

## CHROMATIC reveals chromatinassociated factors contributing to genome topology

## Marc A. Marti-Renom CNAG-CRG · ICREA

http://marciuslab.org http://3DGenomes.org http://cnag.crg.eu



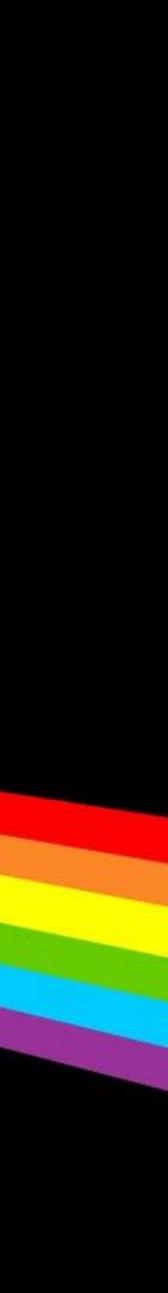


## epigenome

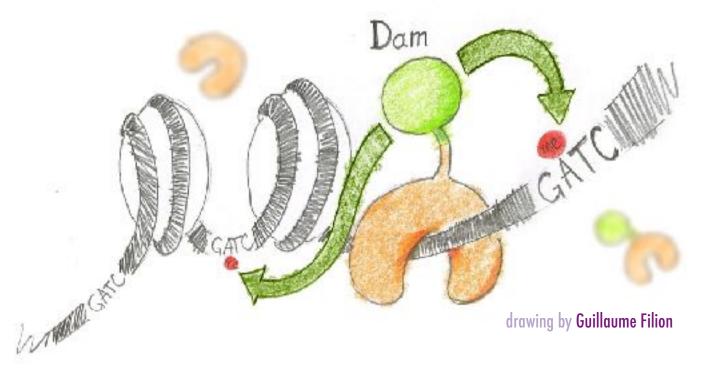
# The genome is a complex system

gene expression

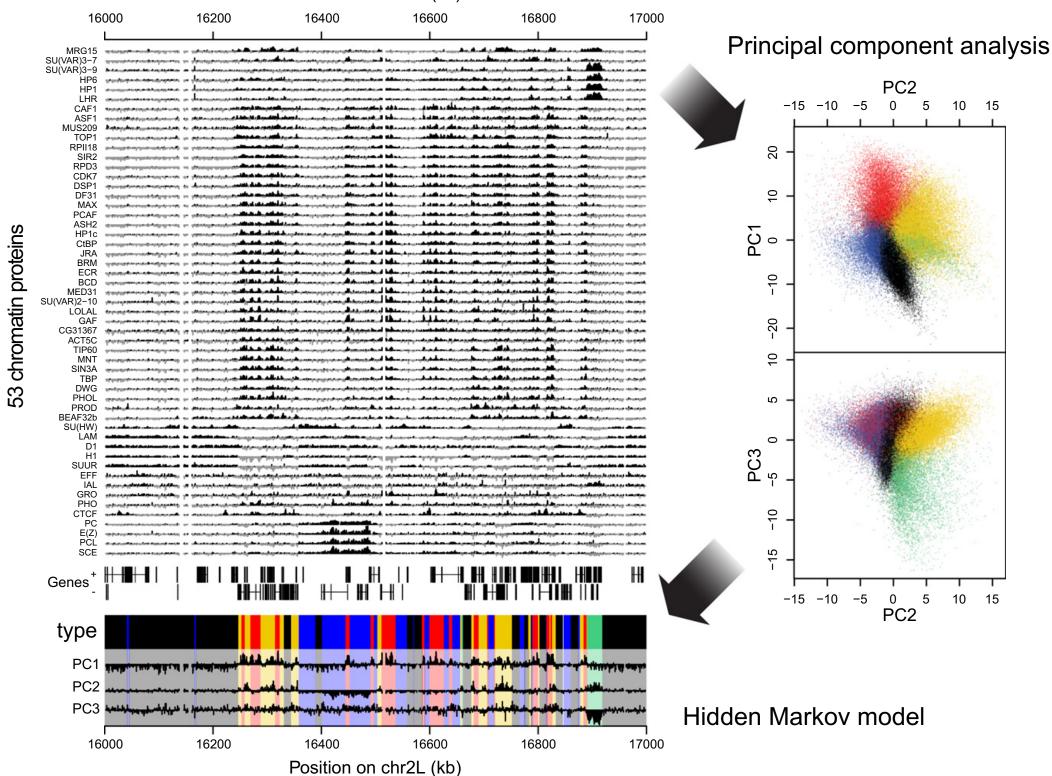


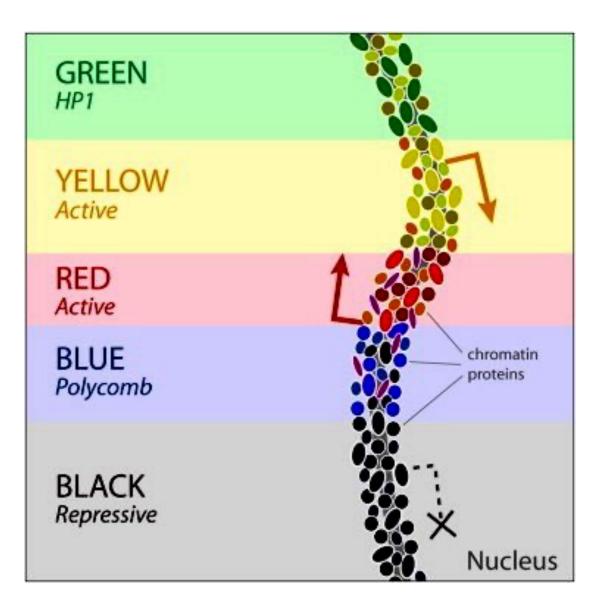


## Fly Chromatin **COLORs** Filion et al. (2010). Cell, 143(2), 212–224.

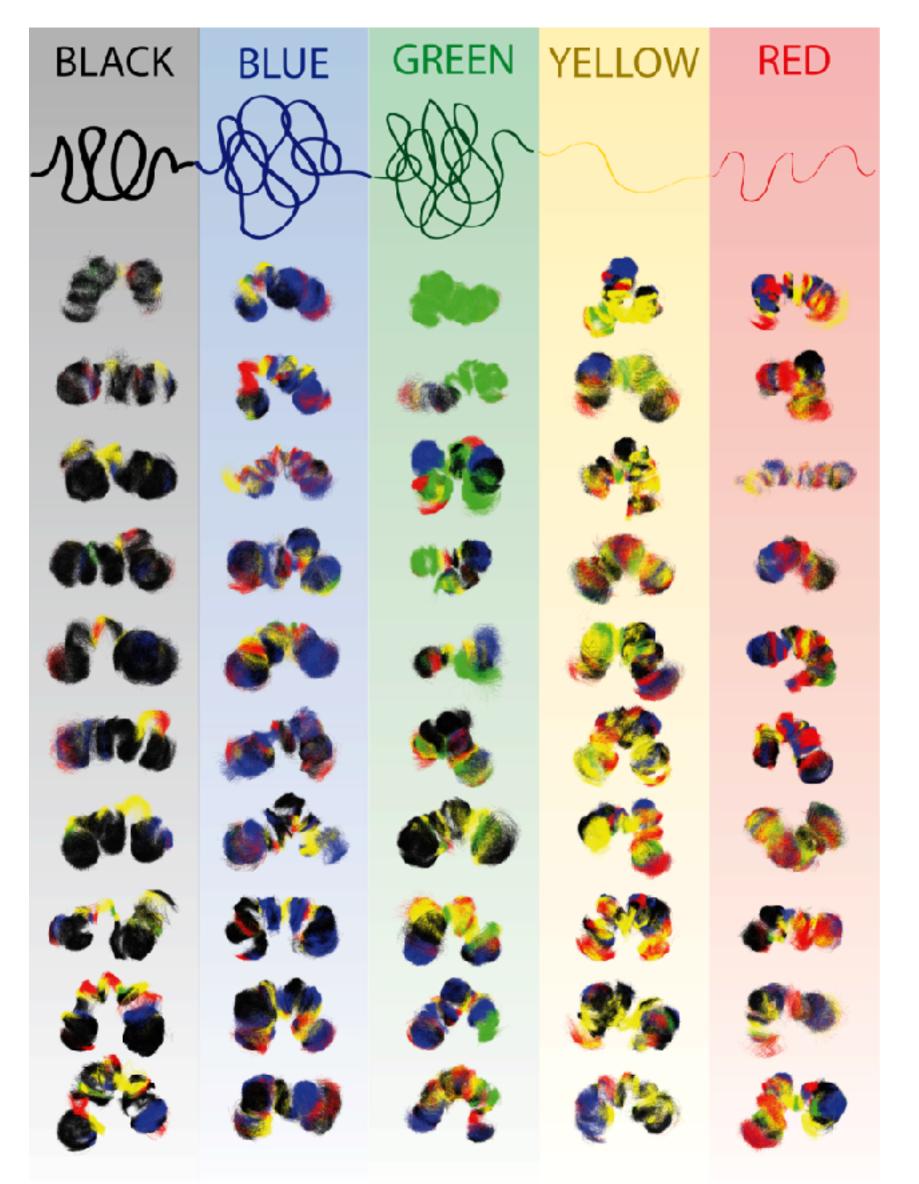


Position on chr2L (kb)





## Who "holds" the genome structure? Serra et al. PLoS Comput Biol (2017) 13(7): e1005665

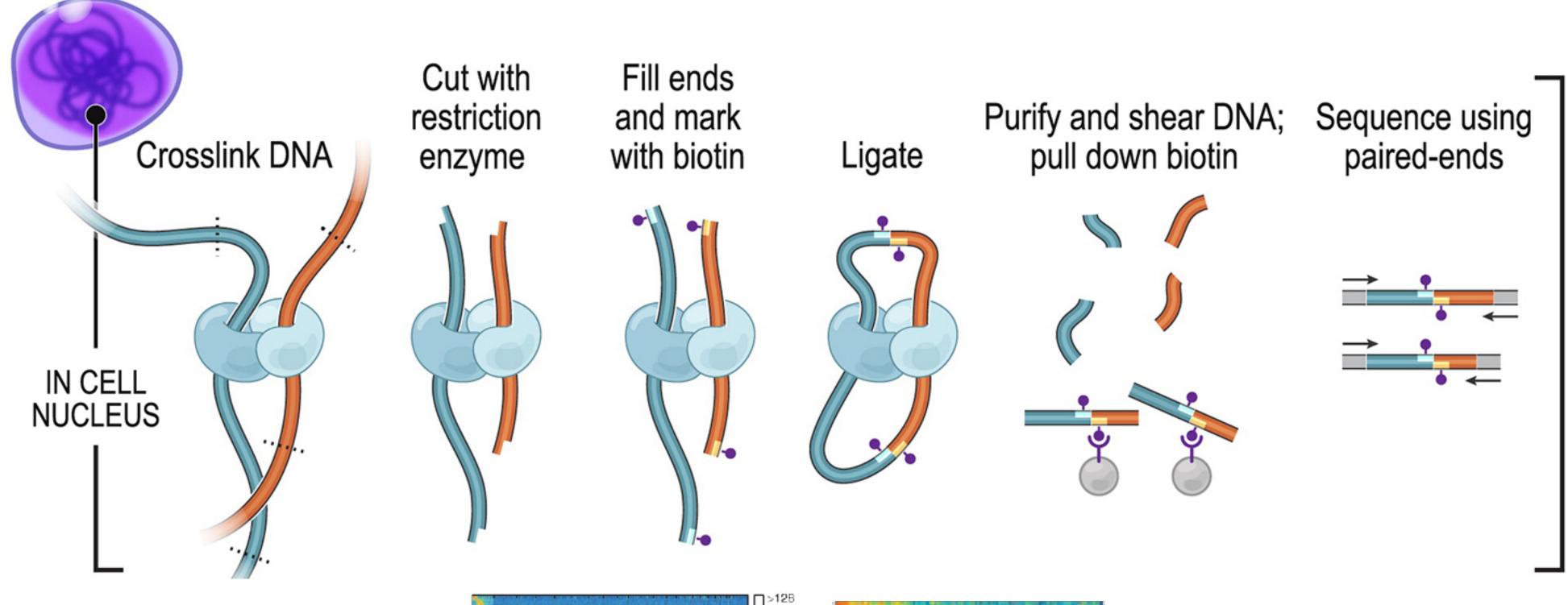


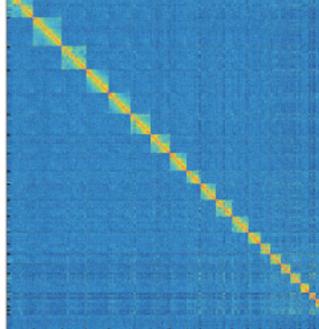
Position on chr2L (kb)

