

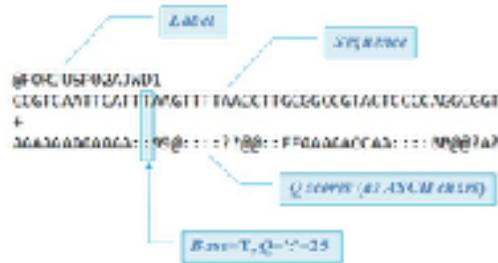
From FASTQ to 3DModels. TADbit...

François Serra, David Castillo & Marc A. Martí-Renom
Structural Genomics Group (CNAG-CRG)

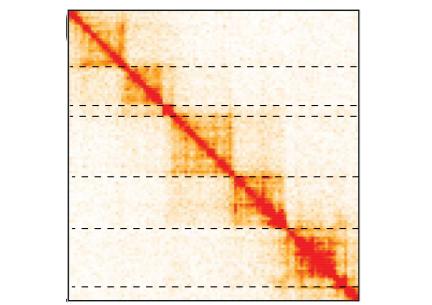




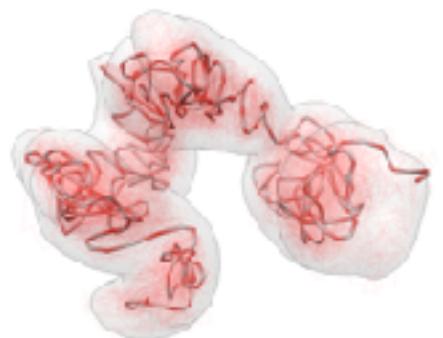
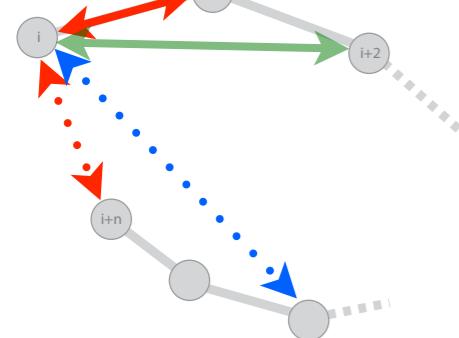
<http://3DGenomes.org>
<http://www.integrativemodeling.org>



FastQ files to Maps

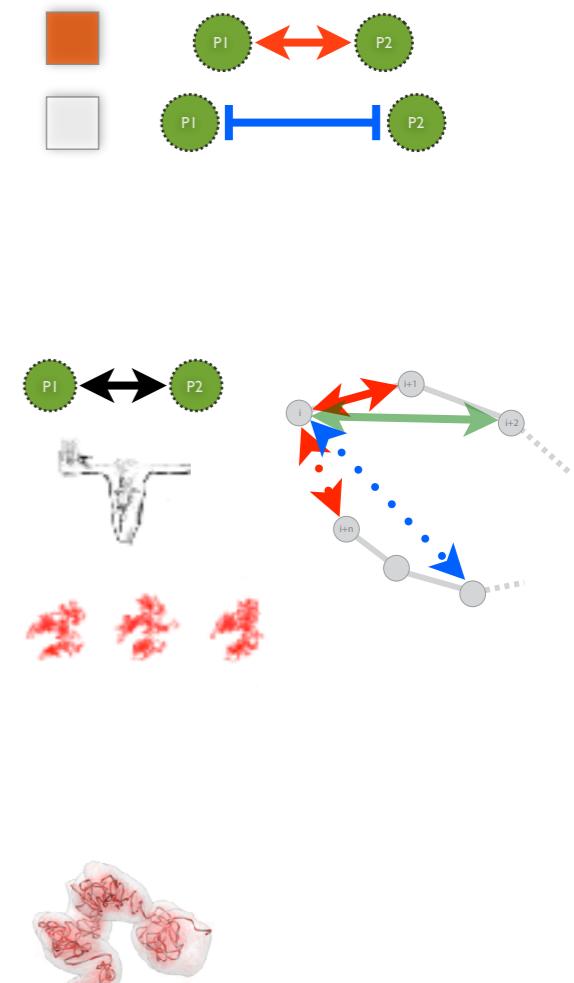
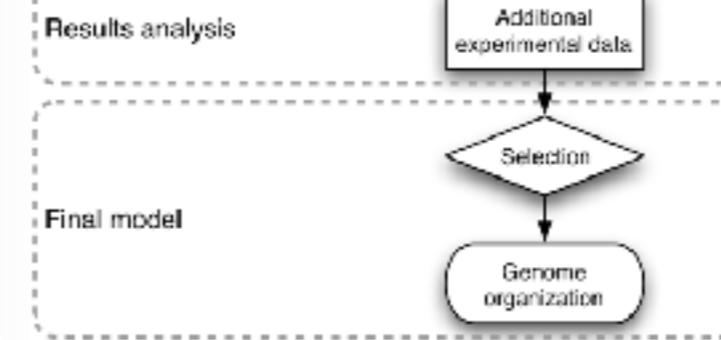
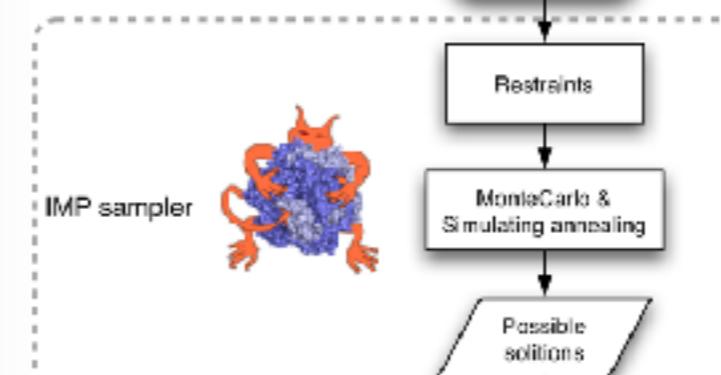
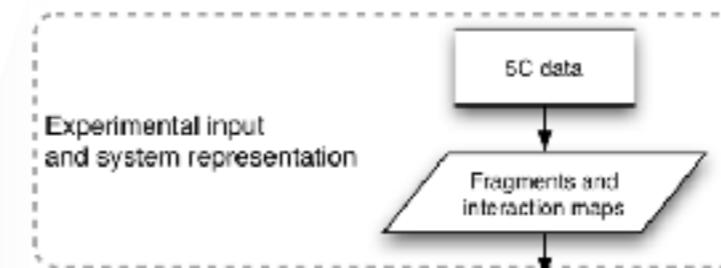


Map analysis



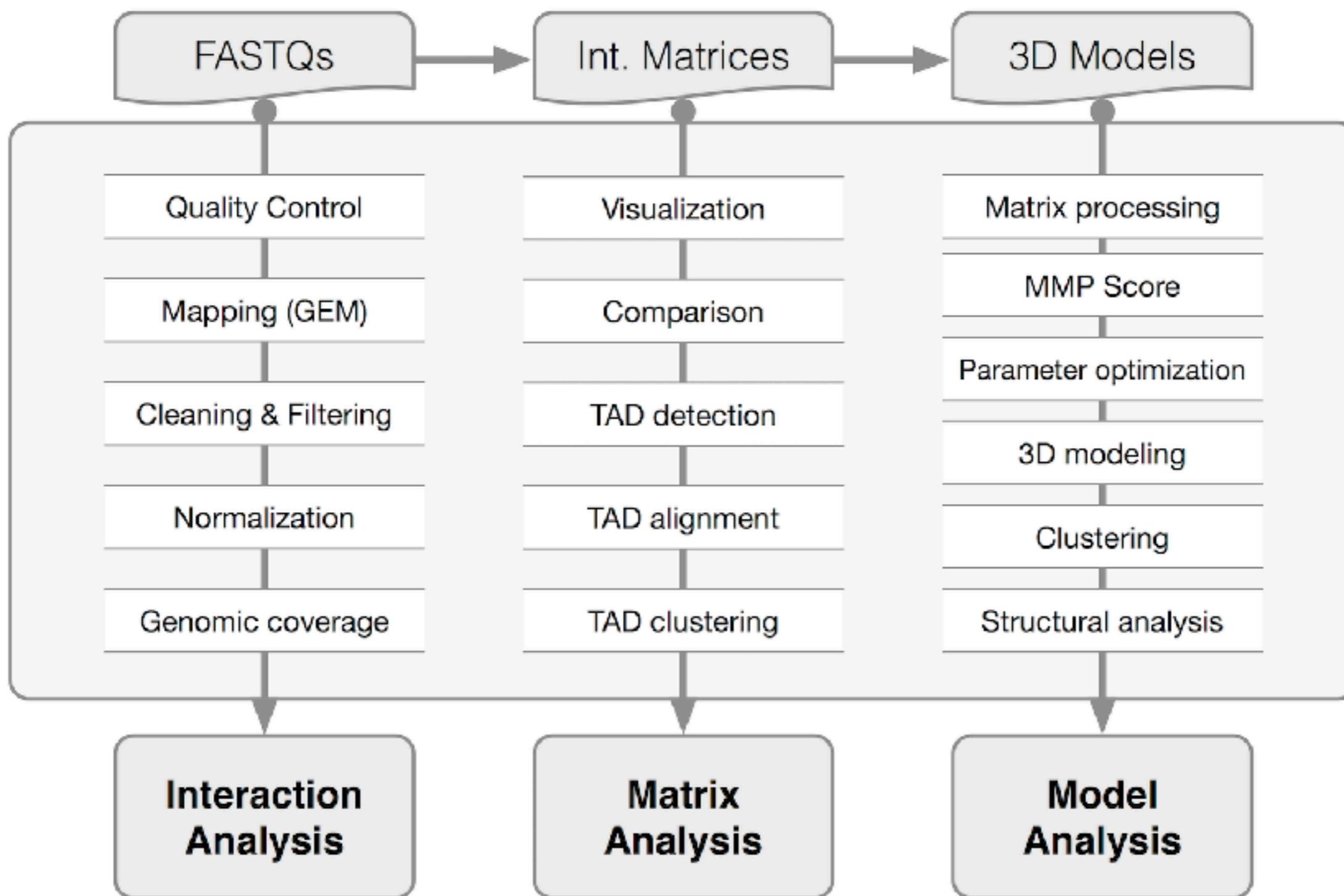
Model building

Model analysis





Serra, Baù, et al. (2017). PLOS CompBio

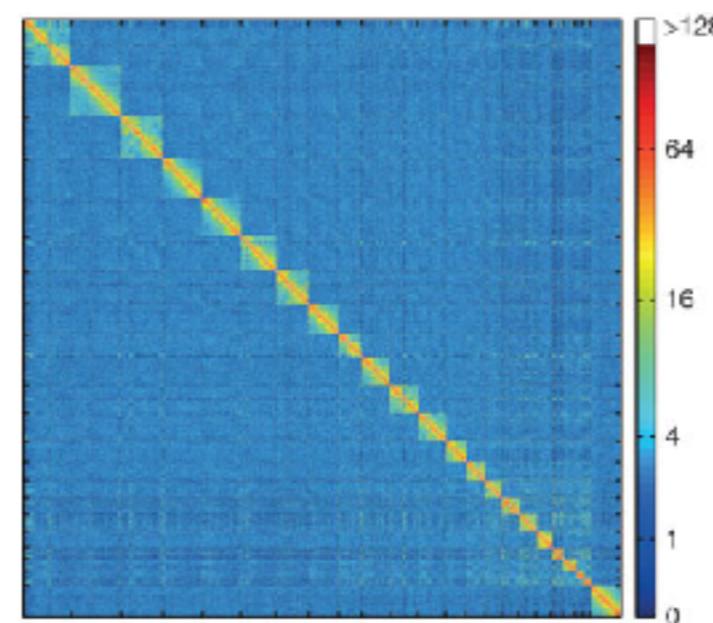
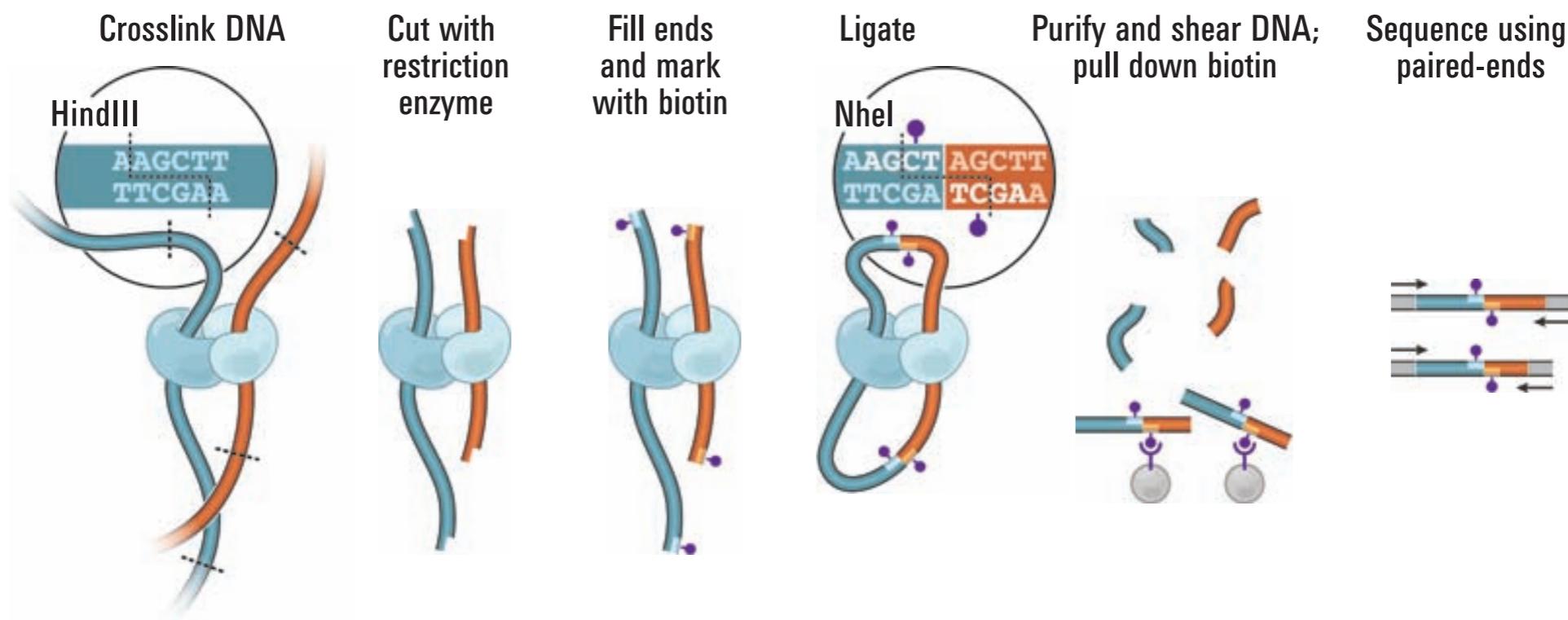




Got FASTQ?

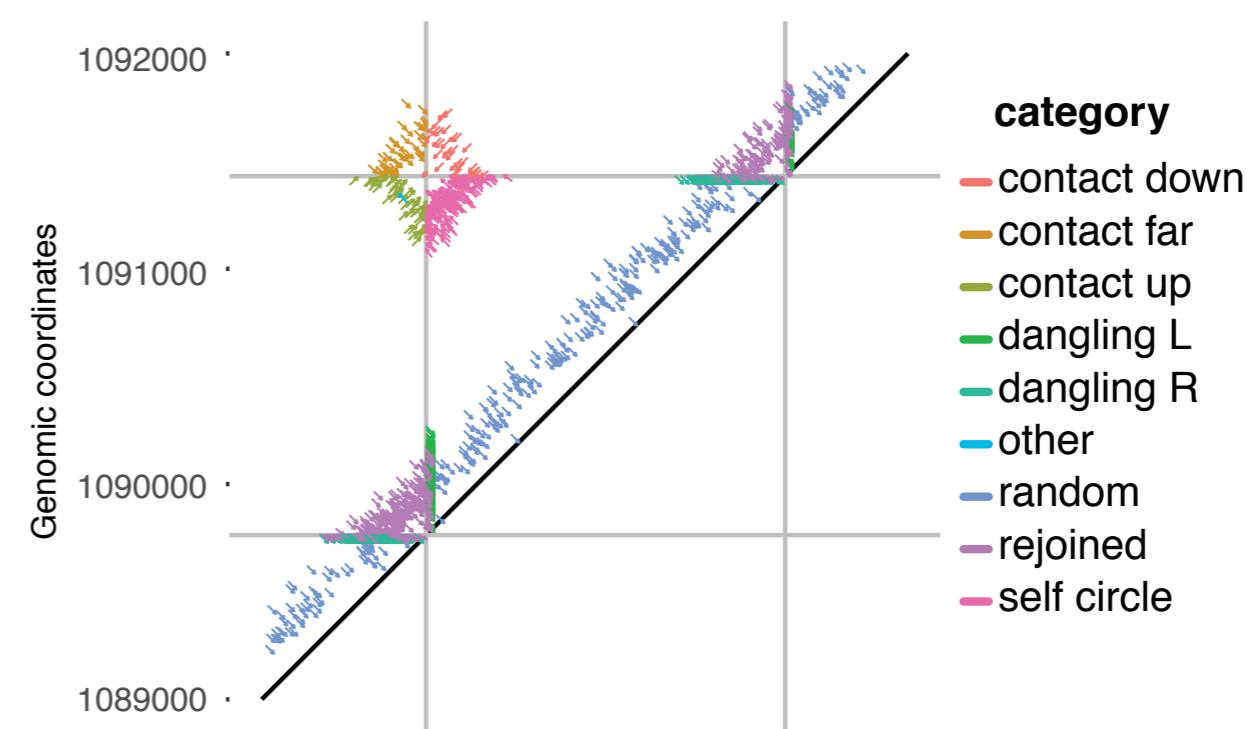
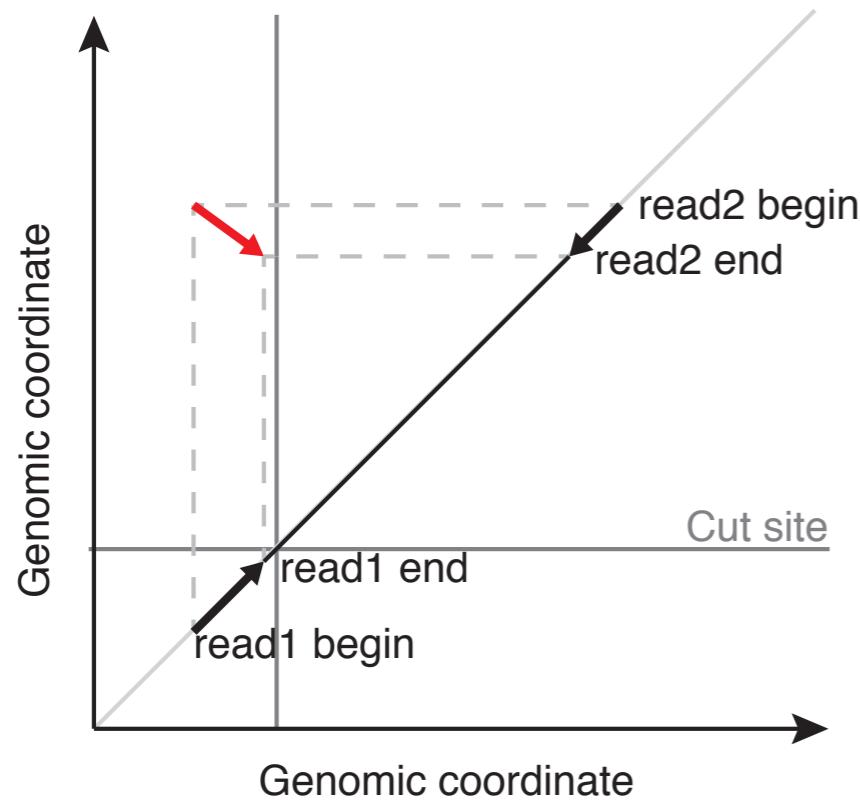
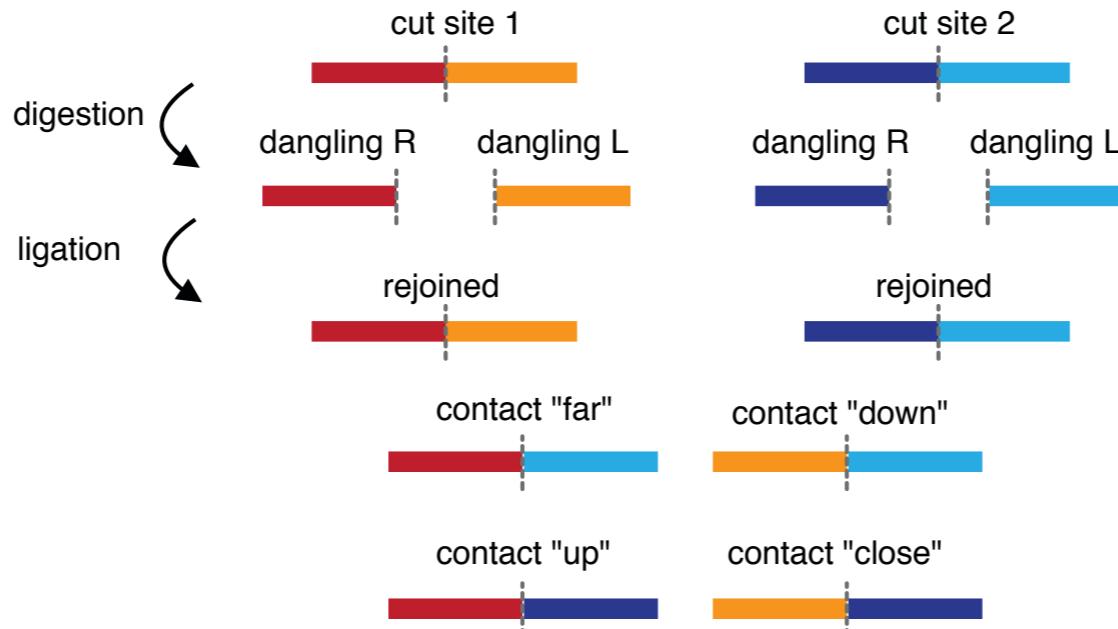
Hi-C experiment

Lieberman-Aiden, E., et al. (2009). Science, 326(5950), 289–293.



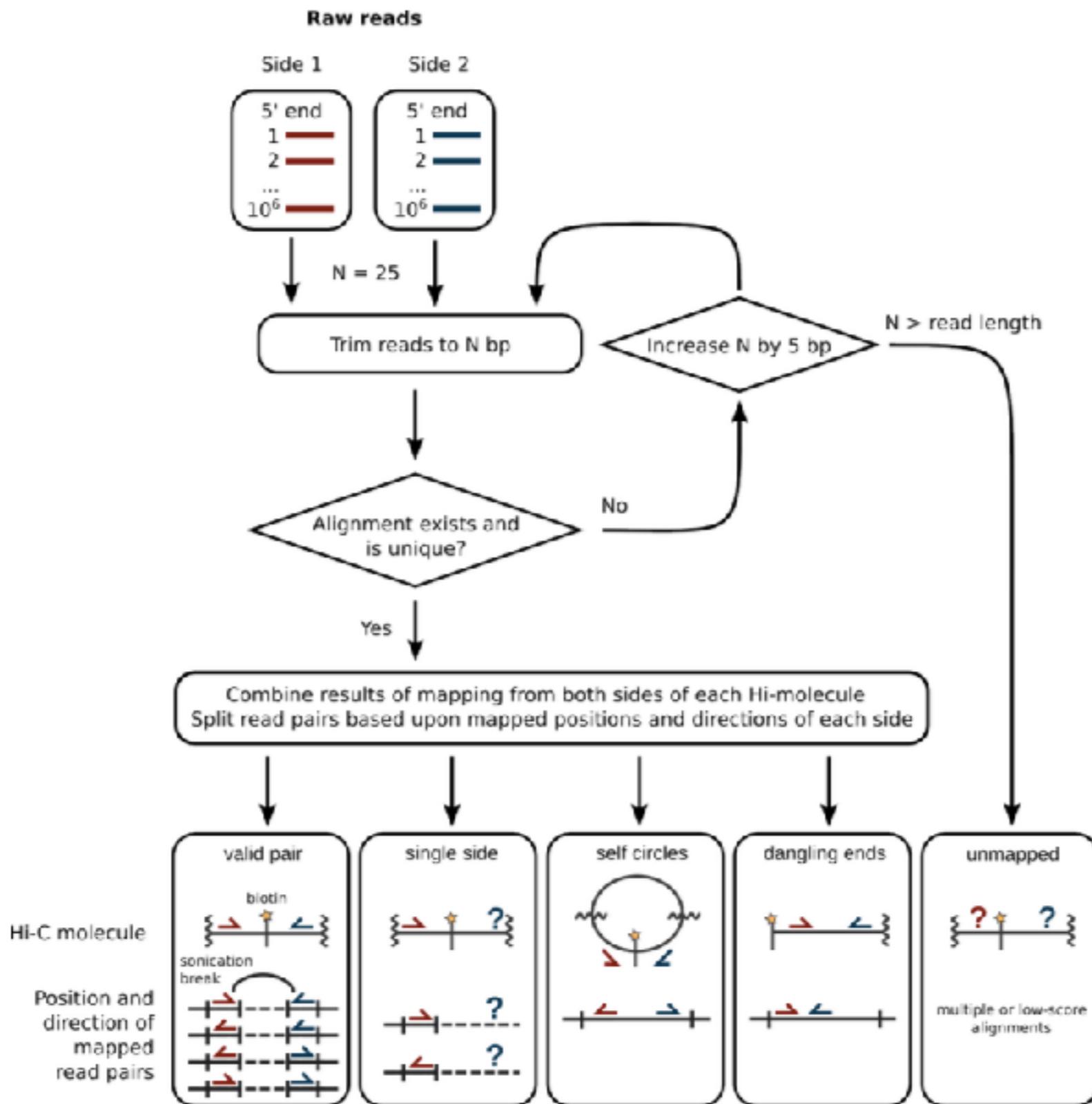
Mapping & Filtering

Imakaev, M. V et al. (2012). Nature Methods, 9(10), 999–1003.



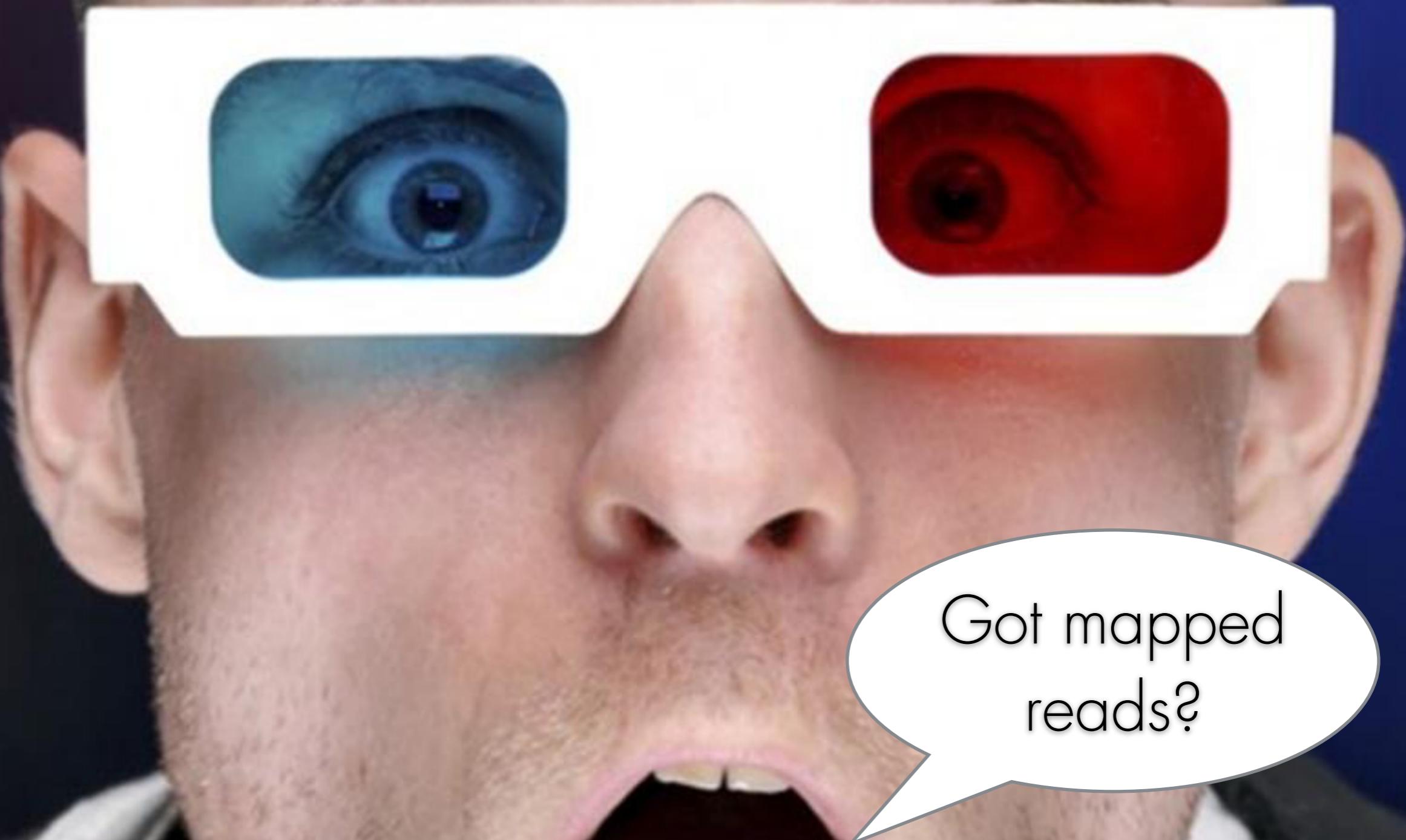
Mapping & Filtering

Imakaev, M. V et al. (2012). Nature Methods, 9(10), 999–1003.



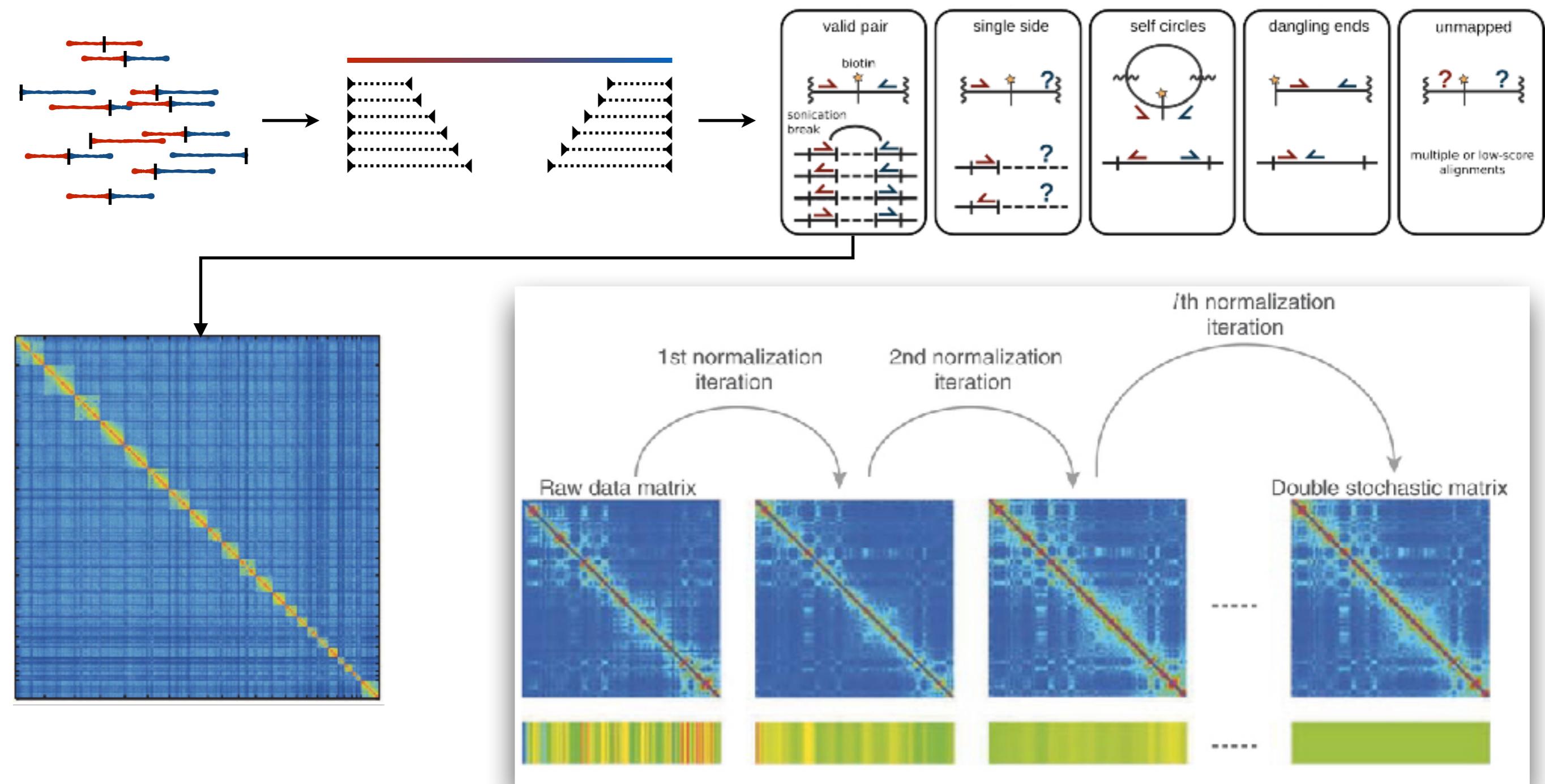
How much you normally map?

