Introduction to Epigenetics

BMI/CS 776

www.biostat.wisc.edu/bmi776/

Spring 2022

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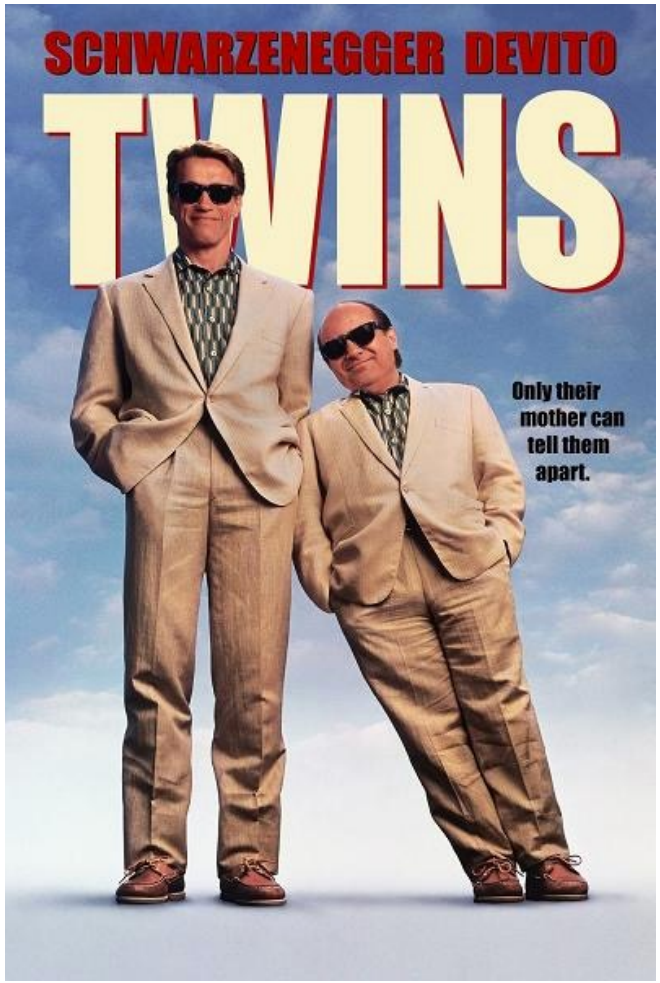
Goals for lecture

Key concepts

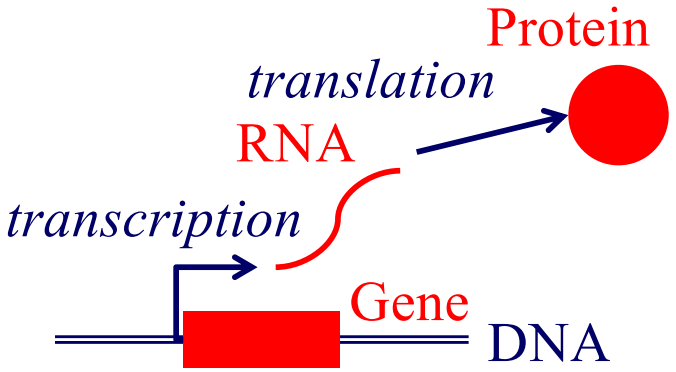
- Importance of epigenetic data for understanding transcriptional regulation
- Use of epigenetic data for predicting transcription factor binding sites

Gene expression and regulation

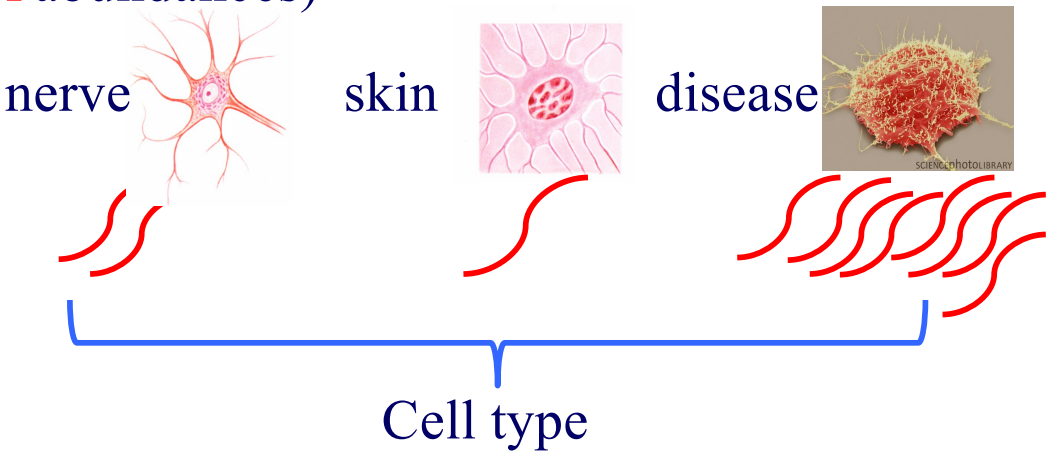
Identical DNA but different gene expression



