

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

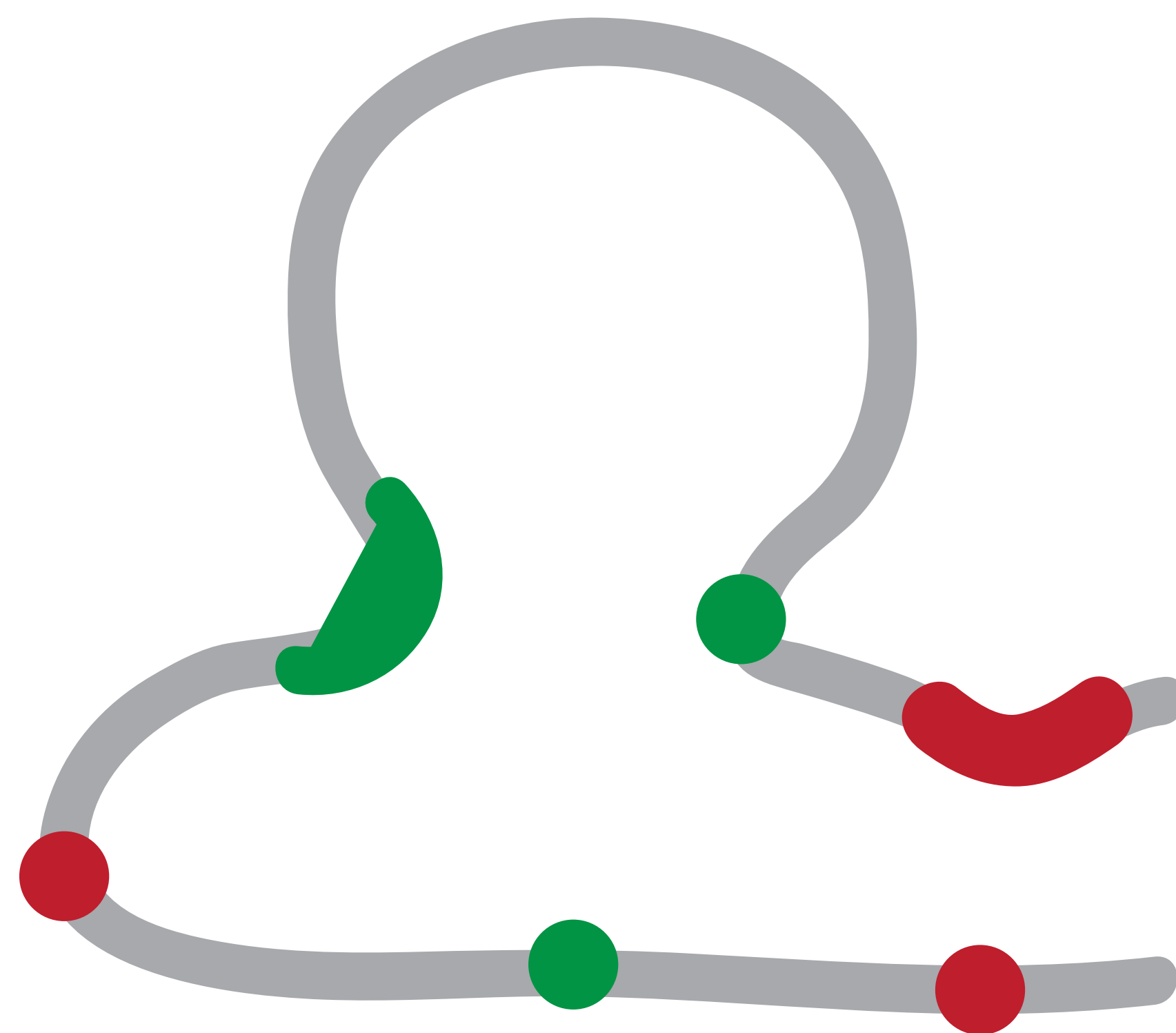
Marc A. Marti-Renom  
Structural Genomics Group (ICREA, CNAG-CRG)

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

**cnag** **CRG**<sup>®</sup>  **ICREA**

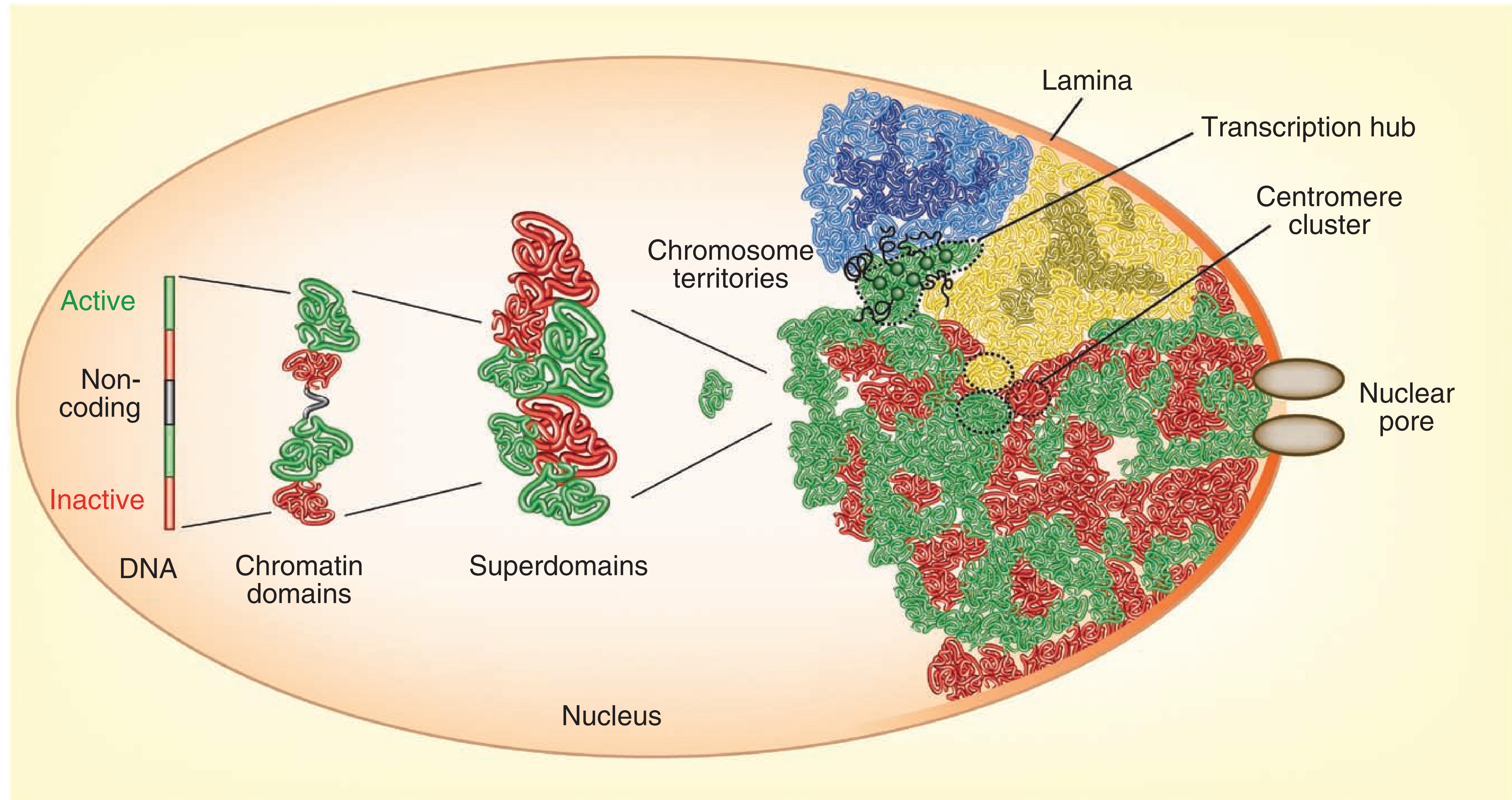






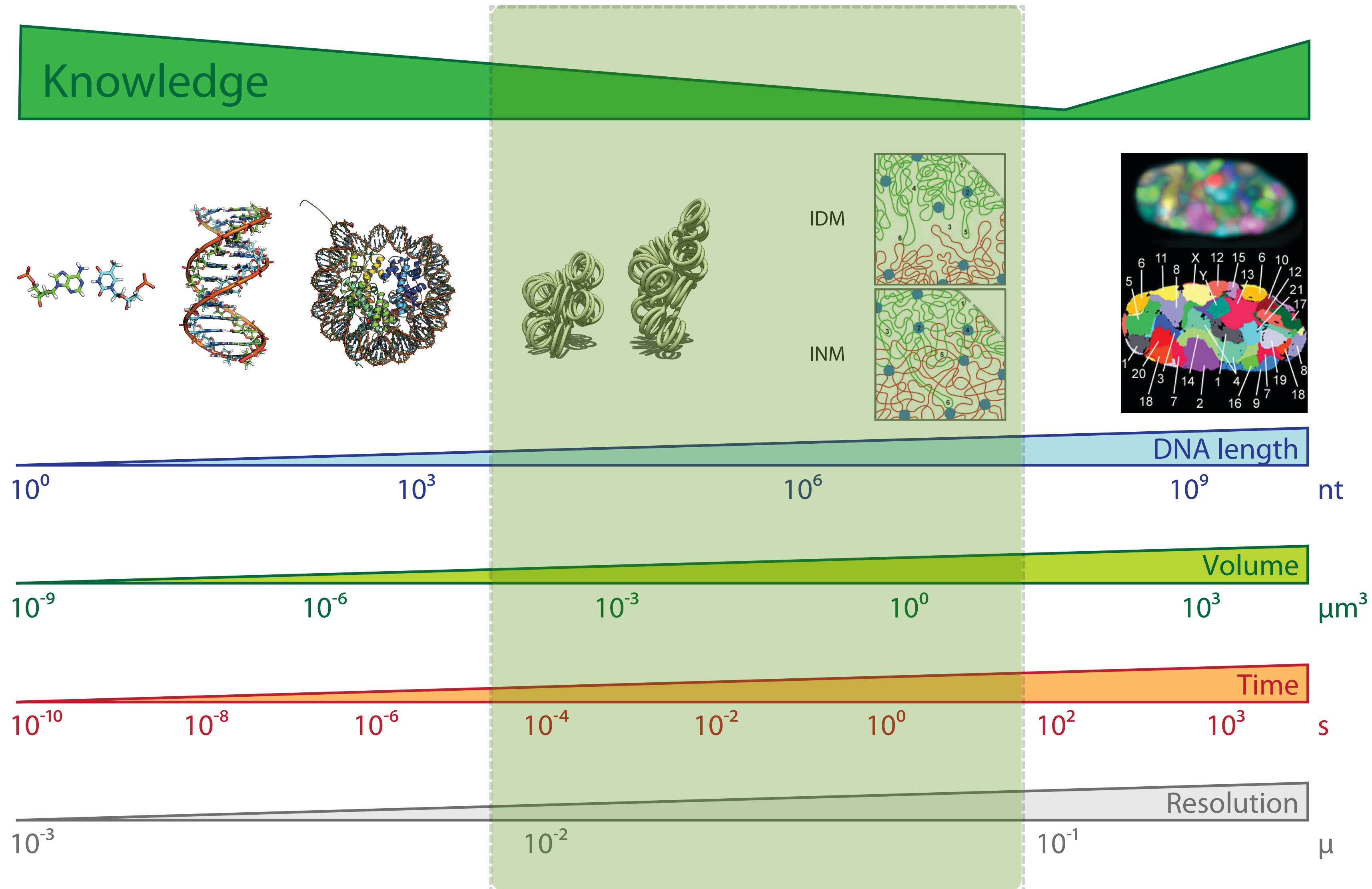
# Complex genome organization

Cavalli, G. & Misteli, T. Functional implications of genome topology. Nat Struct Mol Biol 20, 290–299 (2013).



# Resolution Gap

Marti-Renom, M. A. & Mirny, L. A. PLoS Comput Biol 7, e1002125 (2011)



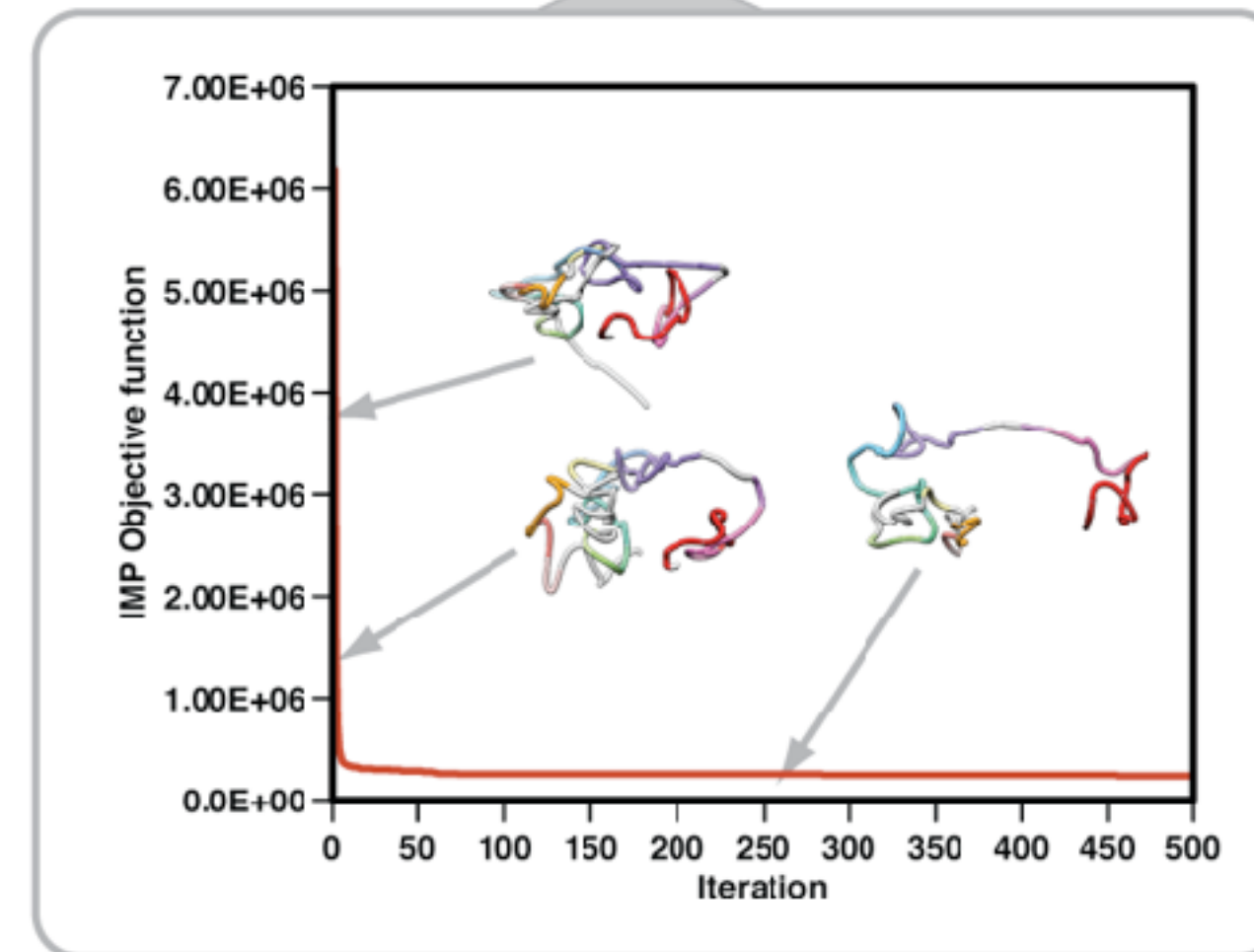
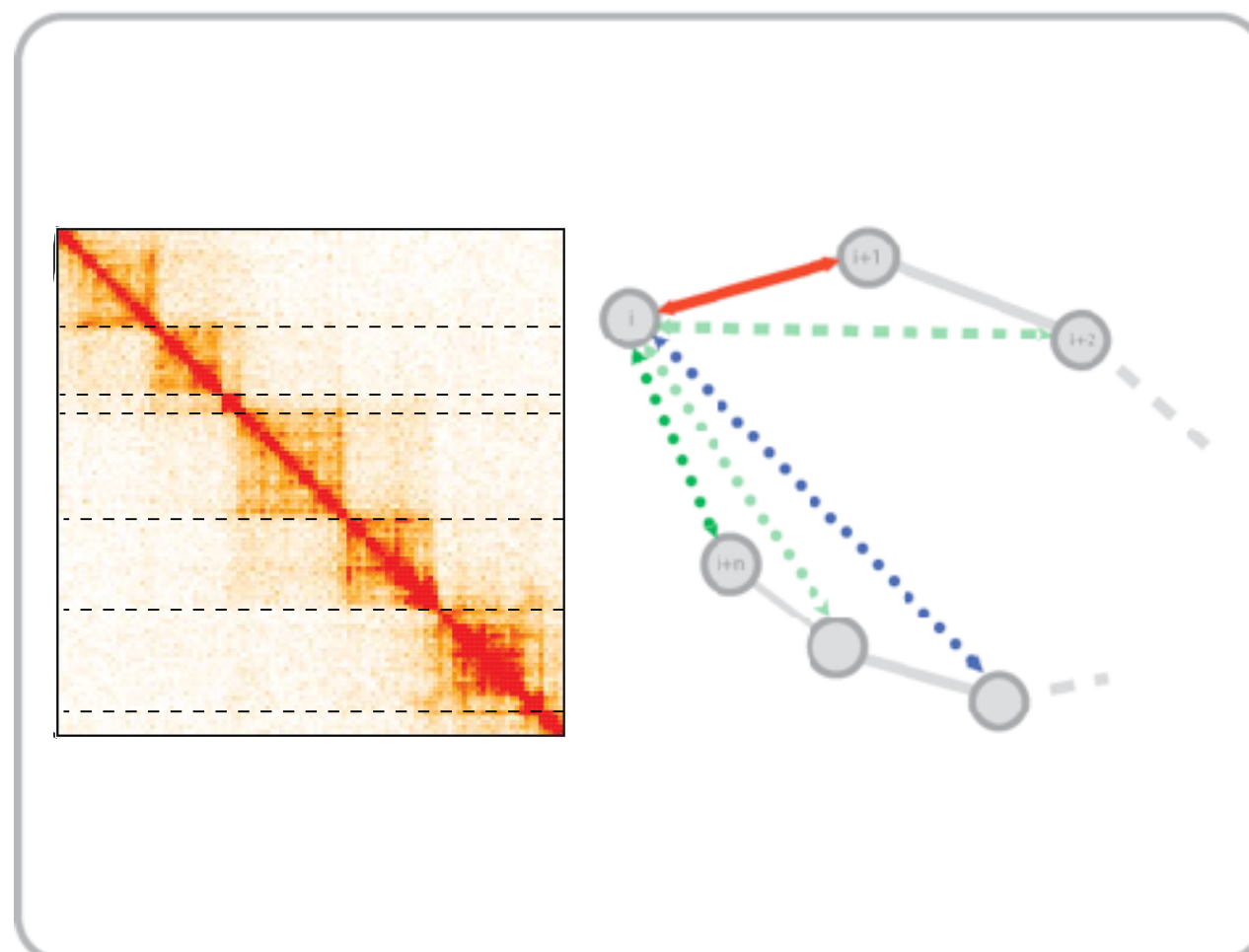
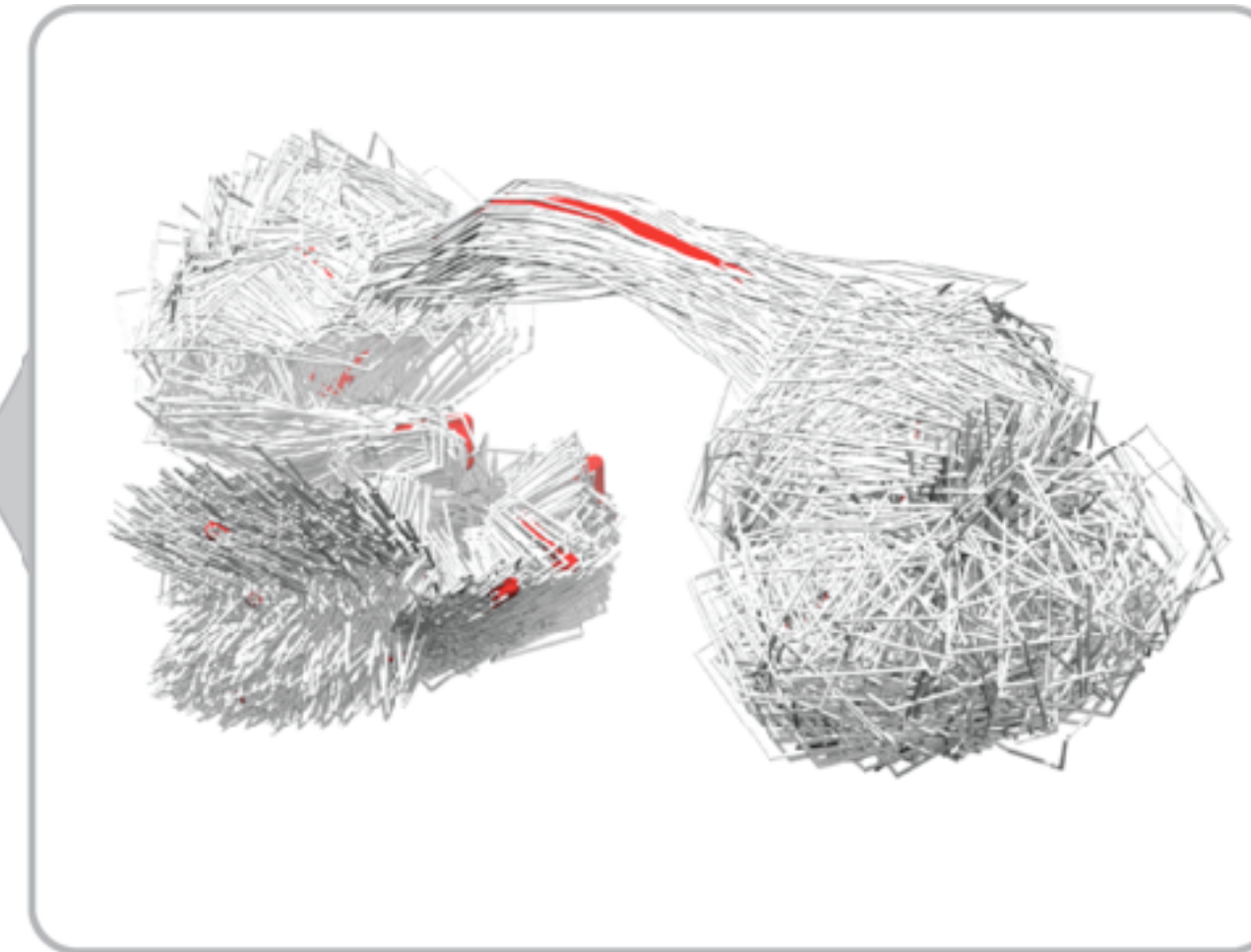
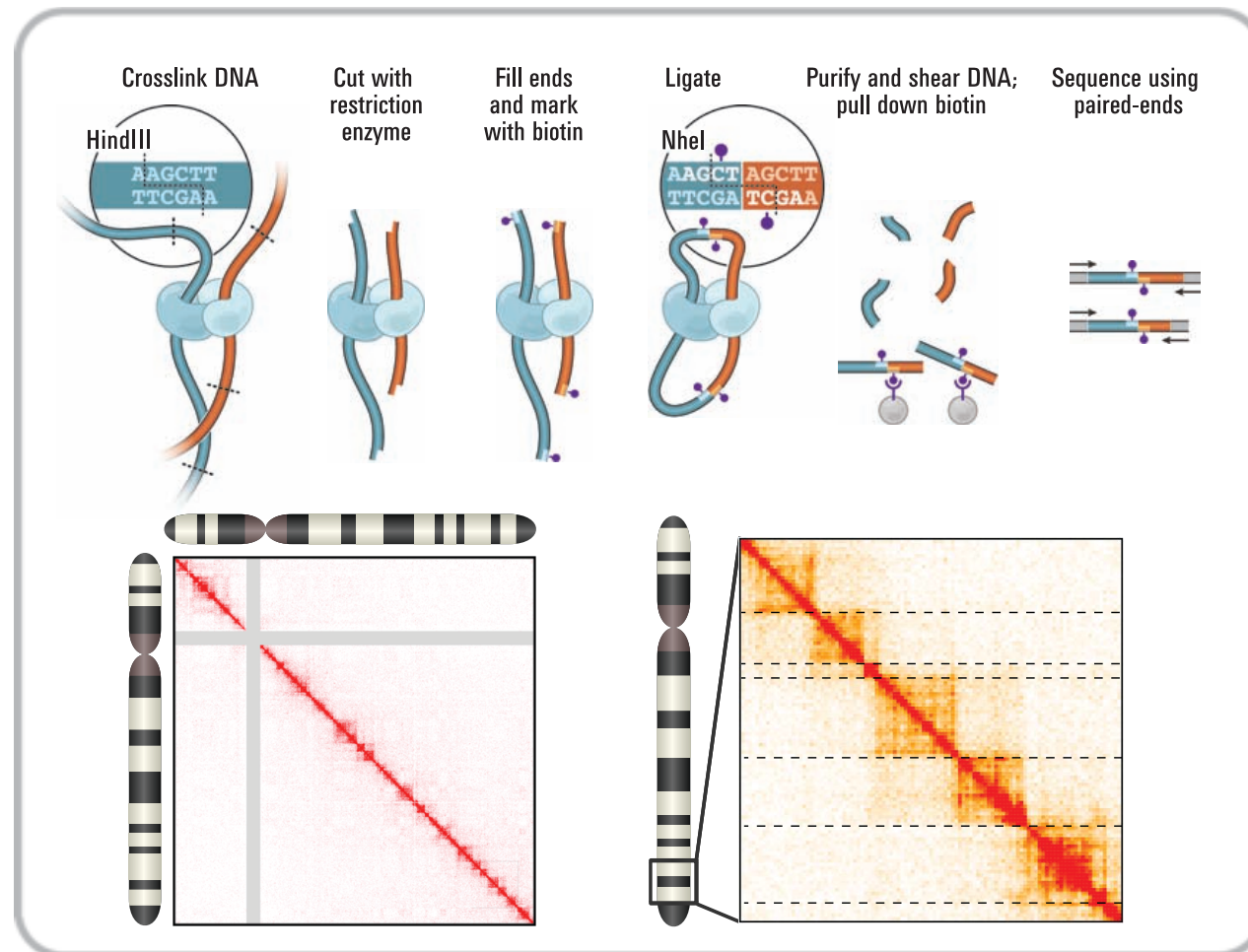


# Hybrid Method

Baù, D. & Martí-Renom, M. A. *Methods* 58, 300–306 (2012).

