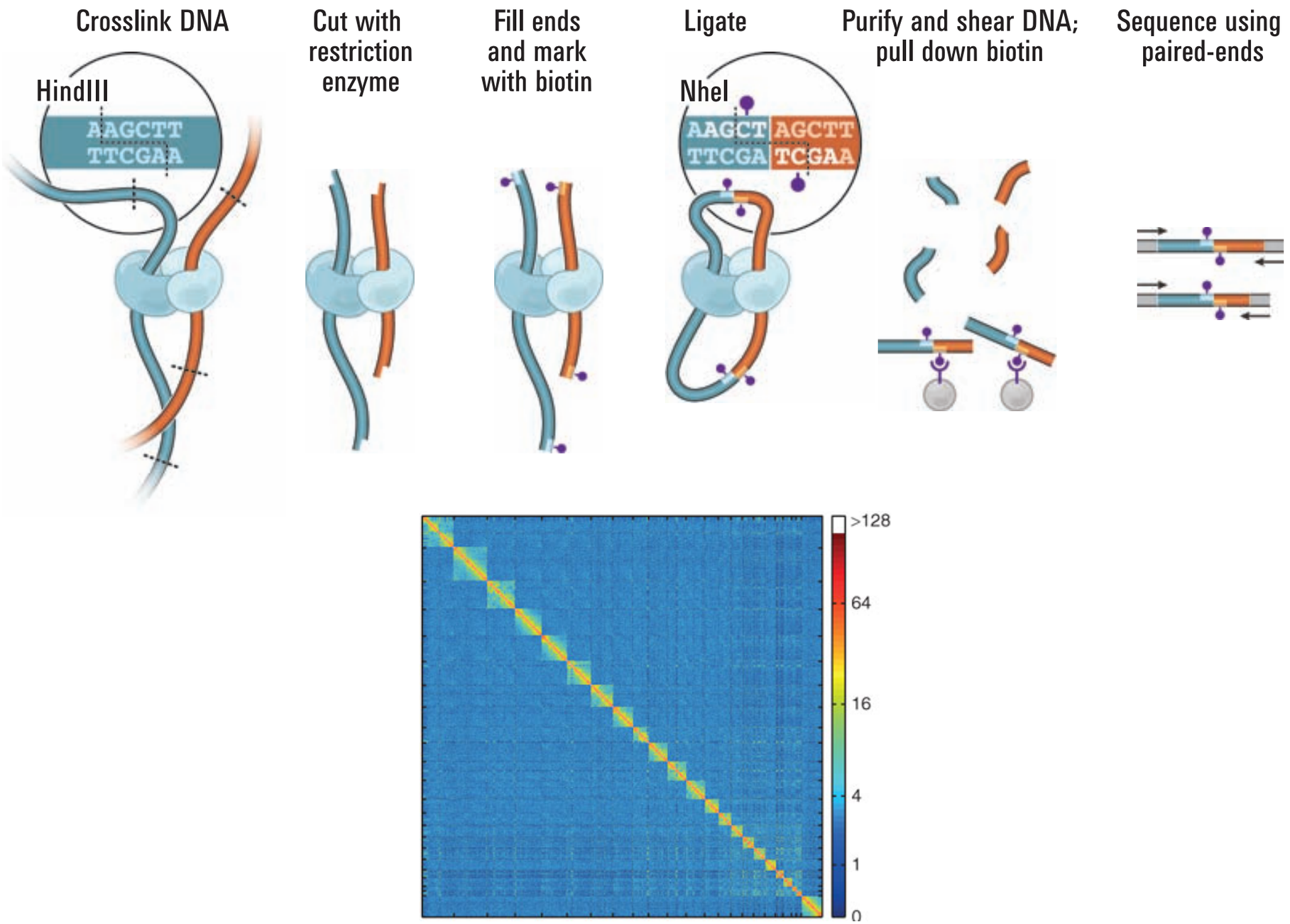
Summary of yesterday lecture

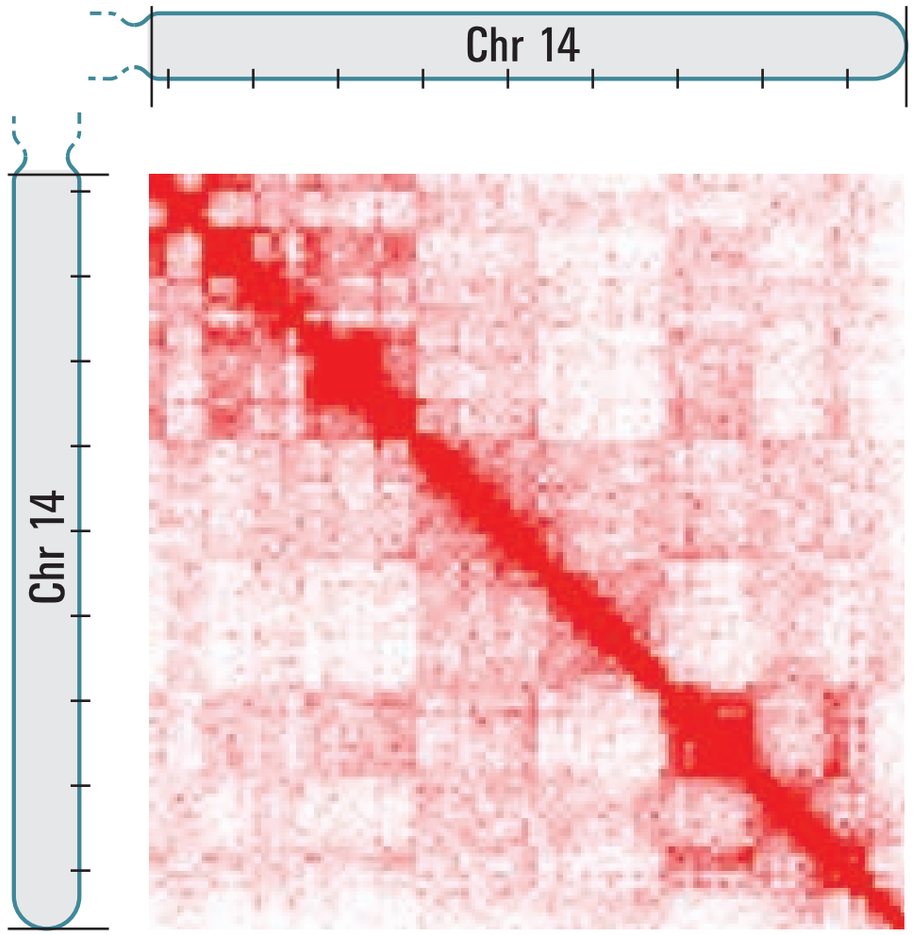
Level IV: Higher-order organization

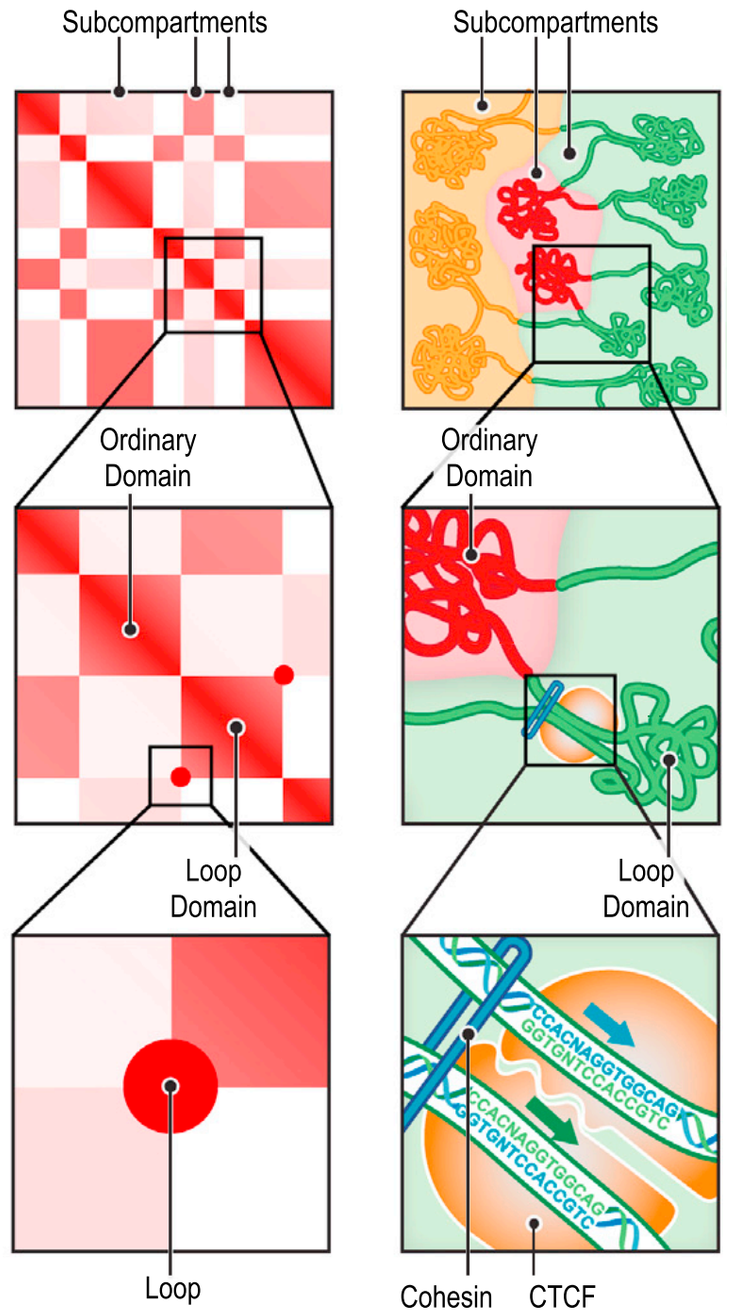


Dekker, J., Rippe, K., Dekker, M., & Kleckner, N. (2002). Science, 295(5558), 1306–1311.
Lieberman-Aiden, E., et al. (2009). Science, 326(5950), 289–293.

