CHROMATIC reveals chromatin-associated factors contributing to genome topology

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CNAG-CRG · ICREA

http://marciuslab.org
http://3DGenomes.org
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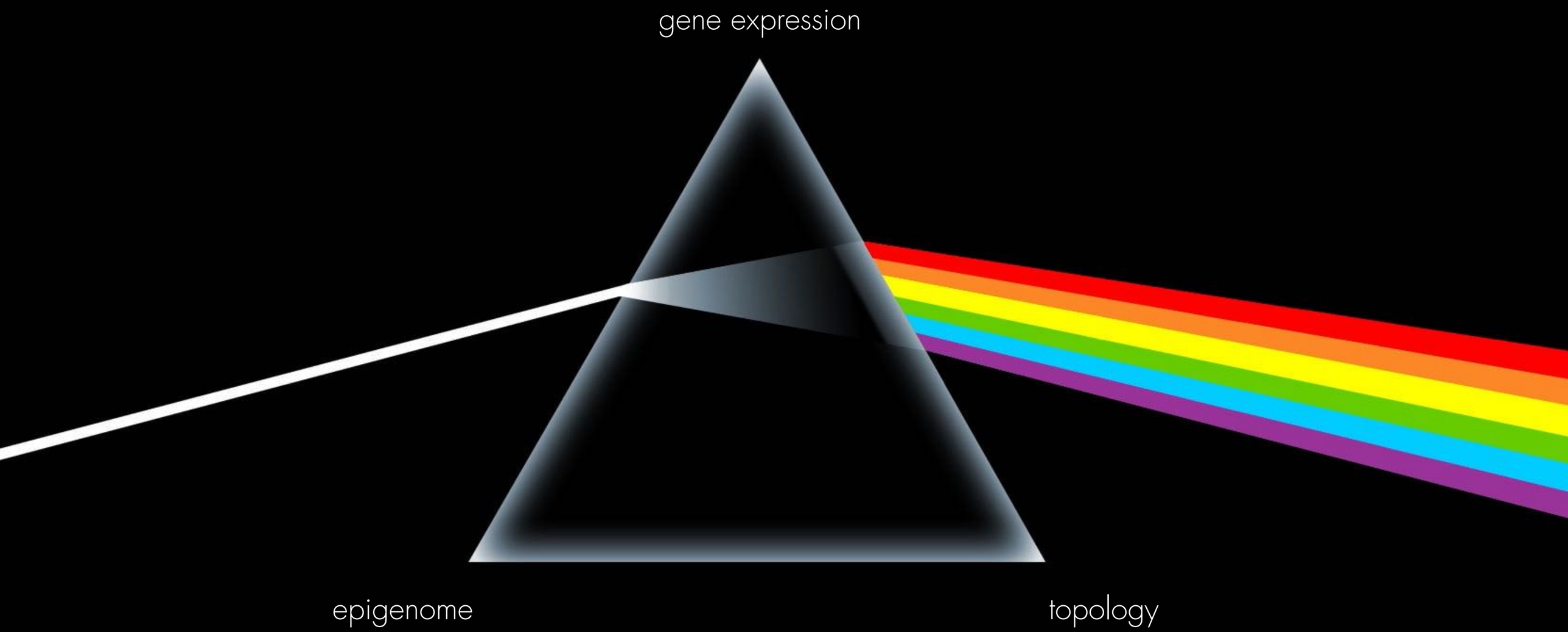
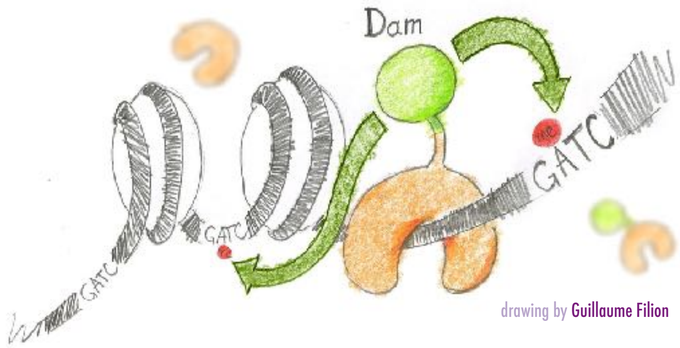
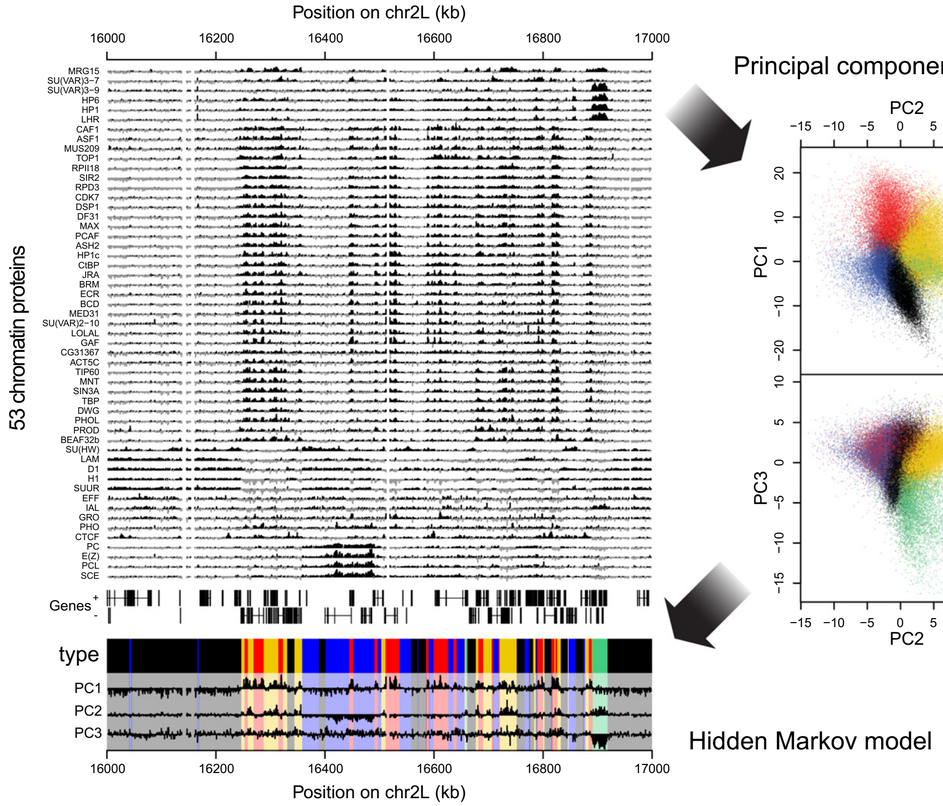
The genome is a complex system



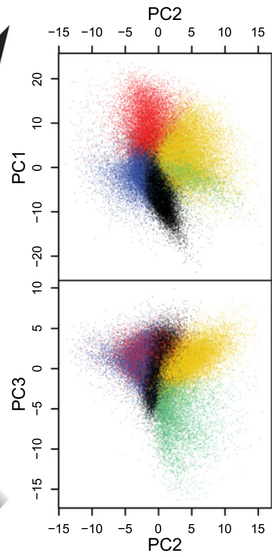
Fly Chromatin COLORs

Filion et al. (2010). Cell, 143(2), 212–224.

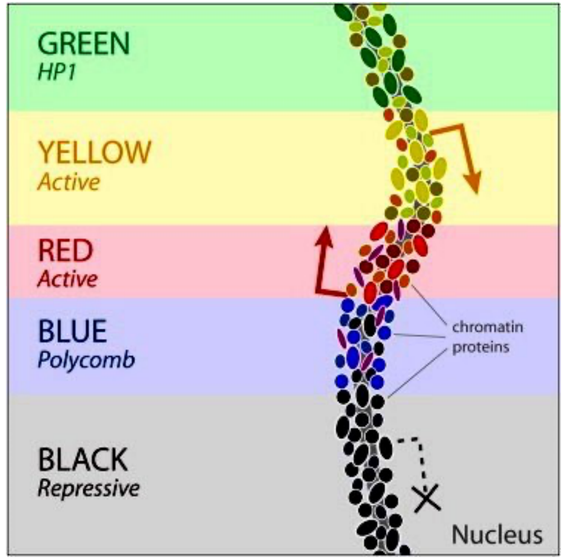




Principal component analysis

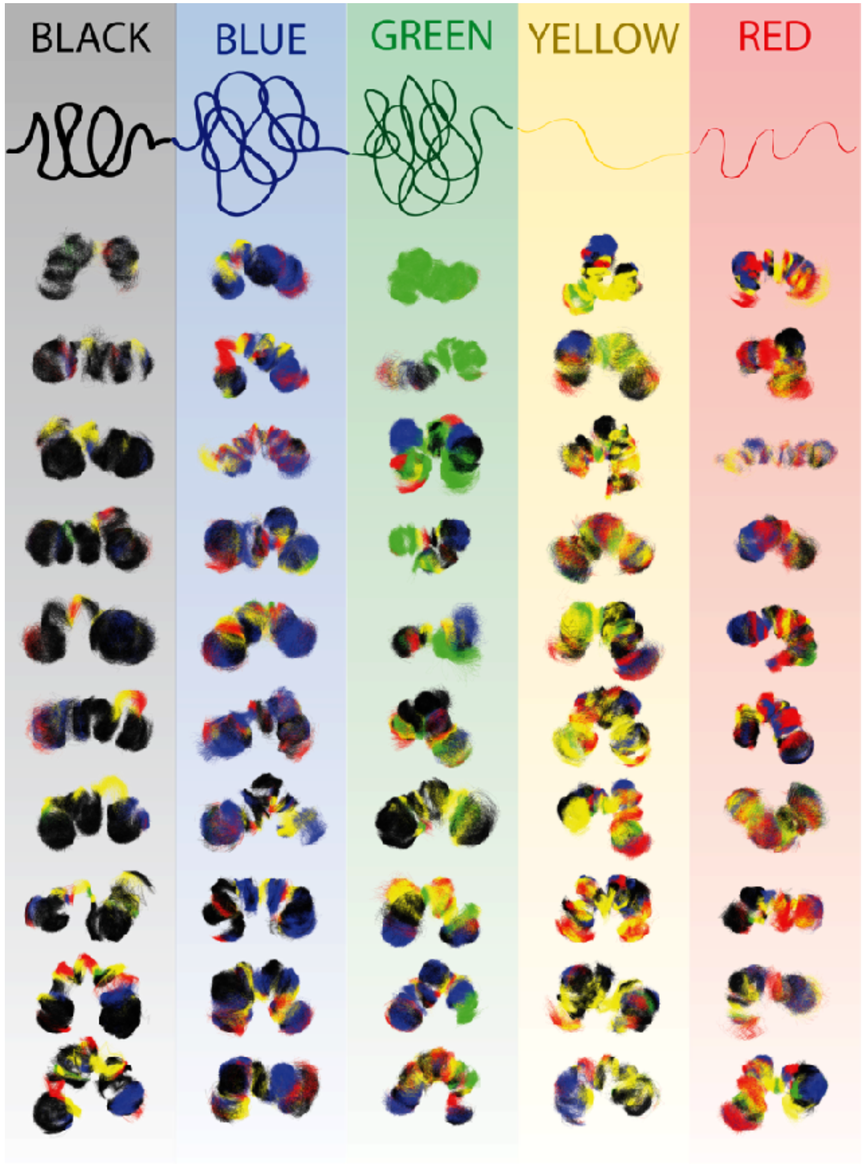


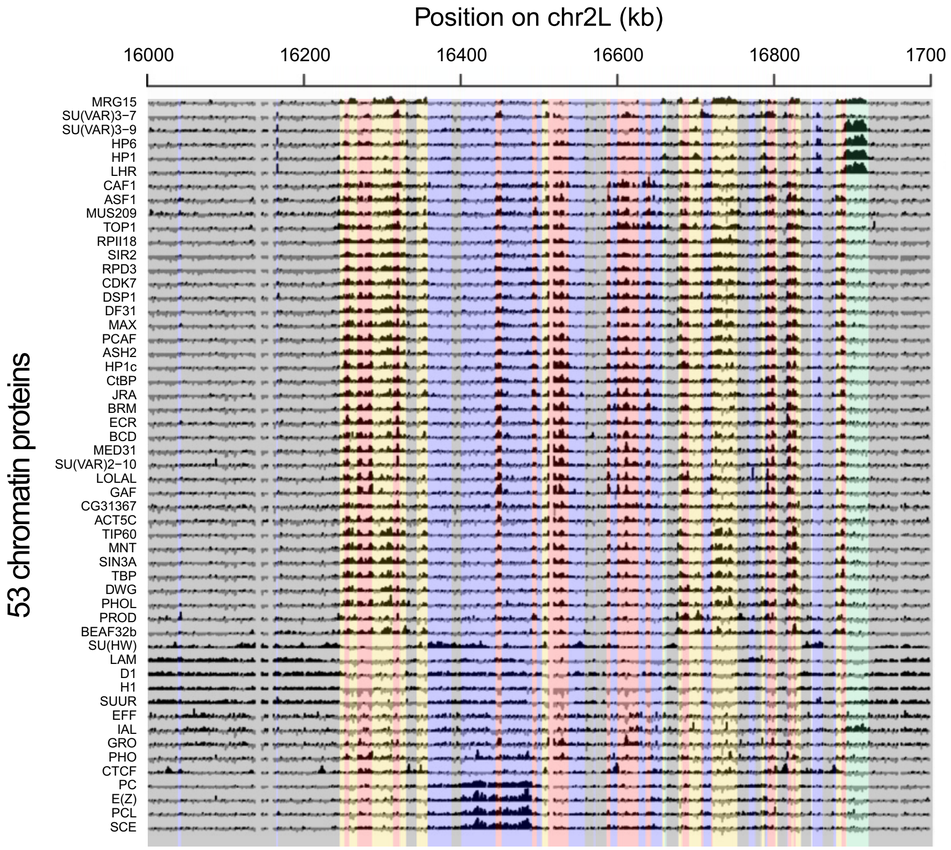
Hidden Markov model



Who "holds" the genome structure?