- 80-90% each end => 60-80% intersection
- ~1% multiple contacts
- Many of intersecting pairs will be lost in filtering...
- Final 40-60% of valid pairs
- One measure of quality is the CIS/TRANS ration
(70-80% good)



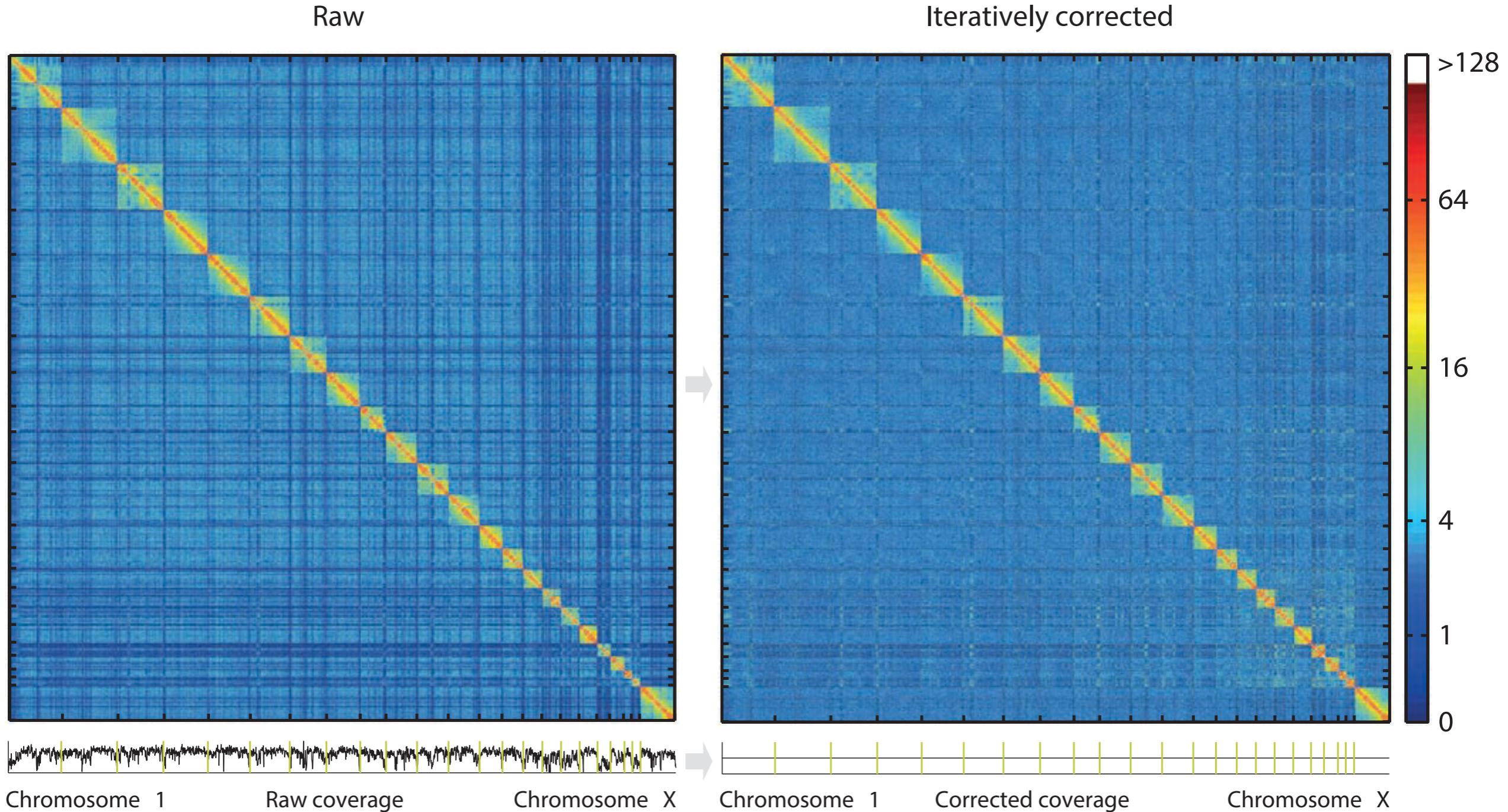
Got mapped
reads?

Interaction matrices



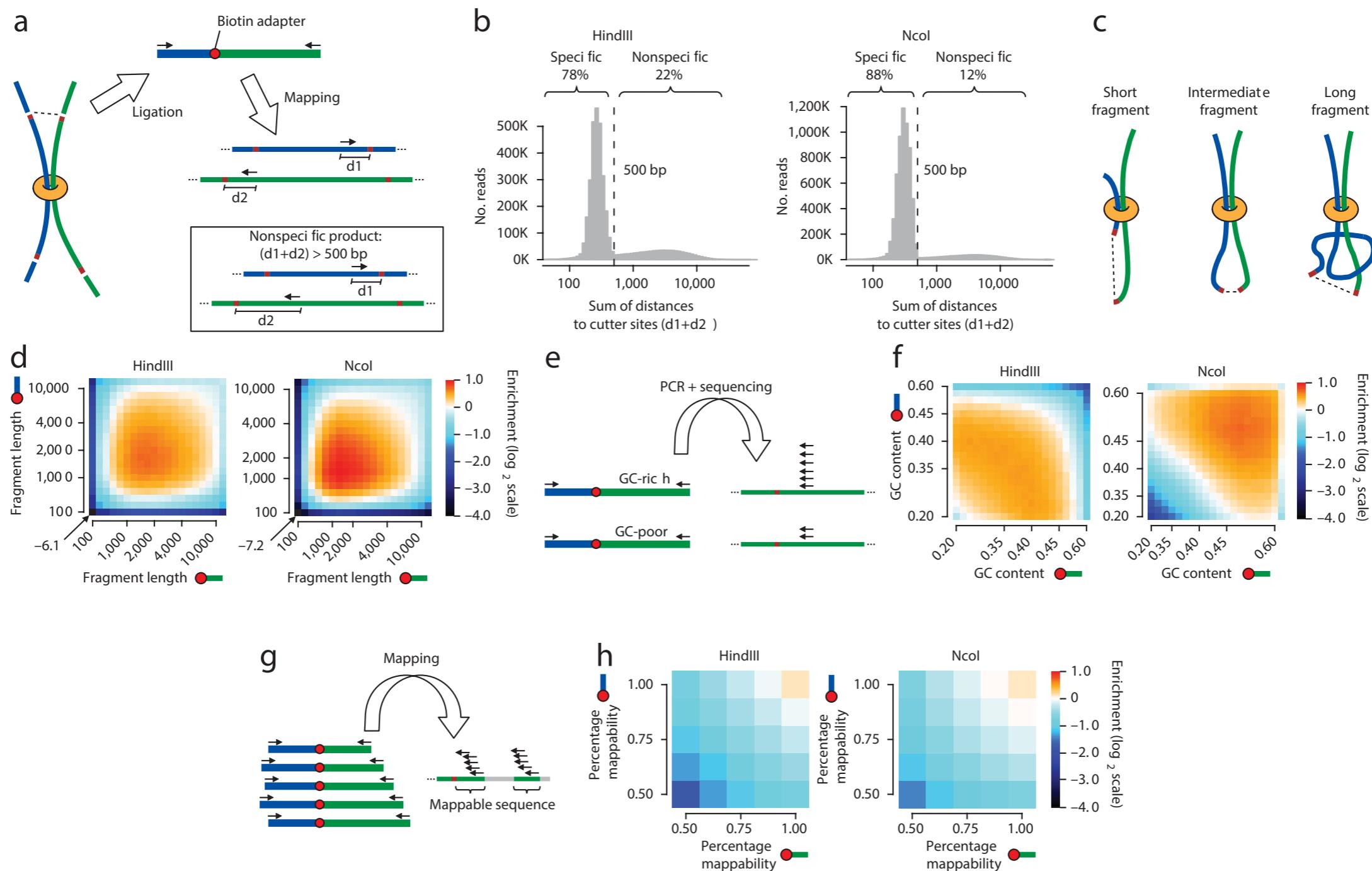
Zooming in on genome organization.
Zhou, X. J., & Alber, F. Nature Methods (2012)

Normalizing HiC data



Normalizing HiC data (a la Tanay)

Yaffe, E., & Tanay, A. (2011). Nature Genetics, 43(11), 1059–1065

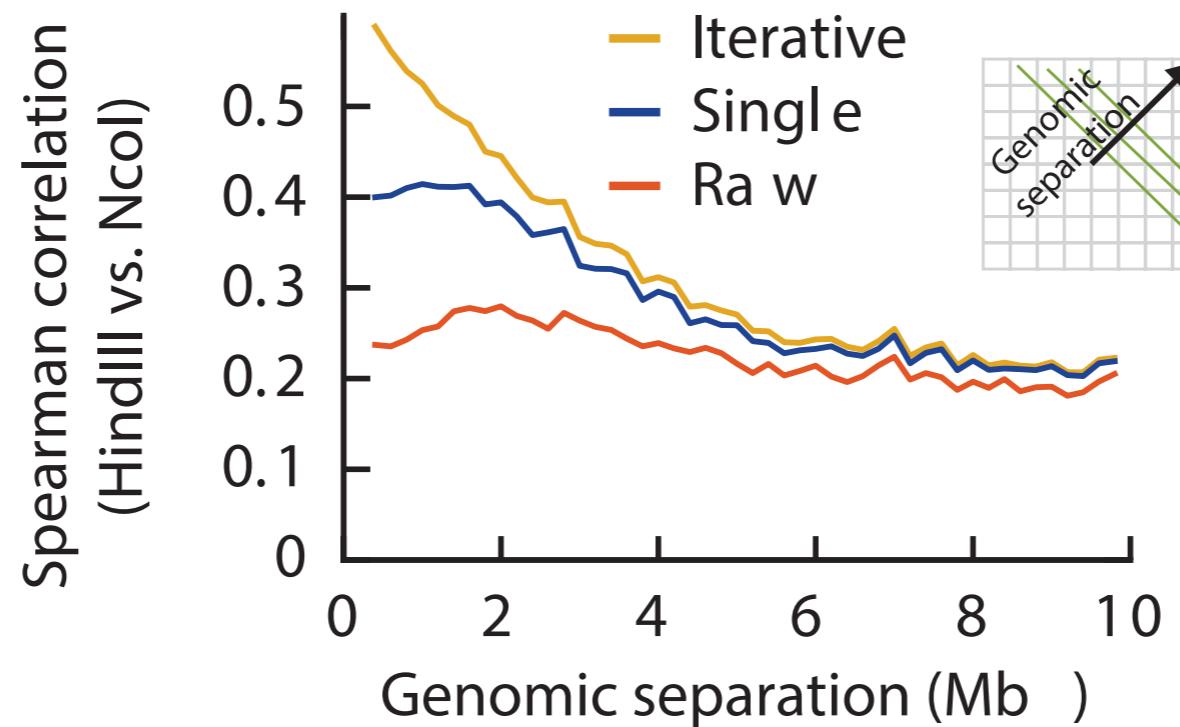
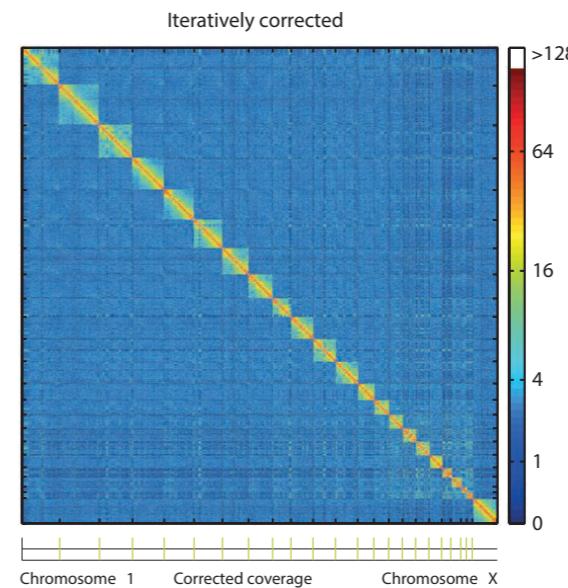


Normalizing HiC data (a la Mirny)

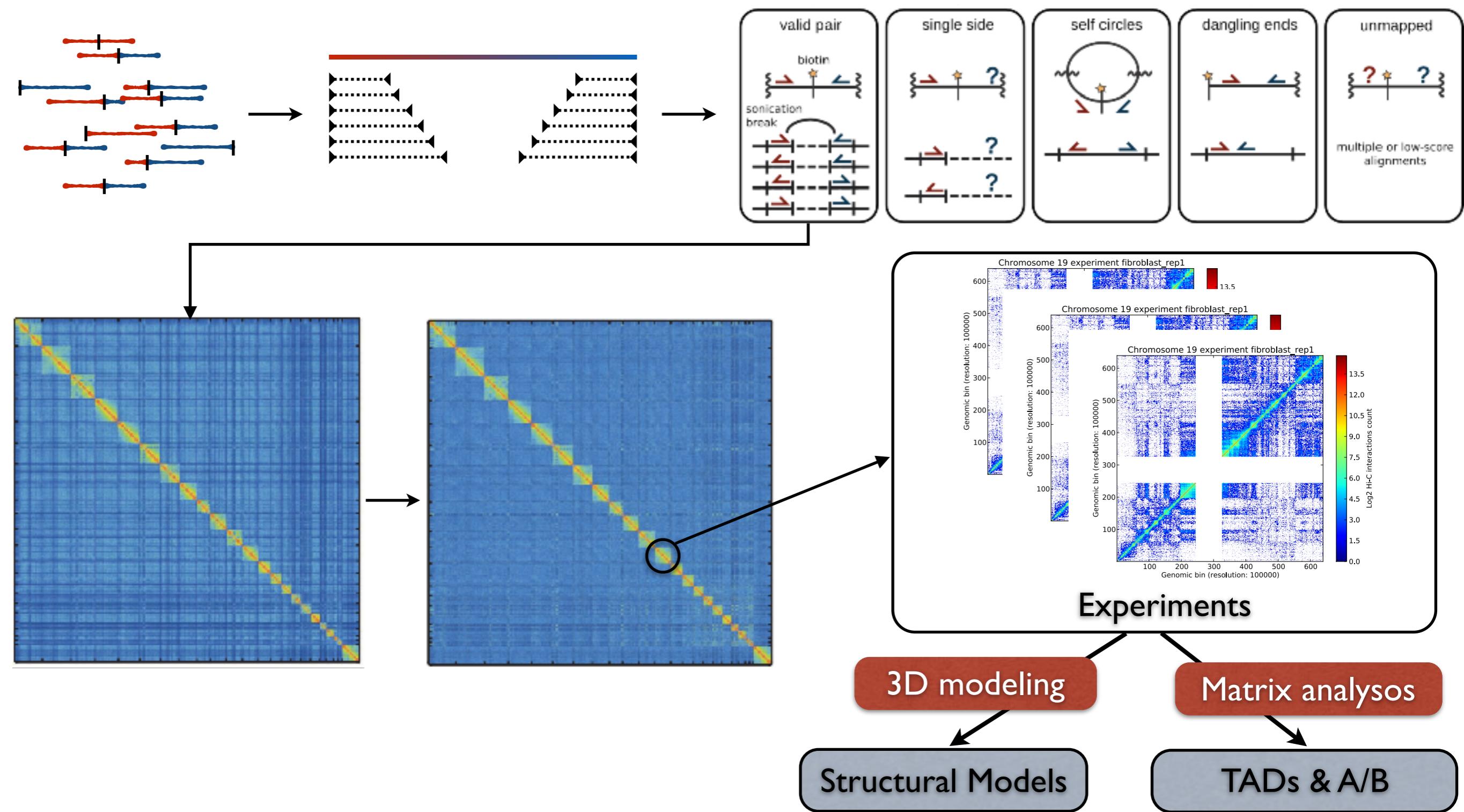
Imakaev, M., Fudenberg, G., McCord, R. P., Naumova, N., Goloborodko, A., Lajoie, B. R., et al. (2012). Nature Methods, 9(10), 999–1003.

$$O_{ij} = B_i B_j T_{ij}$$

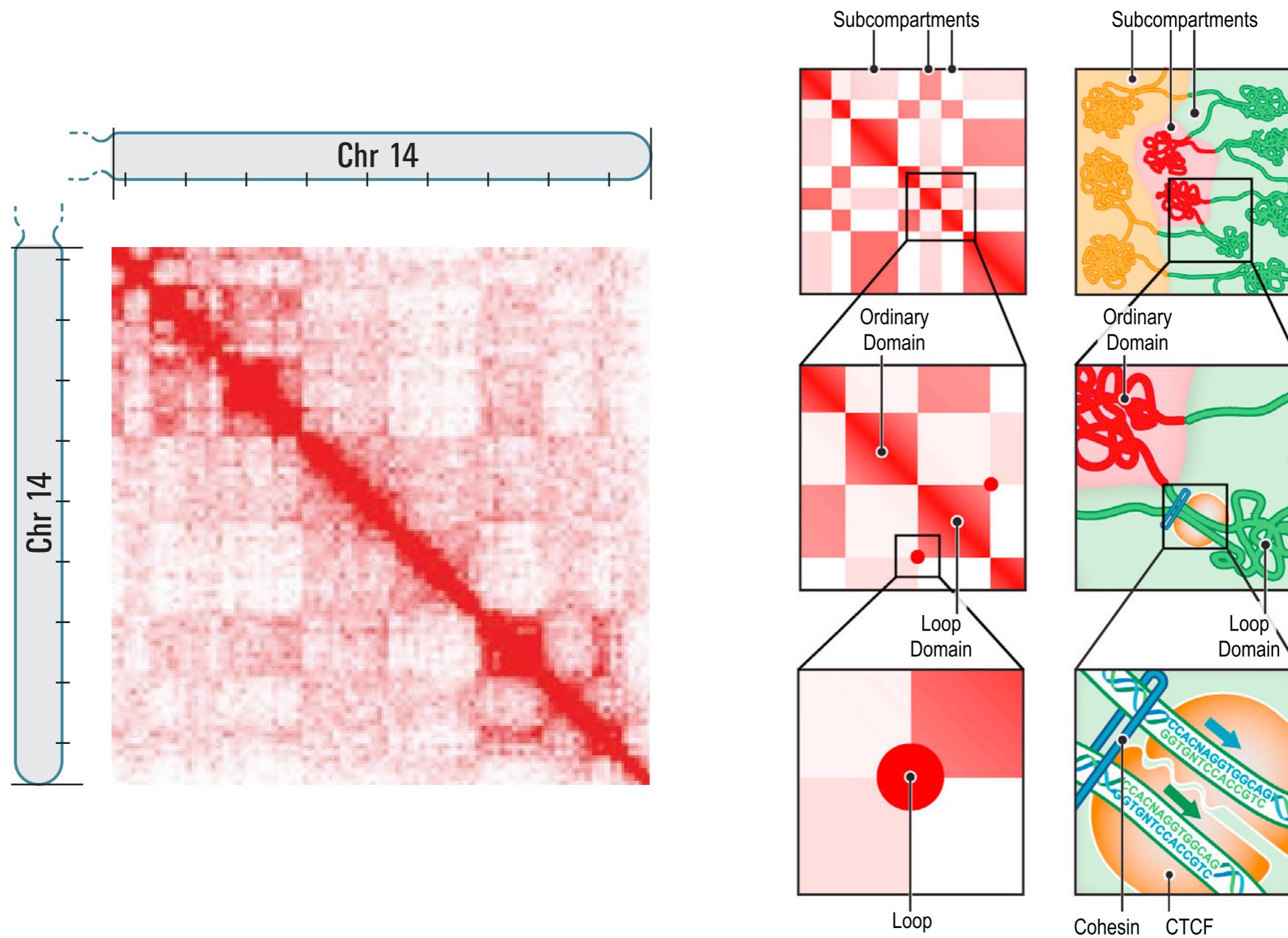
$$\sum_{i=1, |i-j|>1}^N T_{ij} = 1$$



Interaction matrices



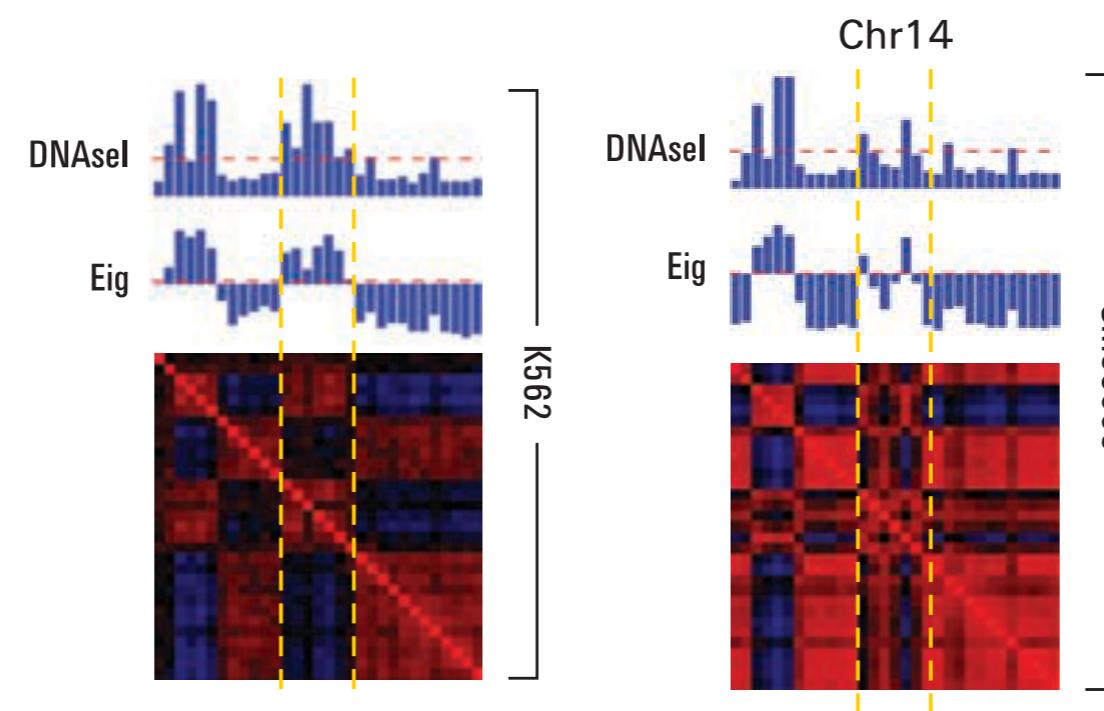
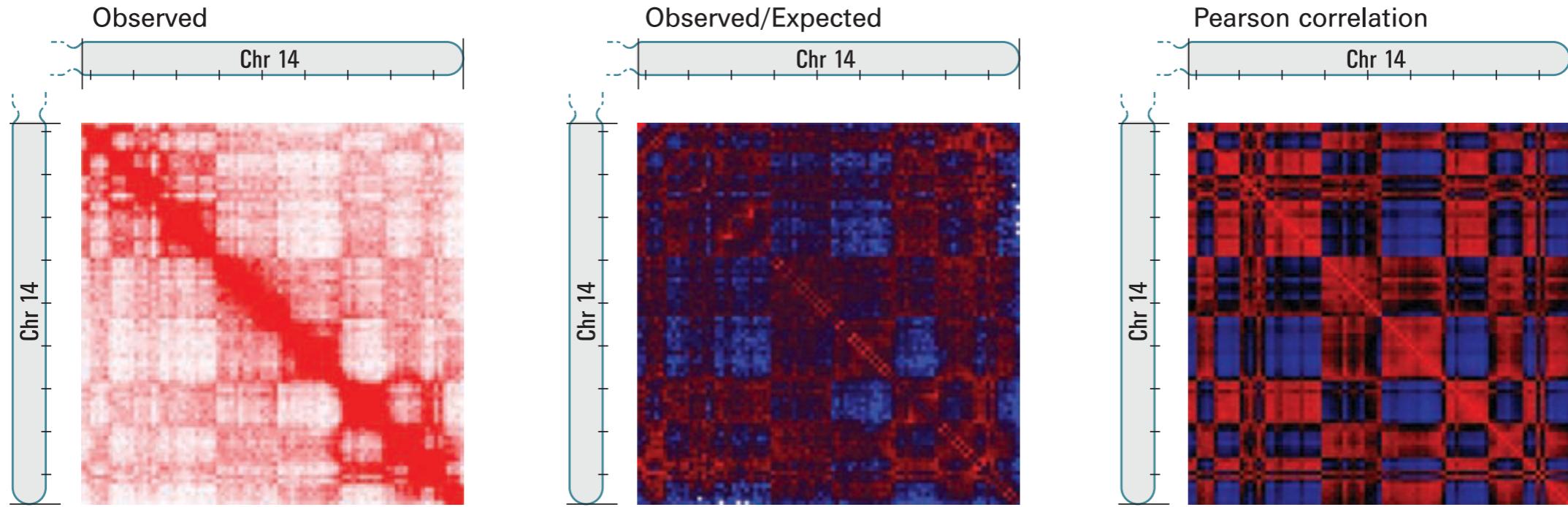
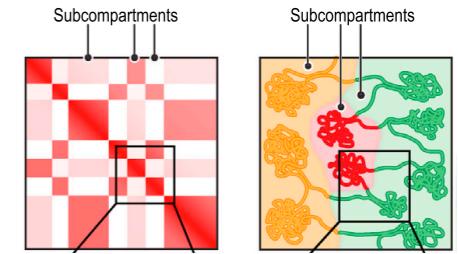
Hierarchical genome organisation



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

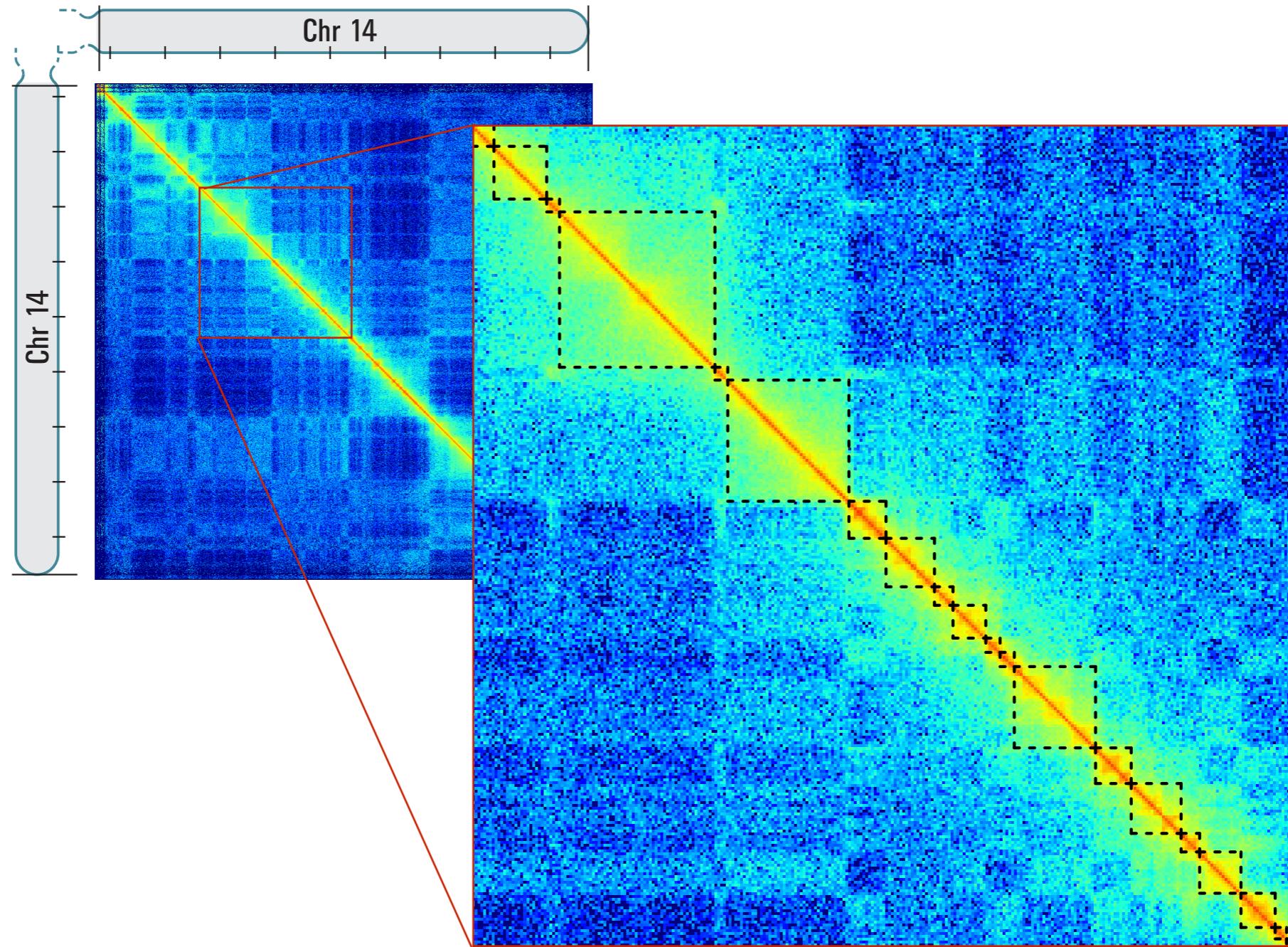
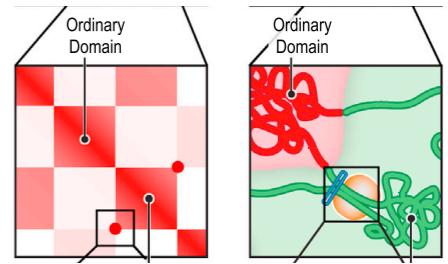
A/B Compartment

Human chromosome 14



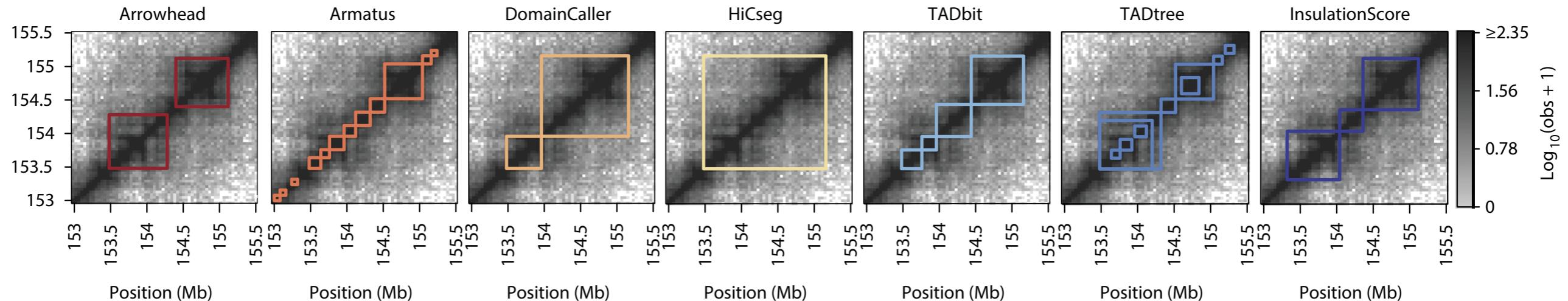
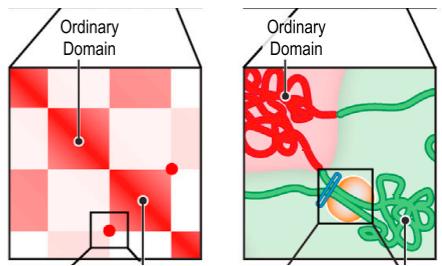
TADs

