Discovering structural units of chromosomal organization with matrix factorization and graph regularization

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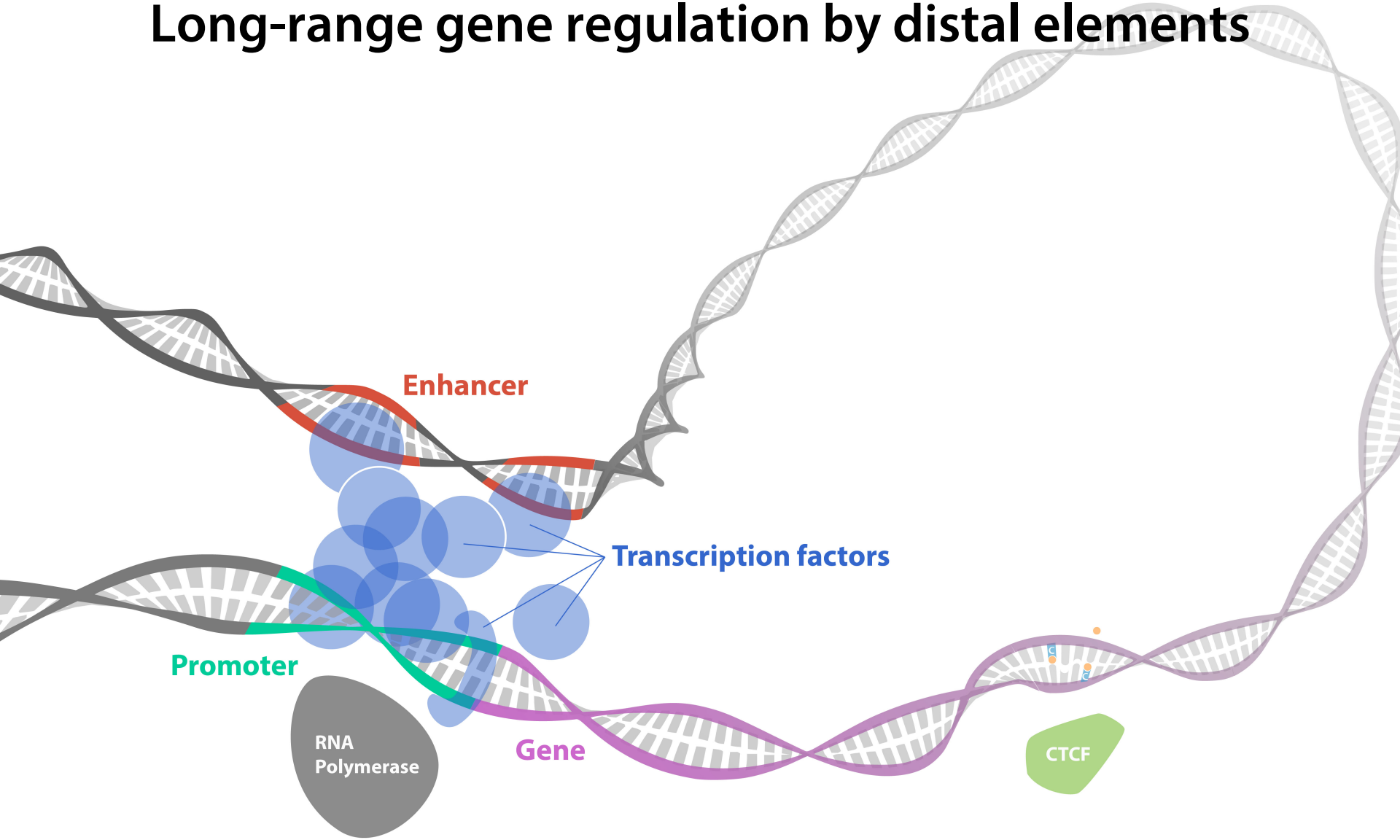
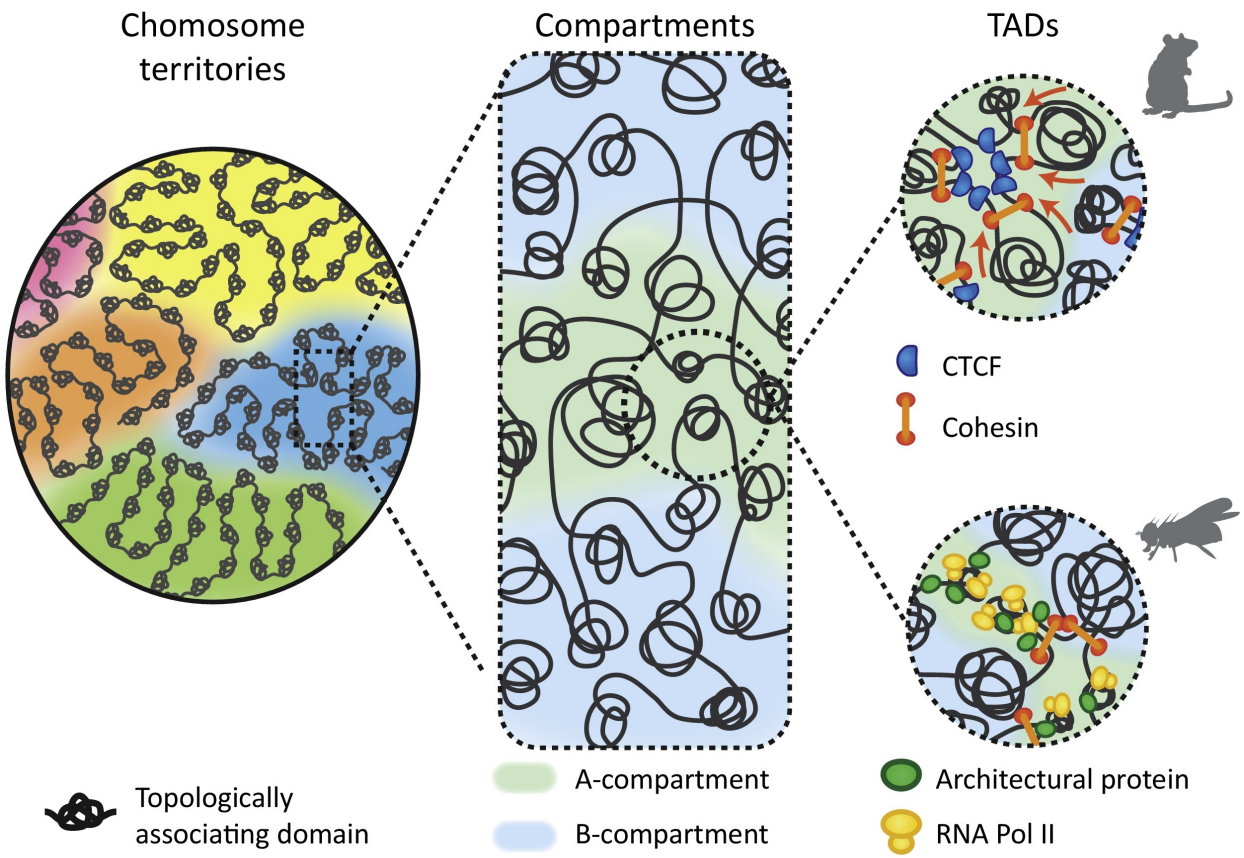
Long-range gene regulation by distal elements



