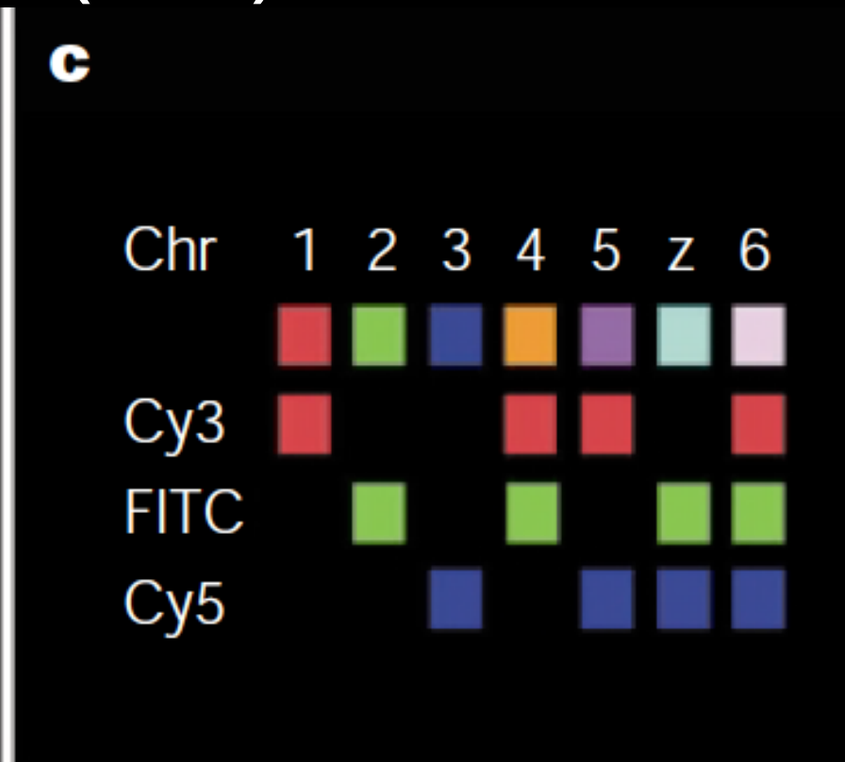
- DNA is **locally** compacted using *histone octamers* to form *nucleosomes*
- DNA is **globally** compacted by way of *chromosomes* (at least, during cell division / mitosis)
- Intermediate packaging mechanisms are subject of heavy speculation

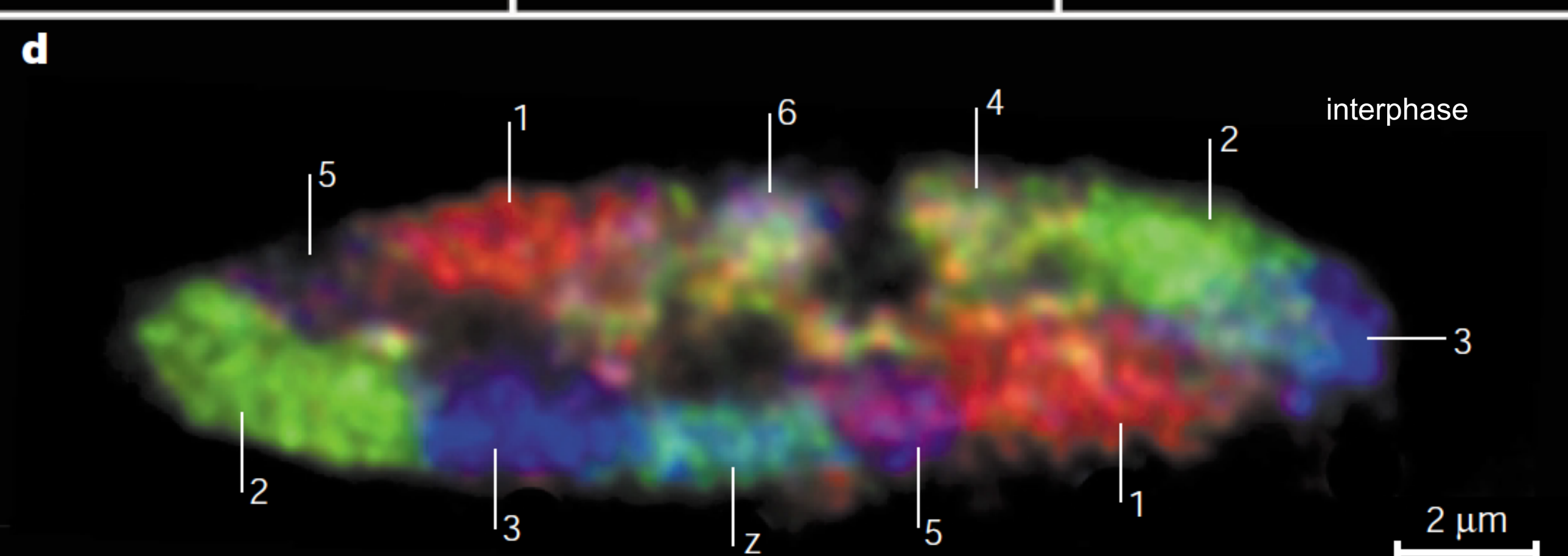


Chromosome territories (CT)





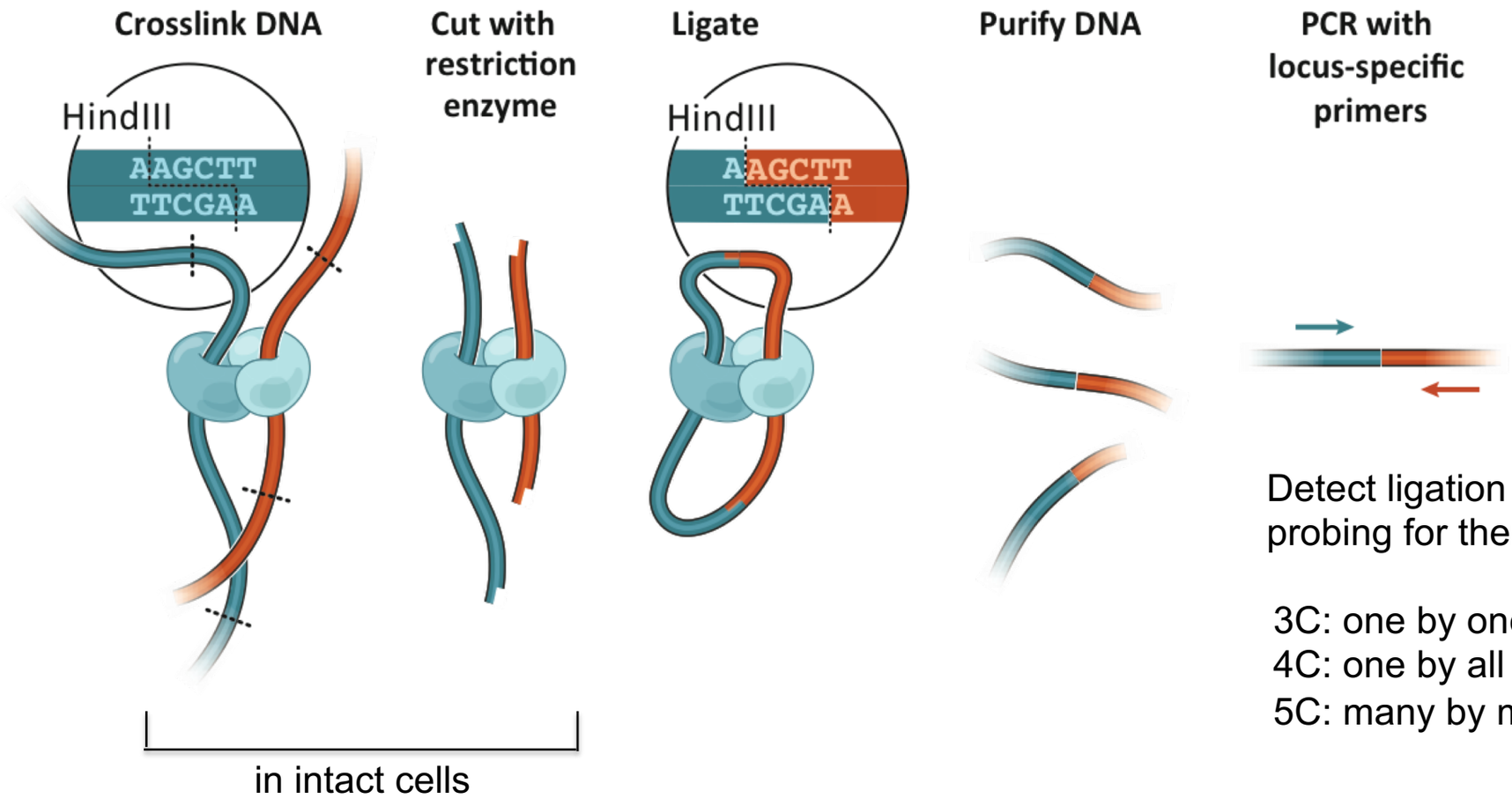




Cremer & Cremer, Nature Review Genetics (2001)

3C: Chromosome Conformation Capture

- Detects physical interactions between genomic elements
- Interacting elements are converted into ***ligation products***



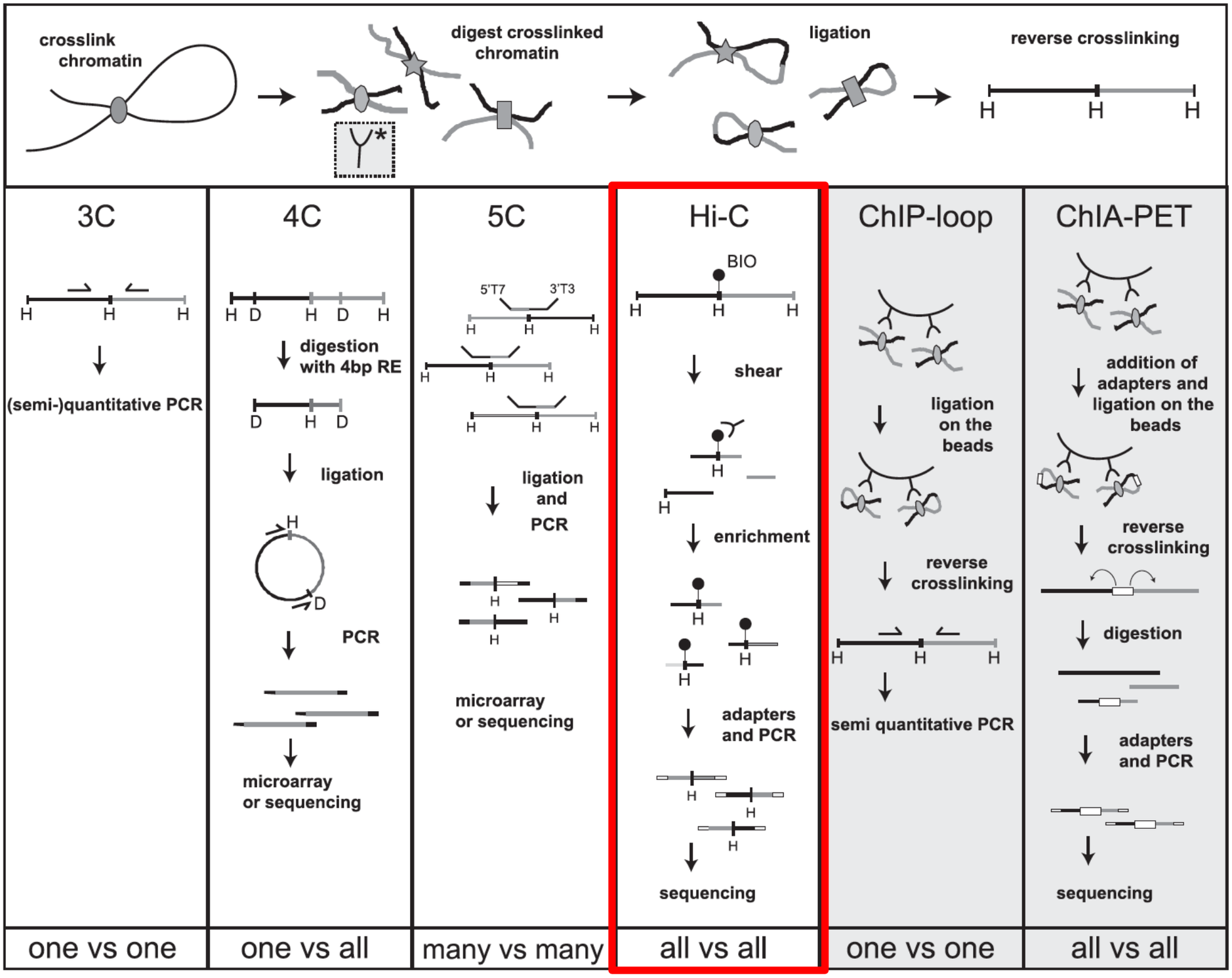
Detect ligation events by probing for them:

3C: one by one (PCR)
4C: one by all (microarray or seq)
5C: many by many (microarray or seq)

Dekker *et al.* Science 2002

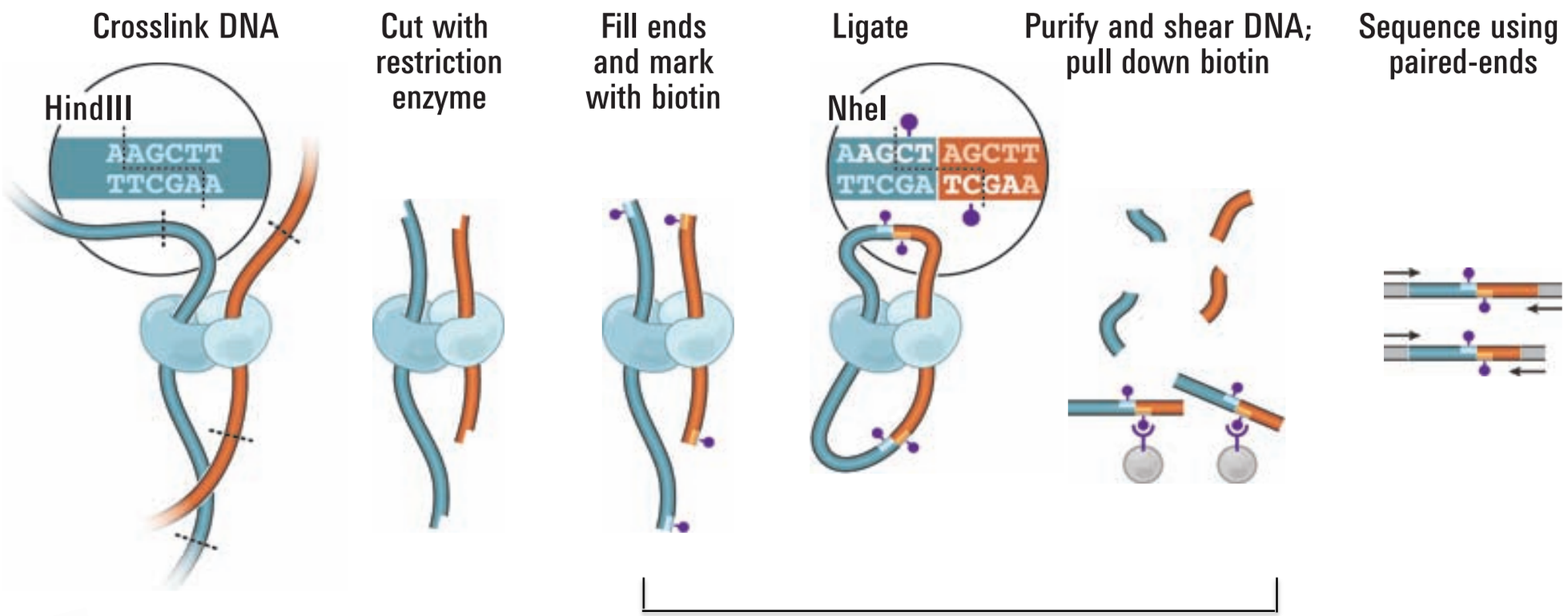
Dostie *et al*. Genome Res. 2006

Chromosome Conformation Capturing (3C) based methods



de Wit & de Laat, Genes & Dev. (2012)

Hi-C: genome-wide 3C

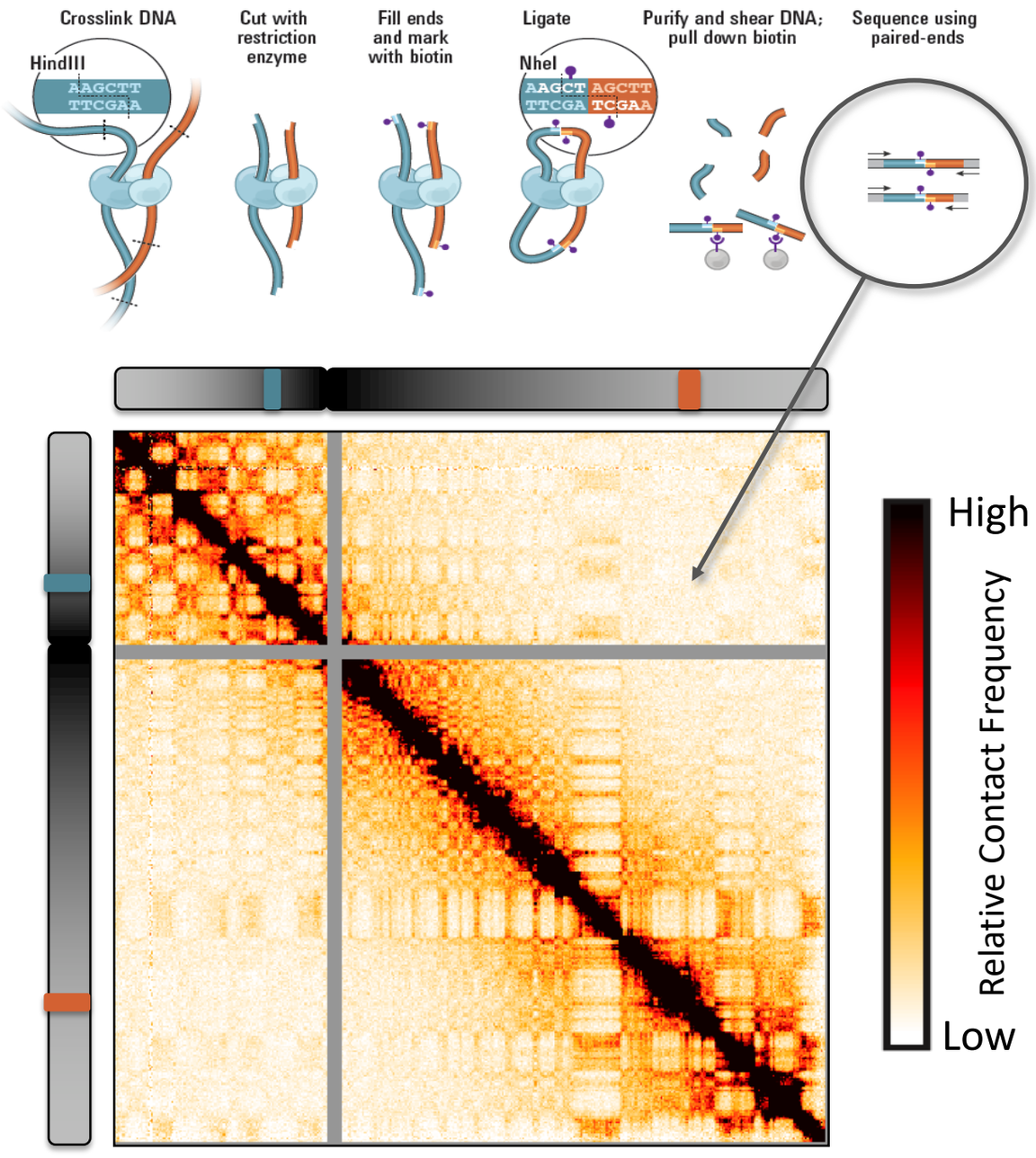


Selectively purify “ligation junctions” from sheared, size-selected DNA

Add adapters and do paired-end sequencing

Lieberman-Aiden, van Berkum *et al.* Science 2009

Hi-C: genome-wide 3C



Ensemble average (over 10^7 cells)
Averages over homologs.
Unless synchronized, averages over the cell cycle as well!

Goal:

Measure direct physical interactions (ensemble average)

Steps:

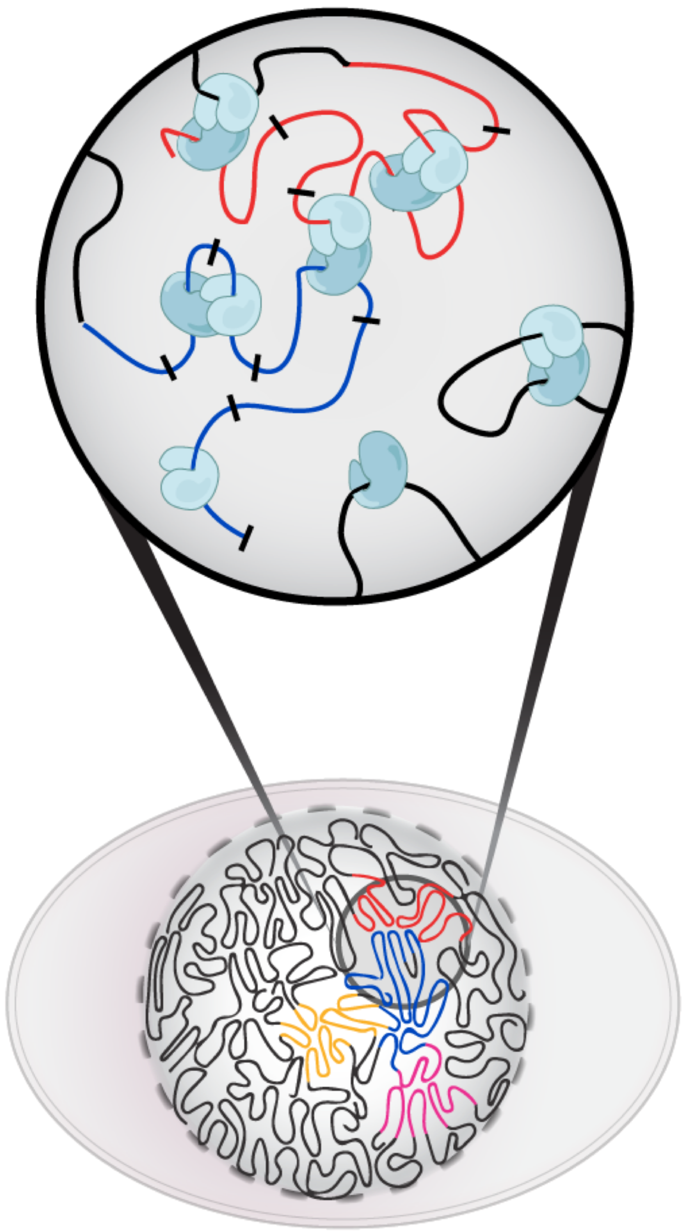
1. Crosslink chromatin (freeze contacts) ➔ "snapshot
2. Cut chromatin with restriction enzyme
3. Ligate: captures spatial proximity between fragment.
4. High-throughput sequencing to identify chimeric reads ➔ interactions

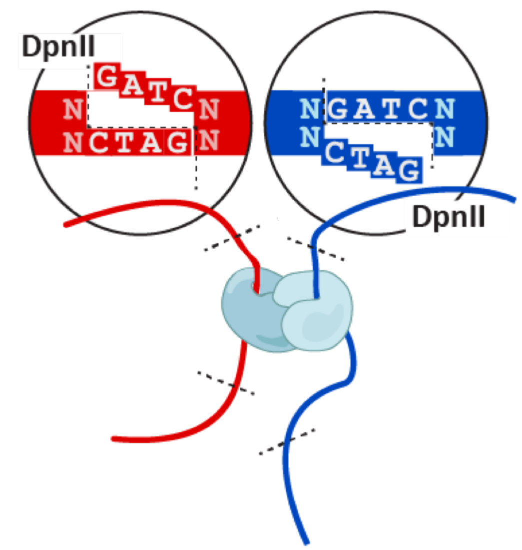
Main features:

- Bright diagonal
- Decay at increasing distances

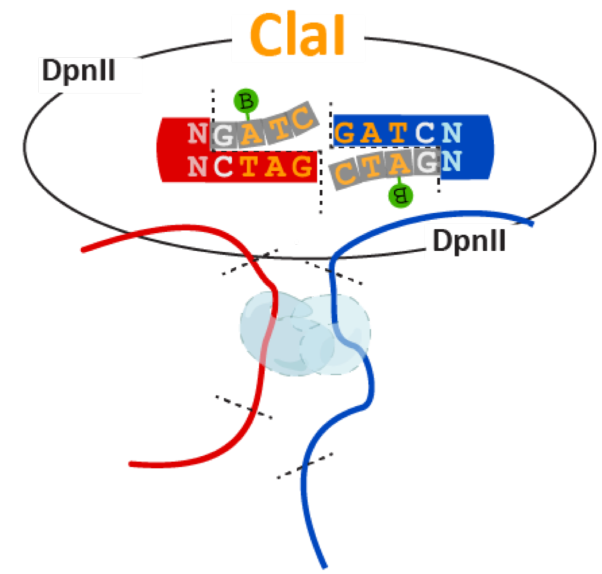
Hi-C vs. What-you-See

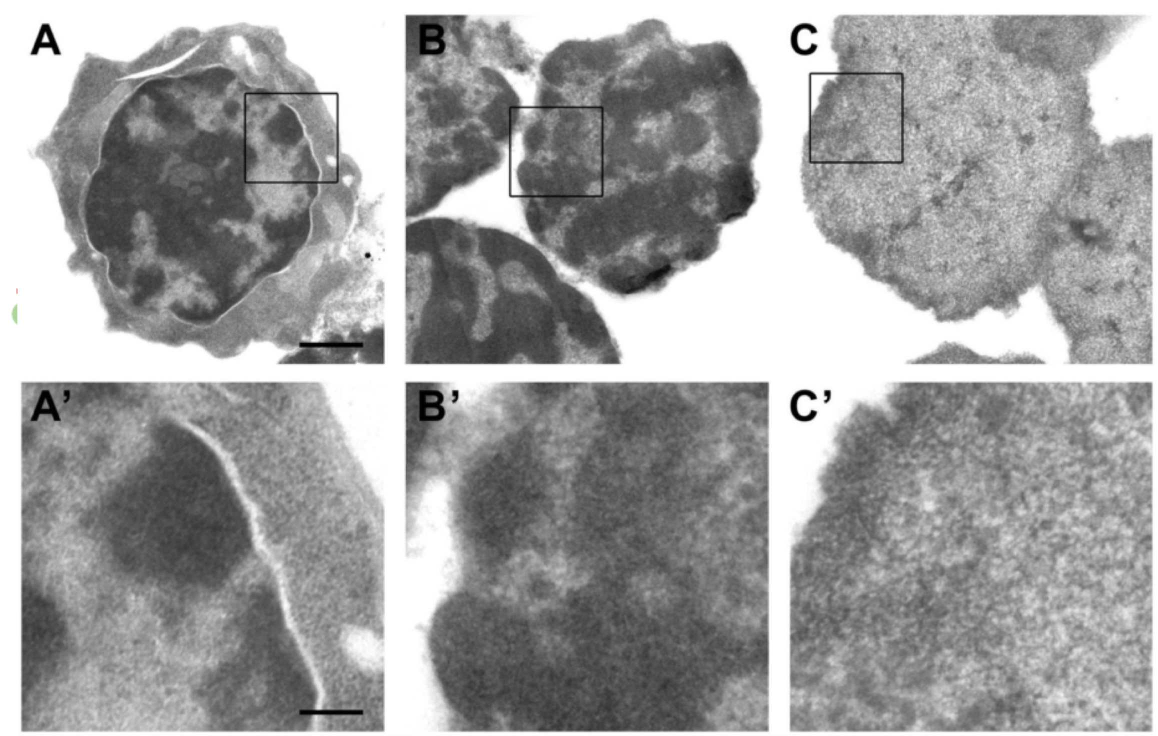
1





2





Critical steps:

1. Crosslinking to fix conformation
2. Digestion and re-ligation
3. Sequencing (biotinylated) junctions

Lieberman-Aiden et al., *Science* 2009

Belaghzal et al., *Methods* 2017

Gavrilov, *NAR* 2013

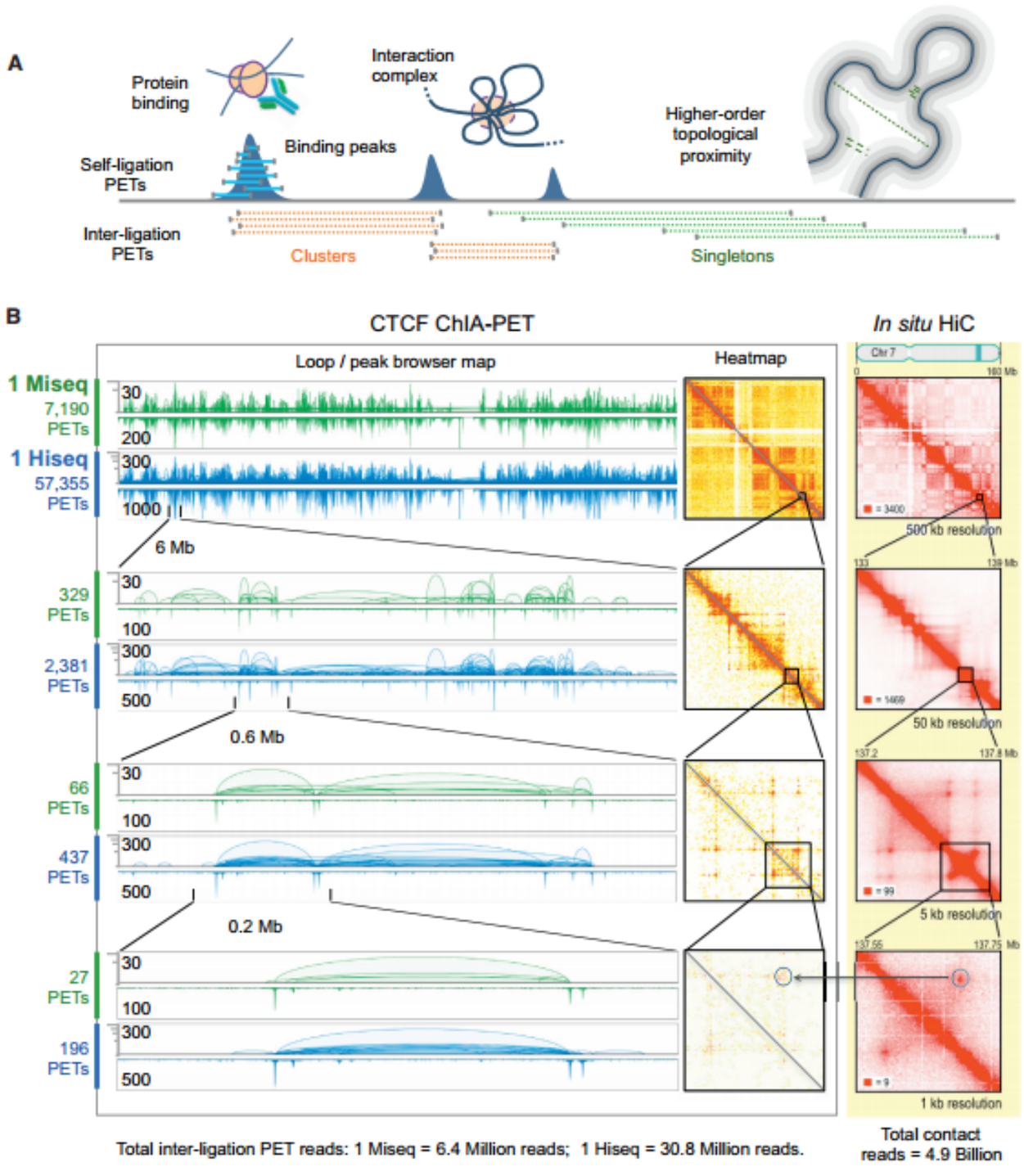
ChIA-PET: Chromatin Interaction Analysis using Paired-End-Tag sequencing

1. self-ligation peaks: binding sites

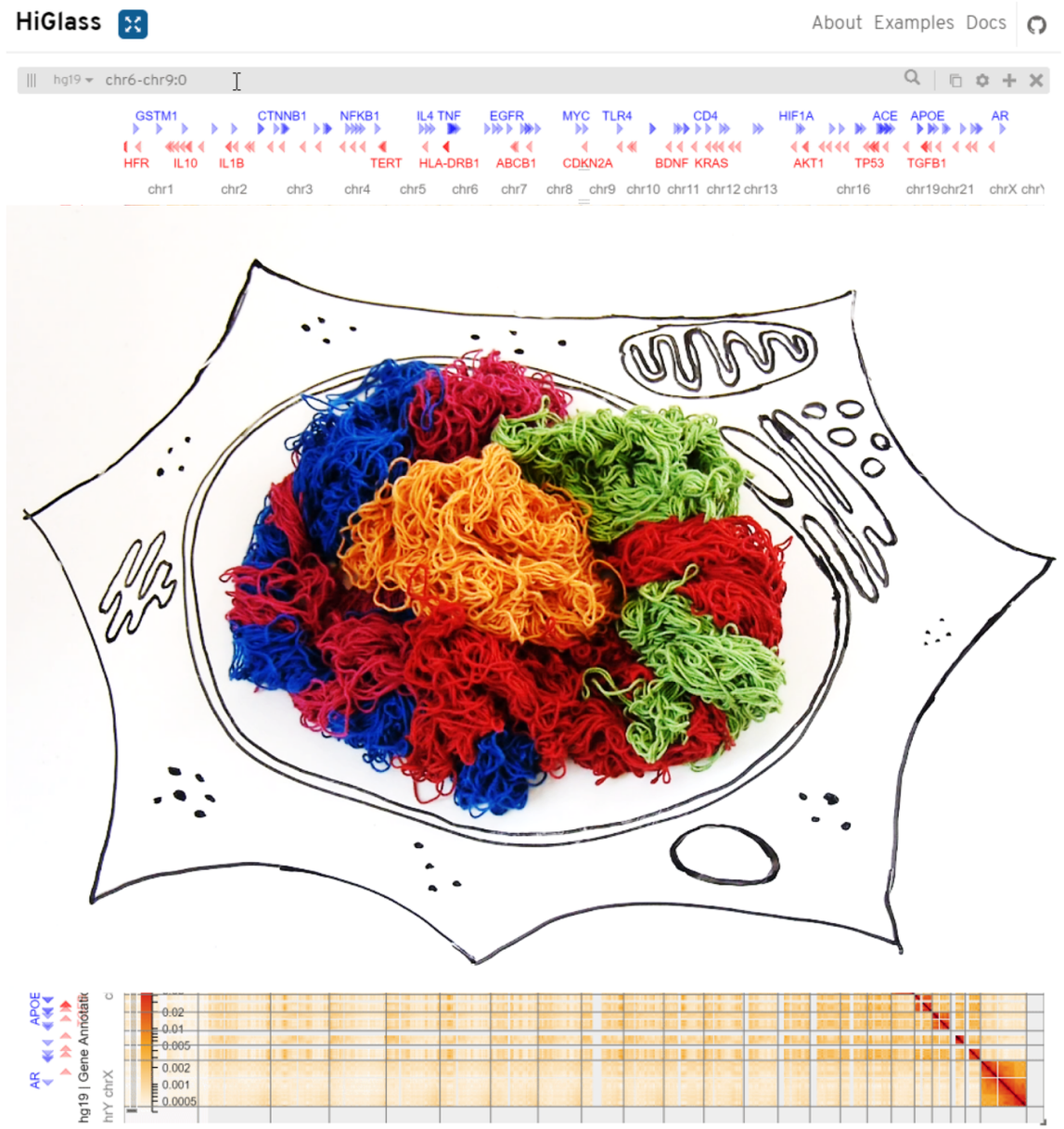
2. Inter-ligation: long range interaction

3. Consistence between CTCF ChIA-PET and Hi-C

4. ChIA-PET has higher resolution than Hi-C

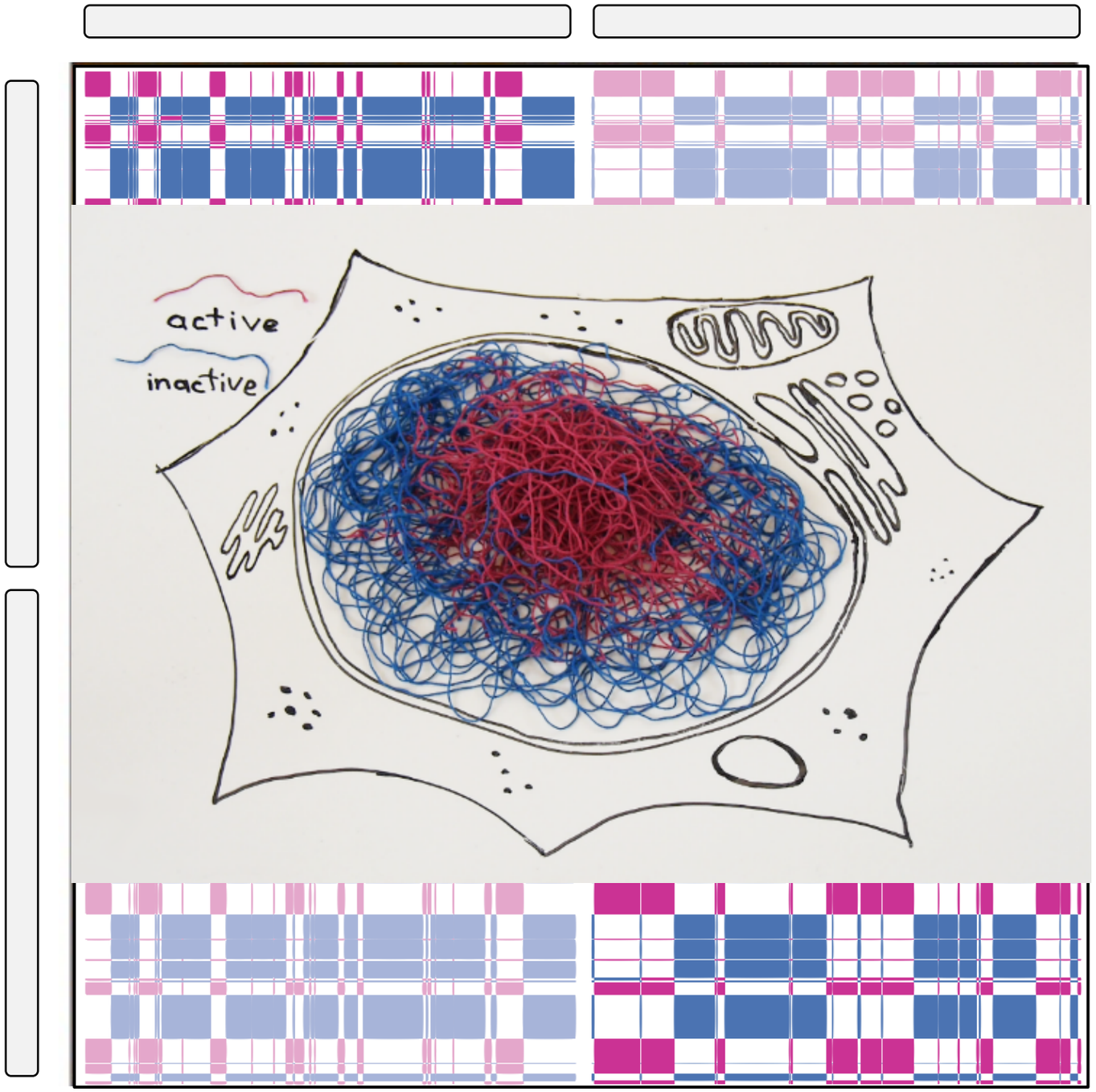


Territoriality

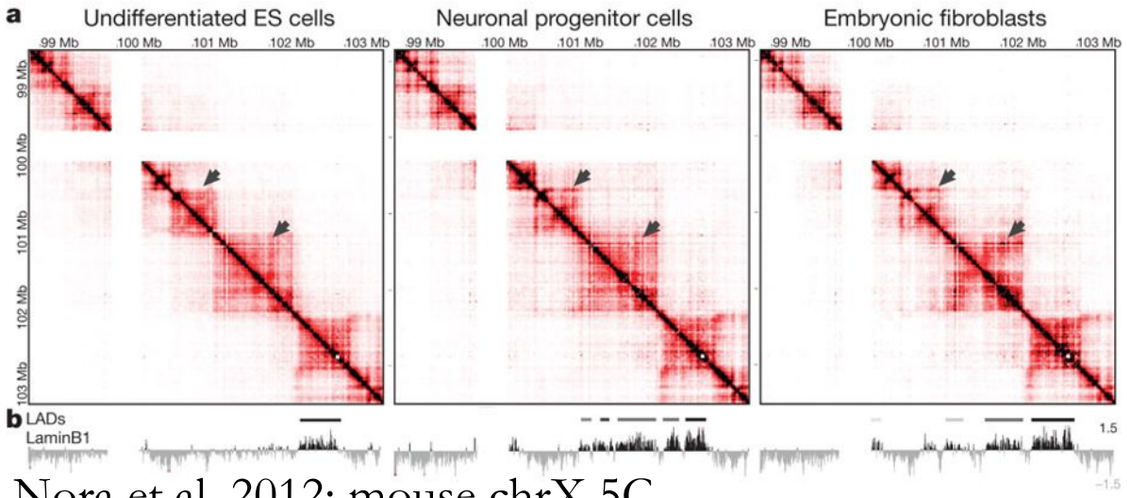


Kerpedjiev P, **Abdennur N**, Lekschas F, McCallum C, Dinkla K, Strobelt H, Luber JM, Ouellette SB, Azhir A, Kumar N, Hwang J, Lee S, Alver BH, Pfister H, Mirny LA, Park PJ, Gehlenborg N. HiGlass: web-based visual exploration and analysis of genome interaction maps. *Genome Biol.* 2018 Aug 24;19(1):125.

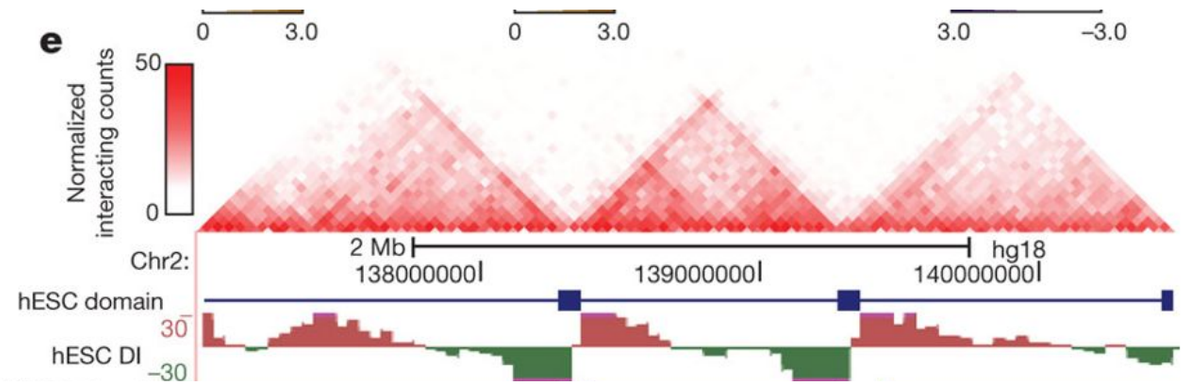
Compartmentalization (segregation)



TADs



Nora et al, 2012: mouse chrX 5C



Dixon et al, 2012: human ESCs and fibroblasts

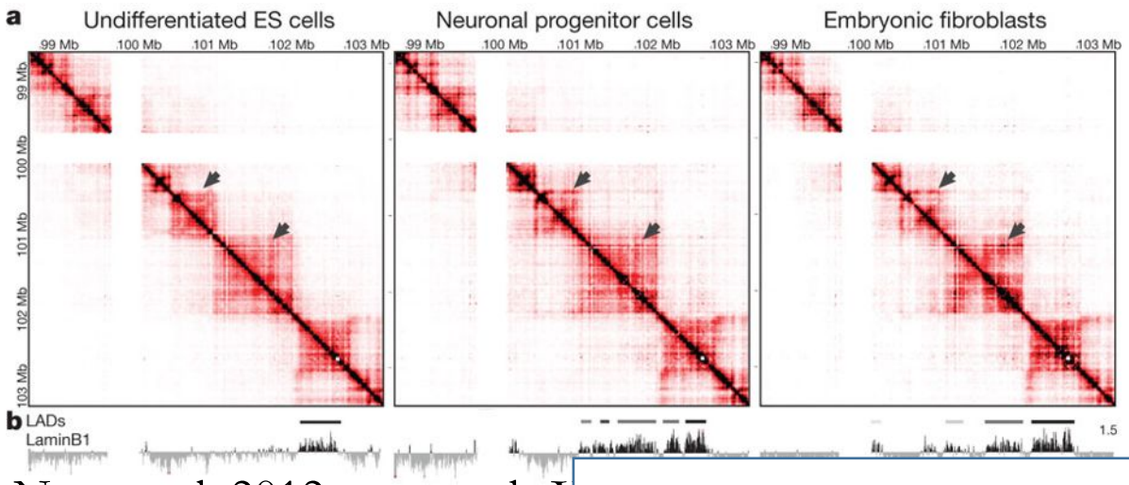
Self-associating intervals, < 1Mb

Sharp boundaries enriched for architectural proteins

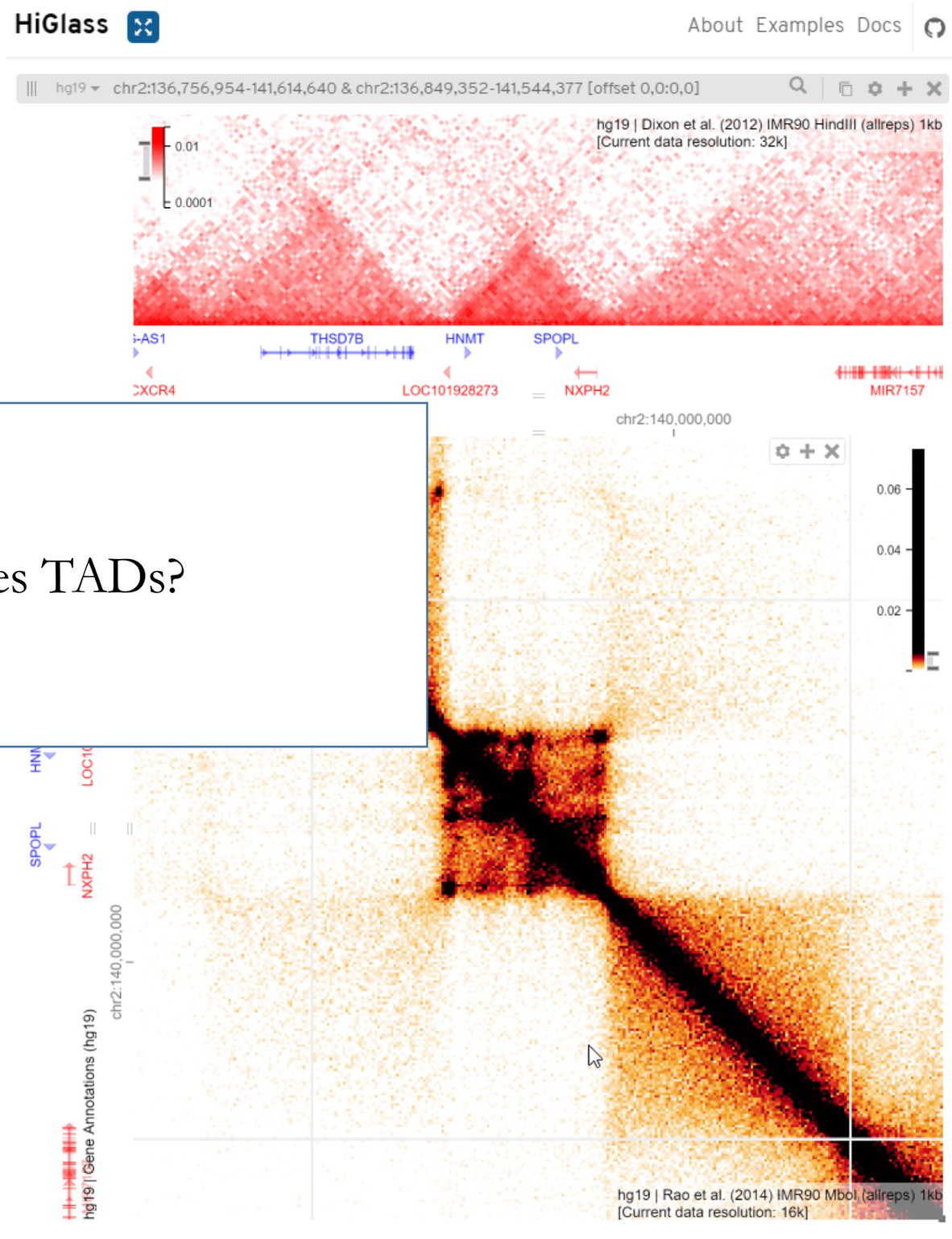
~2-4 fold difference in contact frequency within vs across boundaries

Regulatory neighborhoods

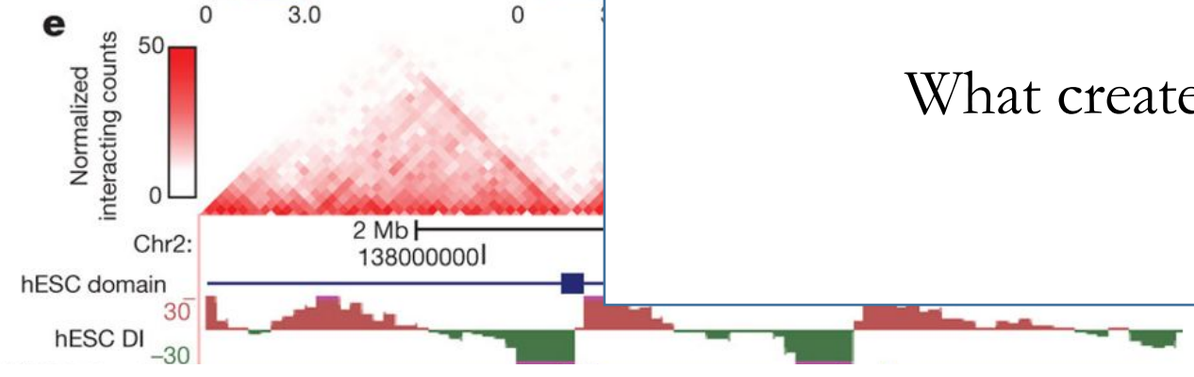
TADs



Nora et al, 2012: mouse chrX



What creates TADs?