Chromosome 14

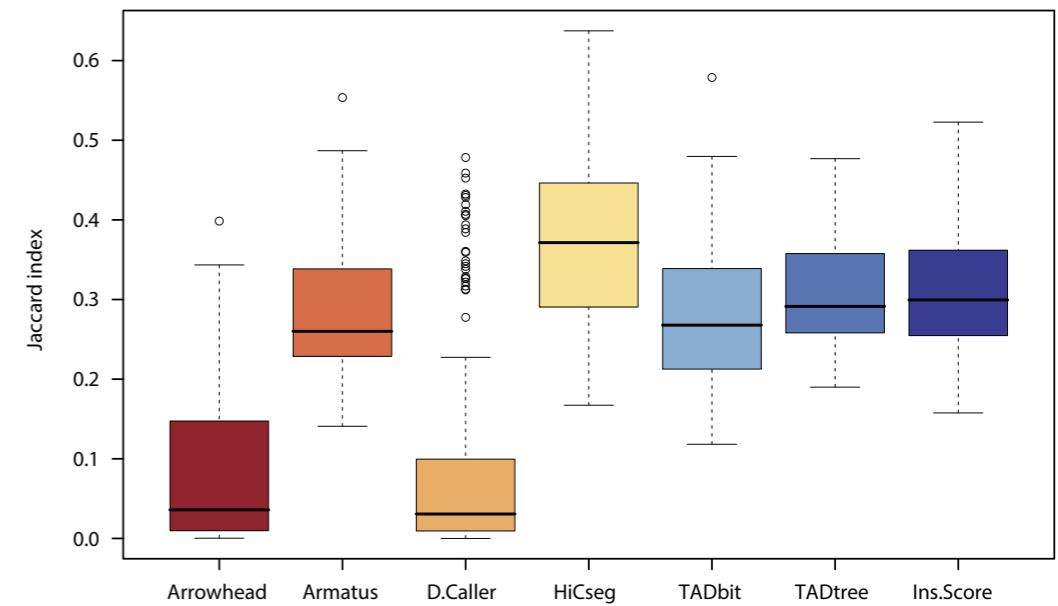
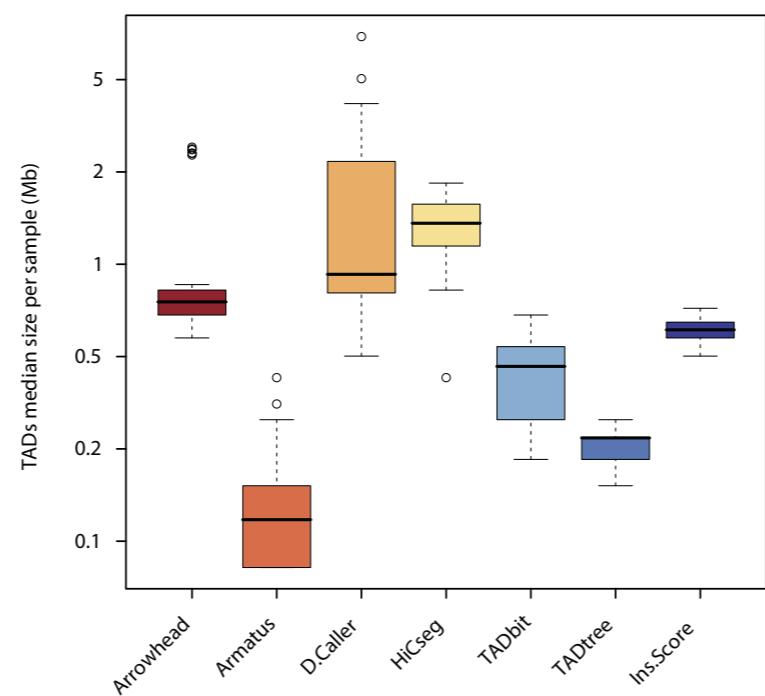
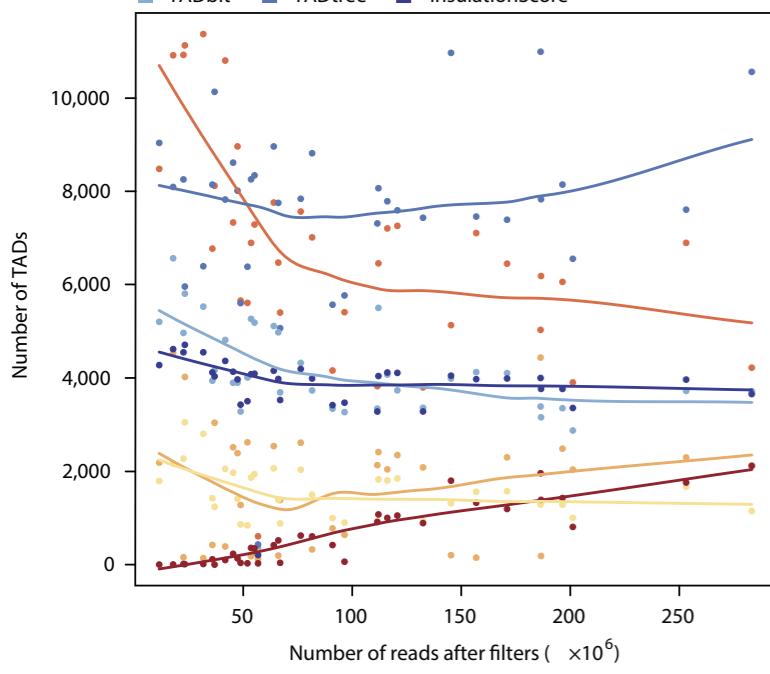


TADs

How well we do...

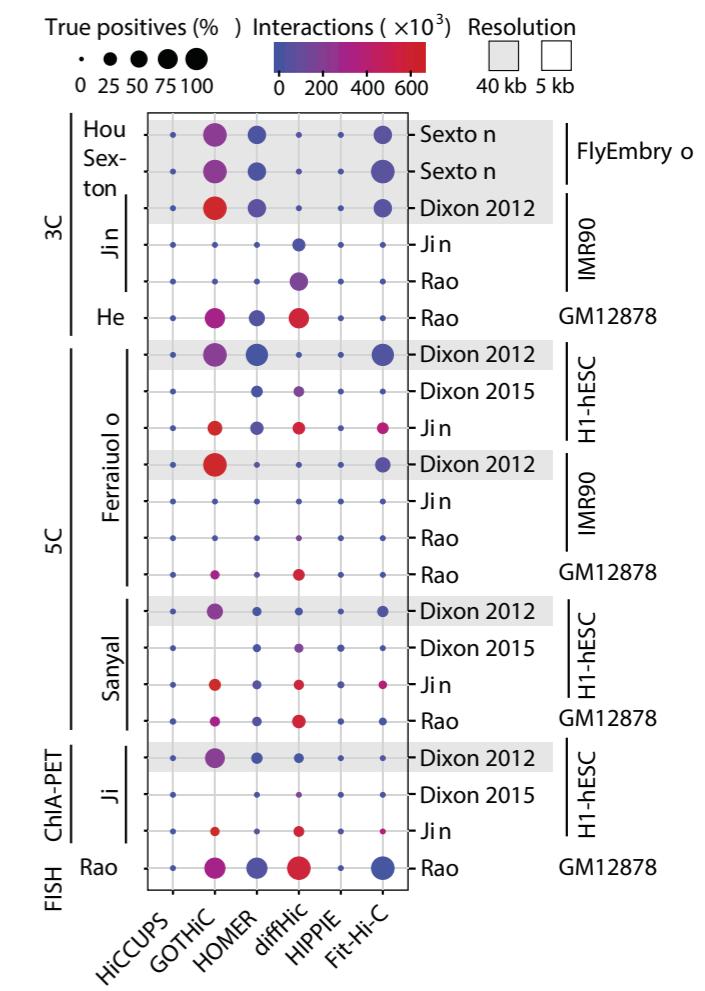
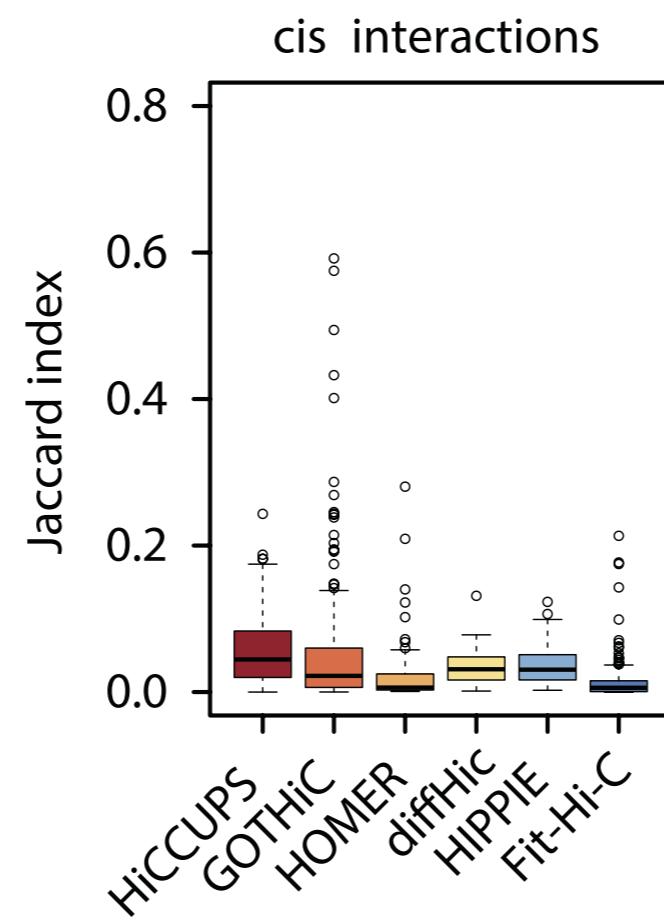
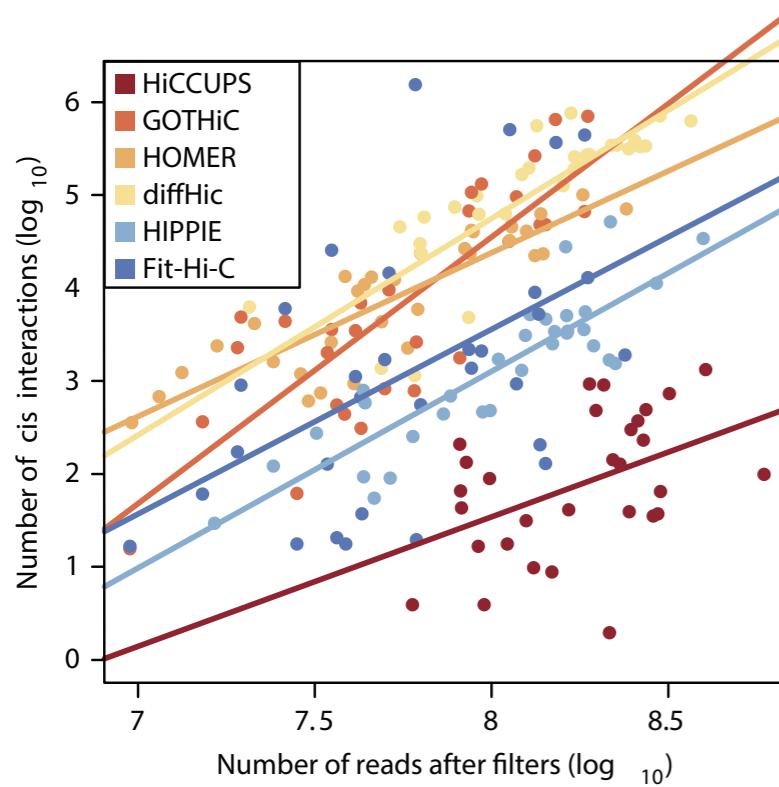
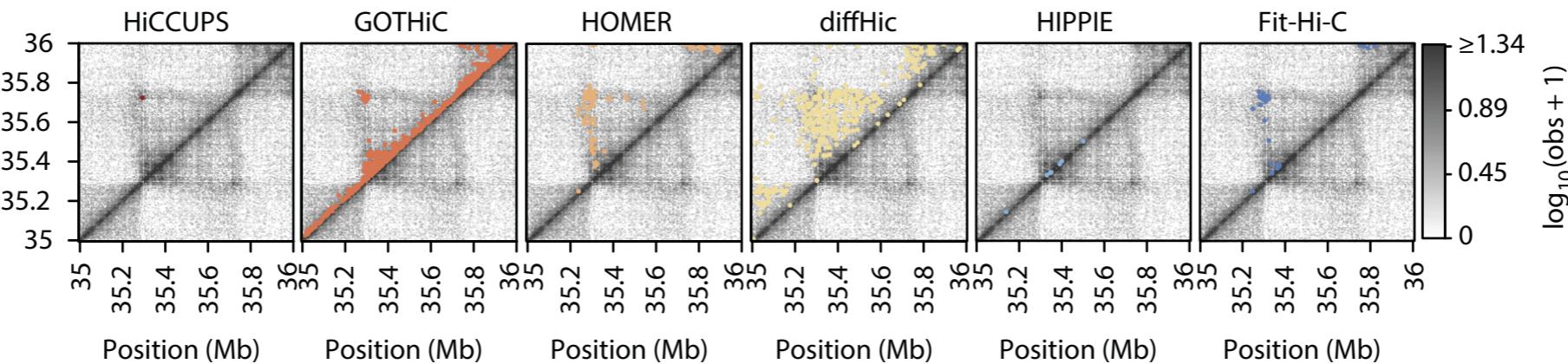
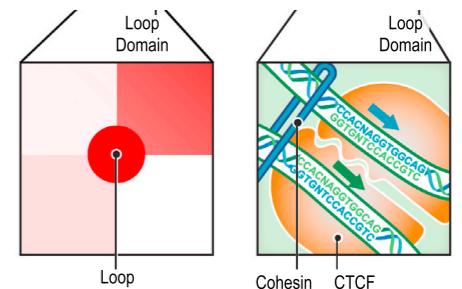


■ Arrowhead ■ Armatus ■ DomainCaller ■ HiCseg
■ TADbit ■ TADtree ■ InsulationScore

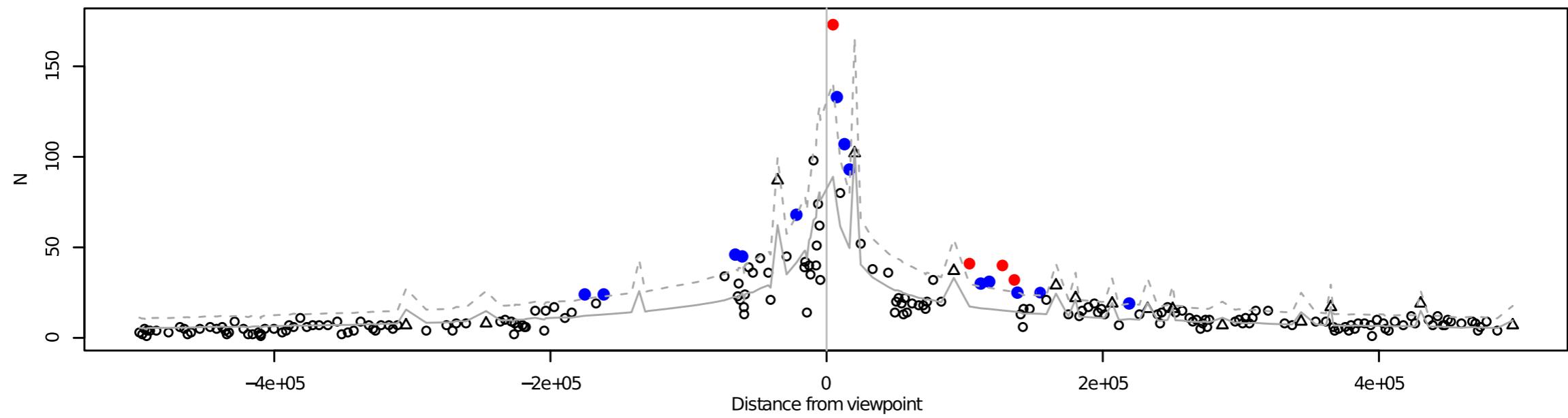
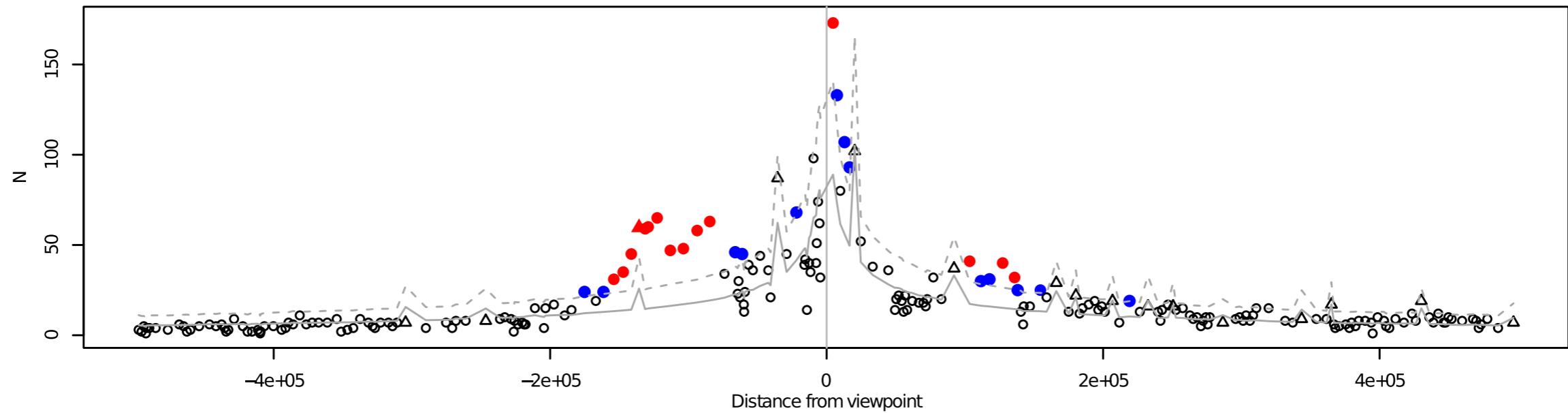


Loops

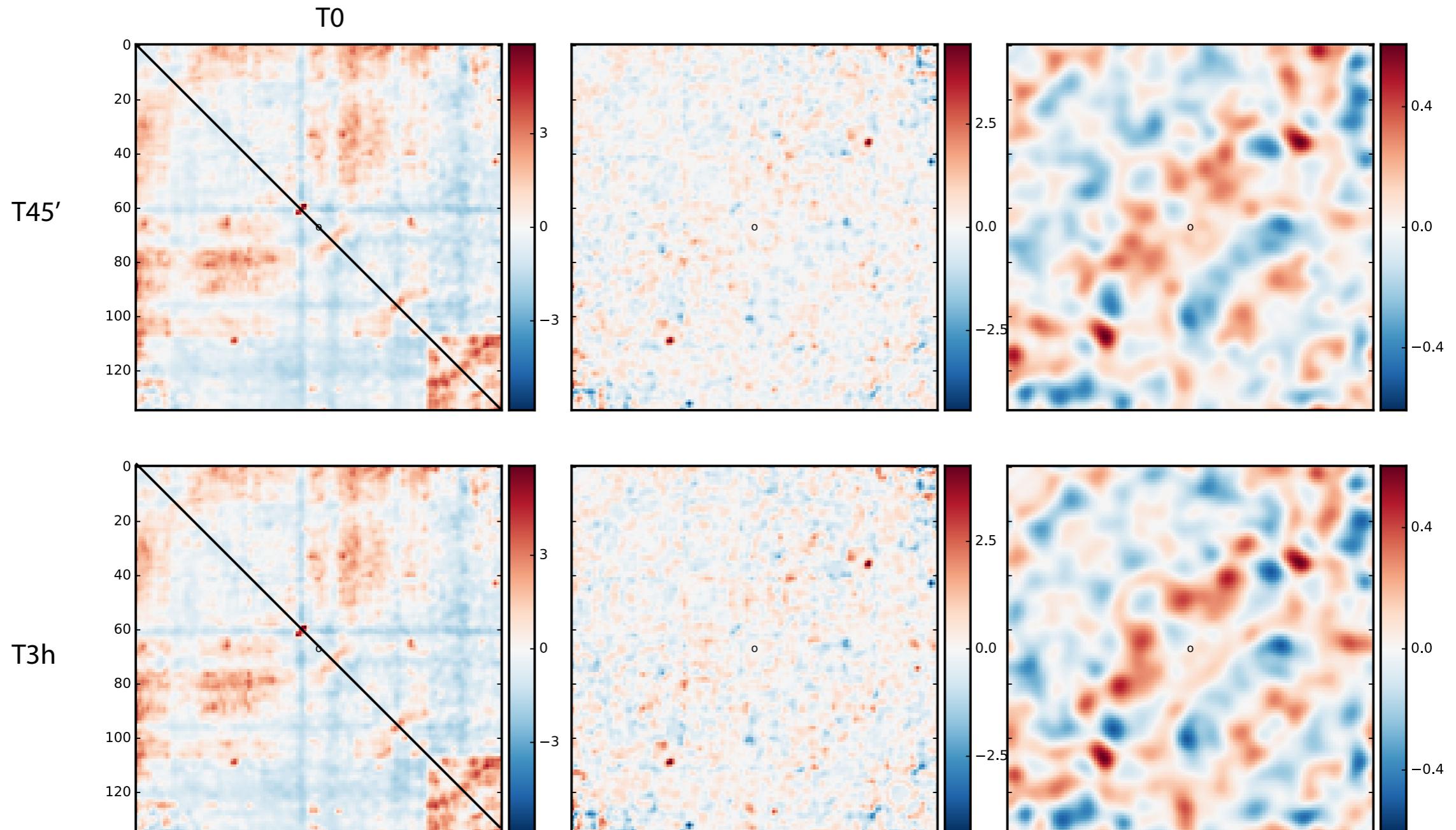
How well we do...



Comparing HiC data



Z-score differences (DekkerLab)



Comparing HiC data (GOTHIC)

Mifsud, B., Tavares-Cadete, F., Young, A. N., Sugar, R., Schoenfelder, S., Ferreira, L., et al. (2015). *Nature Genetics*, 1–12.

ARTICLES

Mapping long-range promoter contacts in human cells with high-resolution capture Hi-C

Borbala Mifsud^{1,2,10}, Filipe Tavares-Cadete^{1,9}, Alice N Young^{3,10}, Robert Sugar¹, Stefan Schoenfelder³, Lauren Ferreira³, Steven W Wingett⁴, Simon Andrews⁴, William Grey⁵, Philip A Ewels³, Bram Herman⁶, Scott Happe⁶, Andy Higgs⁶, Emily LeProust^{6,9}, George A Follows⁷, Peter Fraser³, Nicholas M Luscombe^{1,2,8} & Cameron S Osborne^{3,5}

Transcriptional control in large genomes often requires looping interactions between distal DNA elements, such as enhancers and target promoters. Current chromosome conformation capture techniques do not offer sufficiently high resolution to interrogate these regulatory interactions on a genomic scale. Here we use Capture Hi-C (CHi-C), an adapted genome conformation assay, to examine the long-range interactions of almost 22,000 promoters in 2 human blood cell types. We identify over 1.6 million shared and cell type-restricted interactions spanning hundreds of kilobases between promoters and distal loci. Transcriptionally active genes contact enhancer-like elements, whereas transcriptionally inactive genes interact with previously uncharacterized elements marked by repressive features that may act as long-range silencers. Finally, we show that interacting loci are enriched for disease-associated SNPs, suggesting how distal mutations may disrupt the regulation of relevant genes. This study provides new insights and accessible tools to dissect the regulatory interactions that underlie normal and aberrant gene regulation.

Genome organization influences transcriptional regulation by facilitating interactions between gene promoters and distal regulatory elements. Many contacts have been identified using chromosome conformation capture methodologies^{1–3}. For example, the ChIA-PET (chromatin interaction analysis by paired-end tag sequencing) method has been used to map long-range interactions extending over hundreds of kilobases; however, these studies have only interrogated the subset of interactions involving highly transcriptionally active genes, whereas long-range interactions for weakly expressed and transcriptionally inactive genes remain unknown. Although the 5C (chromatin conformation capture carbon copy) method is not restricted by the nature of interactions, thus far, it has only been applied to a few small genomic regions. The Hi-C method simultaneously captures all genomic interactions, which provides a population-average snapshot of the genome conformation within a single experiment⁴; yet, owing to the enormous complexity of Hi-C libraries, it is costly to sequence to sufficient depth to provide enough spatial resolution to interrogate specific contacts between gene promoters and distal regulatory elements^{5,6}. To circumvent these issues, we have used solution hybridization selection, originally developed for exon sequencing⁷—and recently used to capture the interactions of a few hundred promoters from 3C libraries⁸—to enrich Hi-C libraries for genome-wide, long-range contacts of both active and inactive promoters.

RESULTS

A genome-wide, long-range interaction capture assay

We prepared three HindIII-digested Hi-C libraries from GM12878 cells, a human Epstein-Barr virus (EBV)-transformed lymphoblastoid cell line that has been comprehensively assayed in the Encyclopedia of DNA Elements (ENCODE) Project, and two libraries from *ex vivo* CD34⁺ hematopoietic progenitor cells. One Hi-C library from each cell type was sequenced to examine the di-tag (paired-end read) interaction distribution and depth of read coverage (Supplementary Table 1). As anticipated, we observed a higher density of di-tag interaction reads between restriction fragments in *cis* as compared with fragments in *trans*, with the highest density occurring between fragments separated by less than 20 kb (Supplementary Fig. 1a,b). We also observed demarcation of the genome into distinct contiguous, highly interconnected topologically associated domains (TADs)⁵ (Supplementary Fig. 1c and Supplementary Table 2). The distribution of read coverage was typical for a Hi-C experiment. In our initial comparison, we downsampled all data sets to 45 million unique sequencing reads. Each restriction fragment was represented by an average of 143 and 139 reads in the GM12878 and CD34⁺ libraries, respectively (Supplementary Fig. 1d). We processed the reads using binomial statistics to identify ligation fragments that were significantly enriched ($q < 0.05$). This approach recognizes ligation products between

¹The Francis Crick Institute, London, UK. ²UCL Genetics Institute, University College London, London, UK. ³Nuclear Dynamics Programme, Babraham Institute, Cambridge, UK. ⁴Bioinformatics Group, Babraham Institute, Cambridge, UK. ⁵Department of Medical and Molecular Genetics, King's College London School of Medicine, London, UK. ⁶Diagnostics and Genomics Division, Agilent Technologies, Santa Clara, California, USA. ⁷Department of Haematology, Cambridge University Hospitals National Health Service (NHS) Foundation Trust, Cambridge, UK. ⁸Okinawa Institute of Science and Technology Graduate University, Okinawa, Japan. ⁹Present addresses: Okinawa Institute of Science and Technology Graduate University, Okinawa, Japan (F.T.-C.) and Twist Bioscience, San Francisco, California, USA (E.L.). ¹⁰These authors contributed equally to this work. Correspondence should be addressed to C.S.O. (cameron.osborne@kcl.ac.uk) or N.M.L. (nicholas.luscombe@ucl.ac.uk).

Received 5 December 2014; accepted 2 April 2015; published online 4 May 2015; doi:10.1038/ng.3286

Comparing HiC data (CHICAGO)

Cairns, J., Freire-Pritchett, P., Wingett, S. W., Várnai, C., Dimond, A., Plagnol, V., et al. (2016). *Genome Biology*, 1–17.

Cairns et al. *Genome Biology* (2016) 17:127
DOI 10.1186/s13059-016-0992-2

Genome Biology

METHOD

Open Access

CHiCAGO: robust detection of DNA looping interactions in Capture Hi-C data



CrossMark

Jonathan Cairns^{1†}, Paula Freire-Pritchett^{1†}, Steven W. Wingett^{1,2}, Csilla Várnai¹, Andrew Dimond¹, Vincent Plagnol³, Daniel Zerbino⁴, Stefan Schoenfelder¹, Biola-Maria Javierre¹, Cameron Osborne⁵, Peter Fraser¹ and Mikhail Spivakov^{1*}

Abstract

Capture Hi-C (CHi-C) is a method for profiling chromosomal interactions involving targeted regions of interest, such as gene promoters, globally and at high resolution. Signal detection in CHi-C data involves a number of statistical challenges that are not observed when using other Hi-C-like techniques. We present a background model and algorithms for normalisation and multiple testing that are specifically adapted to CHi-C experiments. We implement these procedures in CHiCAGO (<http://regulatorygenomicsgroup.org/chicago>), an open-source package for robust interaction detection in CHi-C. We validate CHiCAGO by showing that promoter-interacting regions detected with this method are enriched for regulatory features and disease-associated SNPs.

Keywords: Gene regulation, Nuclear organisation, Promoter-enhancer interactions, Capture Hi-C, Convolution background model, *P* value weighting

Background

Chromosome conformation capture (3C) technology has revolutionised the analysis of nuclear organisation, leading to important insights into gene regulation [1]. While the original 3C protocol tested interactions between a single pair of candidate regions (“one vs one”), subsequent efforts focused on increasing the throughput of this technology (4C, “one vs all”; 5C, “many vs many”), culminating in the development of Hi-C, a method that interrogated the whole nuclear interactome (“all vs all”) [1, 2]. The extremely large number of possible pairwise interactions in Hi-C samples, however, imposes limitations on the realistically achievable sequencing depth at individual interactions, leading to reduced sensitivity. The recently developed Capture Hi-C (CHi-C) technology uses sequence capture to enrich Hi-C material for multiple genomic regions of interest (hereafter referred to as “baits”), making it possible to profile the global interaction profiles of many thousands of regions globally (“many vs all”) and at a high resolution (Fig. 1) [3–7].

CHi-C data possess statistical properties that set them apart from other 3C/4C/Hi-C-like methods. First, in contrast to traditional Hi-C or 5C, baits in CHi-C comprise a subset of restriction fragments, while any fragment in the genome can be detected on the “other end” of an interaction. This asymmetry of CHi-C interaction matrices is not accounted for by the normalisation procedures developed for traditional Hi-C and 5C [8–10]. Secondly, CHi-C baits, but not other ends, have a further source of bias associated with uneven capture efficiency. In addition, the need for detecting interactions globally and at a single-fragment resolution creates specific multiple testing challenges that are less pronounced with binned Hi-C data or the more focused 4C and 5C assays, which involve fewer interaction tests. Finally, CHi-C designs such as Promoter CHi-C and HiCap [3–5, 11] involve large numbers (many thousands) of spatially dispersed baits. This presents the opportunity to increase the robustness of signal detection by sharing information across baits. Such sharing is impossible in the analysis of 4C data that focuses on only a single bait and is of limited use in 4C-seq containing a small number of baits [12–14].

These distinct features of CHi-C data have prompted us to develop a bespoke statistical model and a

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Comparing HiC data (diffHiC)

Lun, A. T. L., & Smyth, G. K. (2015). *BMC Bioinformatics*, 1–11.

Lun and Smyth *BMC Bioinformatics* (2015) 16:258
DOI 10.1186/s12859-015-0683-0



SOFTWARE

Open Access



diffHic: a Bioconductor package to detect differential genomic interactions in Hi-C data

Aaron T.L. Lun^{1,2} and Gordon K. Smyth^{1,3*} 

Abstract

Background: Chromatin conformation capture with high-throughput sequencing (Hi-C) is a technique that measures the *in vivo* intensity of interactions between all pairs of loci in the genome. Most conventional analyses of Hi-C data focus on the detection of statistically significant interactions. However, an alternative strategy involves identifying significant changes in the interaction intensity (i.e., differential interactions) between two or more biological conditions. This is more statistically rigorous and may provide more biologically relevant results.