Central dogma

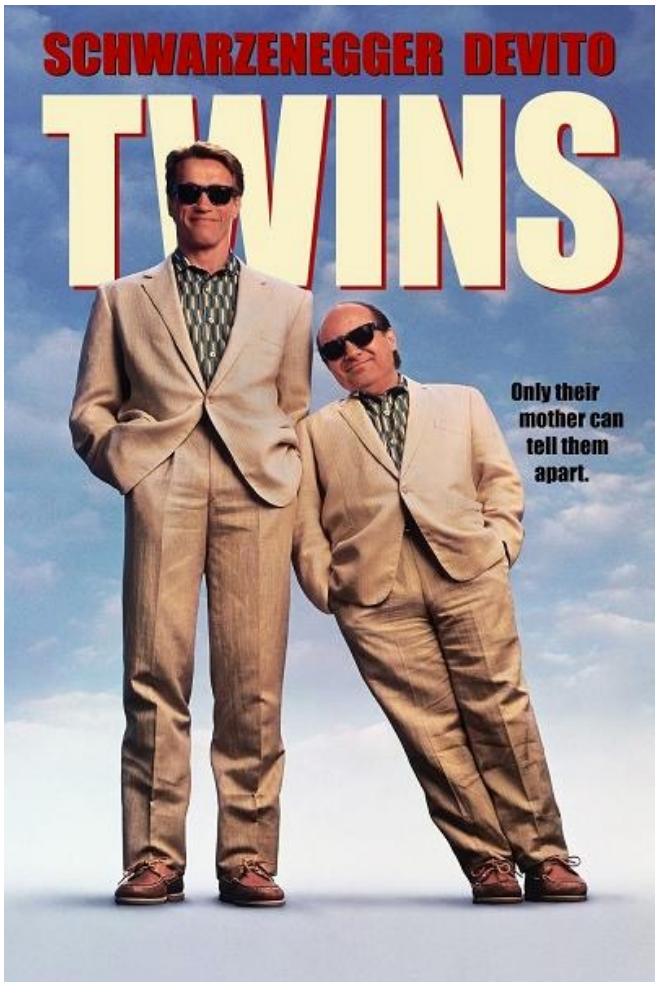


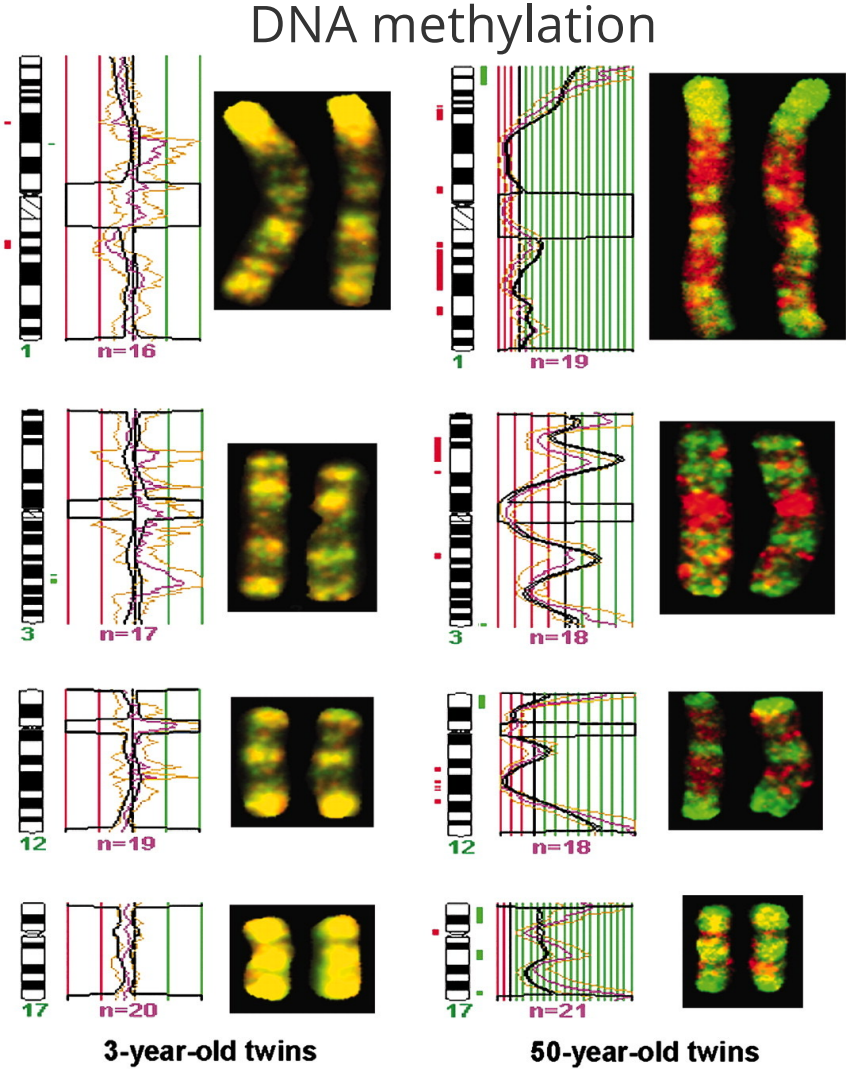
Gene expression levels (e.g., values to quantify RNA abundances)



Gene regulation: which & how genes express?

Identical DNAs but identical fates?



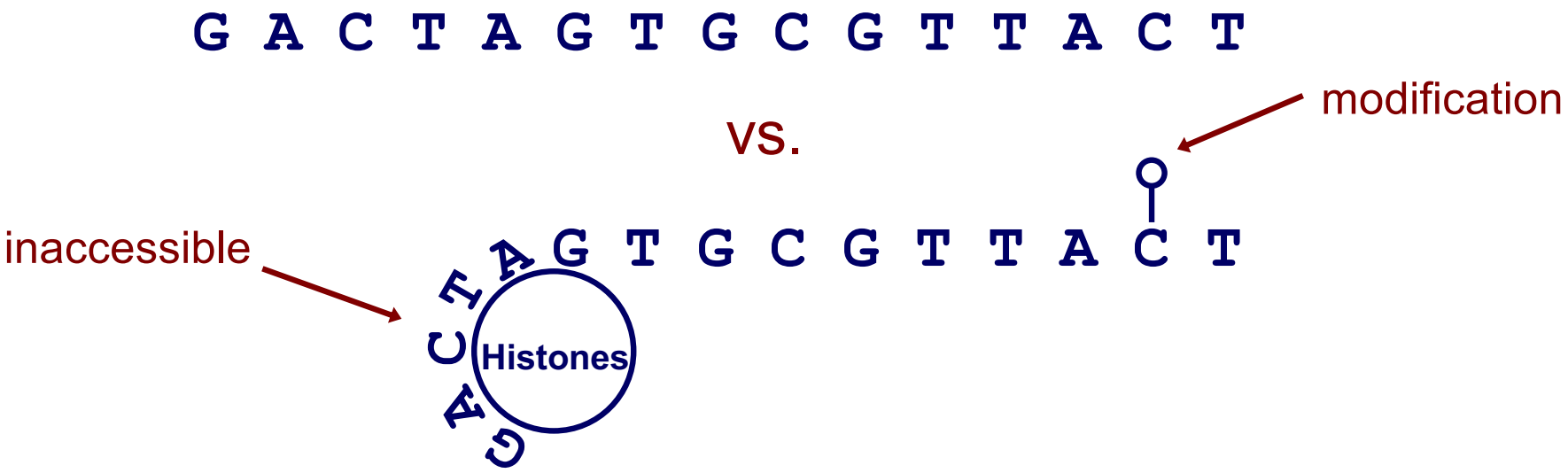


Chromosomes

PNAS July 26, 2005 102 (30) 10604-10609; https://doi.org/10.1073/pnas.0500398102

Defining epigenetics

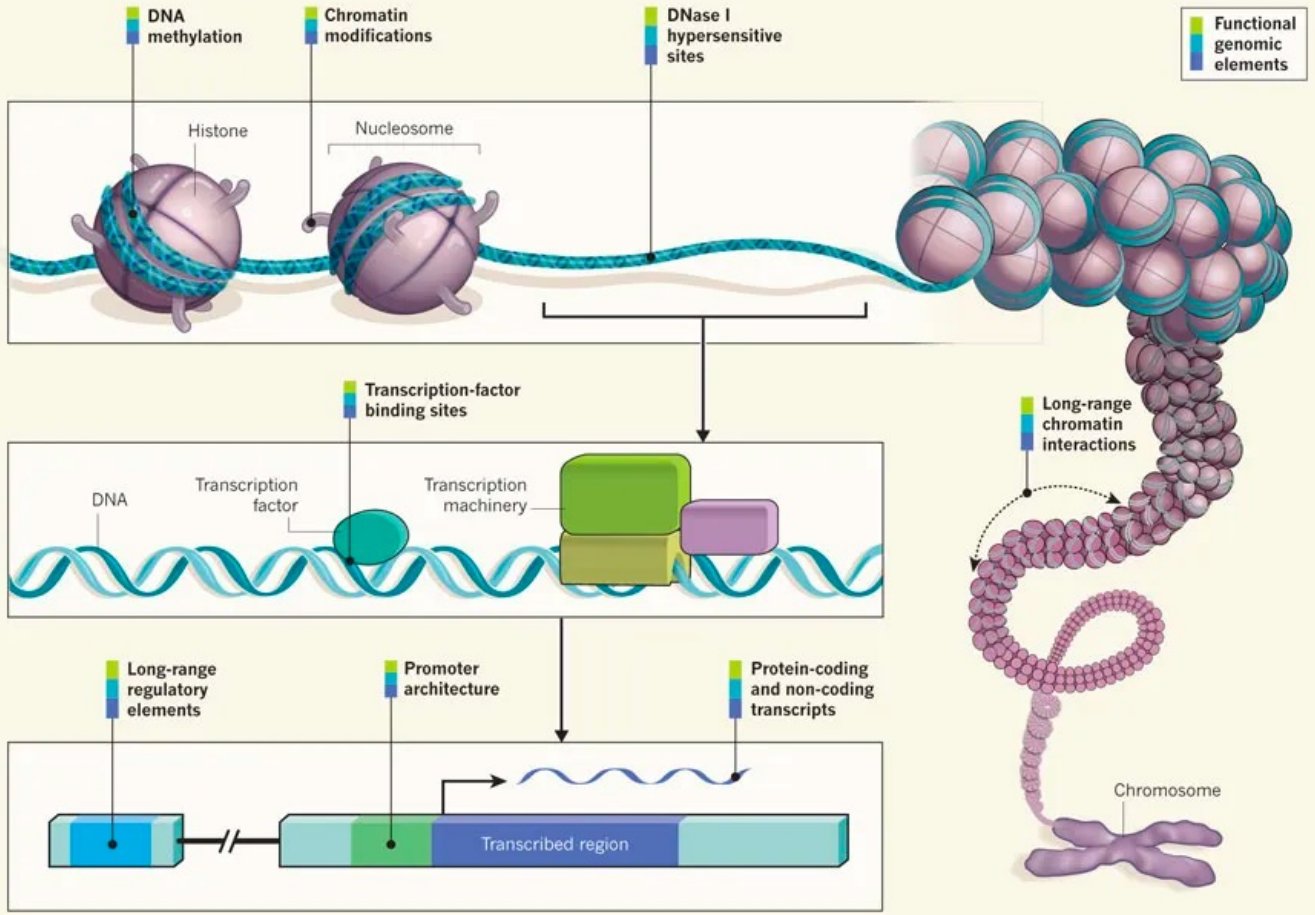
- Formally: attributes that are “in addition to” genetic sequence or sequence modifications
  - “*Epigenetic code*” (vs. genetic code)
- Informally: experiments that reveal the context of DNA sequence
  - DNA has multiple states and modifications