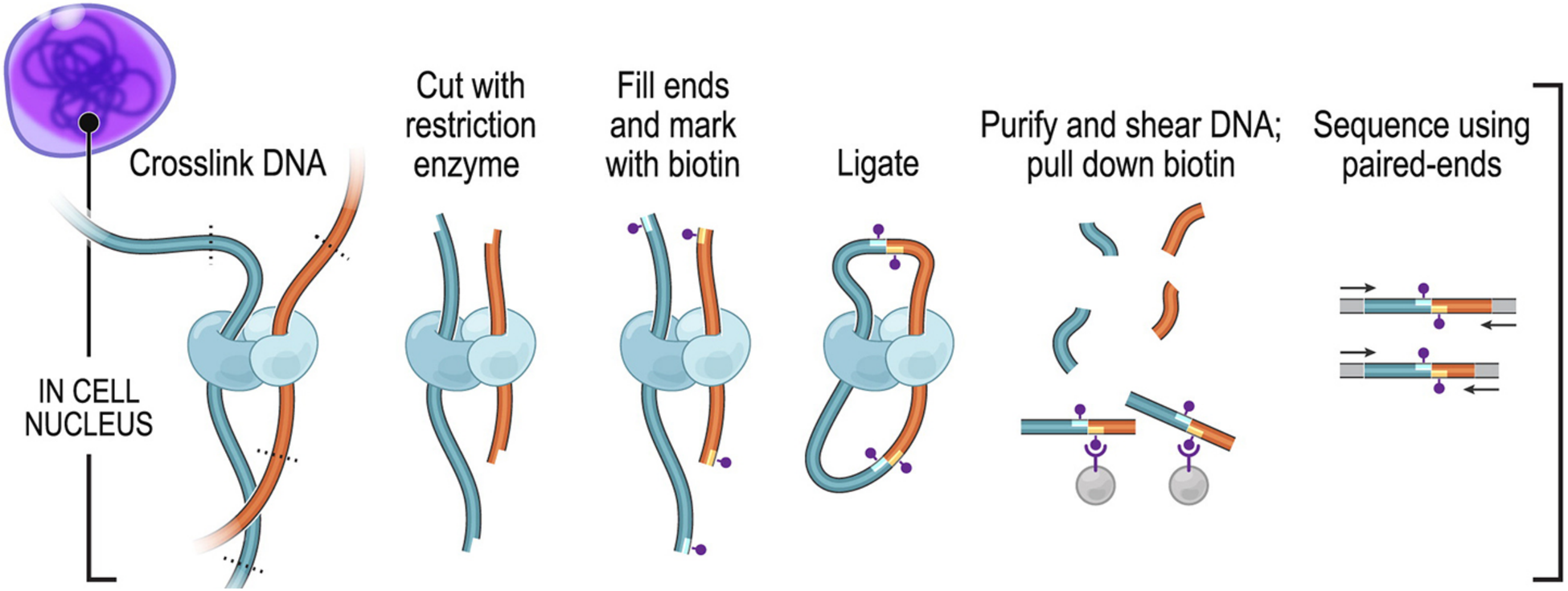
Serra et al. PLoS Comput Biol (2017) 13(7): e1005665

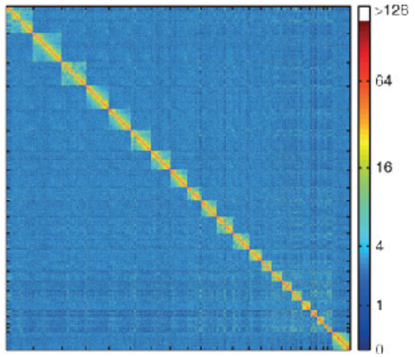


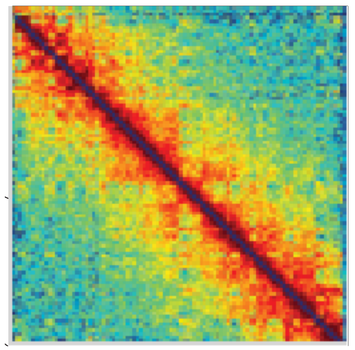


Chromosome Conformation Capture

Dekker, J., Rippe, K., Dekker, M., & Kleckner, N. (2002). Science, 295(5558), 1306–1311.
Lieberman-Aiden, E., et al. (2009). Science, 326(5950), 289–293.

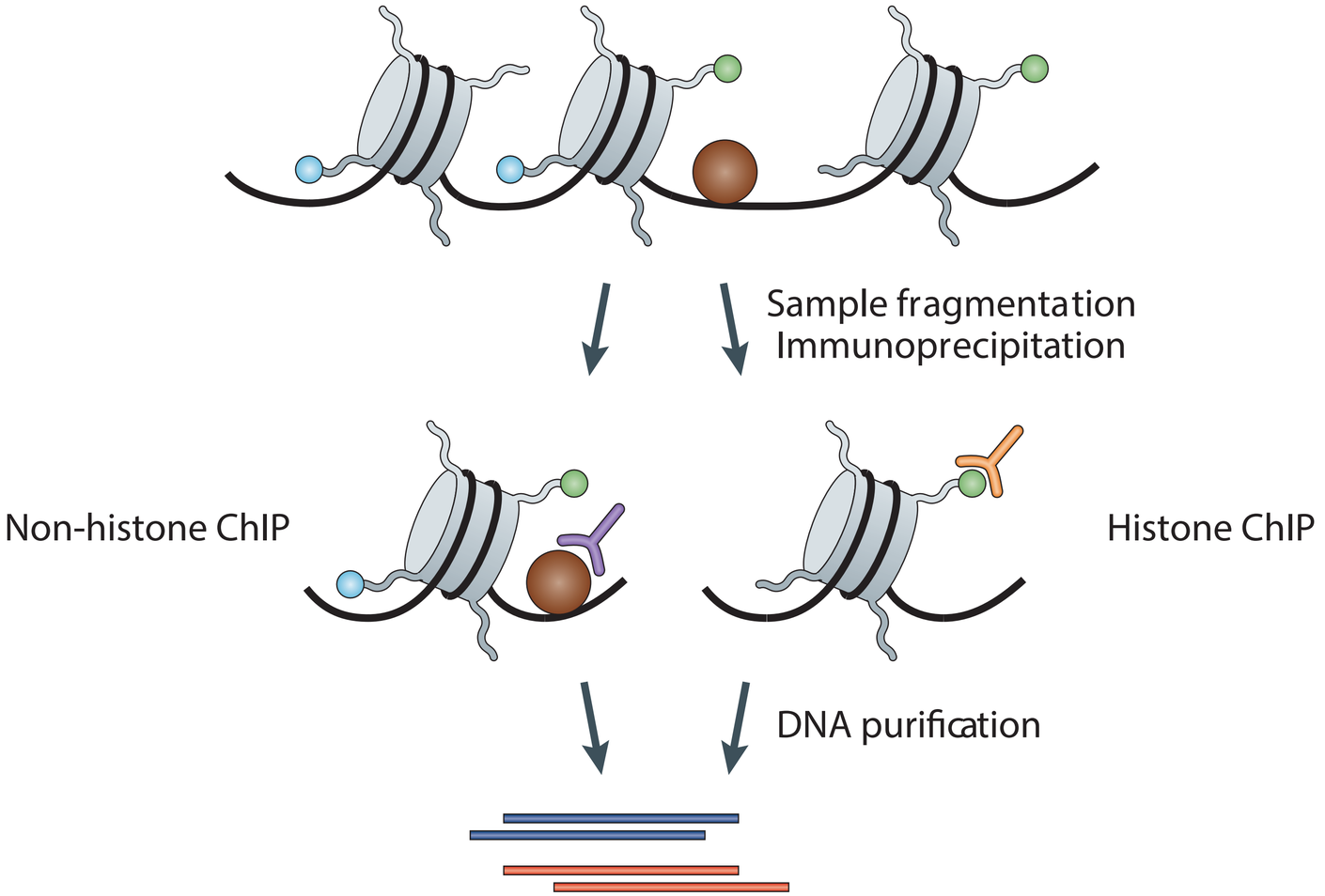




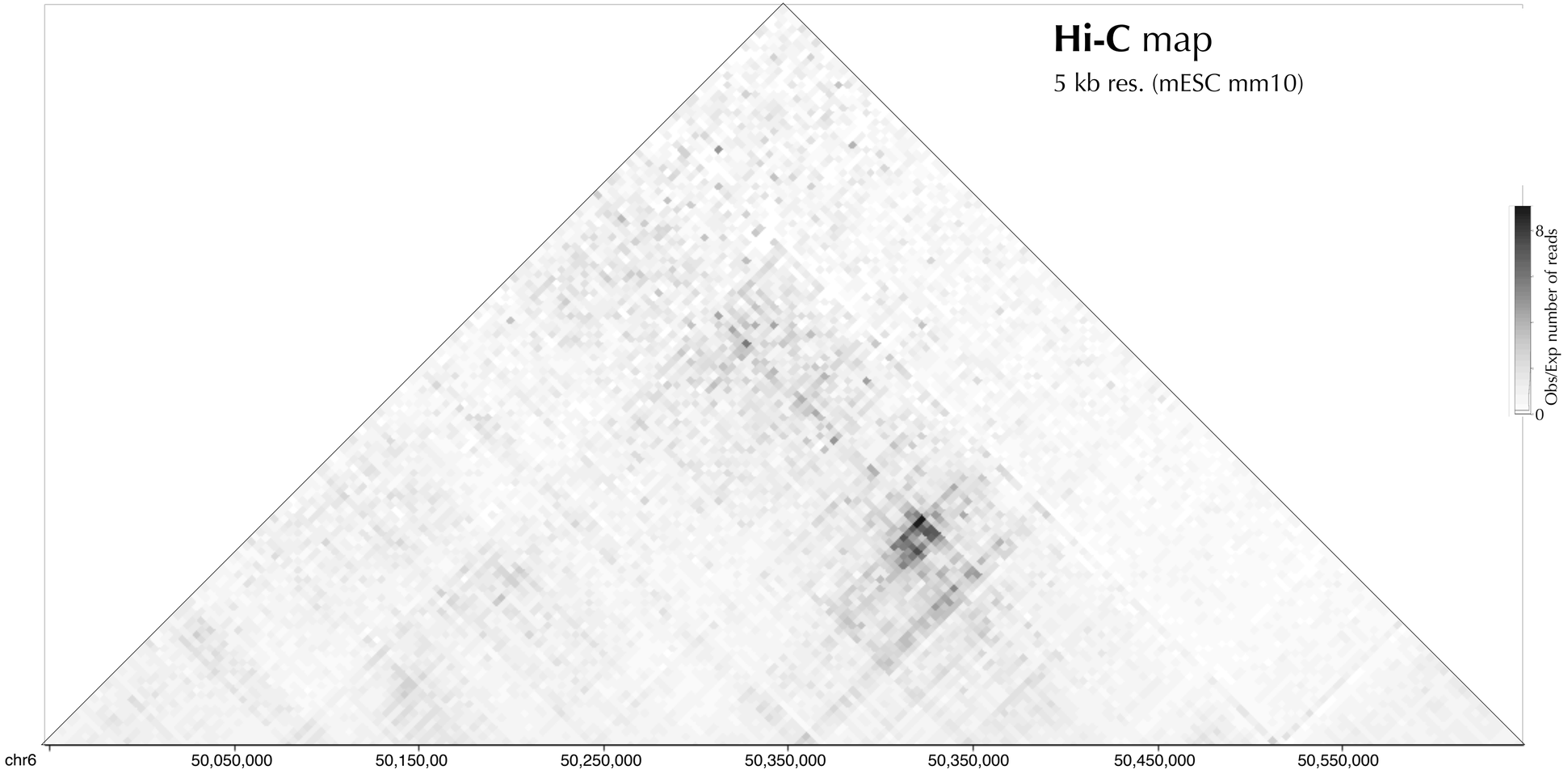


Chromatin Immunoprecipitation (ChIP)

