The Three-Dimensional Architecture of a Bacterial Genome and Its Alteration by Genetic Perturbation

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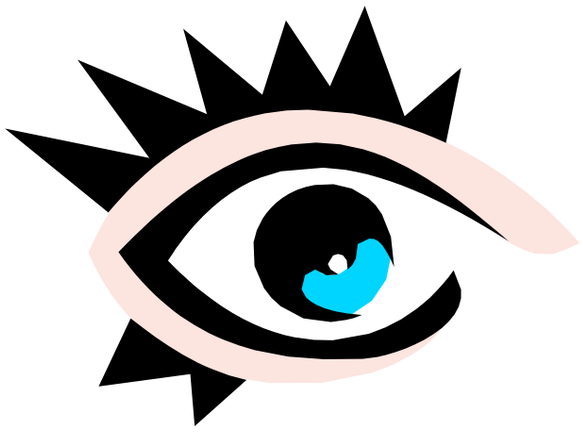
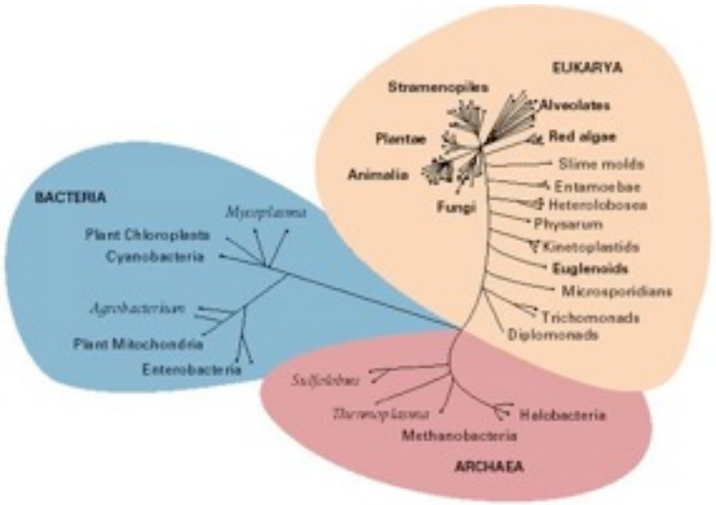
Structural Genomics Group (CRG)

Integrative Modeling Platform

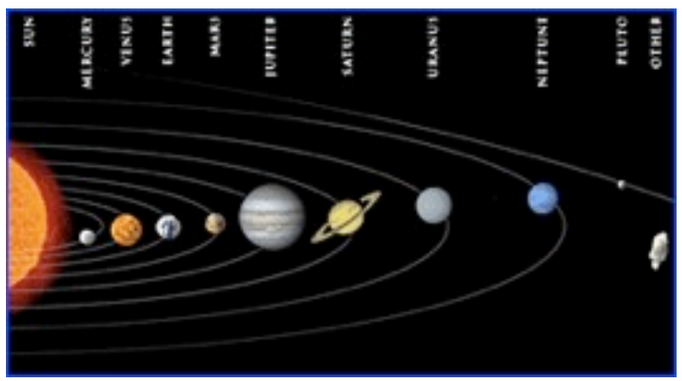
http://www.integrativemodeling.org



Experimental observations

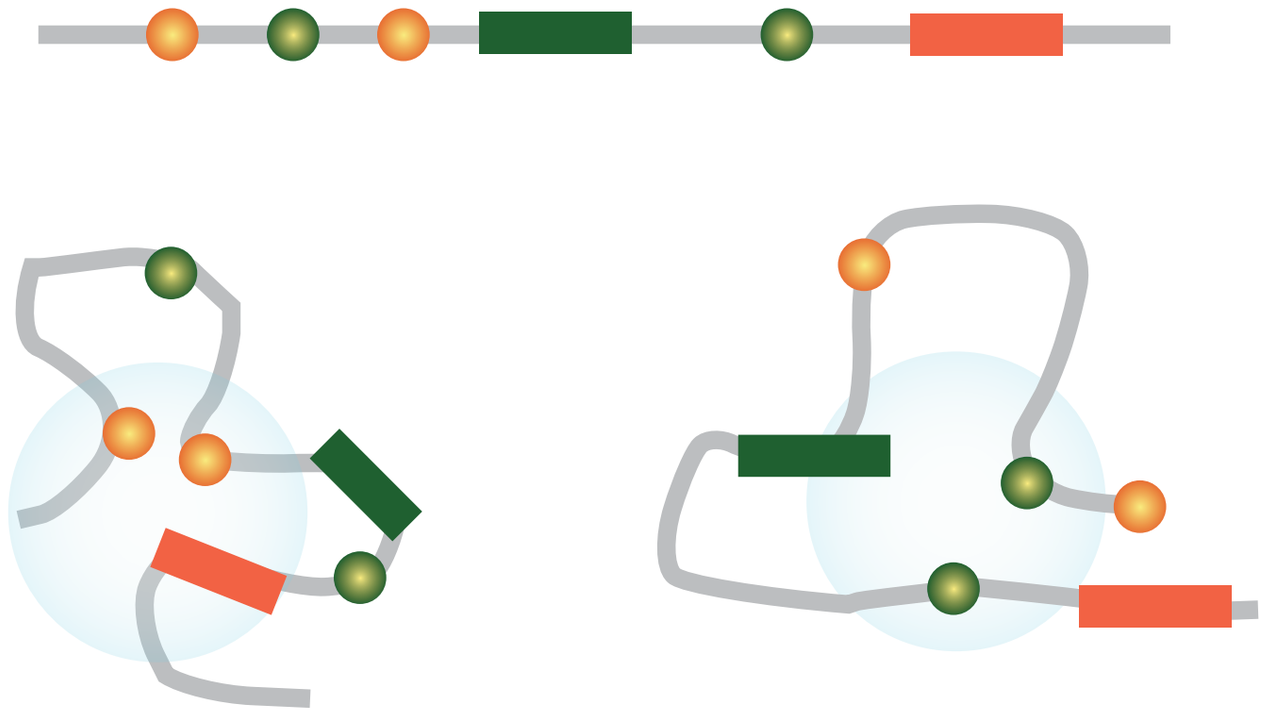


Statistical rules

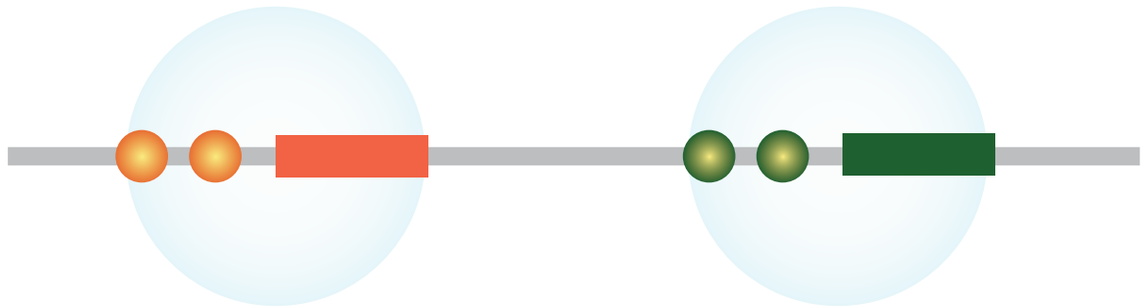


Laws of physics

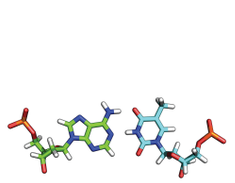
"Complex" genomes

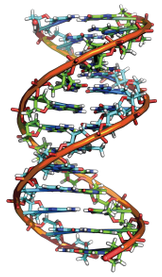


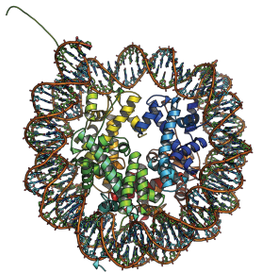
"Simple" genomes

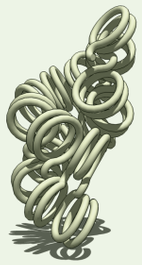


Knowledge



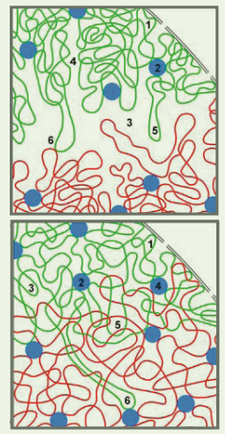


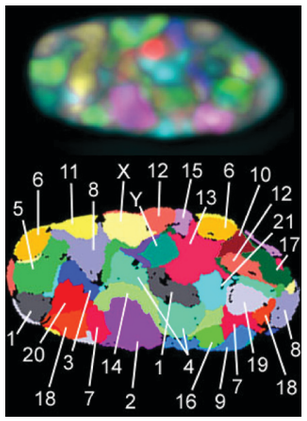




IDM

INM





DNA length

10^0 10^3 10^6 10^9 nt

Volume

10^{-9} 10^{-6} 10^{-3} 10^0 10^3 μm^3

Time

10^{-10} 10^{-8} 10^{-6} 10^{-4} 10^{-2} 10^0 10^2 10^3 s

Resolution

10^{-3} 10^{-2} 10^{-1} µ

Adapted from:

Langowski and Heermann. Semin Cell Dev Biol (2007) vol. 18 (5) pp. 659-67

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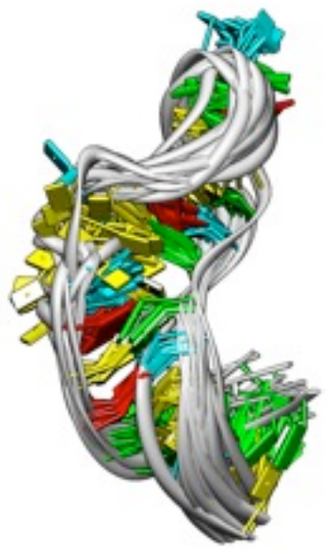
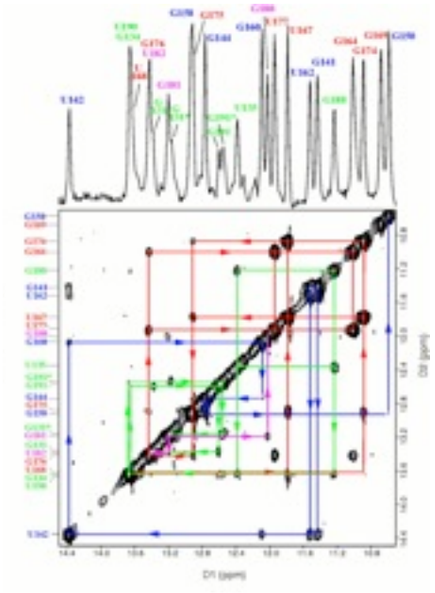
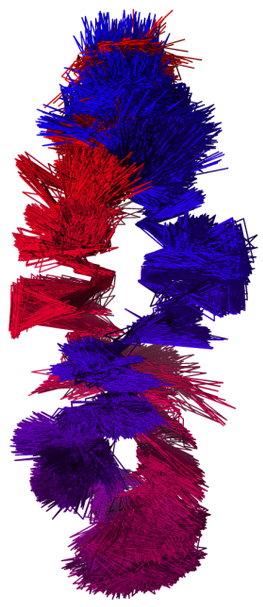
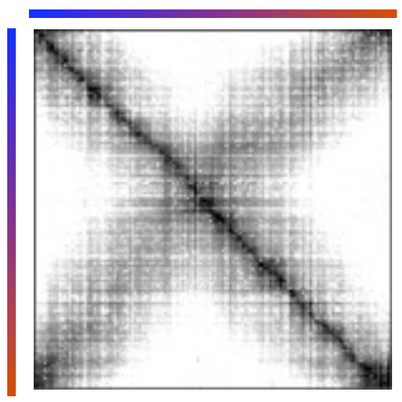