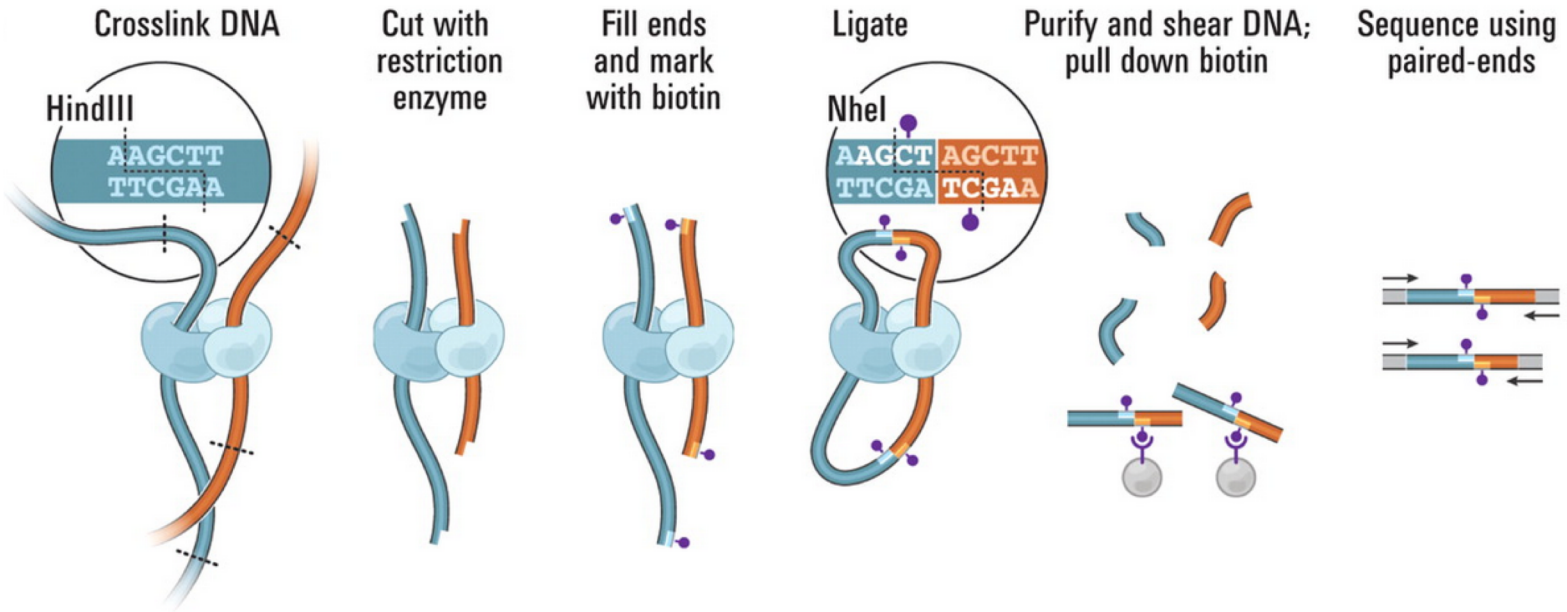
Adapted from illustration by Kelvin Ma

Genome is organized into higher-order domains at multiple scales



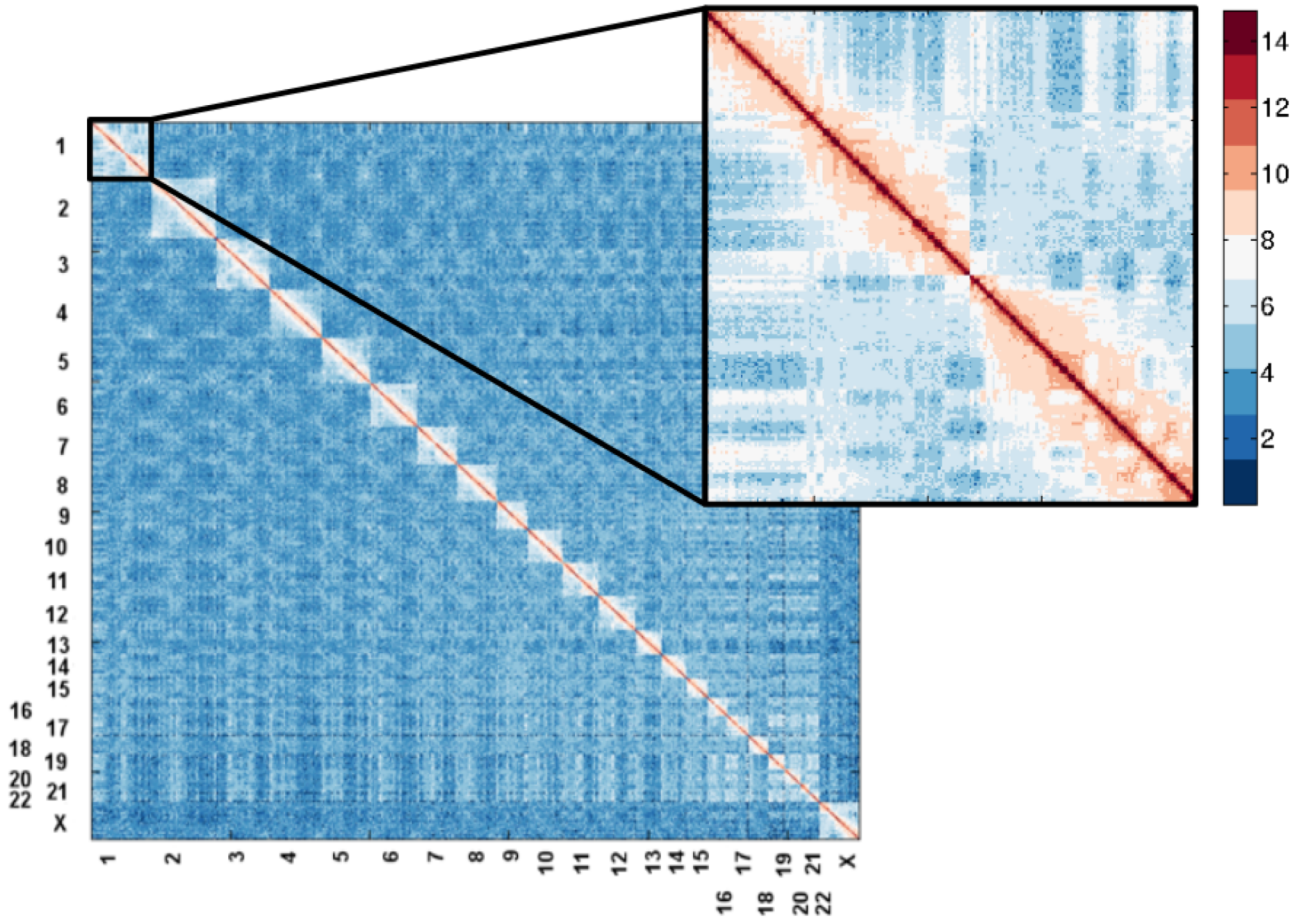
Hug and Vaquerizas. Trends Genet. 2018

Hi-C enables study of 3D genome through pairwise interactions

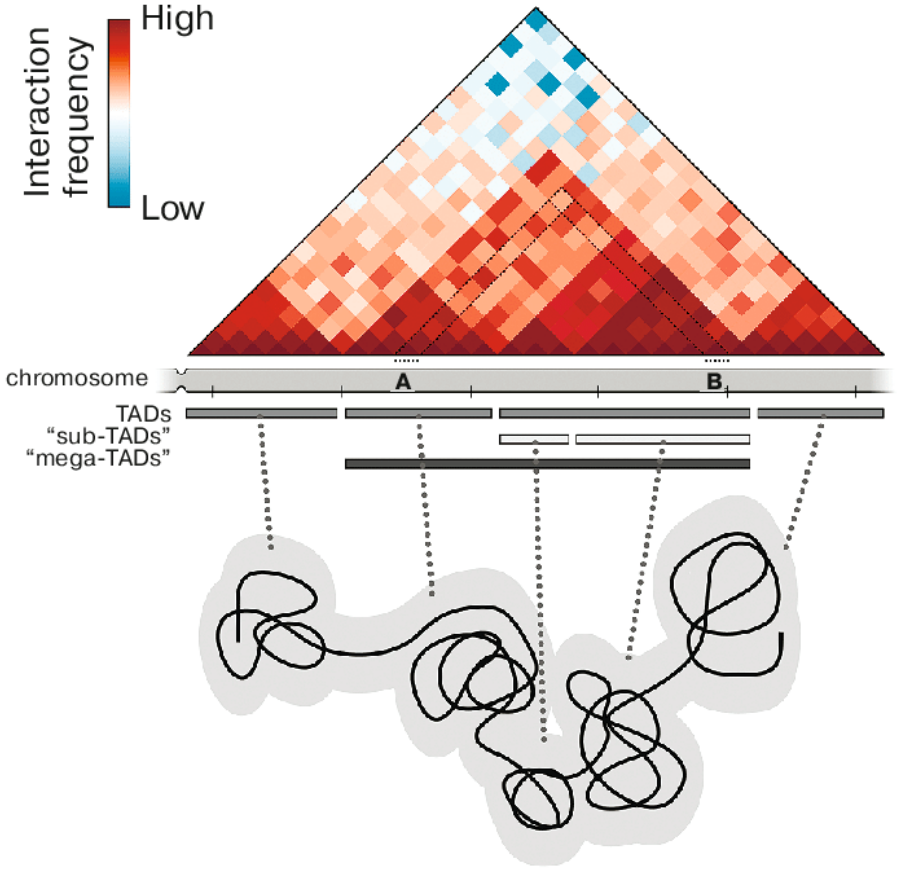


Lieberman-Aiden et al. Science. 2009

Hi-C enables study of 3D genome through pairwise interactions

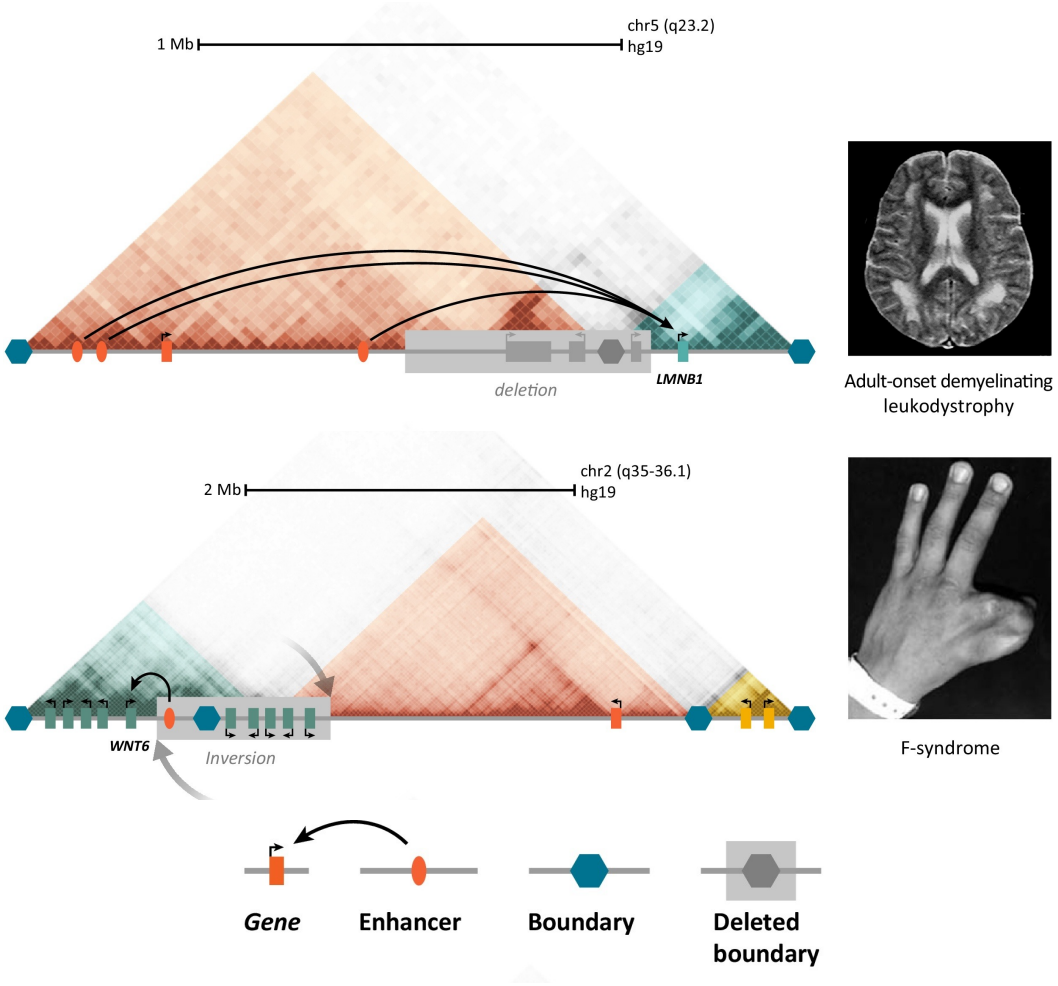


TADs are one of the dominant structural units observed in Hi-C matrices



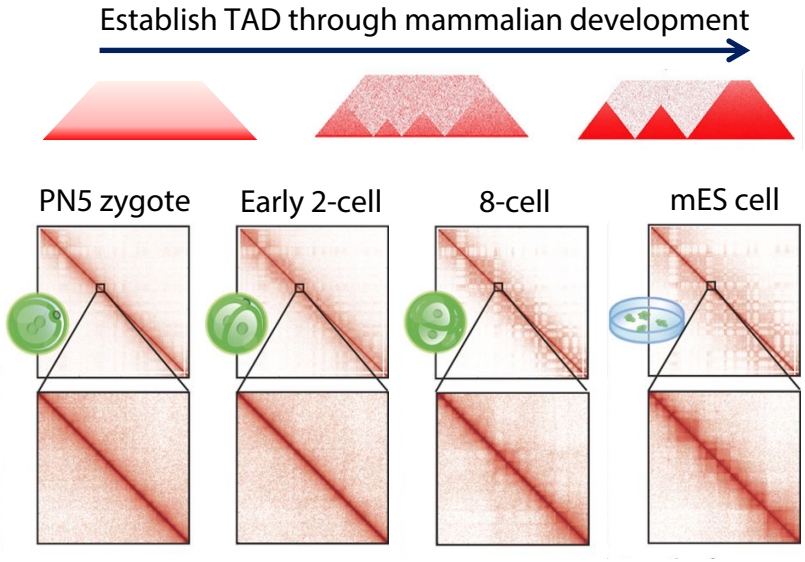
Razin and Gavrilov. Biochemistry (Moscow). 2018

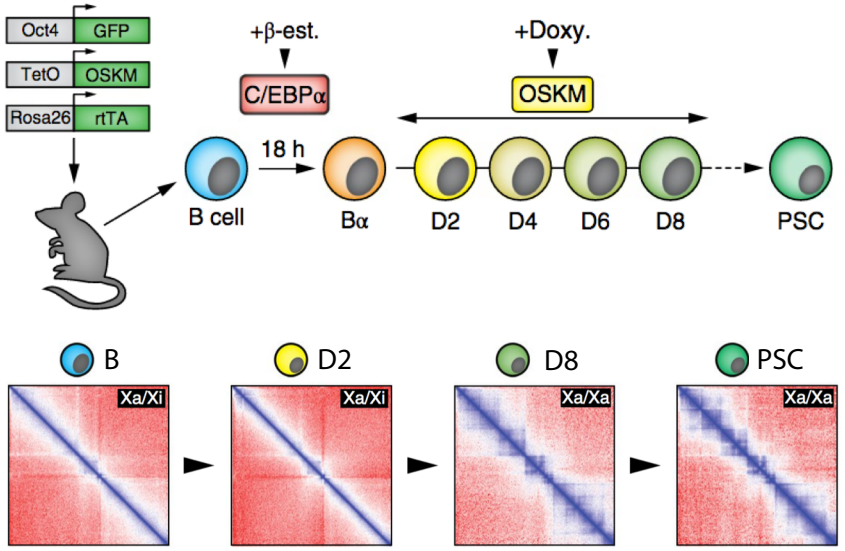
Breaking TADs: alternations in chromatin domains can result in disease