Baù, D. & Marti-Renom, M. A. *Methods* 58, 300–306 (2012).

## Experiments



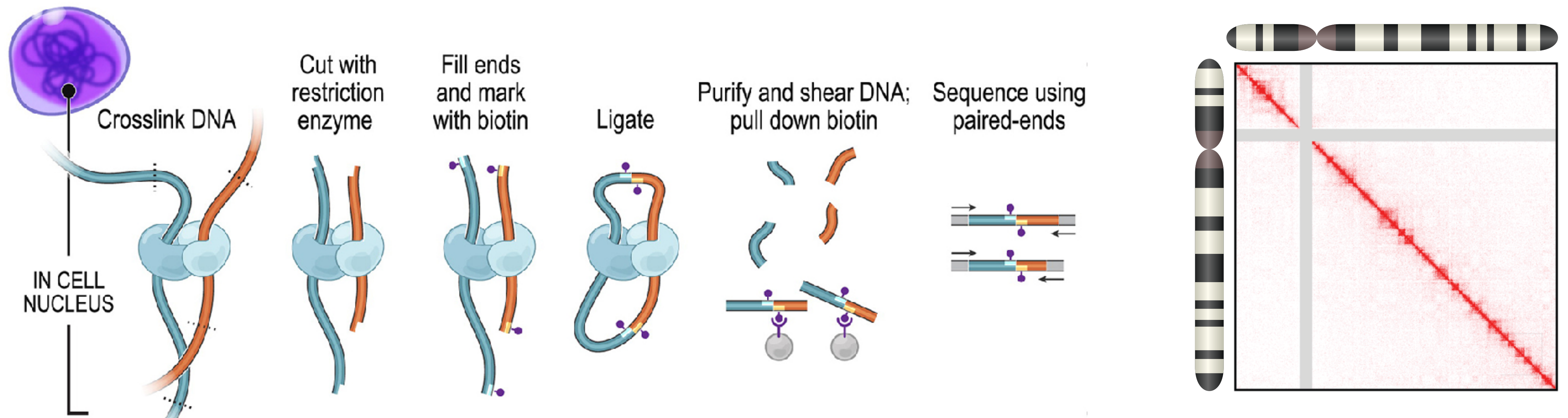
## Computation



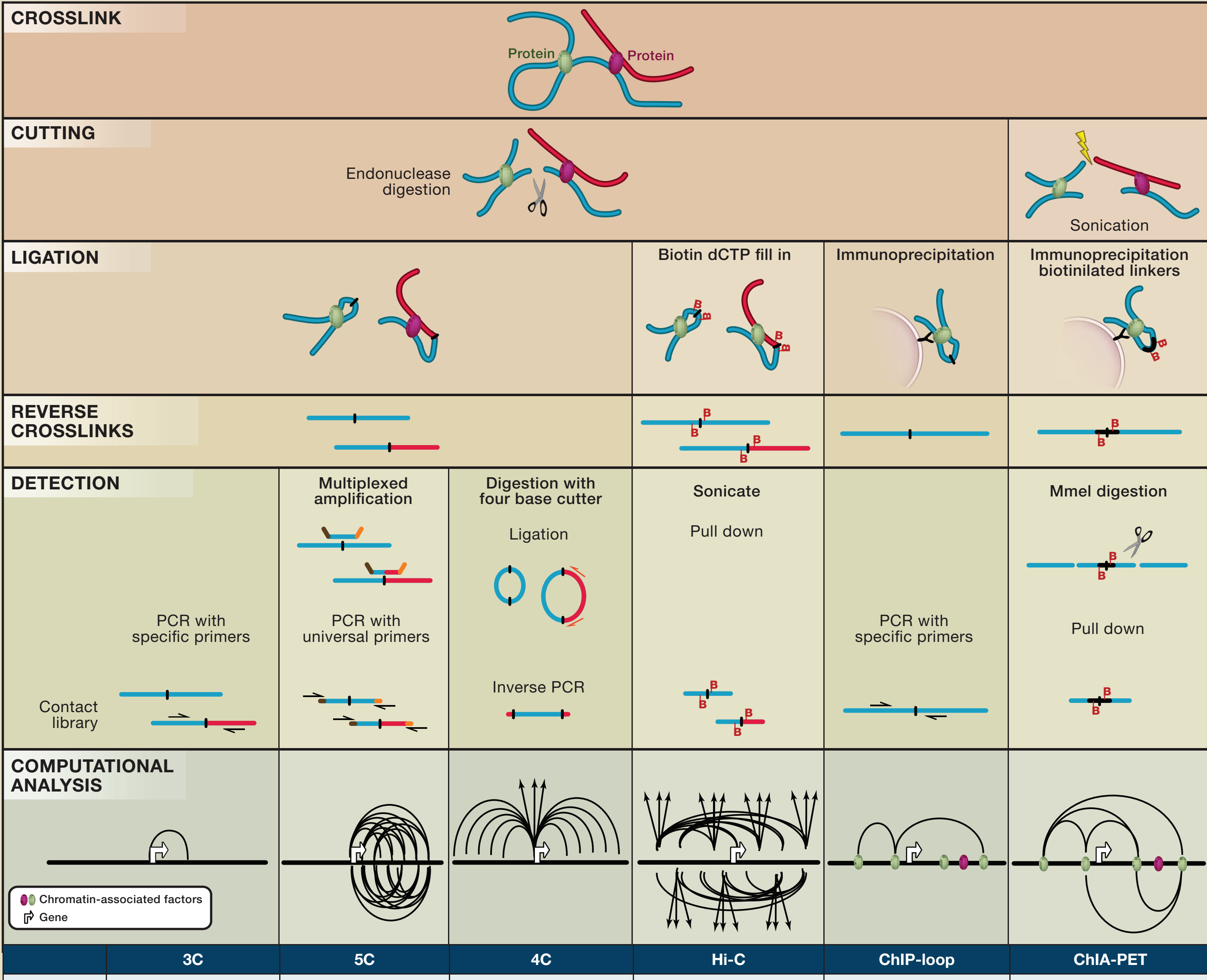
# Chromosome Conformation Capture

Dekker, J., Rippe, K., Dekker, M., & Kleckner, N. (2002). *Science*, 295(5558), 1306–1311.

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



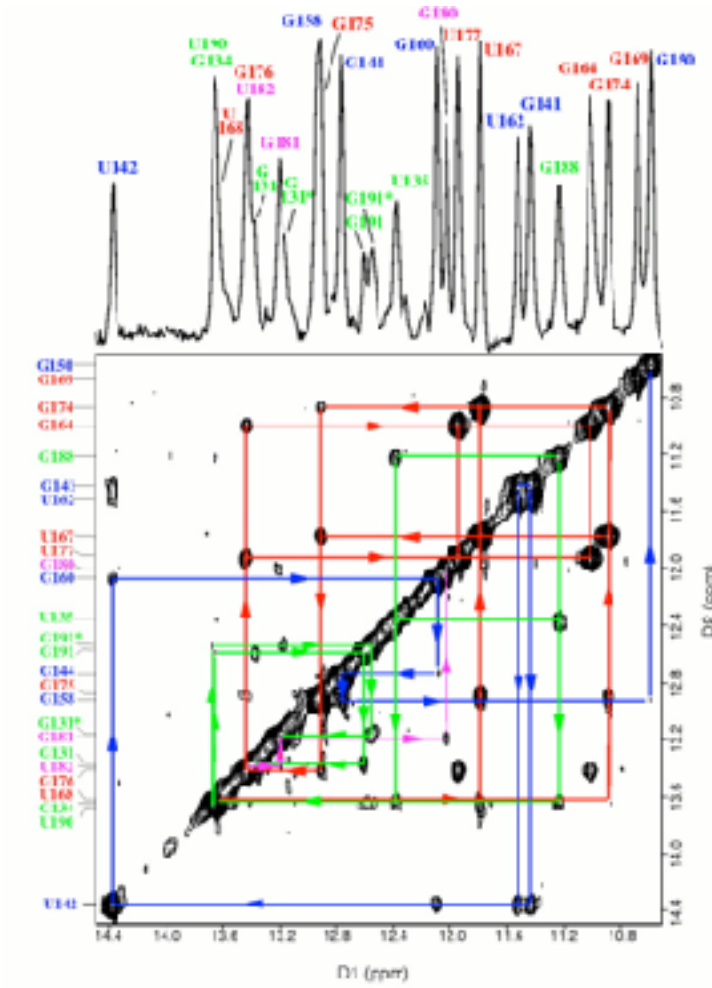
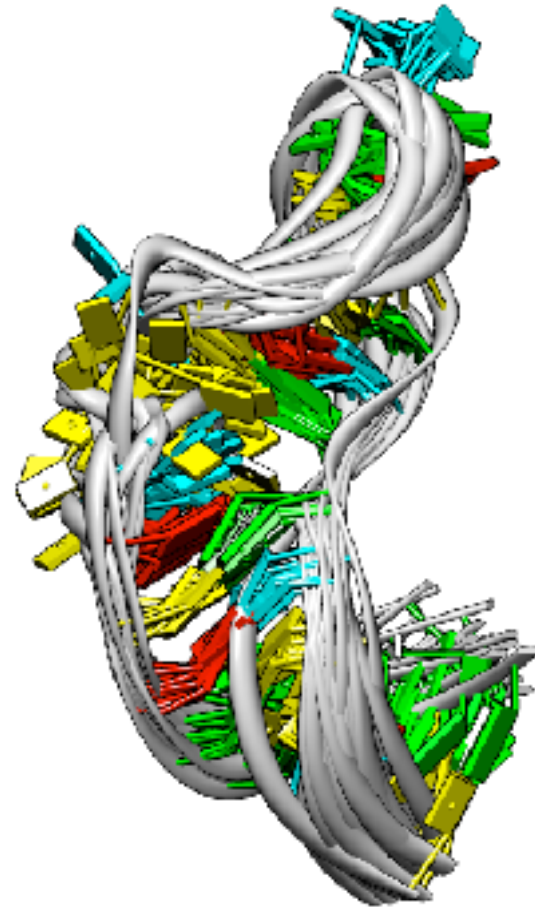
# Chromosome Conformation Capture



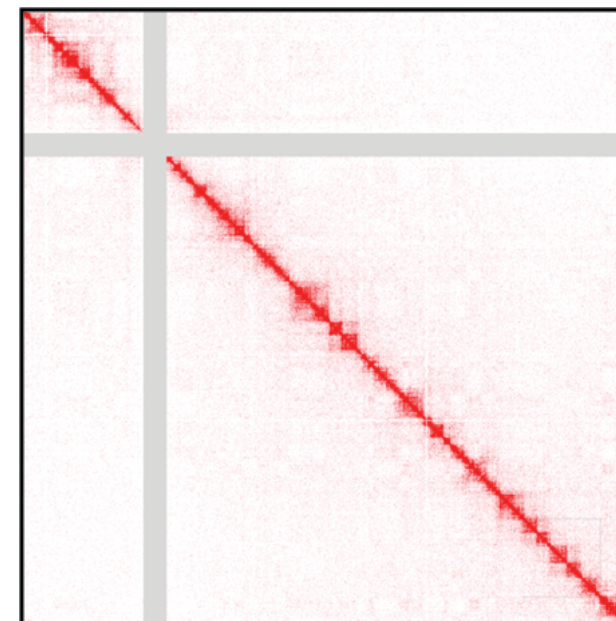
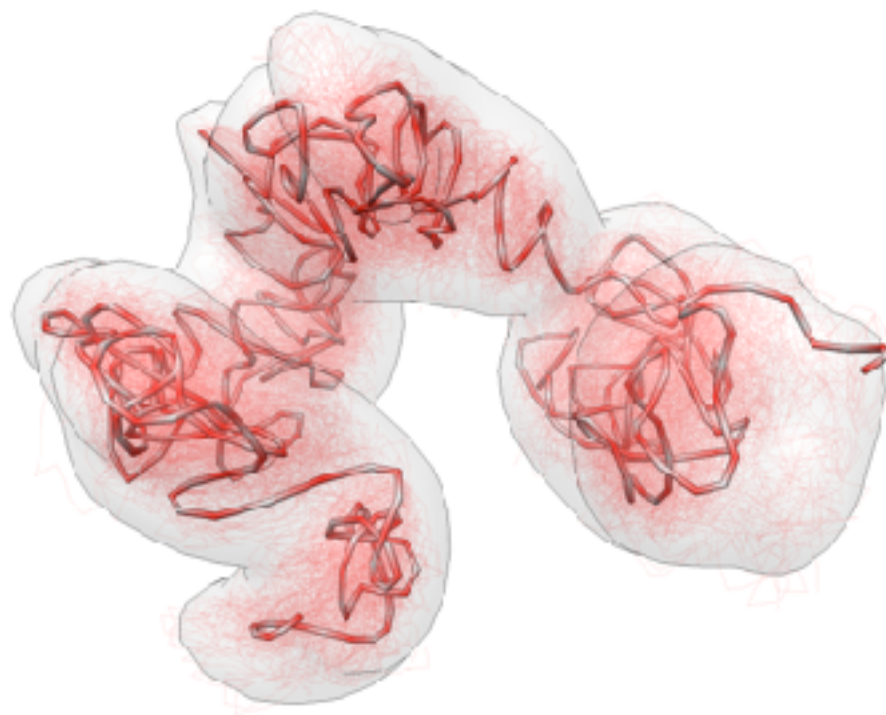


# Restraint-based Modeling

Baù, D. & Marti-Renom, M. A. *Methods* 58, 300–306 (2012).



Biomolecular structure determination  
2D-NOESY data



# Chromosome structure determination

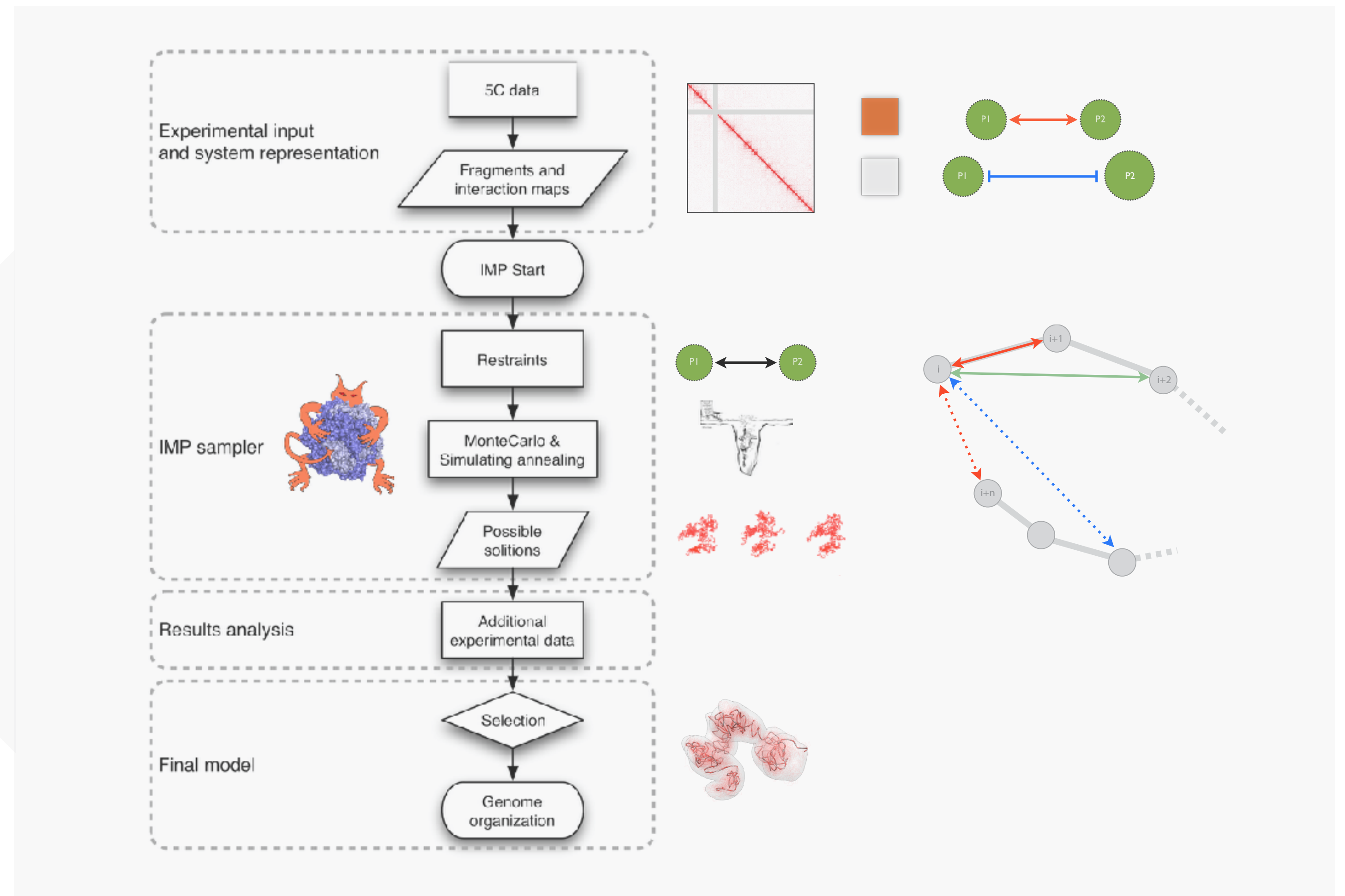
## 3C-based data



## Map analysis

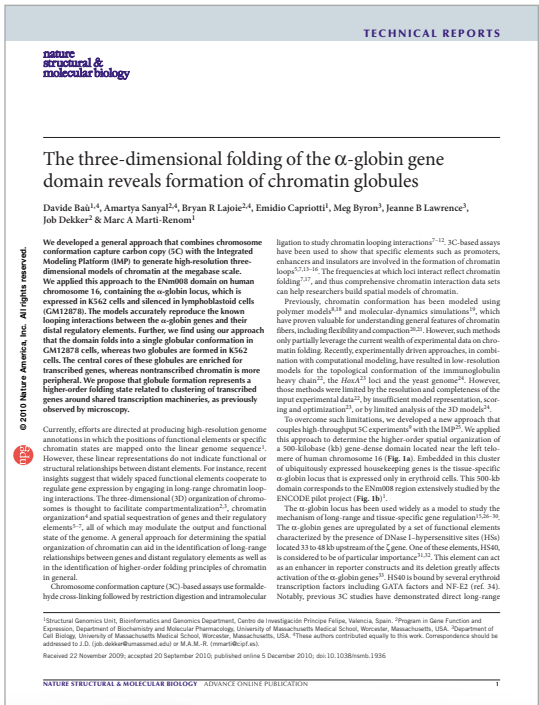
# Model building

## Model analysis

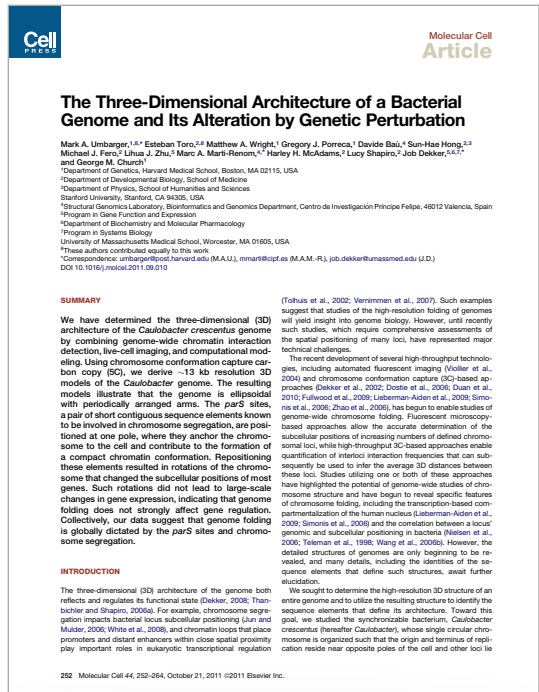




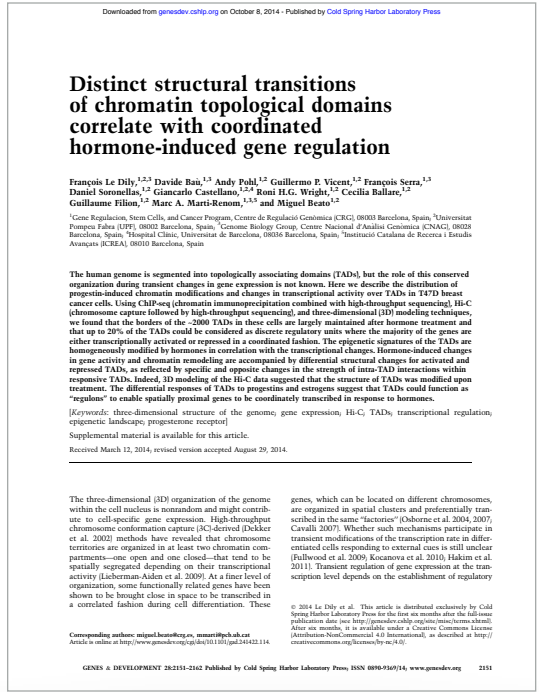
# TADbit previous applications...



