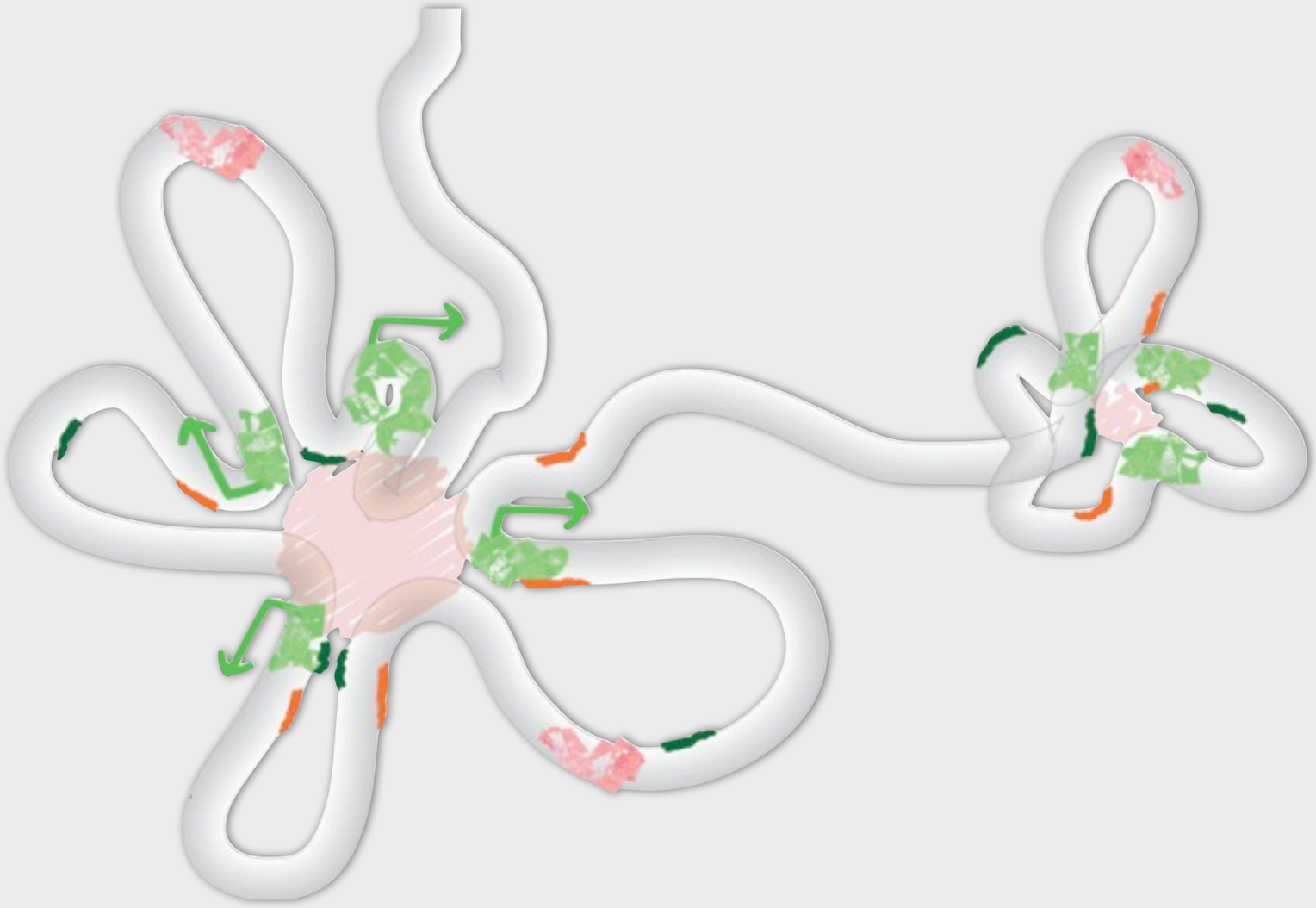
3D folding of chromosomal domains in relation to gene expression



Marc A. Marti-Renom

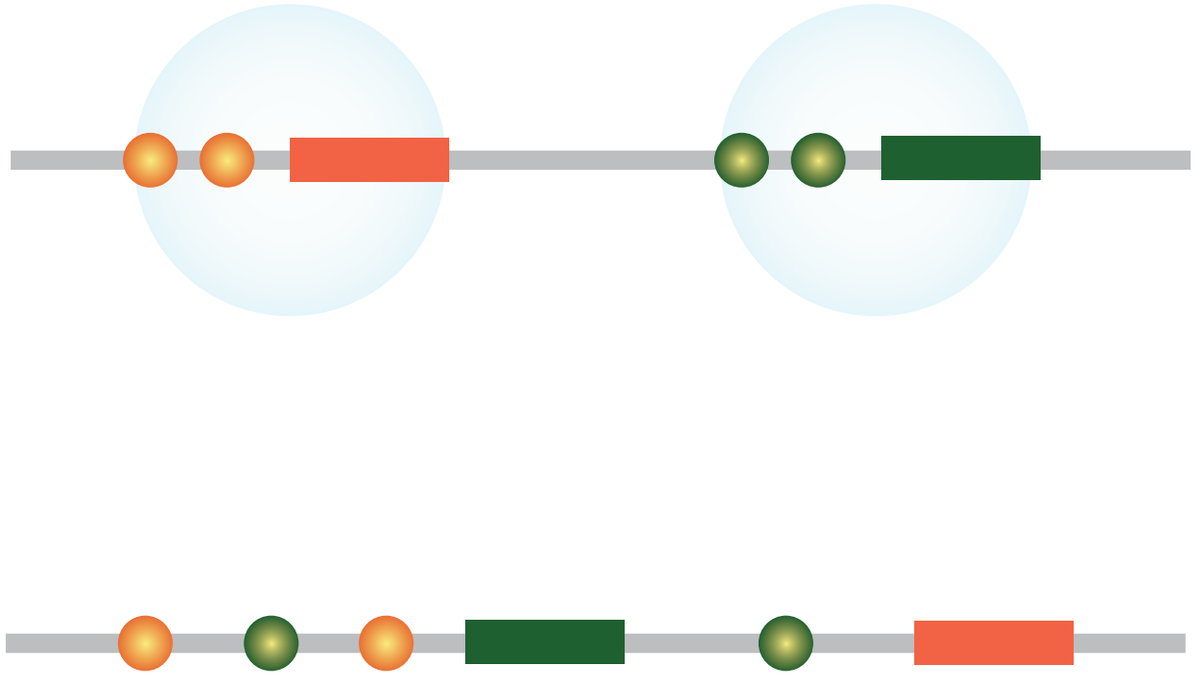
http://sgu.bioinfo.cipf.es

Structural Genomics Unit
Bioinformatics & Genomics Department
Prince Felipe Research Center (CIPF), Valencia, Spain

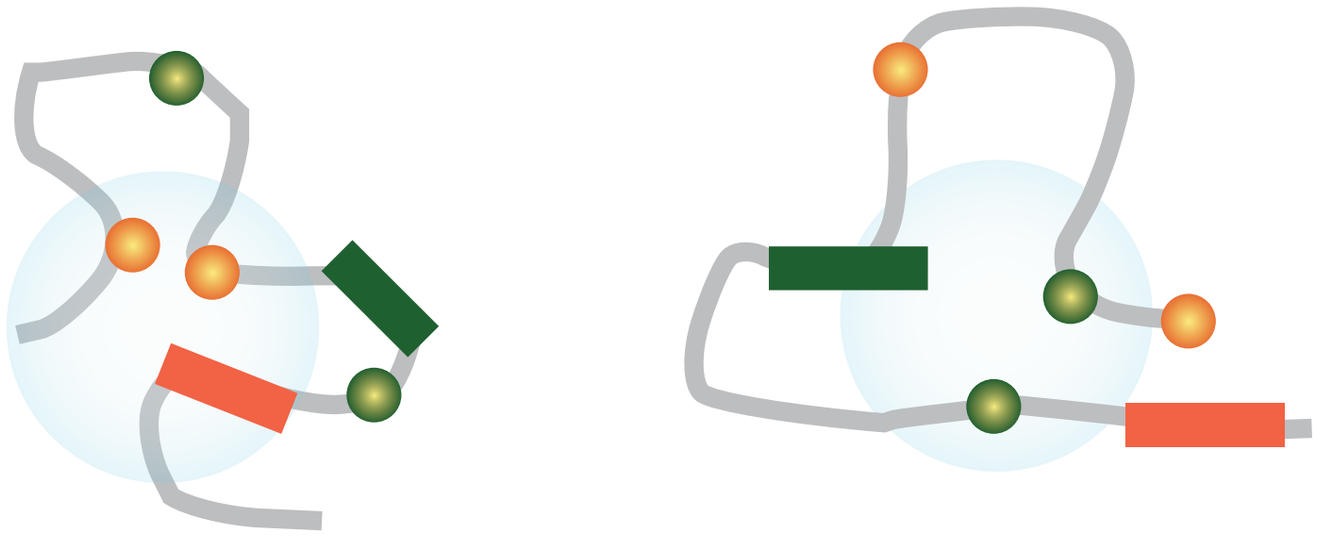
Aim

Can we relate structure and expression?

