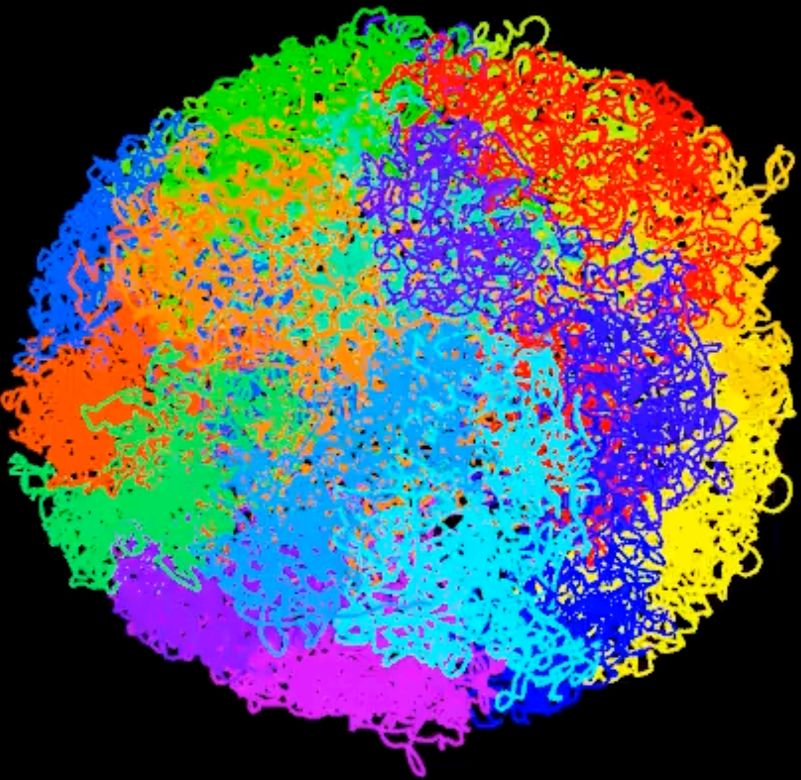
BIO-463
Genomics and bioinformatics

Lecture 13: Chromosome conformation

Dr Jacques Rougemont

EPFL

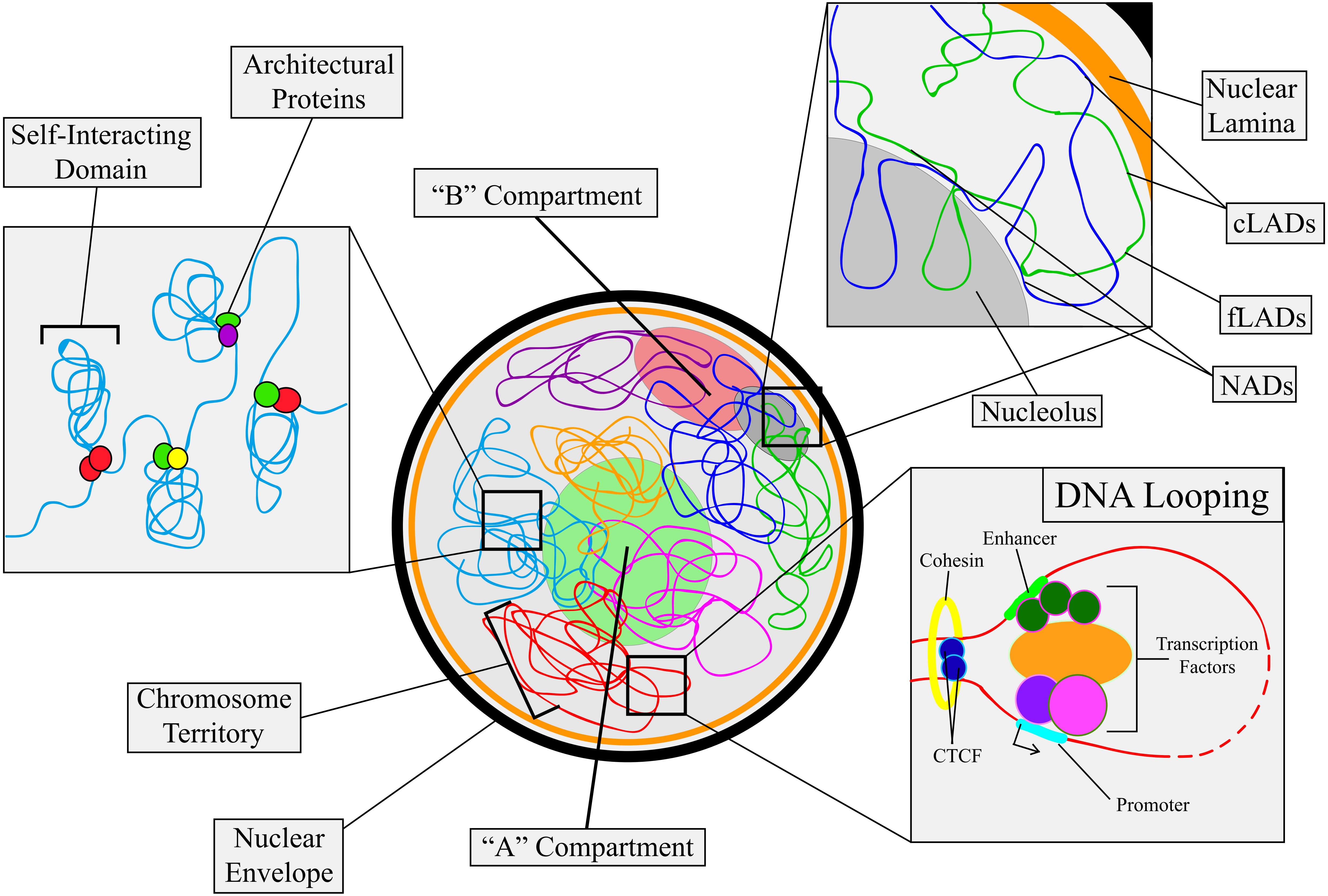
Chromosome conformation



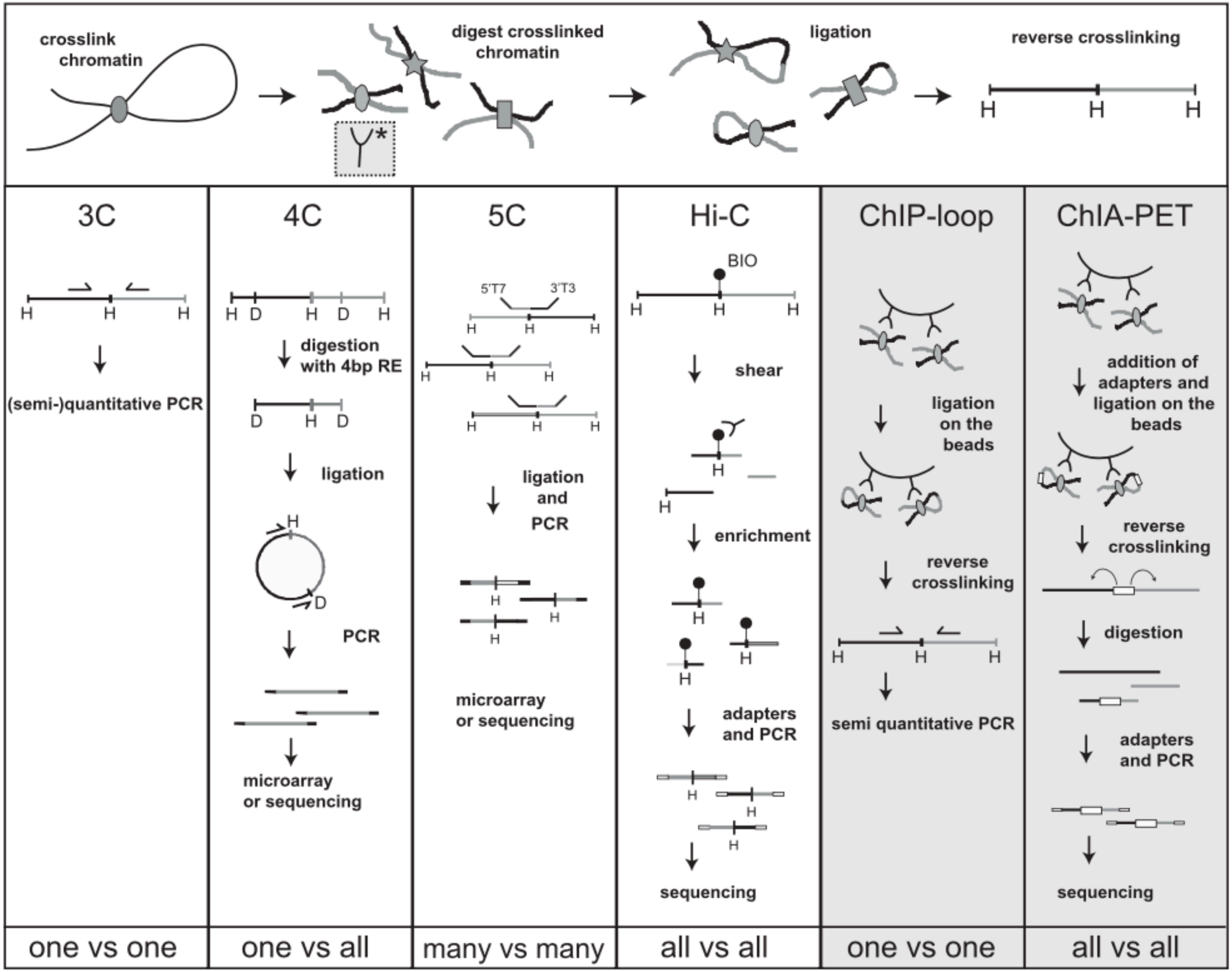
Reconstruction of the most likely chromosome conformations based on **~120'000** contacts observed in **1** mouse stem cell

Stevens TJ et al. Nature (2017)