Baù, D. et al. Nat Struct Mol Biol (2011)



Umbarger, M. A. et al. Mol Cell (2011)

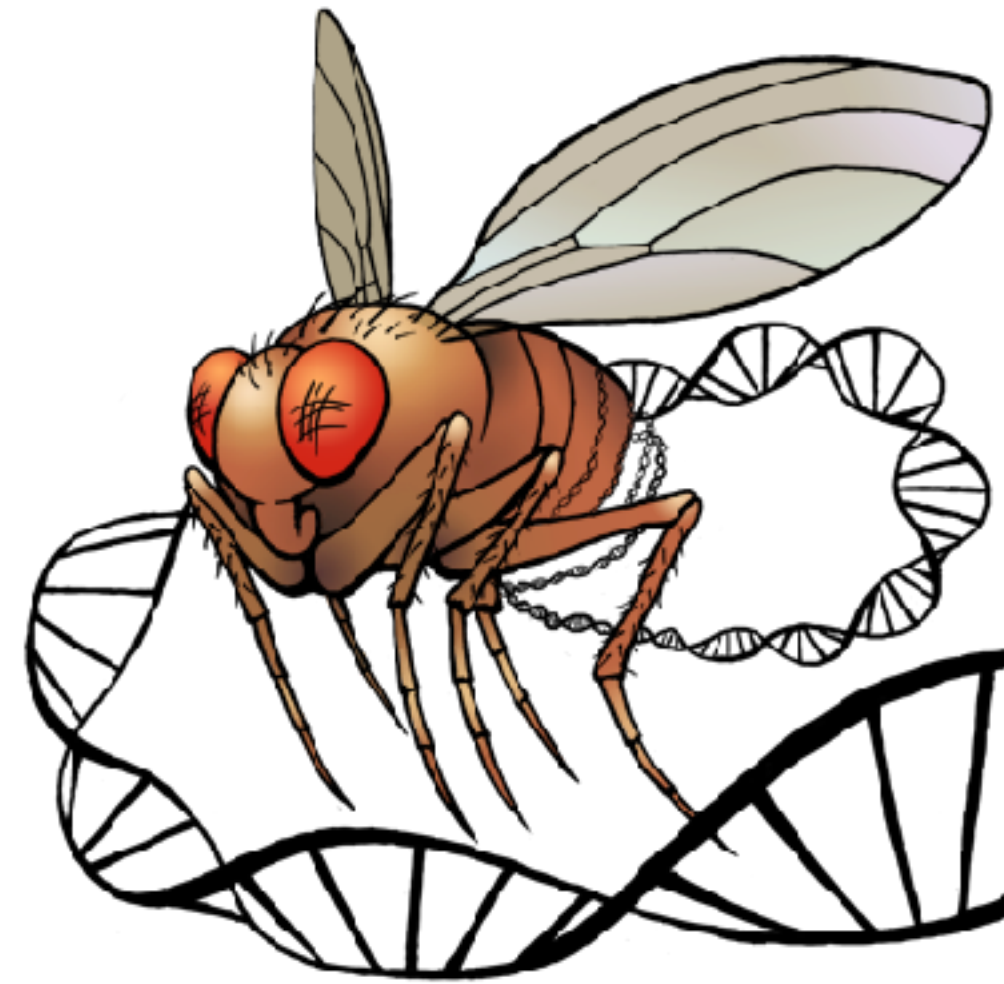


Le Dily, F. et al. Genes & Dev (2014)





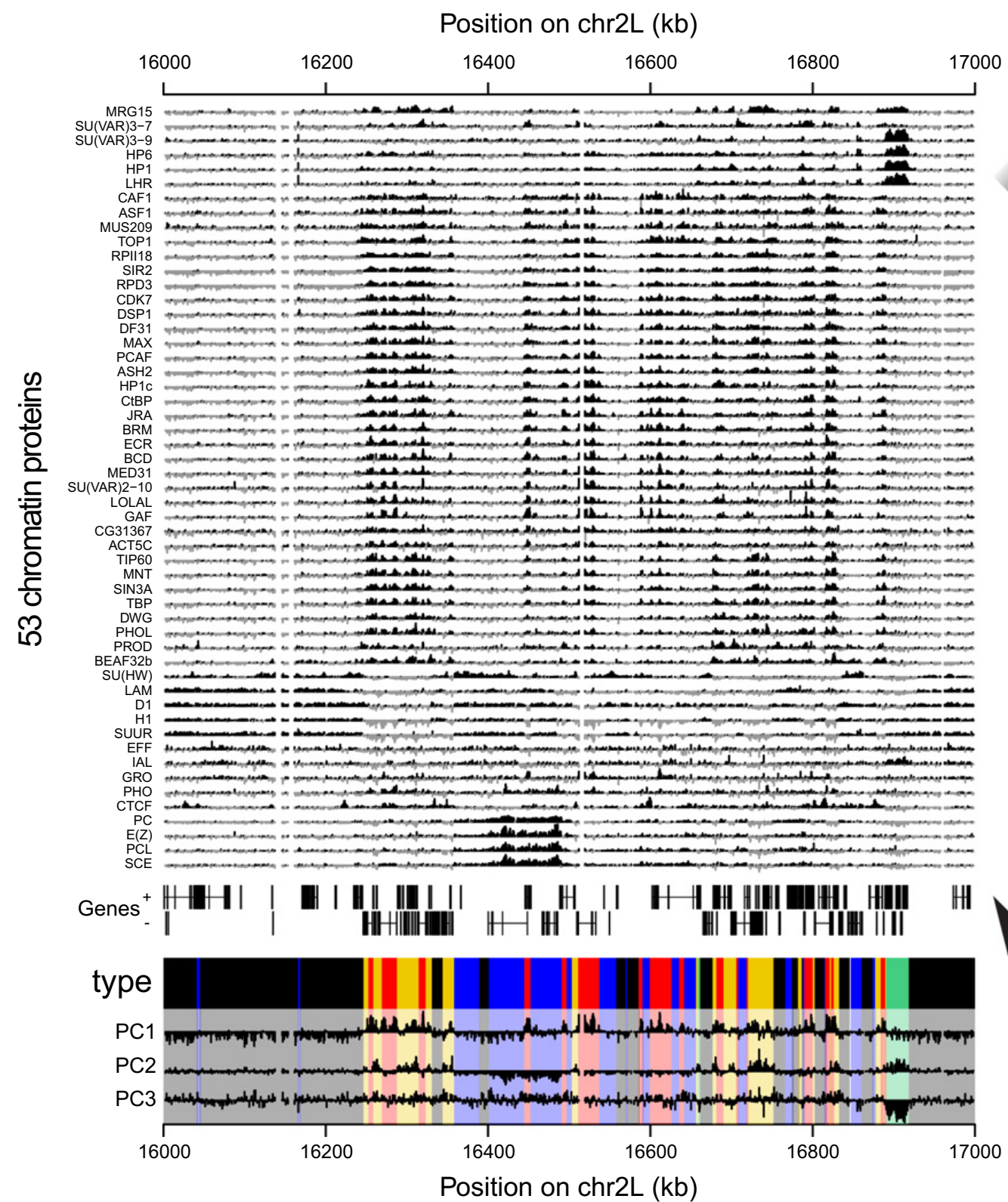
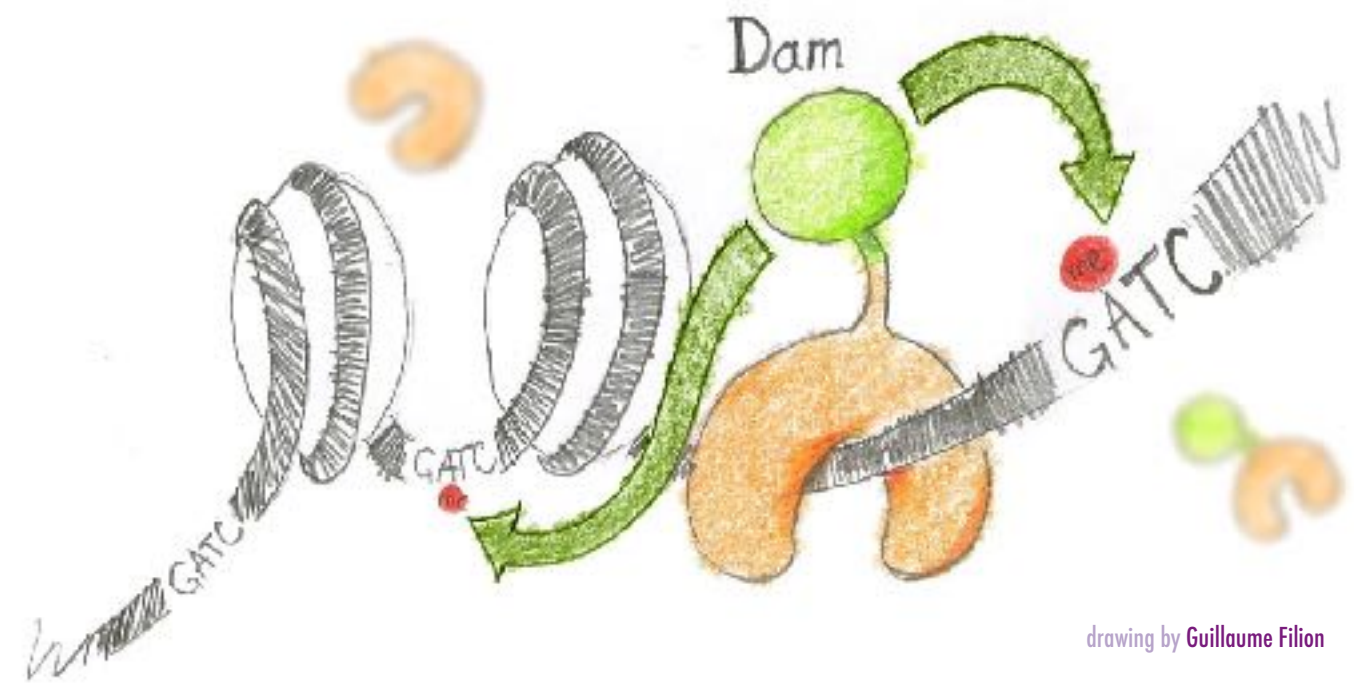
# Structuring the **COLORs** of chromatin



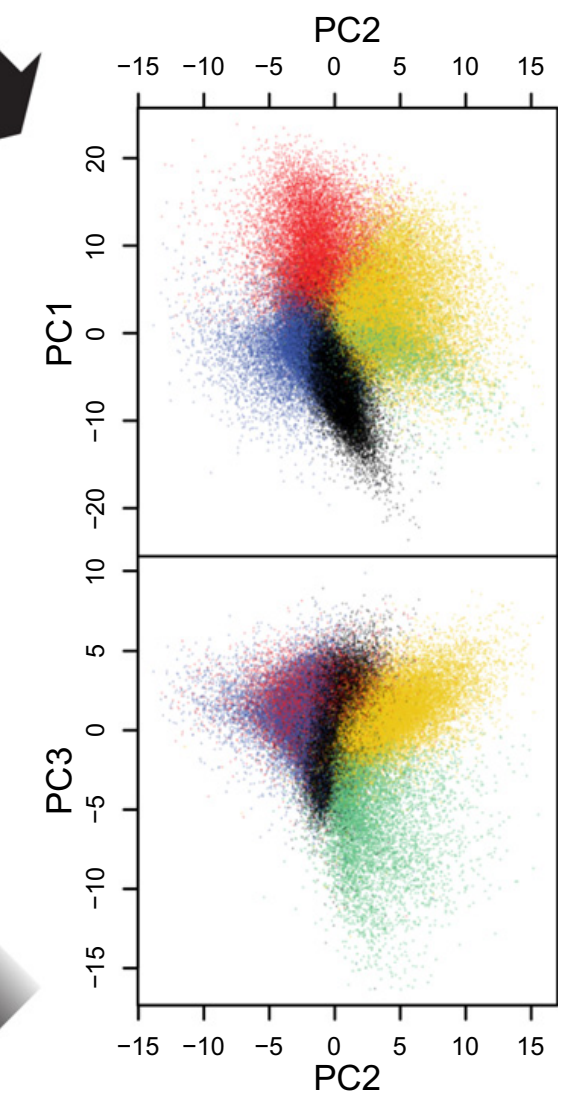


# Fly Chromatin **COLORs**

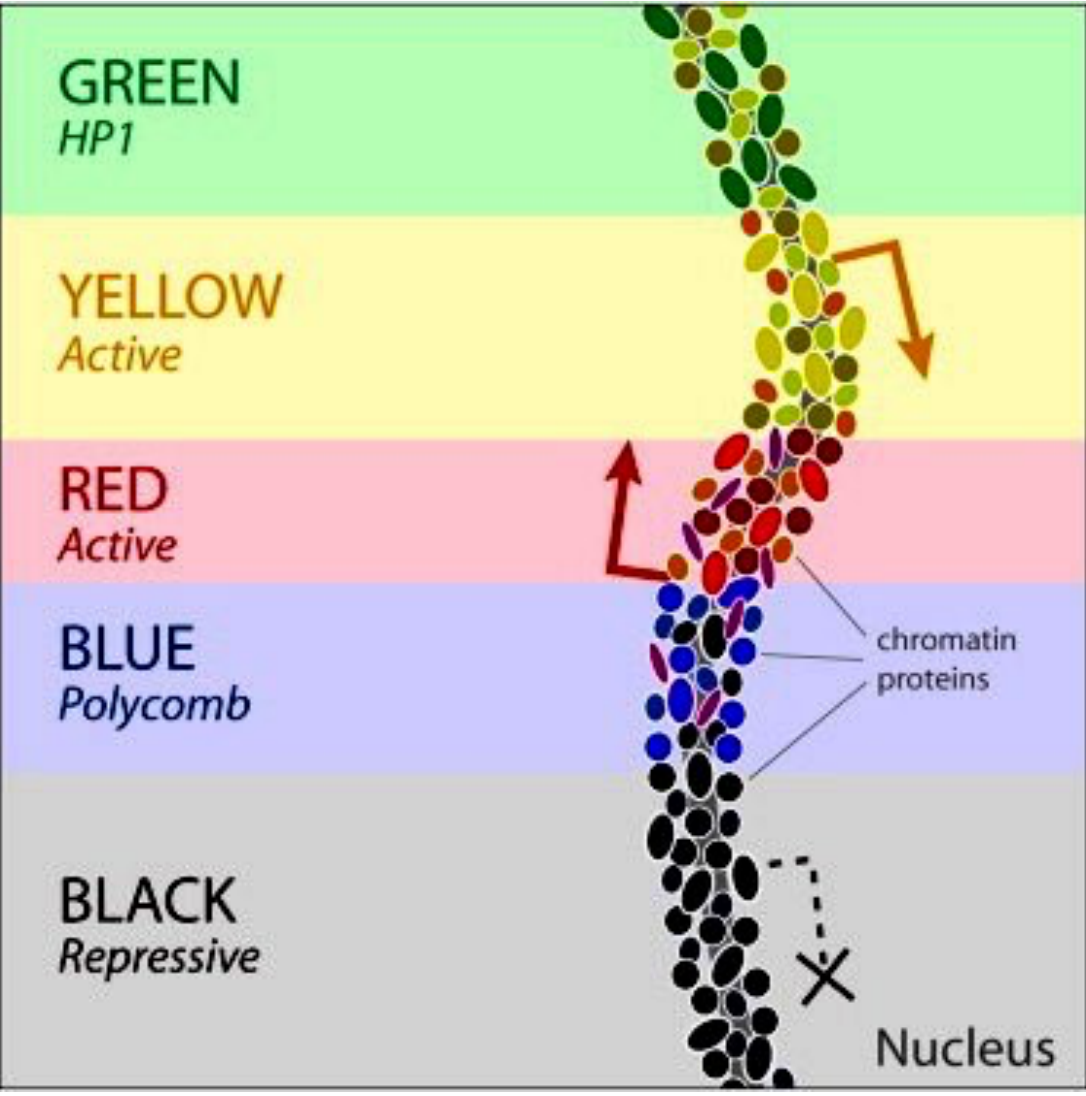
Filion et al. (2010). Cell, 143(2), 212–224.



Principal component analysis



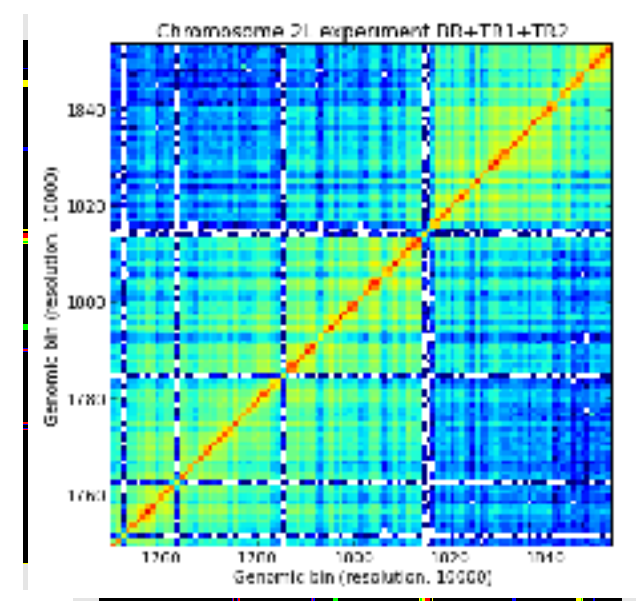
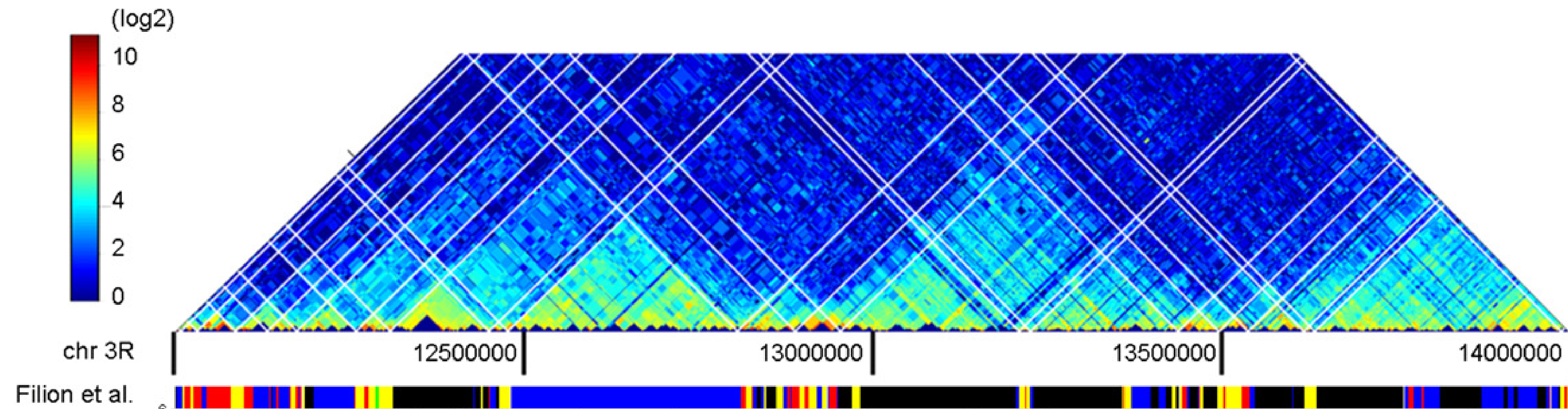
Hidden Markov model





# Fly Chromatin **COLORs**

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

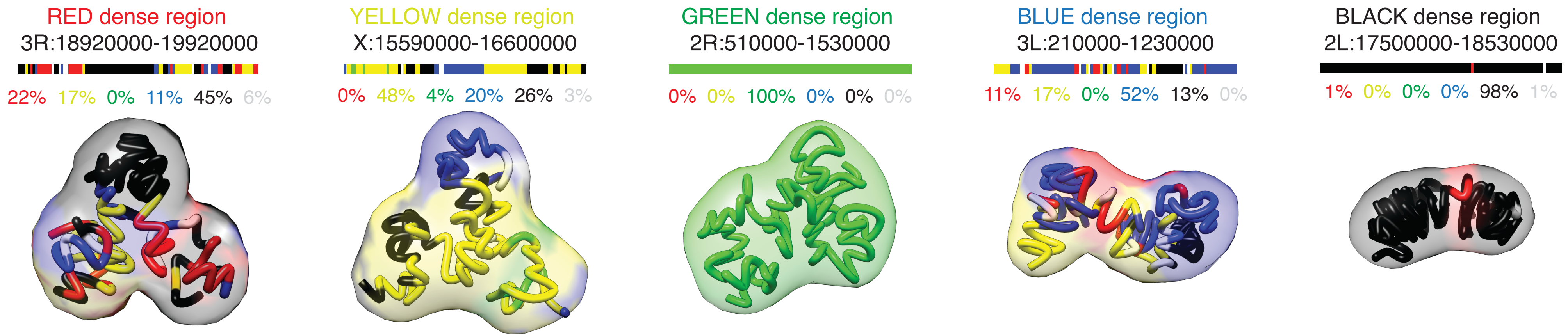


~50 regions of ~1Mb each  
10Kb resolution

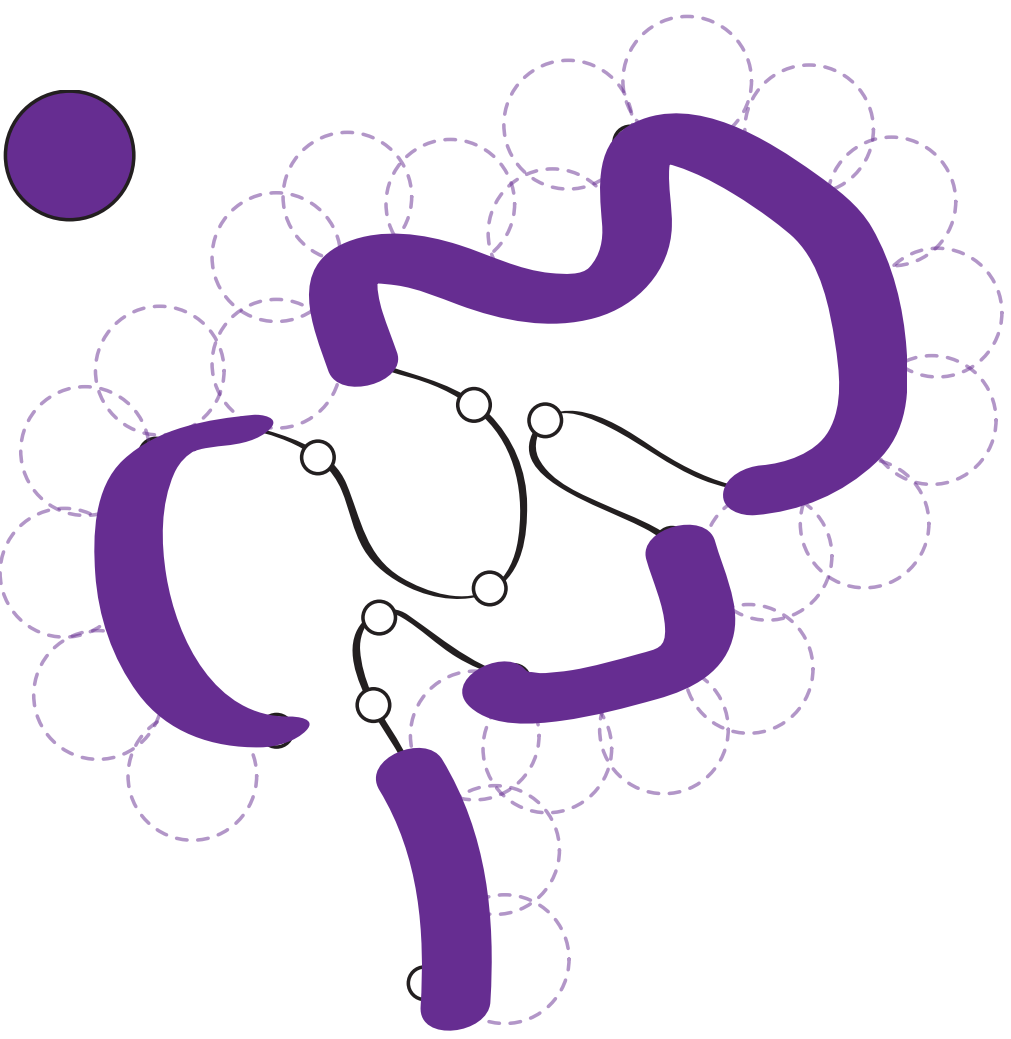


# Structural properties

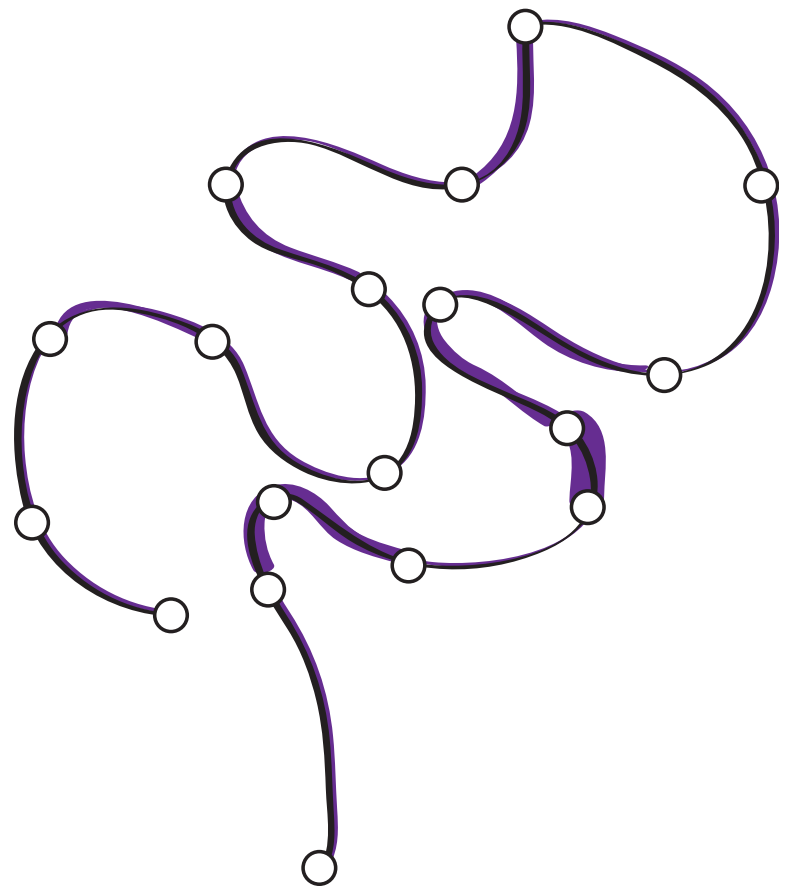
50 1Mb regions. 10 enriched for each color.