Simple genomes



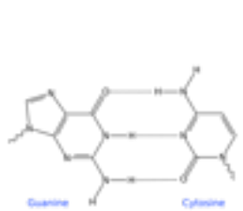
Complex genomes

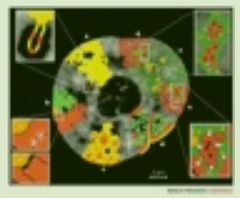


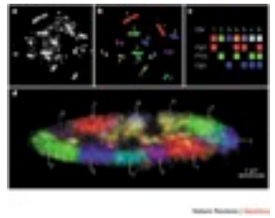
Resolution

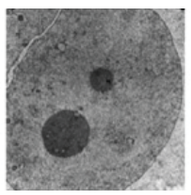
Limited knowledge...

Knowledge









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

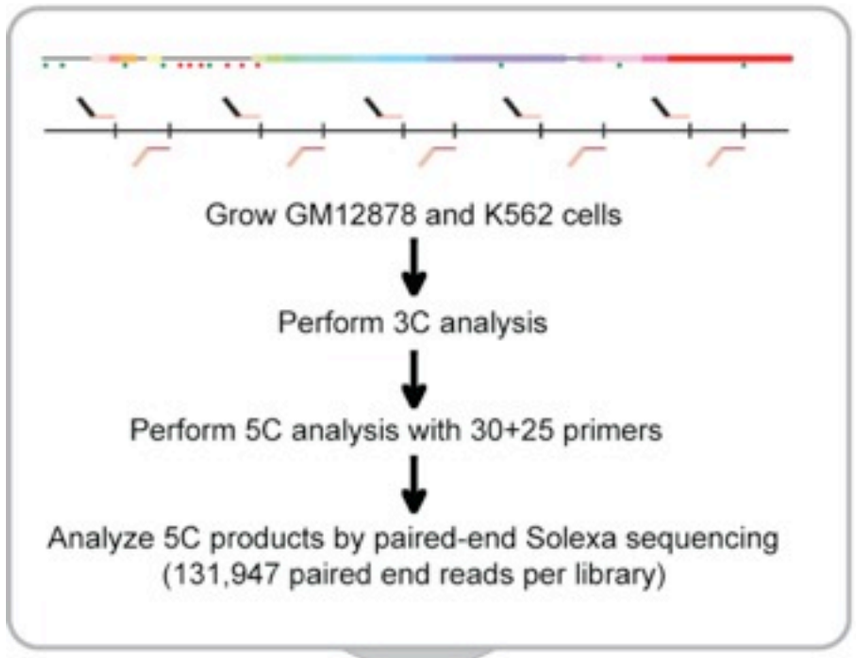
Resolution

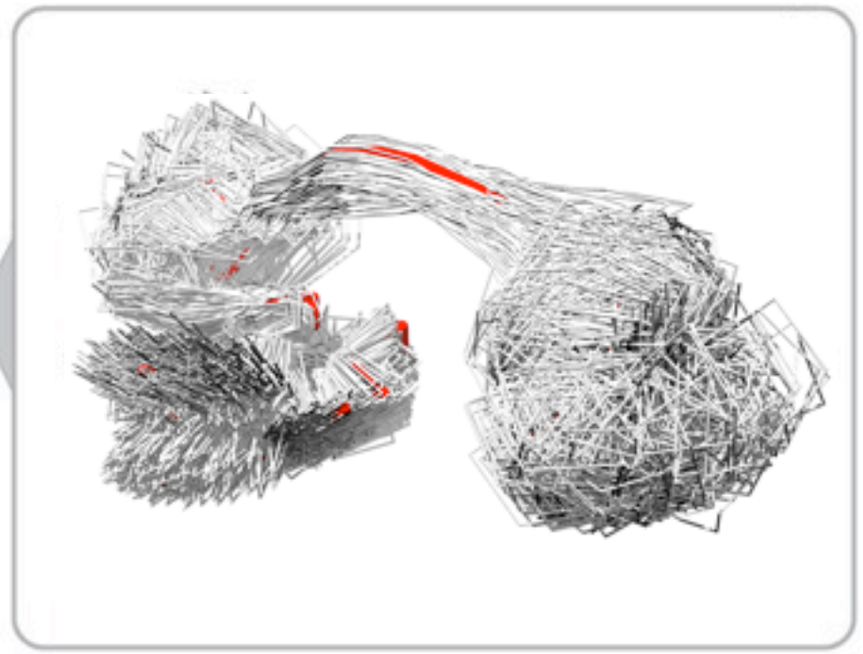
10^{-3} 10^{-2} 10^{-1} µ

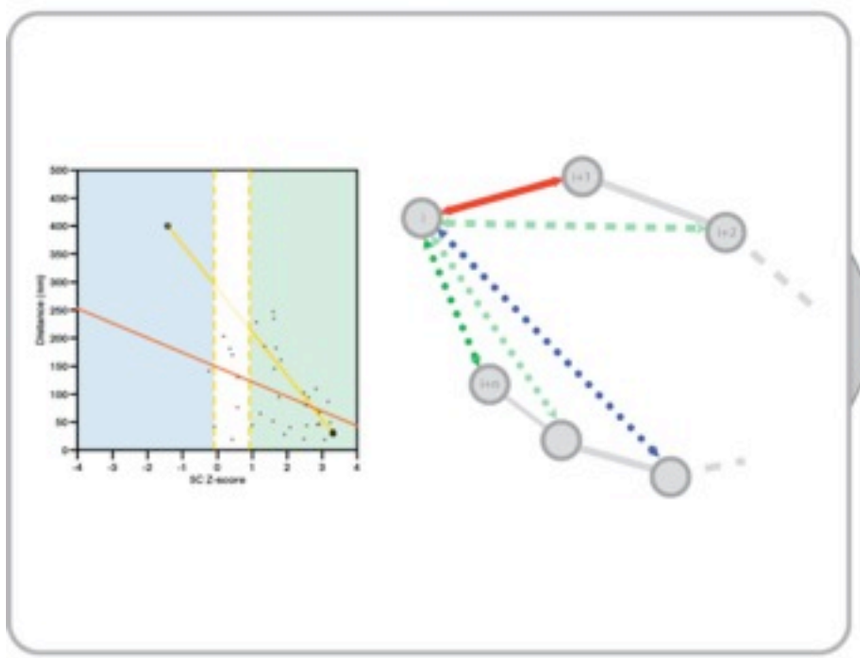
Adapted from:
Langowski and Heermann. Semin Cell Dev Biol (2007) vol. 18 (5) pp. 659-67

