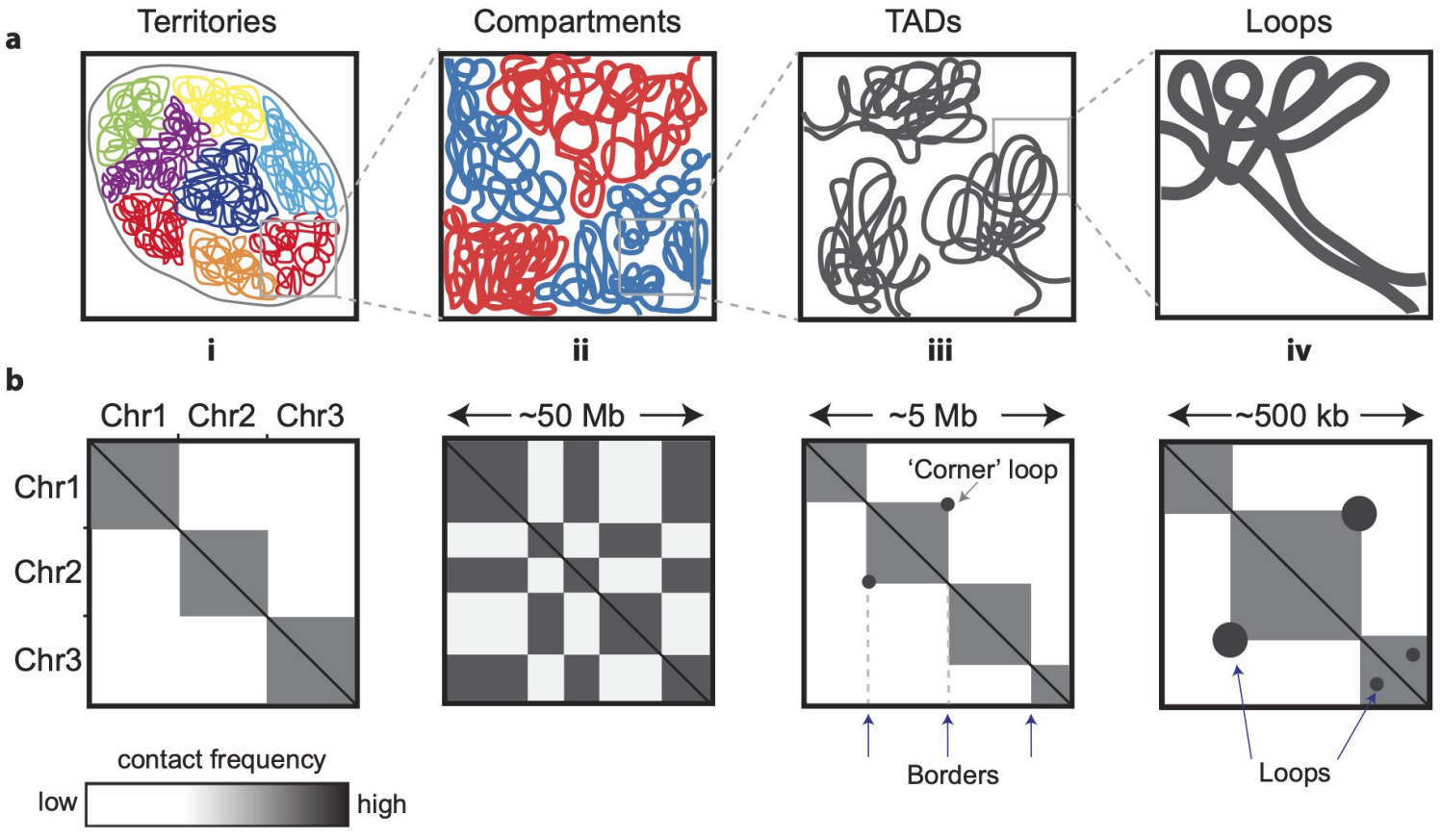
# The 3D Genome

Quantitative Biology 2022
10/14/22

Doctoral Program in
Cell, Molecular, Developmental
Biology, and Biophysics

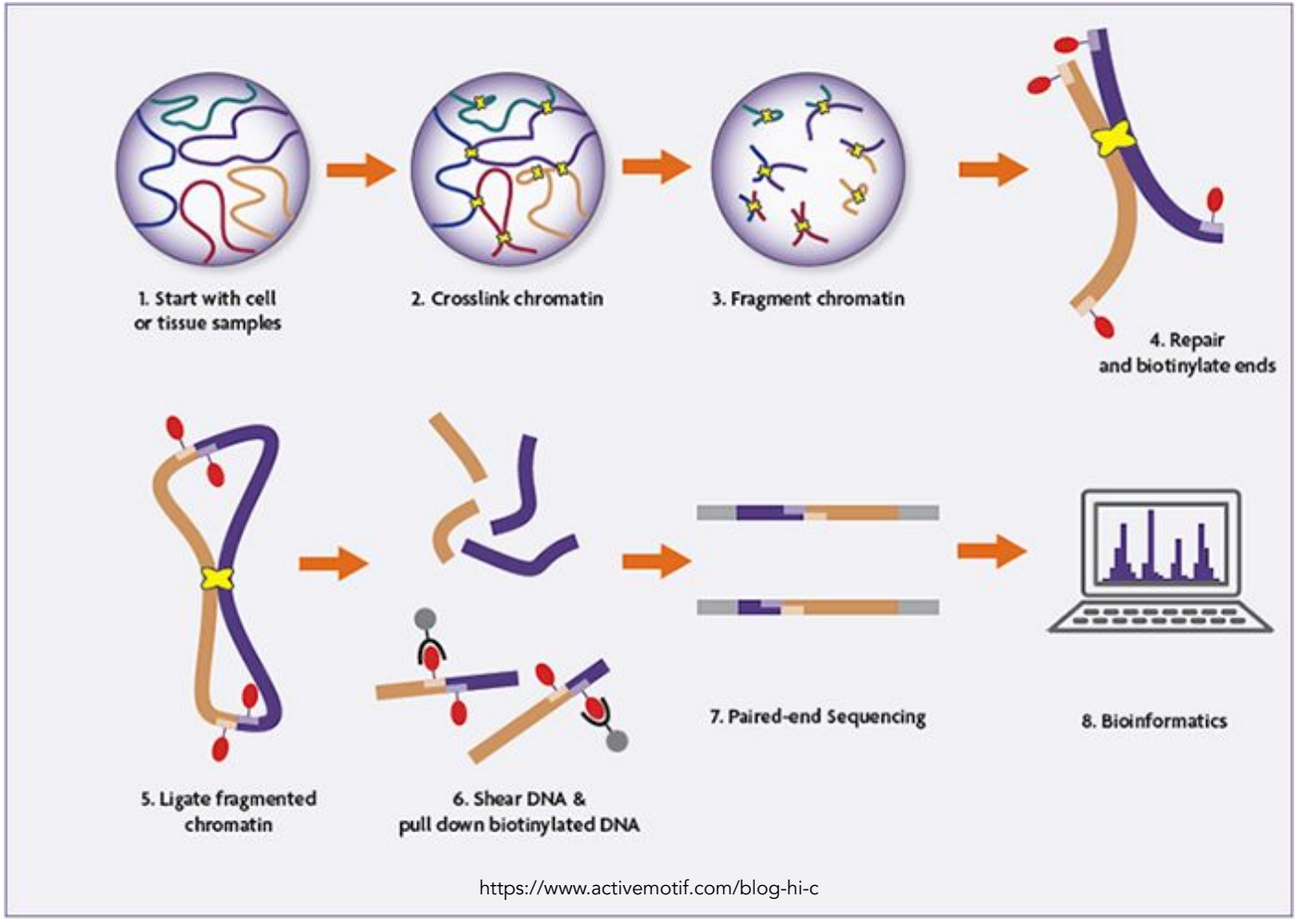
JOHNS HOPKINS
UNIVERSITY

# Scales of chromatin organization



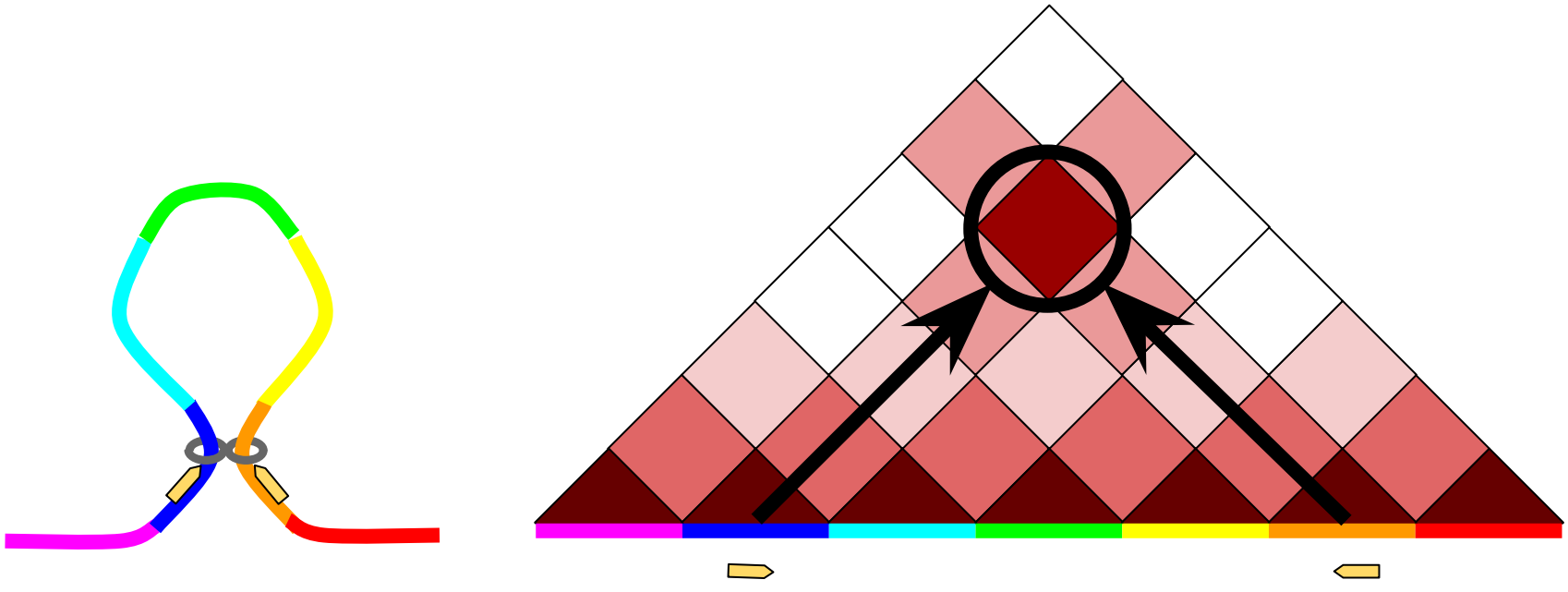

Sikorska N, Sexton T. Defining Functionally Relevant Spatial Chromatin Domains: It is a TAD Complicated. J Mol Biol. 2020 Feb 7;432(3):653-664.