Results: Here, we present the diffHic software package for the detection of differential interactions from Hi-C data. diffHic provides methods for read pair alignment and processing, counting into bin pairs, filtering out low-abundance events and normalization of trended or CNV-driven biases. It uses the statistical framework of the edgeR package to model biological variability and to test for significant differences between conditions. Several options for the visualization of results are also included. The use of diffHic is demonstrated with real Hi-C data sets. Performance against existing methods is also evaluated with simulated data.

Conclusions: On real data, diffHic is able to successfully detect interactions with significant differences in intensity between biological conditions. It also compares favourably to existing software tools on simulated data sets. These results suggest that diffHic is a viable approach for differential analyses of Hi-C data.

Keywords: Hi-C, Genomic interaction, Differential analysis

Background

Chromatin conformation capture with high-throughput sequencing (Hi-C) is a technique that is widely used to study global chromatin organization *in vivo* [1]. Briefly, samples of nuclear DNA are cross-linked and digested with a restriction enzyme to release chromatin complexes into solution (Fig. 1). Each complex may contain multiple restriction fragments, corresponding to an interaction between the associated genomic loci. After some processing, proximity ligation is performed between the ends of the restriction fragments. This favours ligation between restriction fragments in the same complex. The ligated DNA is sheared and purified for high-throughput paired-end sequencing. Each sequencing fragment represents a

ligation product, such that each read in the pair originates from a different genomic locus. The intensity of an interaction between a pair of genomic loci can be quantified as the number of read pairs with one read mapped to each locus. The output from the Hi-C procedure spans the genome-by-genome “interaction space” whereby all pairwise interactions between loci can potentially be detected. As such, careful analysis is required to draw meaningful biological conclusions from this type of data.

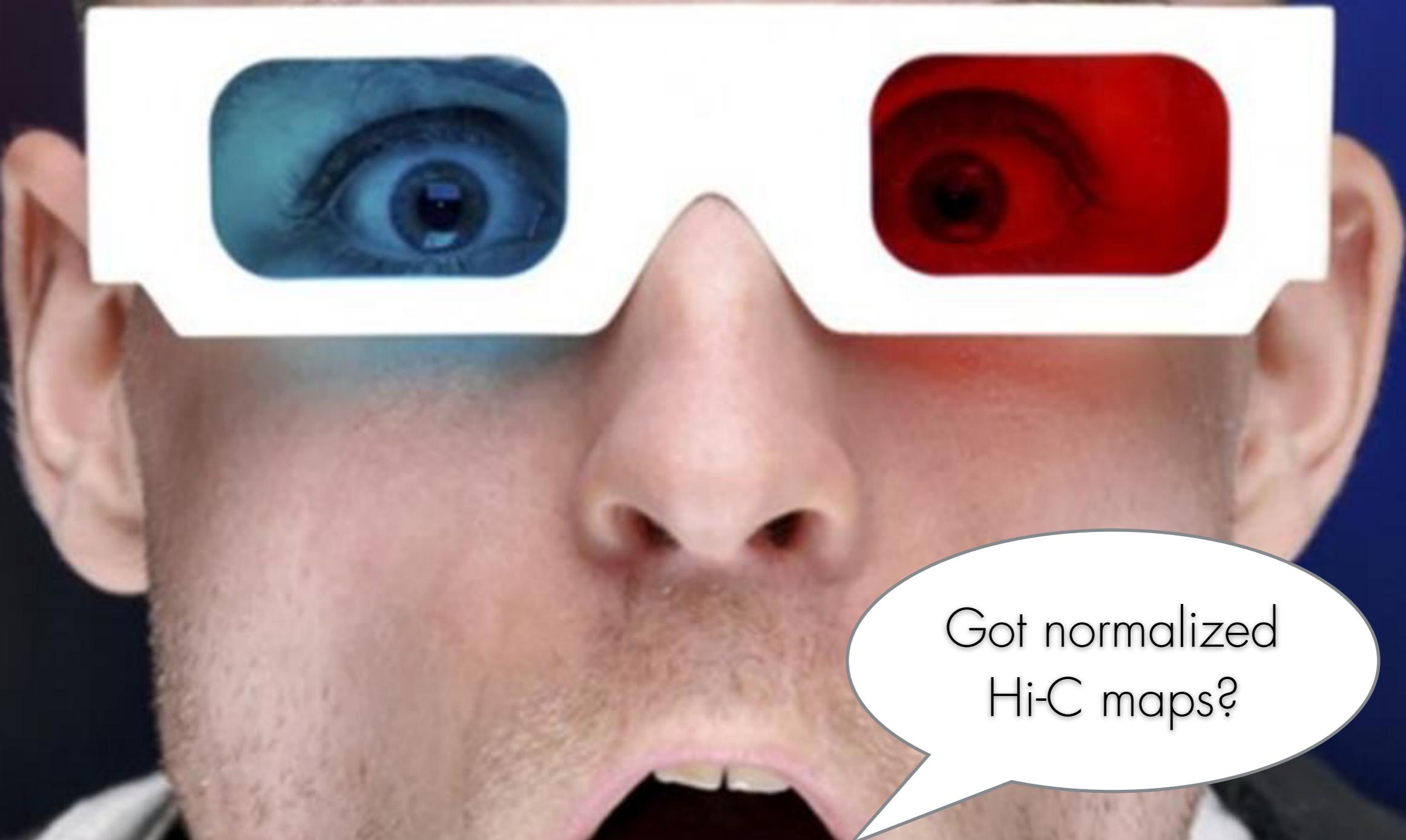
Most analyses of Hi-C data have focused on identifying “significant” interactions from a single sample [2, 3]. This is challenging because non-specific ligation and apparent interactions can arise from a variety of uninteresting technical causes and rigorous analysis requires a precise quantitative understanding of these artifacts. Identifying biologically interesting interactions from a single sample requires elaborate modeling of the background signal in Hi-C experiments in order to correct for systematic biases due to GC content, mappability and fragment length [3]. Such modeling inevitably involves assumptions and approximations. Furthermore, the interaction space

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¹The Walter and Eliza Hall Institute of Medical Research, 1G Royal Parade, Parkville, VIC 3052, Melbourne, Australia

³Department of Mathematics and Statistics, The University of Melbourne, Parkville, VIC 3010, Melbourne, Australia

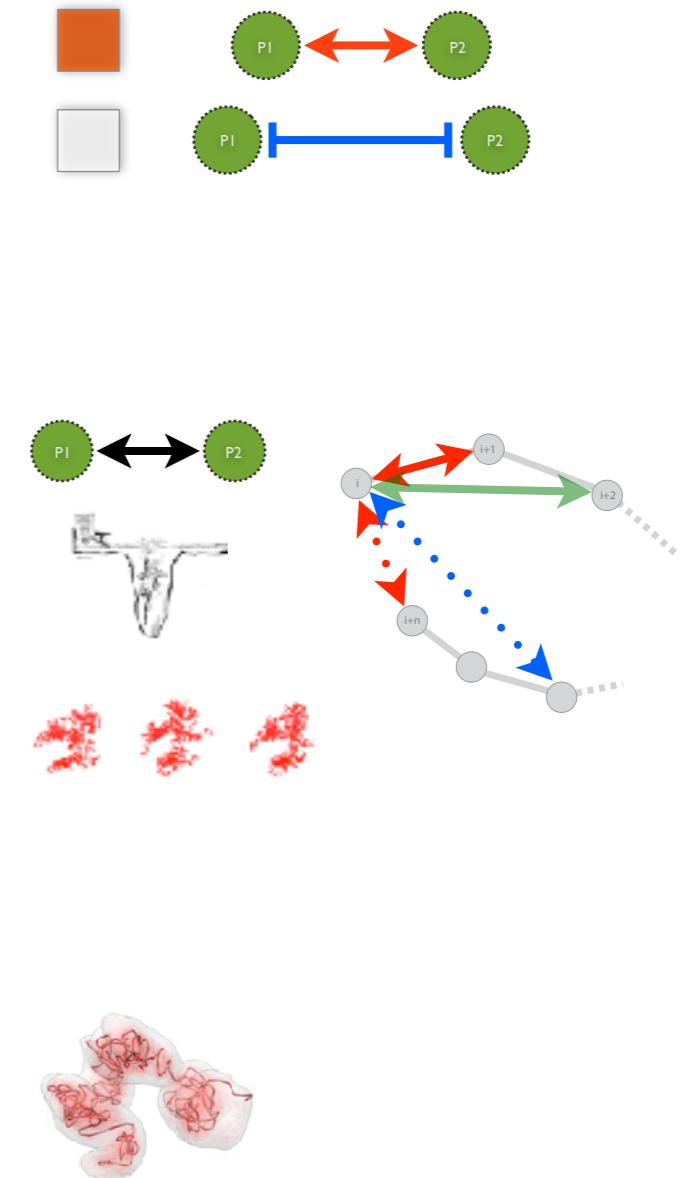
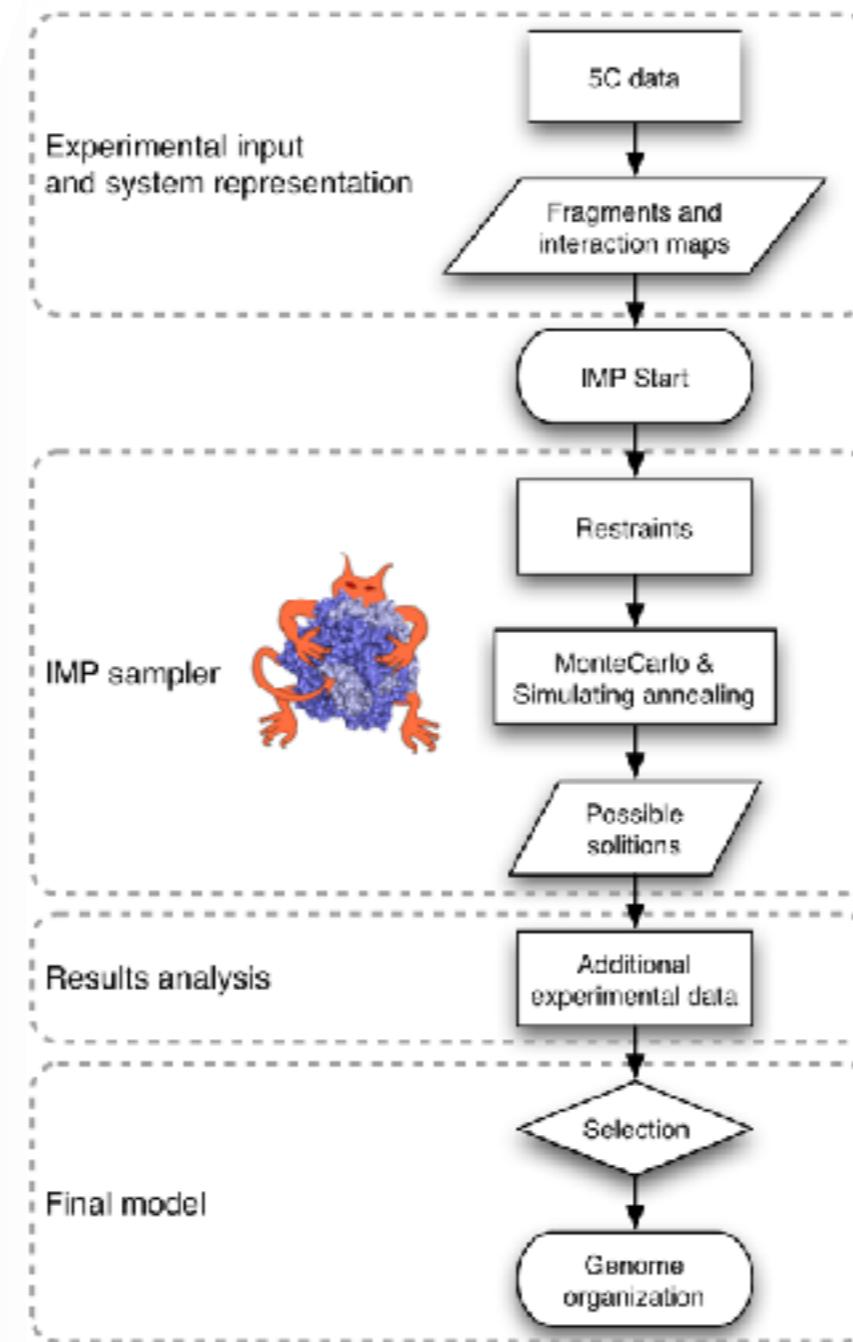
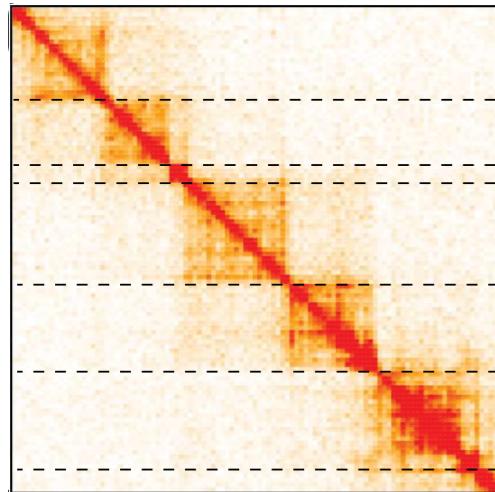
Full list of author information is available at the end of the article



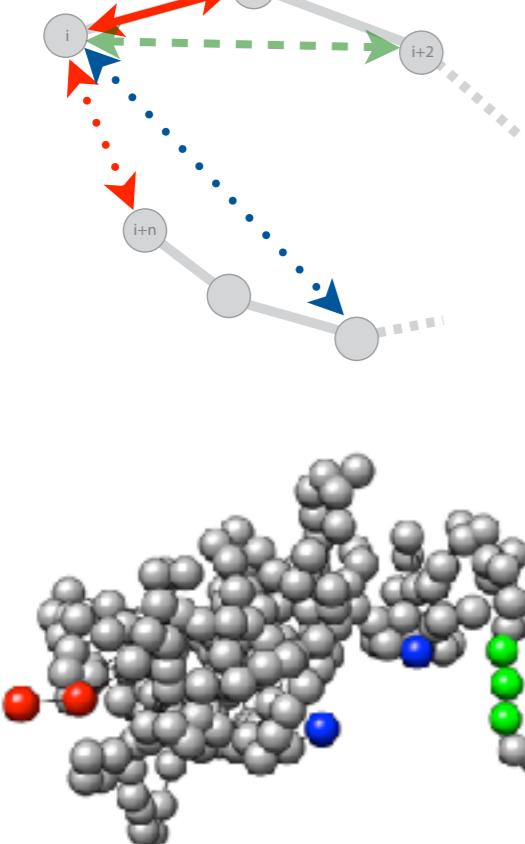
Got normalized
Hi-C maps?



<http://3DGenomes.org>
<http://www.integrativemodeling.org>



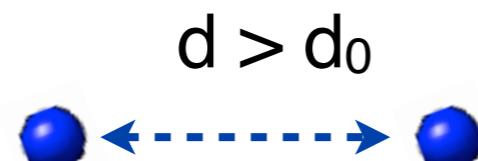
Model representation and scoring



$$d = d_0$$

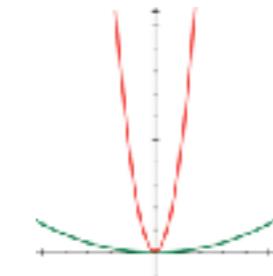


$$d < d_0$$



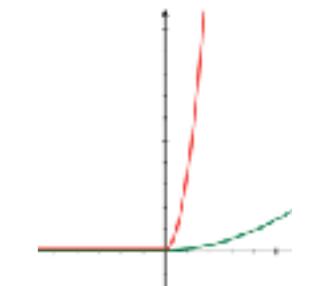
Harmonic

$$H_{i,j} = k(d_{i,j} - d_{i,j}^0)^2$$



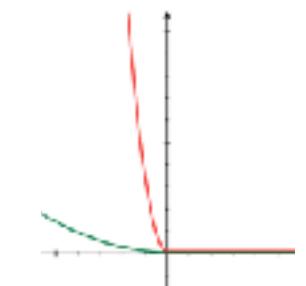
Harmonic Upper Bound

$$\begin{cases} \text{if } d_{i,j} \geq d_{i,j}^0; & ubH_{i,j} = k(d_{i,j} - d_{i,j}^0)^2 \\ \text{if } d_{i,j} < d_{i,j}^0; & ubH_{i,j} = 0 \end{cases}$$

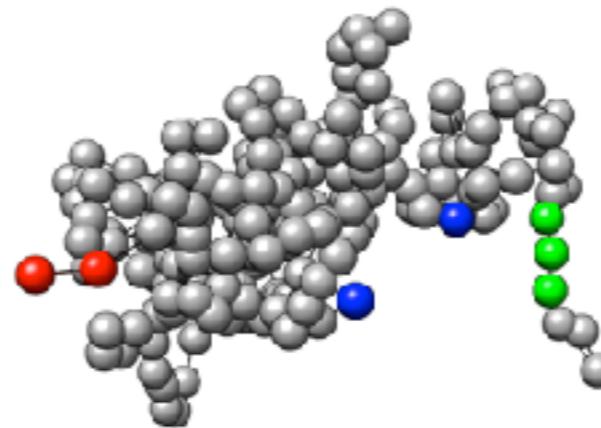


Harmonic Lower Bound

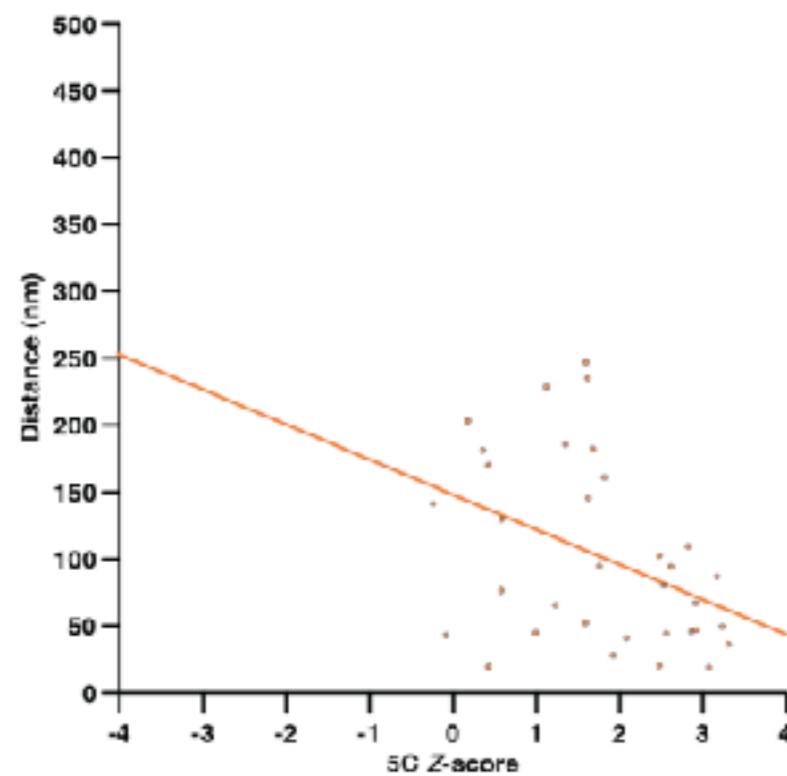
$$\begin{cases} \text{if } d_{i,j} \leq d_{i,j}^0; & lbH_{i,j} = k(d_{i,j} - d_{i,j}^0)^2 \\ \text{if } d_{i,j} > d_{i,j}^0; & lbH_{i,j} = 0 \end{cases}$$



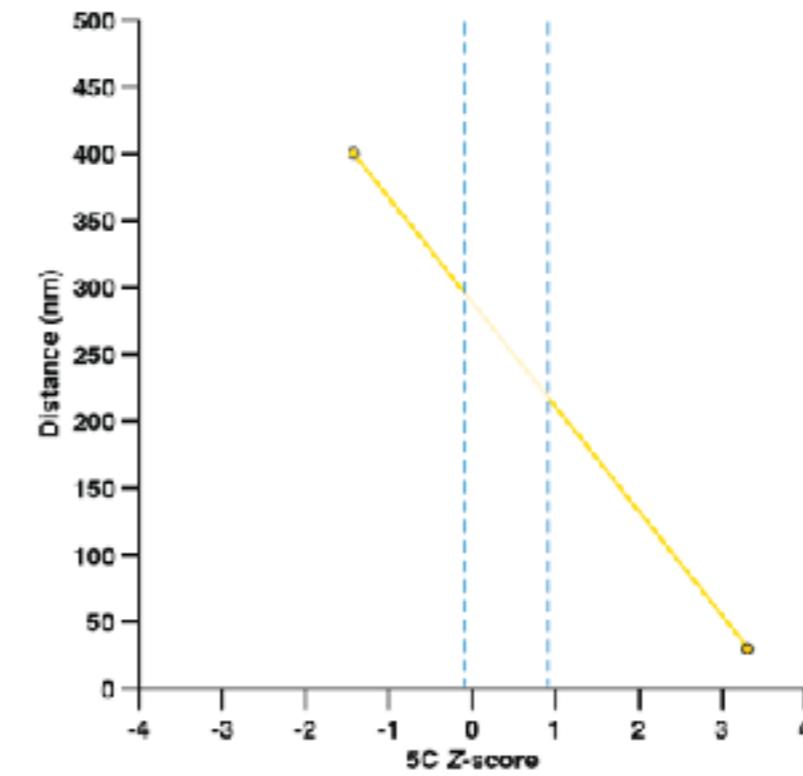
From 3C data to spatial distances



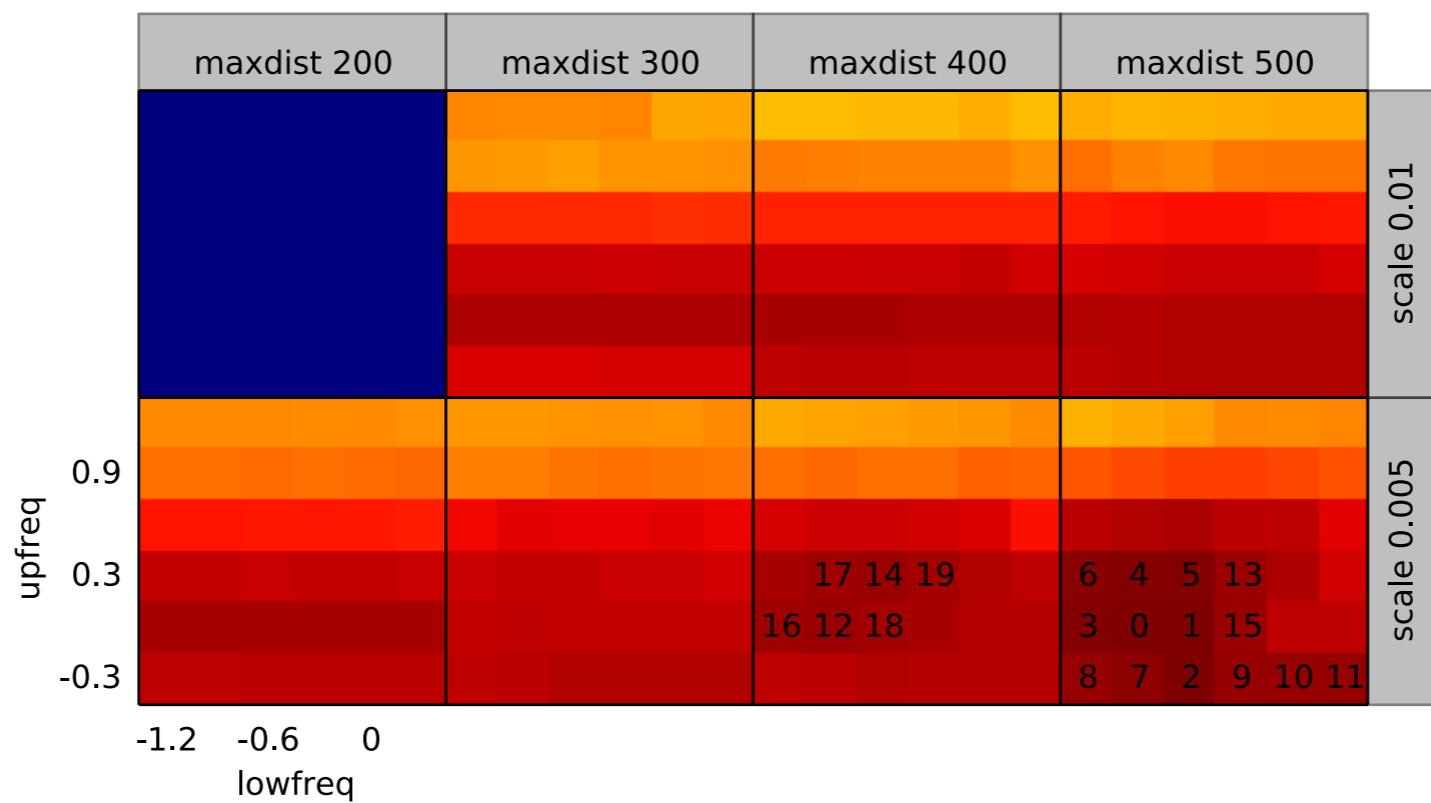
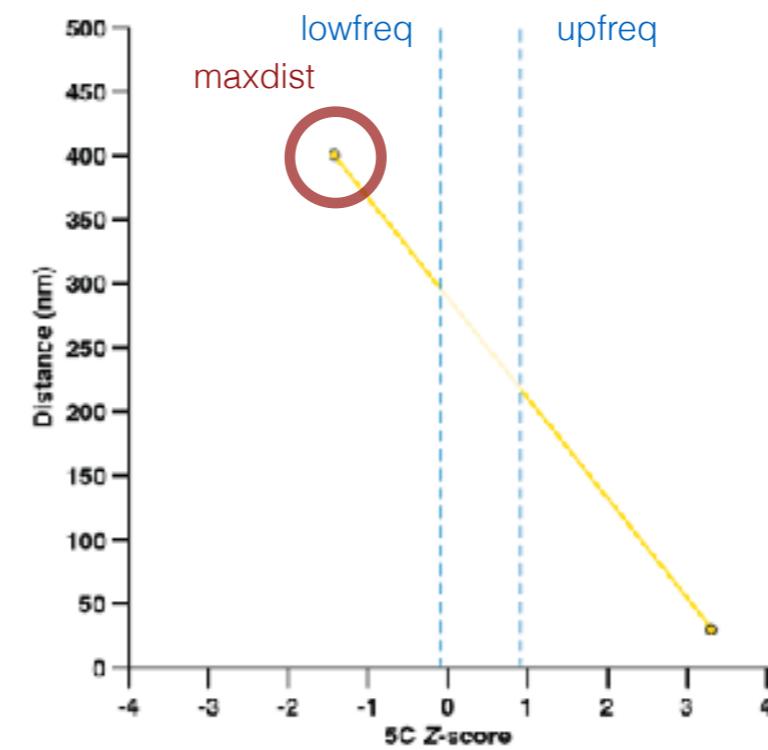
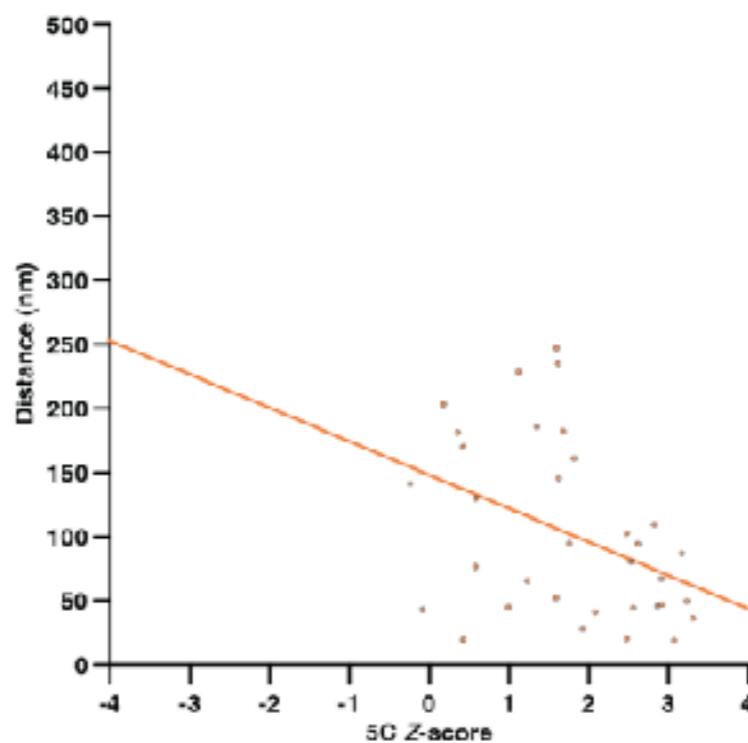
Neighbor fragments