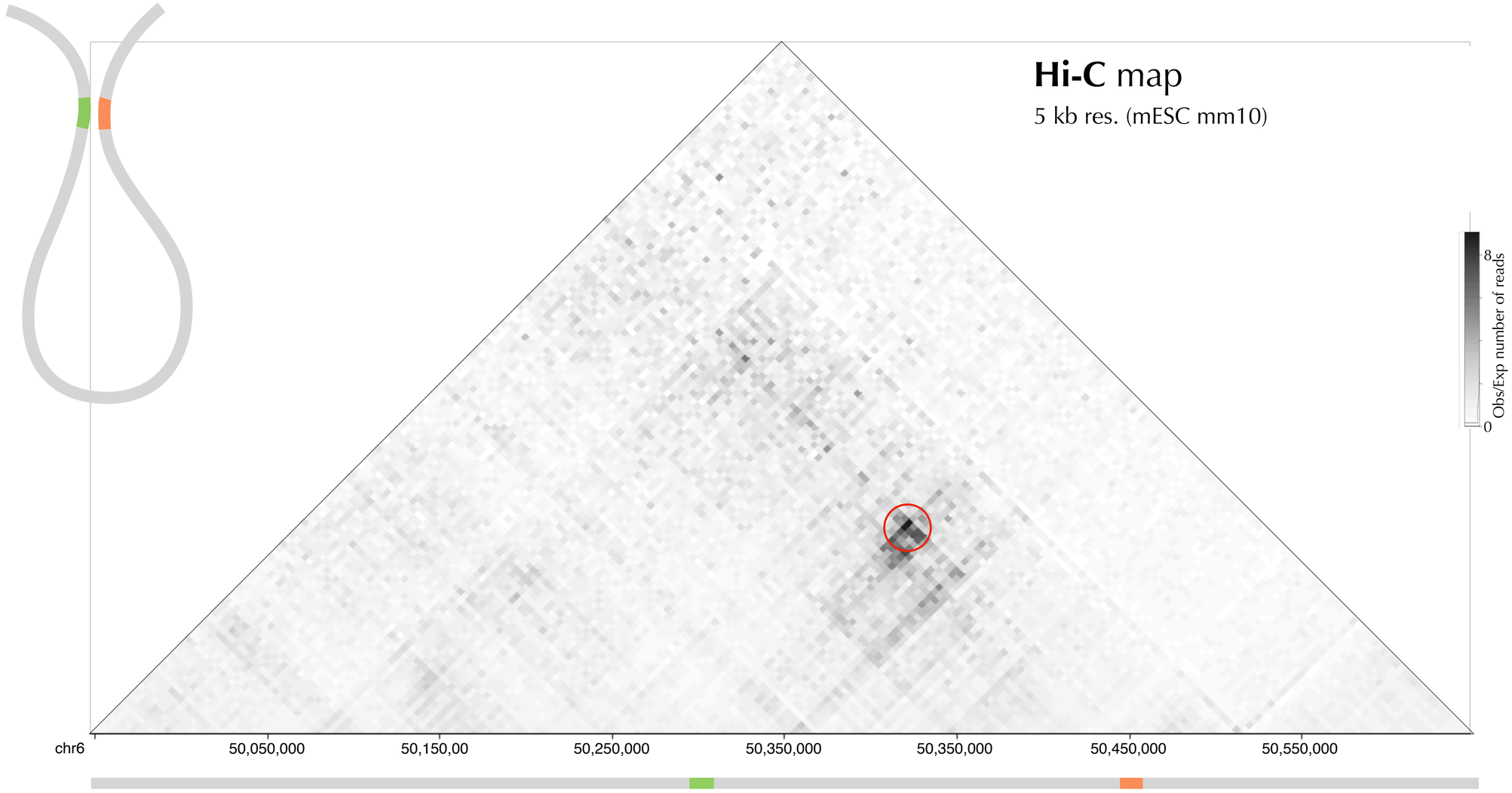
Solomon, M. J., Larsen, P. L. & Varshavsky, A. (1988) Cell 53, 937–947.
Park, P.J. (2009) Nature Reviews Genetics 10, 669–680.



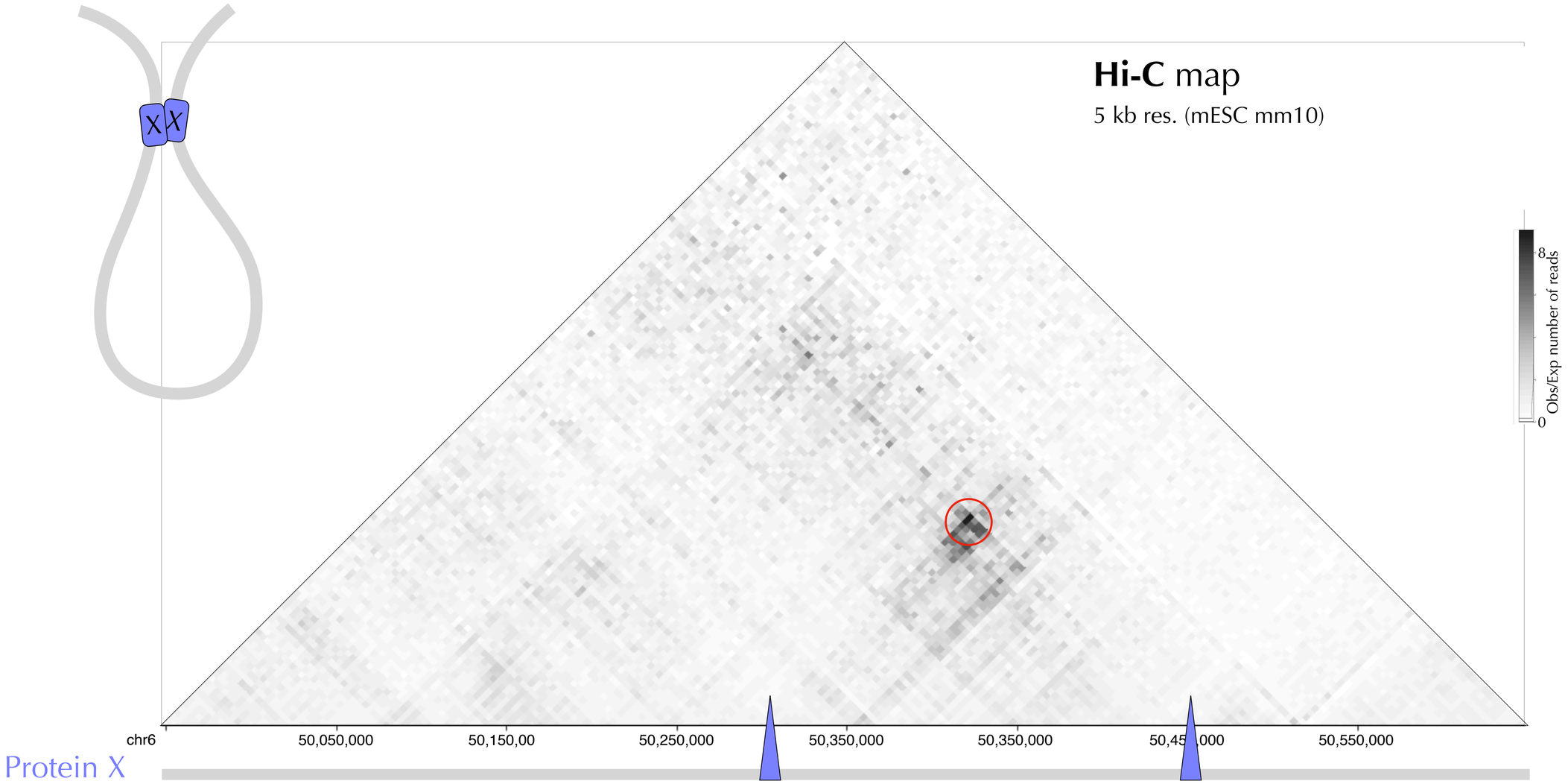
High-throughput Chromosome Conformation Capture (Hi-C)



Chromatin interaction on a Hi-C map

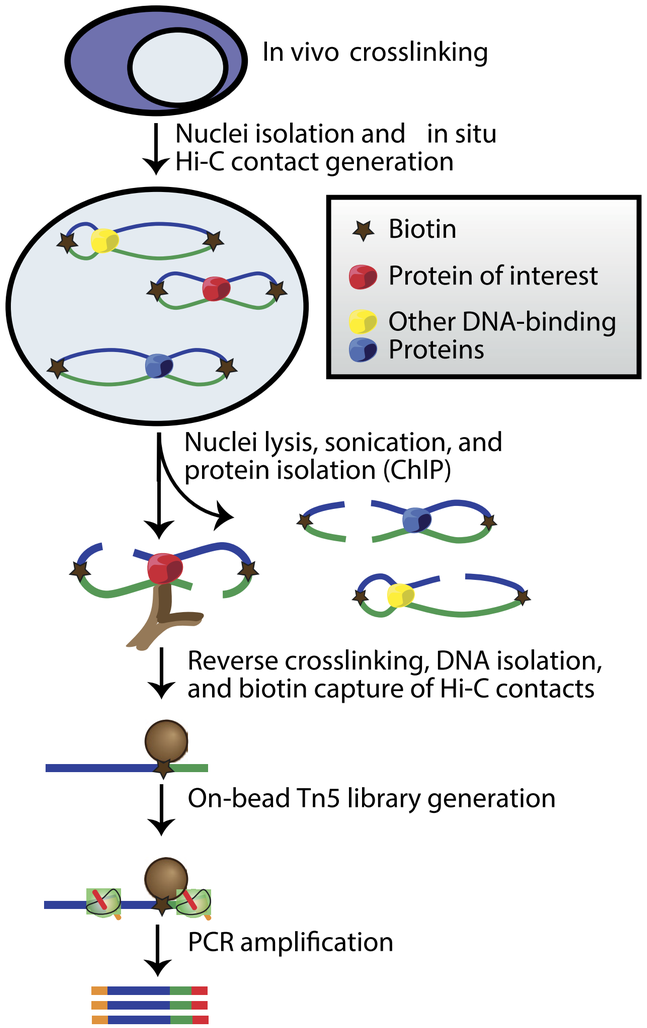


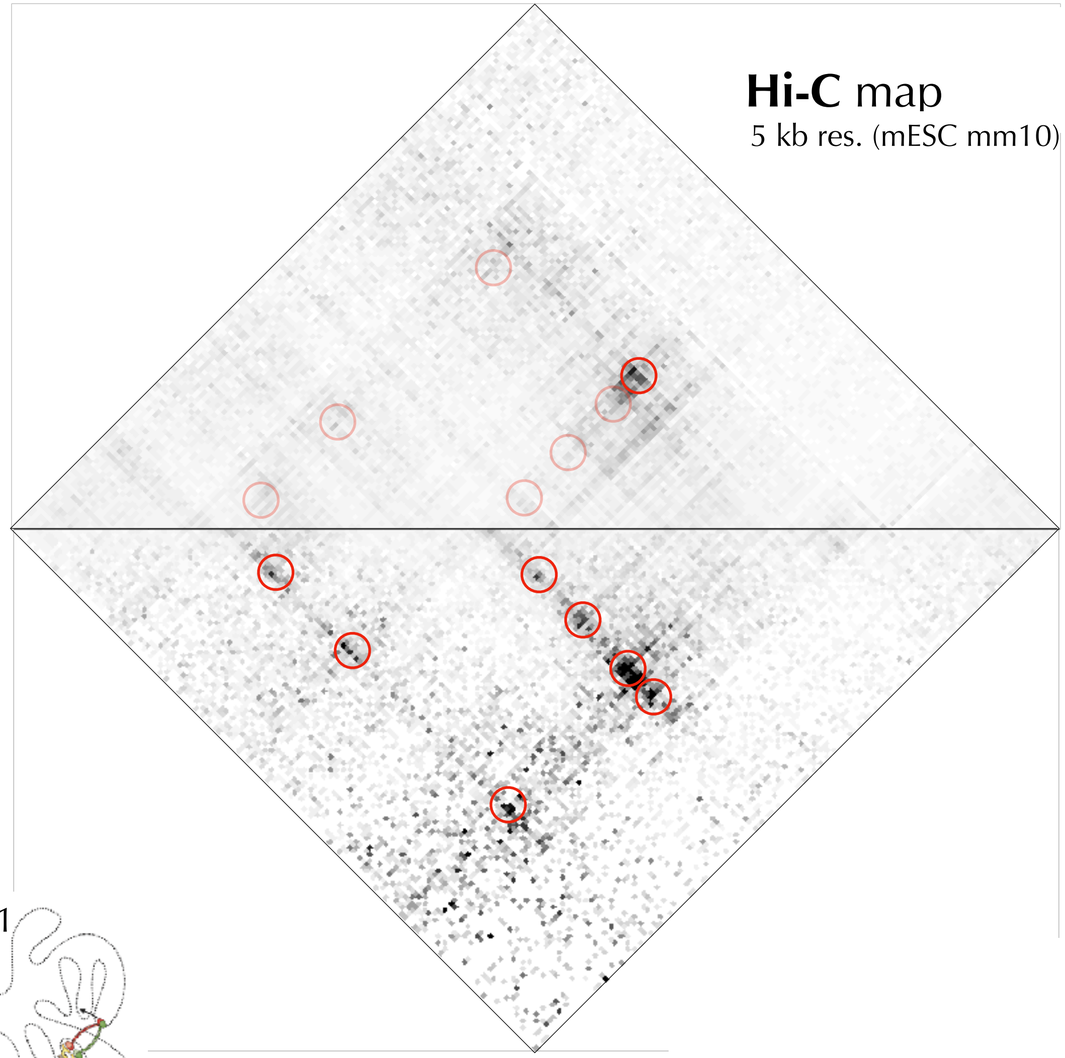
Chromatin interaction "mediated" by a protein

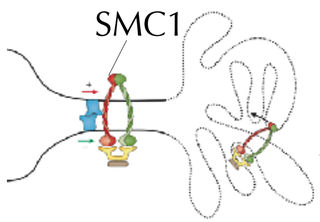


Hi-ChIP: capturing specific protein-mediated interactions

Mumbach, M.R. et al. (2016) Nature Methods 13(11) 919-922.