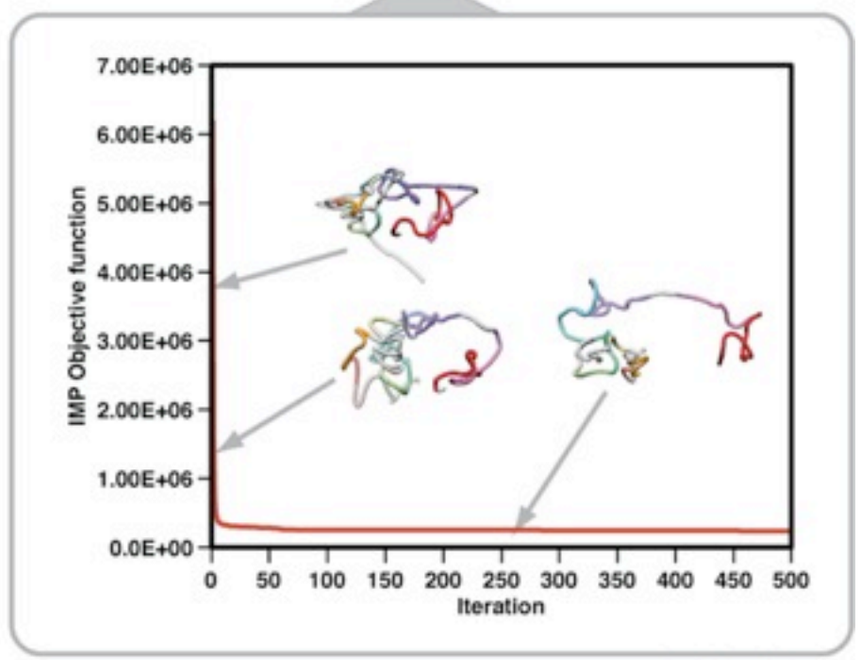
Integrative and iterative approach

Experiments









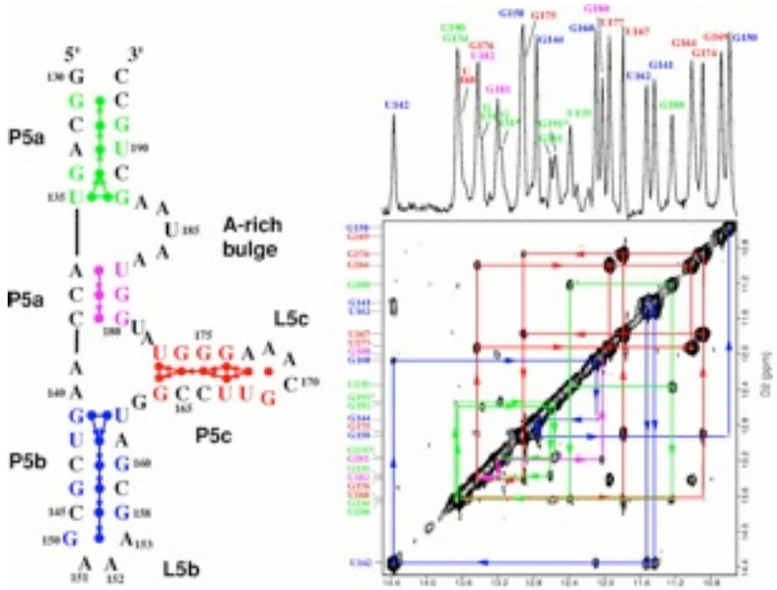
Computation

Structure determination

Integrative Modeling Platform

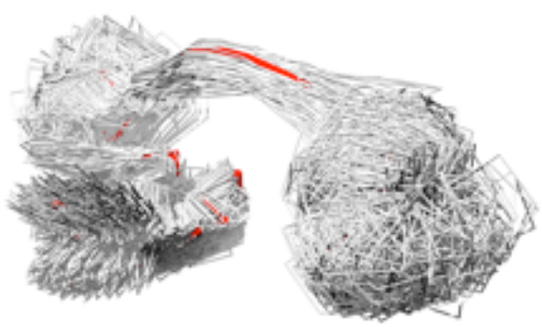
http://www.integrativemodeling.org

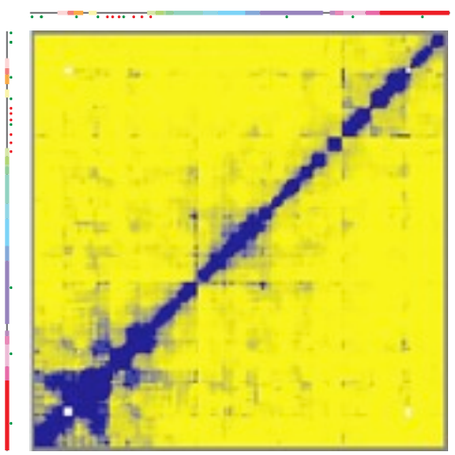
Alber et al. Nature (2007) vol. 450 (7170) pp. 683-94



Biomolecular structure determination

2D-NOESY data





Chromosome structure determination

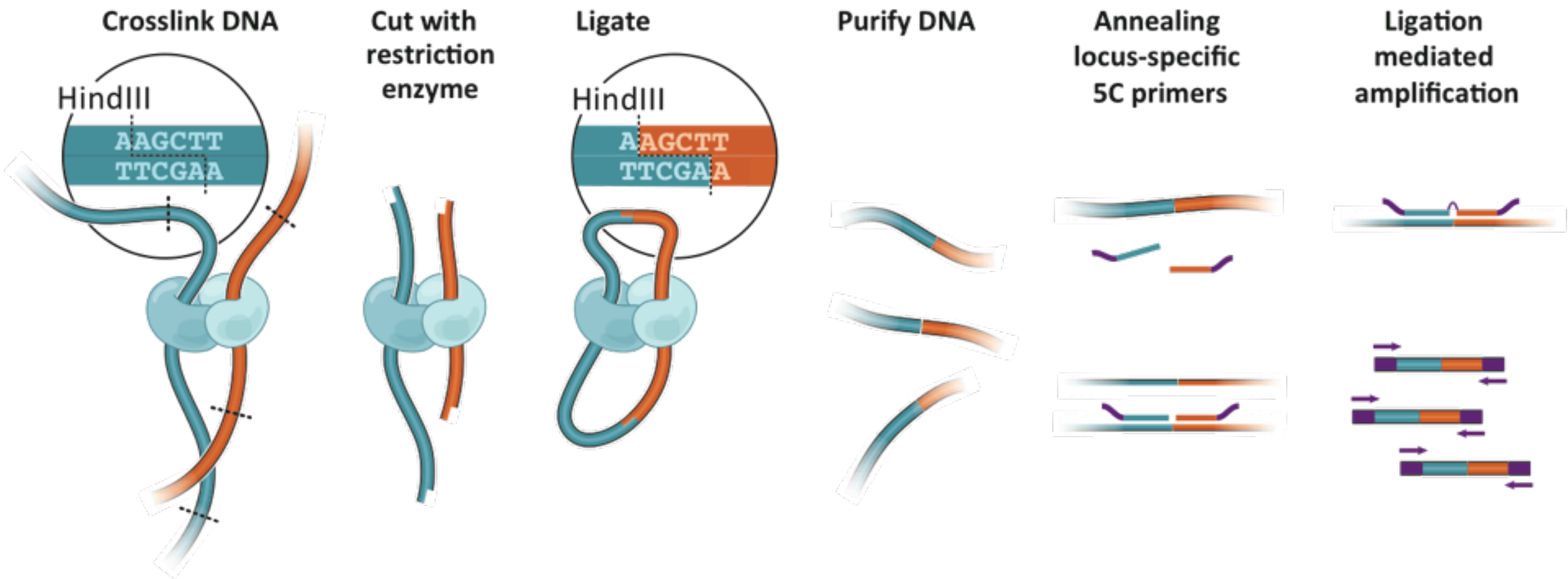
5C data

5C technology

Detecting up to millions of interactions in parallel

http://my5C.umassmed.edu

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



5C “copies” the 3C library into a 5C library containing only ligation junctions

Performed at high levels of multiplexing:

2,000 primers detect 1,000,000 unique interactions in 1 reaction

Human α-globin domain

ENm008 genomic structure and environment

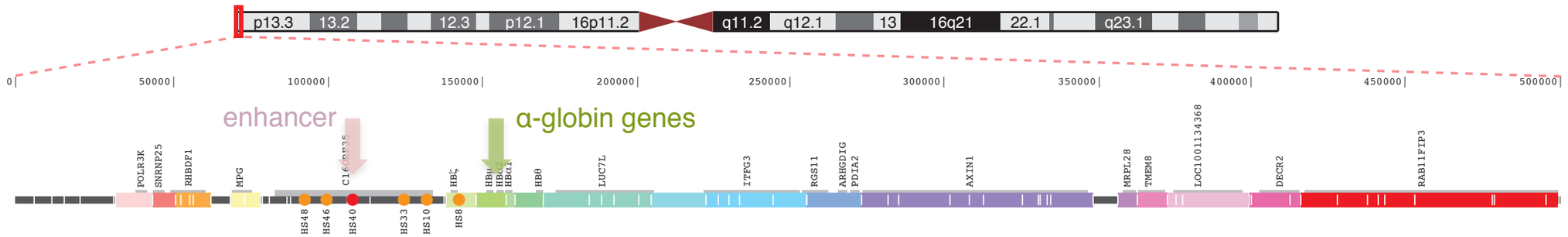
ENCODE Consortium. Nature (2007) vol. 447 (7146) pp. 799-816

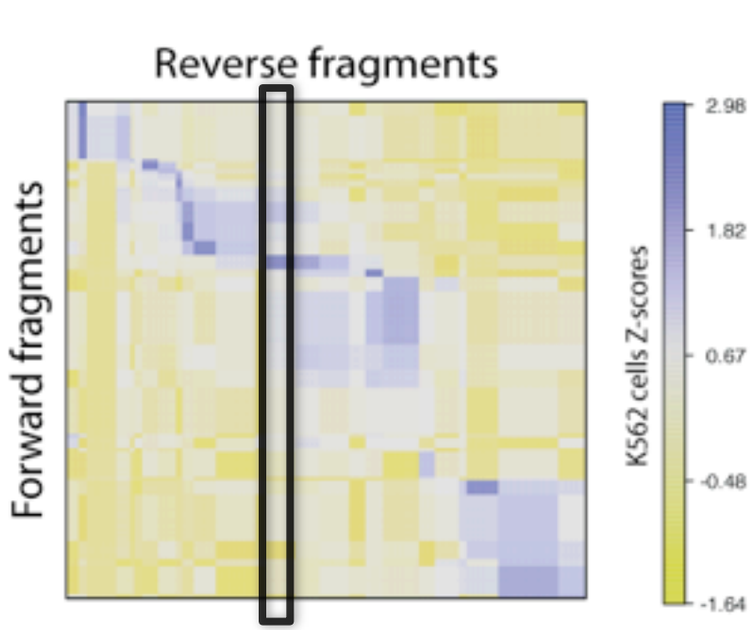
The ENCODE data for ENm008 region was obtained from the UCSC Genome Browser tracks for: RefSeq annotated genes, Affymetrix/CSHL expression data (Gingeras Group at Cold Spring Harbor), Duke/NHGRI DNaseI Hypersensitivity data (Crawford Group at Duke University), and Histone Modifications by Broad Institute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