Biomolecular structure determination

2D-NOESY data





Chromosome structure determination

5C data

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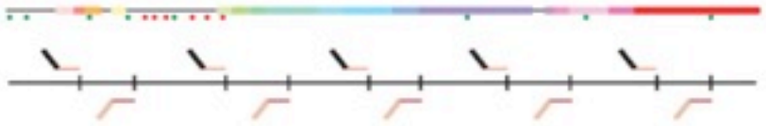
Experiments

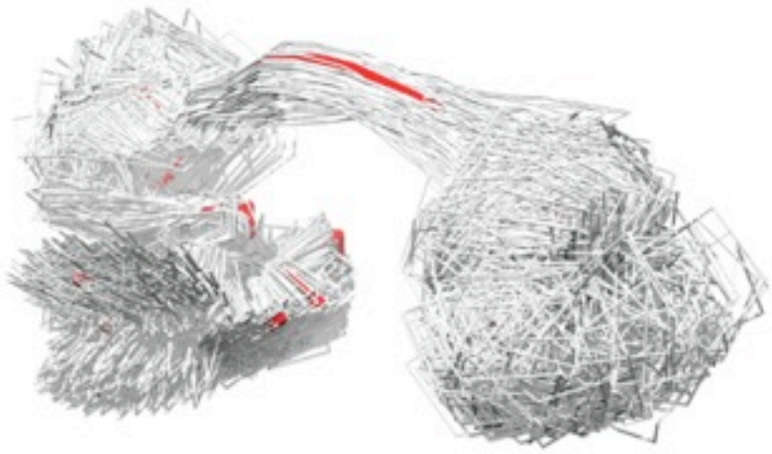


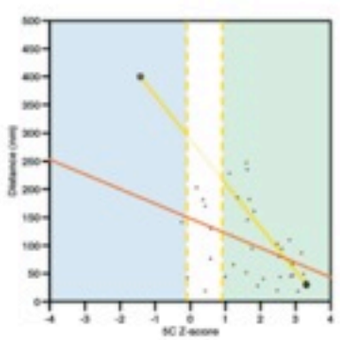
Grow GM12878 and K562 cells

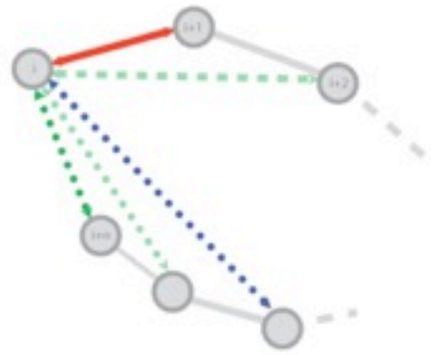
Perform 3C analysis

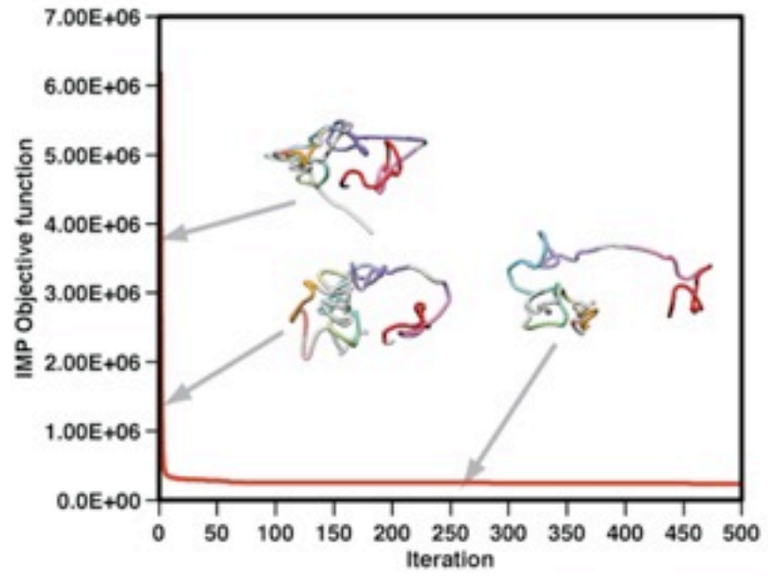
Perform 5C analysis with 30+25 primers

Analyze 5C products by paired-end Solexa sequencing
(131,947 paired end reads per library)





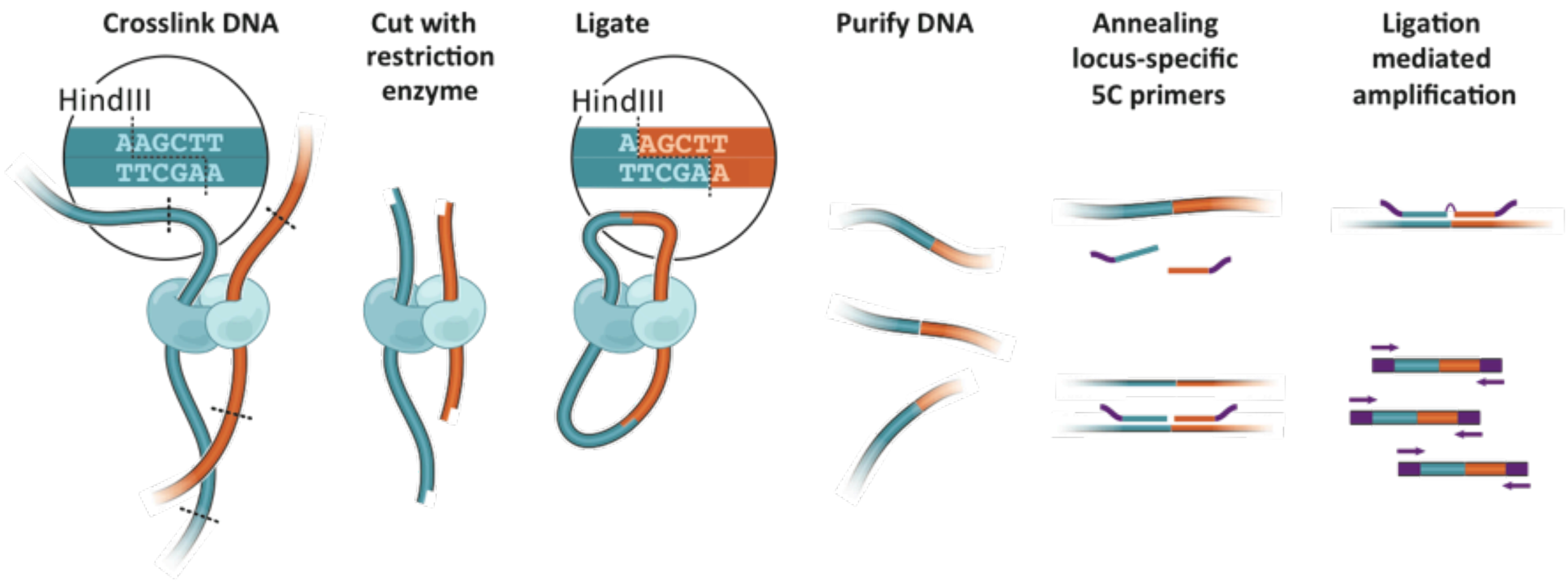




Computation

5C technology

http://my5C.umassmed.edu



Dostie et al. Genome Res (2006) vol. 16 (10) pp. 1299-309

Integrative Modeling

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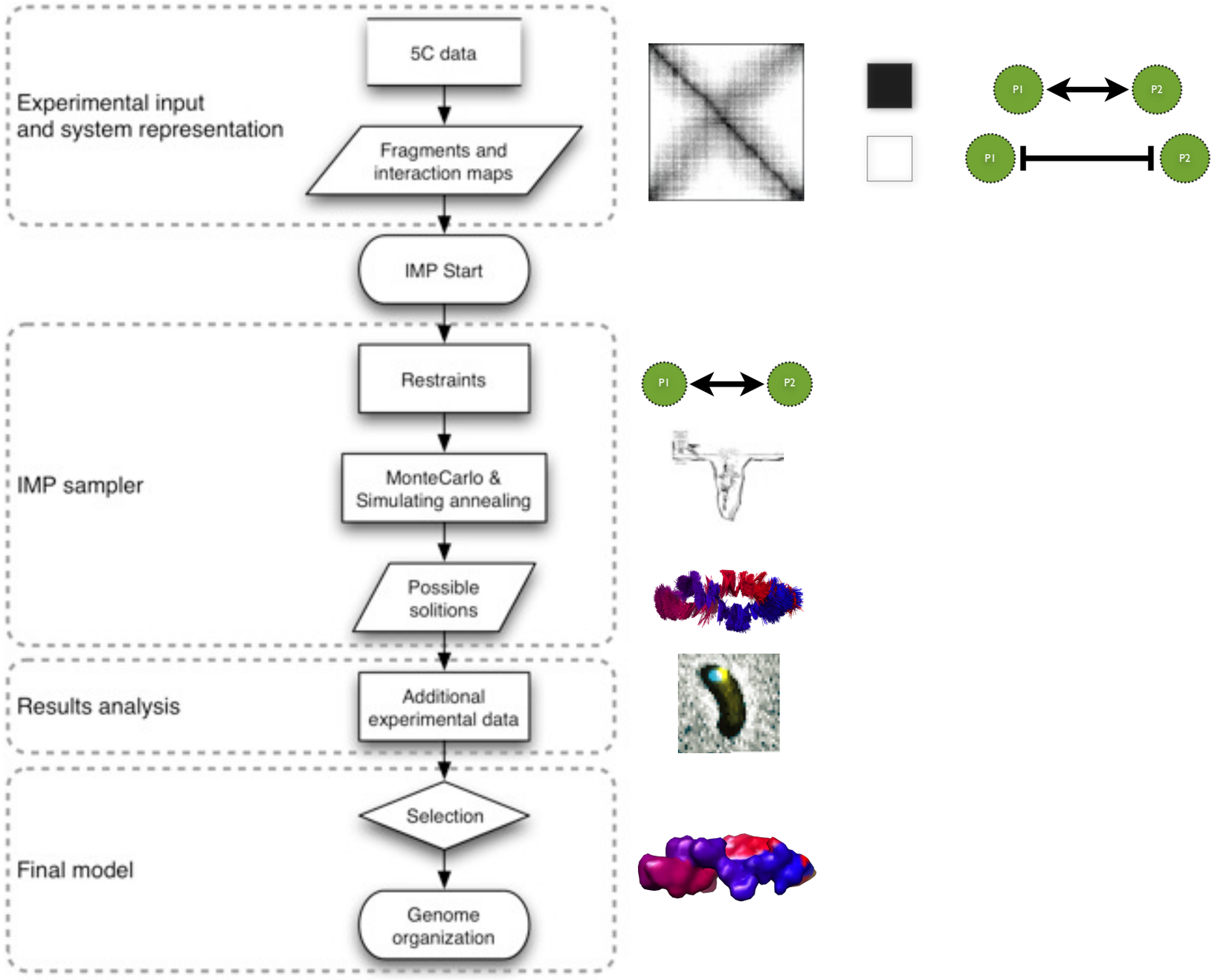
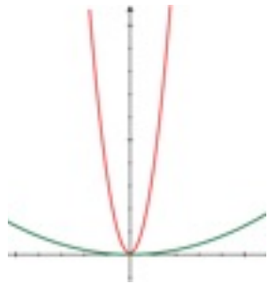


