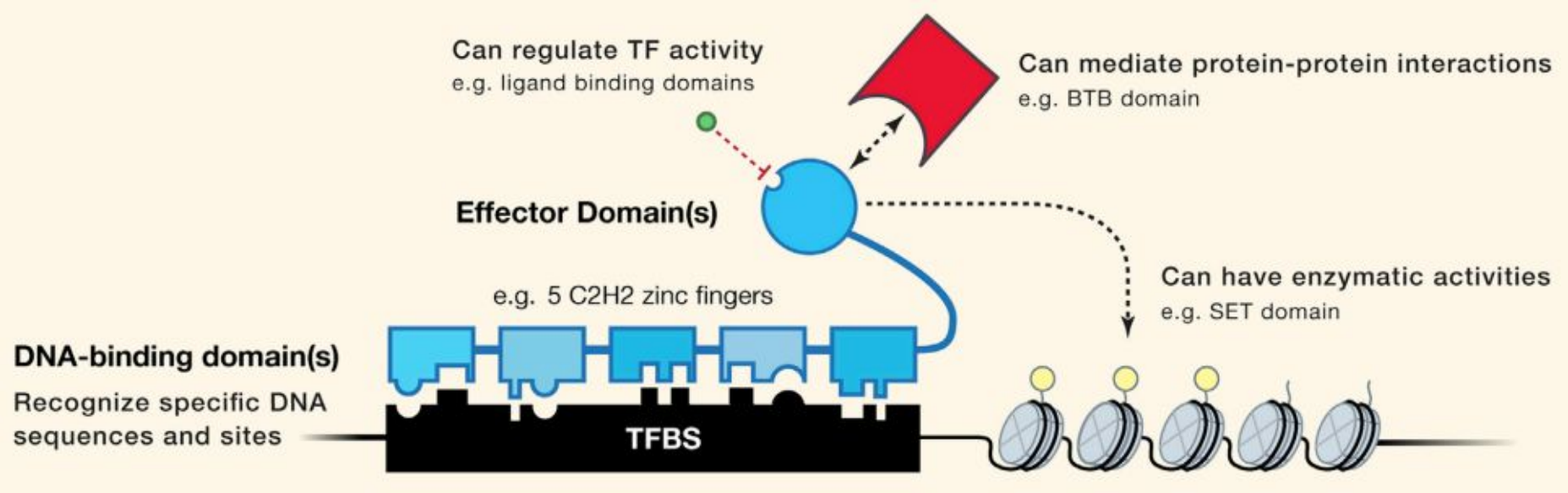
Regulatory genomics

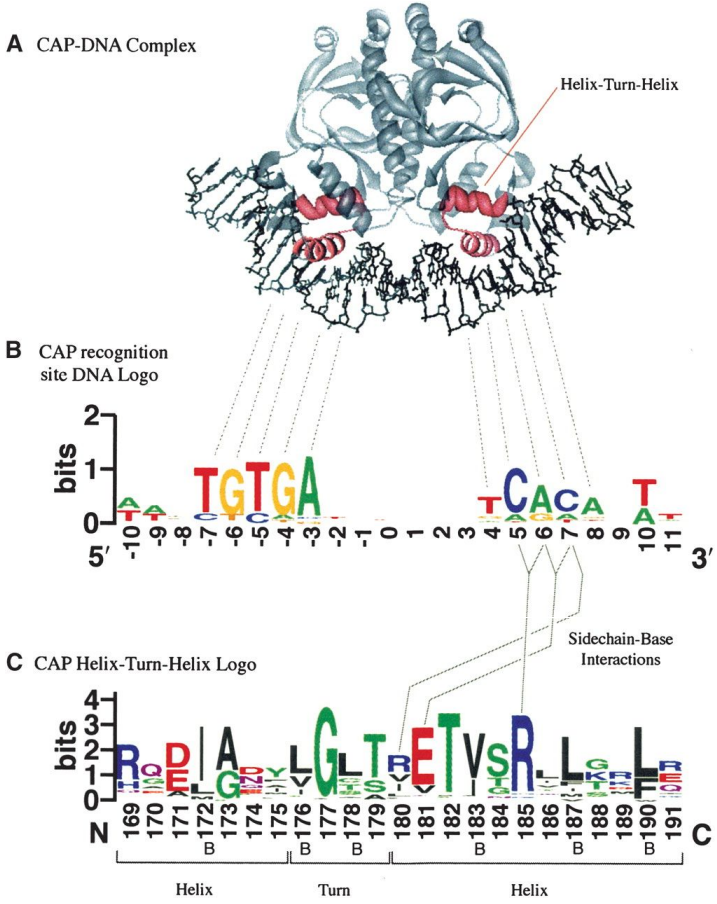
- DNA-binding sites/motifs
- Position-weight matrices
- ChIP-seq
- Motif-finding
  - Expectation-Maximization
  - Gibbs Sampling