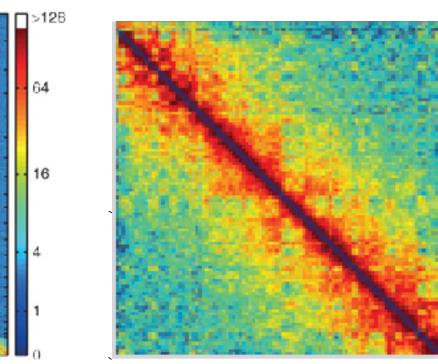
16	000	16200	16400	16600	16800	1700
MRG15	the design of th	and the second sec		And a state of the	Manual Street and Additional	-toutes-to-th
SU(VAR)3-7						-
SU(VAR)3-9						
HP6 HP1	Antheritanian and a strategical and a strategical stra		and the second			- Carling
LHR	an and a state of the state of	and the second se	and the second state of the second second second			
CAF1					at and the state of the second and	
ASF1					and a star of the second black a star same	
MUS209					Brashedder, allebana - sale a creater an	
TOP1					Hand and the affiliation of an article of a first state of the second state of the sec	
RPII18 SIR2	and and a set of the s		and and the state of the second state			410-9
RPD3		a second s	And a surger of the Bullet		the second	
CDK7					and the state of the second state of the second state and a second state and a second state of the second	
DSP1						
DF31						
MAX PCAF					an a	
ASH2					and a state of the second s	
HP1c		maran and and and and the state	Anterior Antonio Bastone & A Baker	and the state of t	day and a set of the same	
CtBP					Actual and a state of the second seco	
JRA					Personal split was able to see a second	
BRM ECR	destations and a second second second				and and a state of the second second strategy and second	
BCD						
MED31	and the second s	manan with the state	and the second state of th	and and an and an and and and and and an	and the state of the second second	diam'r.
SU(VAR)2-10					and the second s	
LOLAL	and the second	And a state of the		and a state of the second	and and a second a se	****
GAF CG31367					an a	
ACT5C					attended and the second distant in such	
TIP60	freihtingestersterstersterste te	and the address of the second	and a state of the	man have a star on all all	and the state of the second second second	and a grade with
MNT						
SIN3A					assessed and the second shift affer a farming	
TBP DWG					and a stand of the second s	
PHOL					terested and a los be believes	
PROD	contrate de construction por en	progenting and the strange of the second	and the second states and states and	and the second state of the second states of the second states of the second states of the second states of the	the second day and and a state of a second second	Annes
BEAF32b	and a Anternation for the second second	man	and the second second second second second	And the state of the second state of the secon	and a state of the same of the same	
SU(HW)	and and a standard and a standard and a standard and a standard at the standar	And and and a second second	And a state of the second s	and the same a factor of a same lagter		
	And a state of the					
D1 H1					and a second	
SUUR						
EFF	a setter statement	Laurent band and and a star and a star	A SALAR ST ALL ST AND A SALAR	and and a set will well and a set of a set	and a second	
IAL						
GRO				a set a s	and the second s	
PHO CTCF					and the state of the second	
PC					A DESCRIPTION OF THE REAL PROPERTY OF THE REAL PROP	
E(Z)	and a summer of the summer of the	and a second state and a second	and the state of t	and a state of the	- and all and the same share a start of the same	Aurona
PČĹ	divelation descentes descentes and a		and the second s	and a star and a subscription of the subscription	A and the day of the strate of	-
SCE	colonity and the second second of	-	At some surface that the second secon			- Carlor Street

# 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.

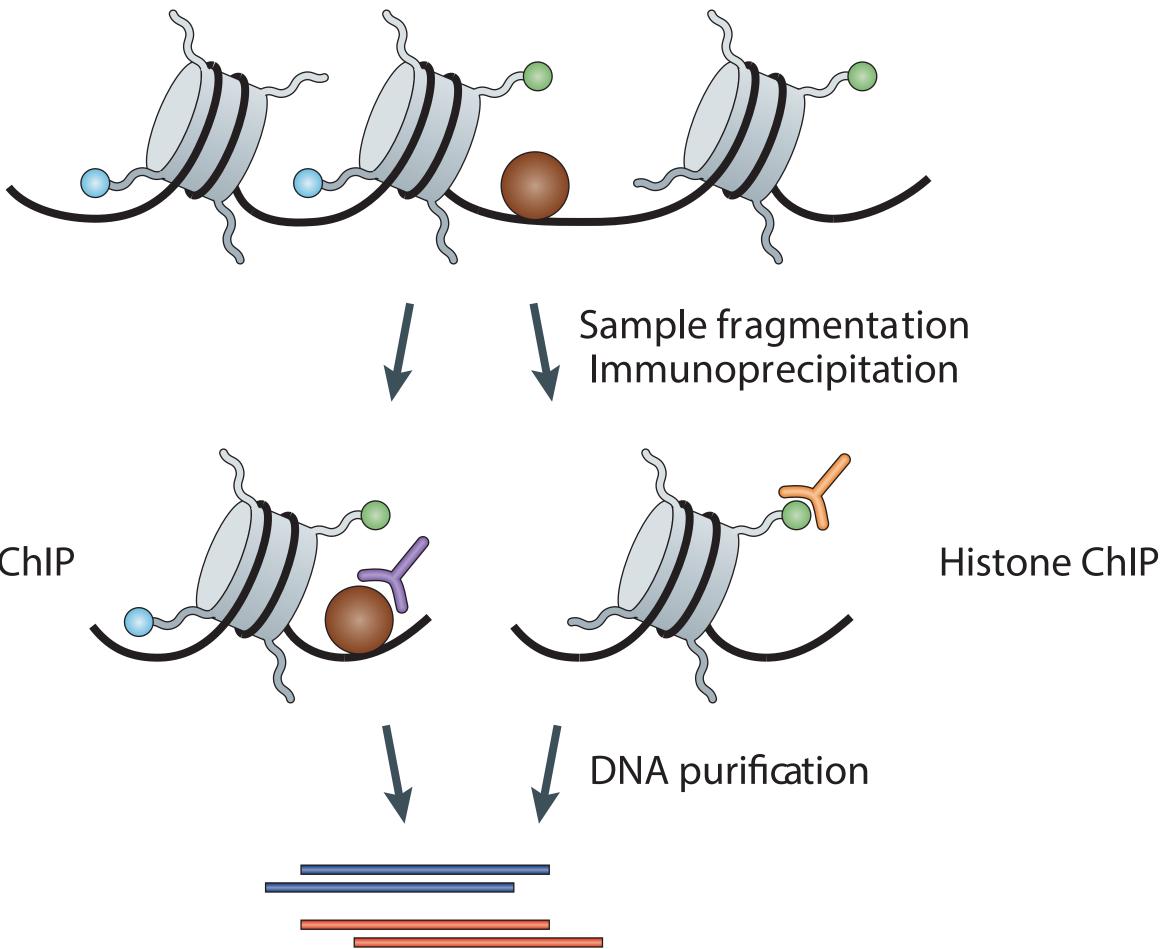


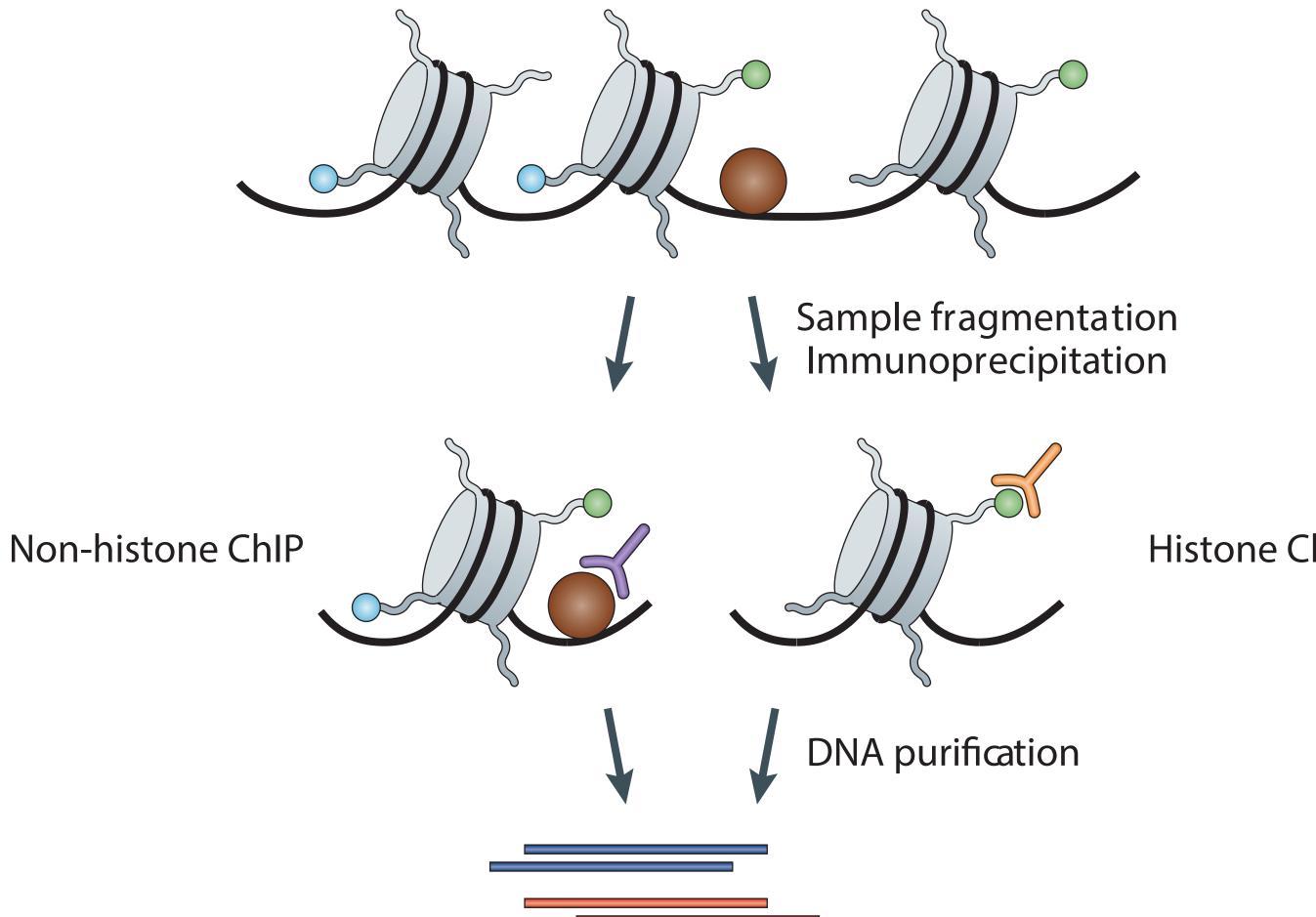




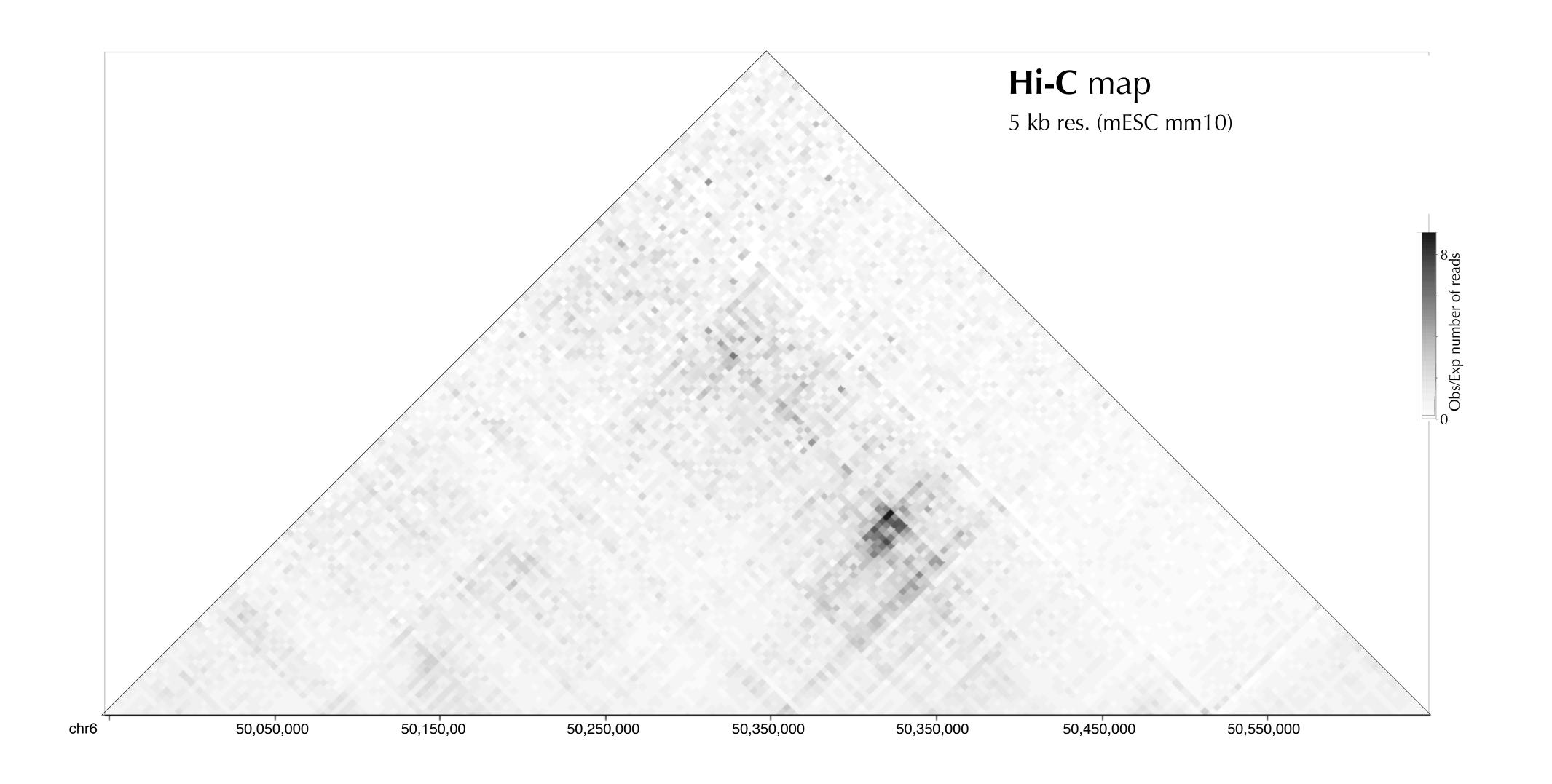
## Chromatin Immunoprecipitation (ChIP)