Chromatin packages DNA around Histones

(pack six feet of DNA into a cell)

NGHRI genetics glossary



Nature **volume 489**, pages52–54(2012)

Importance of epigenetics

Better understand

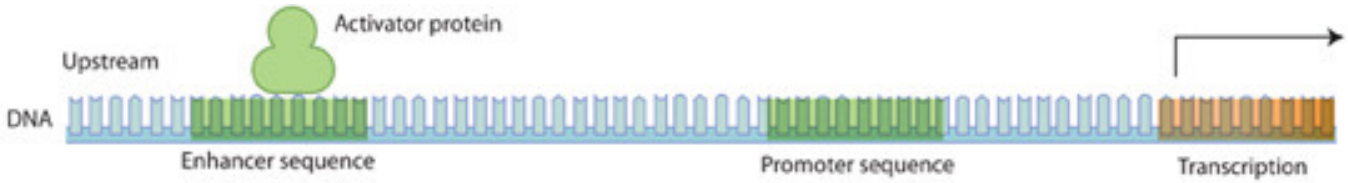
- DNA binding and transcriptional regulation
- Differences between cell and tissue types
- Development and other important processes

PWMs are not enough

- Genome-wide motif scanning is imprecise
- Transcription factors (TFs) bind < 5% of their motif matches
- Same motif matches in all cells and conditions

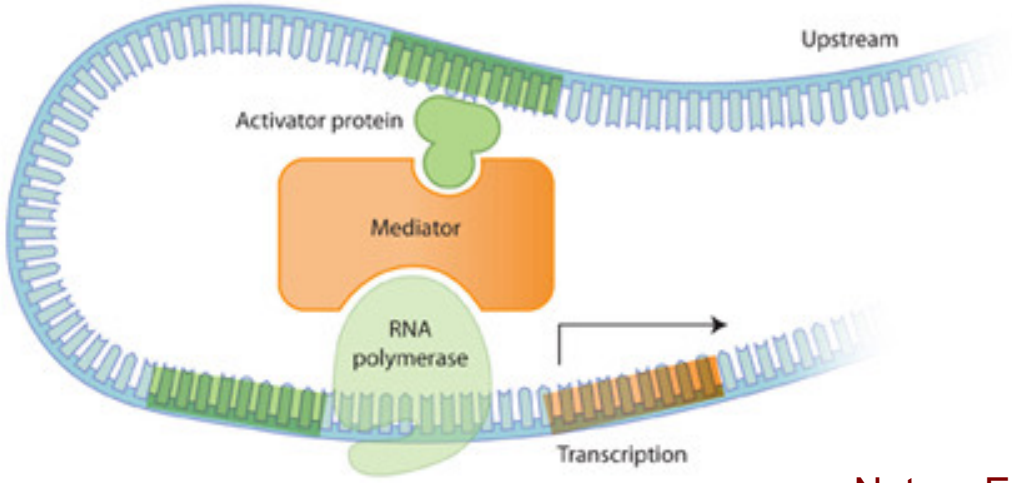
PWMs are not enough

- DNA looping can bring distant binding sites close to transcription start sites
- Which genes does an enhancer regulate?



Enhancer: DNA binding site for TFs, can be far from affected gene

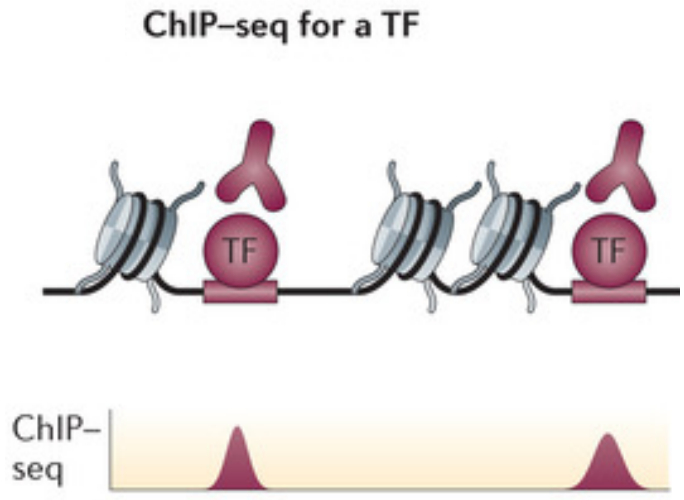
Promoter: DNA binding site for TFs, close to gene transcription start site



Nature Education 2010

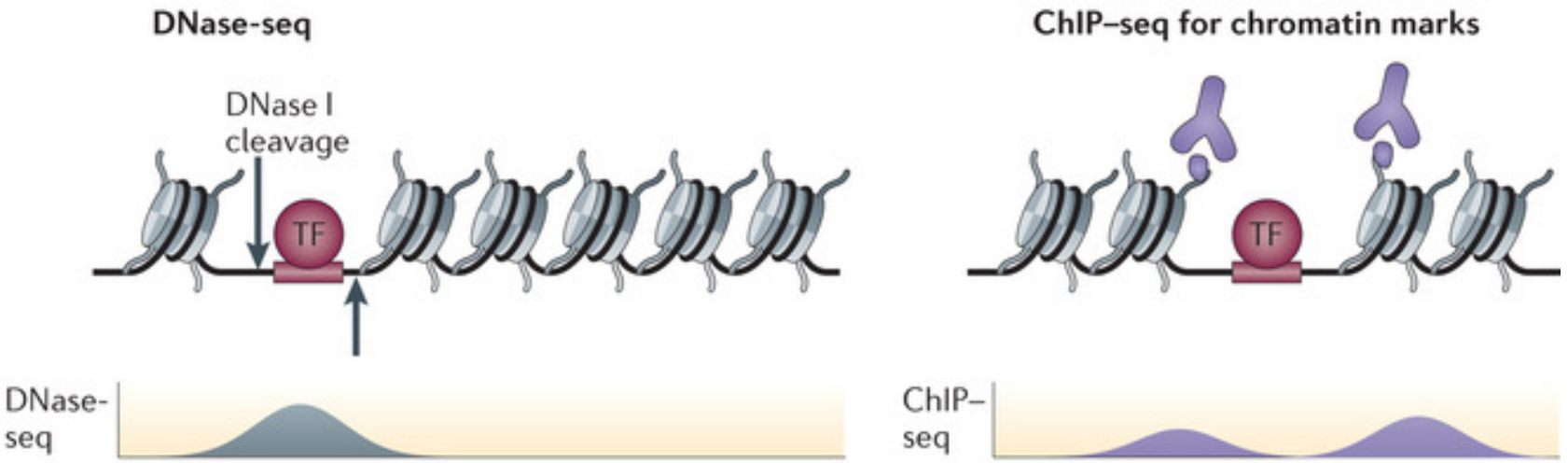
Mapping regulatory elements genome-wide

- Can do much better than motif scanning with additional data
- ChIP-seq measures binding sites for one TF at a time