Level IV: Higher-order organization

Hierarchical genome organisation

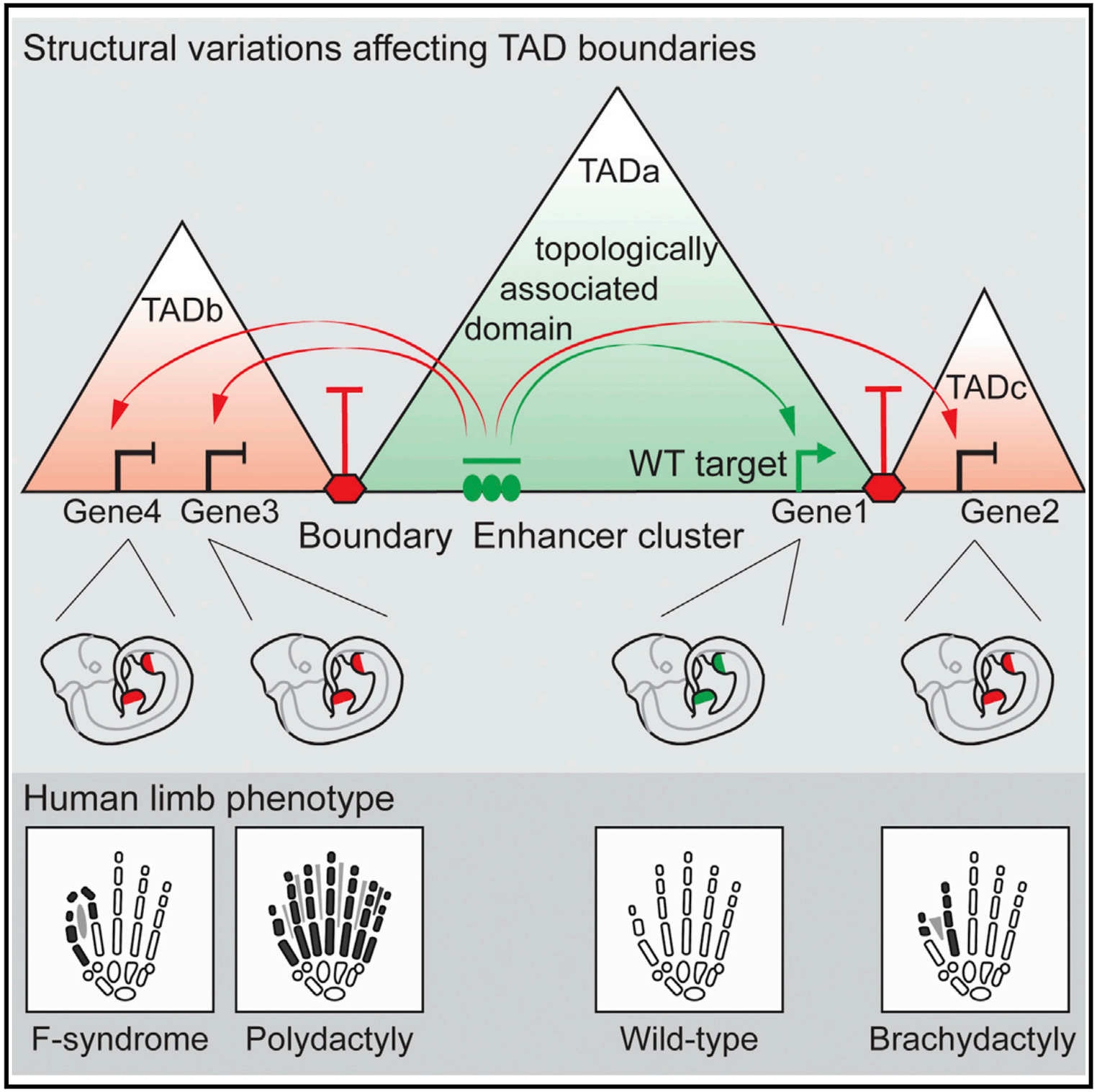




Lieberman-Aiden, E., et al. (2009). Science, 326(5950), 289–293.
Rao, S. S. P., et al. (2014). Cell, 1–29.

Level IV: Higher-order organization

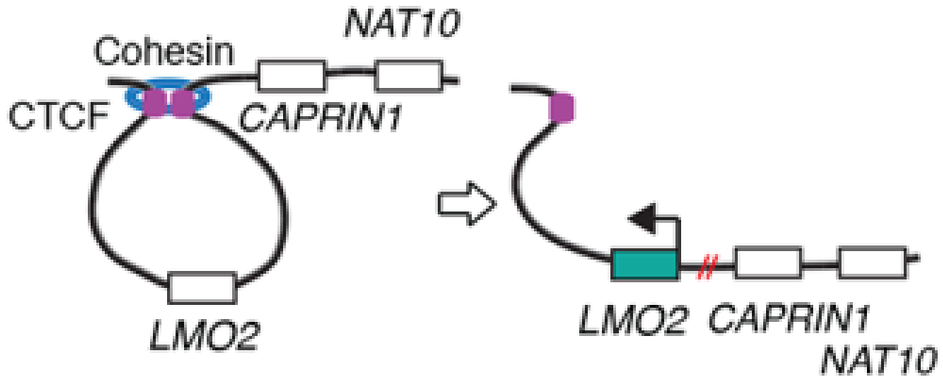
TADs are functional units

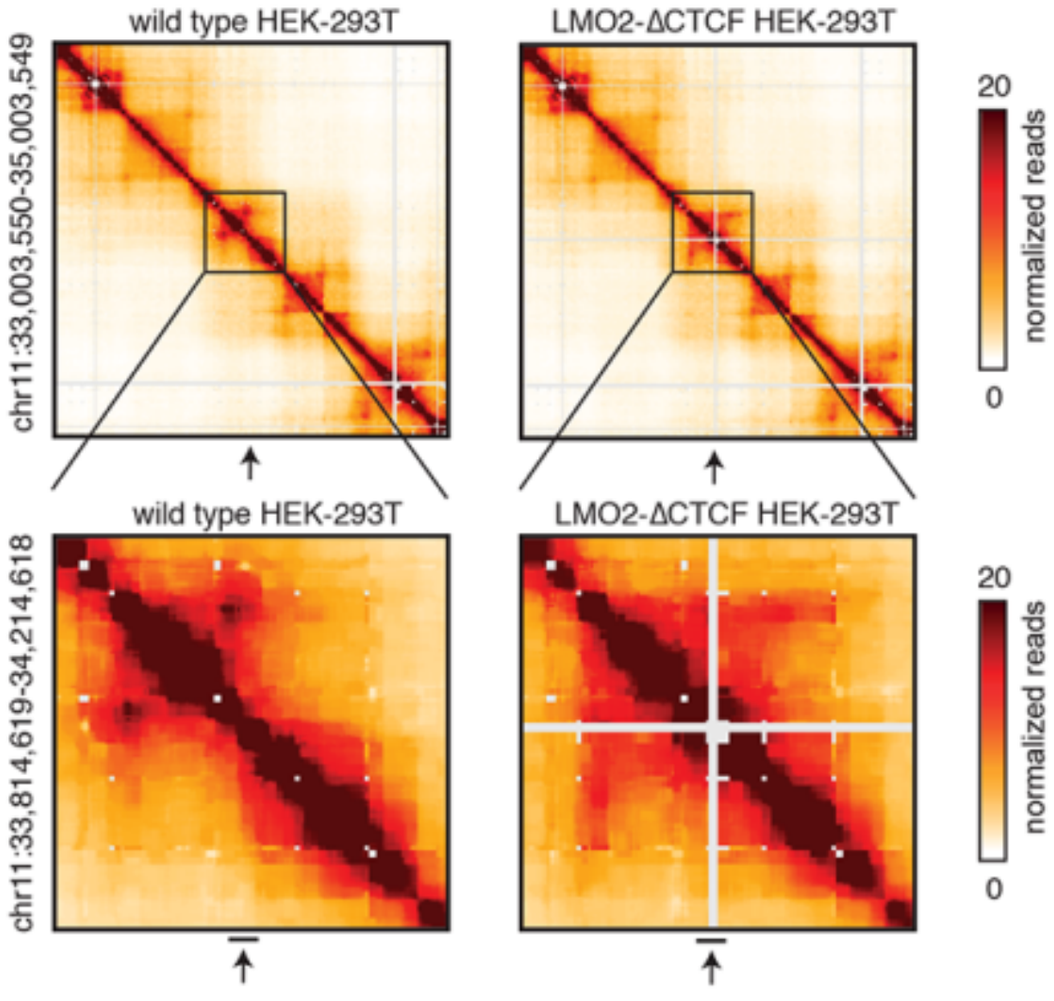


Lupiáñez, et al. (2015). Cell, 1–15.