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

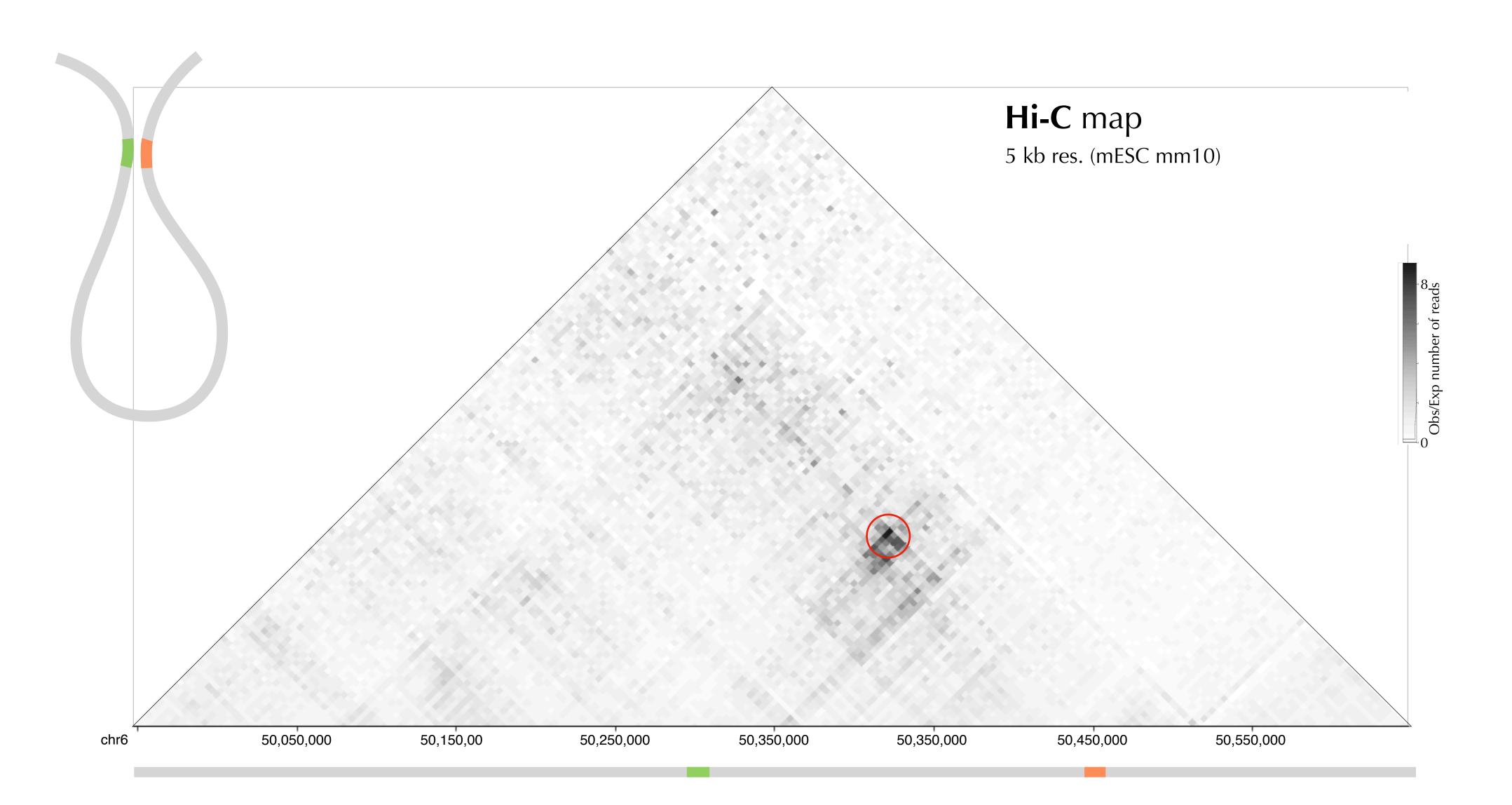


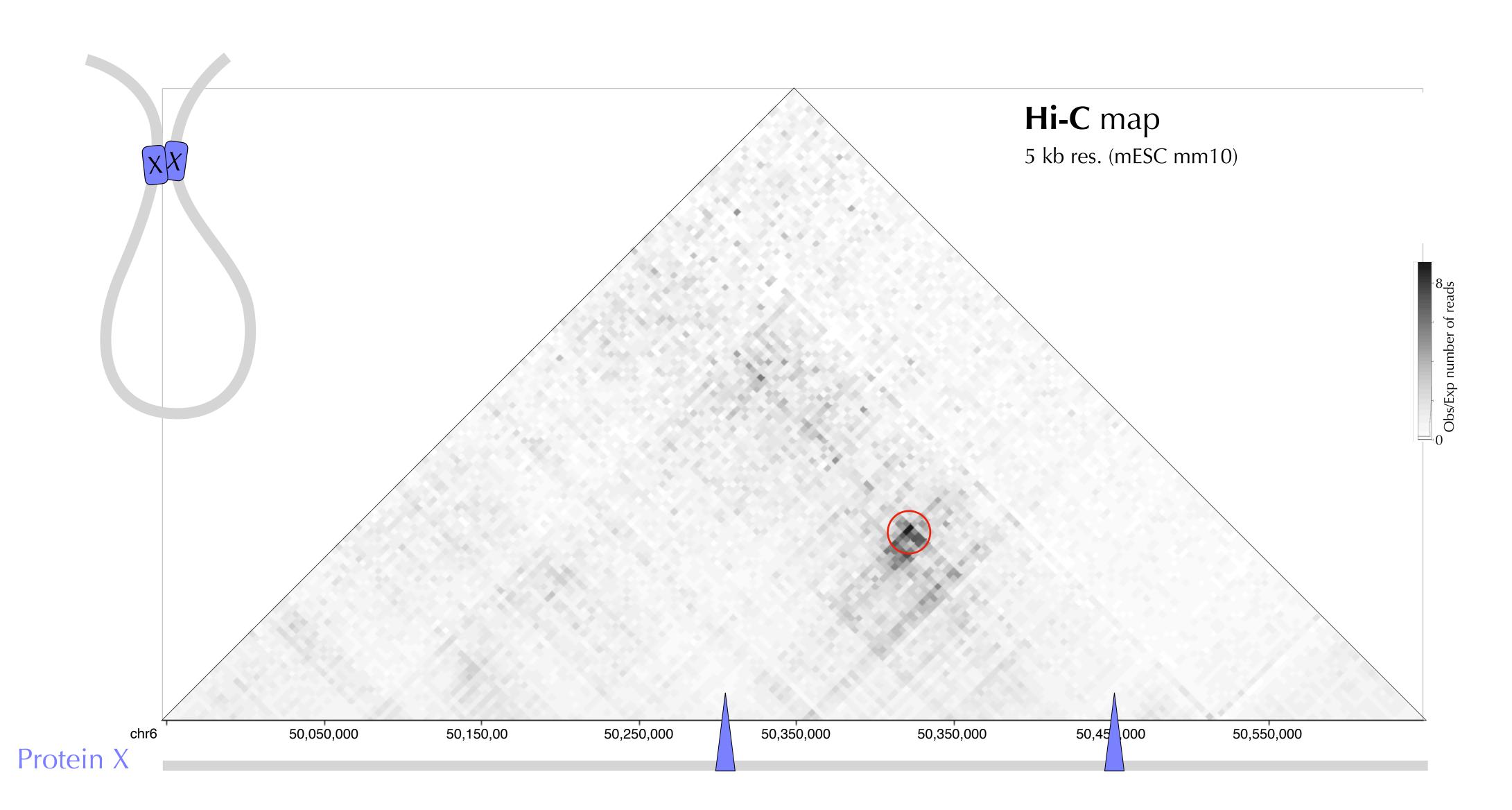


# High-throughput Chromosome Conformation Capture (Hi-C)



## Chromatin interaction on a Hi-C map

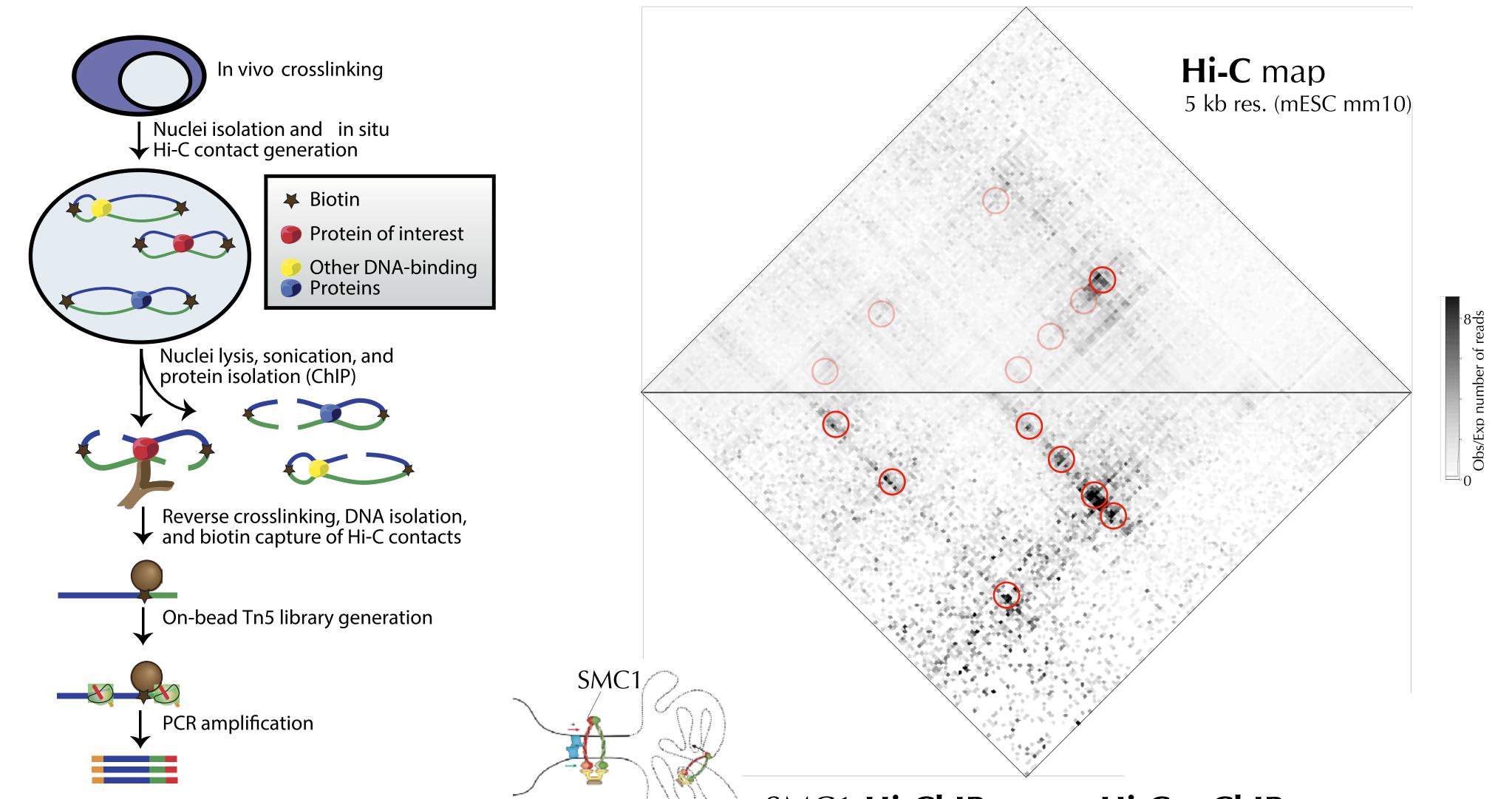




# Chromatin interaction "mediated" by a protein

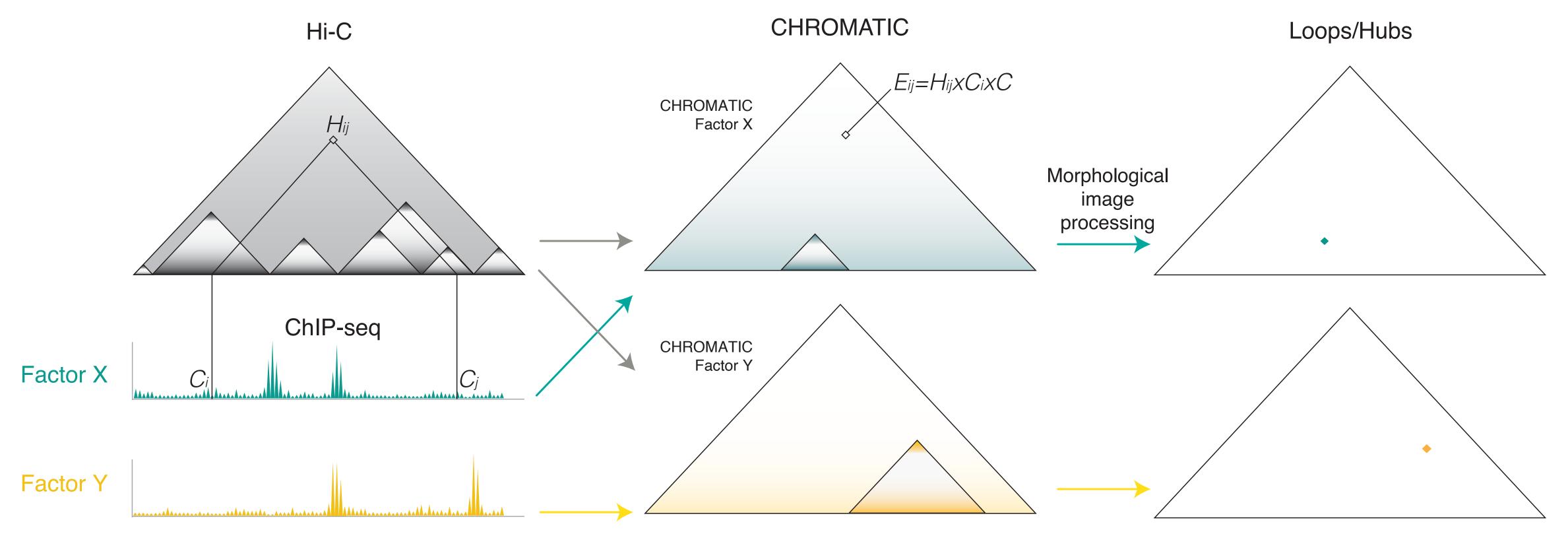
# Hi-ChIP: capturing specific protein-mediated interactions