Human α-globin domain

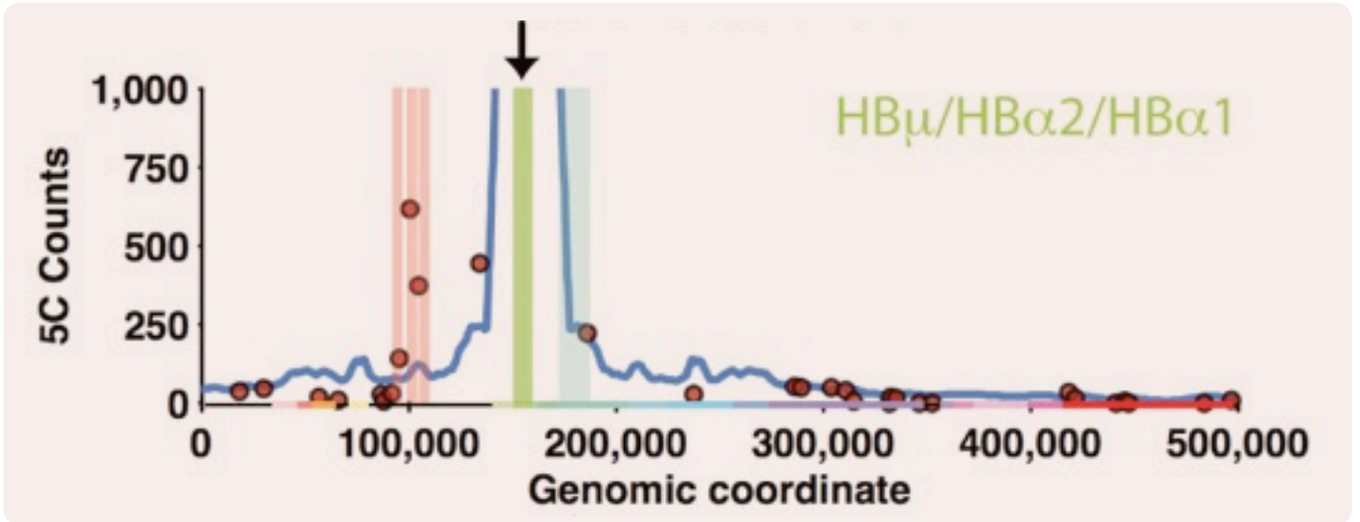
ENm008 genomic structure and environment

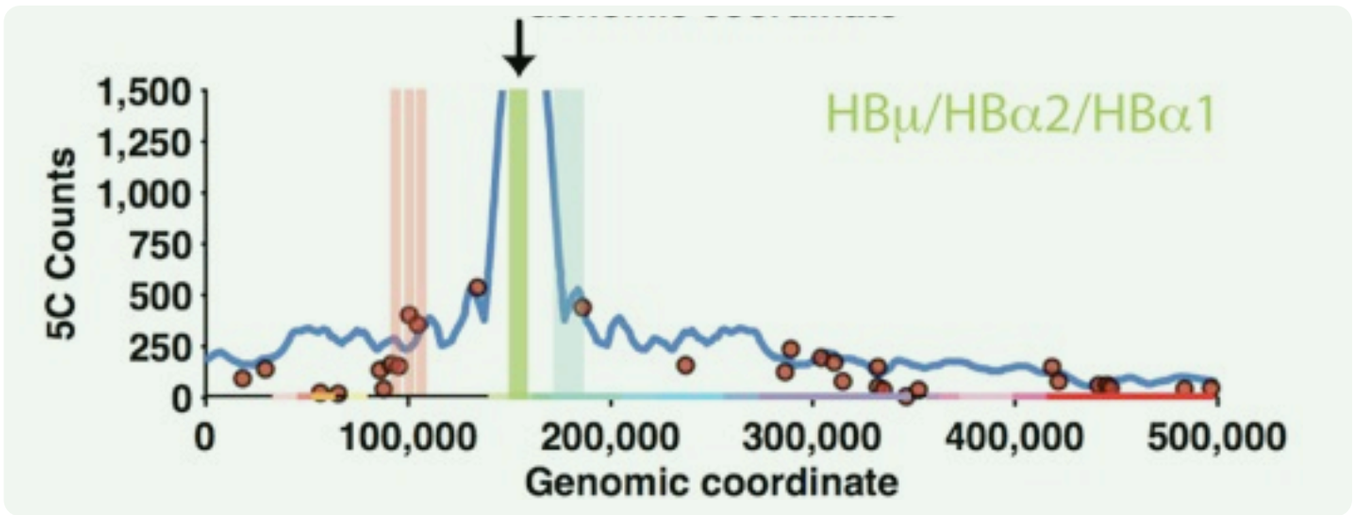
ENCODE Consortium. Nature (2007) vol. 447 (7146) pp. 799-816





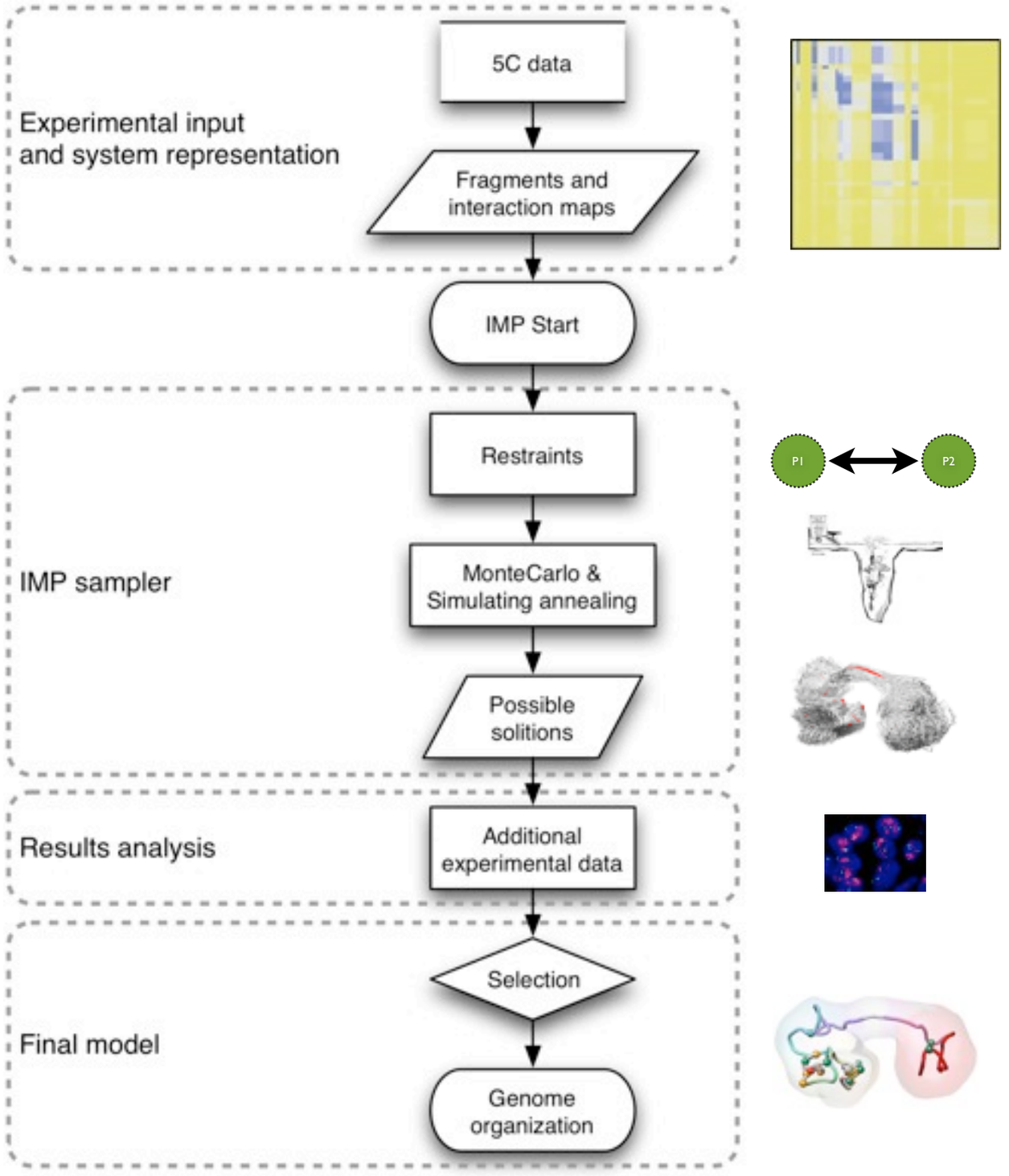
K562 cells:
α-globin genes active





Integrative Modeling

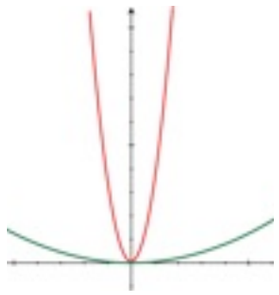
http://www.integrativemodeling.org



Representation

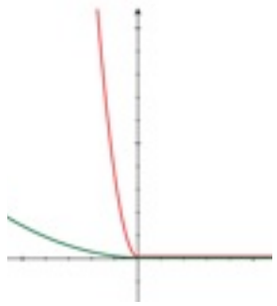
Harmonic

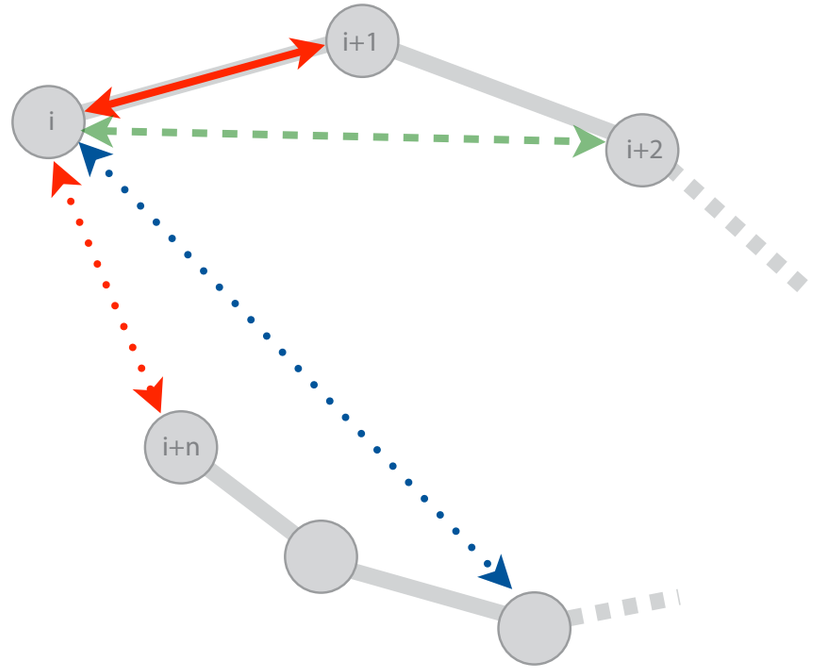
$$H_{i,j} = k\left(d_{i,j} - d^0_{i,j}\right)^2$$