Transcriptional regulation by transcription factors (TFs)



Lambert (2018) Cell

Transcriptional regulation by TFs



(A) 3D protein structure of CAP (Catabolite Activator Protein, also known as CRP), a transcriptional activator that binds at >100 sites within the *Escherichia coli* genome.

(B) CAP binding-site logo (based on 59 binding sites):

- Approximately palindromic - provides two very similar recognition sites, one for each subunit of the dimer.
- The binding site lacks perfect symmetry, possibly due to the inherent asymmetry of the operon promoter region.
- The displacement of the two halves is 11 bp, or approximately one full turn of the DNA helix.
- Additional interactions occur between the protein and the first and last two bases within the DNA minor groove, where the protein cannot easily distinguish A from T, or G from C.

(C) The helix-turn-helix motif from the CAP family of homodimeric DNA binding proteins.

Crooks (2004) Genome Res.

Consensus sequence of DNA-binding sites

EcoRI binds to the 6-mer **GAATTC** (palindrome).

- Occurs once every 4^6 (= **4,096**) bp in a random DNA sequence.

HindII bind to **GTYRAC**.

- **R**: **G** or **A** (purine)
- **Y**: **C** or **T** (pyrimidine)
- Occur once per $4^4 \times 2^2$ (= **1,024**) bp.

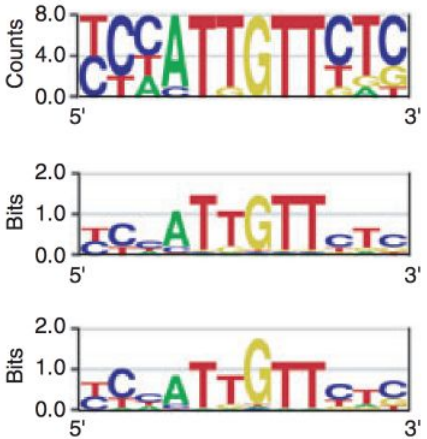
```
HEM13   CCCATTGTTCTC
HEM13   TTTCTGGTTCTC
HEM13   TCAATTGTTTAG
ANB1    CTCATTGTTGTC
ANB1    TCCATTGTTCTC
ANB1    CCTATTGTTCTC
ANB1    TCCATTGTTCGT
ROX1    CCAATTGTTTTG

        YCHATTGTTCTC
```

Motif instances → Motif

```
A 002700000010
C 464100000505
G 000001800112
T 422087088261
```

Position frequency matrix



Sequence logo

D'haeseleer (2016) Nat. Biotech.

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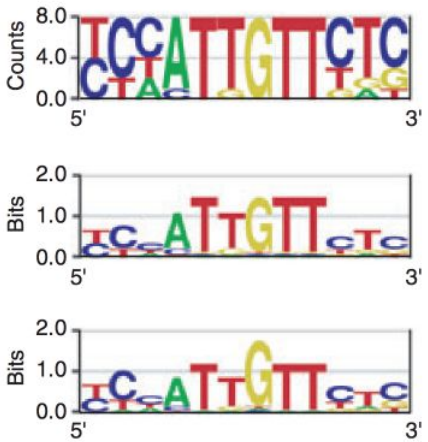

$$I_i = 2 + \sum_b f_{b,i} \log_2 f_{b,i}$$

Scaling sequence logos based on 'information content' than frequency.

- $f_{b,i}$: frequency of base **b** at position **i**.
- Perfectly conserved: 2 bits of information.
- Two of the four bases occur 50% of the time each: 1 bit.
- All four bases occur equally often: no information.

HindII binds to GTYRAC.

- What is its information content?

D'haeseleer (2016) Nat. Biotech.