Representation & Scoring

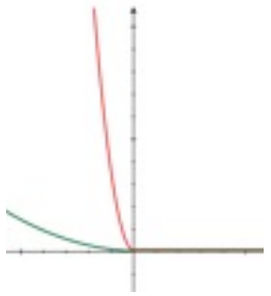
Harmonic

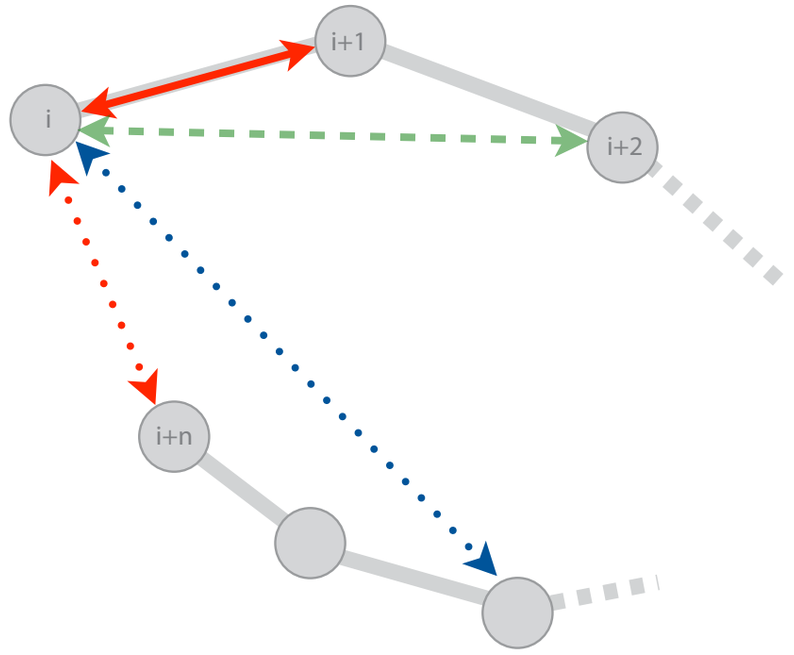
$$H_{i,j} = k\left(d_{i,j} - d^0_{i,j}\right)^2$$



Harmonic Lower Bound

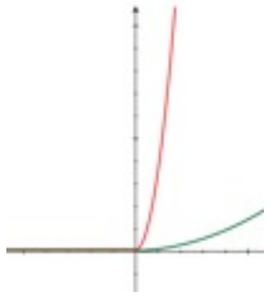
$$\begin{cases} if\ \ d_{i,j} \le d^0_{i,j}; & lbH_{i,j} = k\left(d_{i,j} - d^0_{i,j}\right)^2 \\ if\ \ d_{i,j} > d^0_{i,j}; & lbH_{i,j} = 0 \end{cases}$$





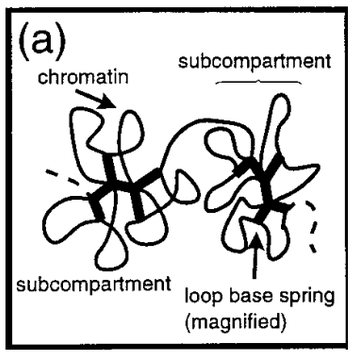
Harmonic Upper Bound

$$\begin{cases} if\ \ d_{i,j} \ge d^0_{i,j}; & ubH_{i,j} = k\left(d_{i,j} - d^0_{i,j}\right)^2 \\ if\ \ d_{i,j} < d^0_{i,j}; & ubH_{i,j} = 0 \end{cases}$$

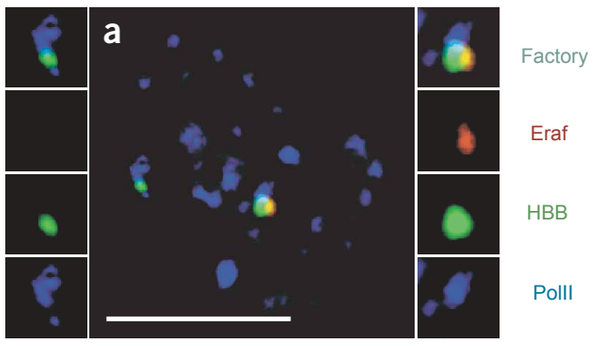


The "Chromatin Globule" model

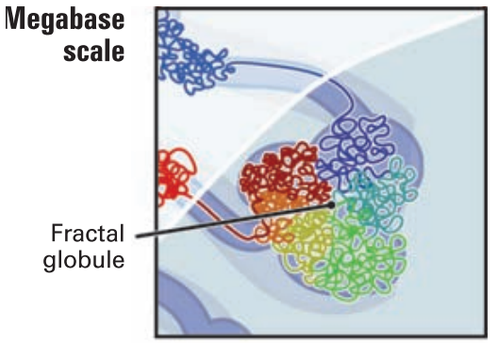
D. Baù et al. Nat Struct Mol Biol (2011) 18:107-14
A. Sanyal et al. Current Opinion in Cell Biology (2011) 23:325–33.



Münkel et al. JMB (1999)



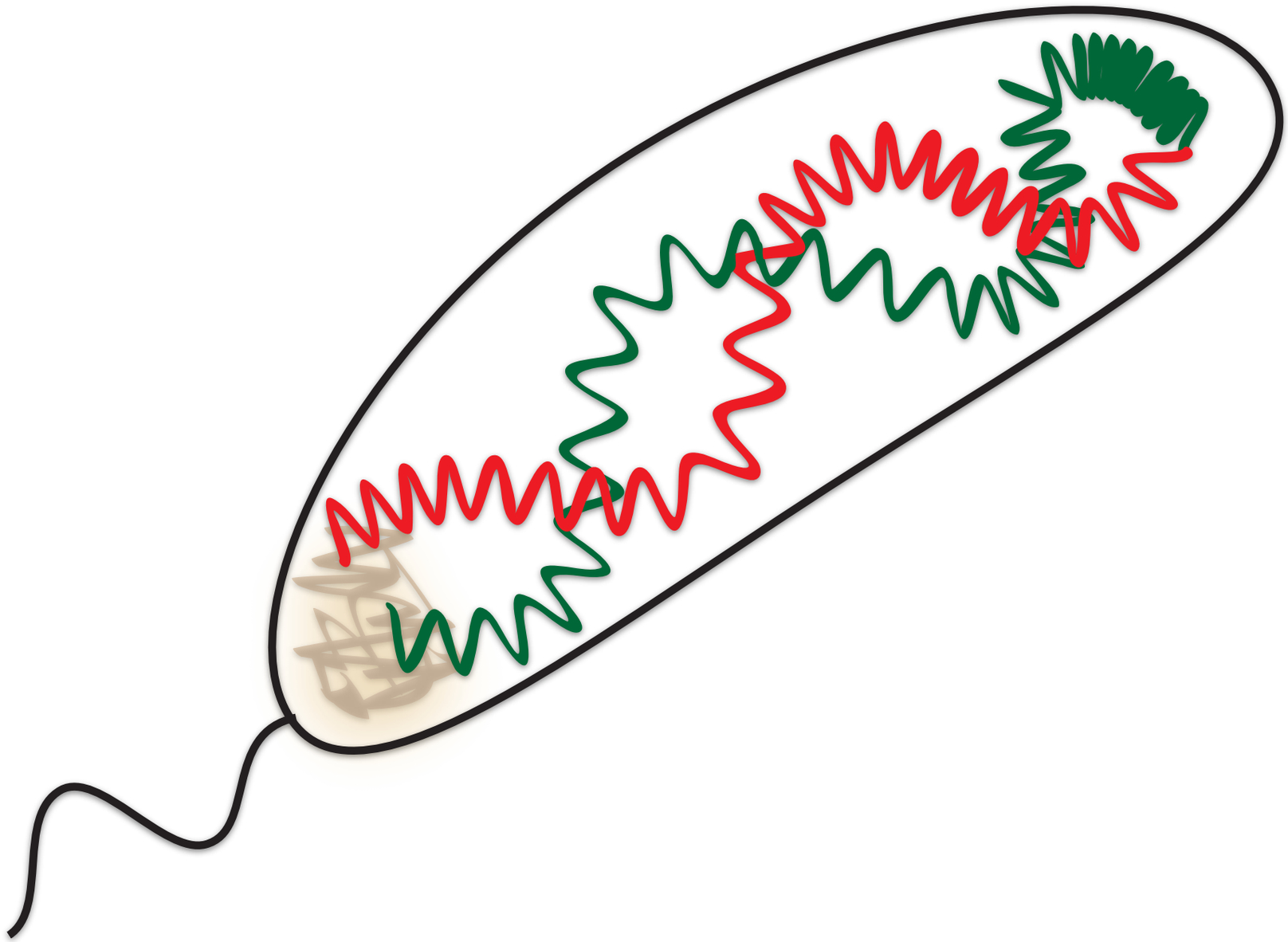
Osborne et al. Nat Genet (2004)



Lieberman-Aiden et al. Science (2009)