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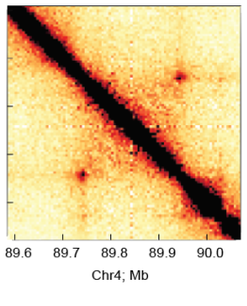
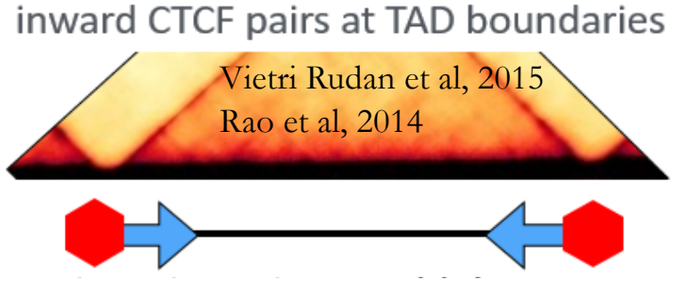
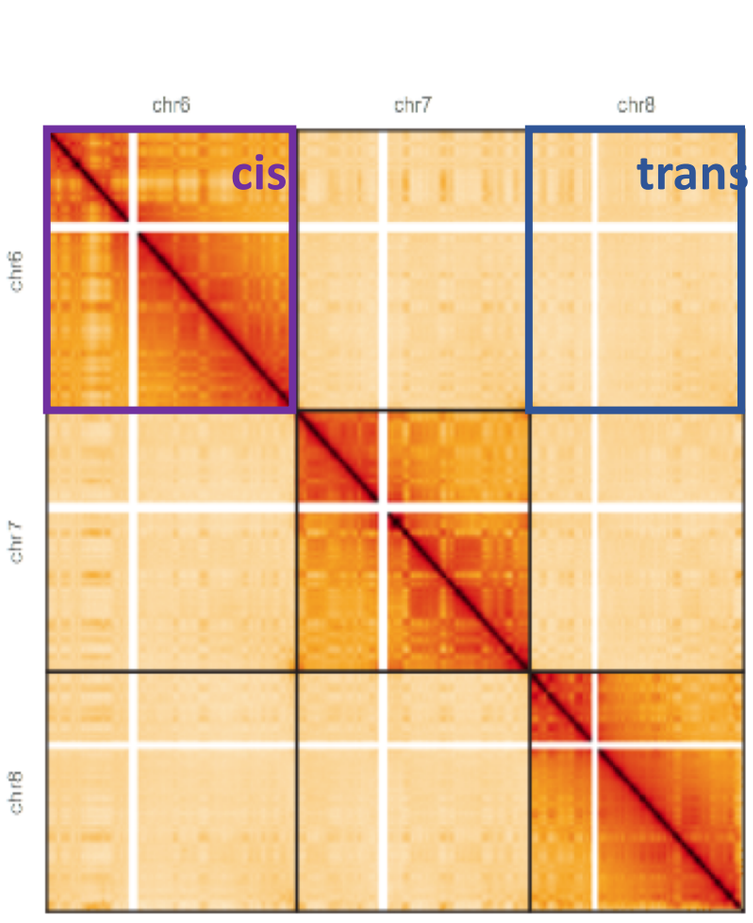


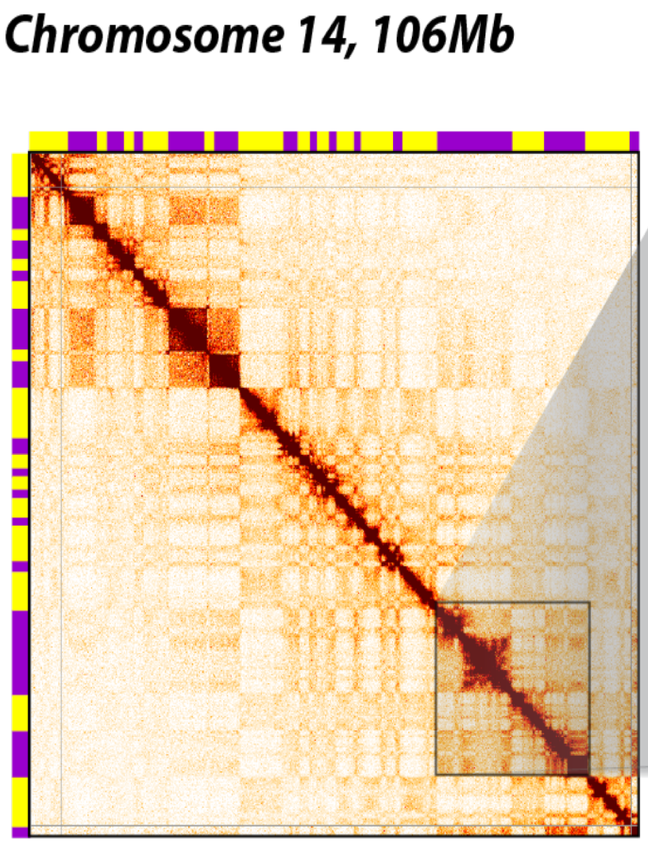
Rao et al, 2014



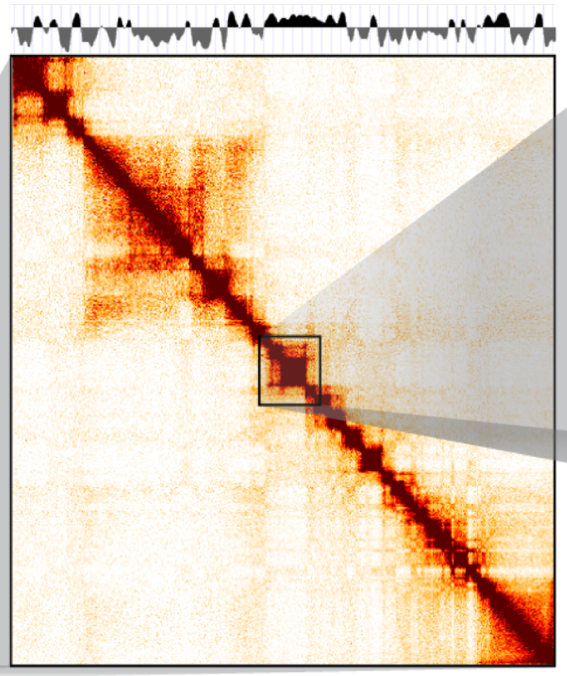
"Loops" (corner peaks)

Scales of organization

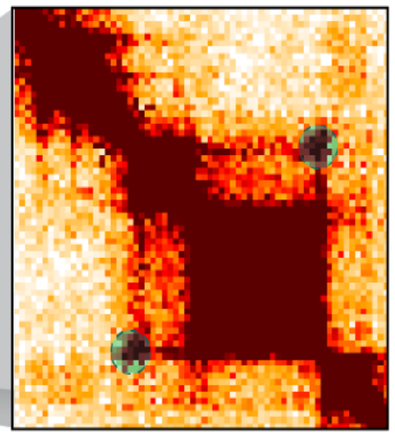




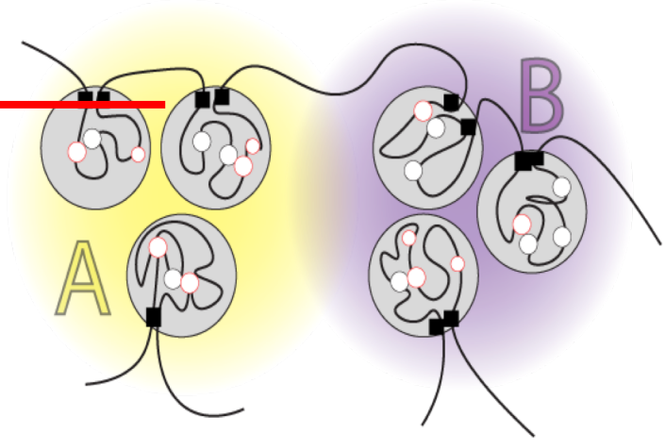
Compartments 1-10 Mb
100-500 Kb bins



TADs 0.1-1Mb
40-100 Kb bins

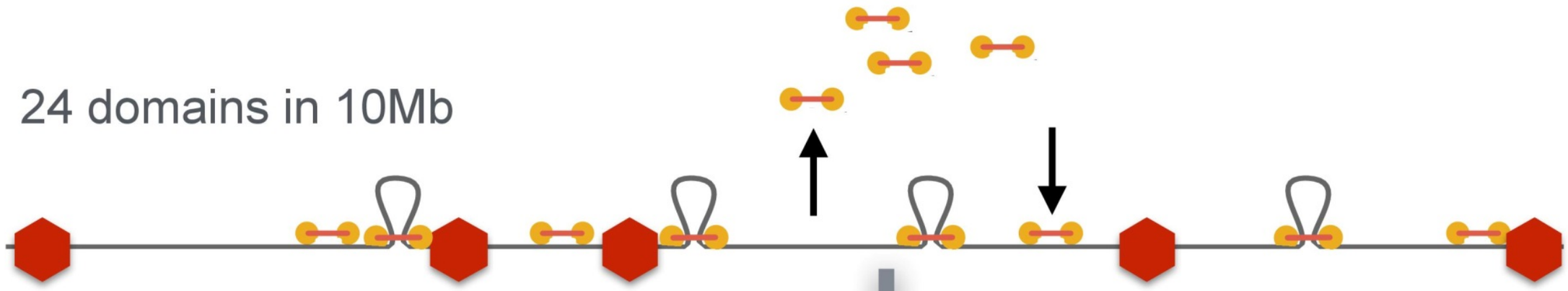


Loops 0.01-0.1Mb
10-40 Kb bins

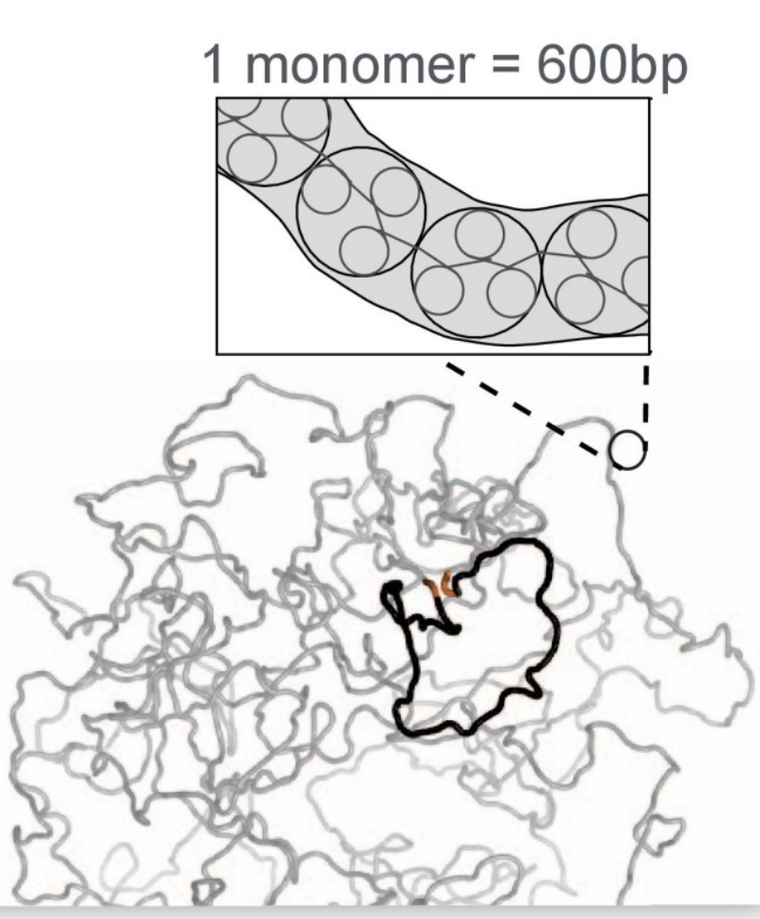


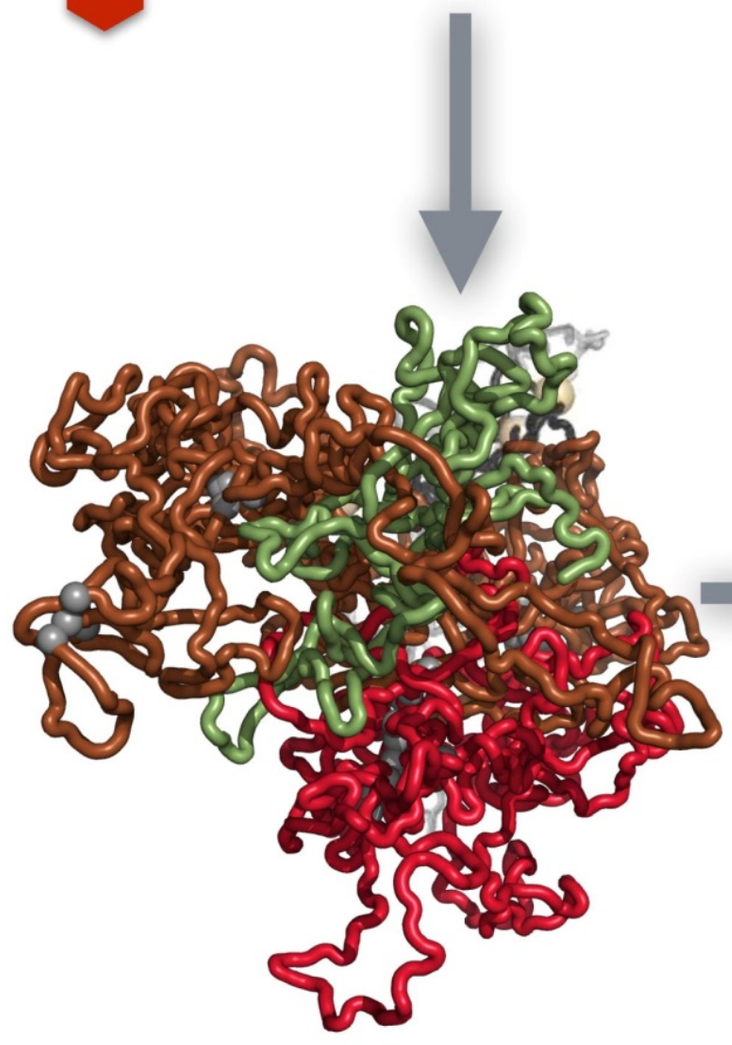
Territories / chromosomes

Loop extrusion + polymer model



3D simulations of polymer dynamics





16,000 monomers

Formation of chromosomal domains by loop extrusion
http://biorxiv.org/content/early/2015/08/14/024620

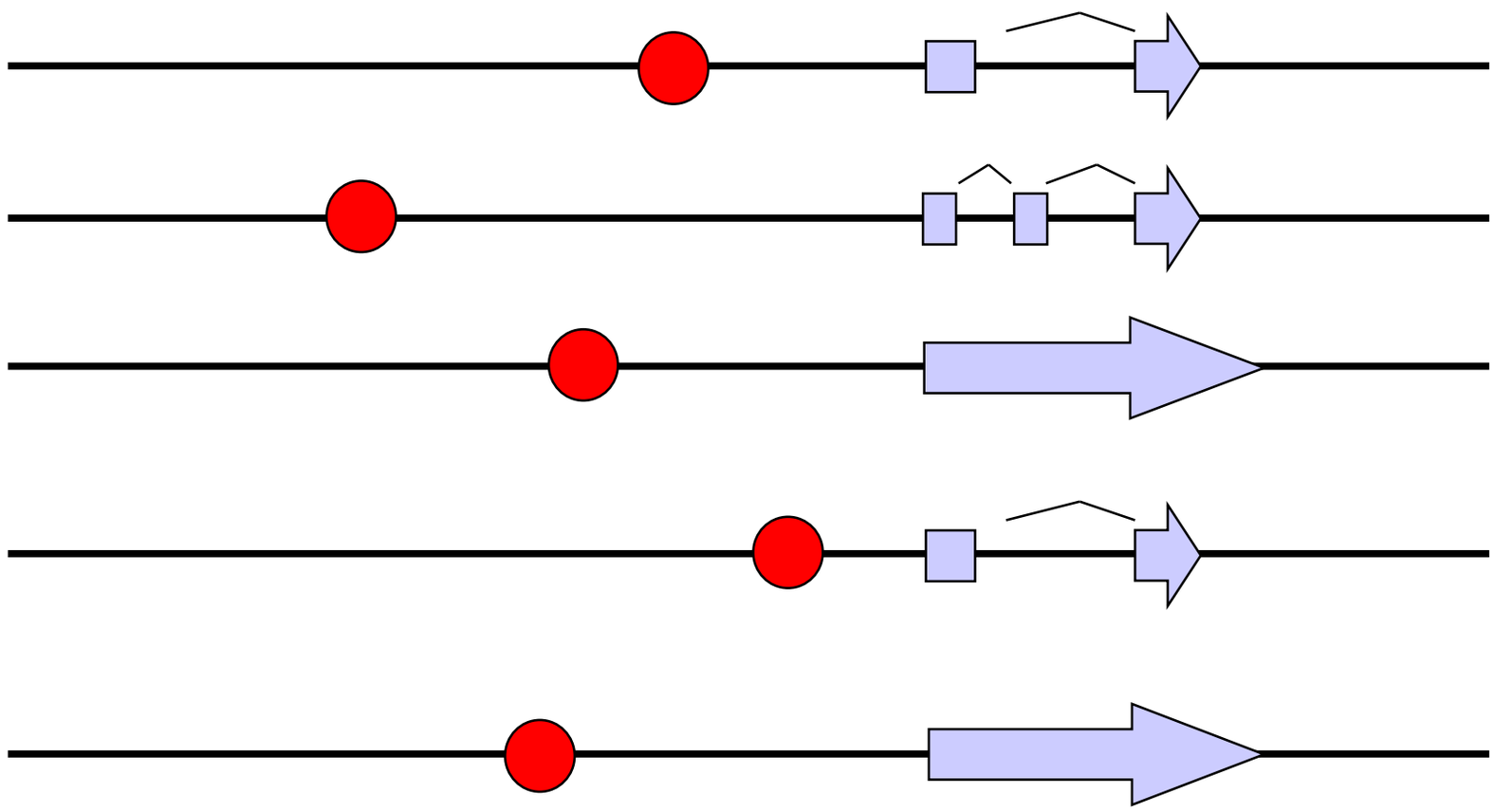
Deep Learning for Regulatory Genomics

1. **Biological foundations: Building blocks of Gene Regulation**
   - Gene regulation: Cell diversity, Epigenomics, Regulators (TFs), Motifs, Disease role
   - Probing gene regulation: TFs/histones: ChIP-seq, Accessibility: DNase/ATAC-seq
   - Three-dimensional chromatin structure, Hi-C, ChIA-PET, TADs, Loop Extrusion
2. **Classical methods for Regulatory Genomics and Motif Discovery**
   - Enrichment-based motif discovery: Expectation Maximization, Gibbs Sampling
   - Experimental: PBMs, SELEX. Comparative genomics: Evolutionary conservation.
3. **Regulatory Genomics CNNs (Convolutional Neural Networks): Foundations**
   - Key idea: pixels ⇔ DNA letters. Patches/filters ⇔ Motifs. Higher ⇔ combinations
   - Learning convolutional filters ⇔ Motif discovery. Applying them ⇔ Motif matches
4. **Regulatory Genomics CNNs/RNNs in Practice: Diverse Architectures**
   - DeepBind: Learn motifs, use in (shallow) fully-connected layer, mutation impact
   - DeepSea: Train model directly on mutational impact prediction
   - Basset: Multi-task DNase prediction in 164 cell types, reuse/learn motifs
   - ChromPuter: Multi-task prediction of different TFs, reuse partner motifs
   - DeepLIFT: Model interpretation based on neuron activation properties
   - DanQ: Recurrent Neural Network for sequential data analysis
5. **Guest Lecture: David Kelley on Basset and Deep Learning for Hi-C looping**

2. Classical regulatory genomics (before Deep Learning)

Enrichment-based discovery methods

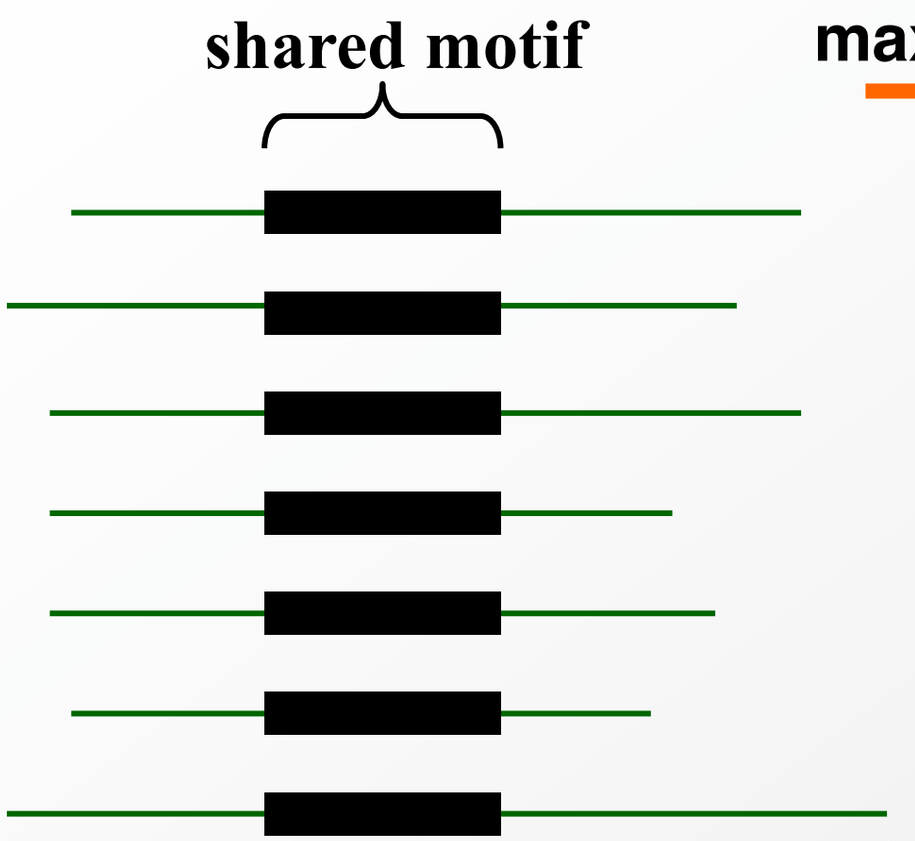
Given a set of co-regulated/functionally related genes, find common motifs in their promoter regions



- **Align the promoters to each other using local alignment**
- **Use expert knowledge for what motifs should look like**
- **Find ‘median’ string by enumeration (motif/sample driven)**
- **Start with conserved blocks in the upstream regions**

Starting positions ⇔ Motif matrix

- given aligned sequences ➔ easy to compute profile matrix



maximization

sequence positions

	1	2	3	4	5	6	7	8
A	0.1	0.3	0.1	0.2	0.2	0.4	0.3	0.1
C	0.5	0.2	0.1	0.1	0.6	0.1	0.2	0.7
G	0.2	0.2	0.6	0.5	0.1	0.2	0.2	0.1
T	0.2	0.3	0.2	0.2	0.1	0.3	0.3	0.1

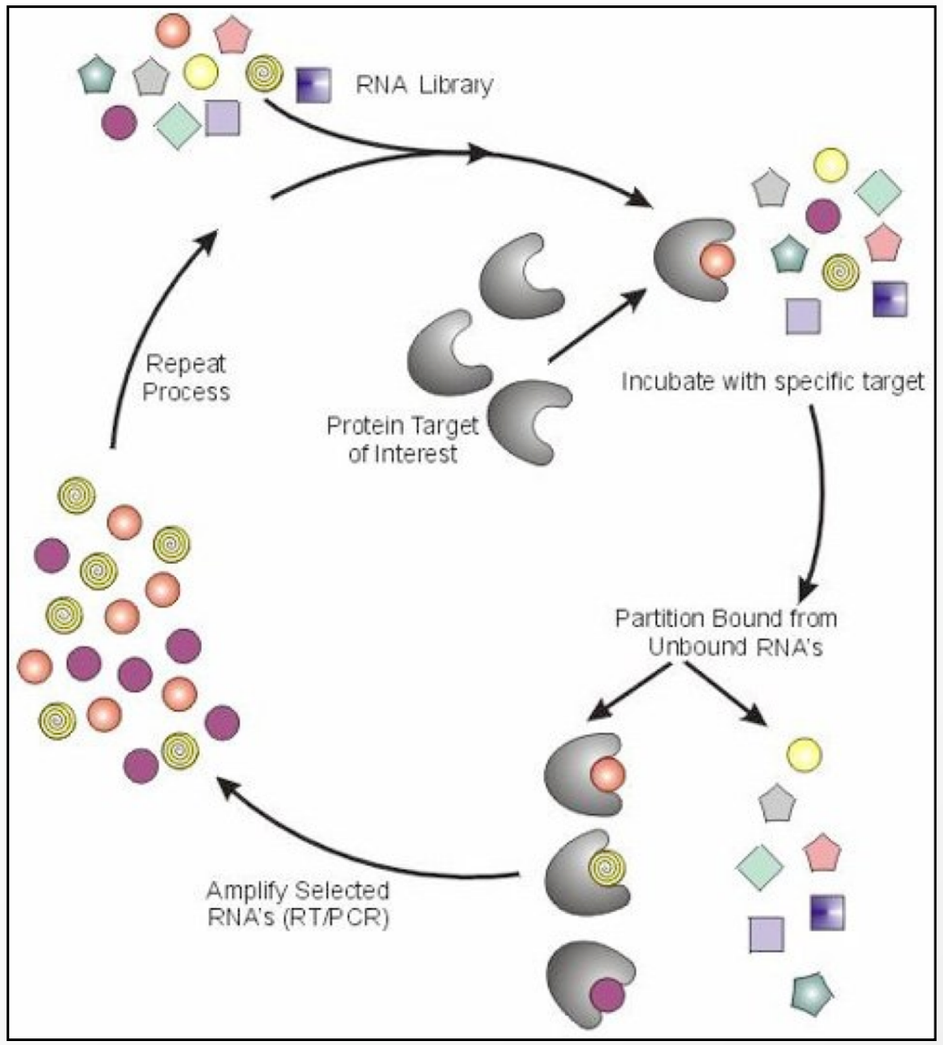
expectation

given profile matrix

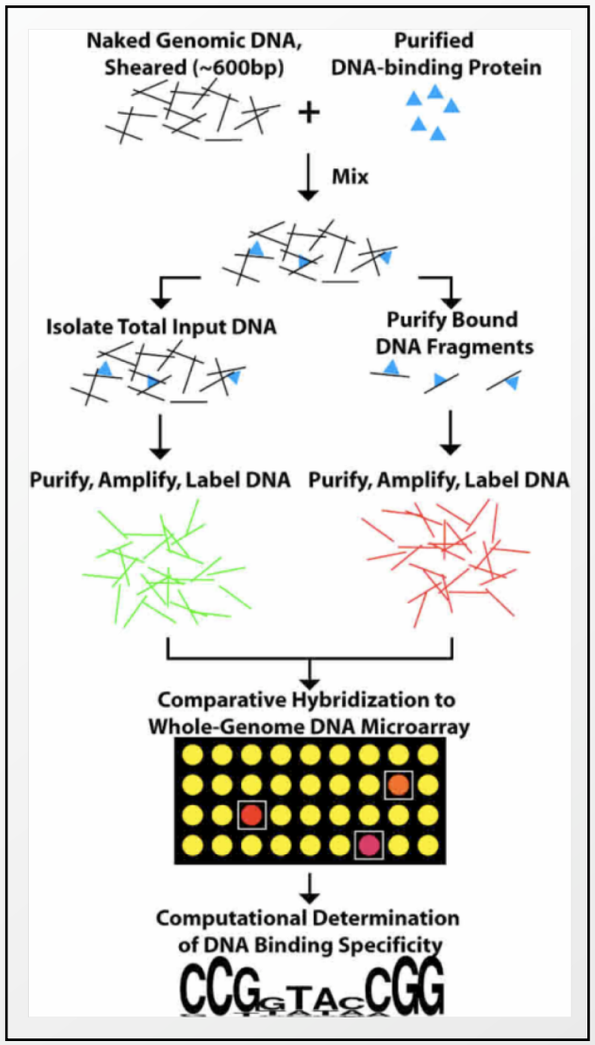
- easy to find starting position probabilities

Key idea: Iterative procedure for estimating both, given uncertainty (learning problem with hidden variables: the starting positions)

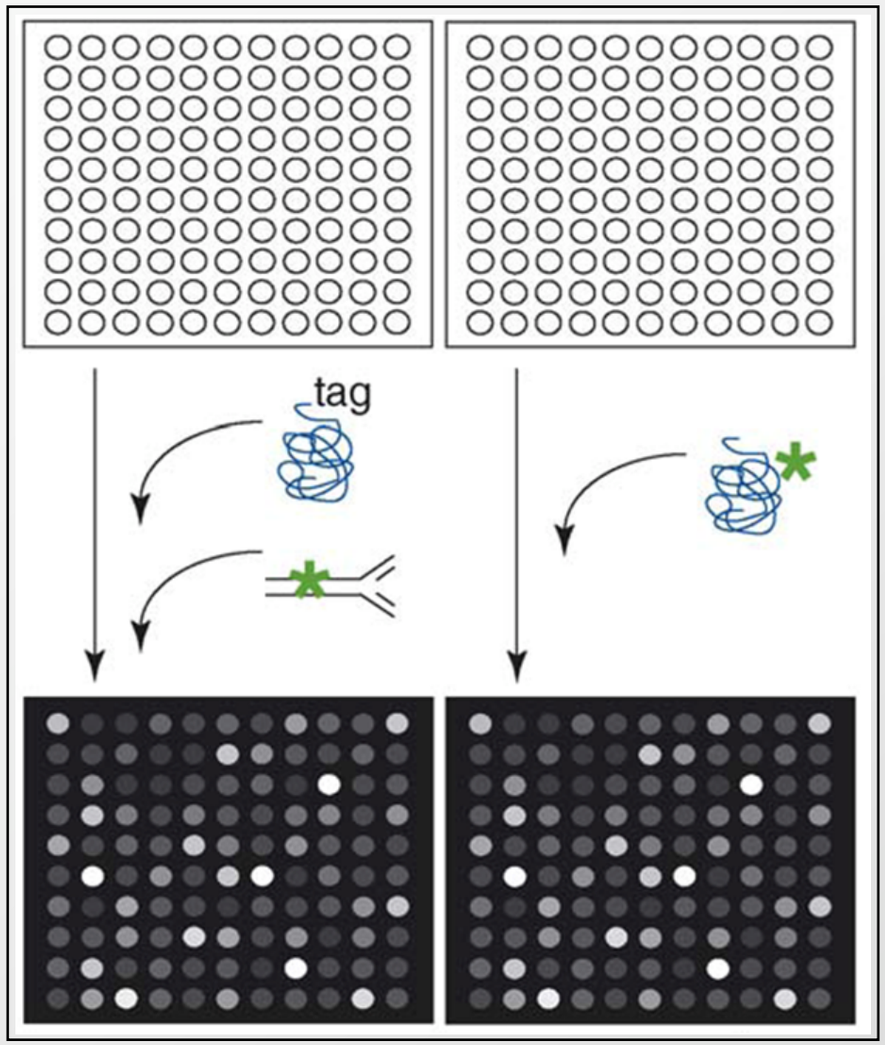
Experimental factor-centric discovery of motifs



SELEX (Systematic Evolution of Ligands by Exponential Enrichment; Klug & Famulok, 1994).



DIP-Chip (DNA-immunoprecipitation with microarray detection; Liu et al., 2005)



PBMs (Protein binding microarrays; Mukherjee, 2004)
Double stranded DNA arrays

Approaches to regulatory motif discovery

Region-based motif discovery

- Expectation Maximization (e.g. MEME)
  - Iteratively refine positions / motif profile
- Gibbs Sampling (e.g. AlignACE)
  - Iteratively sample positions / motif profile
- Enumeration with wildcards (e.g. Weeder)
  - Allows global enrichment/background score
- Peak-height correlation (e.g. MatrixREDUCE)
  - Alternative to cutoff-based approach

Genome-wide

- Conservation-based discovery (e.g. MCS)
  - Genome-wide score, up-/down-stream bias

In vitro / trans

- Protein Domains (e.g. PBMs, SELEX)
  - In vitro motif identification, seq-/array-based

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Deep convolutional neural network

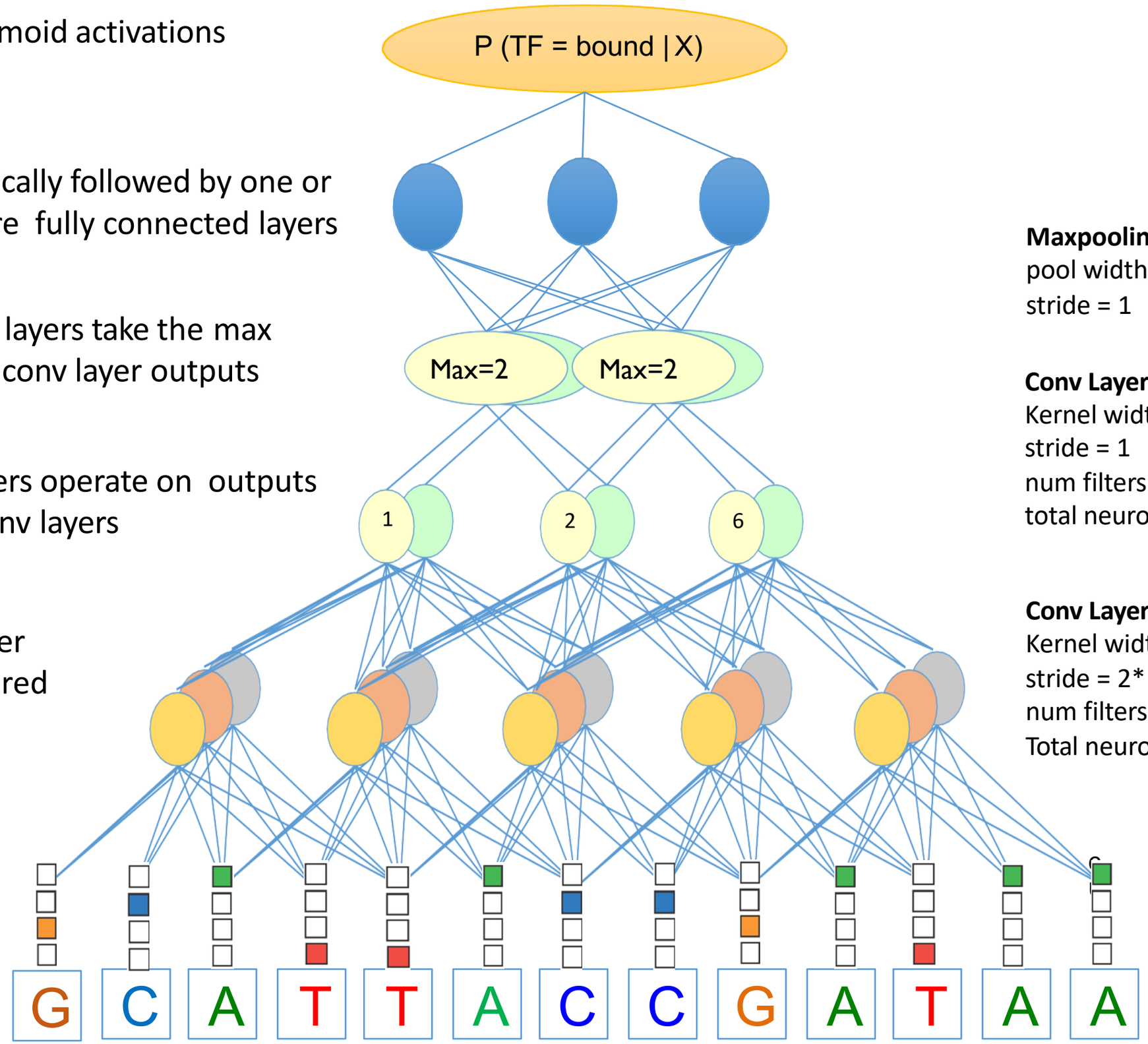
Sigmoid activations

Typically followed by one or more fully connected layers

Maxpooling layers take the max over sets of conv layer outputs

Later conv layers operate on outputs of previous conv layers

Convolutional layer (same color = shared weights)



Maxpooling layer
pool width = 2
stride = 1

Conv Layer 2
Kernel width = 3
stride = 1
num filters / num channels = 2
total neurons = 6

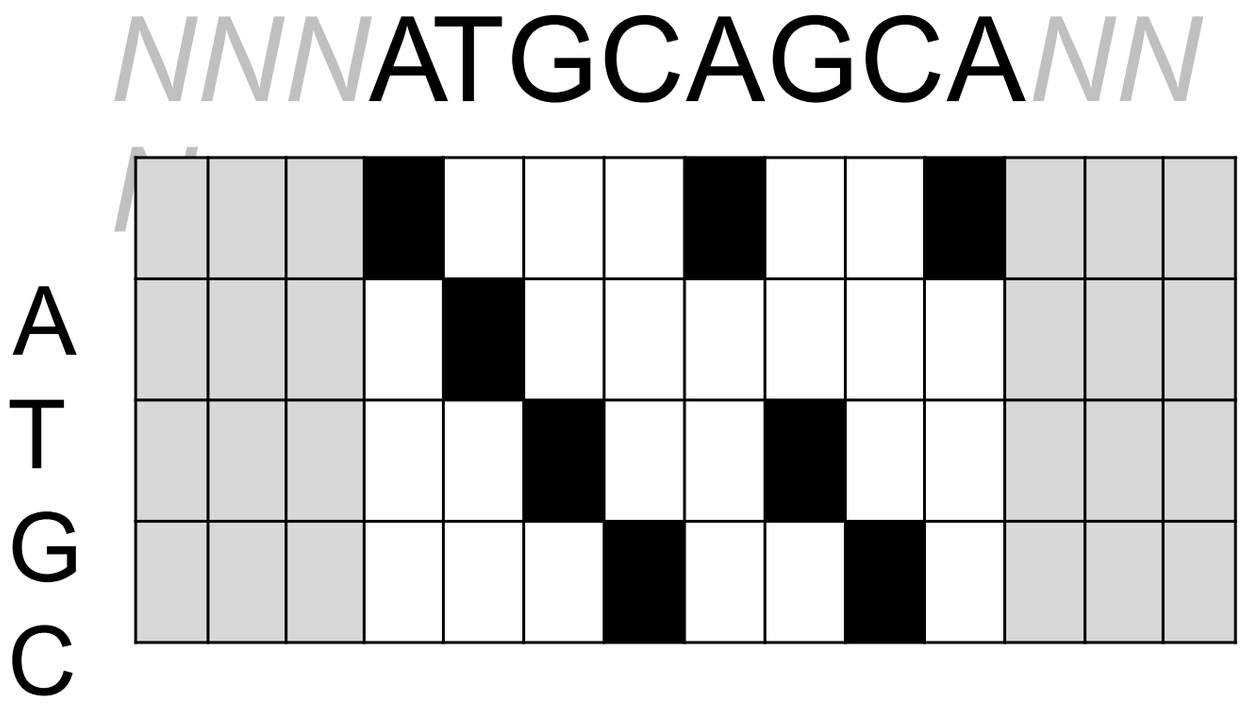
Conv Layer 1
Kernel width = 4
stride = 2*
num filters / num channels = 3
Total neurons = 15

***for genomics, a stride of 1 for conv layers is recommended**

3a. CNNs for Regulatory Genomics Foundations (Low-level features)

An example of using CNN to model DNA sequence

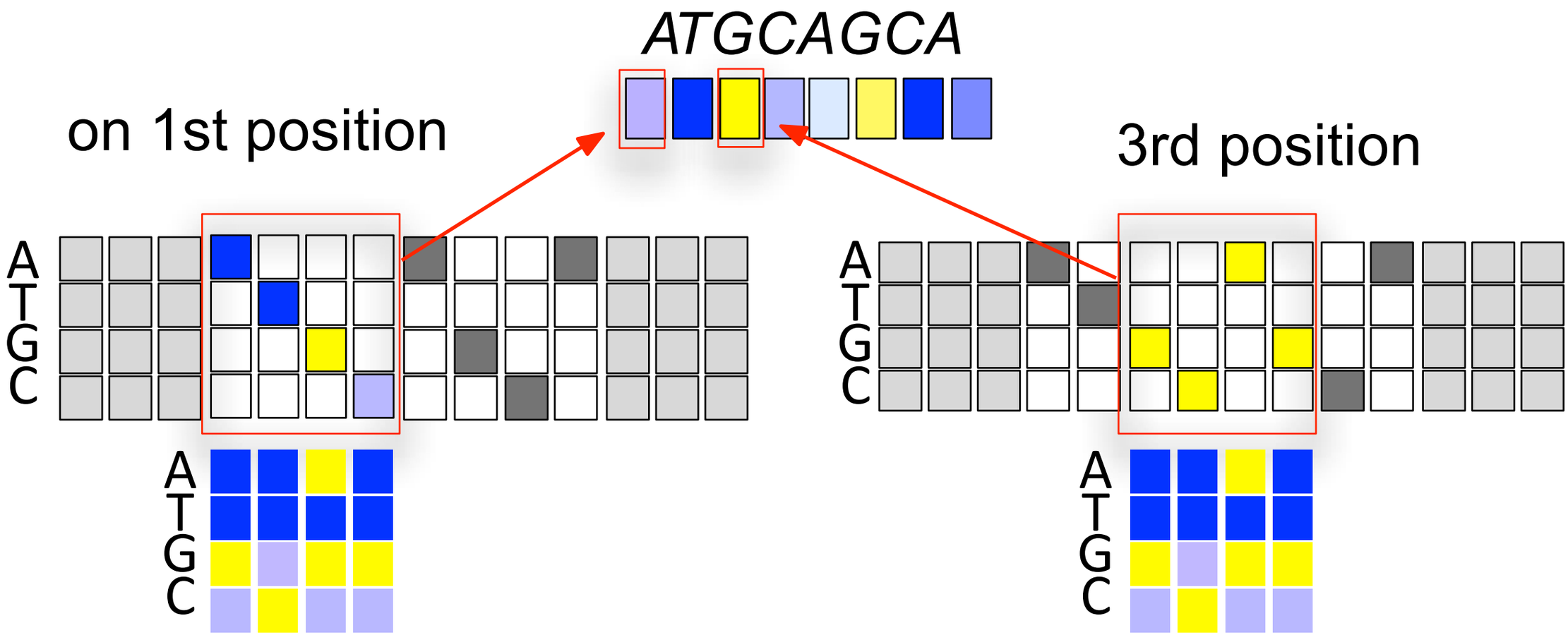
Representing DNA sequence as 2D matrix:



Matrix representation of DNA sequence
(darker = stronger)

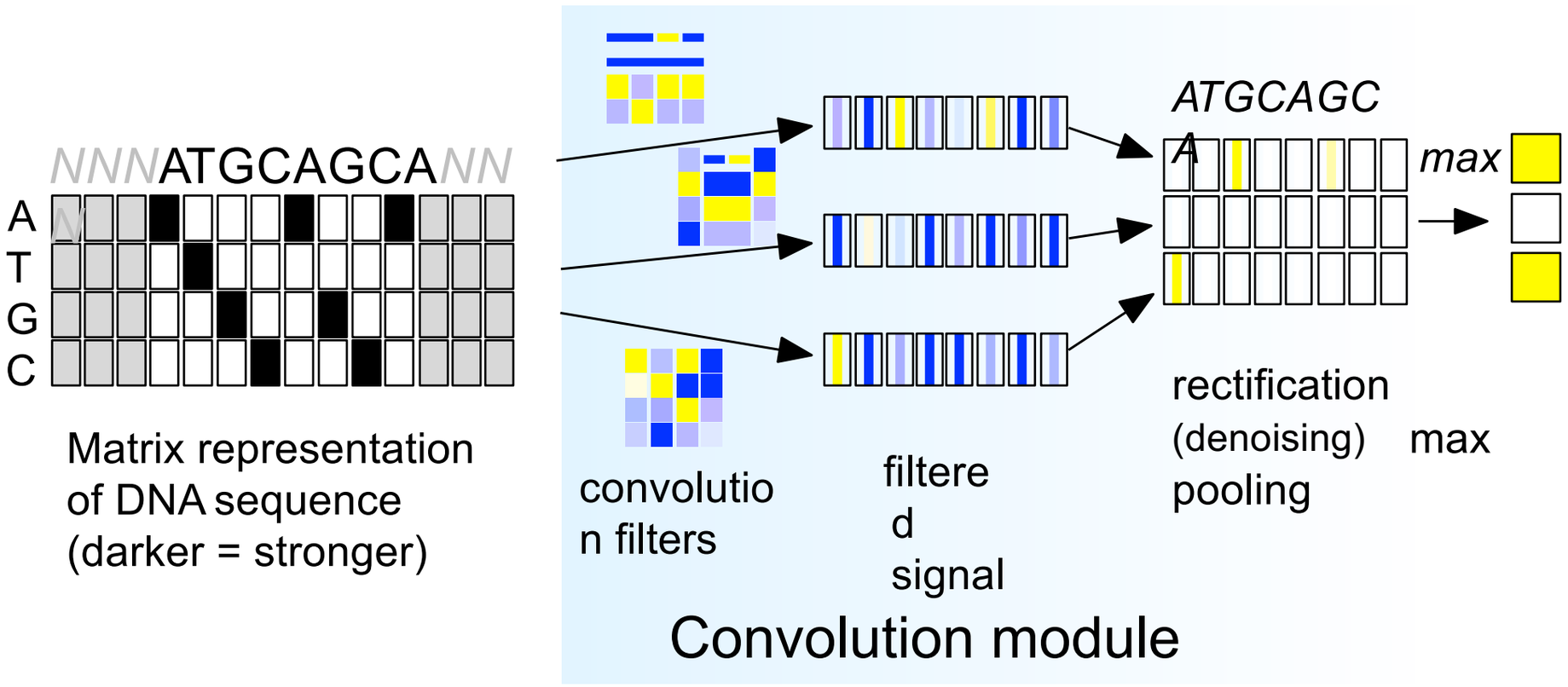
Convolution – extracting invariant feature

Applying 4 bp sequence filter along the DNA matrix:



Yellow = high activity; blue = low activity

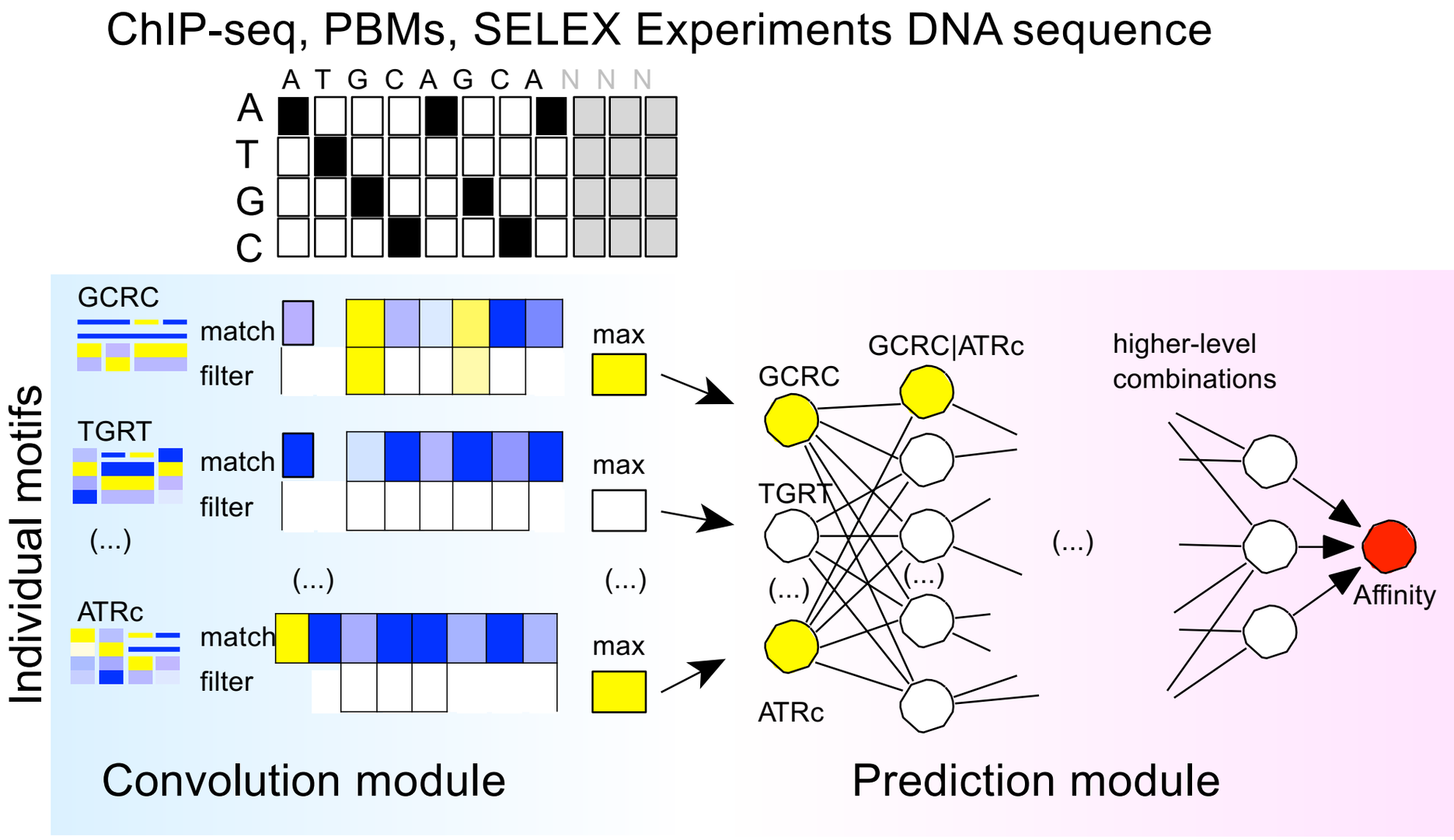
Convolution – extracting invariant feature



Rectification = ignore signals below some threshold.