Chromosome conformation

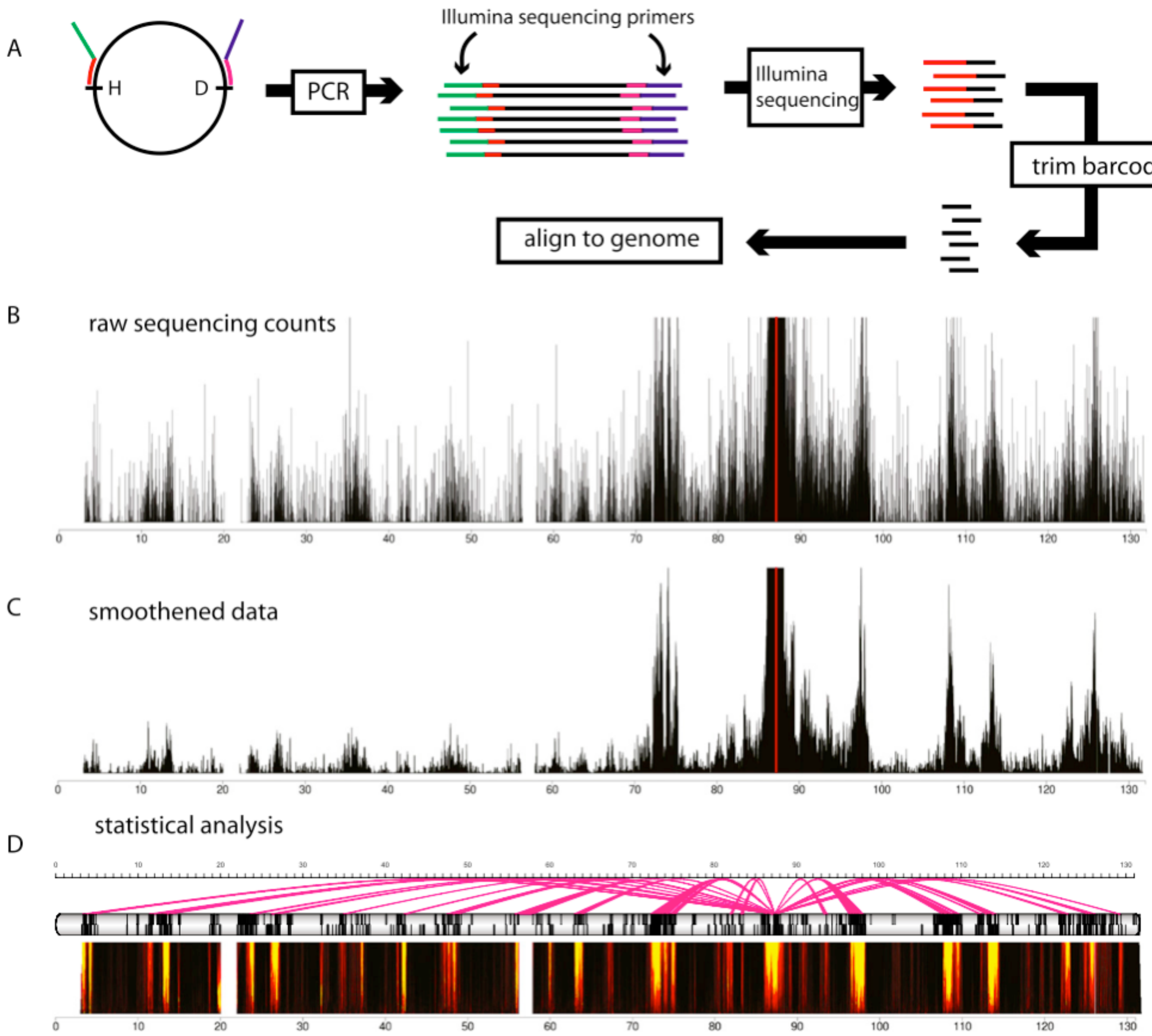


Measuring spatial structure of chromatin

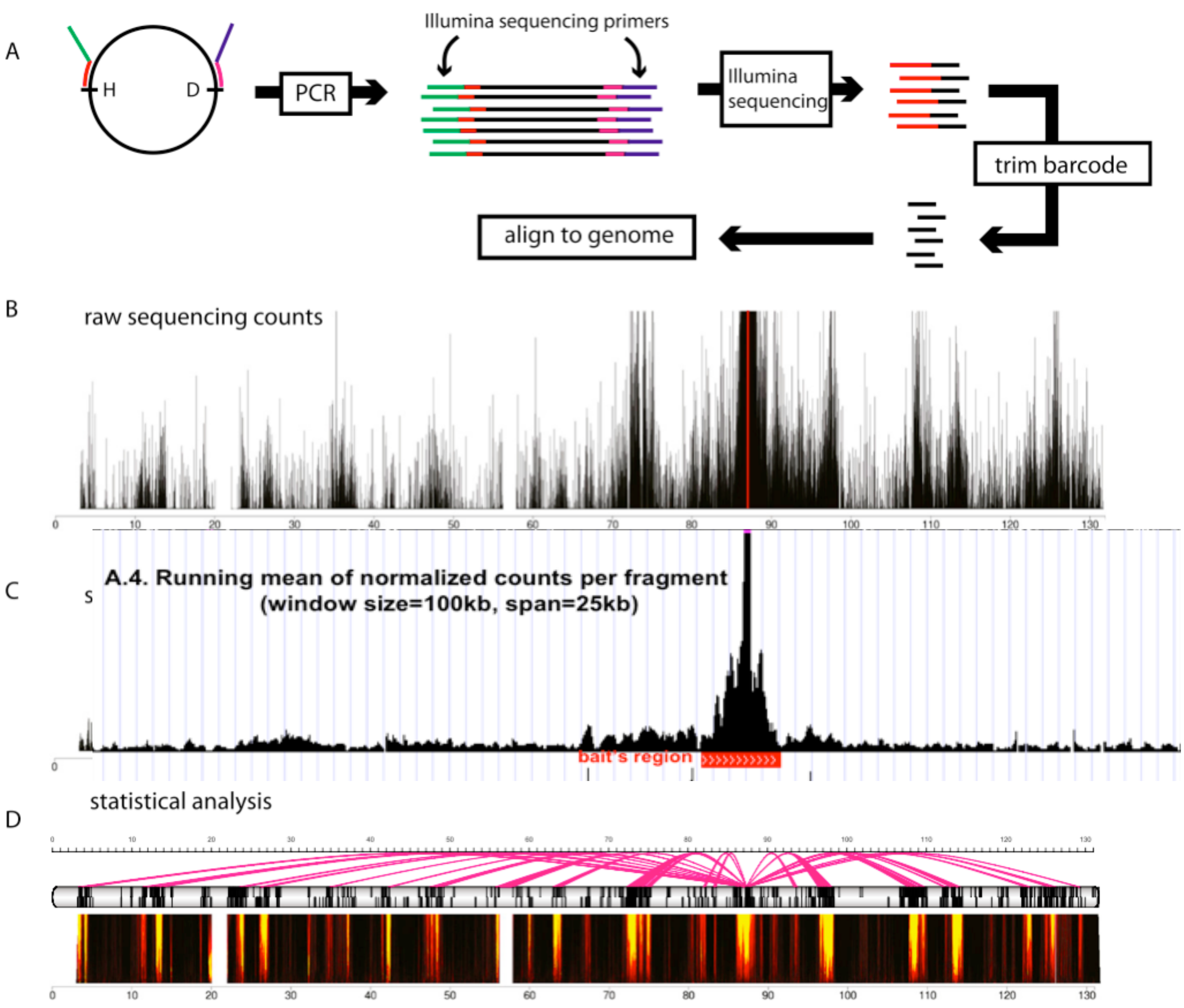


de Wit E & de Laat WA, Genes Dev (2012)

Quantifying interactions



Quantifying interactions

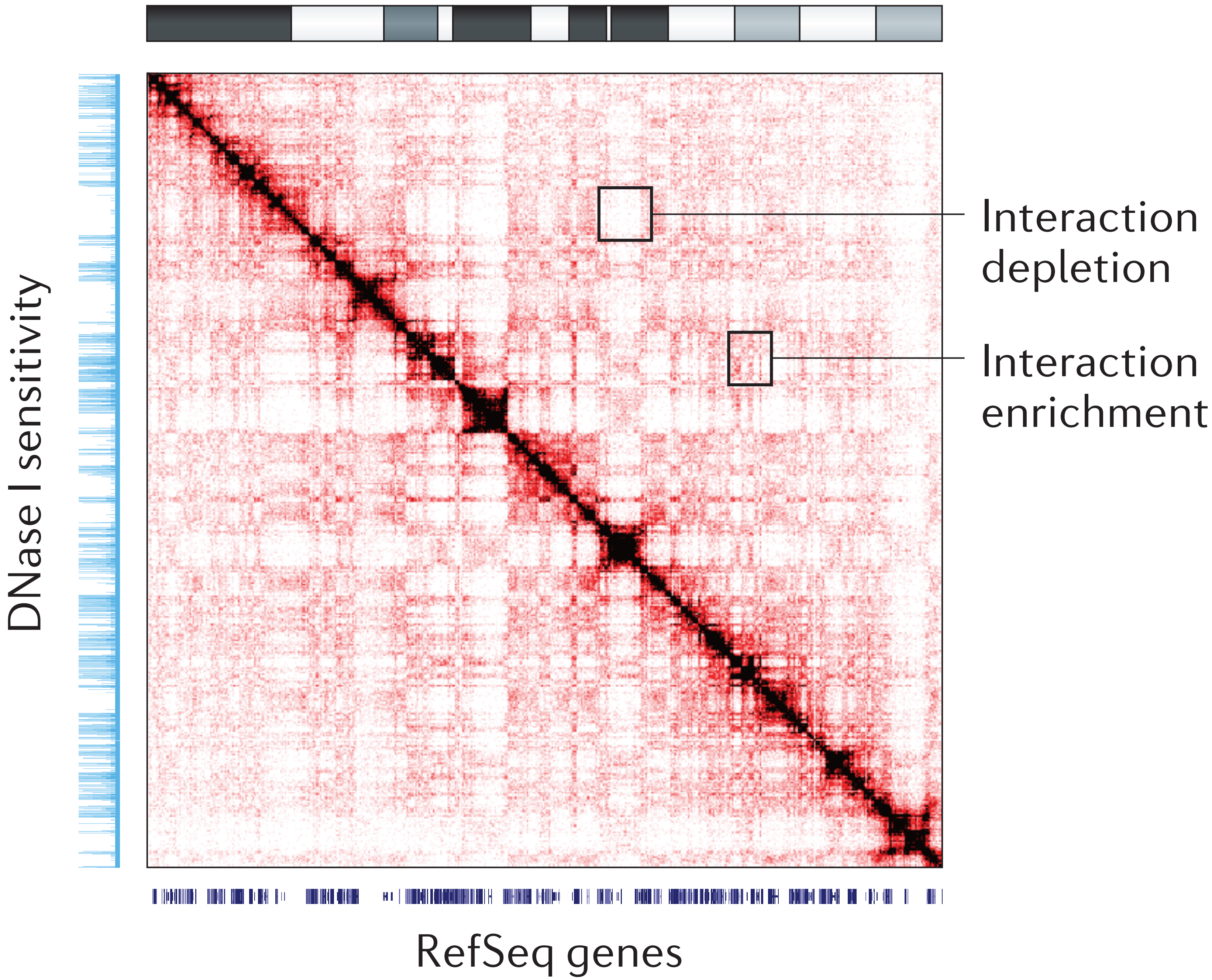


Hi-C contact maps

Mouse chr. 18 (~100Mb)

Bin size: 10 kb -1 Mb

Matrix size: 100 - 10000

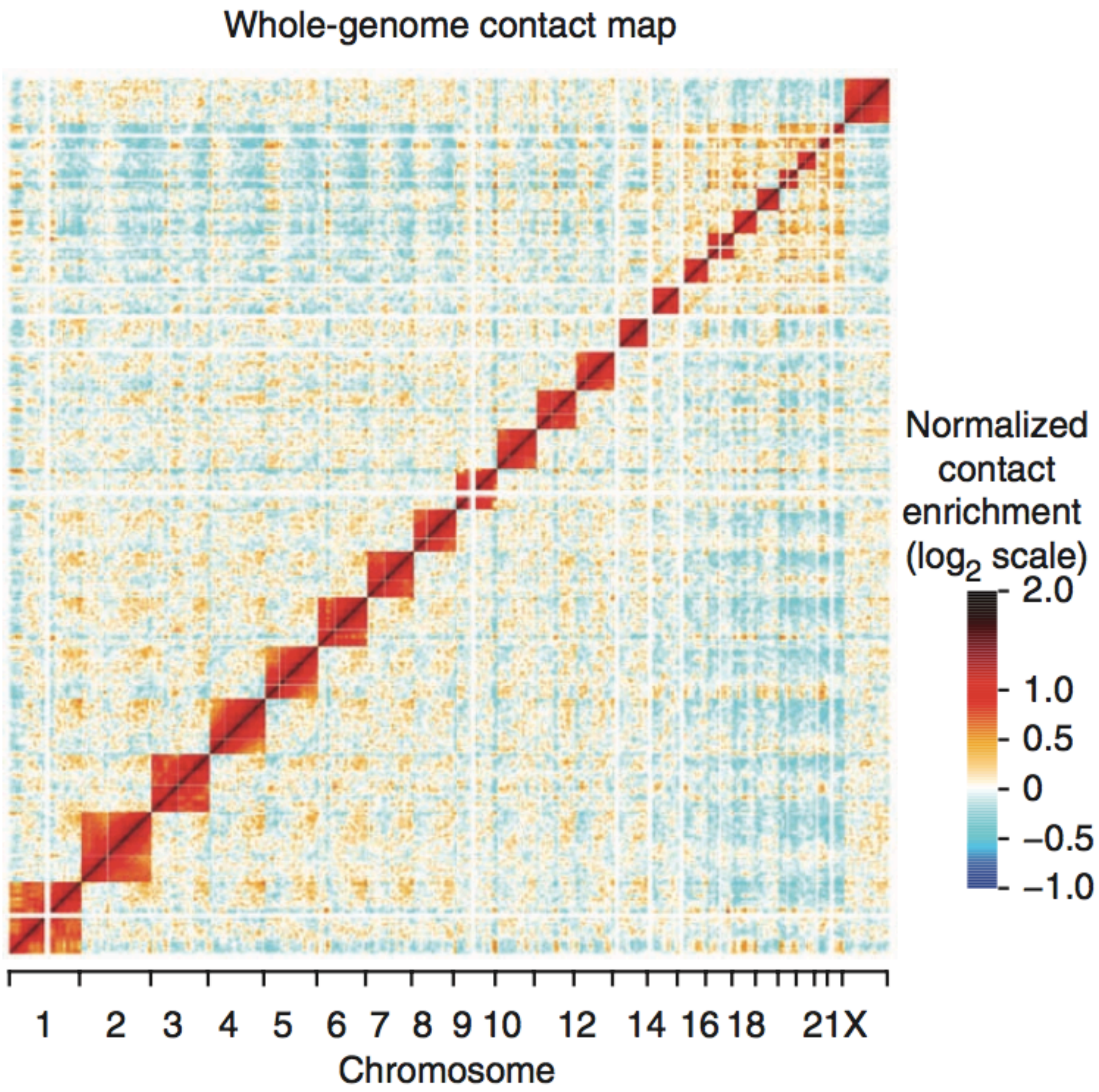


M_{ij} = #read pairs with 1st read in bin i and 2nd read in bin j

Dekker et al. Nat Reviews Genetics (2013)

Hi-C contact maps

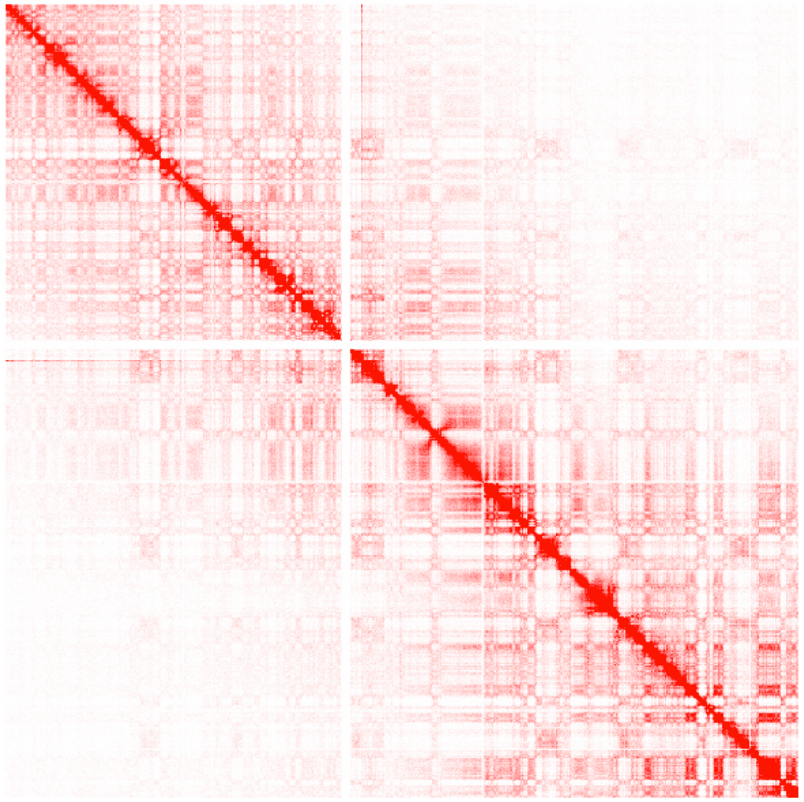
Inter-chromosomal interactions are depleted by dilution effect:



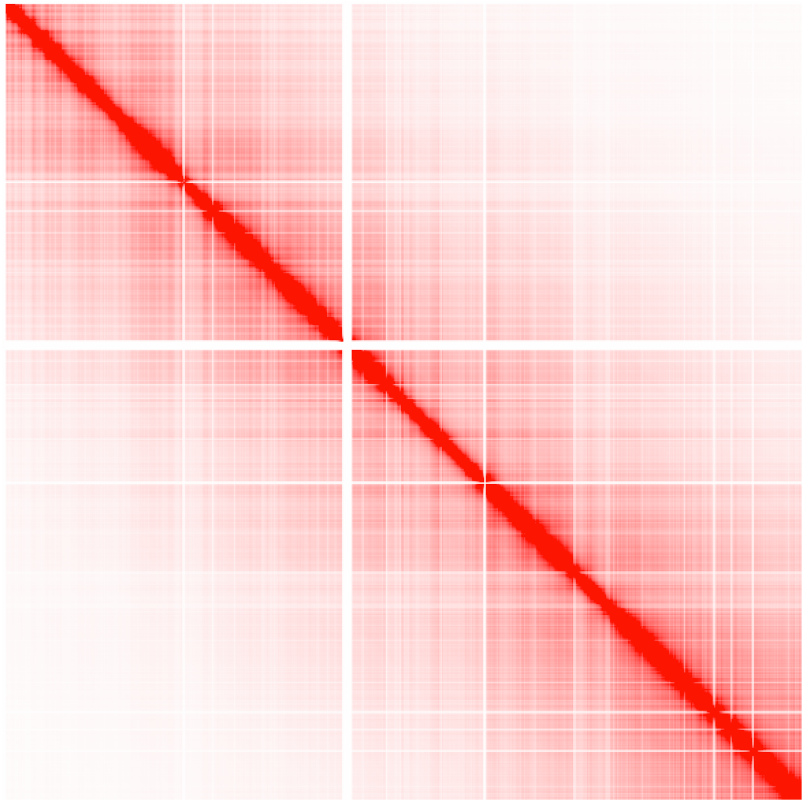
1Mb resolution: matrix is 3000x3000

Yaffe & Tanay Nat Genet (2011)

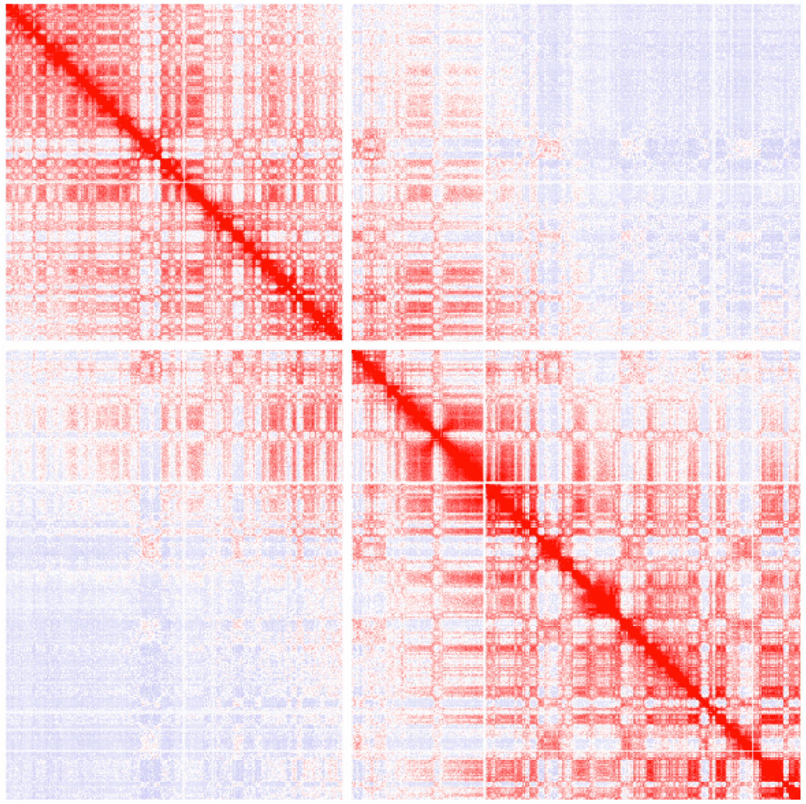
Hi-C normalization



Raw data



Expected



log(Raw / Expected)

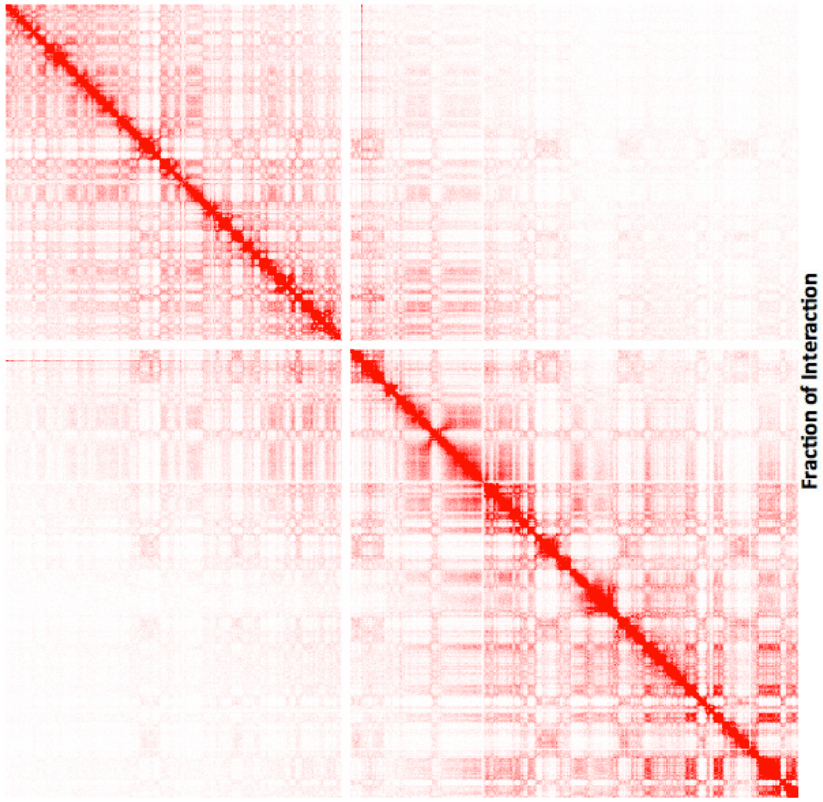
$$E_{ij} = f(|i-j|)\frac{n_i n_j}{N}$$

$$n_i = \sum_k M_{ik}$$

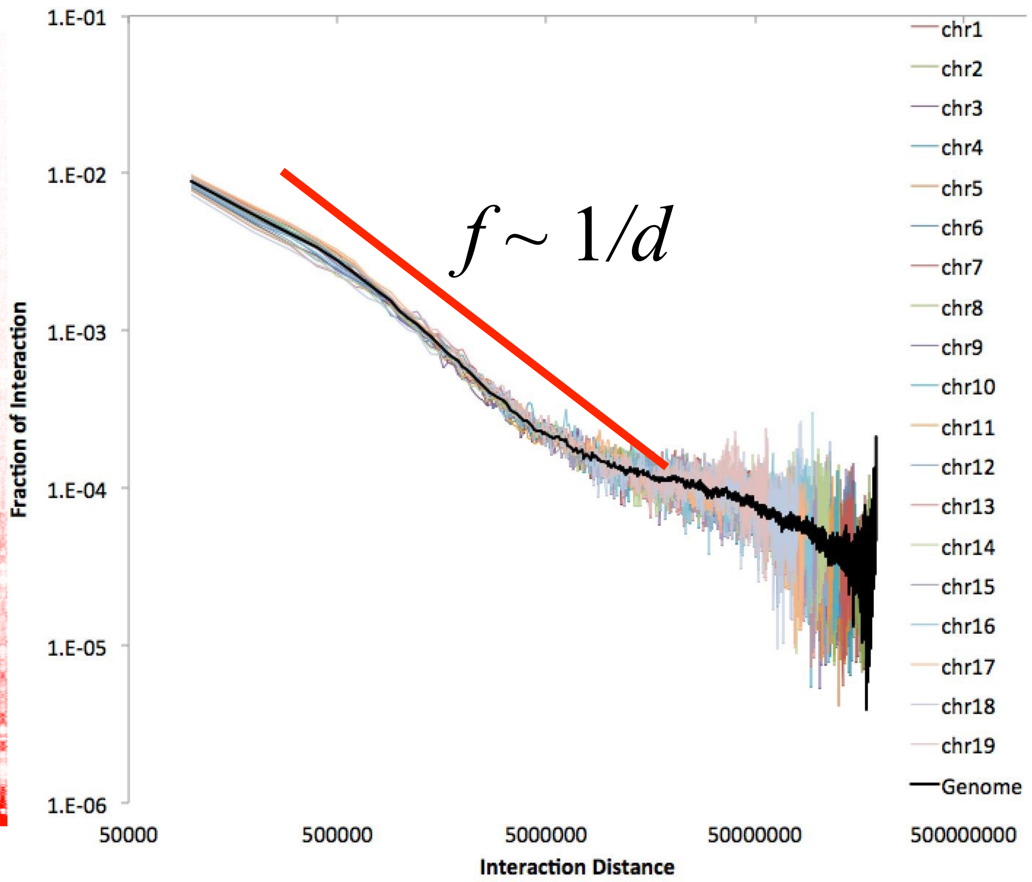
$$N = \sum_k n_k = \sum_{k\ell} M_{k\ell}$$

HOMER:HiCBackground

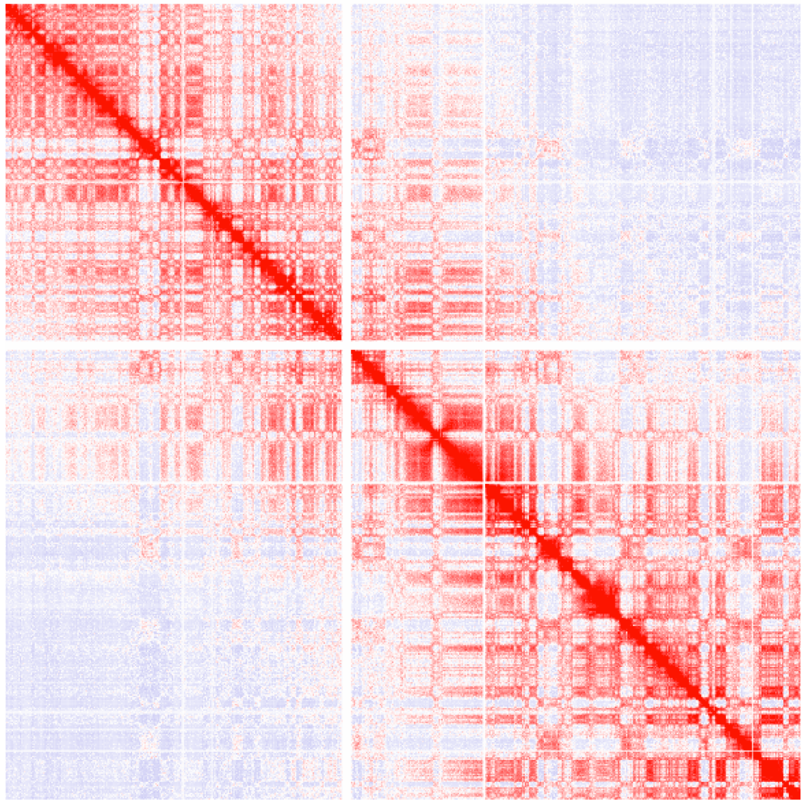
Hi-C normalization



Raw data



Expected



log(Raw / Expected)

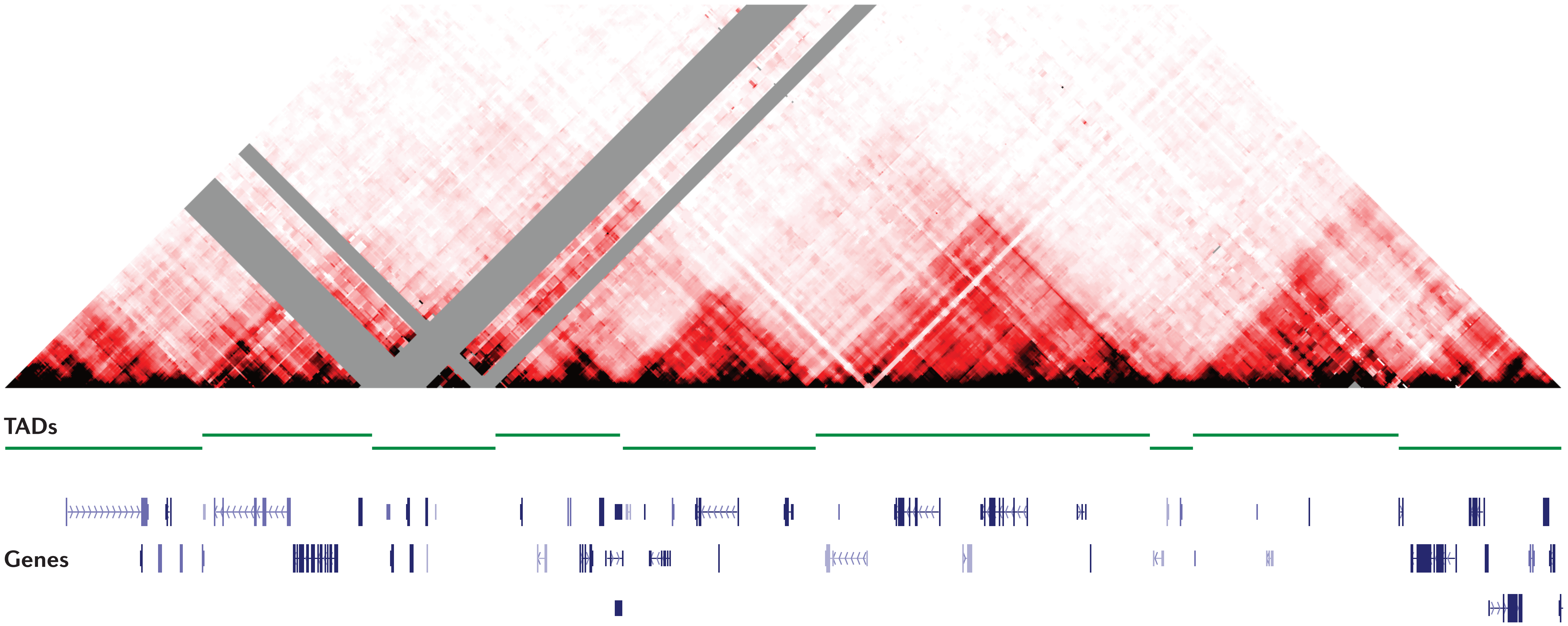
$$E_{ij} = f(|i-j|)\frac{n_i n_j}{N}$$

$$n_i = \sum_k M_{ik}$$

$$N = \sum_k n_k = \sum_{k\ell} M_{k\ell}$$

HOMER:HiCBackground

Topologically Associated Domains



TADs are genome “clusters”:
there are more interactions within TADs than between TADs