Harmonic Lower Bound

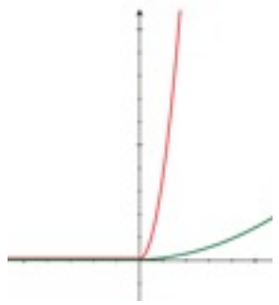
$$\begin{cases} if \;\; d_{i,j} \le d^0_{i,j}; & lbH_{i,j} = k\left(d_{i,j} - d^0_{i,j}\right)^2 \\ if \;\; d_{i,j} > d^0_{i,j}; & lbH_{i,j} = 0 \end{cases}$$





Harmonic Upper Bound

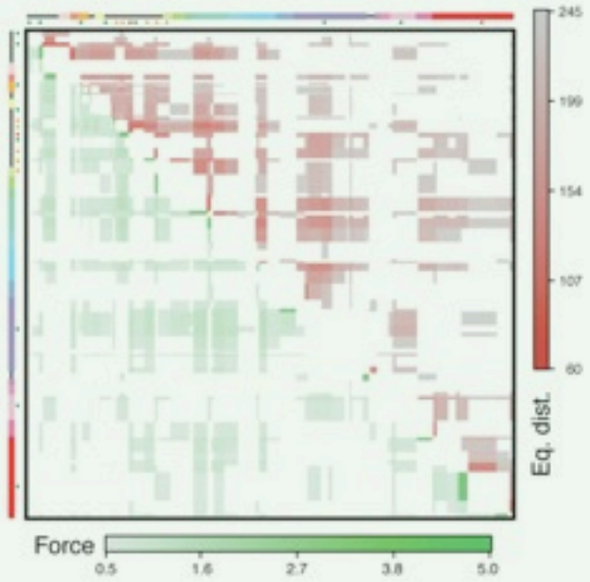
$$\begin{cases} if \;\; d_{i,j} \ge d^0_{i,j}; & ubH_{i,j} = k\left(d_{i,j} - d^0_{i,j}\right)^2 \\ if \;\; d_{i,j} < d^0_{i,j}; & ubH_{i,j} = 0 \end{cases}$$

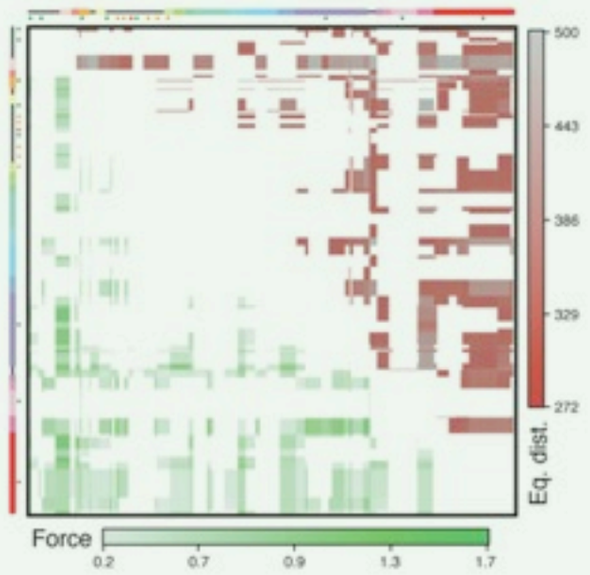


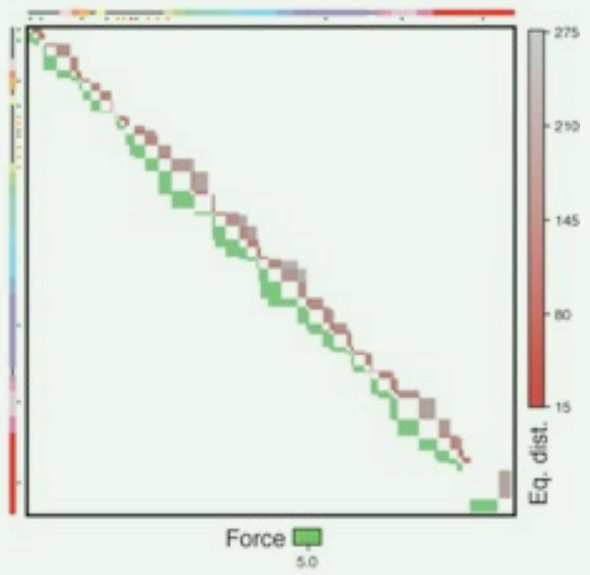
Scoring

GM12878

70 fragments
1,520 restraints



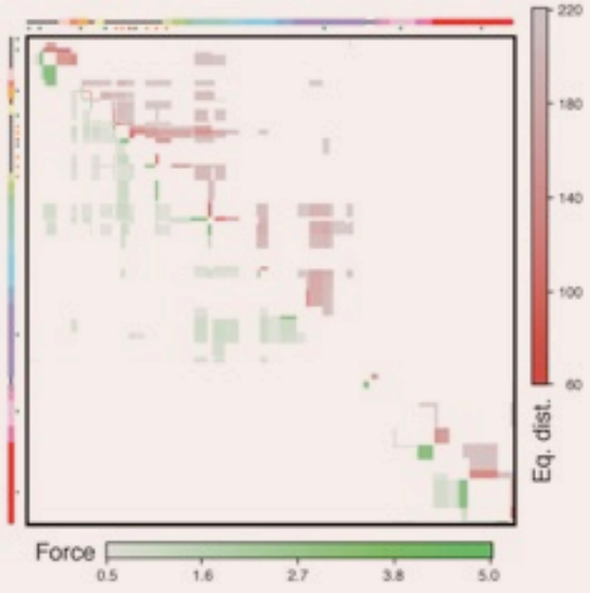


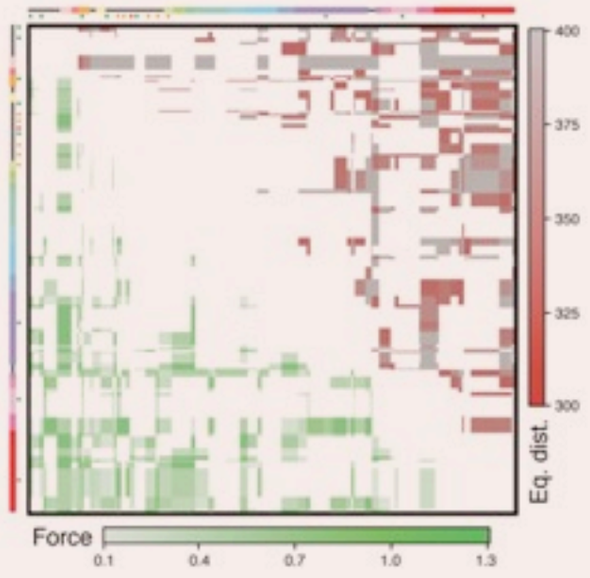


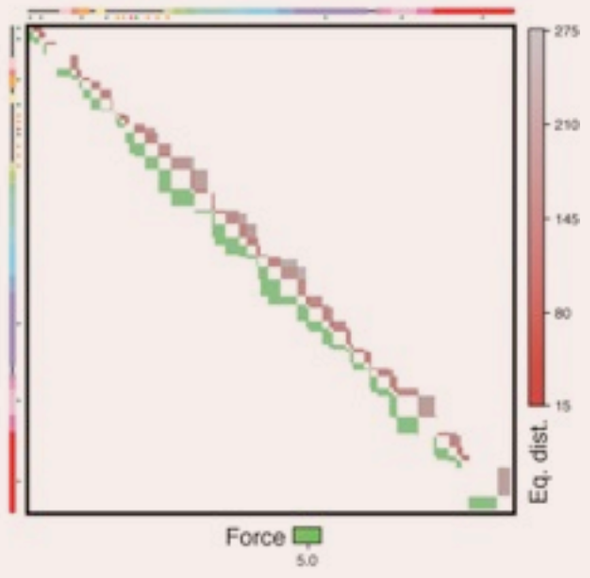
Harmonic | Harmonic Lower Bound | Harmonic Upper Bound