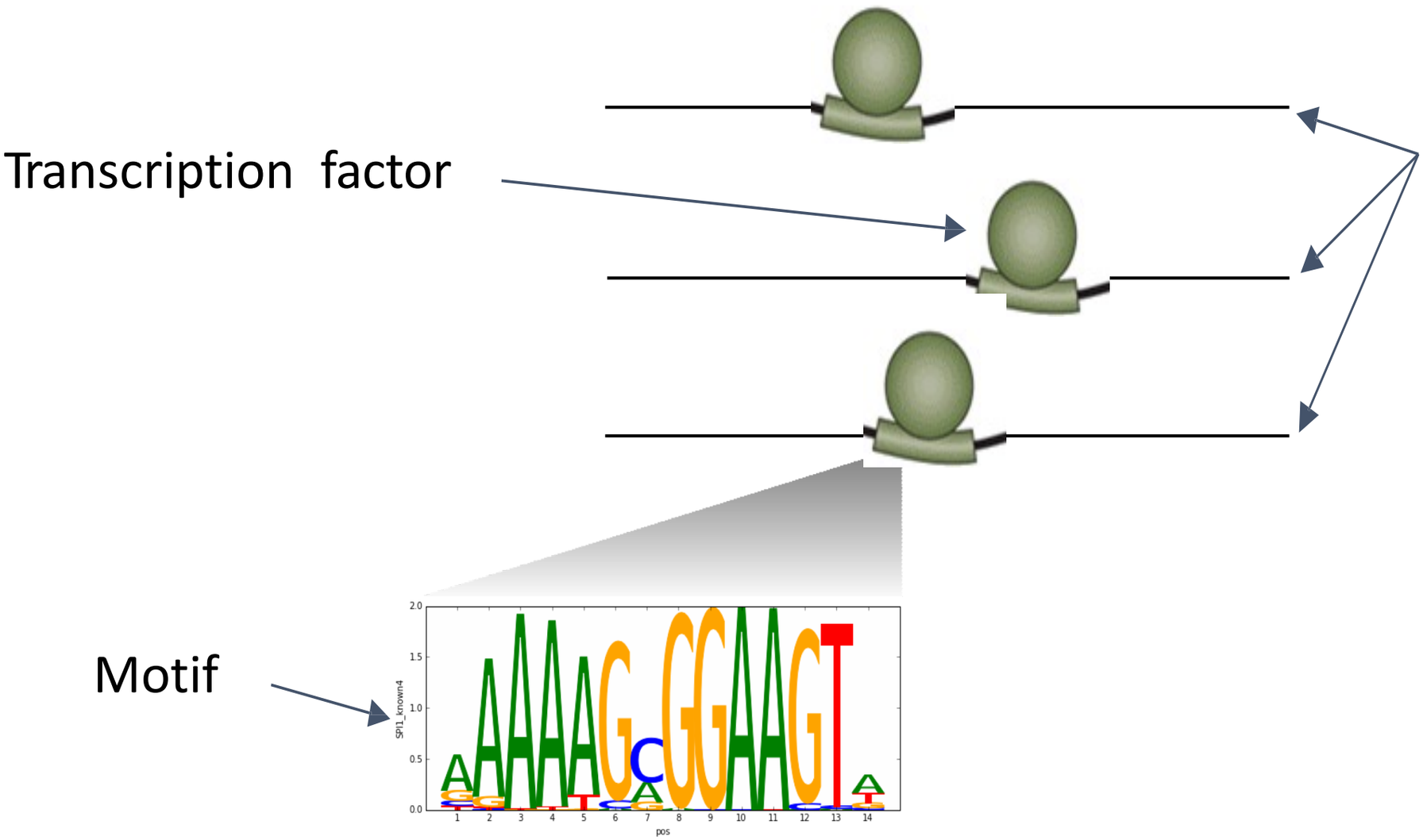
Pooling = summary of each channel by max or average.

Prediction using extracted features map



[Park and Kellis, 2015]

Key properties of regulatory sequence



TRANSCRIPTION FACTOR BINDING

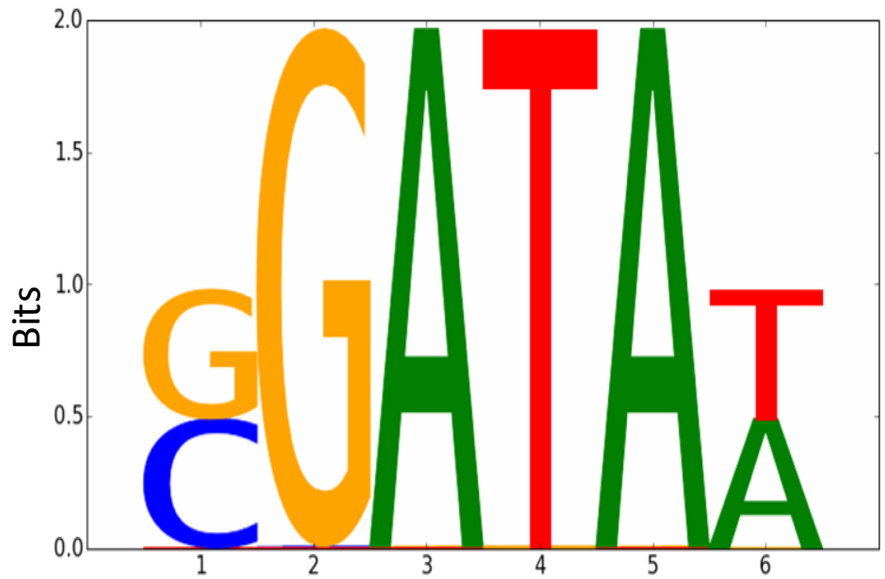
Regulatory proteins called **transcription factors (TFs)** bind to high affinity sequence patterns (**motifs**) in regulatory DNA

Sequence motifs: PWM

GGATAA
CGATAA
CGATAT
GGATAT

$$p_i(x_i = a_i)$$

A	0	0	1	0	1	0.5
C	0.5	0	0	0	0	0
G	0.5	1	0	0	0	0
T	0	0	0	1	0	0.5

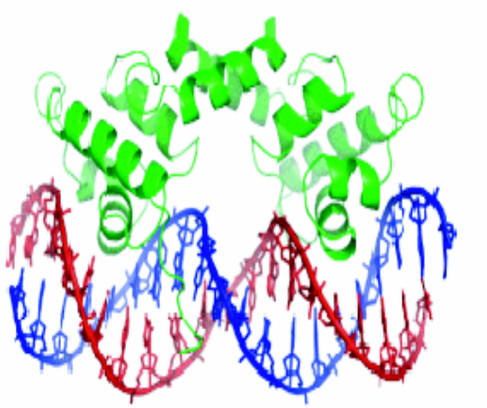


Set of aligned sequences Bound by TF

Position weight matrix (PWM)

PWM logo

https://en.wikipedia.org/wiki/Sequence_logo



The information content (y-axis) of position i is given by:[2]

$$R_i = \log_2(4) - (H_i + e_n)$$

where H_i is the uncertainty (sometimes called the Shannon entropy) of position i

$$H_i = -\sum f_{a,i} \times \log_2 f_{a,i}$$

. The height of letter a in column i is given by

$$\text{height} = f_{a,i} \times R_i$$

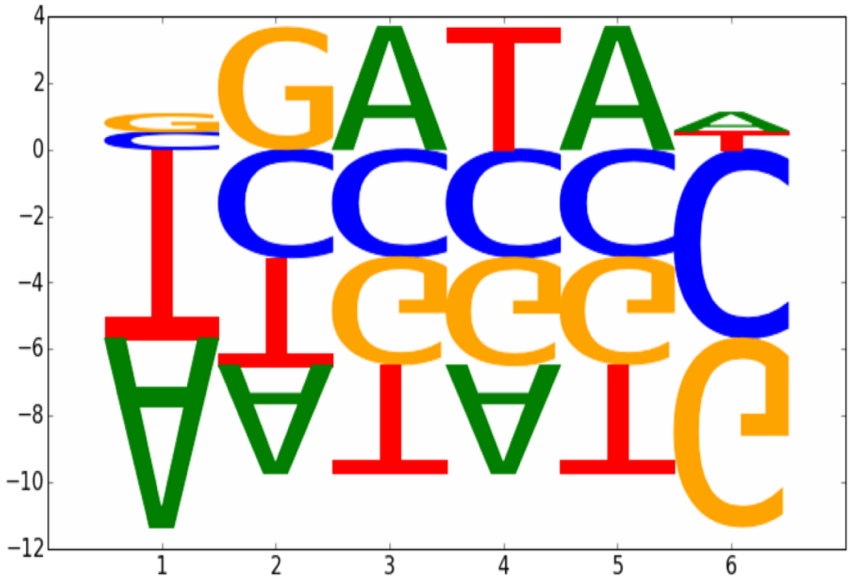
Sequence motifs: PSSM

Accounting for genomic background nucleotide distribution

Position-specific scoring matrix (PSSM)

$$\log_2\left(\frac{p_i(x_i = a_i)}{p_{bg}(x_i = a_i)}\right)$$

A	**-5.7**	**-3.2**	**3.7**	**-3.2**	**3.7**	**0.6**
C	**0.5**	**-3.2**	**-3.2**	**-3.2**	**-3.2**	**-5.7**
G	**0.5**	**3.7**	**-3.2**	**-3.2**	**-3.2**	**-5.7**
T	**-5.7**	**-3.2**	**-3.2**	**3.7**	**-3.2**	**0.5**



PSSM logo

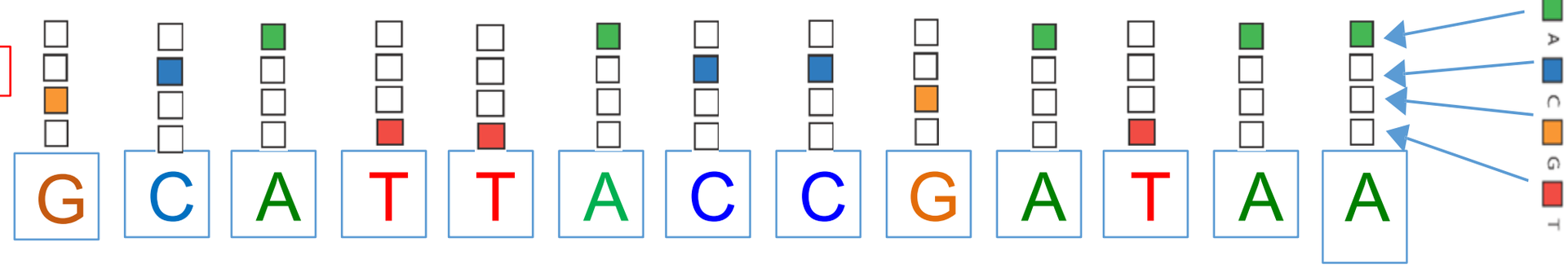
Scoring a sequence with a motif PSSM

PSSM parameters

Scoring weights **W**

A	**-5.7**	**-3.2**	**3.7**	**-3.2**	**3.7**	**0.6**
C	**0.5**	**-3.2**	**-3.2**	**-3.2**	**-3.2**	**-5.7**
G	**0.5**	**3.7**	**-3.2**	**-3.2**	**-3.2**	**-5.7**
T	**-5.7**	**-3.2**	**-3.2**	**3.7**	**-3.2**	**0.5**

One-hot encoding **(X)**



Convolution:
Scoring a sequence with a PSSM

Motif match Scores
sum(W * x)

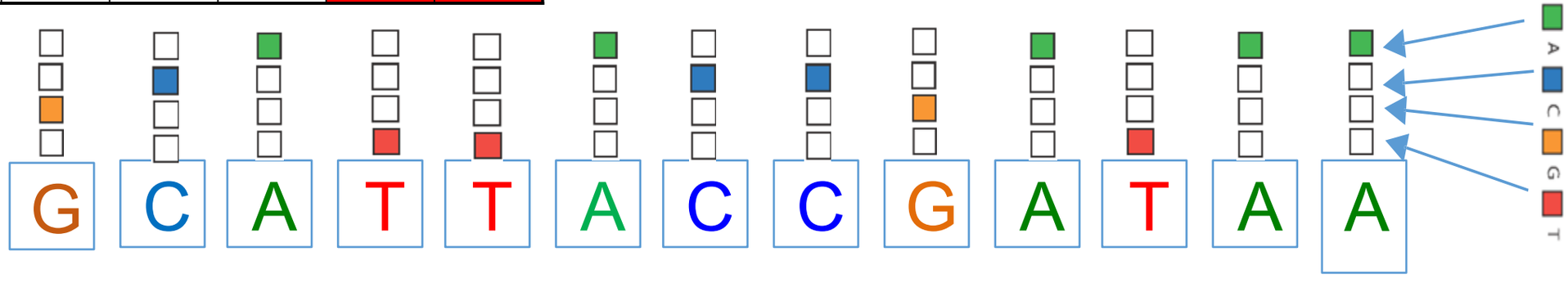
	-5.4										

Scoring weights W

A	**-5.7**	**-3.2**	**3.7**	**-3.2**	**3.7**	**0.6**
C	**0.5**	**-3.2**	**-3.2**	**-3.2**	**-3.2**	**-5.7**
G	**0.5**	**3.7**	**-3.2**	**-3.2**	**-3.2**	**-5.7**
T	**-5.7**	**-3.2**	**-3.2**	**3.7**	**-3.2**	**0.5**

One-hot encoding (X)

Input sequence



Convolution

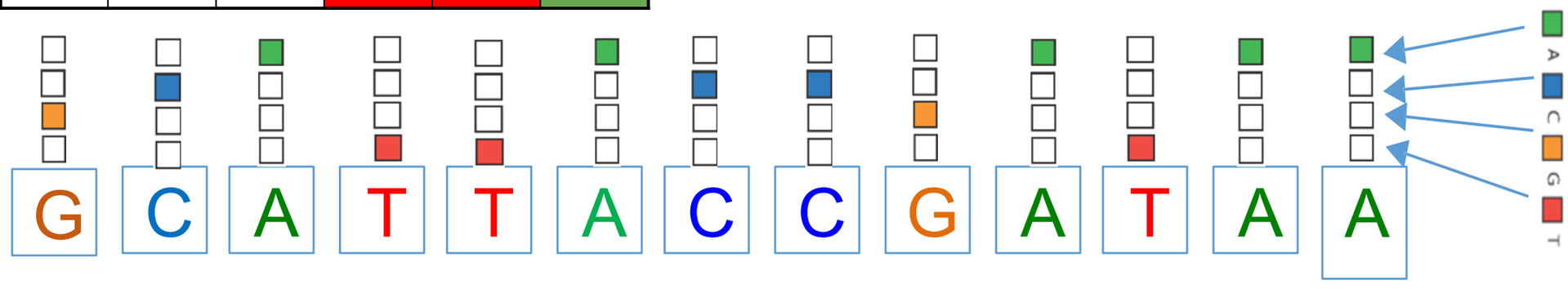
Motif match Scores
sum(W * x)

	-5.4	2.0										

Scoring weights W

A	**-5.7**	**-3.2**	**3.7**	**-3.2**	**3.7**	**0.6**
C	**0.5**	**-3.2**	**-3.2**	**-3.2**	**-3.2**	**-5.7**
G	**0.5**	**3.7**	**-3.2**	**-3.2**	**-3.2**	**-5.7**
T	**-5.7**	**-3.2**	**-3.2**	**3.7**	**-3.2**	**0.5**

One-hot encoding (X)



Input sequence

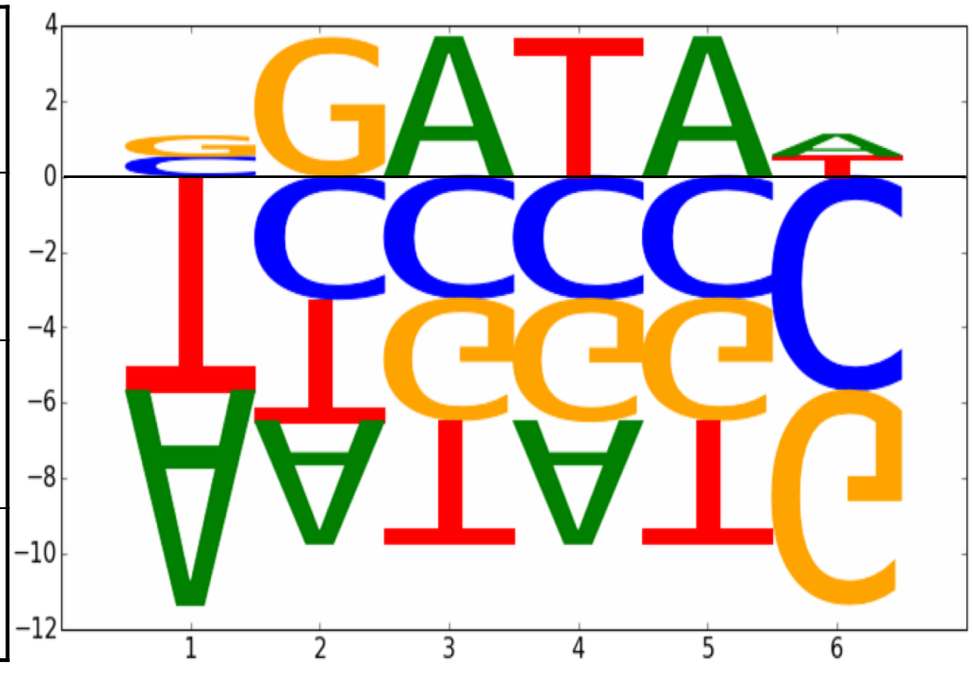
Convolution

Motif match Scores
sum(W * x)

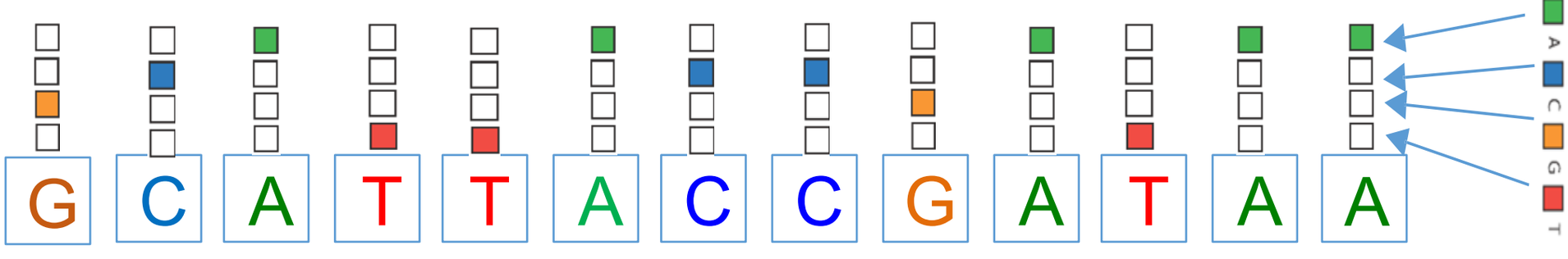
-2.2	-5.4	2.0	-4.3	-24	-17	-18	-11	-12	16	-5.5	-8.5	-5.2

Scoring weights W

A	**-5.7**	**-3.2**	**3.7**	**-3.2**	**3.7**	**0.6**
C	**0.5**	**-3.2**	**-3.2**	**-3.2**	**-3.2**	**-5.7**
G	**0.5**	**3.7**	**-3.2**	**-3.2**	**-3.2**	**-5.7**
T	**-5.7**	**-3.2**	**-3.2**	**3.7**	**-3.2**	**0.5**



One-hot encoding (X)



Input sequence

G C A T T A C C G A T A A

Thresholding scores

Thresholded Motif Scores
max(0, W*x)

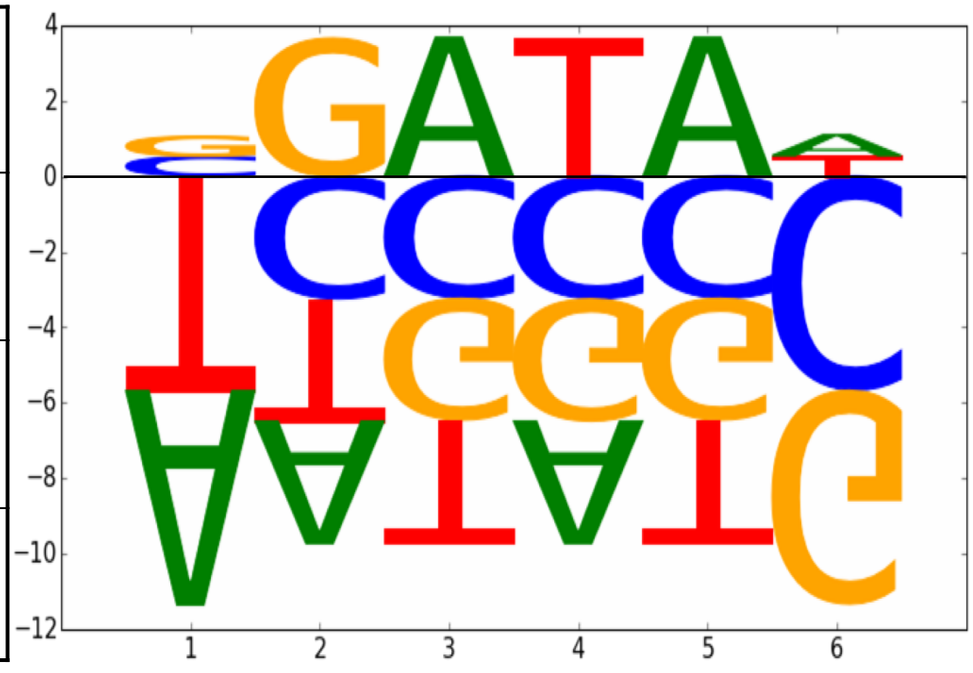
0	0	2.0	0	0	0	0	0	0	16	0	0	0

Motif match Scores W*x

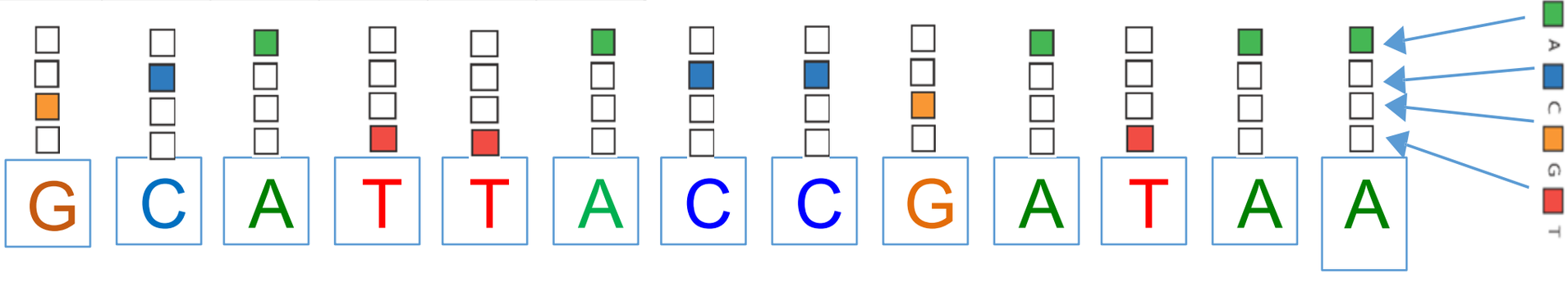
-2.2	-5.4	2.0	-4.3	-24	-17	-18	-11	-12	16	-5.5	-8.5	-5.2

Scoring weights W

A	**-5.7**	**-3.2**	**3.7**	**-3.2**	**3.7**	**0.6**
C	**0.5**	**-3.2**	**-3.2**	**-3.2**	**-3.2**	**-5.7**
G	**0.5**	**3.7**	**-3.2**	**-3.2**	**-3.2**	**-5.7**
T	**-5.7**	**-3.2**	**-3.2**	**3.7**	**-3.2**	**0.5**



One-hot encoding (X)



Input sequence

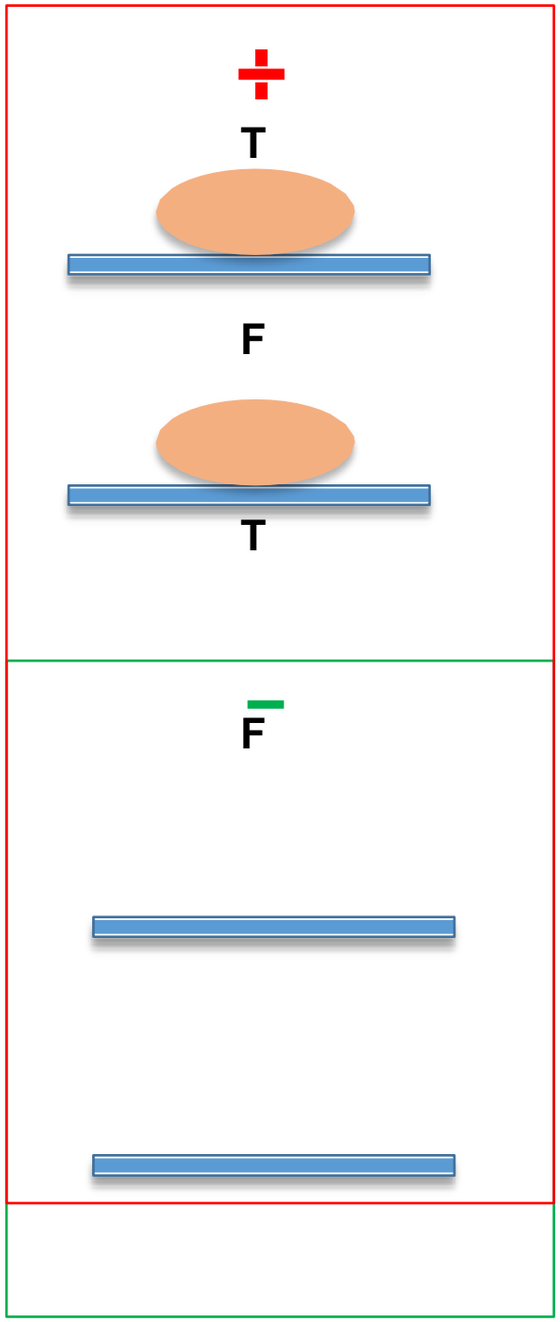
3b. CNNs for Regulatory Genomics Foundations (Higher-level learning)

Learning patterns in regulatory DNA sequence

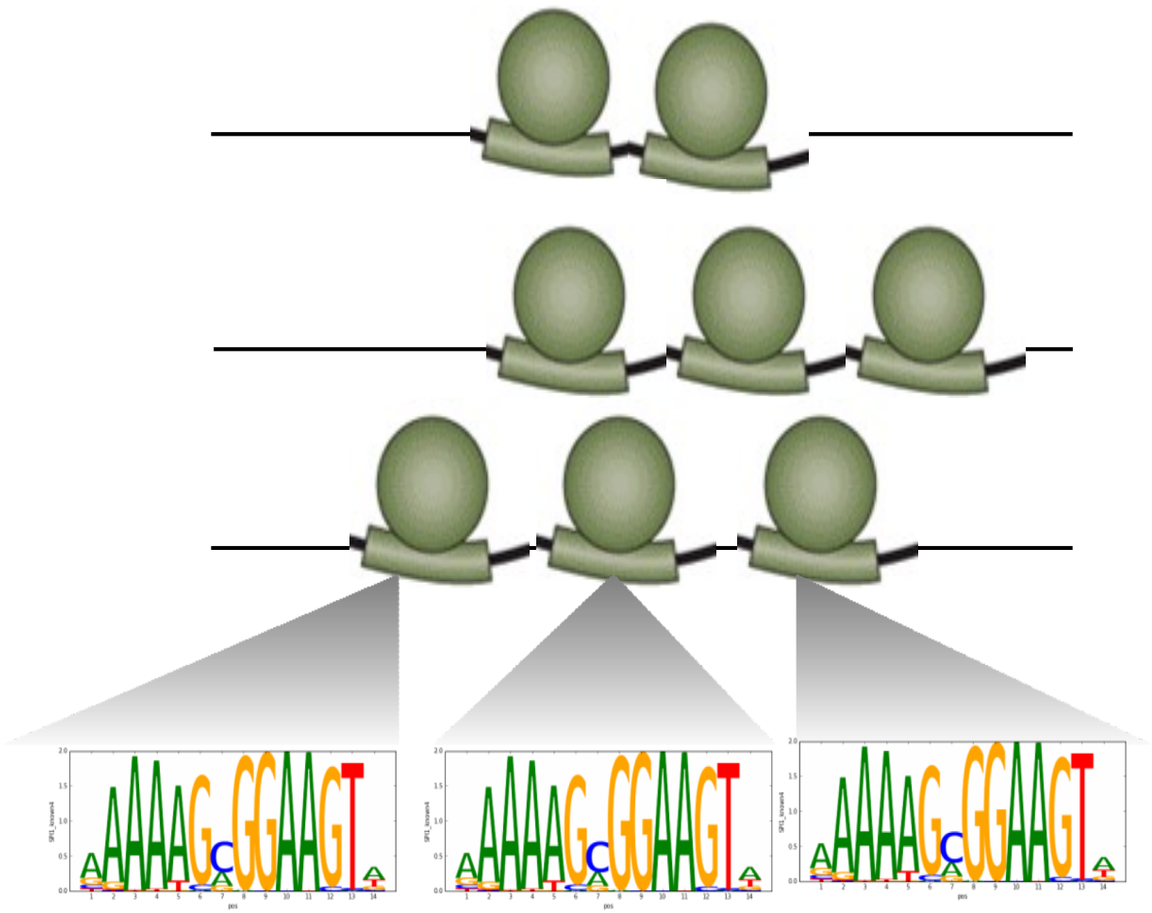
- Positive class of genomic sequences bound a transcription factor of interest

Can we learn patterns in the DNA sequence that distinguish these 2 classes of genomic sequences?

- Negative class of genomic sequences not bound by a transcription factor of interest



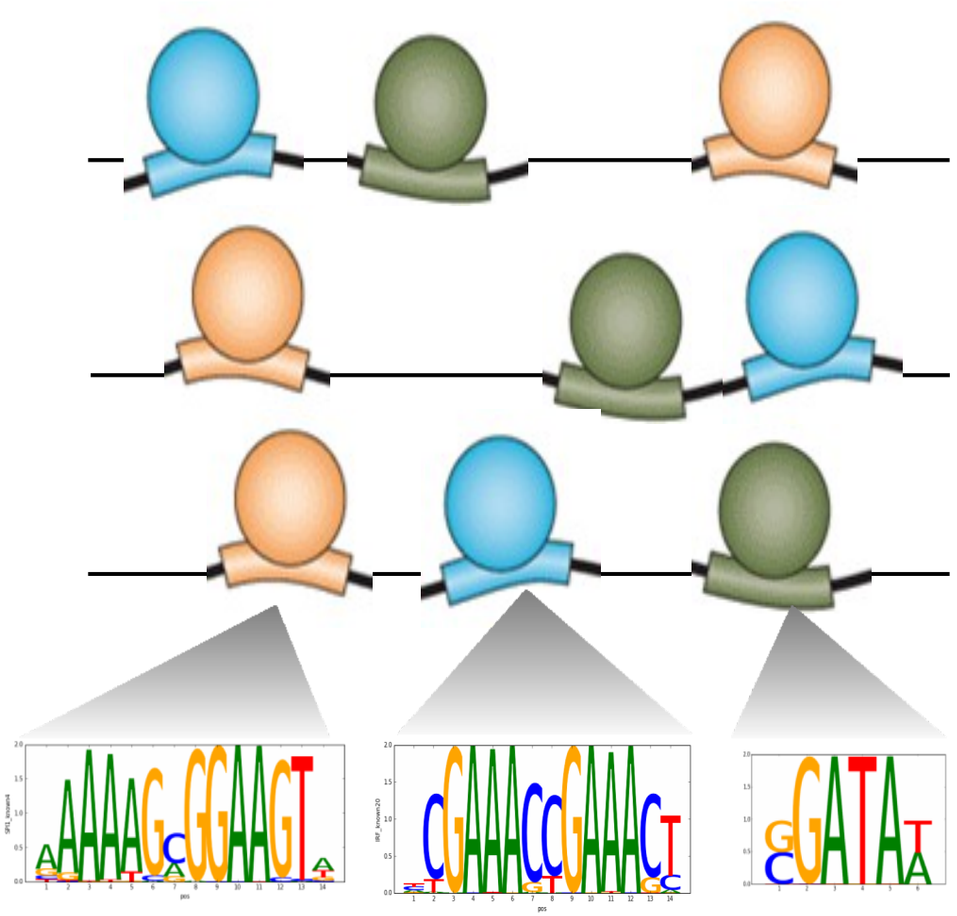
Key properties of regulatory sequence



HOMOTYPIC MOTIF DENSITY

Regulatory sequences often contain **more than one binding instance** of a TF resulting in **homotypic clusters of motifs of the same TF**

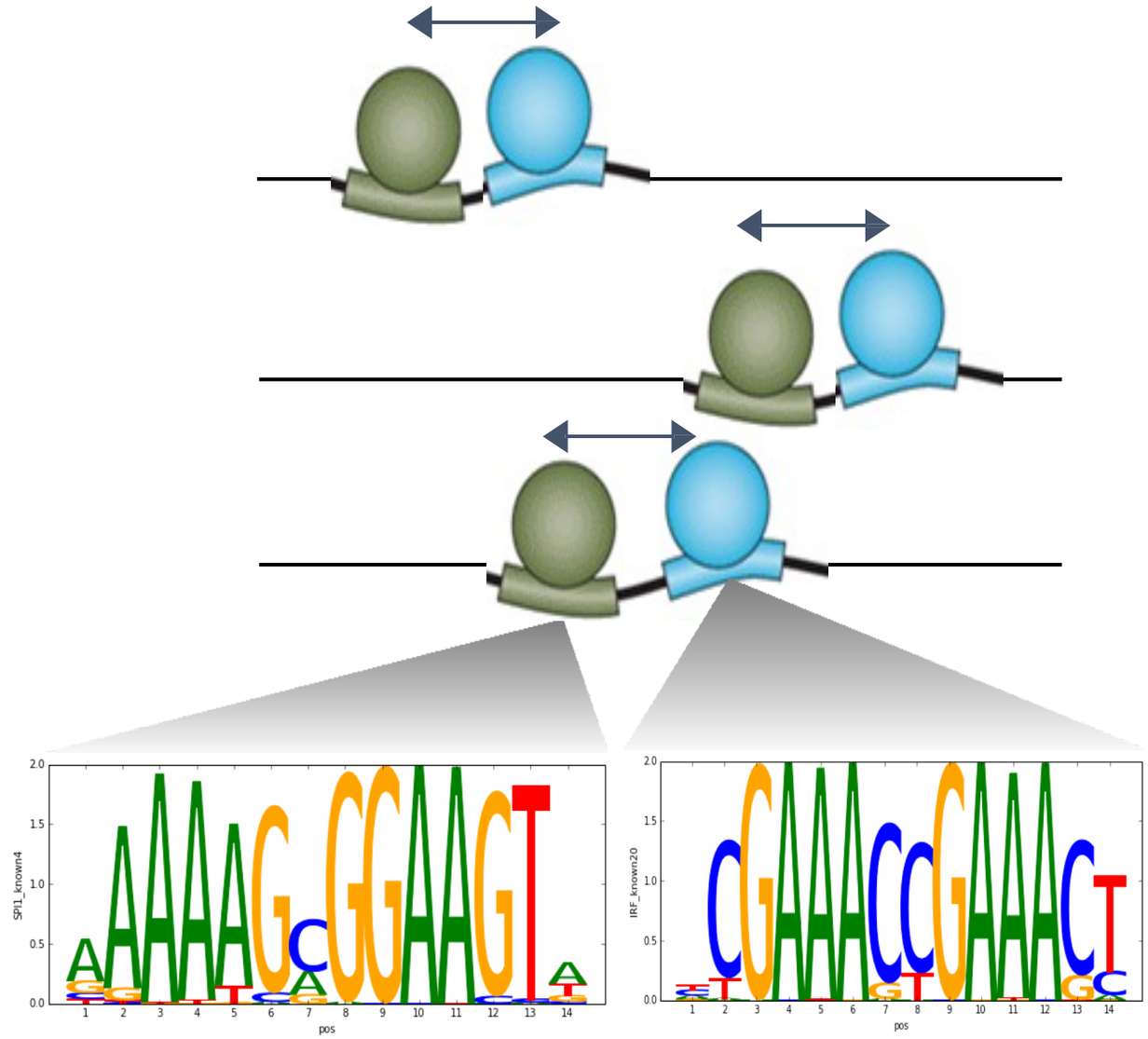
Key properties of regulatory sequence



HETEROTYPIC MOTIF COMBINATIONS

Regulatory sequences often bound by **combinations of TFs** resulting in **heterotypic clusters of motifs of different TFs**

Key properties of regulatory sequence



SPATIAL GRAMMARS OF HETEROTYPIC MOTIF COMBINATIONS

Regulatory sequences are often bound by **combinations of TFs** with specific **spatial and positional constraints** resulting in distinct **motif grammars**

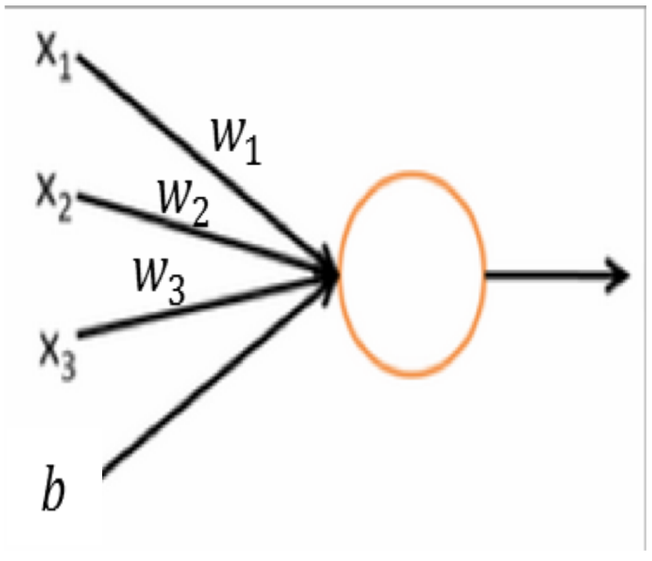
A simple classifier (An artificial neuron)

$$Y = F(x_1, x_2, x_3)$$

parameters

$$Z = w_1.x_1 + w_2.x_2 + w_3.x_3 + b$$

Linear function



Z

Training the neuron means learning the optimal w's and b

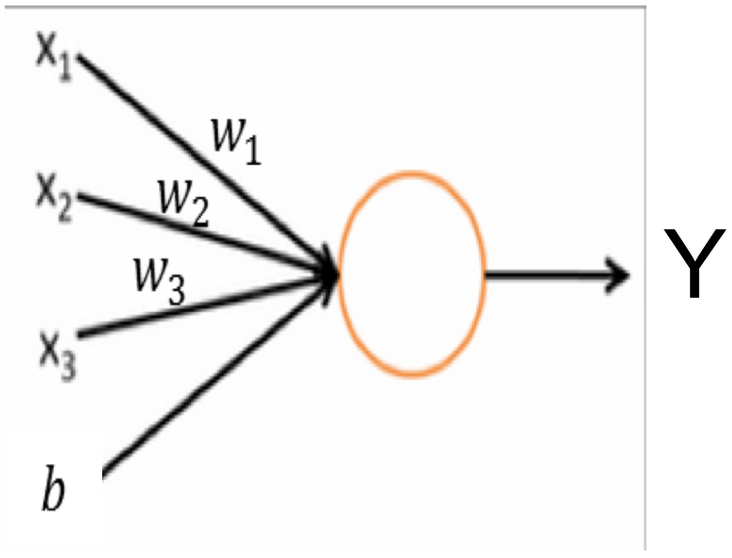
A simple classifier (An artificial neuron)

$$Y = F(x_1, x_2, x_3)$$

parameters

$$Z = w_1.x_1 + w_2.x_2 + w_3.x_3 + b$$

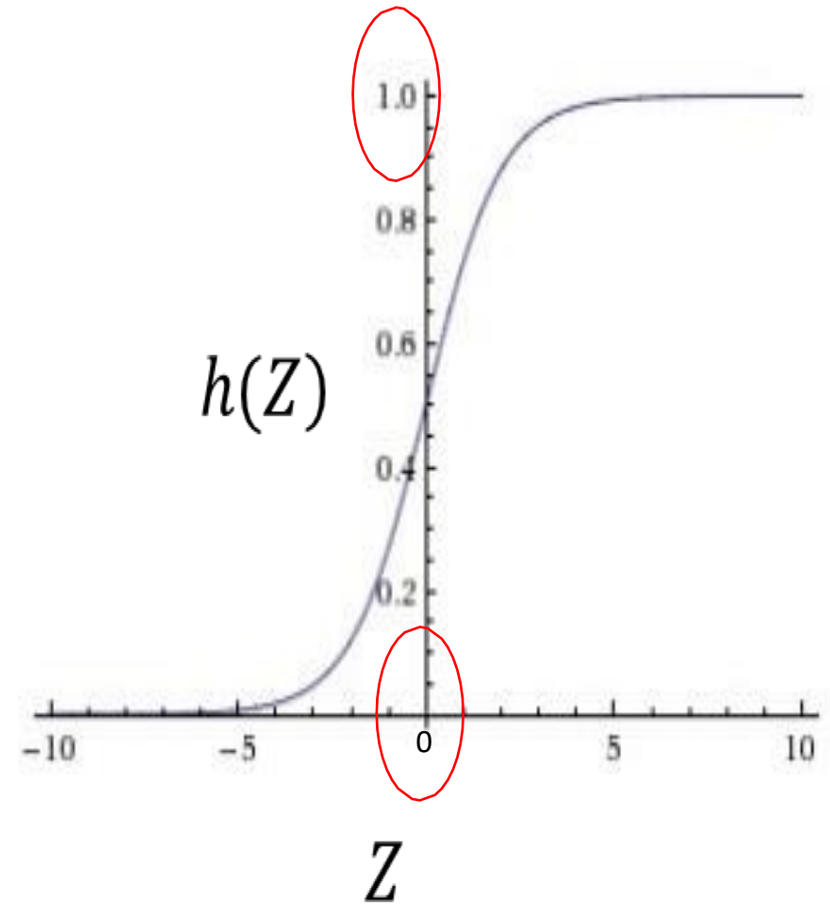
$$Y = h(Z)$$



Logistic / Sigmoid

Useful for predicting probabilitie

Non-linear function



Training the neuron means learning the optimal w's and b

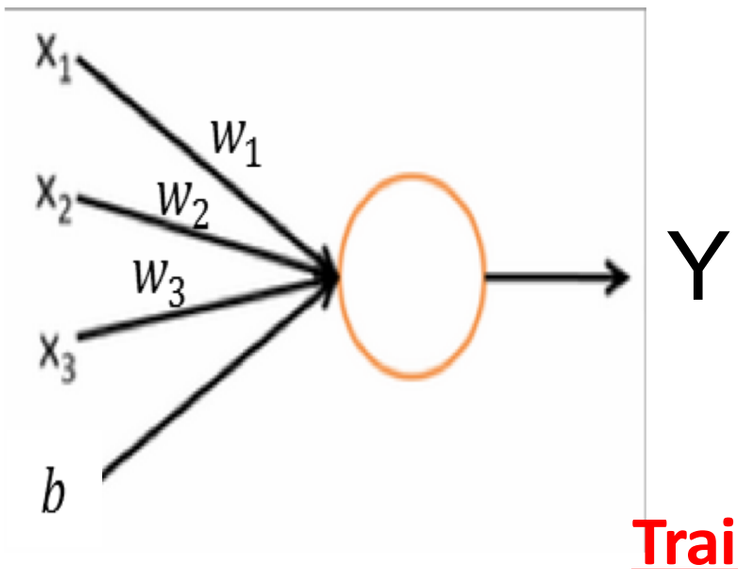
A simple classifier (An artificial neuron)

$$Y = F(x_1, x_2, x_3)$$

parameters

$$Z = w_1.x_1 + w_2.x_2 + w_3.x_3 + b$$

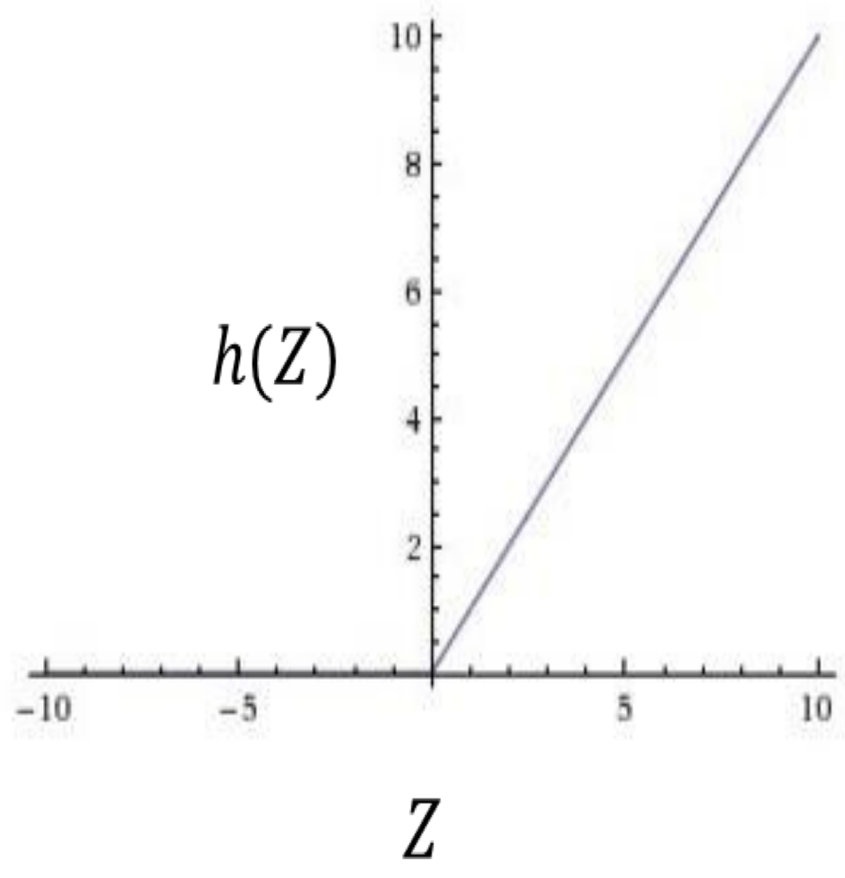
$$Y = h(Z)$$



ReLu (Rectified Linear Unit)

Useful for thresholding

Non-linear function



Training the neuron means learning the optimal w's and b

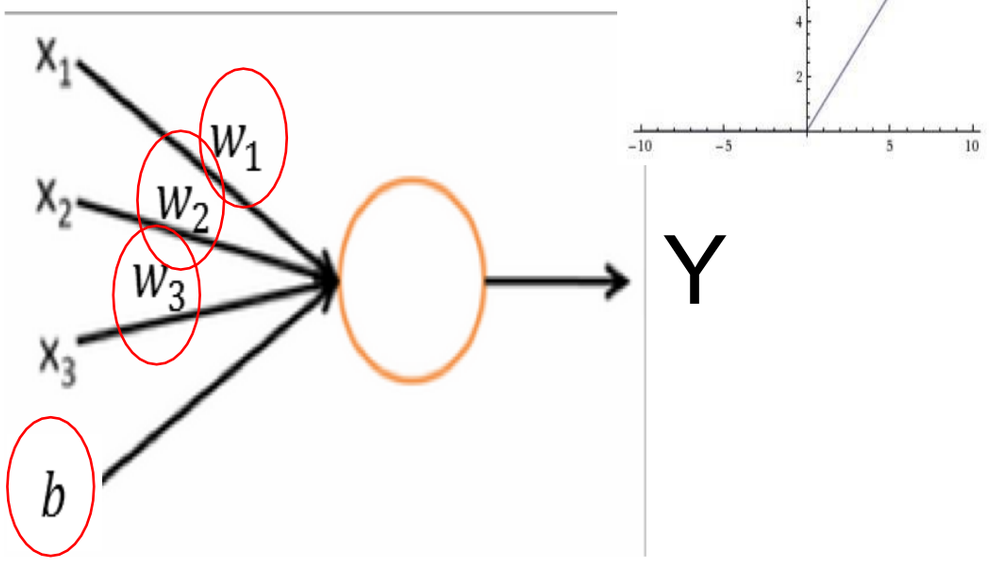
Artificial neuron can represent a motif

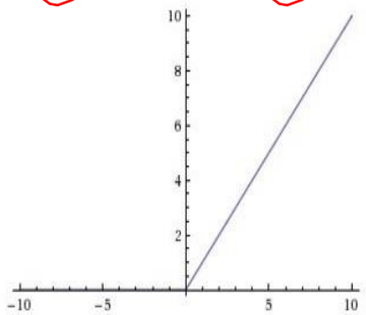
$$Y = F(x_1, x_2, x_3)$$

parameters

$$Z = w_1.x_1 + w_2.x_2 + w_3.x_3 + b$$

$$Y = h(Z)$$





Thresholded Motif Scores max(0, W*x)	0	0	2.0	0	0	0
Motif match Scores sum(W * x)	-2.2	-5.5	2.0	-4.3	-24	-17

