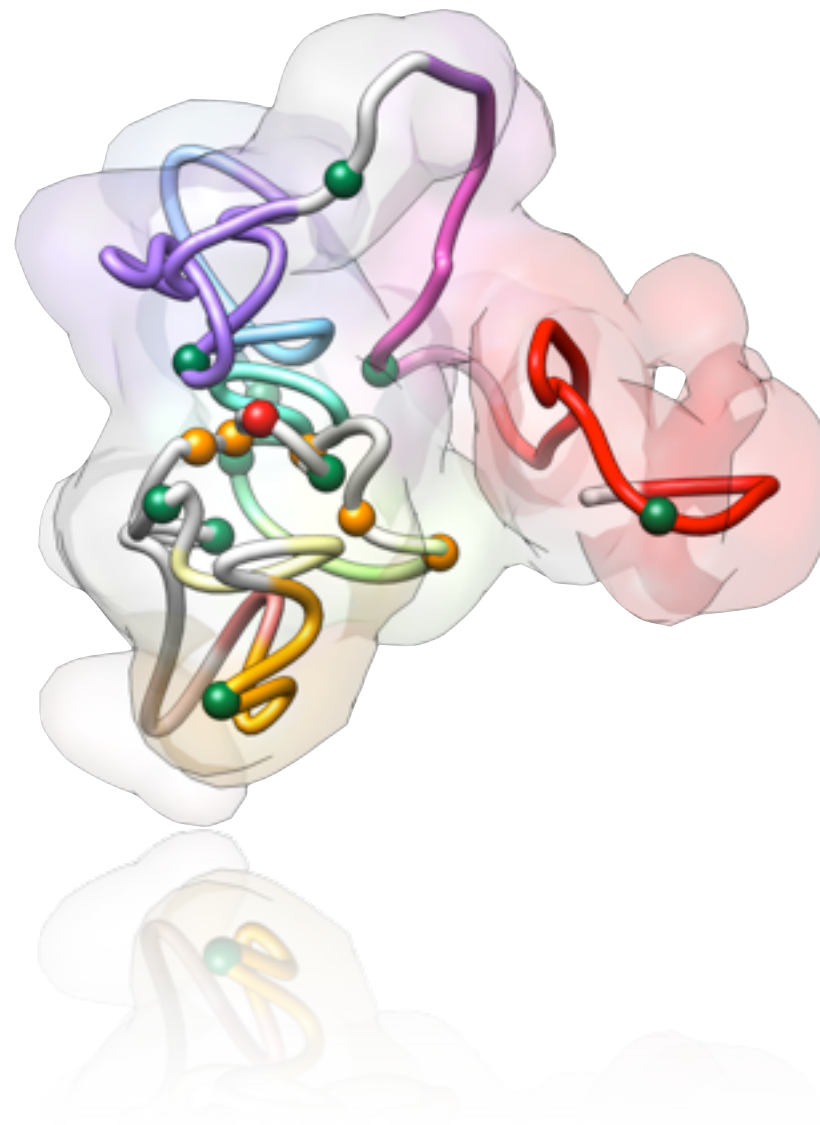
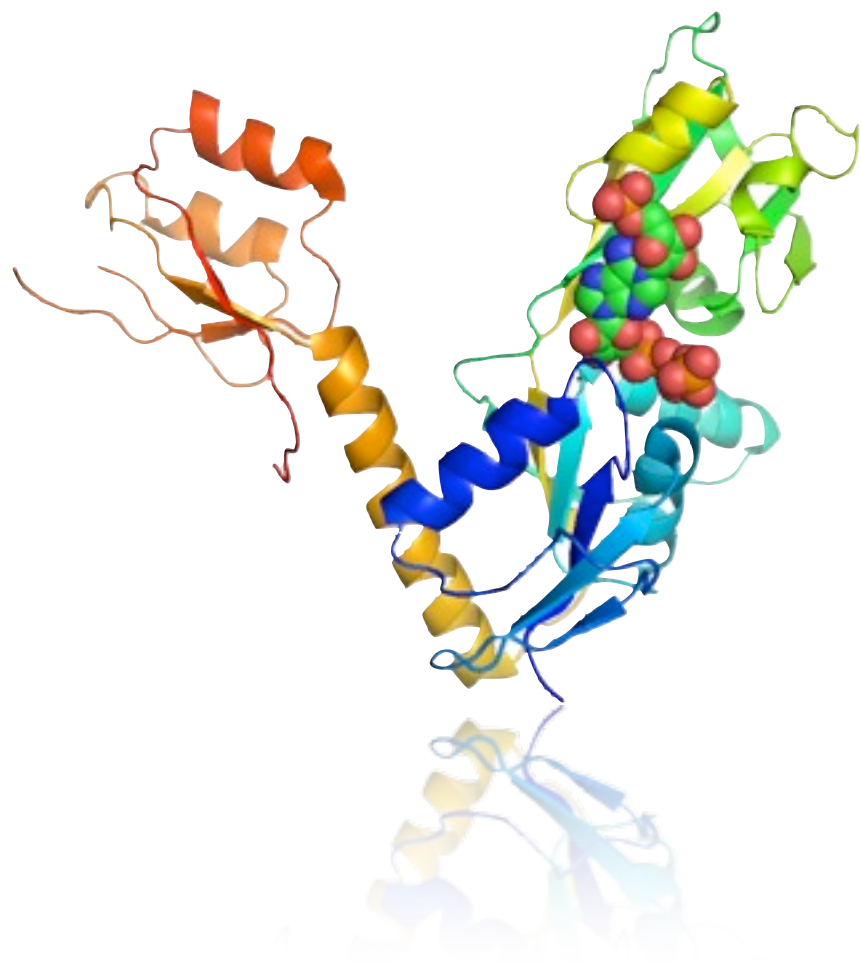


Structure determination of genomes and genomic domains by satisfaction of spatial restraints

Marc A. Marti-Renom

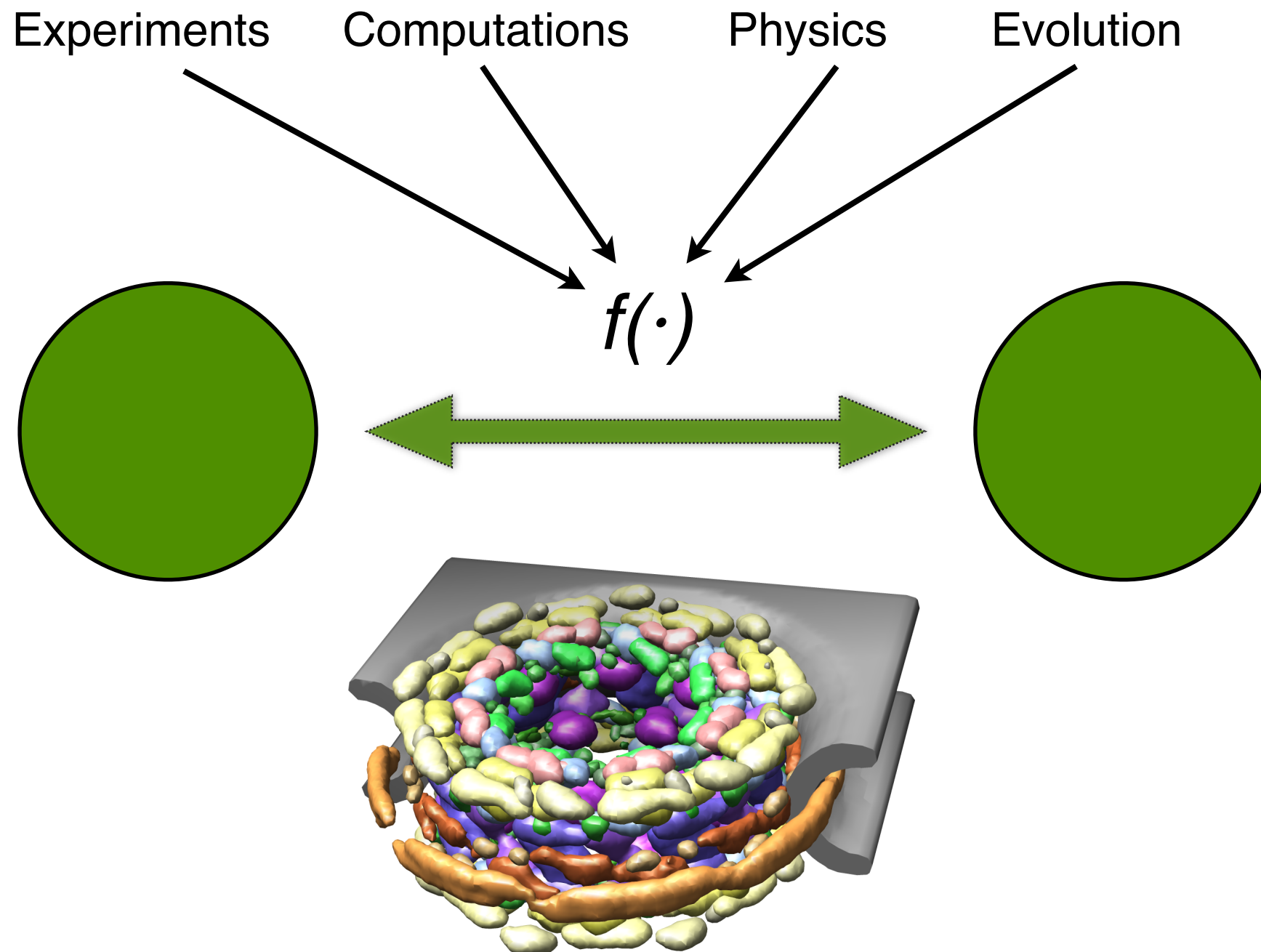
*Genome Biology Group (CNAG)
Structural Genomics Group (CRG)*

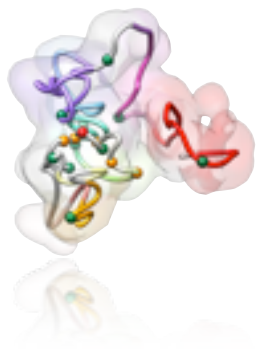


Integrative Modeling Platform

GENERALIZE software development

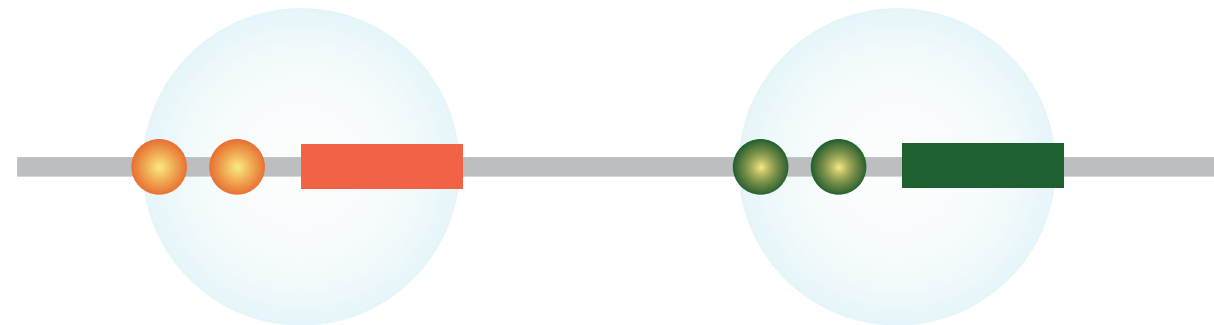
<http://www.integrativemodeling.org>



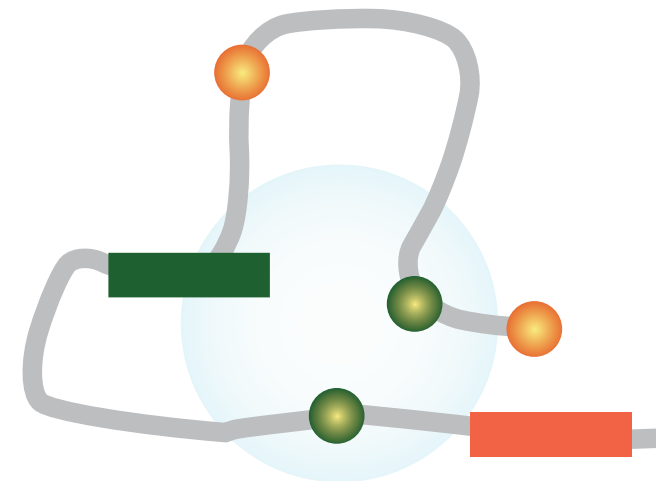
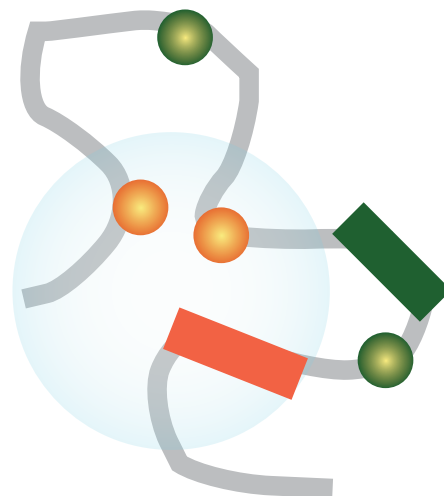