K562

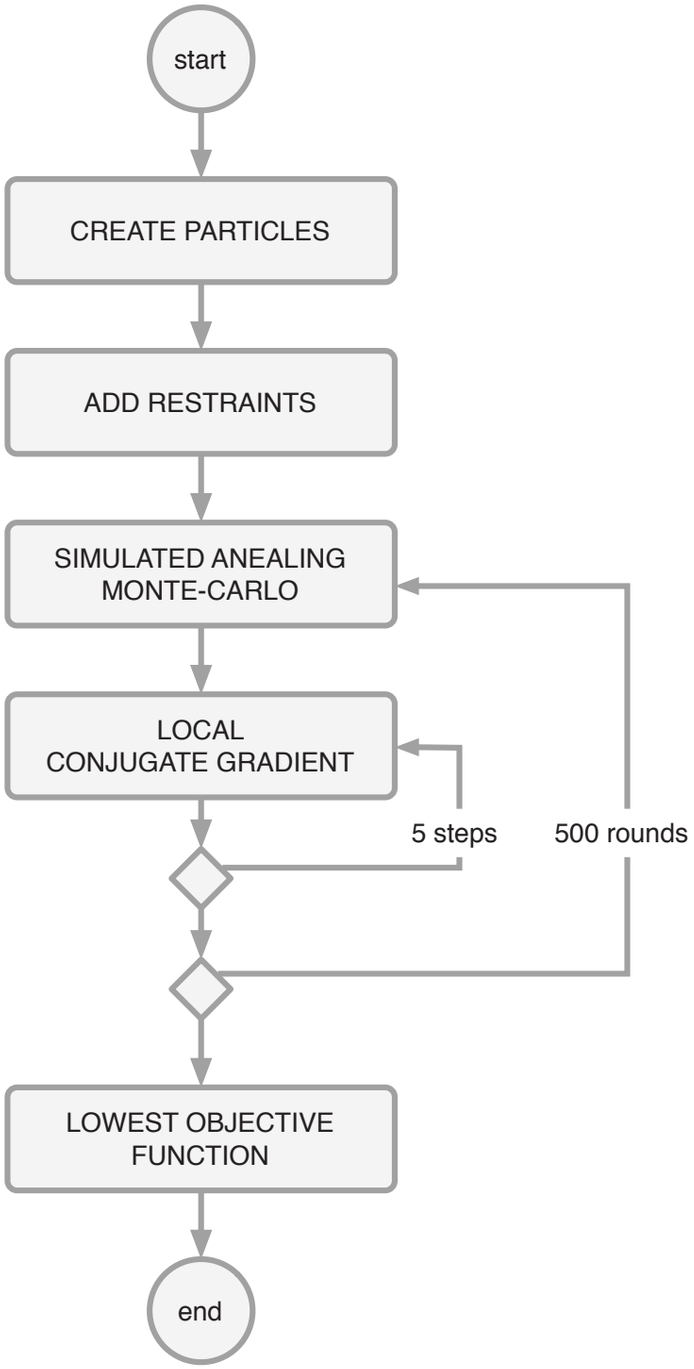
70 fragments
1,049 restraints

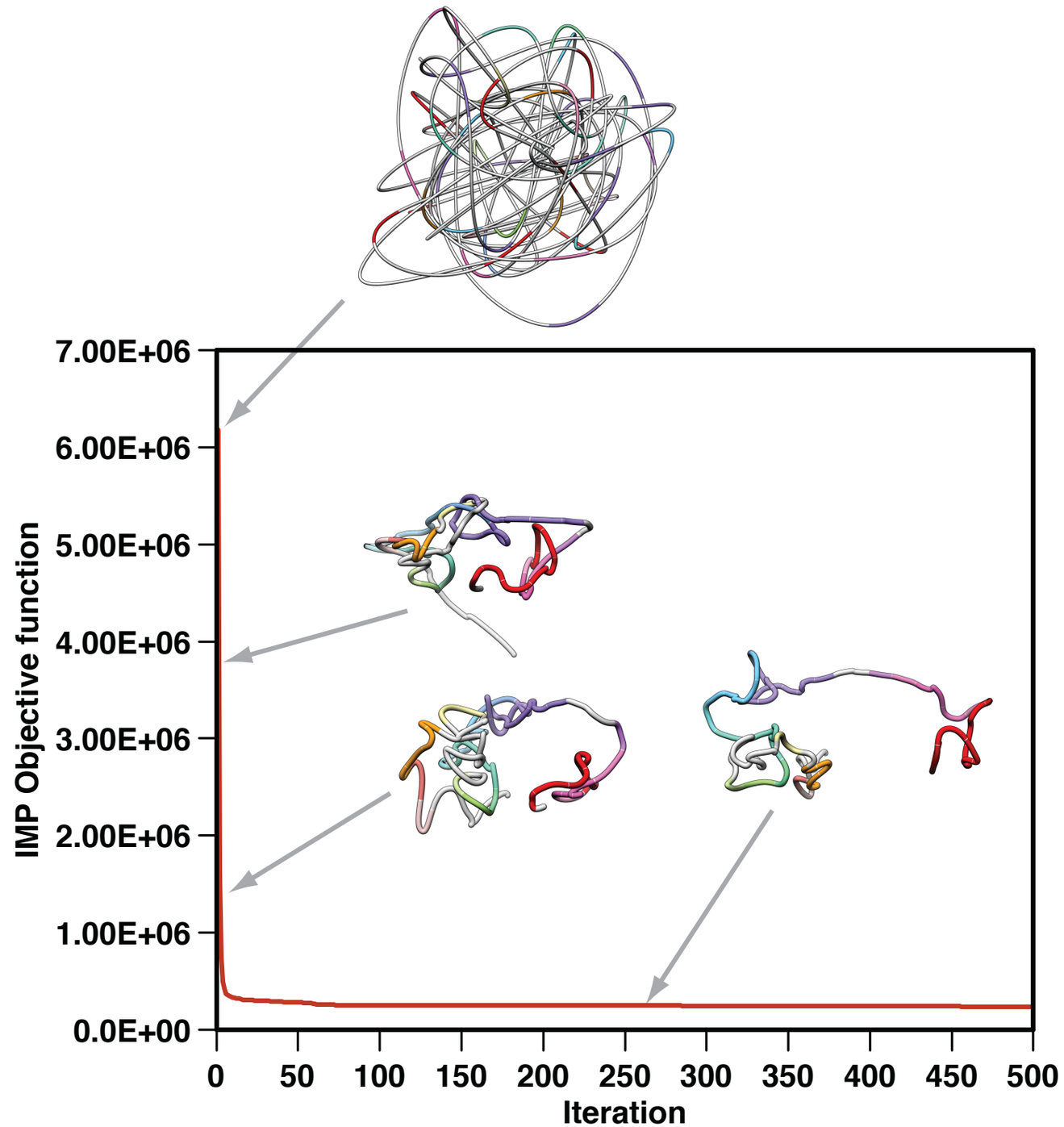




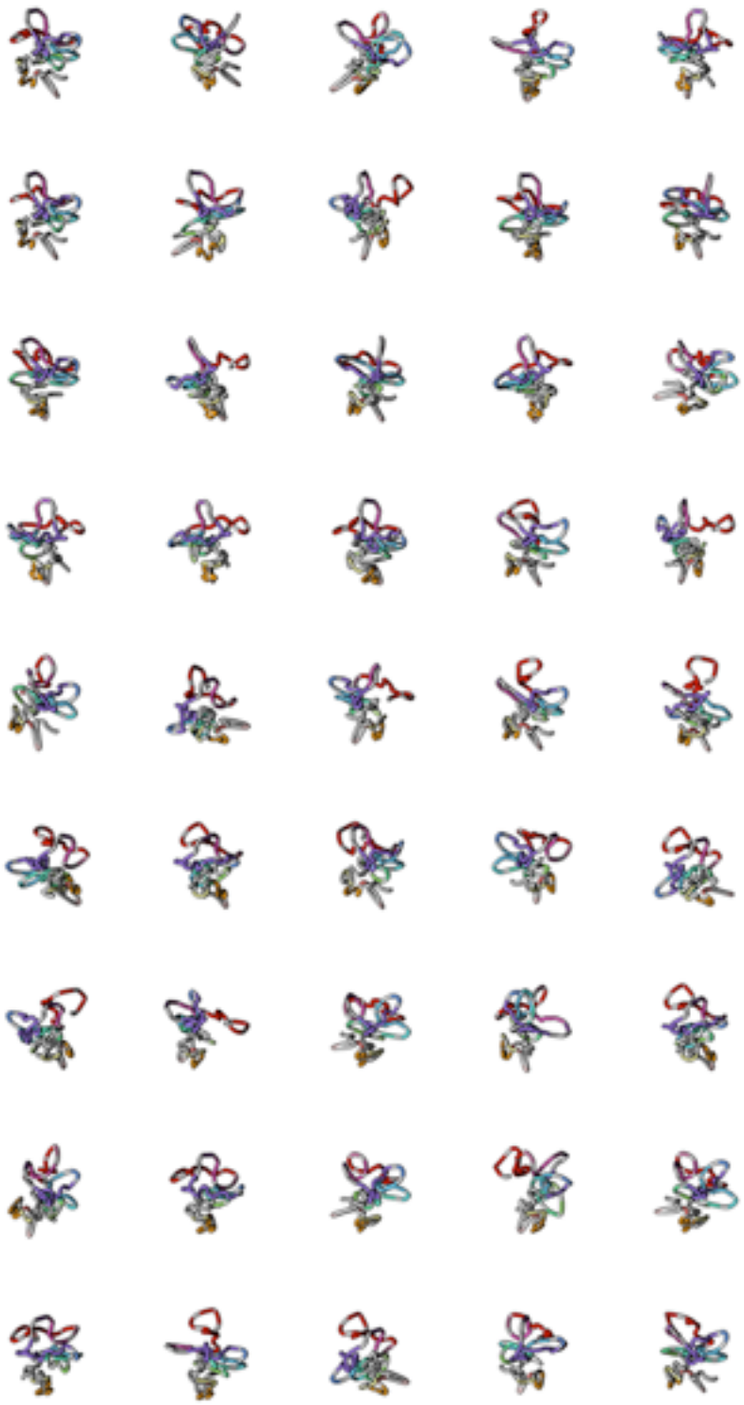


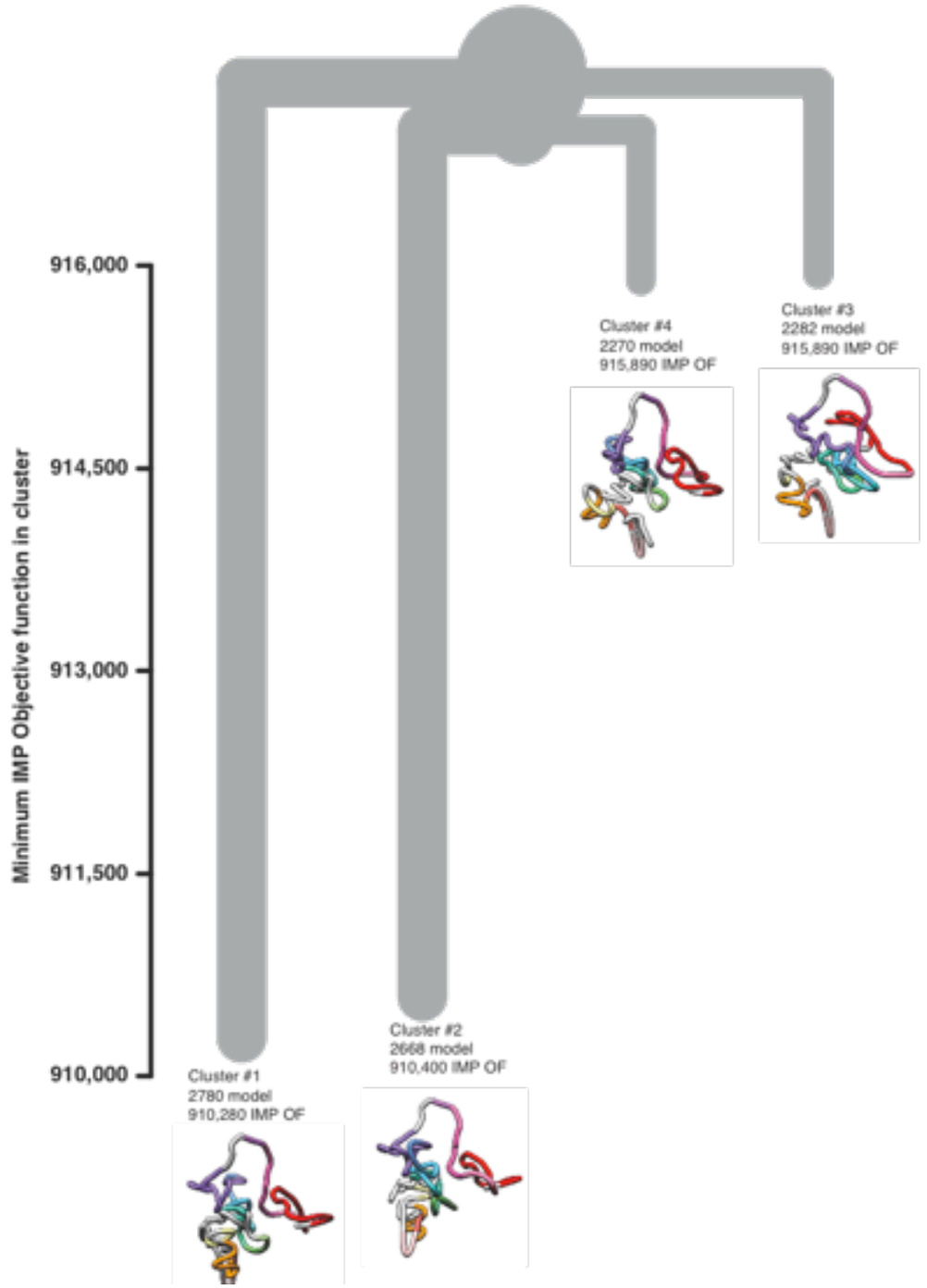
Optimization





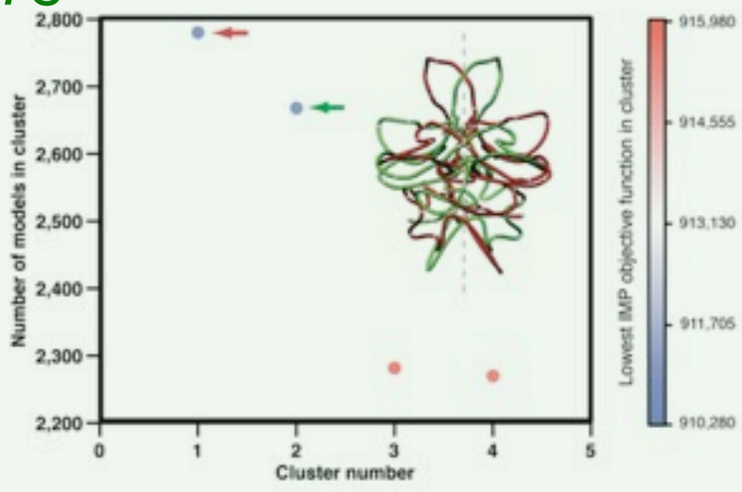
Clustering