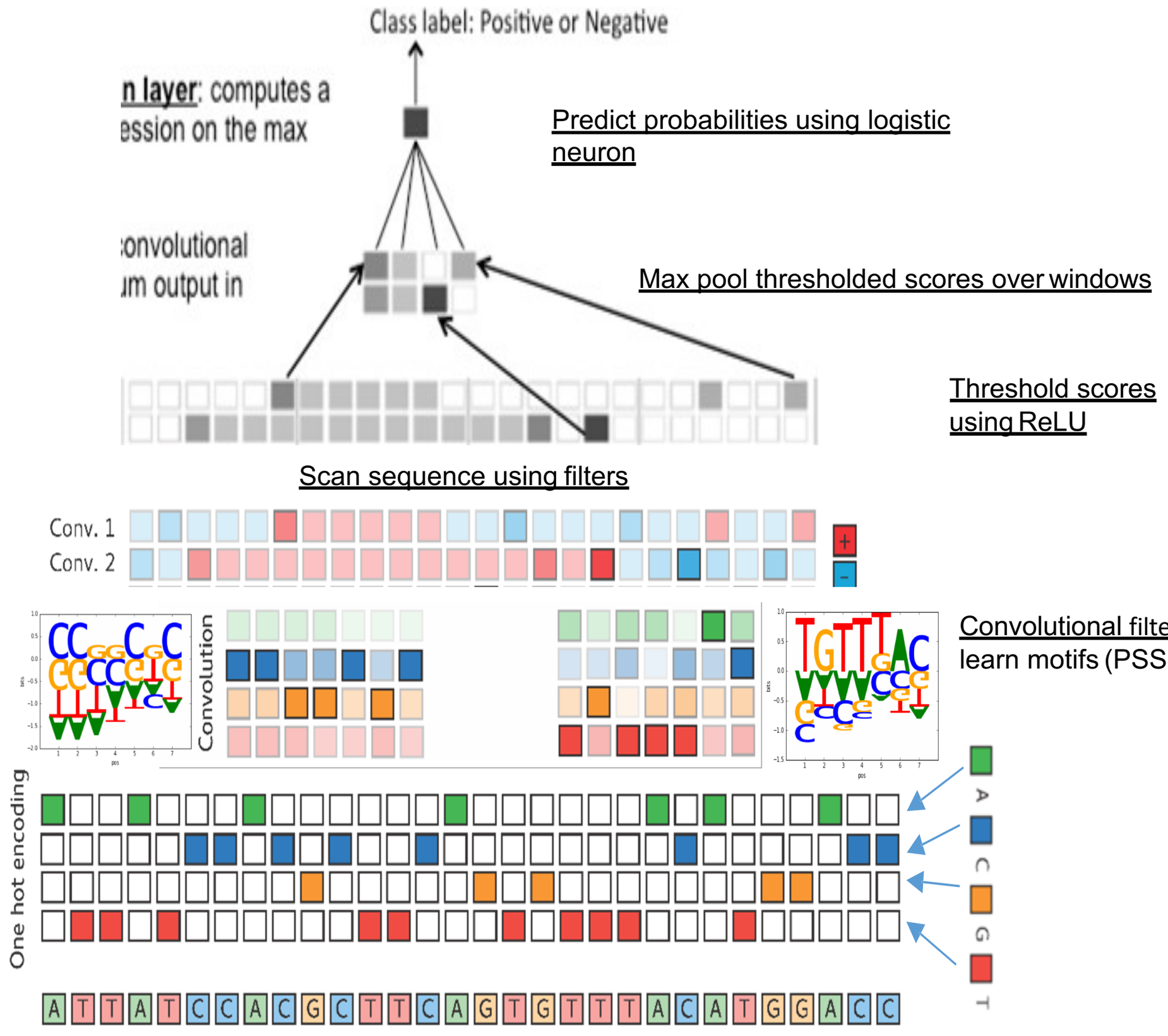
Scoring weights W

A	-5.7	-3.2	3.7	-3.2	3.7	0.6
C	0.5	-3.2	-3.2	-3.2	-3.2	-5.7
G	0.5	3.7	-3.2	-3.2	-3.2	-5.7
T	-5.7	-3.2	-3.2	3.7	-3.2	0.5

One-hot encoding (X)

Input sequence G C A T T A

Biological motivation of Deep CNN



Deep convolutional neural network

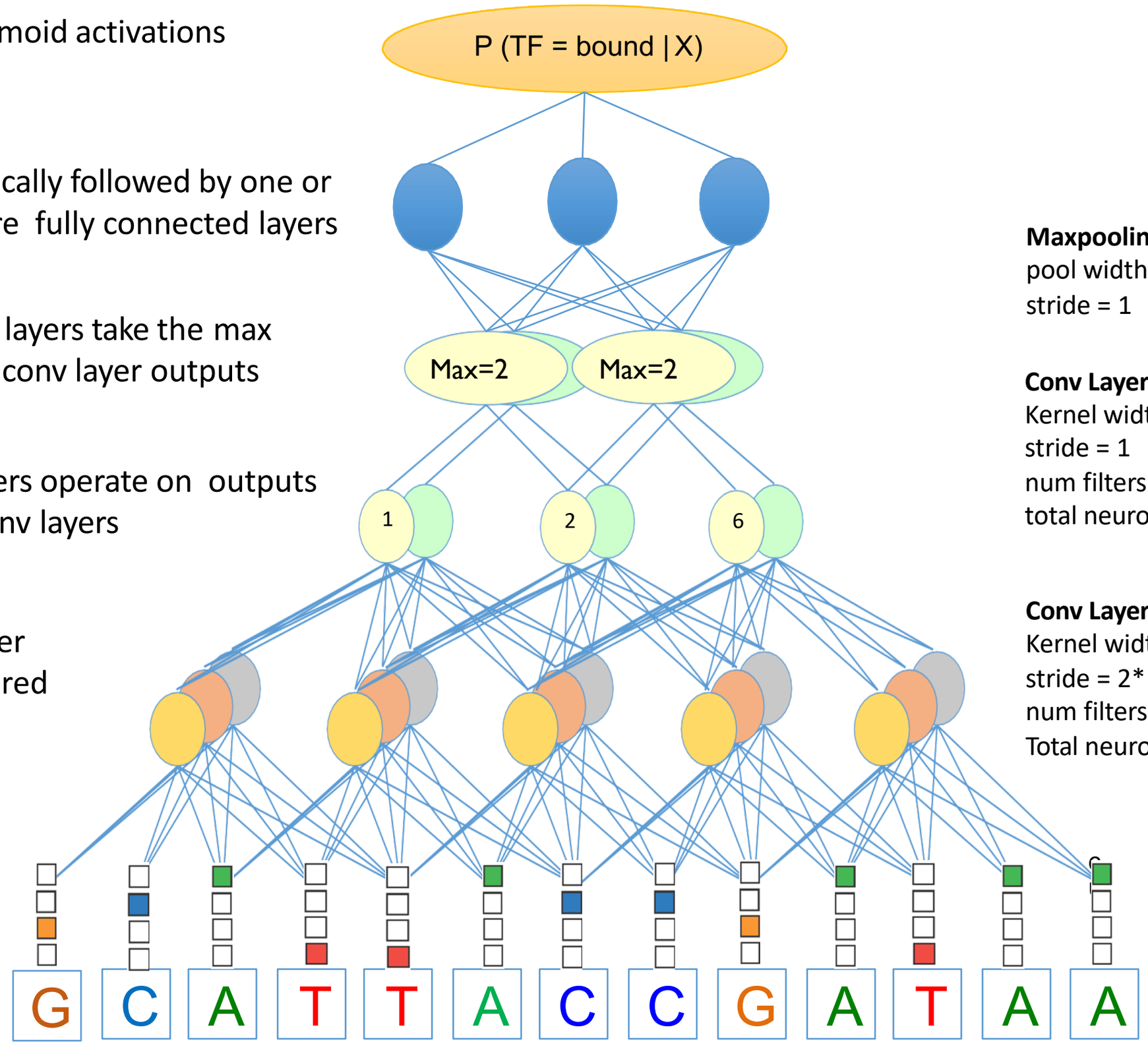
Sigmoid activations

Typically followed by one or more fully connected layers

Maxpooling layers take the max over sets of conv layer outputs

Later conv layers operate on outputs of previous conv layers

Convolutional layer (same color = shared weights)



Maxpooling layer
pool width = 2
stride = 1

Conv Layer 2
Kernel width = 3
stride = 1
num filters / num channels = 2
total neurons = 6

Conv Layer 1
Kernel width = 4
stride = 2*
num filters / num channels = 3
Total neurons = 15

***for genomics, a stride of 1 for conv layers is recommended**

Multi-task CNN

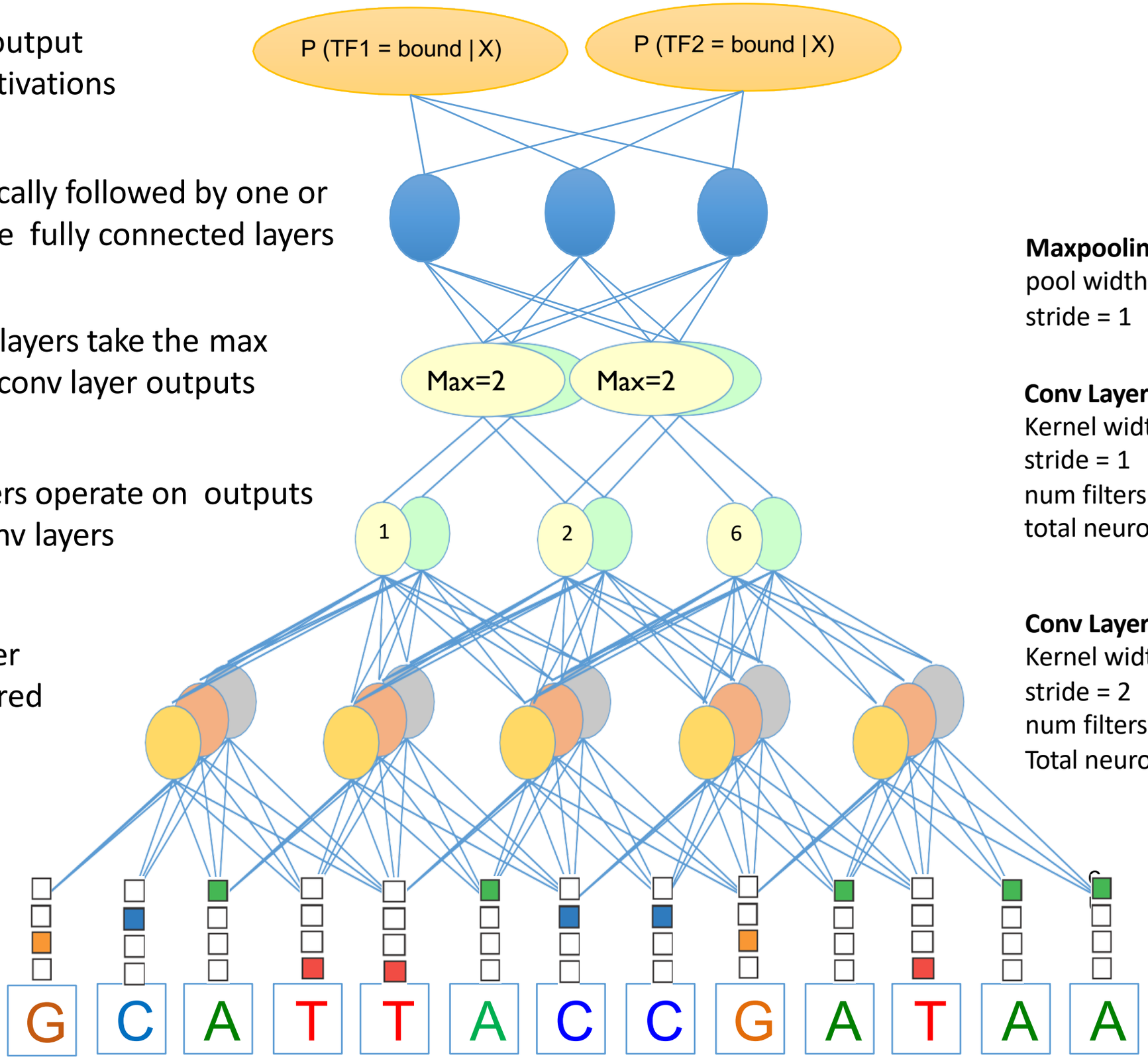
Multi-task output (sigmoid activations here)

Typically followed by one or more fully connected layers

Maxpooling layers take the max over sets of conv layer outputs

Later conv layers operate on outputs of previous conv layers

Convolutional layer (same color = shared weights)



Maxpooling layer
pool width = 2
stride = 1

Conv Layer 2
Kernel width = 3
stride = 1
num filters / num channels = 2
total neurons = 6

Conv Layer 1
Kernel width = 4
stride = 2
num filters / num channels = 3
Total neurons = 15

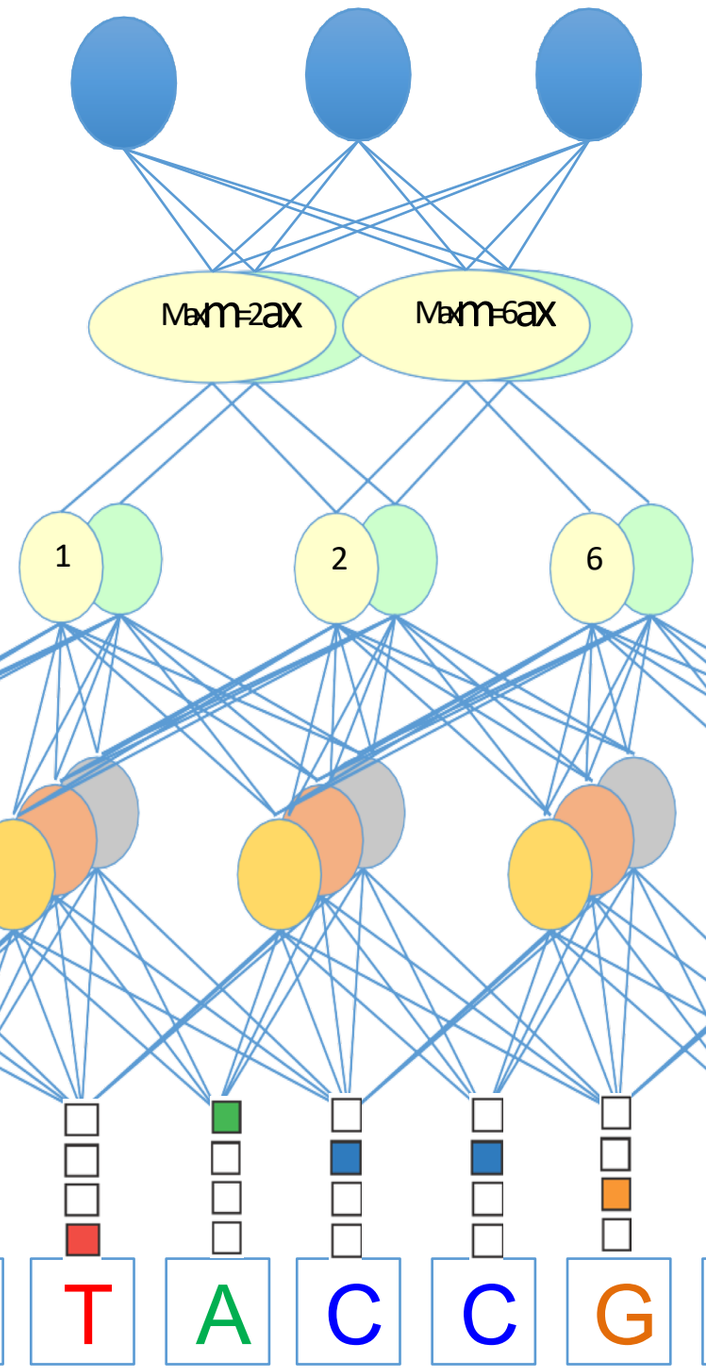
Multi-task CNN

Typically followed by one or more fully connected layers

Maxpooling layers take the max
over sets of conv layer outputs

Later conv layers operate on outputs of previous conv layers

Convolutional layer (same color = shared weights)



Maxpooling layer pool width = 2 stride = 1

Conv Layer 2 Kernel width = 3 stride = 1 num filters / num channels = 2 total neurons = 6

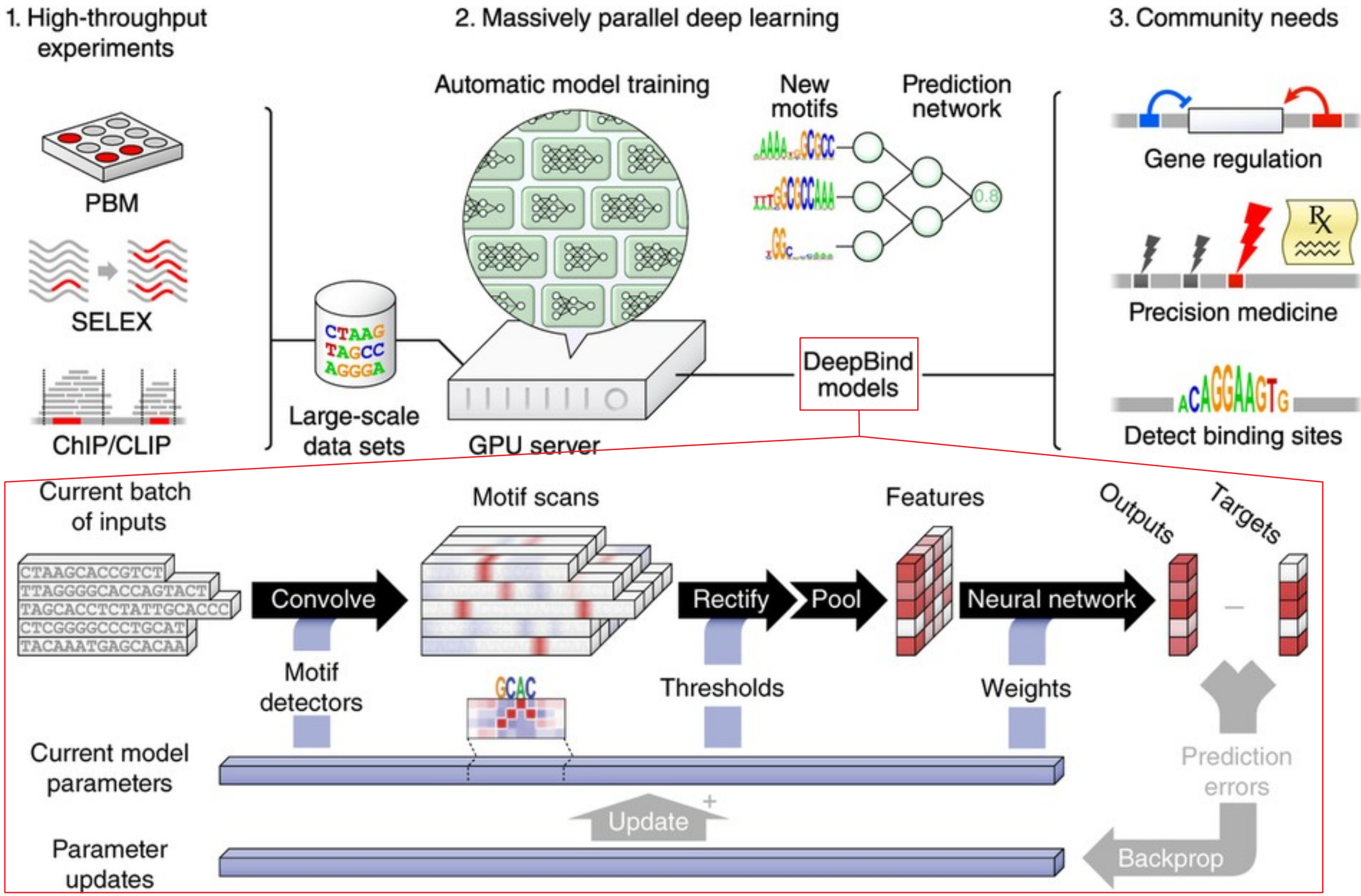
Conv Layer 1 Kernel width = 4 stride = 2* num filters / num channels = 3 Total neurons = 15

Deep Learning for Regulatory Genomics

1. **Biological foundations: Building blocks of Gene Regulation**
   - Gene regulation: Cell diversity, Epigenomics, Regulators (TFs), Motifs, Disease role
   - Probing gene regulation: TFs/histones: ChIP-seq, Accessibility: DNase/ATAC-seq
   - Three-dimensional chromatin structure, Hi-C, ChIA-PET, TADs, Loop Extrusion
2. **Classical methods for Regulatory Genomics and Motif Discovery**
   - Enrichment-based motif discovery: Expectation Maximization, Gibbs Sampling
   - Experimental: PBMs, SELEX. Comparative genomics: Evolutionary conservation.
3. **Regulatory Genomics CNNs (Convolutional Neural Networks): Foundations**
   - Key idea: pixels ⇔ DNA letters. Patches/filters ⇔ Motifs. Higher ⇔ combinations
   - Learning convolutional filters ⇔ Motif discovery. Applying them ⇔ Motif matches
4. **Regulatory Genomics CNNs/RNNs in Practice: Diverse Architectures**
   - DeepBind: Learn motifs, use in (shallow) fully-connected layer, mutation impact
   - DeepSea: Train model directly on mutational impact prediction
   - Basset: Multi-task DNase prediction in 164 cell types, reuse/learn motifs
   - ChromPuter: Multi-task prediction of different TFs, reuse partner motifs
   - DeepLIFT: Model interpretation based on neuron activation properties
   - DanQ: Recurrent Neural Network for sequential data analysis
5. **Guest Lecture: David Kelley on Basset and Deep Learning for Hi-C looping**

4. Regulatory Genomics CNNs in Practice:
(a) DeepBind

DeepBind



[Alipanahi et al., 2015]

NATURE BIOTECHNOLOGY | COMPUTATIONAL BIOLOGY | ANALYSIS

日本語要約

Predicting the sequence specificities of DNA- and RNA-binding proteins by deep learning

Babak Alipanahi, Andrew Delong, Matthew T Weirauch & Brendan J Frey

Affiliations | **Contributions** | **Corresponding author**

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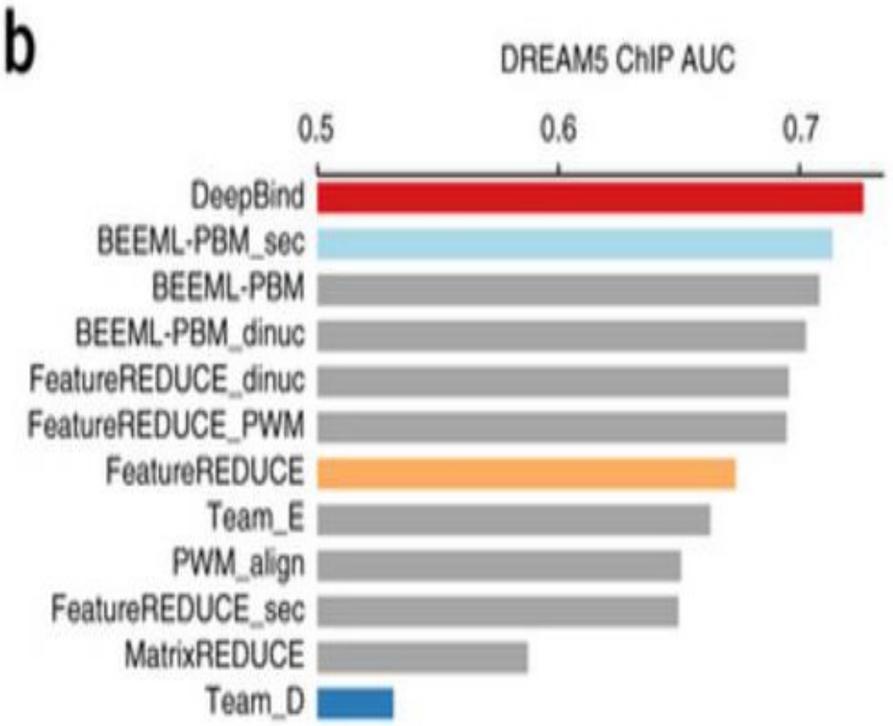
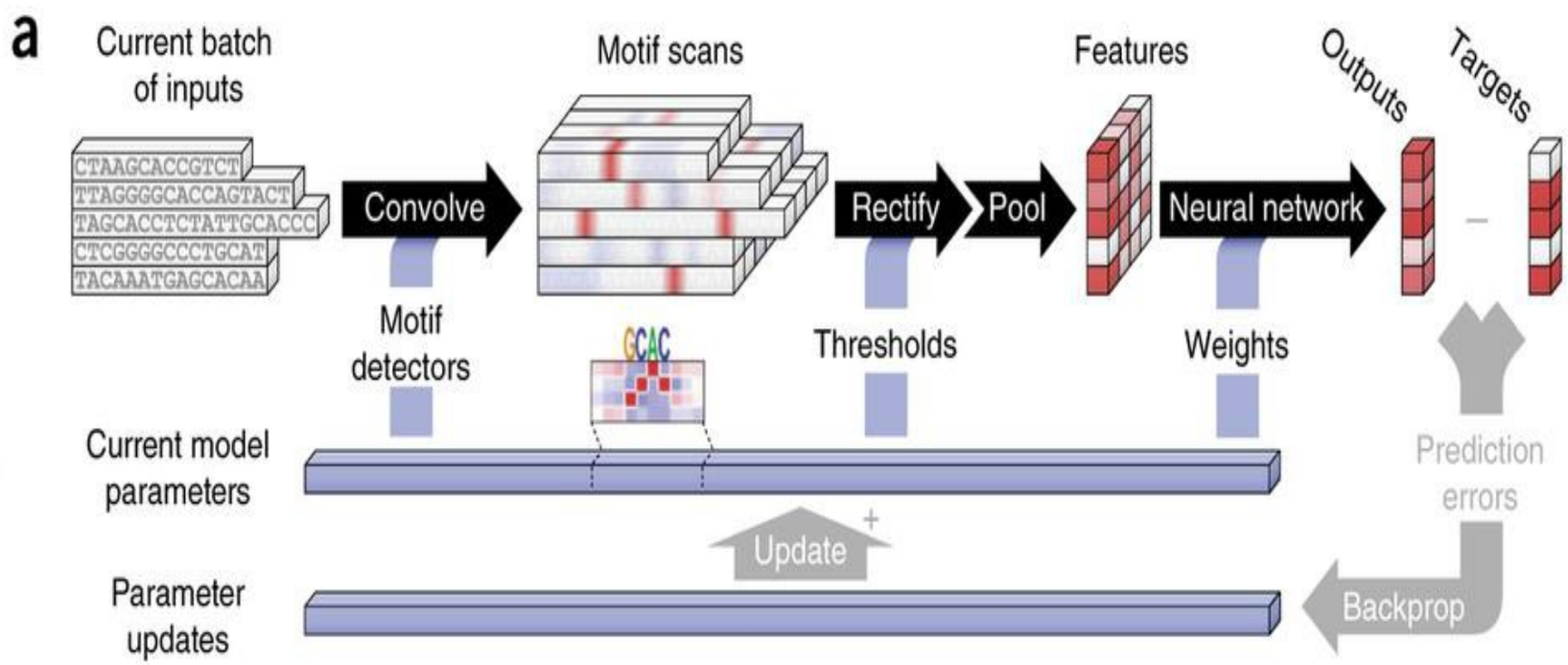
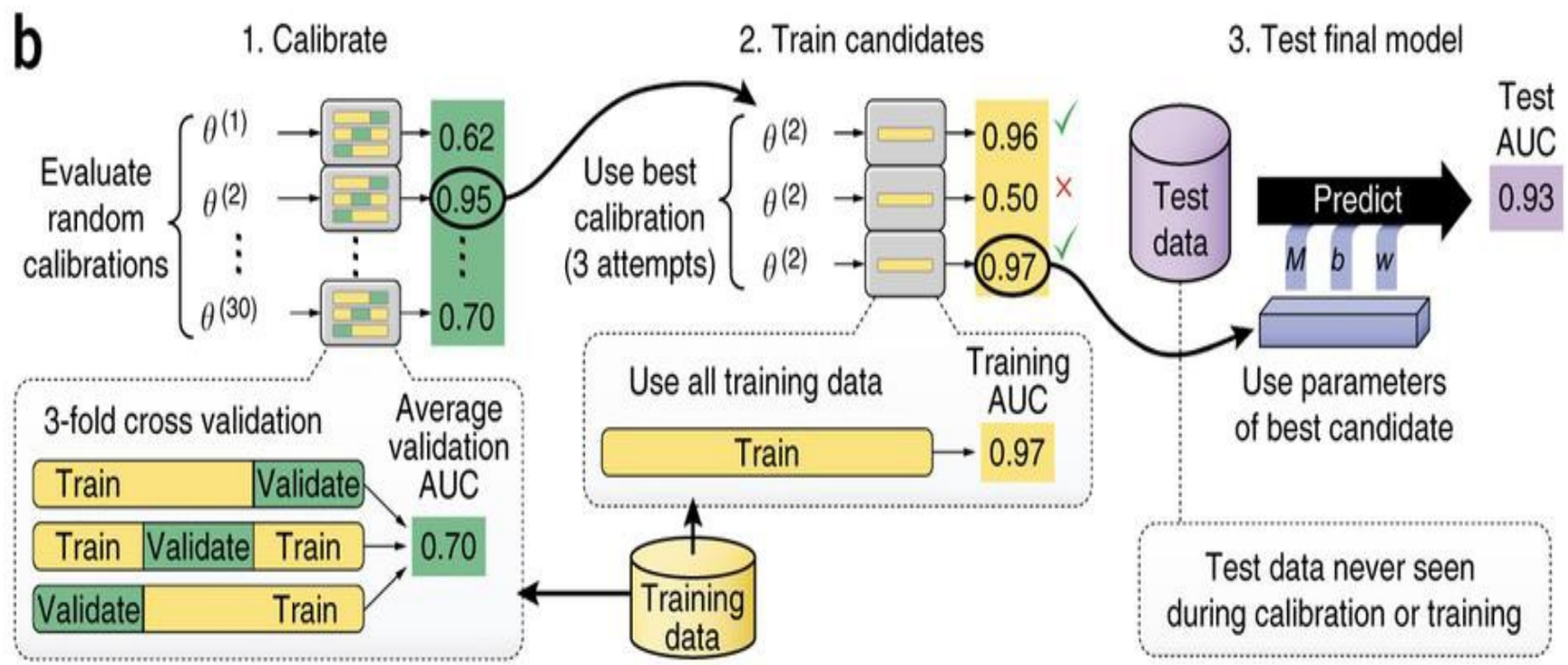
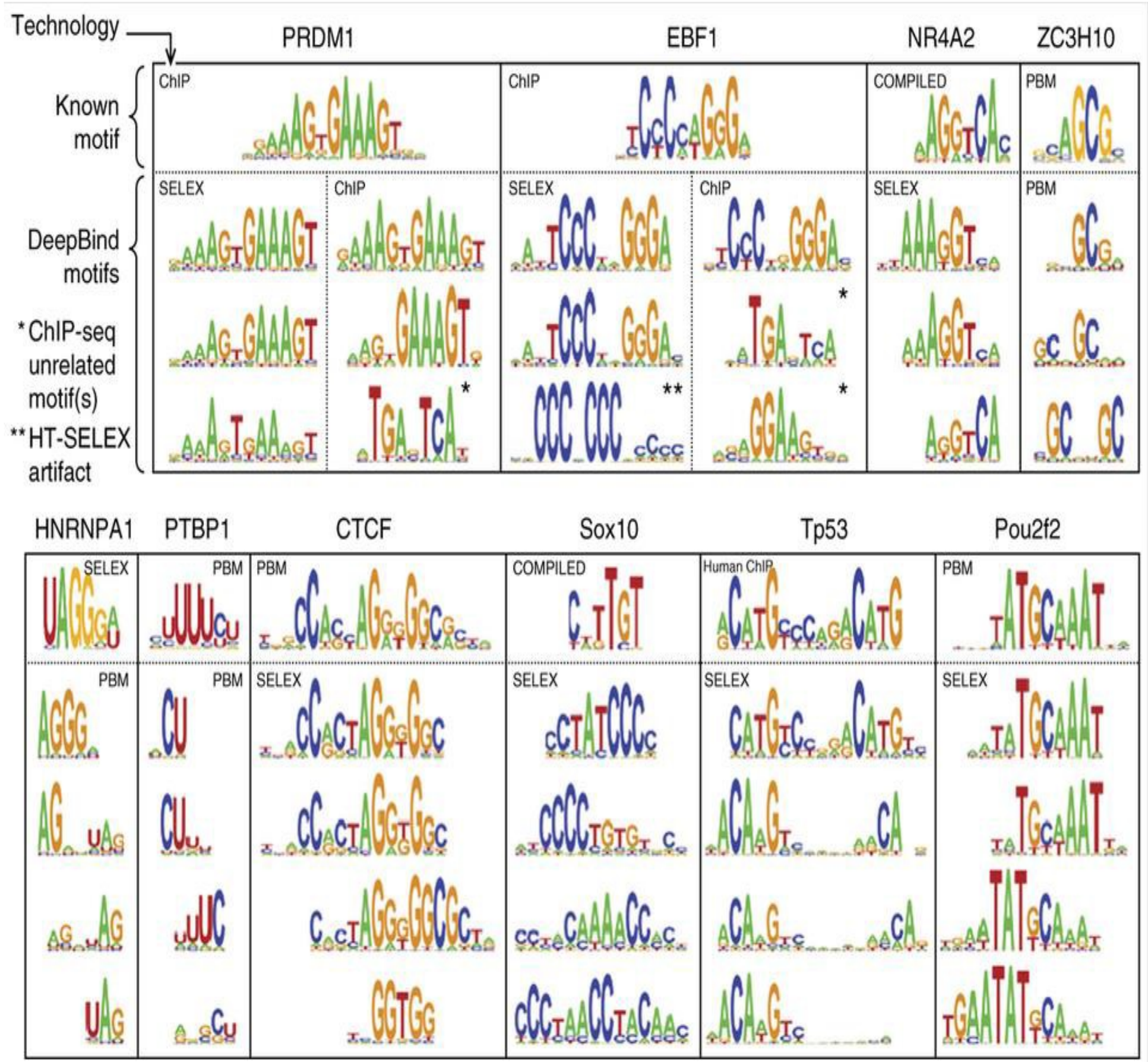


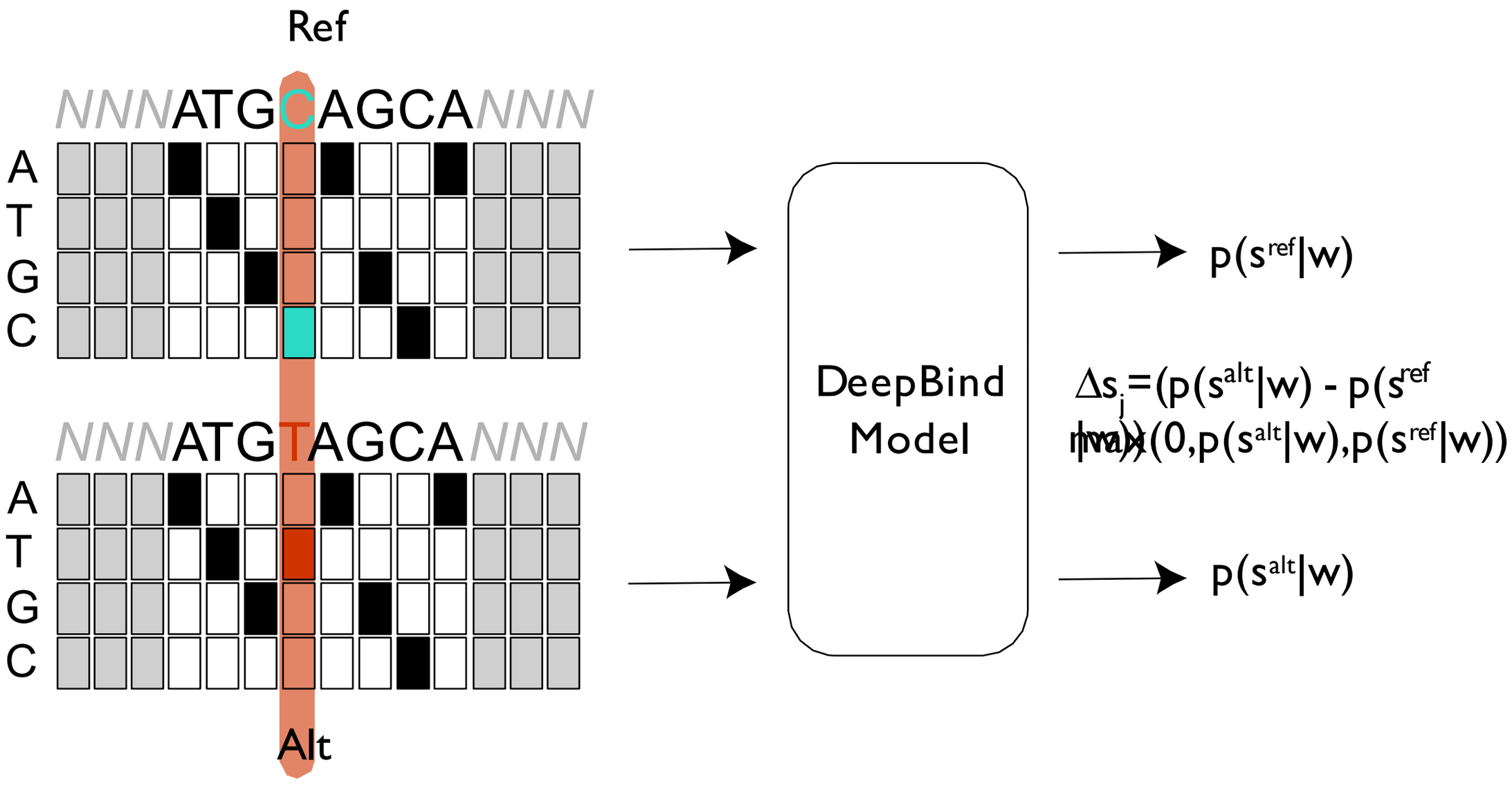




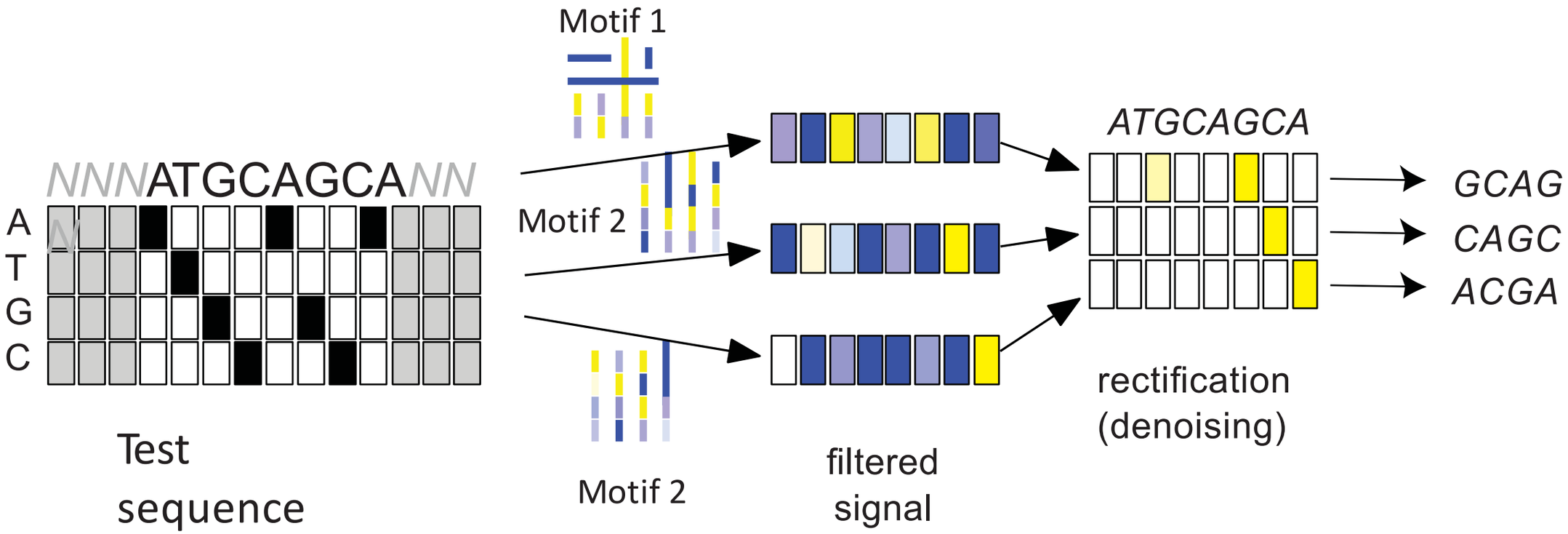
http://www.nature.com/nbt/journal/v33/n8/full/nbt.3300.html


Technology
PRDM1
EBF1
NR4A2
ZC3H10
Known motif
DeepBind motifs
*ChIP-seq unrelated motif(s)
**HT-SELEX artifact
ChIP
SELEX
COMPILED
PBM
HNRNPA1
PTBP1
CTCF
Sox10
Tp53
Pou2f2
Human ChIP

Constructing mutation map



Constructing sequence logo



Motif 1

GCAG
GCTG
GATG
.
.
.
GTAG
GCTG

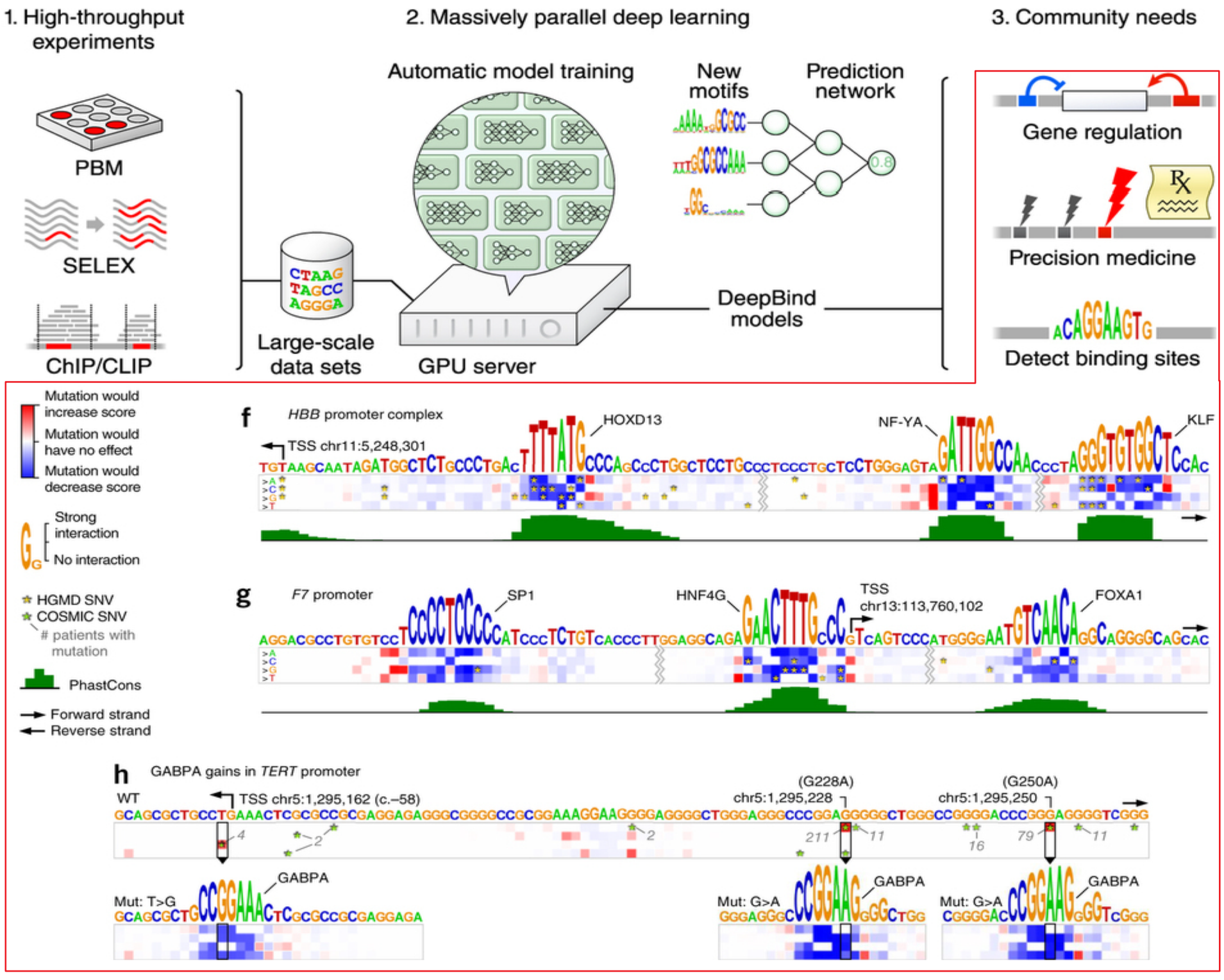
Motif 2

CAGC
GGTC
AGTC
.
.
.
AGGC
GGTG

...