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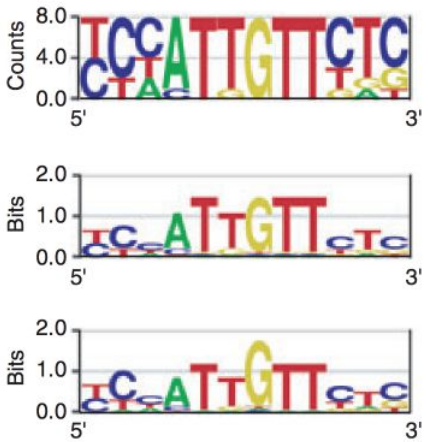

$$I_{seq}(i) = -\sum_b f_{b,i} \log_2 \frac{f_{b,i}}{p_b}$$

Relative entropy (a.k.a. Kullback-Leibler distance) to correct for background nucleotide frequencies.

$$W(b,i) = \log_2 \frac{f_{b,i}}{p_b}$$

Position weight matrix (PWM).

D'haeseleer (2016) Nat. Biotech.

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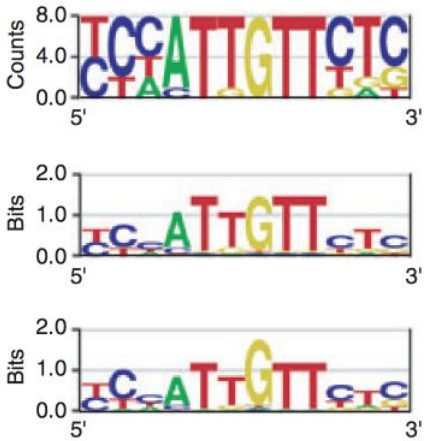

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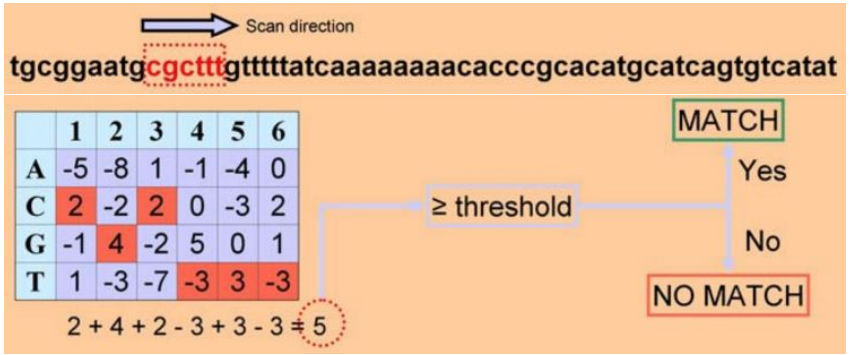

D'haeseleer (2016) Nat. Biotech.

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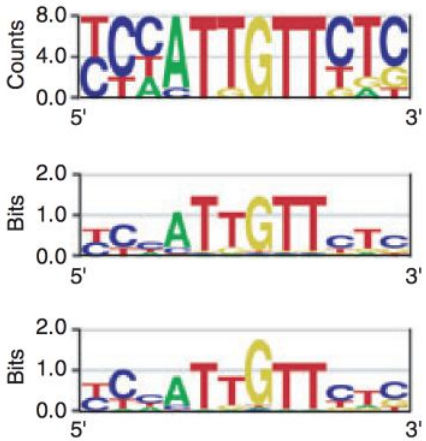
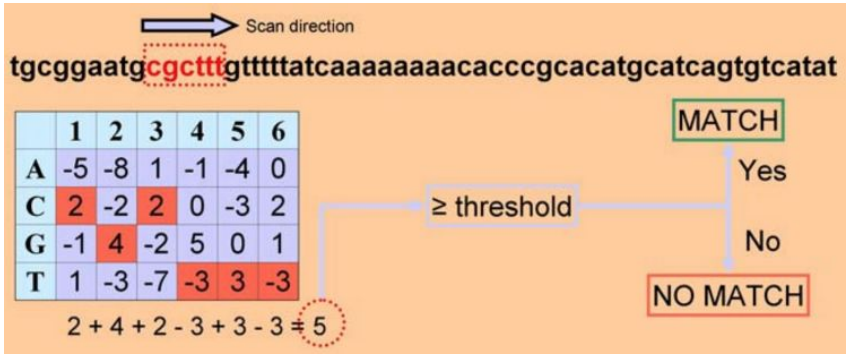


A generative model!