3D Genomics

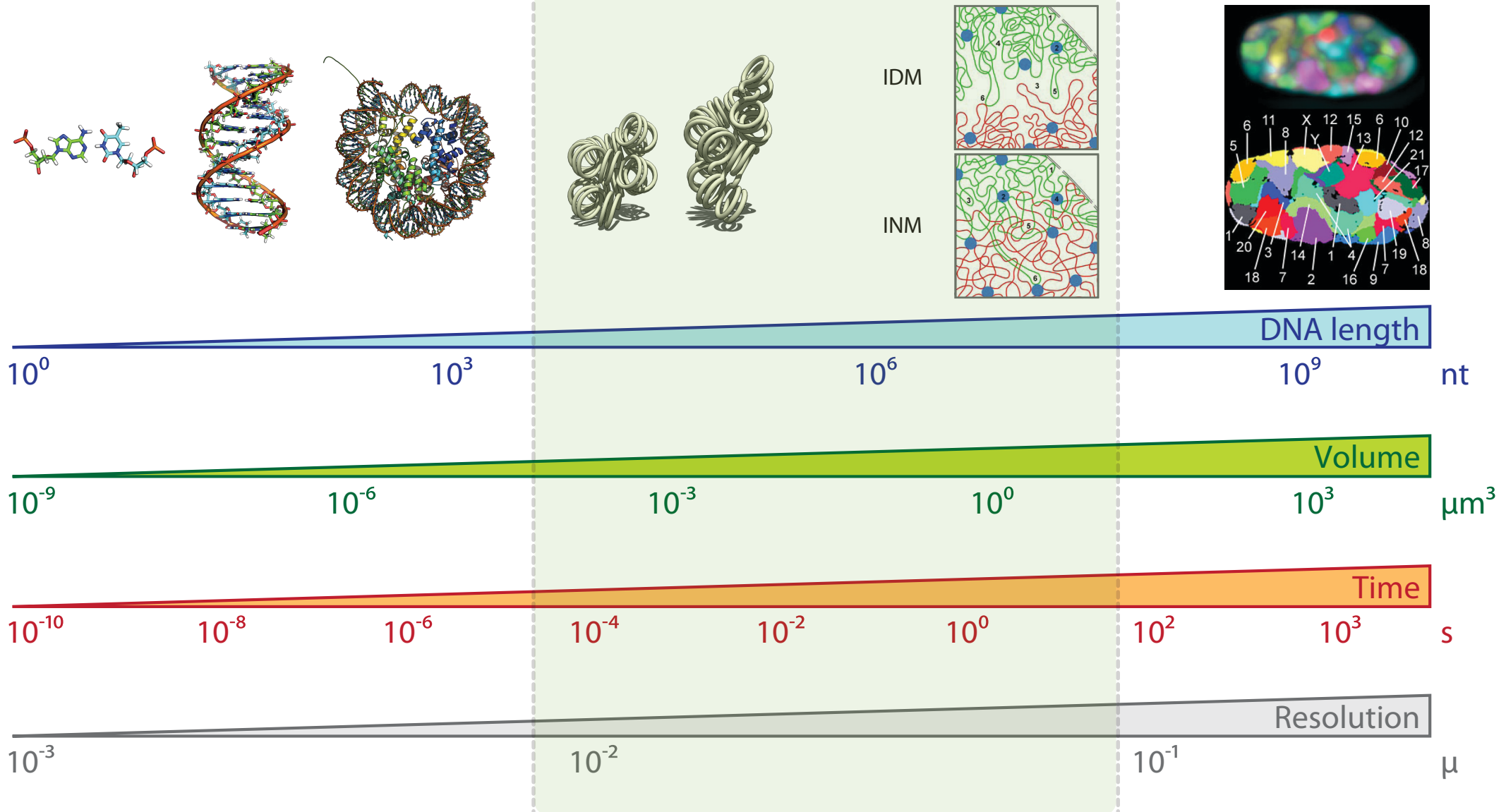
Simple genomes



Complex genomes

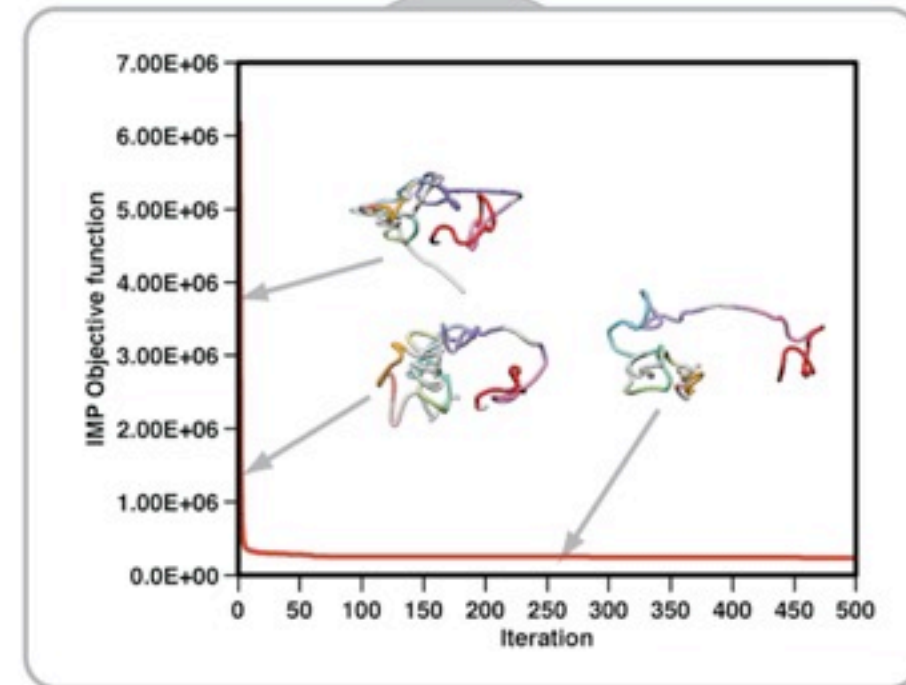
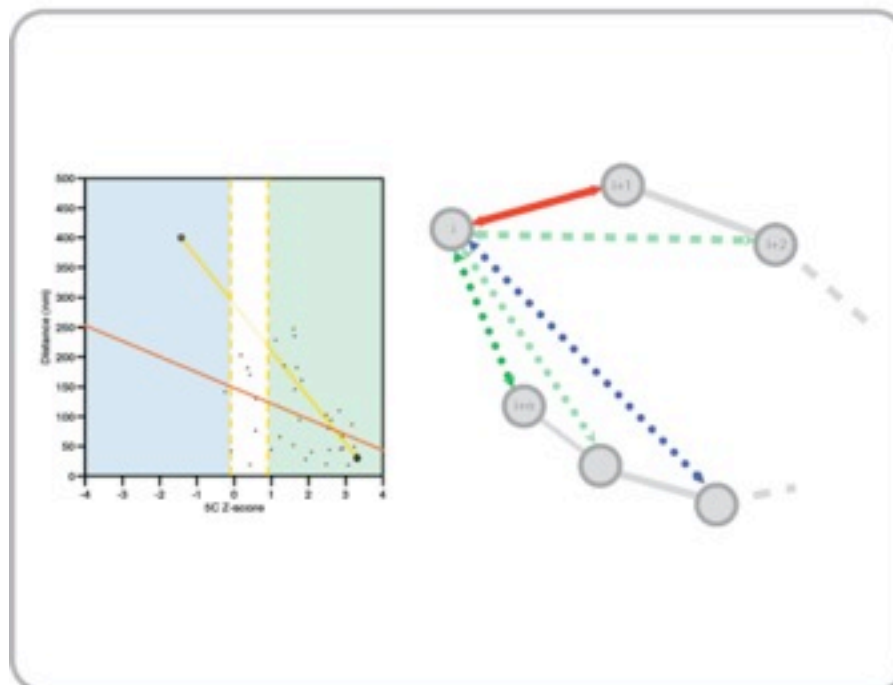
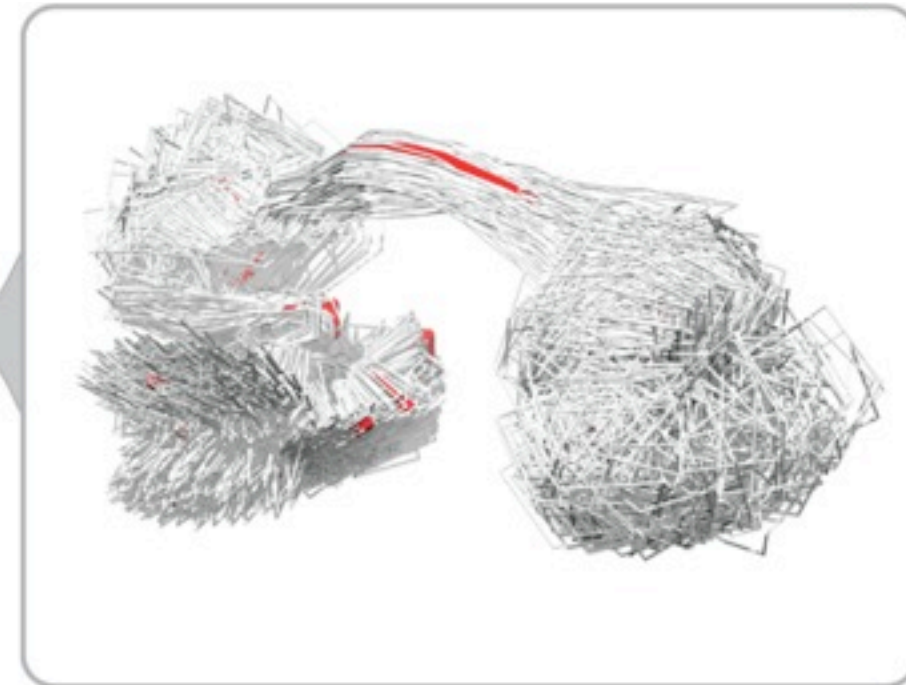
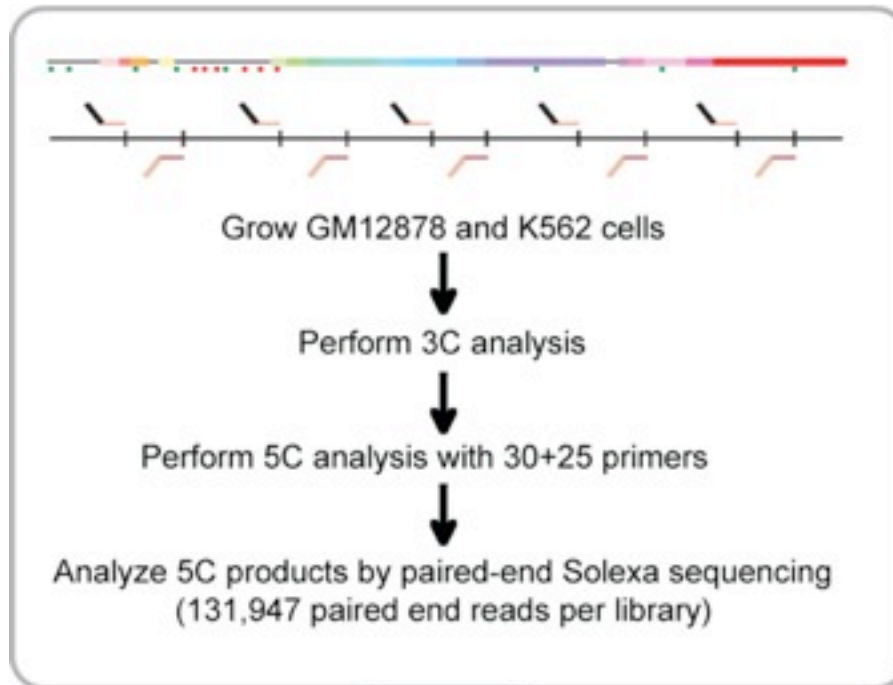


Knowledge

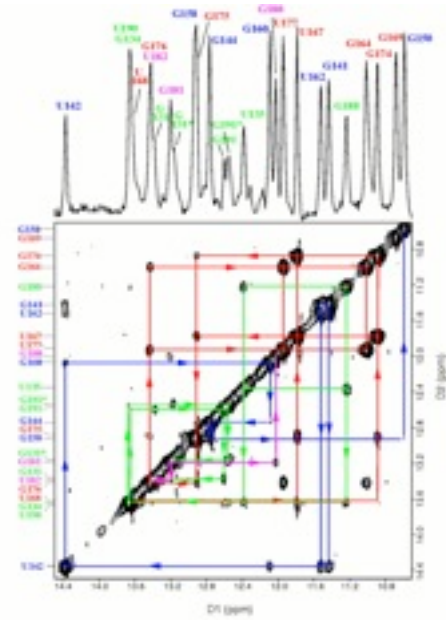
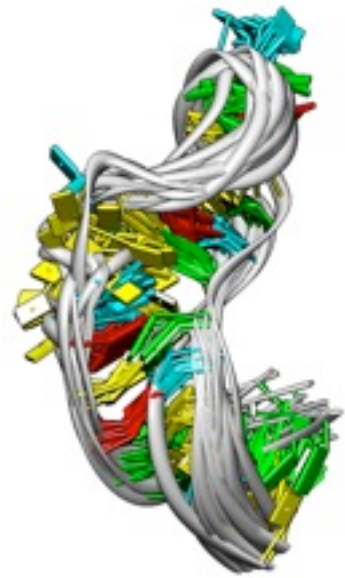


Adapted from:
Langowski and Heermann. *Semin Cell Dev Biol* (2007) vol. 18 (5) pp. 659-67

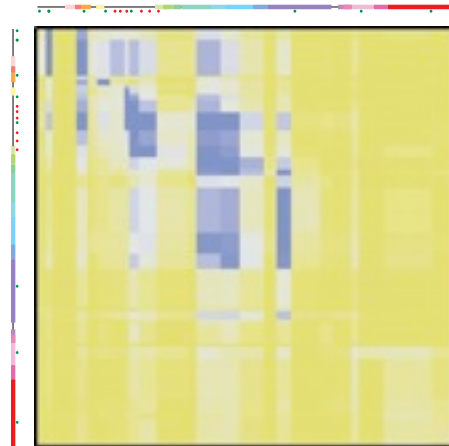
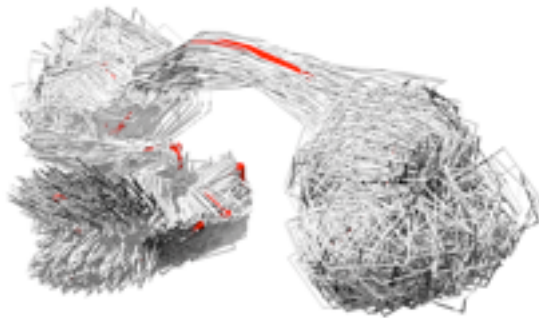
Experiments



Computation



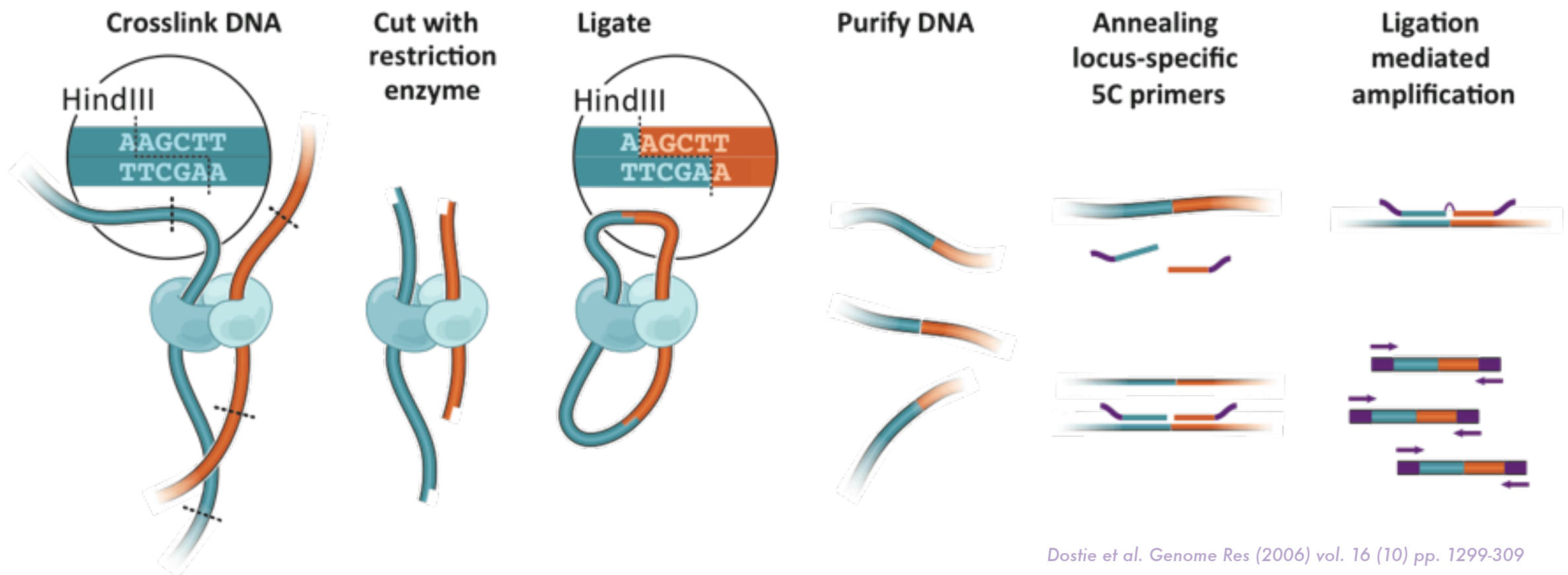
Biomolecular structure determination 2D-NOESY data



Chromosome structure determination 5C data

5C technology

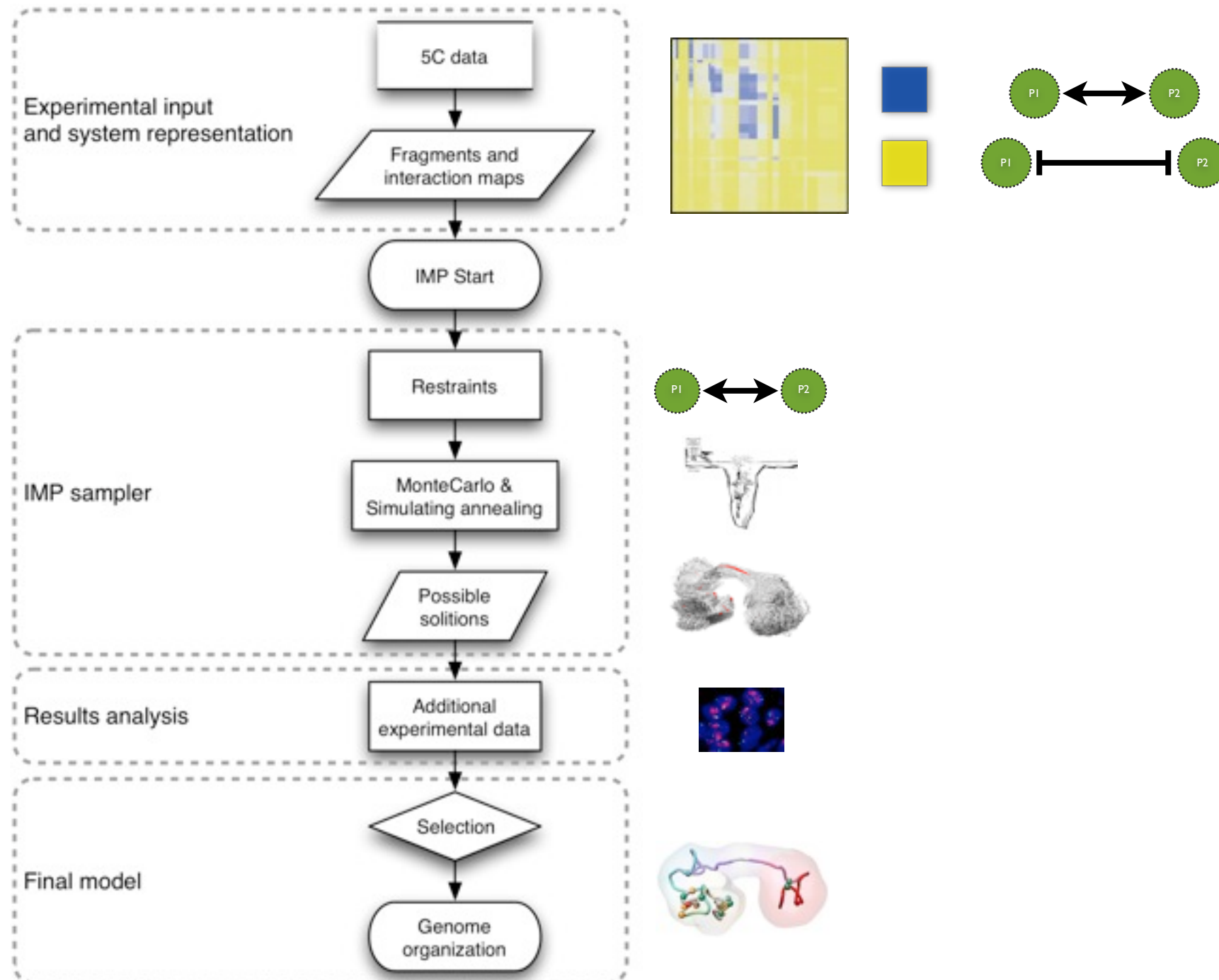
<http://my5C.umassmed.edu>



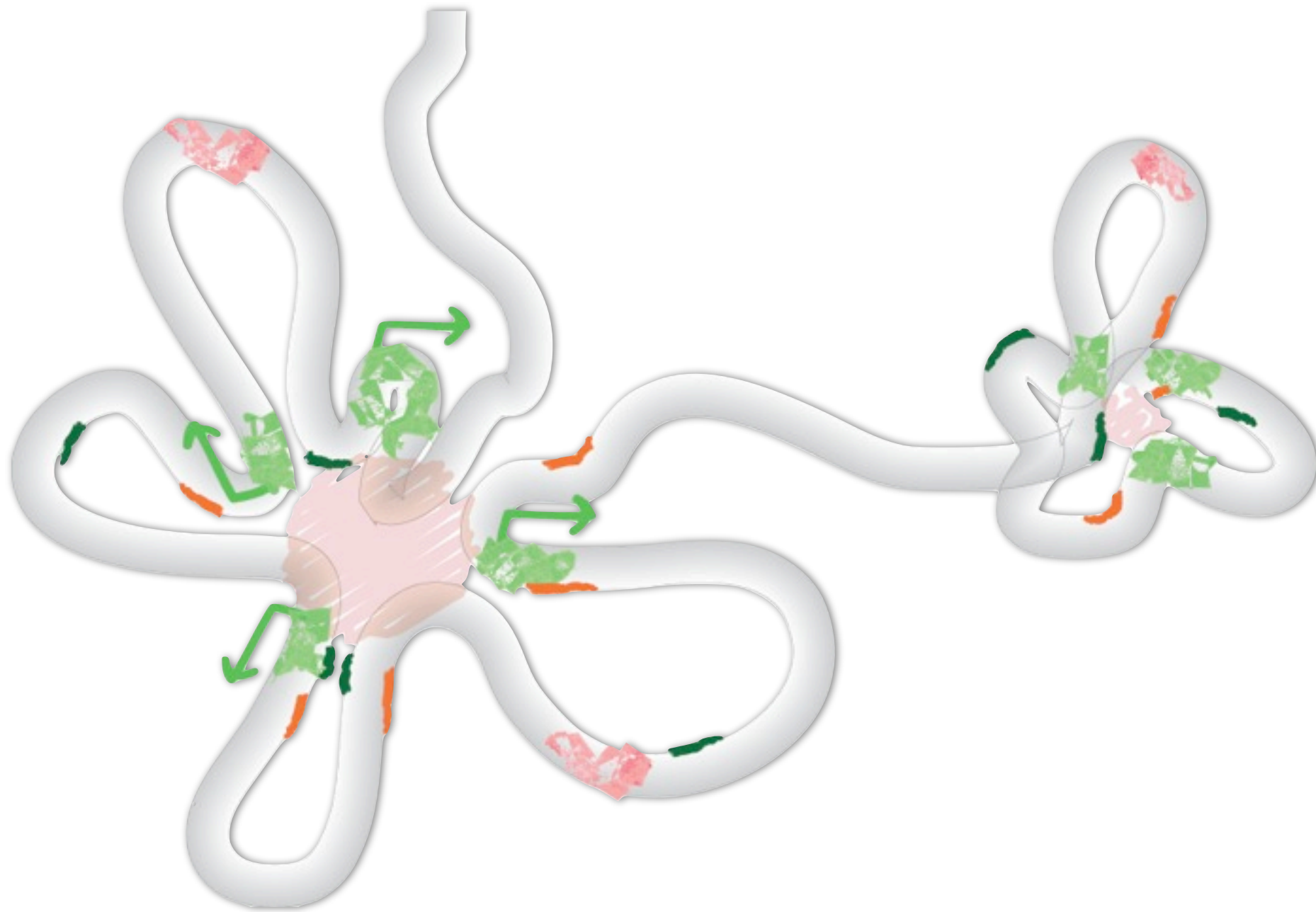
Dostie et al. Genome Res (2006) vol. 16 (10) pp. 1299-309

Integrative Modeling

<http://www.integrativemodeling.org>



Human α -globin domain



Human α -globin domain

ENm008 genomic structure and environment

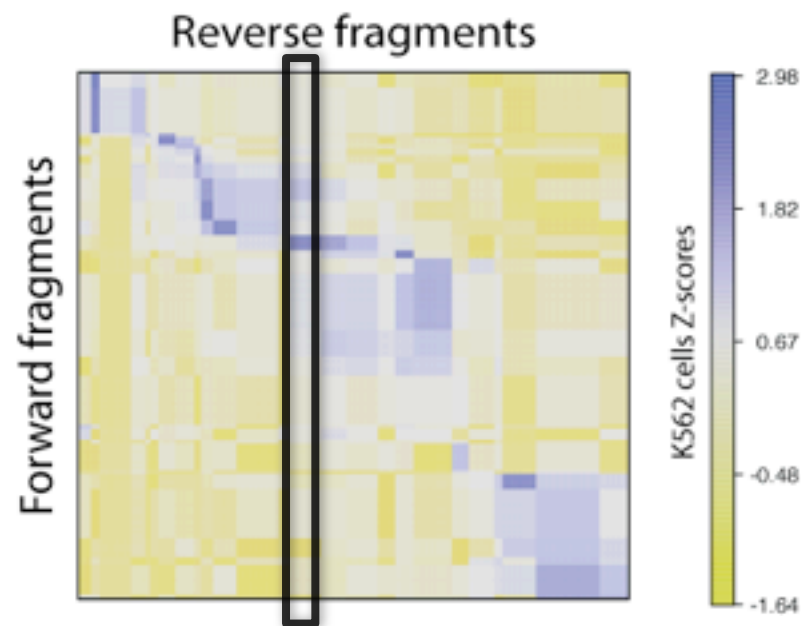
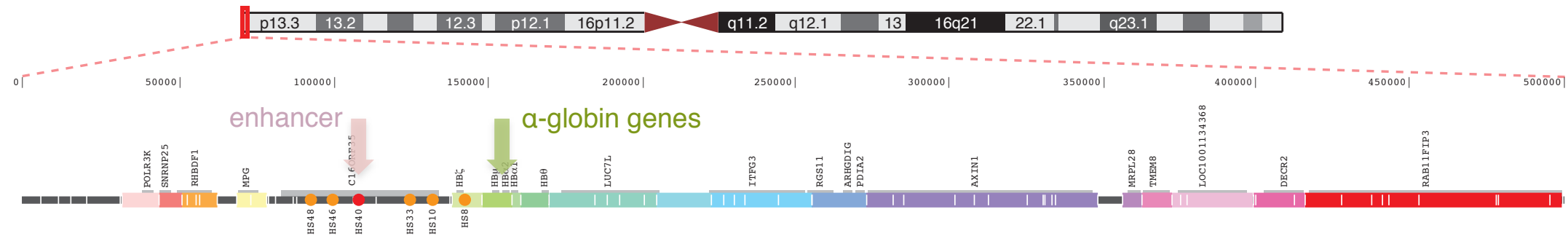