Shlyueva *Nature Reviews Genetics* 2014

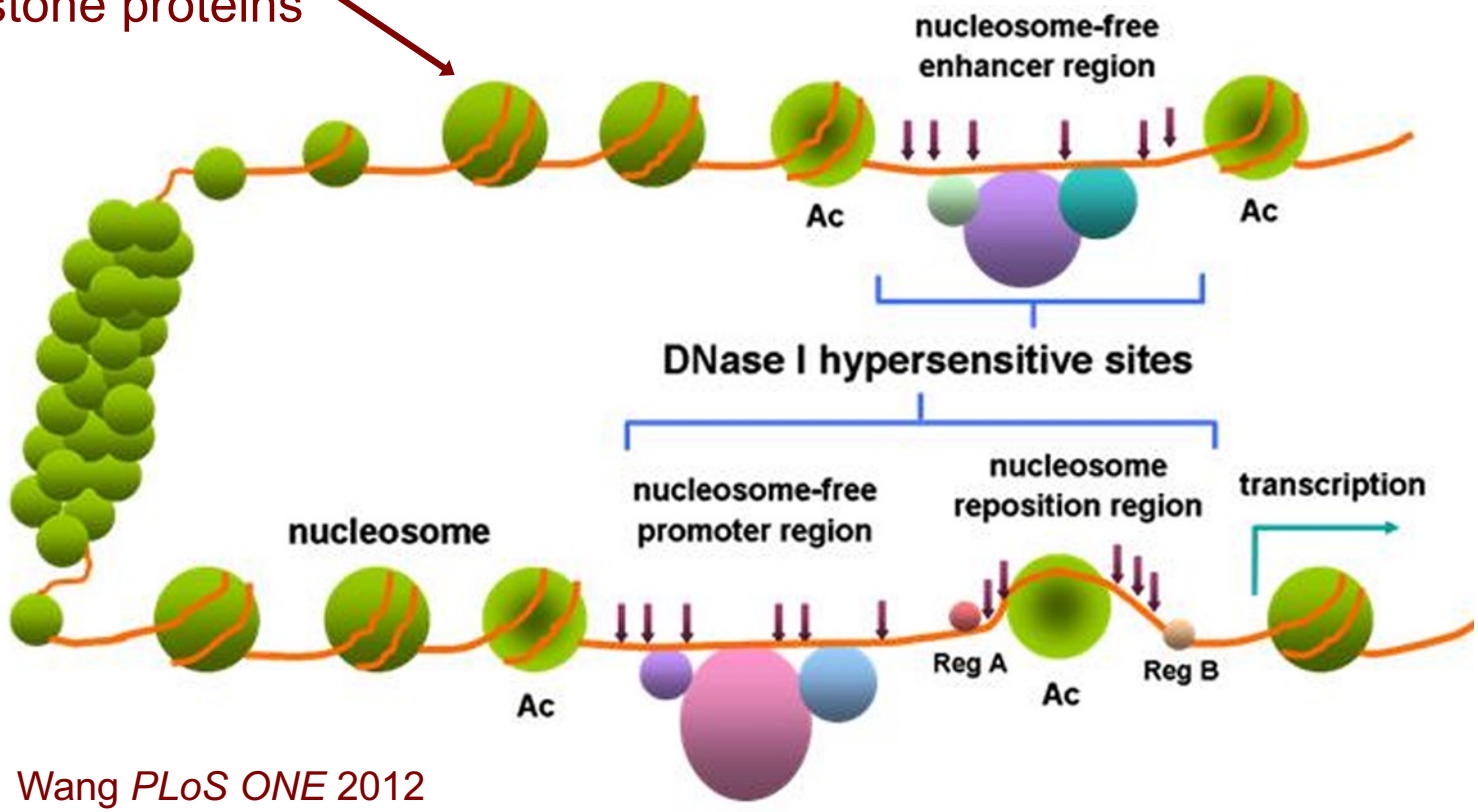
- Epigenetic data suggests where *some* TF binds



DNase I hypersensitivity

- Regulatory proteins bind accessible DNA
- DNase I enzyme cuts open chromatin regions that are not protected by nucleosomes

Nucleosome: DNA wrapped around histone proteins

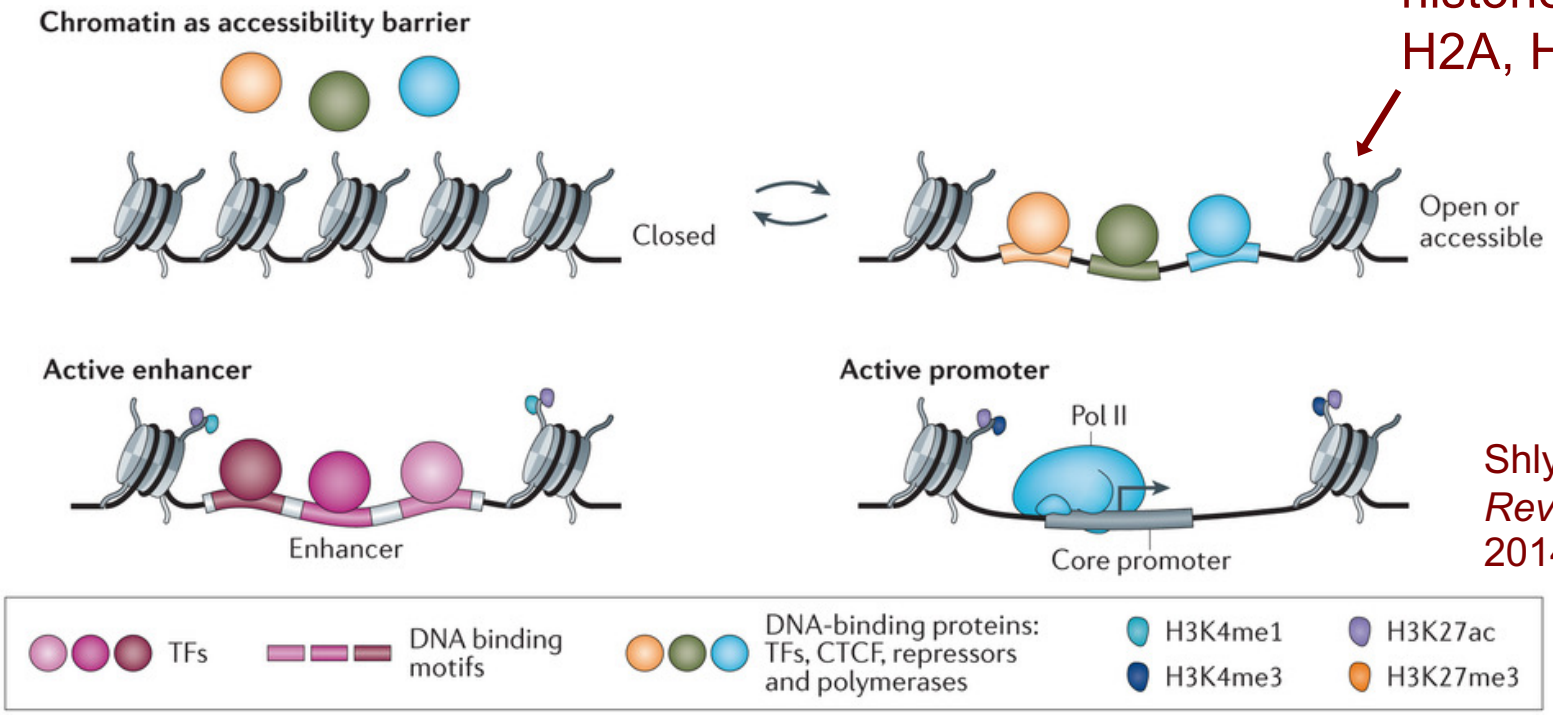


Wang *PLoS ONE* 2012

Histone modifications

- Mark particular regulatory configurations

Two copies of histone proteins H2A, H2B, H3, H4



Shlyueva *Nature Reviews Genetics* 2014

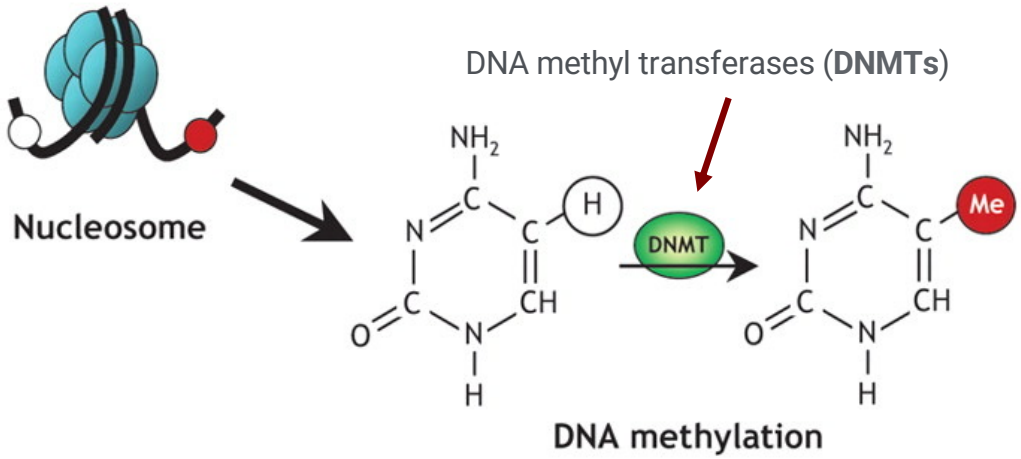
- H3 (protein) K27 (amino acid) ac (modification)

Me, methylation;
Ac, acetylation;
Cit, citrullination;