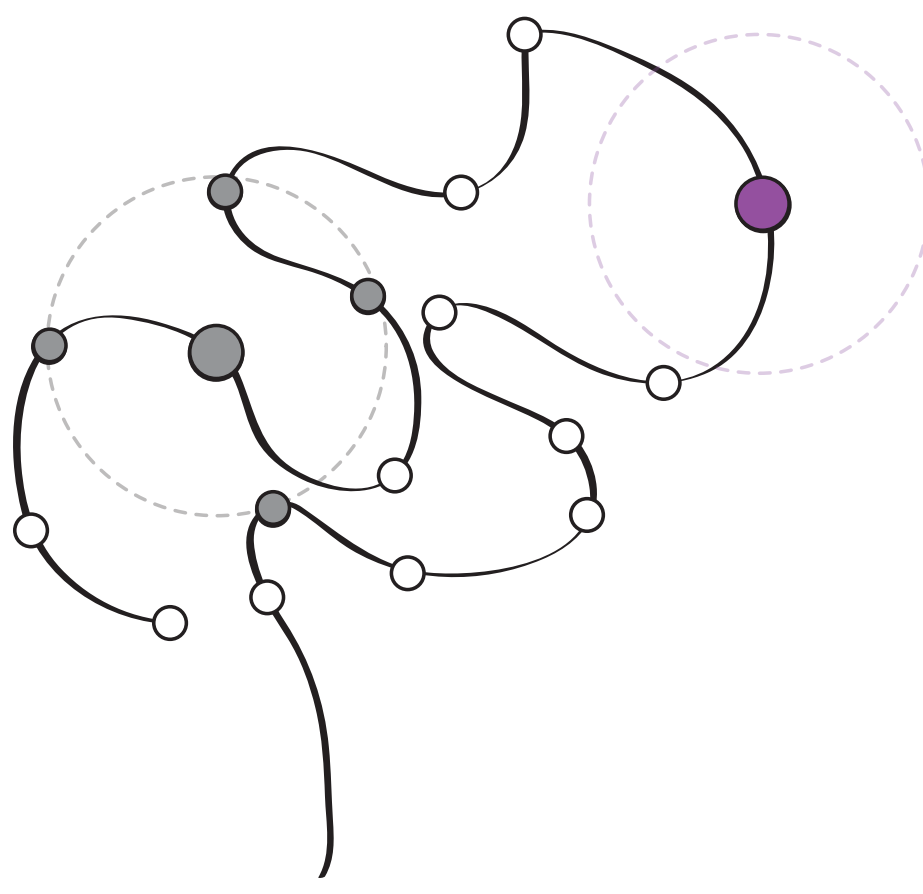
Accessibility (%)



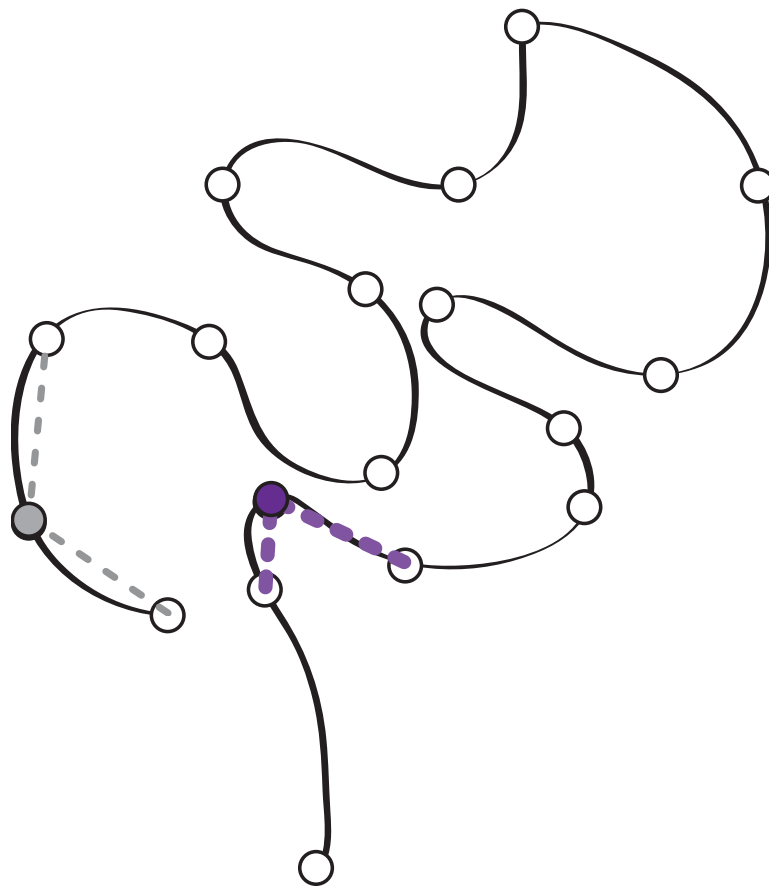
Density (bp/nm)



Interactions



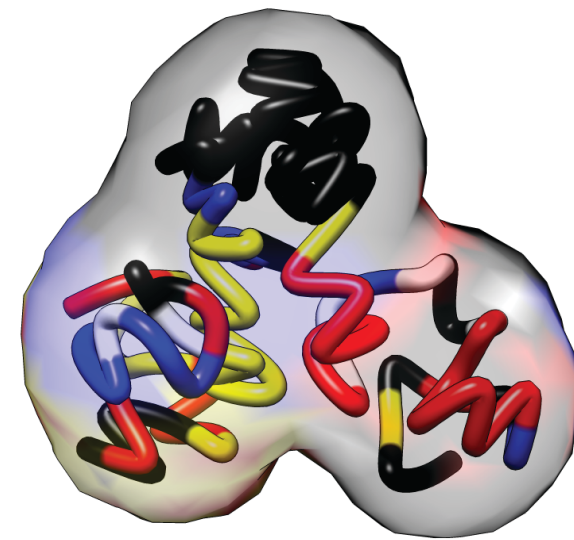
Angle



# Structural **CO**LO**R**s

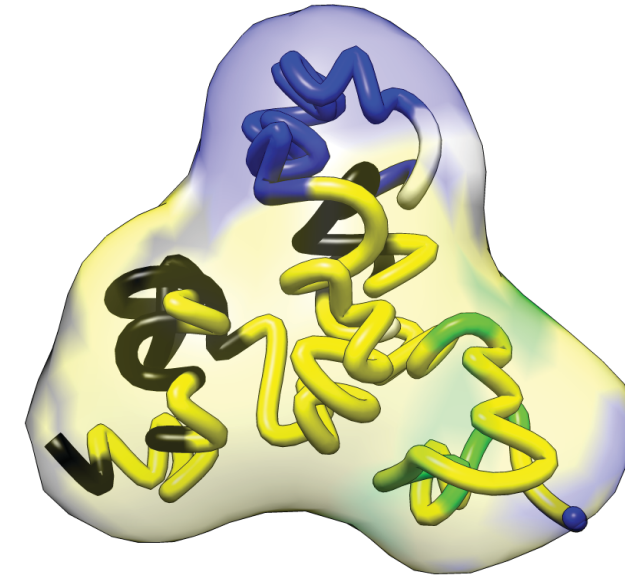
**RED dense region**  
3R:18920000-19920000

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



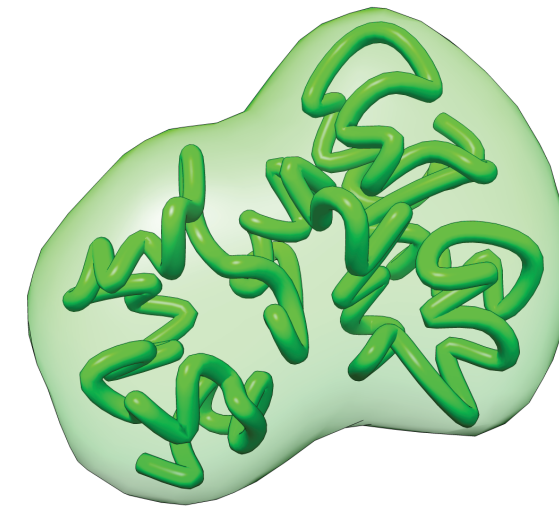
**YELLOW dense region**  
X:15590000-16600000

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



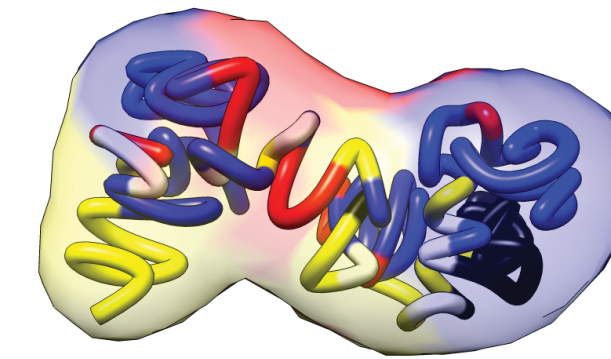
**GREEN dense region**  
2R:510000-1530000

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



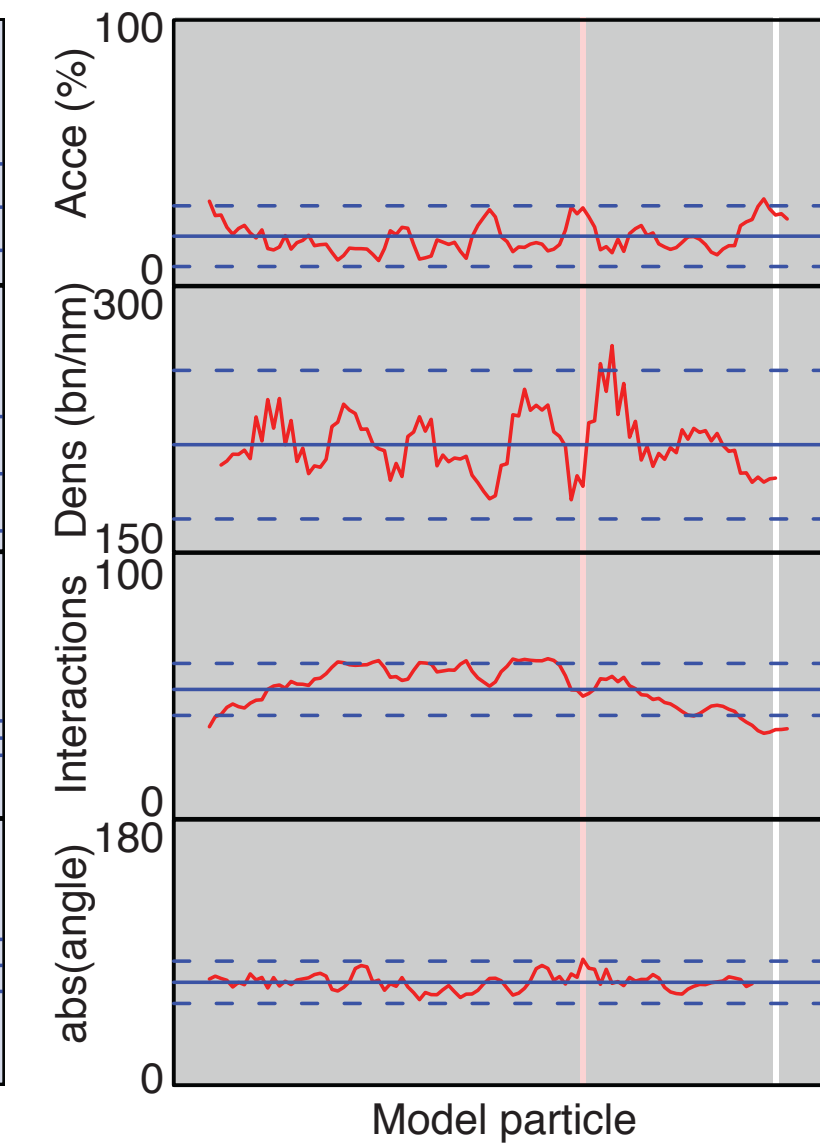
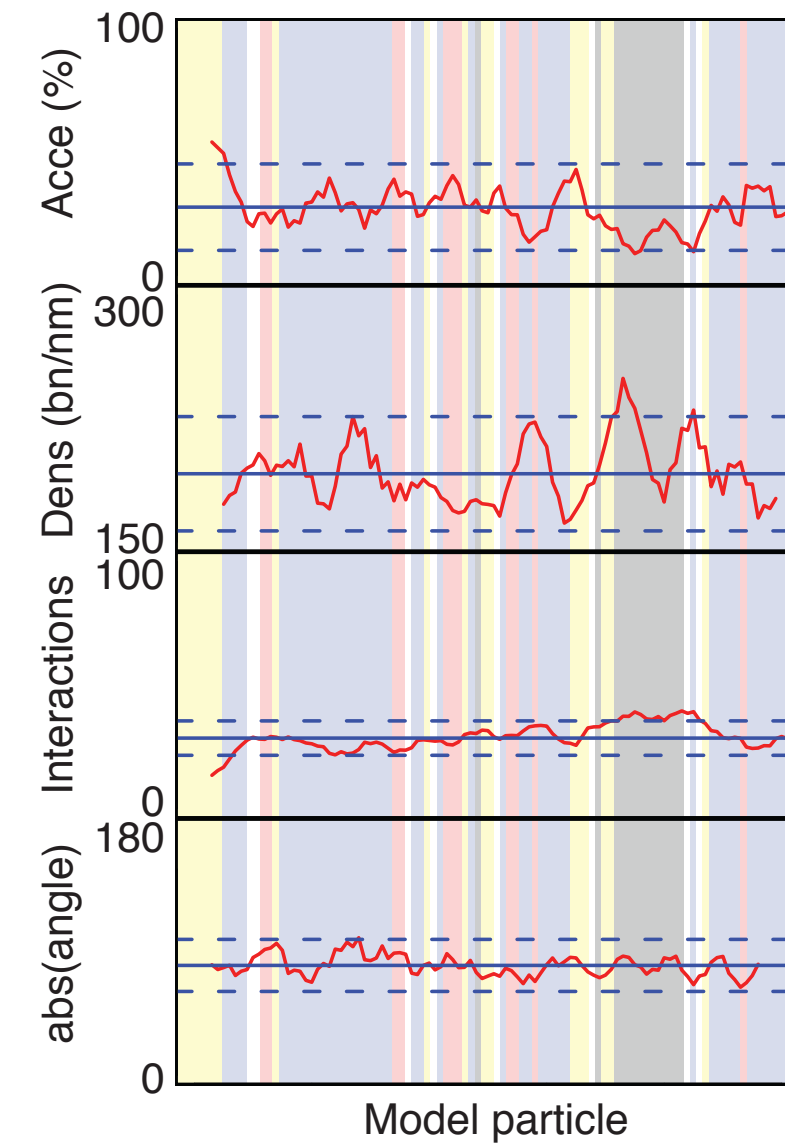
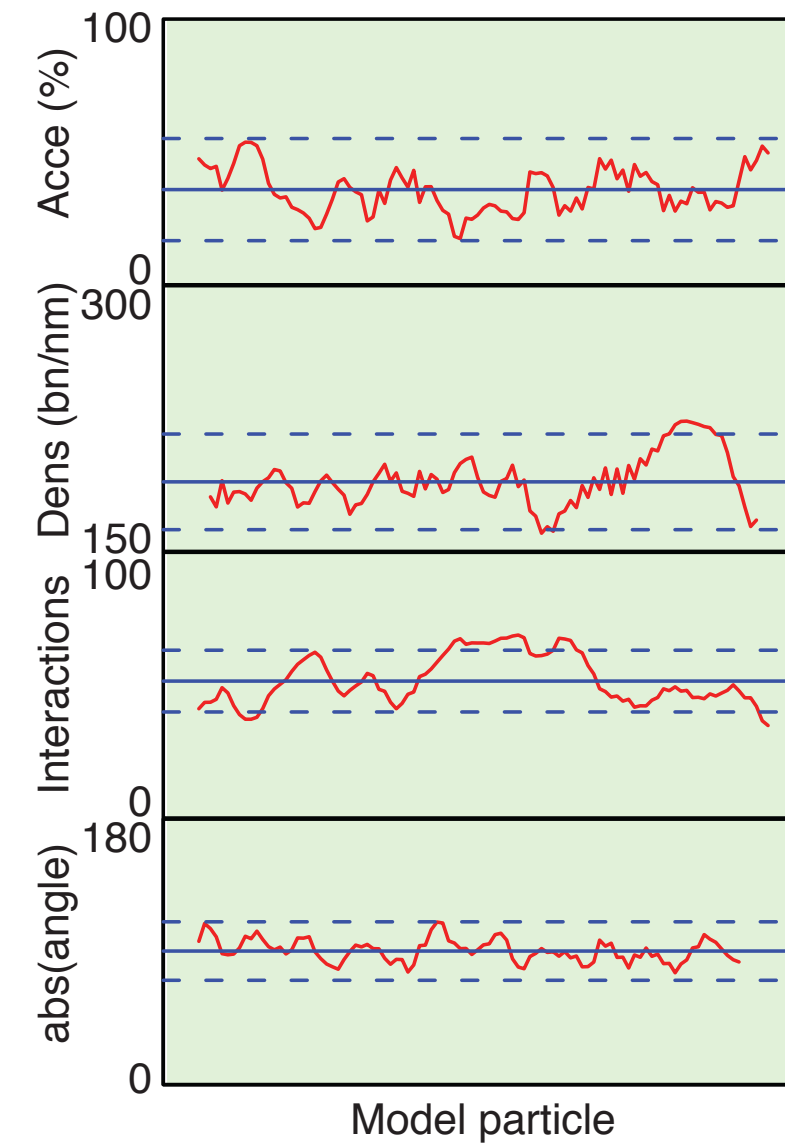
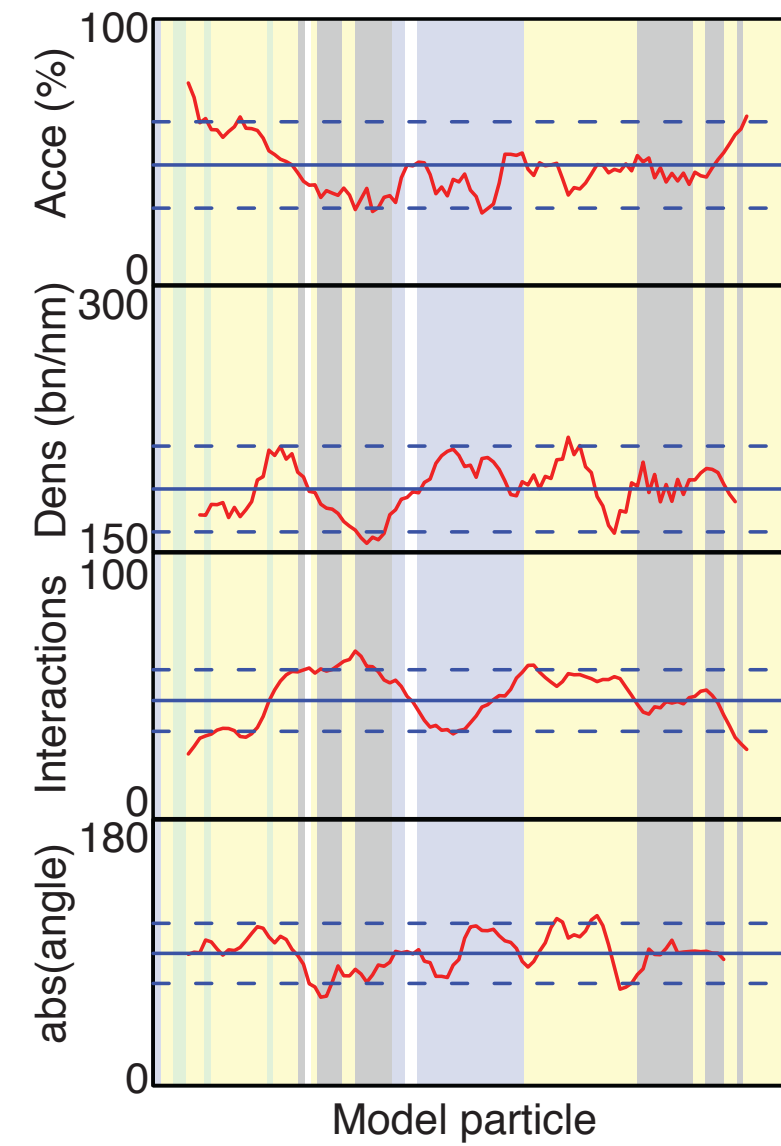
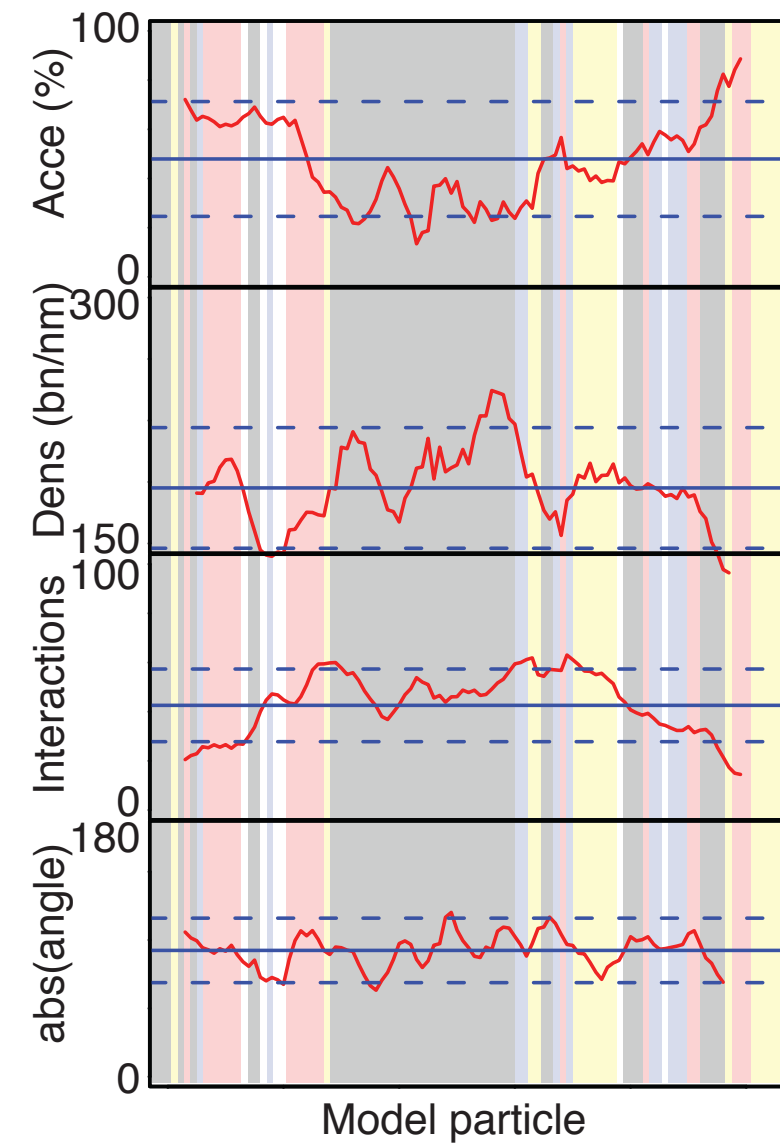
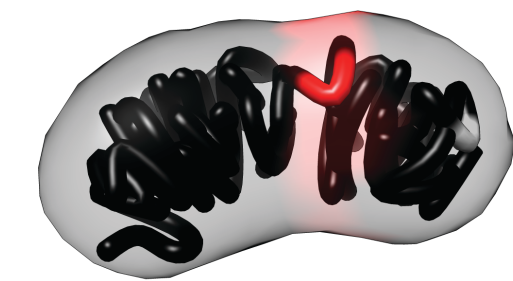
**BLUE dense region**  
3L:210000-1230000