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



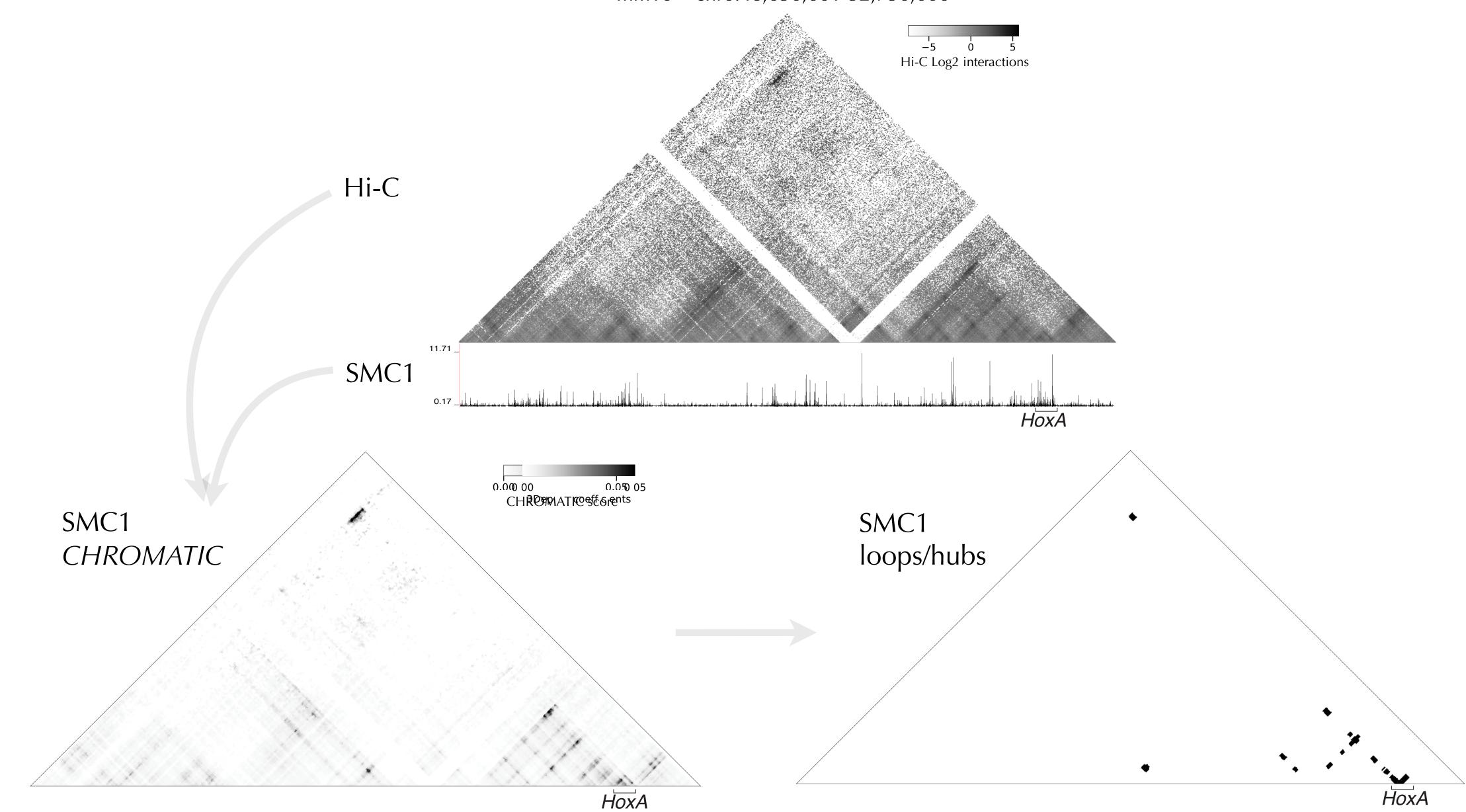
## SMC1 Hi-ChIP map = Hi-C + ChIP

5 kb res. (mESC mm10)



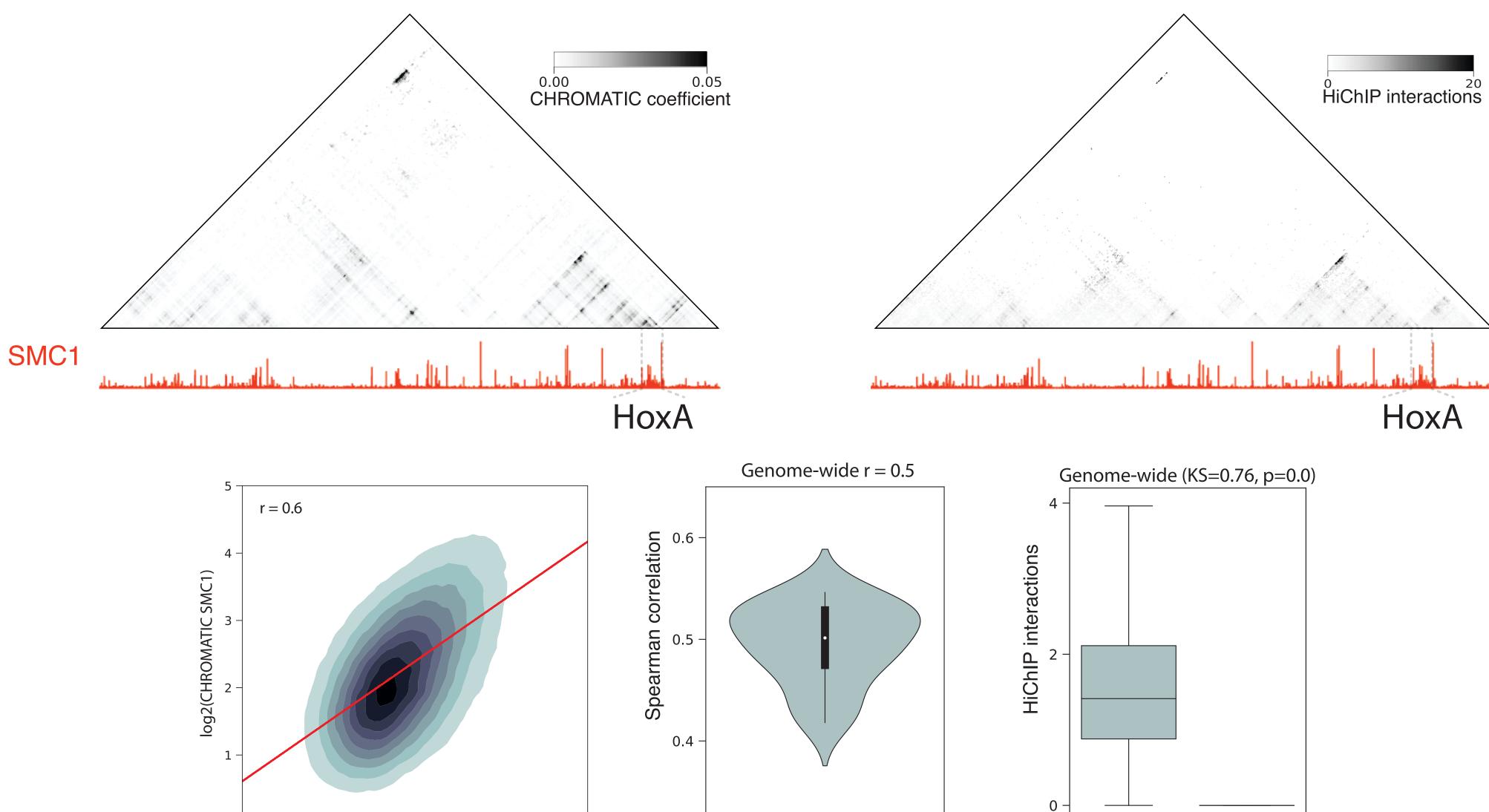
CHROMATIC

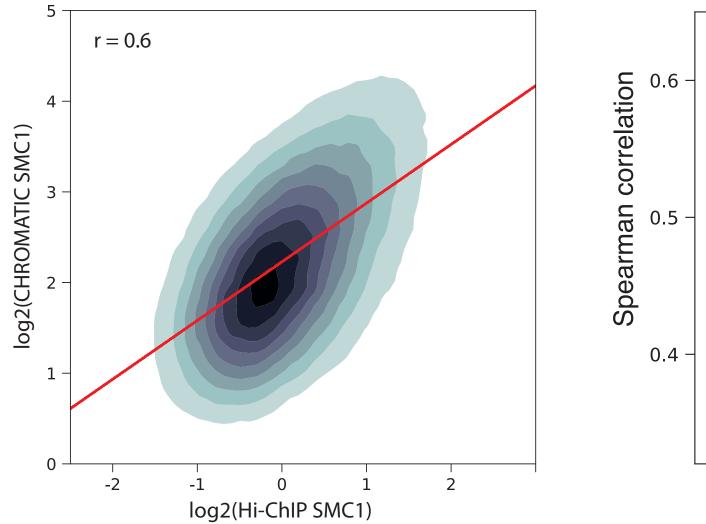




# CHROMATIC example

### mm10 chr6:48,050,001-52,750,006





## Validation with HiChIP as benchmark

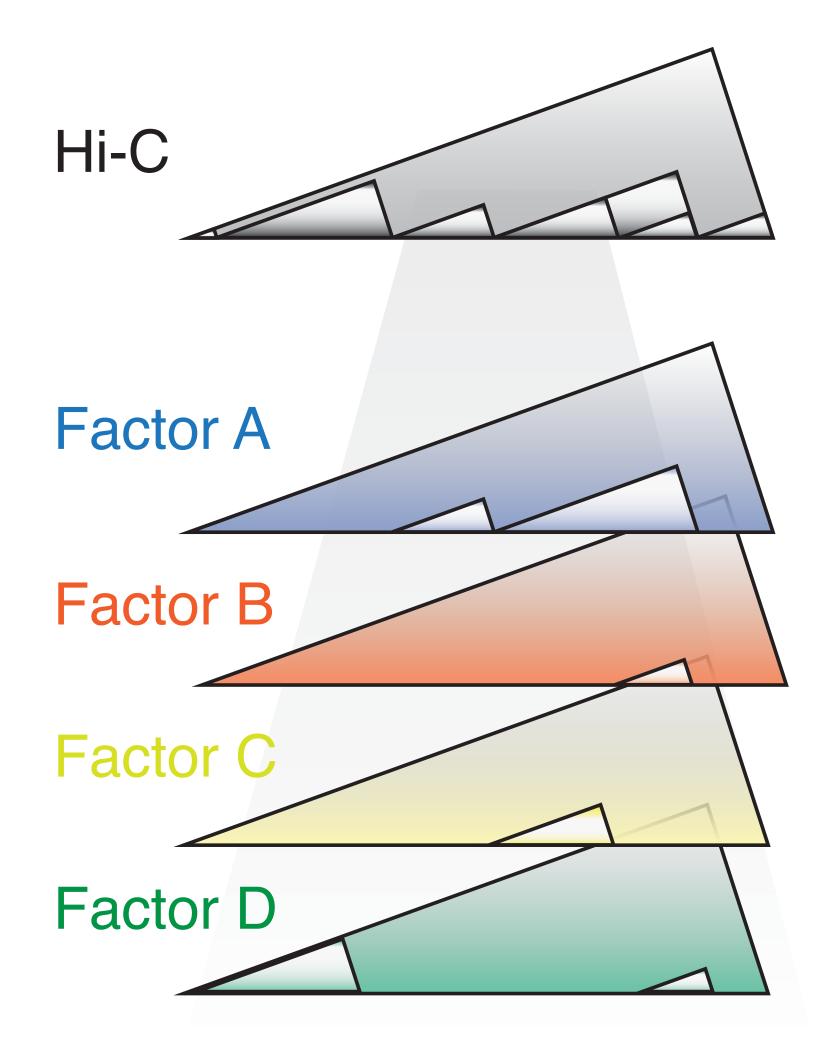
mm10 - mESC - 5kb - chr6:48,050,001-52,750,006