The ENCODE data for ENm008 region was obtained from the UCSC Genome Browser tracks for: RefSeq annotated genes, Affymetrix/CSHL expression data (Gingeras Group at Cold Spring Harbor), Duke/NHGRI DNaseI Hypersensitivity data (Crawford Group at Duke University), and Histone Modifications by Broad Institute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

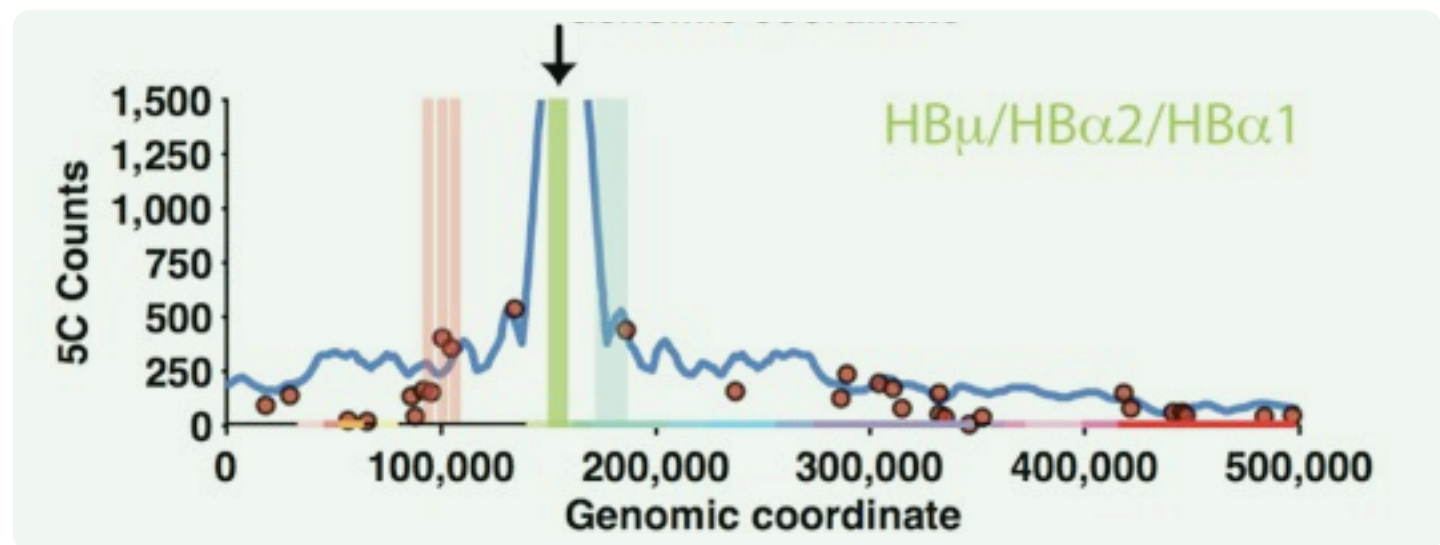
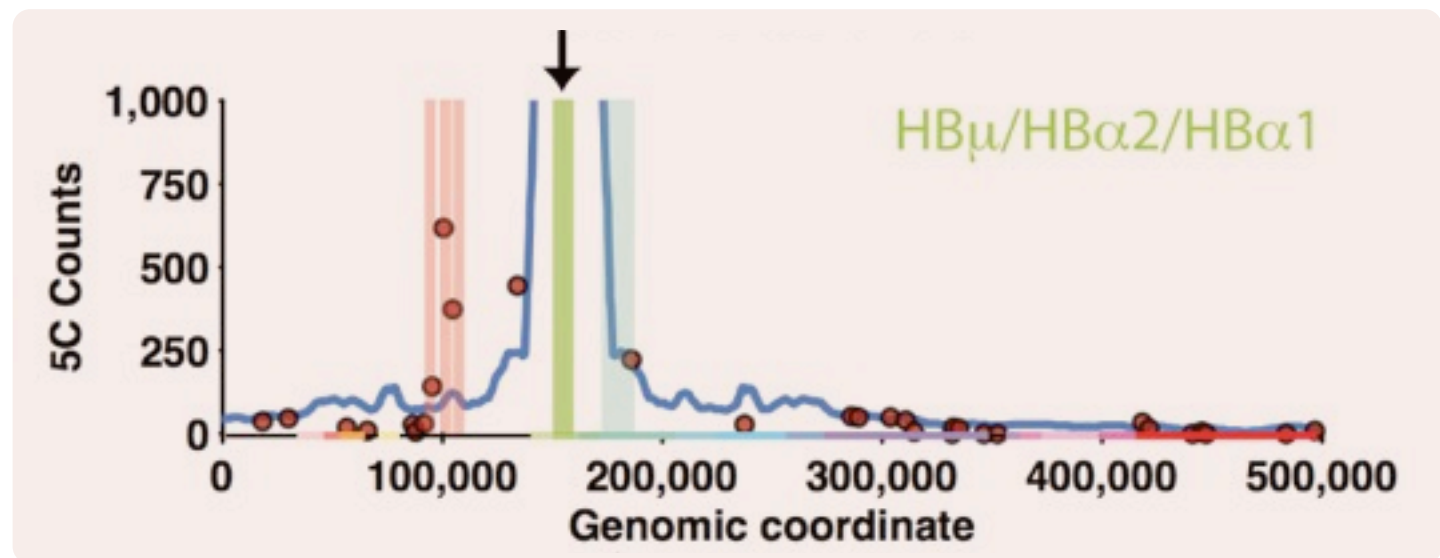
ENCODE Consortium. Nature (2007) vol. 447 (7146) pp. 799-816

Human α -globin domain

ENm008 genomic structure and environment



K562 cells:
 α -globin genes active



Representation

Harmonic

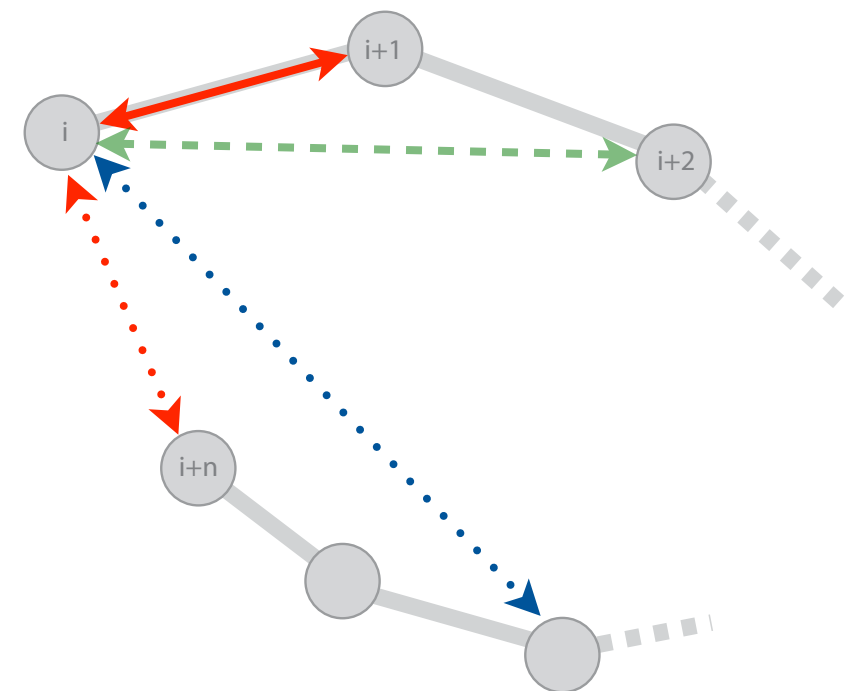
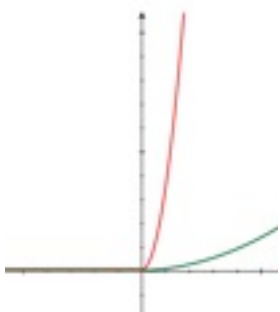
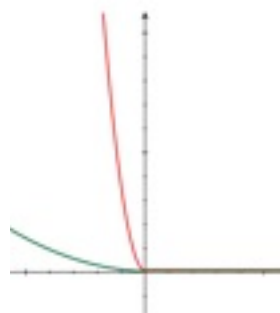
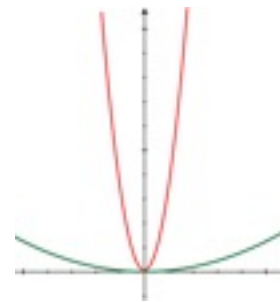
$$H_{i,j} = k(d_{i,j} - d_{i,j}^0)^2$$

Harmonic Lower Bound

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

Harmonic Upper Bound

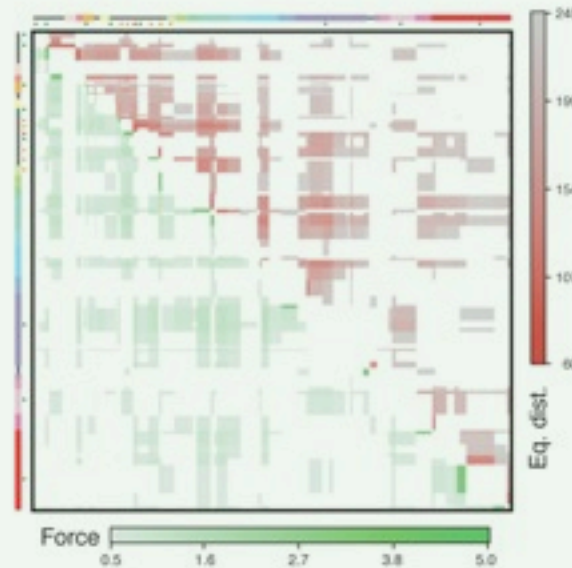
$$\begin{cases} \text{if } d_{i,j} \geq d_{i,j}^0; & ubH_{i,j} = k(d_{i,j} - d_{i,j}^0)^2 \\ \text{if } d_{i,j} < d_{i,j}^0; & ubH_{i,j} = 0 \end{cases}$$



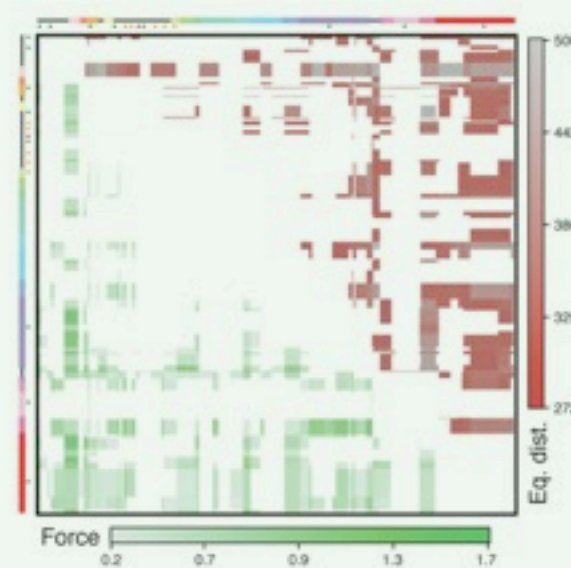
Scoring

GM12878

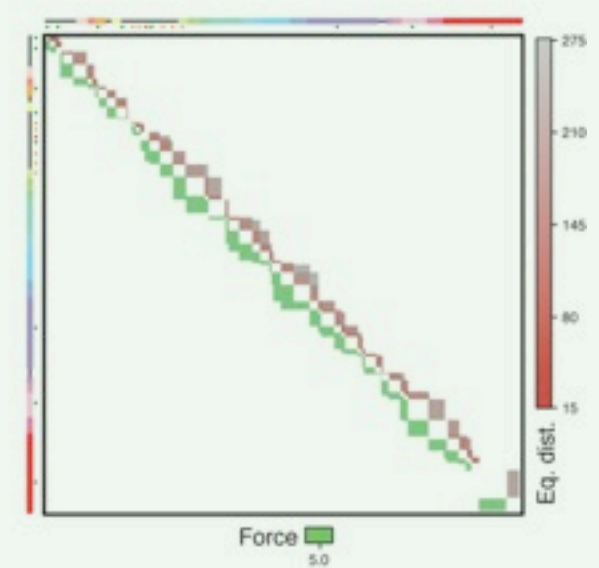
70 fragments
1,520 restraints



Harmonic



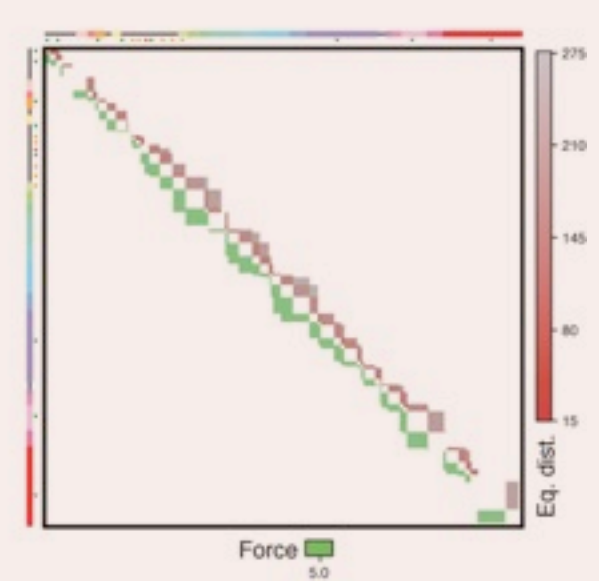
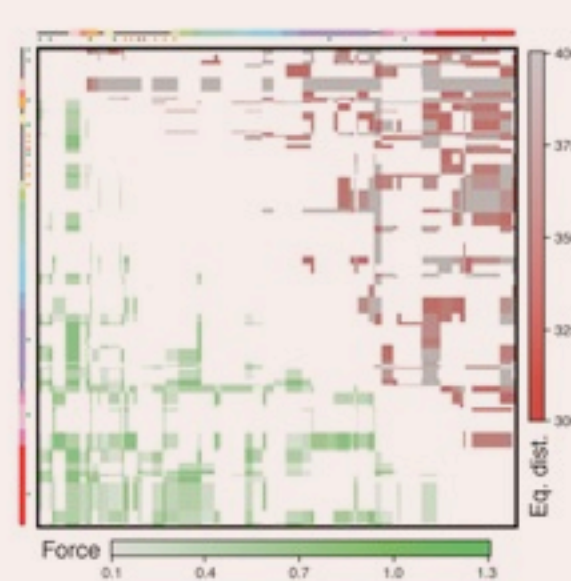
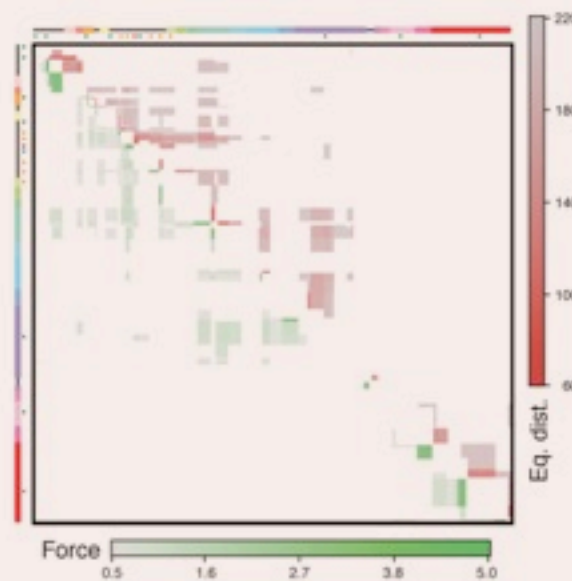
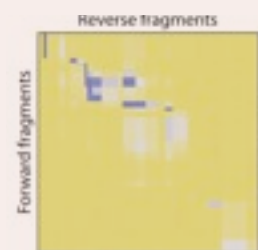
Harmonic Lower Bound