Level IV: Higher-order organization

TADs are functional units



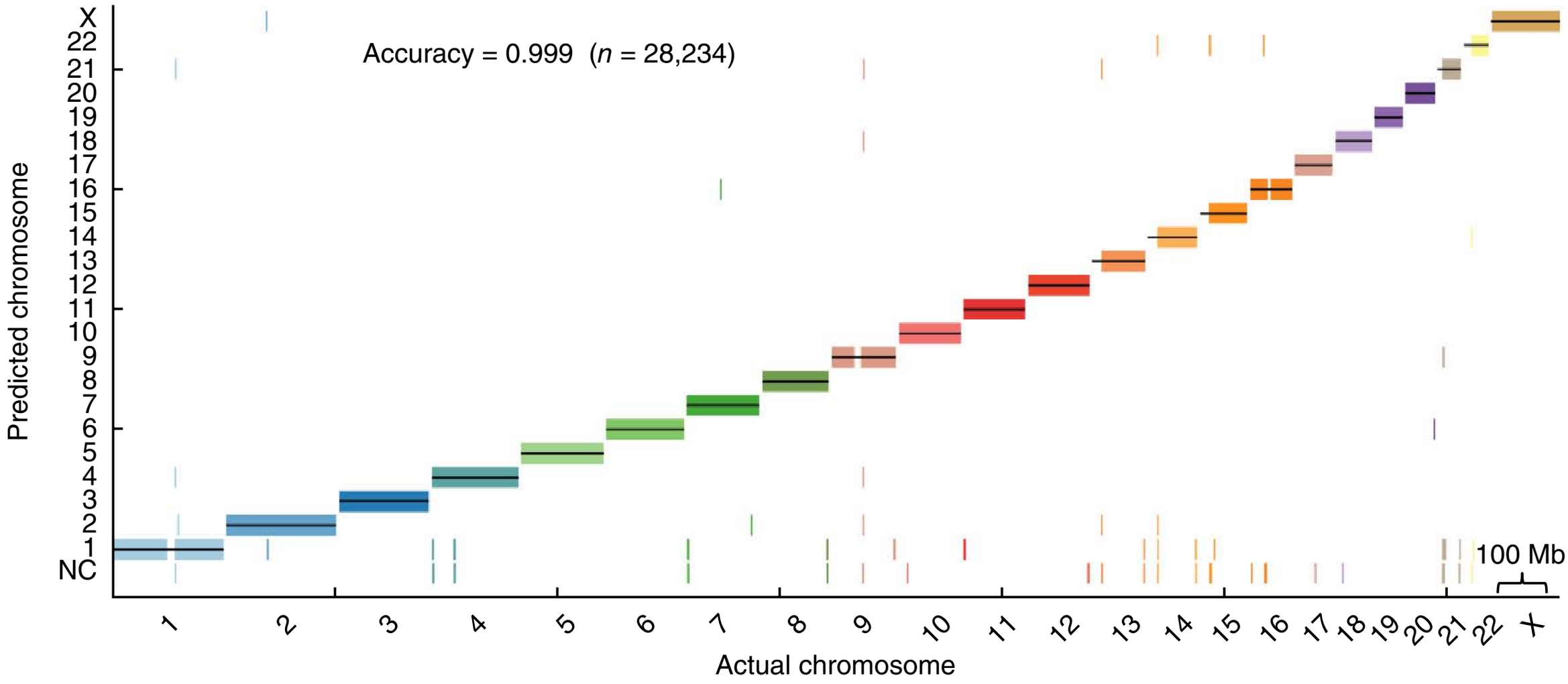


Hnisz, D., et al. (2016). Science, on line

3C Detour…

desirable side effects

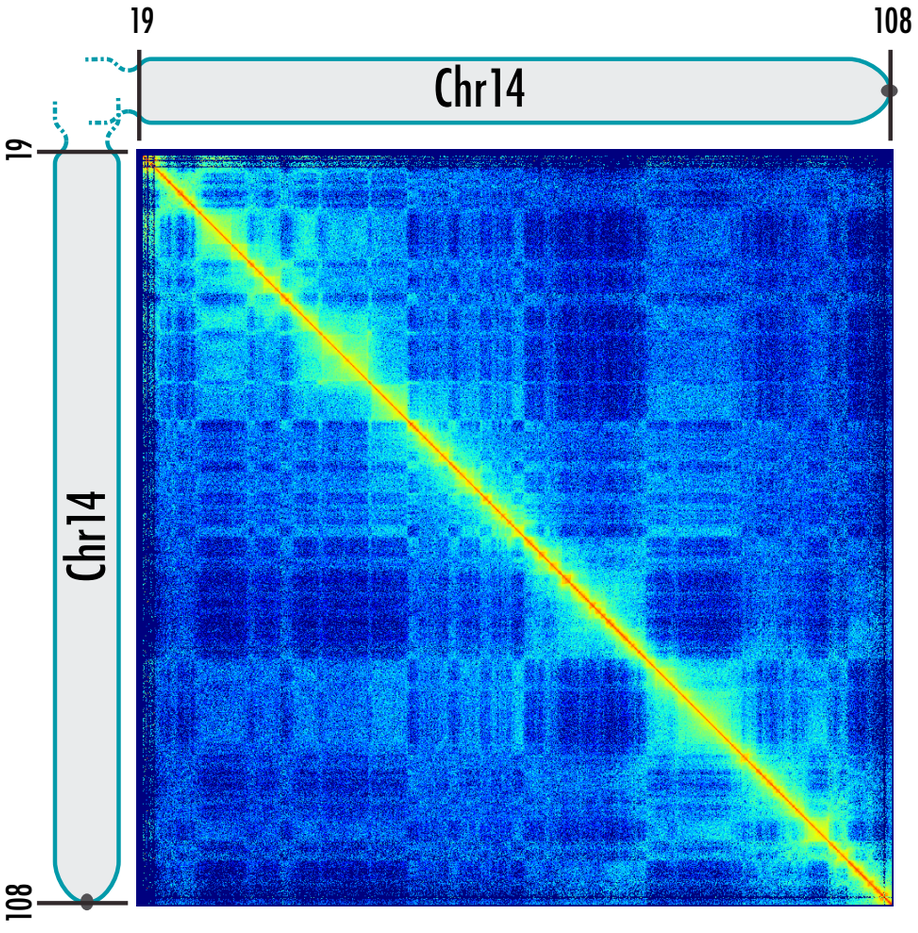
Chromosome Conformation Capture for de-novo assembly

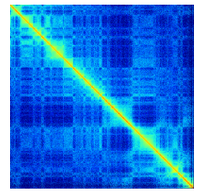


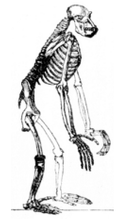
Kaplan, N., & Dekker, J. (2013). High-throughput genome scaffolding from in vivo DNA interaction frequency. Nature Biotechnology, 31(12), 1143–1147.

Great apes lymphoblast maps

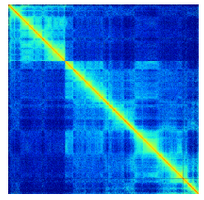
Chromosome 14

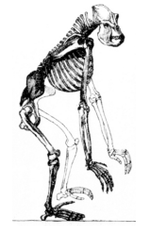




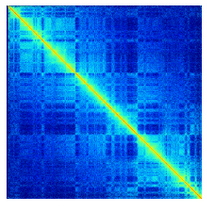


Chimpanzee

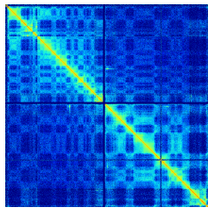




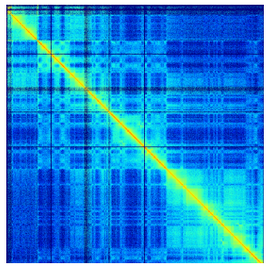
Gorilla



Orangutan



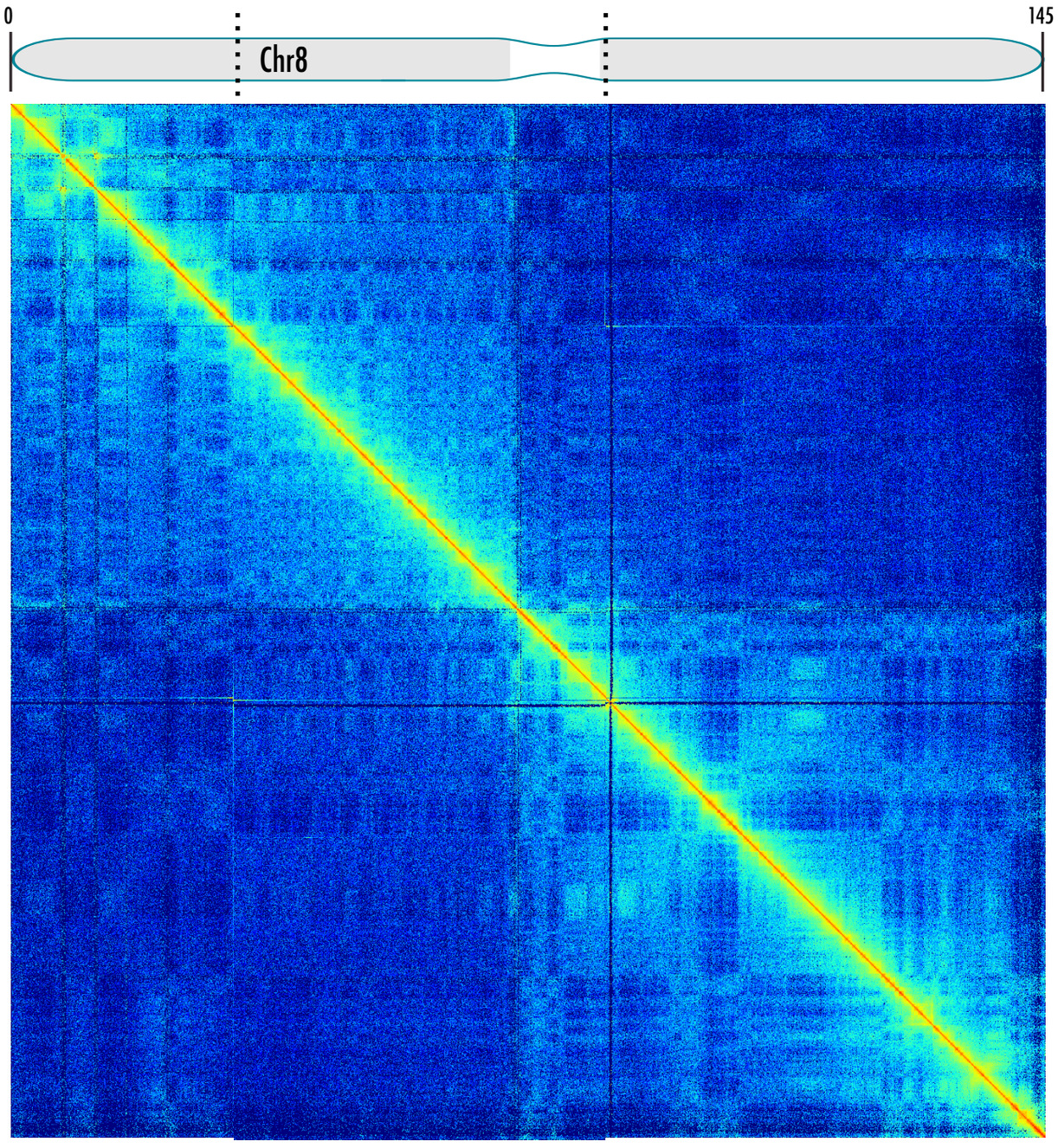
Gibbon



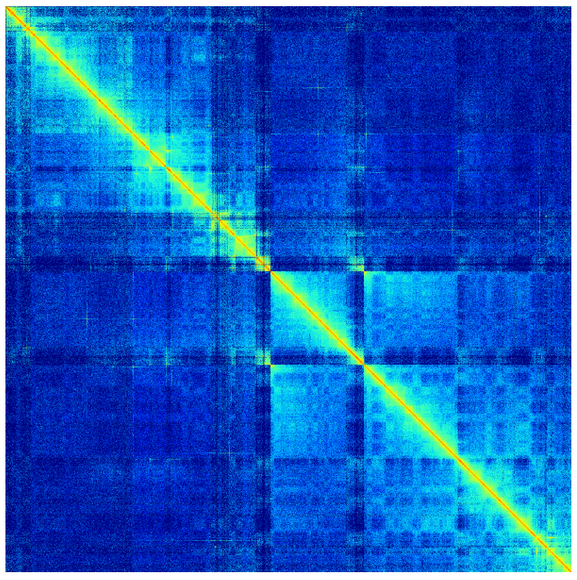
Mouse

Assembly error detection

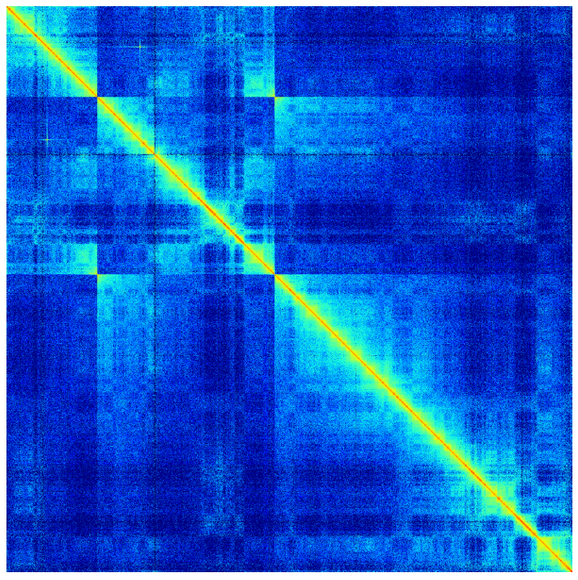
Chromosome 8 Gorilla



Chr 7

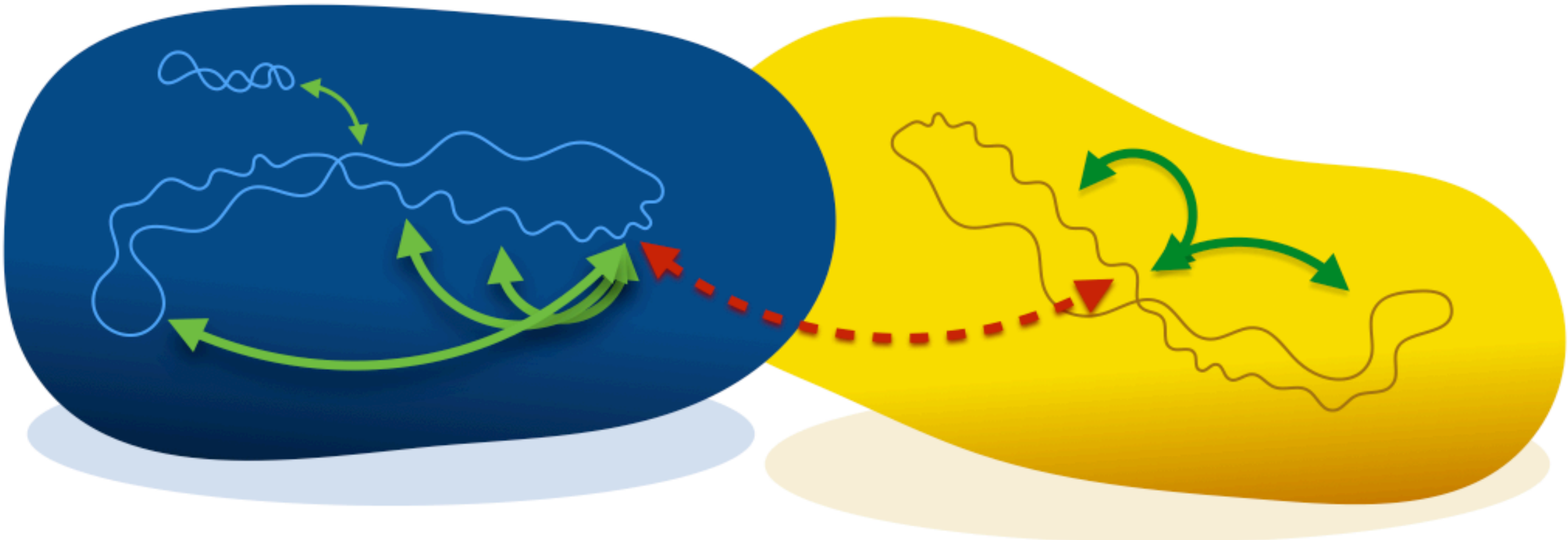


Chr 12



GGO8 has an inversion of the region corresponding to HSA8:30.0-86.9Mb
Aylwyn Scally (Department of Genetics, University of Cambridge)