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



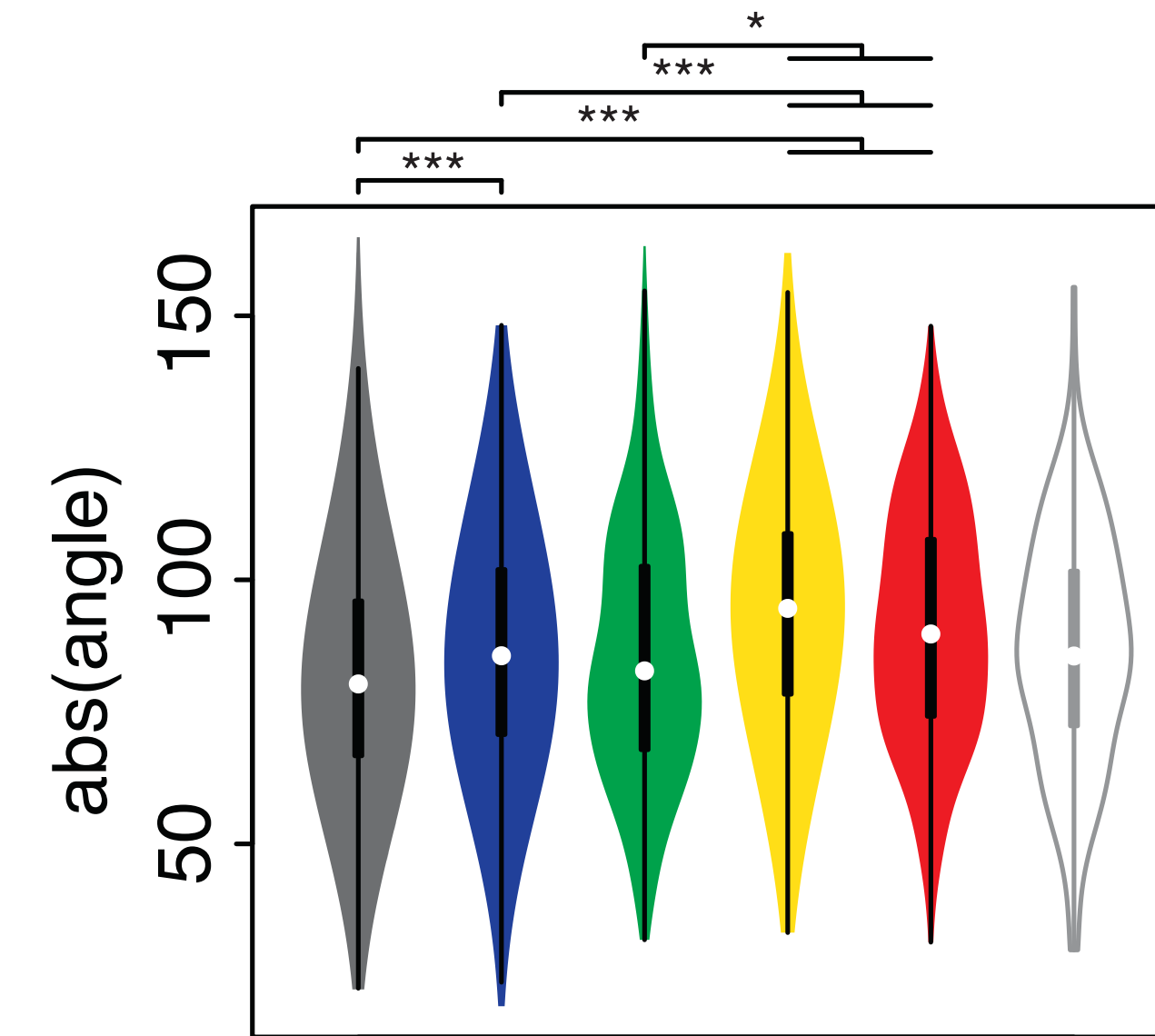
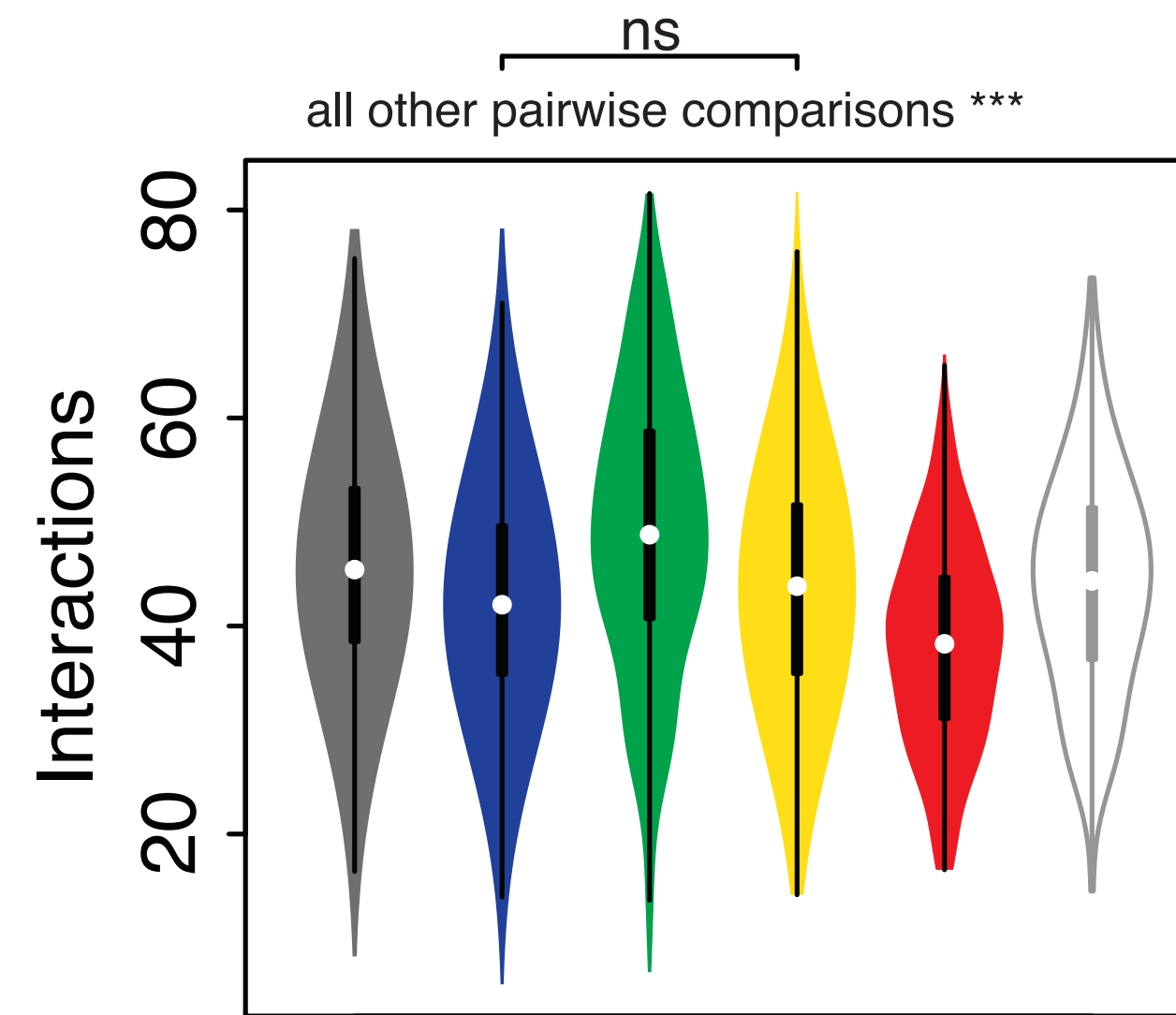
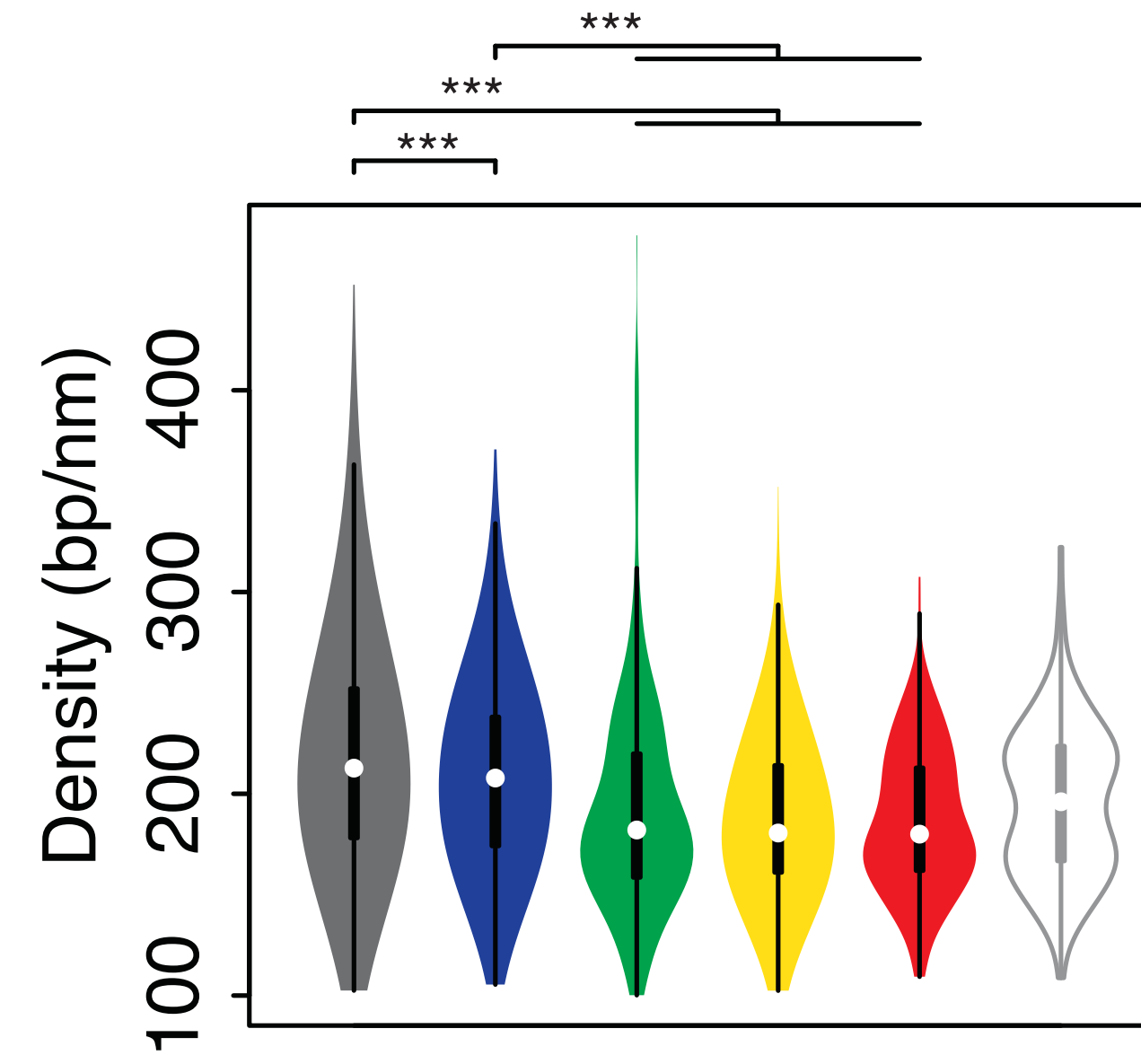
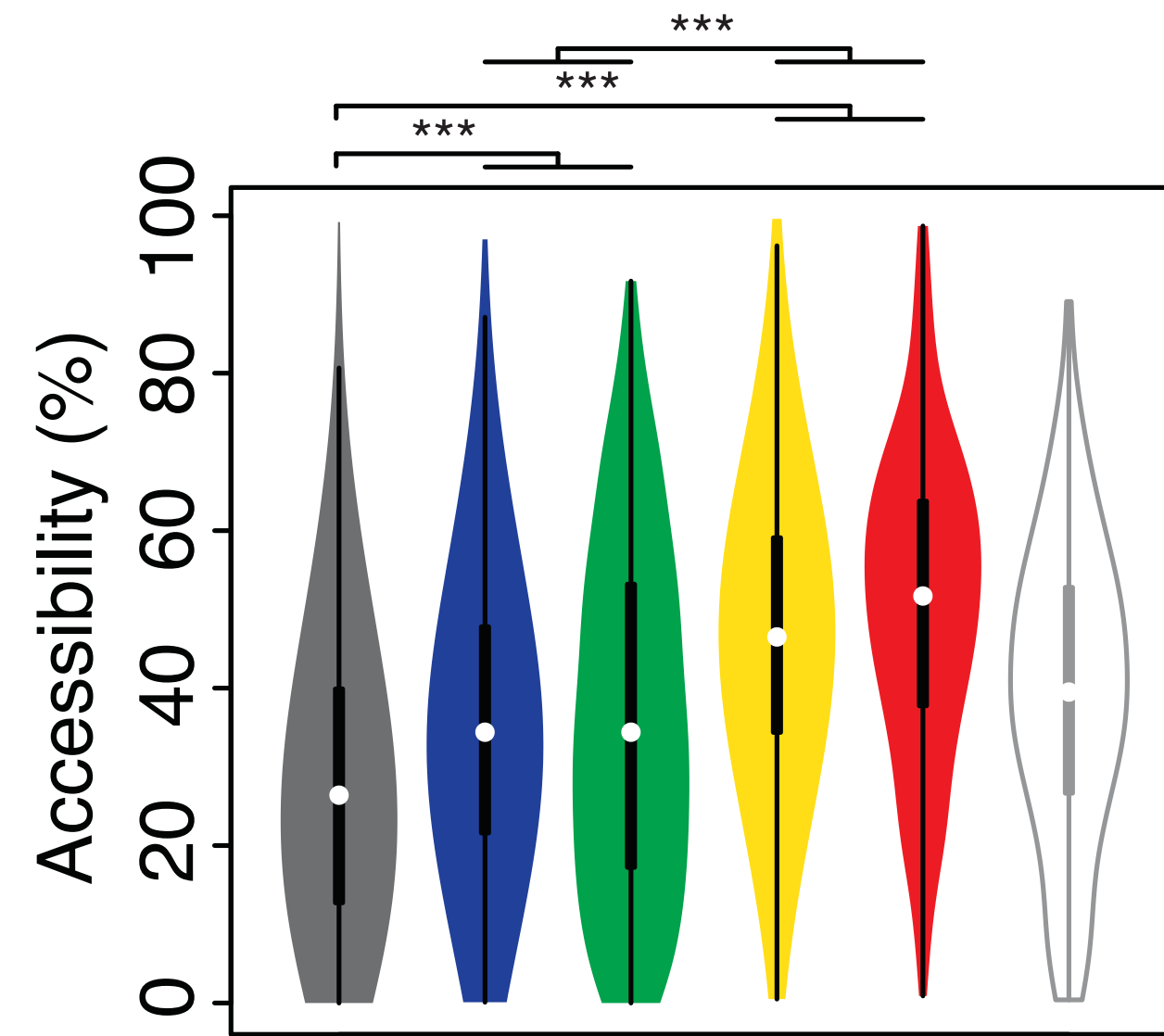
**BLACK dense region**  
2L:17500000-18530000