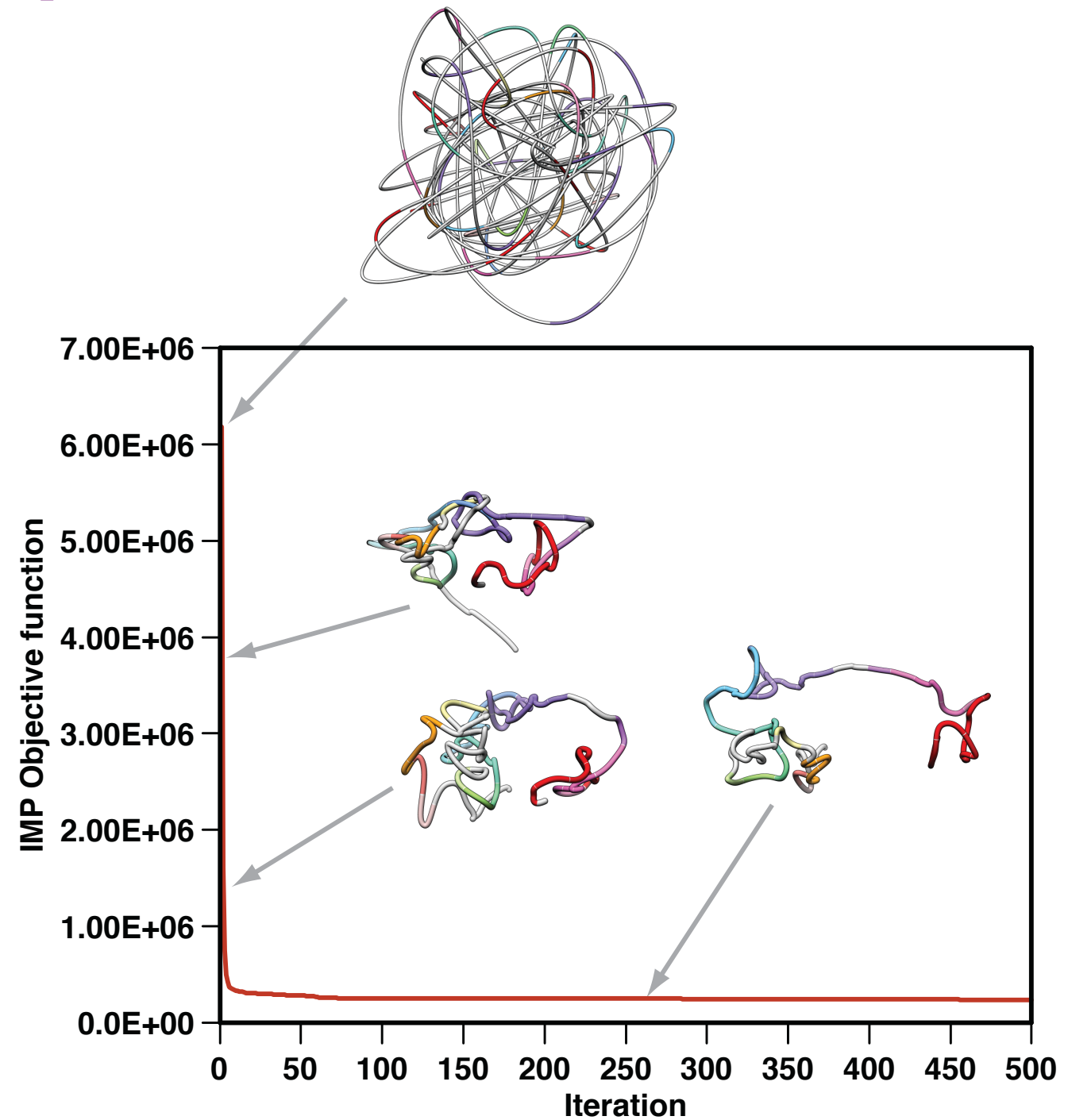
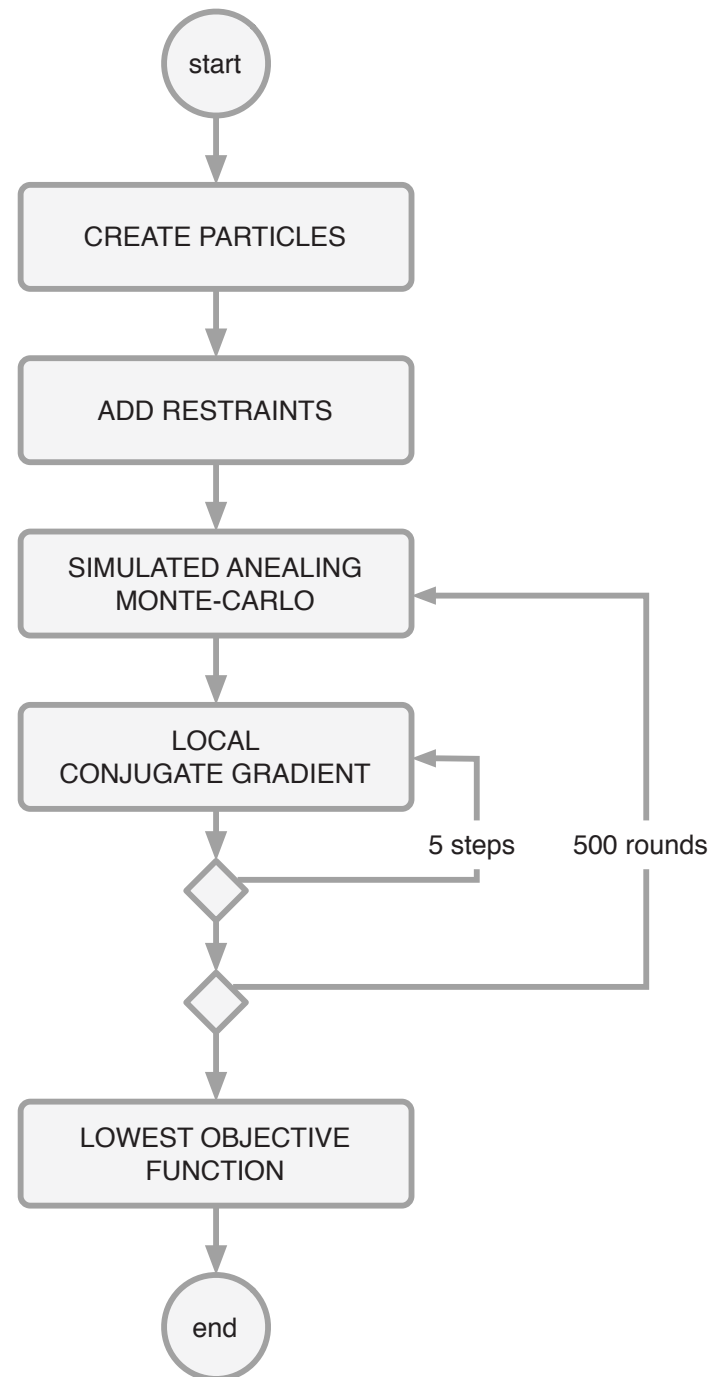
Harmonic Upper Bound

K562

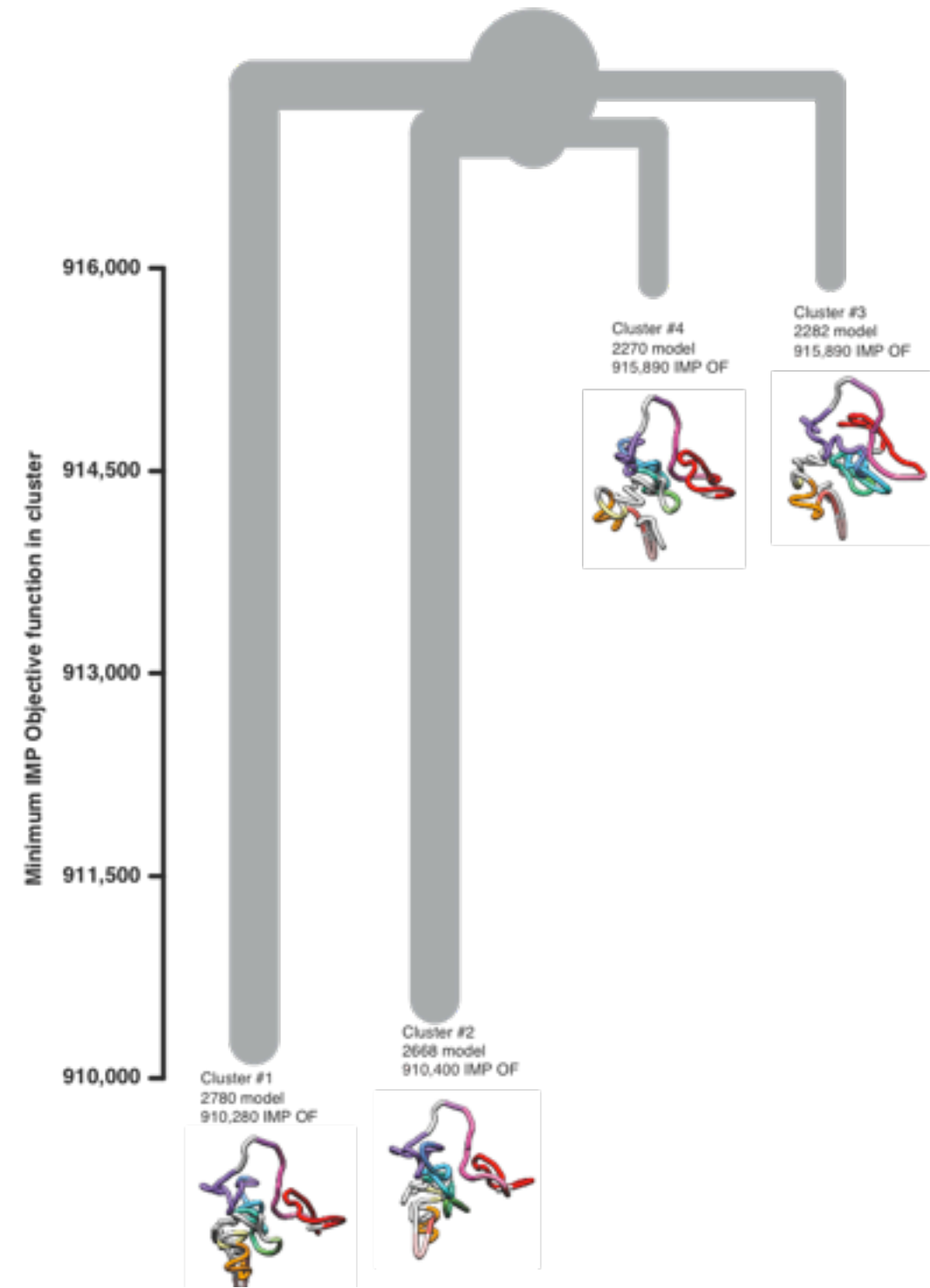
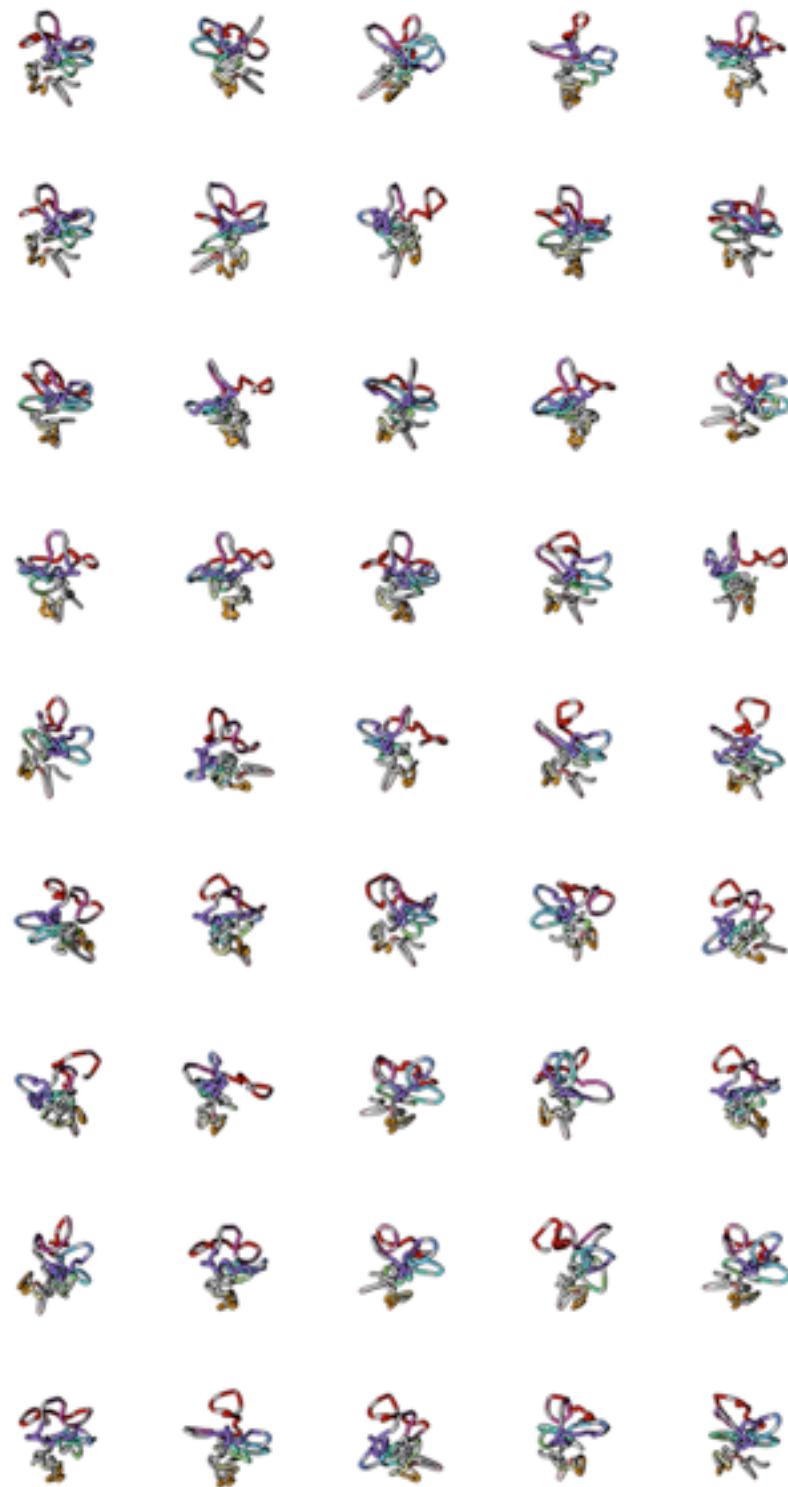
70 fragments
1,049 restraints



Optimization

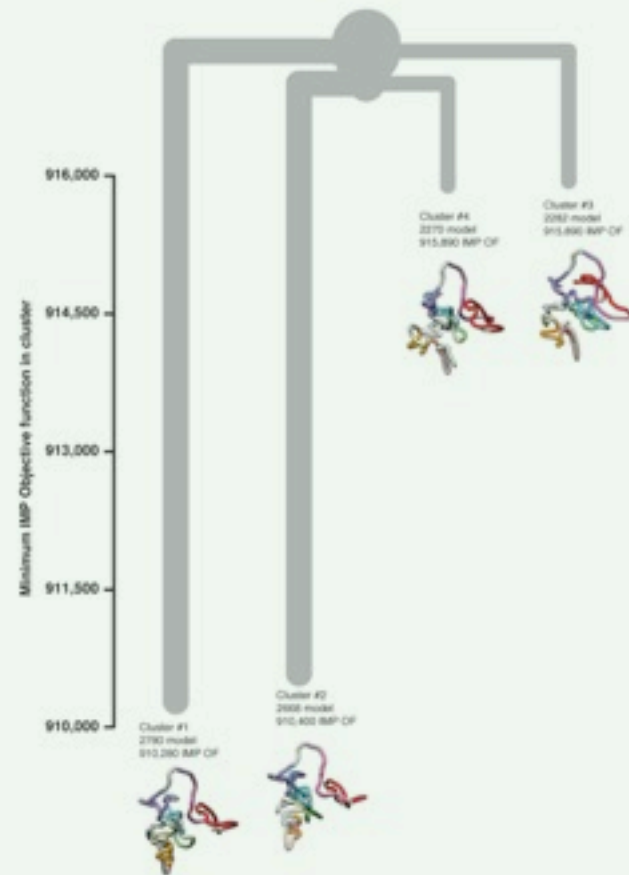
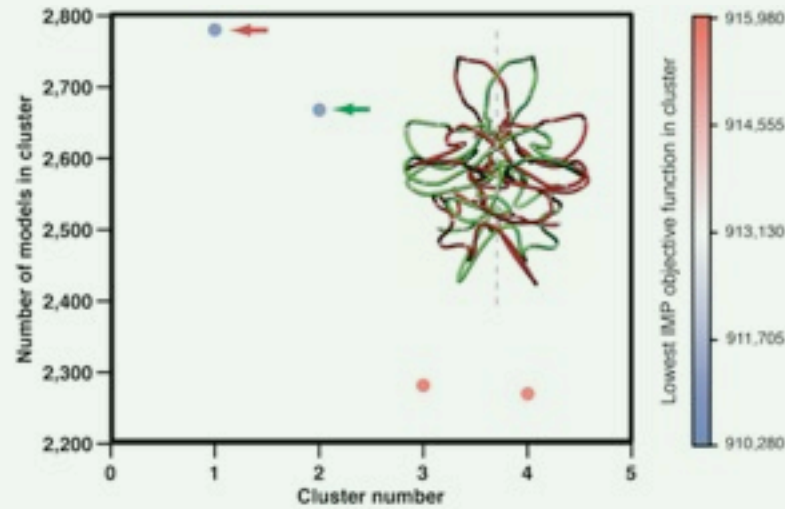


Clustering

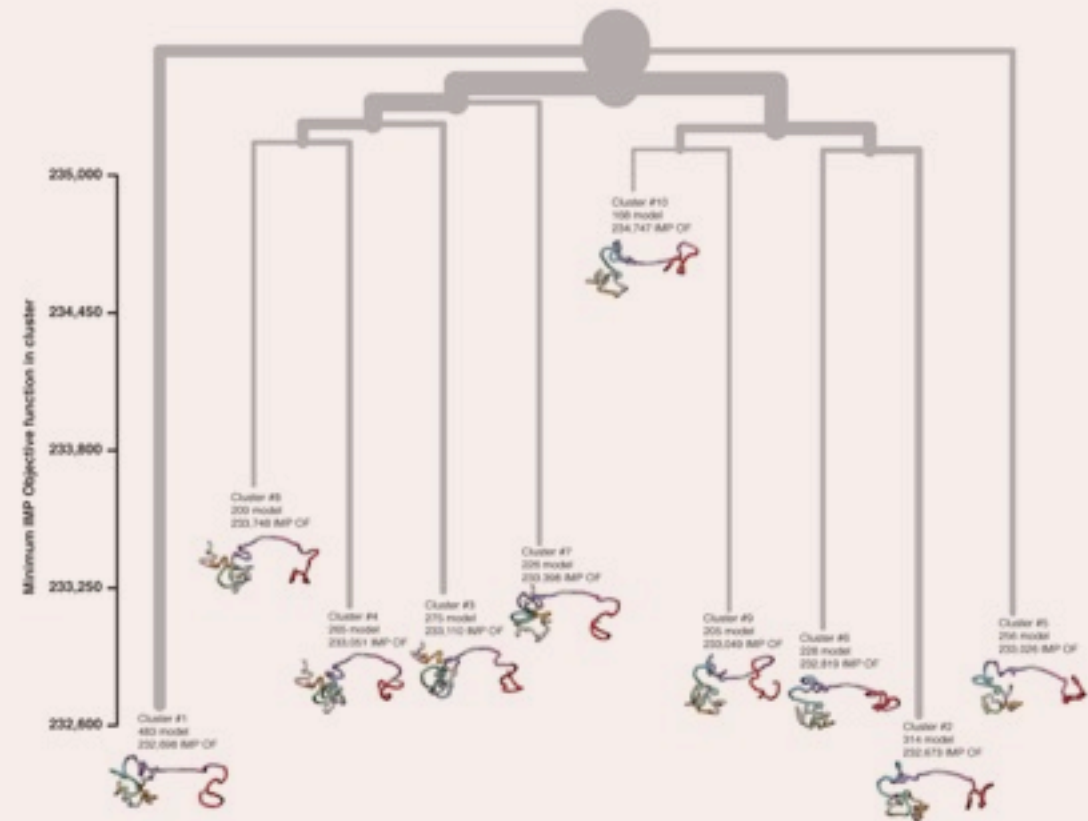
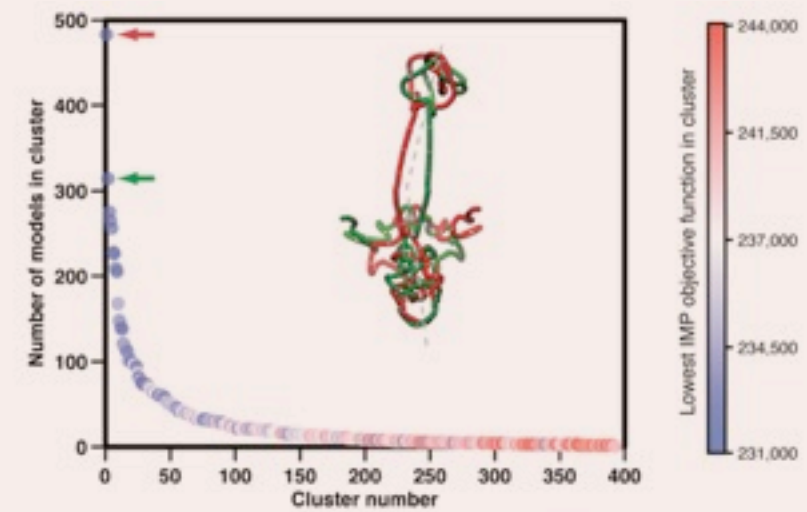