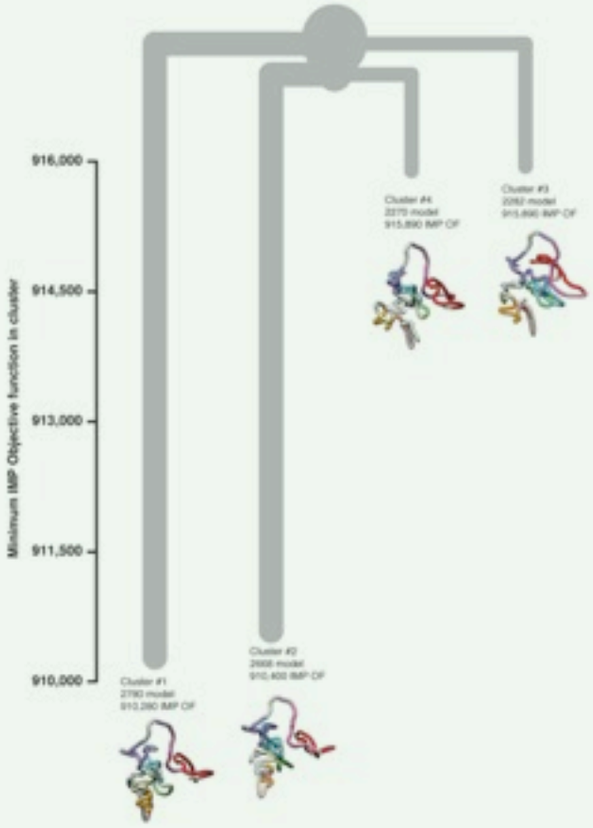



916,000
914,500
913,000
911,500
910,000
Minimum IMP Objective function in cluster
Cluster #4
2270 model
915,890 IMP OF
Cluster #3
2282 model
915,890 IMP OF
Cluster #2
2668 model
910,400 IMP OF
Cluster #1
2780 model
910,280 IMP OF