Lupiáñez et al. Trends Genet. 2016

3D genome organization dynamics during developmental processes





Key et al. Cell. 2017, Du et al. Nature. 2017, Stadhouders et al. Nat. Genet. 2018

Existing methods for finding topological units of chromosomes

Method	Algorithm	Objective
Directionality (Dixon et al. 2012)	HMM	Find a Gaussian mixture model, where a bin can take on one of three states: upstream biased, downstream biased, or not biased
Armatus (Filippova et al. 2014)	Dynamic programming	Find densest subgraph in a network where nodes = genomic regions, edge weights = interaction counts
HiCseg (Lévy-Leduc et al. 2014)	Dynamic programming	Find blocks/contours in Hi-C matrix whose count means form a maximum likelihood mixture model
Insulation Score (Crane et al. 2015)	Aggregation, ratio calculation	Find genomic regions with minimal insulation score, calculated as the mean of interaction counts centered on given region
TopDom (Shin et al. 2016)	Smooth curve fitting	Similar to insulation score
rGMAP (Yu et al. 2017)	Gaussian mixture model	Find a two-component Gaussian mixture model to group interactions to intra-domain and inter-domain contacts
3DNetMod (Norton et al. 2018)	Louvain-like algorithm	Partition a network of genomic regions to maximize modularity

Studies have shown existing methods' sensitivity to low depth and sparsity

nature methods

Analysis | Published: 12 June 2017

Comparison of computational methods for Hi-C data analysis

Mattia Forcato, Chiara Nicoletti, Koustav Pal, Carmen Maria Livi, Francesco Ferrari & Silvio Bicciato

Nature Methods **14**, 679–685 (2017) | Download Citation

Nucleic Acids Research

A critical assessment of topologically associating domain prediction tools

Rola Dali, Mathieu Blanchette

Nucleic Acids Research, Volume 45, Issue 6, 7 April 2017, Pages 2994–3005,
https://doi.org/10.1093/nar/gkx145
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Genome Biology

Research | Open Access

Comparison of computational methods for the identification of topologically associating domains

Marie Zufferey †, Daniele Tavernari †, Elisa Oricchio and Giovanni Ciriello

†Contributed equally

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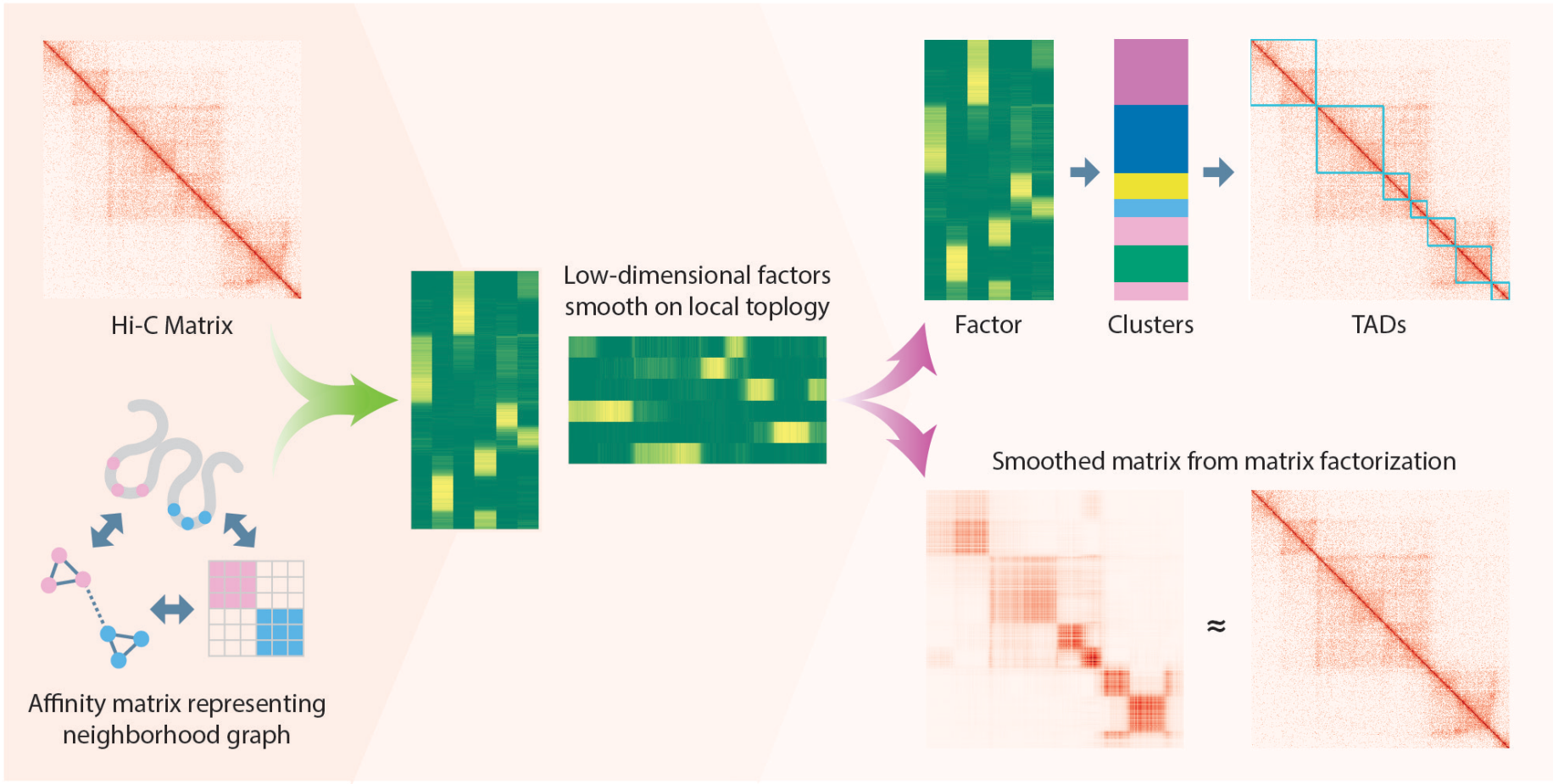
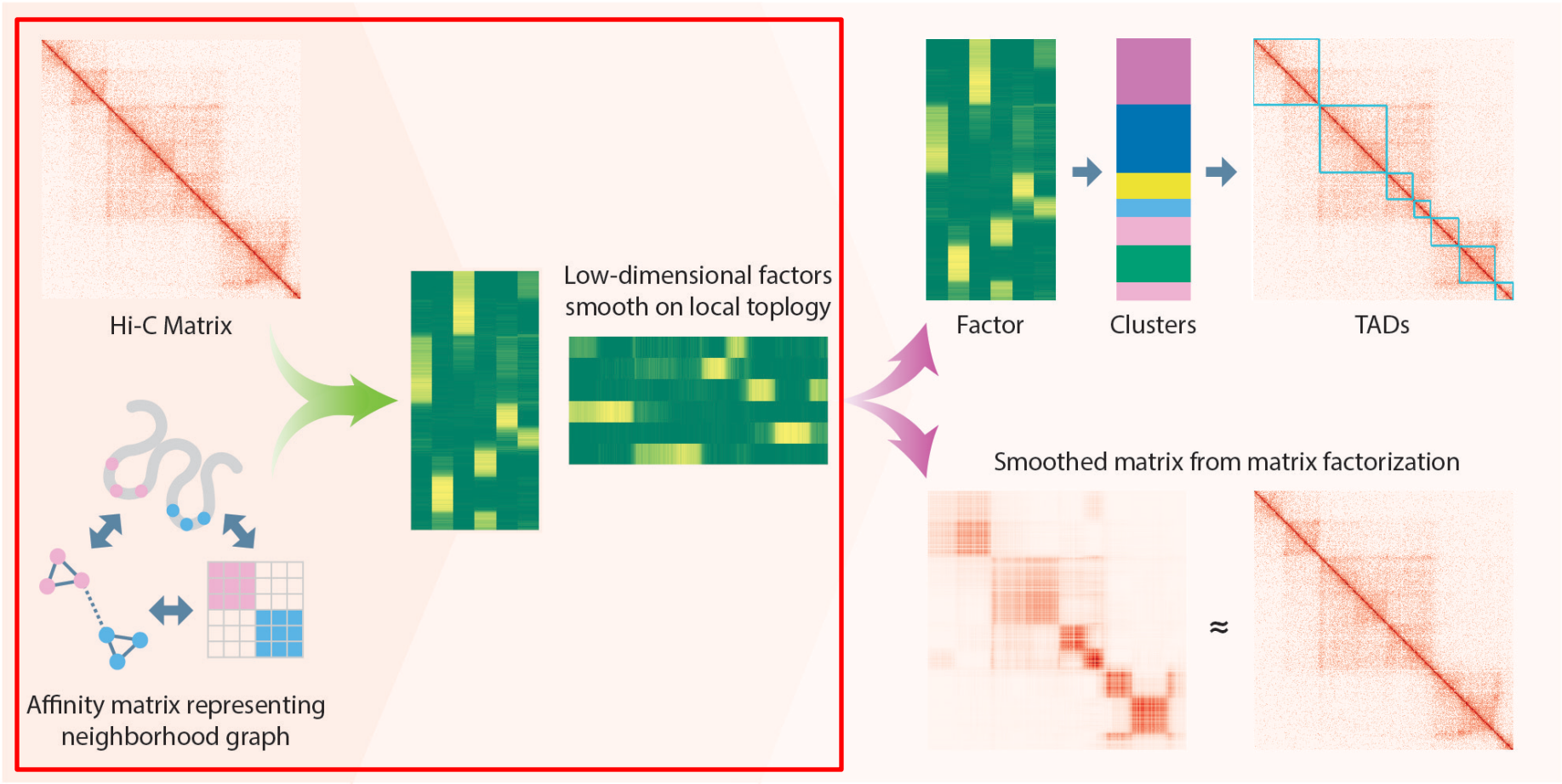
GRiNCH discovers topological units of chromosomes from Hi-C data

- Non-negative factorization (NMF)
- Graph regularization
- Chain-constrained k-medoids clustering