Caulobacter crescentus 3D genome

M.A. Umbarger, et al. Molecular Cell (2011) 44:252–264



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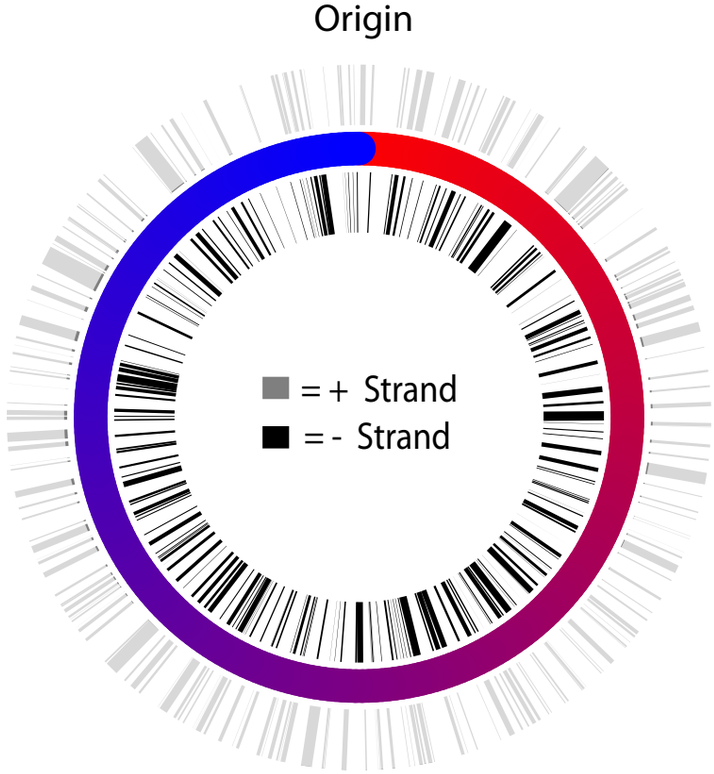
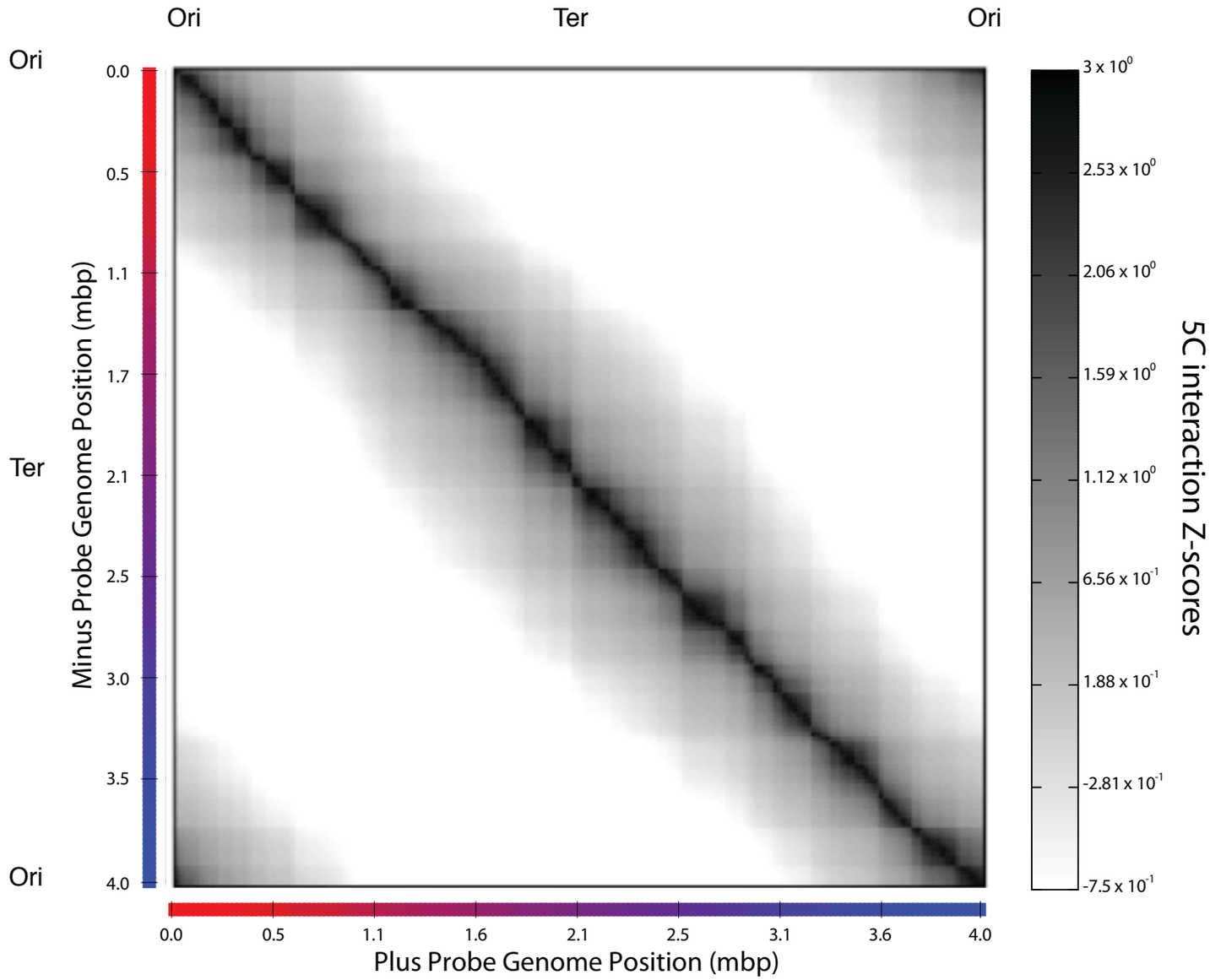
The 3D architecture of Caulobacter Crescentus

4,016,942 bp & 3,767 genes





169 5C primers on + strand

170 5C primers on – strand

28,730 chromatin interactions

~13Kb

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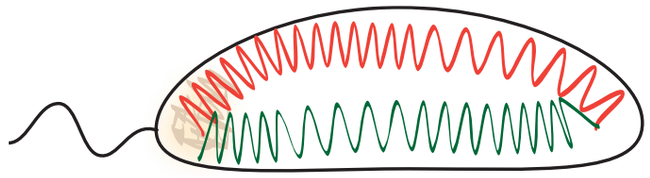
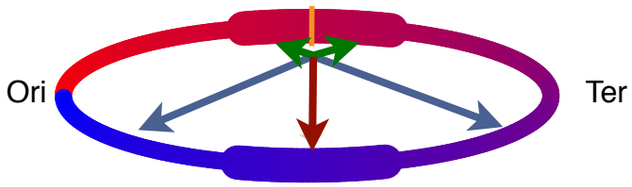
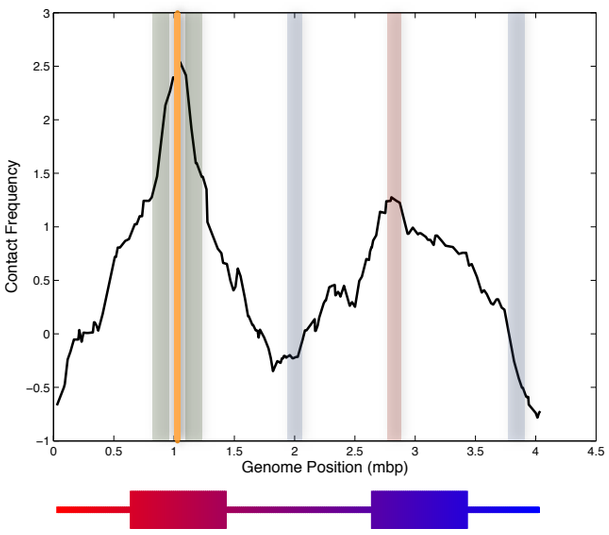
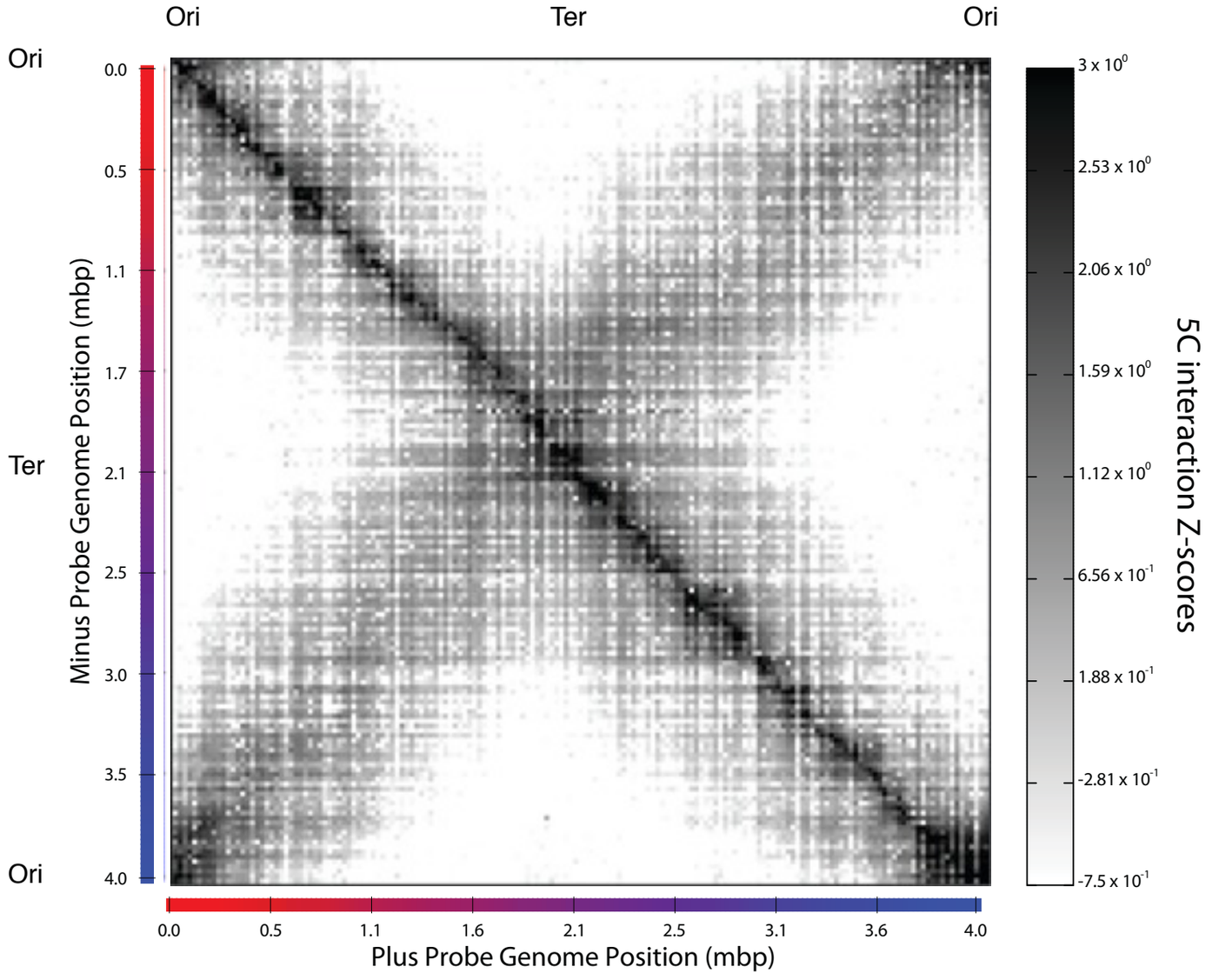
5C interaction matrix