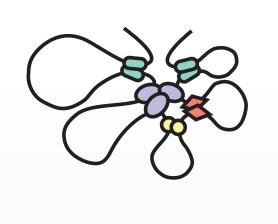
Per chromosome

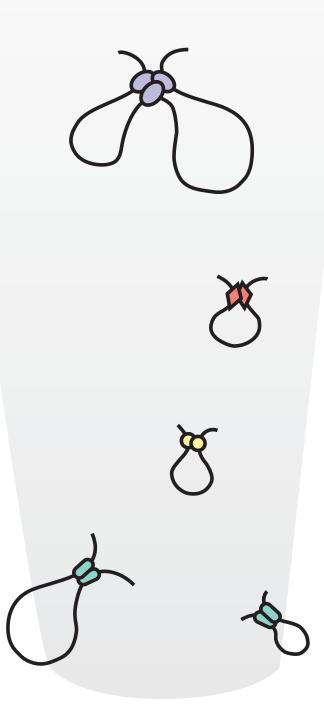
Loops/Hubs

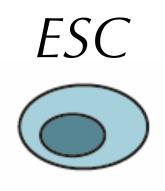
Rest

# The role of chromatin factors in genome topology



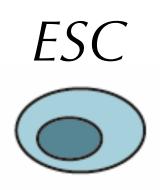


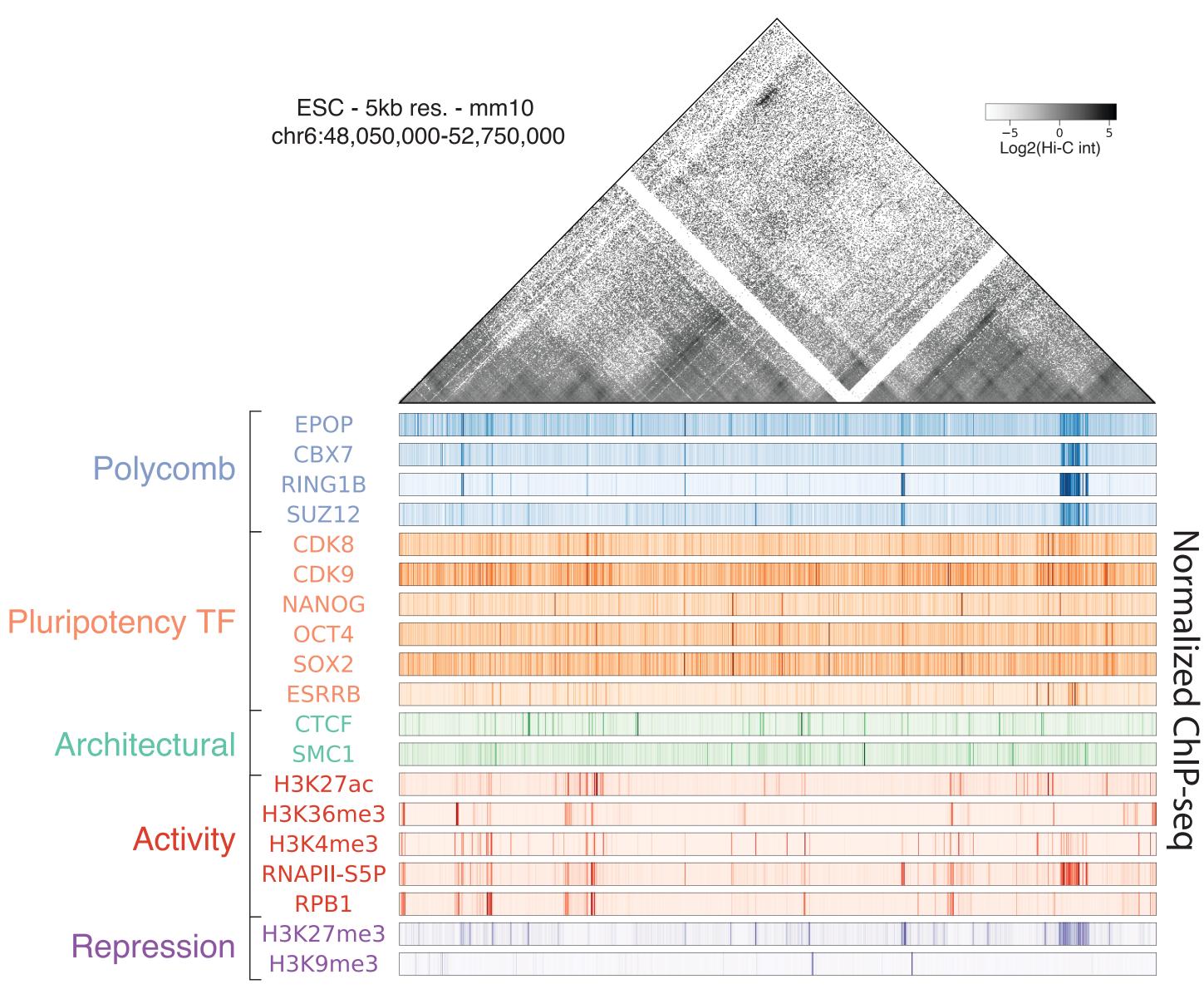








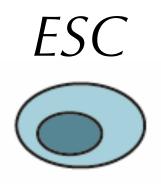


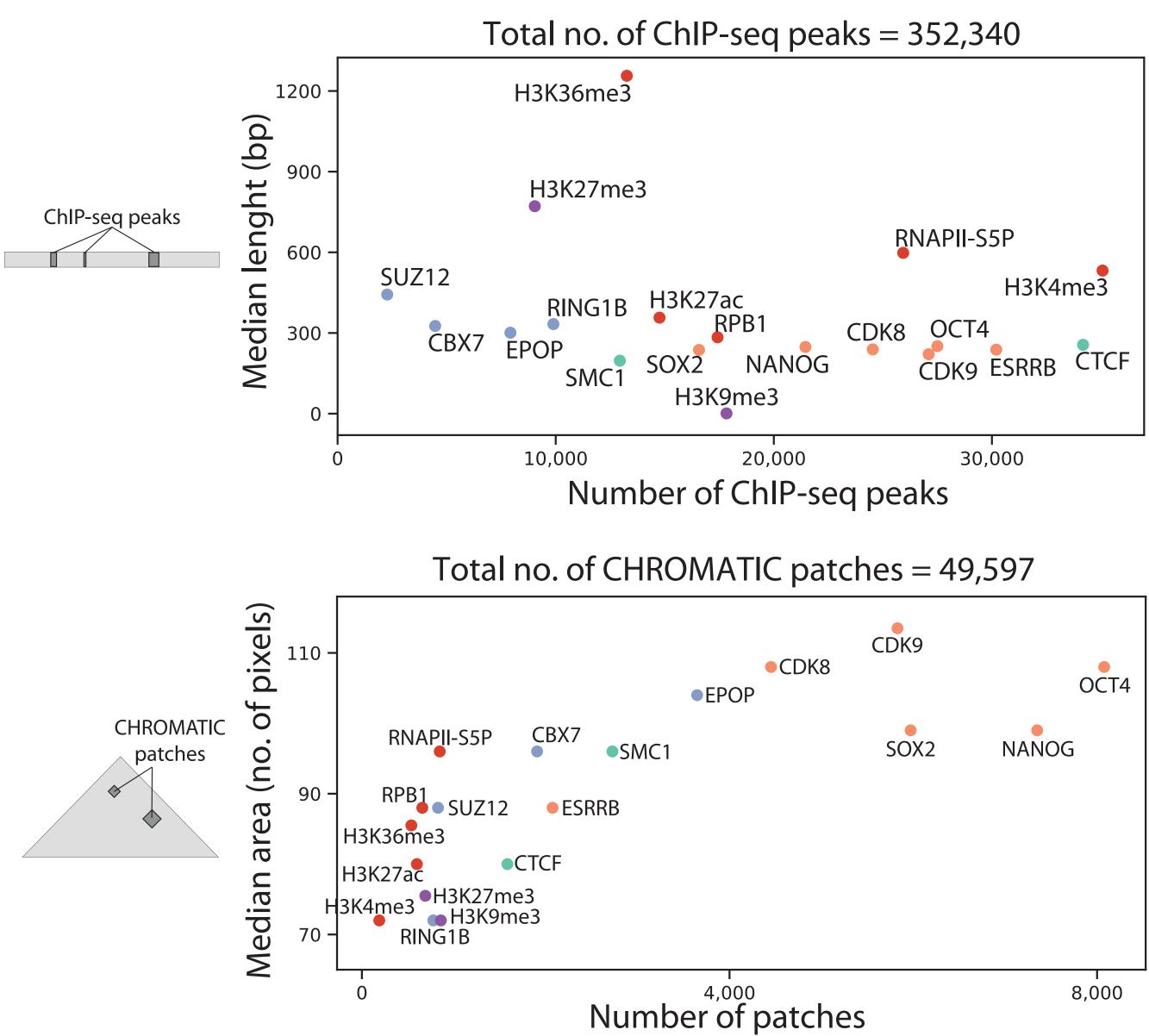


# HoxA cluster (example in ESC)

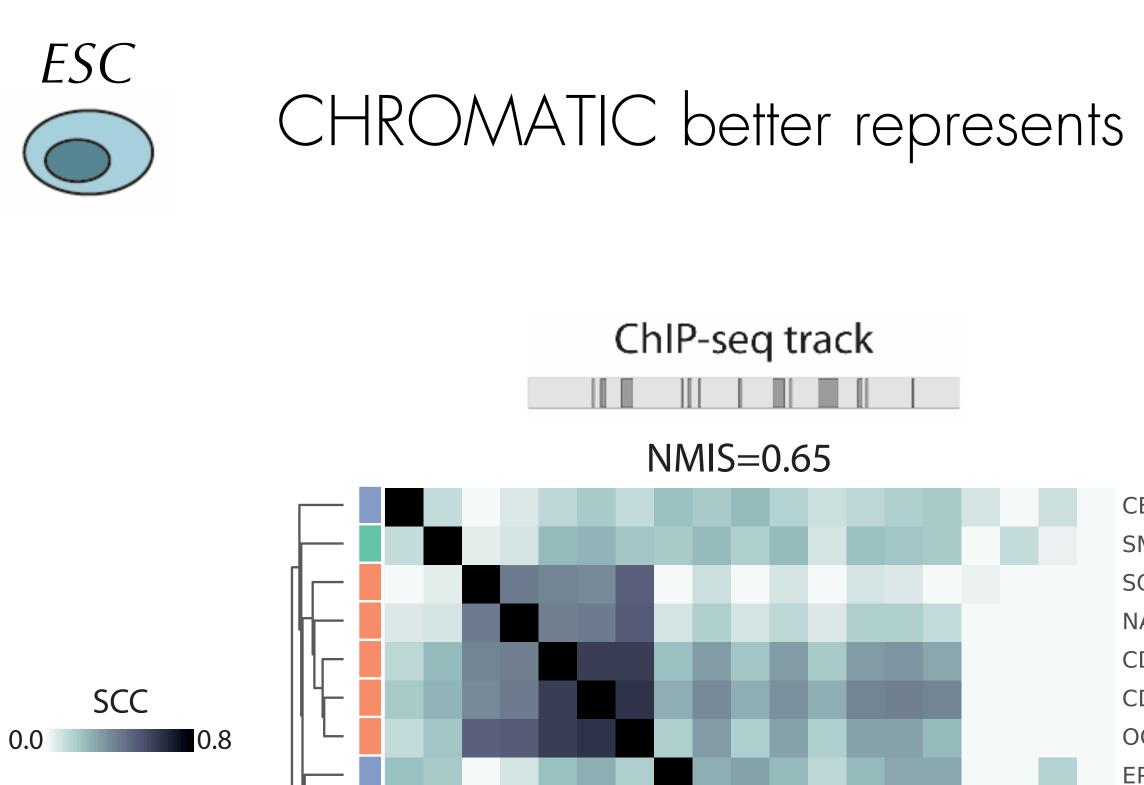
HoxA

## 3D interactions are mostly associated with pluripotent TFs

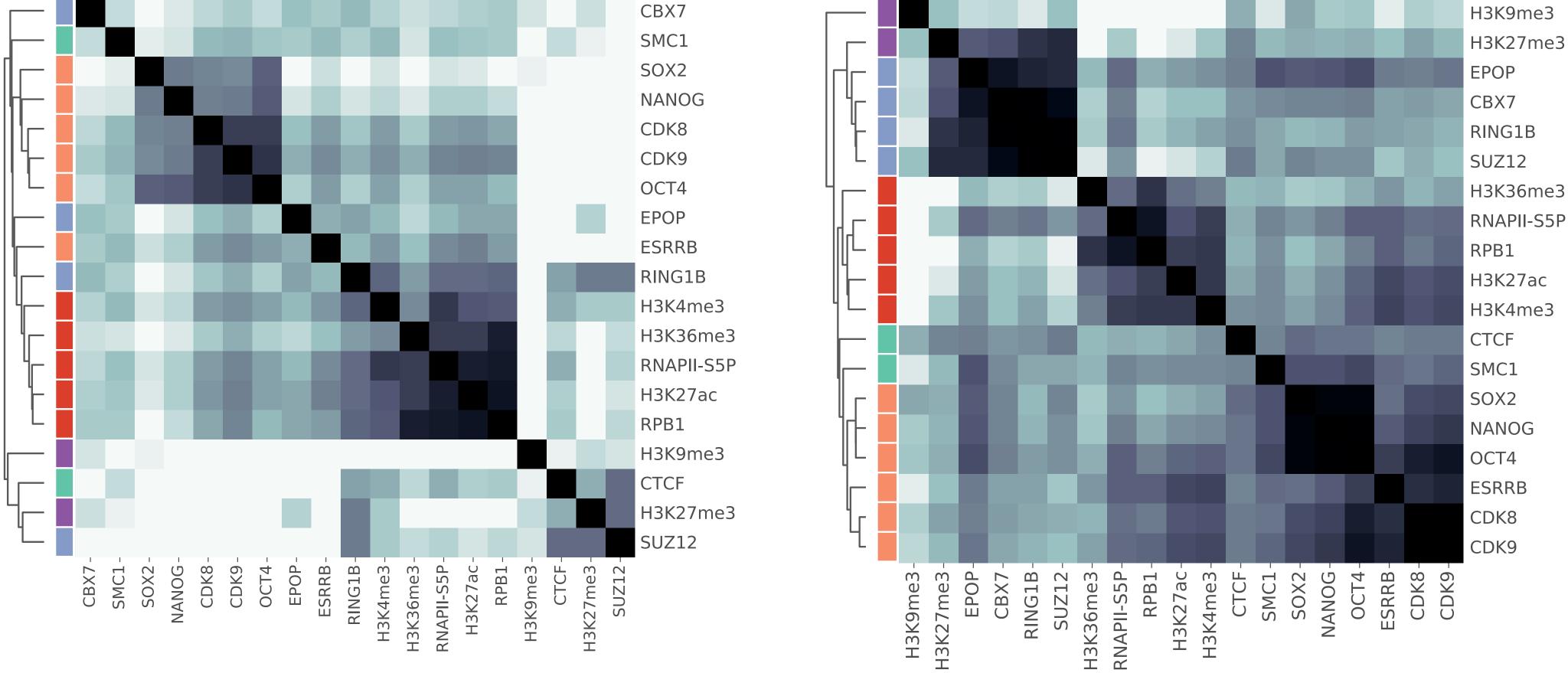




Polycomb **Pluripotency TF** Architectural Activity Repression



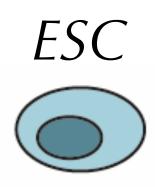
Polycomb Pluripotency TF Architectural Activity Repression