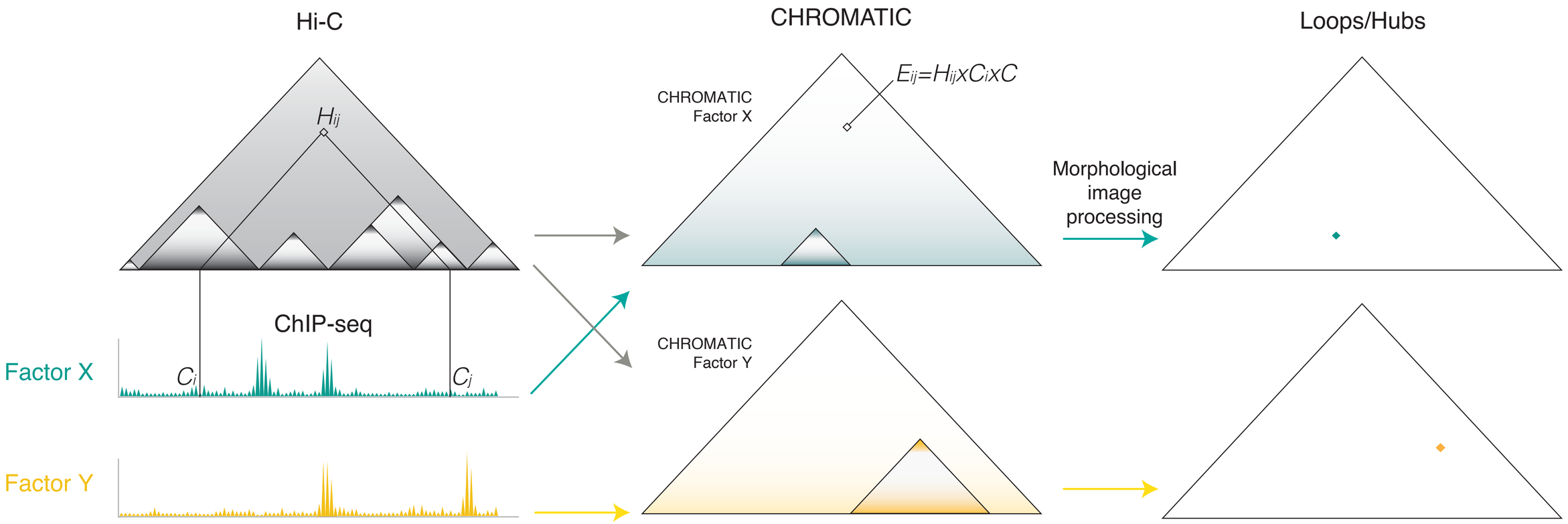




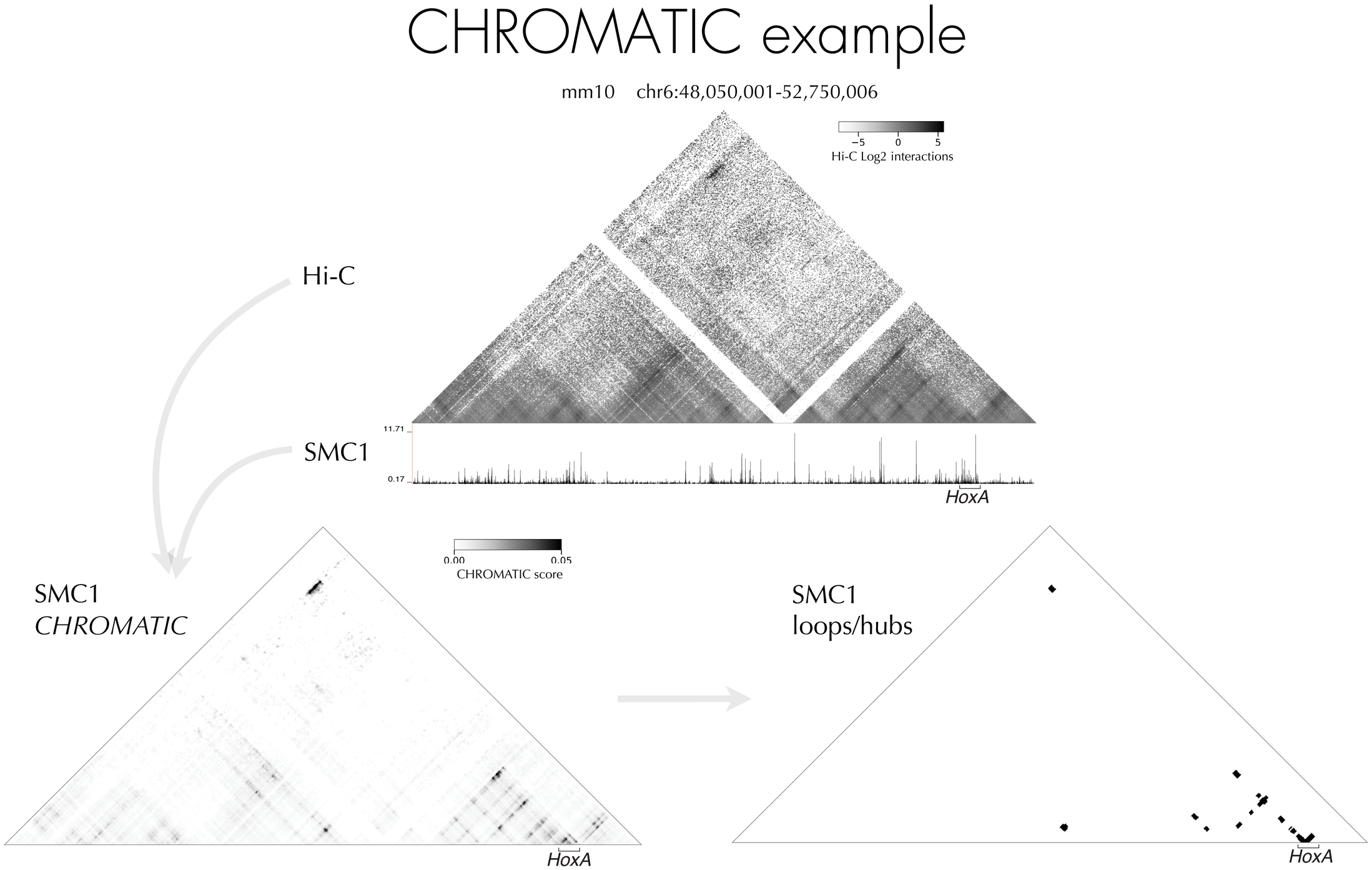
SMC1 **Hi-ChIP** map **= Hi-C + ChIP**

5 kb res. (mESC mm10)

CHROMATIC

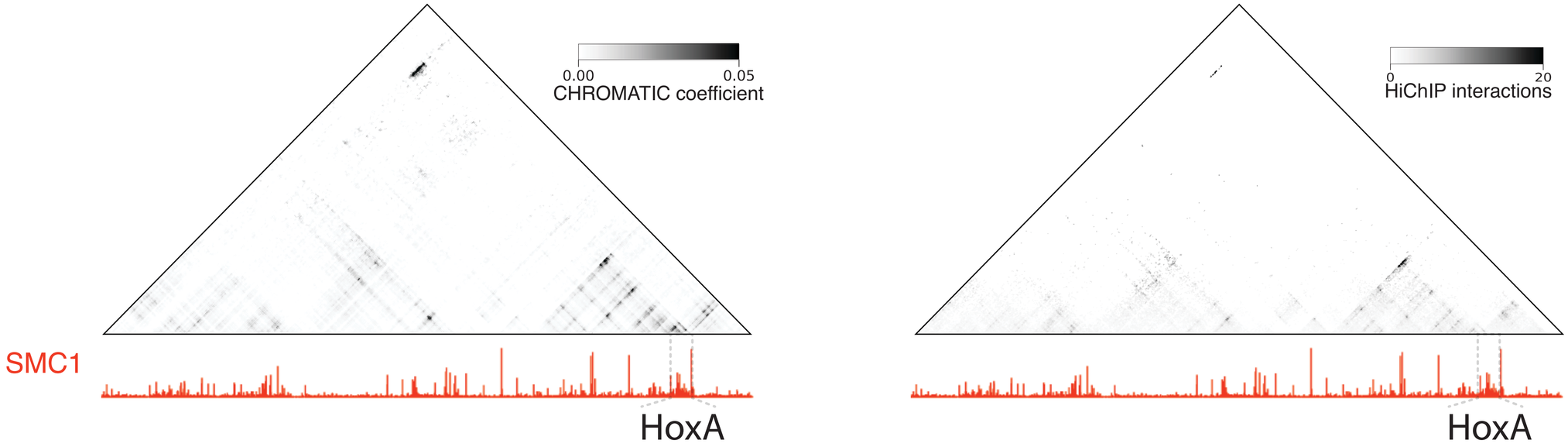

Hi-C
CHROMATIC
Loops/Hubs
H_{ij}
ChIP-seq
Factor X
C_i
C_j
Factor Y
CHROMATIC
Factor X
$E_{ij}=H_{ij}xC_ixC$
CHROMATIC
Factor Y
Morphological
image
processing