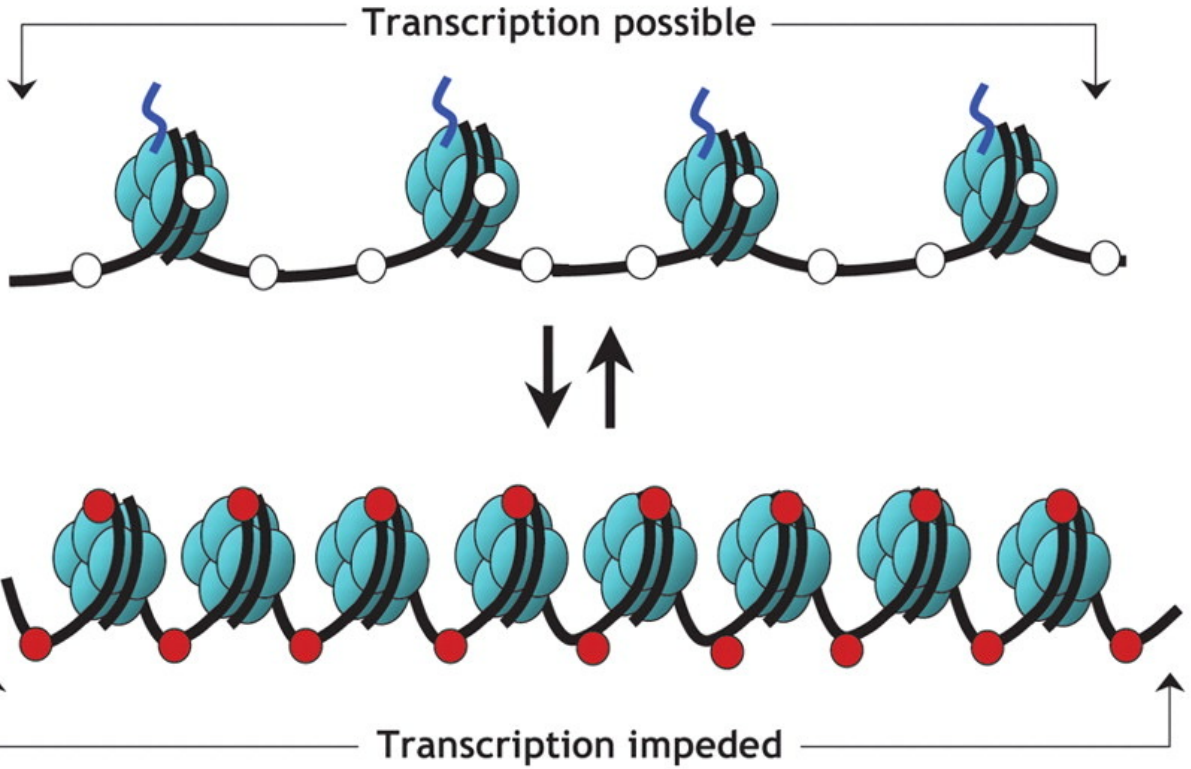
Latham *Nature Structural & Molecular Biology* 2007; Katie Ris-Vicari

DNA methylation

- Reversible DNA modification
- Represses gene expression



Gene "switched on"
- Active (open) chromatin
- Unmethylated cytosines (white circles)
- Acetylated histones

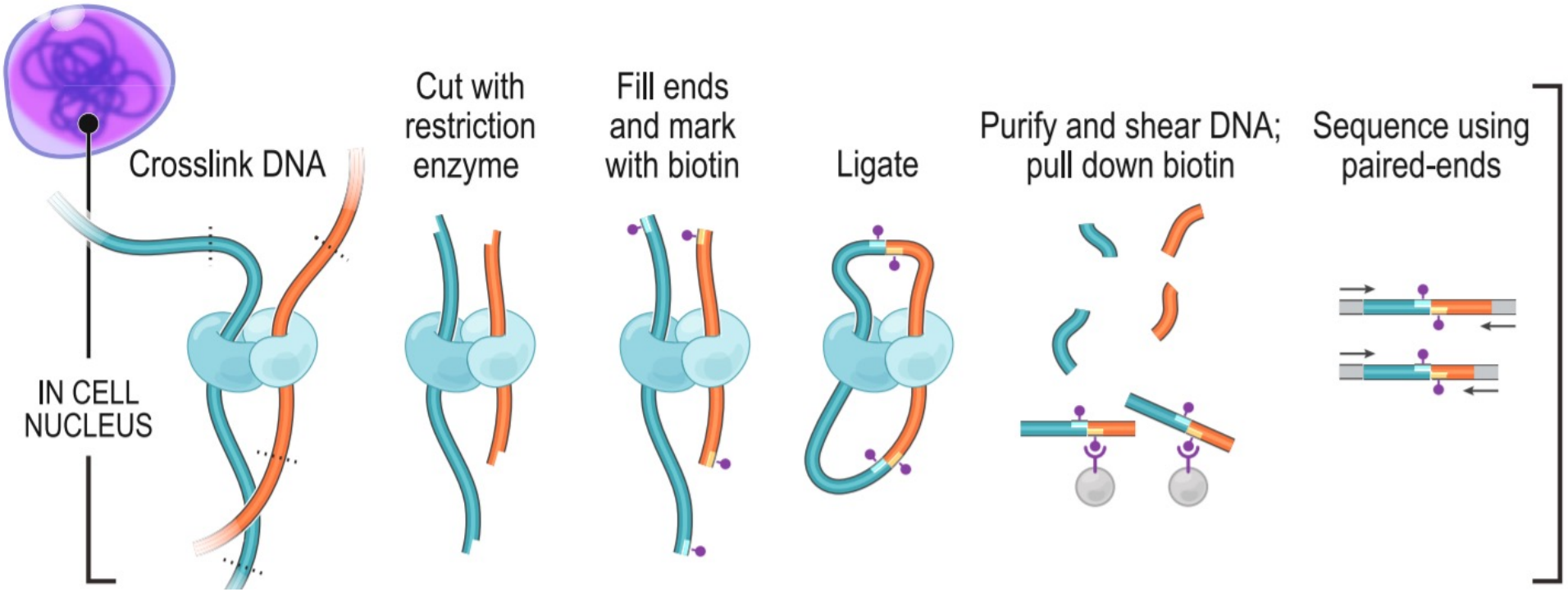


Gene "switched off"
- Silent (condensed) chromatin
- Methylated cytosines (red circles)
- Deacetylated histones