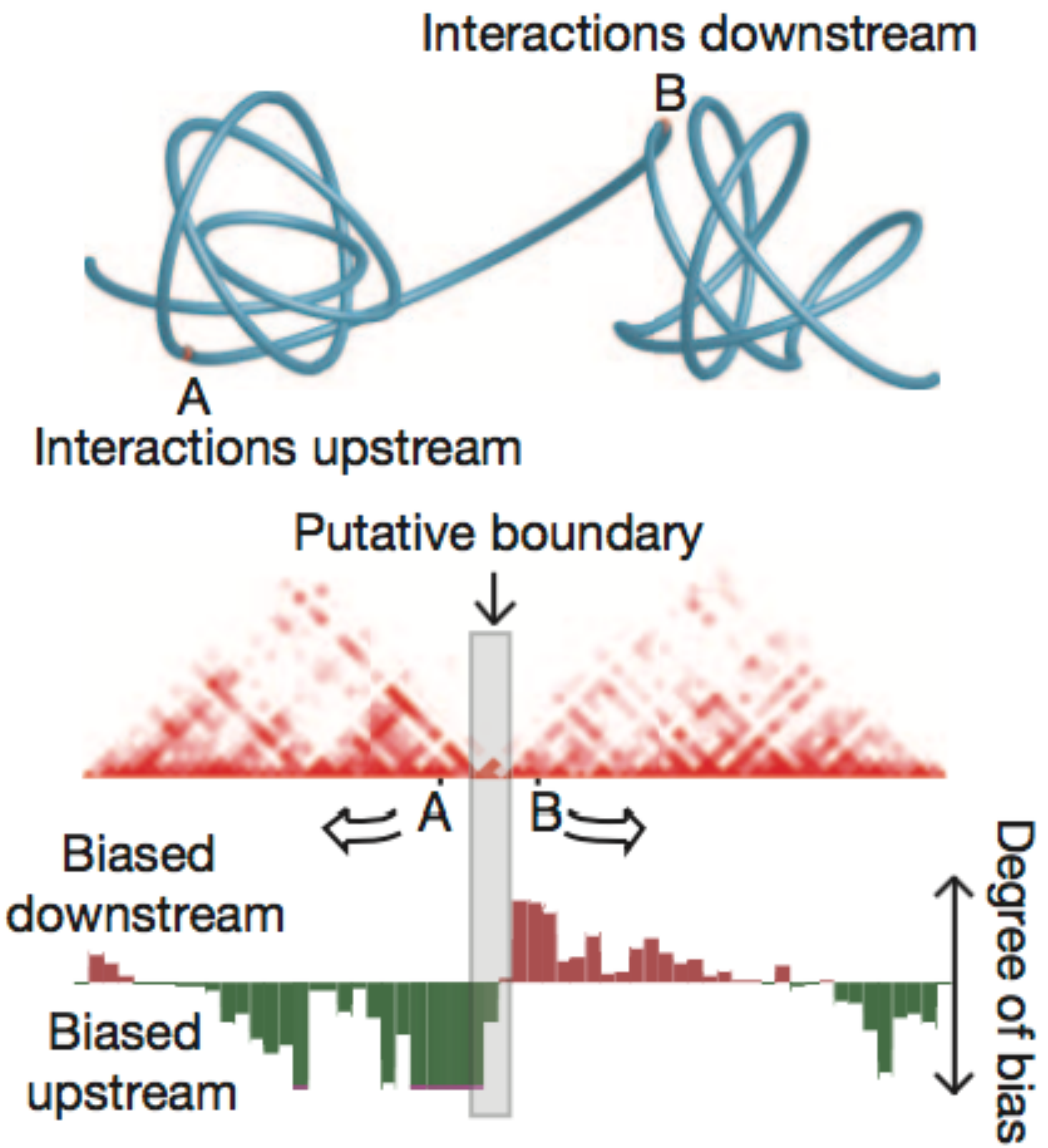
Finding TAD boundaries

DI: directionality index

$$U = \#\{\text{interactions within 2Mb upstream}\}$$

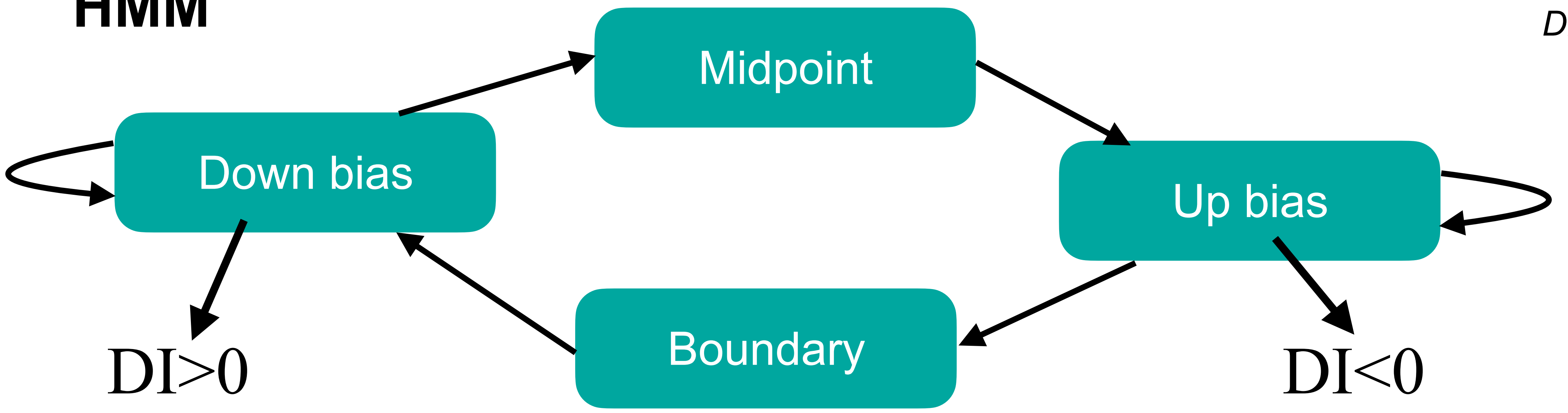
$$D = \#\{\text{interactions within 2Mb downstream}\}$$

$$\mathrm{DI} = \frac{(D-U)^3}{|D^2-U^2|}$$



Dixon et al. Nature (2012)

HMM



Midpoint

Down bias

Up bias

Boundary

DI>0

DI<0

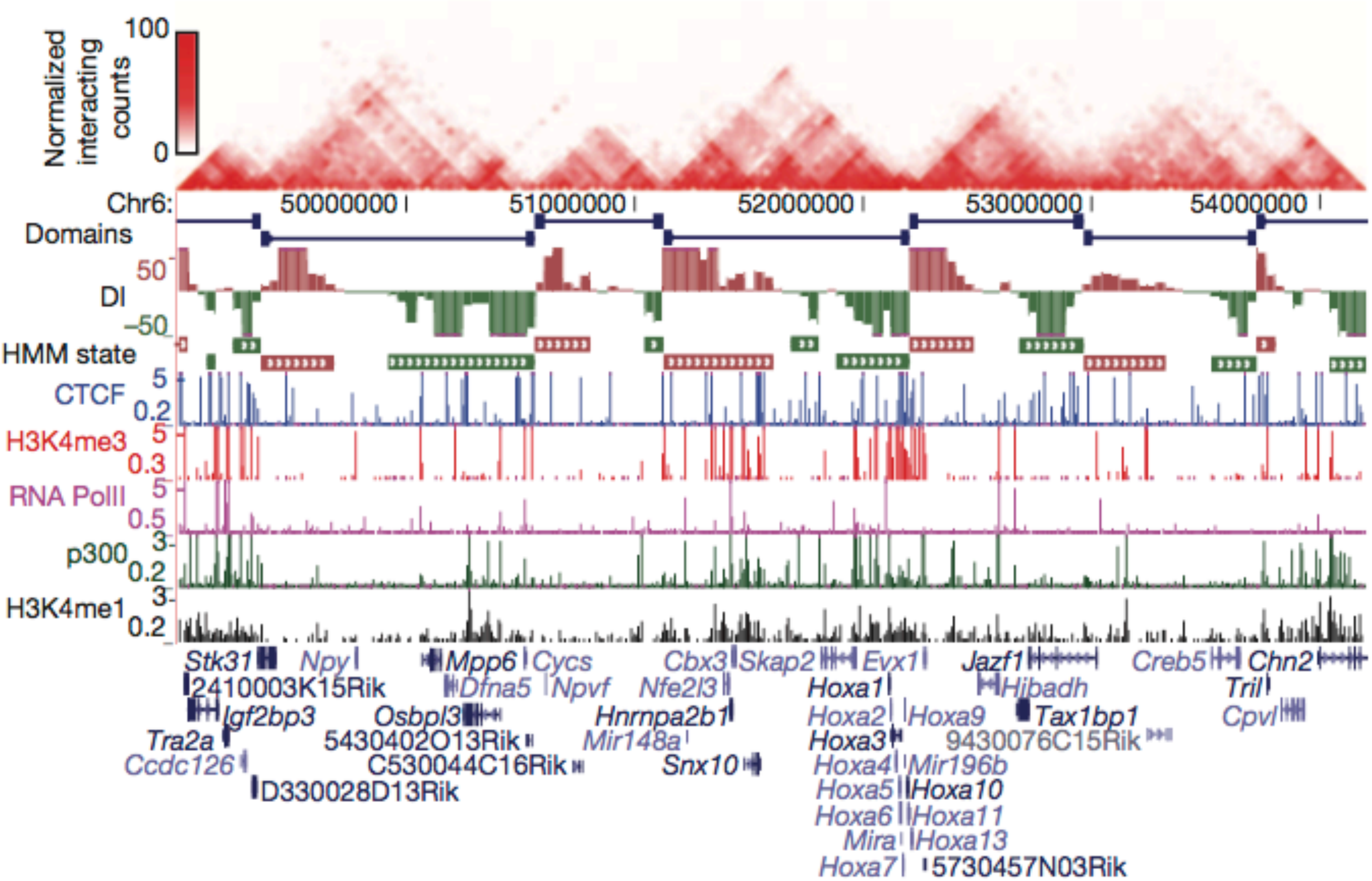
Gene regulation and TADs

Hi-C

TADs

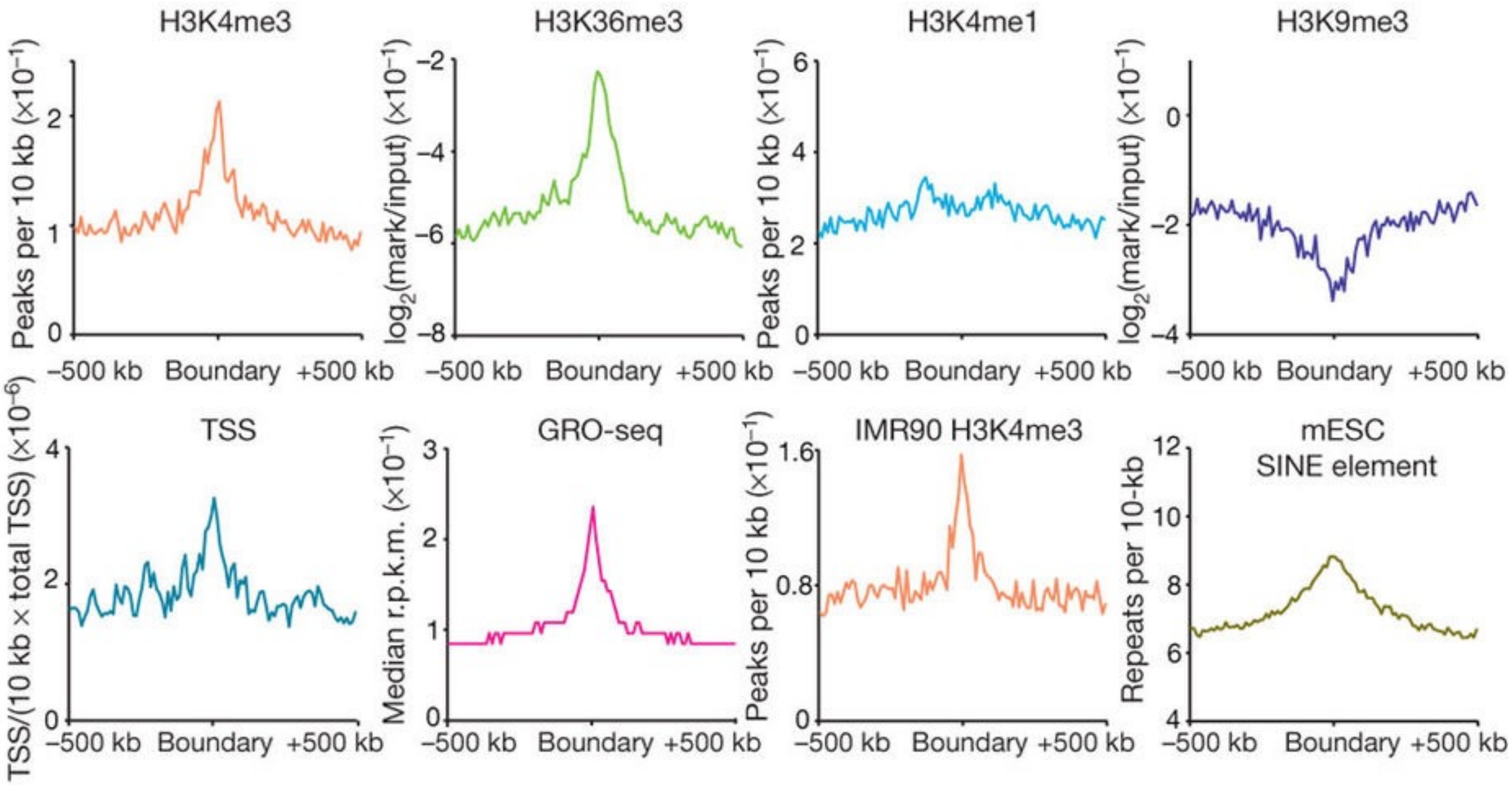
ChIP-seq

Genes



Dixon et al. Nature (2012)