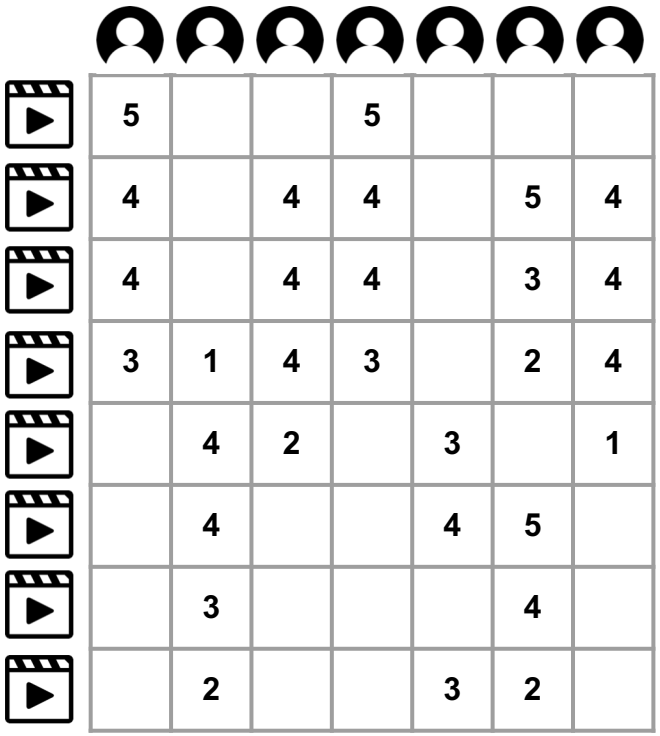
GRiNCH: Graph Regularized NMF and Clustering for Hi-C



GRiNCH: Graph Regularized NMF and Clustering for Hi-C



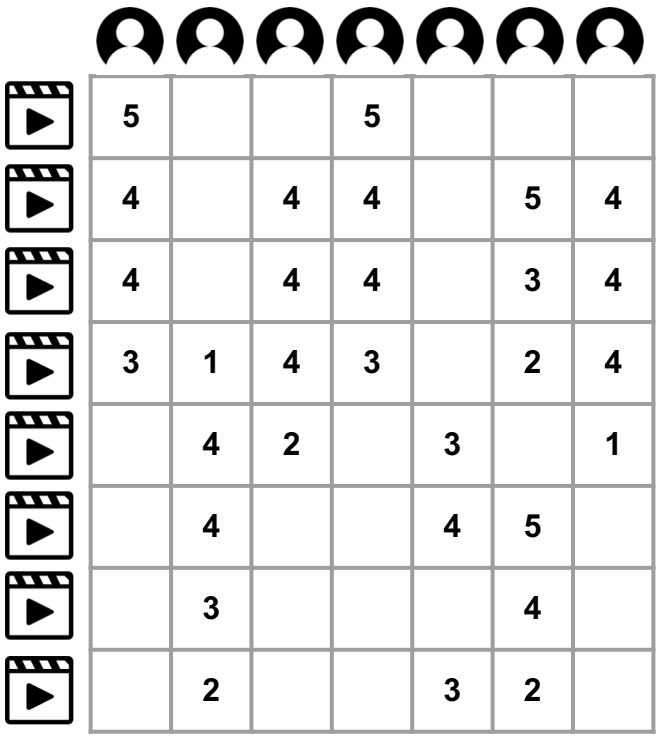
Non-negative matrix factorization (NMF) reduces dimensions of data



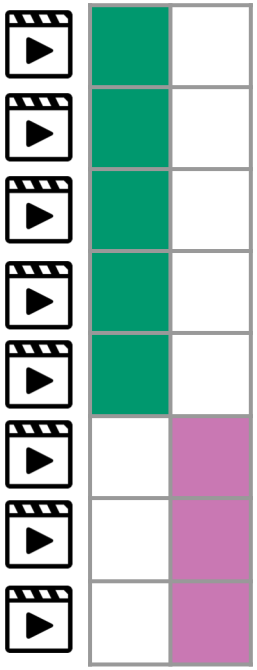
5			5			
4		4	4		5	4
4		4	4		3	4
3	1	4	3		2	4
	4	2		3		1
	4			4	5	
	3				4	
	2			3	2	

$$X = \mathbb{R}^{n \times m}$$

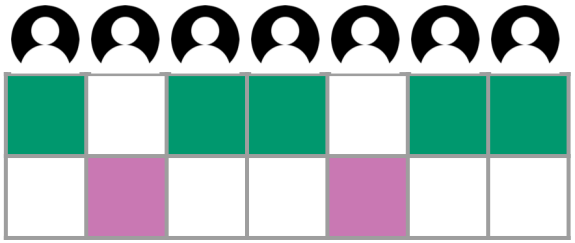
Non-negative matrix factorization (NMF) reduces dimensions of data



$X = \mathbb{R}^{n \times m}$



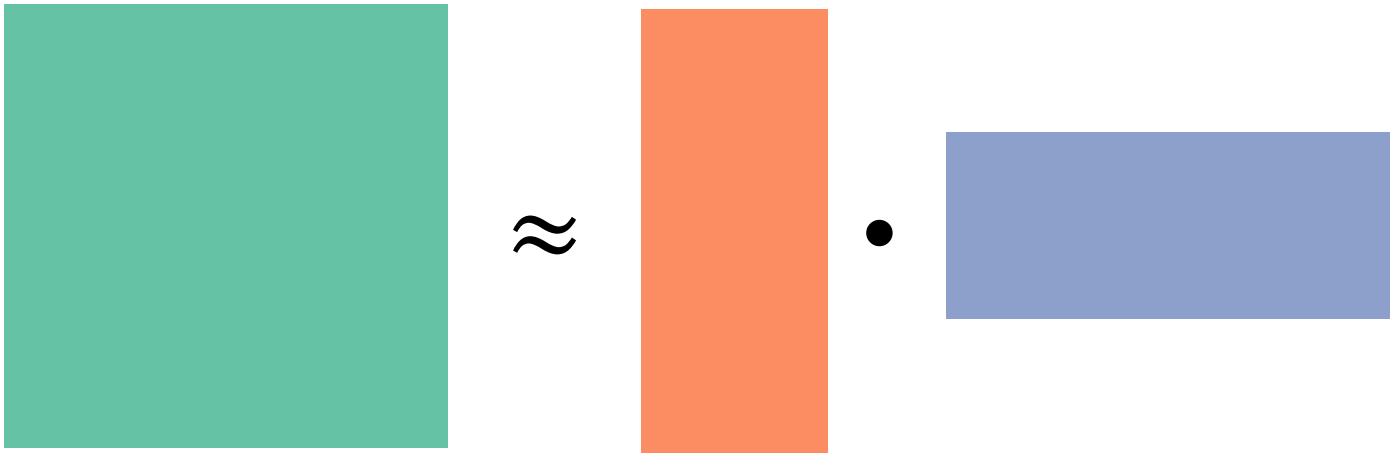
$U = \mathbb{R}^{n \times k}$



$V^T = \mathbb{R}^{k \times m}$

$k << n, m$

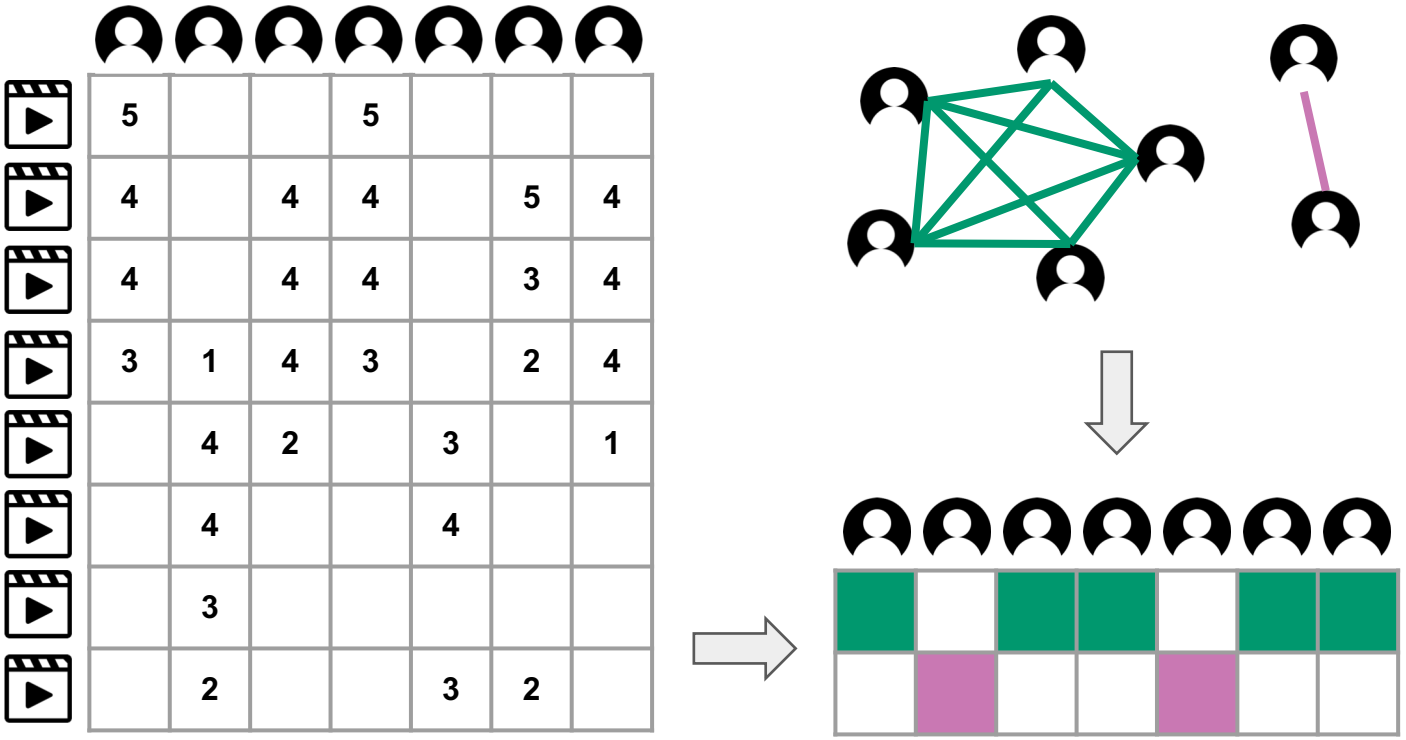
Non-negative matrix factorization (NMF) reduces dimensions of data



Minimize $\| X - UV^T \|^2$

Lee and Seung Adv. Neur. In. 2001

Graph regularization incorporates prior knowledge in network form



Graph regularization incorporates prior knowledge in network form

Minimize $\left\| \mathrm{X} - \mathrm{UV}^{\mathrm{T}} \right\|^2$

Lee and Seung Adv. Neur. In. 2001

Graph regularization incorporates prior knowledge in network form

$$\text{Minimize } \left\| X - UV^T \right\|^2 + \lambda \left(\text{Tr}\left(V^T L V \right) + \text{Tr}\left(U^T L U \right) \right)$$

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Graph regularization incorporates prior knowledge in network form