ELLIPSOID for Caulobacter cresentus

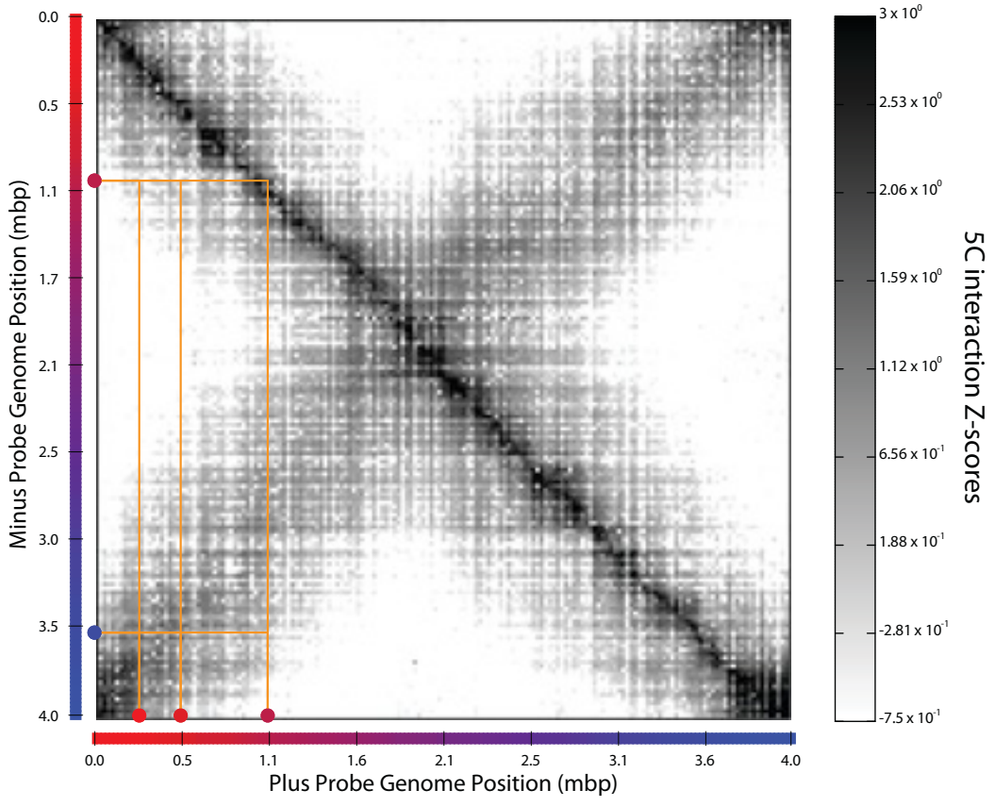




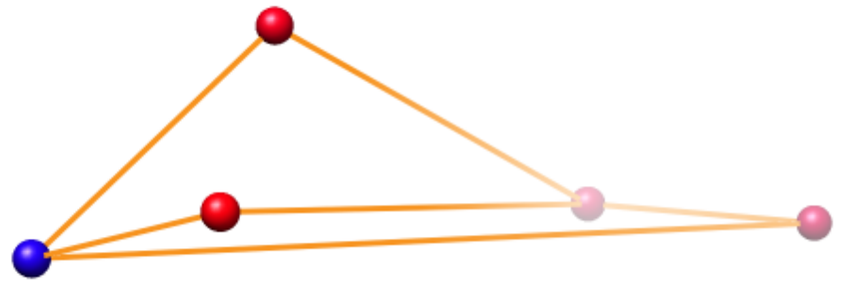


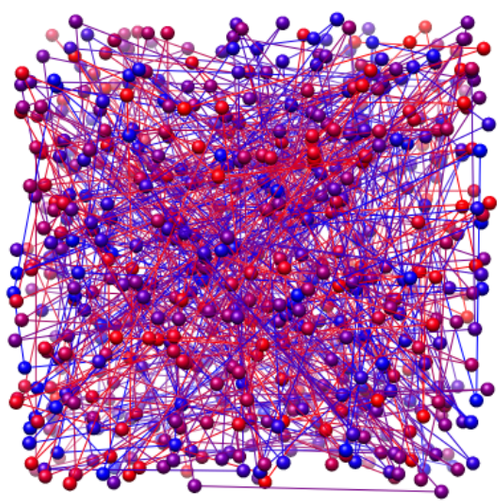


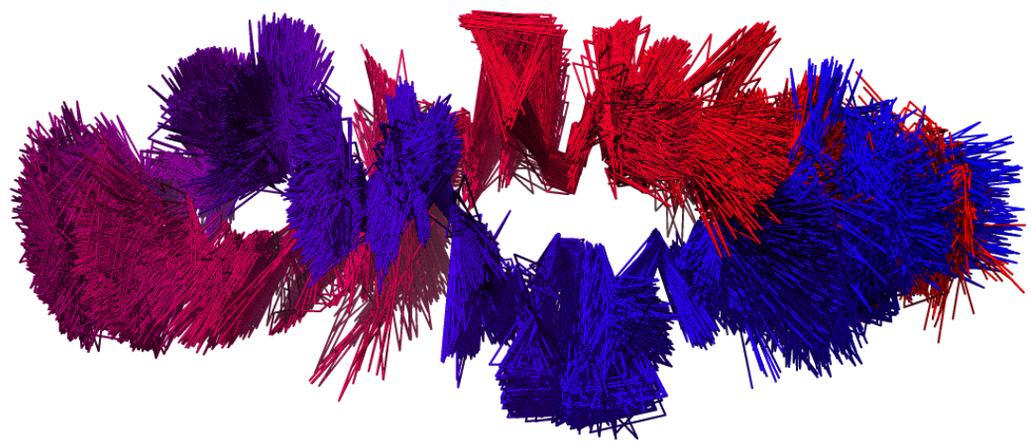
3D model building with the 5C + IMP approach