# Hi-C

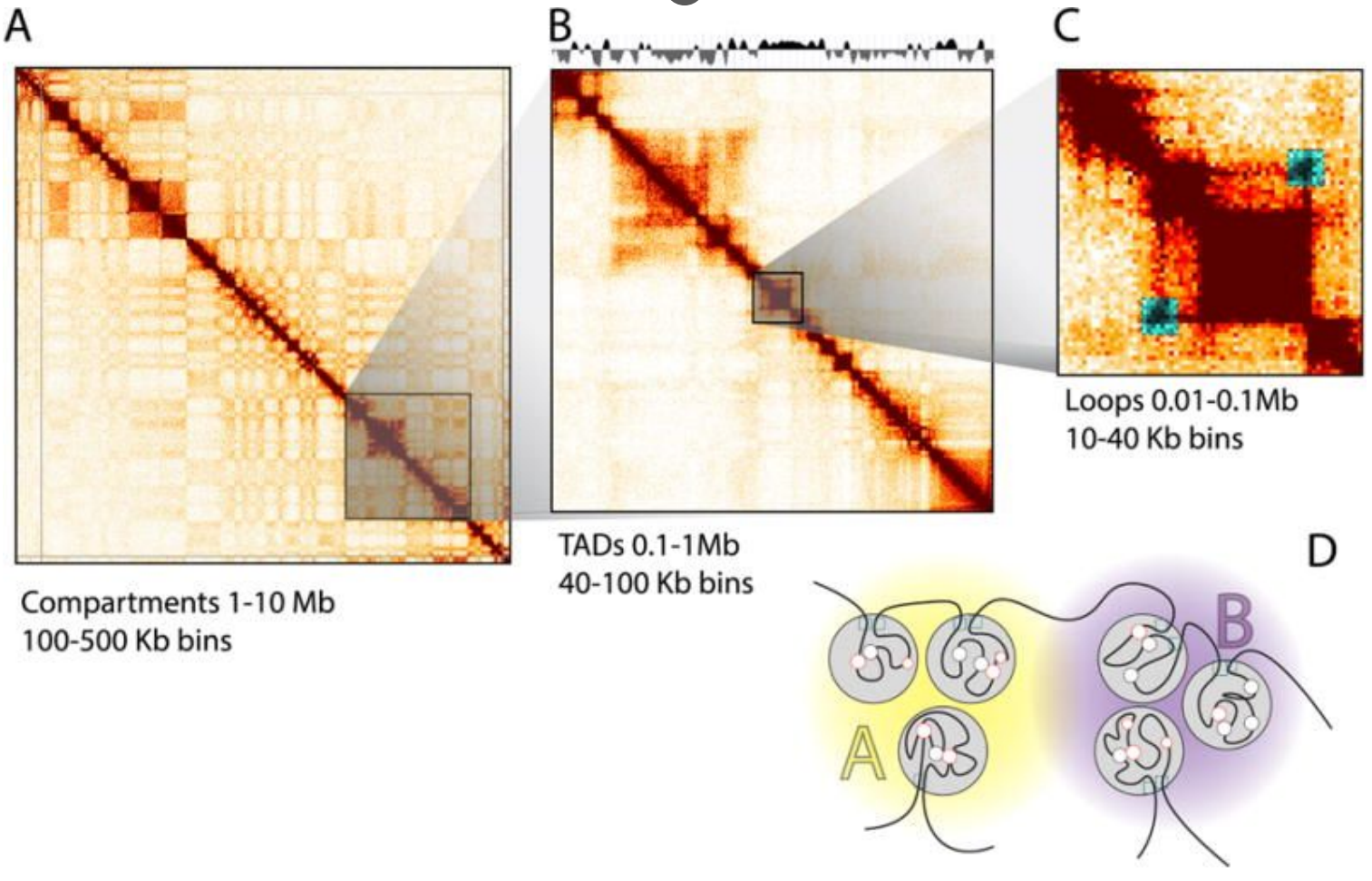



https://www.activemotif.com/blog-hi-c

# Hi-C



# Hi-C




Belaghzal H, Dekker J, Gibcus JH. Hi-C 2.0: An optimized Hi-C procedure for high-resolution genome-wide mapping of chromosome conformation. Methods (San Diego, Calif.). 2017 Jul;123:56-65.

# Hi-C

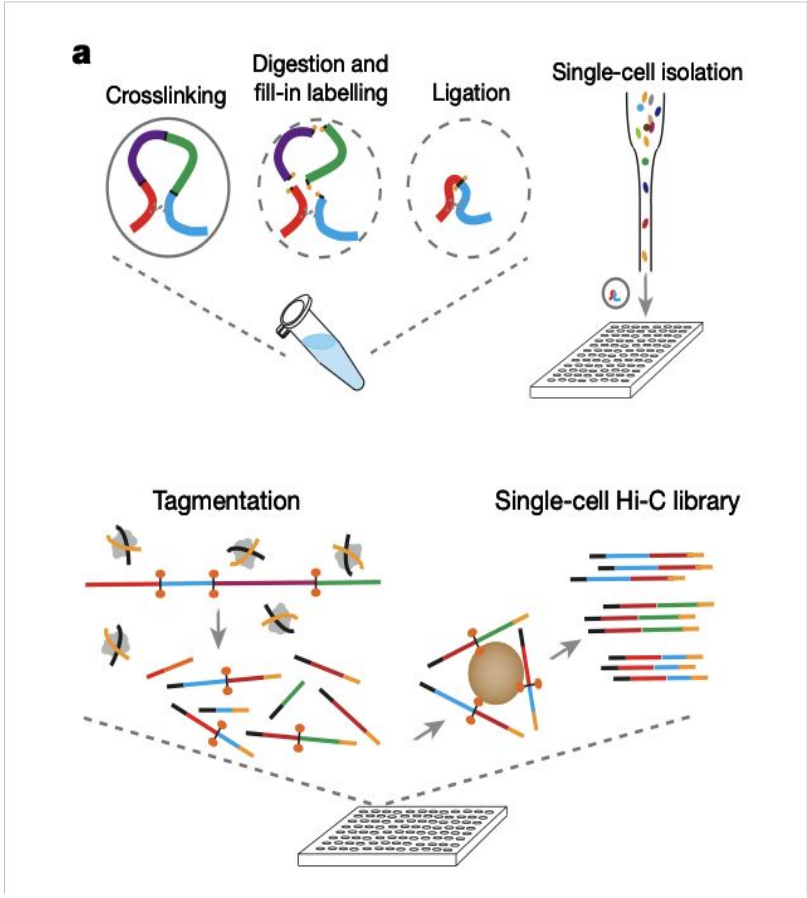
Advantages

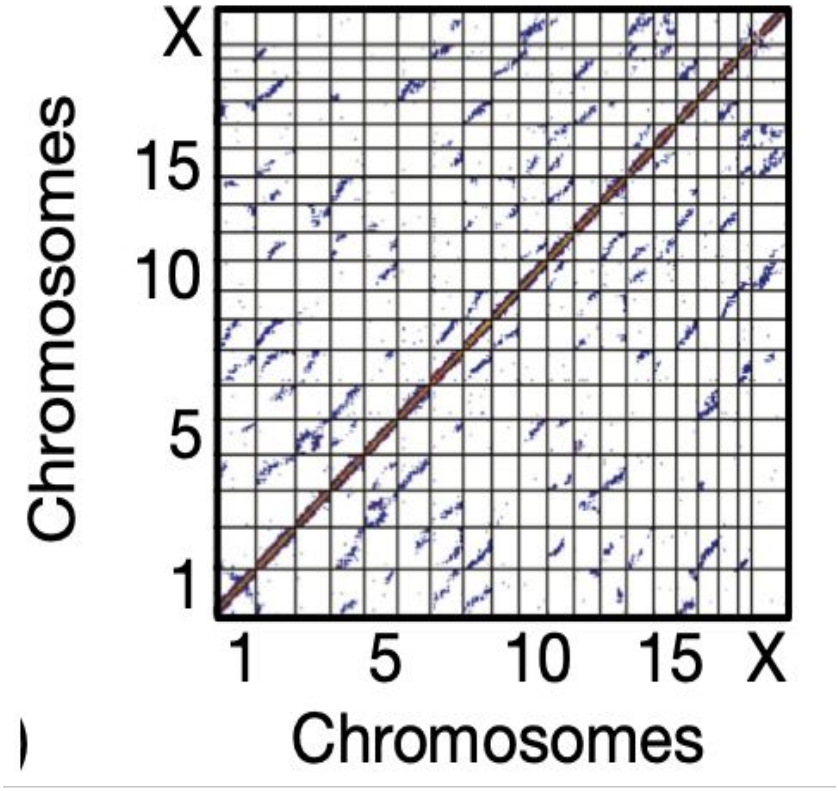
- Whole genome interrogation
- (Relatively) unbiased coverage across all interacting elements

Disadvantages

- Requires a large number of cells (~5M)
- Requires a large number of sequenced reads (50M-2G)
- Does not capture transient interactions well
- Can only look at pairwise interactions