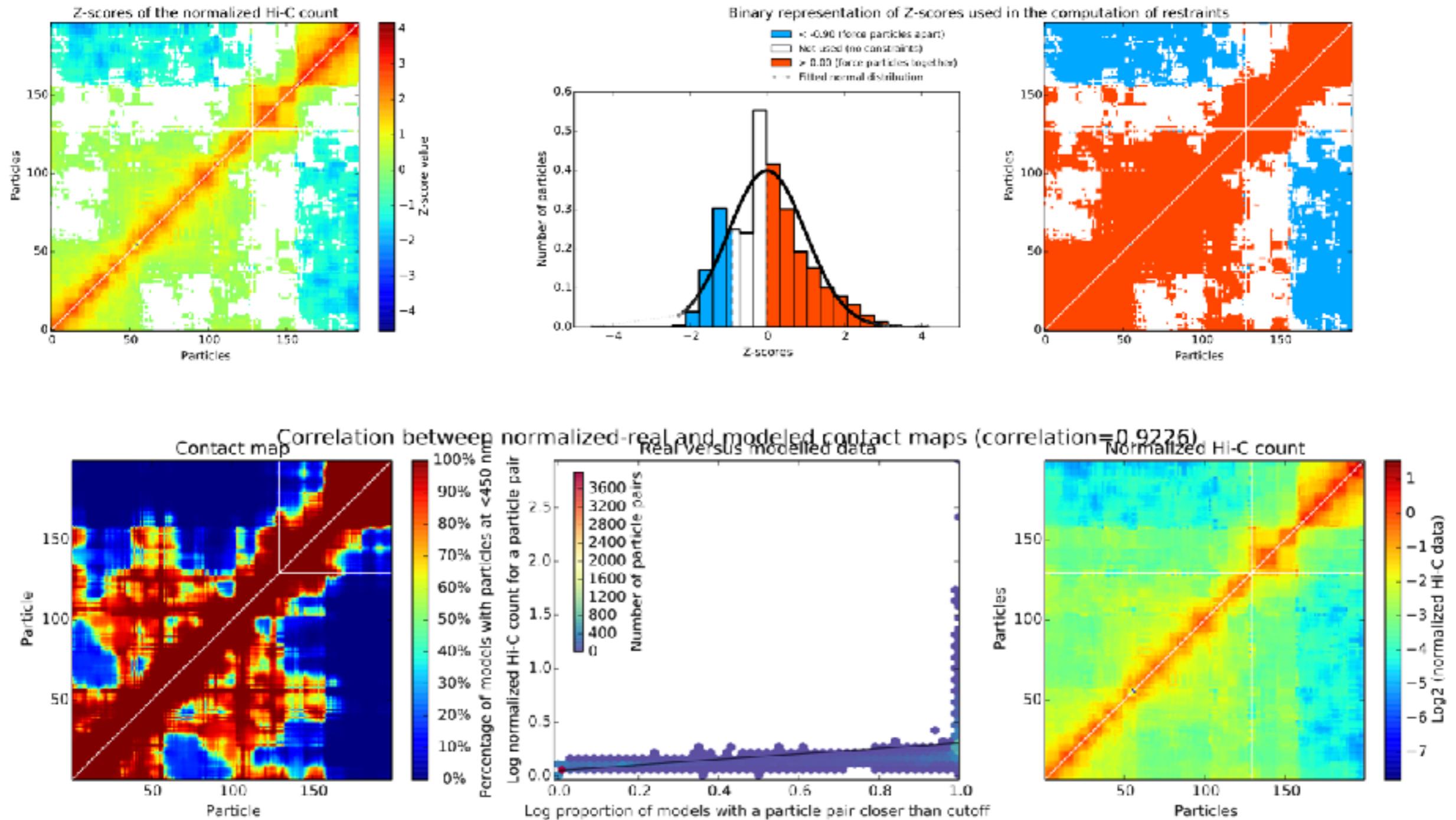
Non-Neighbor fragments



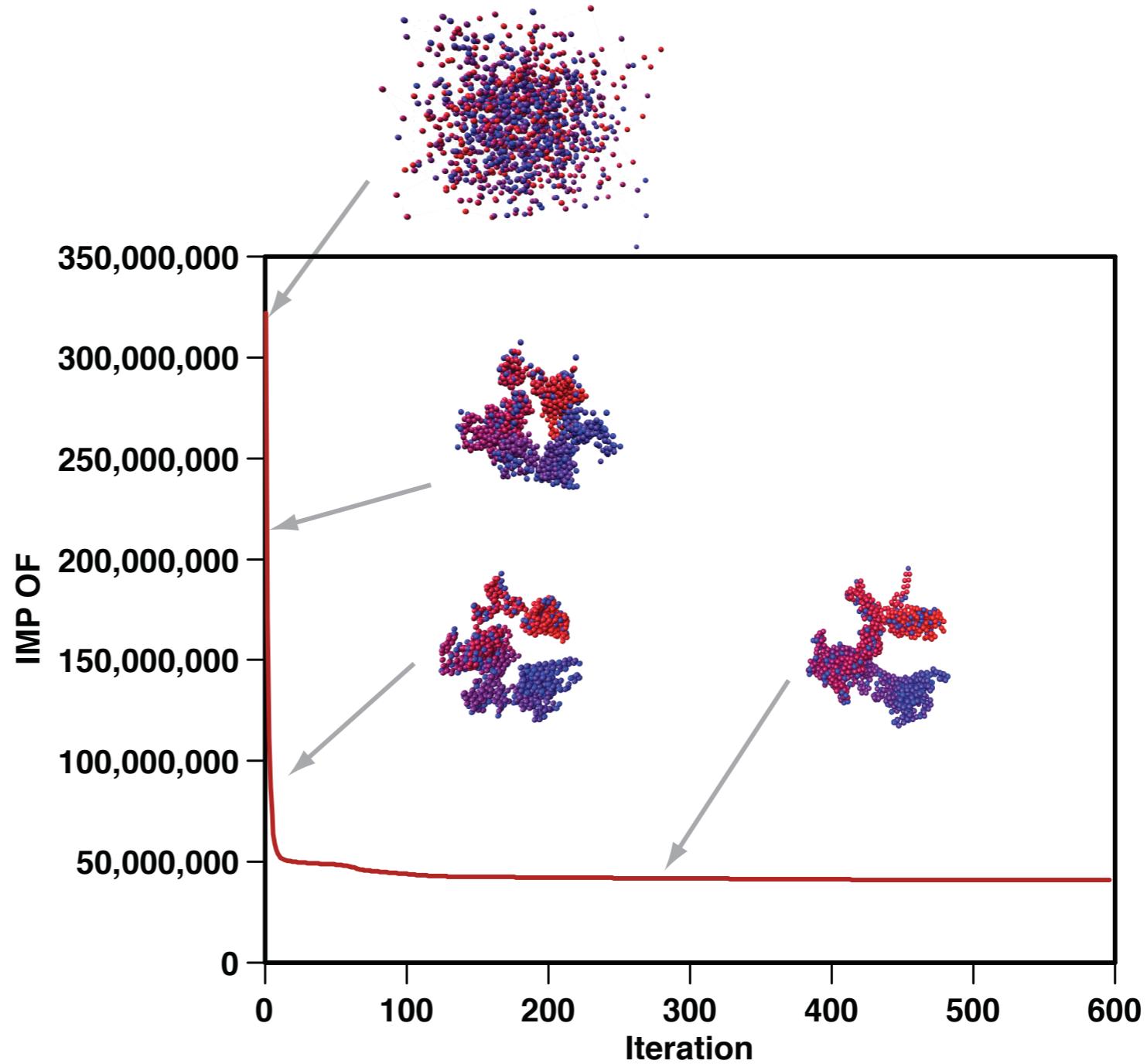
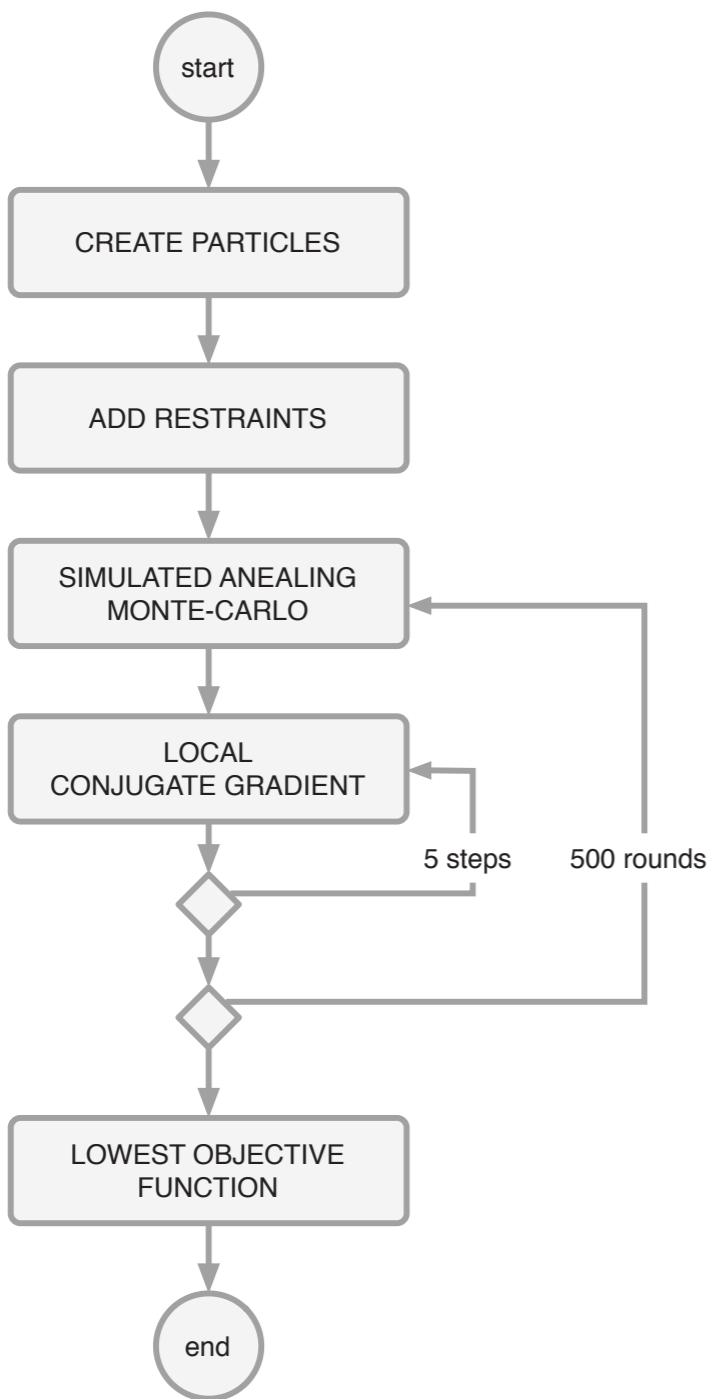
Parameter optimization



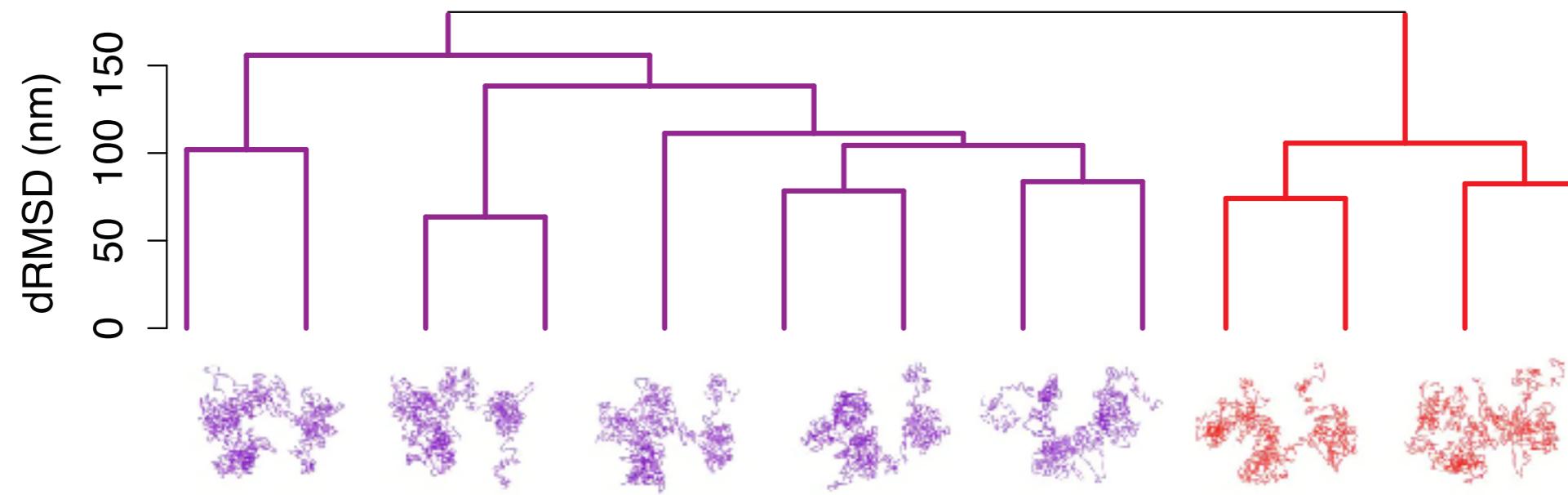
Parameter optimization



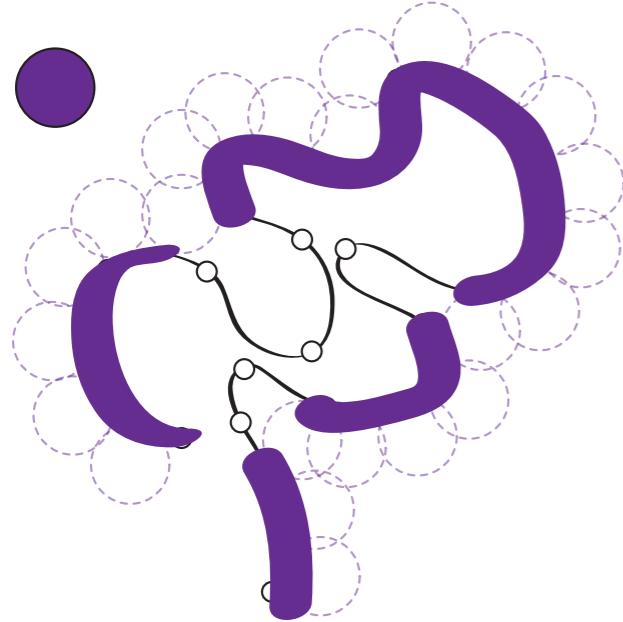
Optimization of the scoring function



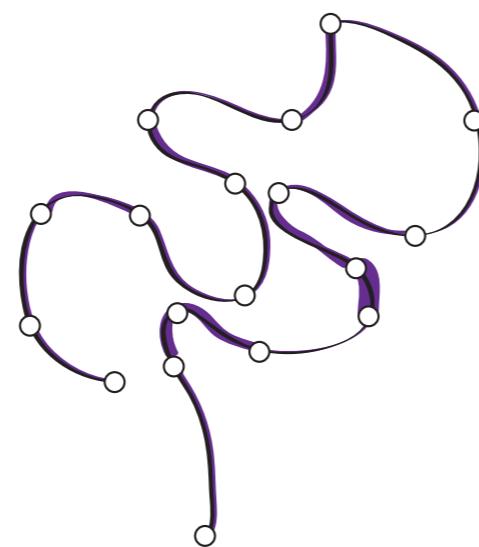
Model analysis: clustering and structural features



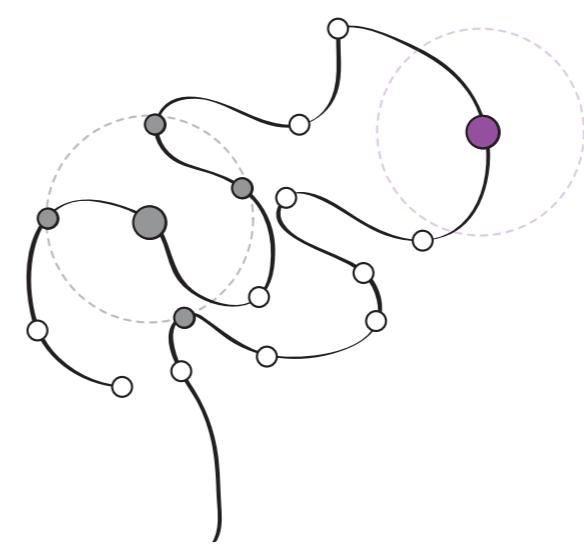
Accessibility (%)



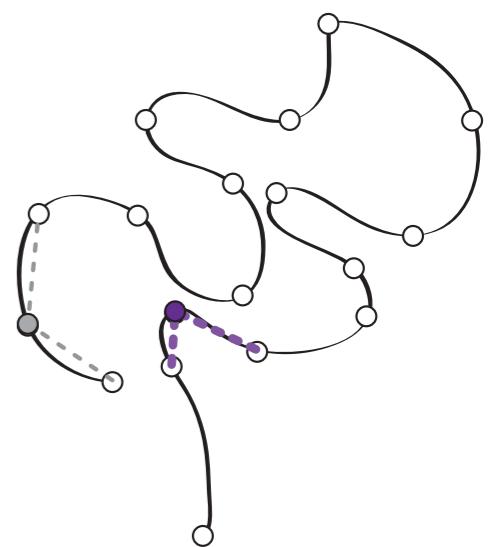
Density (bp/nm)

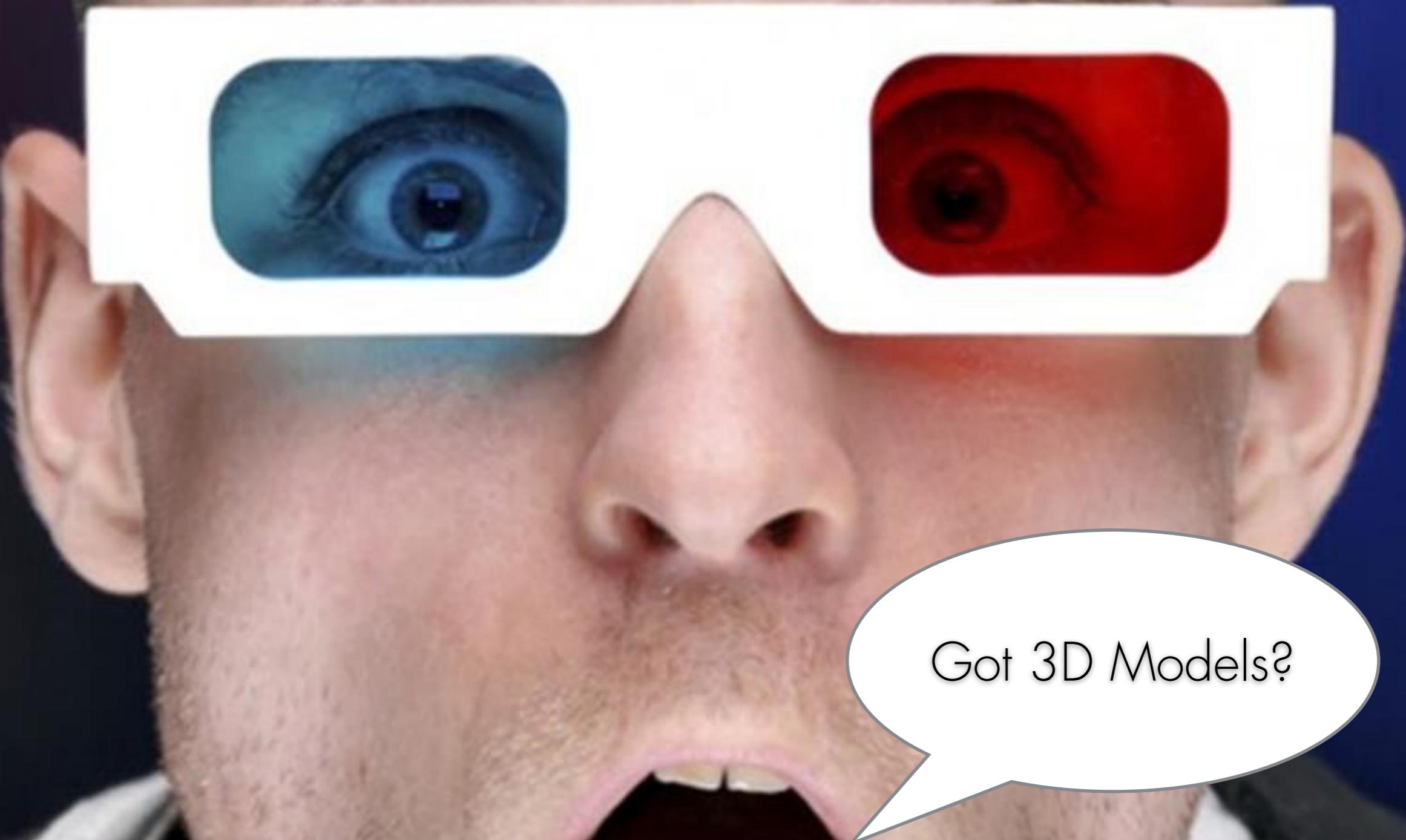


Interactions



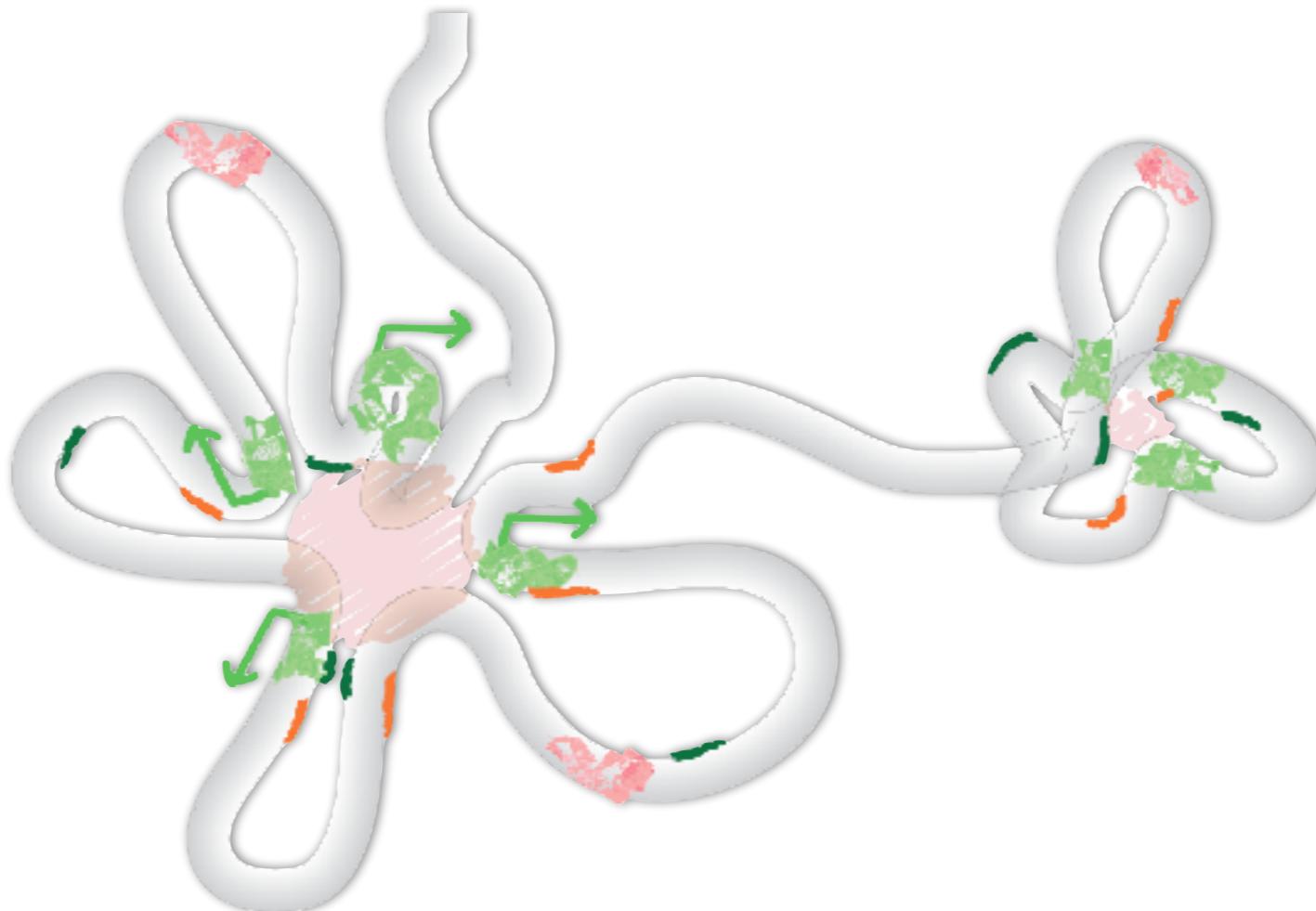
Angle





Got 3D Models?

Human α -globin domain



Davide Baù



Bryan R Lajoie



Amartya Sanyal



Meg Byron



Program in Systems Biology
Department of Biochemistry and Molecular Pharmacology
University of Massachusetts Medical School
Worcester, MA, USA

Human α -globin domain

ENm008 genomic structure and environment

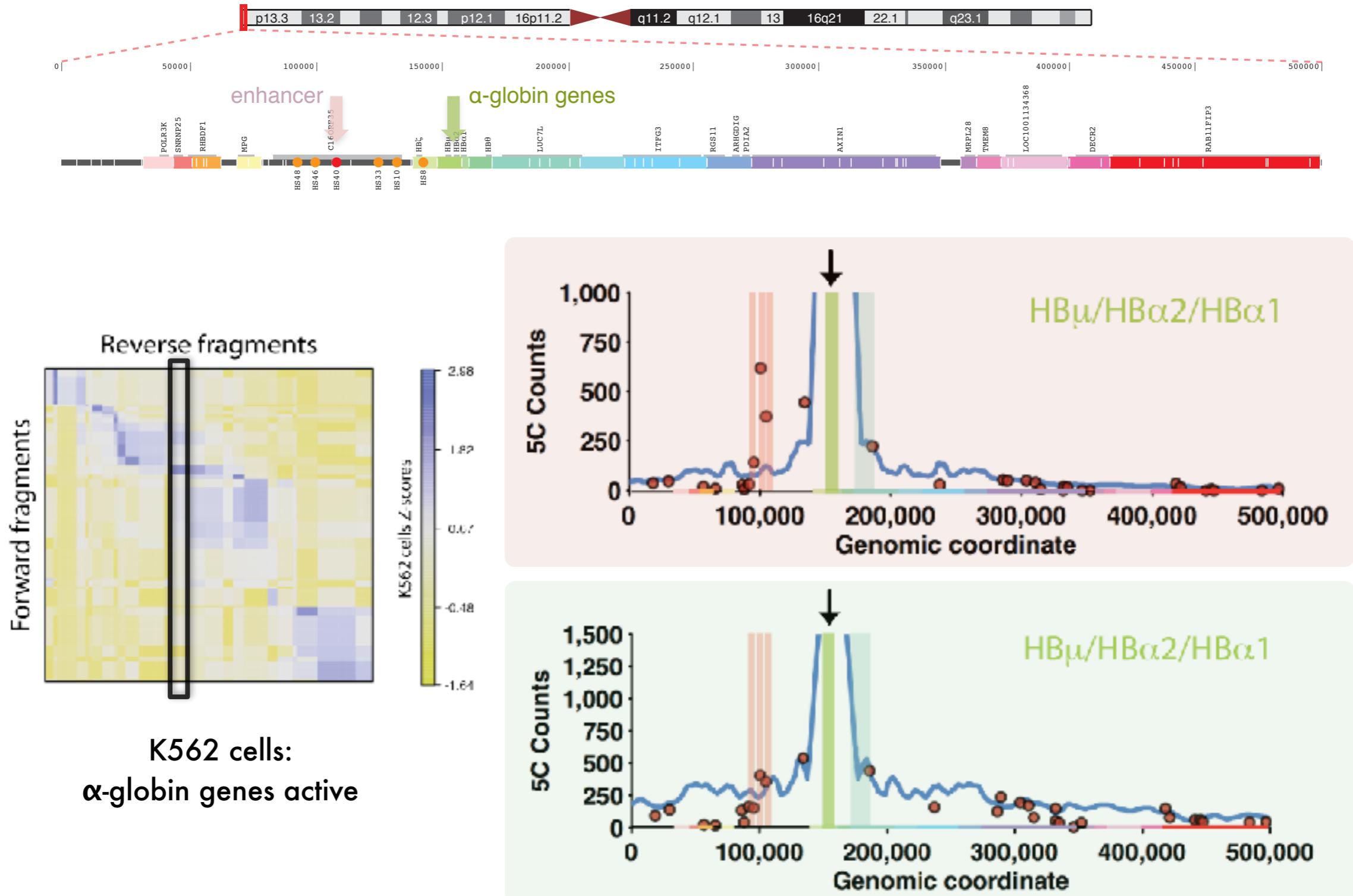


The ENCODE data for ENm008 region was obtained from the UCSC Genome Browser tracks for: RefSeq annotated genes, Affymetrix/CSHL expression data (Gingeras Group at Cold Spring Harbor), Duke/NHGRI DNaseI Hypersensitivity data (Crawford Group at Duke University), and Histone Modifications by Broad Institute ChIP-seq (Bernstein Group at Broad Institute of Harvard and MIT).

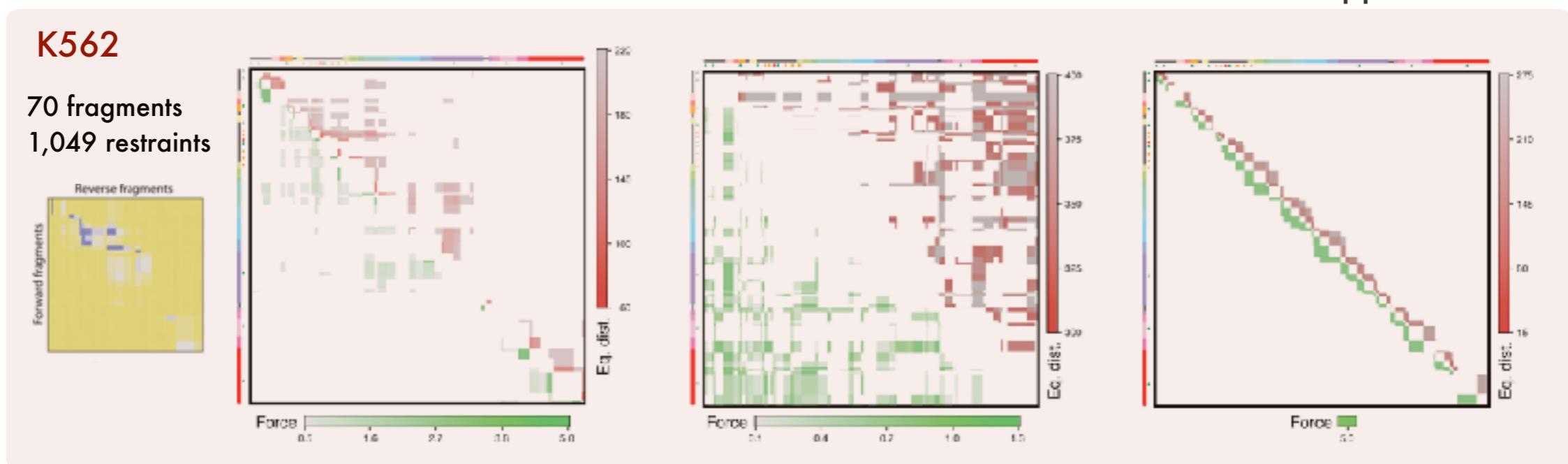
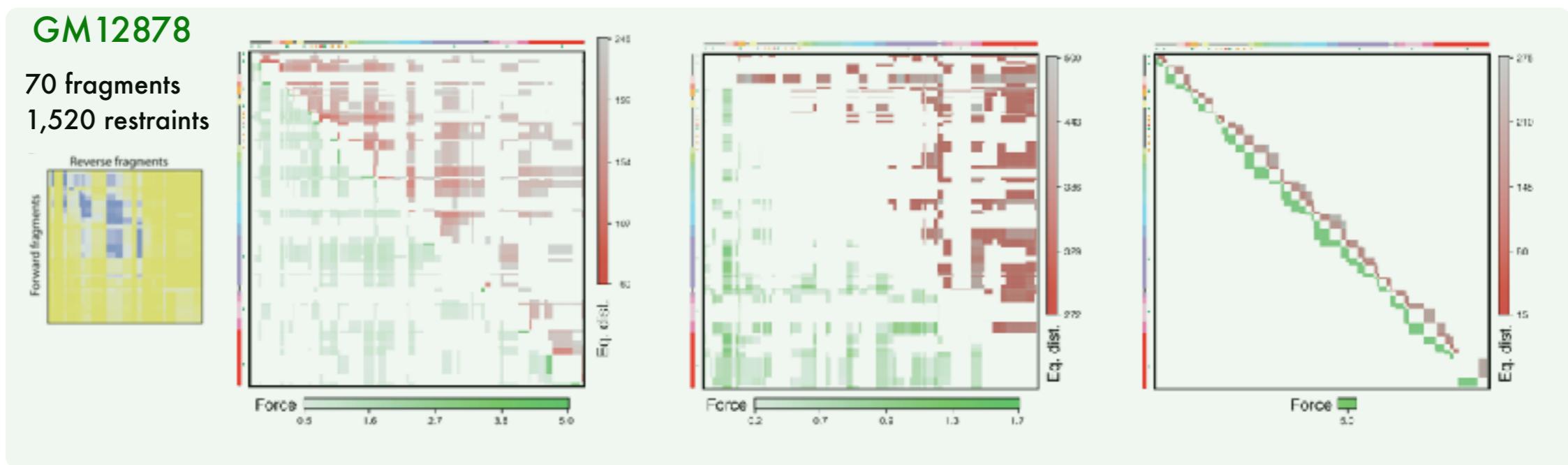
ENCODE Consortium. Nature (2007) vol. 447 (7146) pp. 799-816