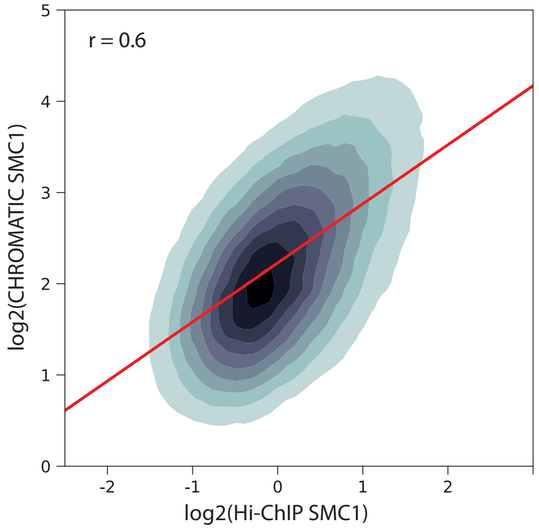
CHROMATIC example

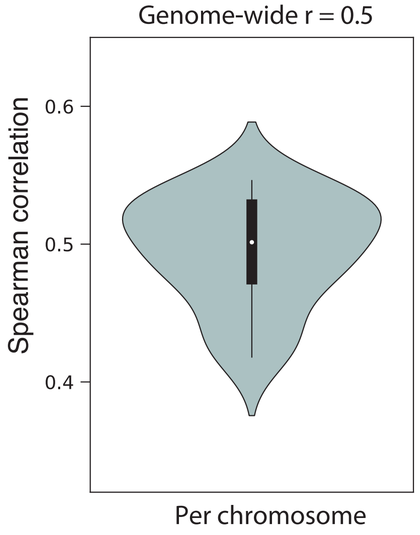


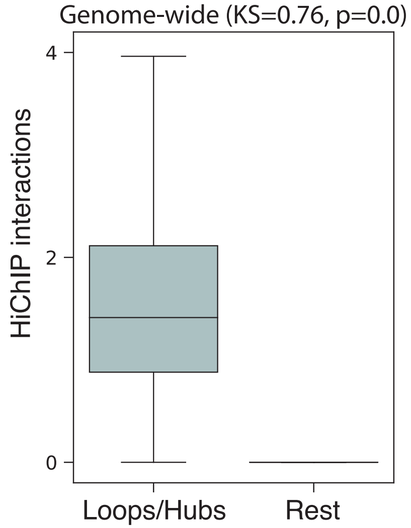
Validation with HiChIP as benchmark

mm10 - mESC - 5kb - chr6:48,050,001-52,750,006

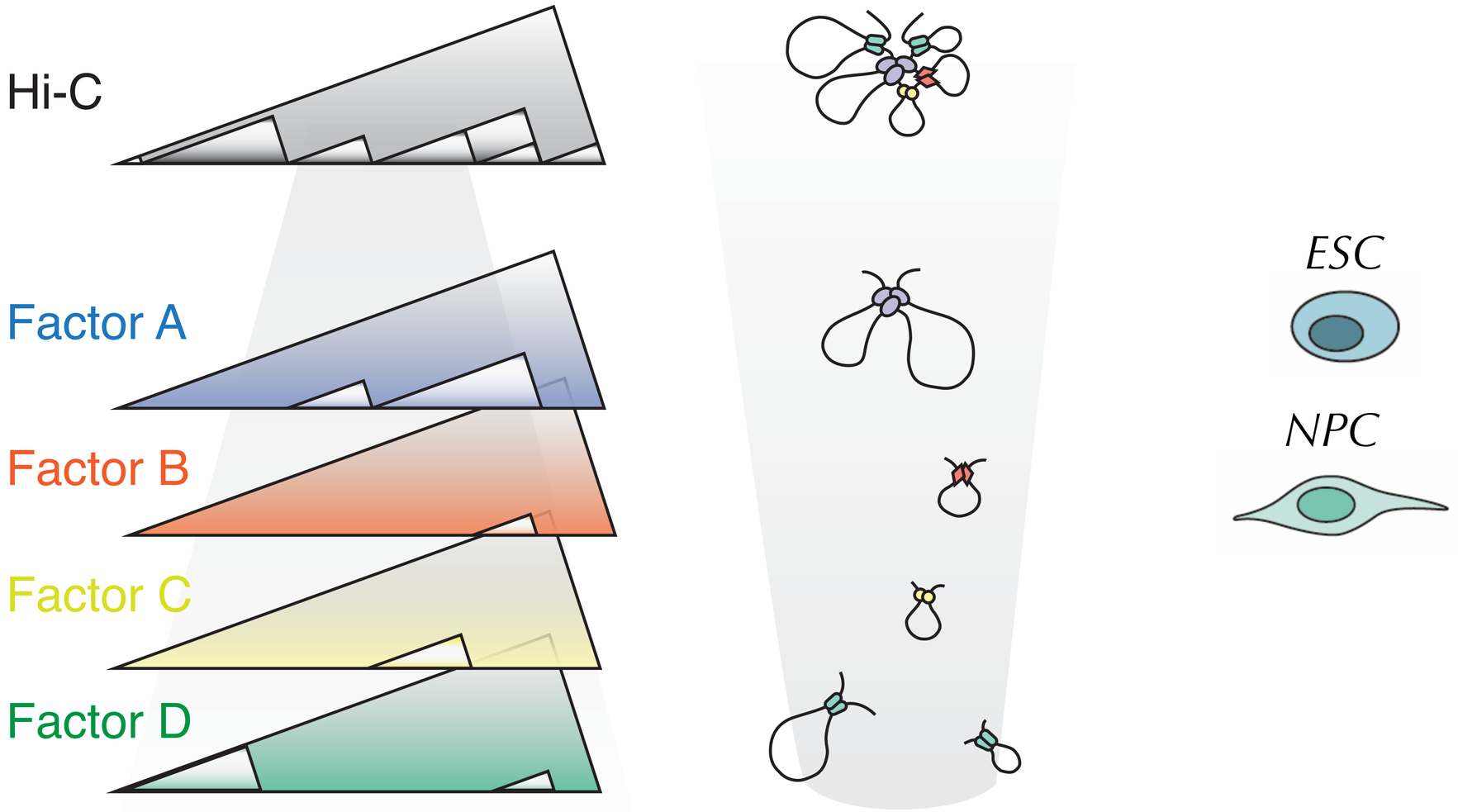




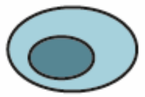




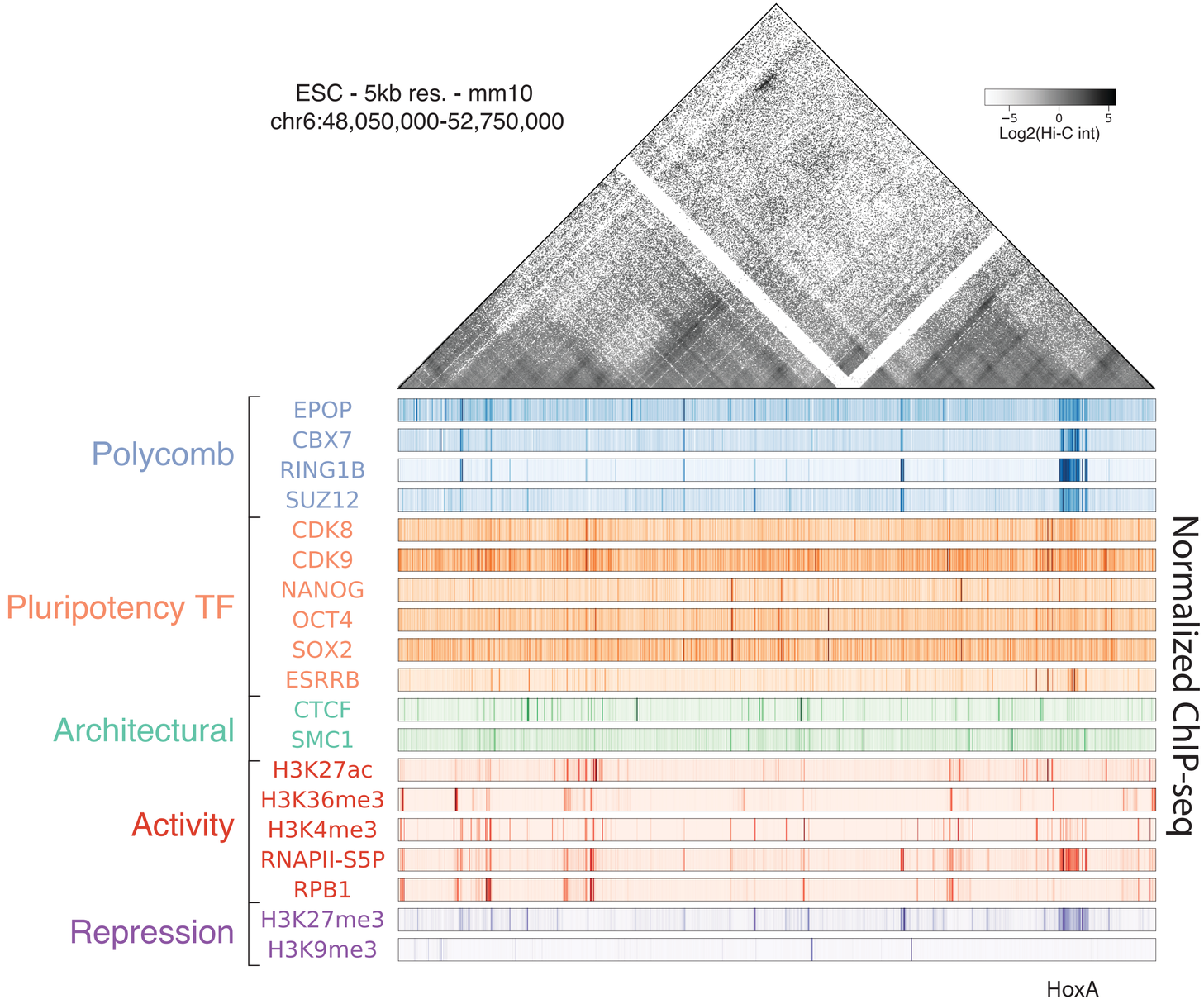
The role of chromatin factors in genome topology



ESC

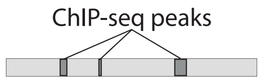


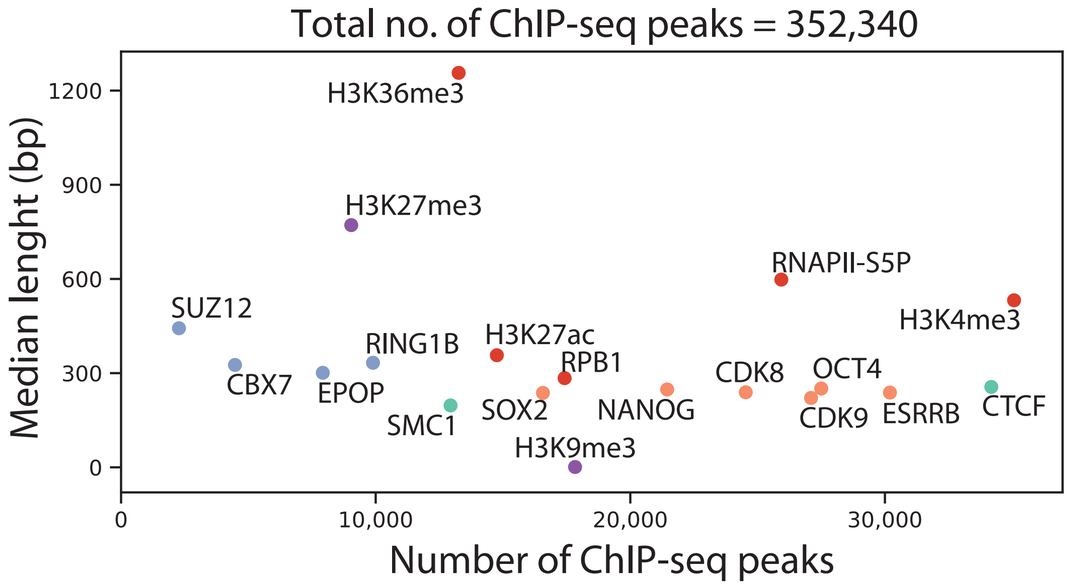
HoxA cluster (example in ESC)



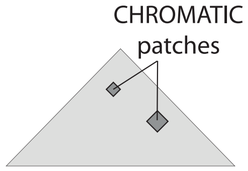
ESC

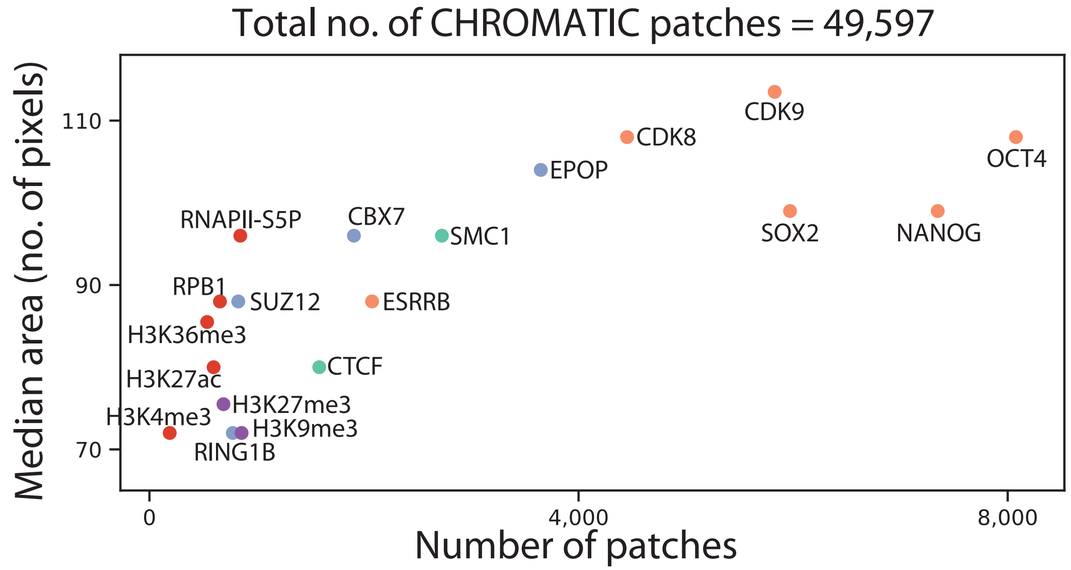
3D interactions are mostly associated with pluripotent TFs





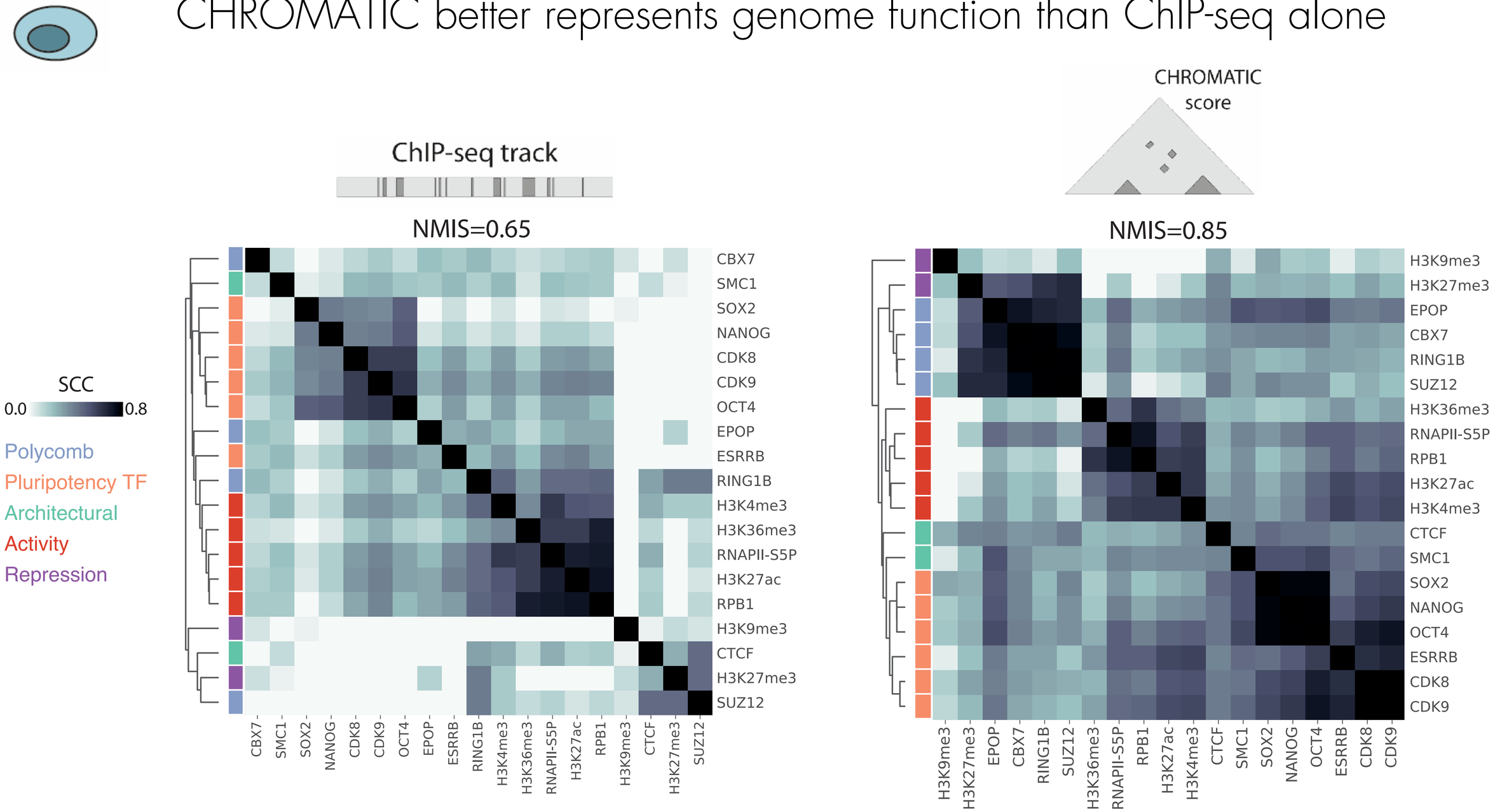
Polycomb
Pluripotency TF
Architectural
Activity
Repression