Assumptions:

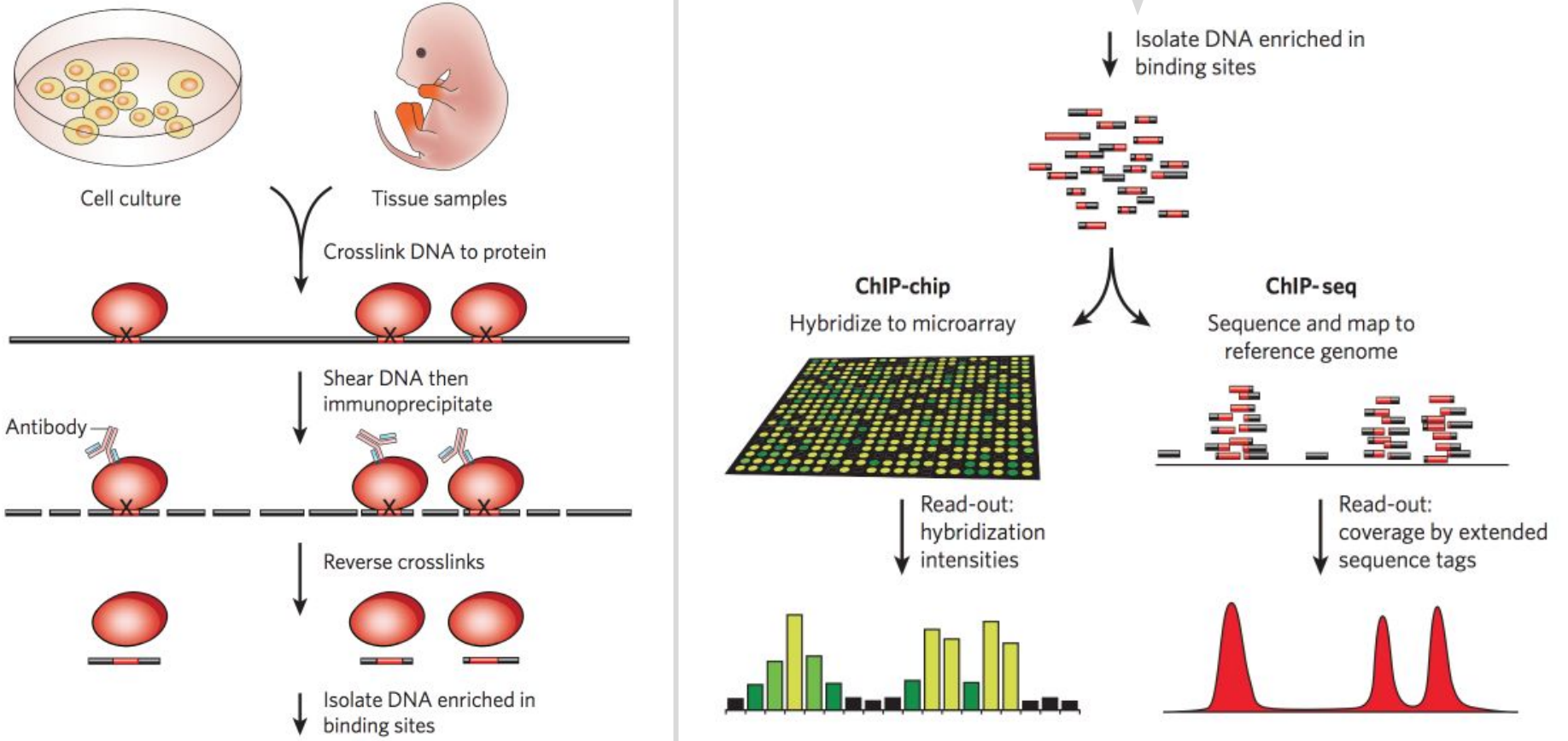
- Independence of positions
- Fixed spacing

Position weight matrix (PWM).



D'haeseleer (2016) Nat. Biotech.