339 mers







Genome organization in Caulobacter crescentus

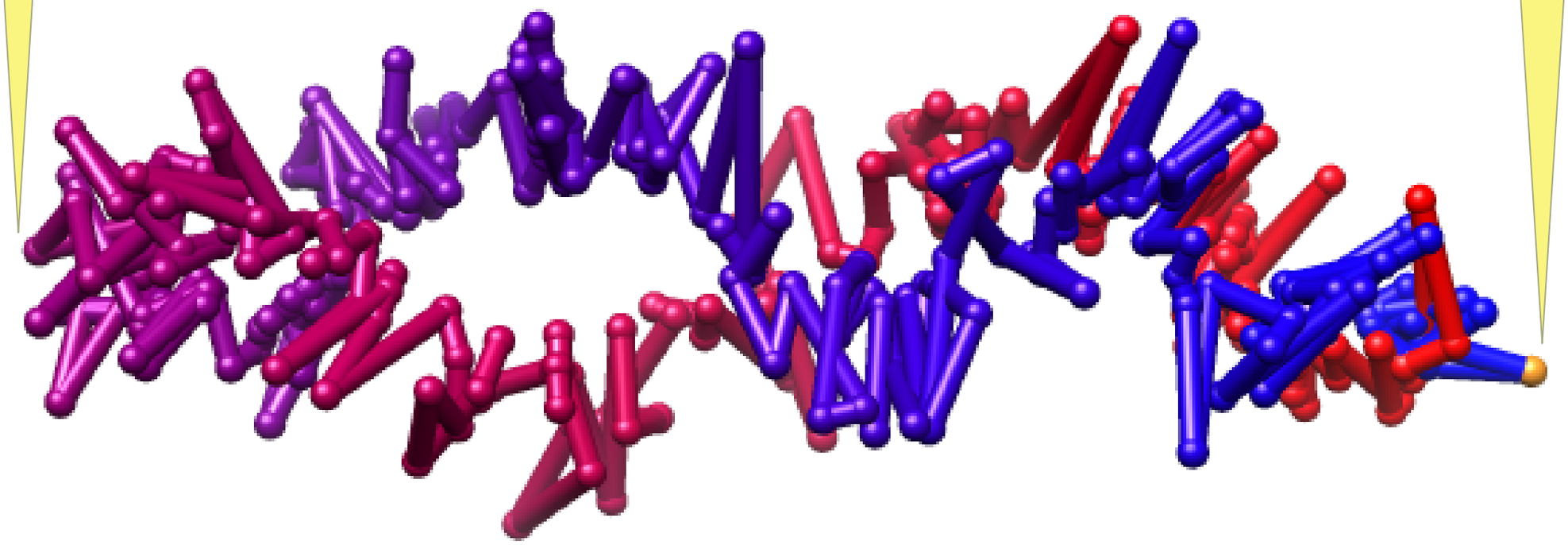
Arms are helical

dif site 47±17Kb from Ter

parS sites 25±17Kb from Ori

Resolution

Centromer-like



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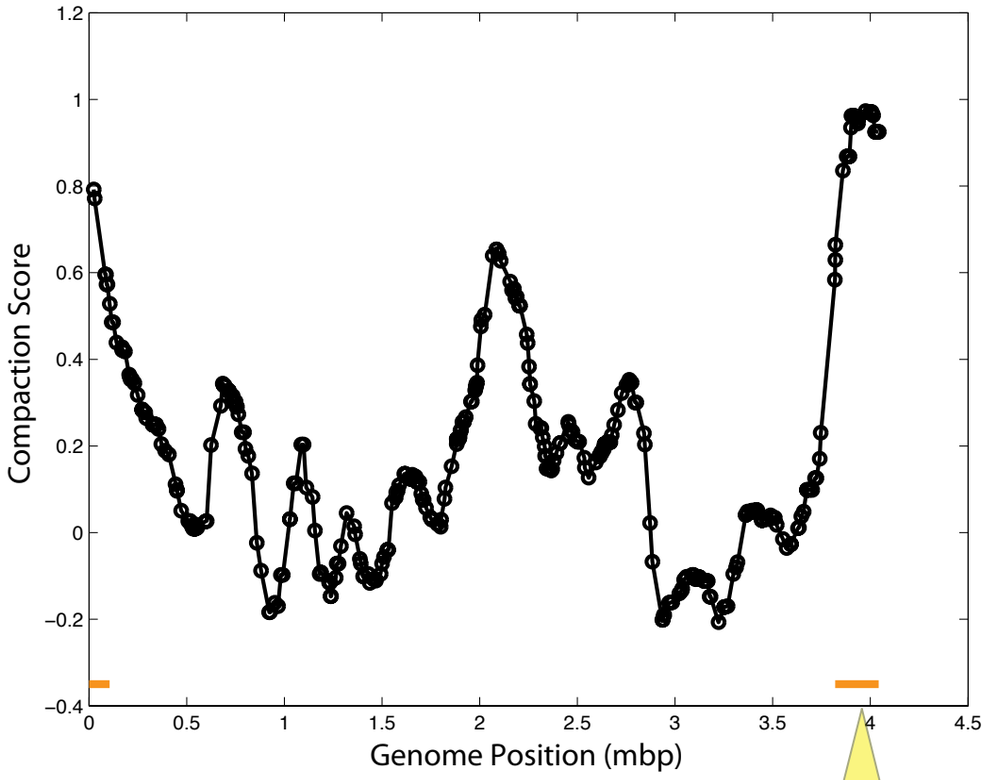
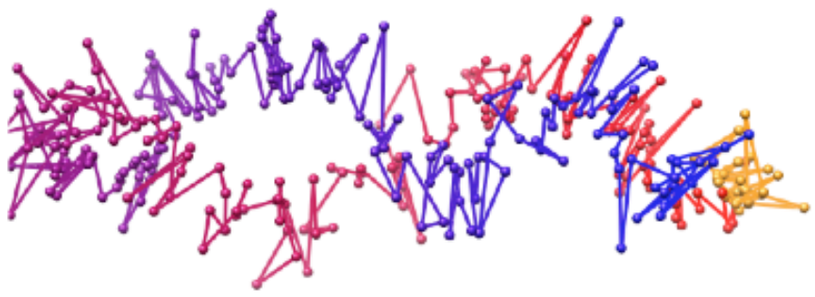
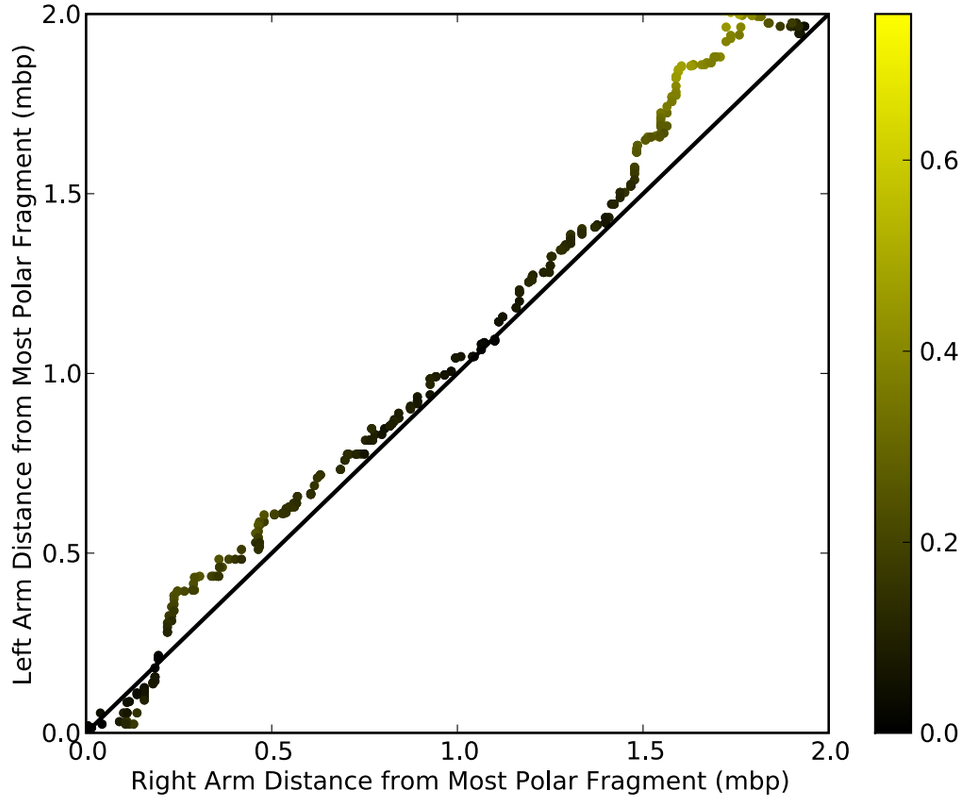
parS sites initiate compact chromatin domain

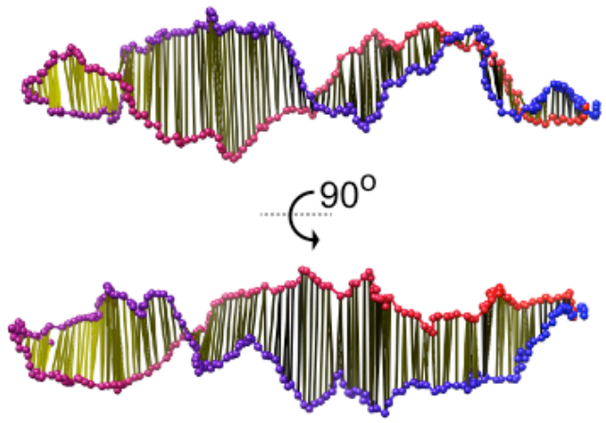


100-200Kb

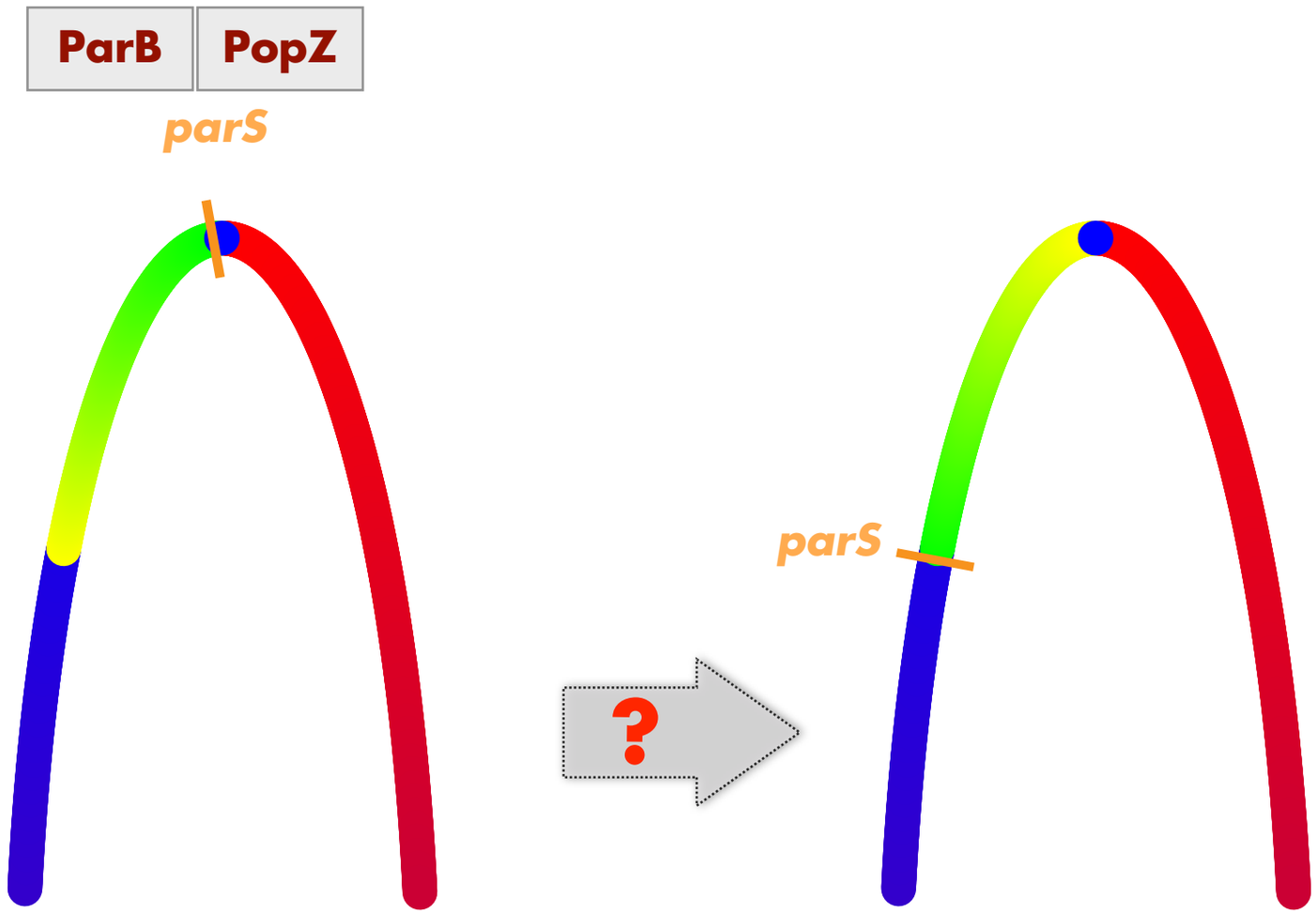


Chromosome arms are equidistant to the cell center





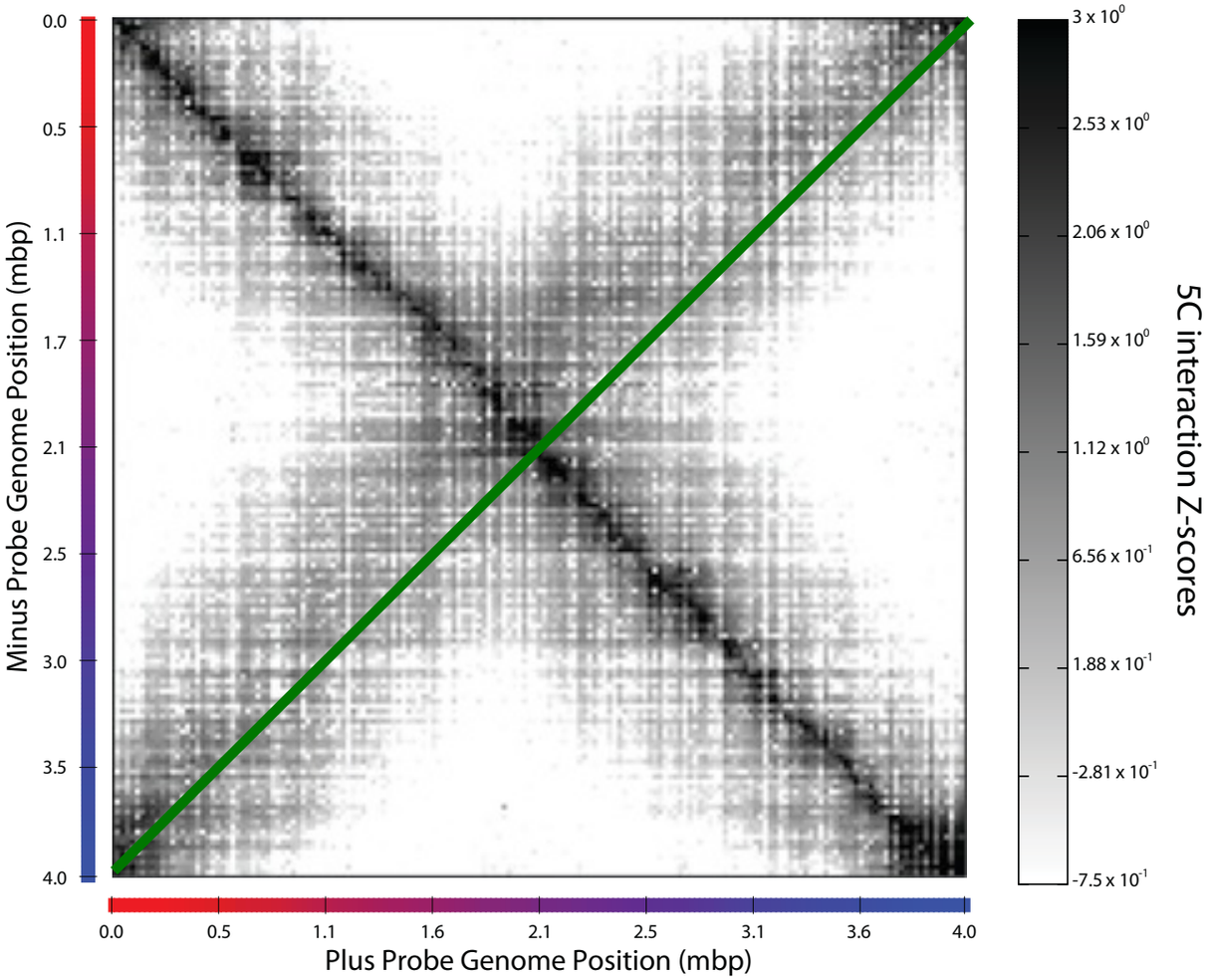
Moving the parS sites 400 Kb away from Ori