Not just *one* solution

GM12878



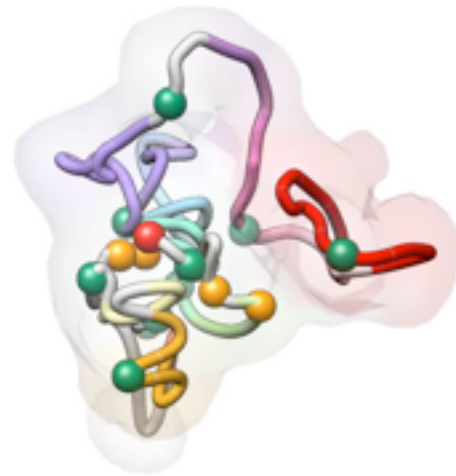
K562



Consistency

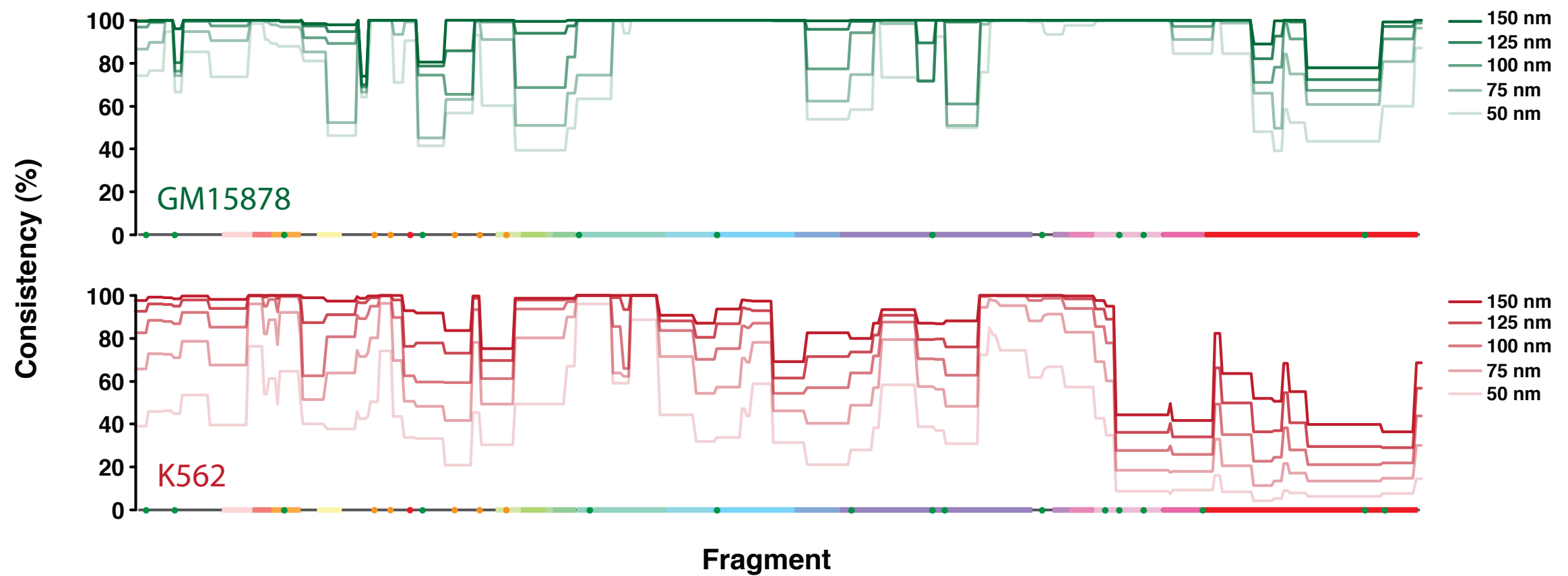
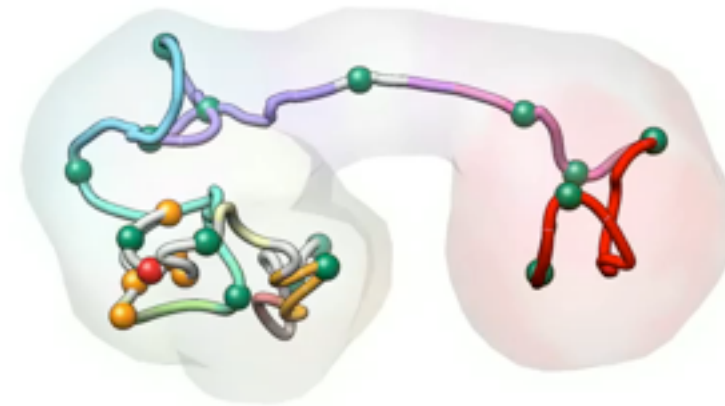
GM12878

Cluster #1
2780 model



K562

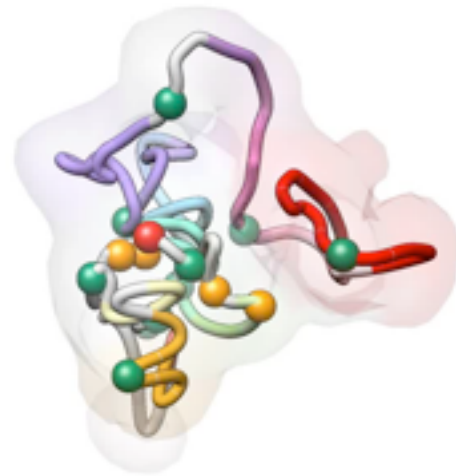
Cluster #2
314 model



Regulatory elements

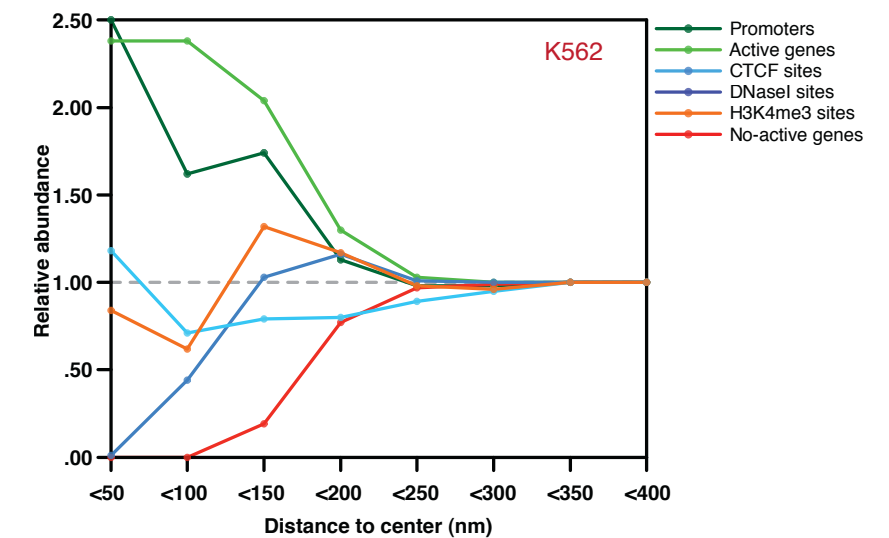
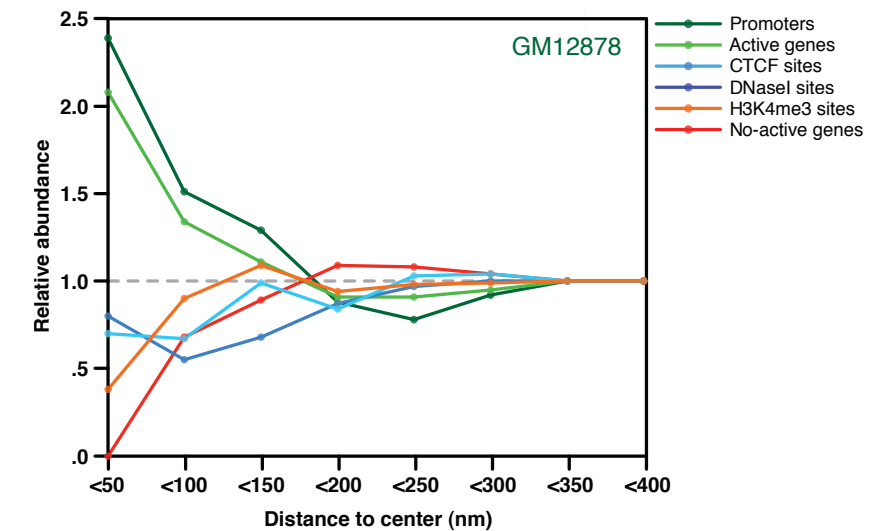
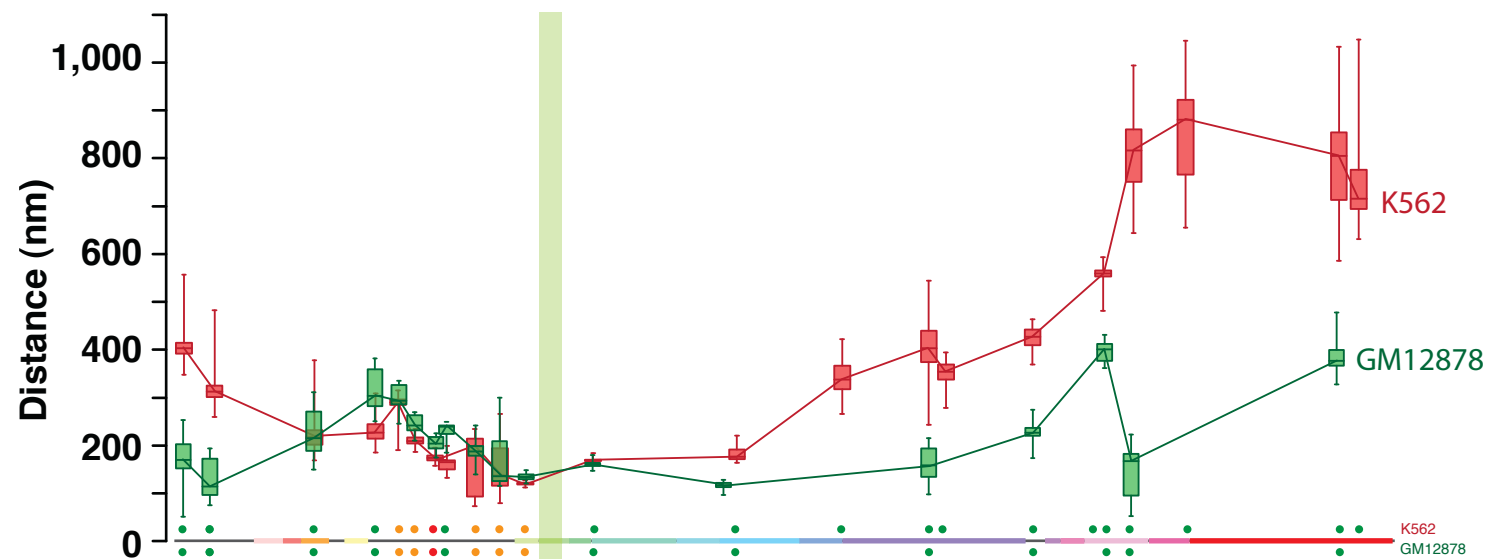
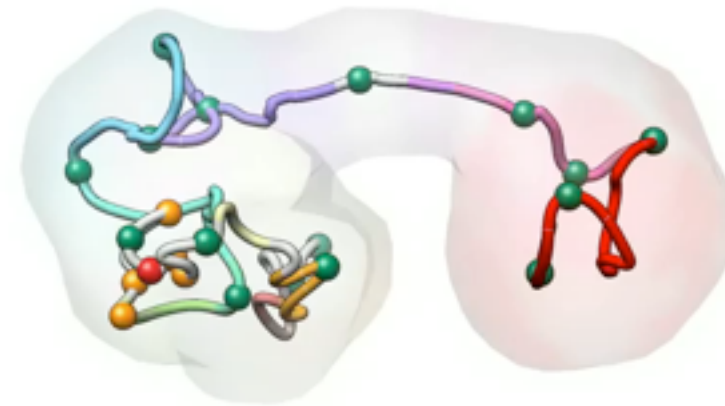
GM12878

Cluster #1
2780 model



K562

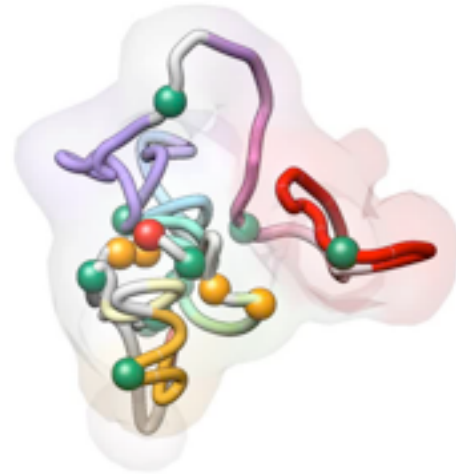
Cluster #2
314 model



Compactness

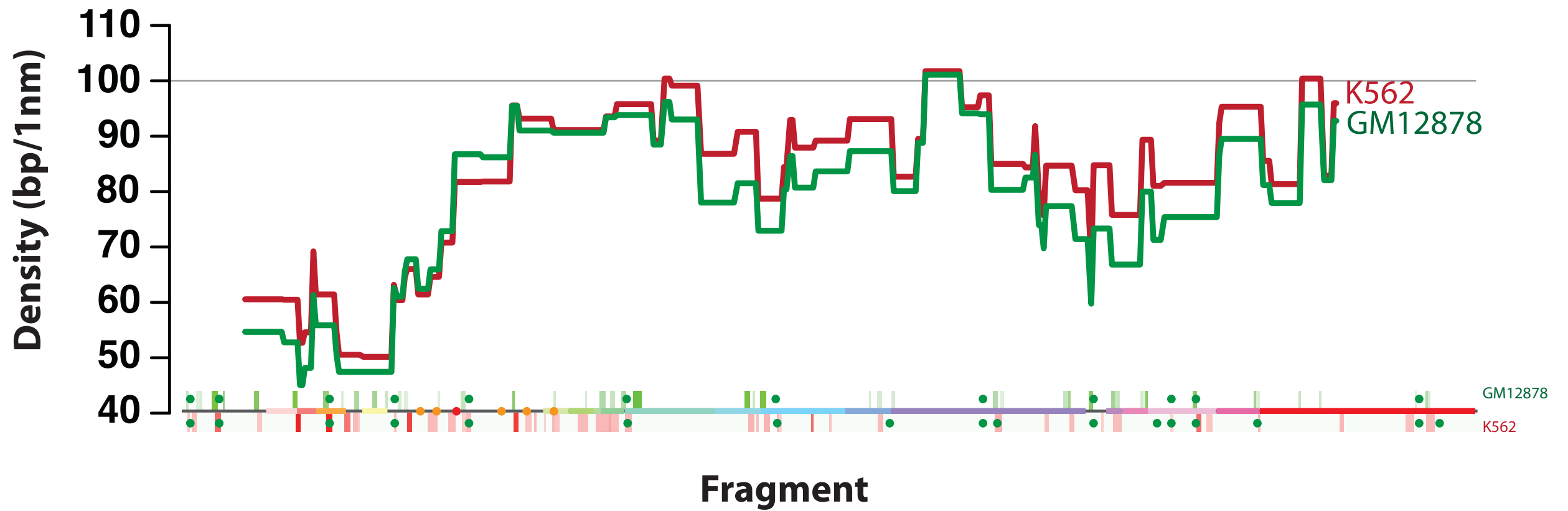
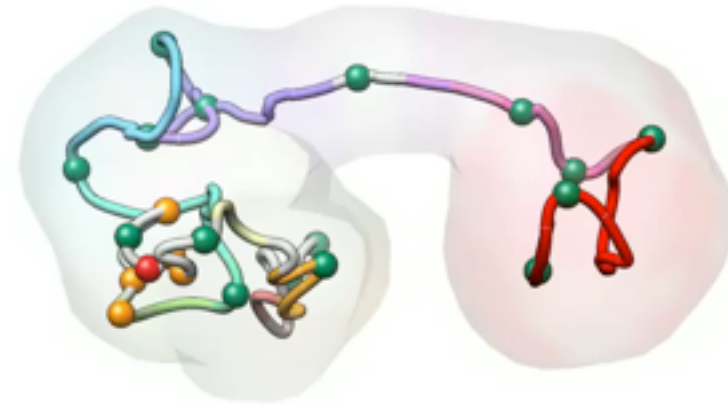
GM12878

Cluster #1
2780 model



K562

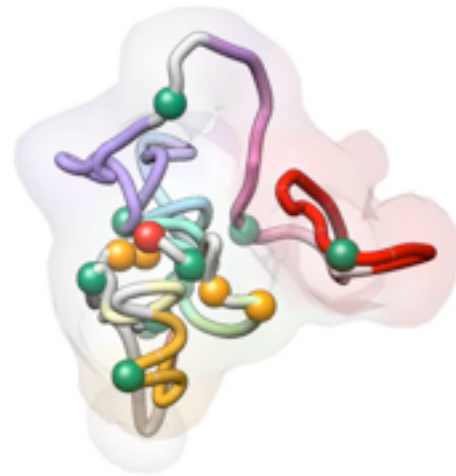
Cluster #2
314 model



Multi-loops

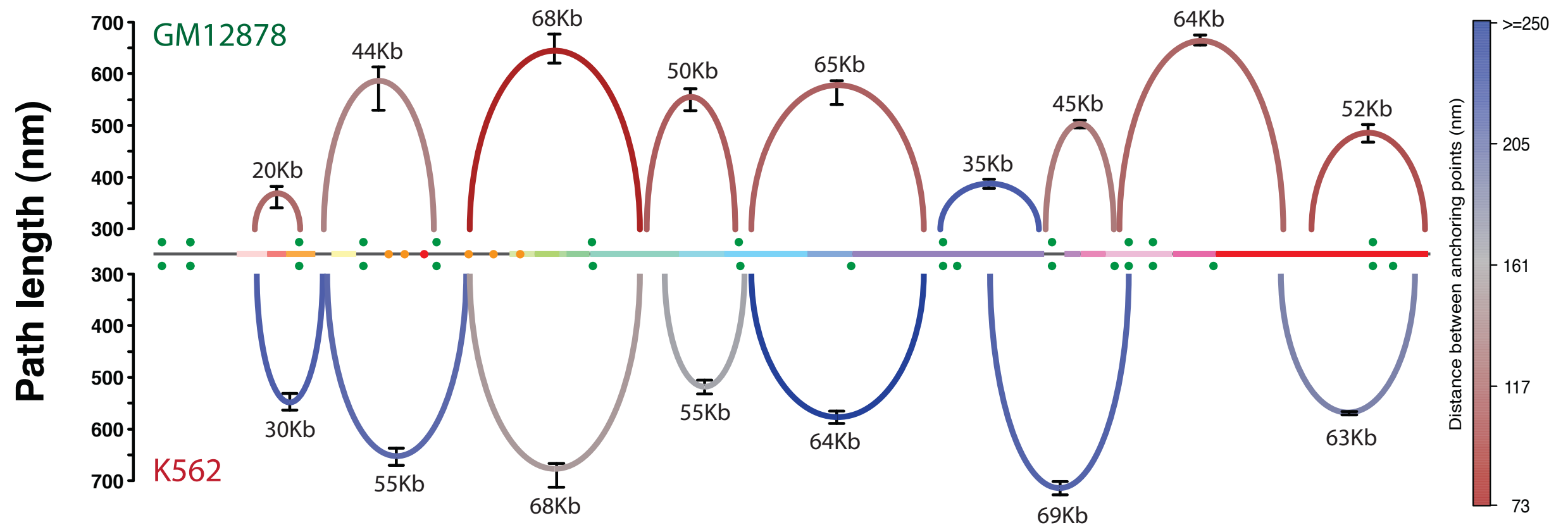
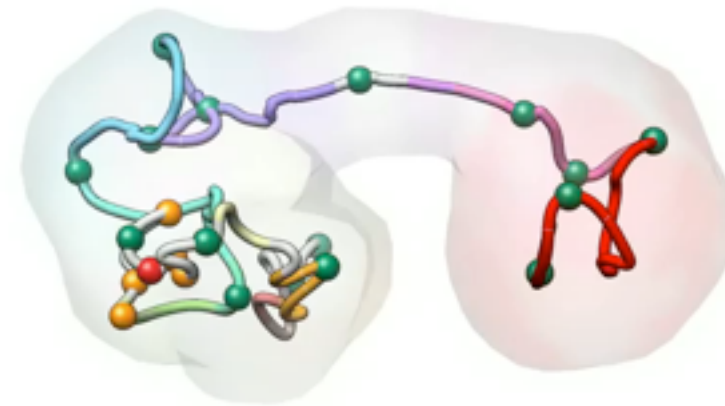
GM12878