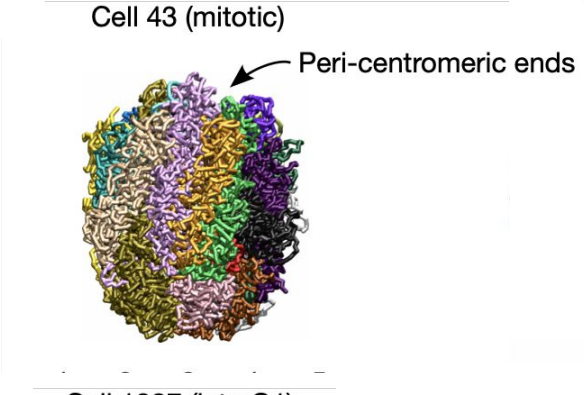
# Single cell Hi-C

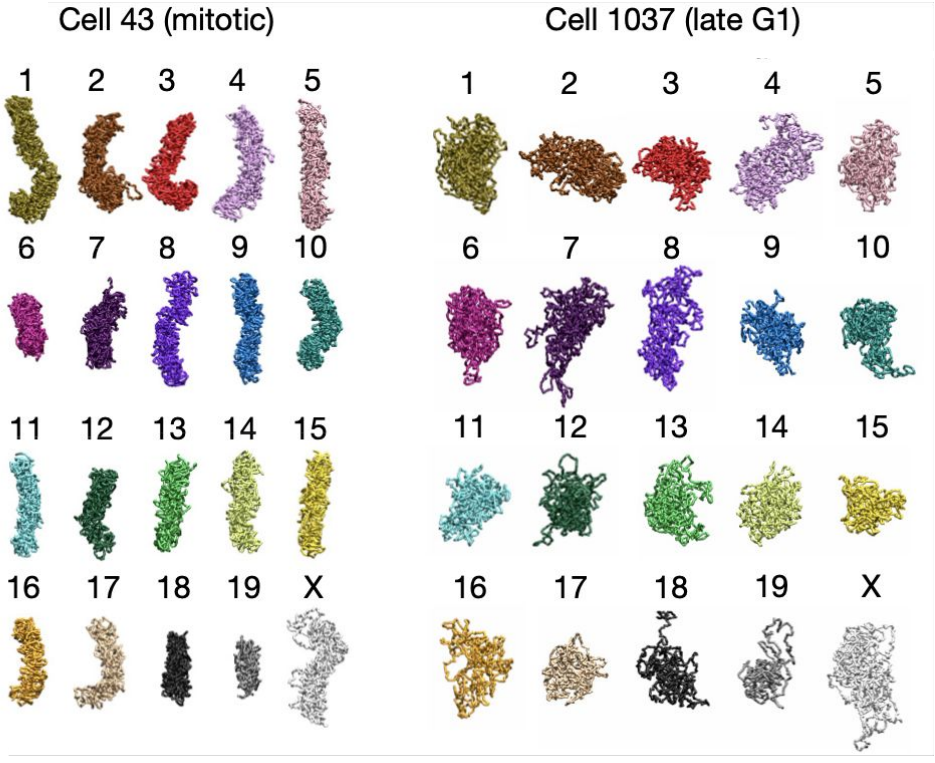



Nagano, T. *et al.* Cell-cycle dynamics of chromosomal organization at single-cell resolution. *Nature* **547,** 61–67 (2017).

# Single cell Hi-C

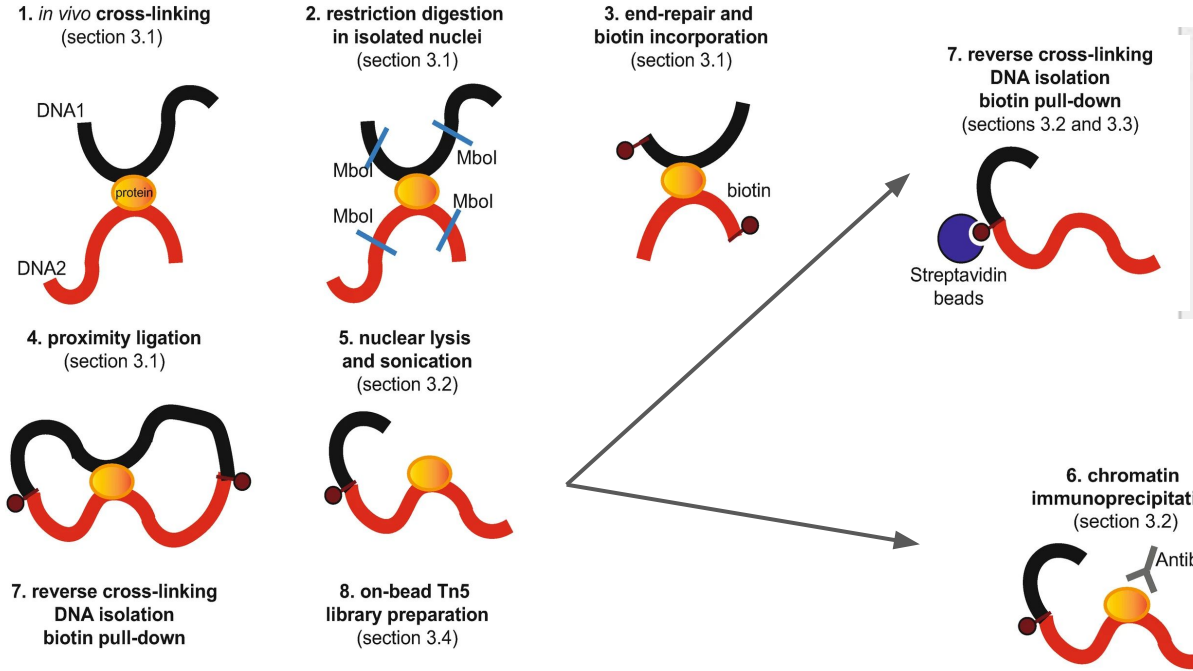



Use molecular dynamic simulation with interactions as attractive constraints to model chromatin configuration

Nagano, T. *et al.* Cell-cycle dynamics of chromosomal organization at single-cell resolution. *Nature* **547,** 61–67 (2017).