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

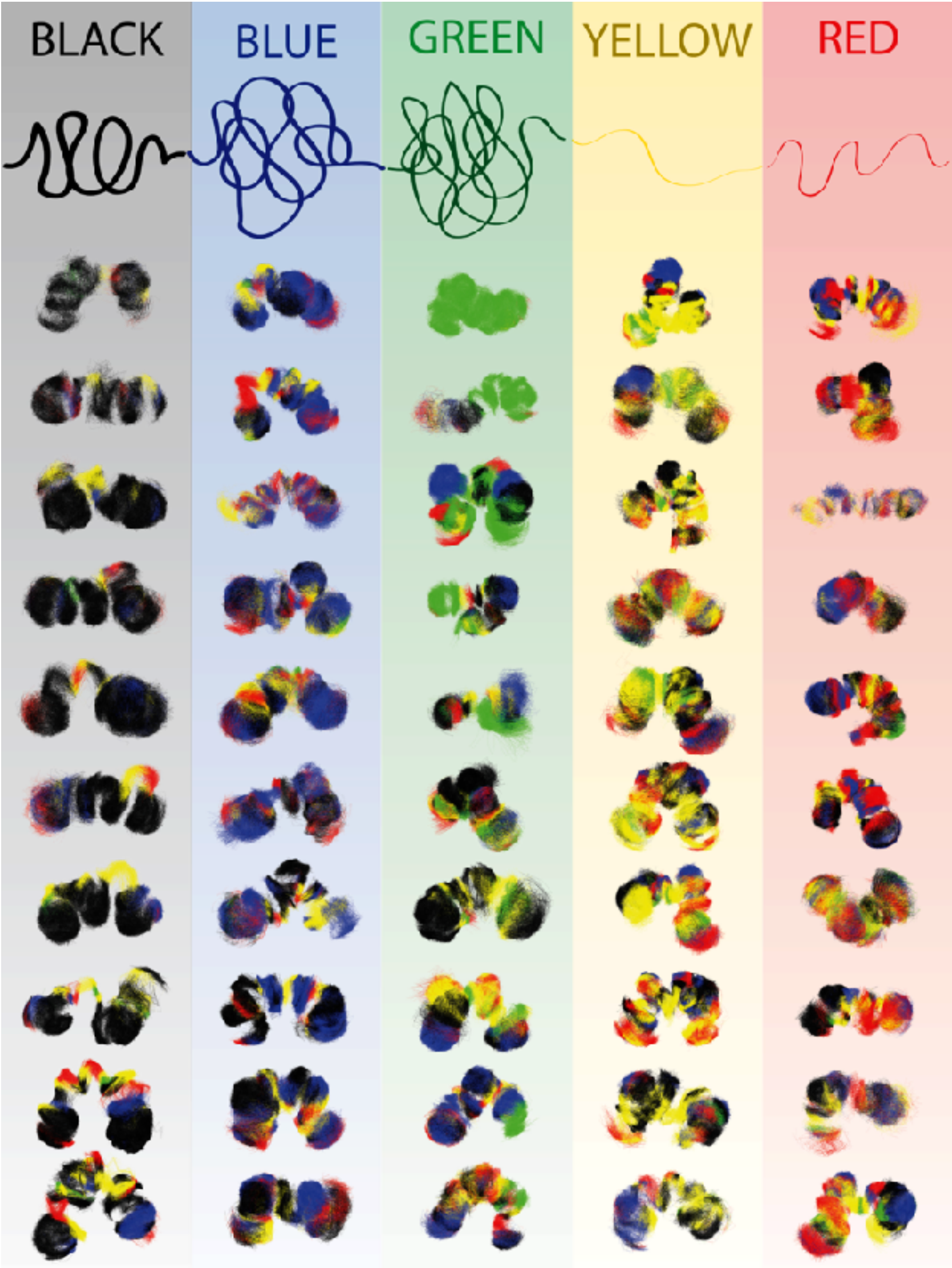




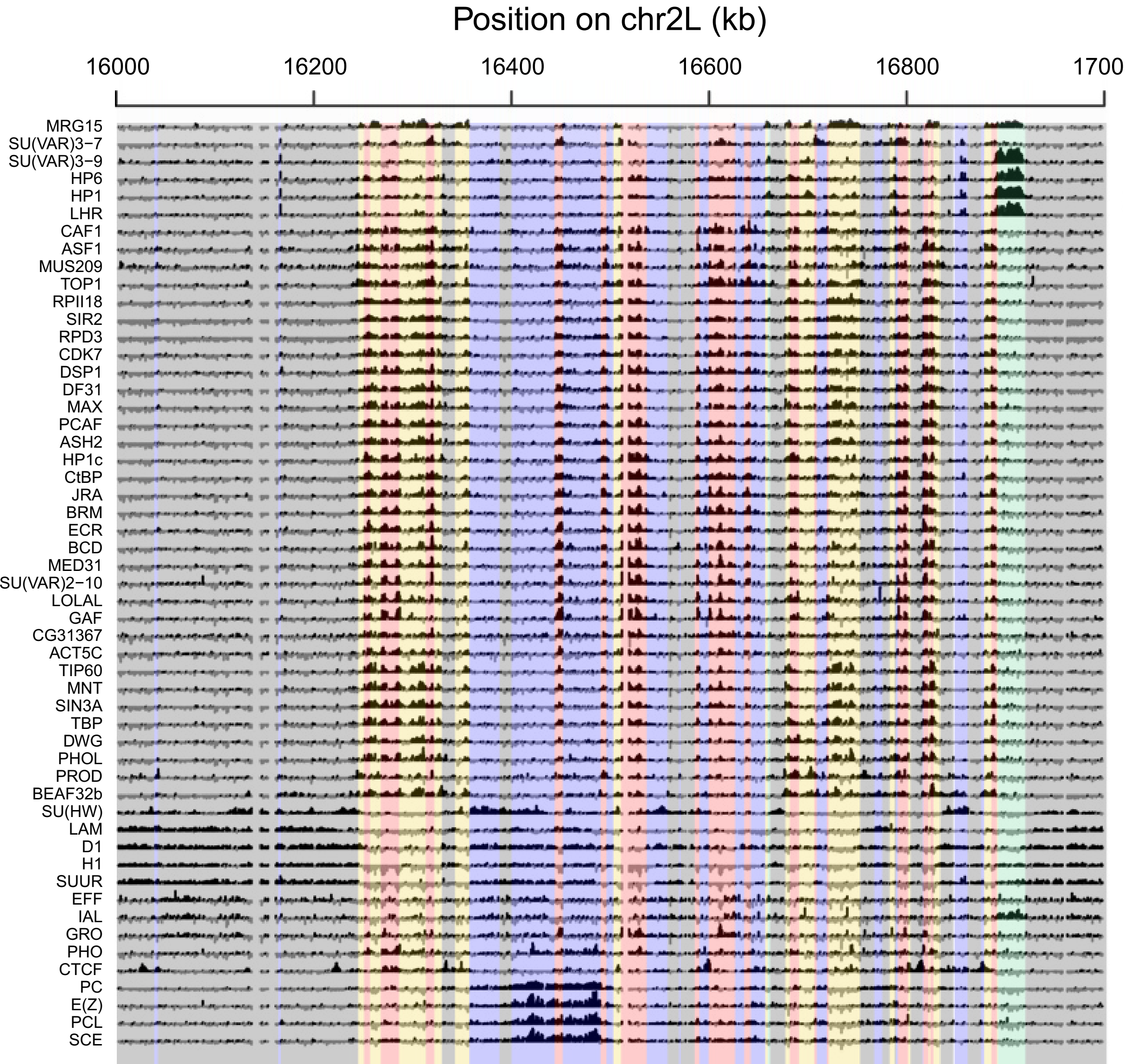
# Structural **COLORs**



StructuralCOLORs



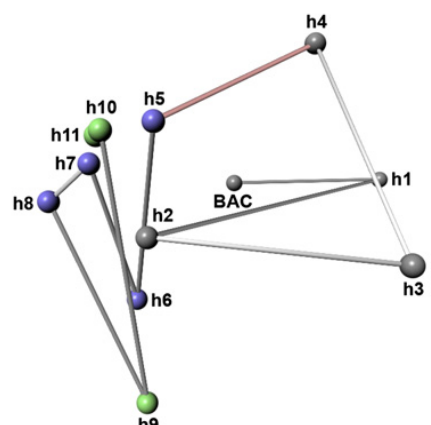
53 chromatin proteins



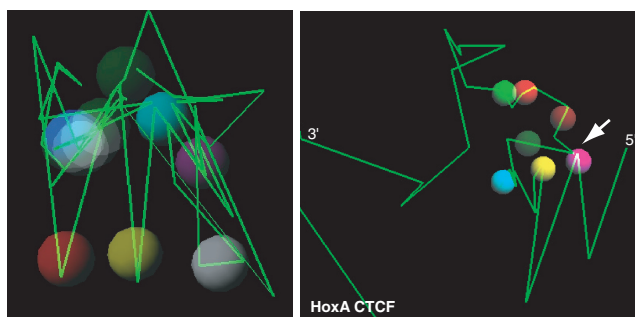


# Are the models correct?

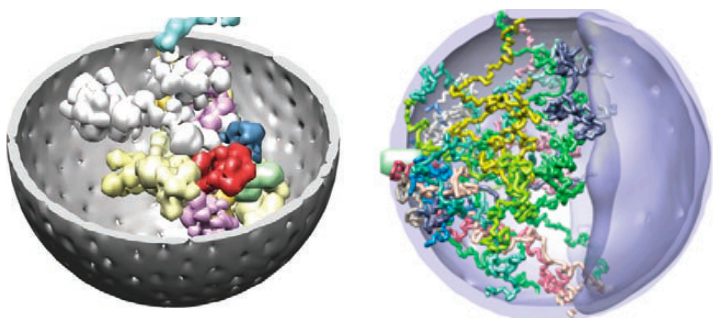
Trussart et al. NAR (2015)



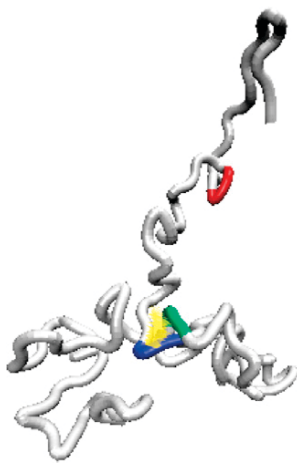
Jhunjunwala (2008) Cell



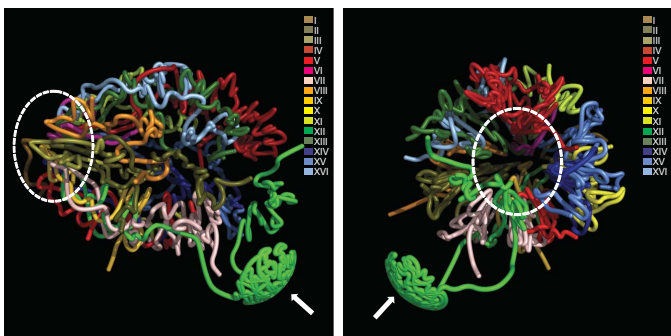
Fraser (2009) Genome Biology  
Ferraiuolo (2010) Nucleic Acids Research



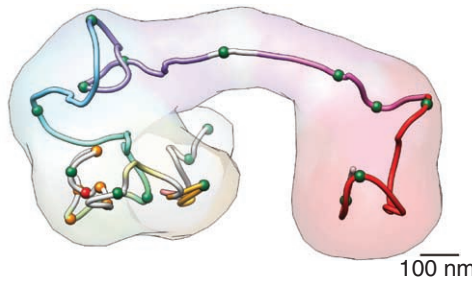
Kalhor (2011) Nature Biotechnology  
Tjong (2012) Genome Research



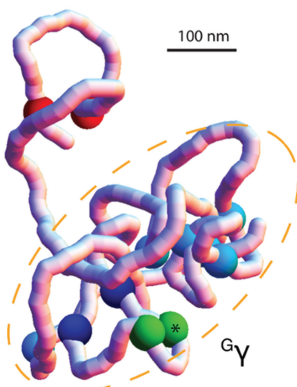
Giorgetti, (2014) Cell



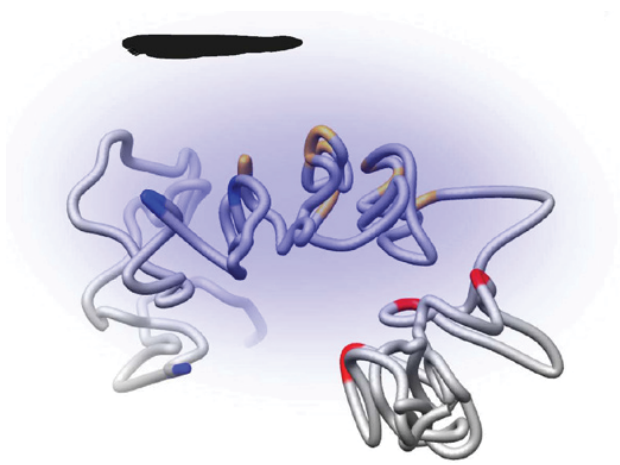
Duan (2010) Nature



Baù (2011) Nature Structural & Molecular Biology



Junier (2012) Nucleic Acids Research



Acemel (2016) Nature Genetics

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

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

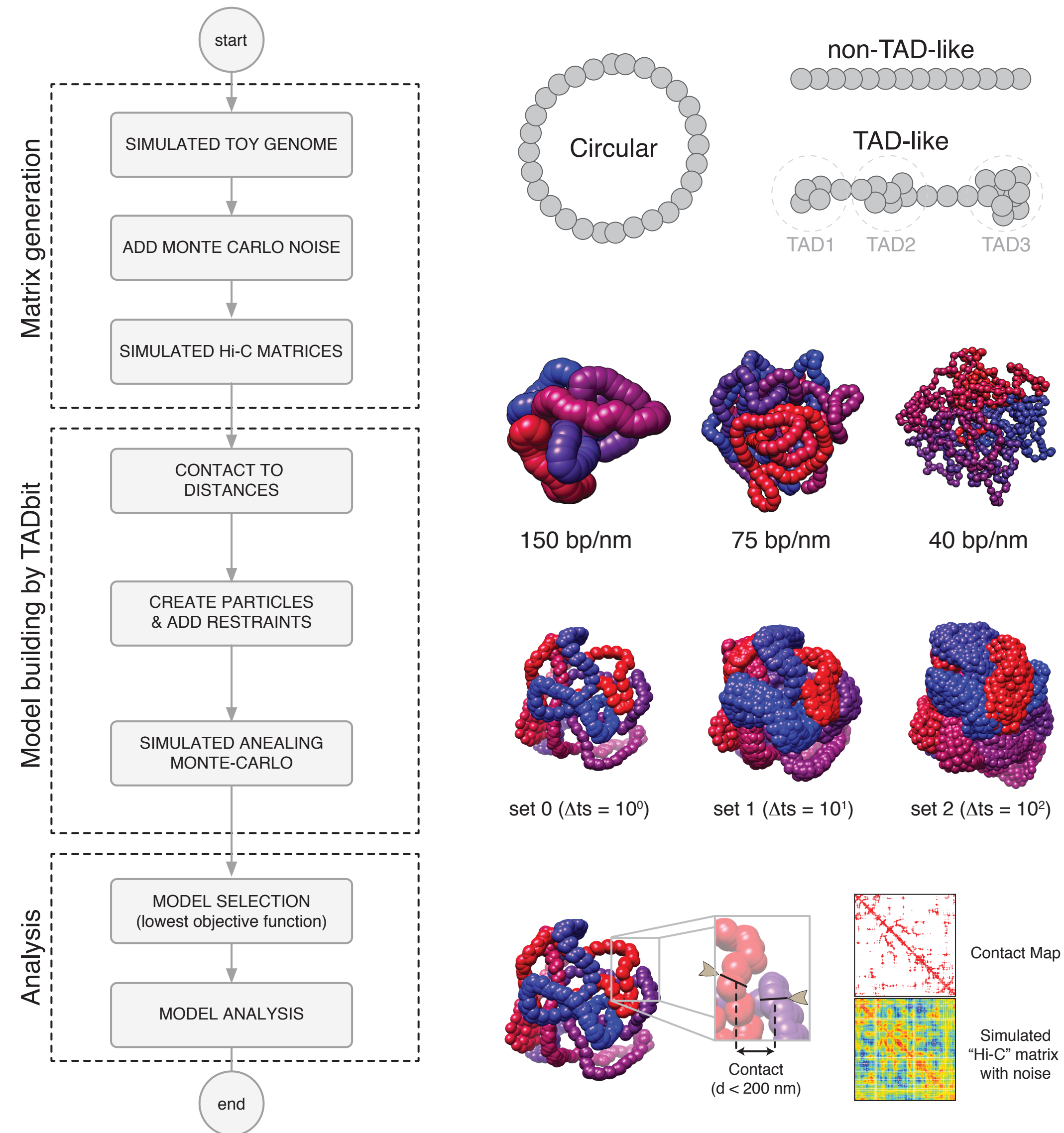
expression regulation and replication (1–6). The advent of the so-called Chromosome Conformation Capture (3C) assays (7), which allowed identifying chromatin-looping interactions between pairs of loci, helped deciphering some of the key elements organizing the genomes. High-throughput derivations of 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://integrativemodelling.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

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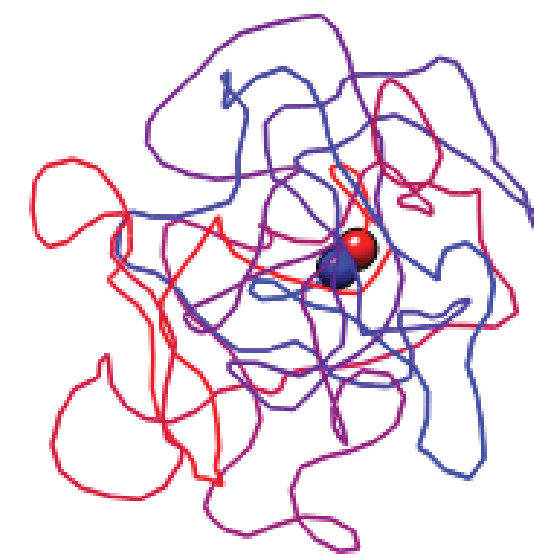
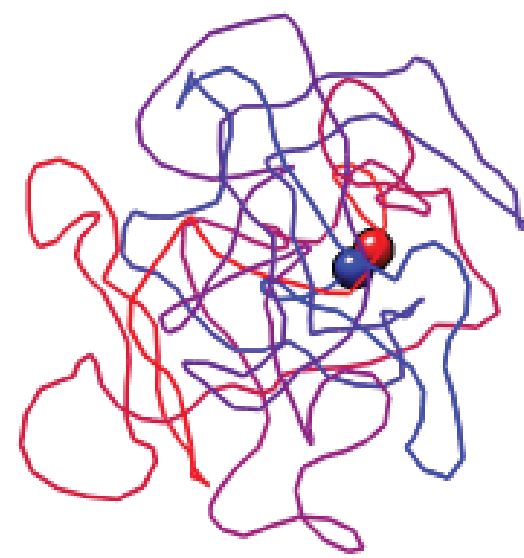
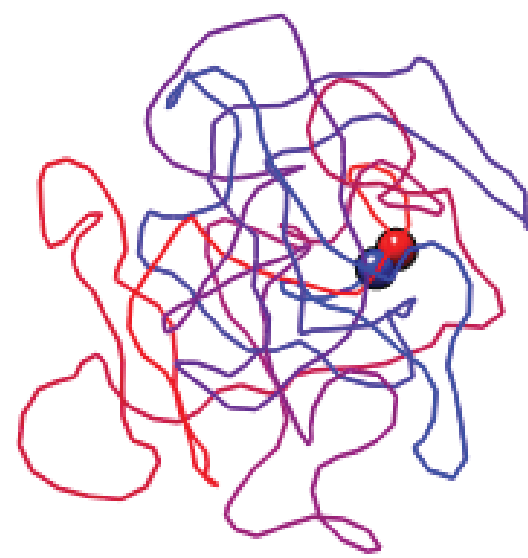
# Toy models (168)



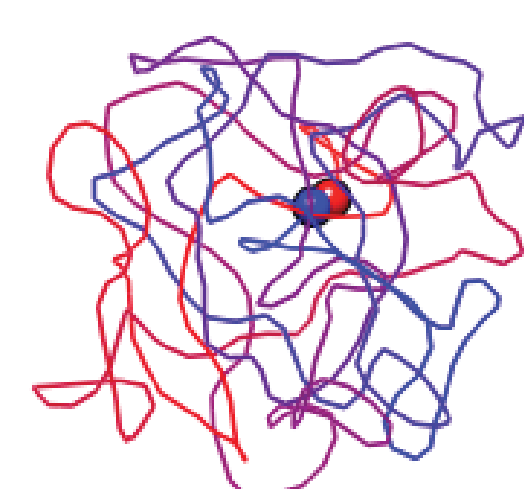
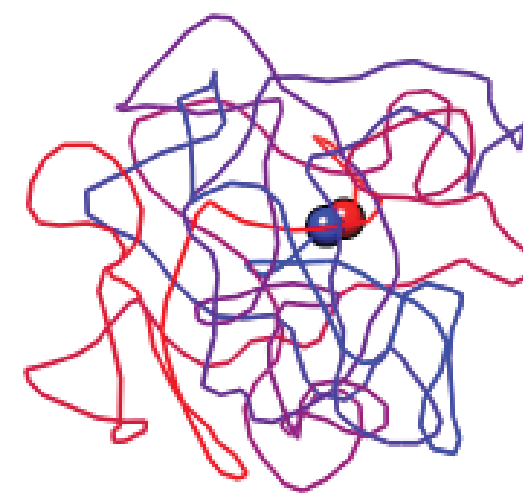
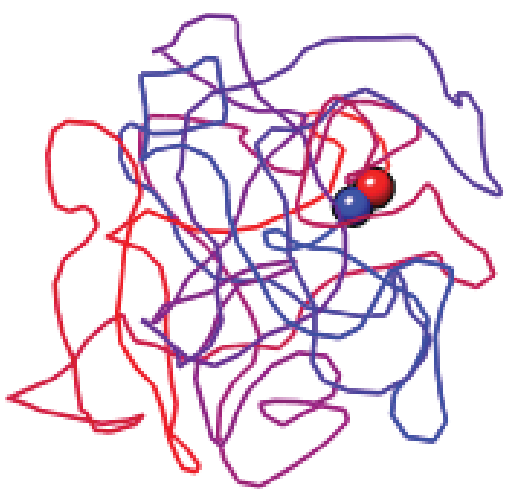
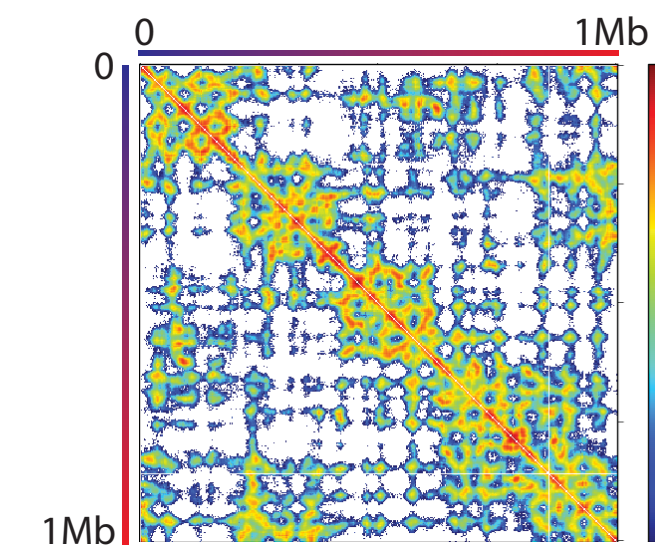
by Ivan Junier



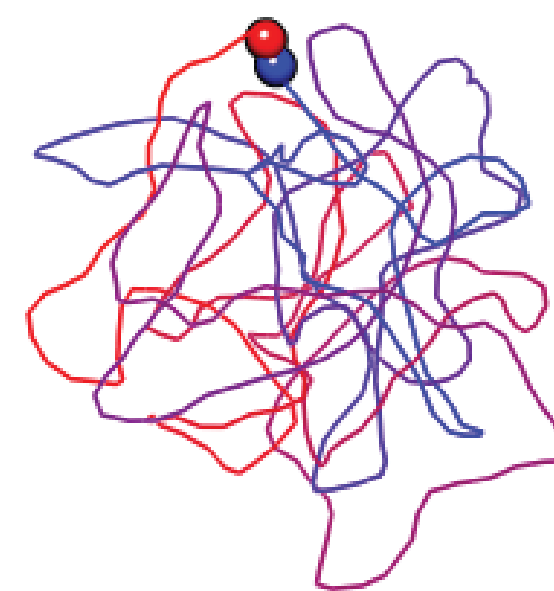
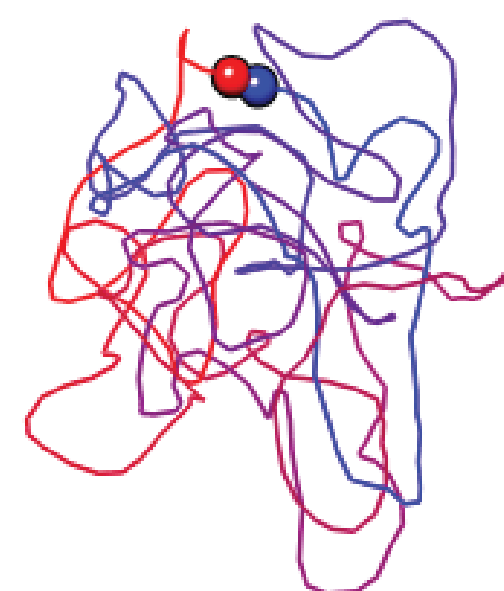
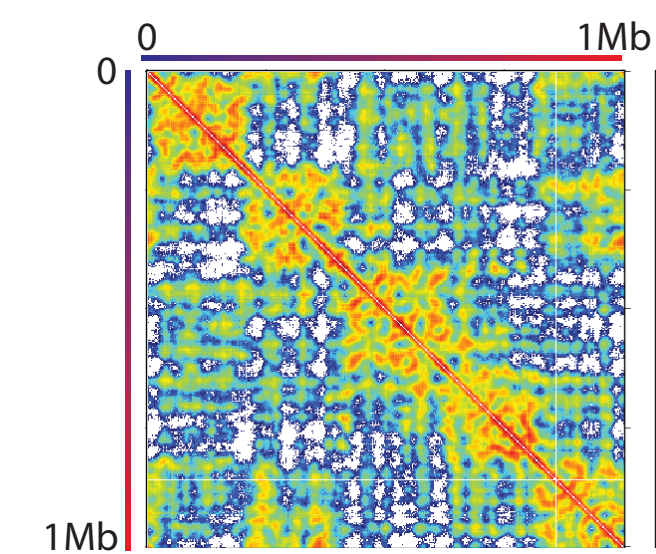
# Toy interaction matrices