ESC

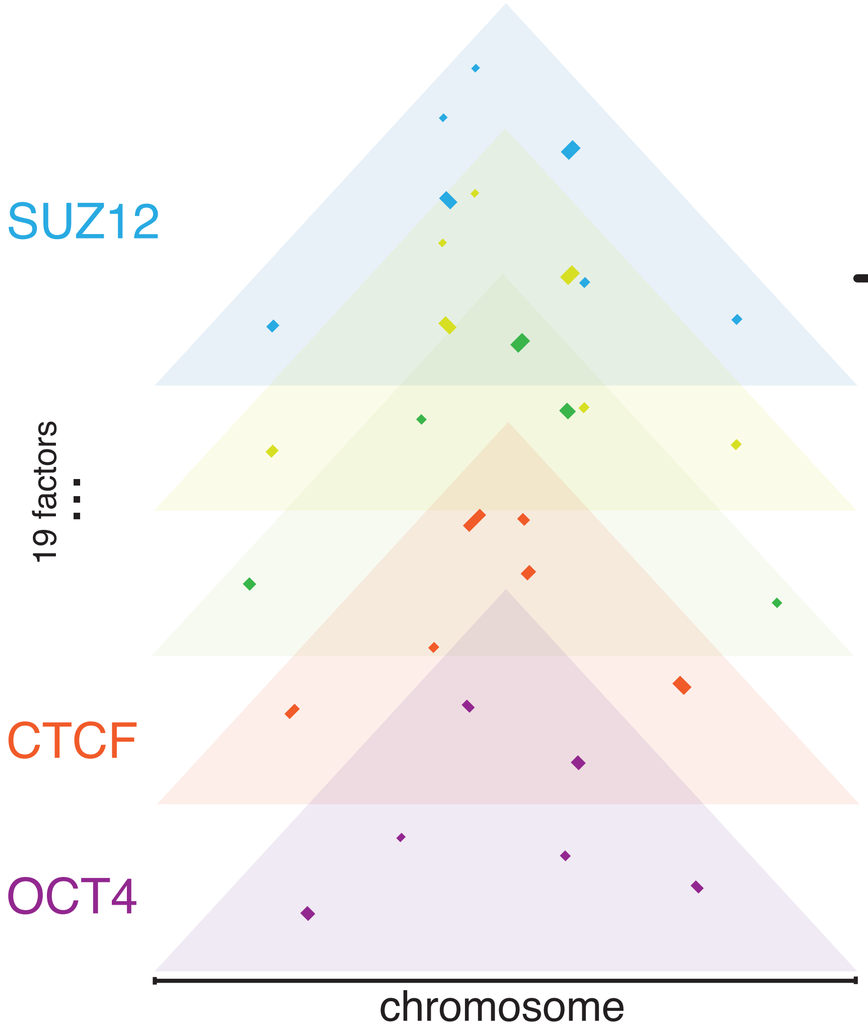
CHROMATIC better represents genome function than ChIP-seq alone



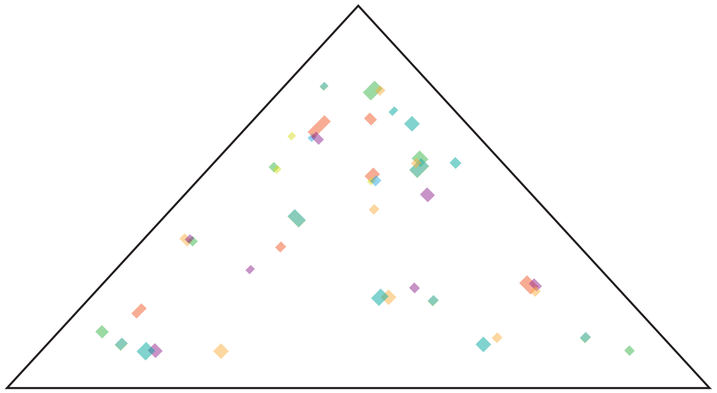
ESC

Measure the 3D co-localization of factors

CHROMATIC interactions



Overlap (19 factors)



8m 54s

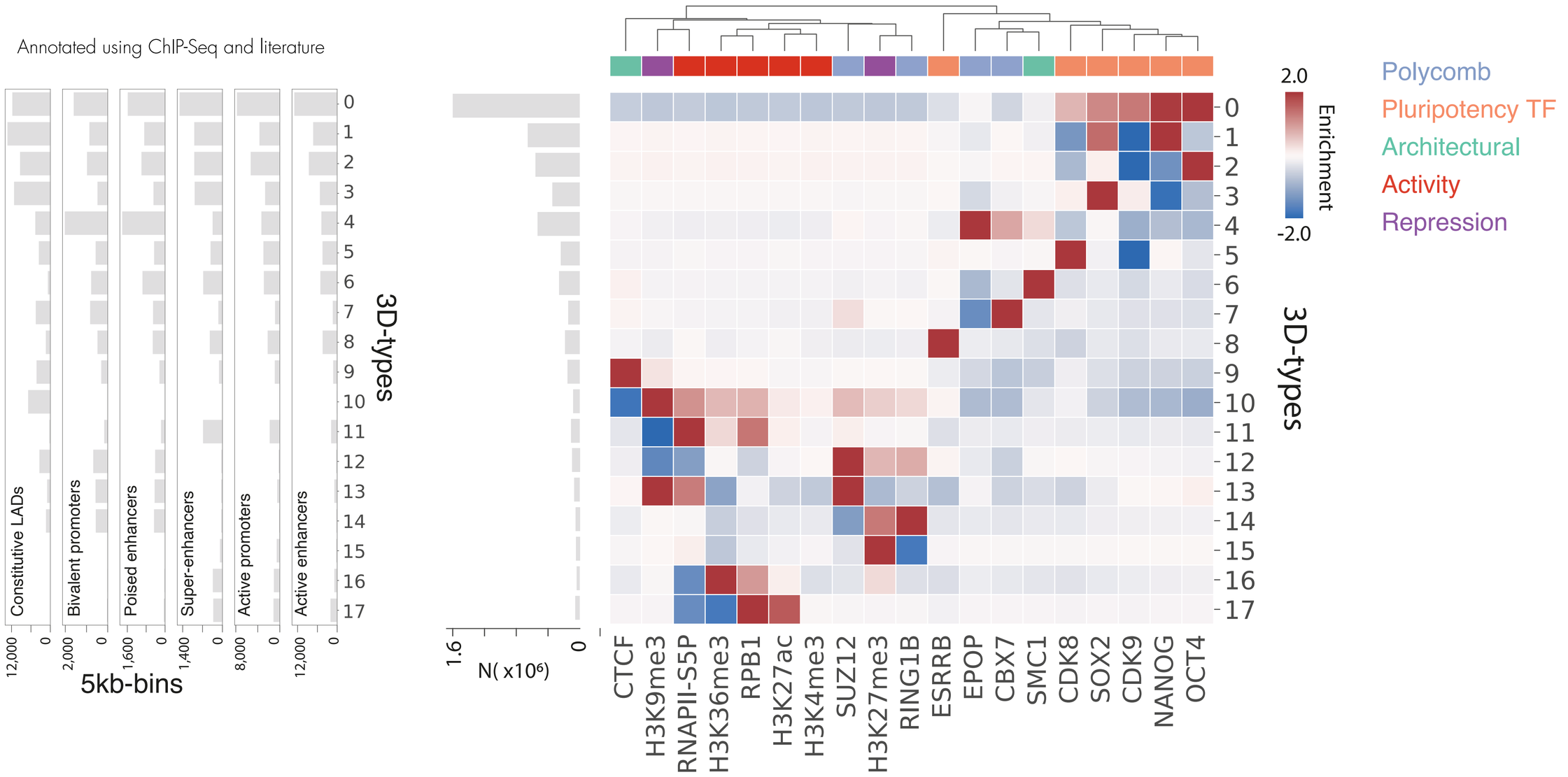
Latent Semantic Analysis

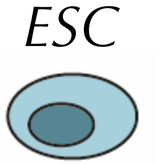
Documents

Doc1: CBX7 NANOG
Doc2: OCT4 CDK8 H3K27ac
Doc3: RING1B
Doc4: H3K36me3 RNAPolIII-S5P
...
...

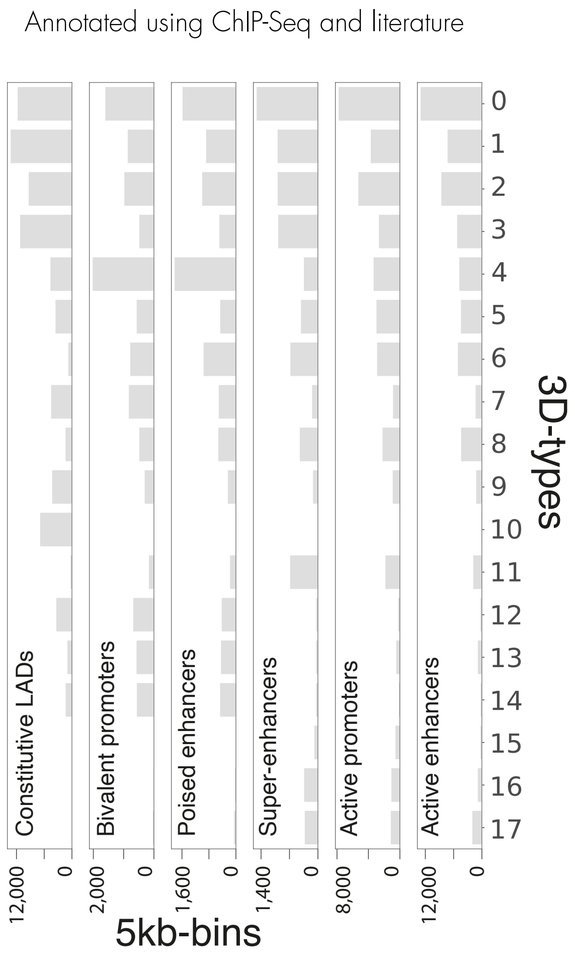
ESC

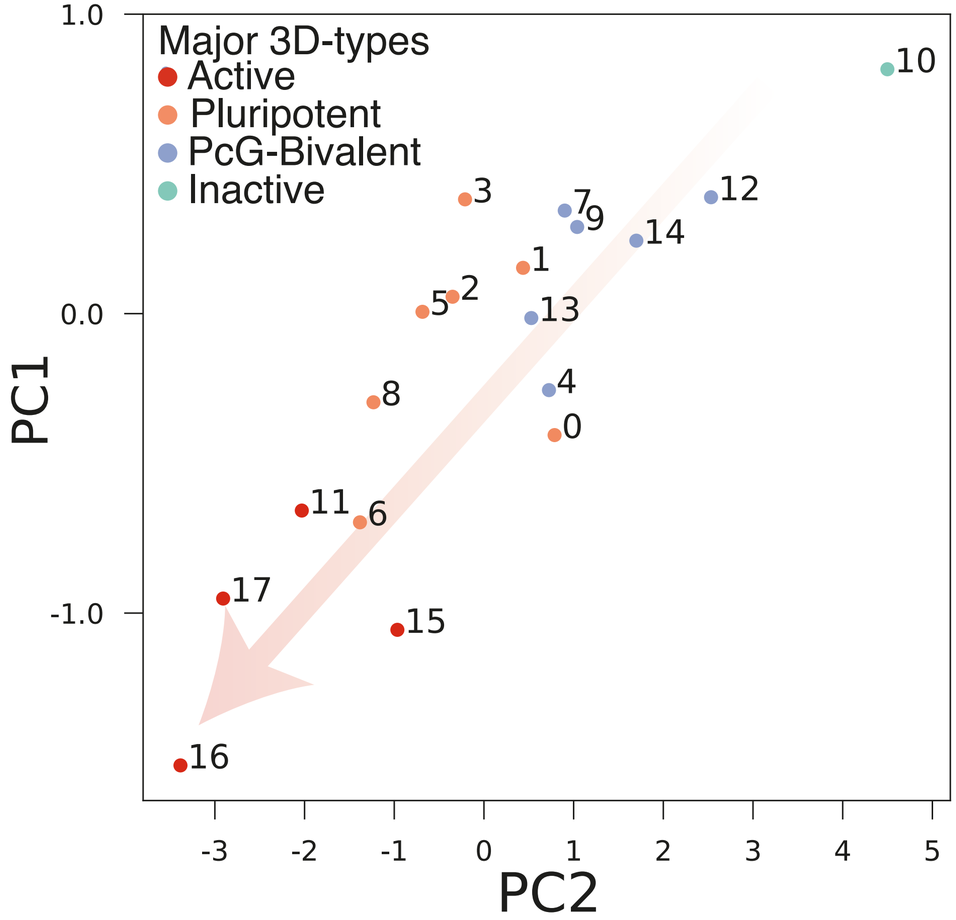
Types of 3D interactions with LSA in ESC

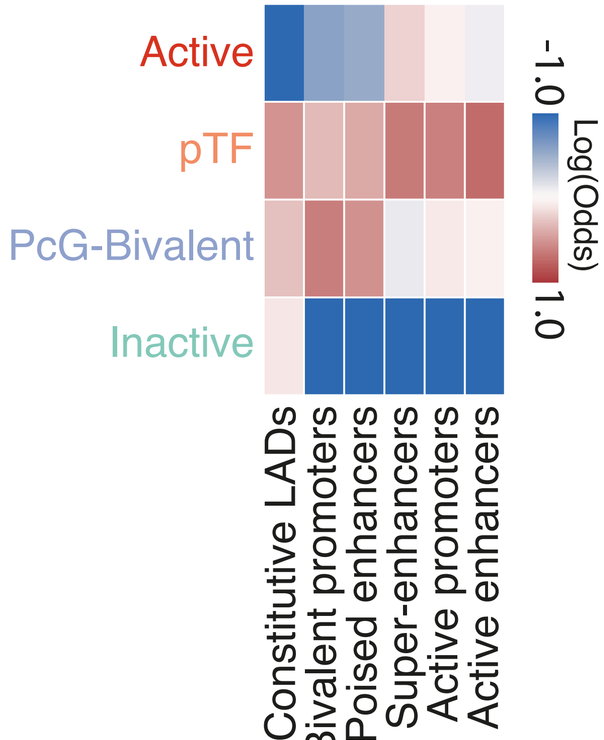




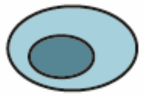
Types of 3D interactions with LSA in ESC