Human α -globin domain

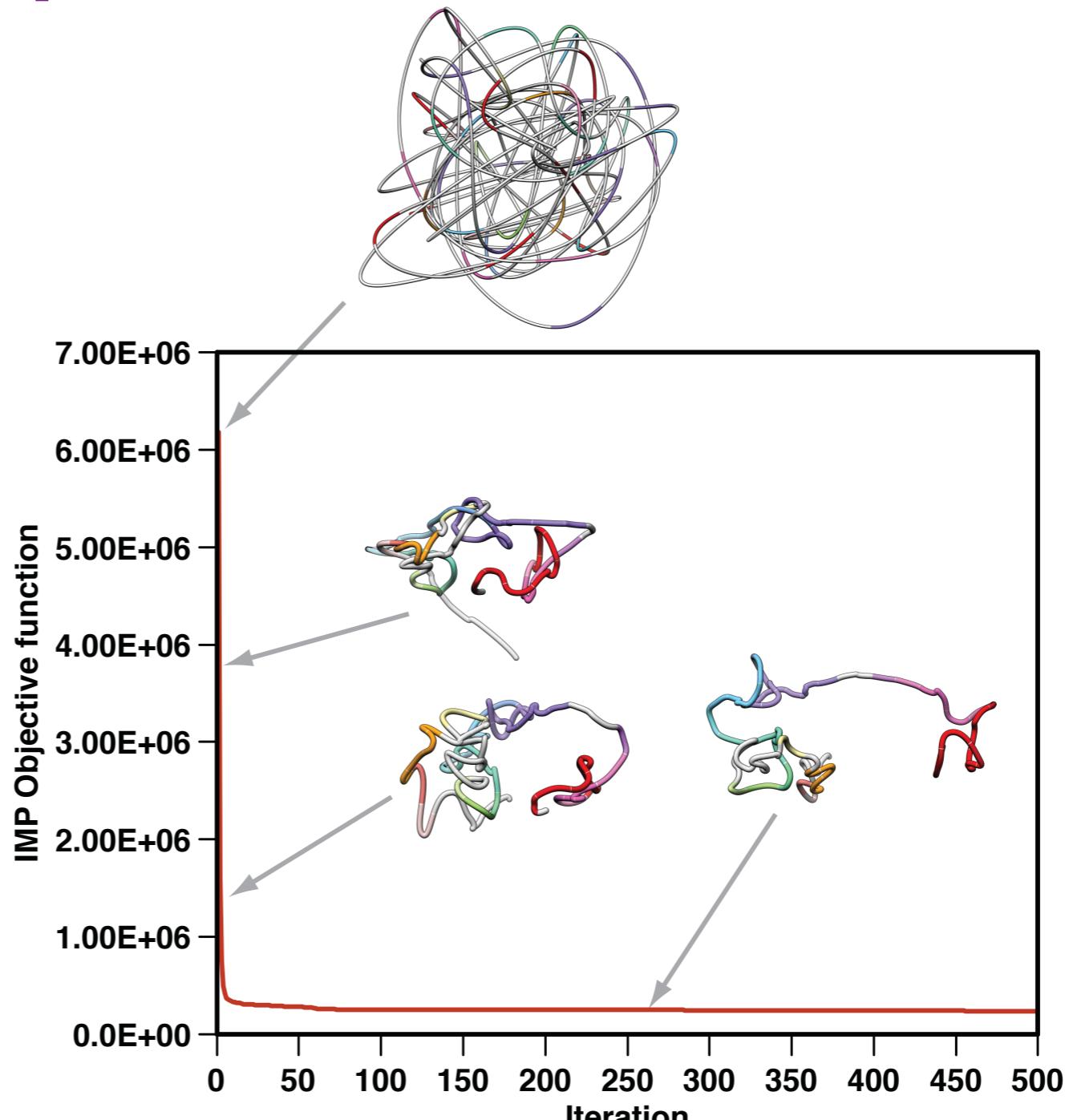
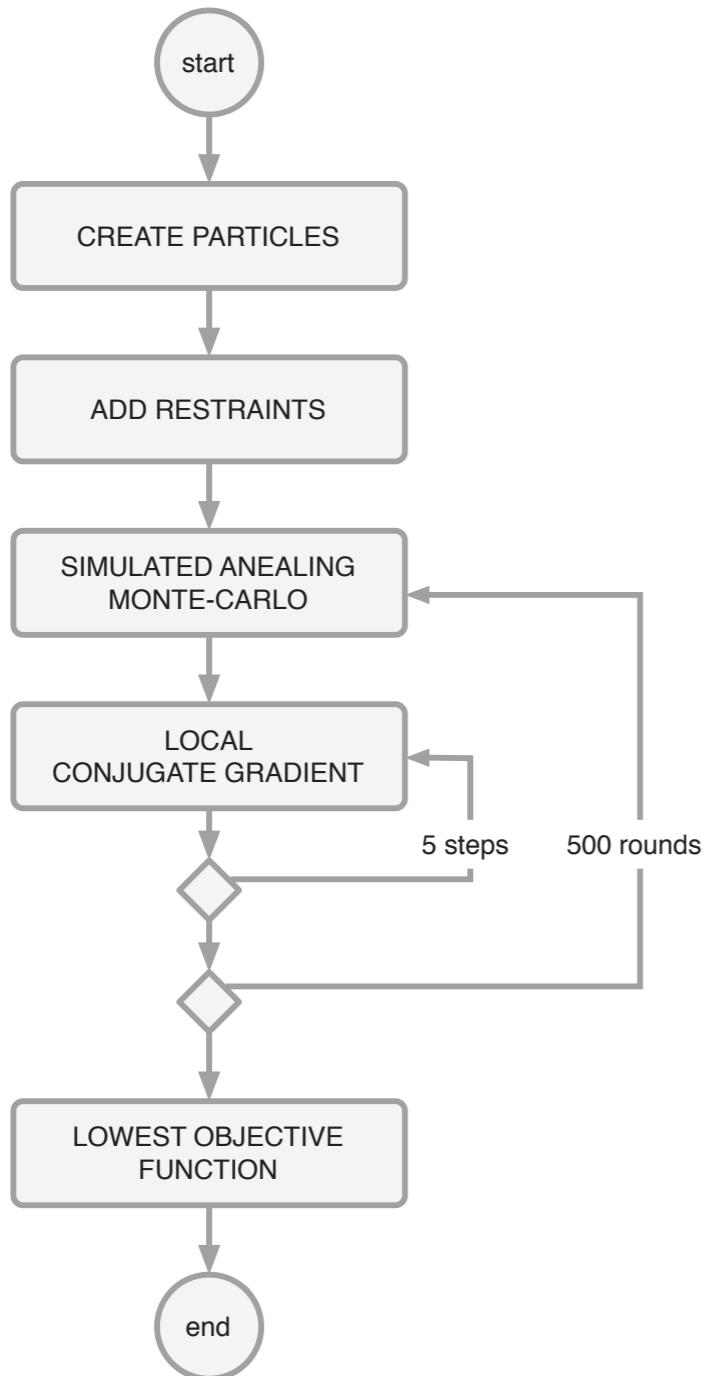
ENm008 genomic structure and environment



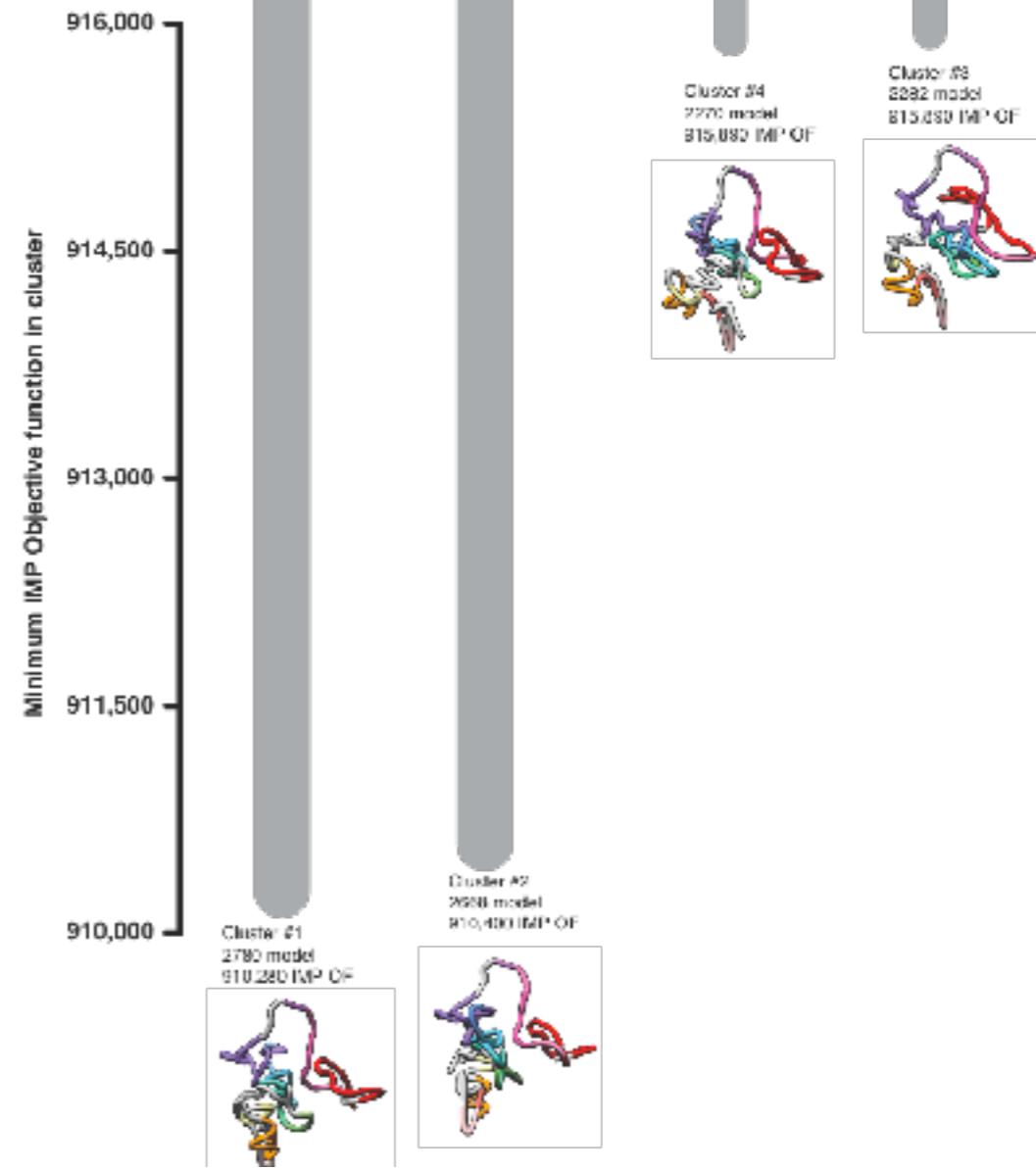
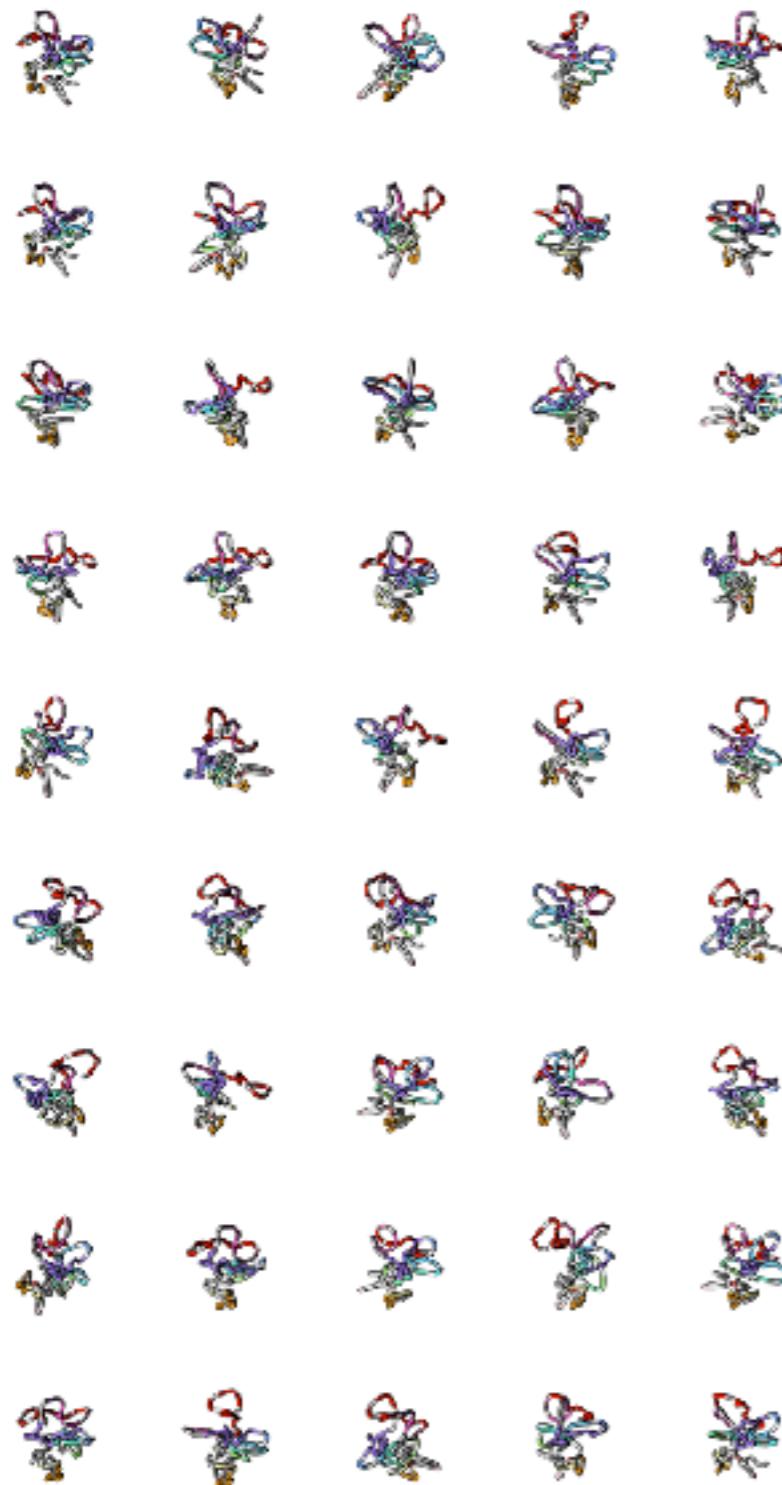
Scoring



Optimization

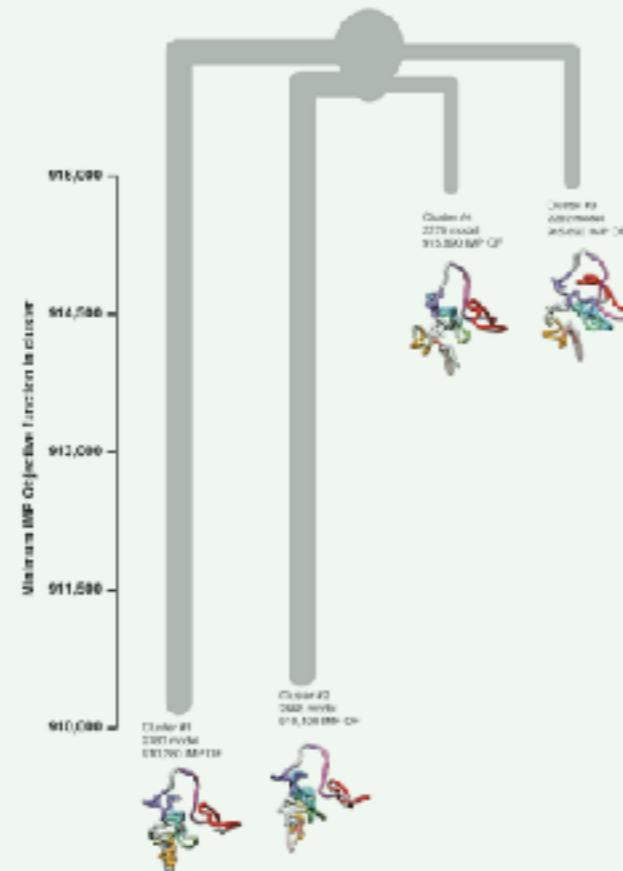
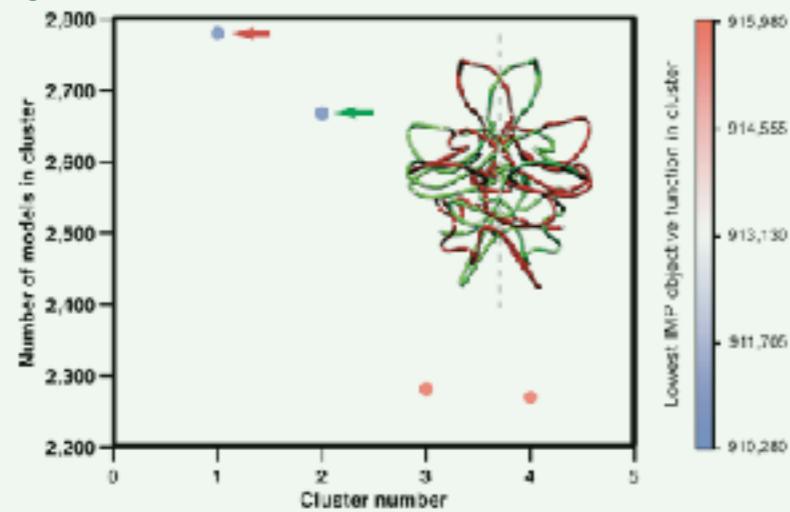


Clustering

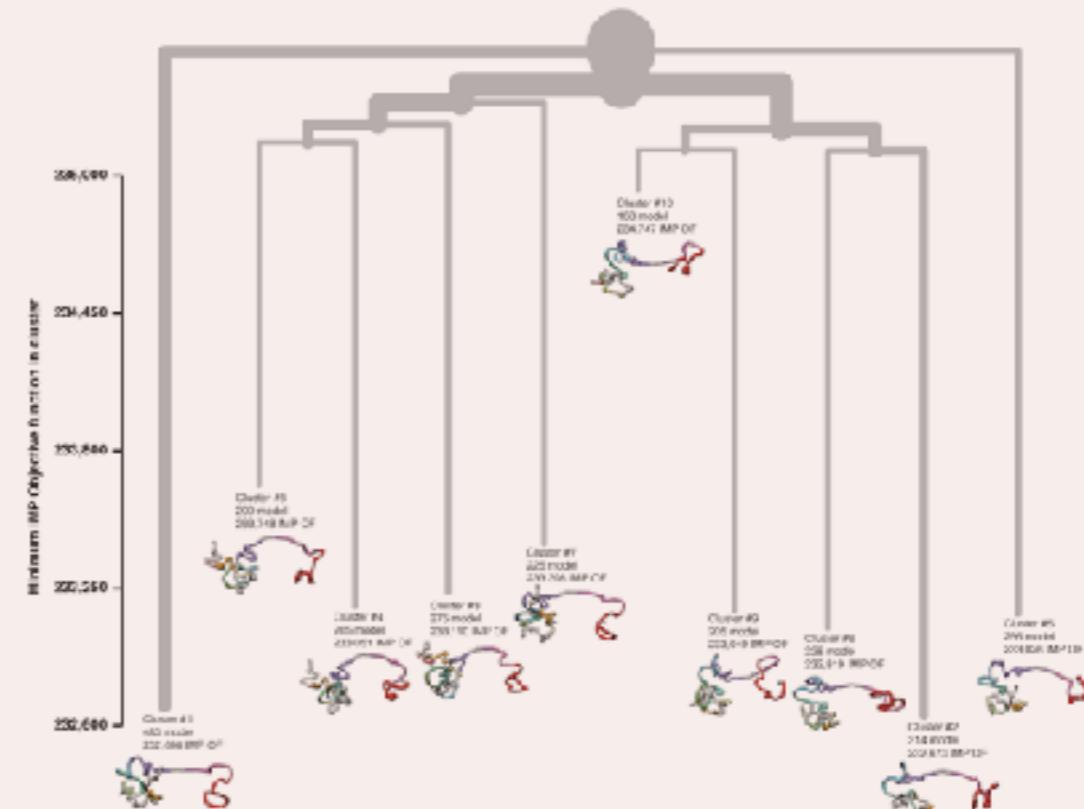
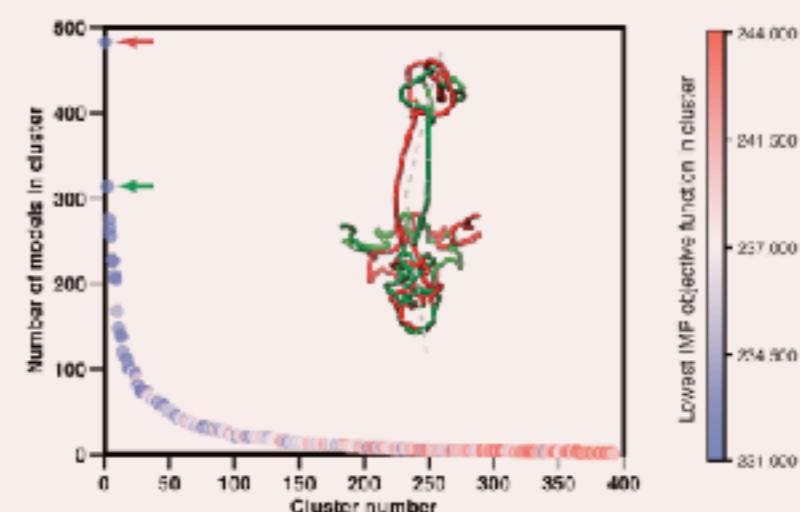


Not just one solution

GM12878



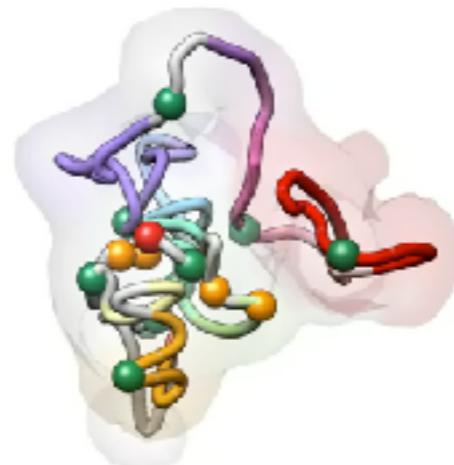
K562



Regulatory compartmentalization

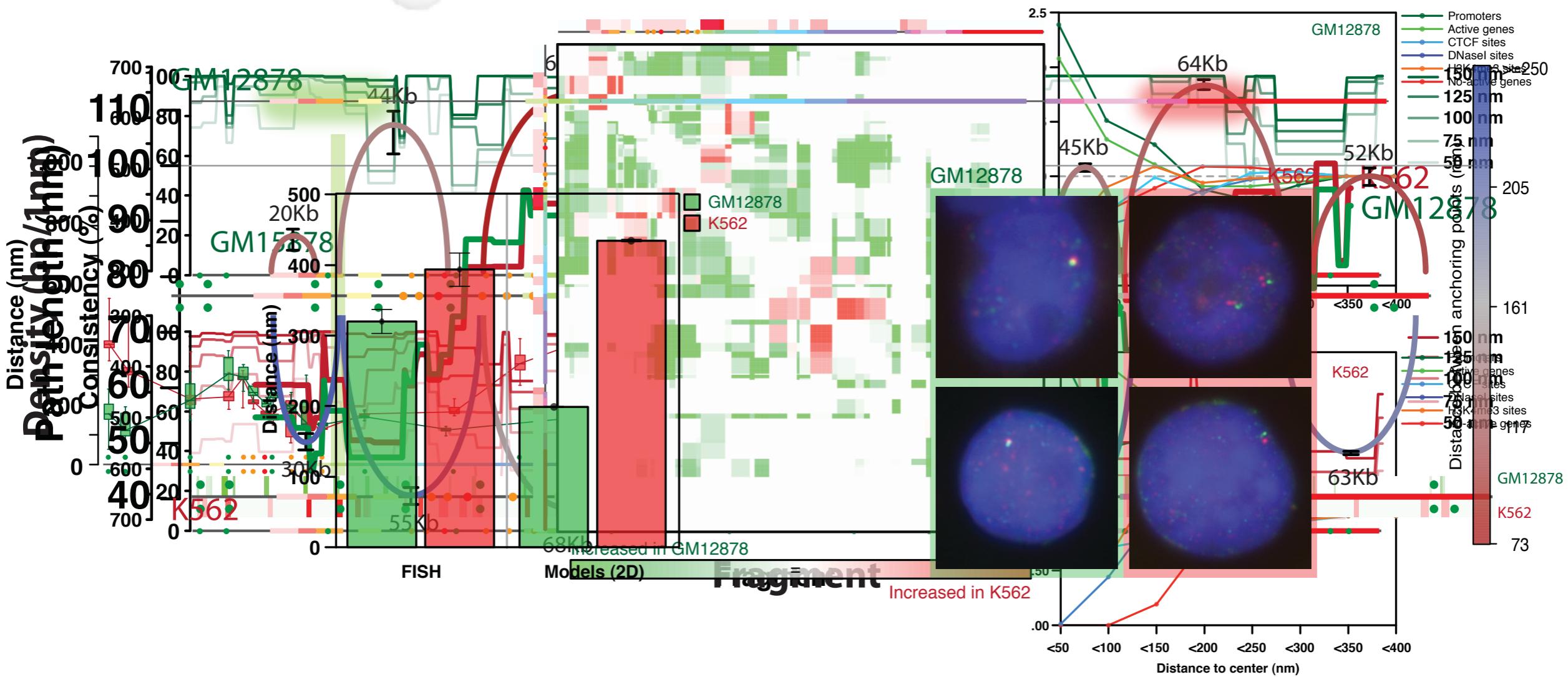
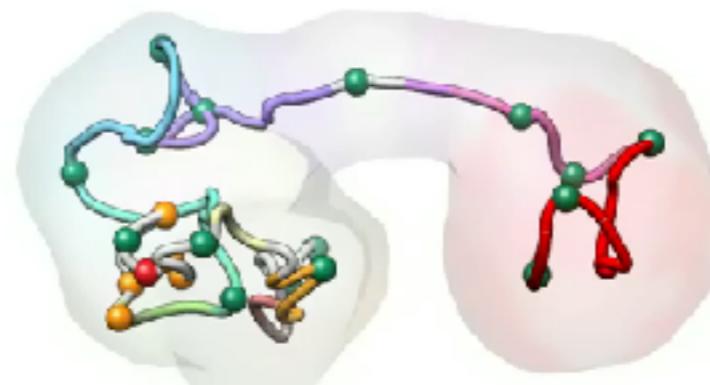
GM12878

Cluster #1
2780 model

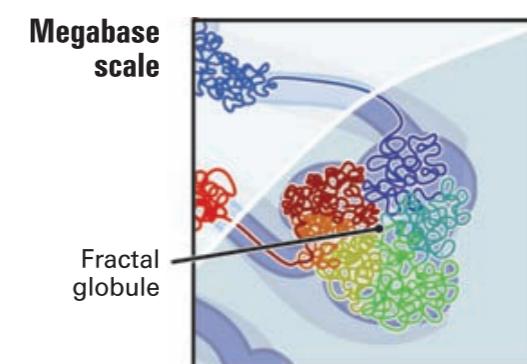
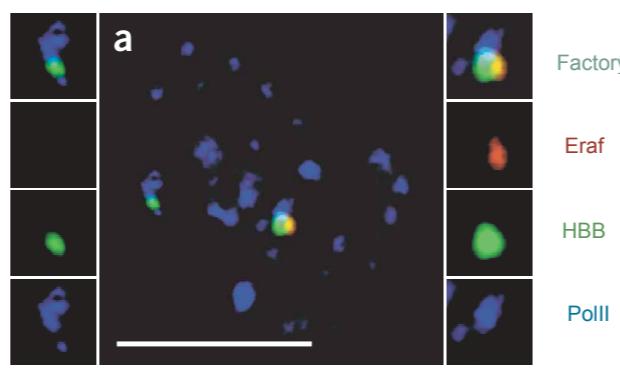
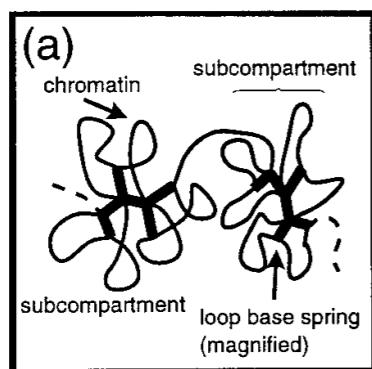
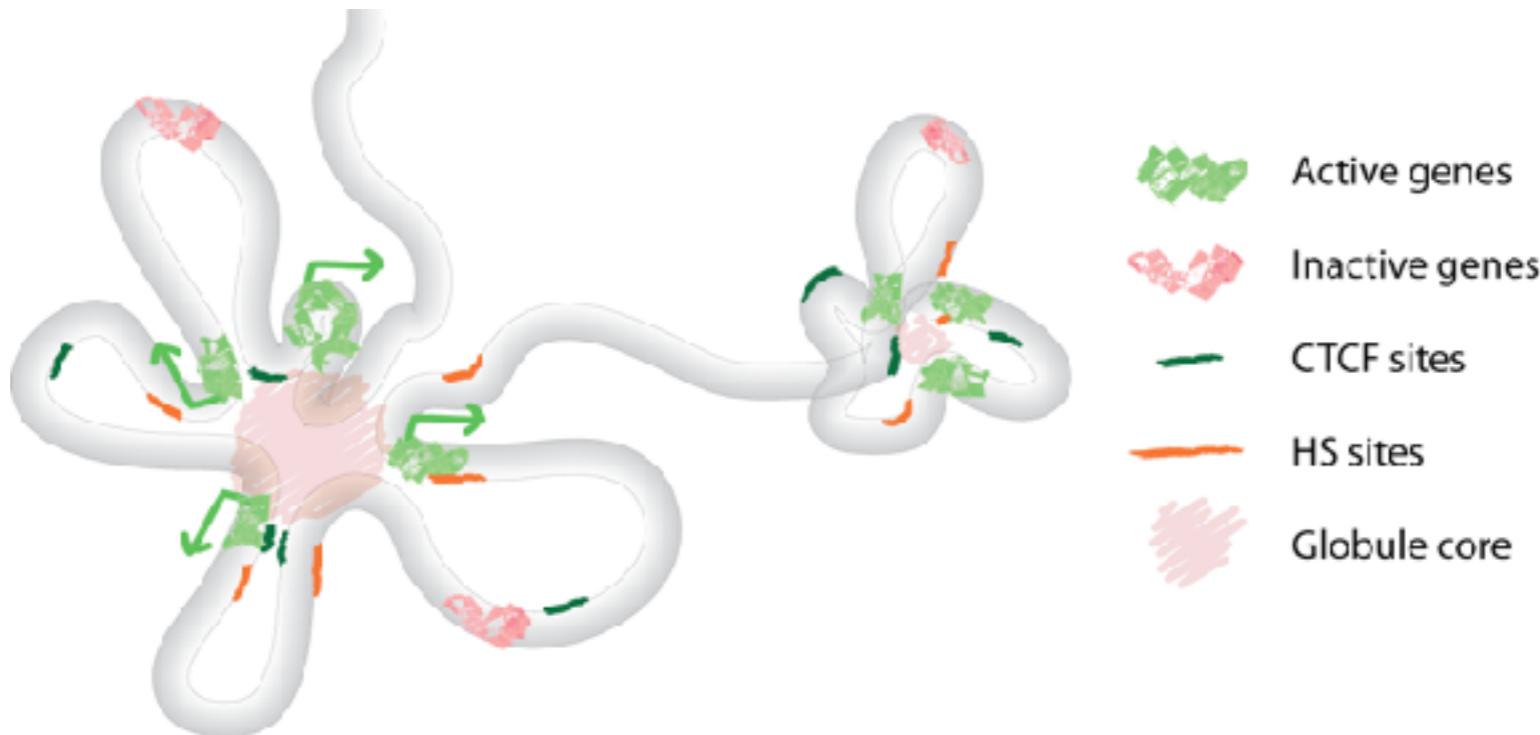