Cluster #1
2780 model



K562

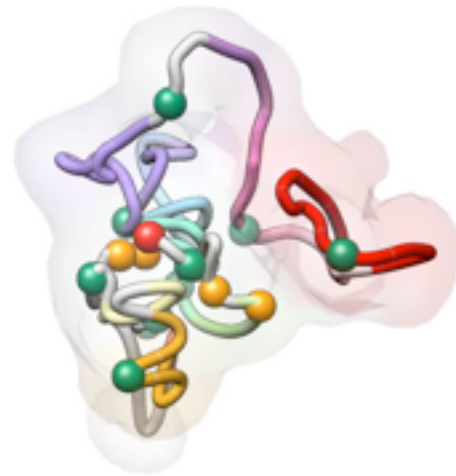
Cluster #2
314 model



Expression

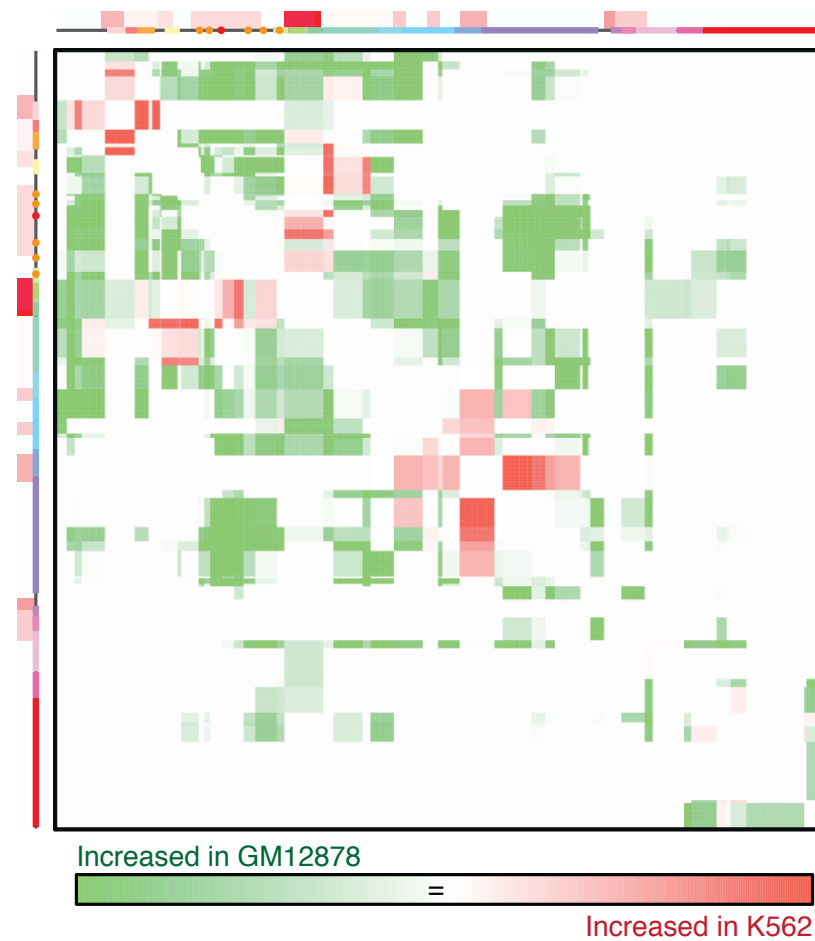
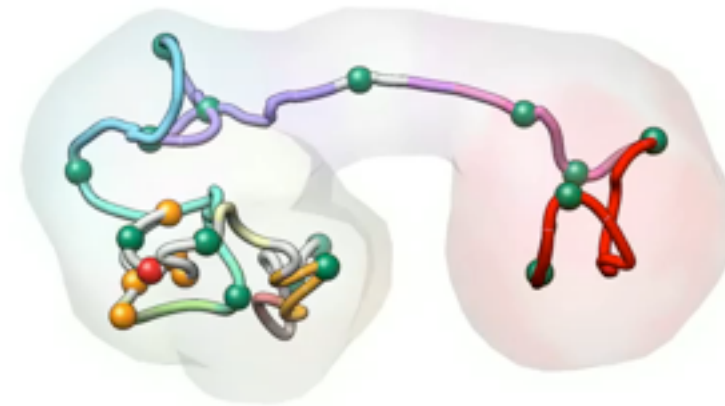
GM12878

Cluster #1
2780 model



K562

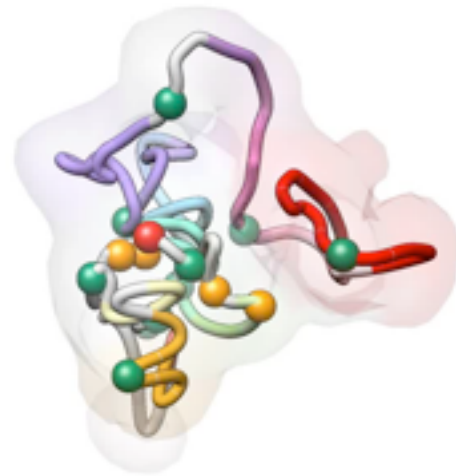
Cluster #2
314 model



FISH validation

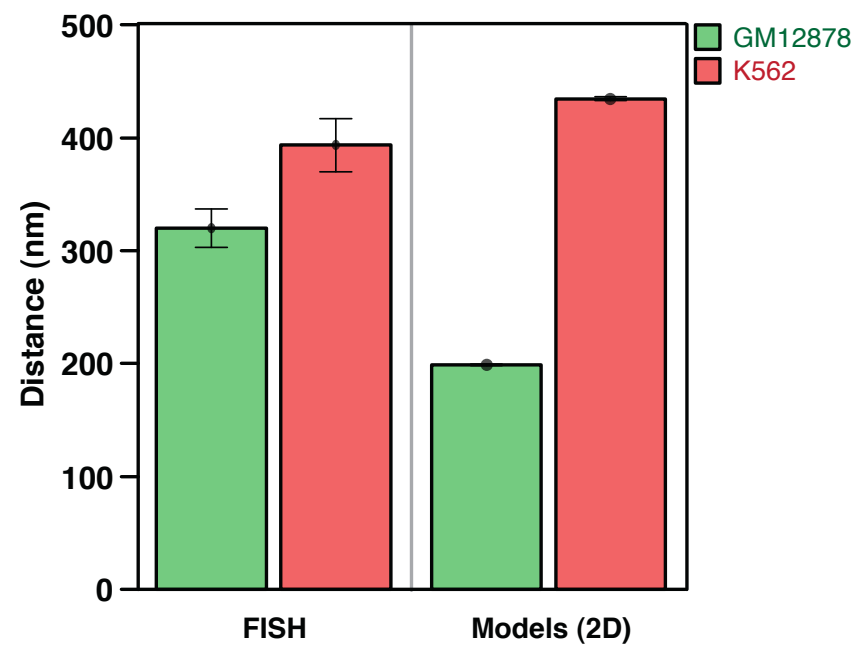
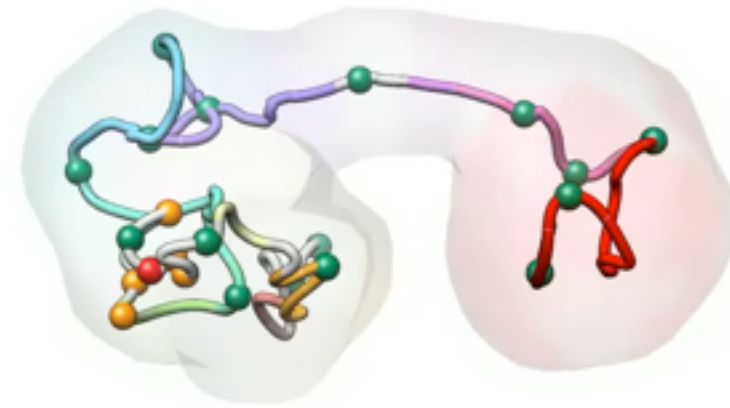
GM12878

Cluster #1
2780 model



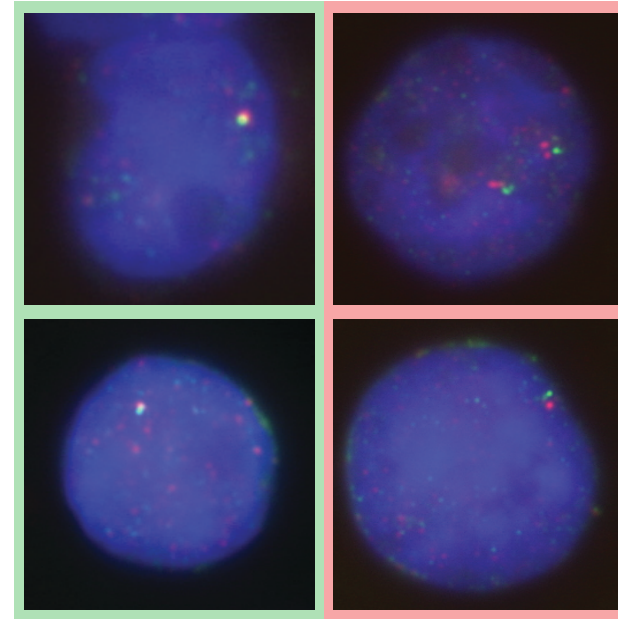
K562

Cluster #2
314 model

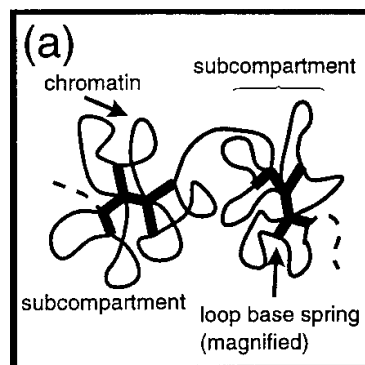


GM12878

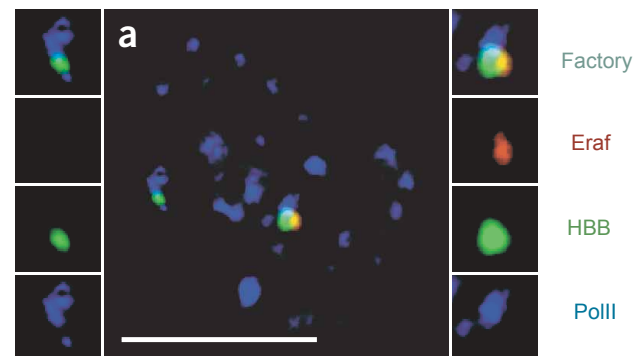
K562



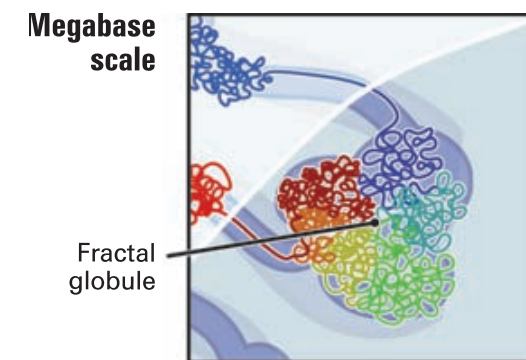
The “Chromatin Globule” model



Münkel et al. JMB (1999)



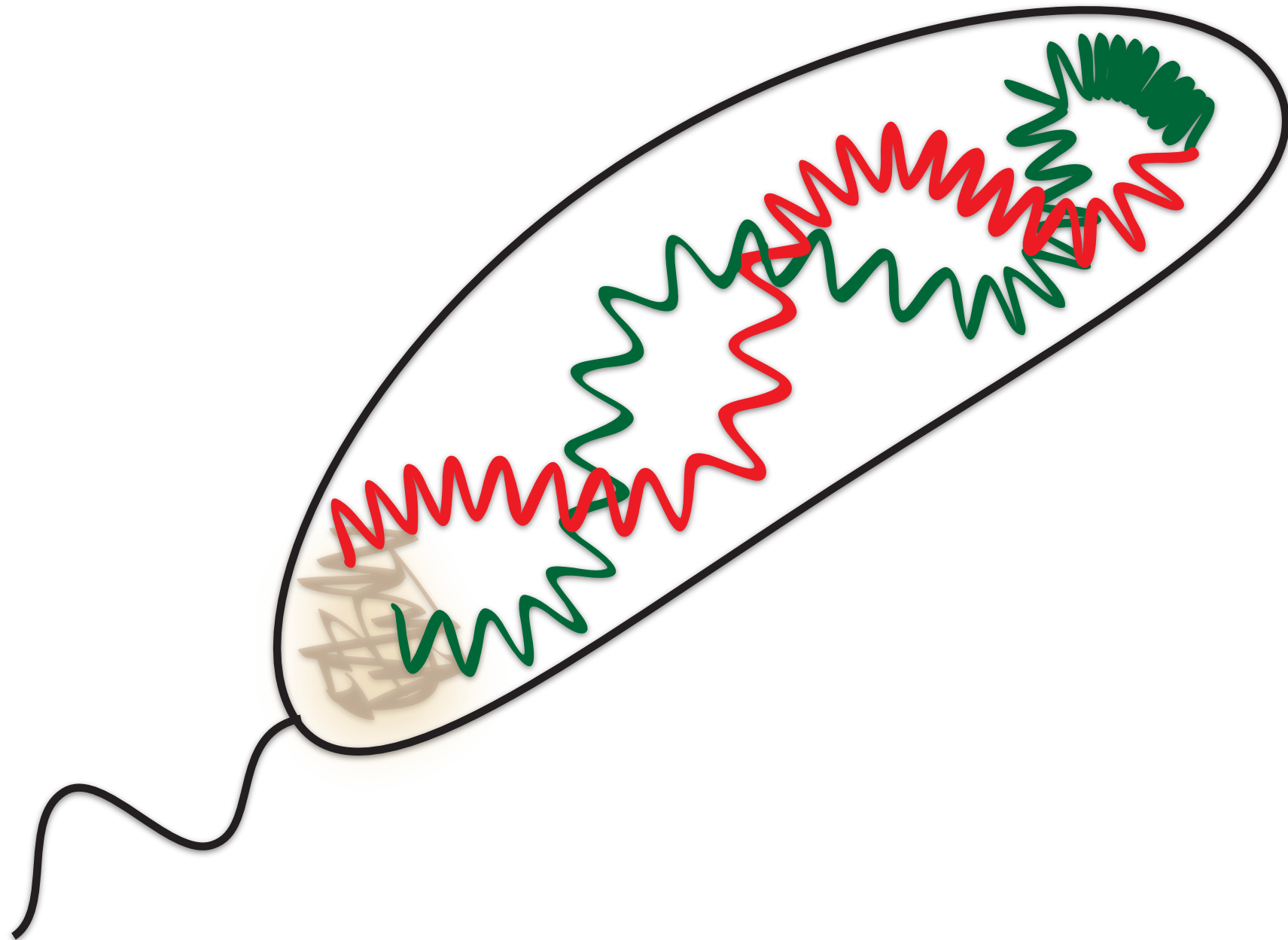
Osborne et al. Nat Genet (2004)



Lieberman-Aiden et al. Science (2009)

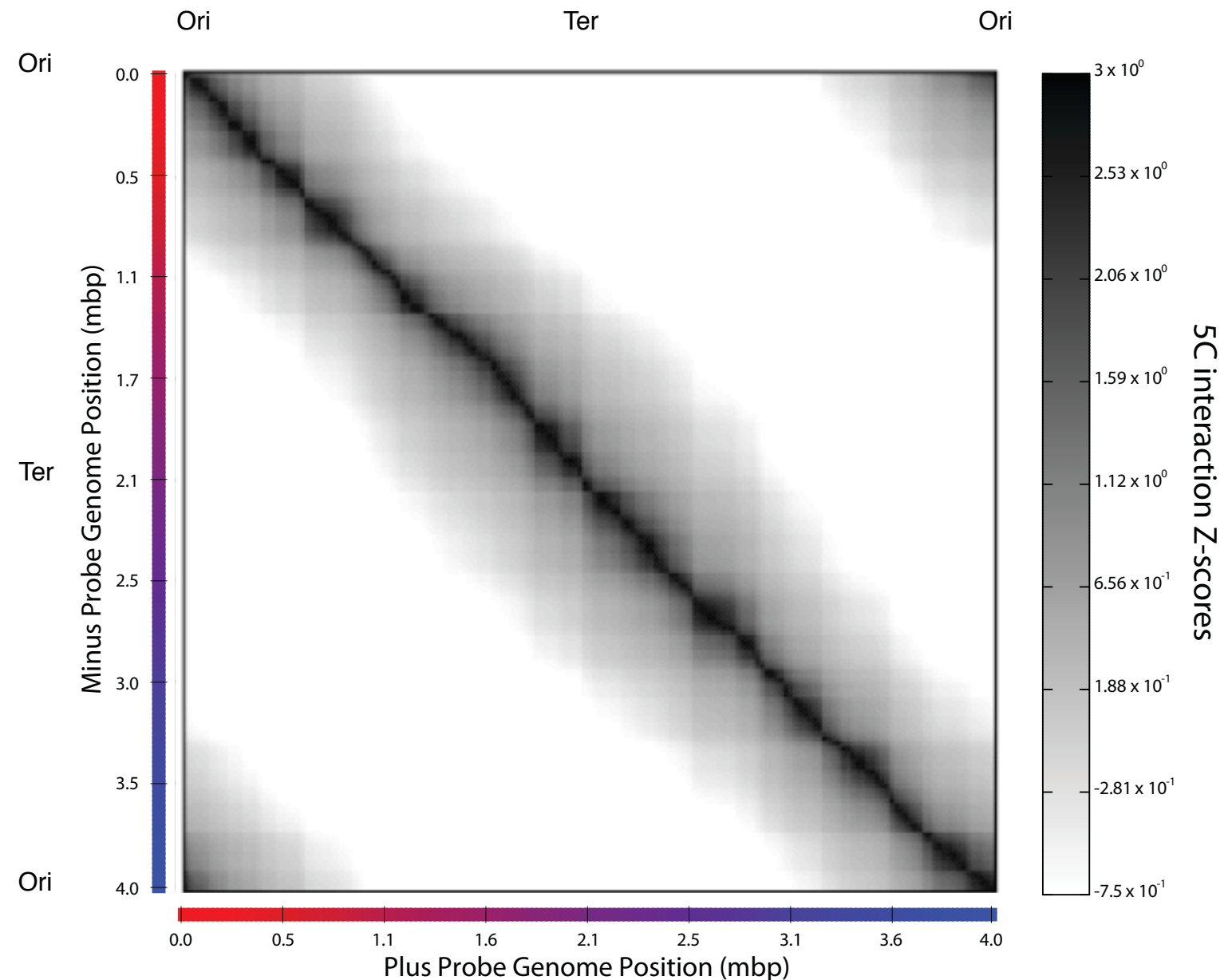
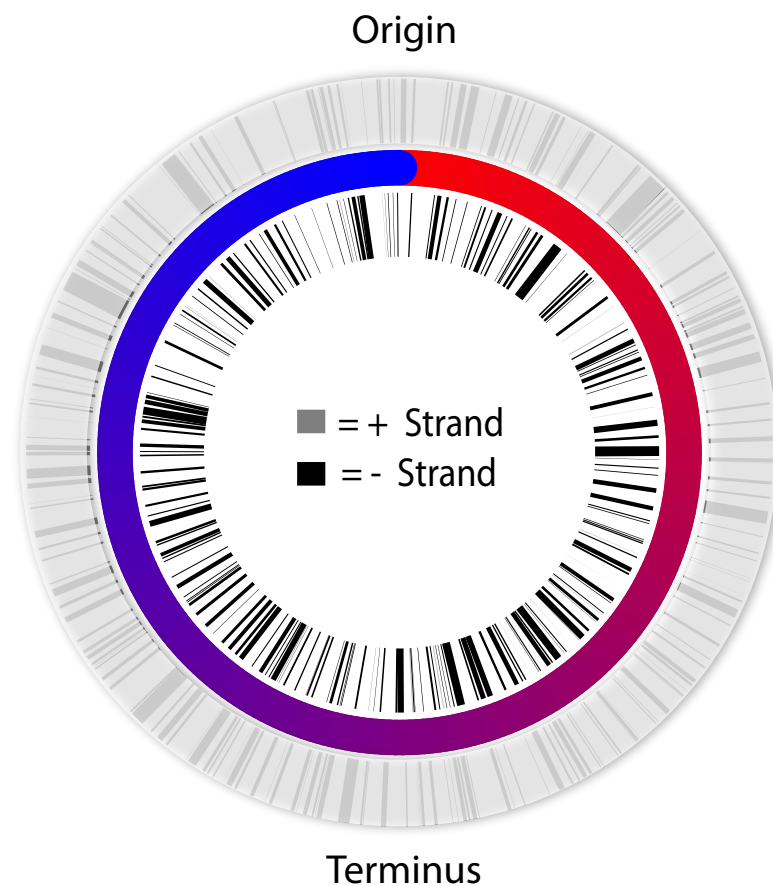
D. Baù et al. **Nat Struct Mol Biol** (2011) 18:107-14
A. Sanyal et al. **Current Opinion in Cell Biology** (2011) 23:325–33.