Gene regulation and TADs

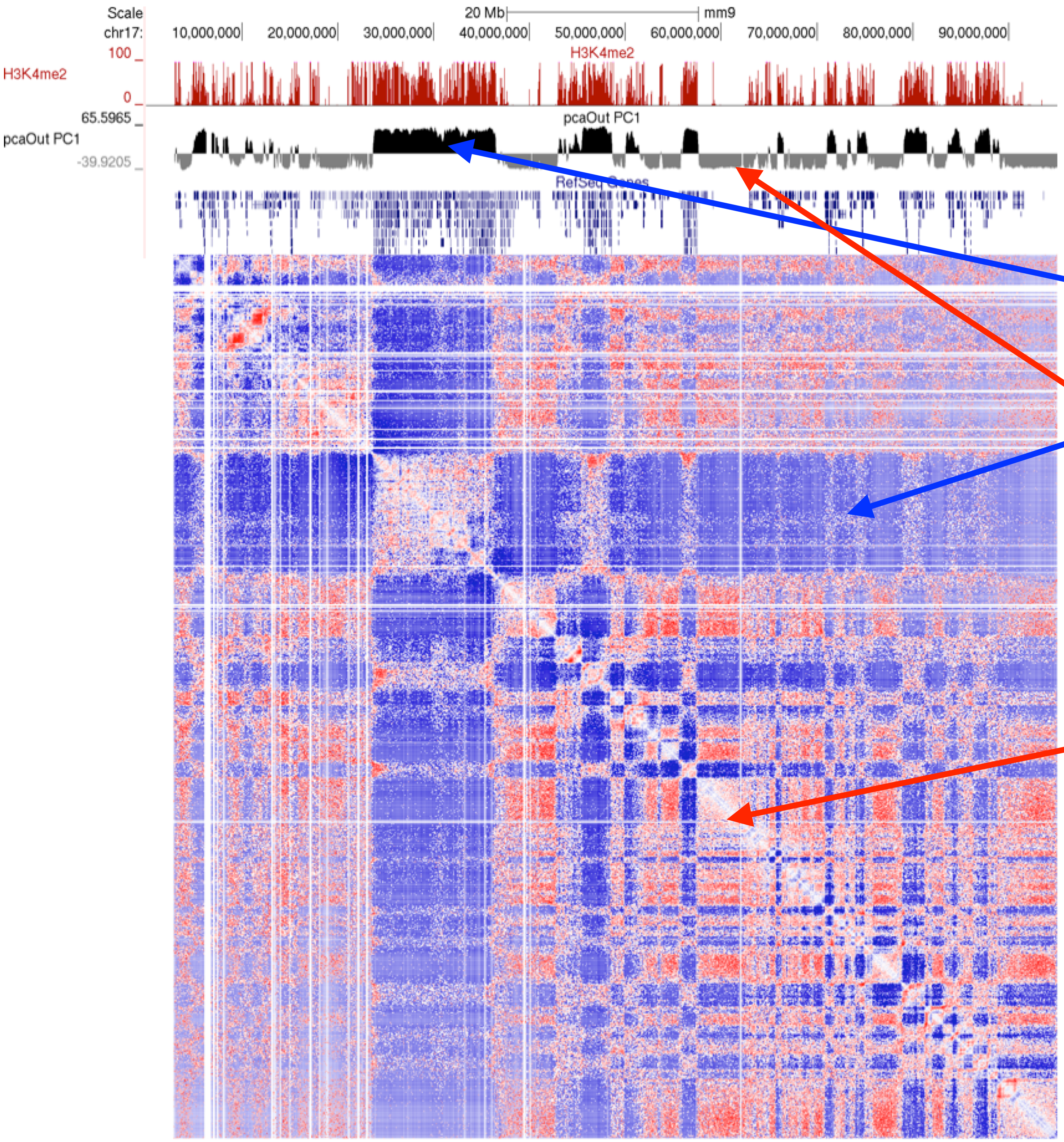


Marks of active transcription associate with boundaries

Dixon et al. Nature (2012)

Correlation analysis

First eigenvector



Compartment A

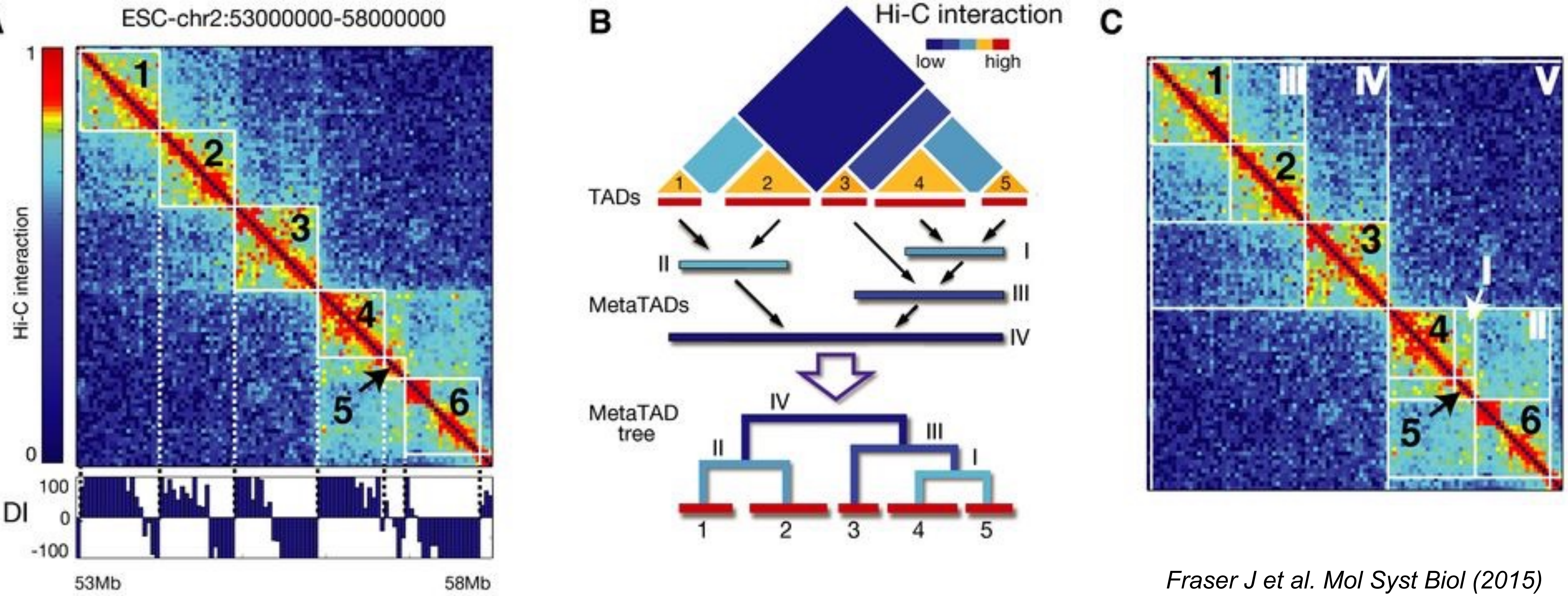
Compartment B

Matrix of row correlations

Lieberman-Aiden E et al. Science (2009)

HOMER:HiCpca

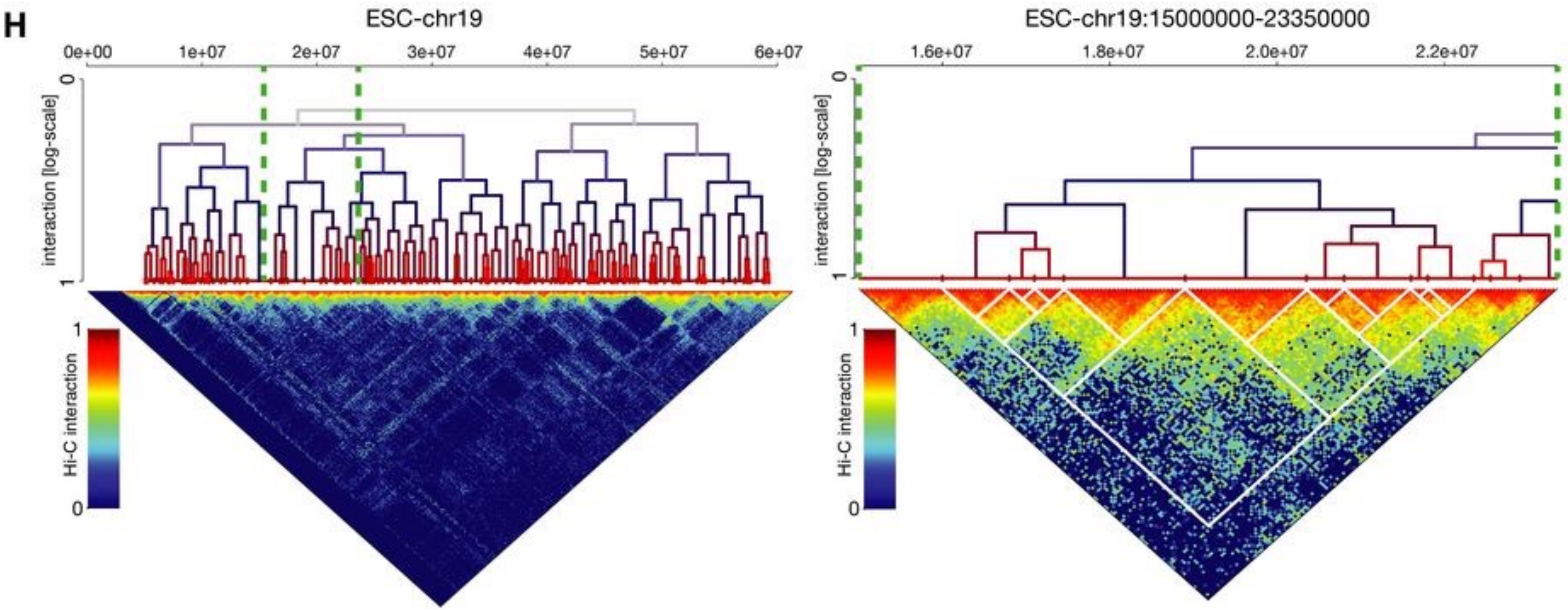
TAD hierarchy



Fraser J et al. Mol Syst Biol (2015)