Chromosome Conformation Capture for meta genomics



Beitel, C. W., Froenicke, L., Lang, J. M., Korf, I. F., Michelmore, R. W., Eisen, J. A., & Darling, A. E. (2014). Strain- and plasmid-level deconvolution of a synthetic metagenome by sequencing proximity ligation products. doi:10.7287/peerj.preprints.260v1

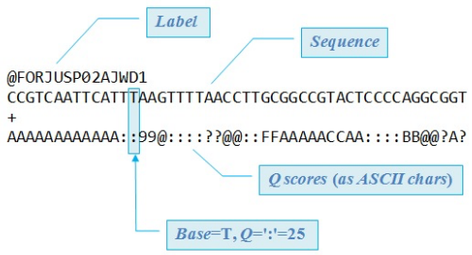
Structure determination of genomes and genomic domains by satisfaction of spatial restraints

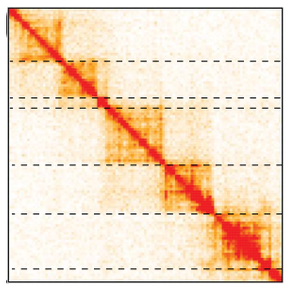
Marc A. Marti-Renom
Structural Genomics Group (ICREA, CNAG-CRG)

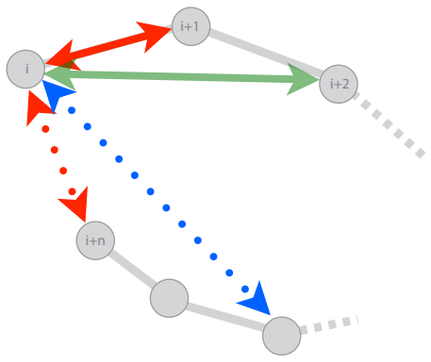
http://marciuslab.org
http://3DGenomes.org
http://cnag.crg.eu