Mapping of regulatory elements using ChIP-chip and ChIP-seq



Visel (2009) Nature

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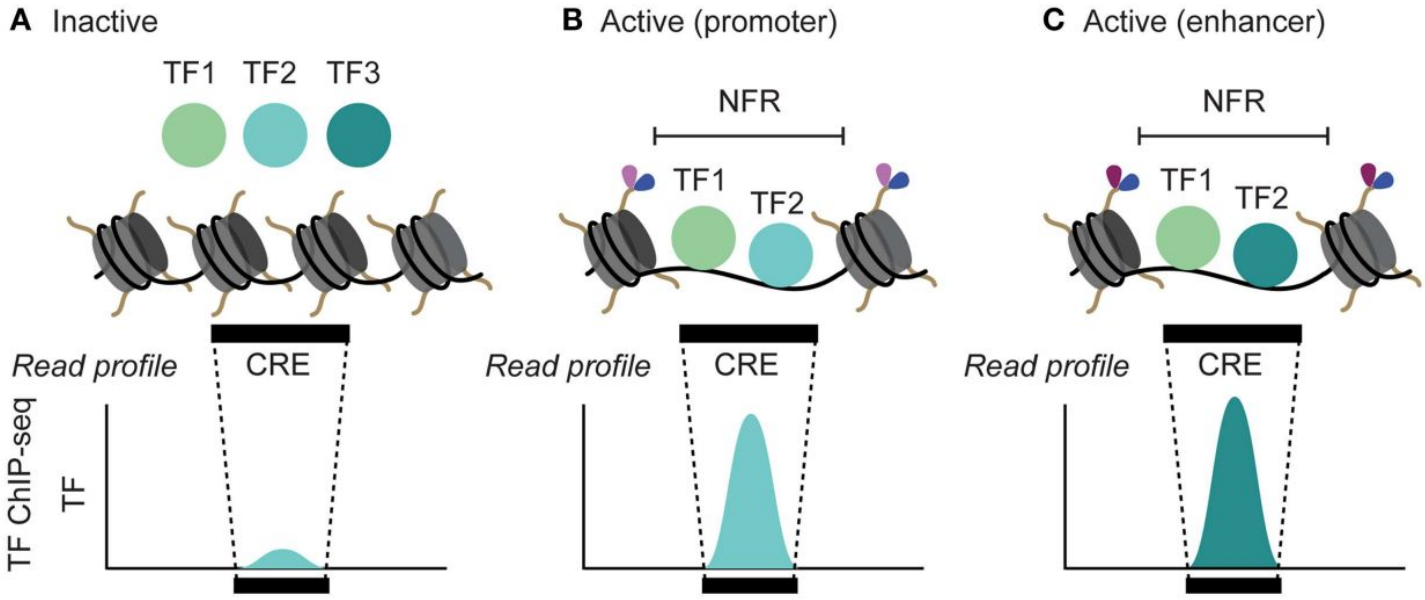

Pundhir (2015) Front. Genet.

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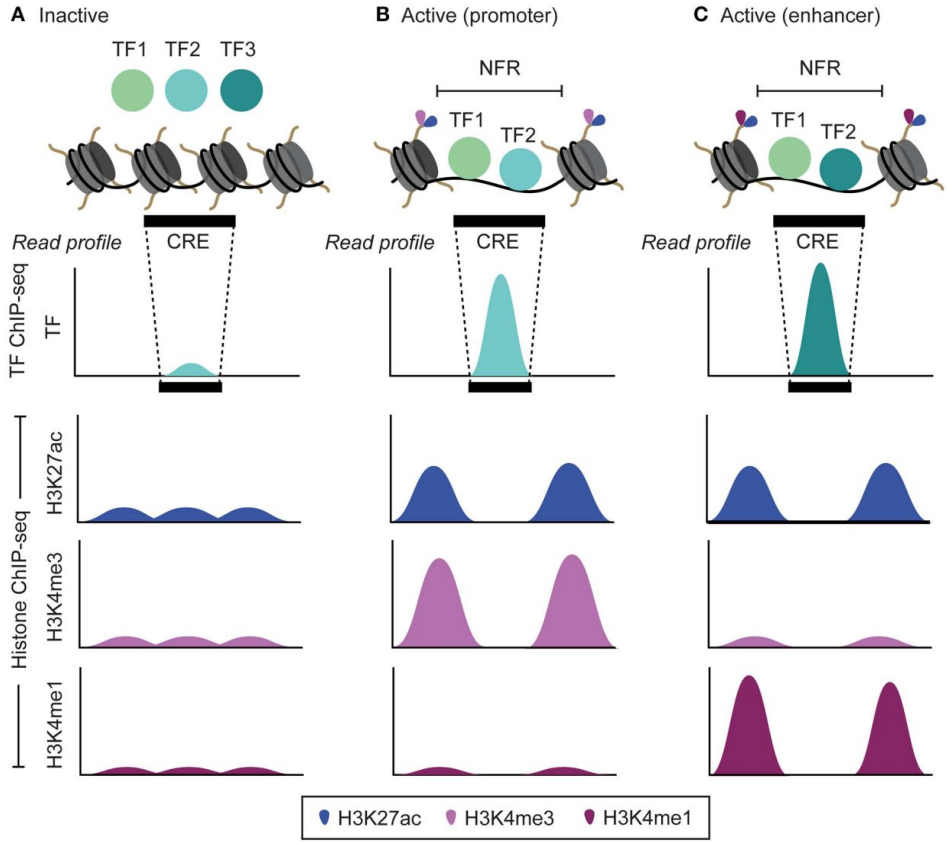