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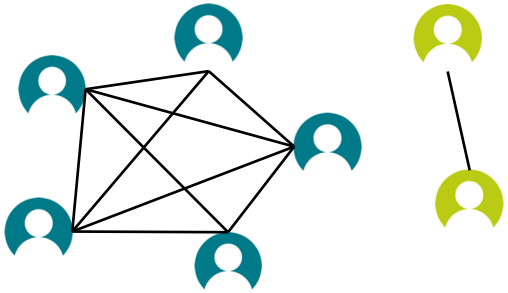
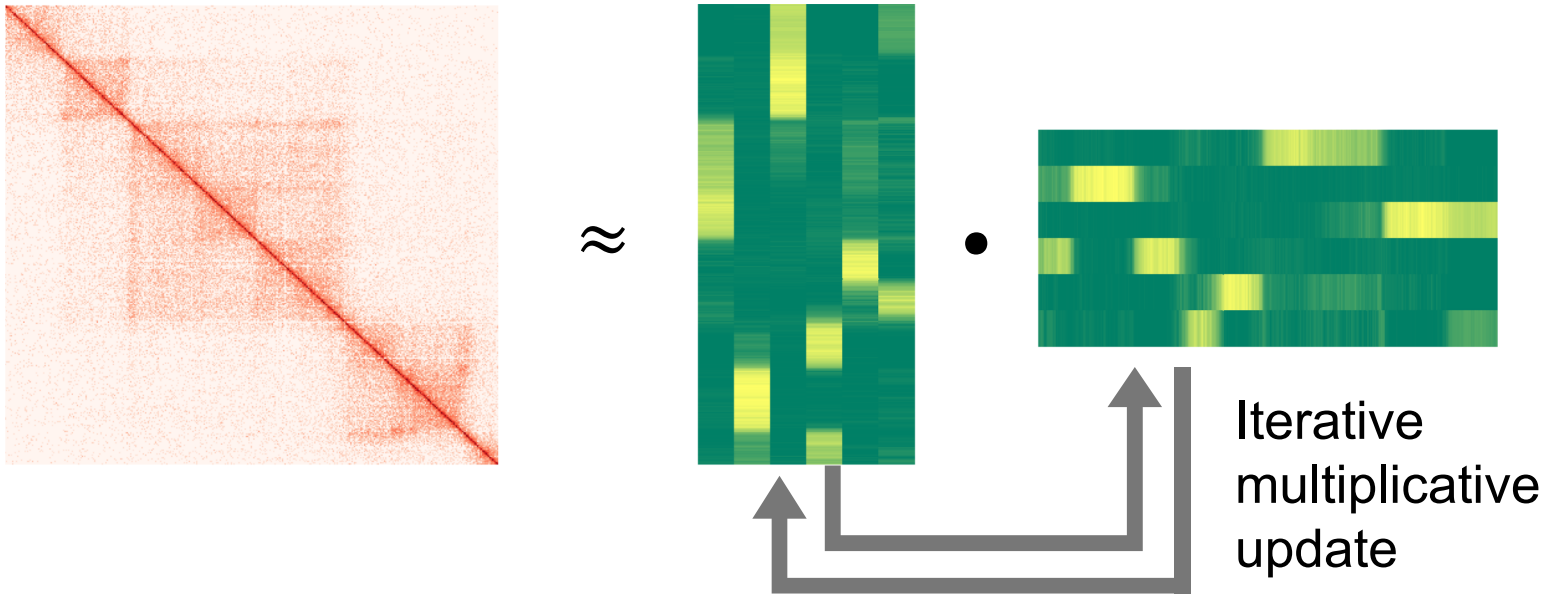


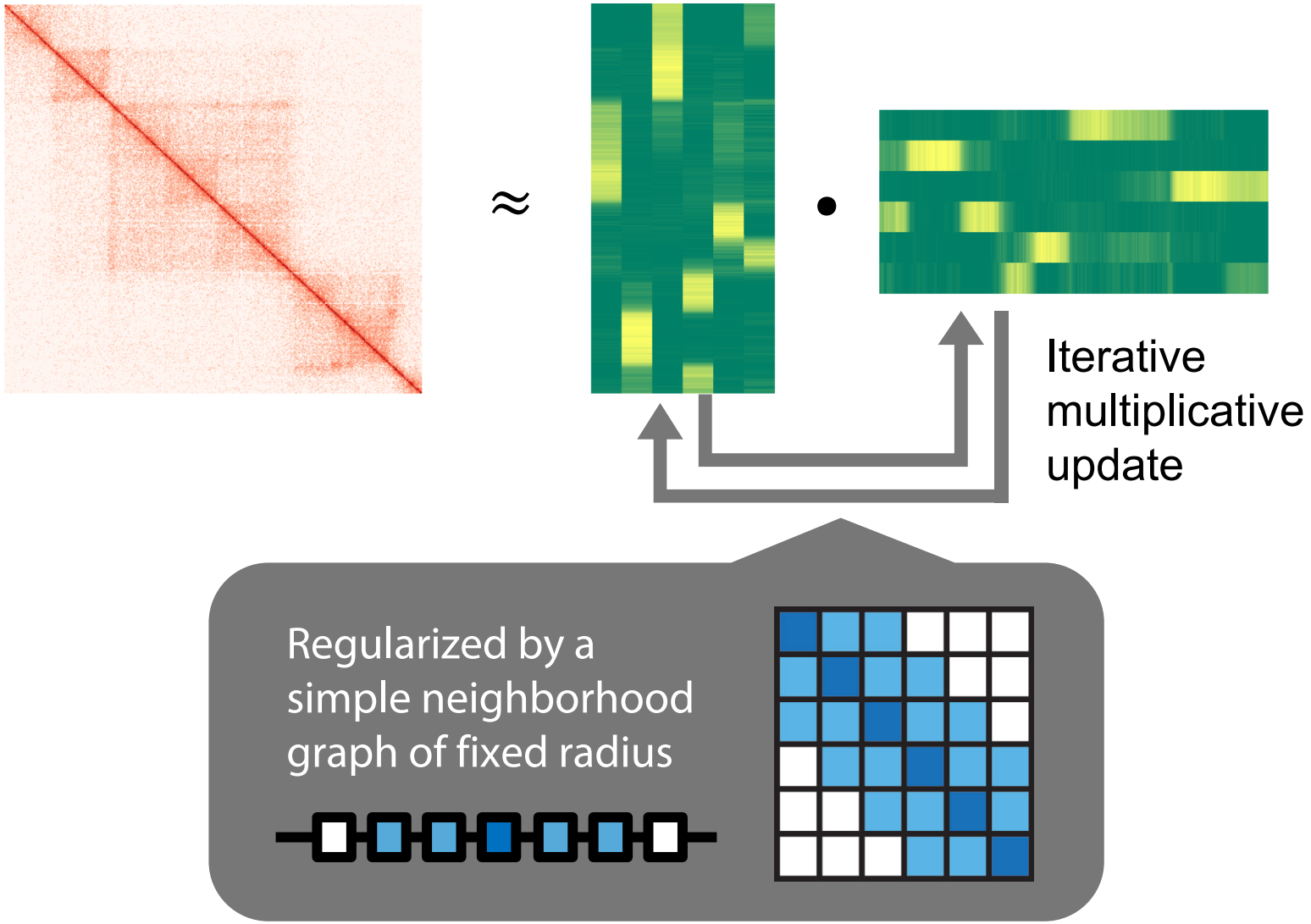
$$\begin{bmatrix} 3 & -1 & -1 & -1 & -1 & 0 & 0 \\ -1 & 4 & -1 & -1 & -1 & 0 & 0 \\ -1 & -1 & 3 & -1 & -1 & 0 & 0 \\ -1 & -1 & -1 & 4 & -1 & 0 & 0 \\ -1 & -1 & -1 & -1 & 4 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 1 & -1 \\ 0 & 0 & 0 & 0 & 0 & -1 & 1 \end{bmatrix}$$