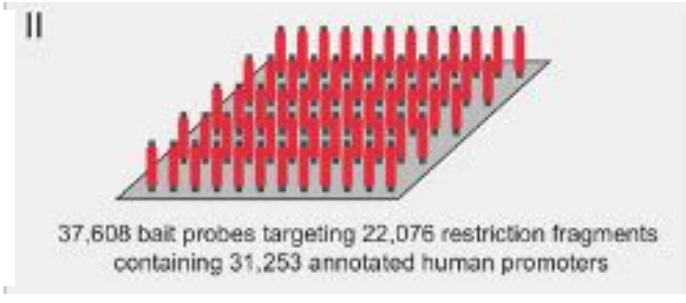
# Hi-ChIP vs. capture-Hi-C



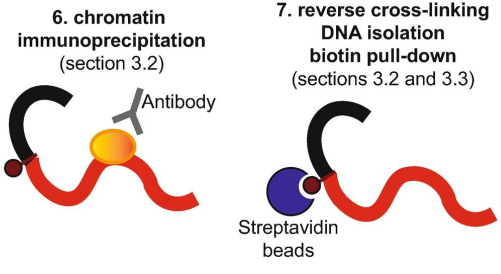




capture Hi-C



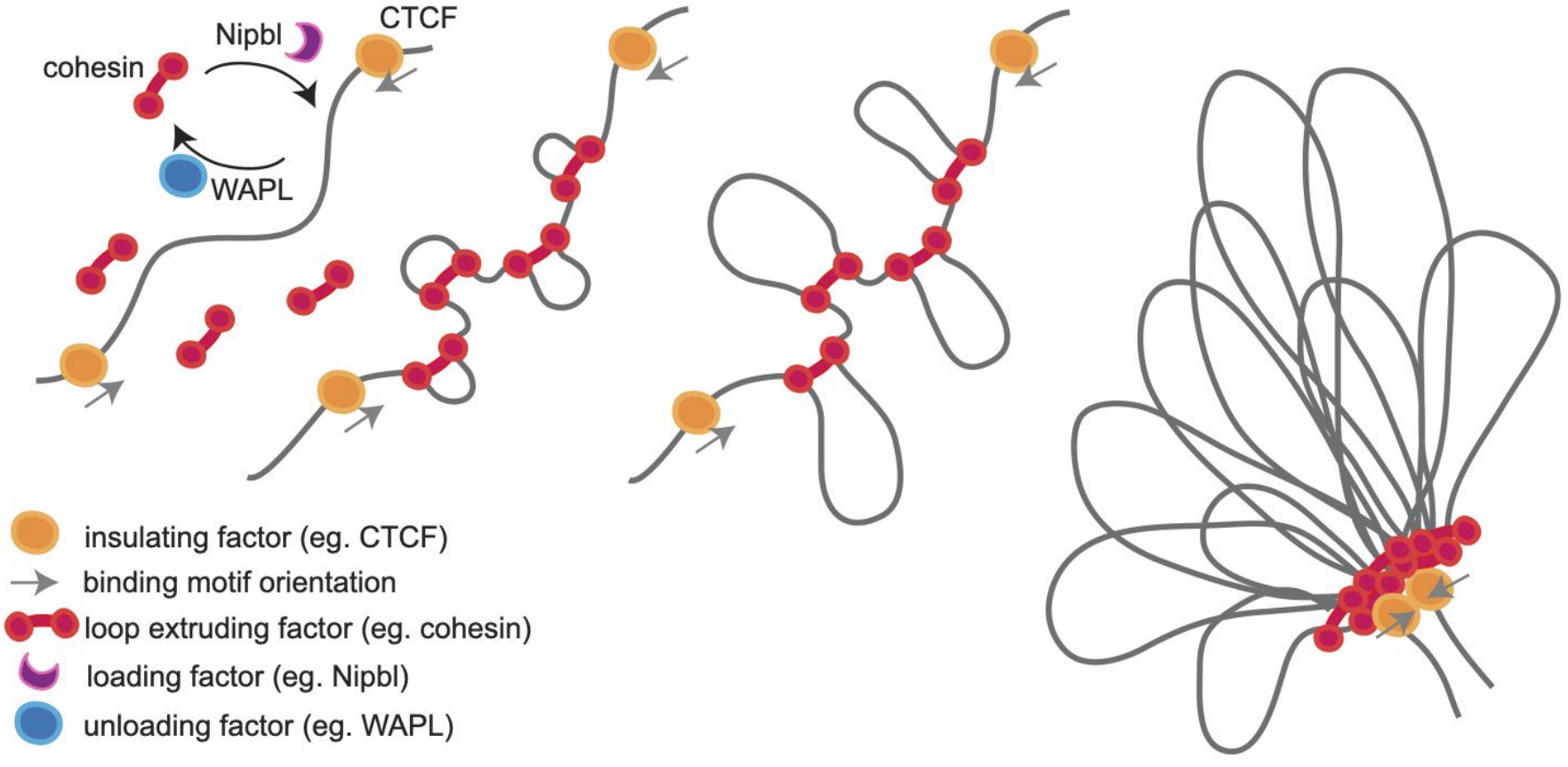

Hi-ChIP




https://link.springer.com/protocol/10.1007/978-1-0716-2497-5_7/figures/1

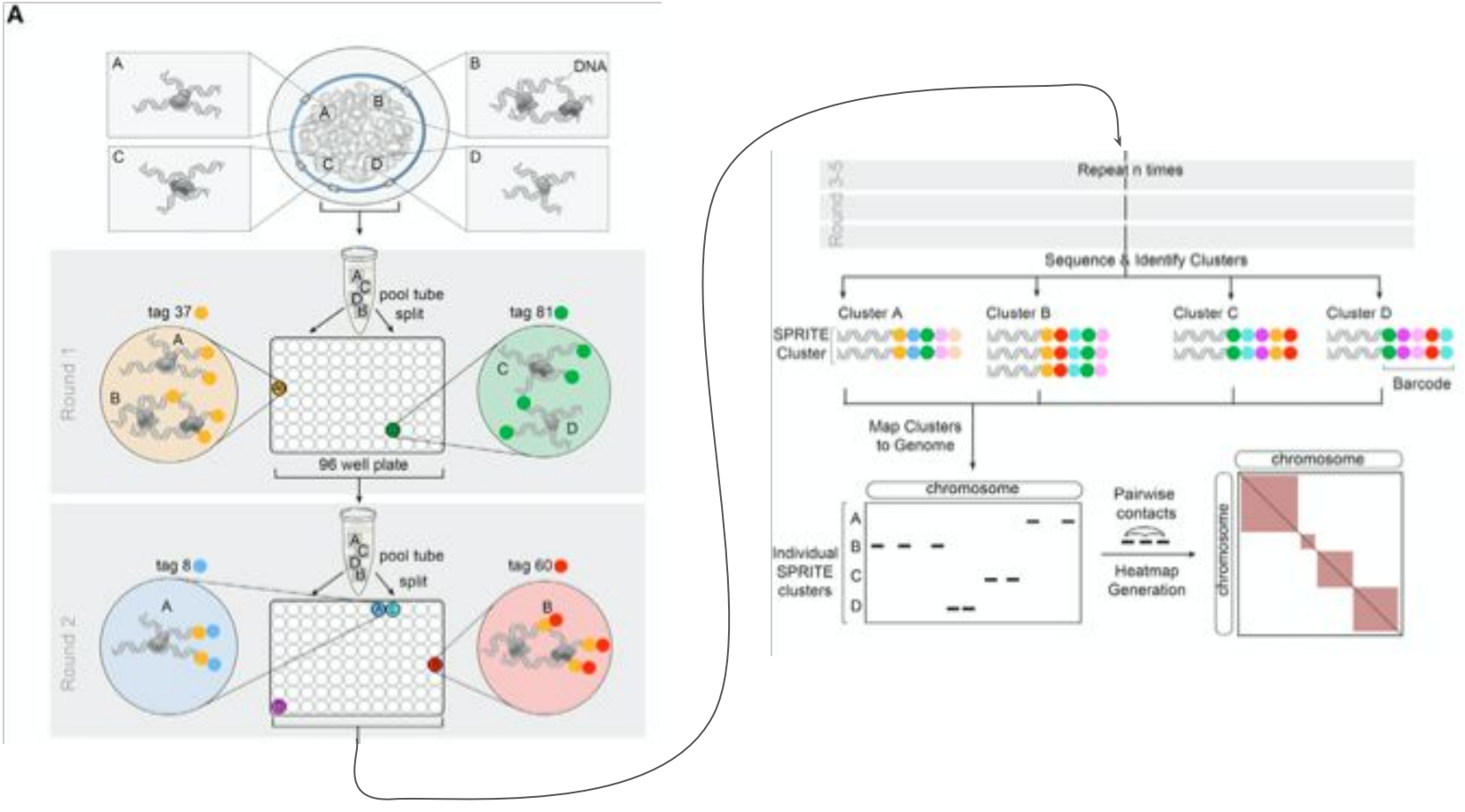
Schoenfelder S, Javierre BM, Furlan-Magaril M, Wingett SW, Fraser P. Promoter Capture Hi-C: High-resolution, Genome-wide Profiling of Promoter Interactions. J Vis Exp. 2018 Jun 28;(136):57320.

# Pairwise or multiway interactions?



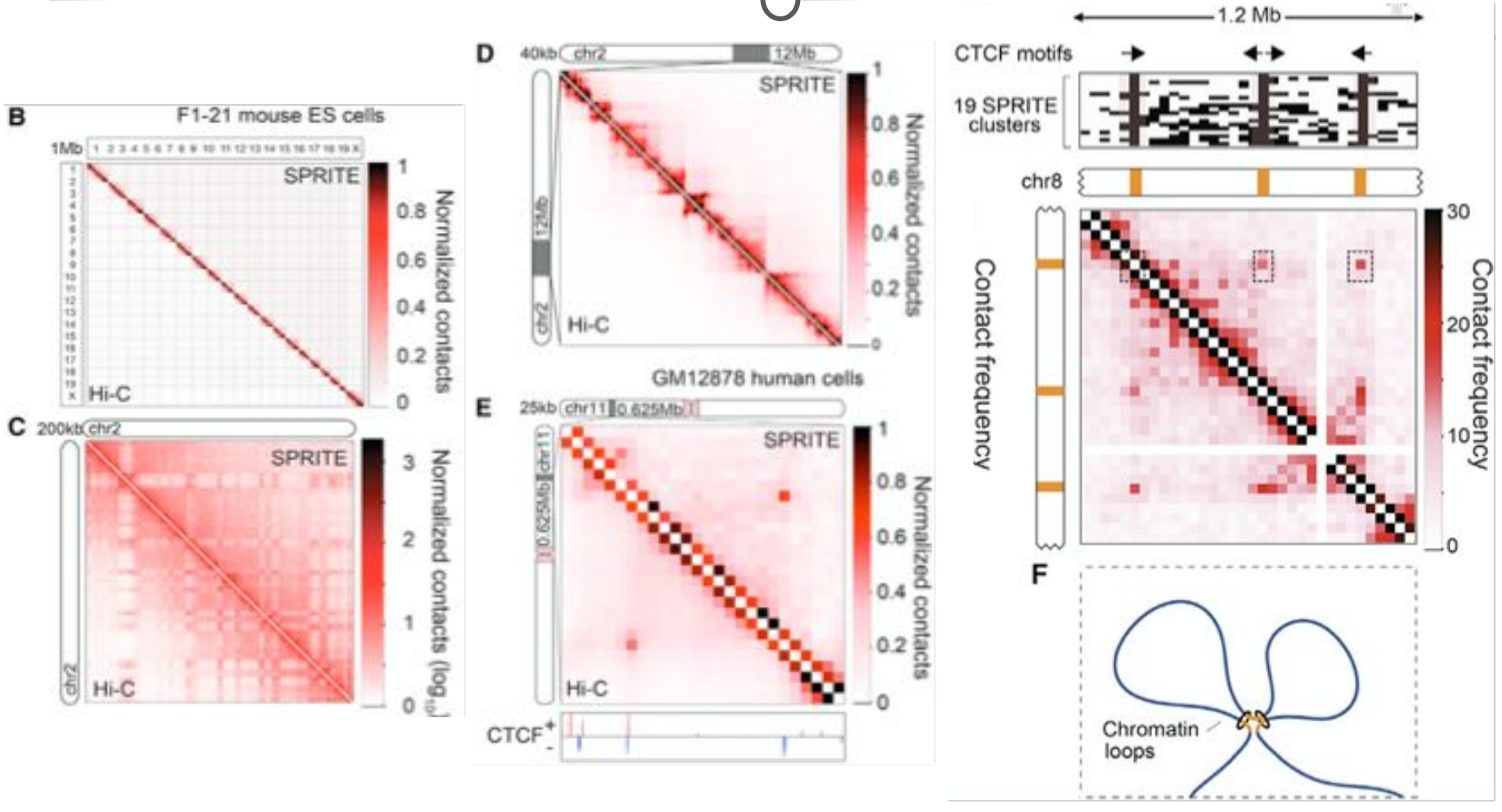

Sikorska N, Sexton T. Defining Functionally Relevant Spatial Chromatin Domains: It is a TAD Complicated. J Mol Biol. 2020 Feb 7;432(3):653-664.

# SPRITE (Split-Pool Recognition of Interactions by Tag Extension)




Quinodoz, S. A. *et al.* Higher-Order Inter-chromosomal Hubs Shape 3D Genome Organization in the Nucleus. *Cell* **0,** (2018).

# SPRITE (Split-Pool Recognition of Interactions by Tag Extension)




Quinodoz, S. A. *et al.* Higher-Order Inter-chromosomal Hubs Shape 3D Genome Organization in the Nucleus. *Cell* **0,** (2018).