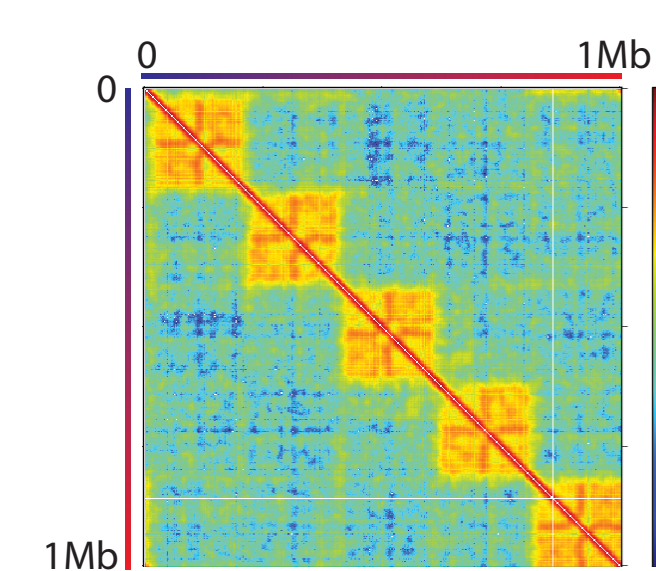
**set 0 ( $\Delta ts=10^0$ )**



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

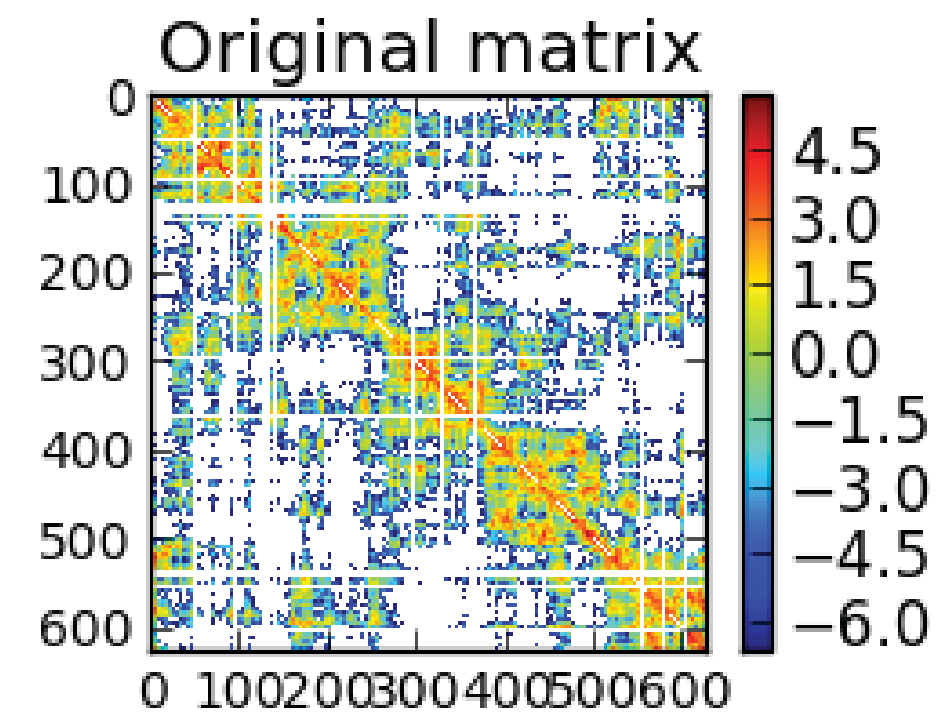
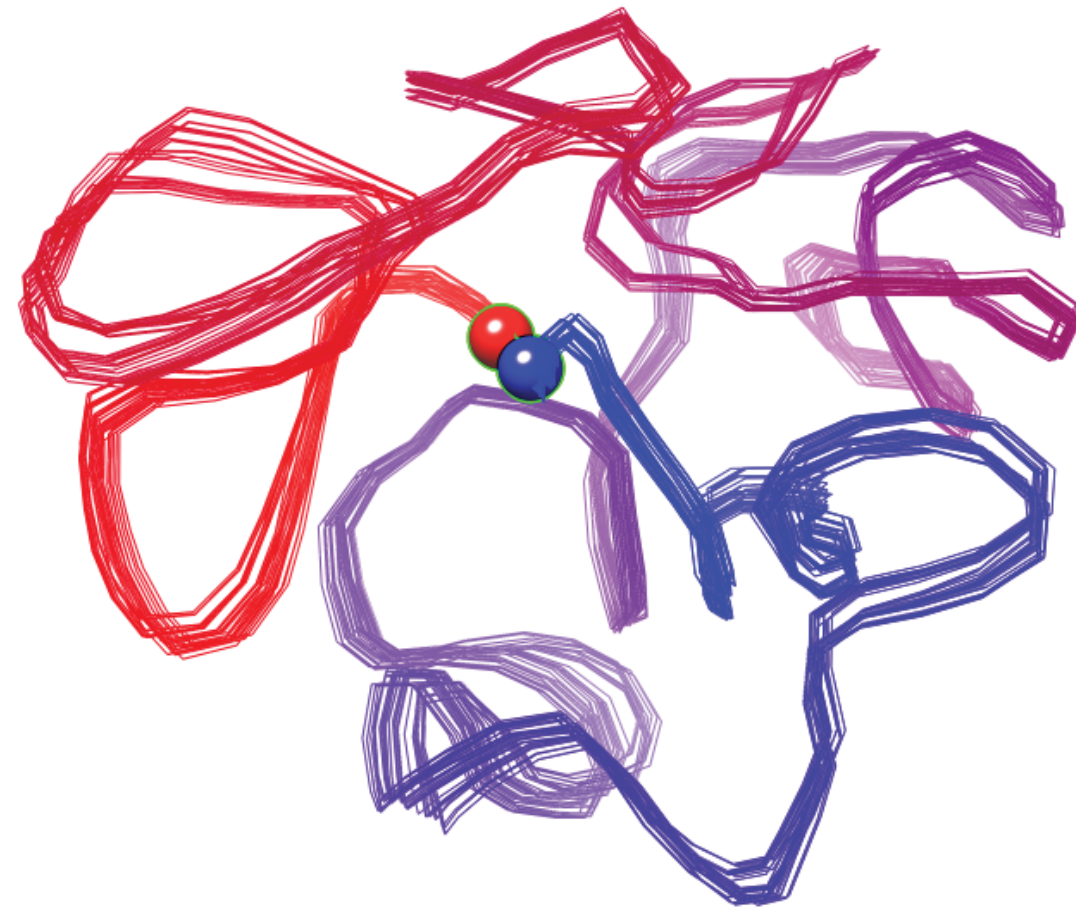


**set 6 ( $\Delta ts=10^6$ )**





# Reconstructing toy models



**chr40\_TAD**

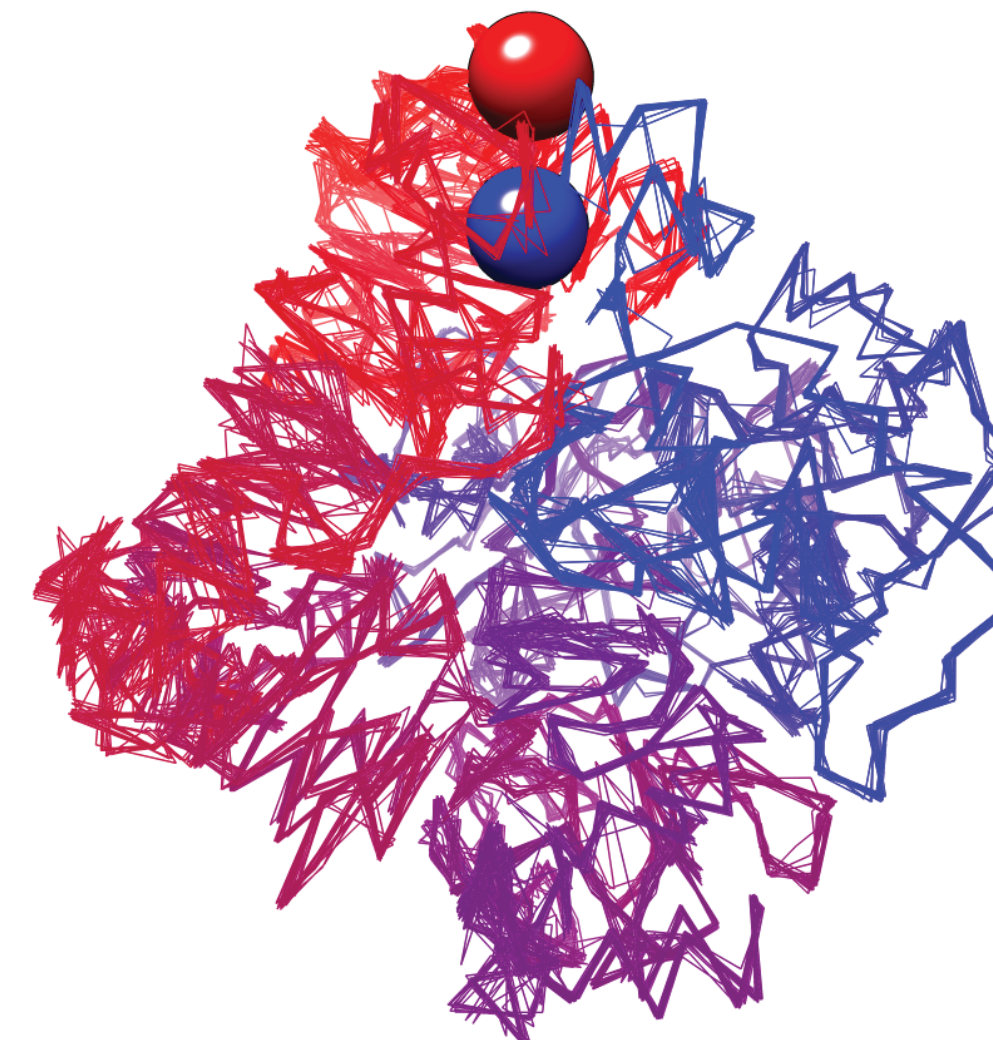
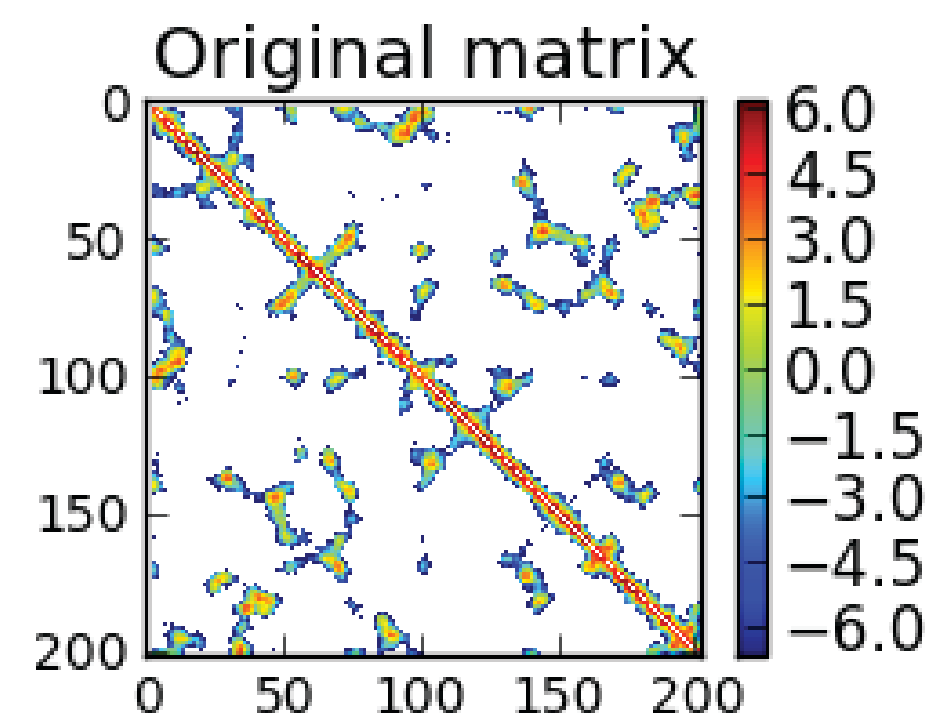
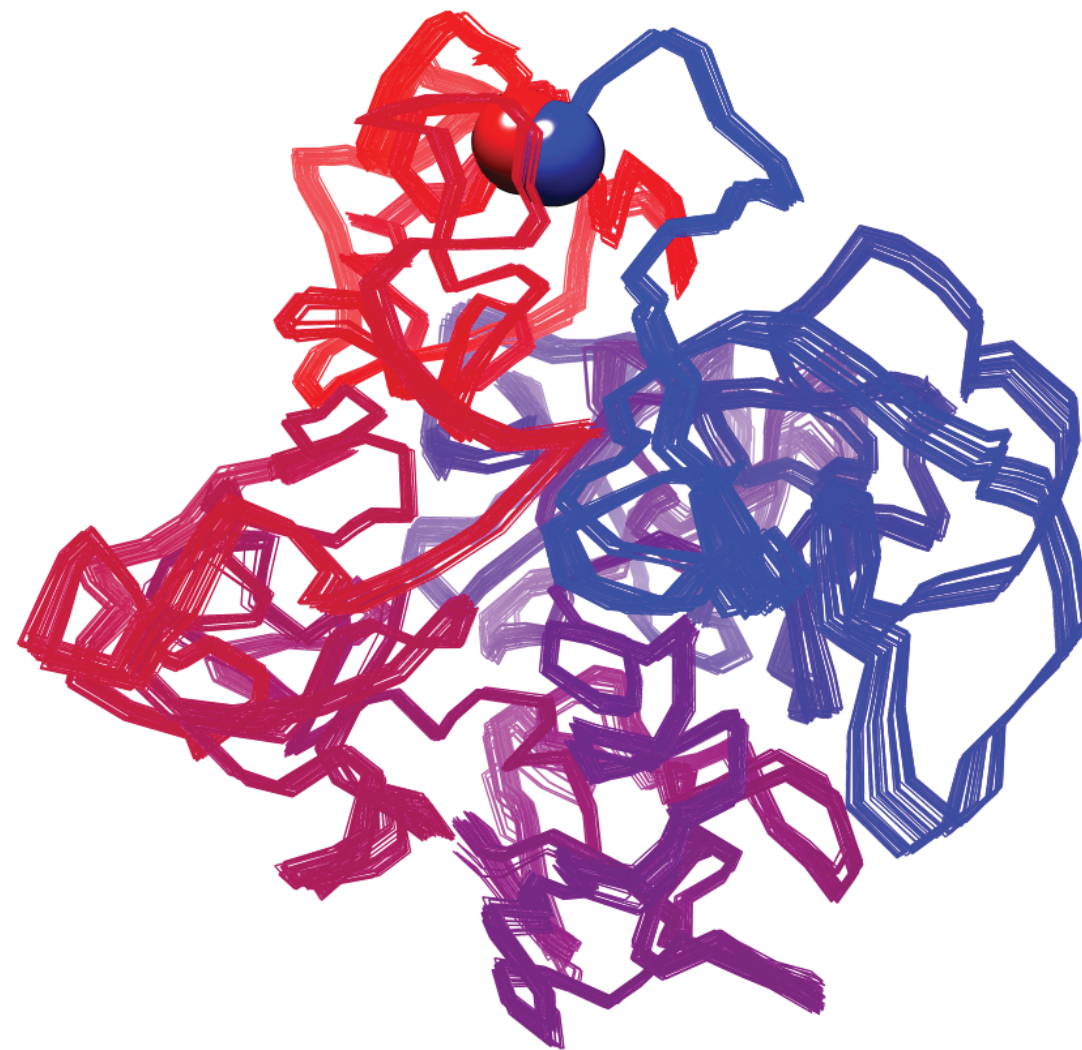
$\alpha=100$

$\Delta t_s=10$

TADbit-SCC: 0.91

**$\langle d\text{RMSD} \rangle$ : 32.7 nm**

**$\langle d\text{SCC} \rangle$ : 0.94**



**chr150\_TAD**

$\alpha=50$

$\Delta t_s=1$

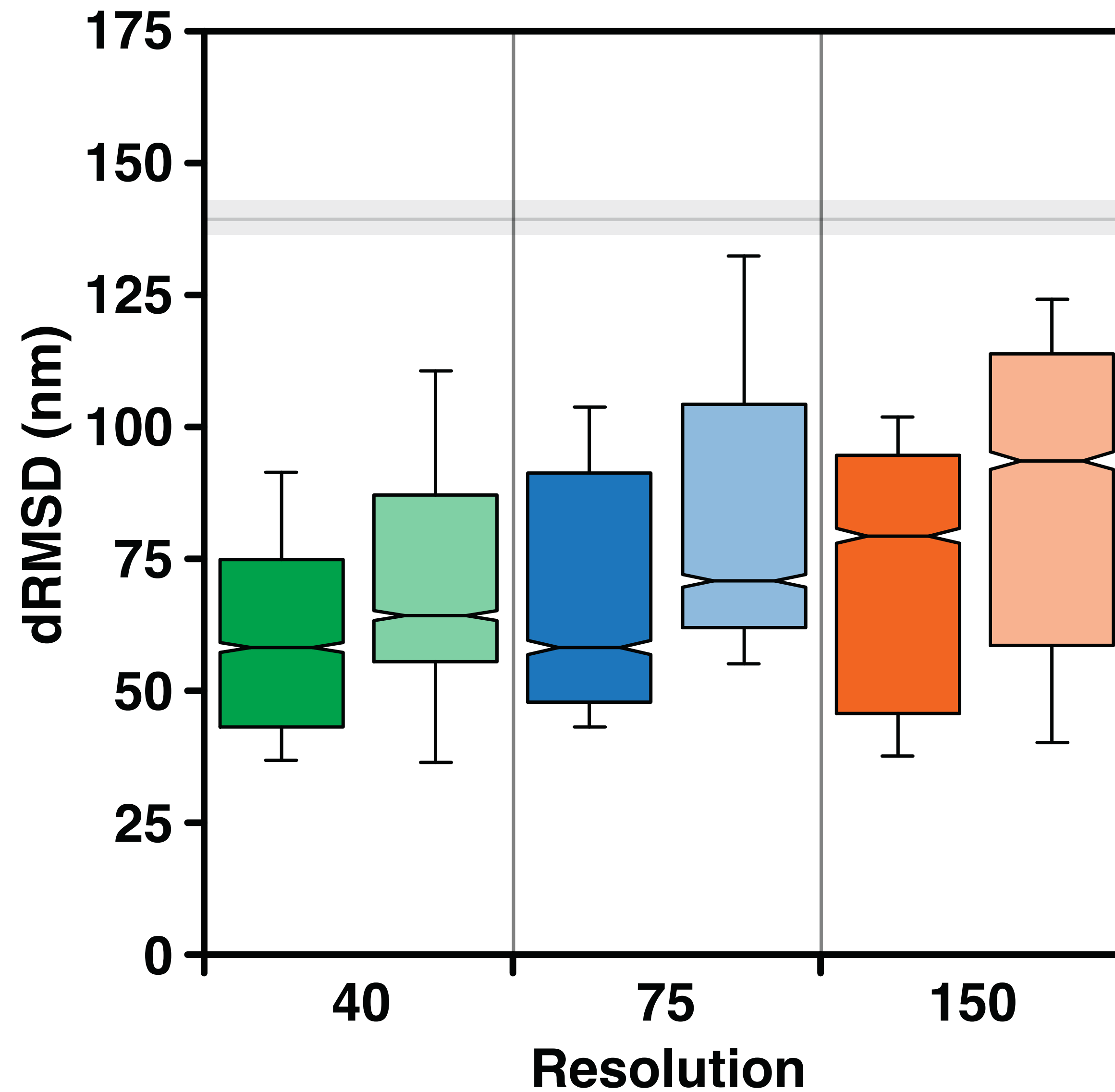
TADbit-SCC: 0.82

**$\langle d\text{RMSD} \rangle$ : 45.4 nm**

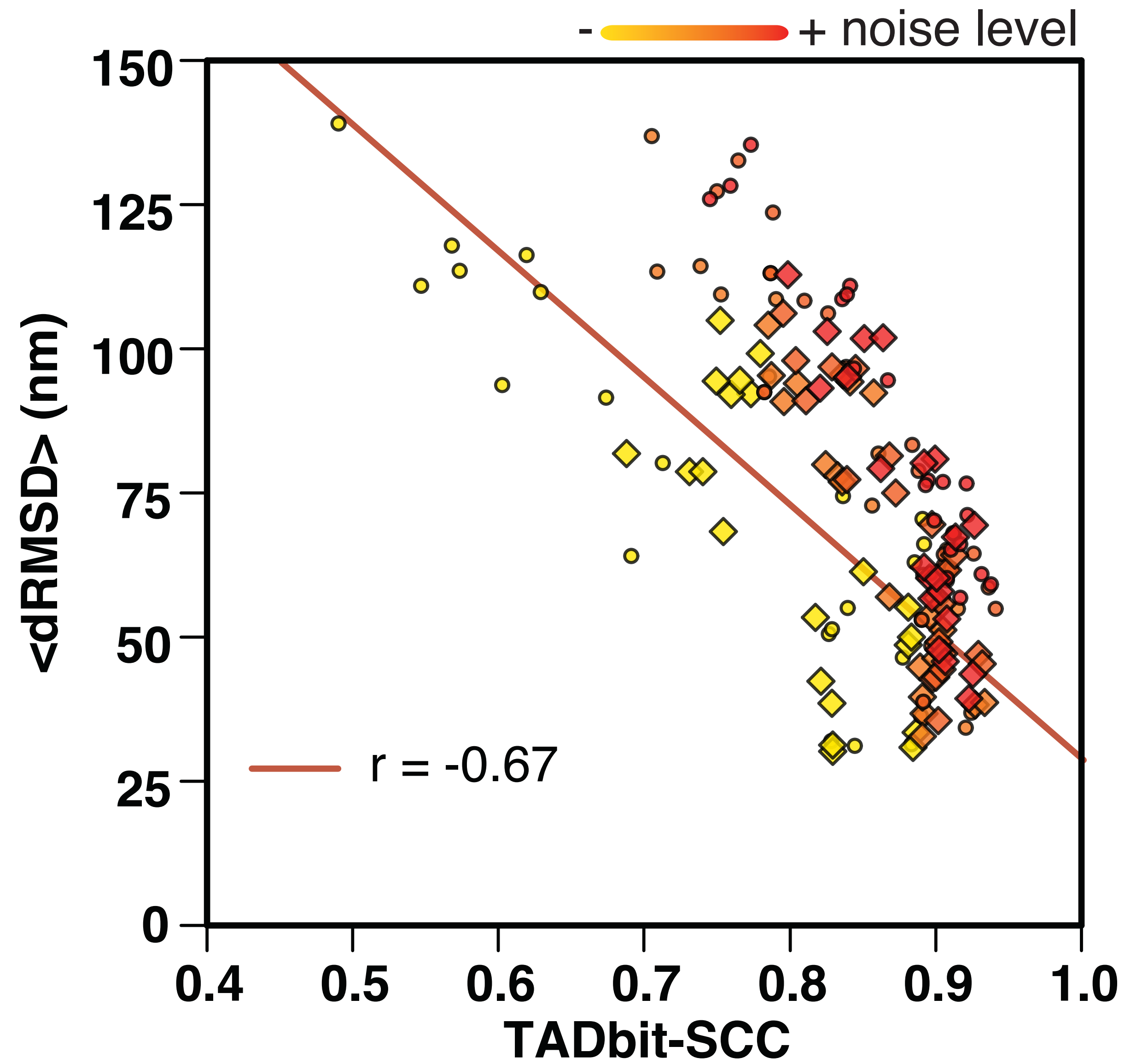
**$\langle d\text{SCC} \rangle$ : 0.86**



TADs & higher-res are "good"

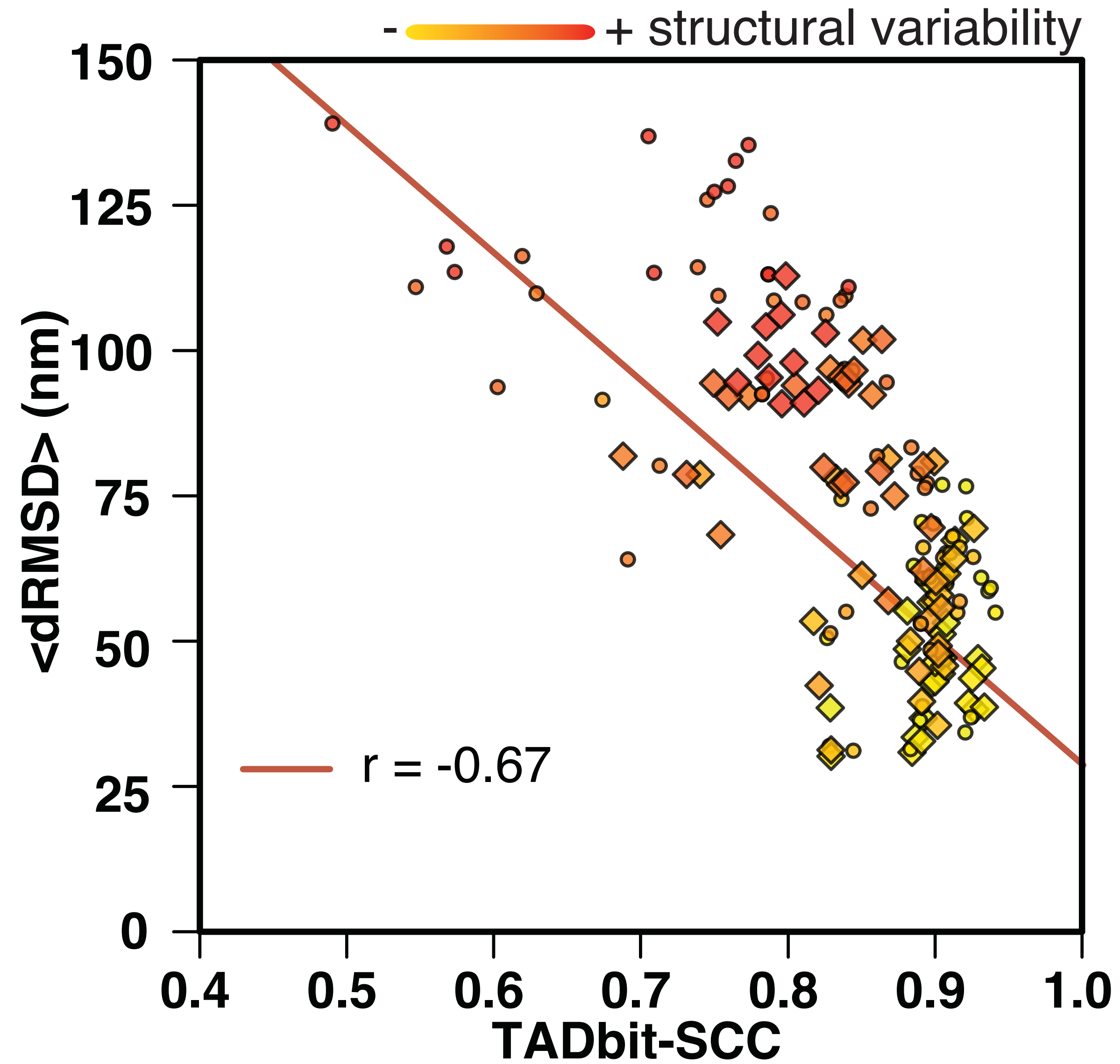


Noise is "OK"