Lee and Seung Adv. Neur. In. 2001

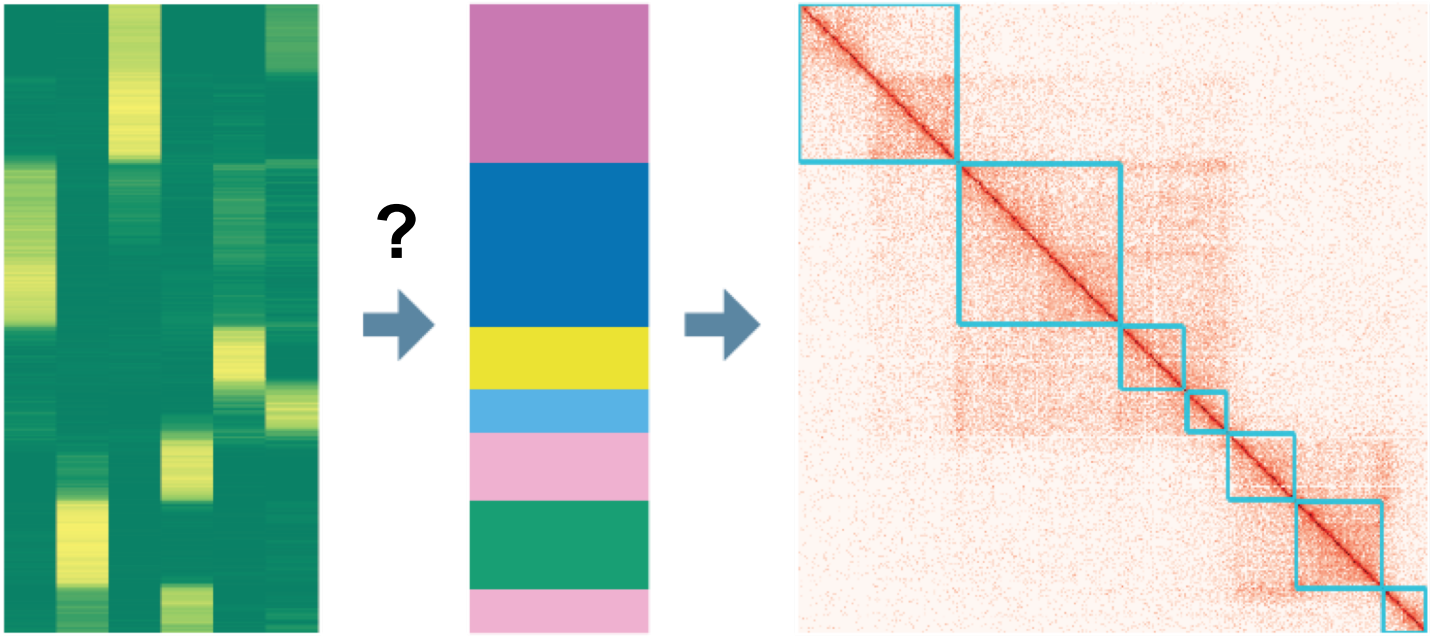
Graph regularized NMF on Hi-C data



Graph regularized NMF on Hi-C data



Lower-dimension factors to clusters



Chain-constrained k-medoids clustering

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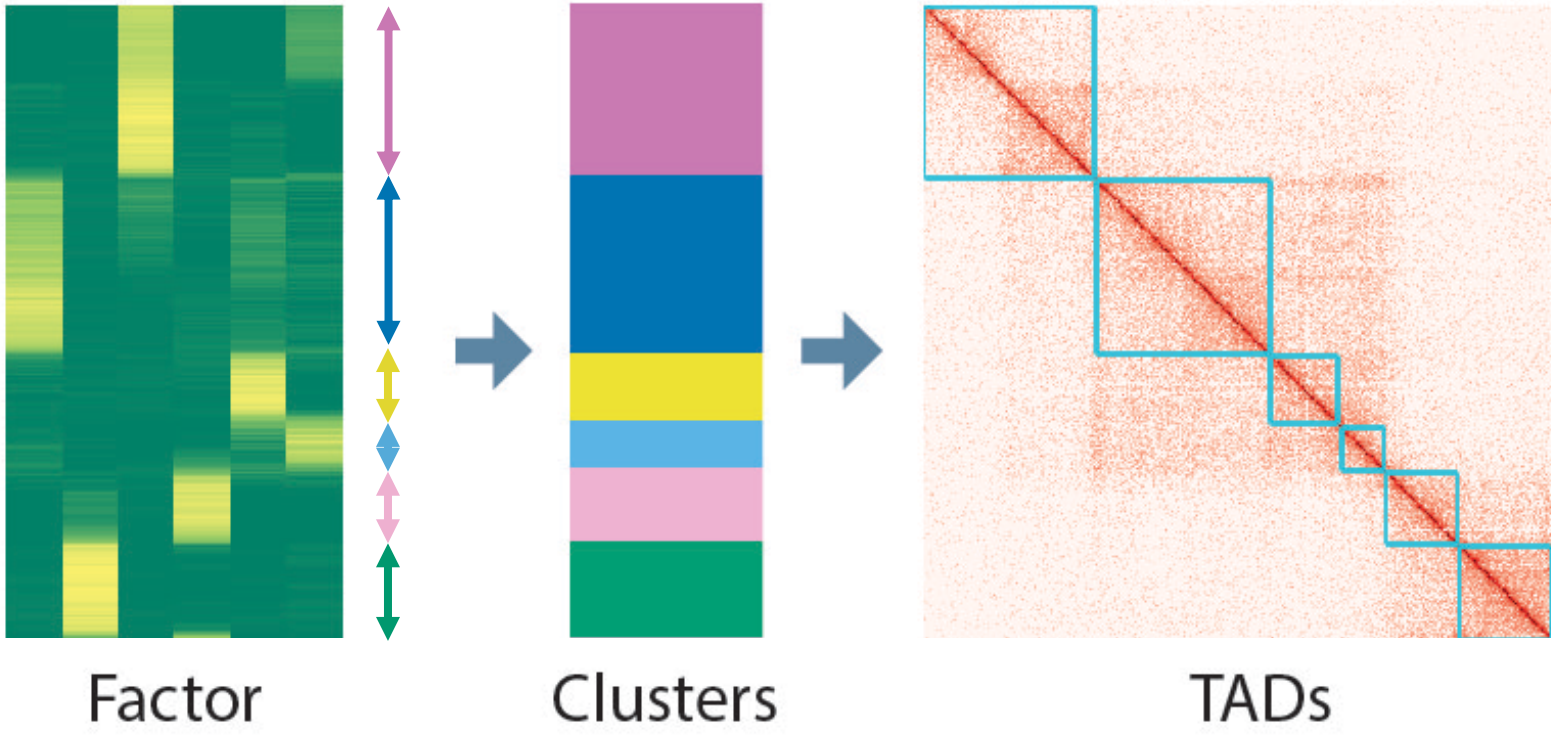
Chain-constrained k-medoids clustering

Chain-constrained k-medoids clustering

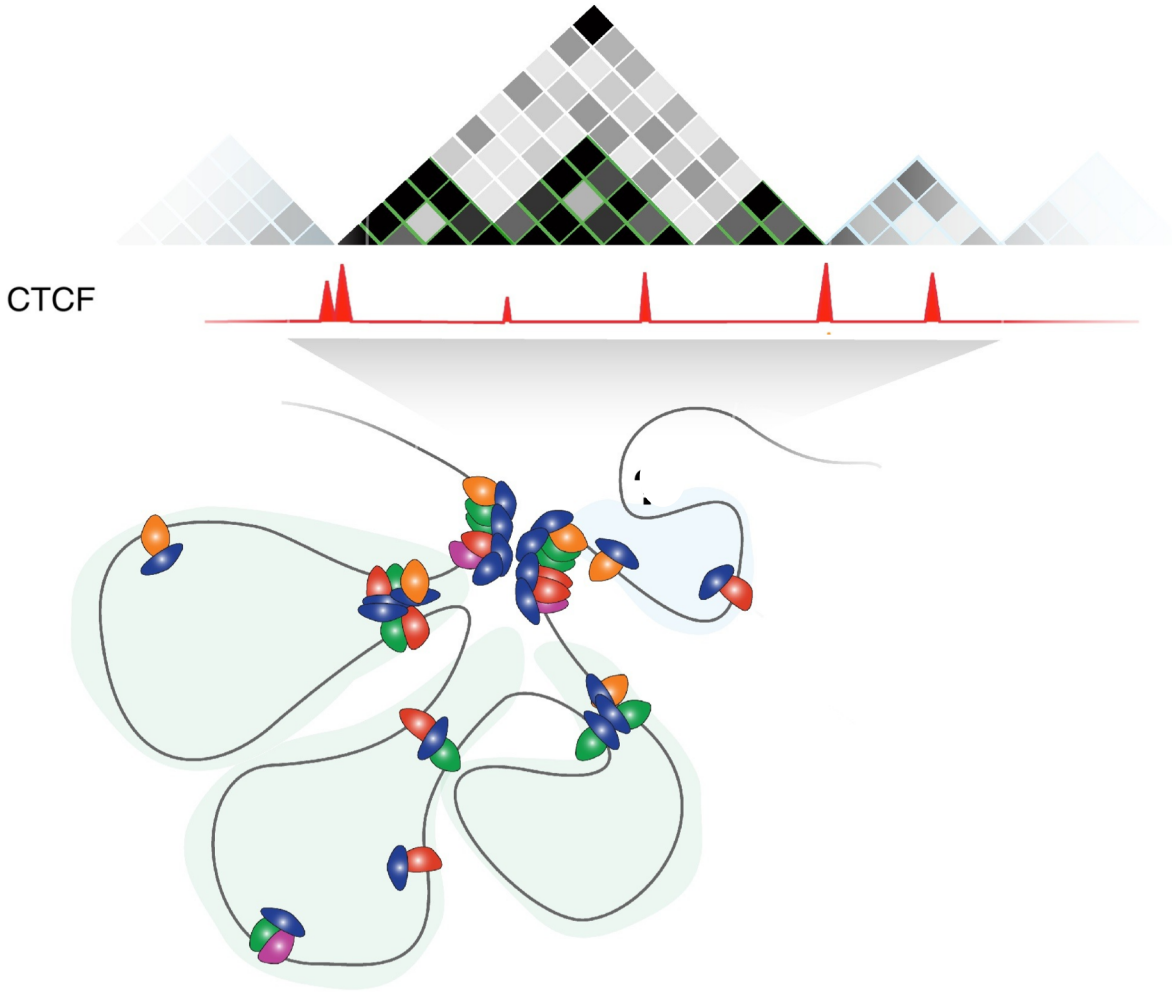
Chain-constrained k-medoids clustering on lower-dimensional factor



Evaluating effectiveness of GRiNCH

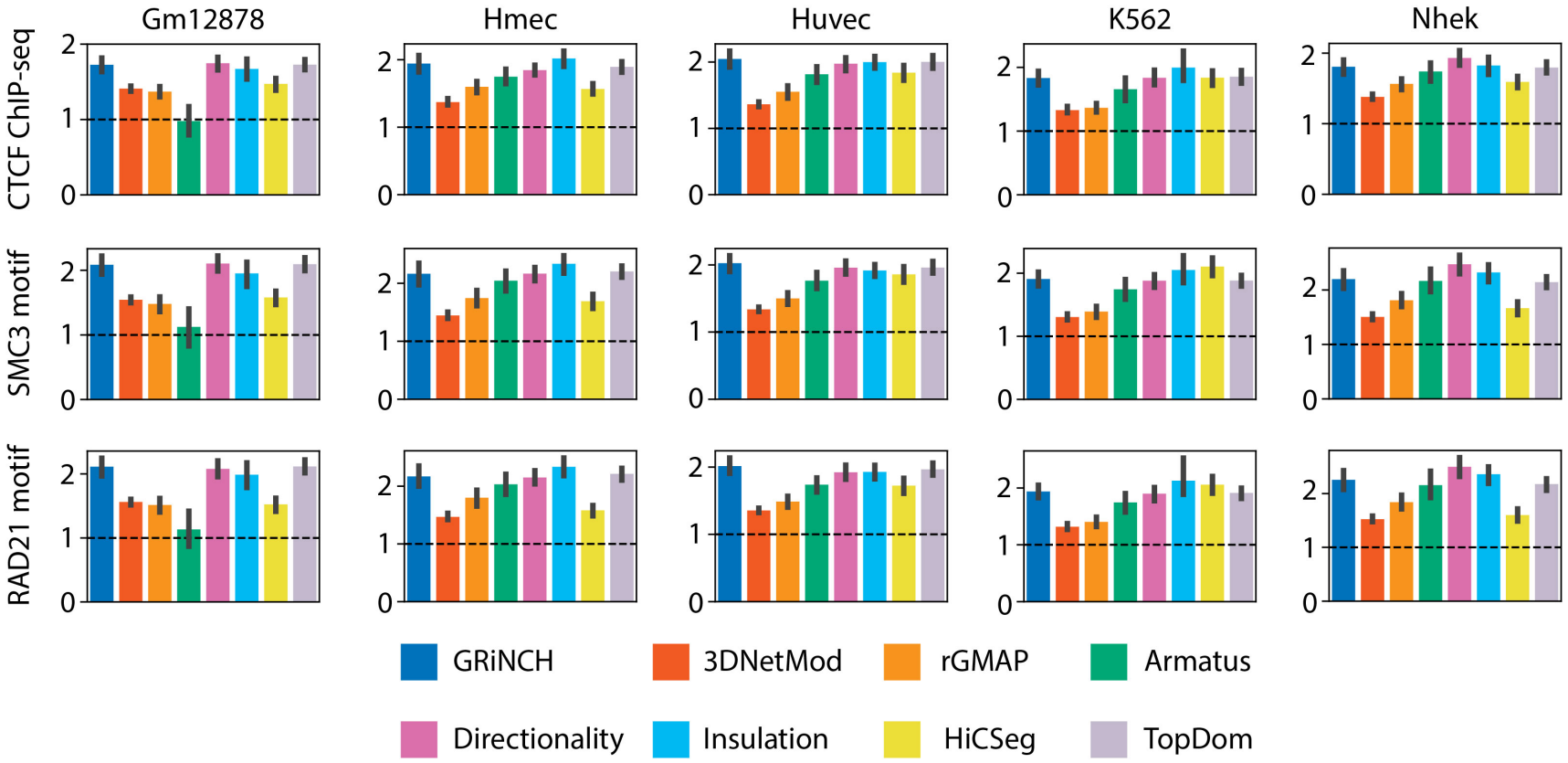
- CTCF and cohesion enrichment in TAD boundaries
- Stability of TADs to low-depth data
- Recovery of TADs and significant interactions from smoothed low-depth data