PFM

Predicting disease mutations



[Alipanahi et al., 2015]

DeepBind summary

The key deep learning techniques:

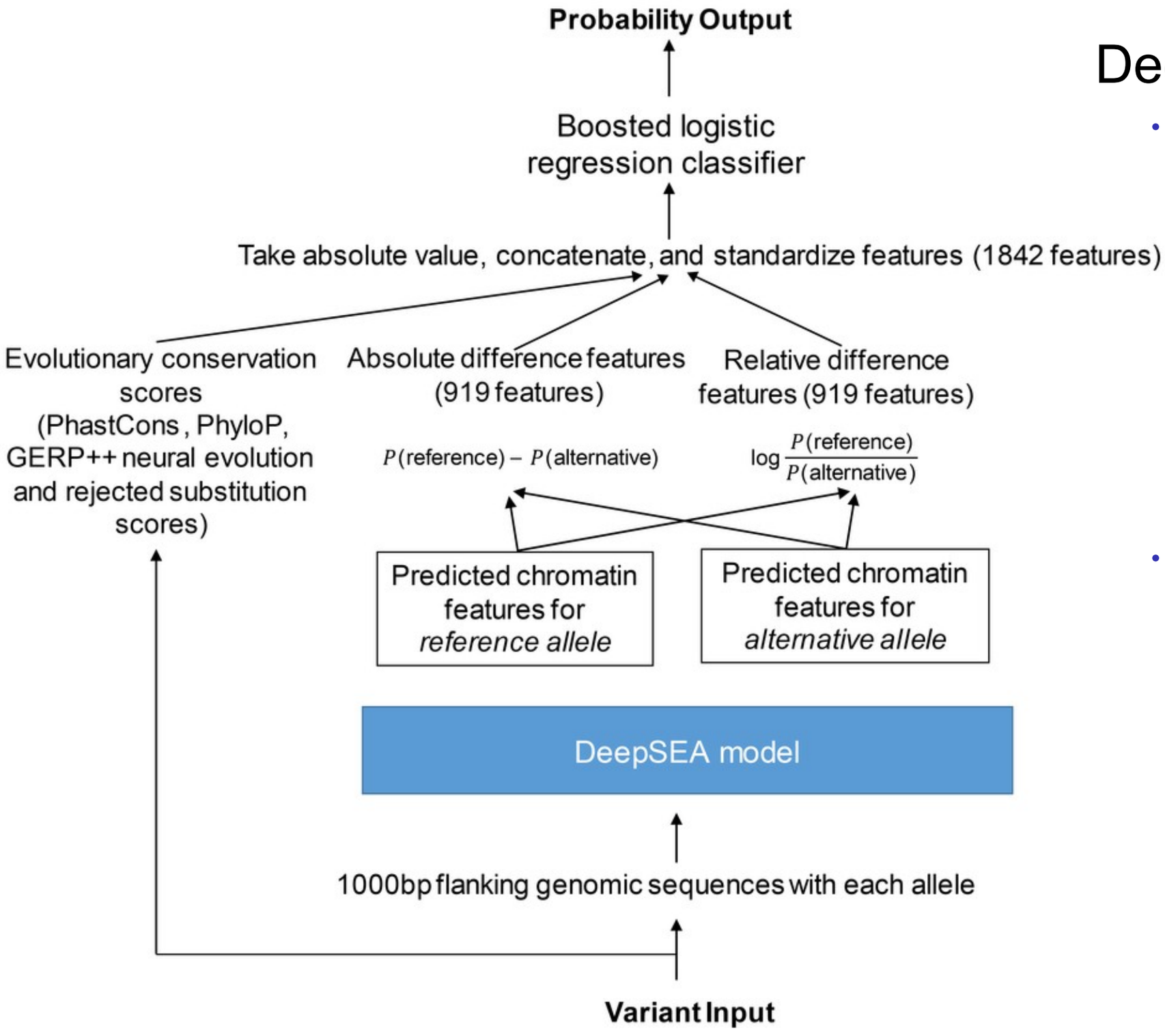
- Convolutional learning
- Representational learning
- Back-propagation and stochastic gradient
- Regularization and dropout
- Parallel GPU computing especially useful for hyperparameter search

Limitations in DeepBind:

- Require defining negative training examples, which is often arbitrary
- Using observed mutation data only as post-hoc evaluation
- Modeling each regulatory dataset separately

Regulatory Genomics CNNs in Practice:
(b) DeepSEA

DeepSea



DeepSea:

- Similar as DeepBind but trained a separate CNN on each of the ENCODE/Roadmap Epigenomic chromatin profiles 919 chromatin features (125 DNase features, 690 TF features, 104 histone features).
- It uses the Δs mutation score as input to train a linear logistic regression to predict GWAS and eQTL SNPs defined from the GRASP database with a P-value cutoff of 1E-10 and GWAS SNPs from the NHGRI GWAS Catalog

[Zhou and Troyanskaya, 2015]

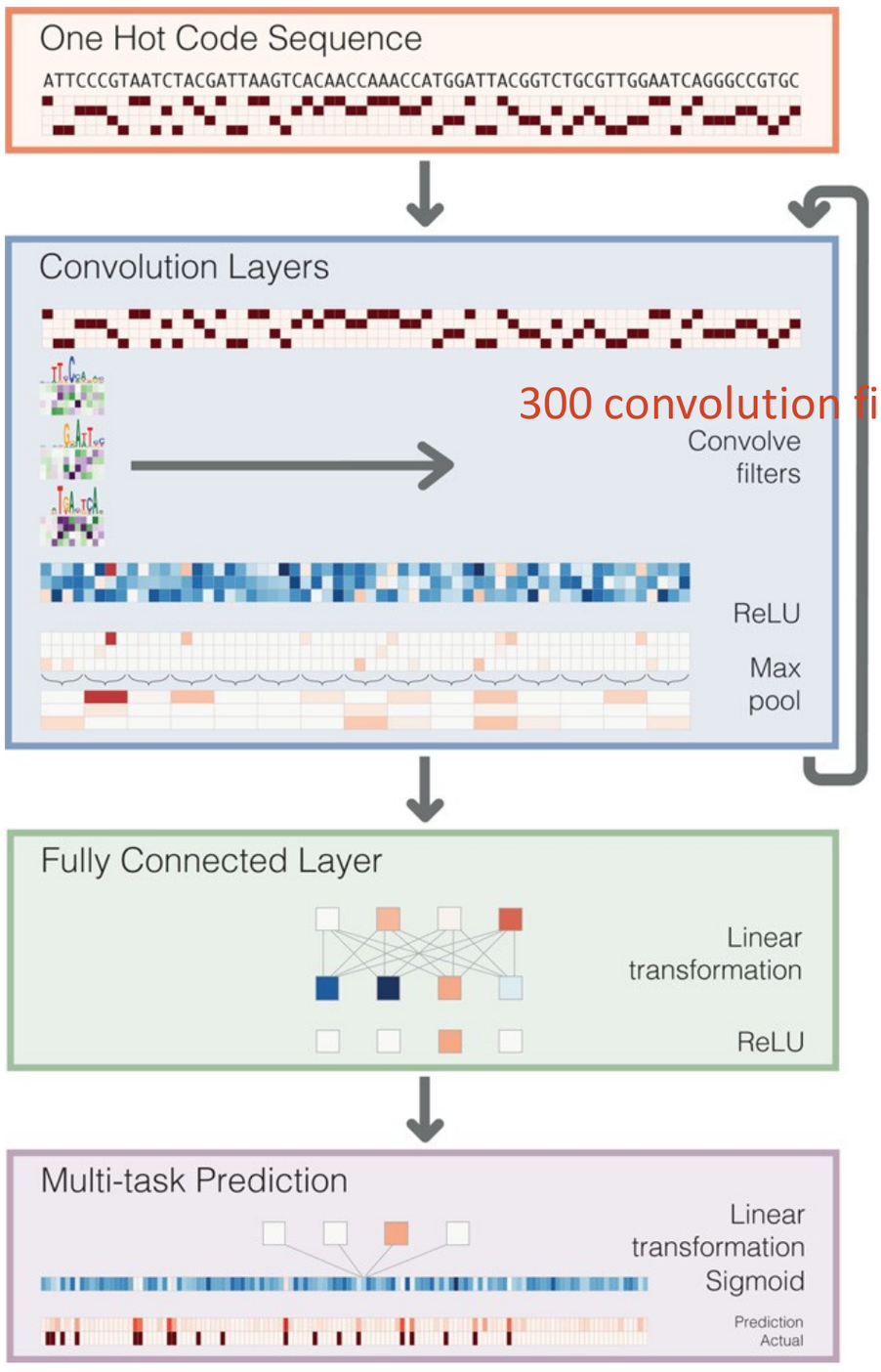
Regulatory Genomics CNNs in Practice:
(c) Basset

Basset: Learning the regulatory code of the accessible genome with deep convolutional neural networks.

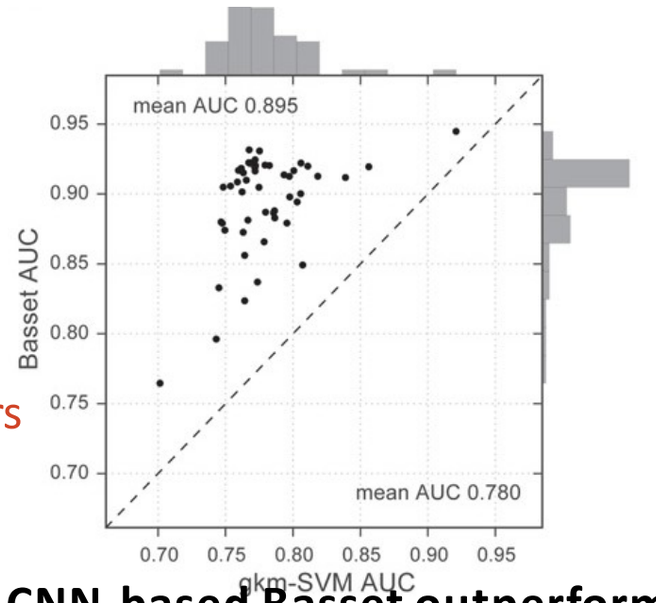
David R. Kelley
Jasper Snoek
John L. Rinn

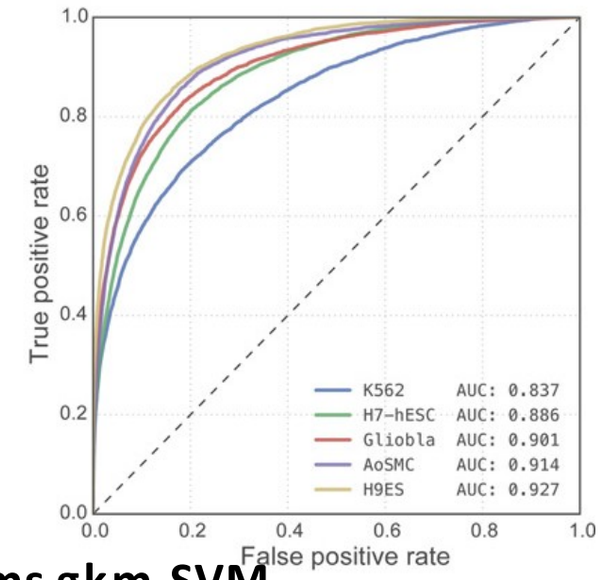
Genome Research, March 2016

Basset

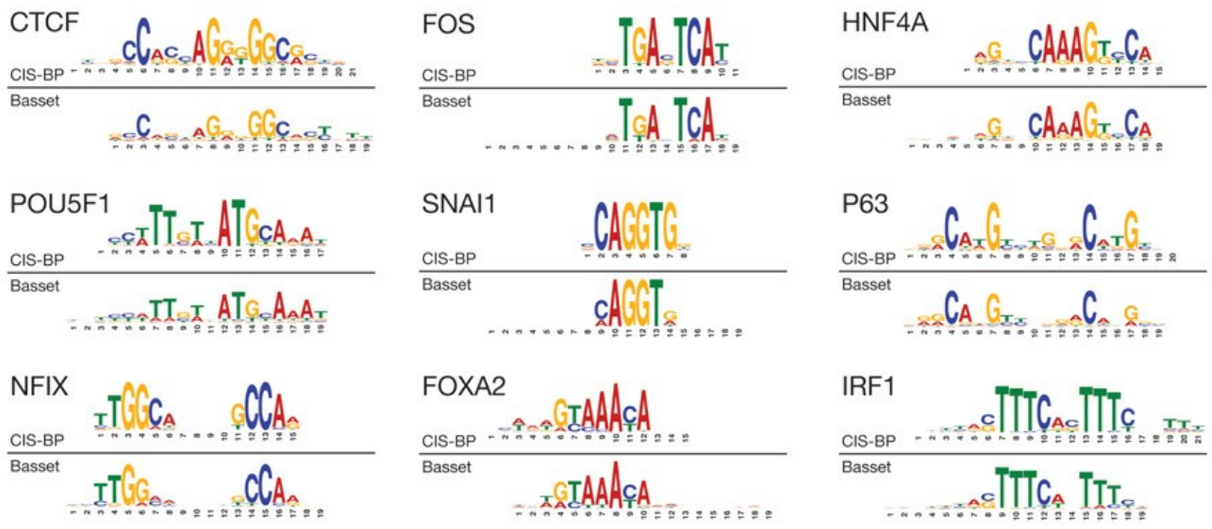


Simultaneously predicting DNase sites in 164 cell types





CNN-based Basset outperforms gkm-SVM



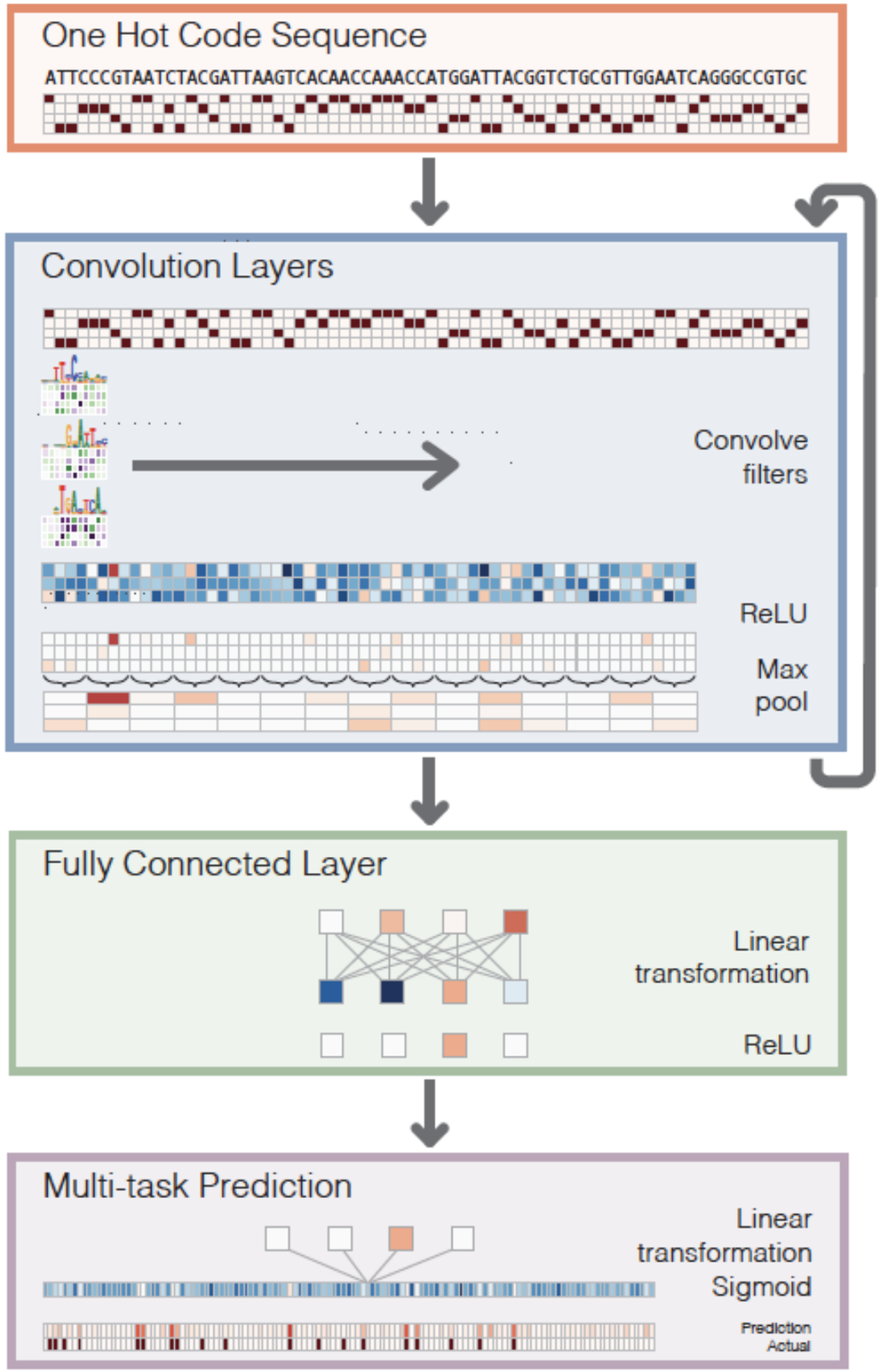
Convolutional filters connected to the input sequence recapitulate some known TF motifs

[Kelley et al., 2016]

Bassett architecture for accessibility prediction

Input:
600 bp

1.9 million
training examples



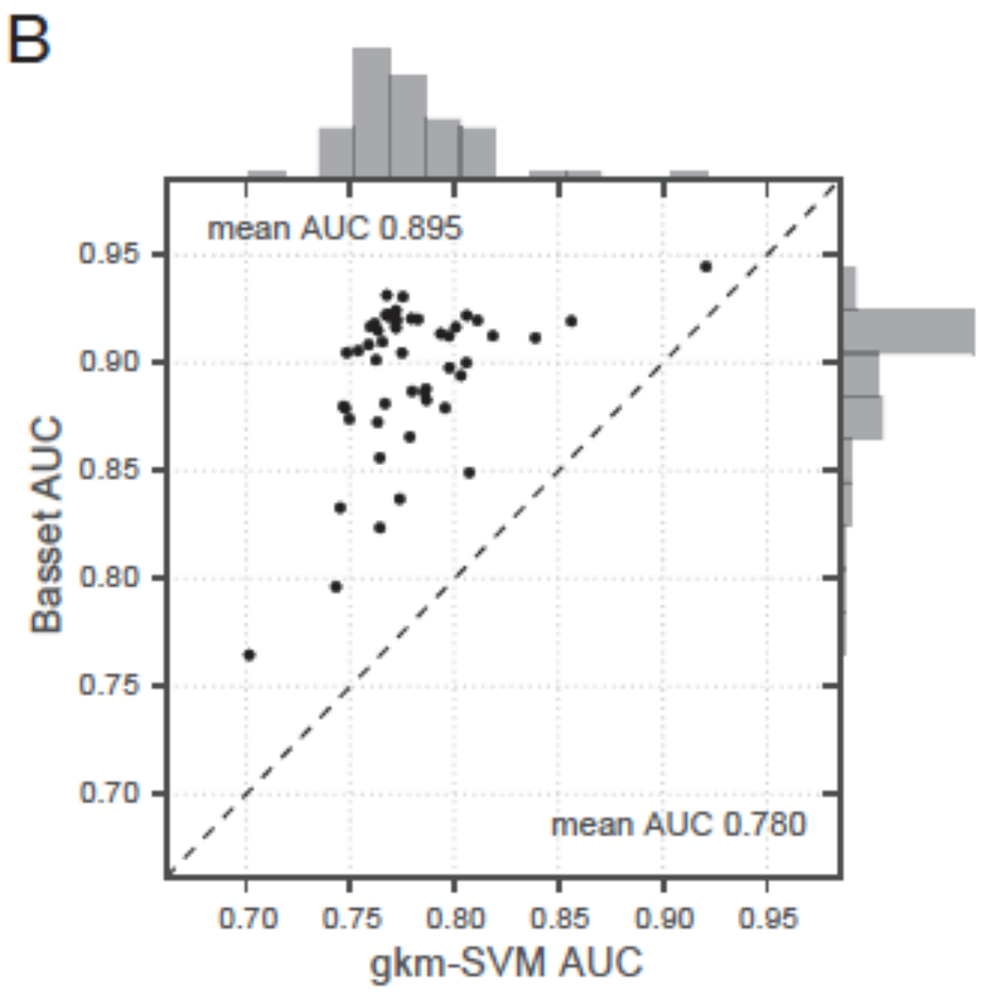
300 filters
3 conv layers
3 FC layers

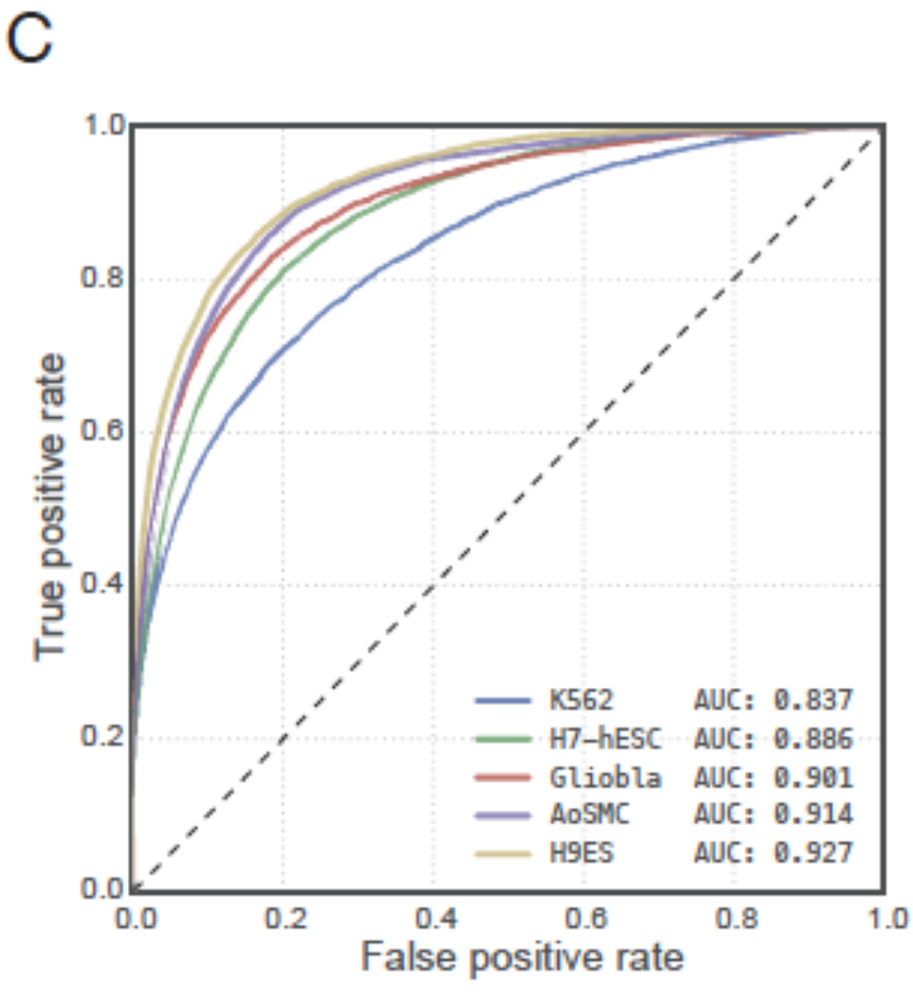
3 fully connected layers

Output:
168 bits

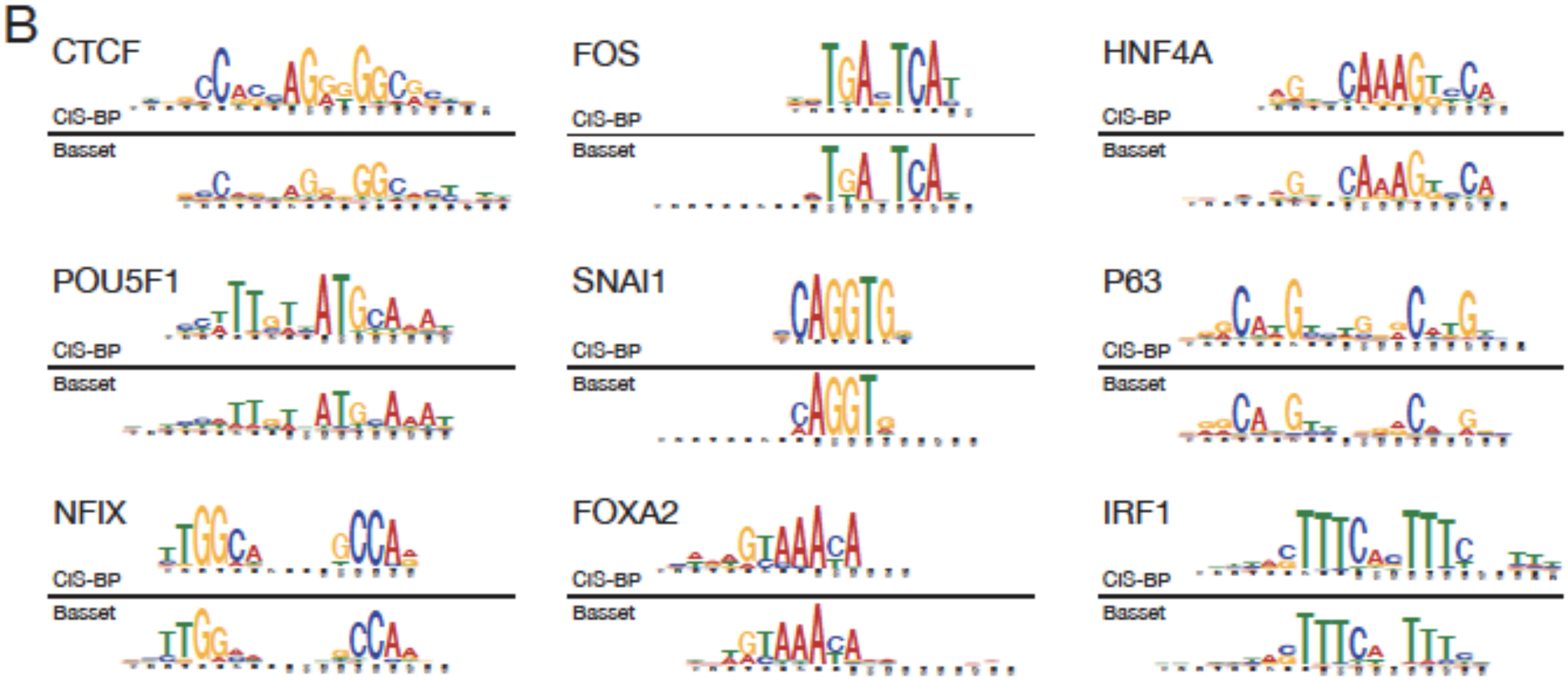
168 outputs
(1 per cell type)

Bassett AUC performance vs. gkm-SVM



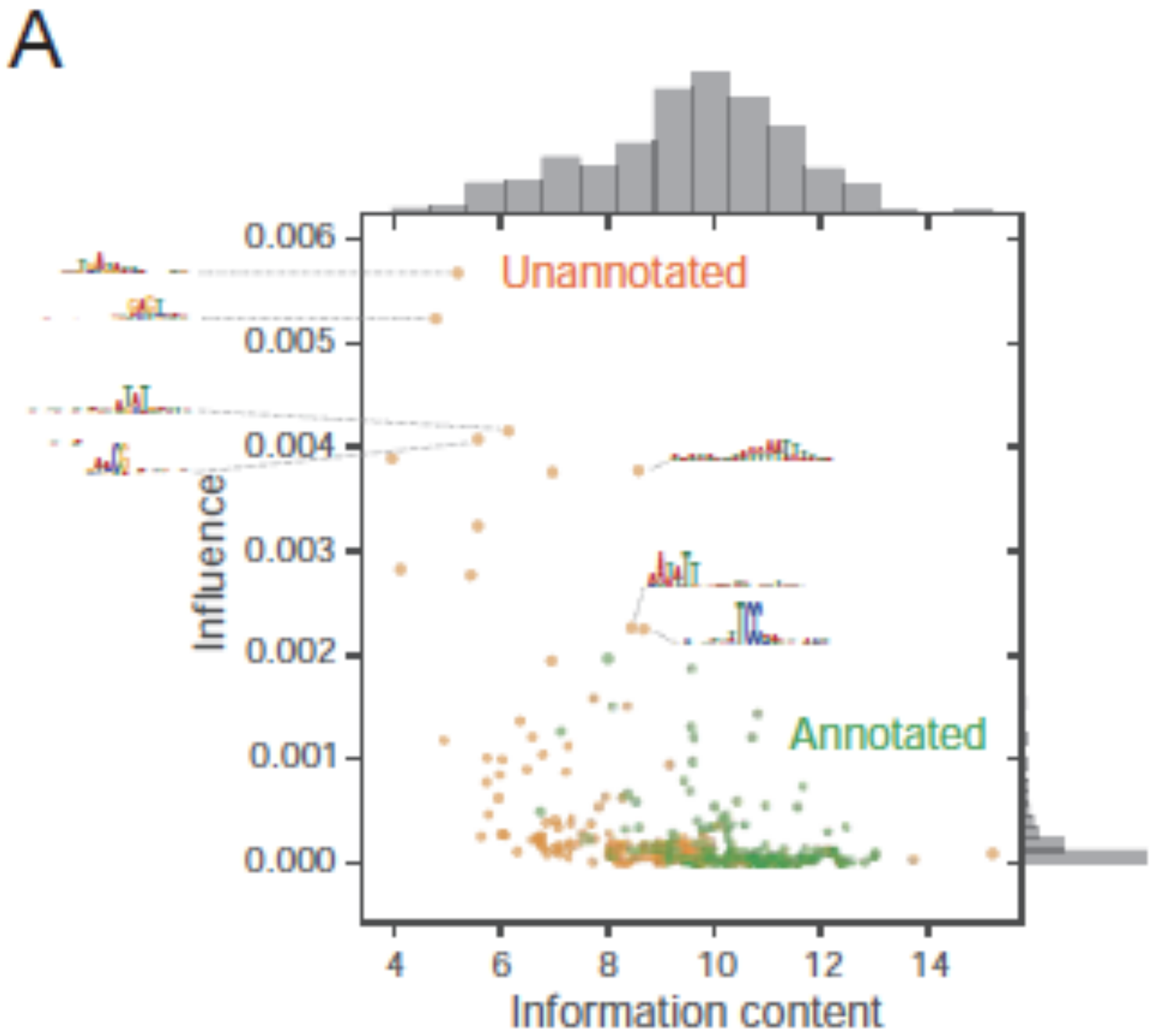


45% of filter derived motifs are found in the CIS-BP database

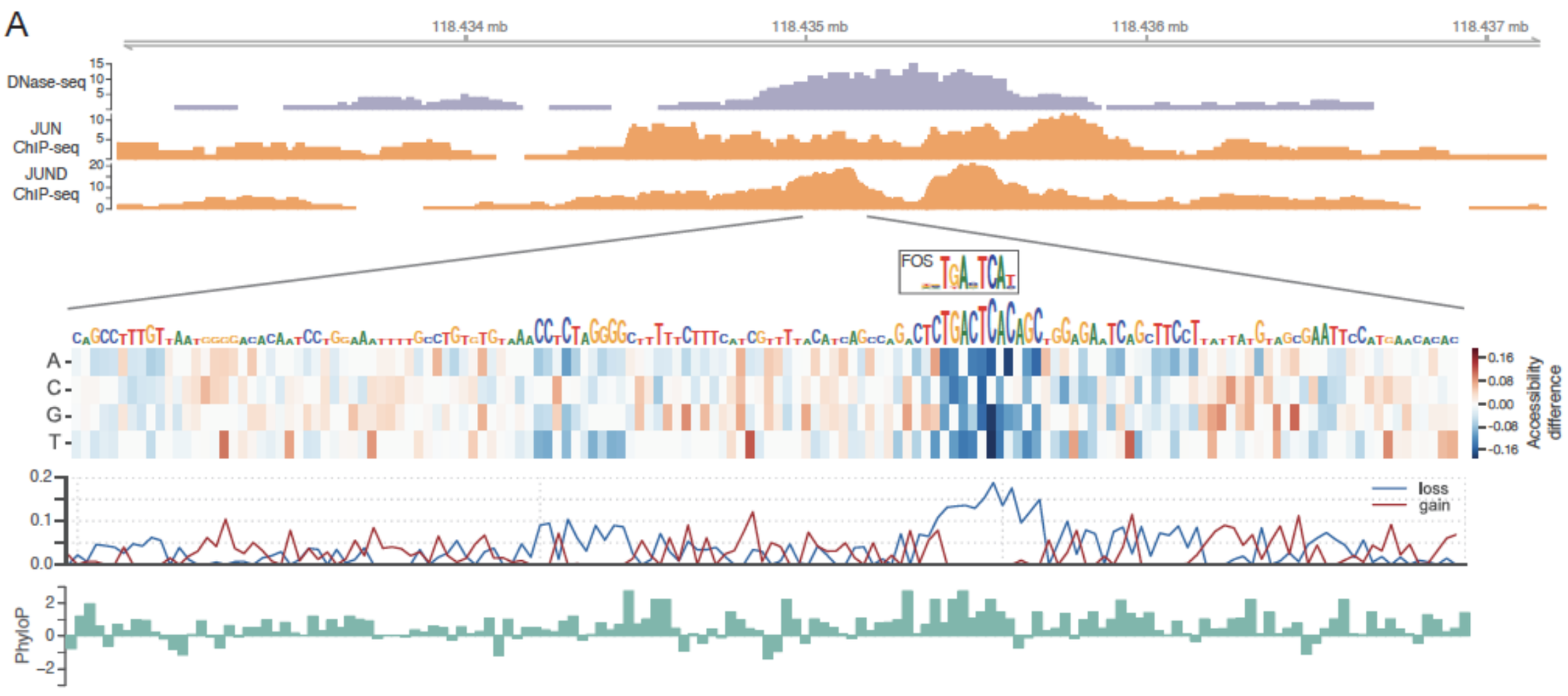


Motifs created by clustering matching input sequences and computing PWM

Motif derived from filters with more information tend to be annotated

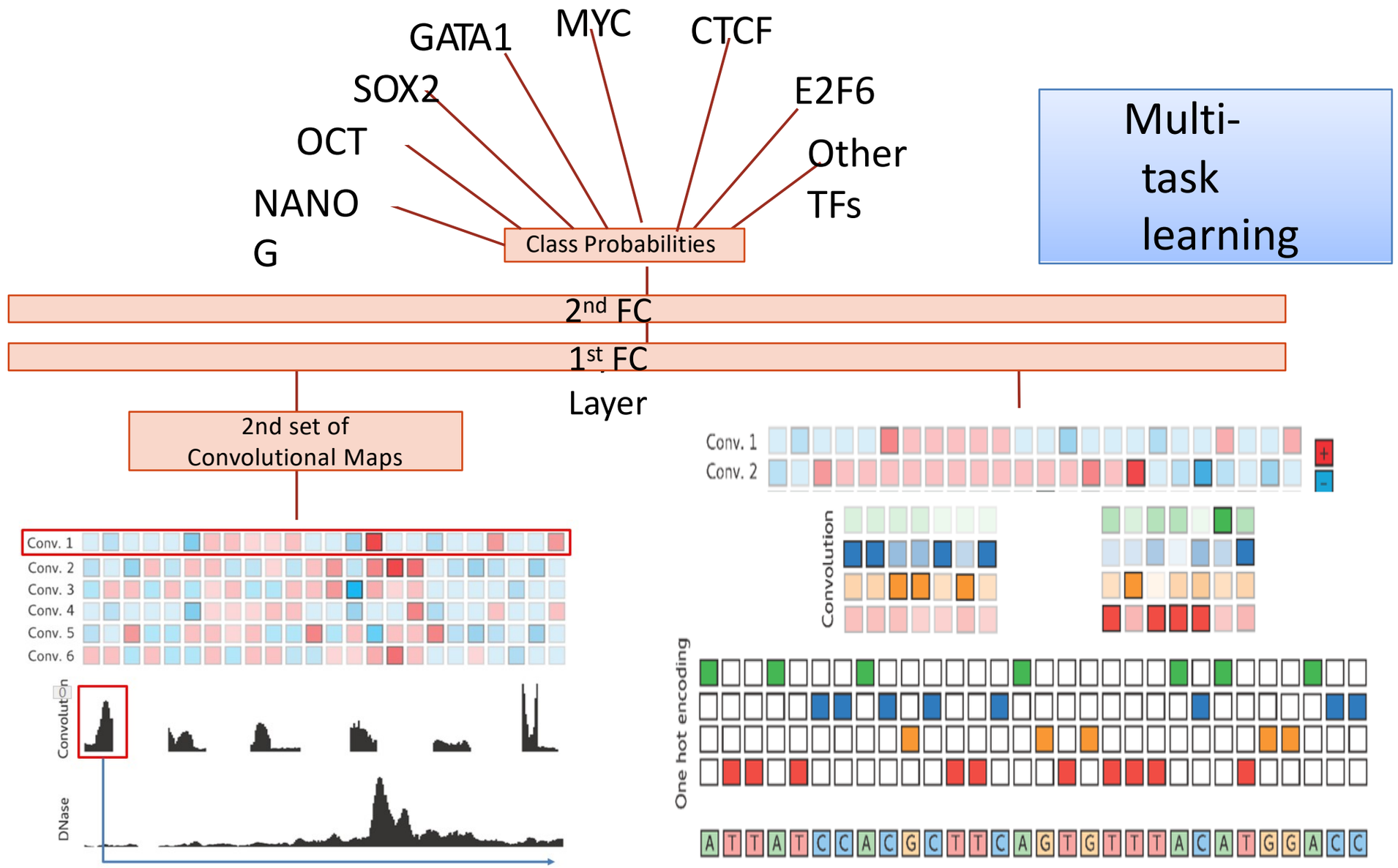


Computational saturation mutagenesis of an AP-1 site reveals loss of accessibility



Regulatory Genomics CNNs in Practice:
(d) Chromputer

ChromPuter

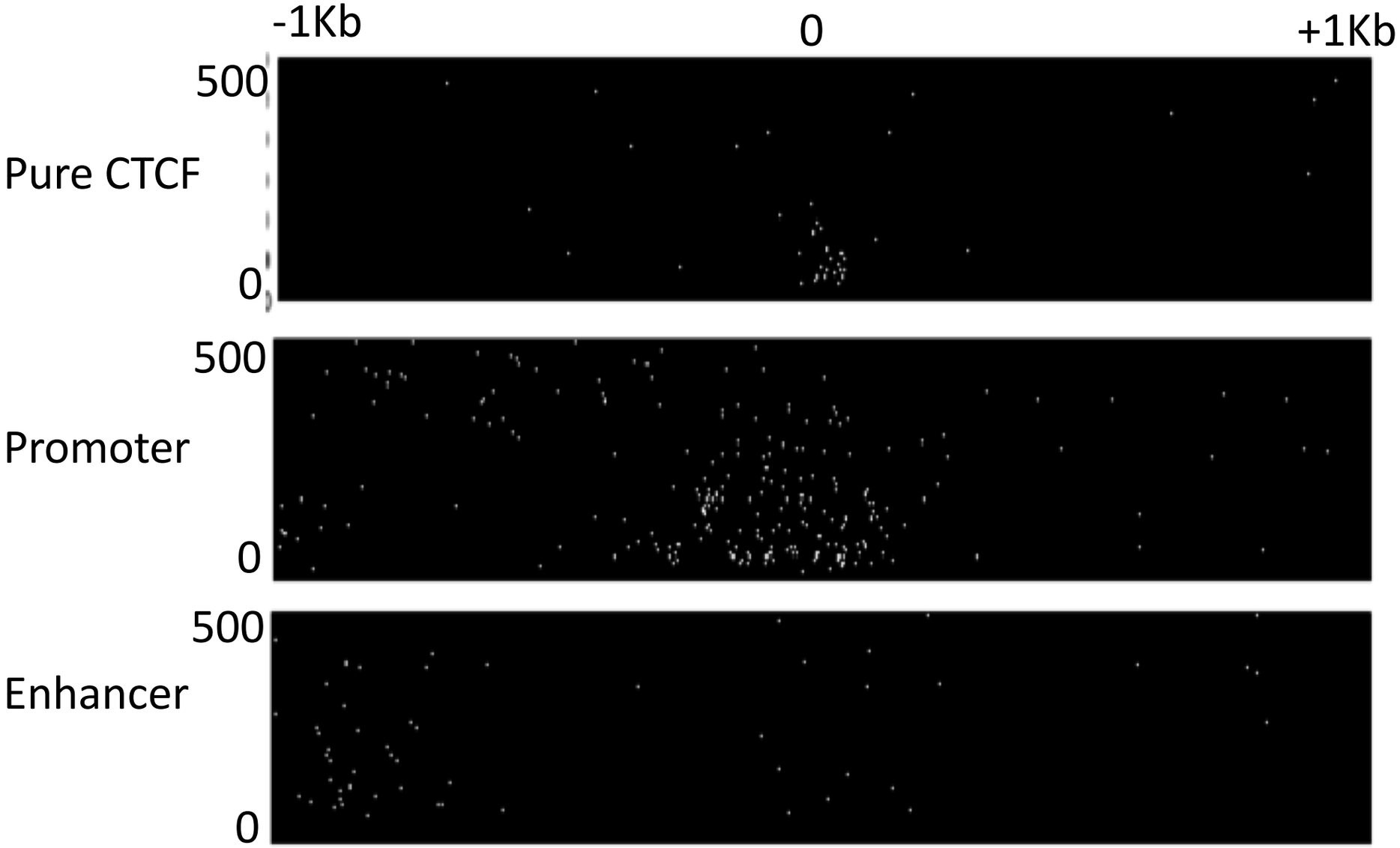


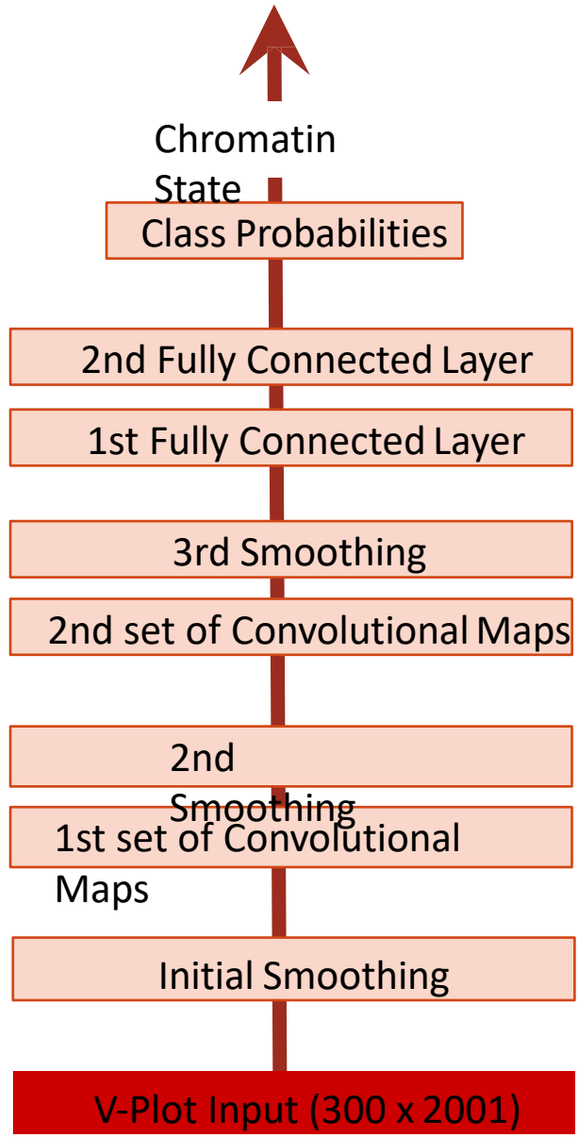
1D DNase-seq/ATAC-seq profile

DNA sequence

(Anshul Kundaje's group from Stanford)

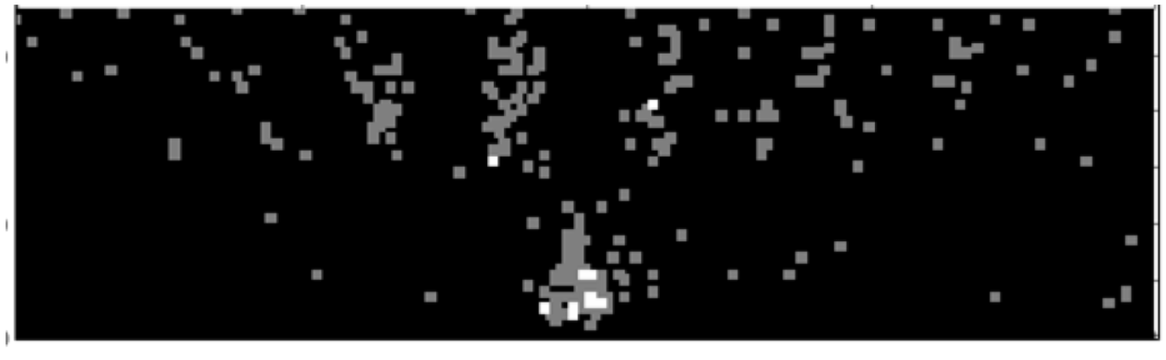
How does a deep conv. neural network transform the raw V-plot input at each layer



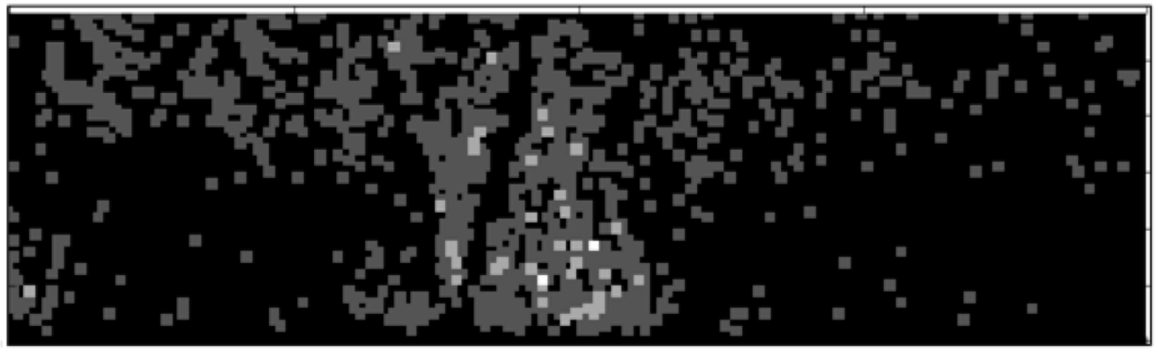


After initial pooling (smoothing)