# SPRITE (Split-Pool Recognition of Interactions by Tag Extension)

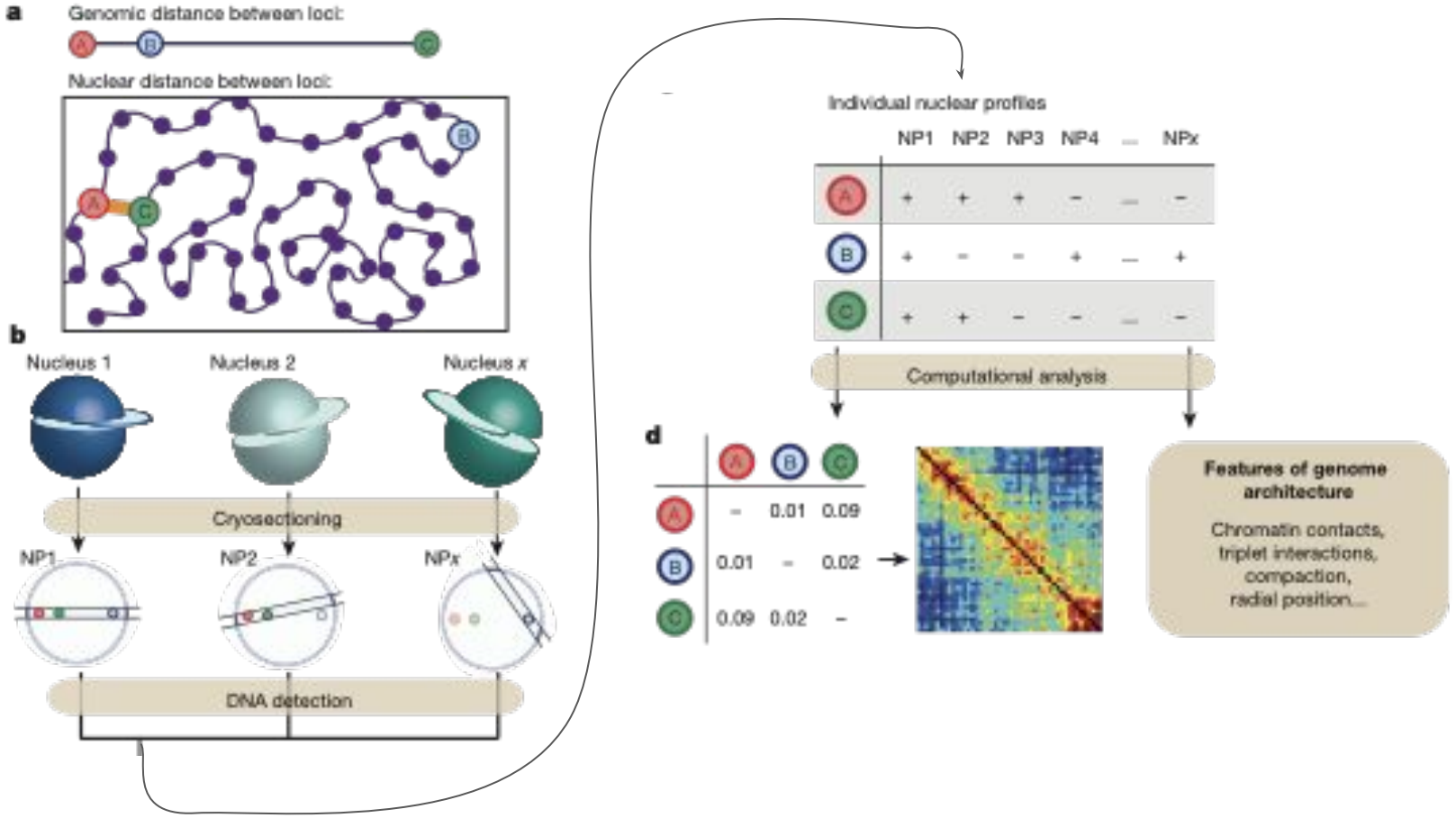
Advantages

- Can identify multi-way interactions
- Can identify interactions when DNA is too far apart to ligate

Disadvantages

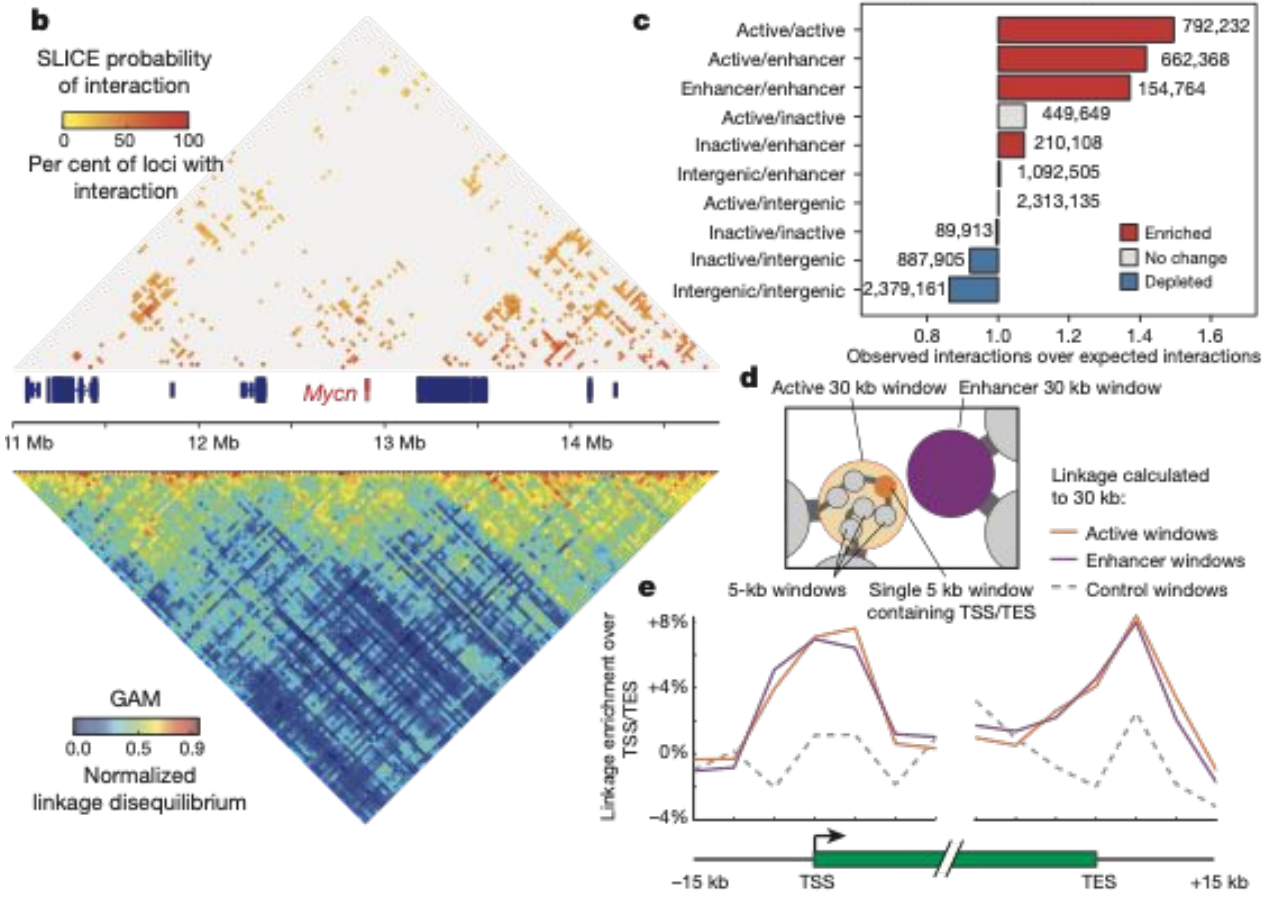
- Requires large number of cells (10M)
- Requires a large number of mapped reads (50M-500M)
- Laborious to perform

# GAM (genome architecture mapping)




Beagrie, R. A. *et al*. Complex multi-enhancer contacts captured by genome architecture mapping. *Nature* **543,** 519–524 (2017).

# GAM (genome architecture mapping)




Beagrie, R. A. *et al.* Complex multi-enhancer contacts captured by genome architecture mapping. *Nature* **543,** 519–524 (2017).

# GAM (genome architecture mapping)

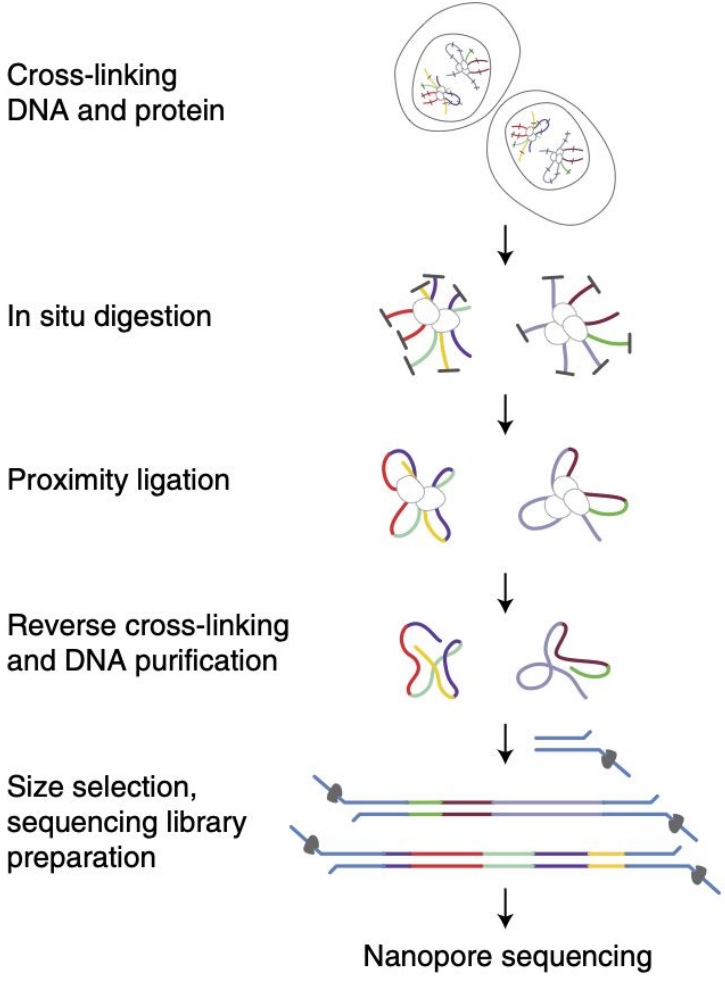
Advantages

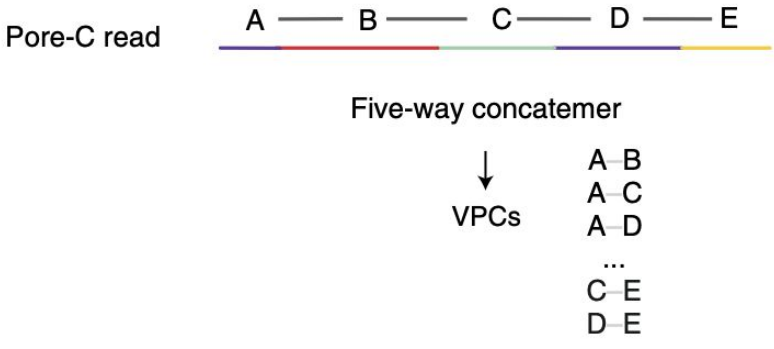
- Can identify multi-way interactions
- Can identify any DNA regions in close proximity
- Requires a small number of cells (100s)
- Provides single-cell information

Disadvantages

- Requires a large number of mapped reads (100M-1G)