## CHROMATIC better represents genome function than ChIP-seq alone

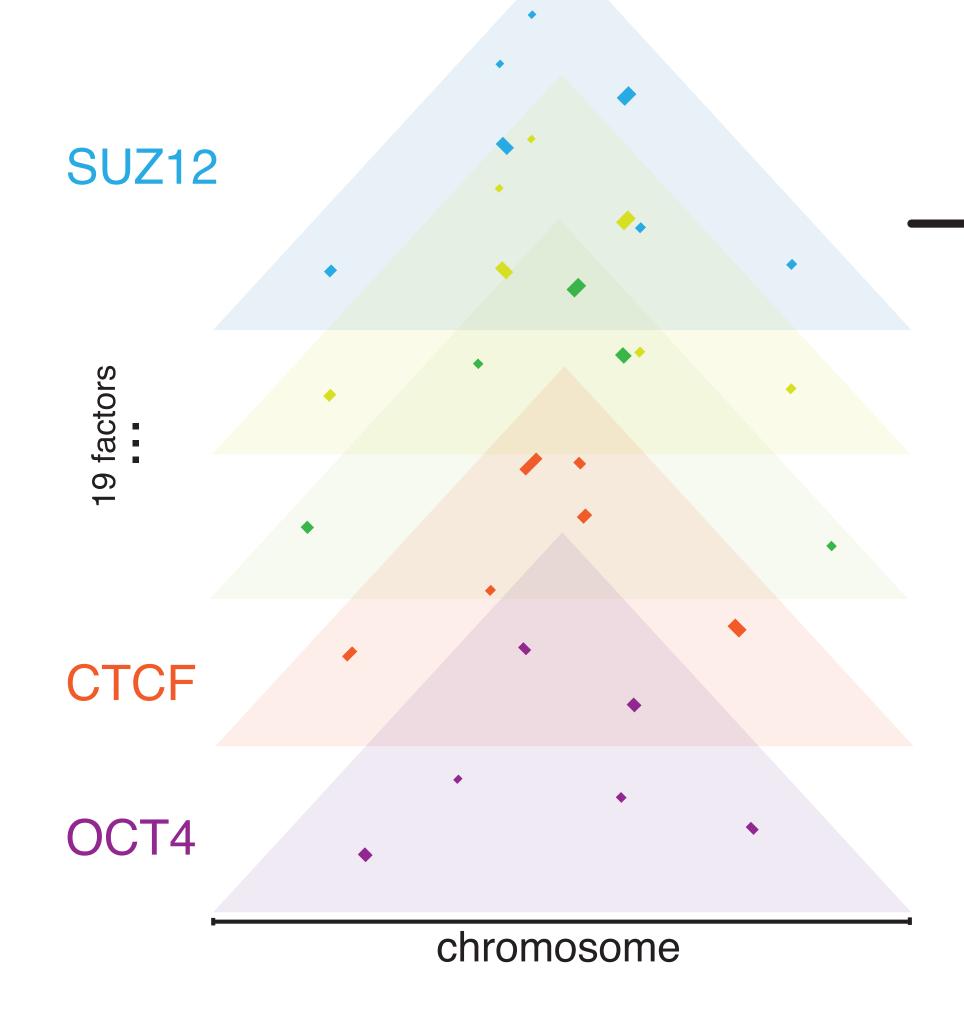


NMIS=0.85

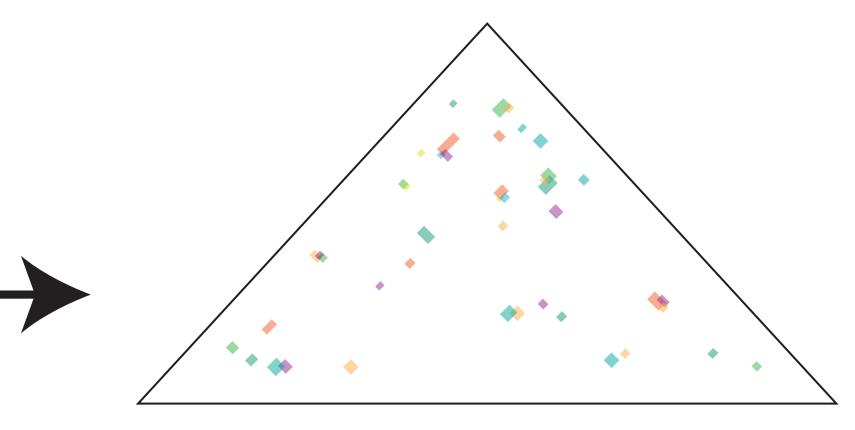


## Measure the 3D co-localization of factors

CHROMATIC interactions



Overlap (19 factors)

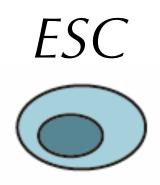




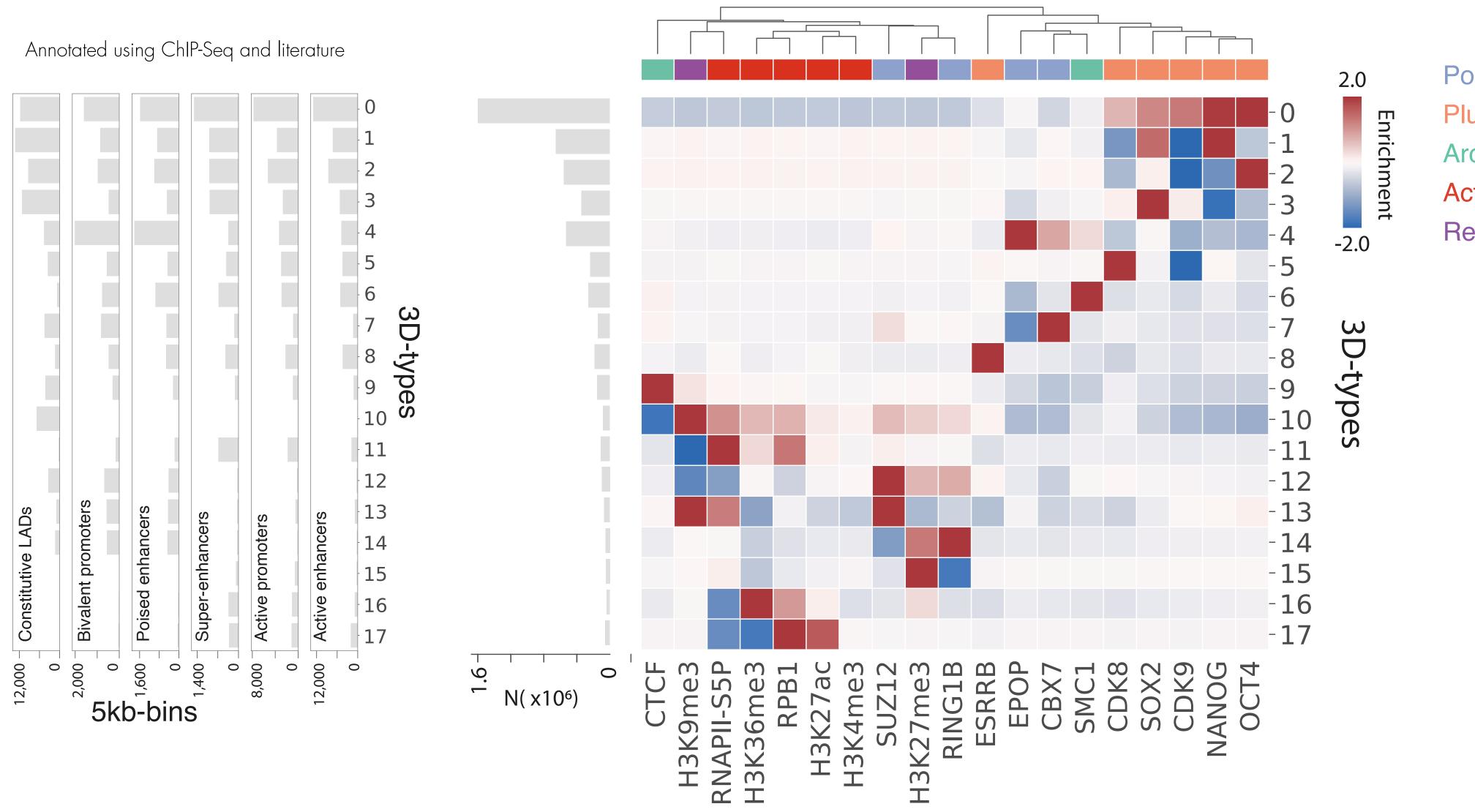
8m 54s

Latent Semantic Analysis

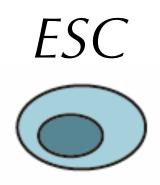
. . .