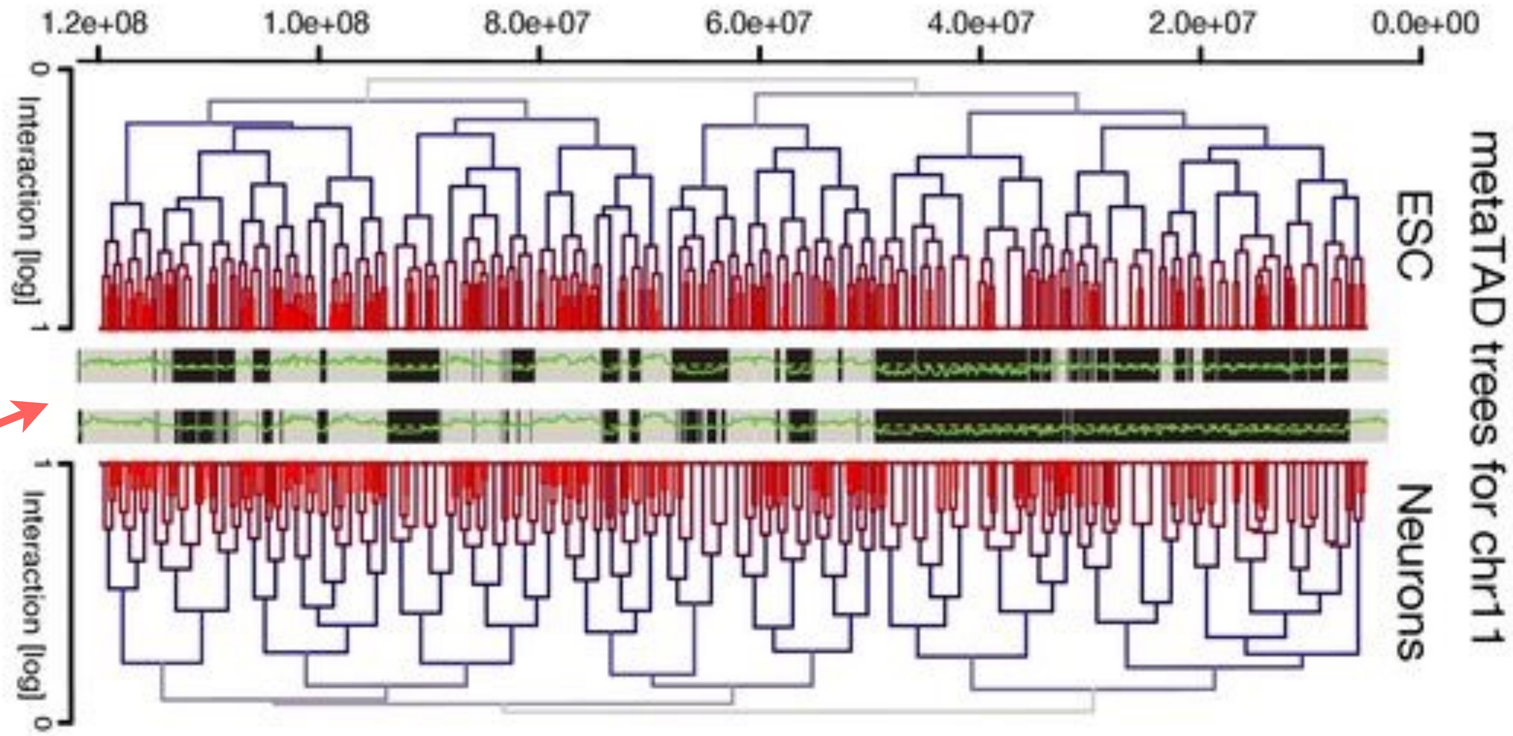
UPGMA algorithm on average TAD-TAD interactions

TAD hierarchy



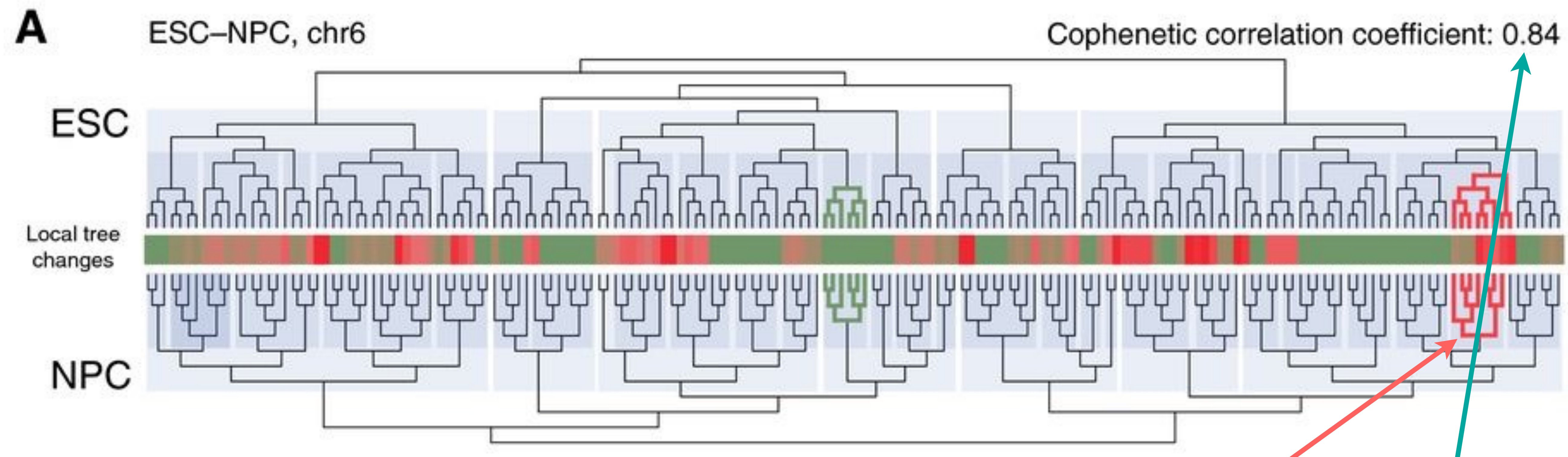
Fraser J et al. Mol Syst Biol (2015)

TAD hierarchy associates with A/B compartments



A/B compartments

TAD hierarchy



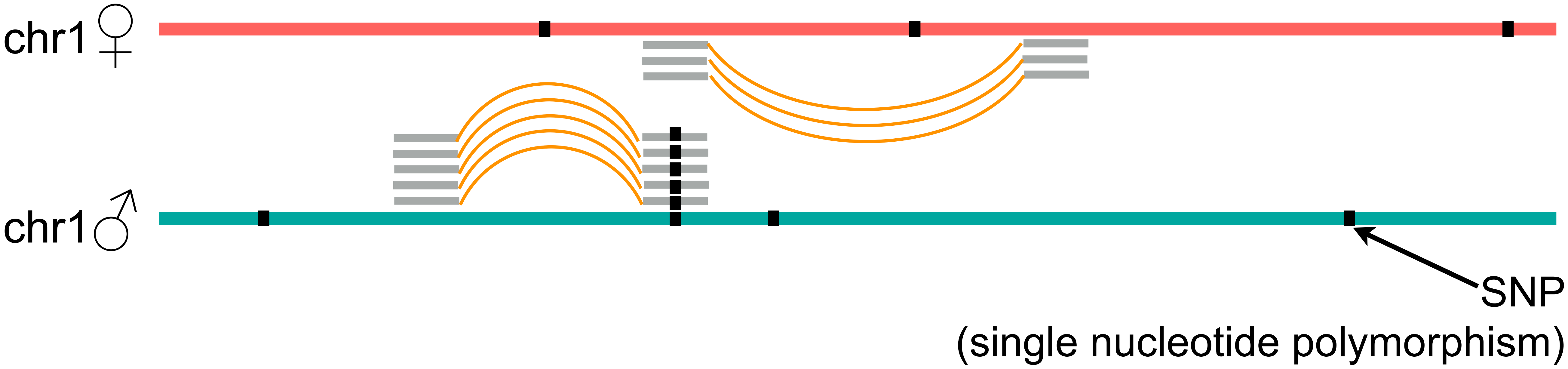
Fraser J et al. Mol Syst Biol (2015)

Changes in tree topology reflect changes in gene regulation

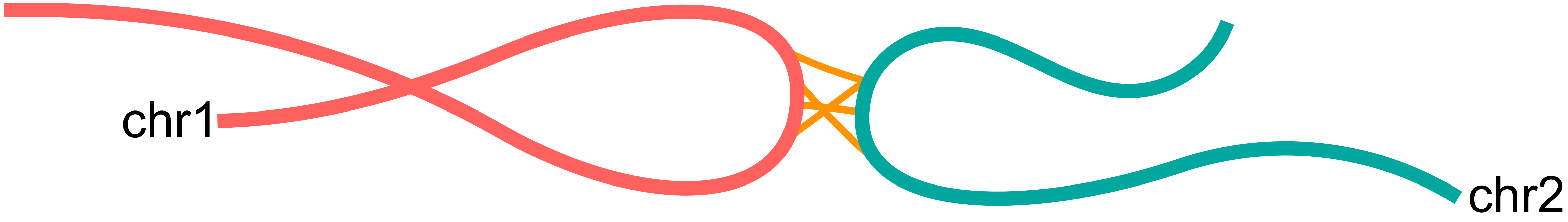
There are few overall changes in topology across cell types

Single-cell+diploid

How to separate “maternal” and “paternal” chromosome?

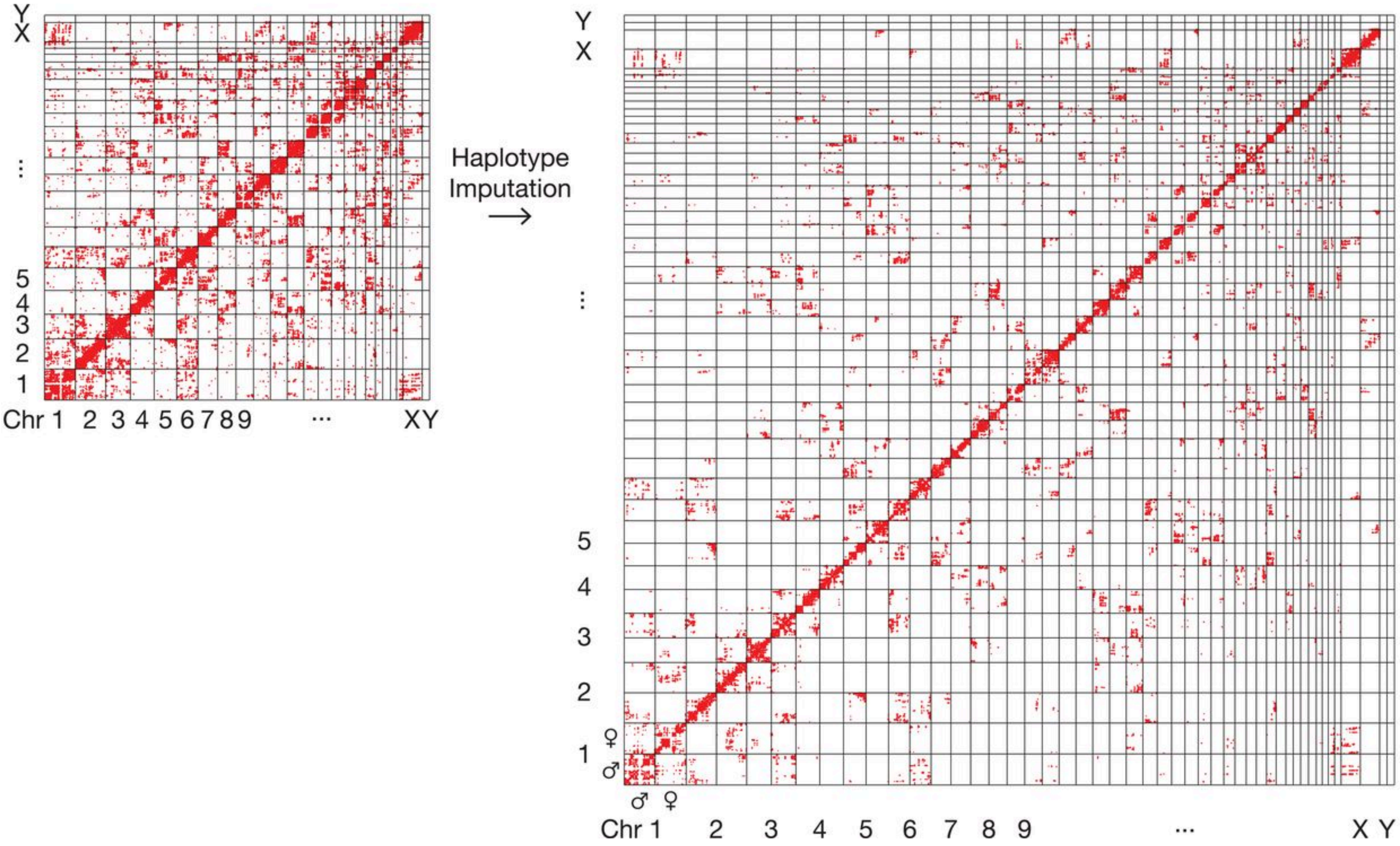


- Use SNPs to attribute reads to haplotype
- Propagate to contacting loci along chromosome
- Use statistical model to split pairs without SNPs between haplotypes
- Observation: “proximity effect” also works between chromosomes



Tan L et al. Science (2018)