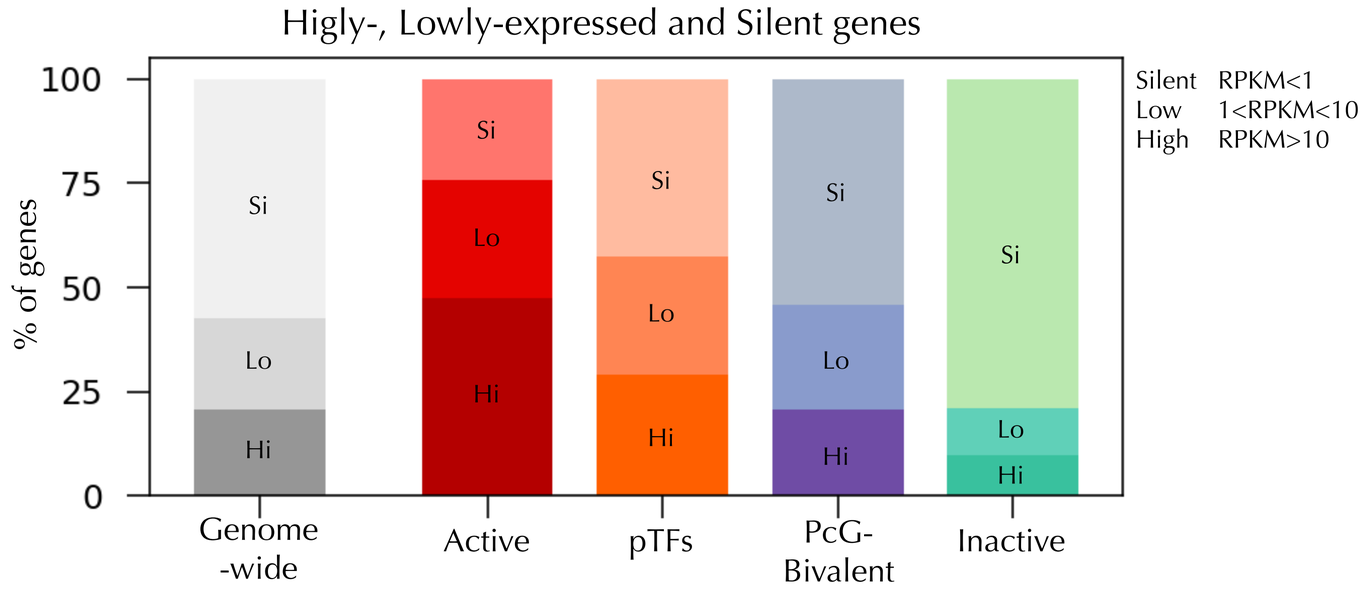


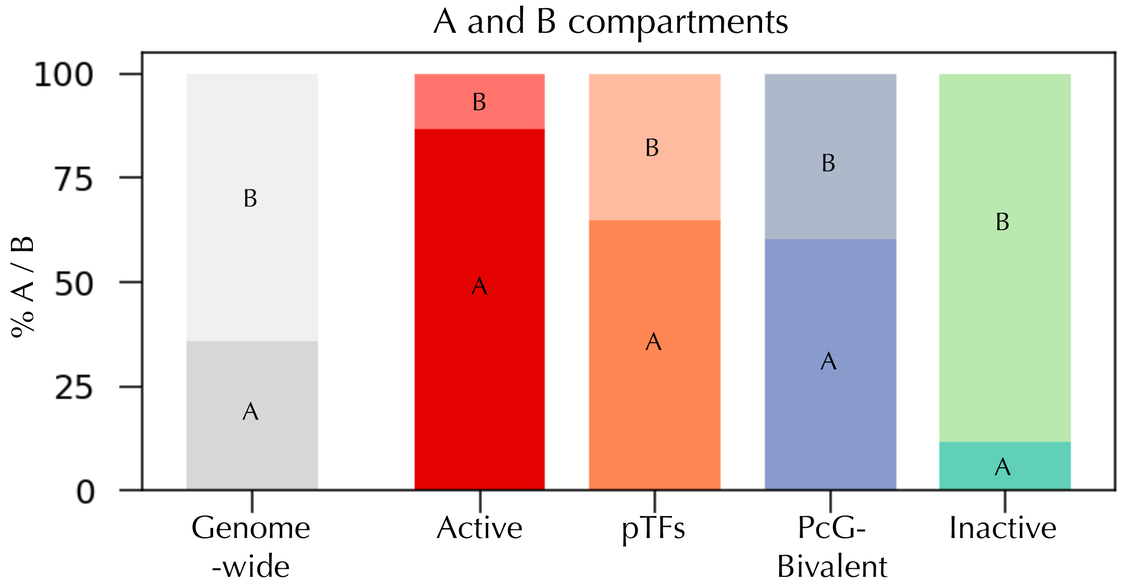


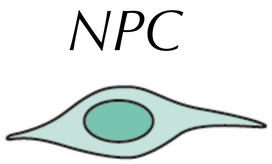
ESC



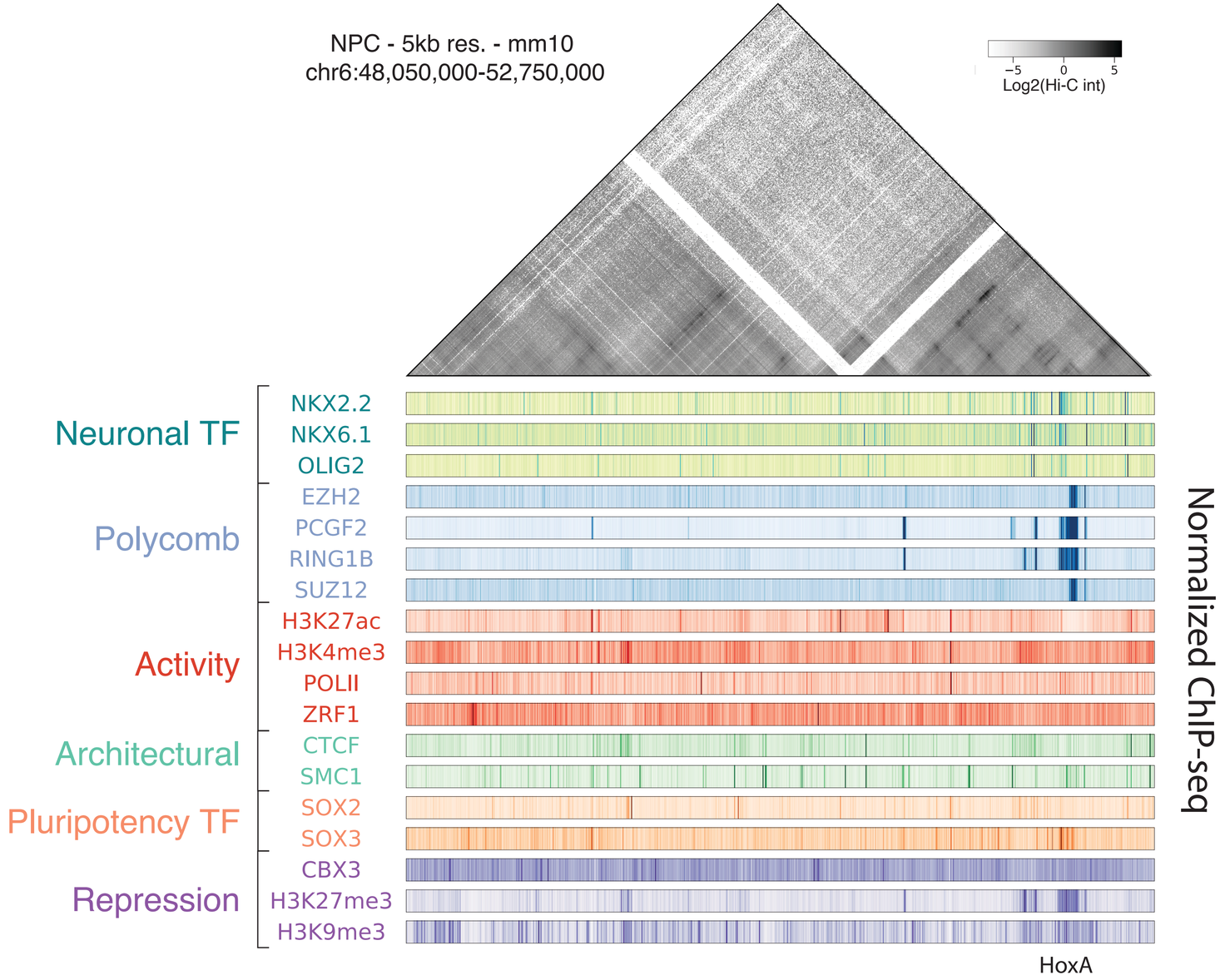
4 major types of 3D interactions in ESC



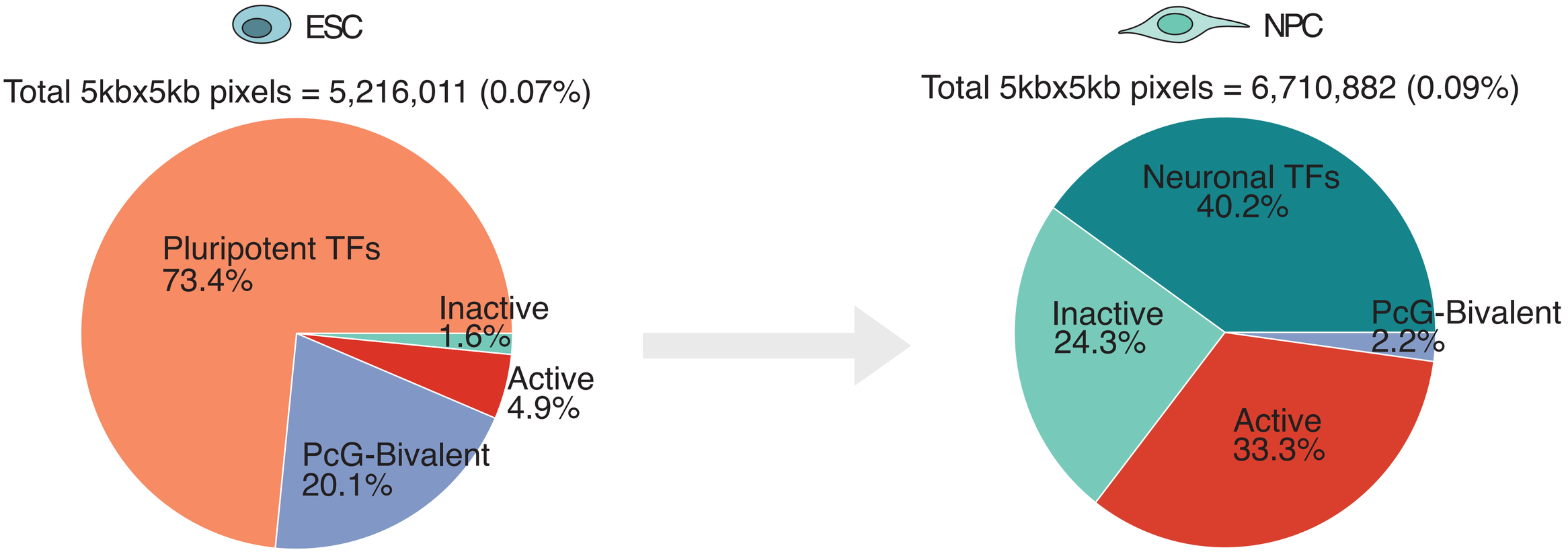




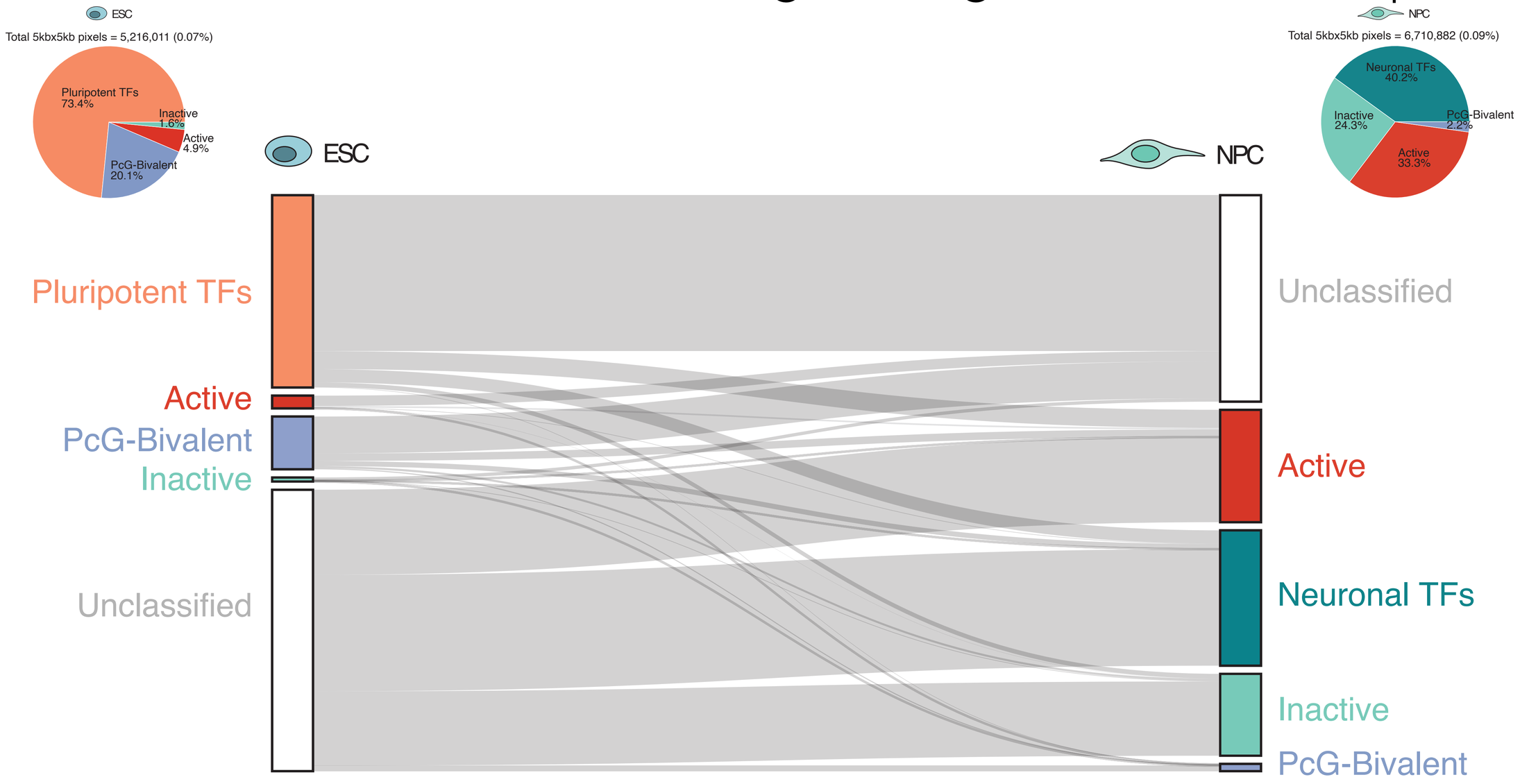
HoxA cluster (example in NPC)