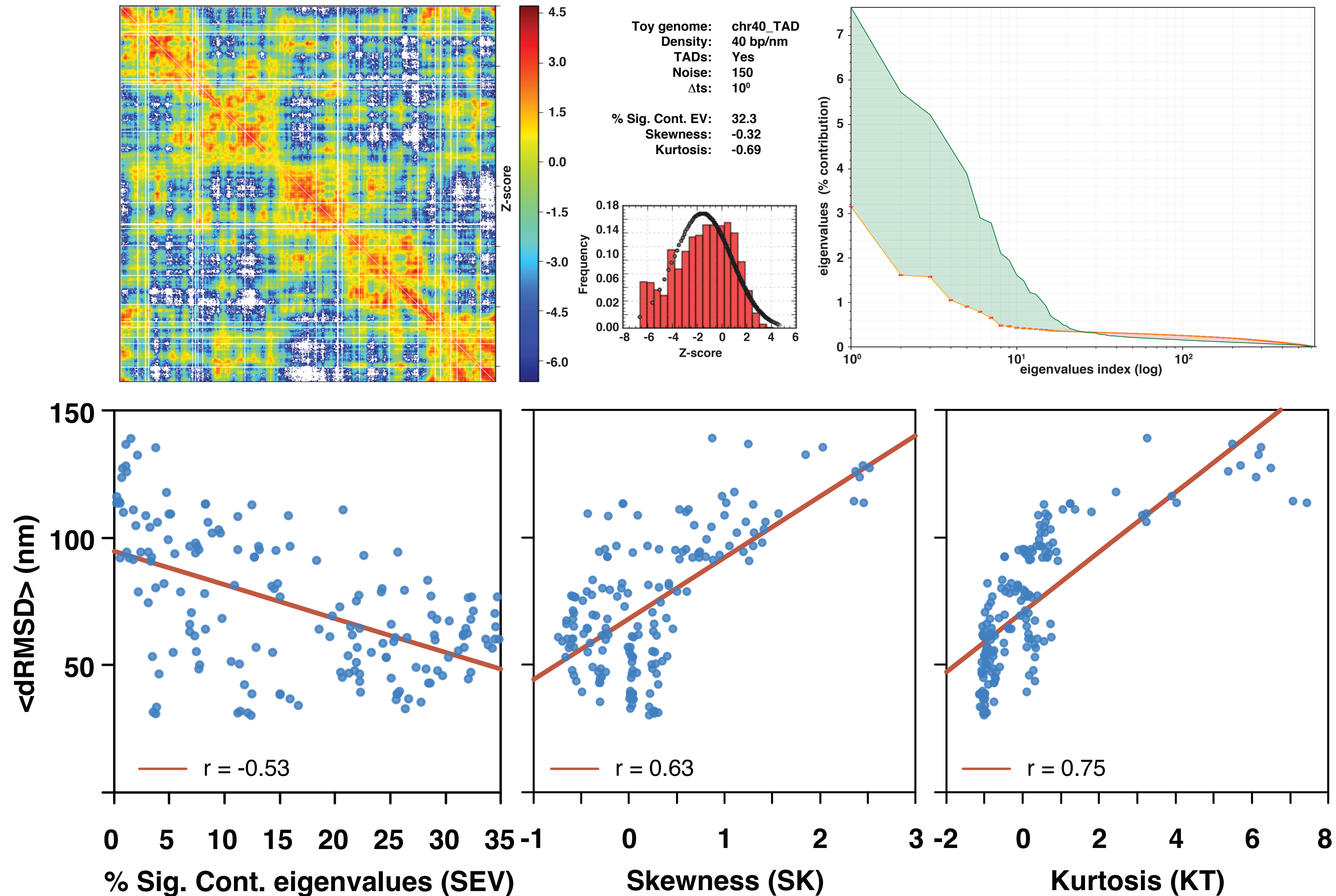




Structural variability is "NOT OK"

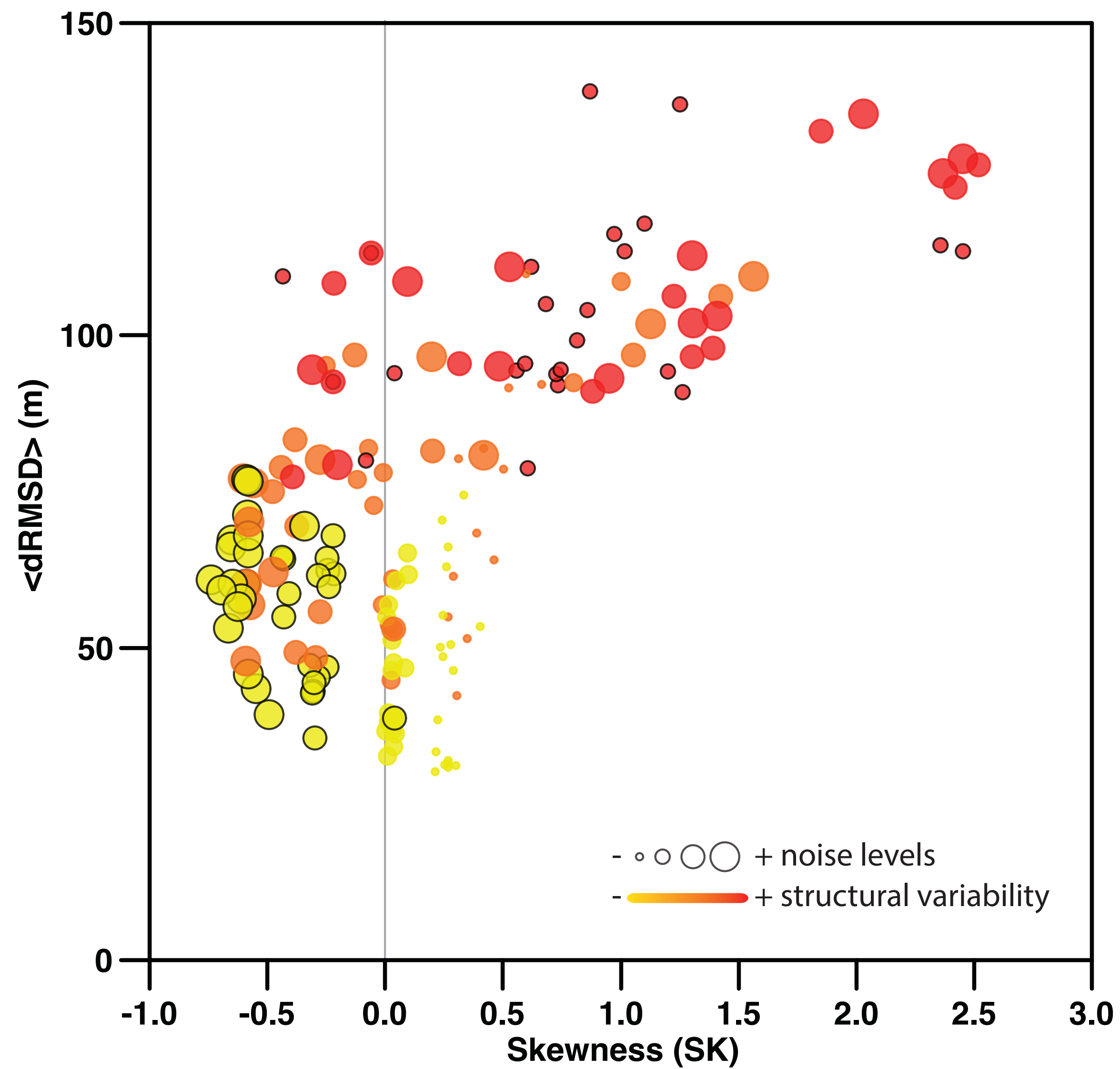
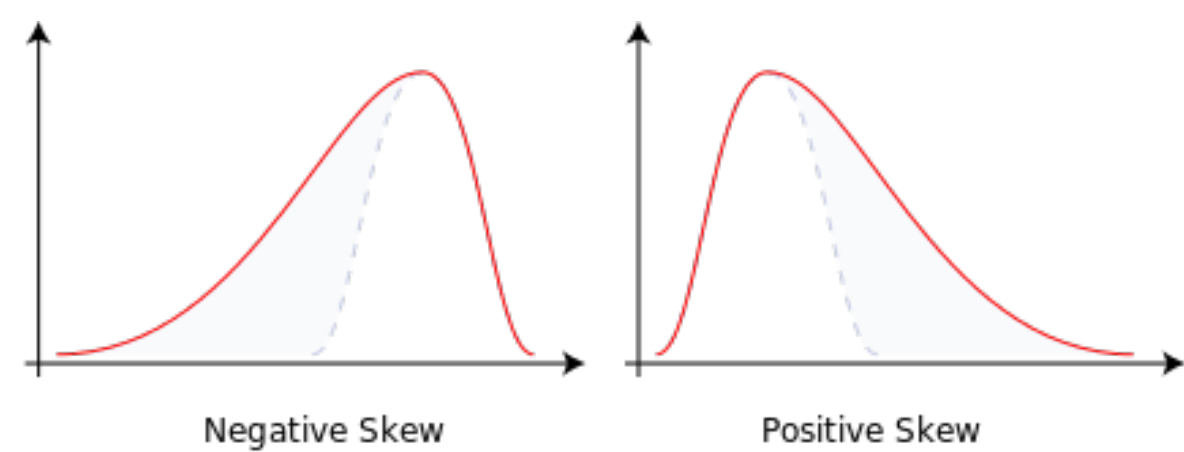


# Can we predict the accuracy of the models?



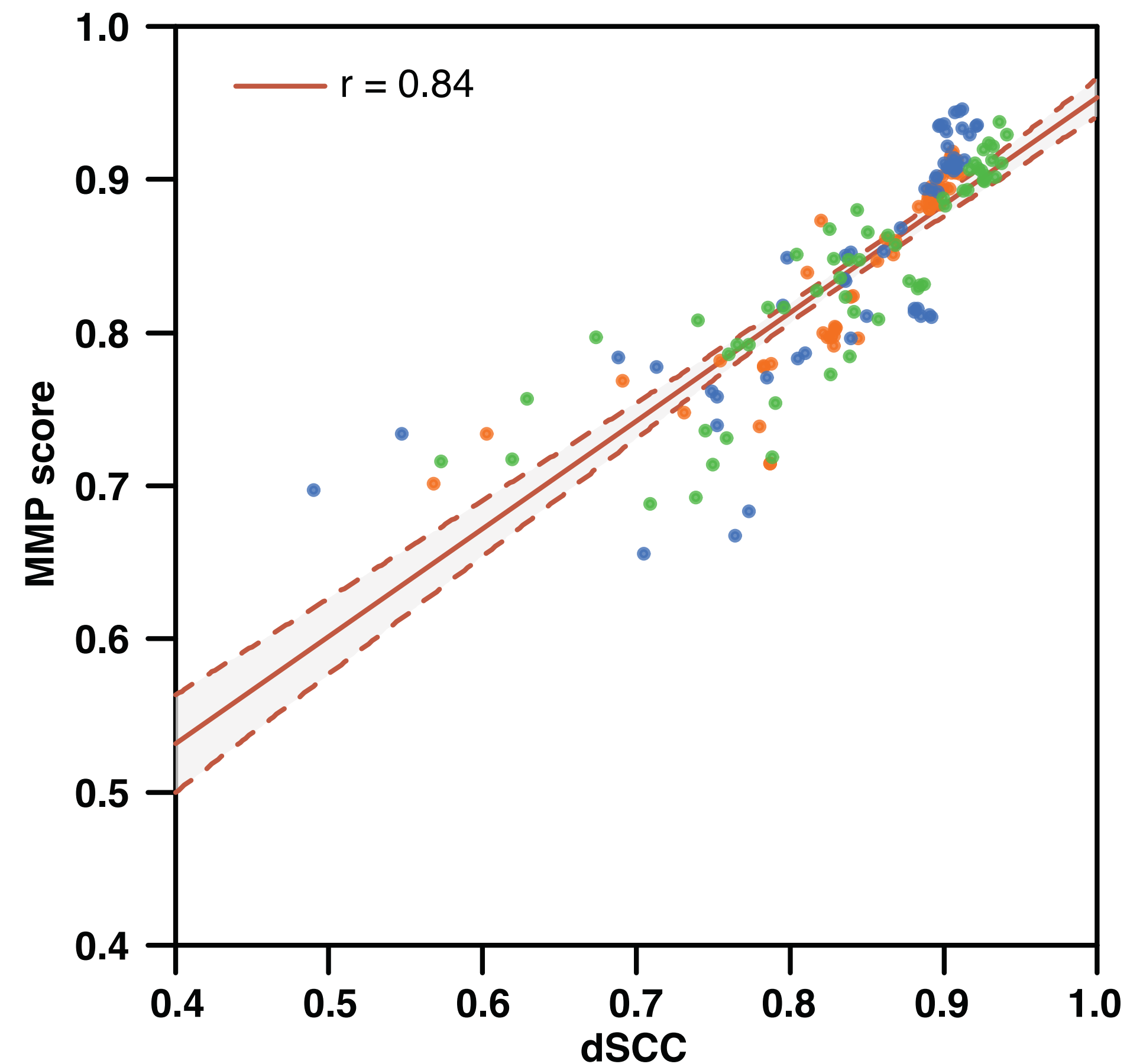


# Skewness "side effect"



# Can we predict the accuracy of the models?

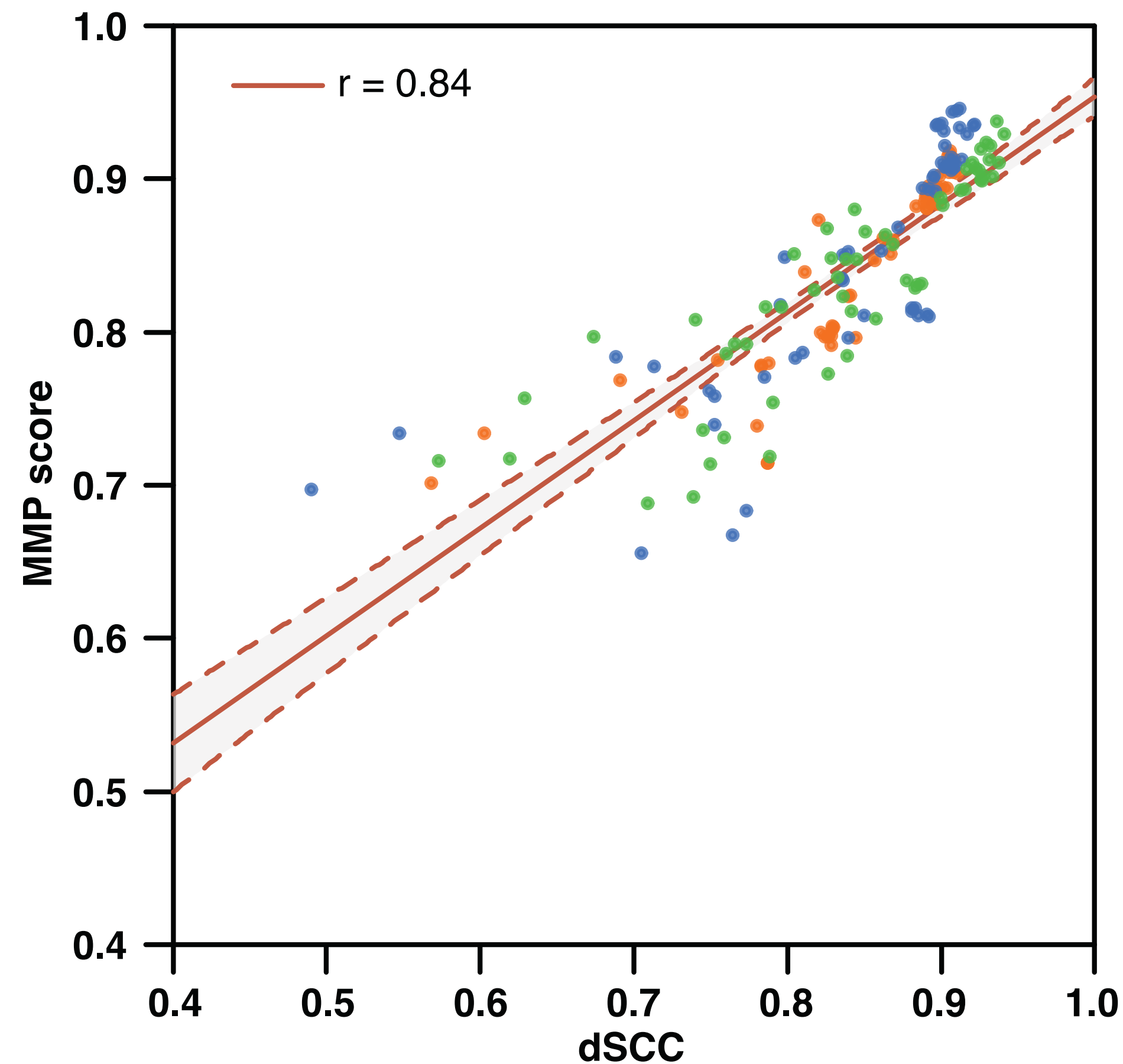
$$\text{MMP} = -0.0002 * \text{Size} + 0.0335 * \text{SK} - 0.0229 * \text{KU} + 0.0069 * \text{SEV} + 0.8126$$



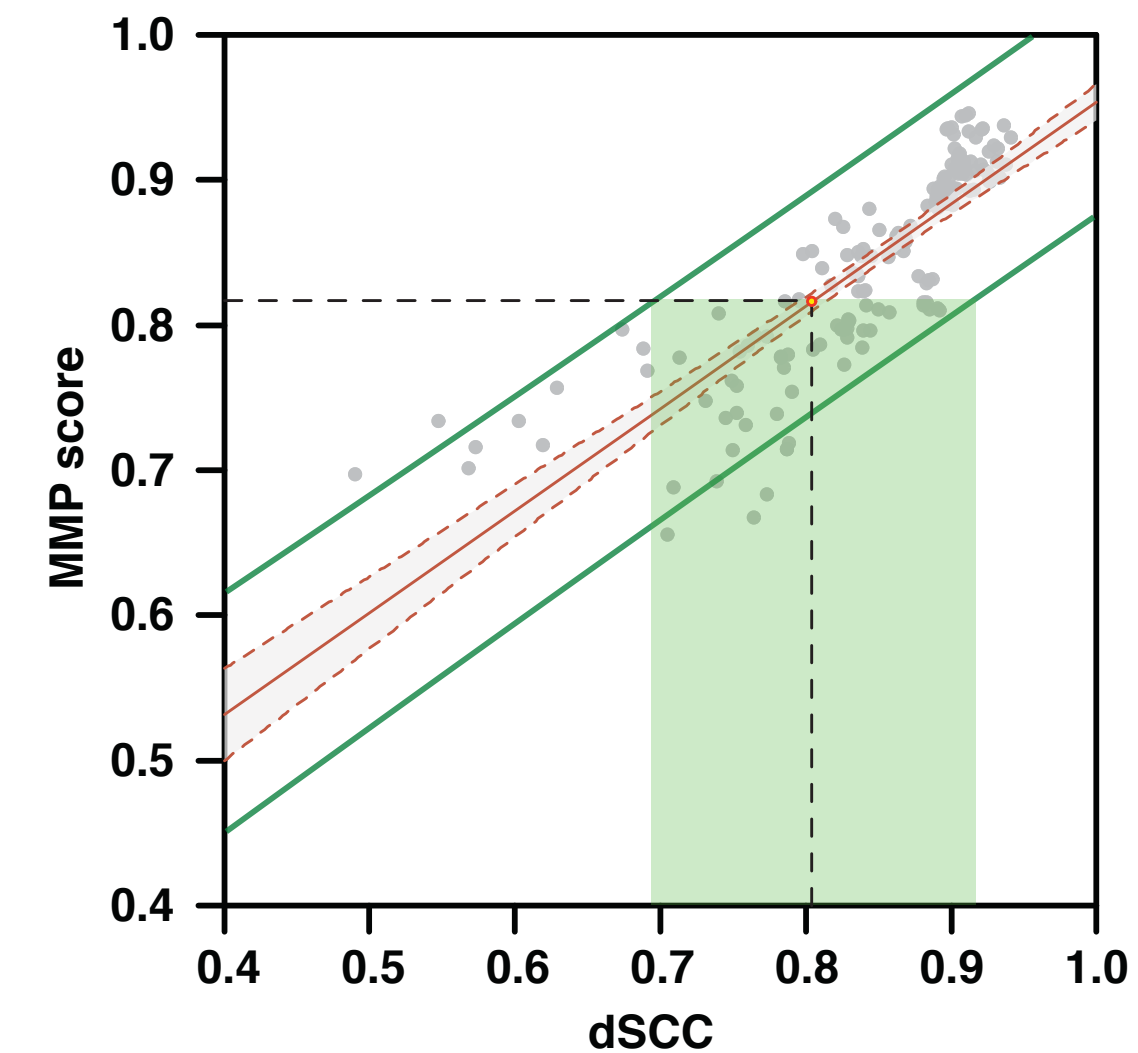
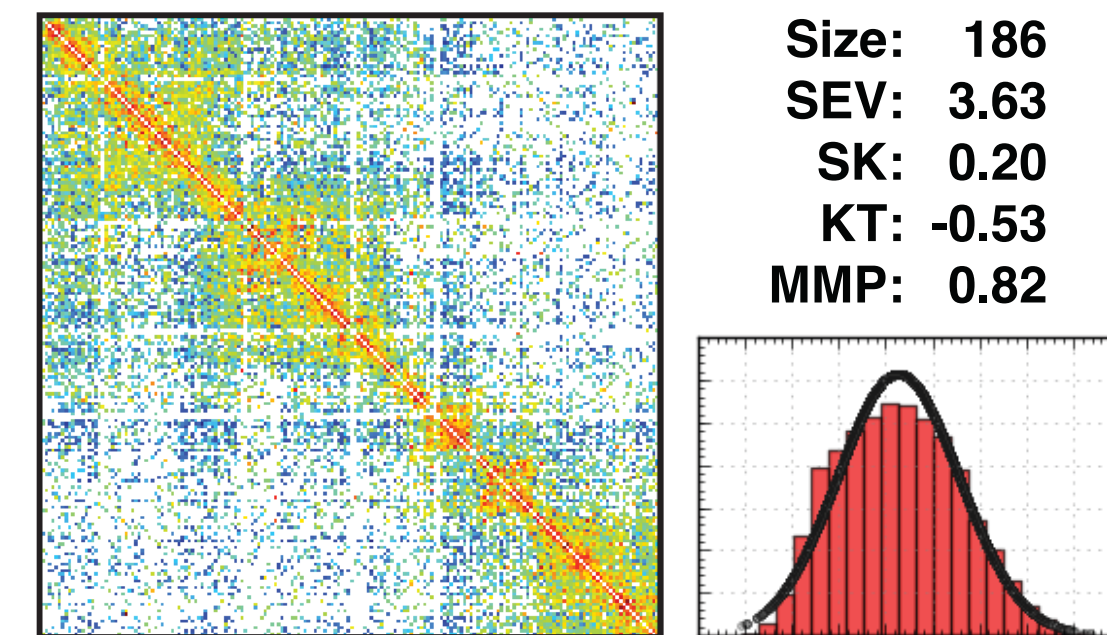


# Can we predict the accuracy of the models?

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



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





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