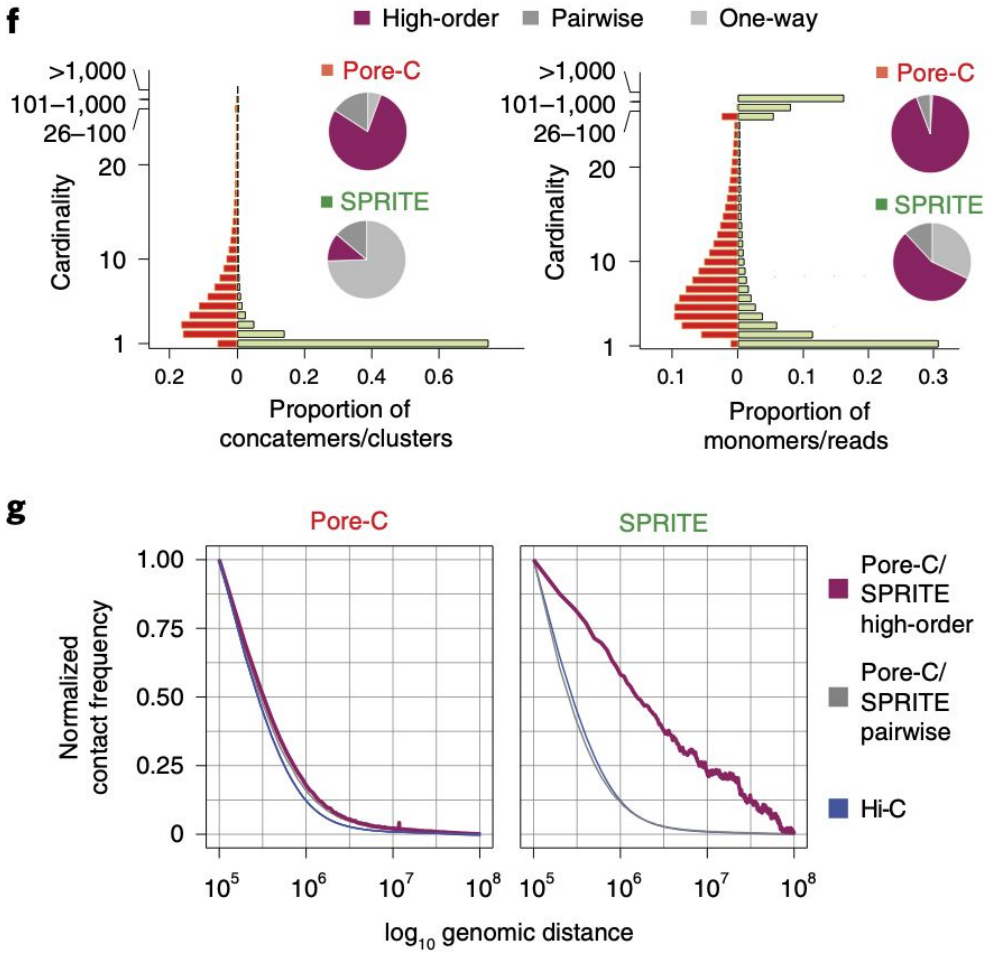
# Pore-C (Nanopore Concatemer Sequencing)



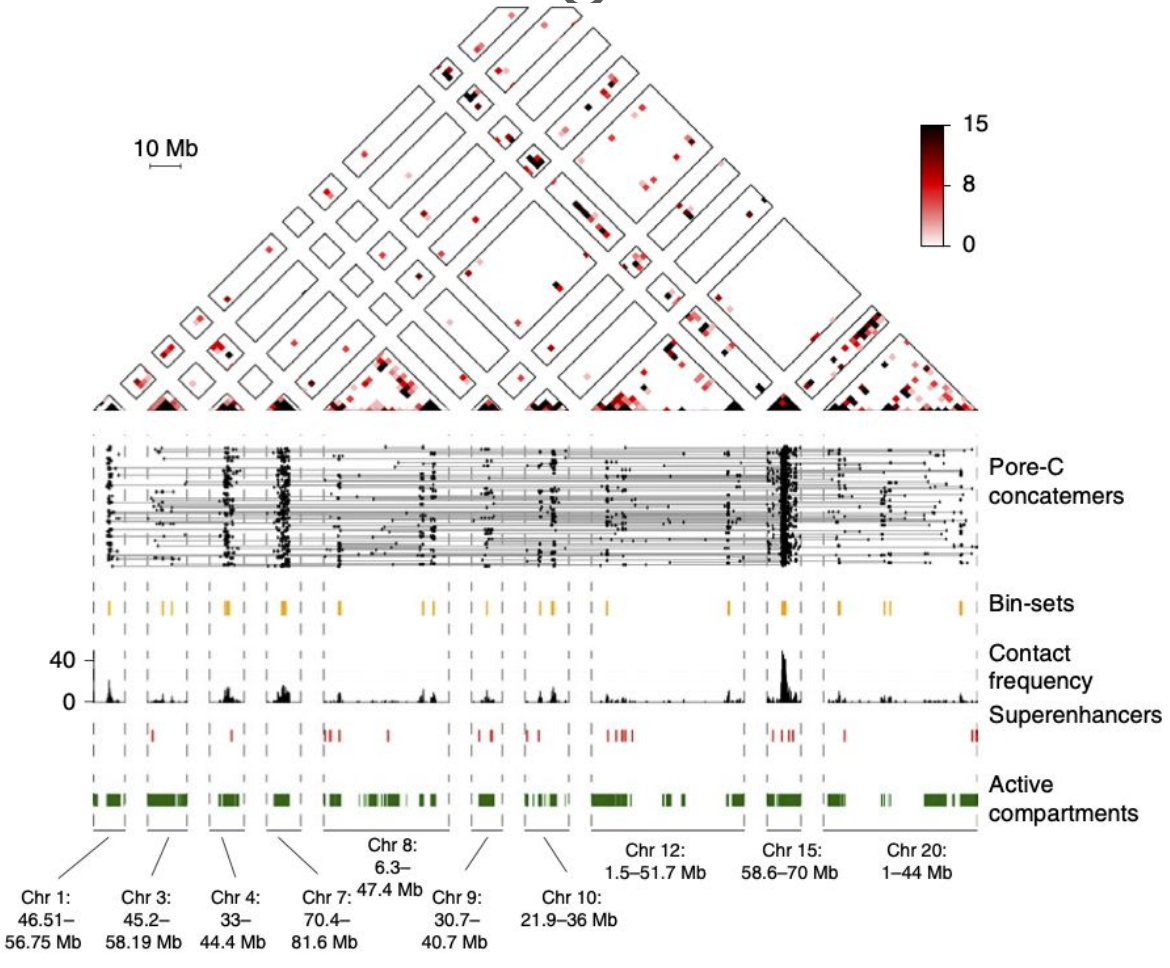

Deshpande, A. S. et al. (2022). Identifying synergistic high-order 3D chromatin conformations from genome-scale nanopore concatemer sequencing. *Nature Biotechnology*, *40*(10), 1488–1499.

# Pore-C (Nanopore Concatemer Sequencing)




Deshpande, A. S. et al. (2022). Identifying synergistic high-order 3D chromatin conformations from genome-scale nanopore concatemer sequencing. *Nature Biotechnology*, *40*(10), 1488–1499.

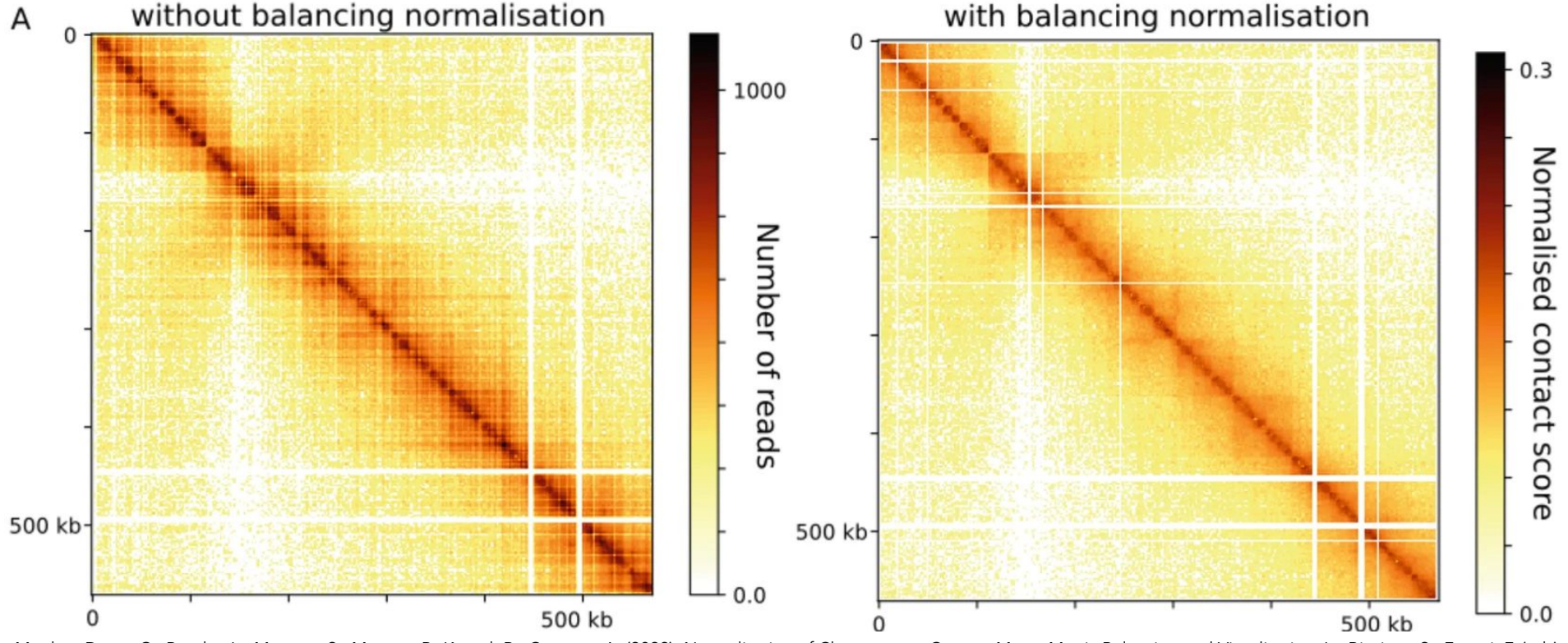
# Pore-C (Nanopore Concatemer Sequencing)




Deshpande, A. S. et al. (2022). Identifying synergistic high-order 3D chromatin conformations from genome-scale nanopore concatemer sequencing. *Nature Biotechnology*, *40*(10), 1488–1499.