Single-cell+diploid

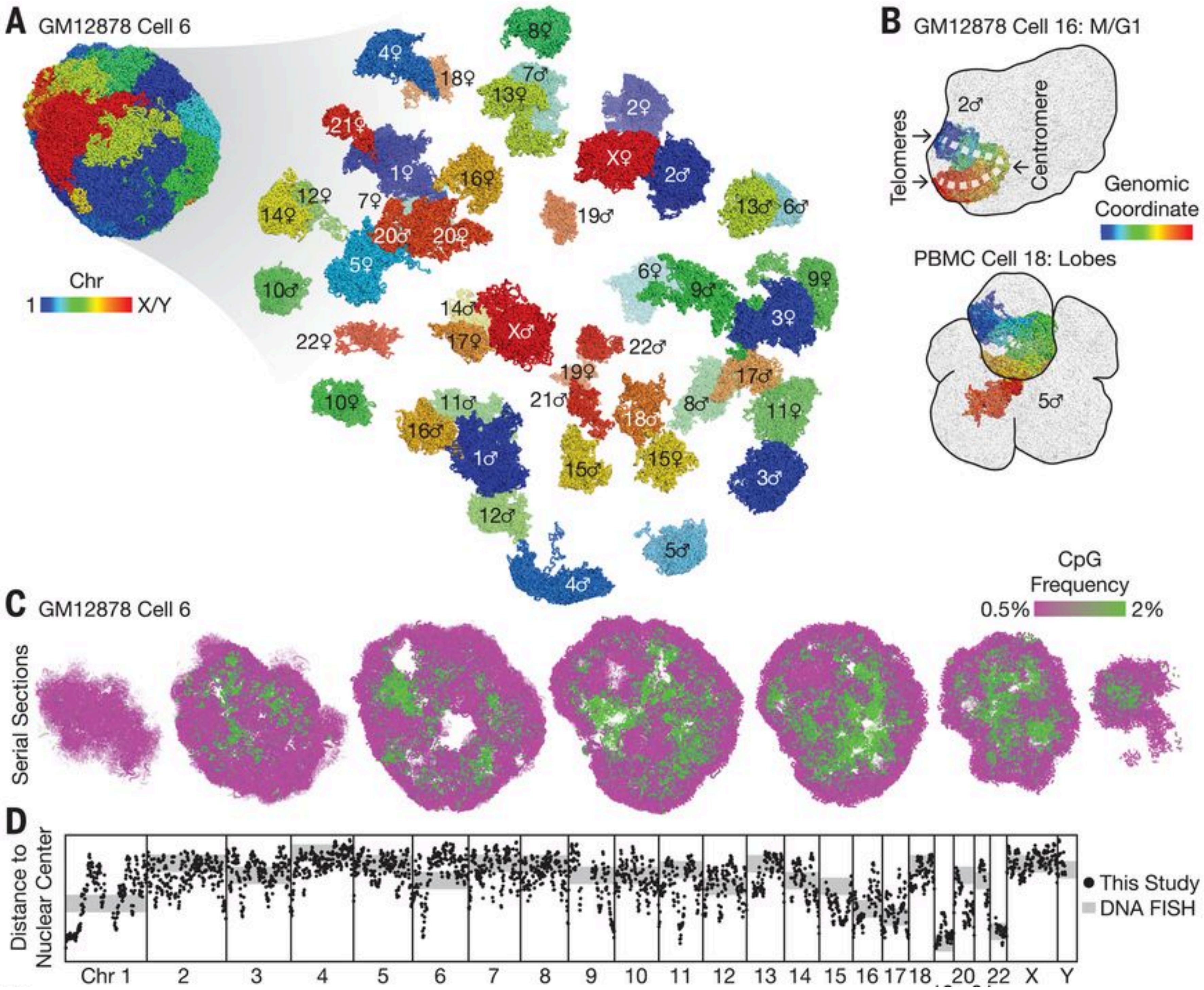


Resolution is 20kB, ~ 1M contacts × 18 cells

Tan L et al. Science (2018)

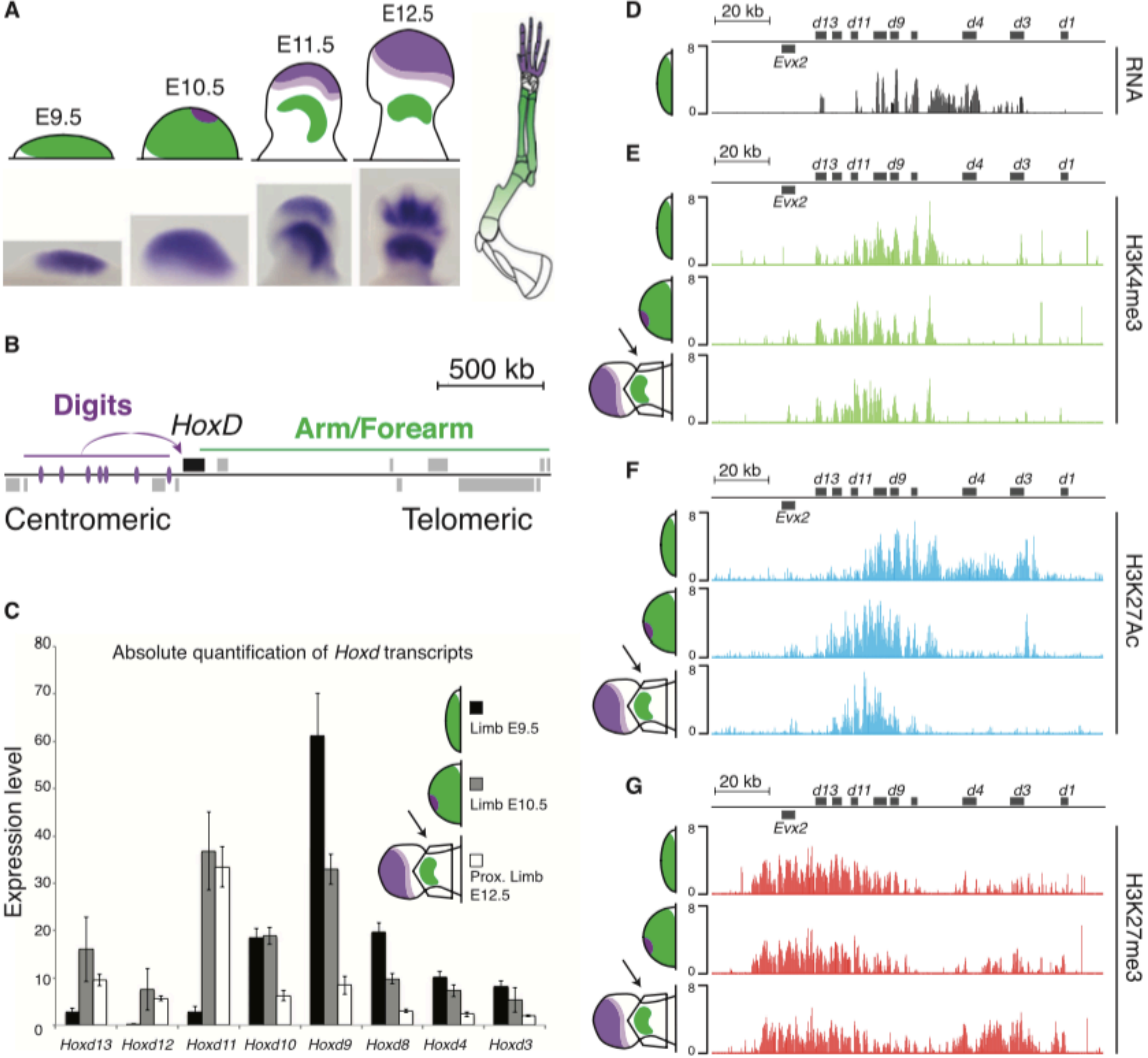
Single-cell+diploid

- Chromosome territories
- Mitotic / abnormal cell
- Eu/Heterochromatin
- Preferred distance to center of nucleus



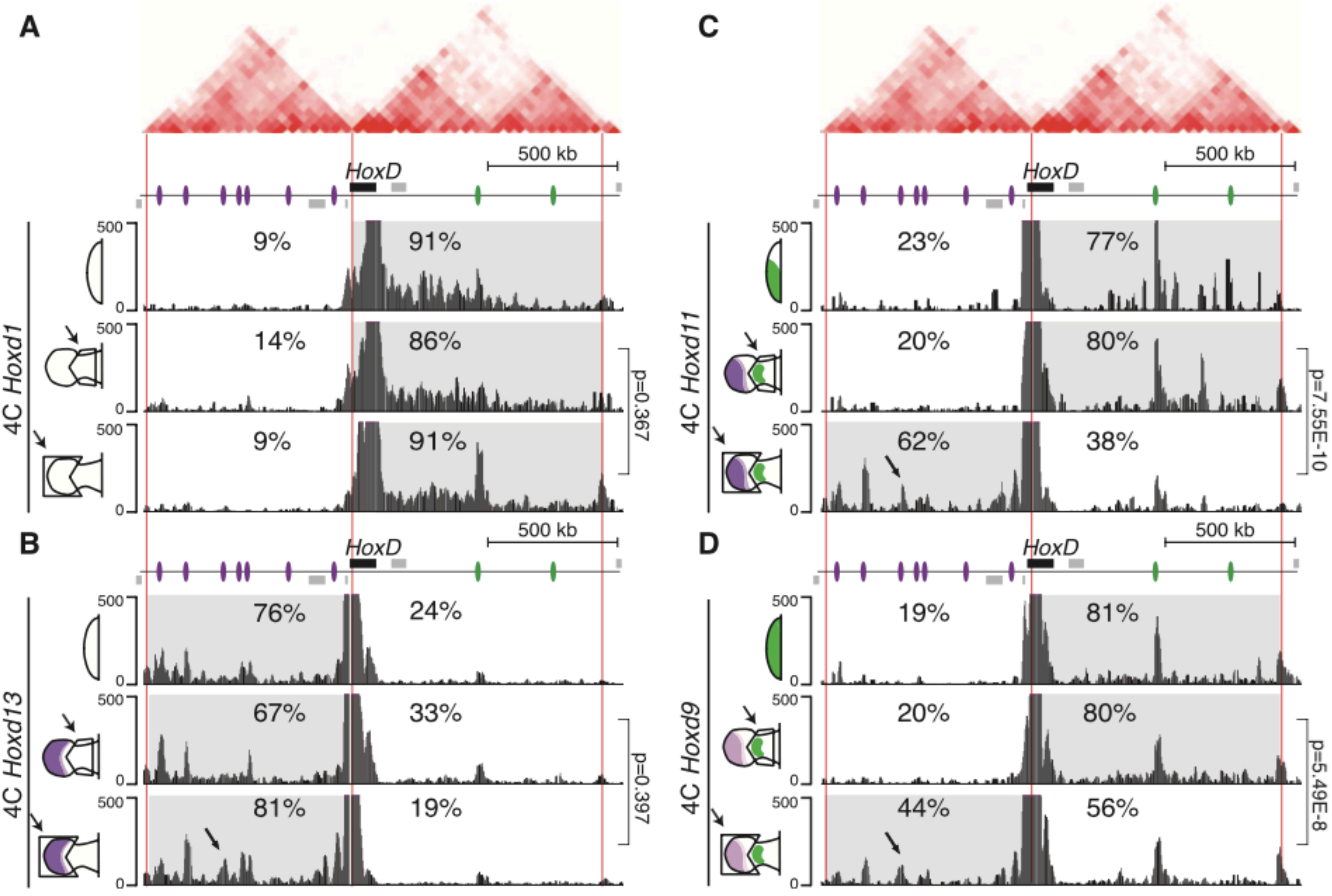
Tan L et al. Science (2018)

Regulation and structure



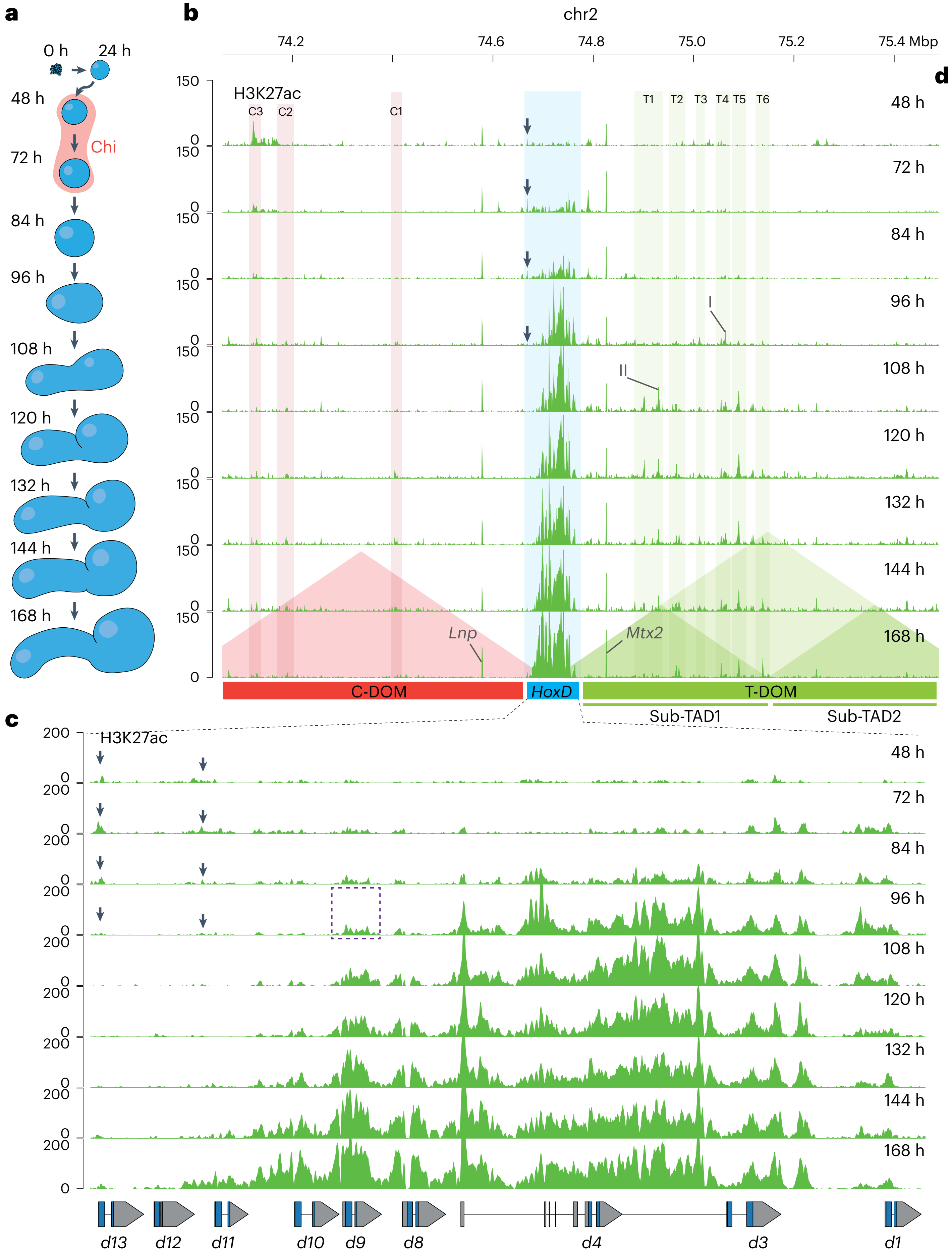
Andrey et al. Science (2013)