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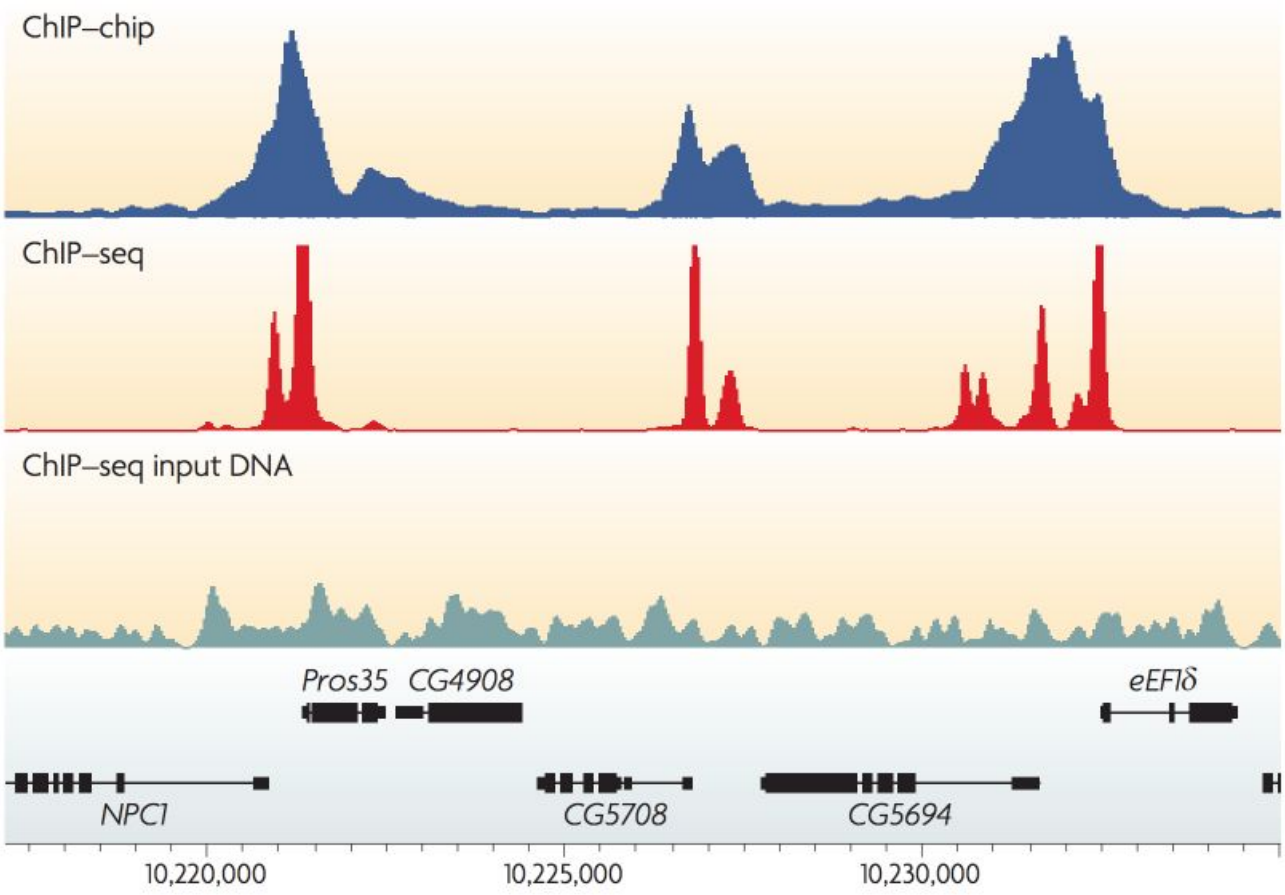

Park (2009) Nat. Rev. Genet.