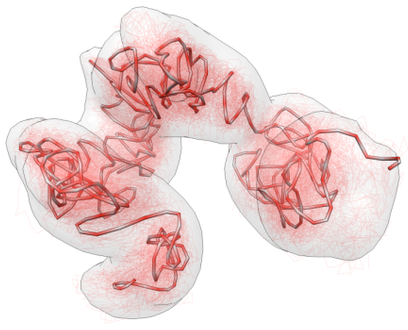
TADbit

http://3DGenomes.org







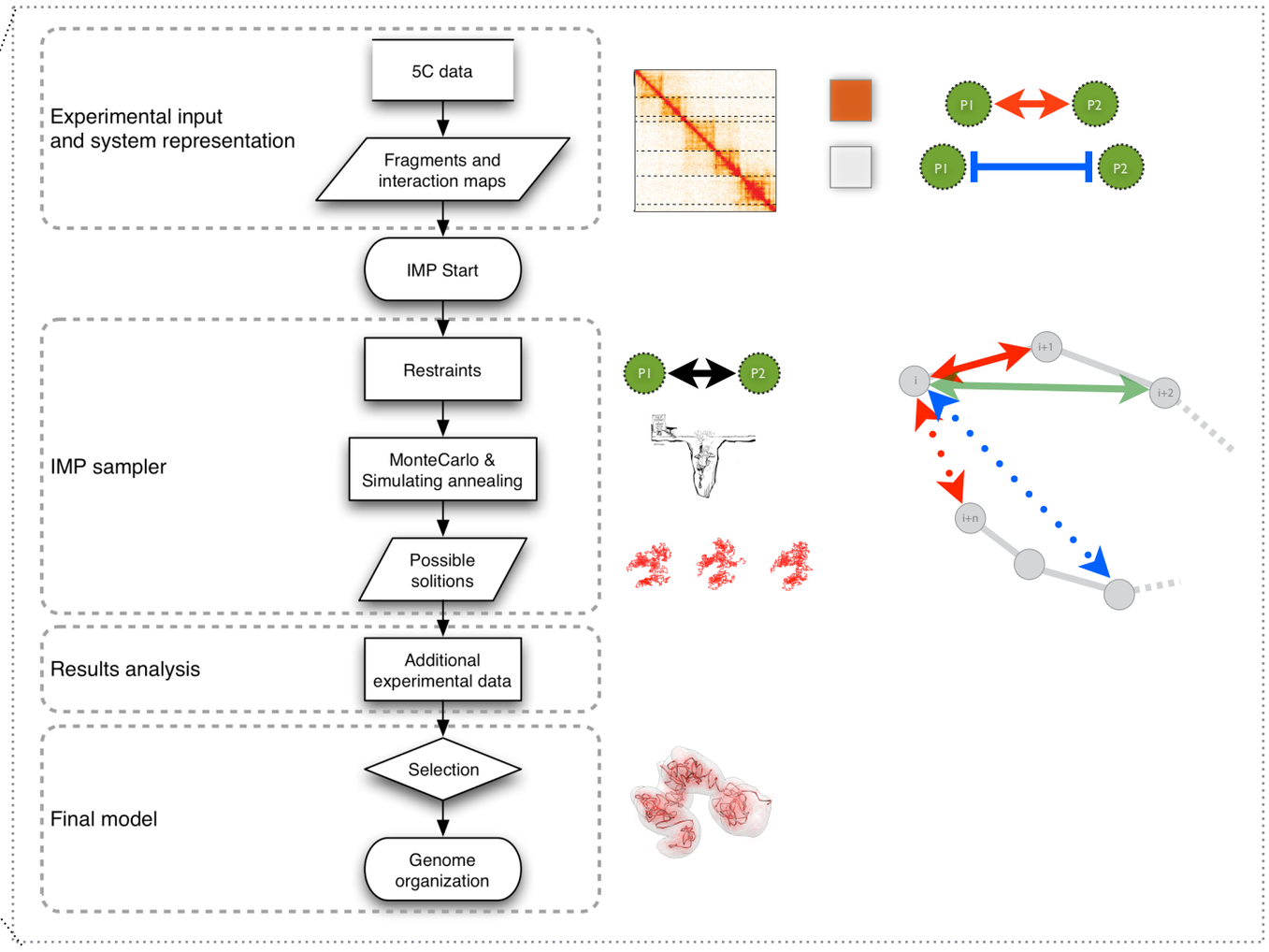


FastQ files to Maps

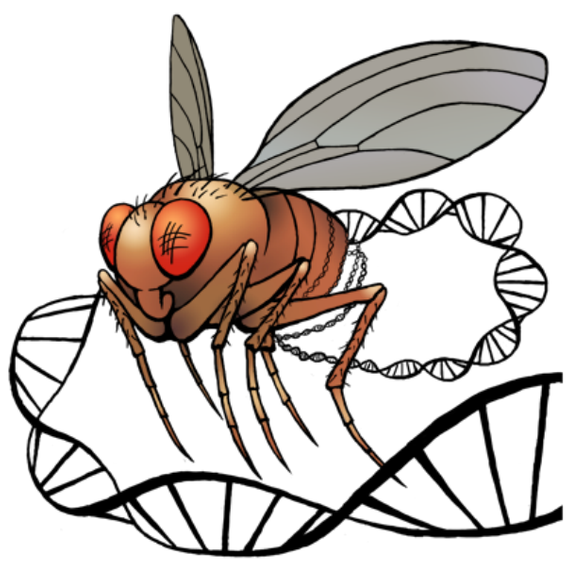
Map analysis

Model building

Model analysis

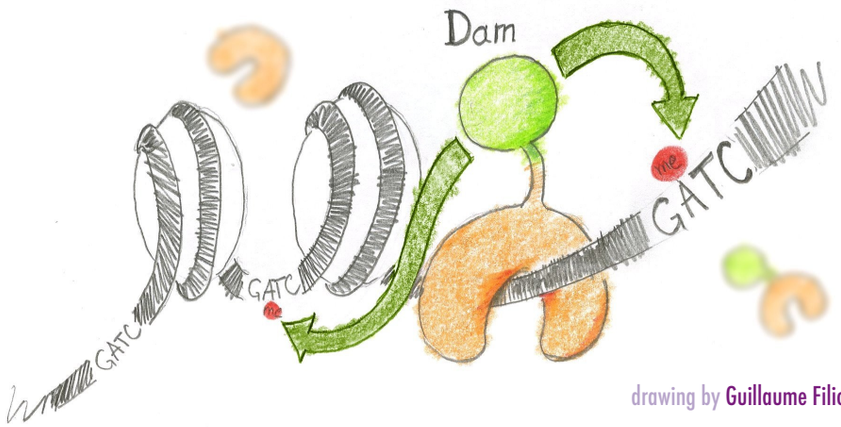


Structuring the COLORs of chromatin

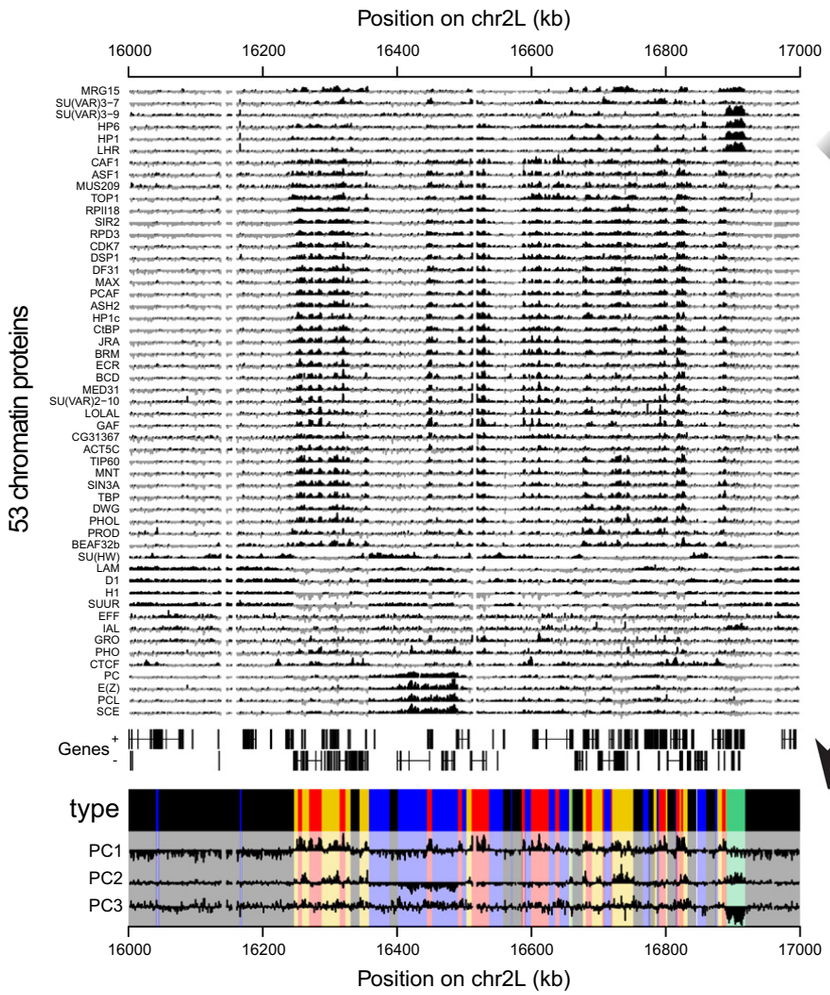


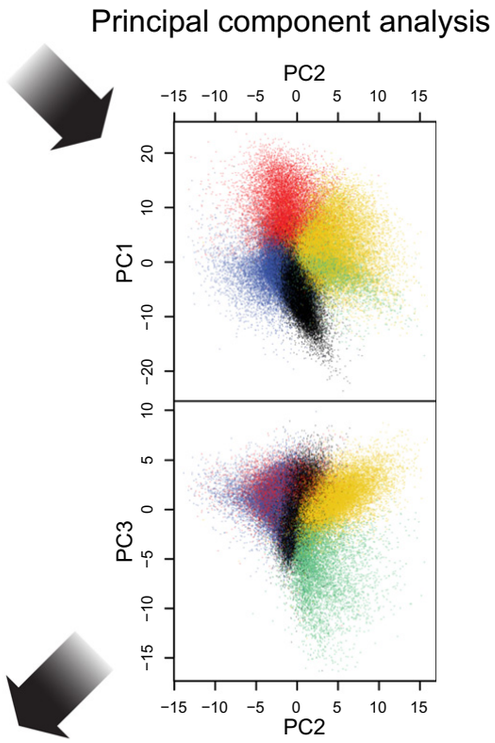
Fly Chromatin COLORs

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

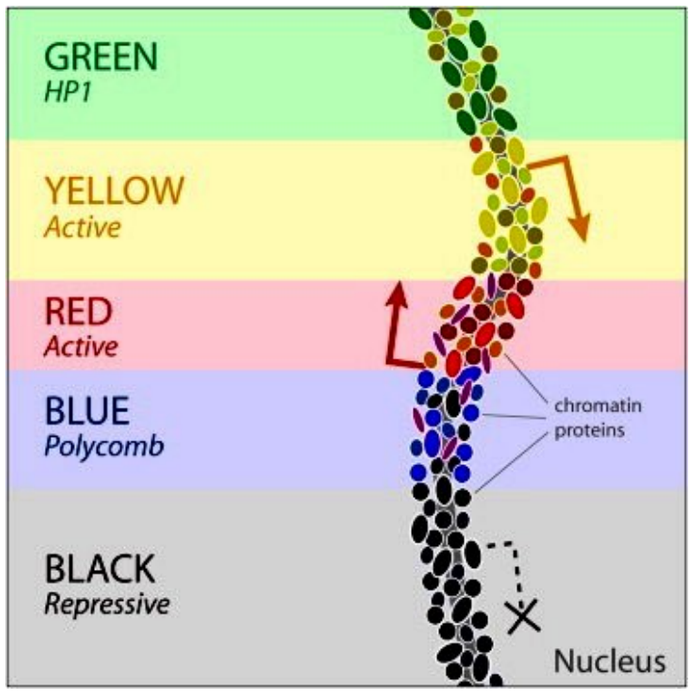


drawing by Guillaume Filion



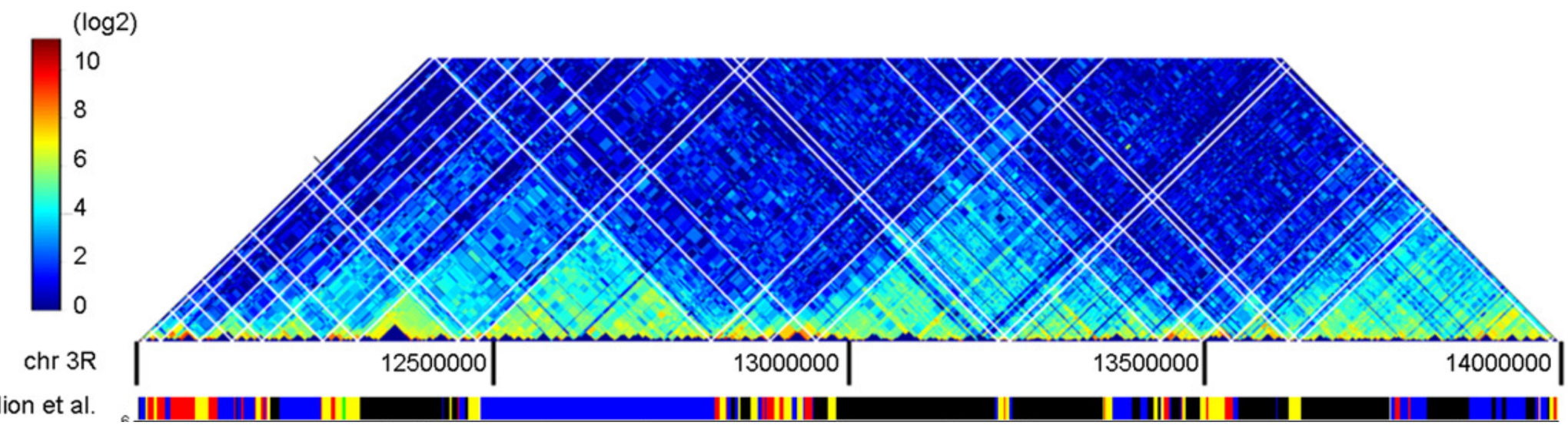


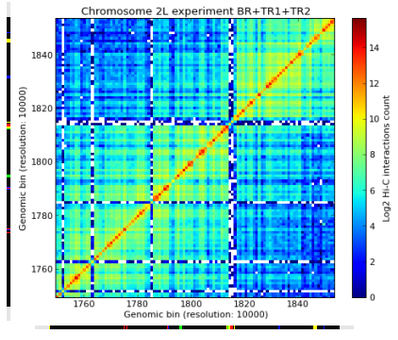
Hidden Markov model

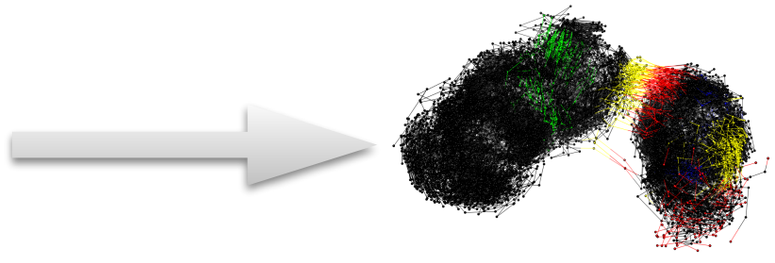


Fly Chromatin COLORs

Hou et al. (2012). Molecular Cell, 48(3), 471–484.



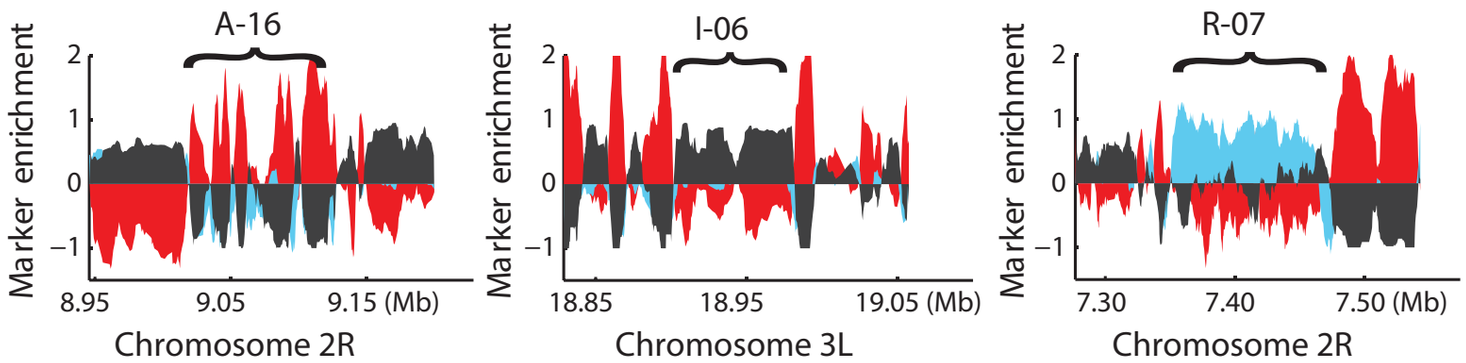


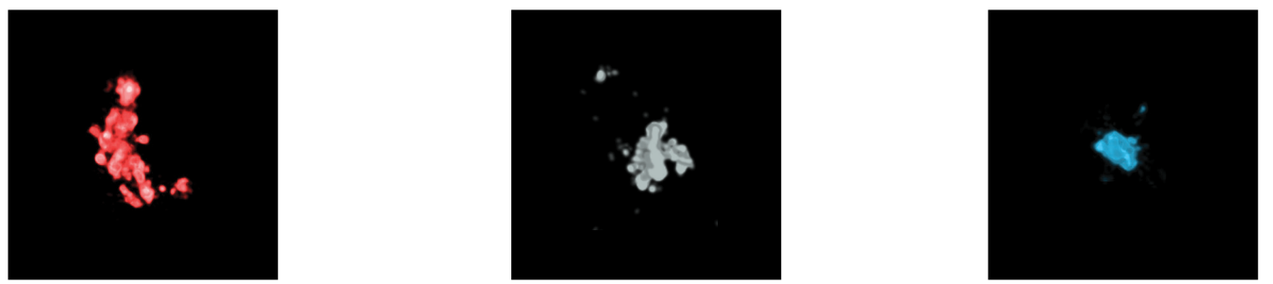


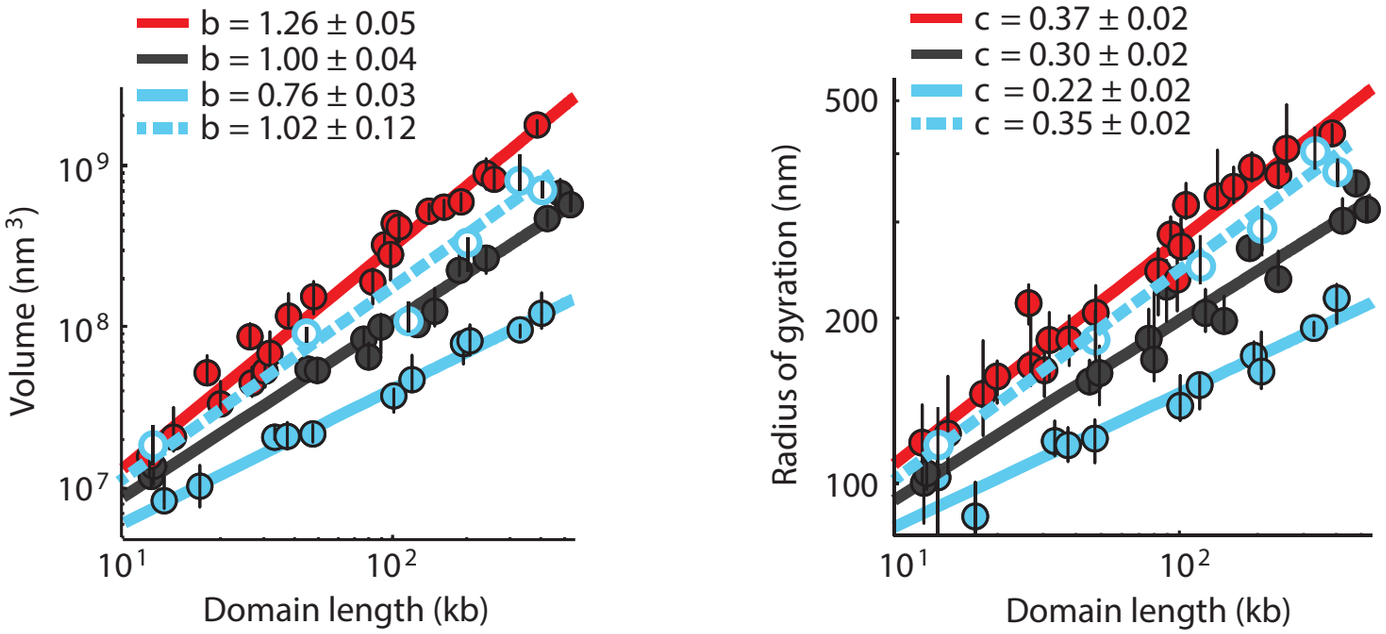
~200 regions of ~5Mb each
2Kb resolution

Model accuracy

Boettiger, A. N., et al. (2016). Nature, 1–15.