K562

Cluster #2
314 model



The “Chromatin Globule” model

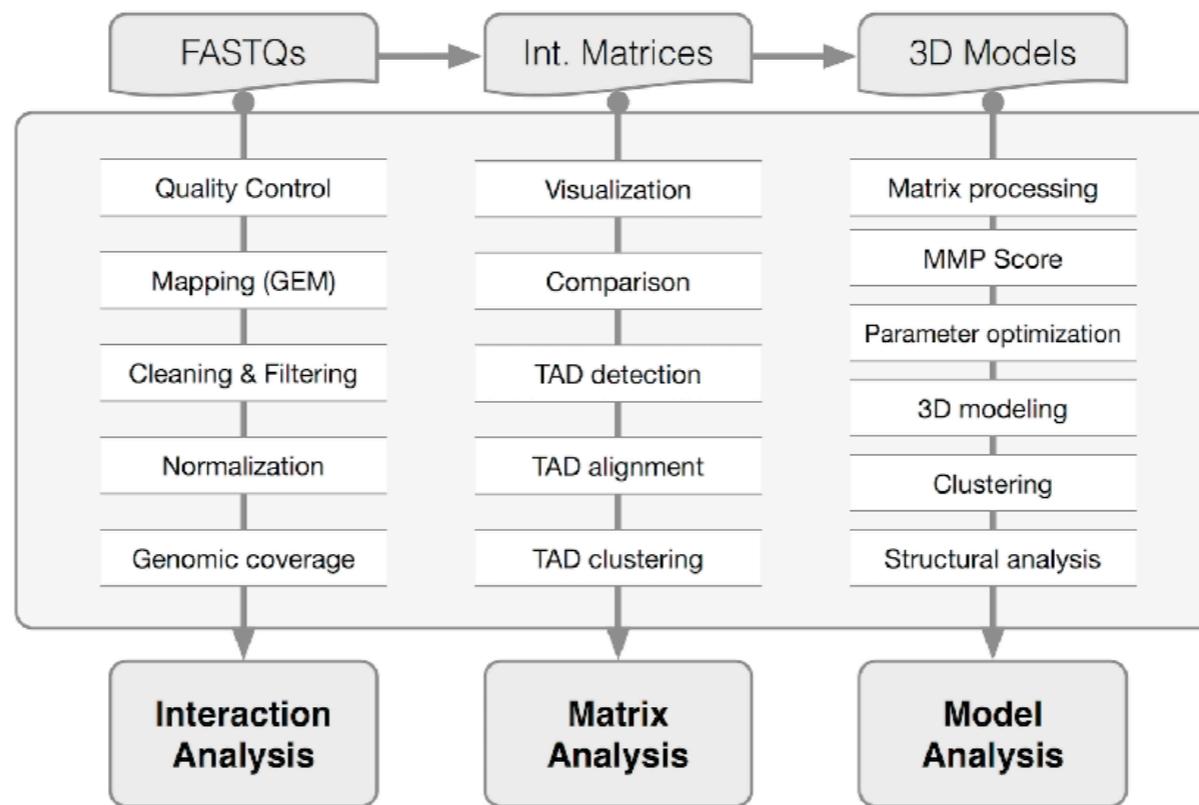


D. Baù et al. **Nat Struct Mol Biol** (2011) 18:107-14

A. Sanyal et al. **Current Opinion in Cell Biology** (2011) 23:325–33.

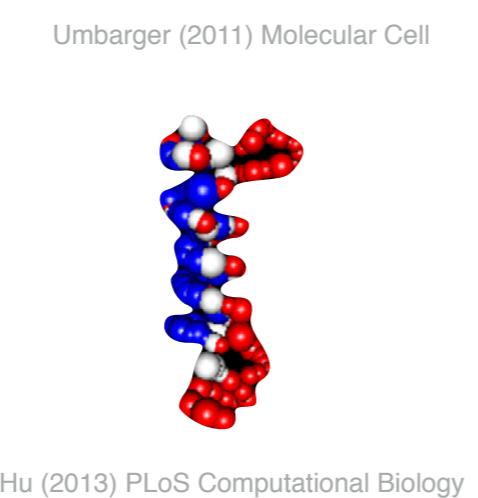
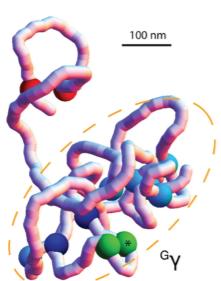
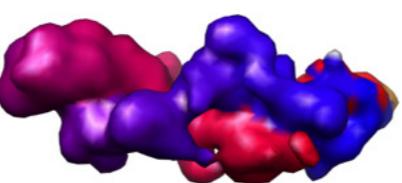
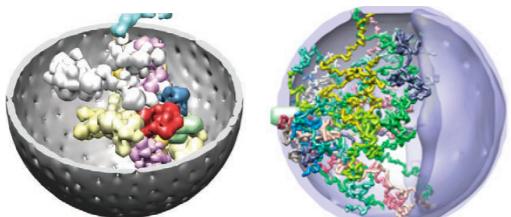
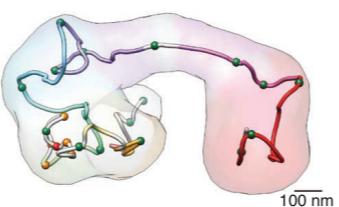
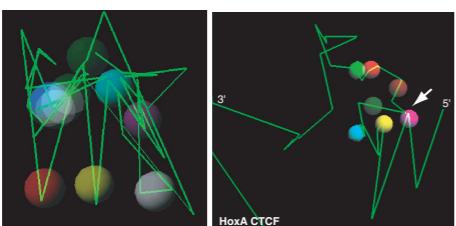
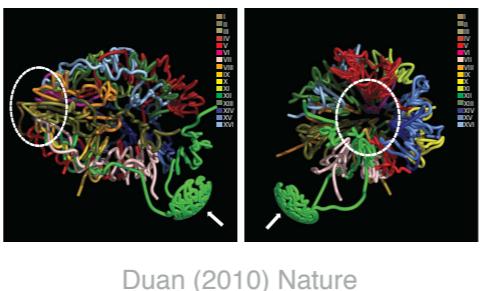
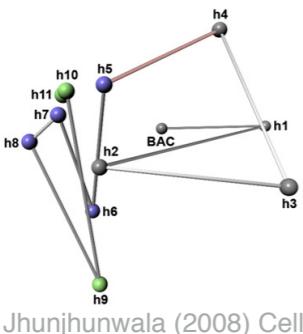


Serra, Baù, et al. (2017). PLOS CompBio



- Baù, D. et al. Nat Struct Mol Biol (2011)
- Umbarger, M. A. et al. Mol Cell (2011)
- Le Dily, F. et al. Genes & Dev (2014)
- Belton, J.M. et al. Cell Reports (2015)
- Trussart M. et al. Nature Communication (2017)
- Cattoni, D. et al. Nature Communication (2017)
- Stadhouders R. et al. Nature Genetics (2018)
- Kojic, A., Cuadrado, A. et al. Nat Struct Mol Biol (2018)
- Beekman R. et al. Nature Medicine (2018)
- Mas, G. et al. Nature Genetics (2018) in press

Are the models correct?



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

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

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

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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 restraint-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).

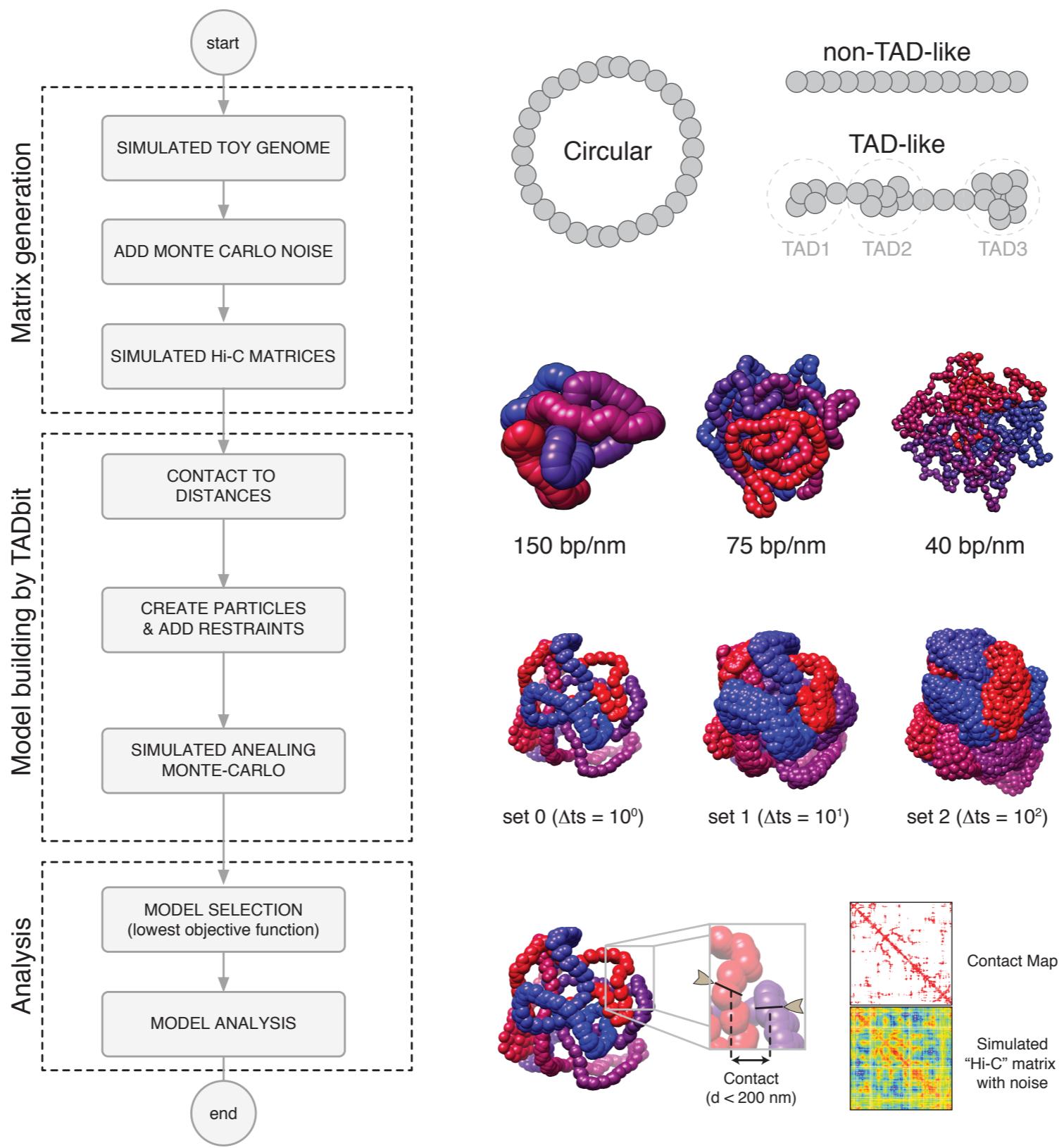
We recently developed a mean-field method for modeling 3D structures of genomes and genomic domains based on 3C interaction data (9). Our approach, called TADbit, was developed around the Integrative Modeling Platform (IMP, <http://integrativemodeling.org>), a general framework for restraint-based modeling 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 eukaryotic and prokaryotic 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

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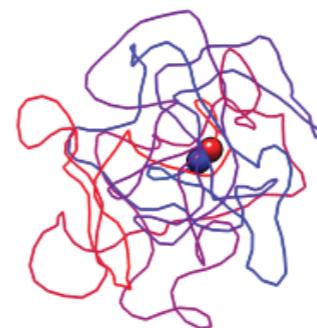
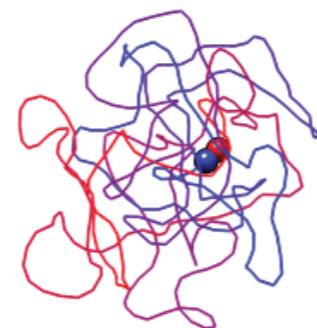
Trussart, et al. (2015). Nucleic Acids Research.

Toy models

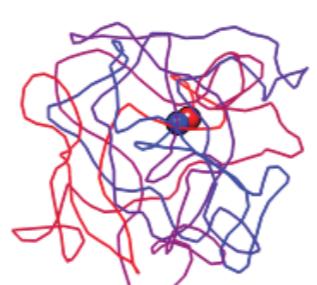
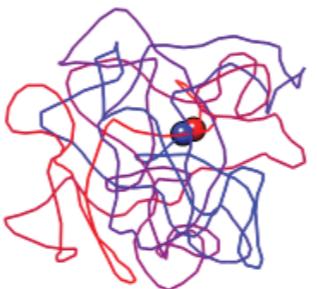
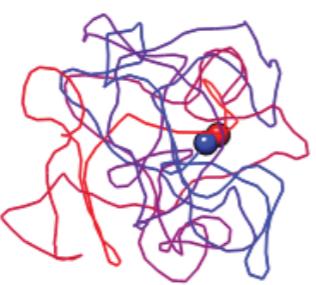
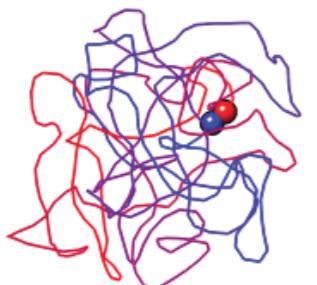
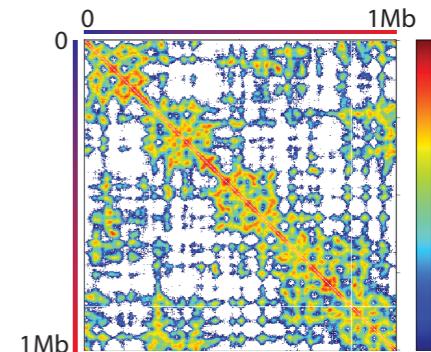


by Ivan Junier

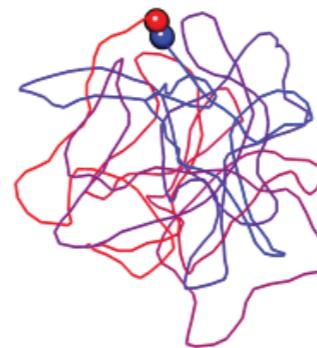
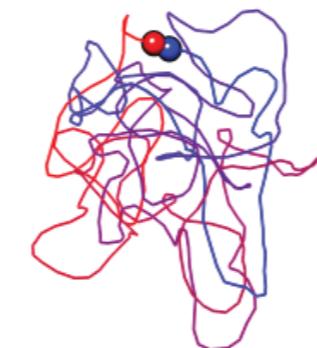
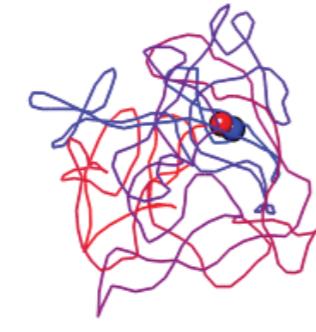
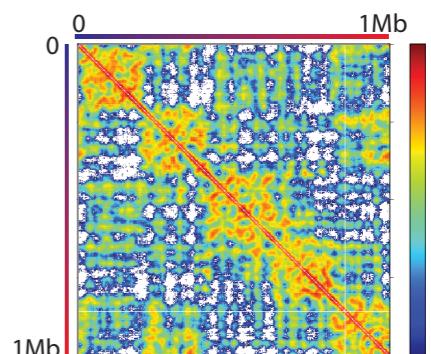
Toy interaction matrices



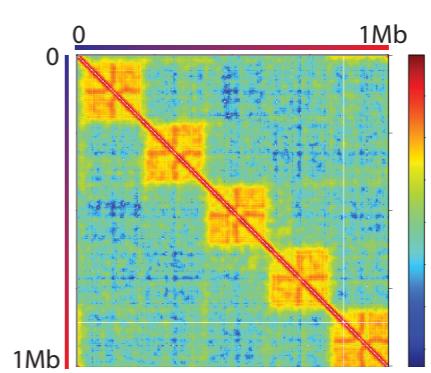
set 0 ($\Delta ts=10^0$)



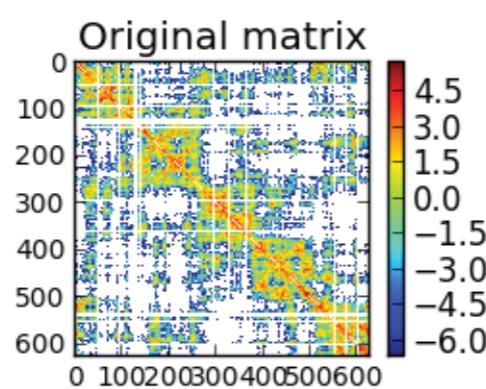
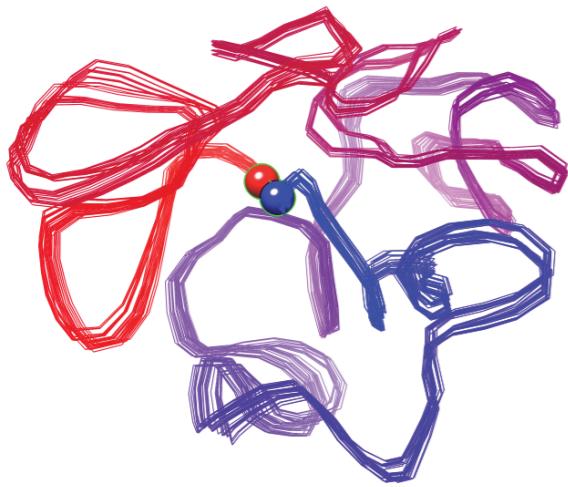
set 4 ($\Delta ts=10^4$)



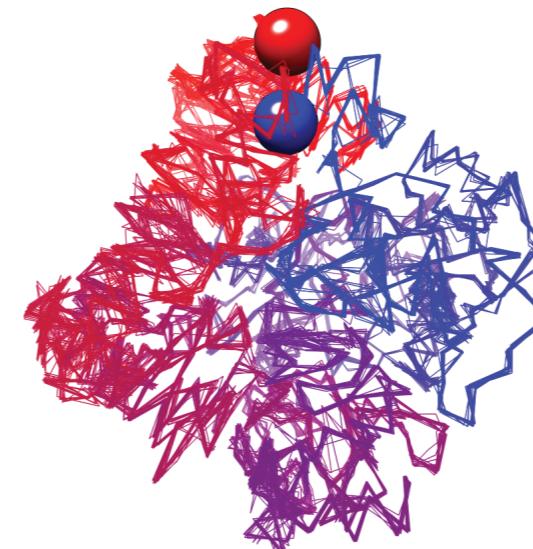
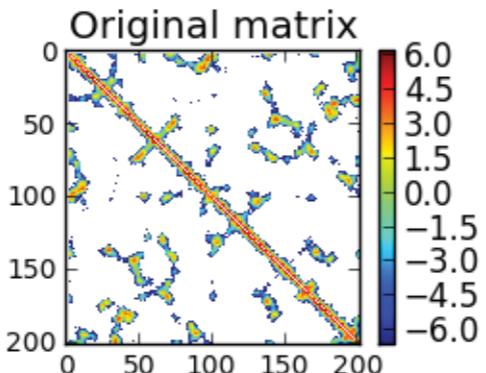
set 6 ($\Delta ts=10^6$)



Reconstructing toy models

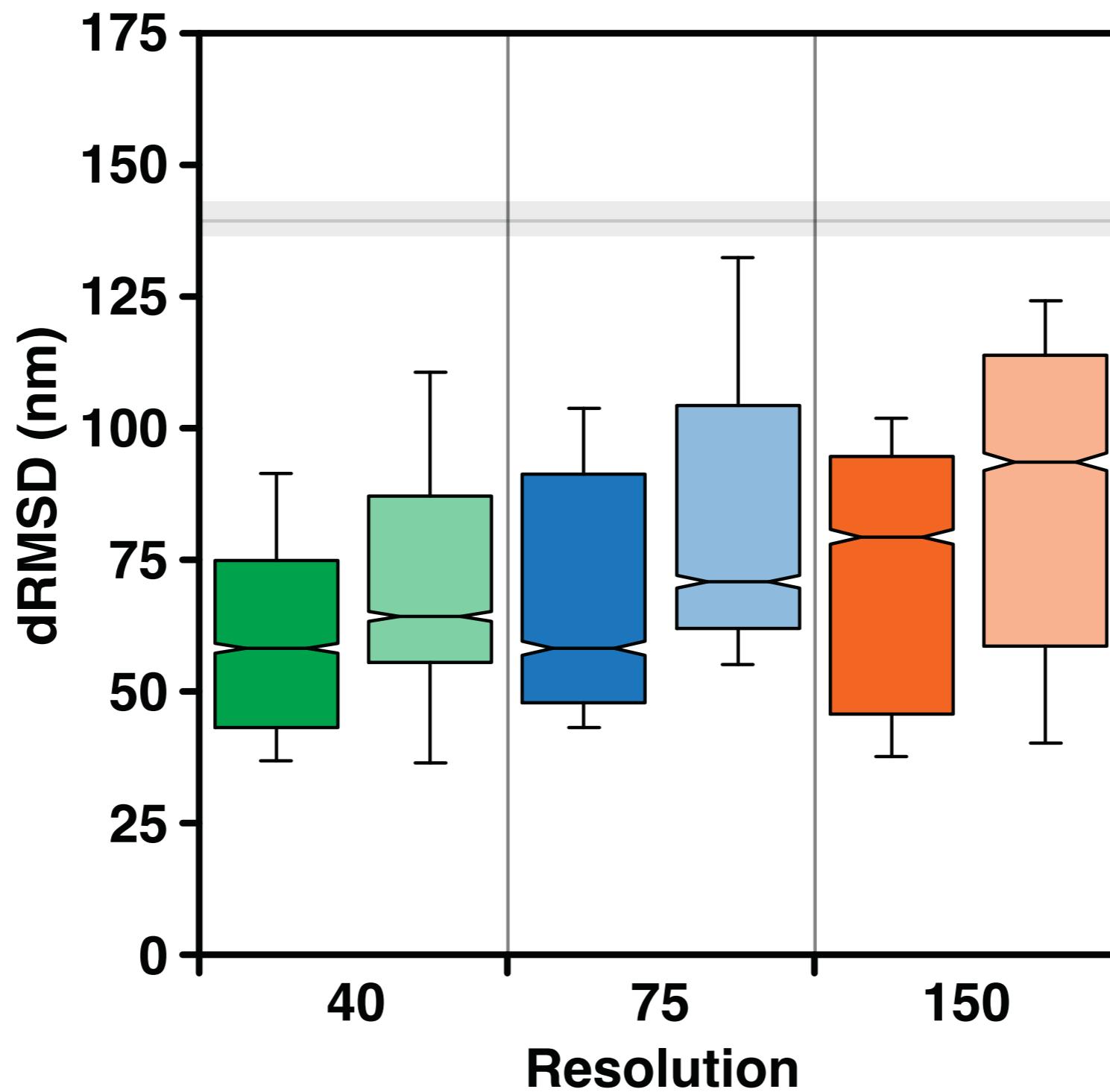


chr40_TAD
 $\alpha=100$
 $\Delta ts=10$
TADbit-SCC: 0.91
 $\langle dRMSD \rangle$: 32.7 nm
 $\langle dSCC \rangle$: 0.94

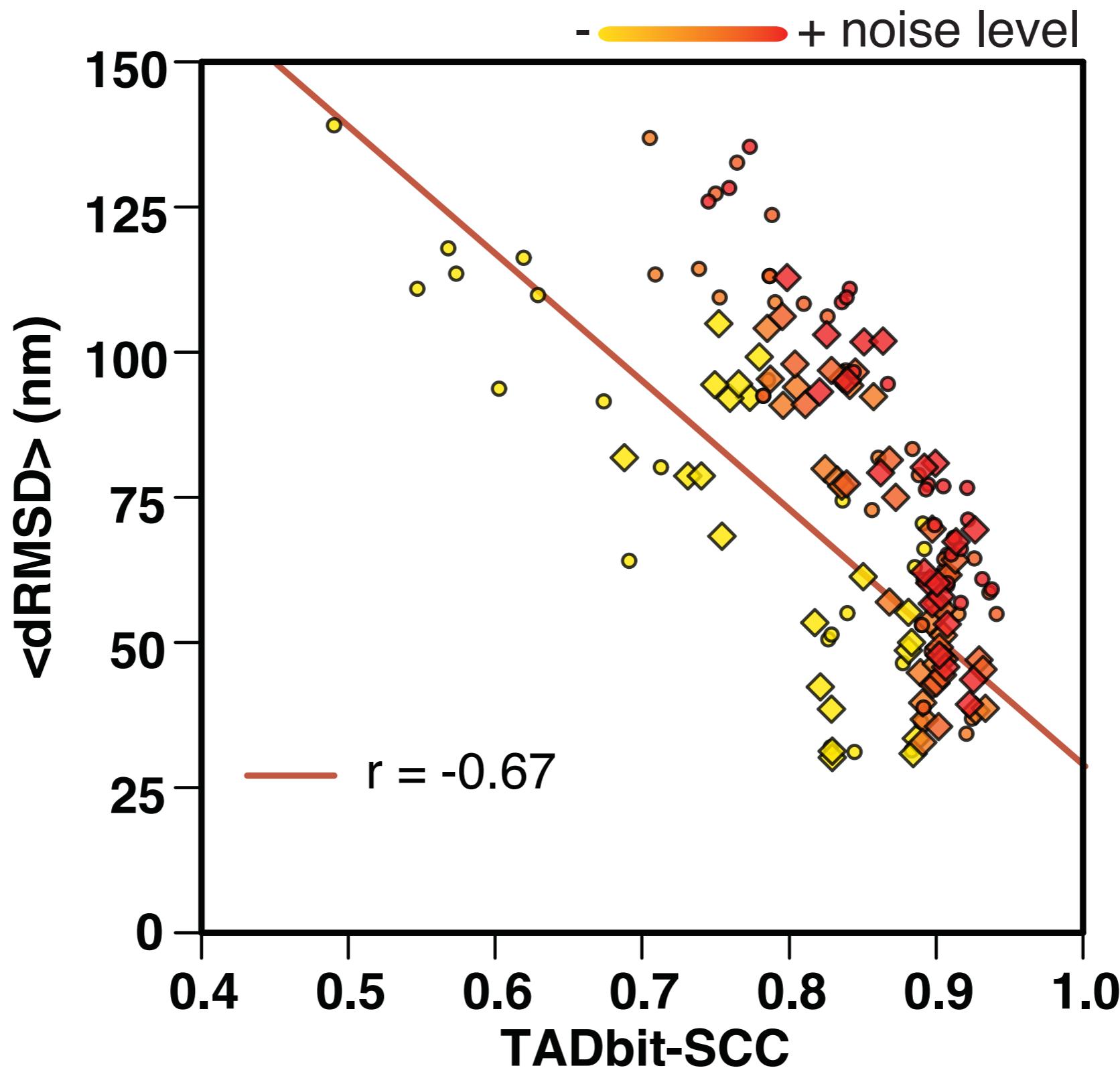


chr150_TAD
 $\alpha=50$
 $\Delta ts=1$
TADbit-SCC: 0.82
 $\langle dRMSD \rangle$: 45.4 nm
 $\langle dSCC \rangle$: 0.86

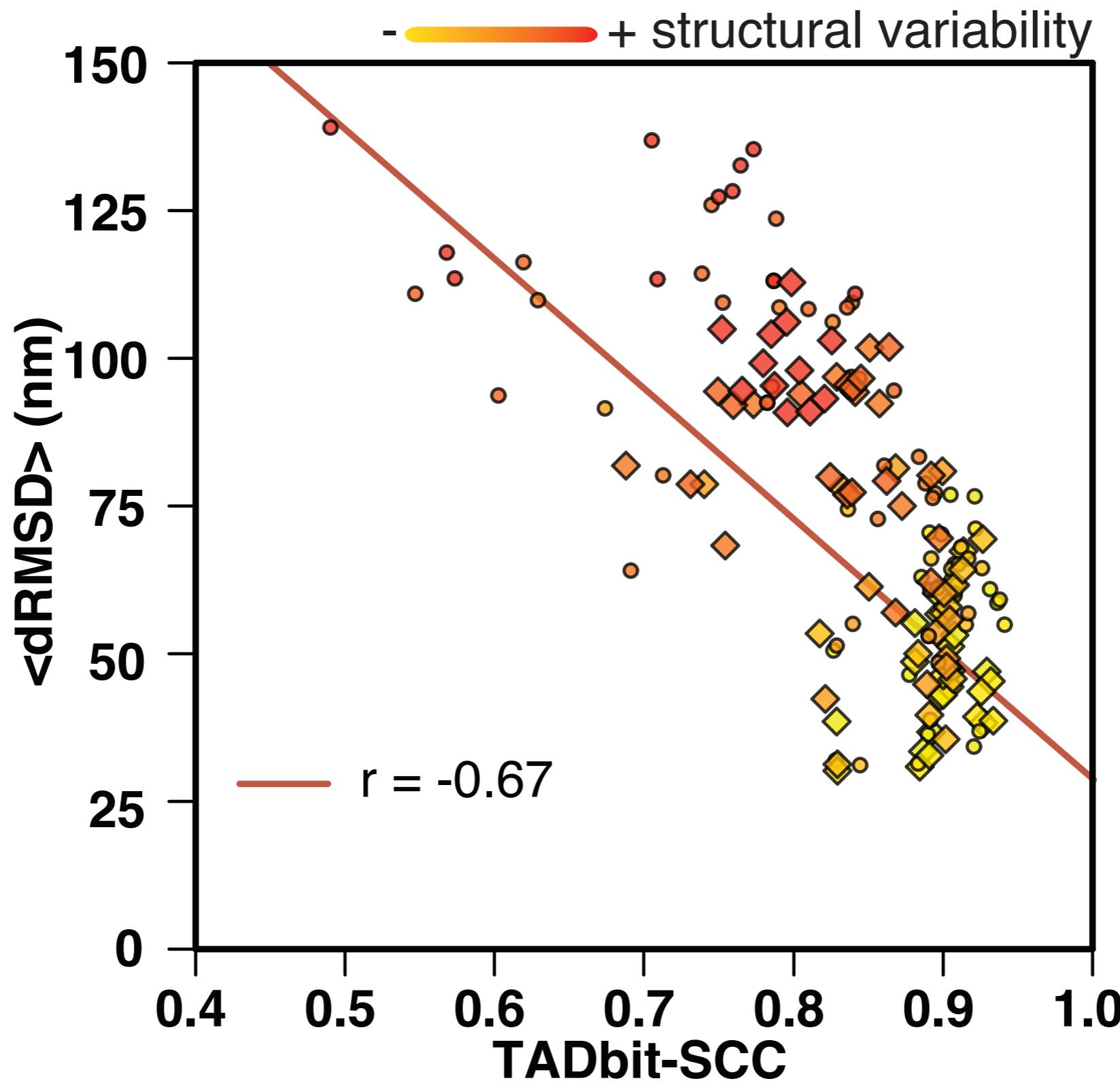
TADs & higher-res are “good”



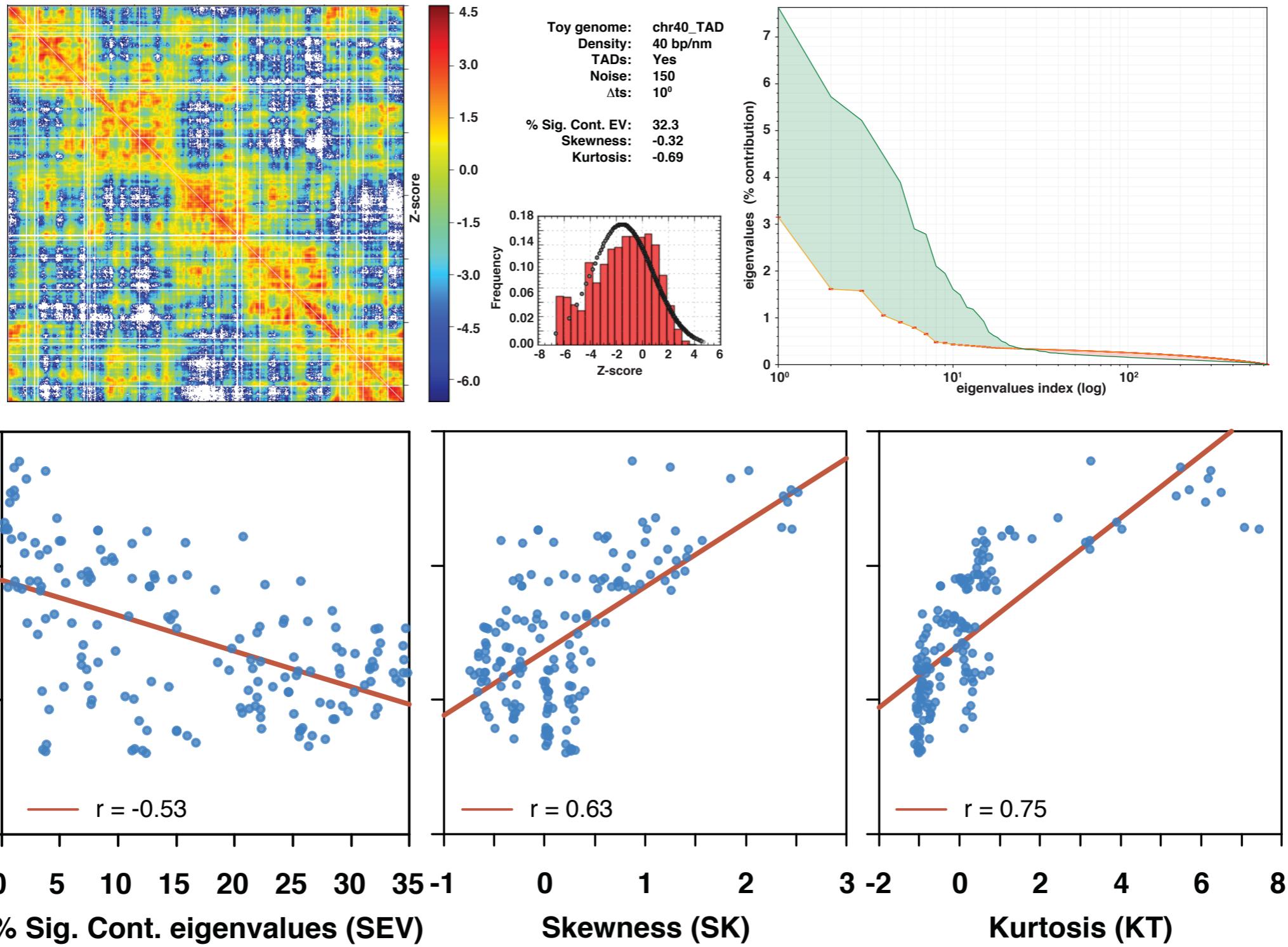
Noise is "OK"



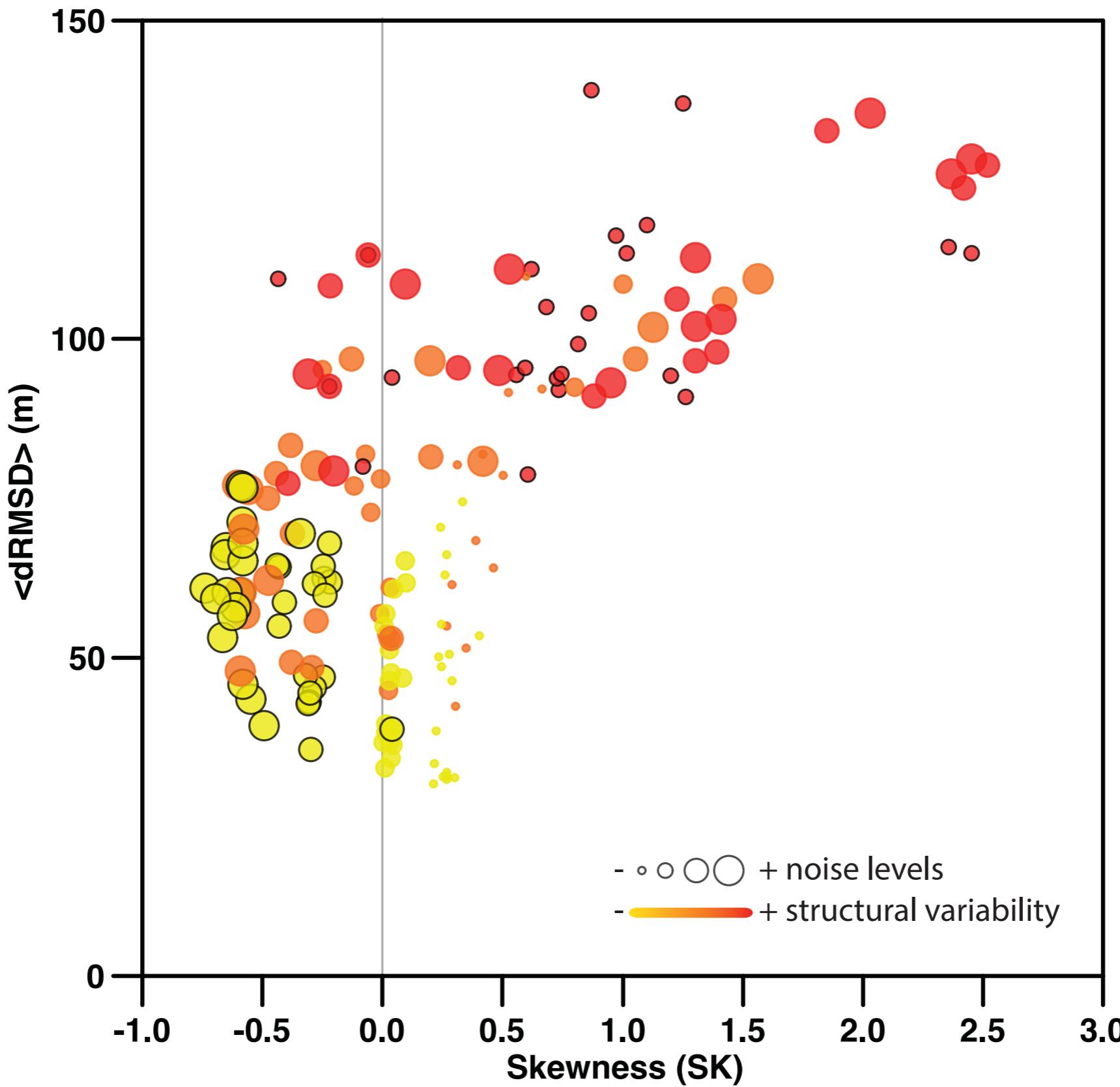
Structural variability is “NOT OK”



Can we predict the accuracy of the models?