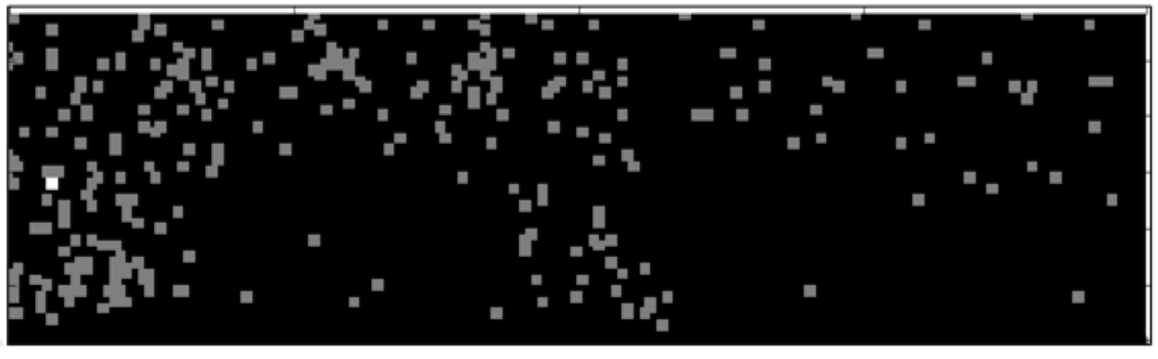
Pure CTCF

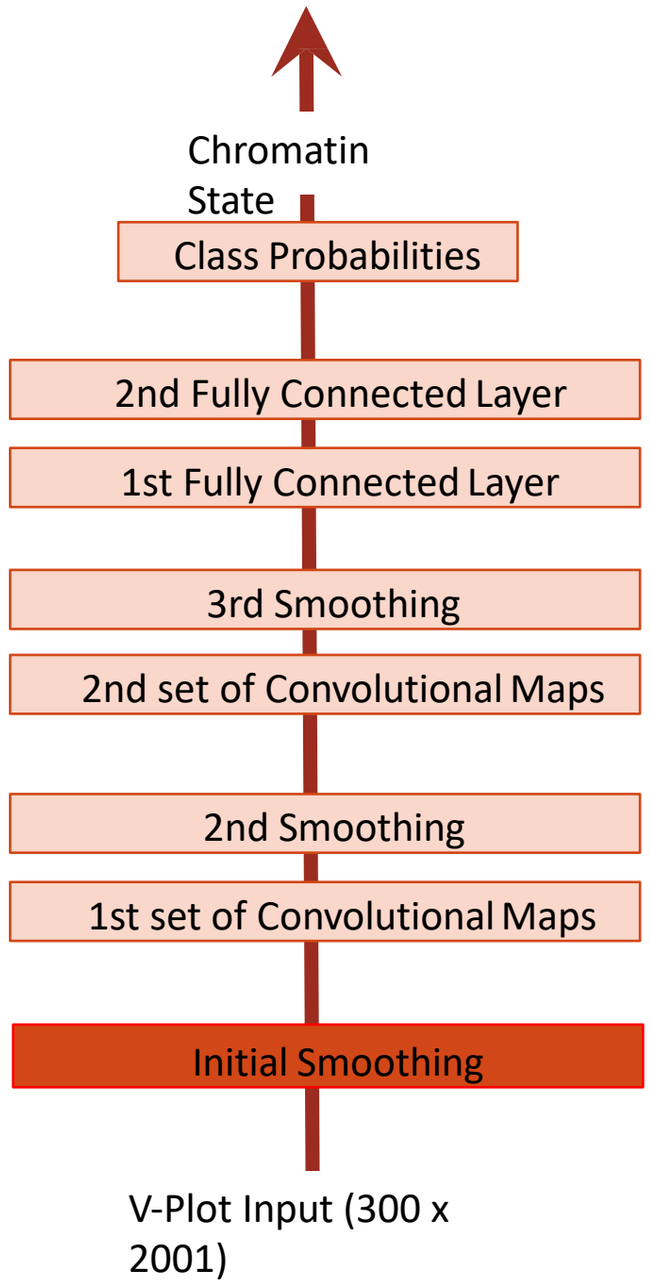


Promoter



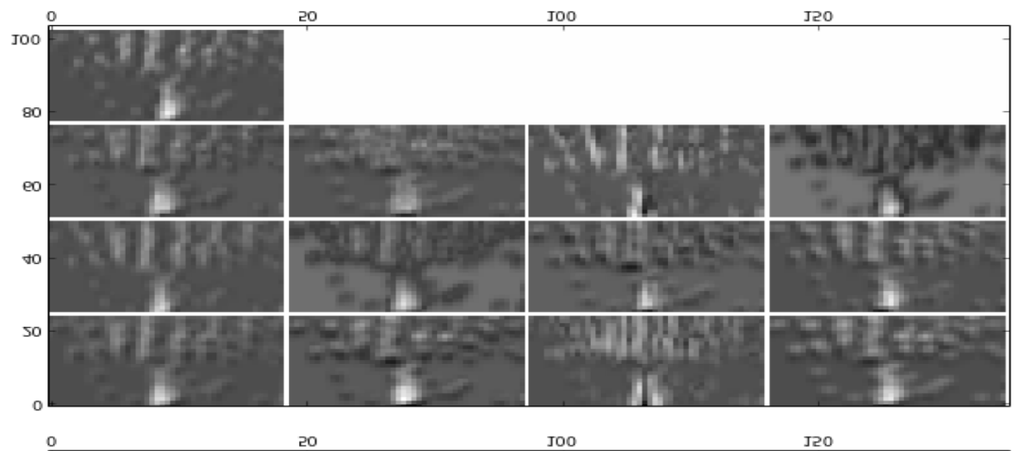
Enhancer



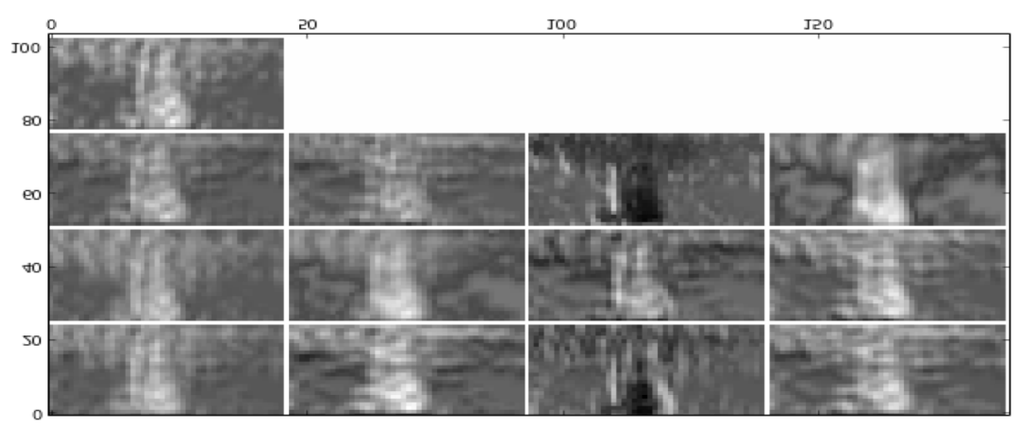


Second set of convolutional maps

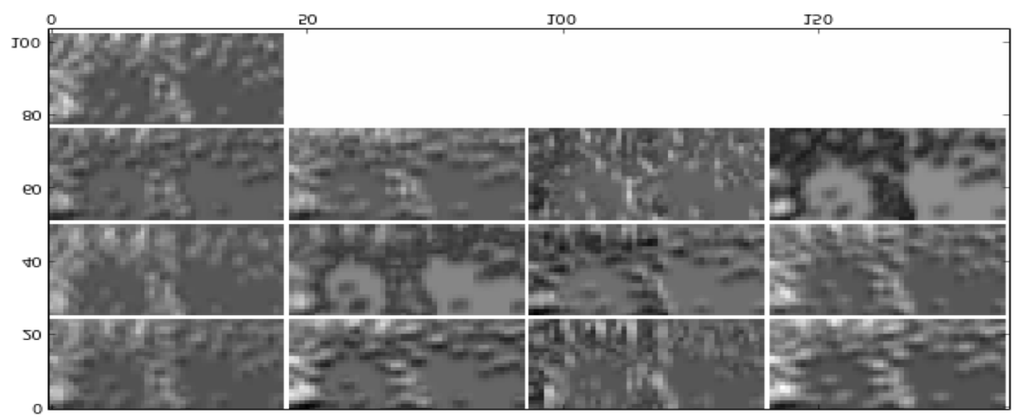
Pure CTCF

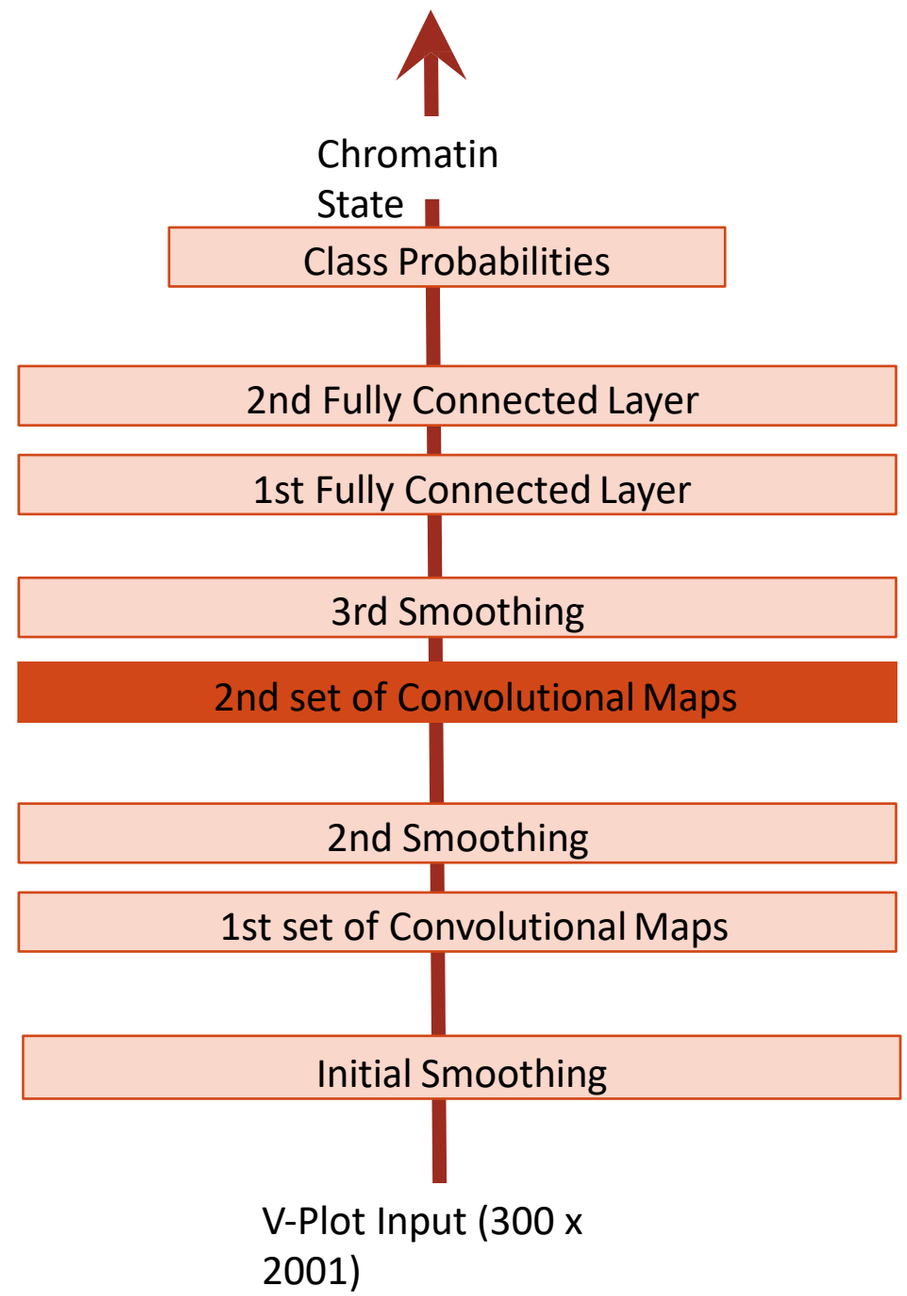


Promoter



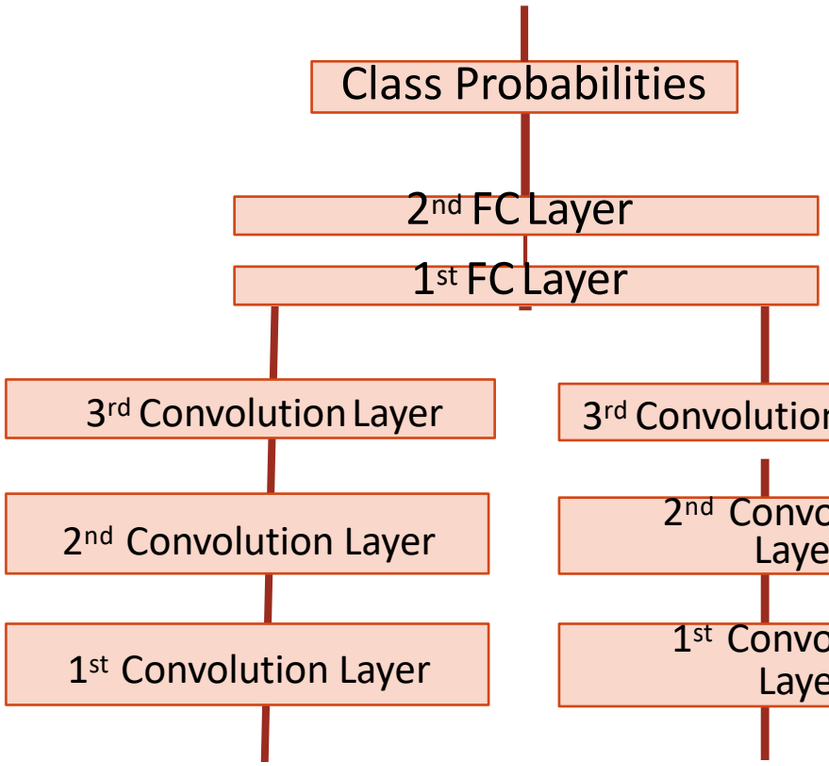
Enhancer



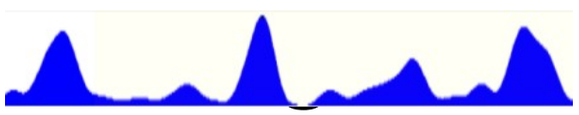


Learning from **multiple 1D functional data** (e.g. DNase, MNase)

Chromatin State

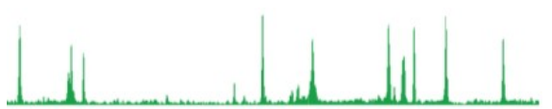


1D MNase

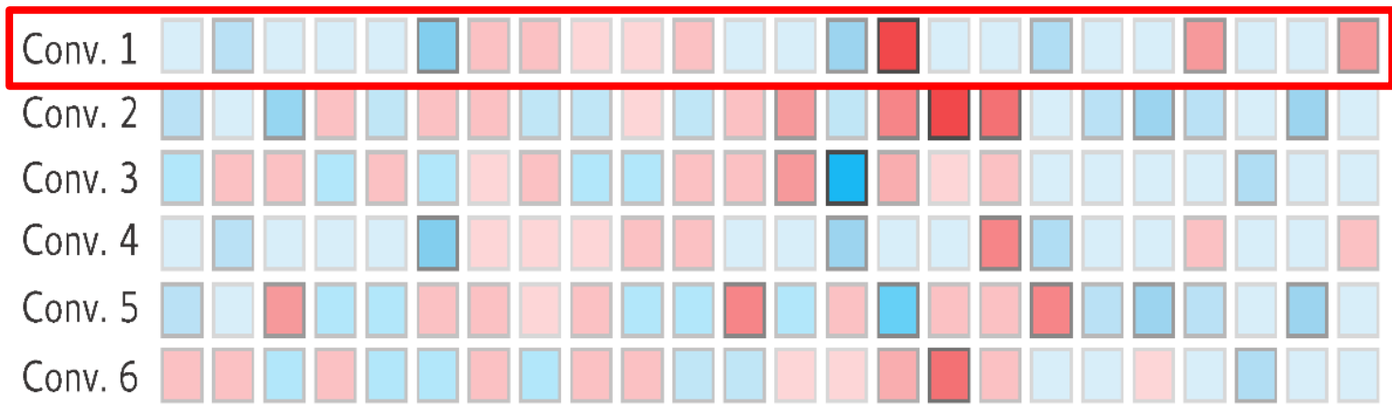


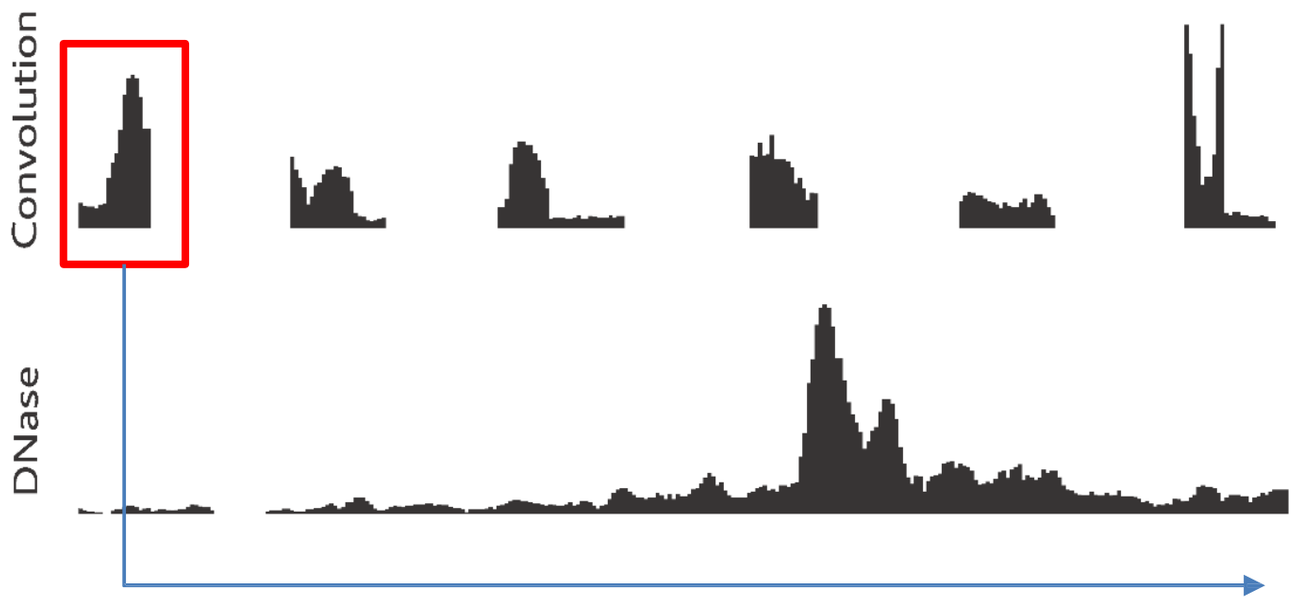
(1 x 2001)

1D DNase



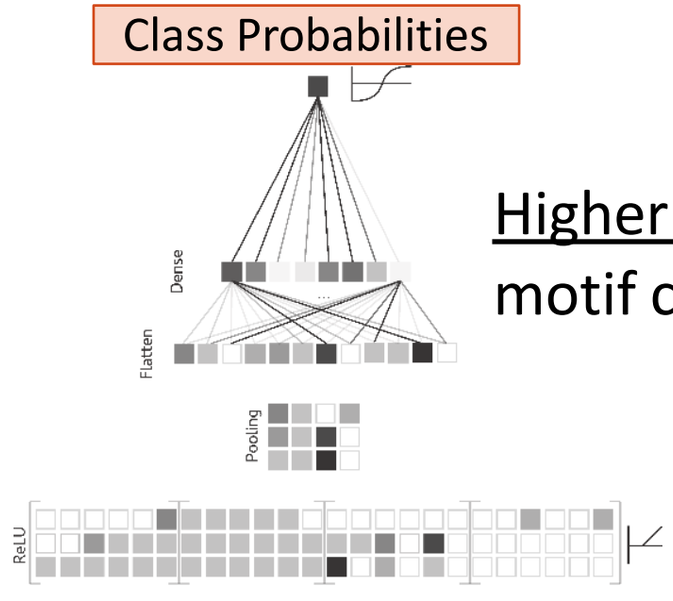
(1 x 2001)





Scan DNase profile using filter

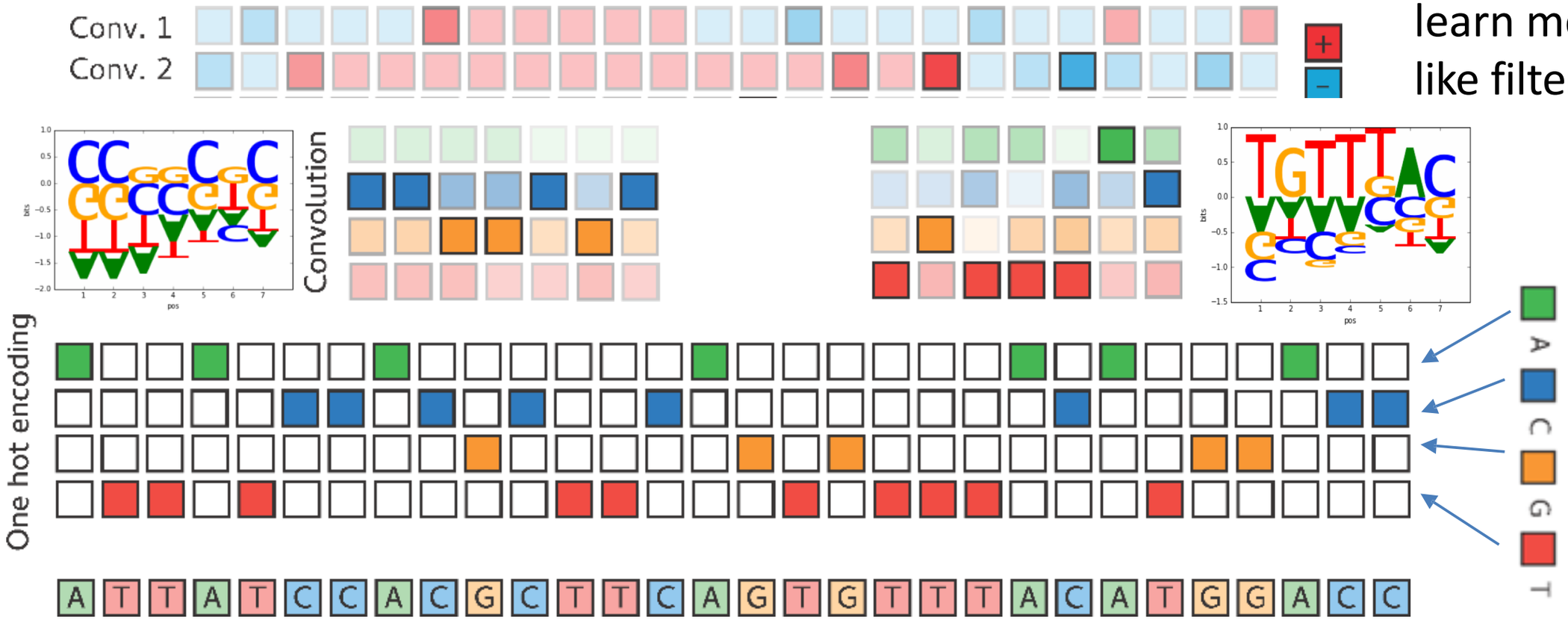
Learning from raw DNA sequence



Higher layers learn motif combinations

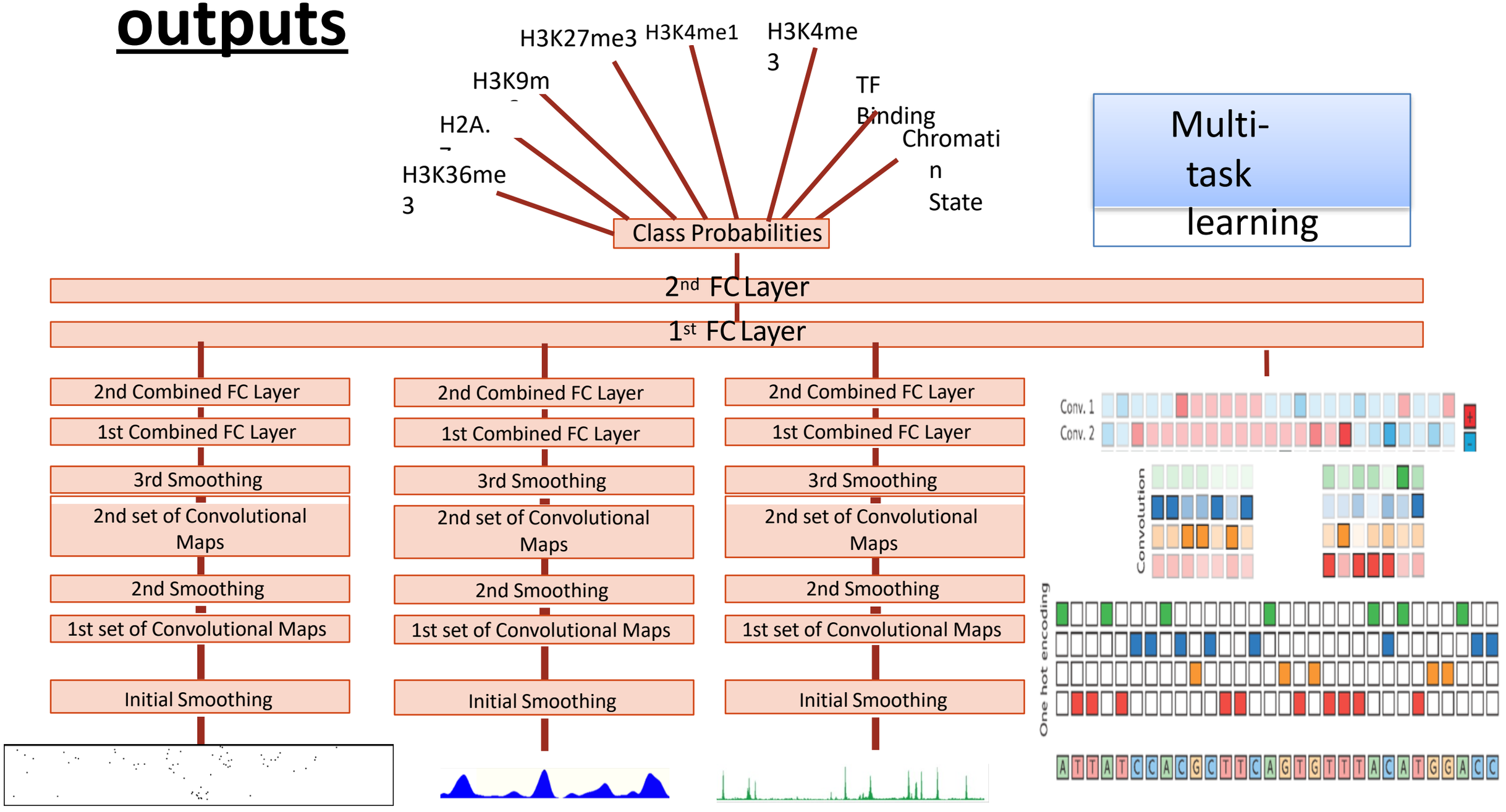
Score sequence using filters

Convolutional layers learn motif (PWM) like filters



The Chromputer

Integrating multiple inputs (1D, 2D signals, sequence) to simulatenously **predict multiple outputs**



Chromatin architecture can predict **chromatin state** in held out chromosome (same cell type)

Model + Input data types	8-class chromatin state accuracy (%)
Majority class (baseline)	**42%**
Gene proximity	59%
Random Forest: **ATAC-seq** (150M reads)	**61%**
Chromputer: **DNase** (60M reads)	68.1%
Chromputer: **Mnase** (1.5B reads)	69.3%
Chromputer: **ATAC-seq** (150M reads)	**75.9%**
Chromputer: **DNase** + **MNase**	**81.6%**
Chromputer: **ATAC-seq** + **sequence**	83.5%
Chromputer: **DNase** + **MNase** + **sequence**	**86.2%**
Label accuracy across replicates (upper bound)	**88%**

High cross cell-type chromatin state prediction

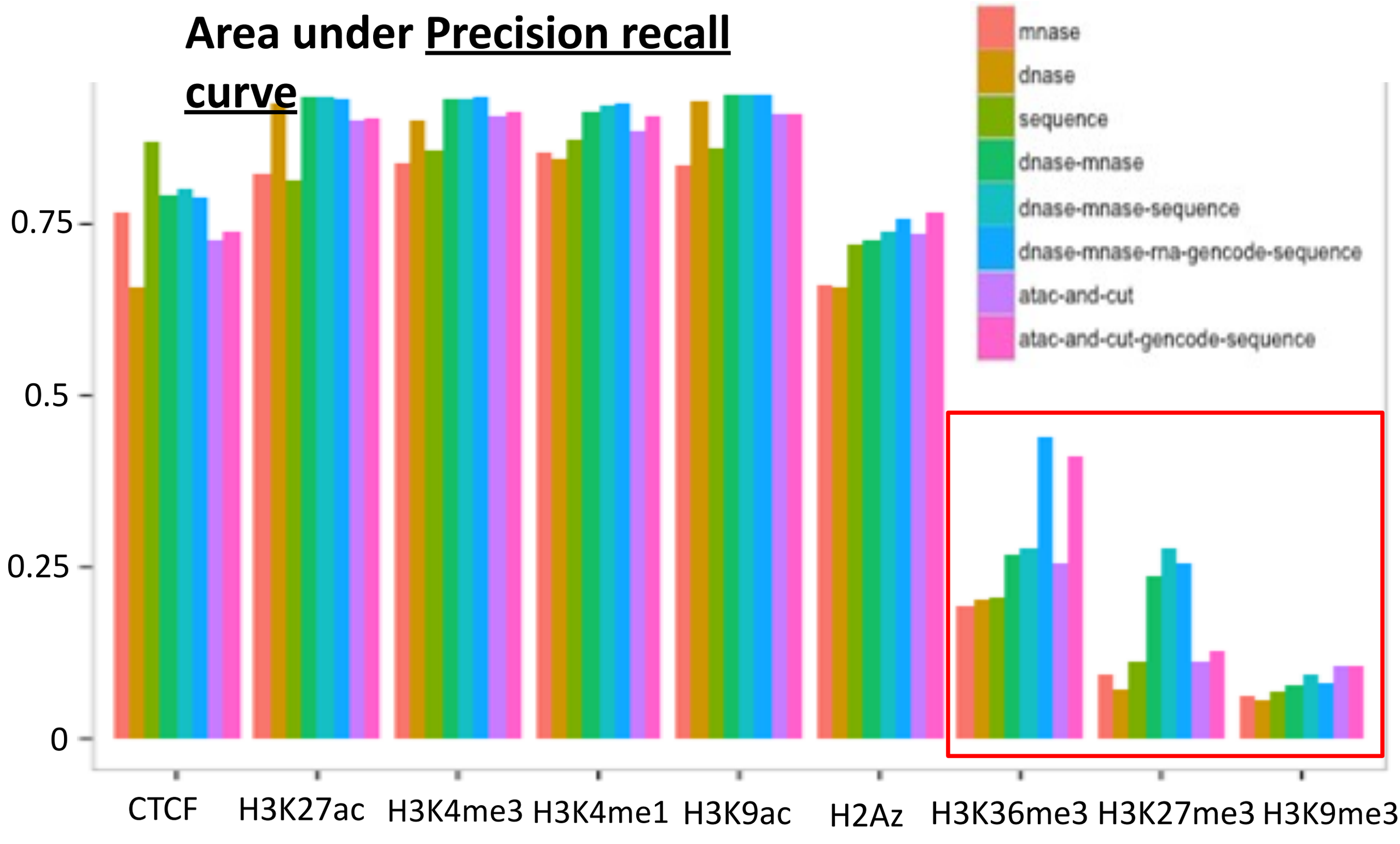
- Learn model on **DNase and MNase only**
- **Learn on GM12878, predict on K562 (and vice versa)**
- **Requires local normalization** to make signal comparable

8 class chromatin state accuracy

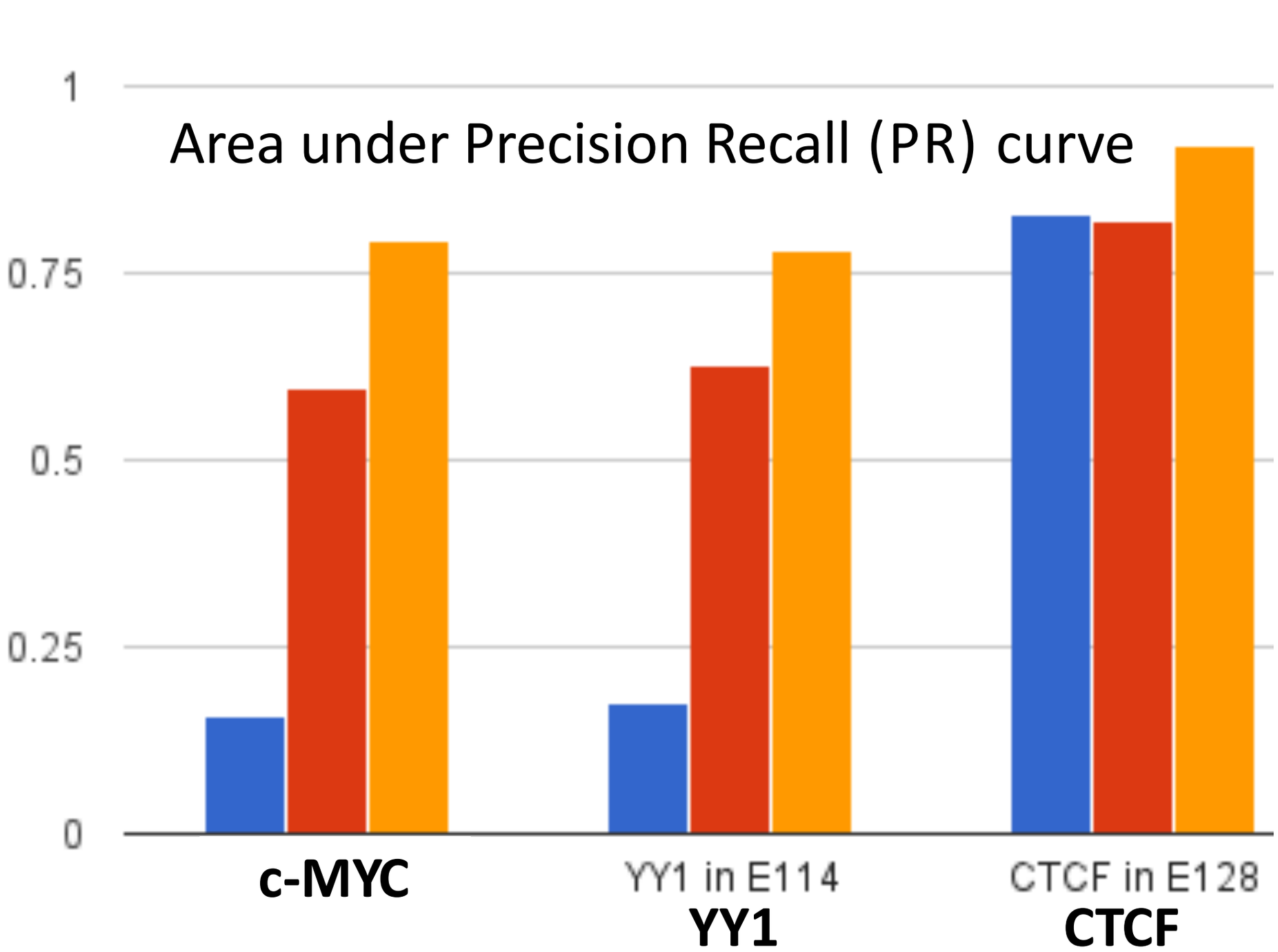
Train ↓ / Test →	GM12878	K562
GM12878	0.816	**0.818**
K562	**0.769**	0.844

Predicting individual histone marks from ATAC/DNase/MNase/Sequence

Area under <u>Precision recall curve</u>



Chromputer trained on TF ChIP-seq predicts cross cell-type in-vivo TF binding with high accuracy

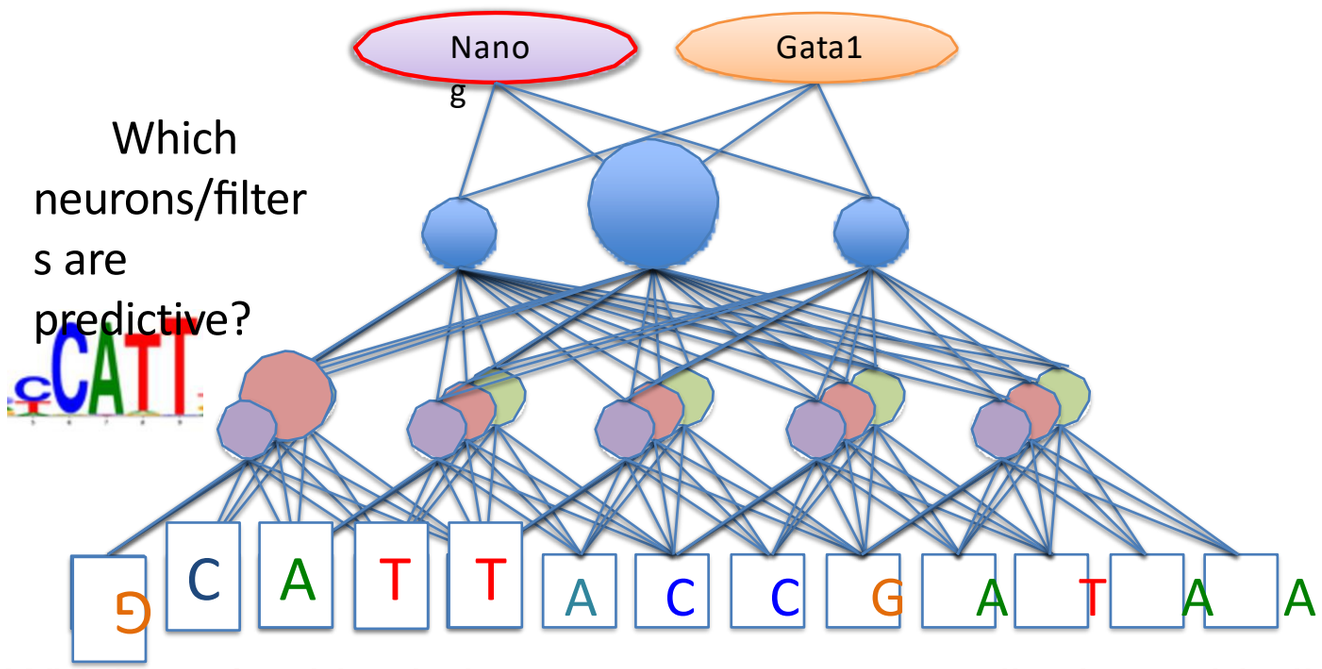


DeepBind
DeepSEA
Chromputer

Inputs: Seq + DNA shape + DNase profile
Positives: Reproducible ChIP-seq peaks
Negatives: All other DNase peaks + flanks + matched random sites

Test sets: Held out chromosomes in held out cell types

DeepLift reveals feature importance at the input layer



Key idea:

- ReLU is piece-wide linear
- Backpropagation differences of outputs using observed and reference inputs (e.g., inputs of all zeros) to obtain gradient w.r.t. the input
- Importance of any input to any output is the gradients weighted by the input itself

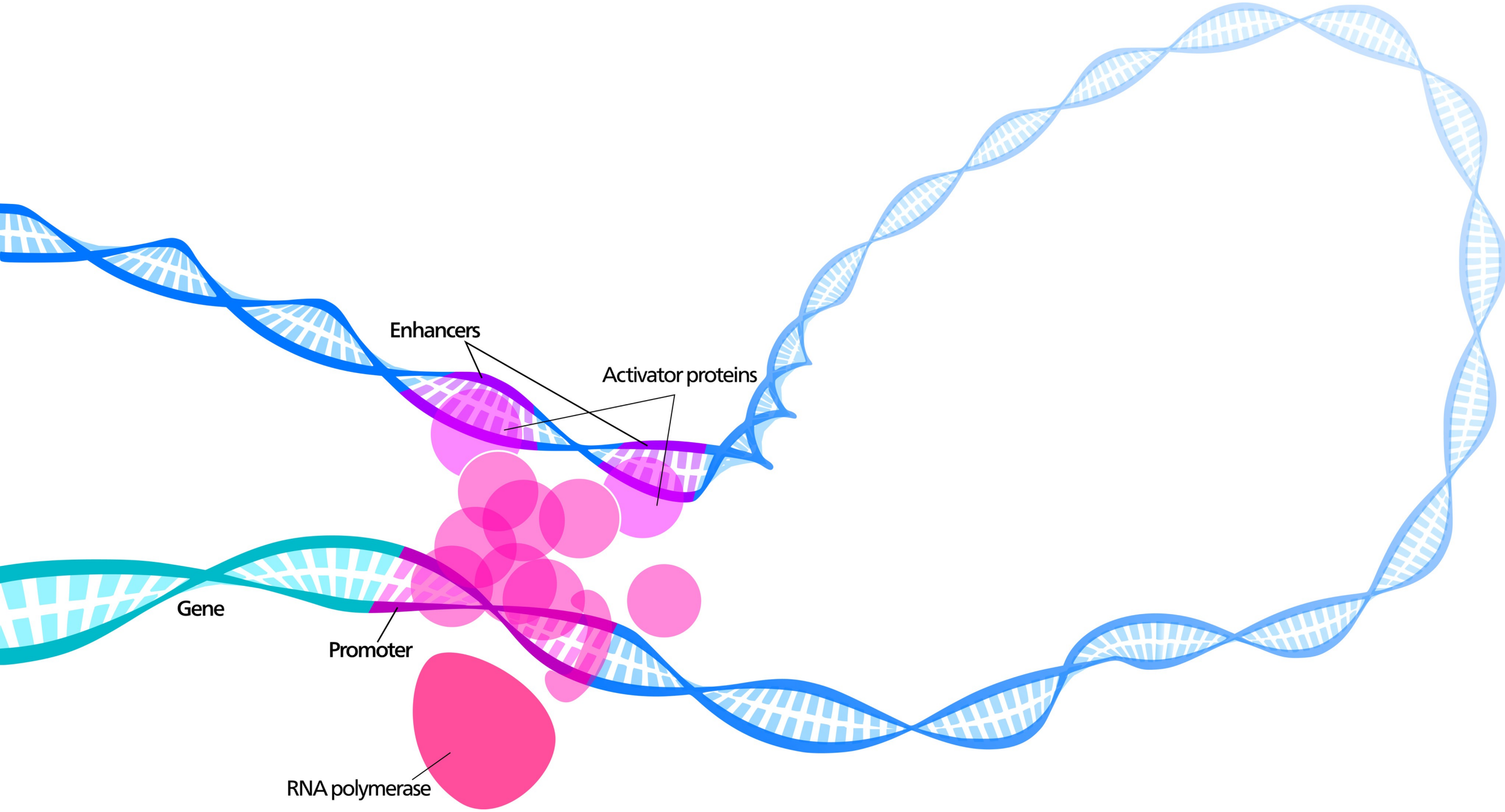
(Anshul Kundaje's group from Stanford)

Deep Learning for Regulatory Genomics

1. **Biological foundations: Building blocks of Gene Regulation**
   - Gene regulation: Cell diversity, Epigenomics, Regulators (TFs), Motifs, Disease role
   - Probing gene regulation: TFs/histones: ChIP-seq, Accessibility: DNase/ATAC-seq
   - Three-dimensional chromatin structure, Hi-C, ChIA-PET, TADs, Loop Extrusion
2. **Classical methods for Regulatory Genomics and Motif Discovery**
   - Enrichment-based motif discovery: Expectation Maximization, Gibbs Sampling
   - Experimental: PBMs, SELEX. Comparative genomics: Evolutionary conservation.
3. **Regulatory Genomics CNNs (Convolutional Neural Networks): Foundations**
   - Key idea: pixels ⇔ DNA letters. Patches/filters ⇔ Motifs. Higher ⇔ combinations
   - Learning convolutional filters ⇔ Motif discovery. Applying them ⇔ Motif matches
4. **Regulatory Genomics CNNs/RNNs in Practice: Diverse Architectures**
   - DeepBind: Learn motifs, use in (shallow) fully-connected layer, mutation impact
   - DeepSea: Train model directly on mutational impact prediction
   - Basset: Multi-task DNase prediction in 164 cell types, reuse/learn motifs
   - ChromPuter: Multi-task prediction of different TFs, reuse partner motifs
   - DeepLIFT: Model interpretation based on neuron activation properties
   - DanQ: Recurrent Neural Network for sequential data analysis
5. **Guest Lecture: David Kelley on Basset and Deep Learning for Hi-C looping**

David Kelley 1 - Basset

How are genes regulated?



Where/when does this sequence generate transcription?

TTACCGCGCAGGTTCACCGTTGGCTAACCGATCGCGAGTATGGGTCATTGTCGCTGTTCTTAGCTGCATTCGGCGATCCCGATCTCCACAGCGCCAAATTTCGGTAAGAACATCCCGTGCTTACTATAGCAACCGGAGGTGCTGTTTT
TACGGTCGCGAATAGCCTGAGGCAGTGTAGGTATACCACCTCACGTGGGGCGAACCAATTTTAGATTTAGGGCGACGAGCTATACGTCTGATGCAATAAGACTATTATGTTGCTGGCGCATAGGGTGCGAGTGCCTTCTCCCGGGCTT
GAGCTAACTAAAGACACCGCTGTAAAACCGAACAGTATTGGTATATGTAGCTGGTTCTTTAATAAACGACTTGGTATCGTTGAAGATTATTGGCCGCCTAATCACTCTCGCACTCCTGGCATTAGTTTATGCTCGTATATGTTCCTGG
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CGTGTGAGACTTCTGCGATTTTCCCCTAACCGTAAGCTCTCCTCAAGATATGTAATTTATAACCAGGCTGACTATAGTTCTCACAGCGTACCCTTCAGGAACGTGATACGGTTTAAGATGTCATCGCTCATCGAGGCTTCCATGGAGT
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How about now?

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Biological sequence representations

ACGTGATTACAACGT

Biological sequence representations

ACGTGATTACAACGT

ACGT 1

Biological sequence representations

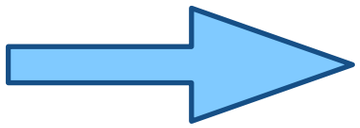
ACGTGATTACAACGT

ACGT	1
CGTG	1

Biological sequence representations

ACGTGATTACAACGT

AACG	1
ACAA	1
ACGT	2
ATTA	1
CAAC	1
CGTG	1
GATT	1
GTGA	1
TACA	1
TGAT	1
TTAC	1
_____	0



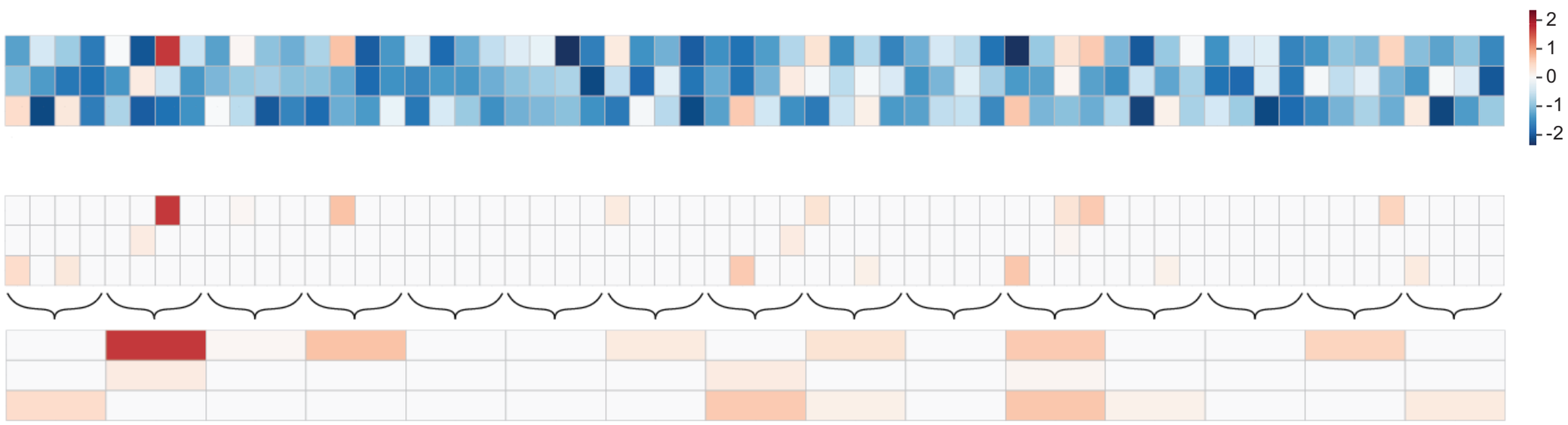
Can we learn better representations?

DNA convolutional neural network

ATTCCCGTAATCTACGATTAAGTCACAACCAAACCATGGATTACGGTCTGCGTTGGAATCAGGGCCGTGC

A
C
G
T

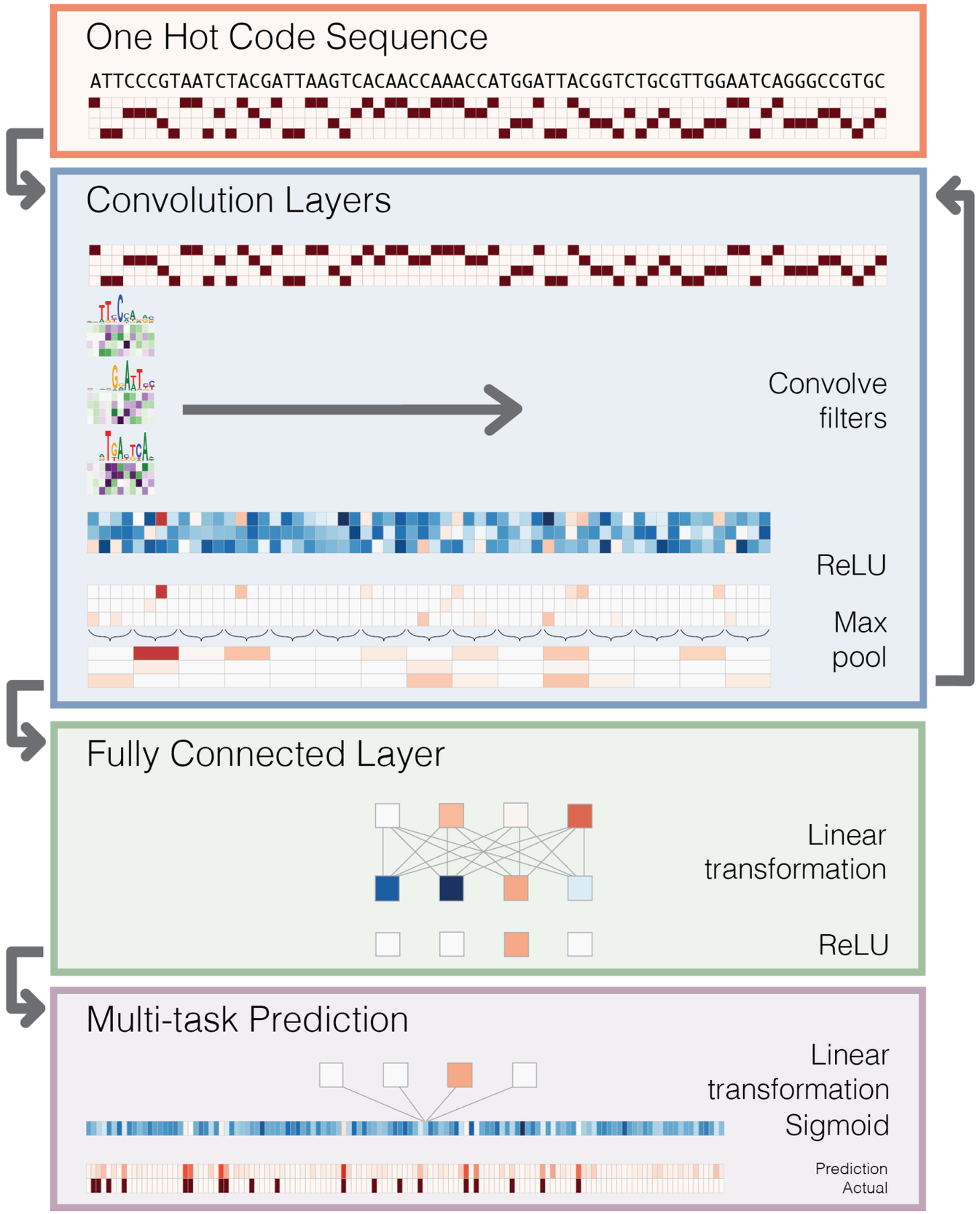
Convolve filters



ReLU

Max pool

DNA convolutional neural network



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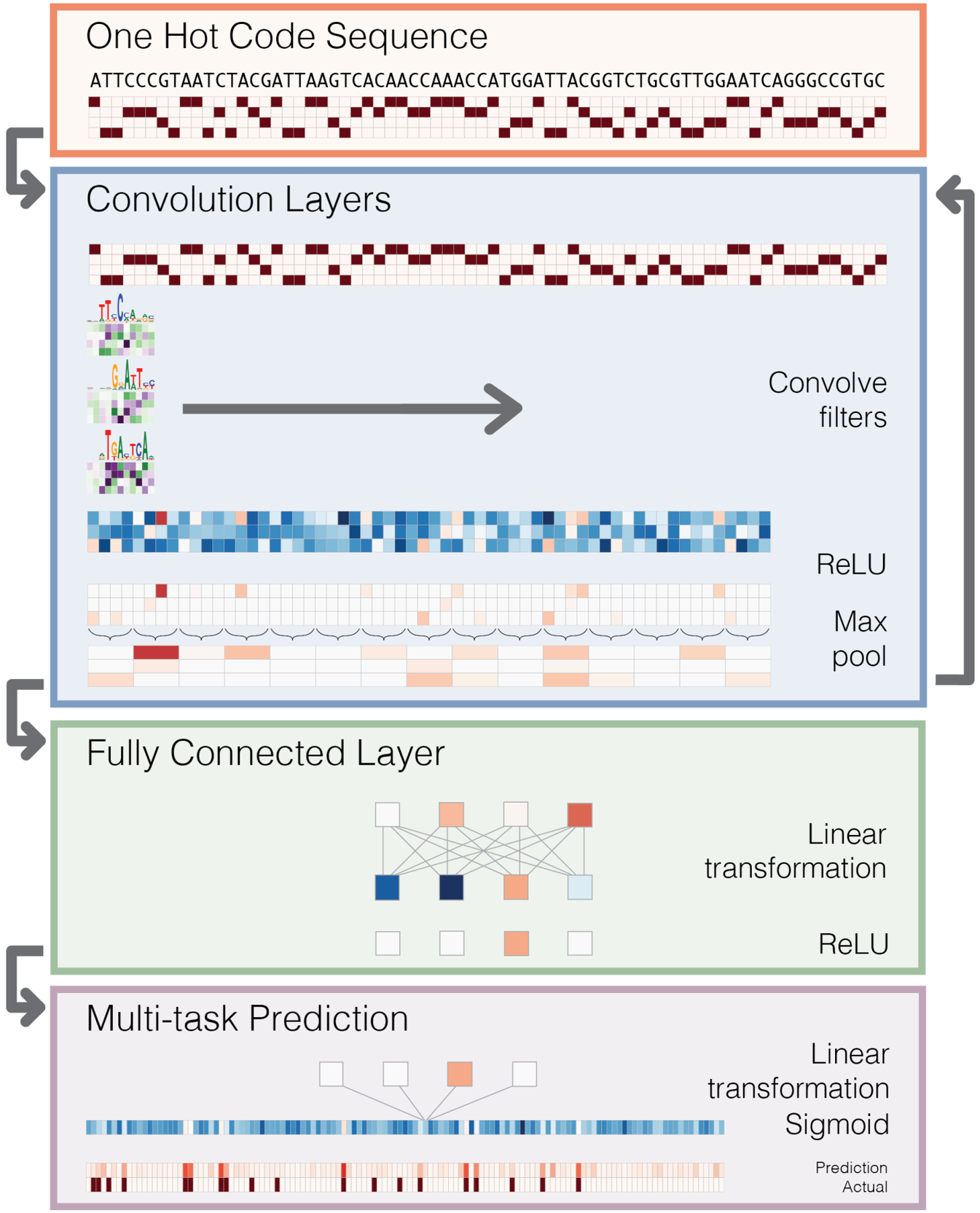
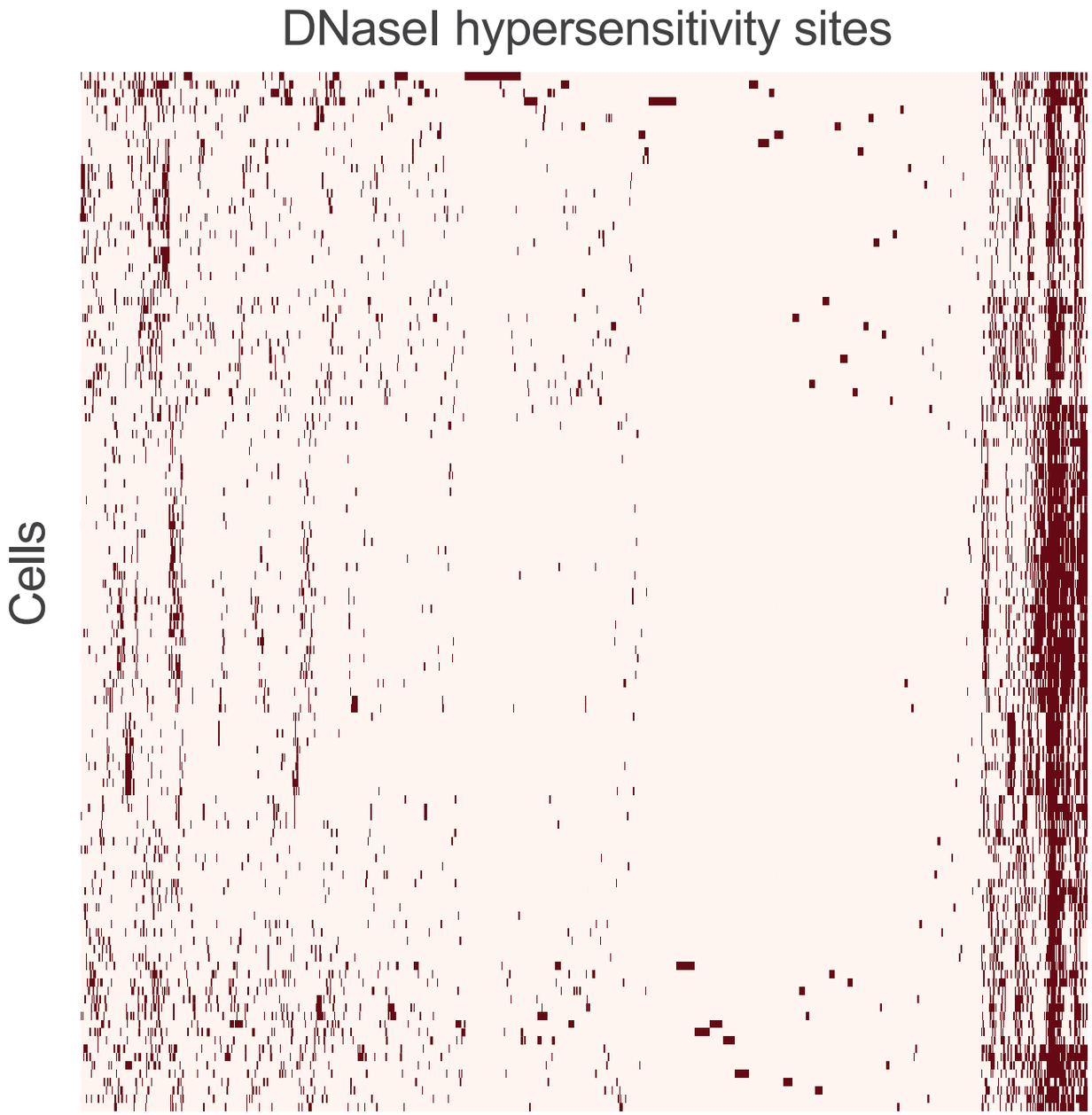