Caulobacter crescentus genome



The 3D architecture of *Caulobacter Crescentus*

4,016,942 bp & 3,767 genes

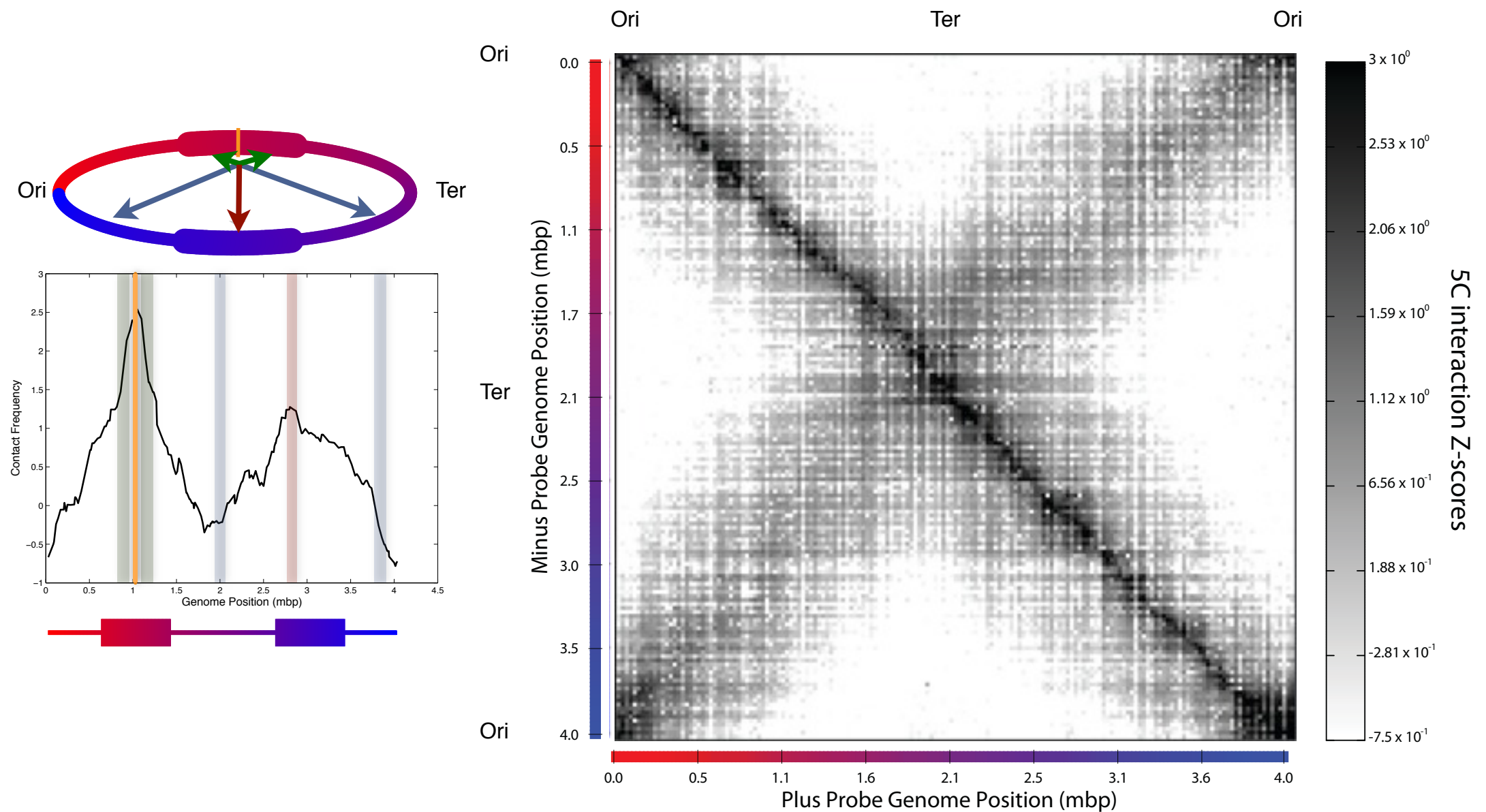
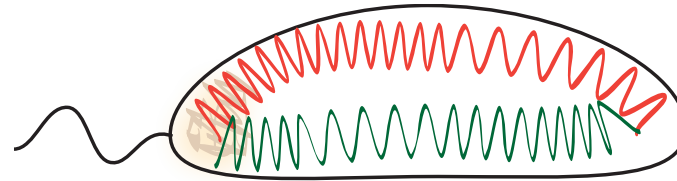


169 5C primers on + strand
170 5C primers on - strand
28,730 chromatin interactions

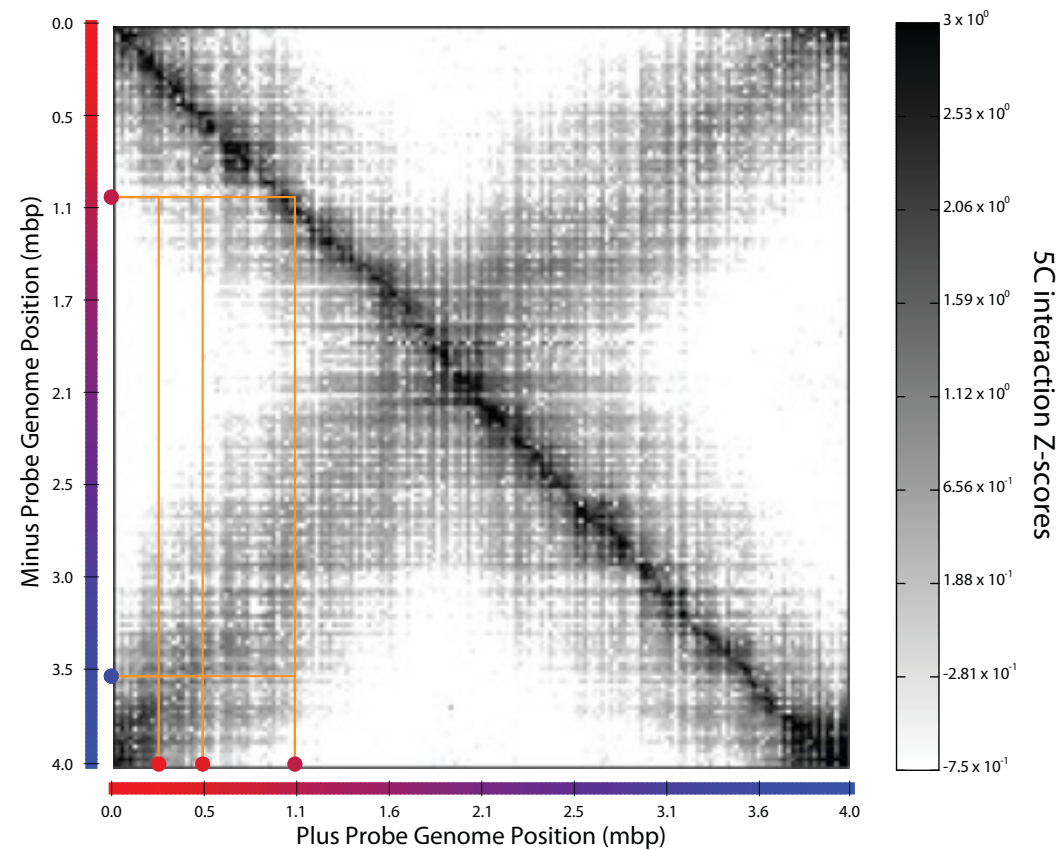
~13Kb

5C interaction matrix

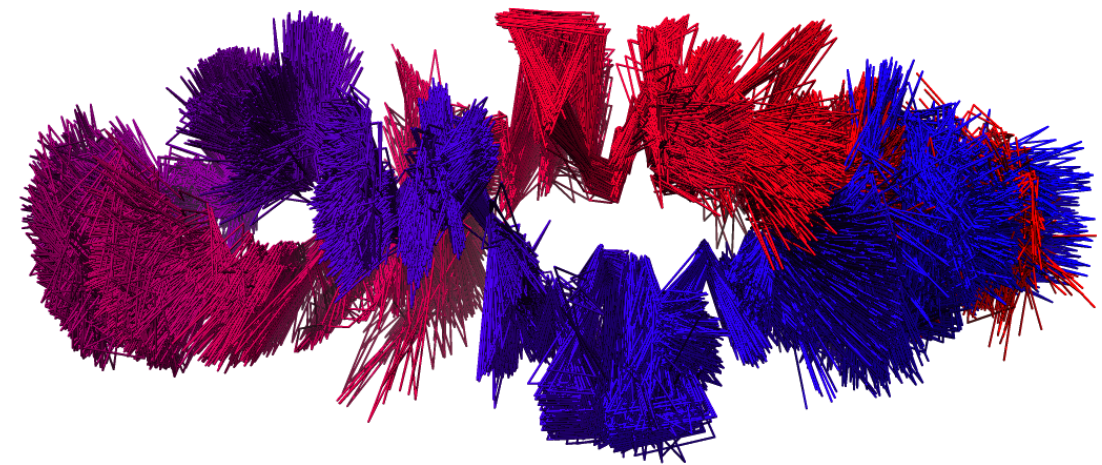
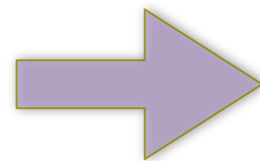
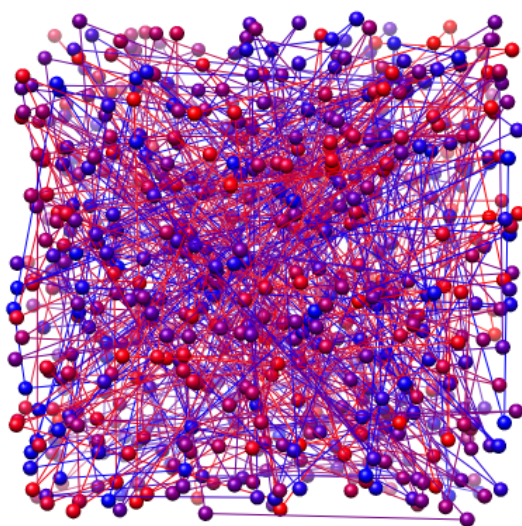
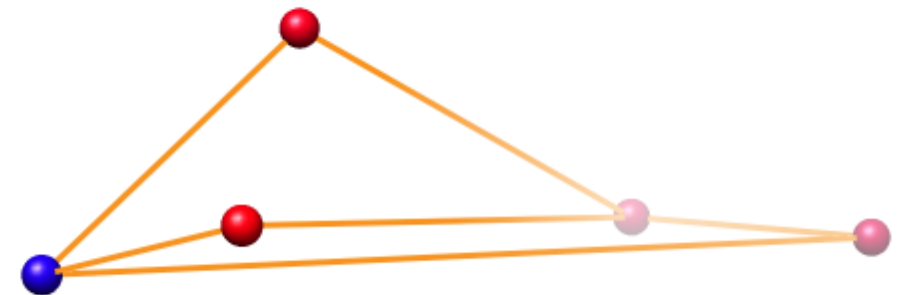
ELLIPSOID for *Caulobacter crescentus*