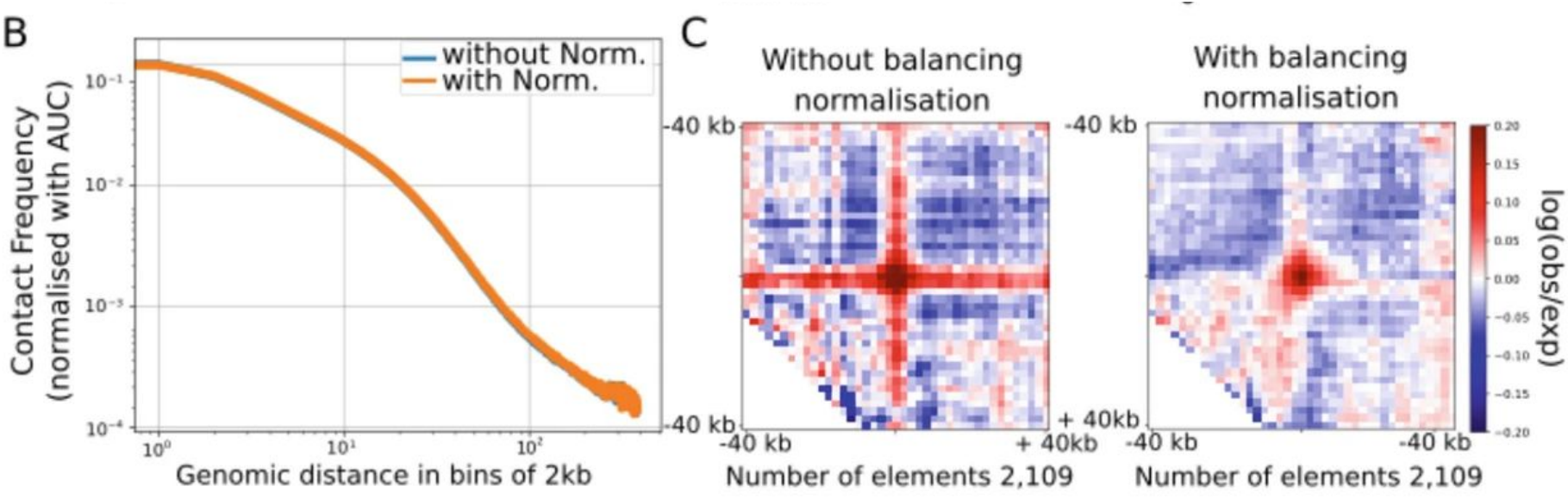
# Hi-C Bias

Given a symmetric matrix, multiply rows and columns by some vector of values such that the marginal means are all 1.



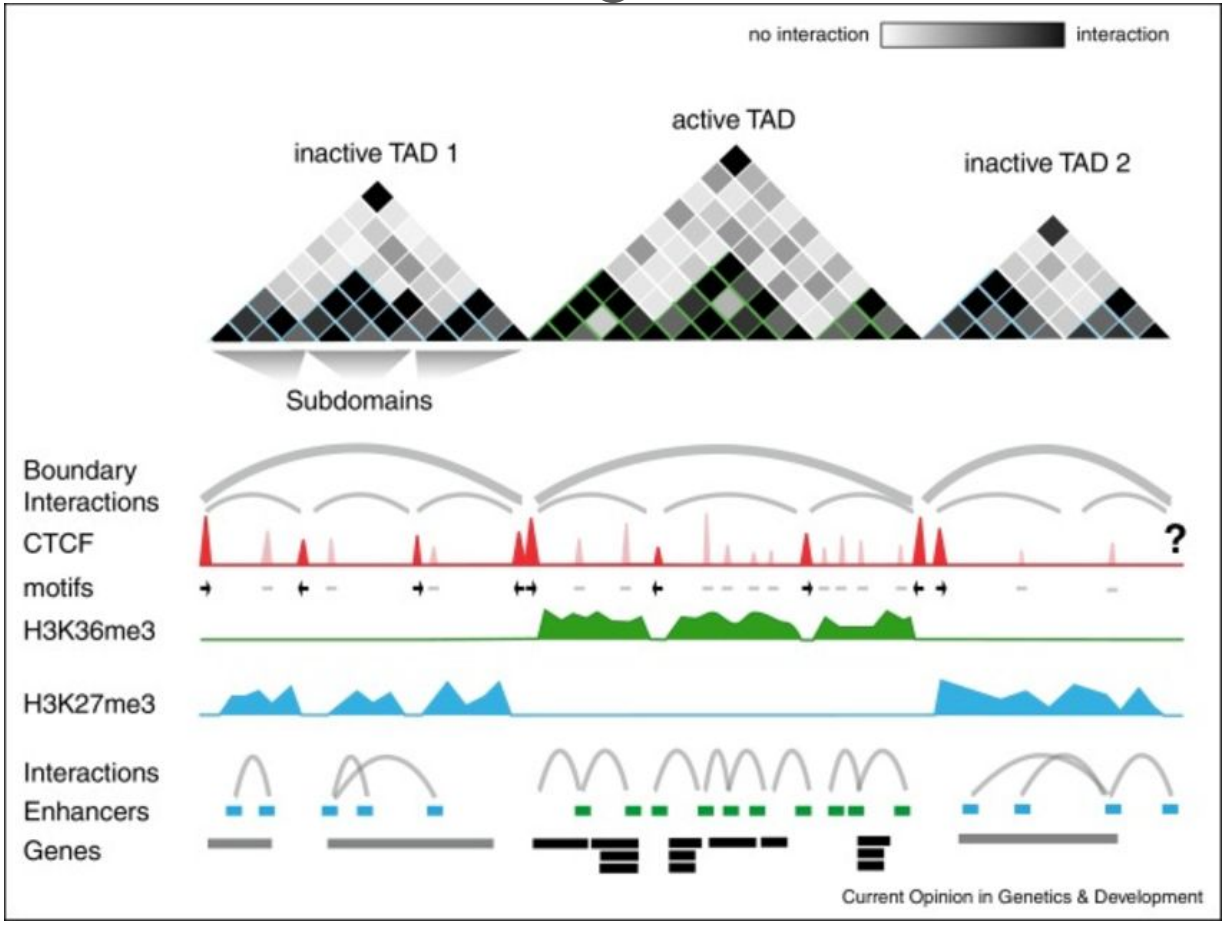

Matthey-Doret, C., Baudry, L., Mortaza, S., Moreau, P., Koszul, R., Cournac, A. (2022). Normalization of Chromosome Contact Maps: Matrix Balancing and Visualization. In: Bicciato, S., Ferrari, F. (eds) Hi-C Data Analysis. Methods in Molecular Biology, vol 2301. Humana, New York, NY.

# Hi-C Bias



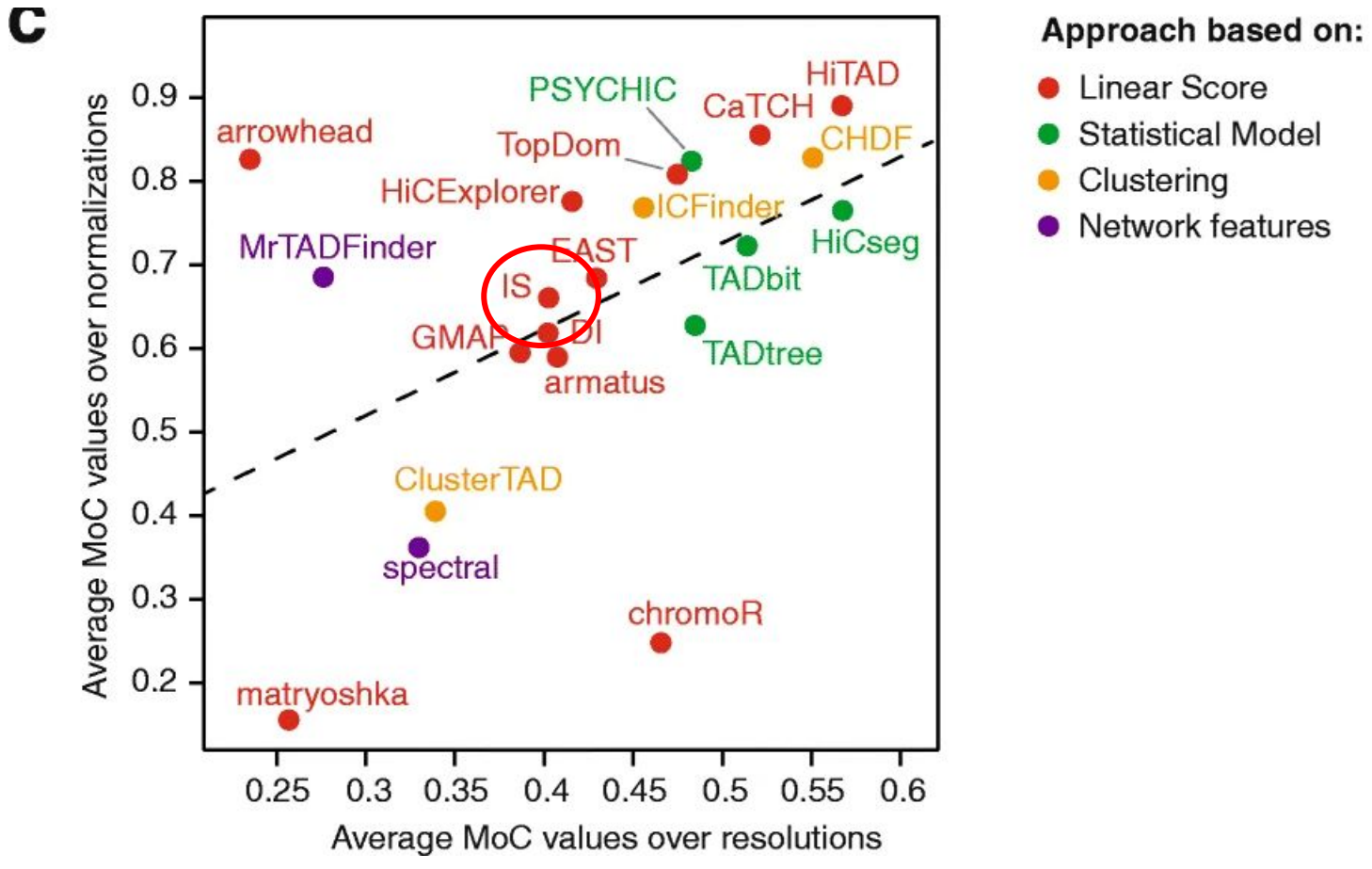

Matthey-Doret, C., Baudry, L., Mortaza, S., Moreau, P., Koszul, R., Cournac, A. (2022). Normalization of Chromosome Contact Maps: Matrix Balancing and Visualization. In: Bicciato, S., Ferrari, F. (eds) Hi-C Data Analysis. Methods in Molecular Biology, vol 2301. Humana, New York, NY.