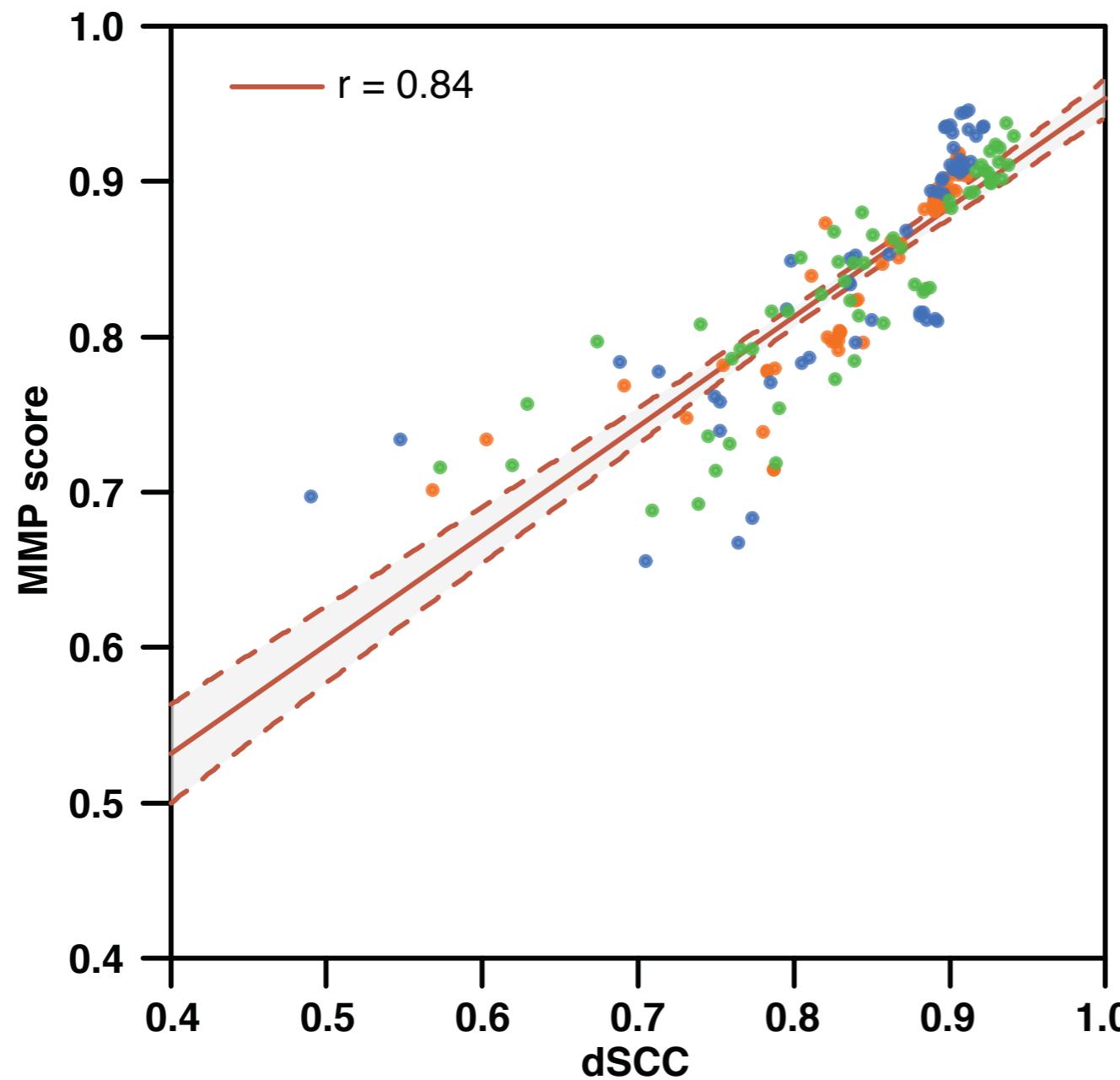


Skewness "side effect"

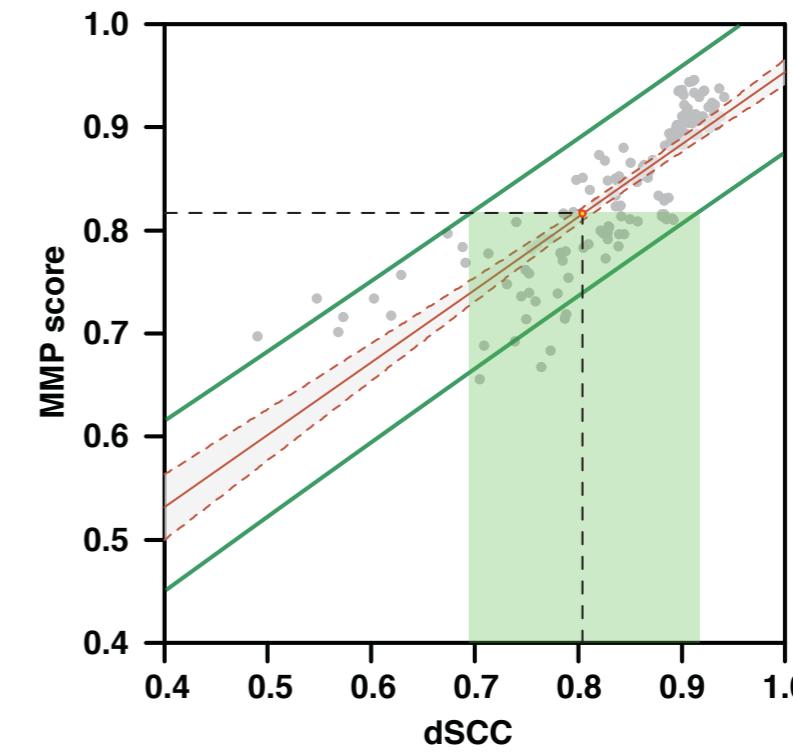
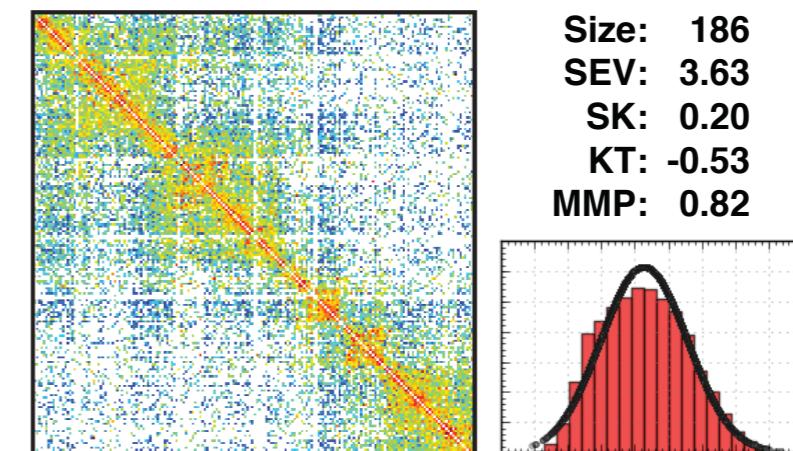


Can we predict the accuracy of the models?

$$\text{MMP} = -0.0002 * \text{Size} + 0.0335 * \text{SK} - 0.0229 * \text{KU} + 0.0069 * \text{SEV} + 0.8126$$



Human Chr1:120,640,000-128,040,000



Higher-res is “good”

put your \$\$ in sequencing

Noise is “OK”

no need to worry much

Structural variability is “NOT OK”

homogenize your cell population!

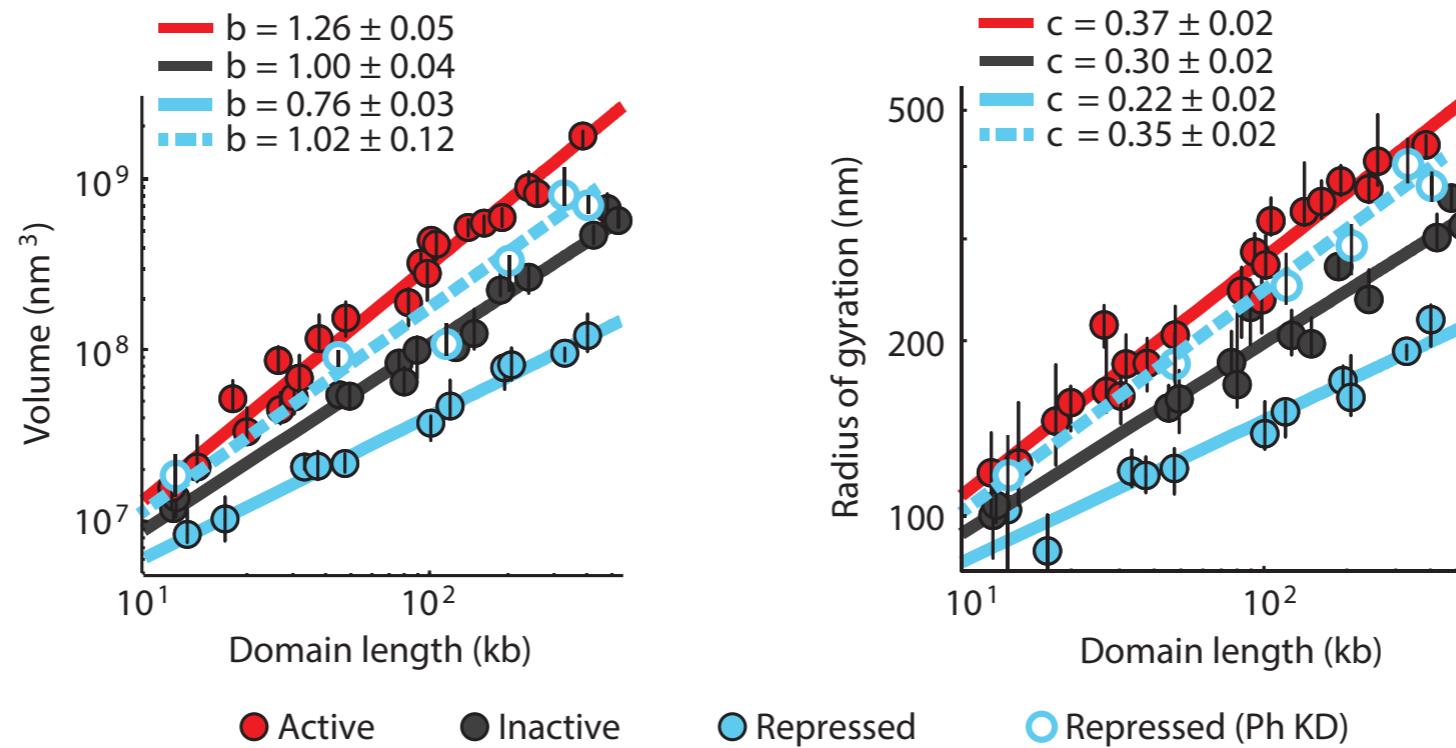
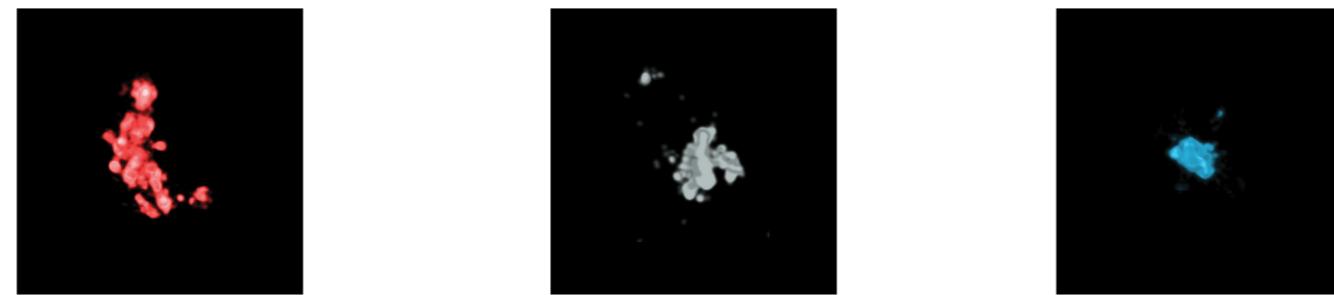
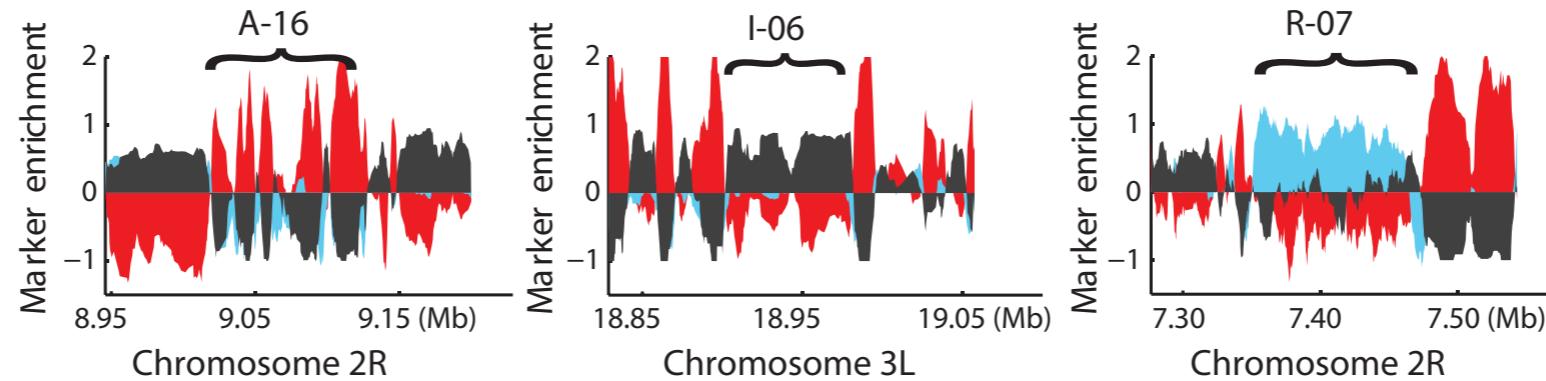
...but we can differentiate between noise and structural variability

and we can a priori predict the accuracy of the models

But... what about direct validation of models?

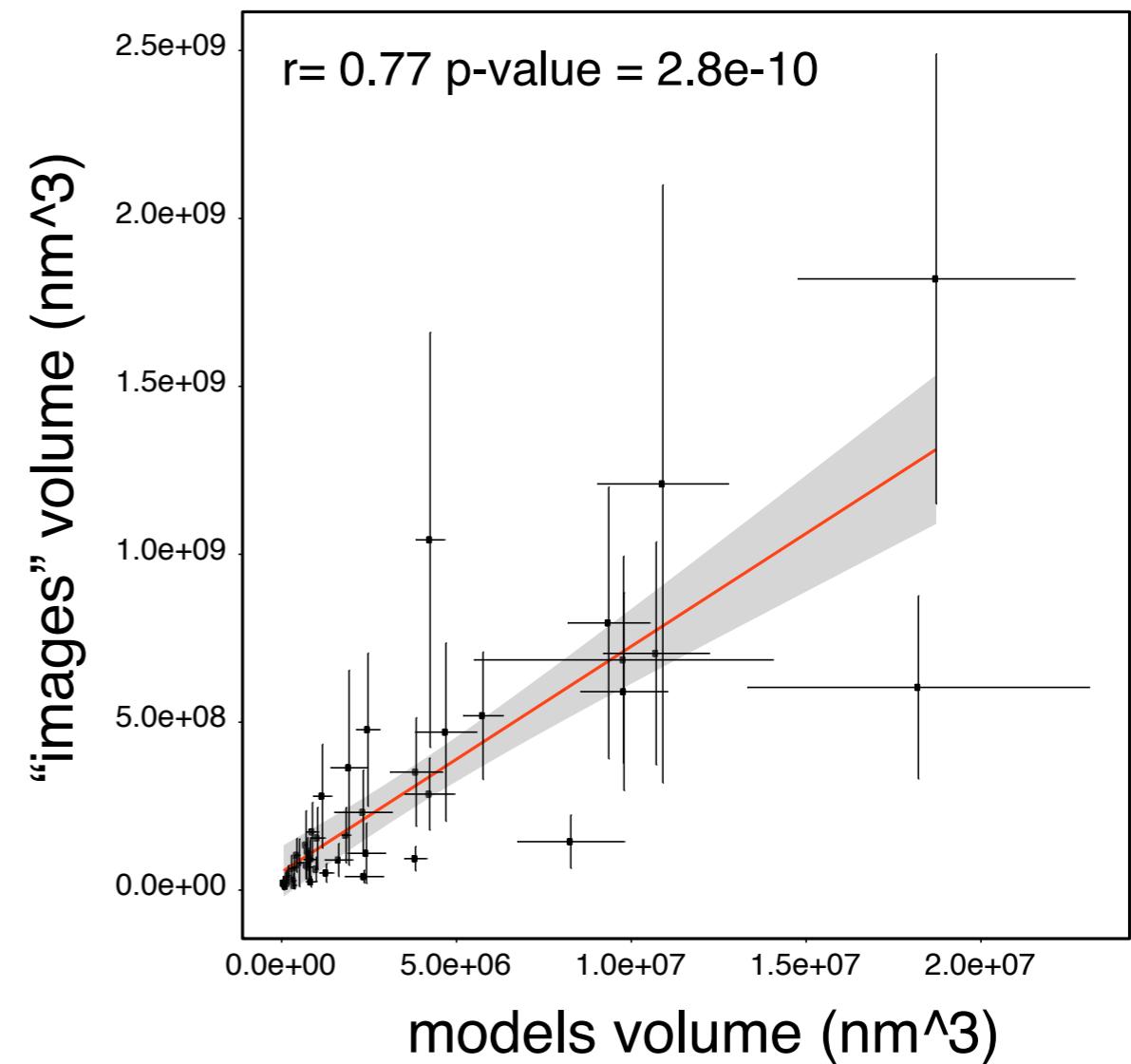
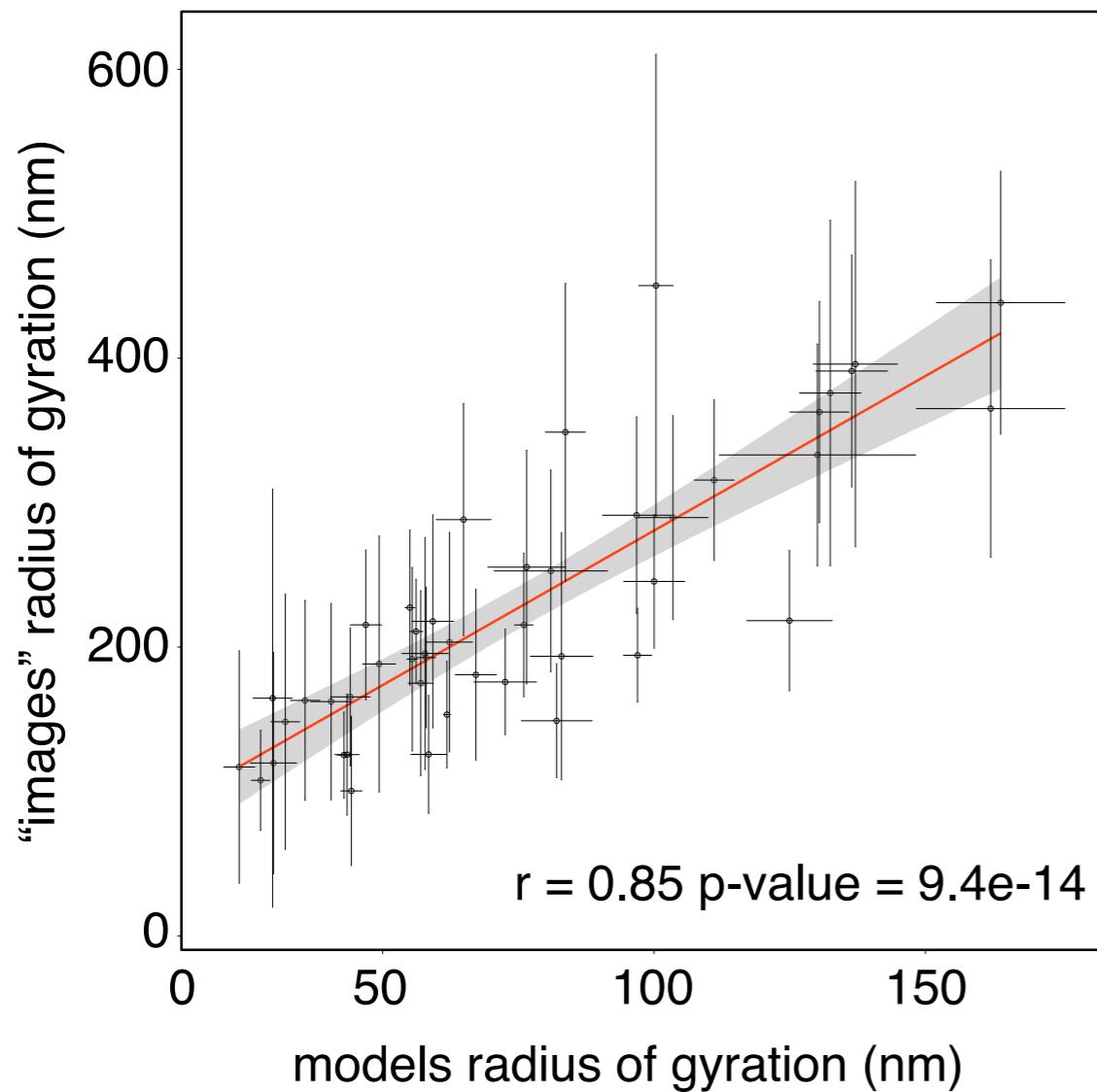
Model accuracy

Boettiger, A. N., et al. (2016). Nature, 529, 418–422.



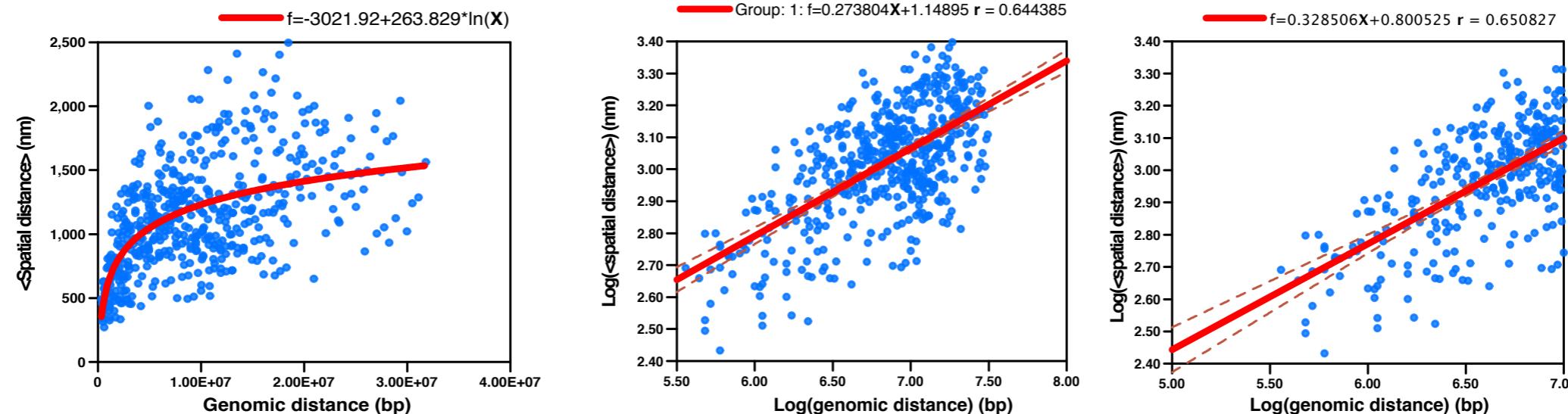
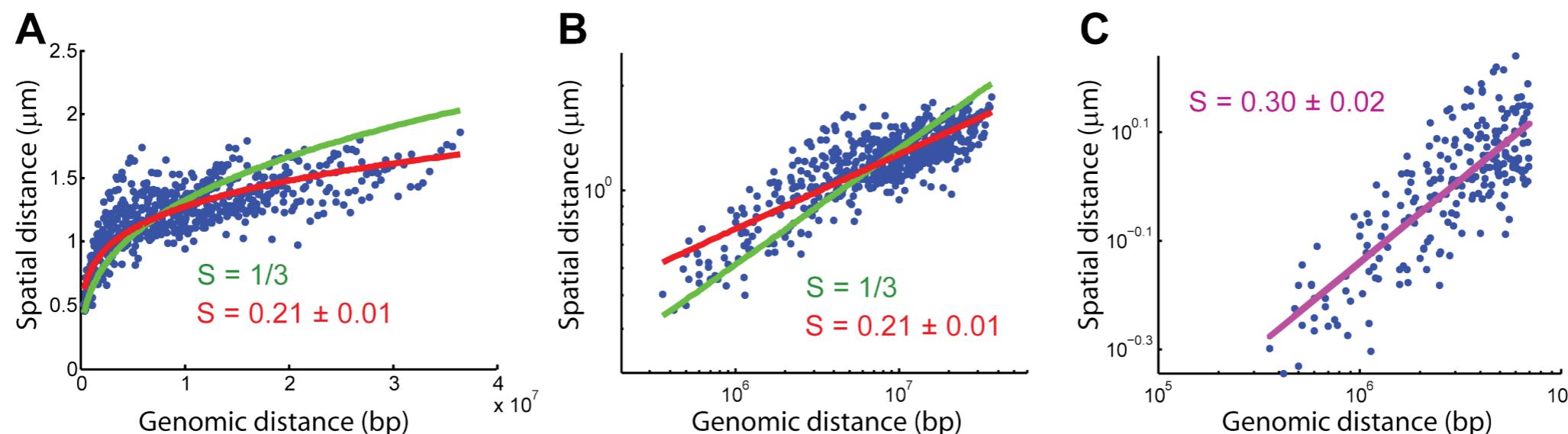
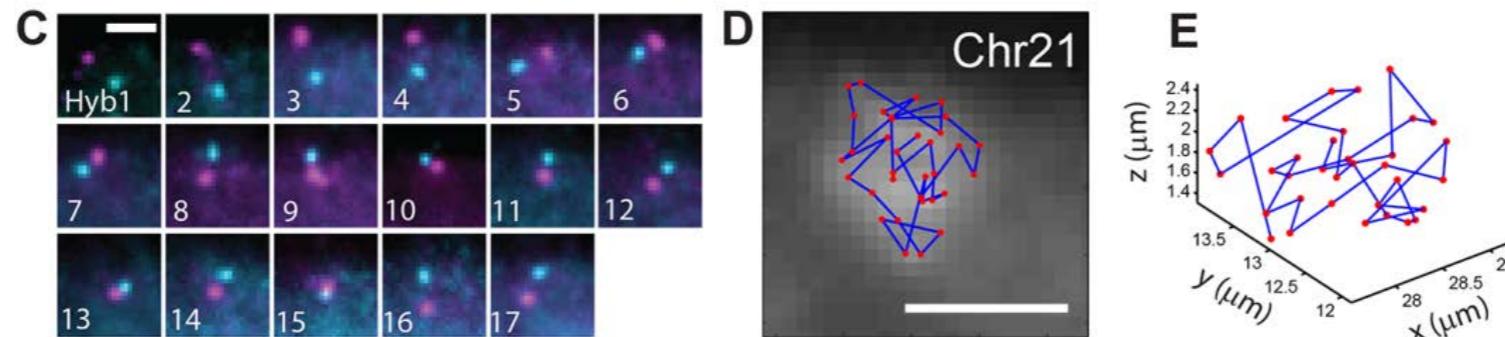
Model accuracy (fly@2Kb)

Boettiger, A. N., et al. (2016). Nature, 529, 418–422.



Model accuracy (Human Chr21@40Kb)

Wang, S., et al. (2016). Science 353, 598–602.



Model accuracy (Human Chr21@40Kb)

Wang, S., et al. (2016). Science 353(6299), 598–602.