CTCF binding is associated with TAD boundaries

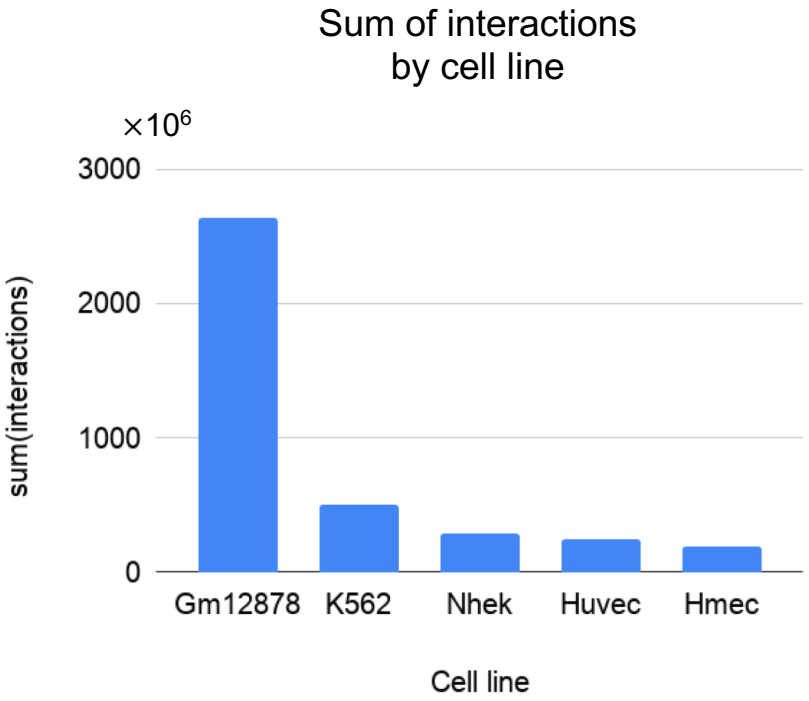


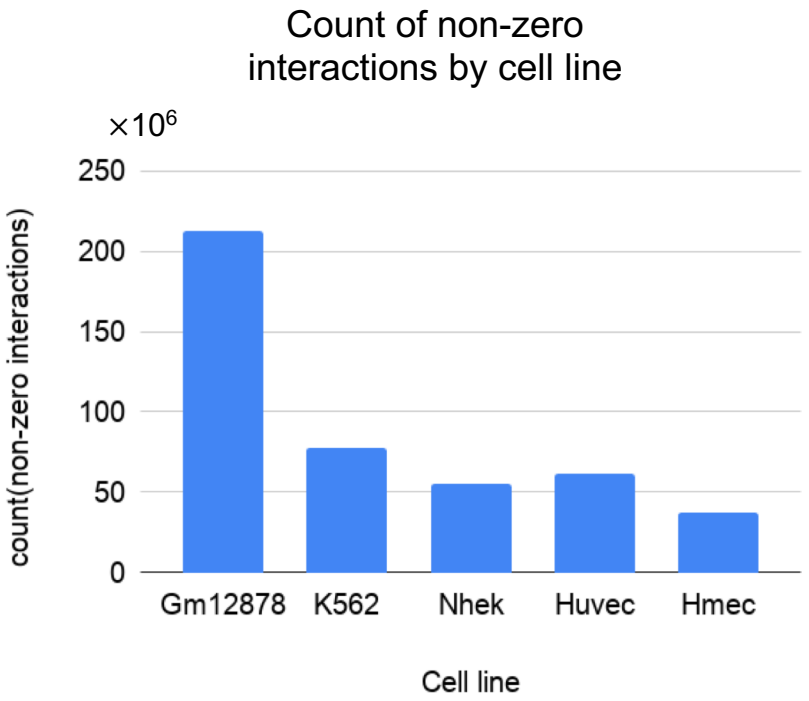
Ali et al. Curr. Opin. Genet. Dev. 2016

GRiNCH cluster boundaries are significantly enriched in CTCF and cohesin binding



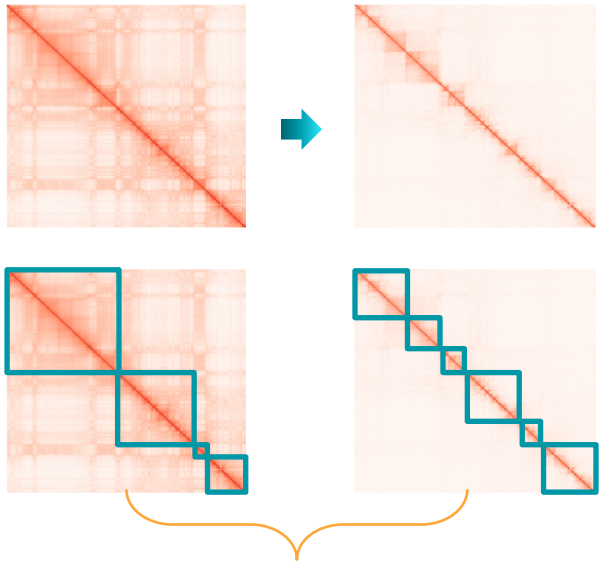
Many public high-resolution Hi-C datasets have low sequence depth



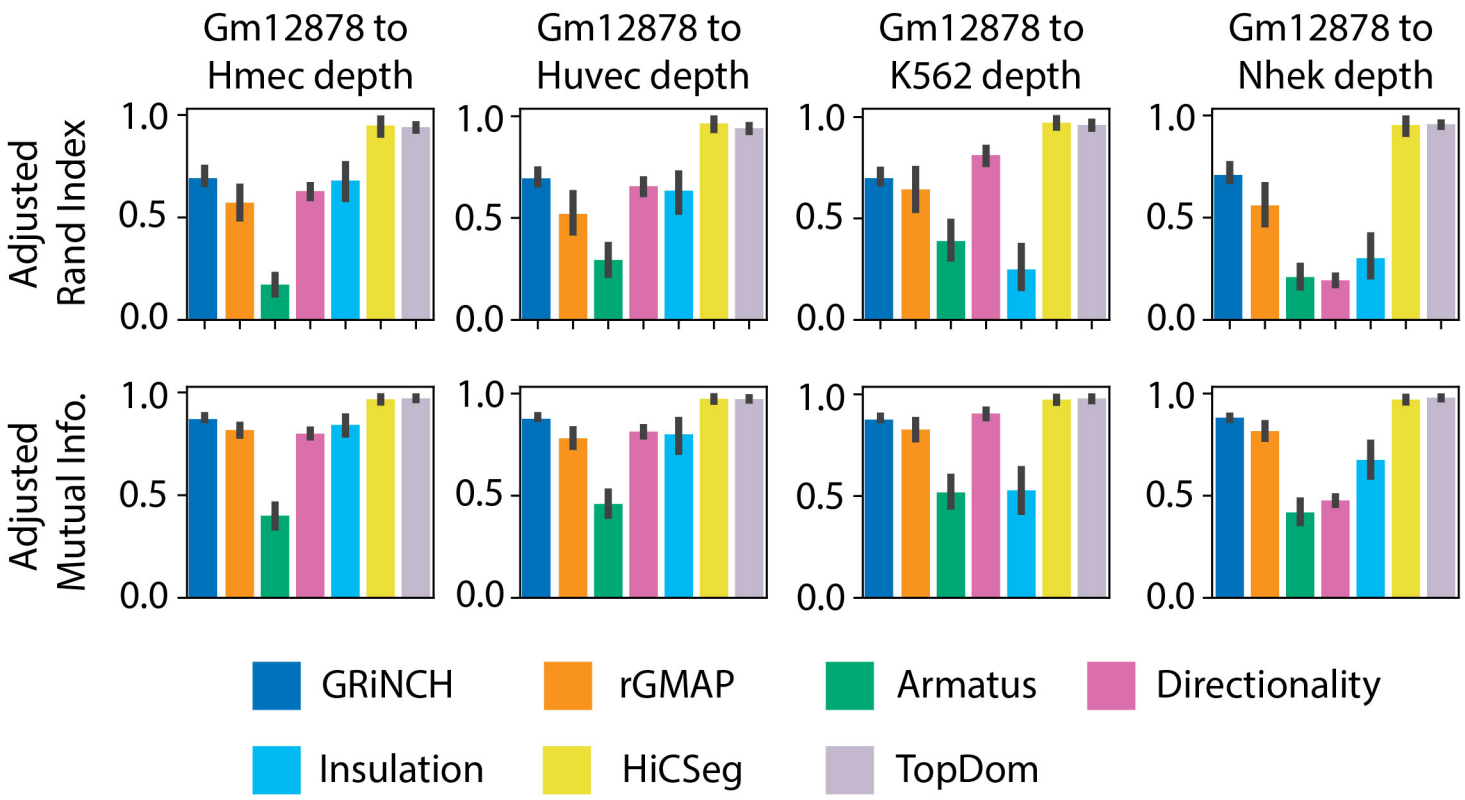


Evaluating stability to low depth data with downsampling and cluster similarity

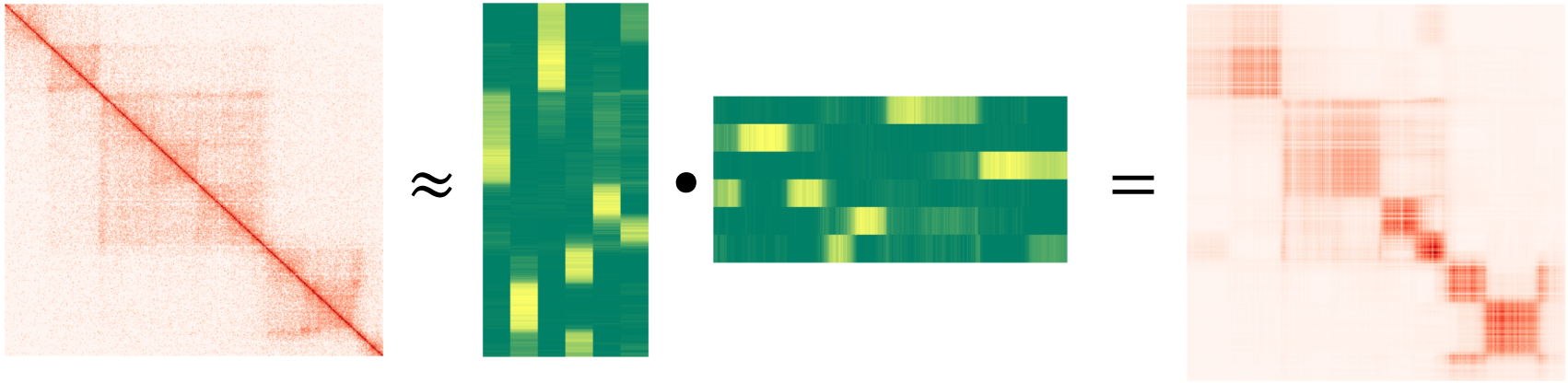
1. Downsample high-depth dataset to the depth of lower-depth dataset.
2. Find TADs in the original high-depth data and in the downsampled data.
3. Measure the similarity of TADs from high-depth vs low-depth data.