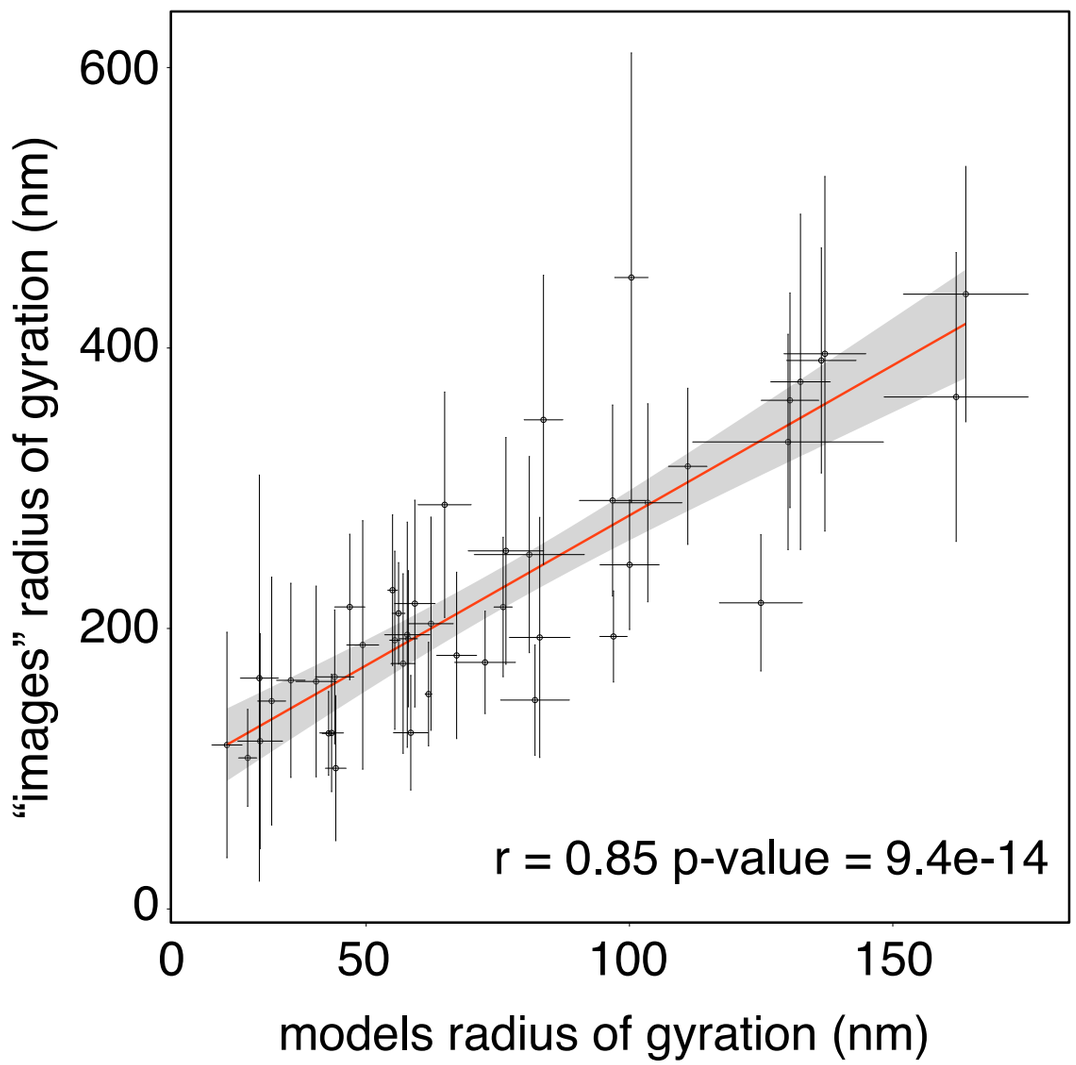


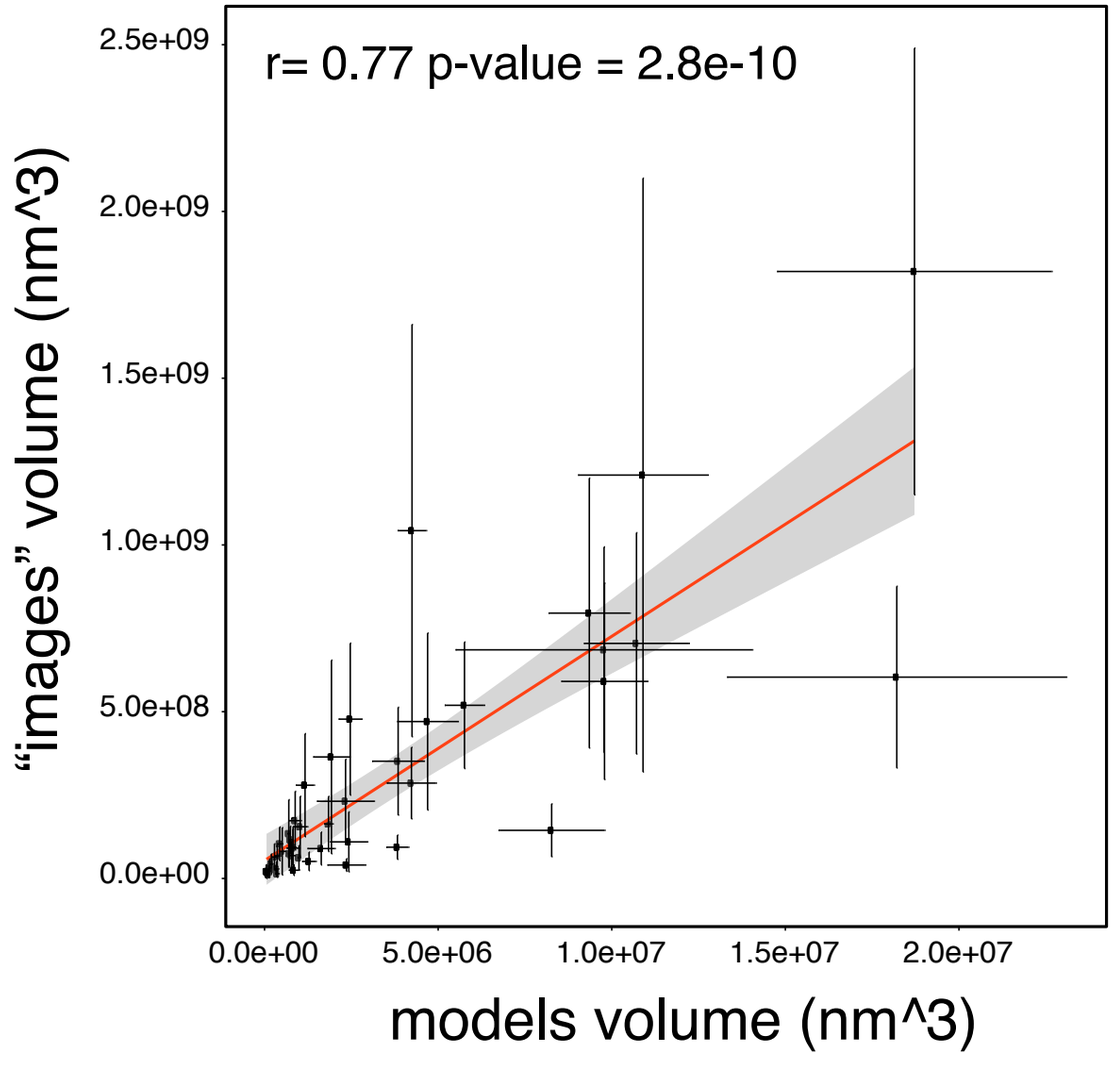




Model accuracy

Boettiger, A. N., et al. (2016). Nature, 1–15.



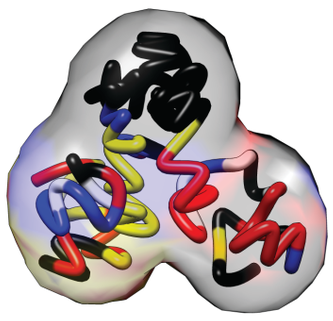


Structural properties

50 1Mb regions. 10 enriched for each color.