# Types of 3D interactions with LSA in ESC

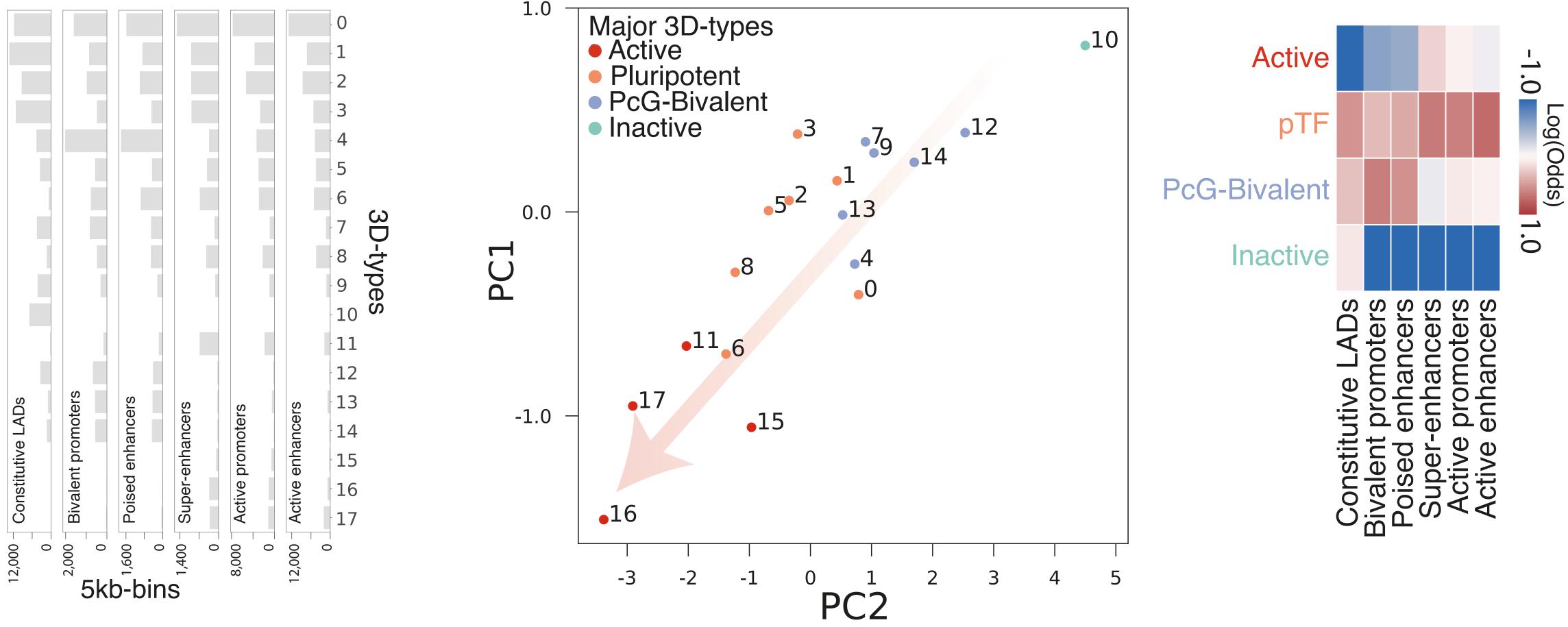


Polycomb Pluripotency TF Architectural Activity Repression

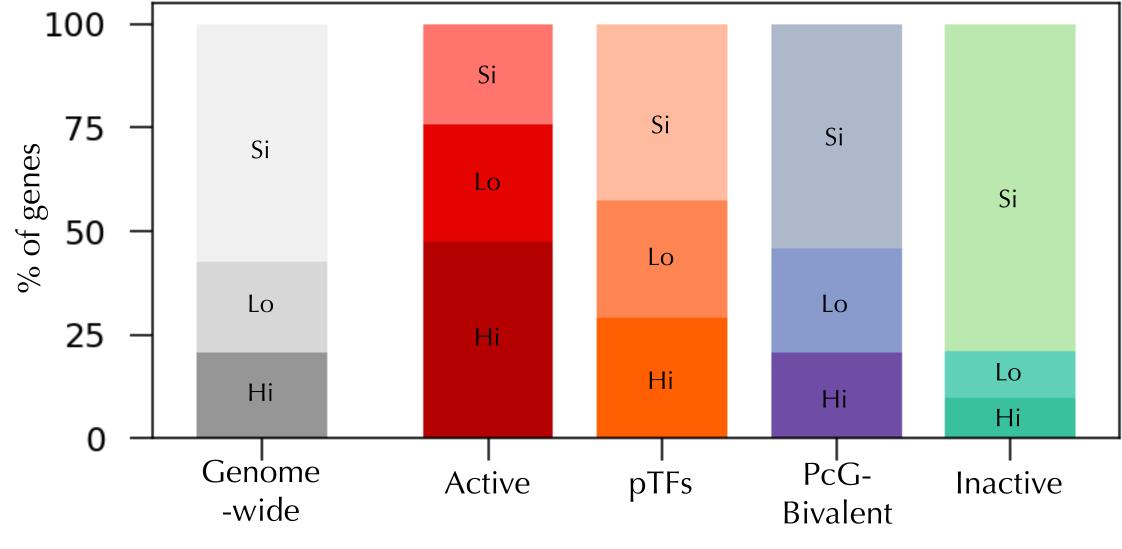


# Types of 3D interactions with LSA in ESC

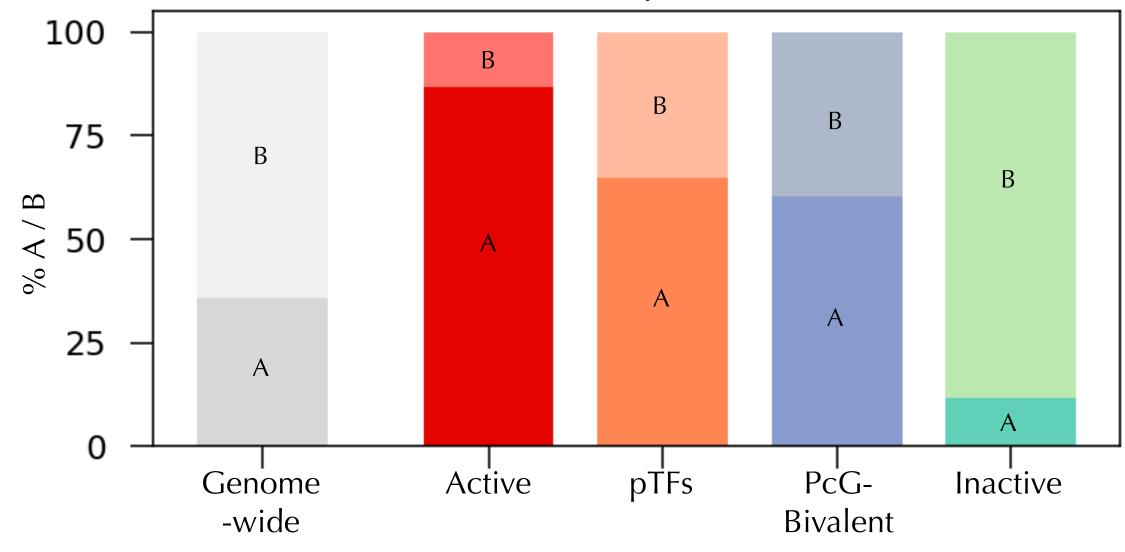
Annotated using ChIP-Seq and literature

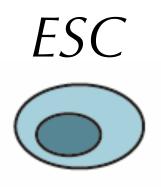


# 4 major types of 3D interactions in ESC





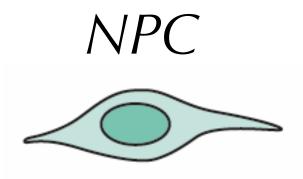


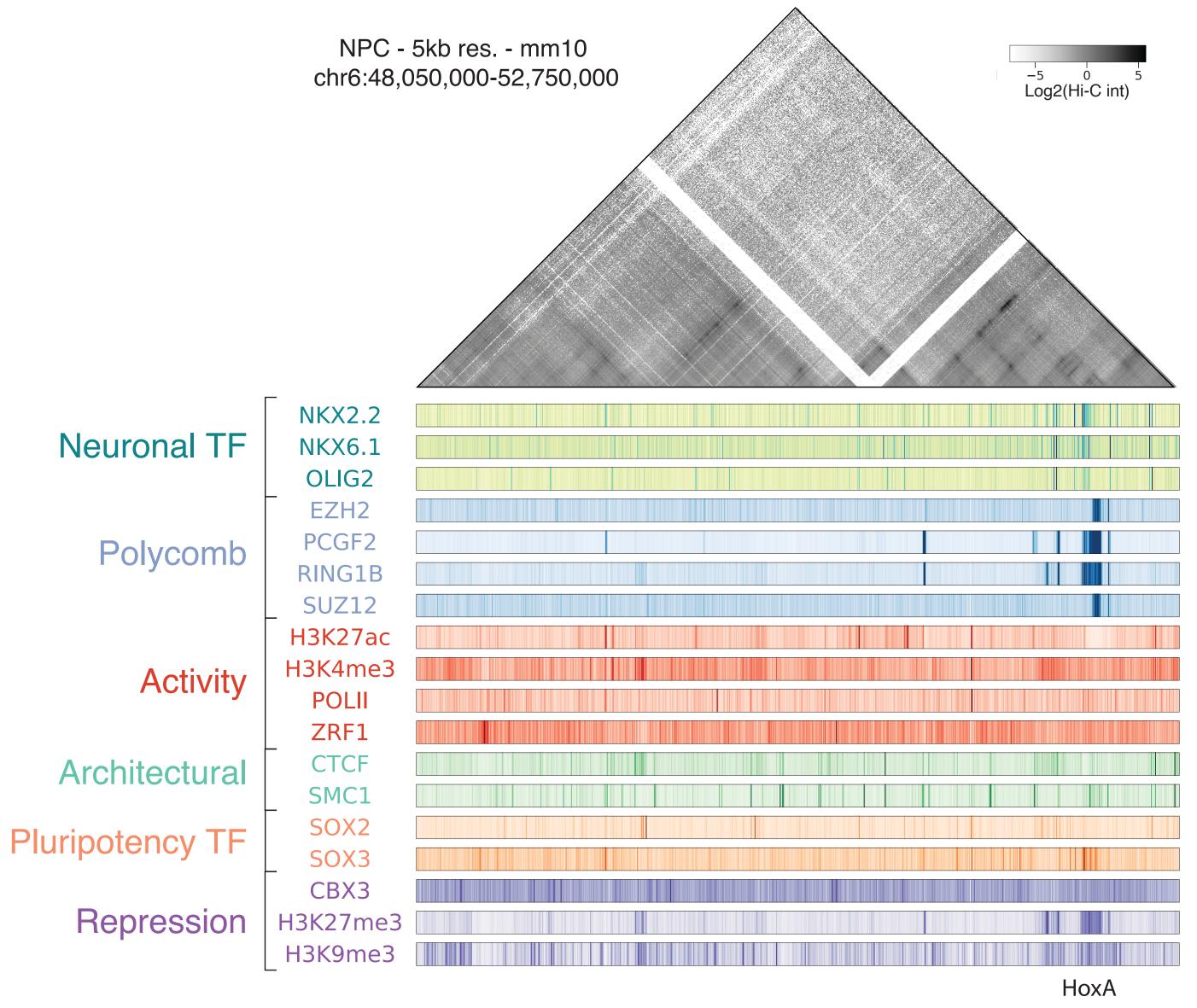


### Higly-, Lowly-expressed and Silent genes

Silent RPKM<1 1<RPKM<10 Low High RPKM>10

### A and B compartments





# HoxA cluster (example in NPC)

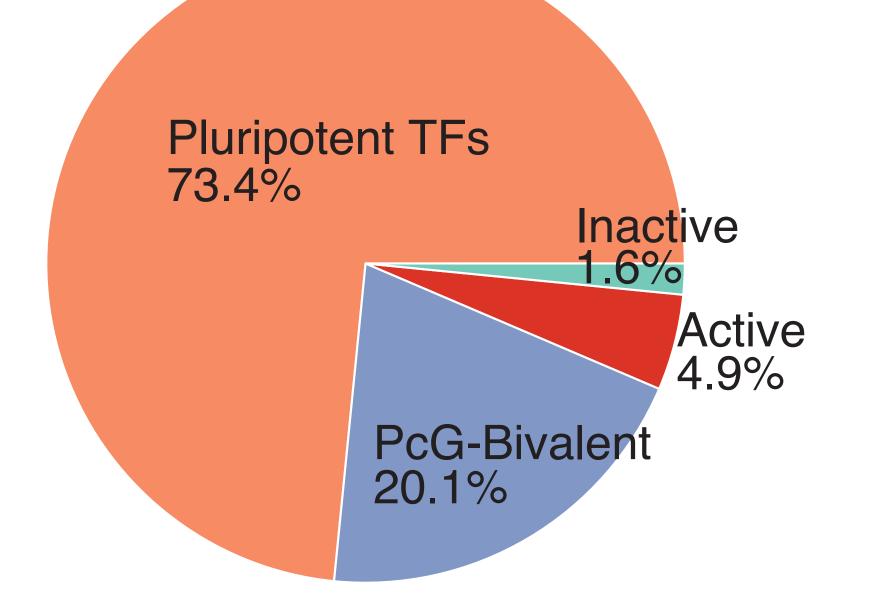
Normalized

ChIP-seq

## Global 3D interactions rewiring during mouse development

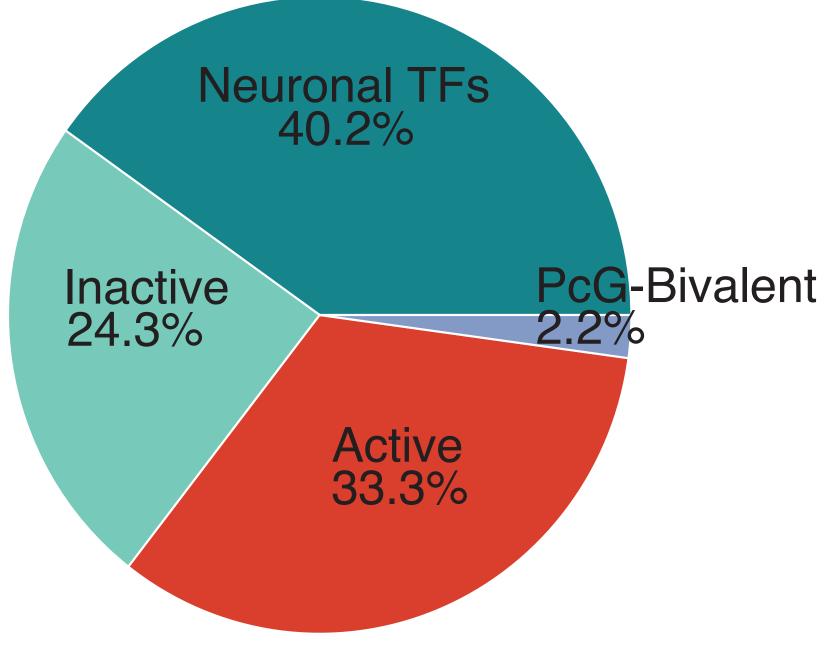


## Total 5kbx5kb pixels = 5,216,011 (0.07%)

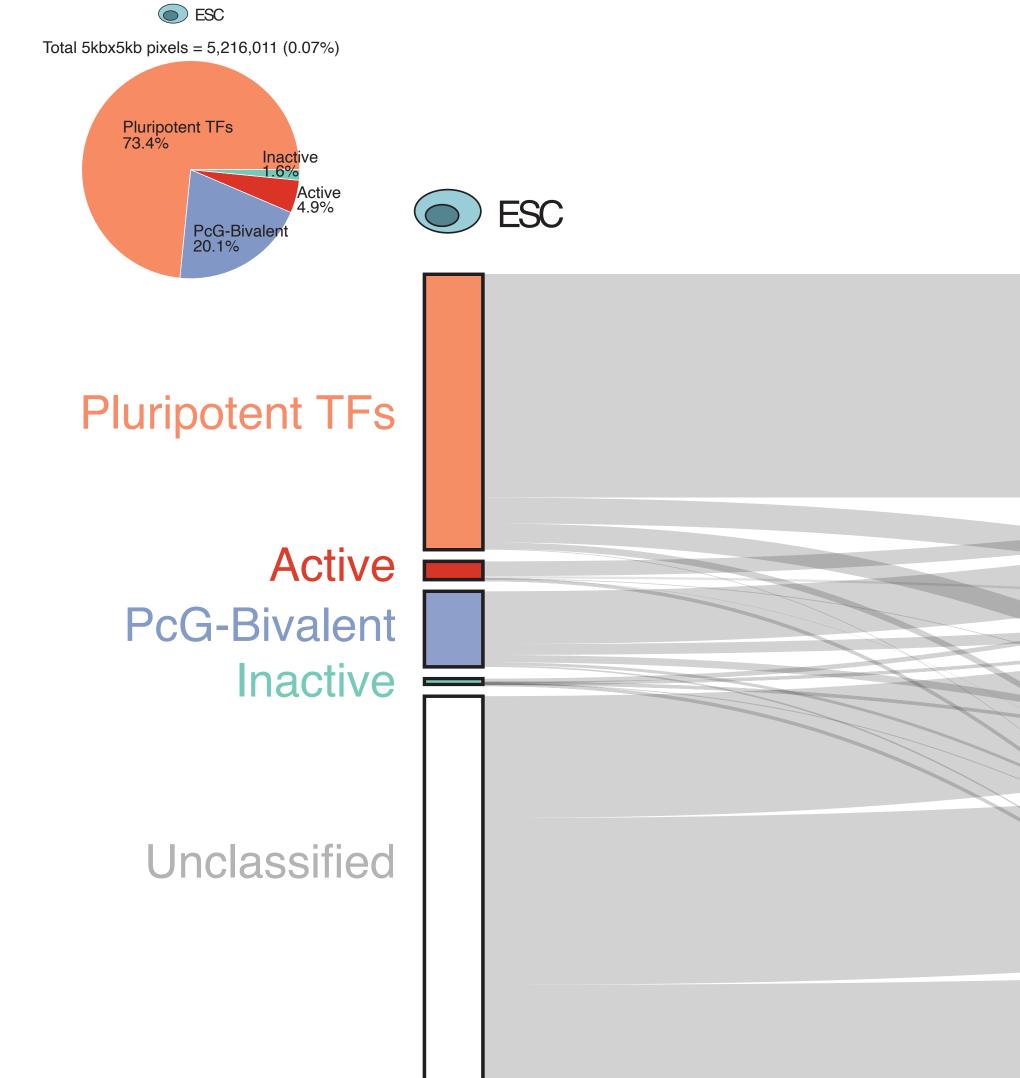




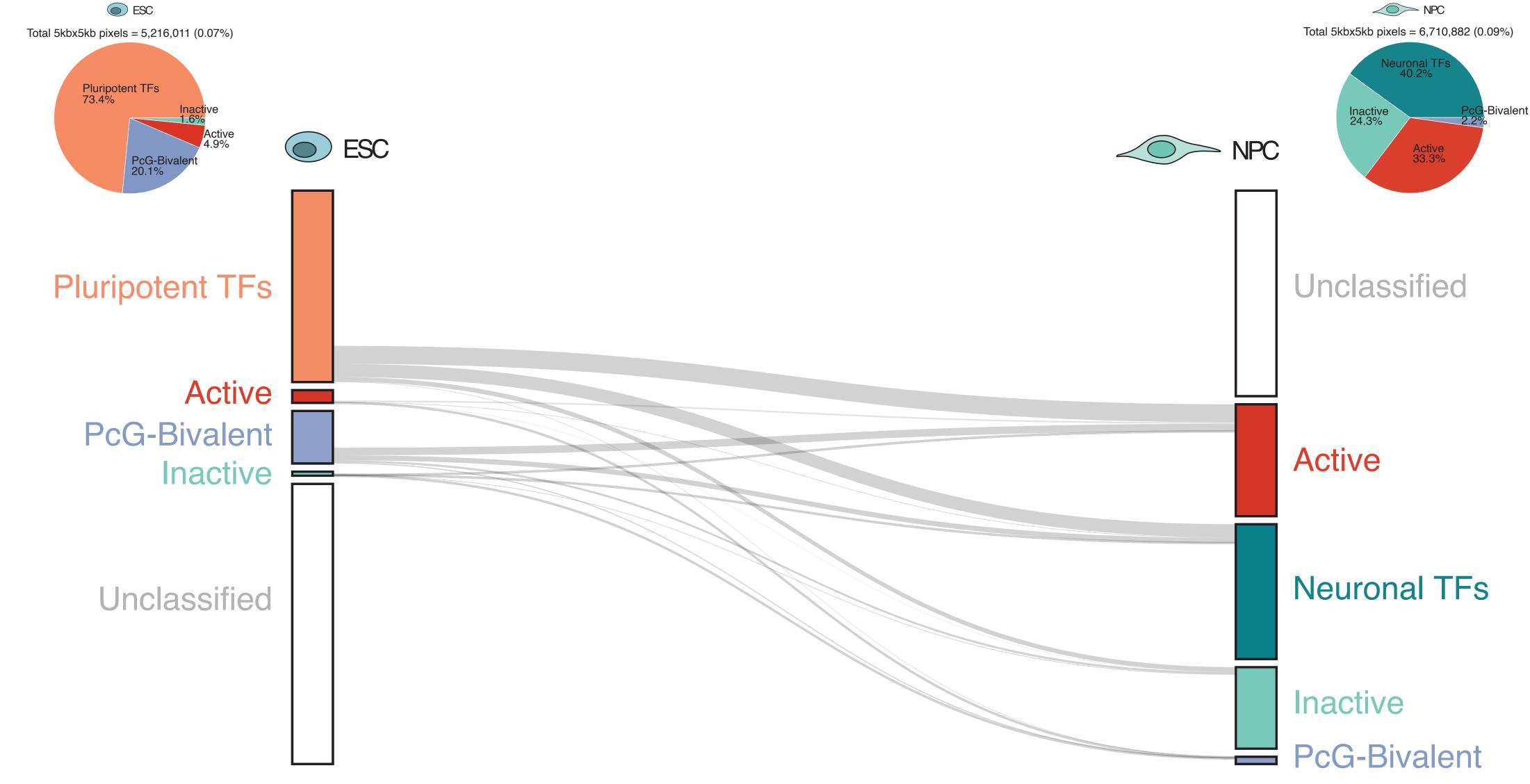
## Total 5kbx5kb pixels = 6,710,882 (0.09%)



### Global 3D interactions rewiring during mouse development ( ESC Total 5kbx5kb pixels = 6,710,882 (0.09%) Total 5kbx5kb