3D model building with the 5C + IMP approach



339 mers



Genome organization in *Caulobacter crescentus*

Arms are helical

Resolution

Centromer-like

dif site 47 ± 17 Kb from Ter

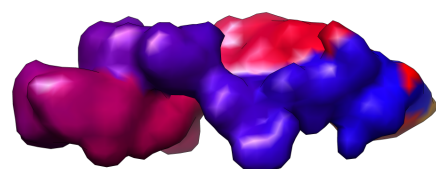
parS sites 25 ± 17 Kb from Ori

Cluster 1

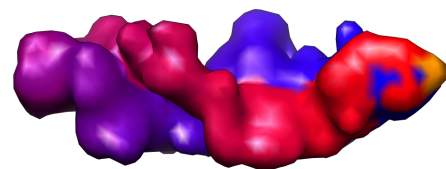
Cluster 2

Cluster 3

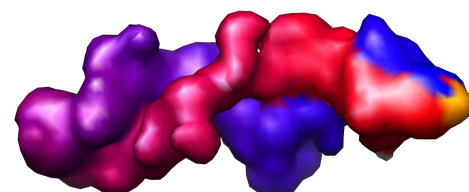
Cluster 4



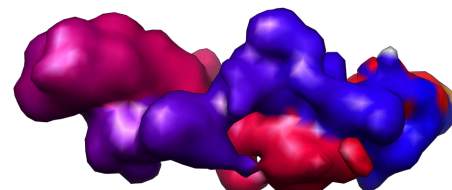
180°



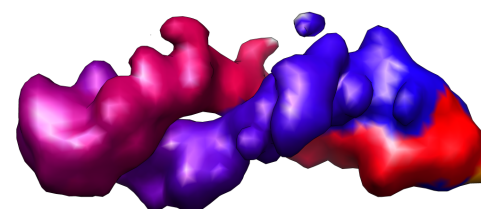
500 nm



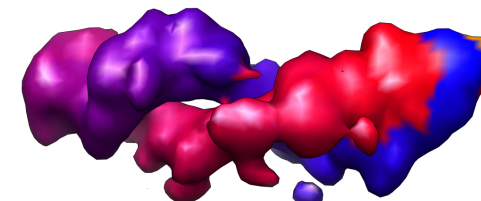
180°



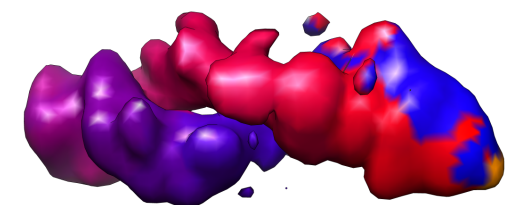
500 nm



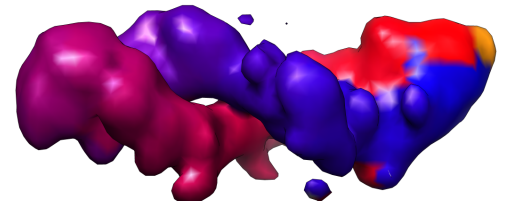
180°



500 nm



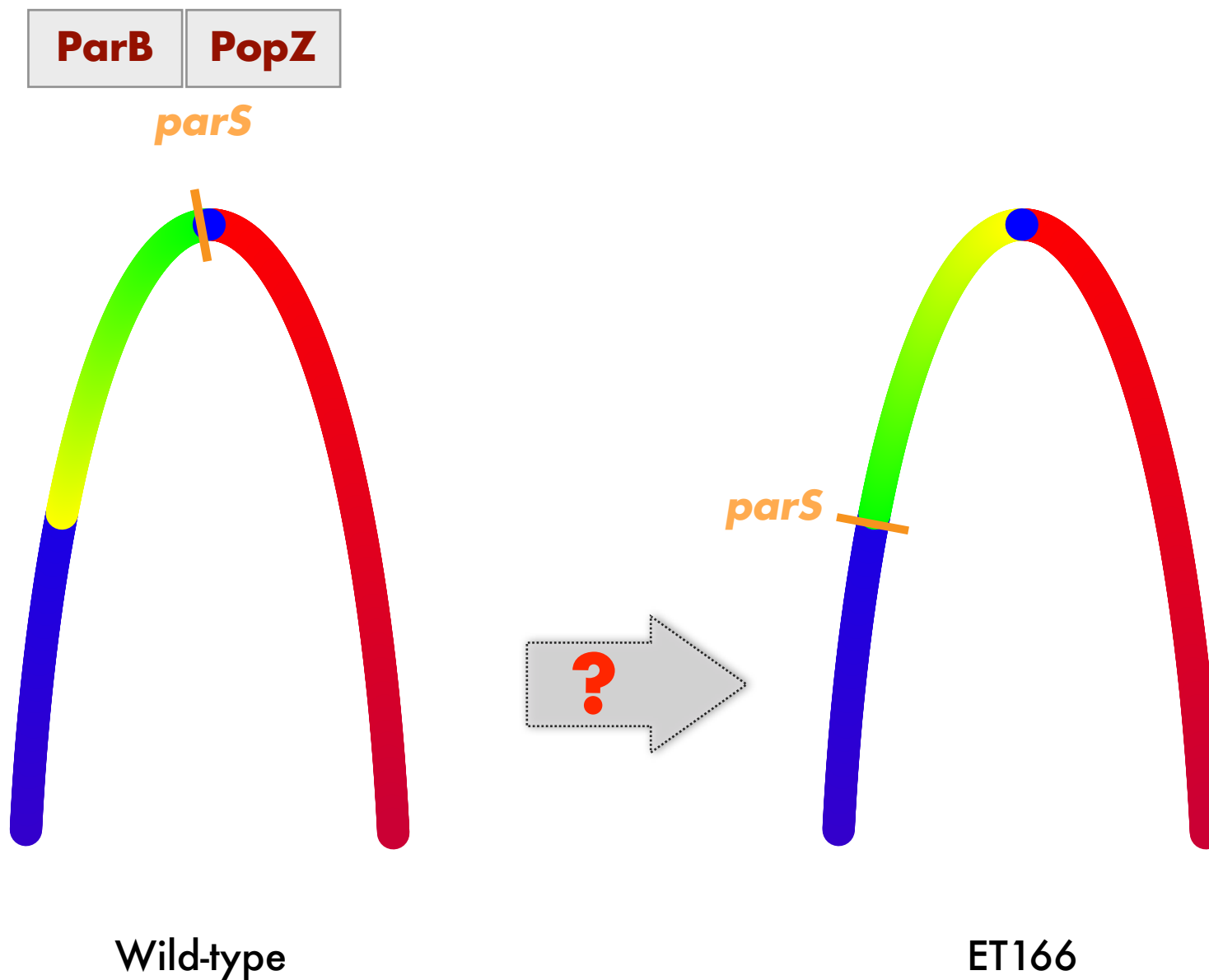
180°



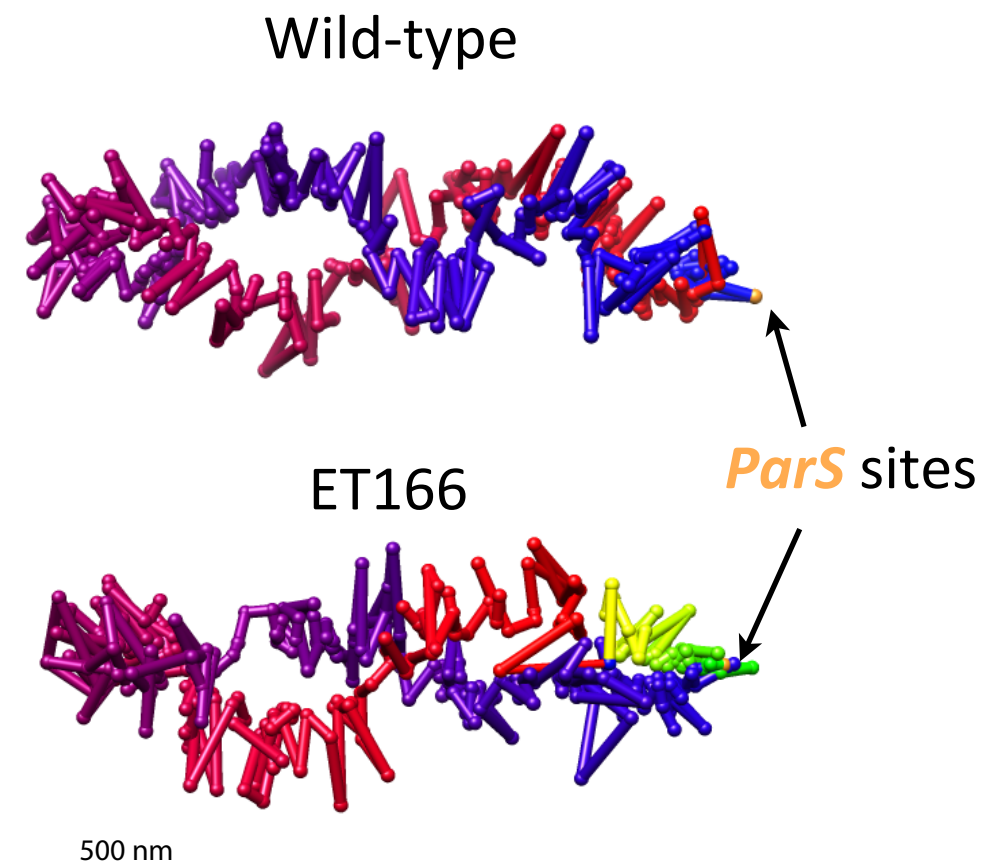
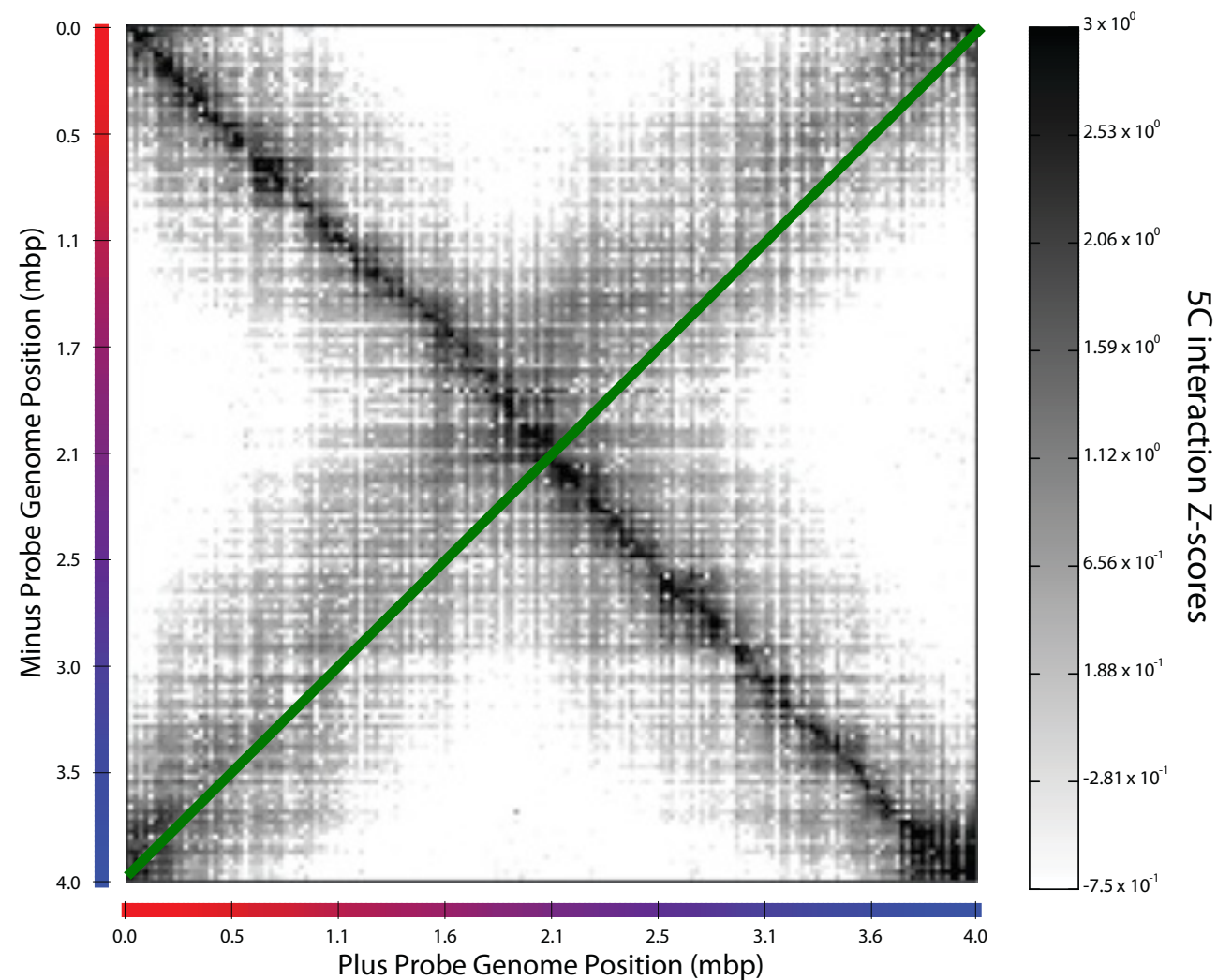
500 nm

MIRRORS!

Moving the **parS** sites 400 Kb away from Ori

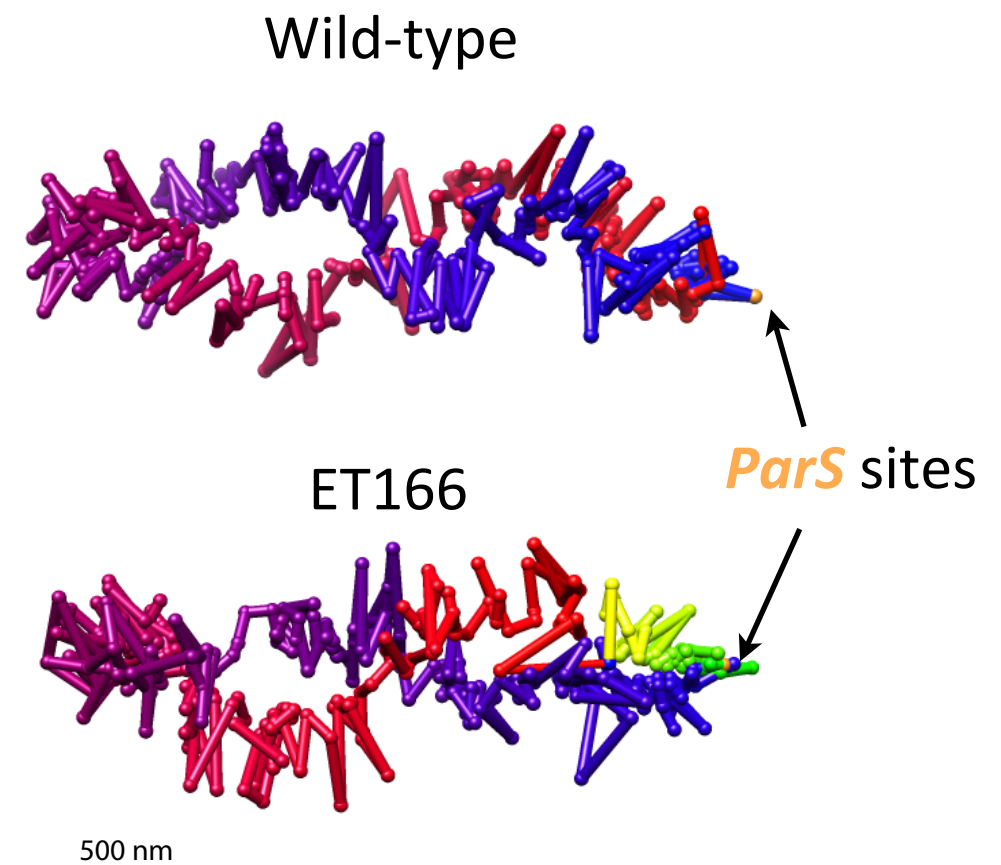
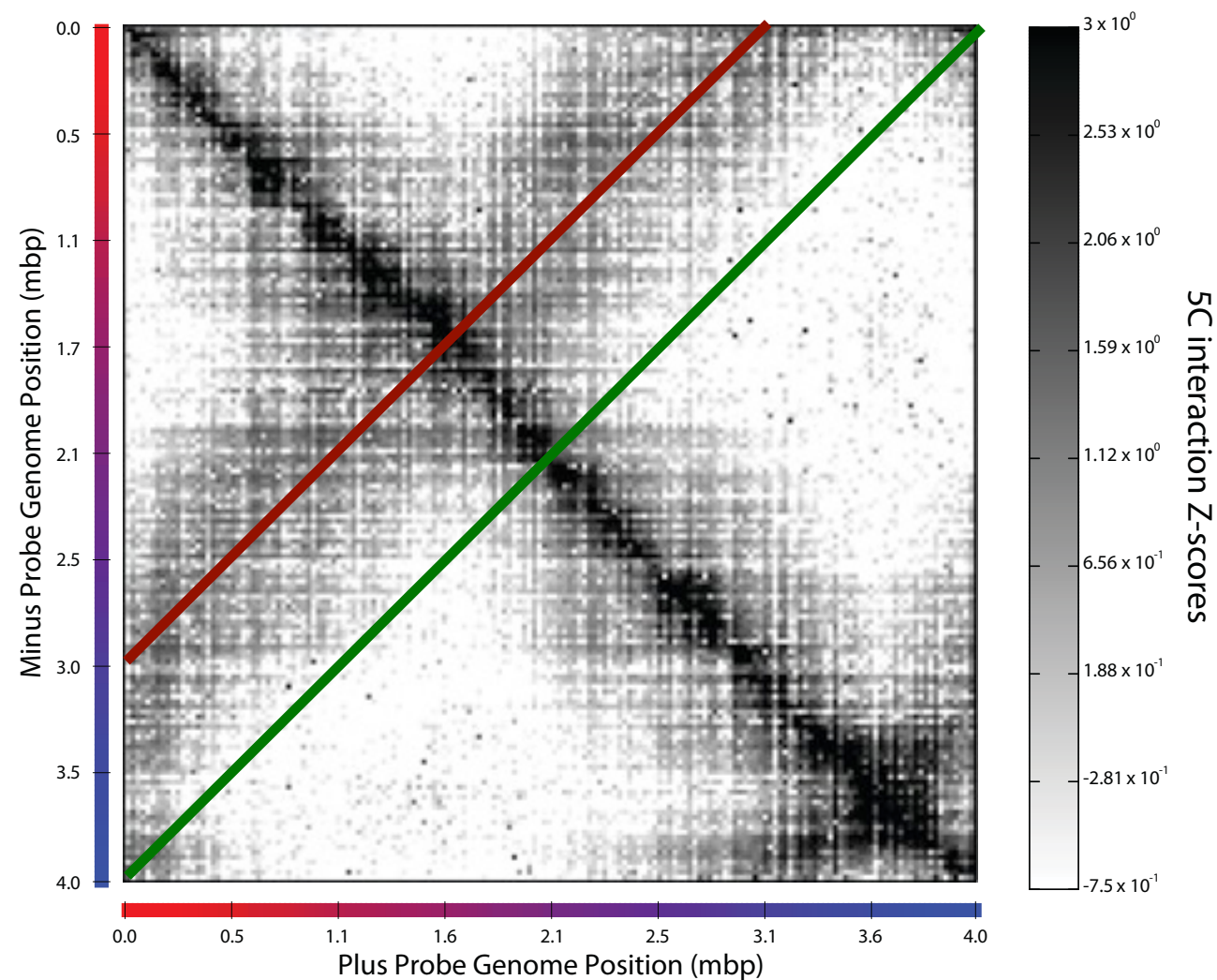


Moving the **parS** sites results in whole genome rotation!



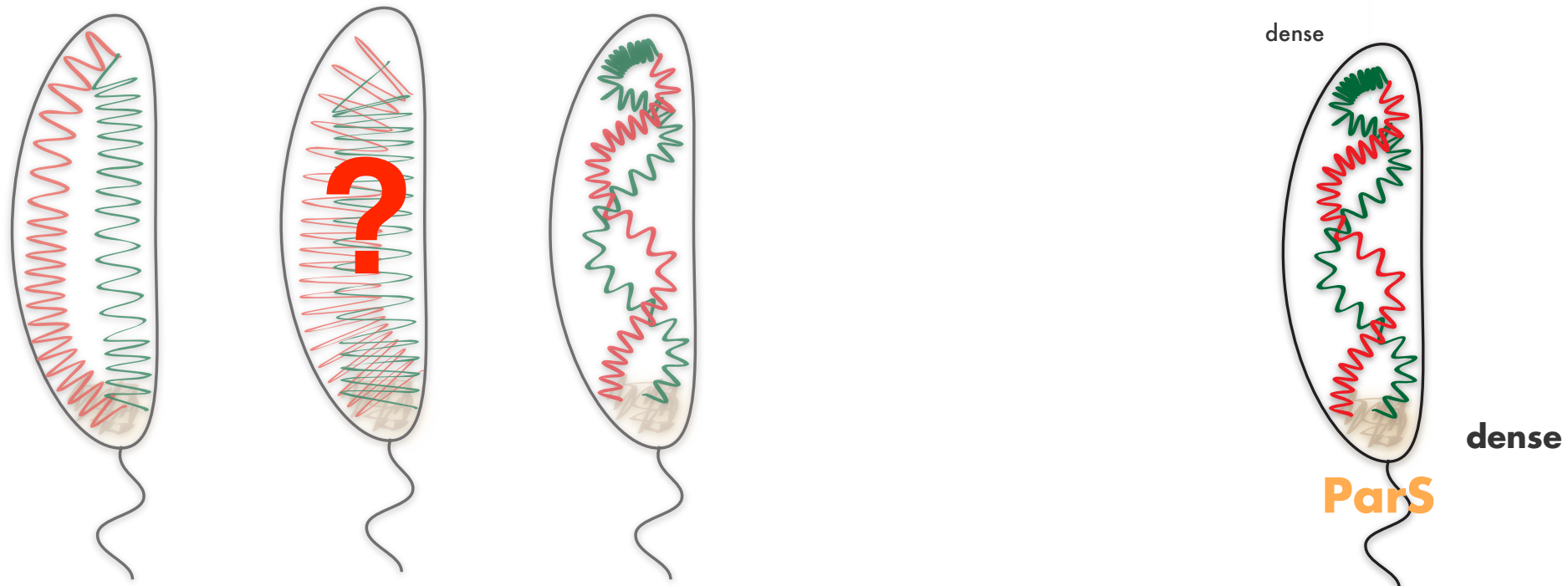
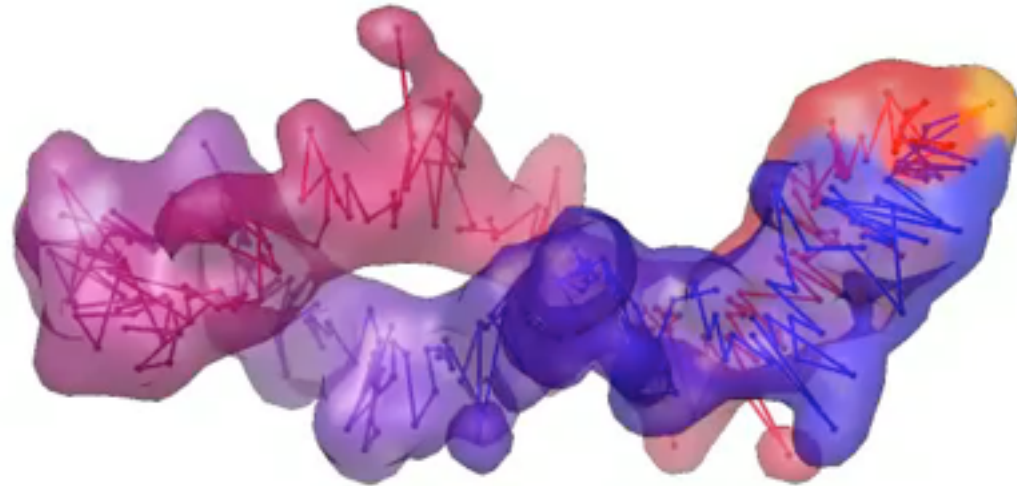
Arms are **STILL** helical

Moving the *parS* sites results in whole genome rotation!



Arms are **STILL** helical

Genome architecture in *Caulobacter*

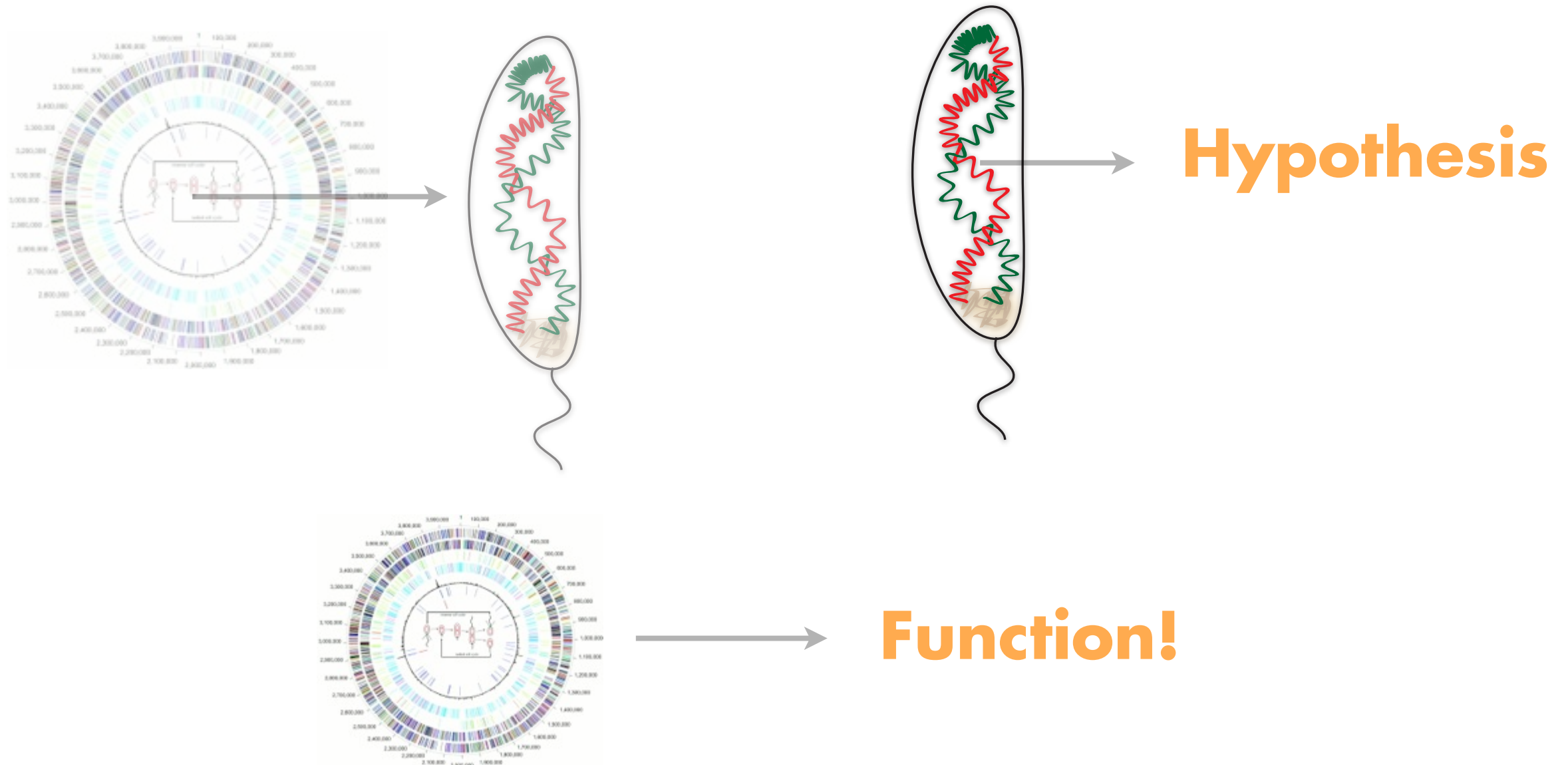


M.A. Umbarger, et al. **Molecular Cell** (2011) **44**:252–264

From Sequence to Function

5C + IMP

Technology



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

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