OpenStax CNX

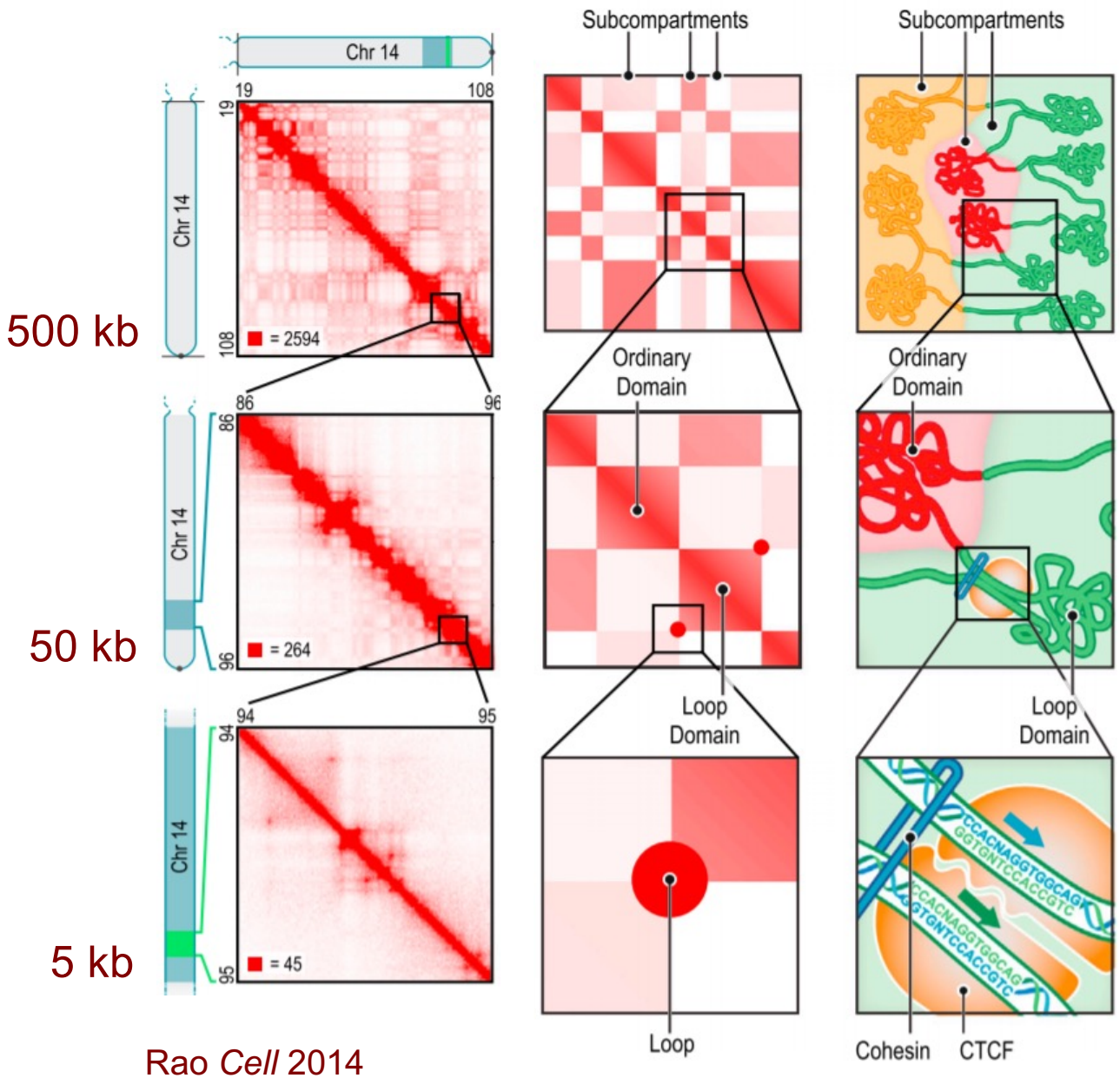
3D organization of chromatin

- YouTube: The 3D Organization of Our Genome
- Algorithms to predict long range enhancer-promoter interactions
- Or measure with chromosome conformation capture (3C, Hi-C, etc.)



Rao *Cell* 2014

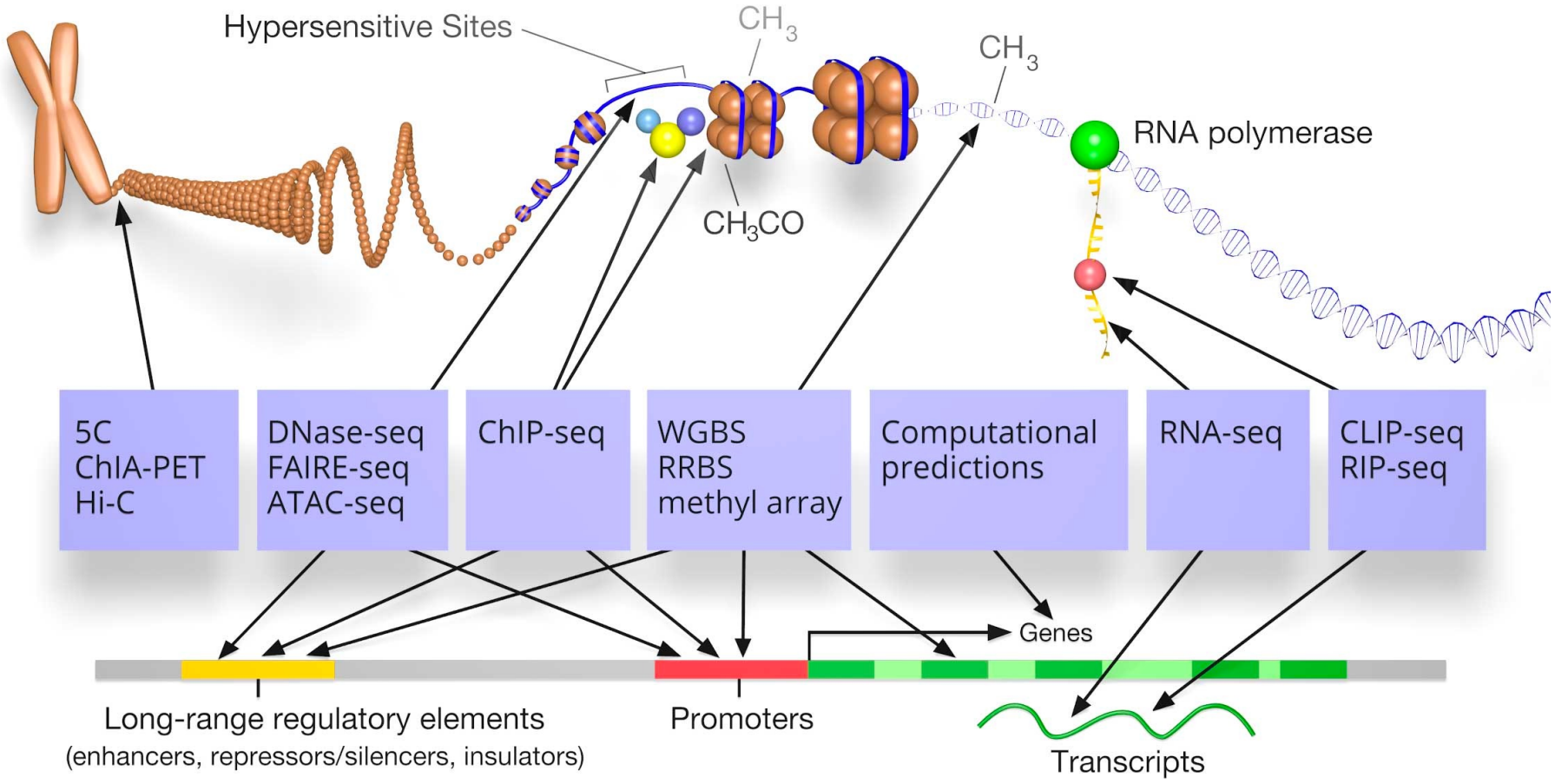
3D organization of chromatin



Rao *Cell* 2014

- Hi-C produces 2D chromatin contact maps
- Learn domains, enhancer-promoter interactions