GRiNCH clusters are stable to low depth and sparsity

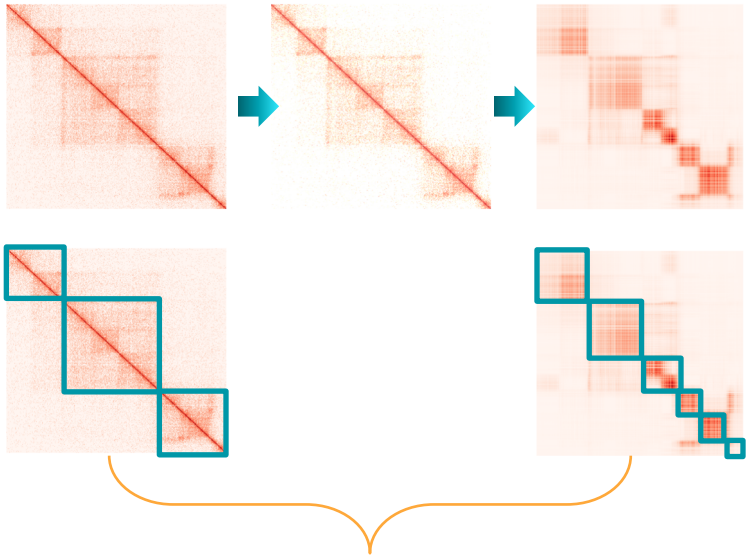


GRiNCH can smooth Hi-C matrix through matrix completion

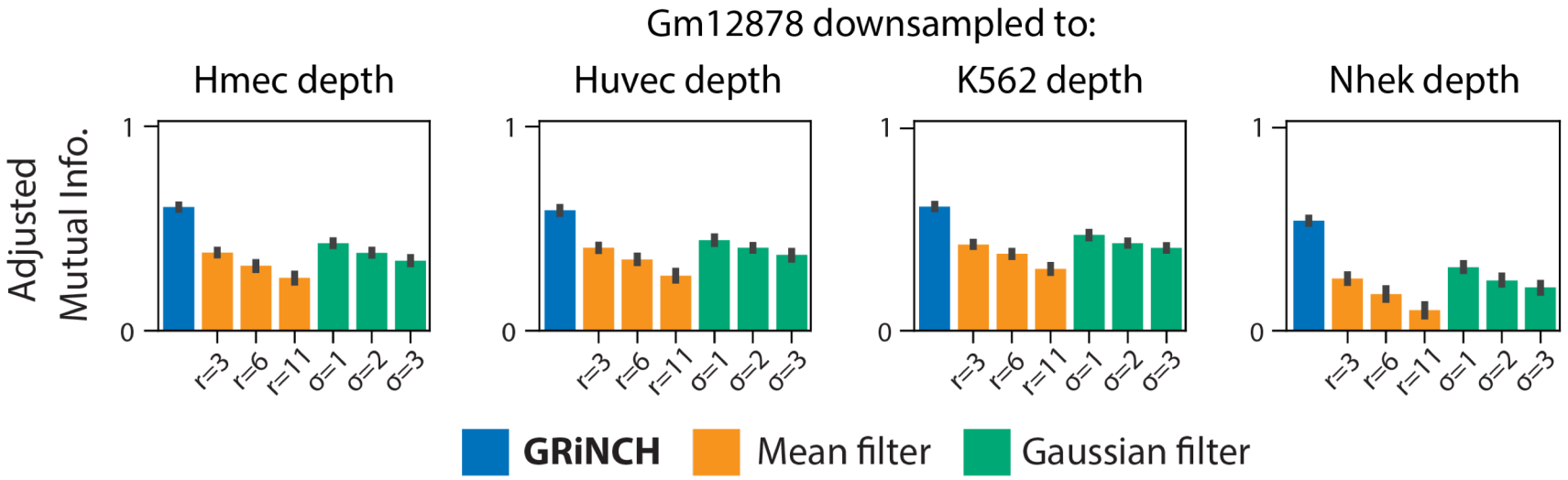


Evaluating structure recovery after smoothing using an independent TAD-calling method

1. Downsample high-depth datasets then smooth.
2. Find TADs using TopDom in the original and the smoothed data.
3. Measure the similarity of TADs from original vs smoothed data.



GRiNCH smoothing can help recover structure in low-depth Hi-C data

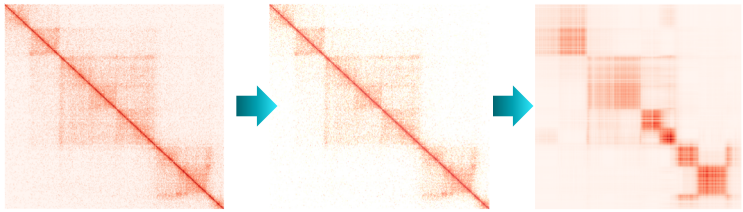


Evaluating recovery of significant interactions after smoothing

1. Downsample high-depth datasets then smooth.

2. Find significant interactions using FitHiC in the original and smoothed data.

3. Measure precision and recall

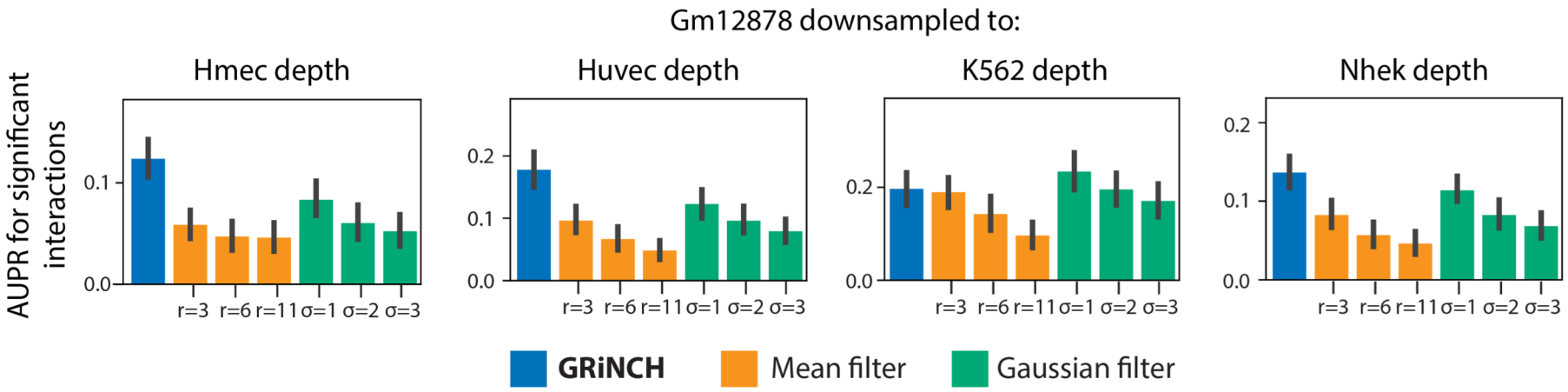


"True" significant interactions

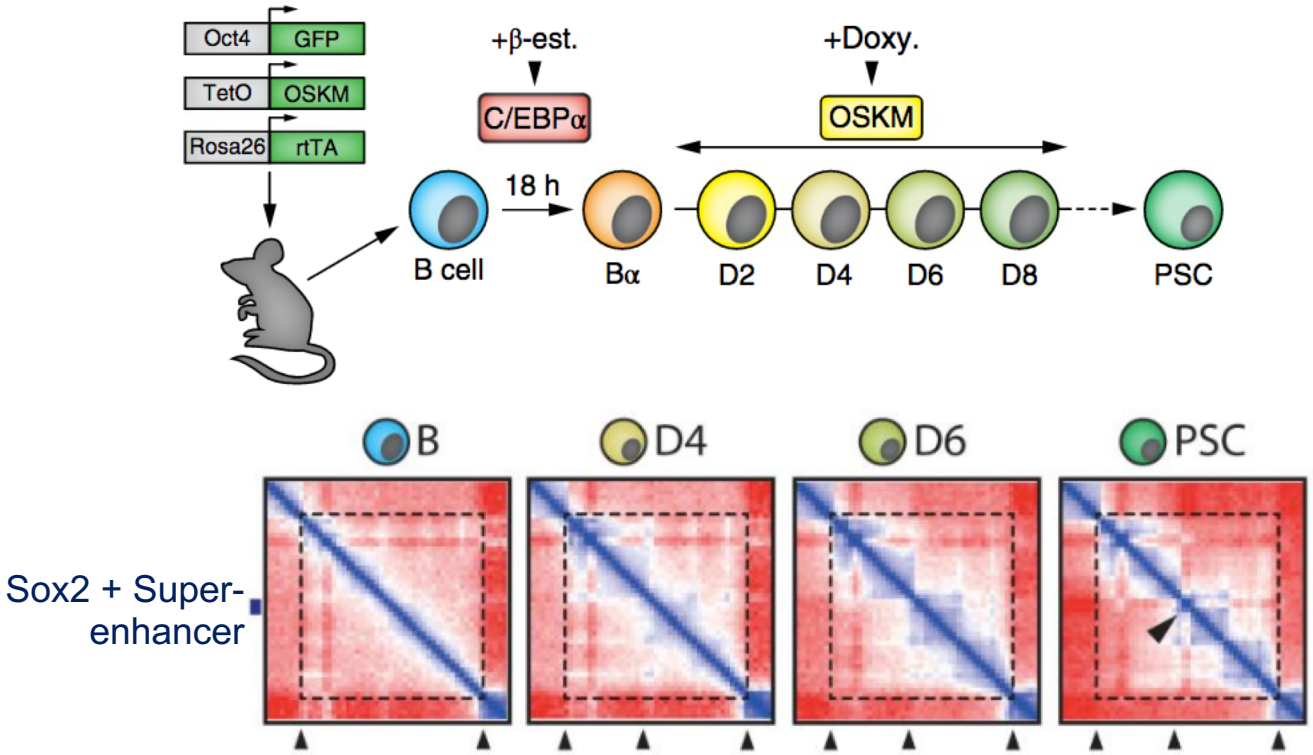
"Predicted" sig. interactions

Area under precision and recall curve = 0.3

GRiNCH smoothing can help recover significant interactions in low-depth Hi-C data

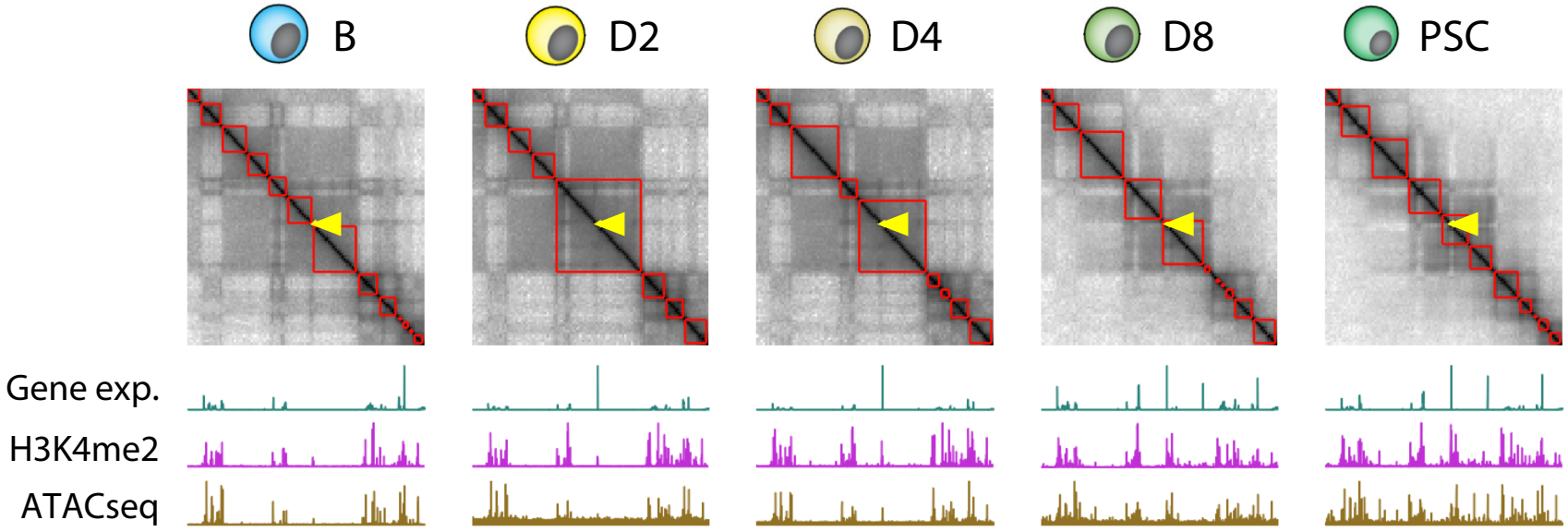


3D genome organization dynamics during cell reprogramming



Stadhouders et al. Nat. Genet. 2018

GRiNCH clusters align with epigenetic changes during reprogramming



Stadhouders et al. Nat. Genet. 2018

Conclusion

- GRiNCH is an NMF-based method with graph regularization to find structural units of the genome.
- GRiNCH finds clusters with significant boundary element enrichment.
- GRiNCH is stable to low-depth, sparse datasets.
- GRiNCH can smooth input Hi-C matrix.

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Poster E-53 in Session A