One Hot Code Sequence
ATTCCCGTAATCTACGATTAAGTCACAACCAAACCATGGATTACGGTCTGCGTTGGAATCAGGGCCGTGC
Convolution Layers
Convolve filters
ReLU
Max pool
Fully Connected Layer
Linear transformation
ReLU
Multi-task Prediction
Linear transformation
Sigmoid
Prediction
Actual

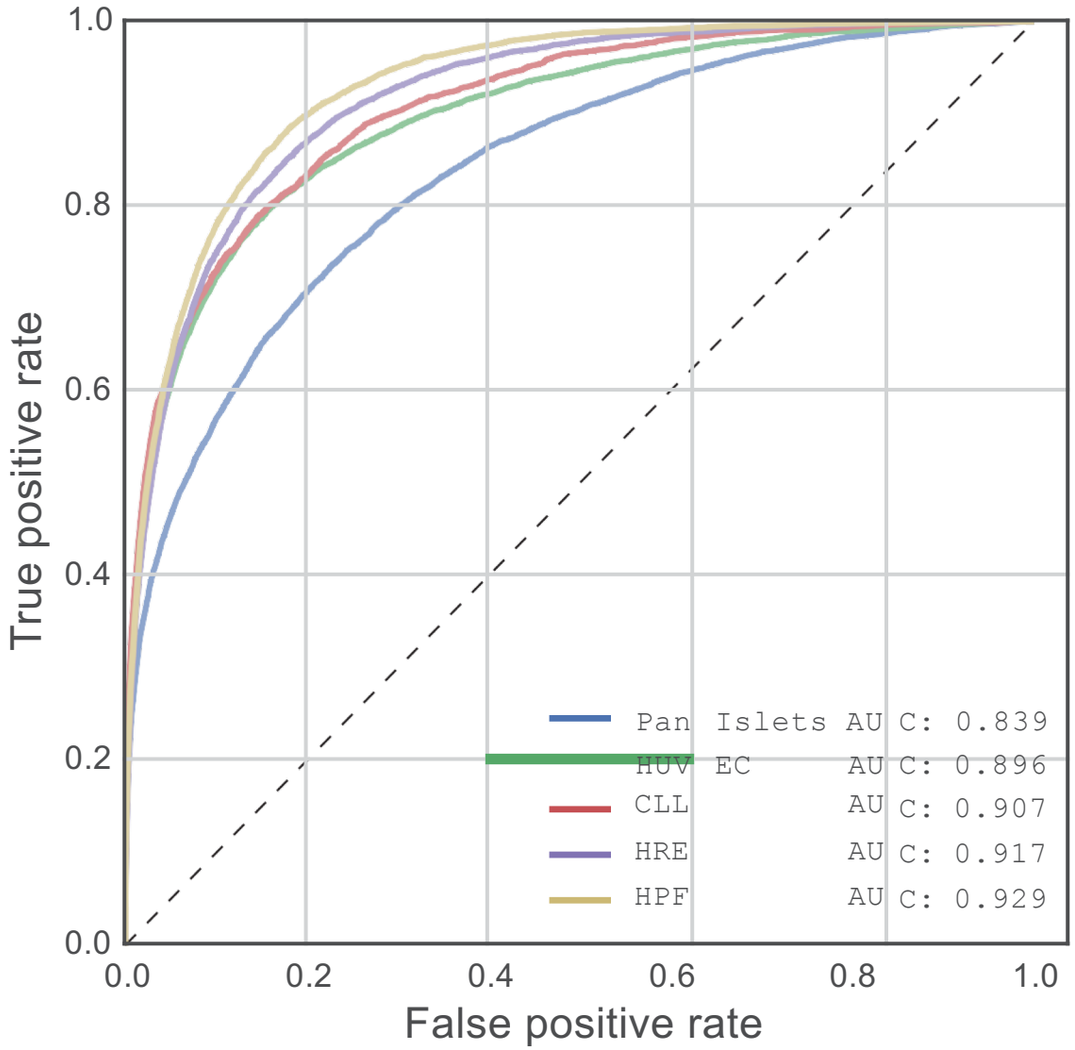
Demonstration: DNaseI hypersensitivity

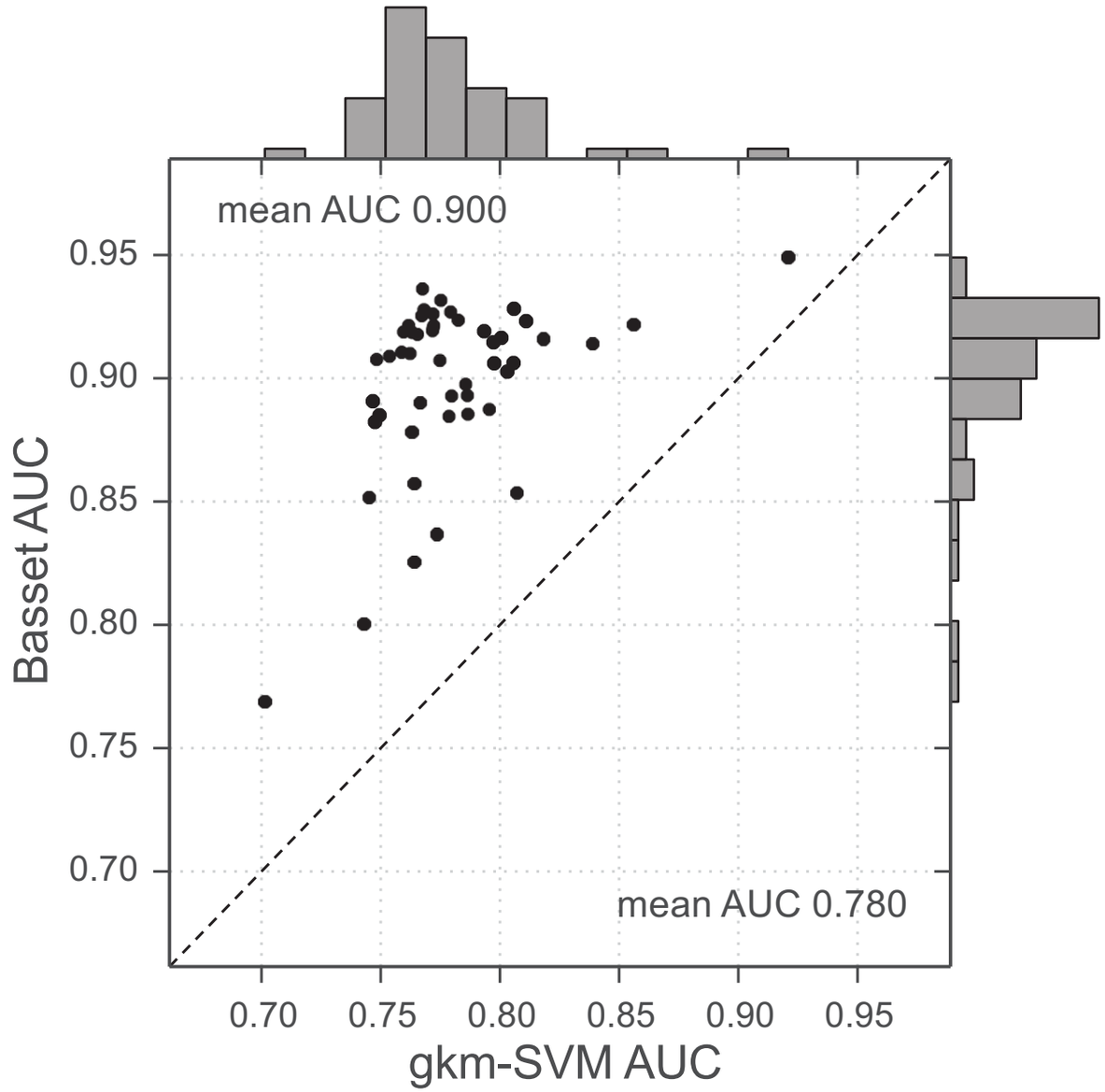
- DNaseI-seq from 164 cell types from ENCODE and Epigenomics Roadmap.

- 2 million sites—broken into training, validation, and test sets.



Conv nets accurately predict DNase hypersensitivity





Ghandi, Lee et al. Enhanced Regulatory Sequence Prediction Using Gapped k-mer Features. PLoS Comp Bio, 2014.

Filters recapitulate known TF binding motifs

OCT4

CIS-BP

Filters recapitulate known TF binding motifs

CTCF

CIS-BP

Basset

FOS

CIS-BP

Basset

HNF4A

CIS-BP

Basset

OCT4

CIS-BP

Basset

SNAI1

CIS-BP

Basset

P63

CIS-BP

Basset

NFIX

CIS-BP

Basset

FOXA2

CIS-BP

Basset

IRF1

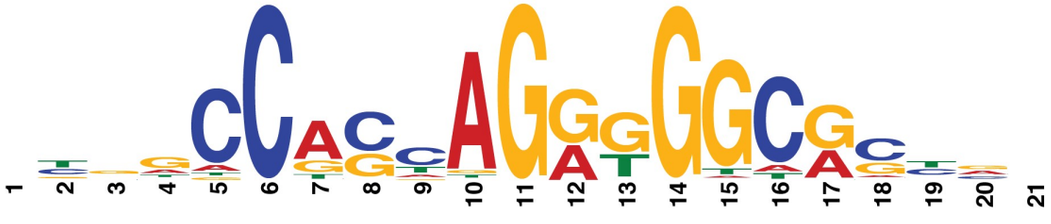
CIS-BP

Basset

Multiple filters capture motif variants

CTCF

CIS-BP



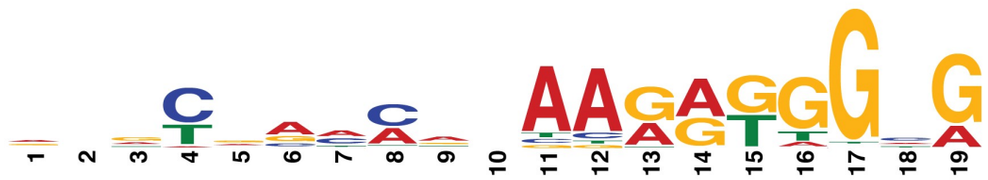
Basset

filter9

filter185

filter200

filter147

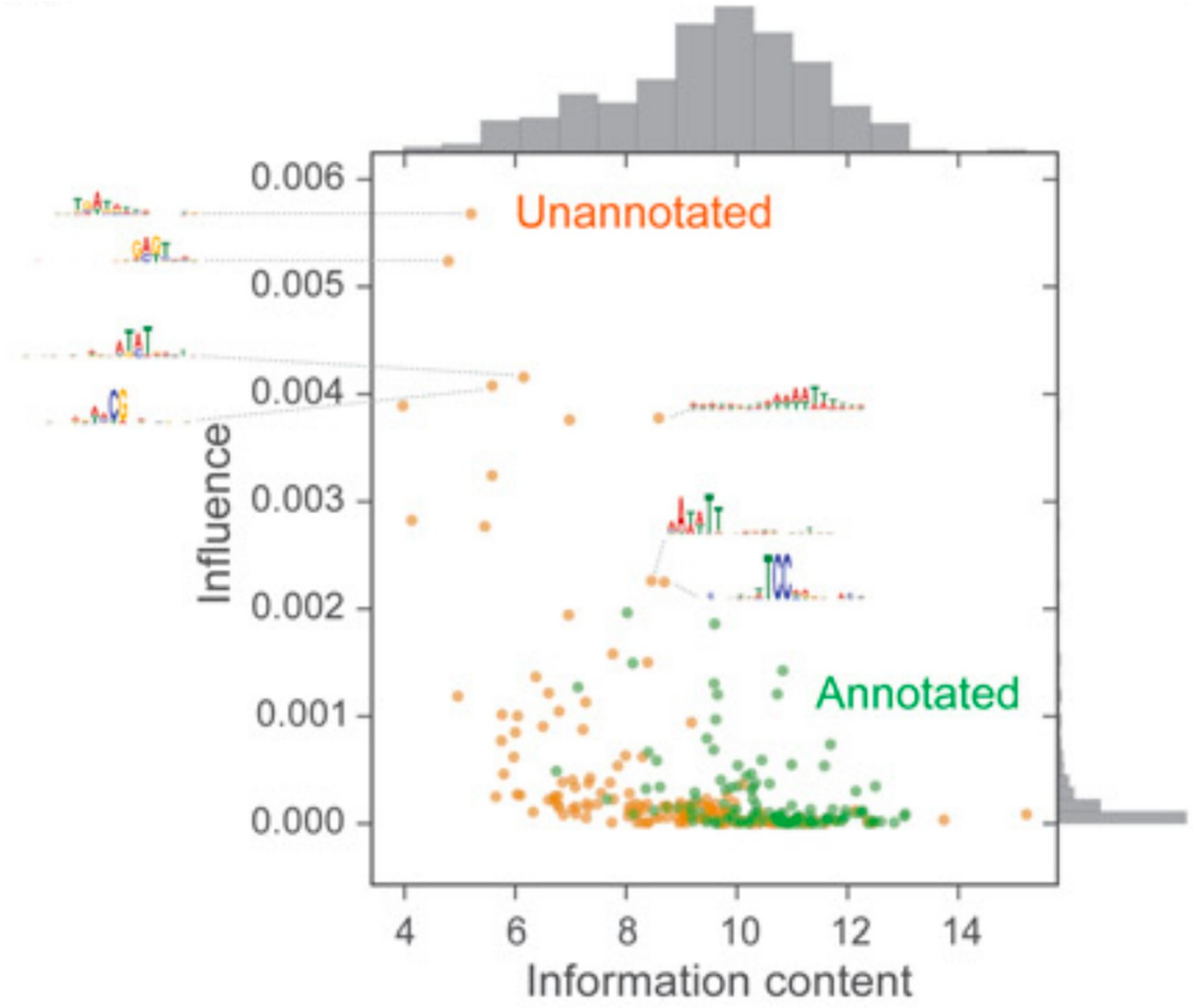


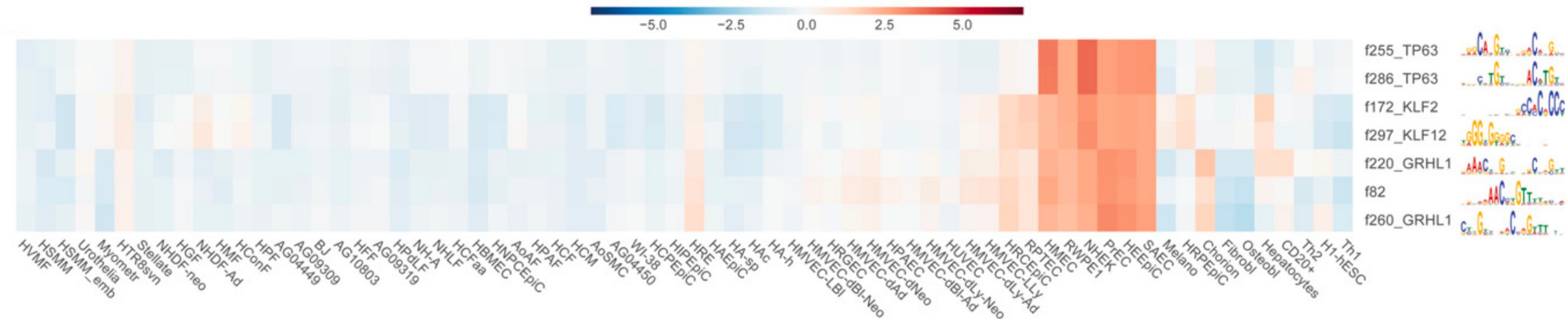
filter231

filter106

filter68

Dense representations challenge filter interpretation





Known motif injection

GGTGTCAGCAGCAGCCCCGCTTTCCGATTCGGACTCCATGCGGCGCAAGCGGCGGATCCACTTCTCTGGGCCCAAACGCCTCCCAGAGTCAGCTCTGCGCGACGACGCGGAACTCGAGCC

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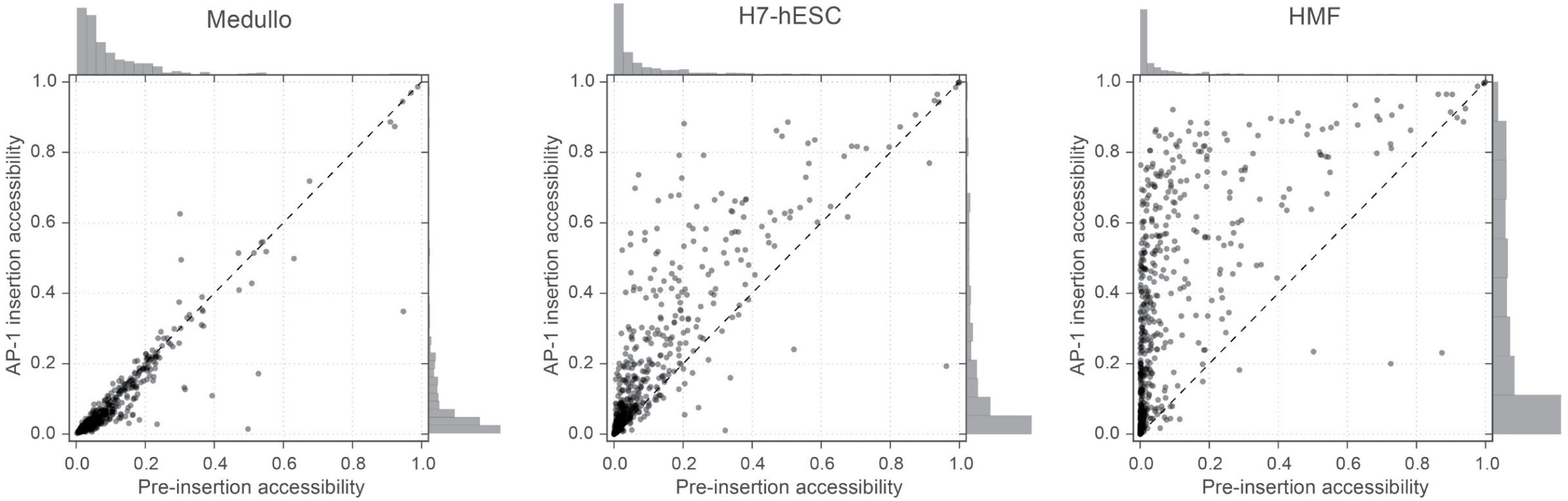
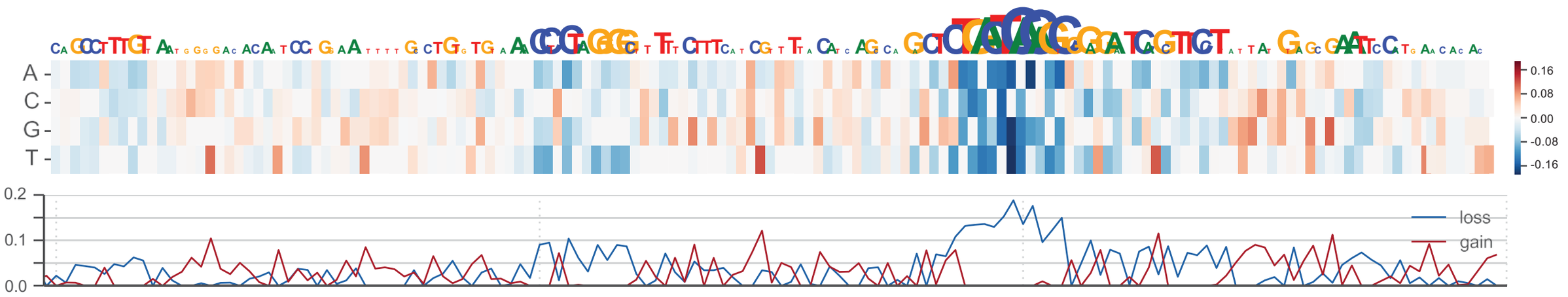
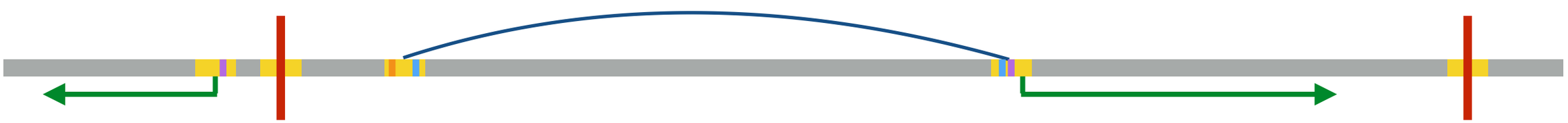


Annotate nucleotide influence



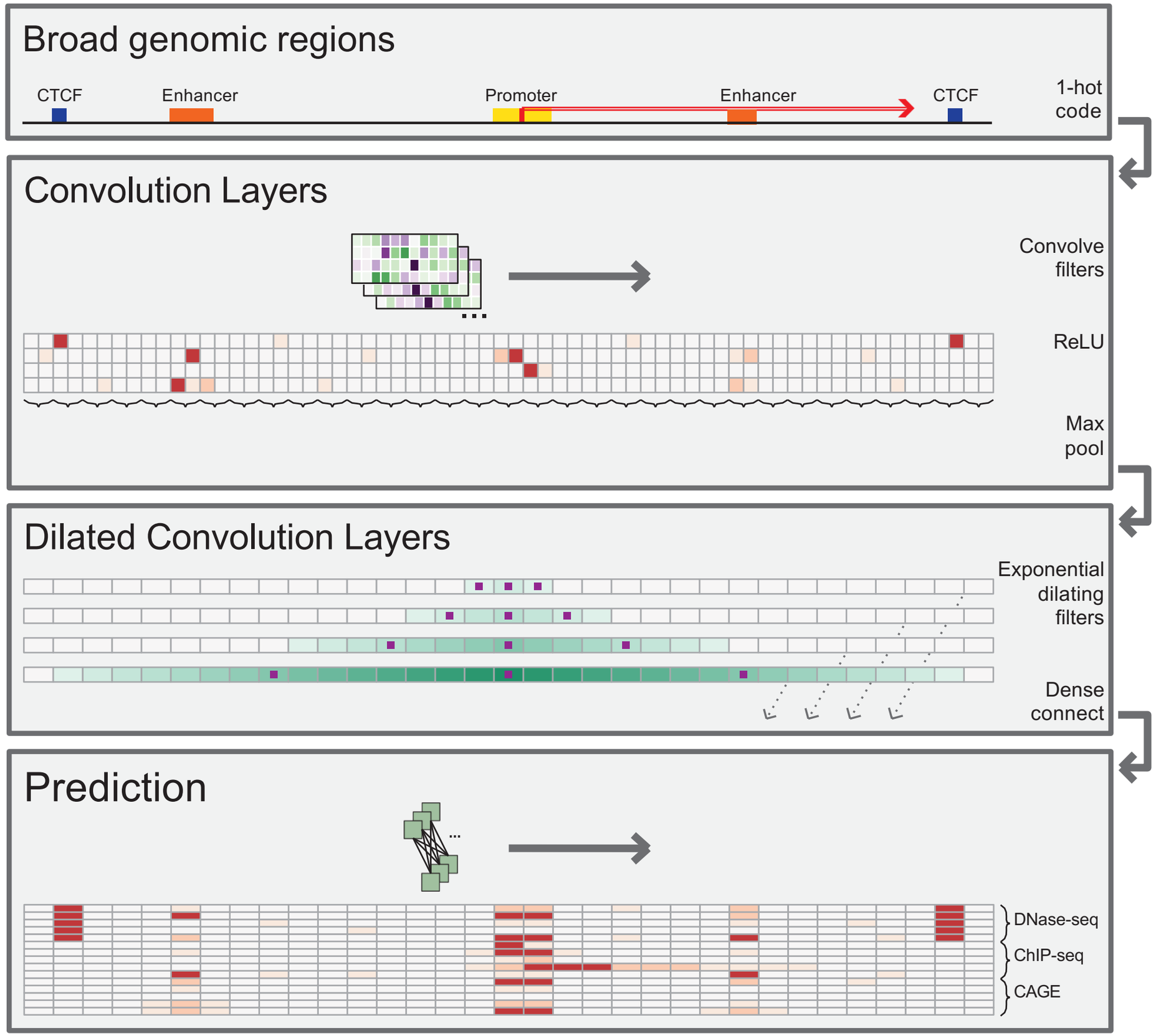
Can we predict transcription?



f( )

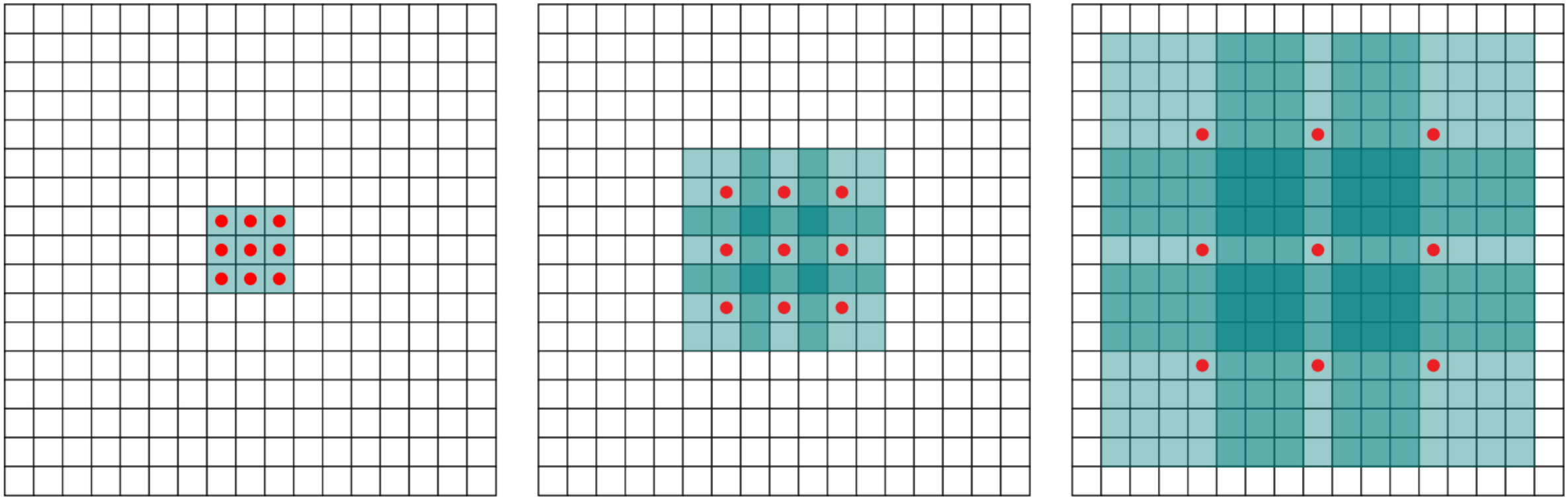
David Kelley 2 – Incorporating broader context

Sequential regulatory activity prediction



Kelley, D., et al. Sequential regulatory activity prediction across chromosomes with convolutional neural networks. Genome Research, 2018.

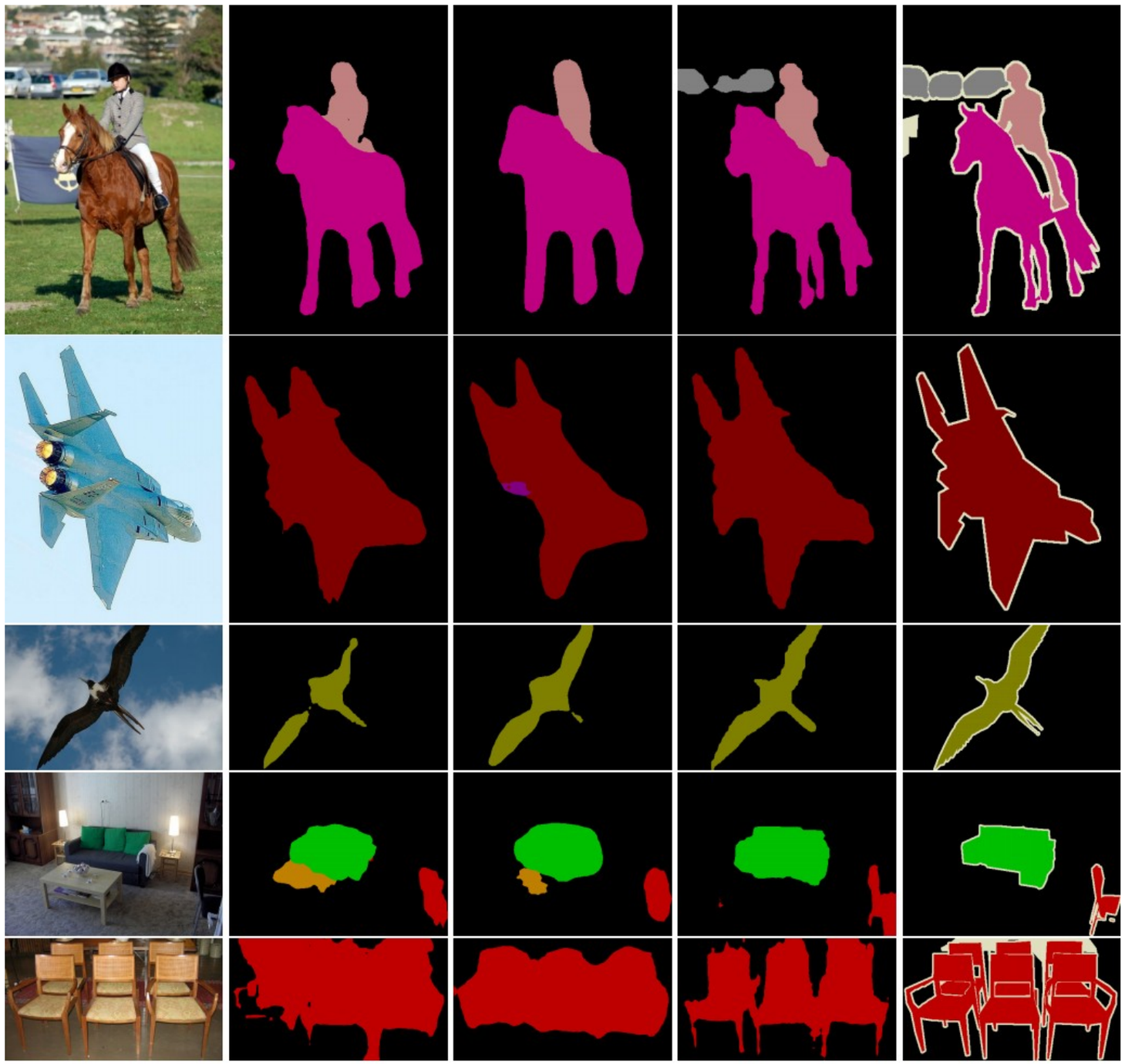
Dilated convolution



- Parameters grow linearly.
- Receptive field grows exponentially.

Yu, Koltun. Multi-scale context aggregation by dilated convolutions. ICLR, 2016.

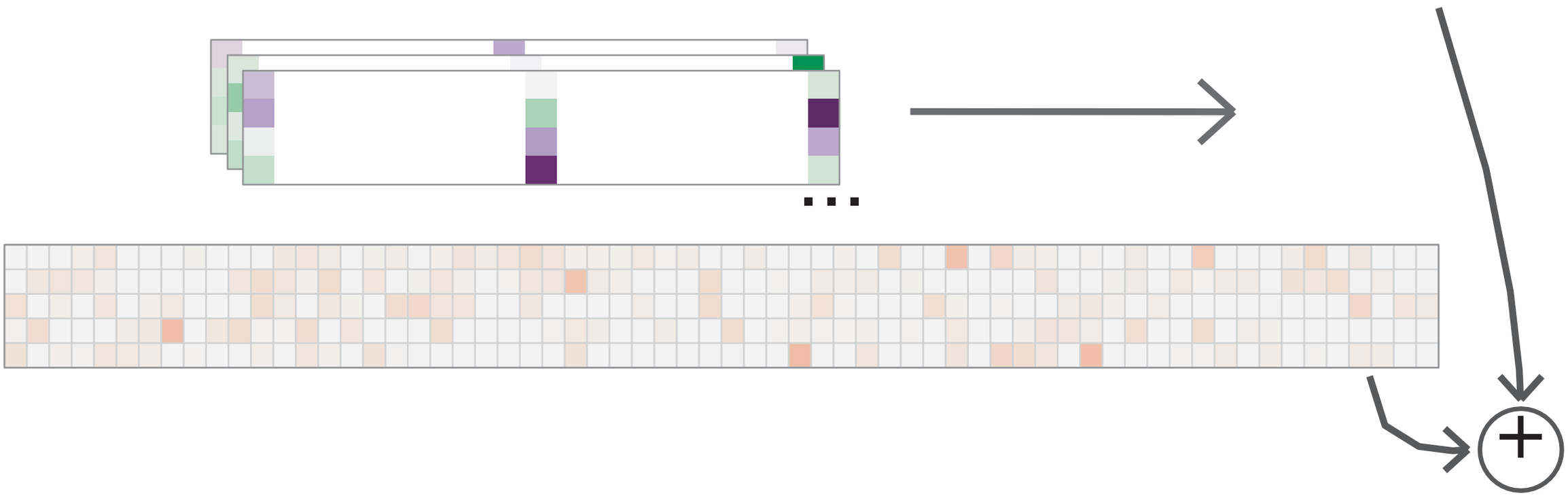
Dilated convolution for image segmentation



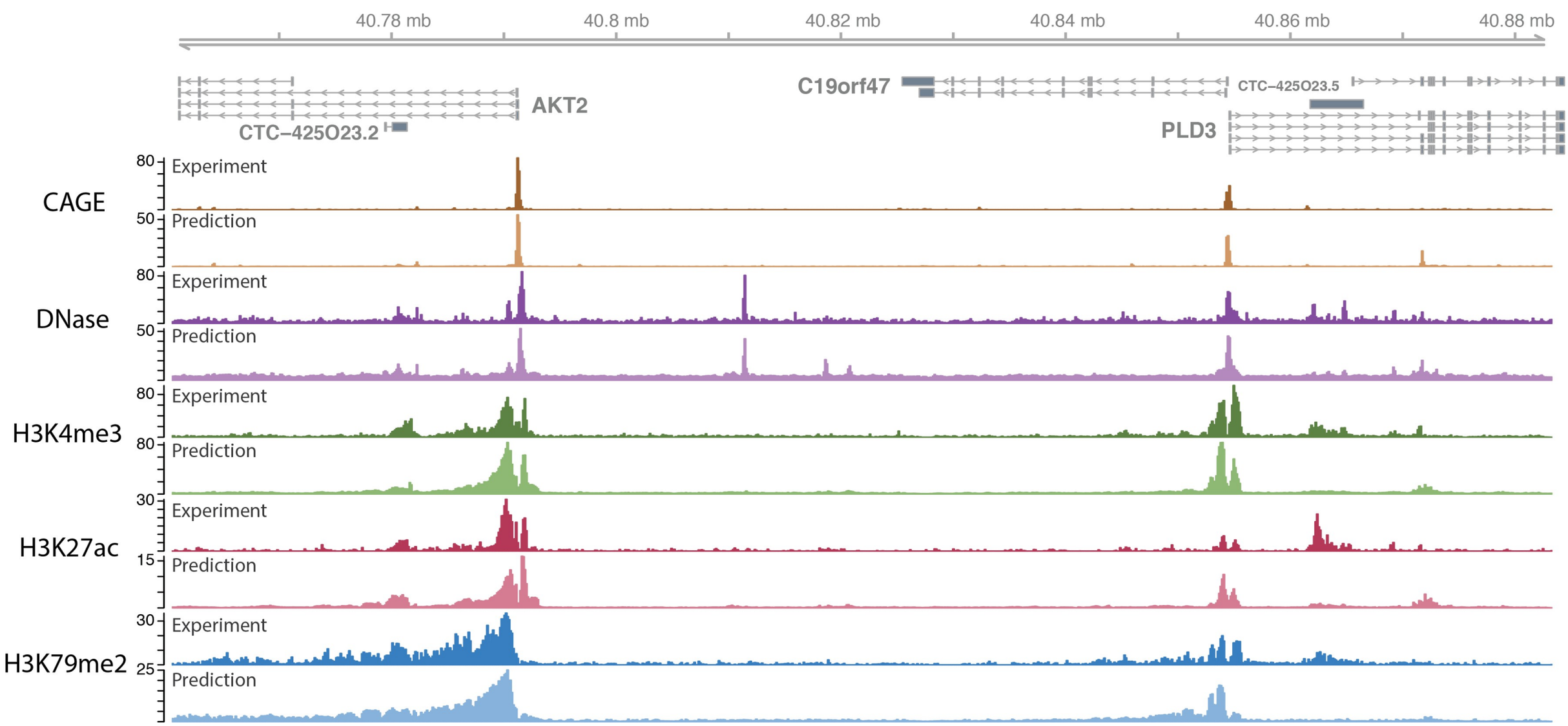
(a) Image (b) FCN-8s (c) DeepLab (d) Our front end (e) Ground truth

Yu, Koltun. Multi-scale context aggregation by dilated convolutions. ICLR, 2016.

Dilated convolution with residual connections

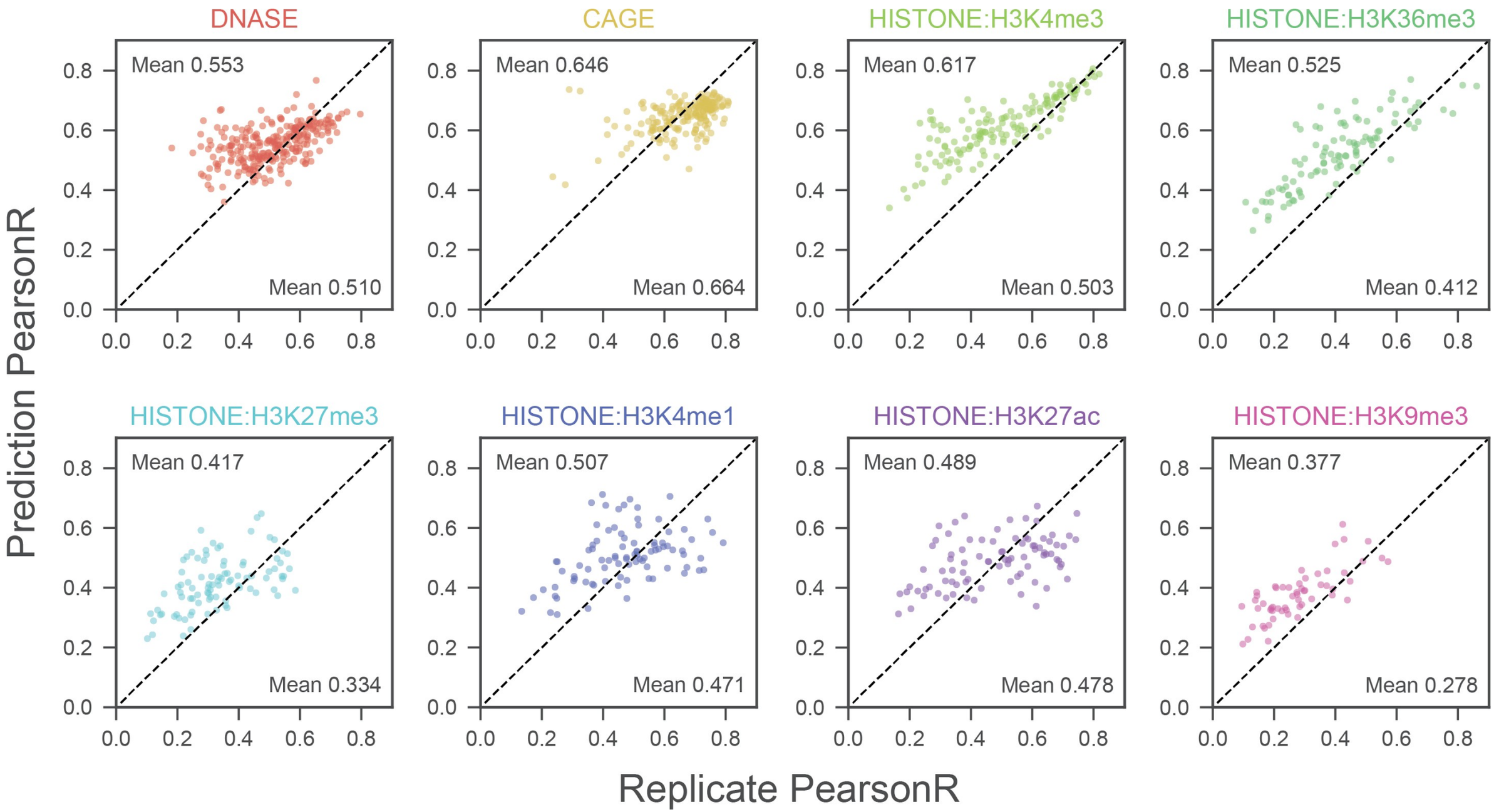


Model generalizes to held out sequences



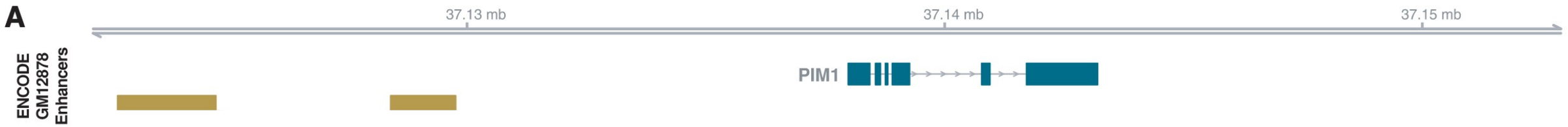
Kelley, D., et al. Sequential regulatory activity prediction across chromosomes with convolutional neural networks. Genome Research, 2018.

Predictions rival replicate experiment correlation

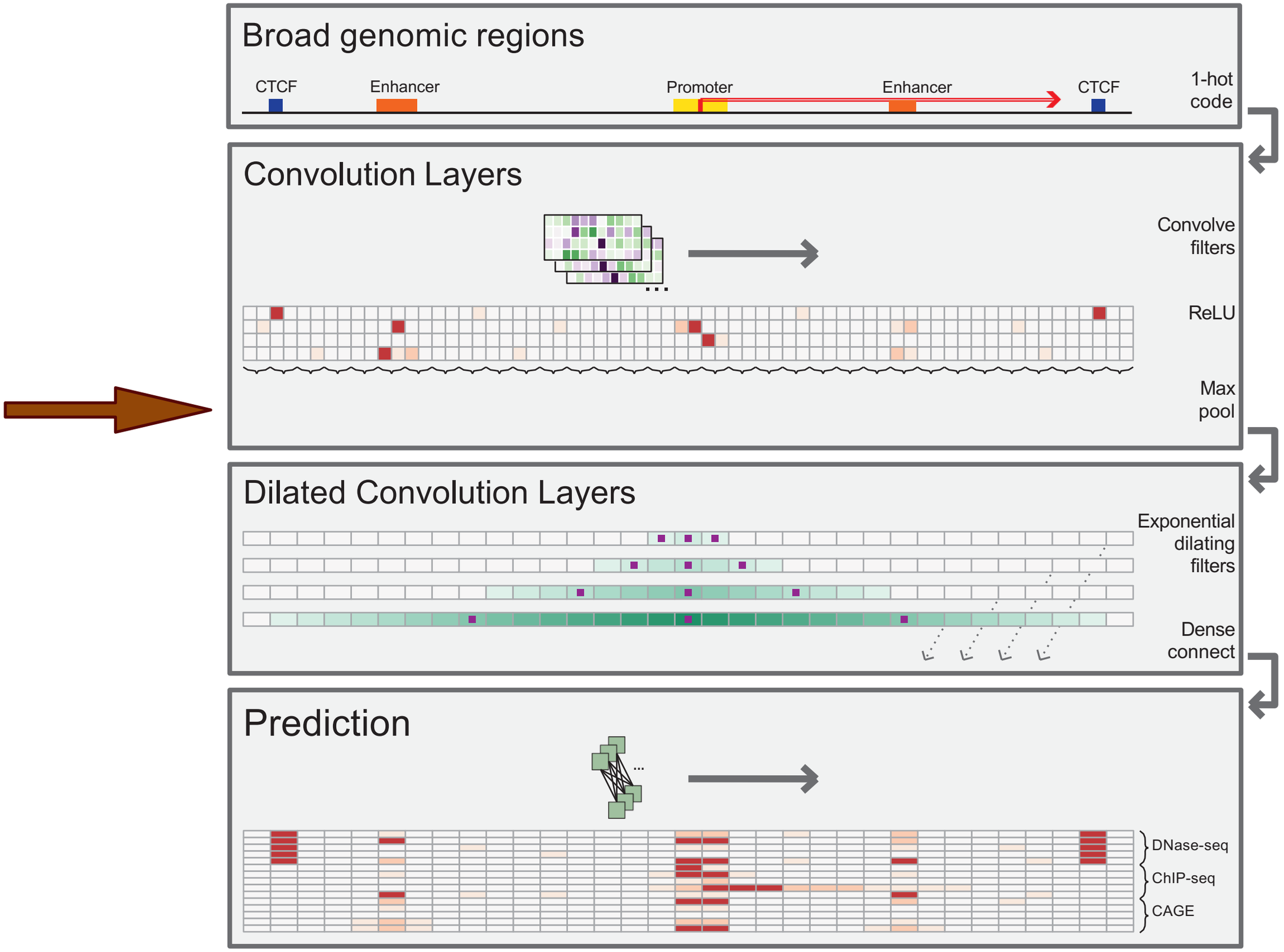


Kelley, D., et al. Sequential regulatory activity prediction across chromosomes with convolutional neural networks. Genome Research, 2018.

Does the model use sequence beyond the promoter?