Next Generation Sequencing (NGS) for epigenomics

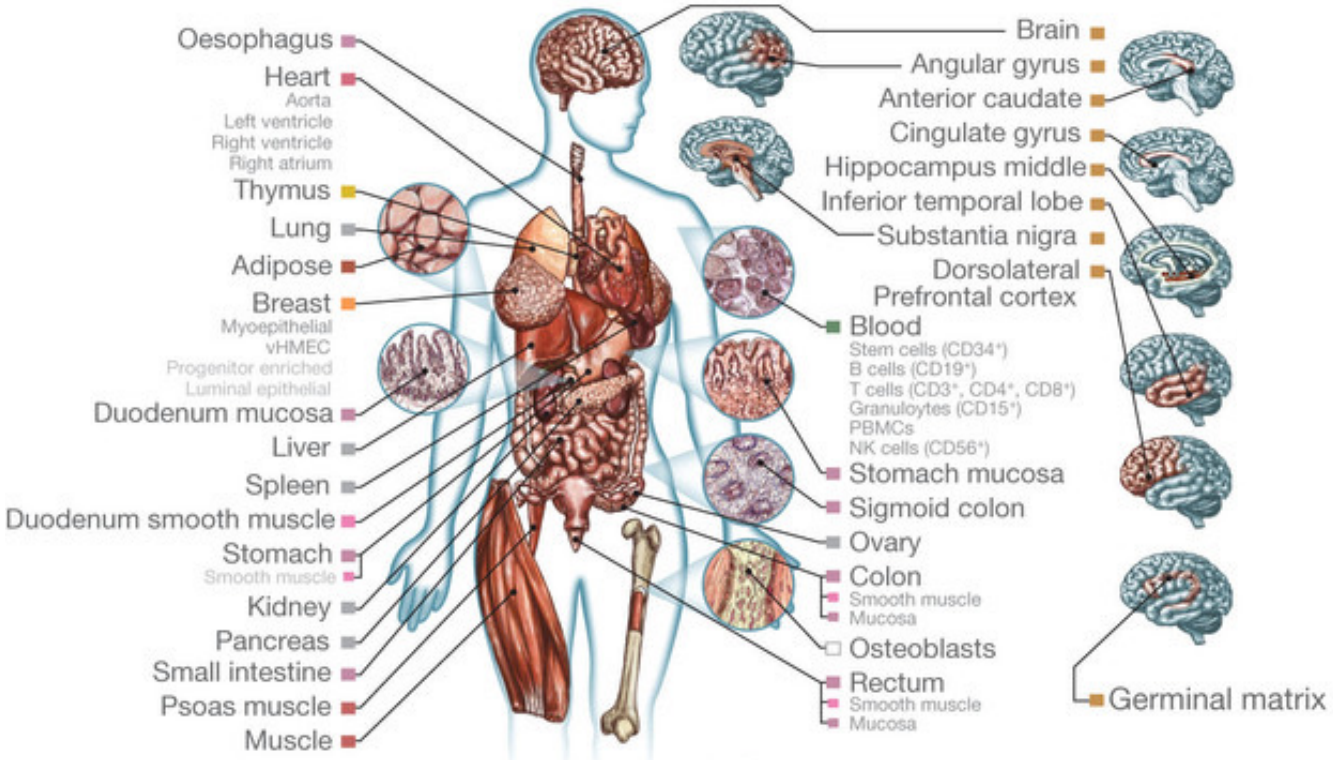


ENCODE

Based on an image by Darryl Leja (NHGRI), Ian Dunham (EBI), Michael Pazin (NHGRI)

Large-scale epigenetic maps

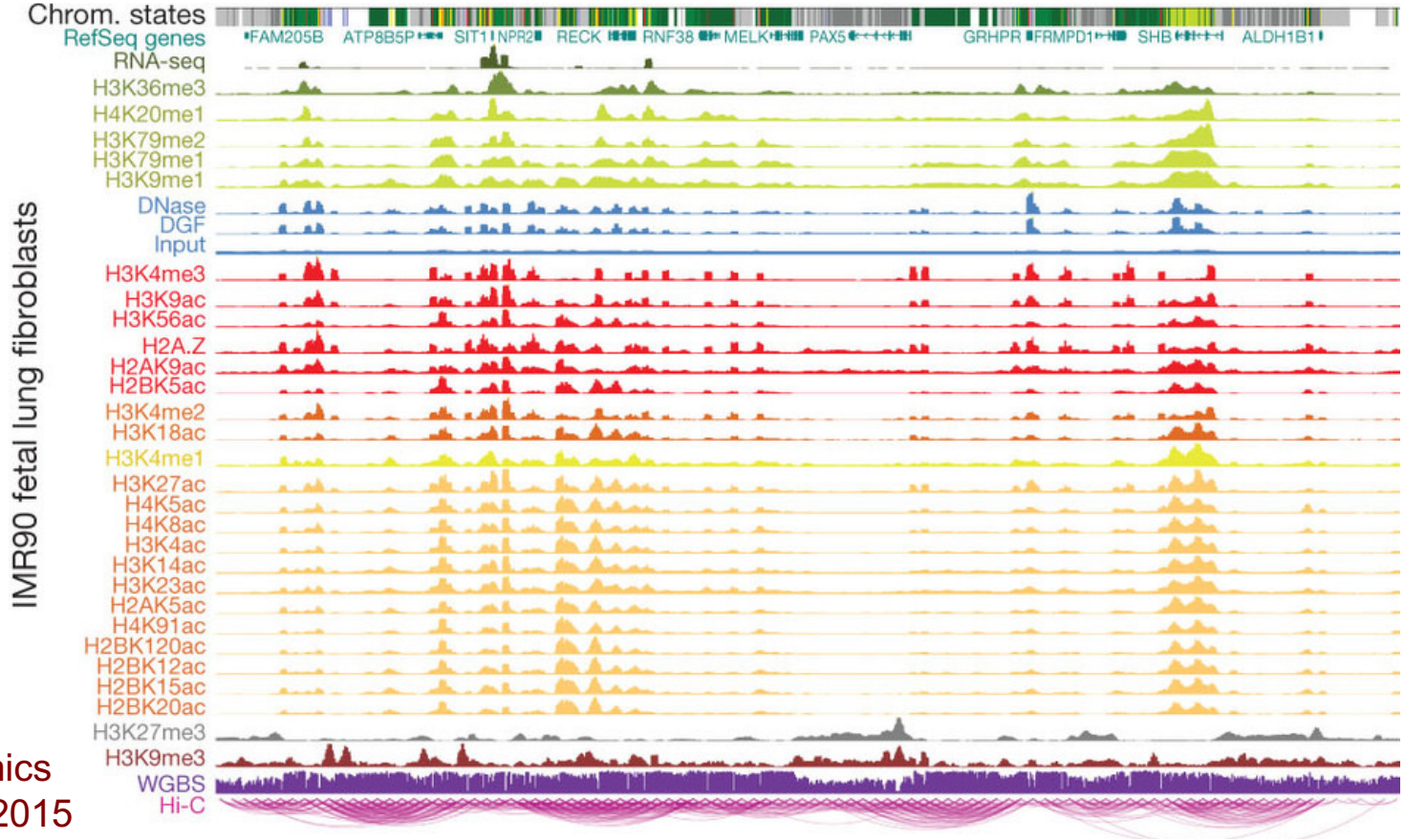
- Epigenomes are condition-specific
- Roadmap Epigenomics Consortium and ENCODE surveyed over 100 types of cells and tissues



Roadmap Epigenomics Consortium *Nature* 2015

Genome annotation

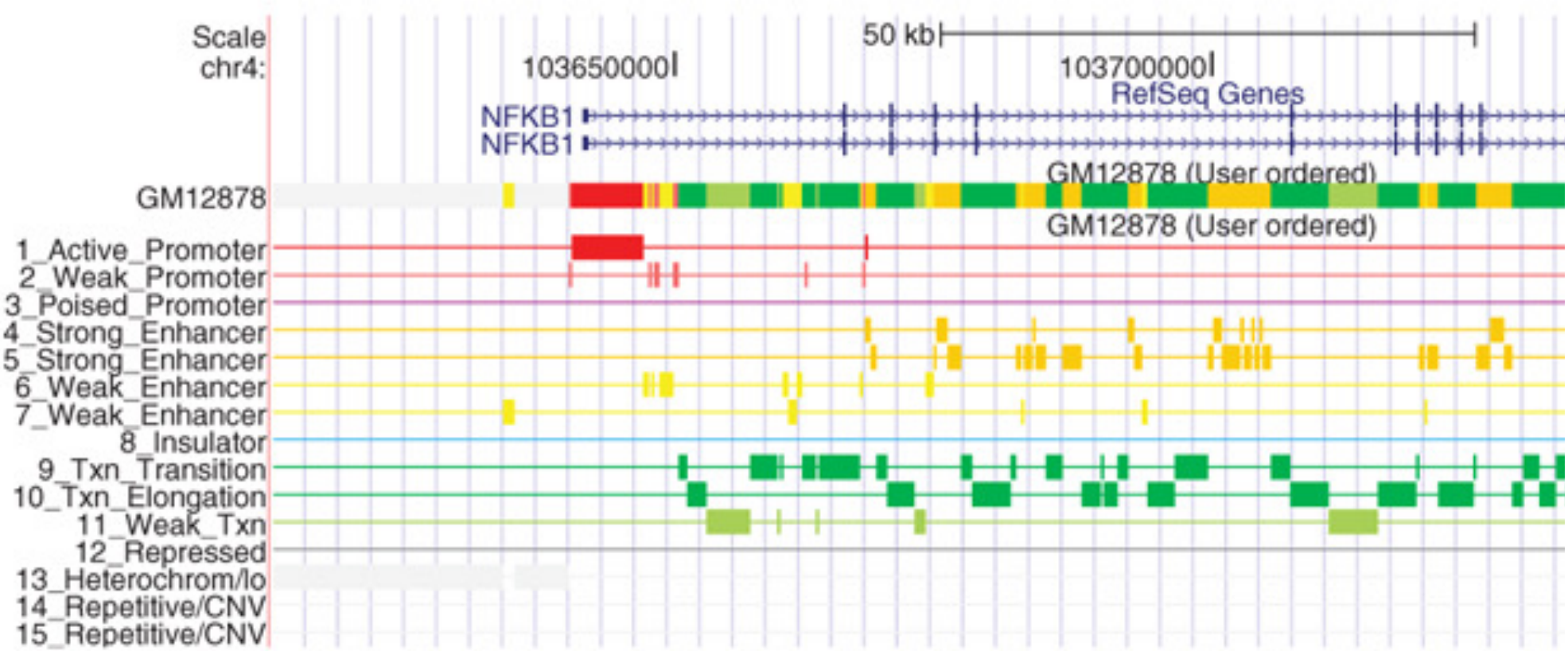
- Combinations of epigenetic signals can predict functional state
  - ChromHMM: Hidden Markov Model
  - Segway: Dynamic Bayesian network