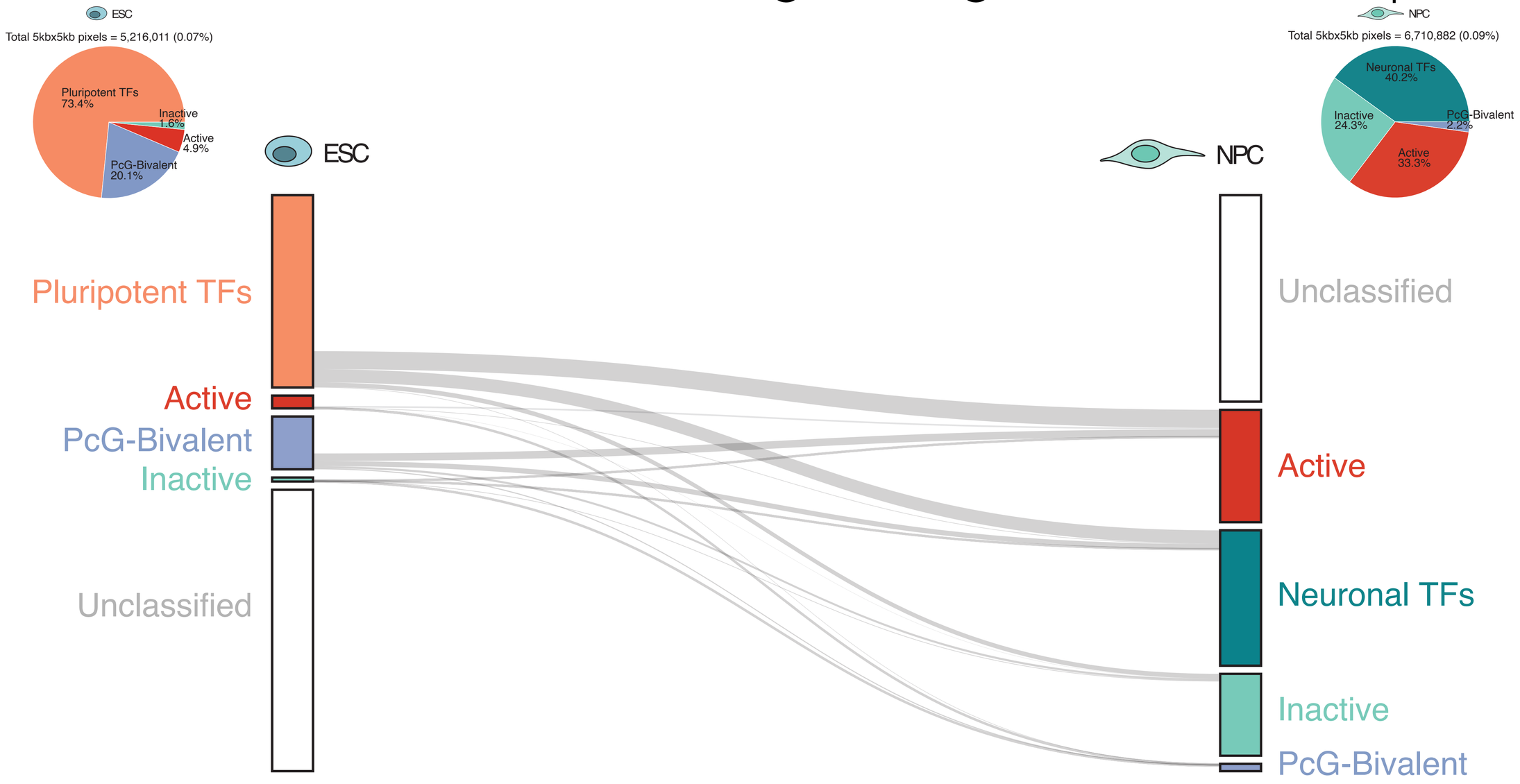
Global 3D interactions rewiring during mouse development



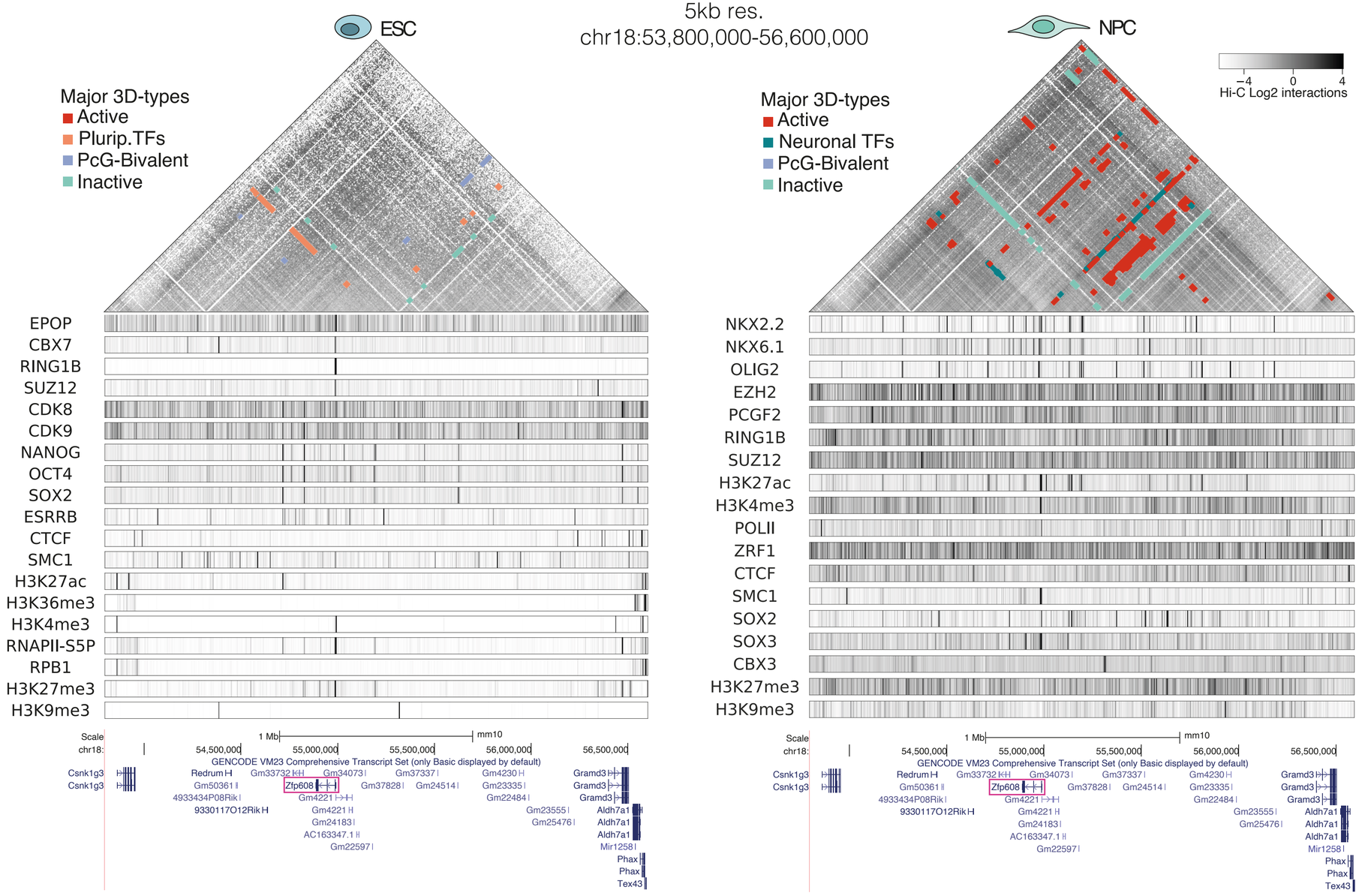
Global 3D interactions rewiring during mouse development



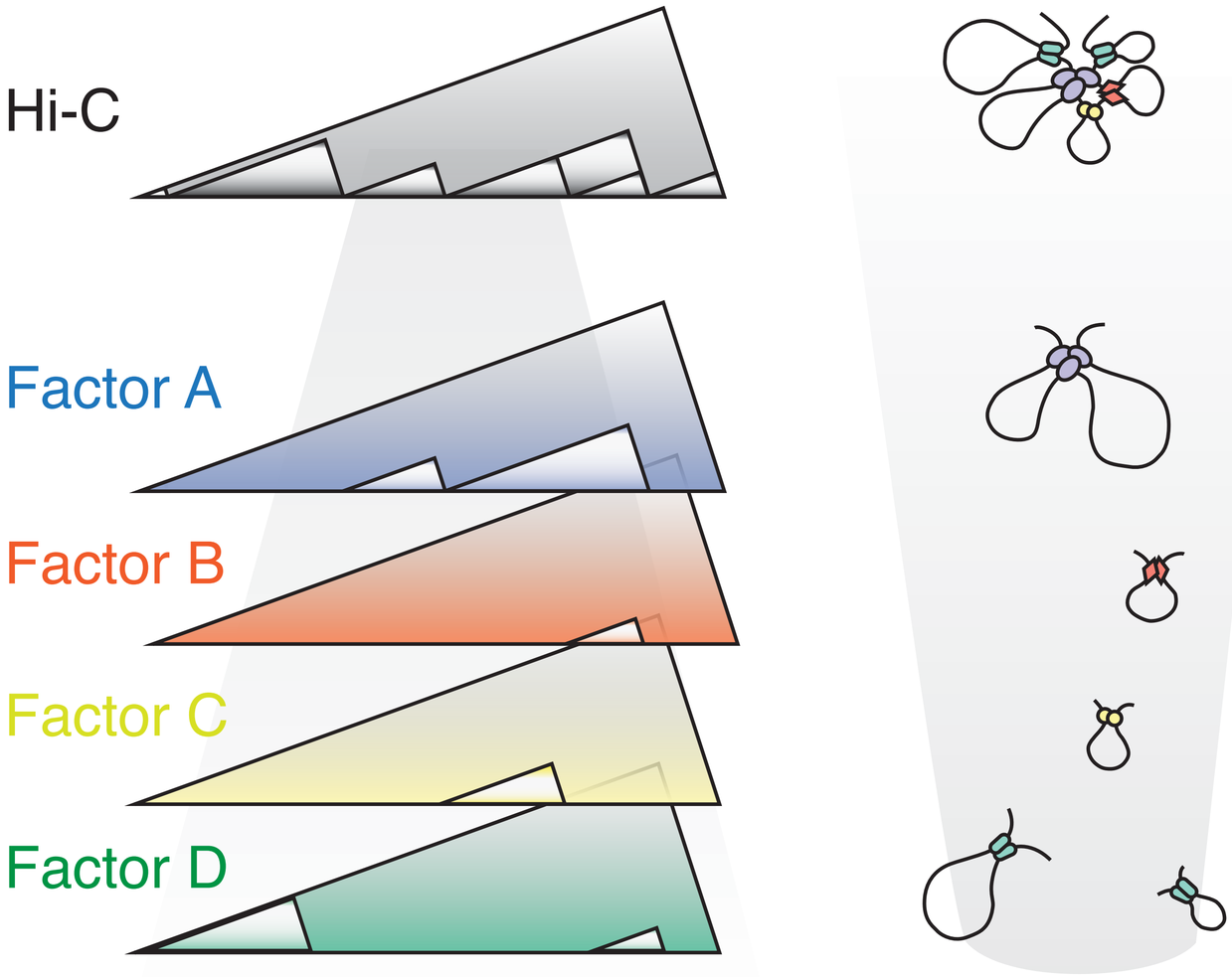
Global 3D interactions rewiring during mouse development



3D interactions rewiring at Zfp608 locus during mouse neural development



Take home message…



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Marc A. Marti-Renom serves as a consultant to Acuity Spatial Genomics, Inc., and receives compensation for these services.