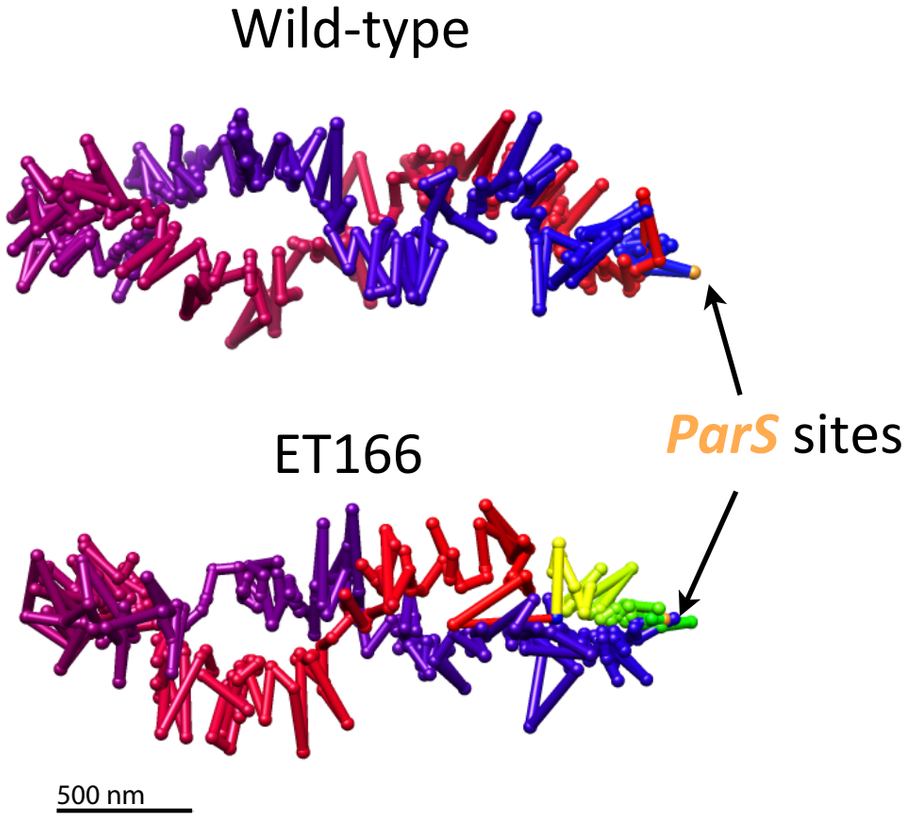


Wild-type

ET166

Moving the parS sites results in whole genome rotation!

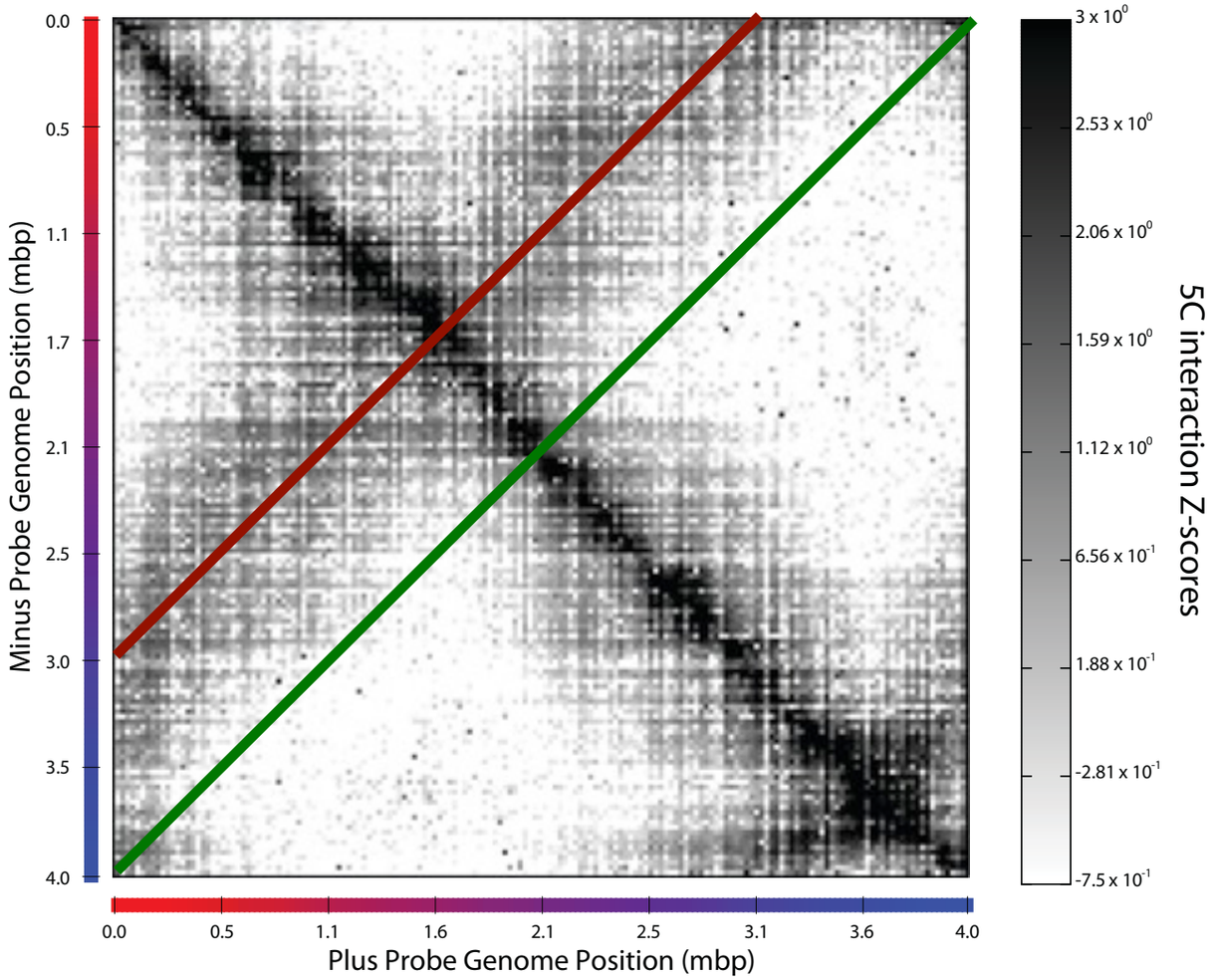


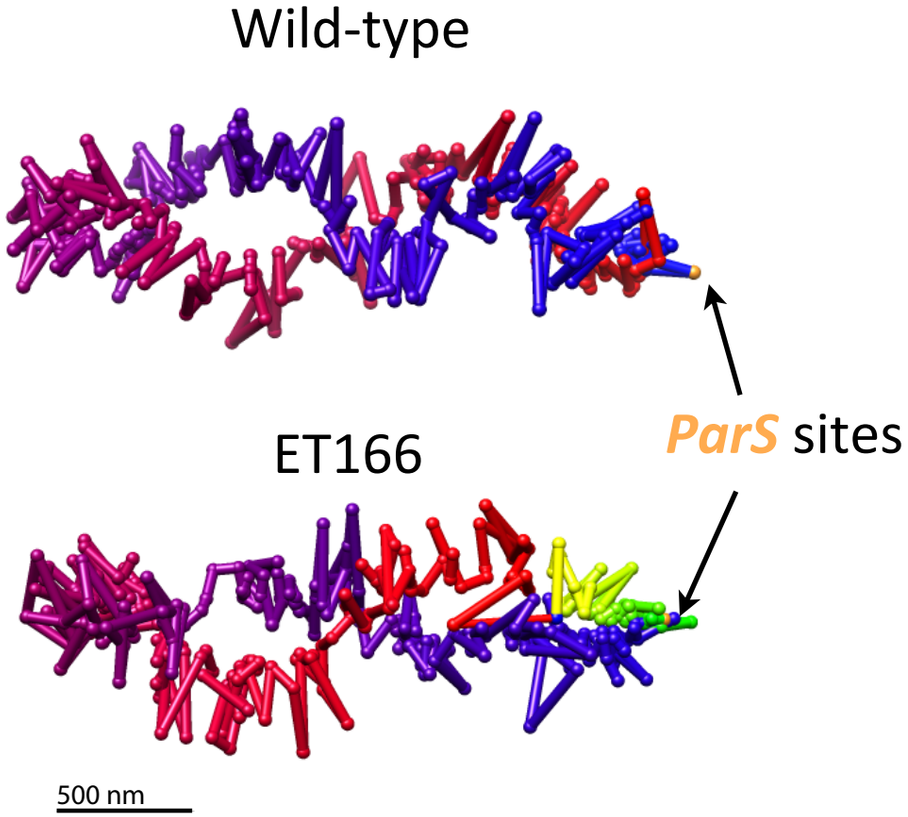


Arms are **STILL** helical

Structure & function PRESERVED!!!

Moving the parS sites results in whole genome rotation!