# TADs (topologically associated domains)

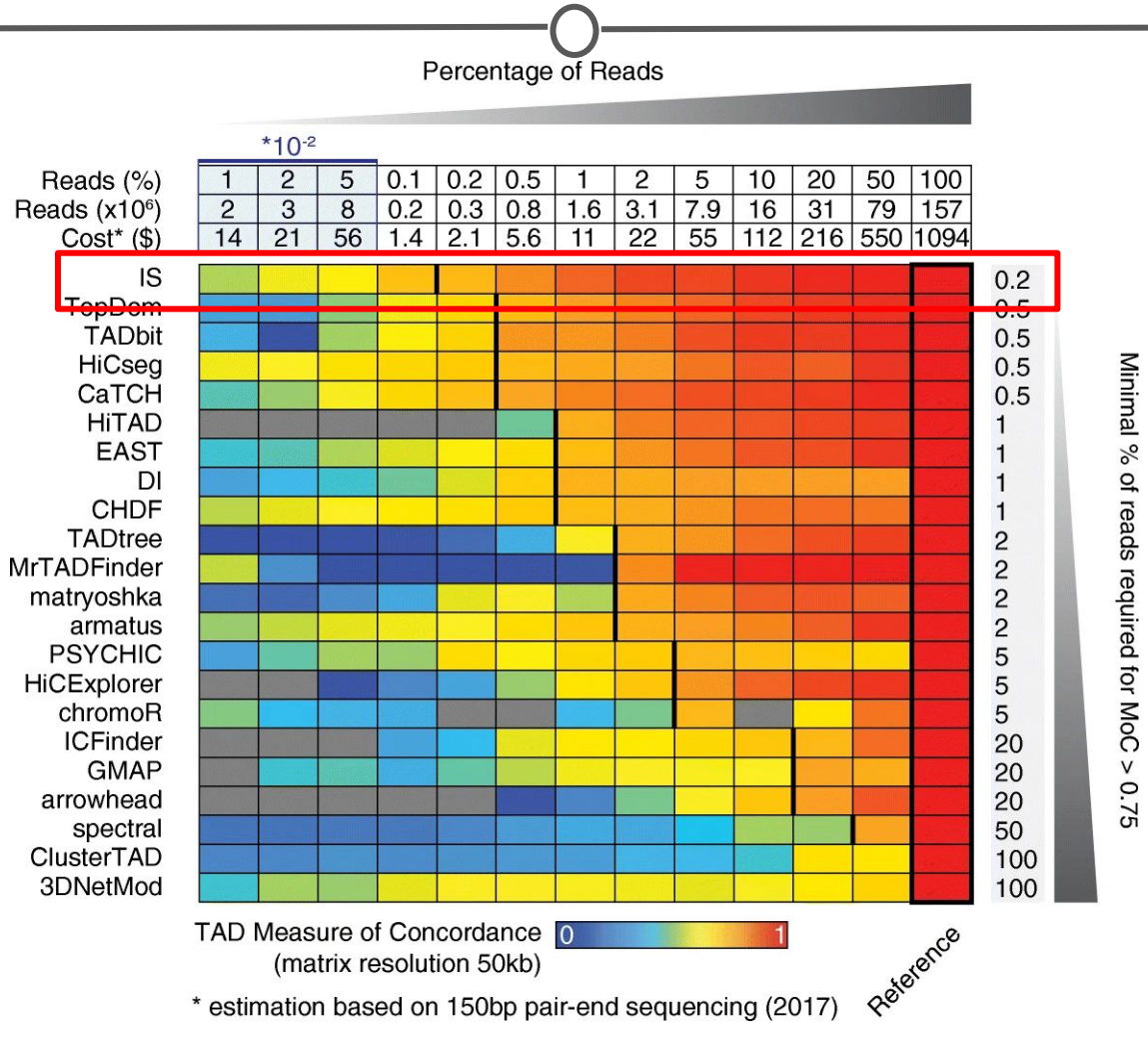



Ali, Tamer & Renkawitz, Rainer & Bartkuhn, Marek. (2016). Insulators and domains of gene expression. Current Opinion in Genetics & Development. 37.

# The world of TAD finders

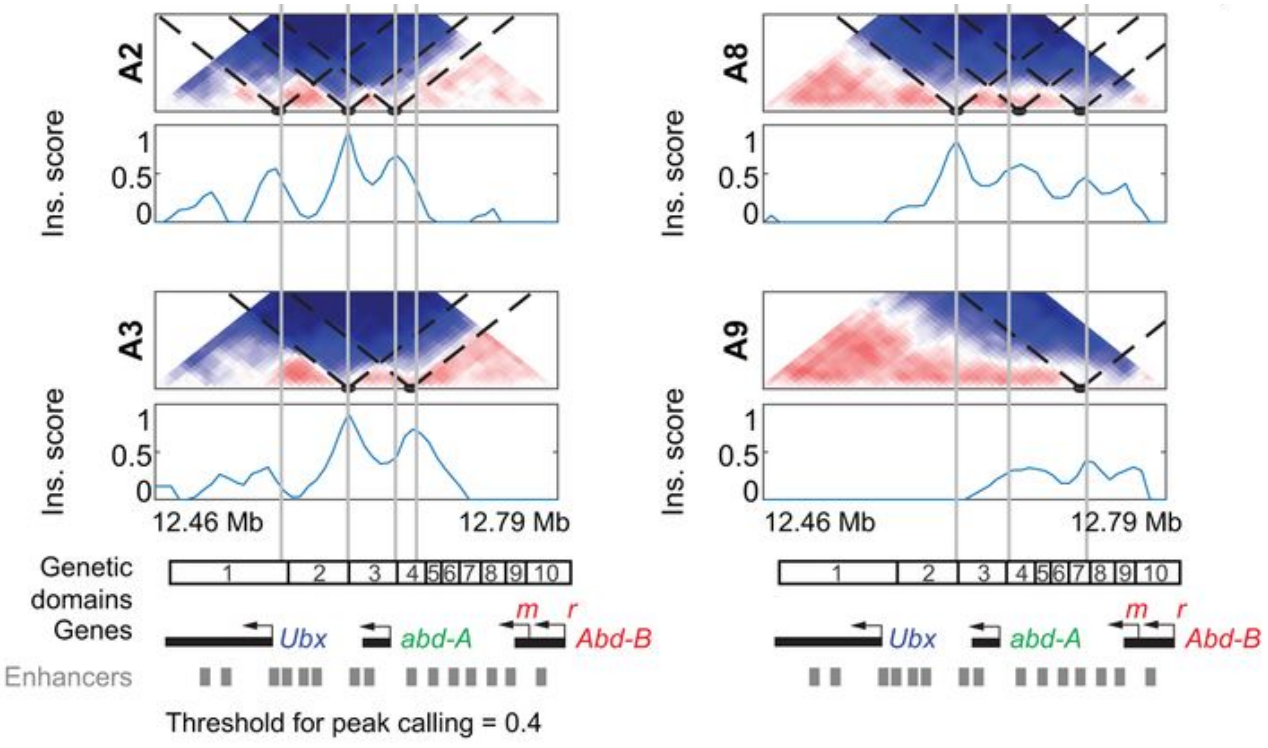



Zufferey, M., Tavernari, D., Oricchio, E. *et al.* Comparison of computational methods for the identification of topologically associating domains. *Genome Biol* 19, 217 (2018).



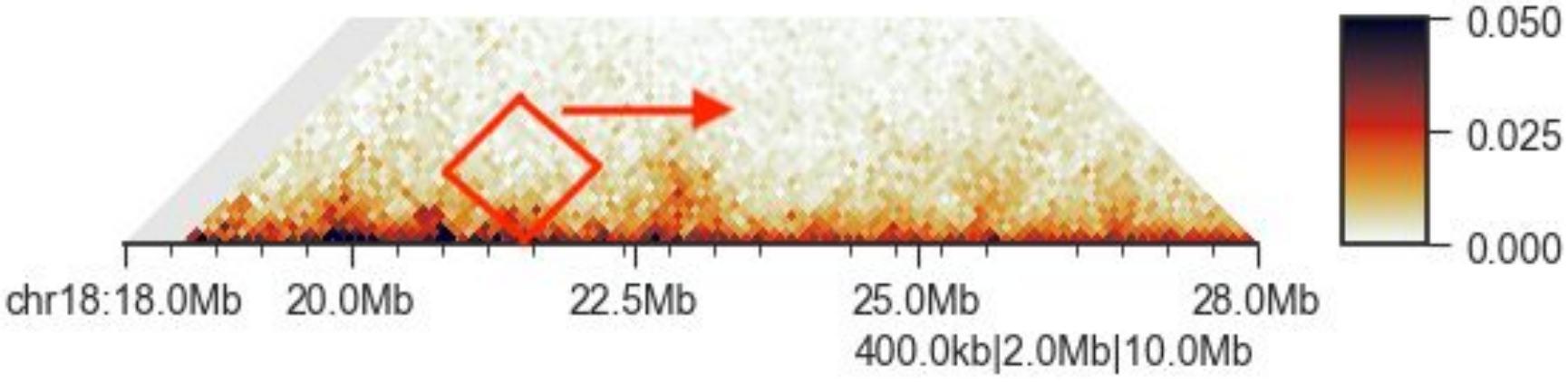

Zufferey, M., Tavernari, D., Oricchio, E. *et al.* Comparison of computational methods for the identification of topologically associating domains. *Genome Biol* 19, 217 (2018).

# Insulation Score




Mateo LJ, Murphy SE, Hafner A, Cinquini IS, Walker CA, Boettiger AN. Visualizing DNA folding and RNA in embryos at single-cell resolution. Nature. 2019 Apr;568(7750):49-54. doi: 10.1038/s41586-019-1035-4. Epub 2019 Mar 18.

# Calculating the insulation score




Crane, E., Bian, Q., McCord, R. *et al.* Condensin-driven remodelling of X chromosome topology during dosage compensation. *Nature* 523, 240–244 (2015).