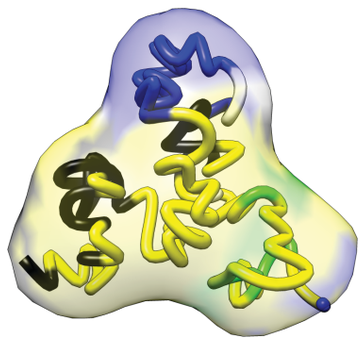
RED dense region
3R:18920000-19920000

22% 17% 0% 11% 45% 6%



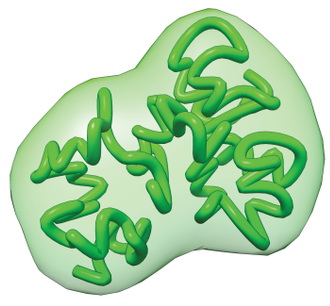
YELLOW dense region
X:15590000-16600000

0% 48% 4% 20% 26% 3%



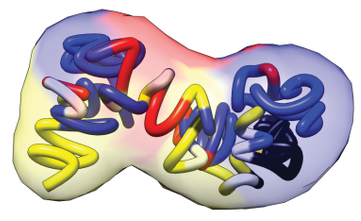
GREEN dense region
2R:510000-1530000

0% 0% 100% 0% 0% 0%



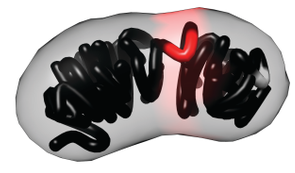
BLUE dense region
3L:210000-1230000

11% 17% 0% 52% 13% 0%

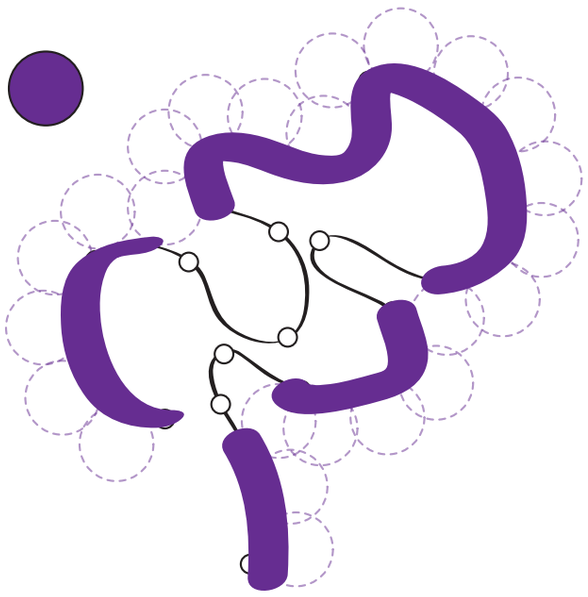


BLACK dense region
2L:17500000-18530000

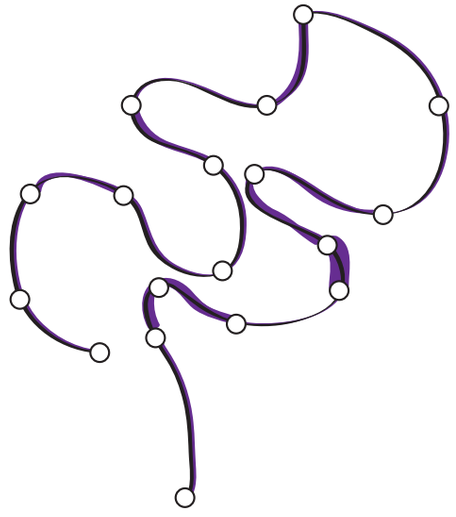
1% 0% 0% 0% 98% 1%



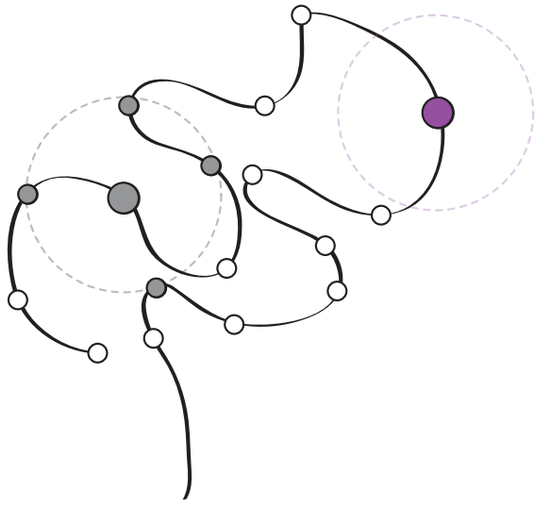
Accessibility (%)



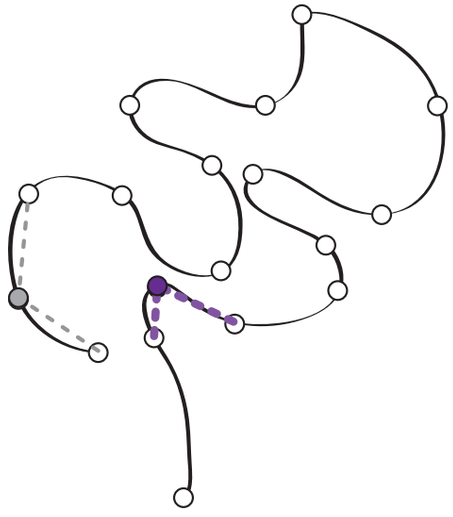
Density (bp/nm)