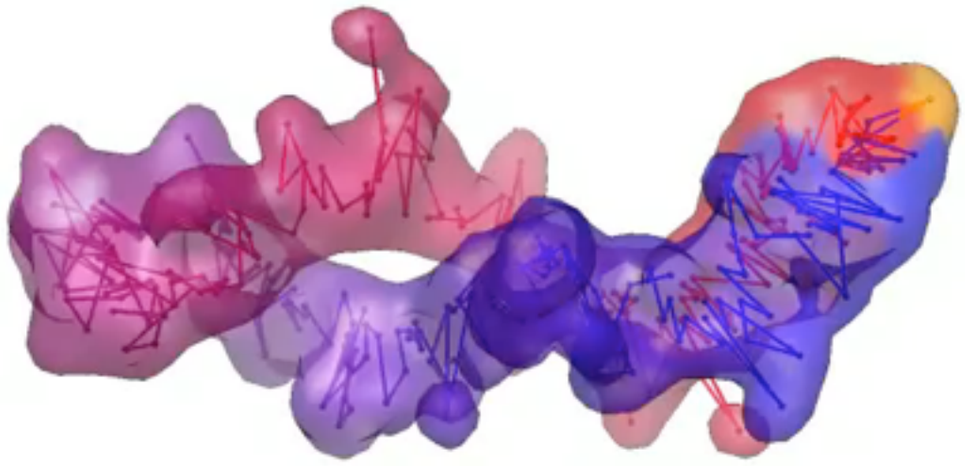


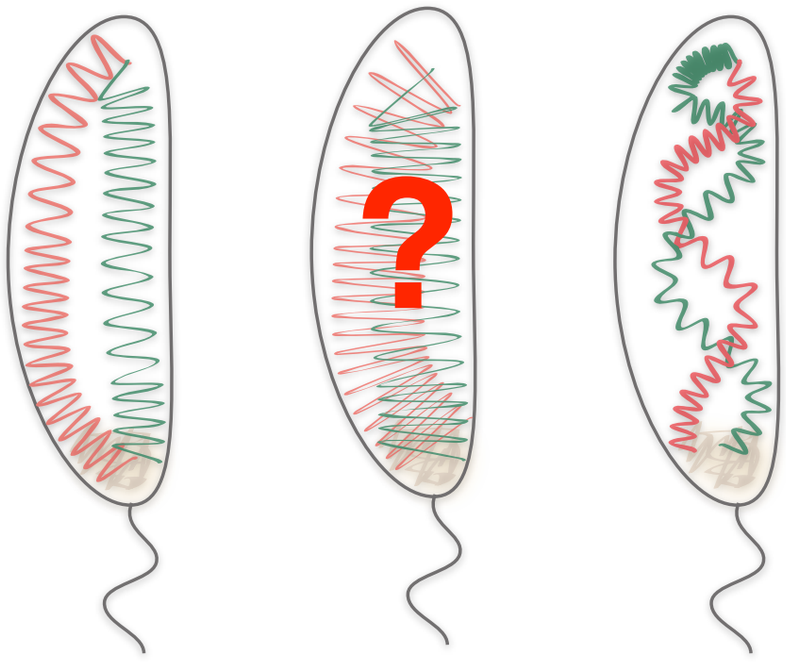
Arms are **STILL** helical

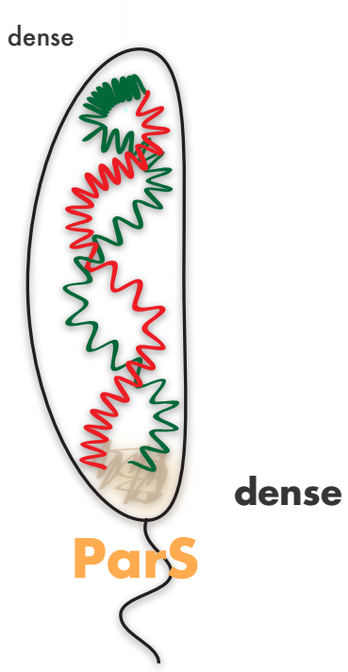
Structure & function PRESERVED!!!

Genome architecture in Caulobacter

M.A. Umbarger, et al. Molecular Cell (2011) 44:252–264







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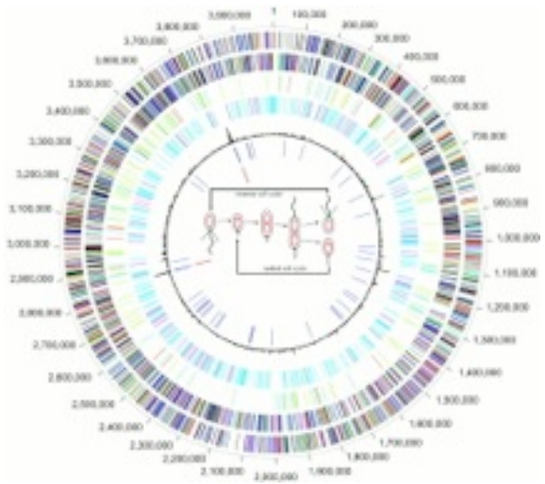
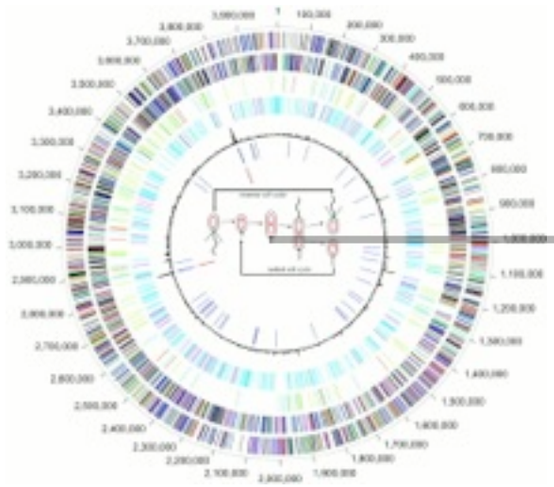
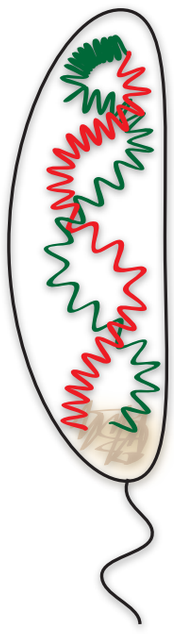
From Sequence to Function

D. Baù and M.A. Marti-Renom Chromosome Res (2011) 19:25-35.



Function!





Function!

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Review

Bridging the Resolution Gap in Structural Modeling of 3D Genome Organization

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Abstract: Over the last decade, and especially after the advent of fluorescent *in situ* hybridization imaging and chromosome conformation capture methods, the availability of experimental data on genome three-dimensional organization has dramatically increased. We now have access to unprecedented details of how genomes organize within the interphase nucleus. Development of new computational approaches to leverage this data has already resulted in the first three-dimensional structures of genomic domains and genomes. Such approaches expand our knowledge of the chromatin folding principles, which has been classically studied using polymer physics and molecular simulations. Our outlook describes computational approaches for integrating experimental data with polymer physics, thereby bridging the resolution gap for structural determination of genomes and genomic domains.

This is an "Editors' Outlook" article for *PLoS Computational Biology*

Recent experimental and computational advances are resulting in an increasingly accurate and detailed characterization of how genomes are organized in the three-dimensional (3D) space of the nucleus (Figure 1) [1]. At the lowest level of chromatin organization, naked DNA is packed into nucleosomes, which forms the so-called chromatin fiber composed of DNA and proteins. However, this initial packing, which reduces the length of the DNA by about seven times, is not sufficient to explain the higher-order folding of chromosomes during interphase and metaphase. It is now accepted that chromosomes and genes are non-randomly and dynamically positioned in the cell nucleus during the interphase, which challenges the classical representation of genomes as linear static sequences. Moreover, compartmentalization, chromatin organization, and spatial location of genes are associated with gene expression and the functional status of the cell. Despite the importance of 3D genomic architecture, we have a limited understanding of the molecular mechanisms that determine the higher-order organization of genomes and its relation to function. Computational biology plays an important role in the plethora of new technologies aimed at addressing this knowledge gap [2]. Indeed, Thomas Cremer, a pioneer in studying nuclear organization using light microscopy, recently highlighted the importance of computational science in complementing and leveraging experimental observations of genome organization [2]. Therefore, computational approaches to integrate experimental observations with chromatin physics are needed to determine the architecture (3D) and dynamics (4D) of genomes.

We present two complementary approaches to address this challenge: (i) the first approach aims at developing simple polymer models of chromatin and determining relevant interactions (both physical and biological) that explain experimental observations; (ii) the second approach aims at integrating diverse experimental observations into a system of spatial restraints to be satisfied, thereby constraining possible structural models of the chromatin. The goal of both approaches is dual: to obtain most accurate 3D and 4D representation of chromatin architecture and to understand physical constraints and biological phenomena that determine its organization. These approaches are reminiscent of the protein-folding field where the first strategy was used for characterizing protein "foldability" and the second was implemented for modeling the structure of proteins using nuclear magnetic resonance and other experimental constraints. In fact, our outlook consistently returns to the many connections between the two fields.

What Does Technology Show Us?

Today, it is possible to quantitatively study structural features of genomes at diverse scales that range from a few specific loci, through chromosomes, to entire genomes (Table 1) [3]. Broadly, there are two main approaches for studying genomic organization: light microscopy and cell/molecular biology (Figure 2). Light microcopy [4], both with fixed and living cells, can provide images of a few loci within individual cells [5,6], as well as their dynamics as a function of time [7] and cell state [8]. On a larger scale, light microscopy combined with whole-chromosome staining reveals chromosomal territories during interphase and their reorganization upon cell division. Immunofluorescence with fluorescent antibodies in combination with RNA, and DNA fluorescence *in situ* hybridization (FISH) has been used to determine the co-localization of loci and nuclear substructures.

Using cellular and molecular biology, novel chromosome conformation capture (3C)-based methods such 3C [9], 3C-on-chip or circular 3C (the so-called 4C) [10,11], 3C carbon copy (5C) [12], and Hi-C [13] quantitatively measure frequencies of spatial contacts between genomic loci averaged over a large

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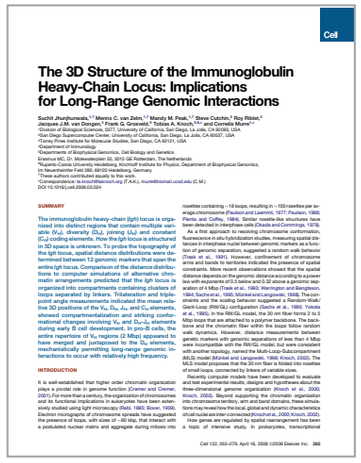

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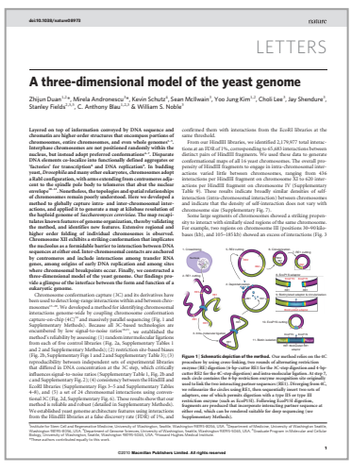

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