Roadmap Epigenomics Consortium *Nature* 2015

Genome annotation

- States are more interpretable than raw data

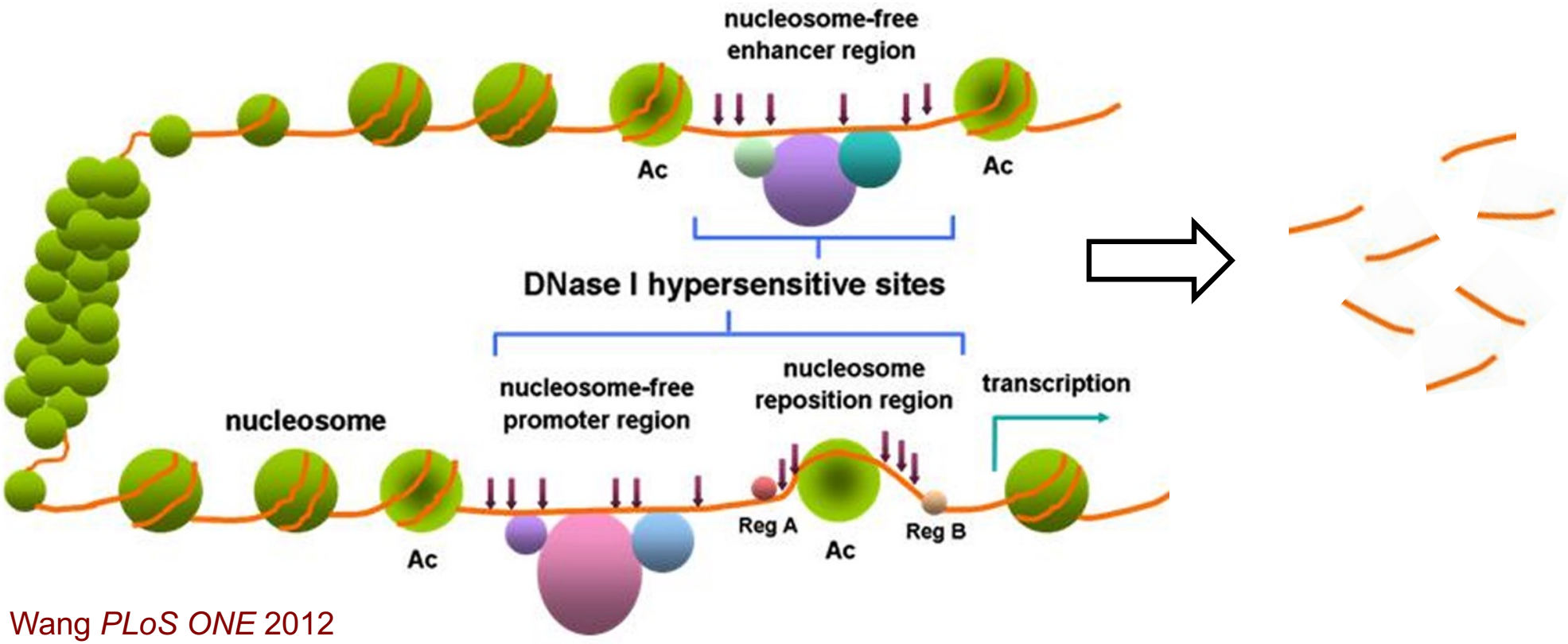


Ernst and Kellis *Nature Methods* 2012

Predicting TF binding with DNase-Seq

DNase I hypersensitive sites

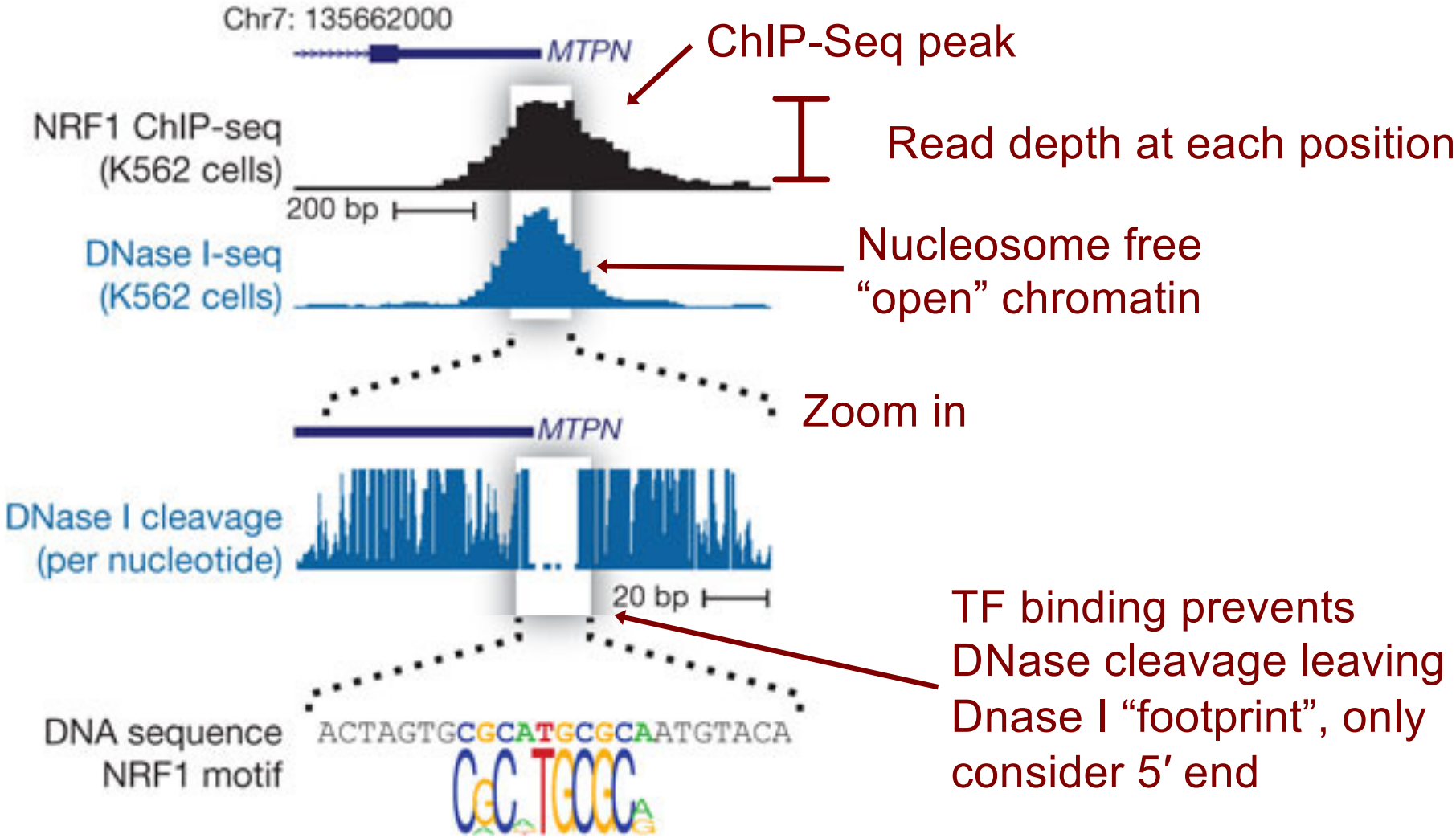
- Arrows indicate DNase I cleavage sites
- Obtain short reads that we map to the genome



Wang *PLoS ONE* 2012

DNase I footprints

- Distribution of mapped reads is informative of open chromatin and specific TF binding sites



Neph *Nature* 2012

DNase I footprints to TF binding predictions

- DNase footprints suggest that ***some*** TF binds that location

- We want to know ***which*** TF binds that location

- Two ideas:
  - Search for DNase footprint patterns, then match TF motifs
  - Search for motif matches in genome, then model proximal DNase-Seq reads

We'll consider this approach