Intermediate gradient



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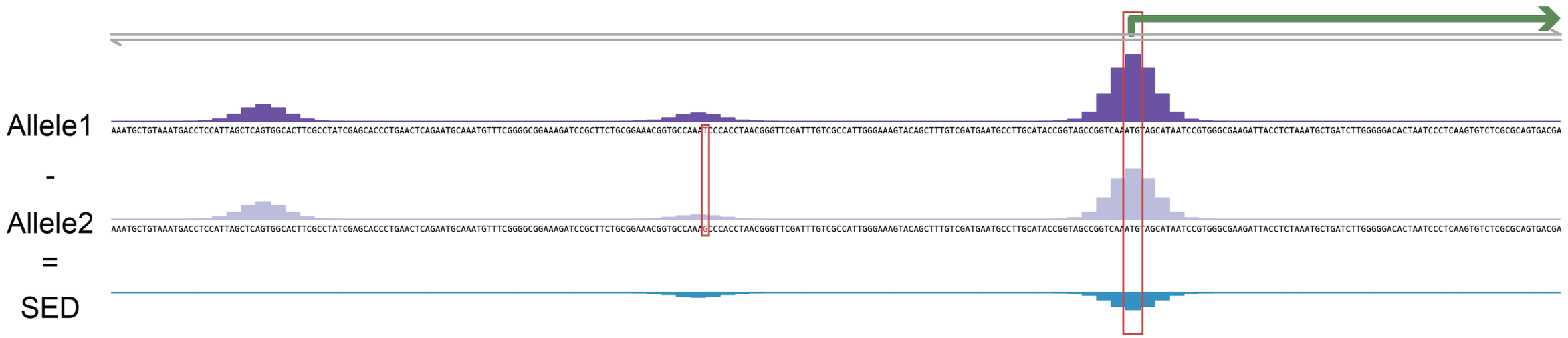
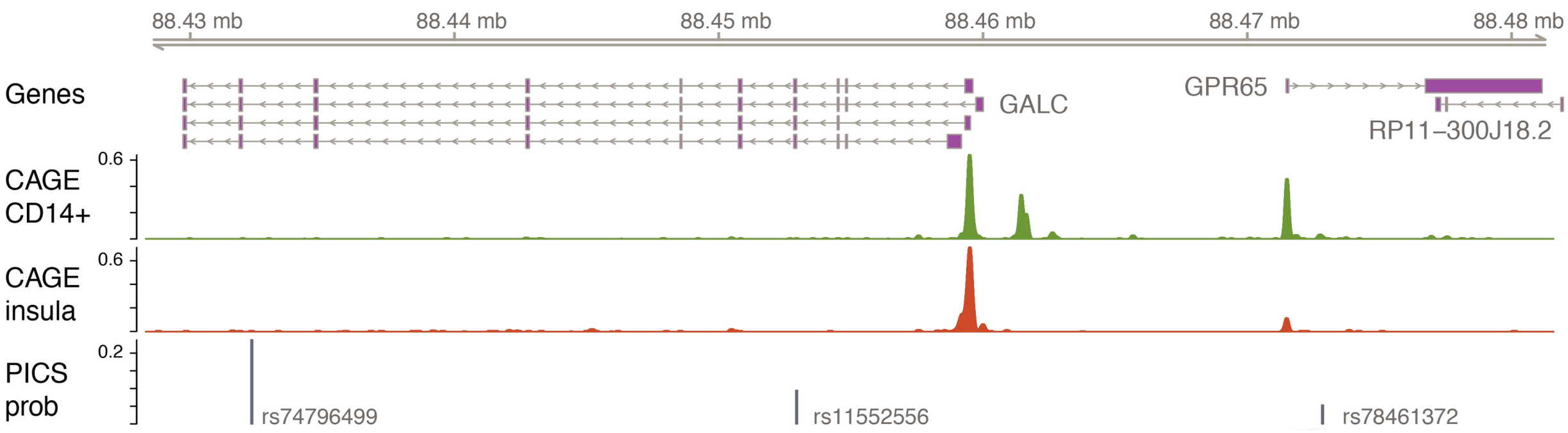
Enhancer maps

Kelley, D., et al. Sequential regulatory activity prediction across chromosomes with convolutional neural networks. Genome Research, 2018.

Predicting noncoding variant effects



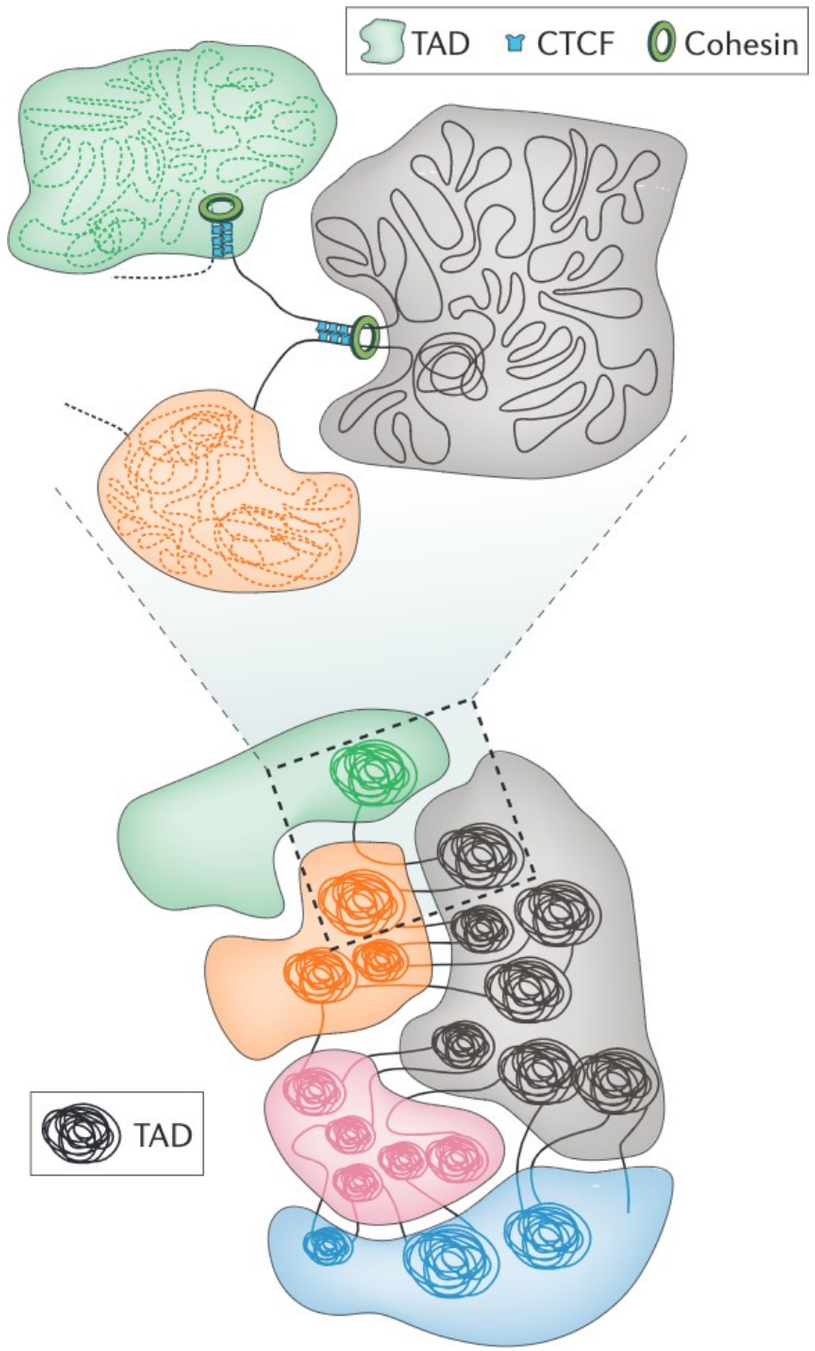
Case study: multiple sclerosis

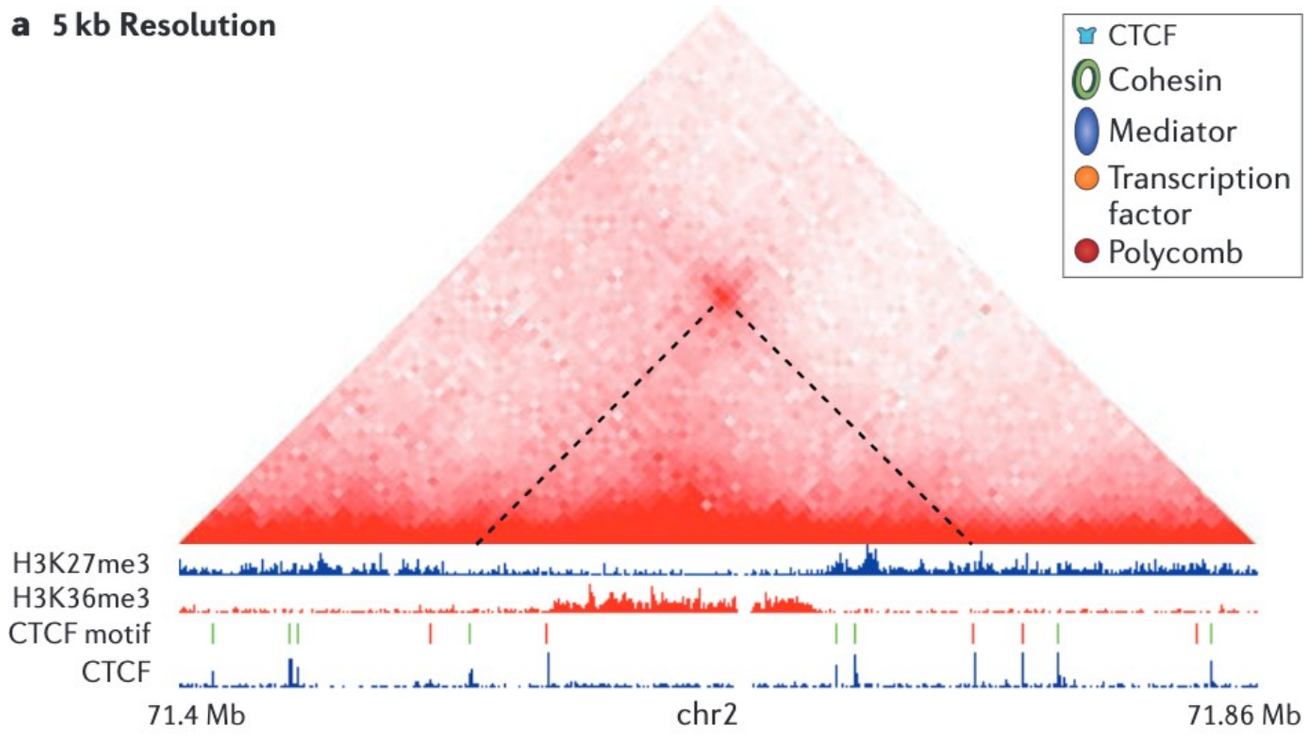


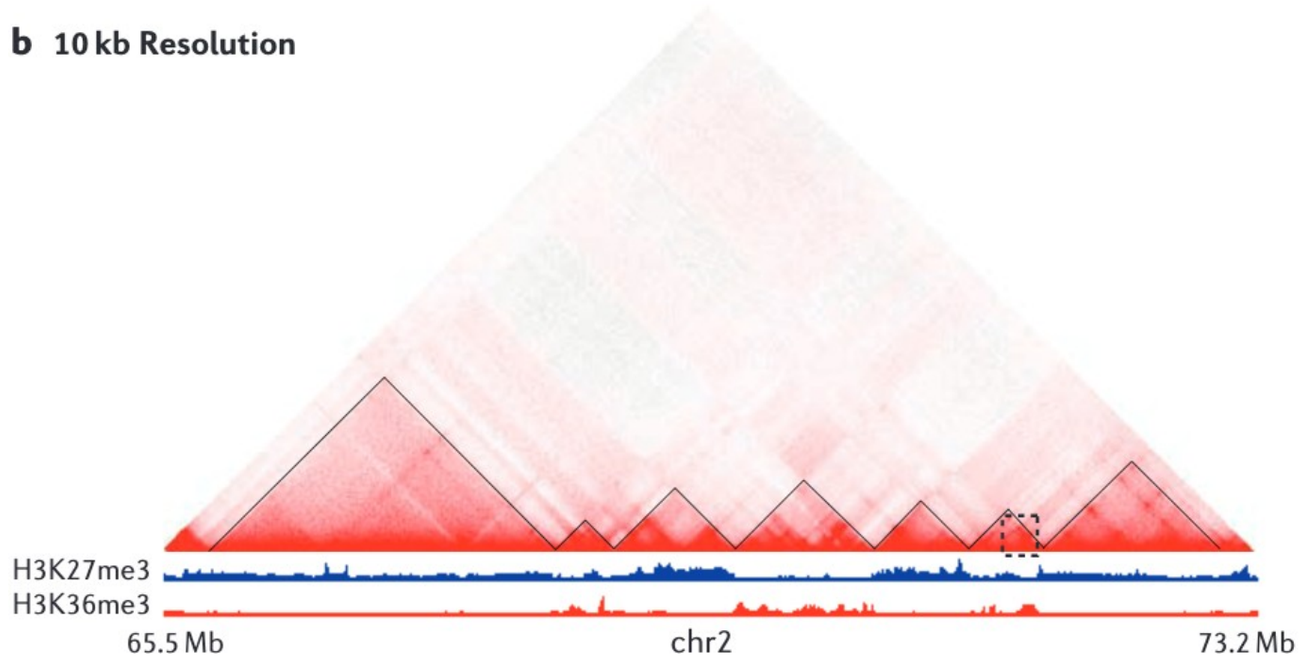
Kelley, D., et al. Sequential regulatory activity prediction across chromosomes with convolutional neural networks. Genome Research, 2018.

David Kelley 3 – Incorporating spatial information

3D contact and gene regulation

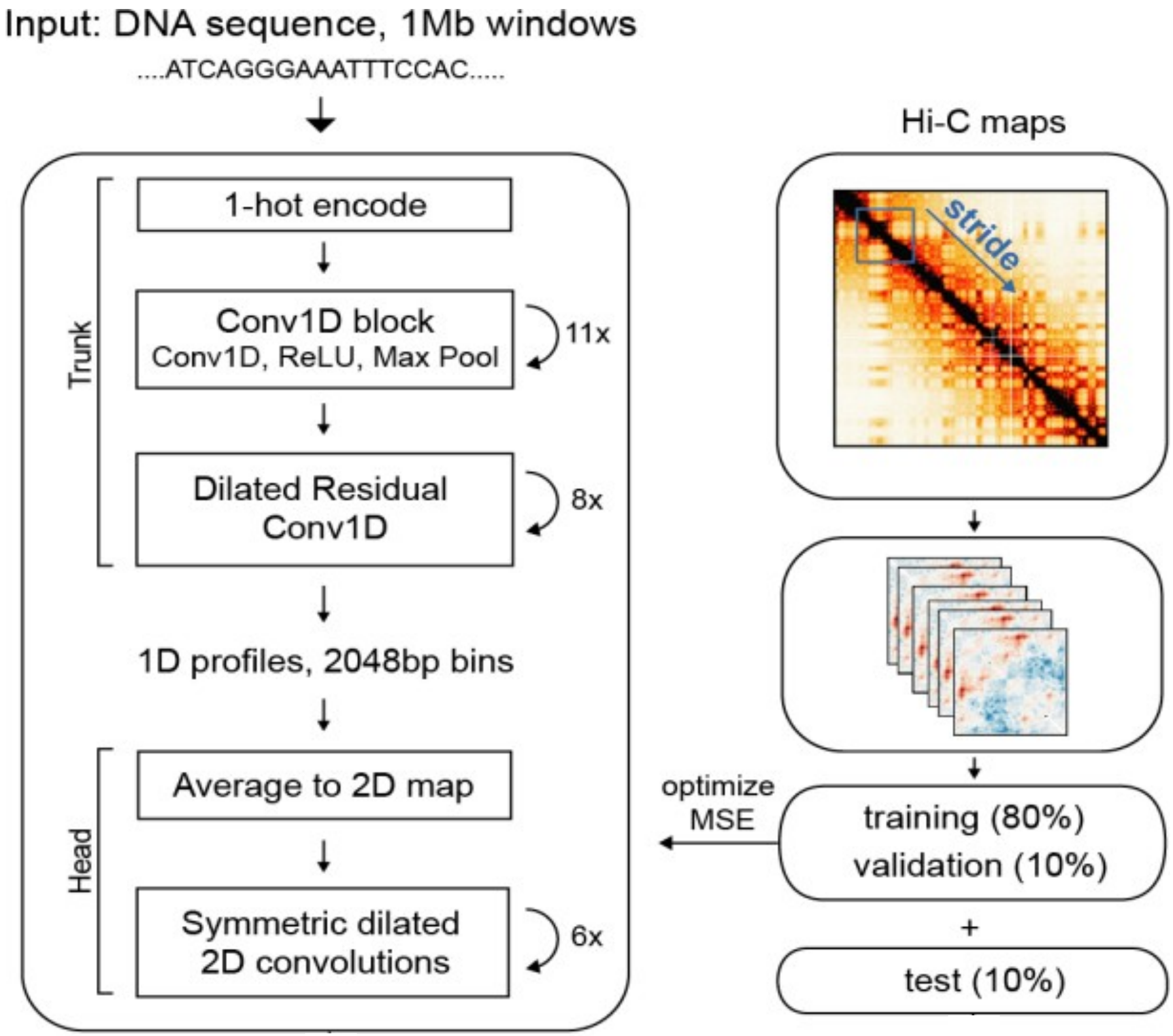






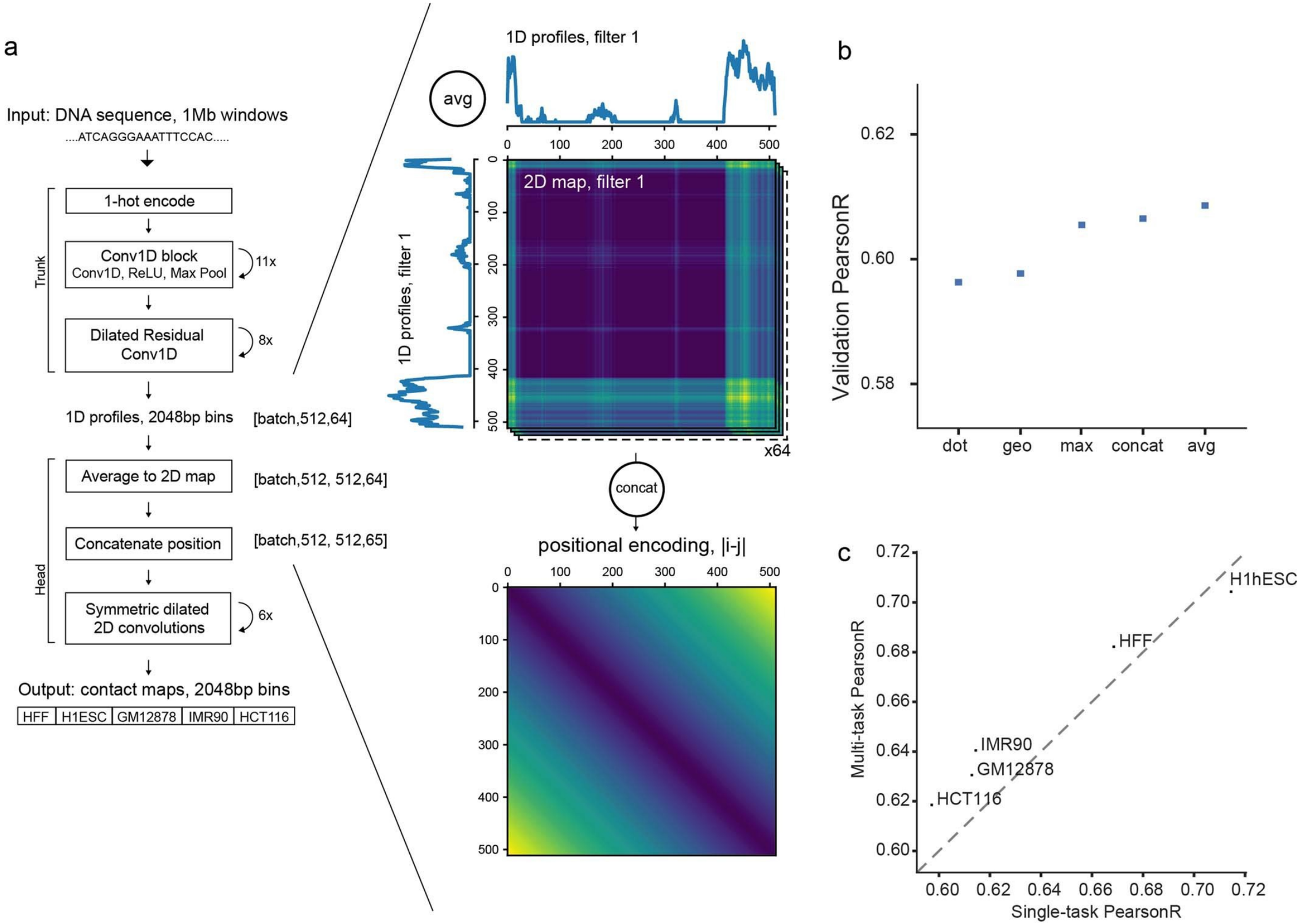
Bonev, Cavalli. Organization and function of the 3D genome. Nature Reviews Genetics, 2016.

Can we predict 3D contacts from DNA?



Fudenberg, Kelley, Pollard. Predicting 3D genome folding from DNA sequence. Nature Methods, 2020.

1D profiles to 2D maps



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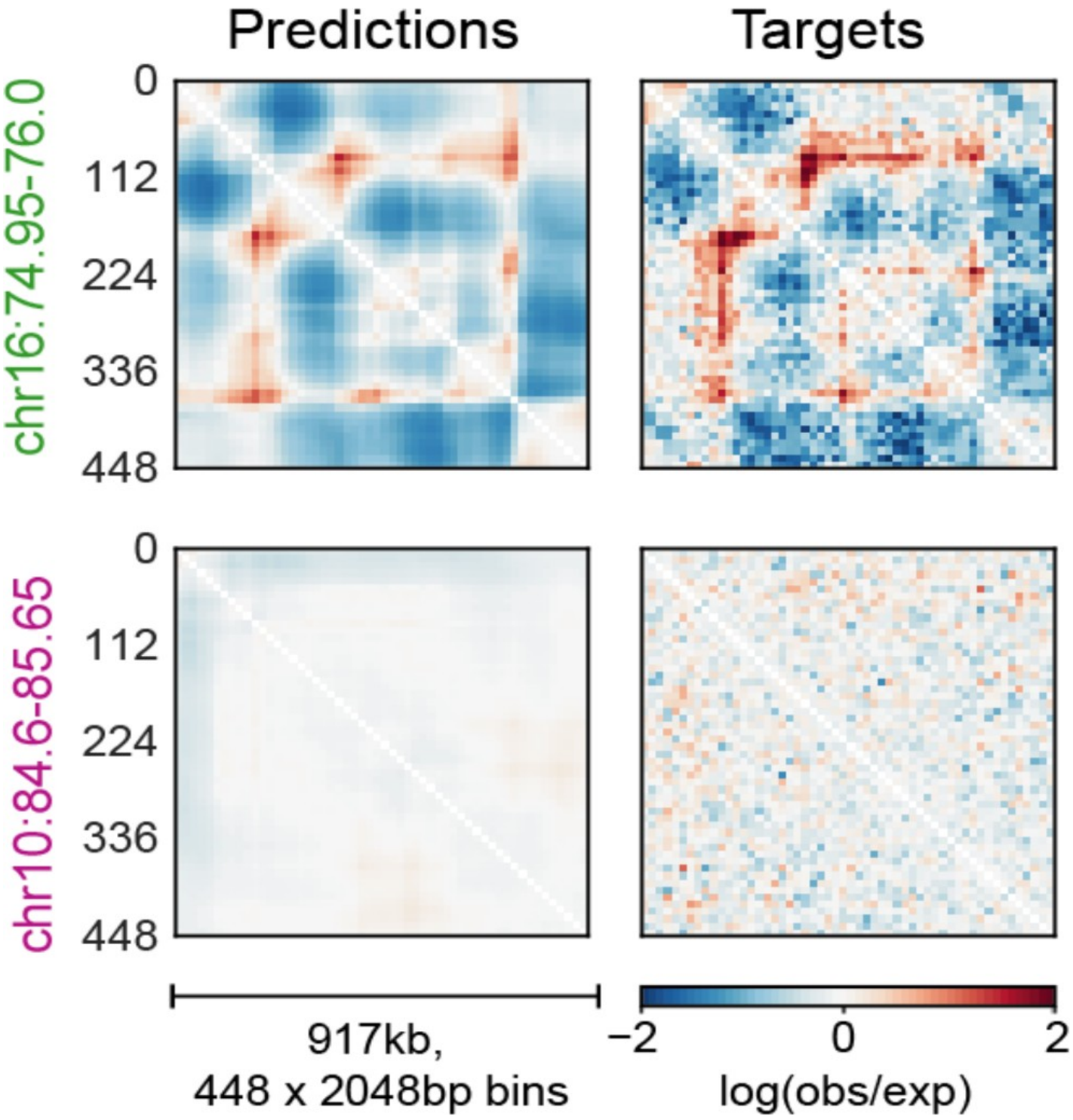
Predictions recover Hi-C contacts



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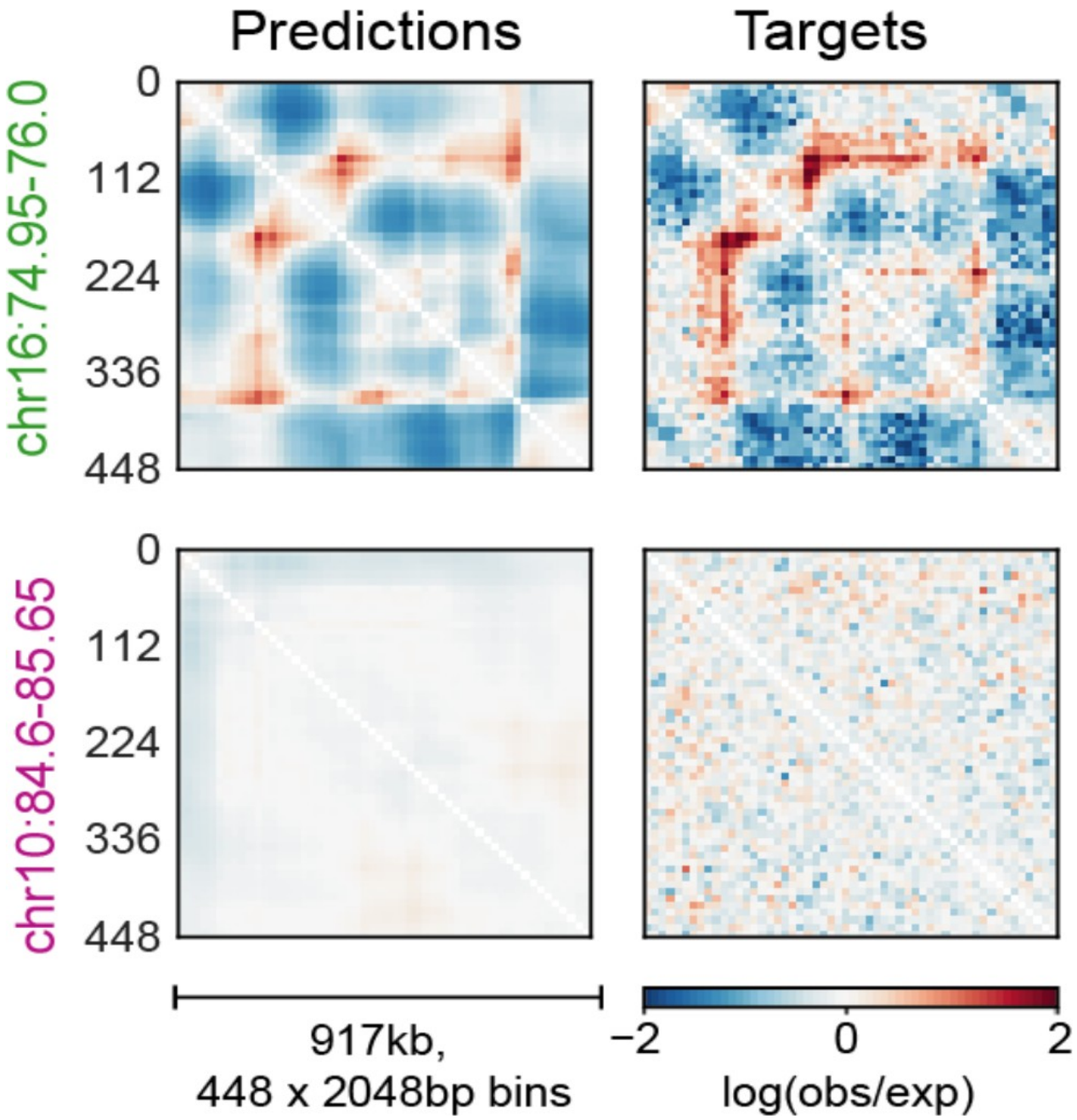
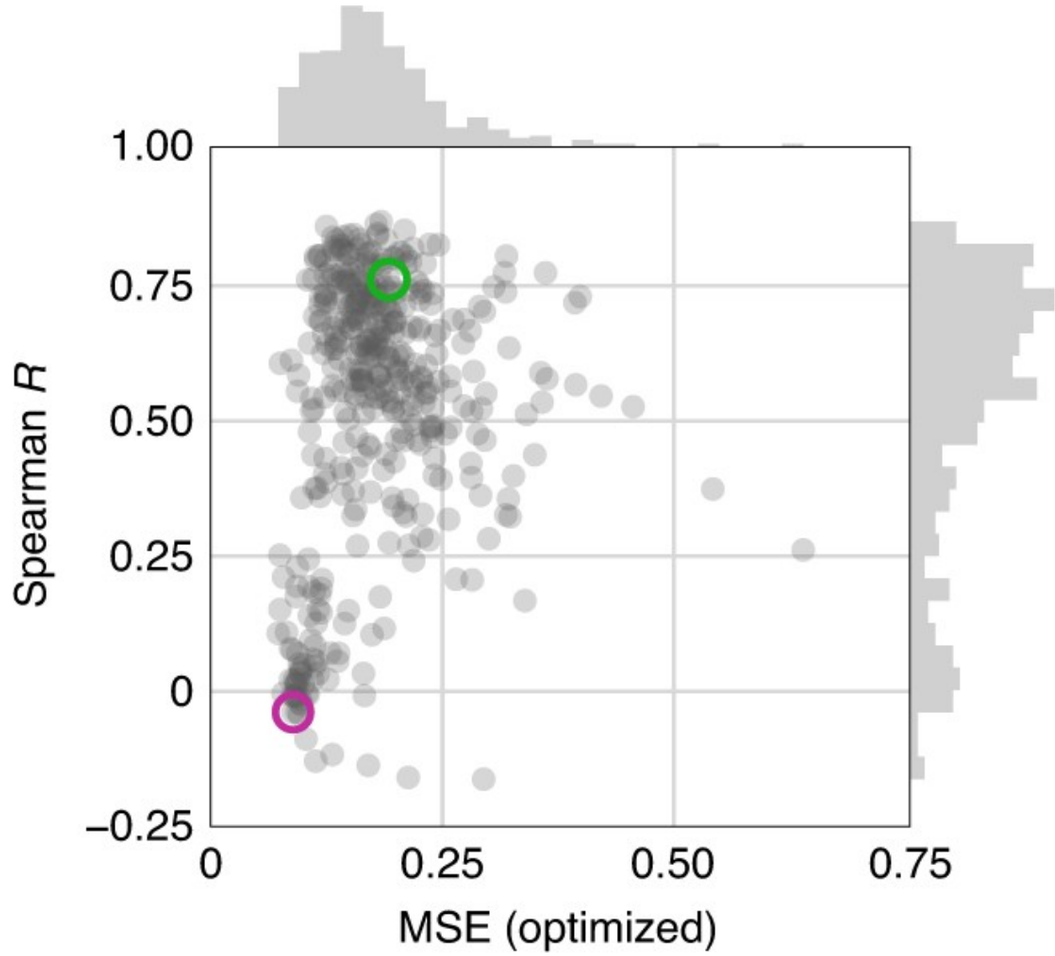
Predictions recover Hi-C contacts





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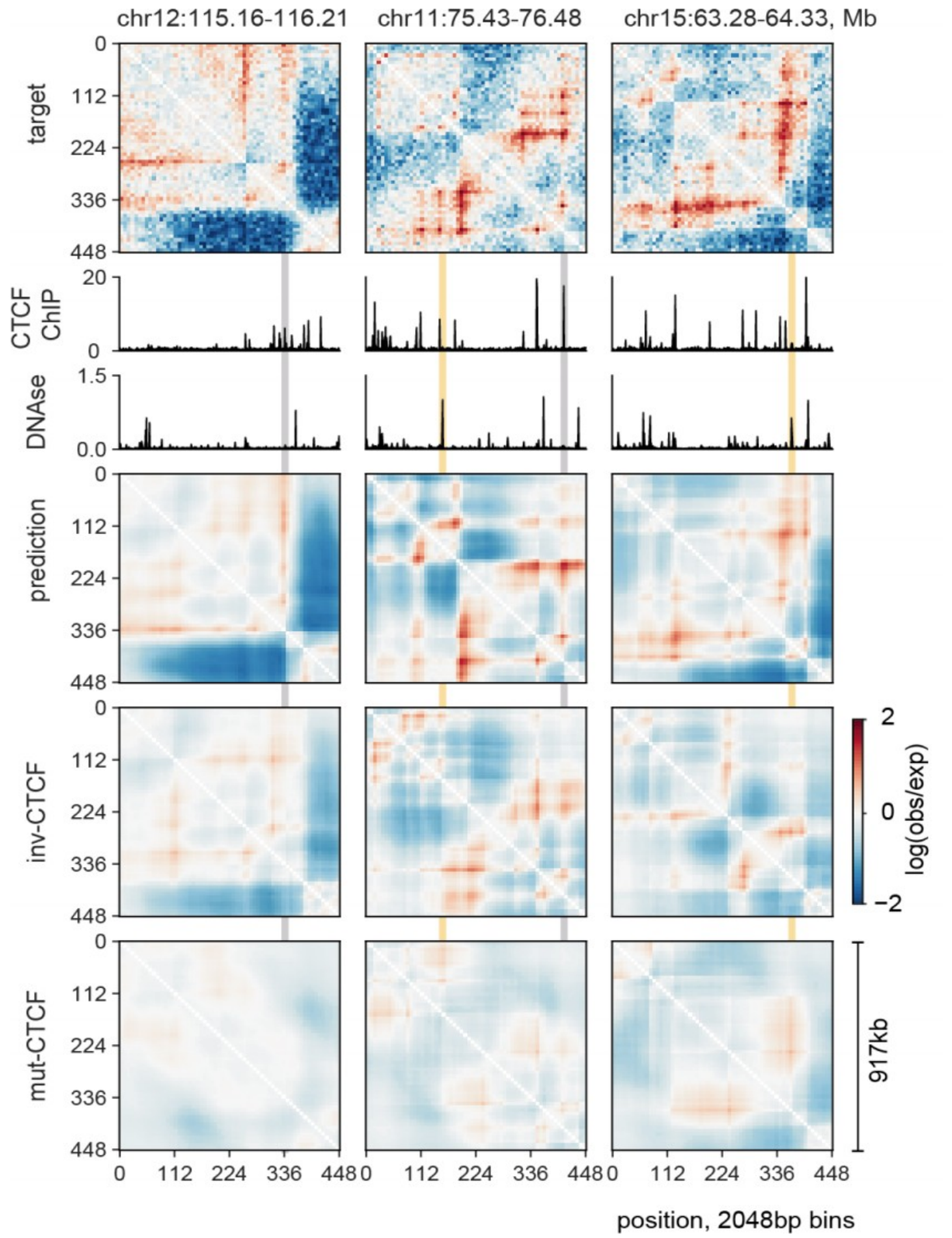
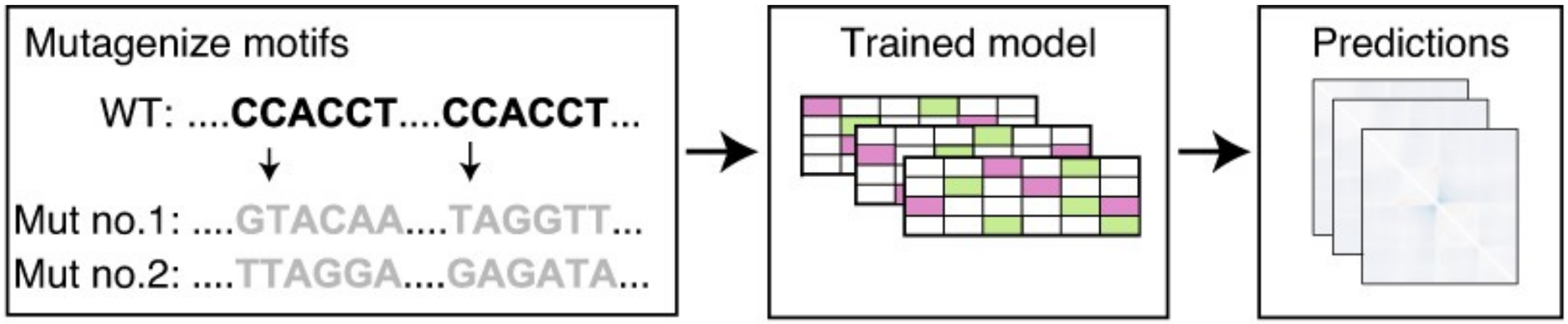
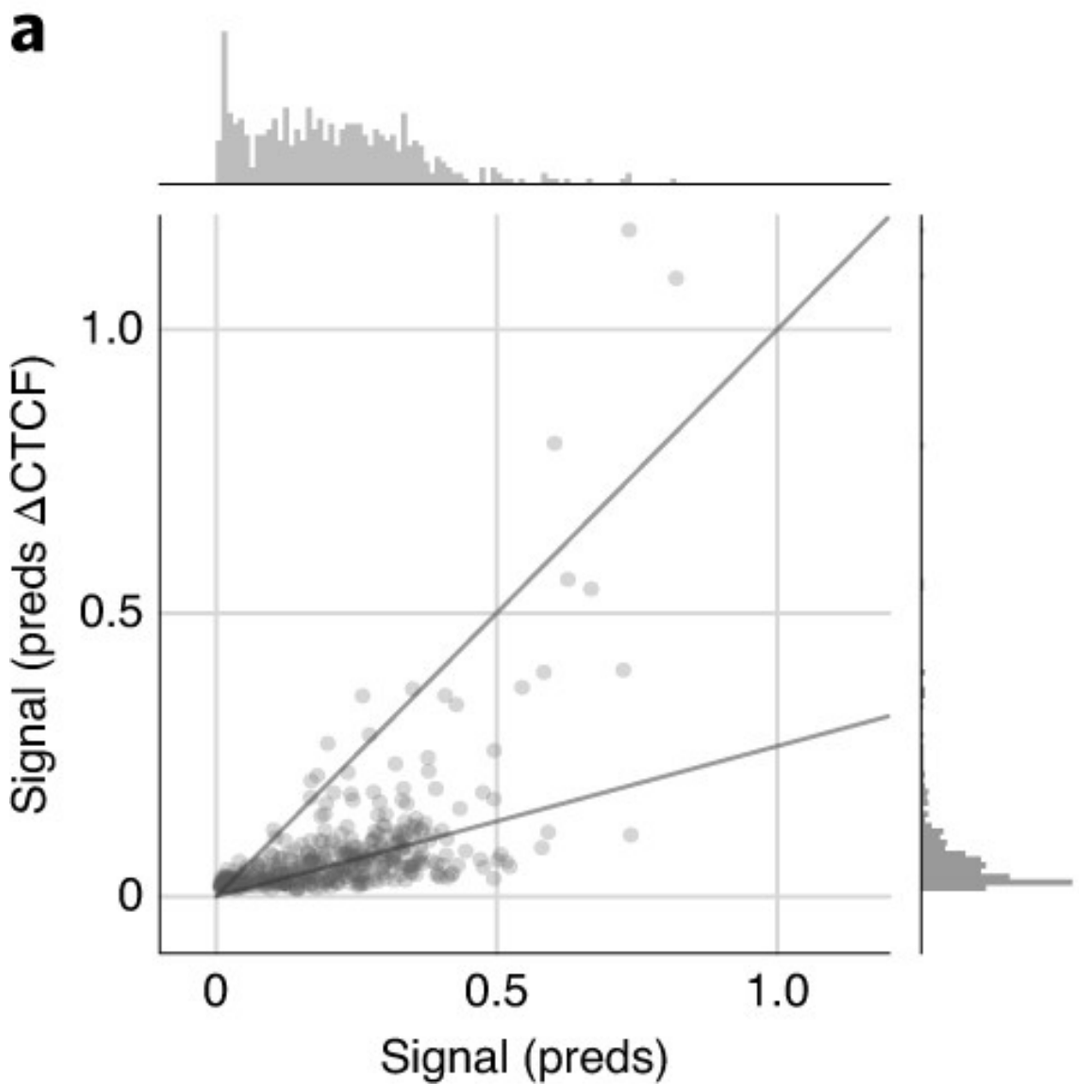
Contacts depend on CTCF and other elements

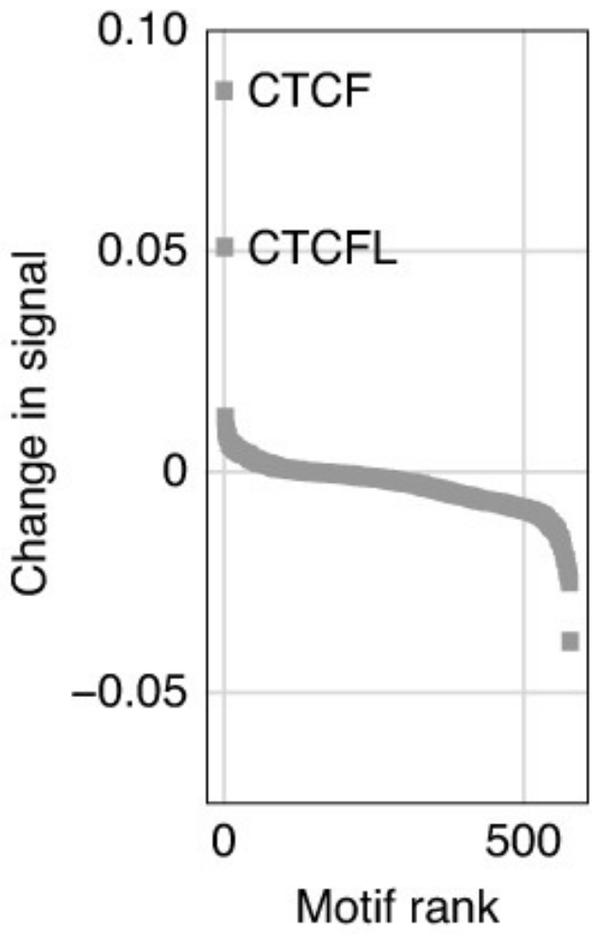


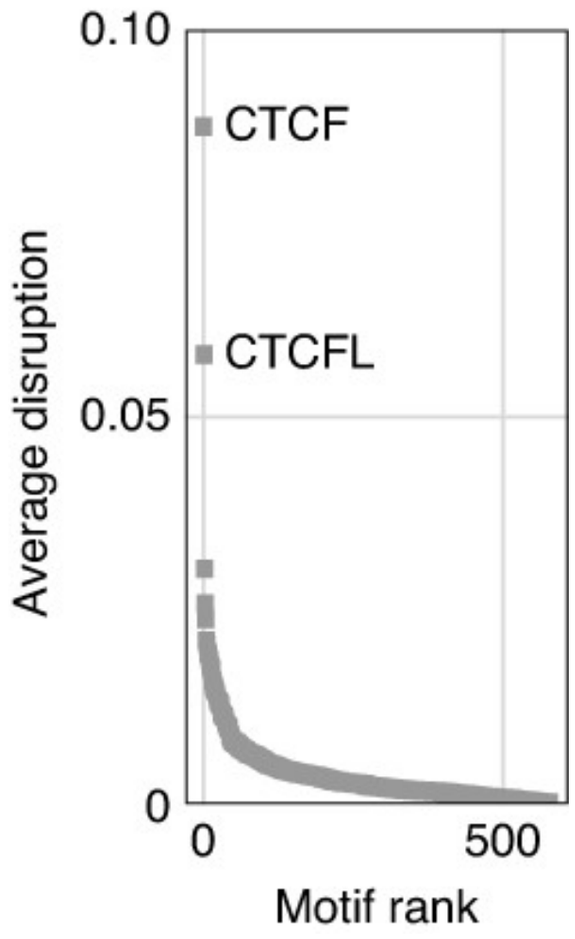
Fudenberg, Kelley, Pollard. Predicting 3D genome folding from DNA sequence. Nature Methods, 2020.

CTCF is the only truly relevant TF motif









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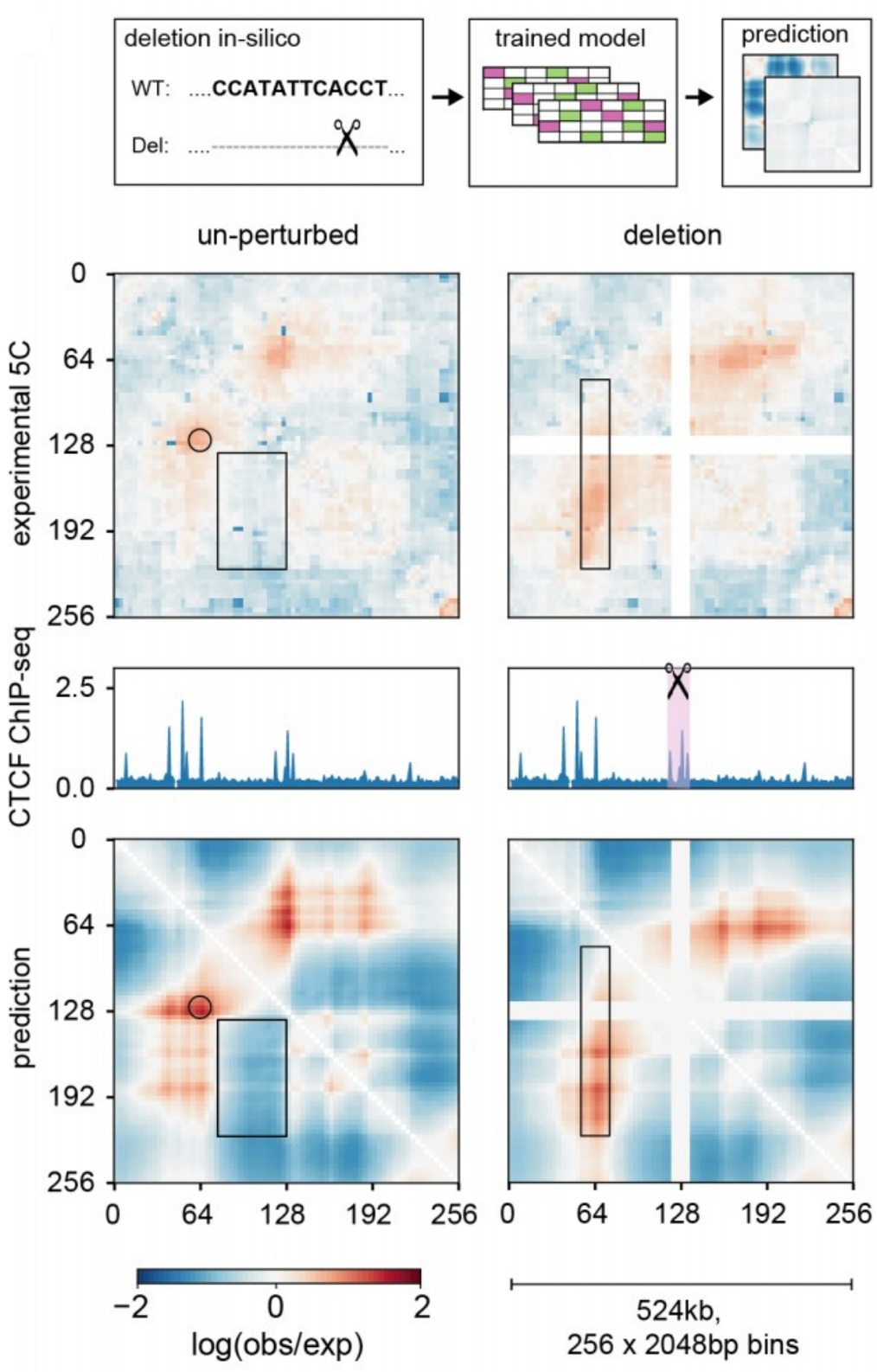
Model predicts deletion effects



Fudenberg, Kelley, Pollard. Predicting 3D genome folding from DNA sequence. Nature Methods, 2020.

Deep Learning for Regulatory Genomics

1. **Biological foundations: Building blocks of Gene Regulation**
   - Gene regulation: Cell diversity, Epigenomics, Regulators (TFs), Motifs, Disease role
   - Probing gene regulation: TFs/histones: ChIP-seq, Accessibility: DNase/ATAC-seq
   - Three-dimensional chromatin structure, Hi-C, ChIA-PET, TADs, Loop Extrusion
2. **Classical methods for Regulatory Genomics and Motif Discovery**
   - Enrichment-based motif discovery: Expectation Maximization, Gibbs Sampling
   - Experimental: PBMs, SELEX. Comparative genomics: Evolutionary conservation.
3. **Regulatory Genomics CNNs (Convolutional Neural Networks): Foundations**
   - Key idea: pixels ⇔ DNA letters. Patches/filters ⇔ Motifs. Higher ⇔ combinations
   - Learning convolutional filters ⇔ Motif discovery. Applying them ⇔ Motif matches
4. **Regulatory Genomics CNNs/RNNs in Practice: Diverse Architectures**
   - DeepBind: Learn motifs, use in (shallow) fully-connected layer, mutation impact
   - DeepSea: Train model directly on mutational impact prediction
   - Basset: Multi-task DNase prediction in 164 cell types, reuse/learn motifs
   - ChromPuter: Multi-task prediction of different TFs, reuse partner motifs
   - DeepLIFT: Model interpretation based on neuron activation properties
   - DanQ: Recurrent Neural Network for sequential data analysis
5. **Guest Lecture: David Kelley on Basset and Deep Learning for Hi-C looping**