Interactions



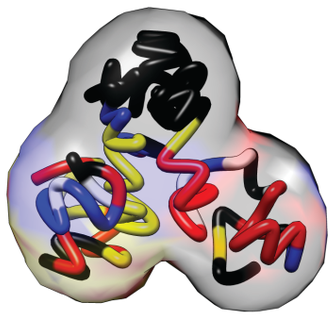
Angle



Structural COLORs

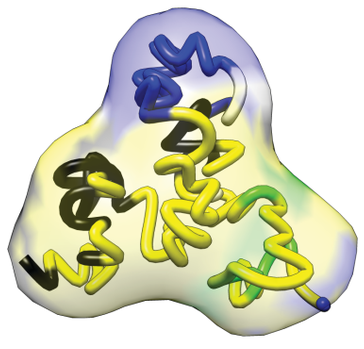
RED dense region
3R:18920000-19920000

22% 17% 0% 11% 45% 6%



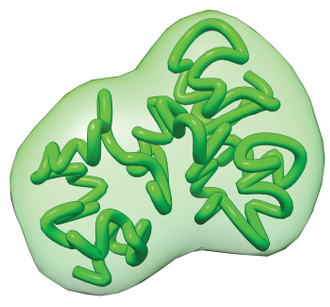
YELLOW dense region
X:15590000-16600000

0% 48% 4% 20% 26% 3%



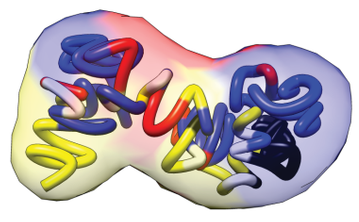
GREEN dense region
2R:510000-1530000

0% 0% 100% 0% 0% 0%



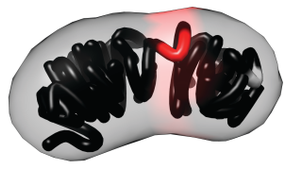
BLUE dense region
3L:210000-1230000

11% 17% 0% 52% 13% 0%

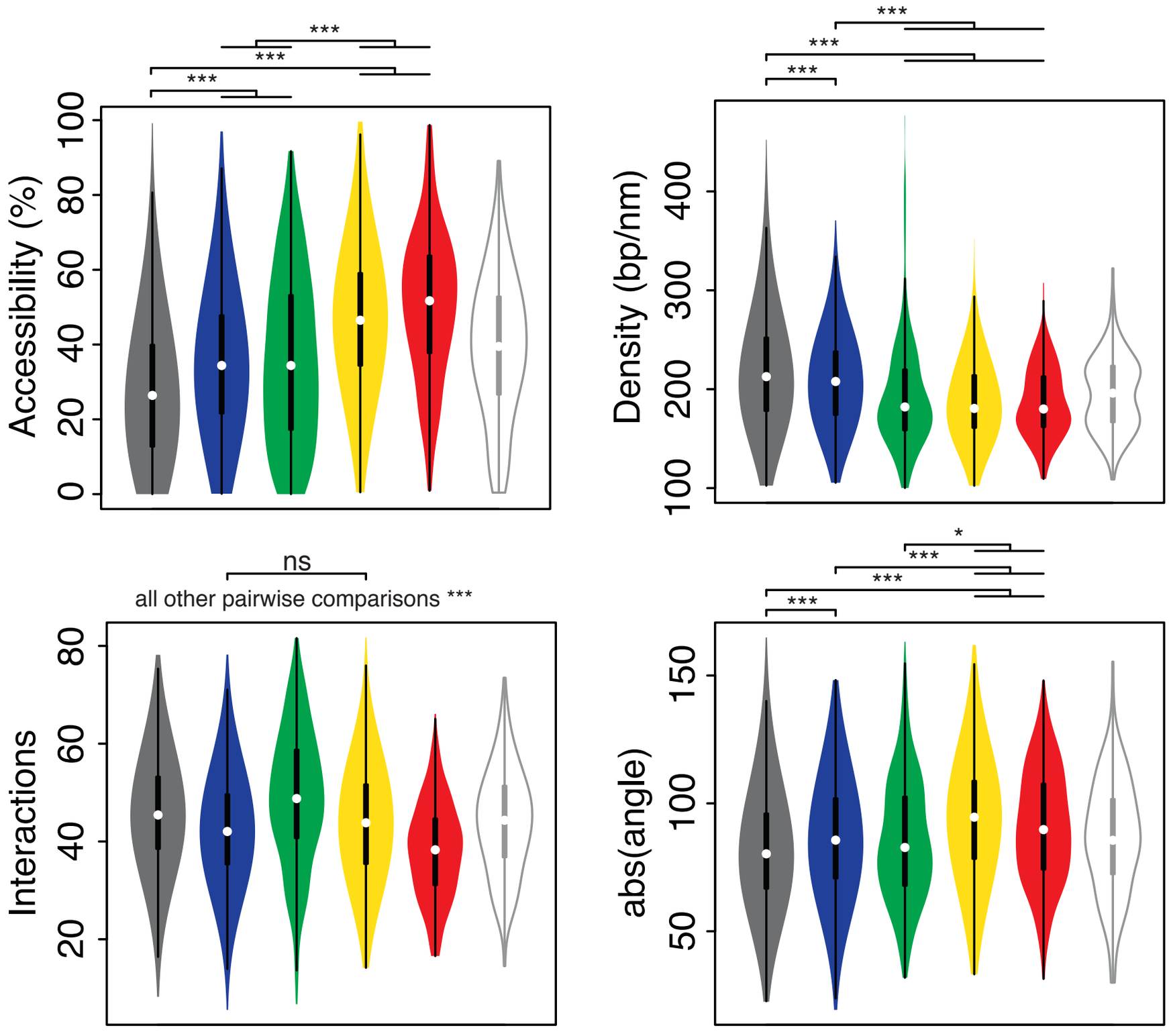


BLACK dense region
2L:17500000-18530000

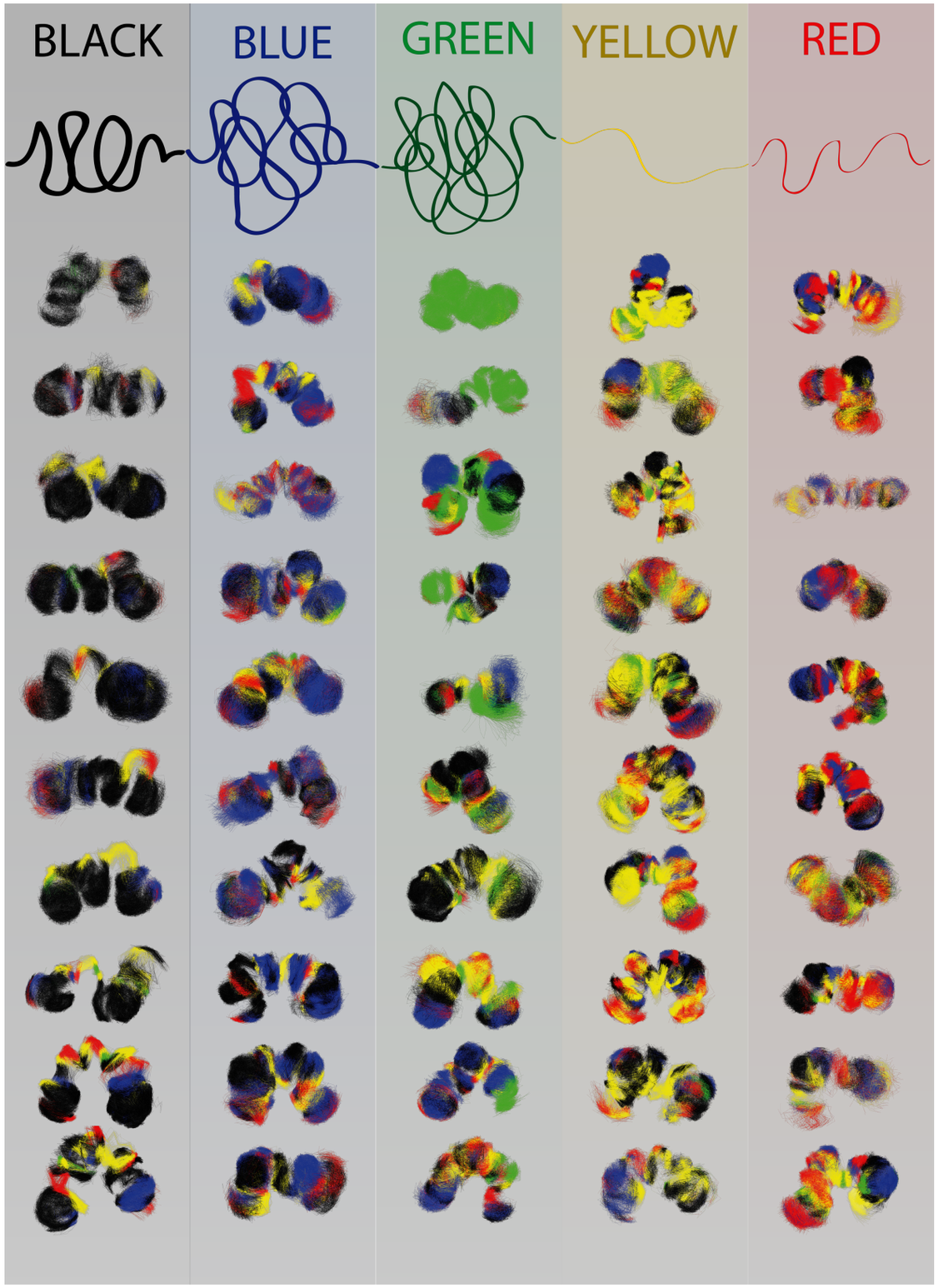
1% 0% 0% 0% 98% 1%

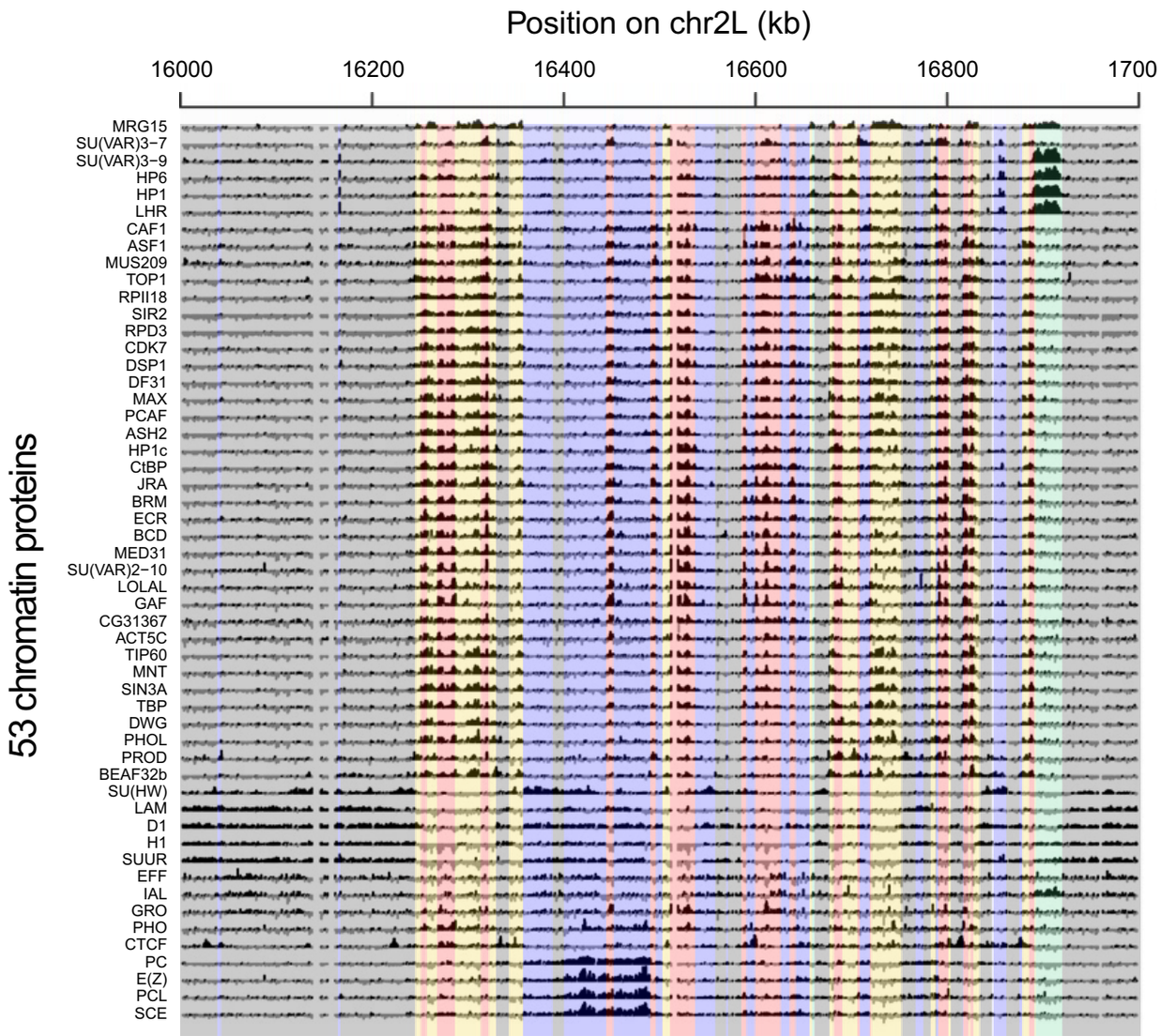


Structural COLORs

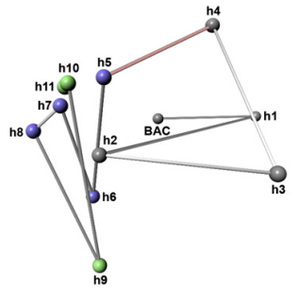


Structural COLORs

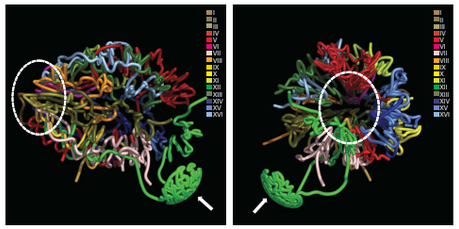




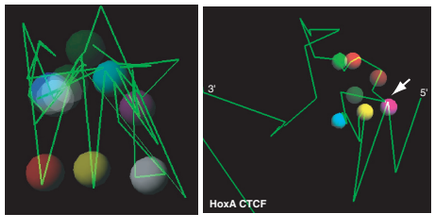
Are the models correct?



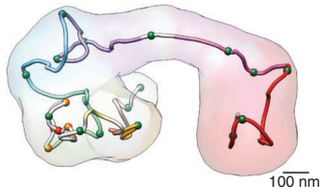
Jhunjhunwala (2008) Cell



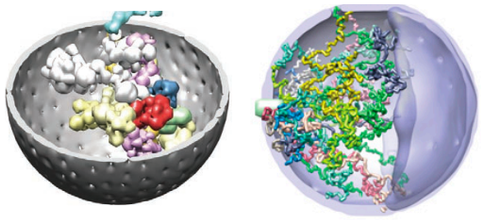
Duan (2010) Nature



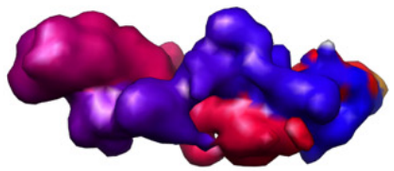
Fraser (2009) Genome Biology
Ferraiuolo (2010) Nucleic Acids Research



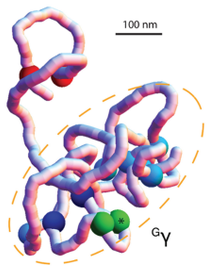
Baù (2011) Nature Structural & Molecular Biology



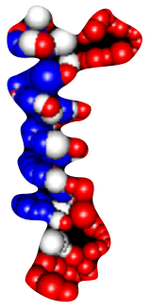
Kalhor (2011) Nature Biotechnology
Tjong (2012) Genome Research



Umbarger (2011) Molecular Cell



Junier (2012) Nucleic Acids Research



Hu (2013) PLoS Computational Biology

Nucleic Acids Research Advance Access published March 23, 2015

Nucleic Acids Research, 2015 **1**
doi: 10.1093/nar/gkv221

Assessing the limits of restraint-based 3D modeling of genomes and genomic domains

Marie Trussart[1,2], François Serra[3,4], Davide Baù[3,4], Ivan Junier[2,3], Luís Serrano[1,2,5] and Marc A. Marti-Renom[3,4,5,*]

[1]EMBL/CRG Systems Biology Research Unit, Centre for Genomic Regulation (CRG), Barcelona, Spain, [2]Universitat Pompeu Fabra (UPF), Barcelona, Spain, [3]Gene Regulation, Stem Cells and Cancer Program, Centre for Genomic Regulation (CRG), Barcelona, Spain, [4]Genome Biology Group, Centre Nacional d'Anàlisi Genòmica (CNAG), Barcelona, Spain and [5]Institució Catalana de Recerca i Estudis Avançats (ICREA), Barcelona, Spain

Received January 16, 2015; Revised February 16, 2015; Accepted February 22, 2015

ABSTRACT

Restraint-based modeling of genomes has been recently explored with the advent of Chromosome Conformation Capture (3C-based) experiments. We previously developed a reconstruction method to resolve the 3D architecture of both prokaryotic and eukaryotic genomes using 3C-based data. These models were congruent with fluorescent imaging validation. However, the limits of such methods have not systematically been assessed. Here we propose the first evaluation of a mean-field restraint-based reconstruction of genomes by considering diverse chromosome architectures and different levels of data noise and structural variability. The results show that: first, current scoring functions for 3D reconstruction correlate with the accuracy of the models; second, reconstructed models are robust to noise but sensitive to structural variability; third, the local structure organization of genomes, such as Topologically Associating Domains, results in more accurate models; fourth, to a certain extent, the models capture the intrinsic structural variability in the input matrices and fifth, the accuracy of the models can be *a priori* predicted by analyzing the properties of the interaction matrices. In summary, our work provides a systematic analysis of the limitations of a mean-field restrain-based method, which could be taken into consideration in further development of methods as well as their applications.

INTRODUCTION

Recent studies of the three-dimensional (3D) conformation of genomes are revealing insights into the organization and the regulation of biological processes, such as gene expression regulation and replication (1–6). The advent of the so-called Chromosome Conformation Capture (3C) assays (7), which allowed identifying chromatin-looping interactions between pairs of loci, helped deciphering some of the key elements organizing the genomes. High-throughput derivations of genome-wide 3C-based assays were established with Hi-C technologies (8) for an unbiased identification of chromatin interactions. The resulting genome interaction matrices from Hi-C experiments have been extensively used for computationally analyzing the organization of genomes and genomic domains (5). In particular, a significant number of new approaches for modeling the 3D organization of genomes have recently flourished (9–14). The main goal of such approaches is to provide an accurate 3D representation of the bi-dimensional interaction matrices, which can then be more easily explored to extract biological insights. One type of methods for building 3D models from interaction matrices relies on the existence of a limited number of conformational states in the cell. Such methods are regarded as mean-field approaches and are able to capture, to a certain degree, the structural variability around these mean structures (15).

We recently developed a mean-field method for modeling 3D structures of genomes and genomic domains based on 3C interaction data (9). Our approach, called TADbit, was developed around the Integrative Modeling Platform (IMP, http://integrativemodeing.org), a general framework for restraint-based modeling of 3D bio-molecular structures (16). Briefly, our method uses chromatin interaction frequencies derived from experiments as a proxy of spatial proximity between the ligation products of the 3C libraries. Two fragments of DNA that interact with high frequency are dynamically placed close in space in our models while two fragments that do not interact as often will be kept apart. Our method has been successfully applied to model the structures of genomes and genomic domains in eukaryote and prokaryote organisms (17–19). In all of our studies, the final models were partially validated by assessing their

*To whom correspondence should be addressed. Tel: +34 934 020 542; Fax: +34 934 037 279; Email: mmarti@pcb.ub.cat

Trussart, et al. (2015). Nucleic Acids Research.

IMGR: a truly integrative method for chromatin path detection