pixels = 5,216,011 (0.07%) leuronal Tl 40.2% Pluripotent TFs 73.4% Inactive 24.3% Bivalent Active ESC NPC Active 33.3% PcG-Biva 20.1% **Pluripotent TFs** Unclassified Active **PcG-Bivalent** Active Inactive Neuronal TFs Unclassified Inactive **PcG-Bivalent**

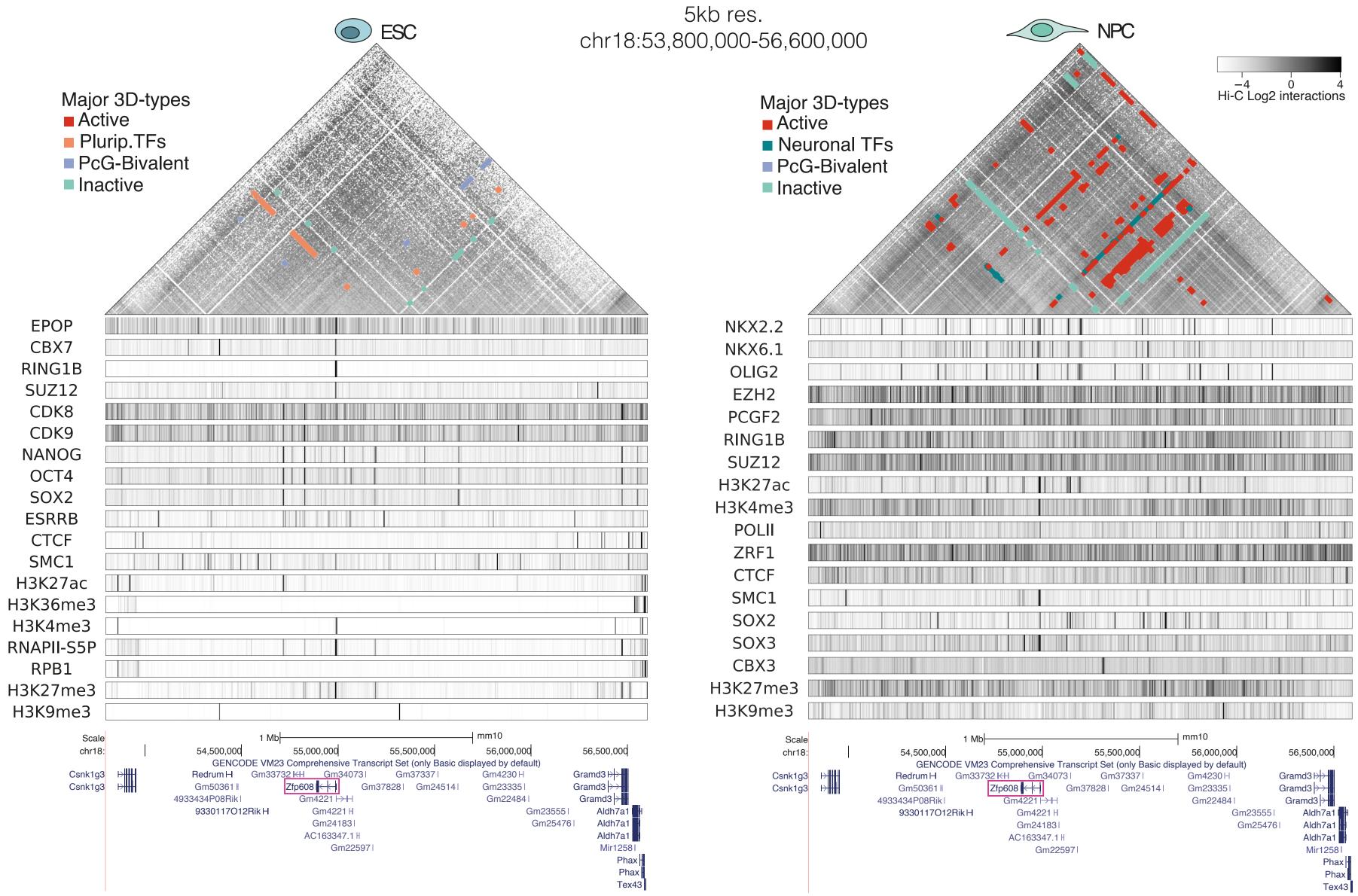


# Global 3D interactions rewiring during mouse development

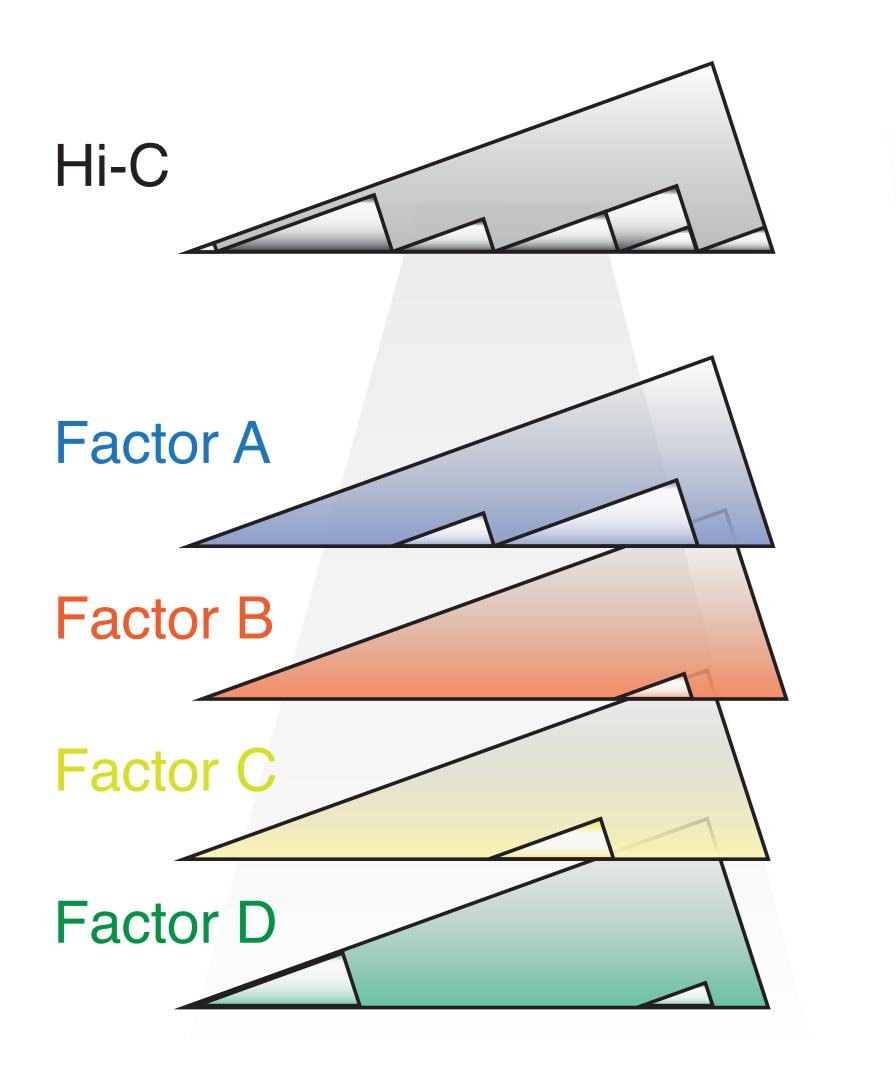


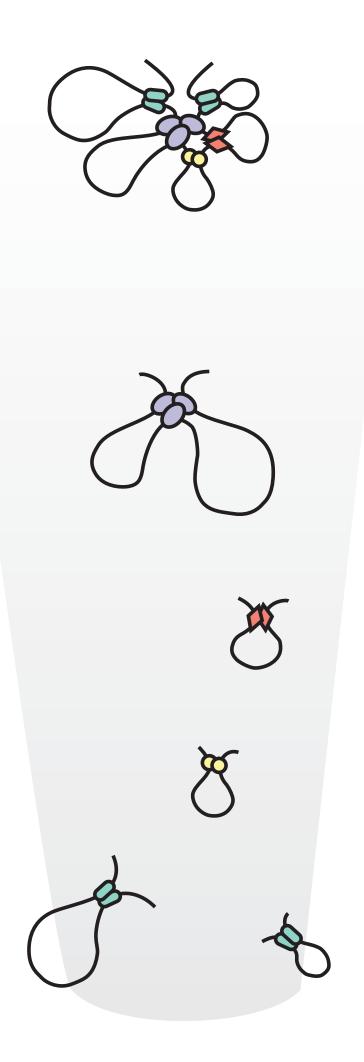
t

## 3D interactions rewiring at Zfp608 locus during mouse neural development



## Take home message...





### http://marciuslab.org http://3DGenomes.org



Ronan Duchesne Irene Farabella Alicia Hernández lana Kim François Le Dily lago Maceda Maria Marti-Marimon Francesca Mugianesi Meritxell Novillo Aleksandra Sparavier Leo Zuber



### In collaboration with the Di Croce Lab @CRG



















David Castillo Marco Di Stefano Juan A. Rodriguez

.: Our current sponsors :.

🔇 Obra Social "la Caixa"





**National Human Genome Research Institute** 

.: Conflict of Interest Statement :.

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