Regulation and structure

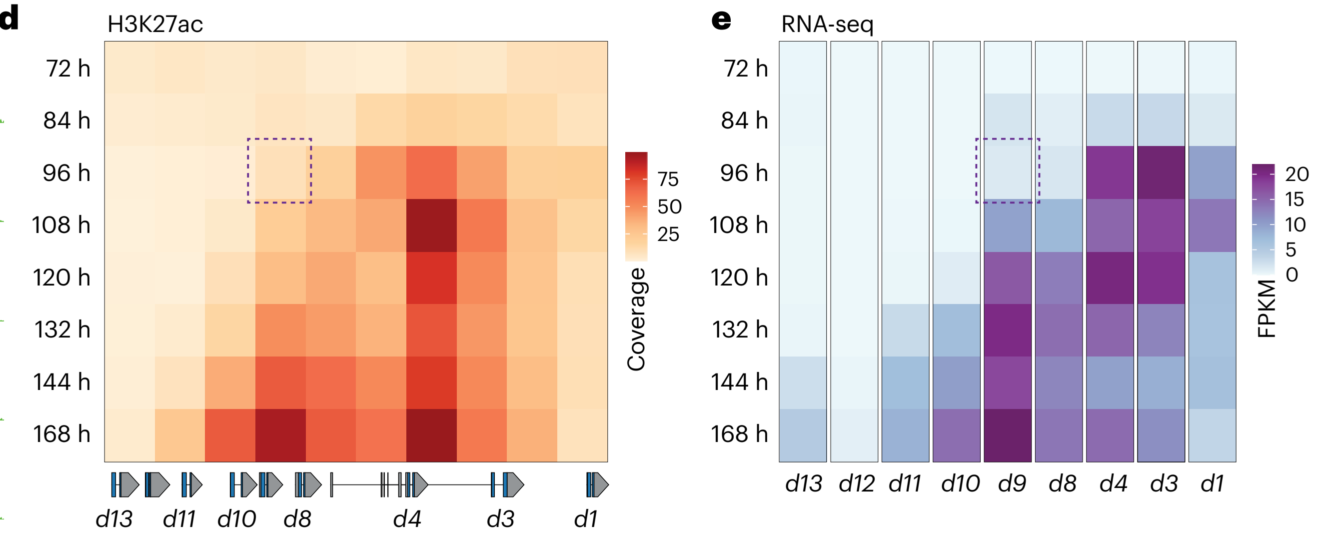


Andrey et al. Science (2013)

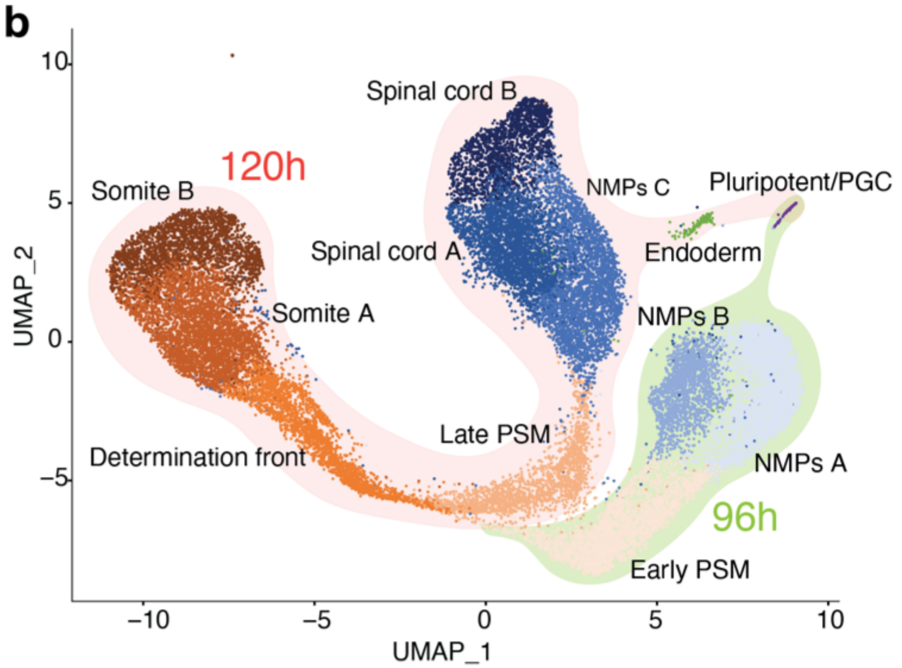
Stembryos



Rekaik et al. Nat. Genet (2023)

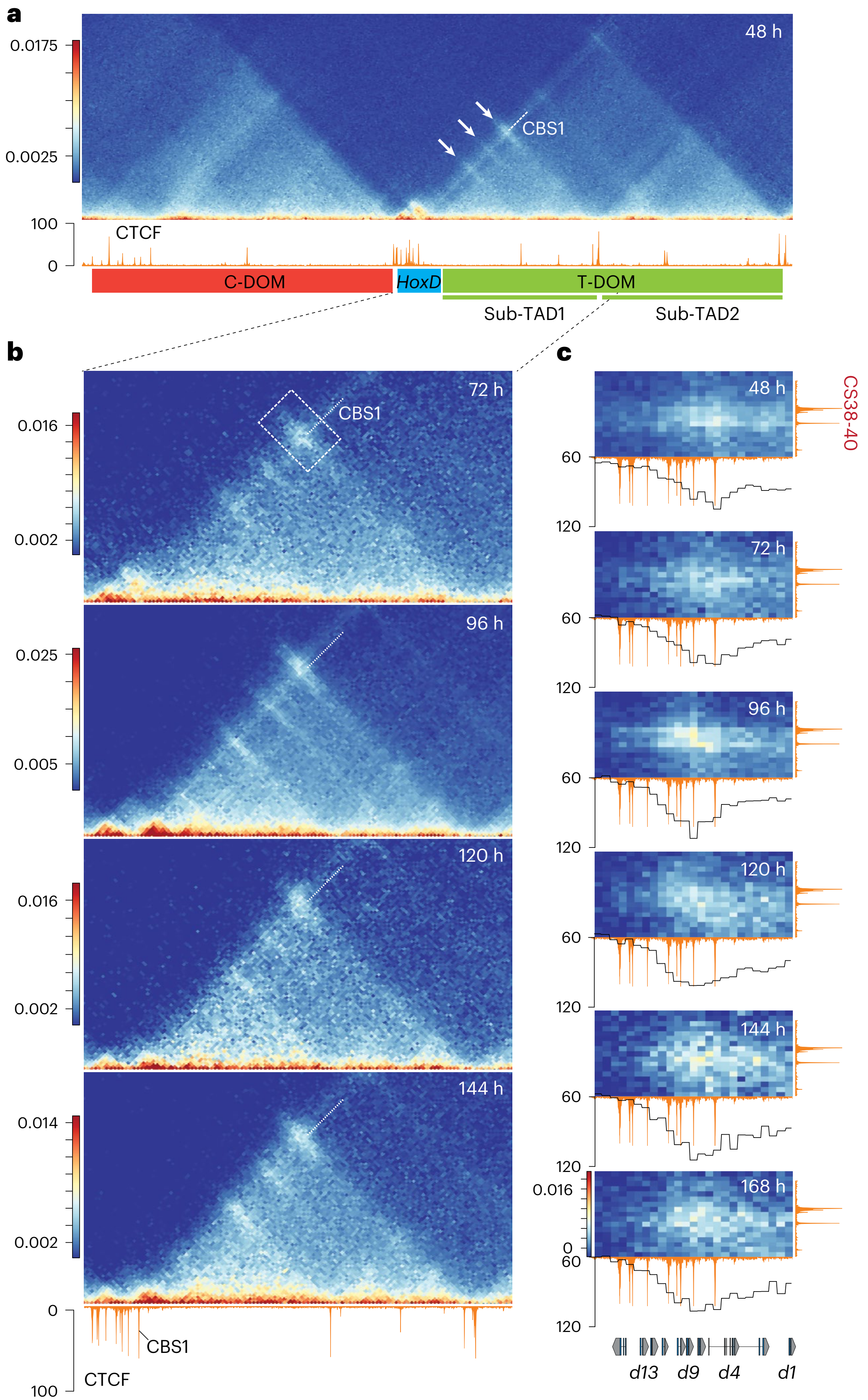


- Lab-induced tail-bud growth from stem cells
- H3K27ac ChIP-seq and RNA-seq show the expected sequential activation
- ChIP-seq peaks appear at contacted loci



Stembryos

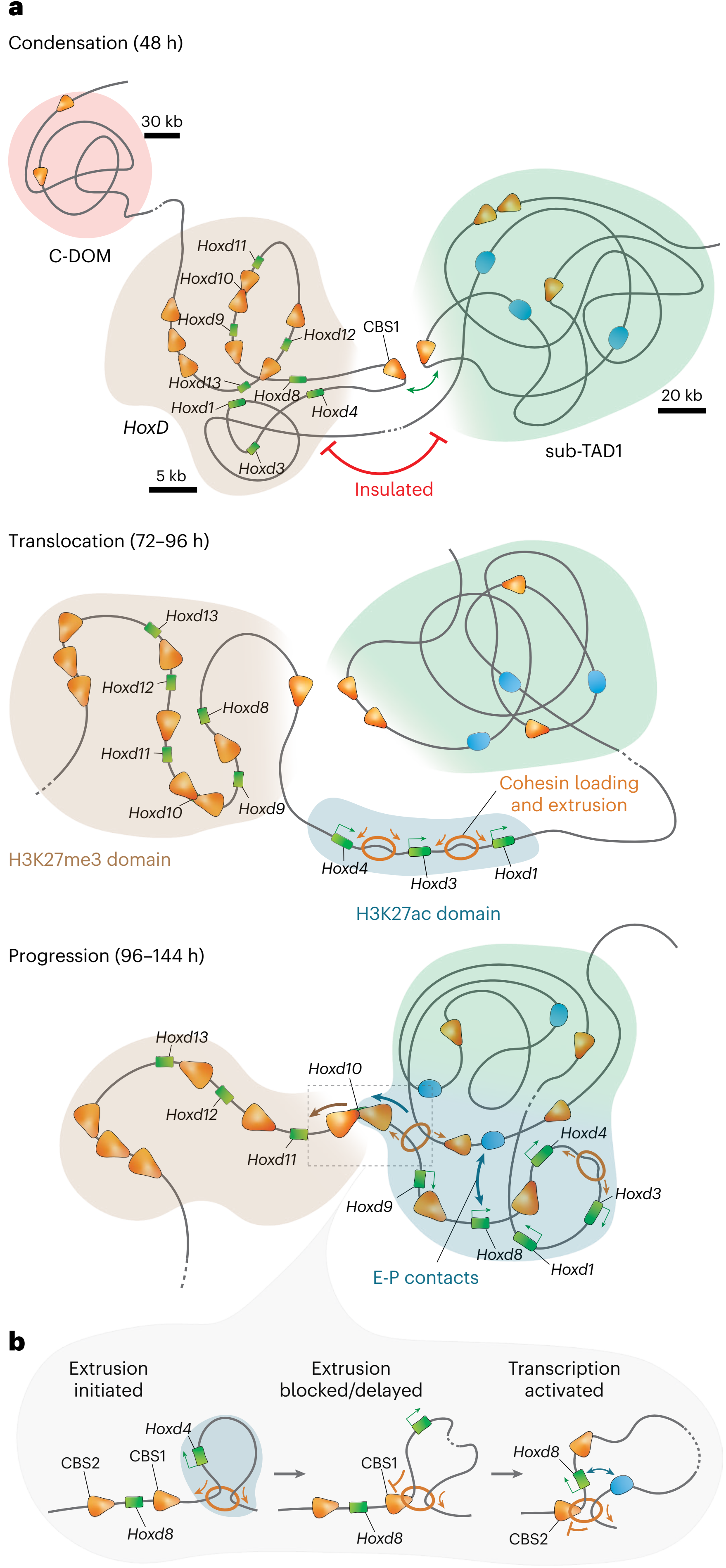
Rekaik et al. Nat. Genet (2023)



- CHi-C (capture Hi-C: restrict to contact from chr2:72'240'000-76'840'000) at 5kb resolution
- Compare with CTCF binding
- Contacts progressively transfer to T-DOM

Stembryos

Rekaik et al. Nat. Genet (2023)



Current model based on

- expression (RNA)
- transcriptional activity (PolII, H3K27ac)
- structural proteins binding (CTCF, Cohesin)
- chromatin compartments (Hi-C, CHi-C)
- Plus: genetics (deletions, inversions) and engineering (stembryos)

References

- Lieberman-Aiden, E. et al. Comprehensive mapping of long-range interactions reveals folding principles of the human genome. Science 326, 289–293 (2009).
- Yaffe, E. & Tanay, A. Probabilistic modeling of Hi-C contact maps eliminates systematic biases to characterize global chromosomal architecture. Nat Genet 43, 1059–1065 (2011).
- de Wit, E. & de Laat, W. A decade of 3C technologies: insights into nuclear organization. Genes Dev 26, 11–24 (2012).
- Dixon, J. R. et al. Topological domains in mammalian genomes identified by analysis of chromatin interactions. Nature 485, 376–380 (2012).
- Andrey, G. et al. A switch between topological domains underlies HoxD genes collinearity in mouse limbs. Science 340, 1234167 (2013).
- Dekker, J., Marti-Renom, M. A. & Mirny, L. A. Exploring the three-dimensional organization of genomes: interpreting chromatin interaction data. Nat Rev Genet 14, 390–403 (2013).
- Fraser, J. et al. Hierarchical folding and reorganization of chromosomes are linked to transcriptional changes in cellular differentiation. Mol Syst Biol 11, 852 (2015).
- Tan, L. et al. Three-dimensional genome structures of single diploid human cells. Science 361, 924–928 (2018).
- Rekaik, H. et al. Sequential and directional insulation by conserved CTCF sites underlies the Hox timer in stembryos. Nat Genet 55, 1164-1175 (2023).