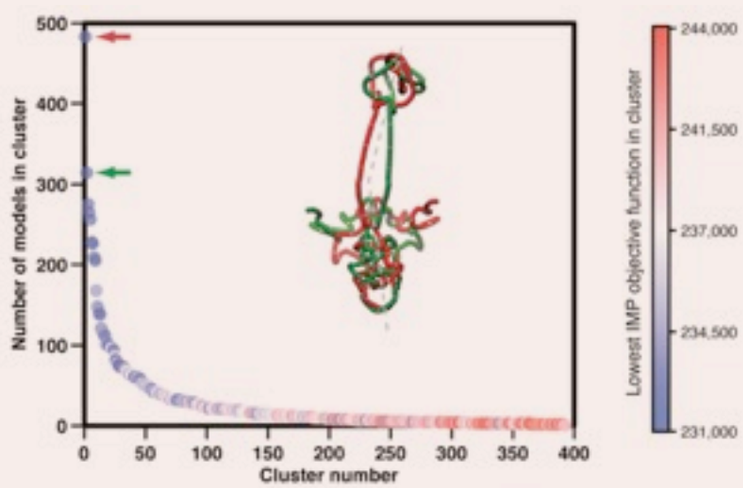
Not just *one* solution

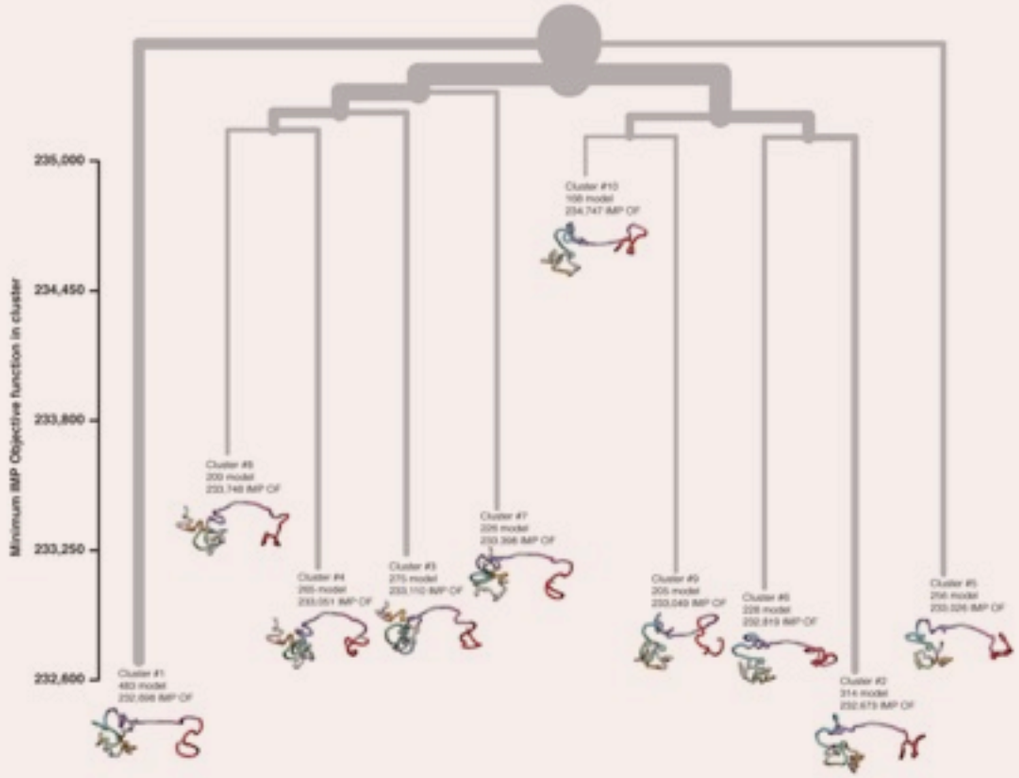
GM12878





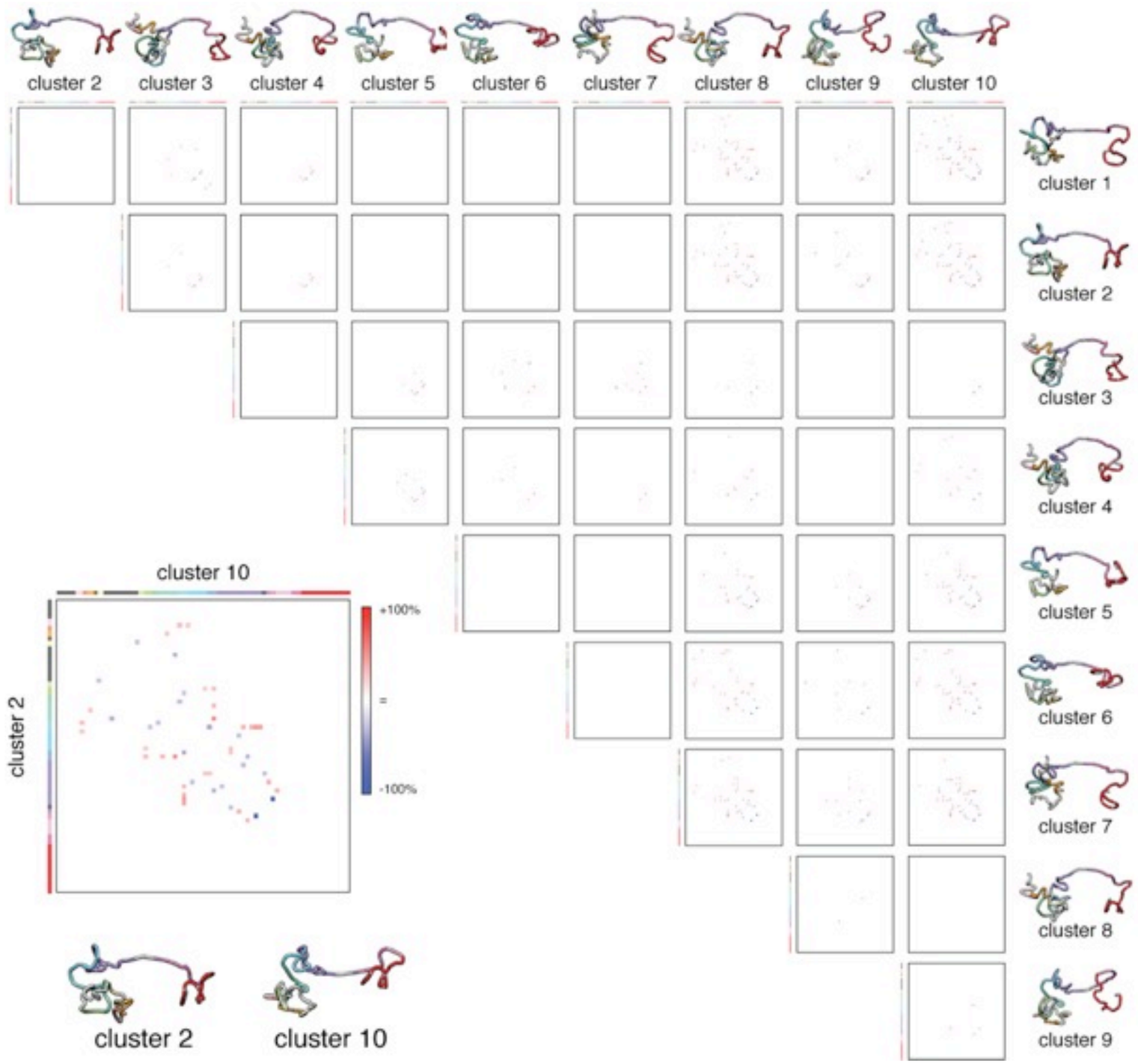
K562





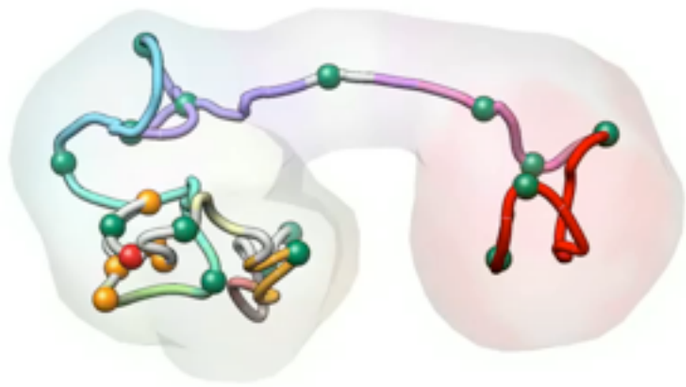
Not just *one* solution

and we can de-convolute them!

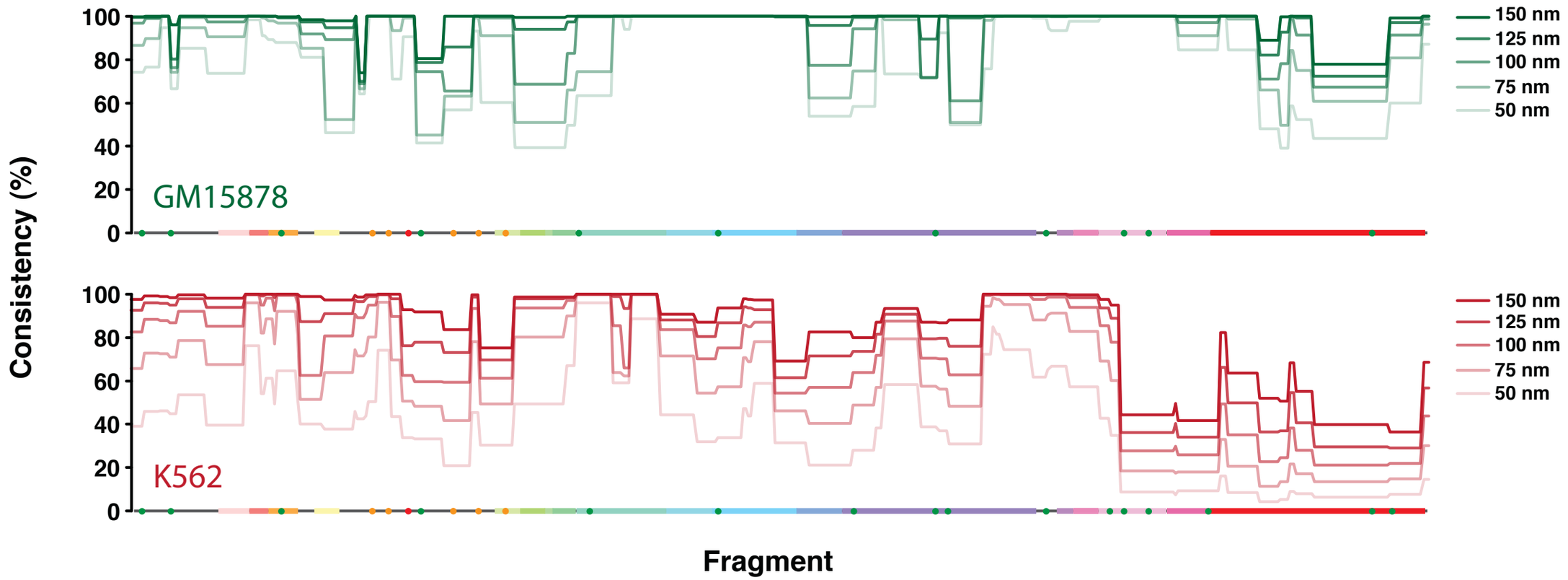


Consistency

GM12878
Cluster #1
2780 model



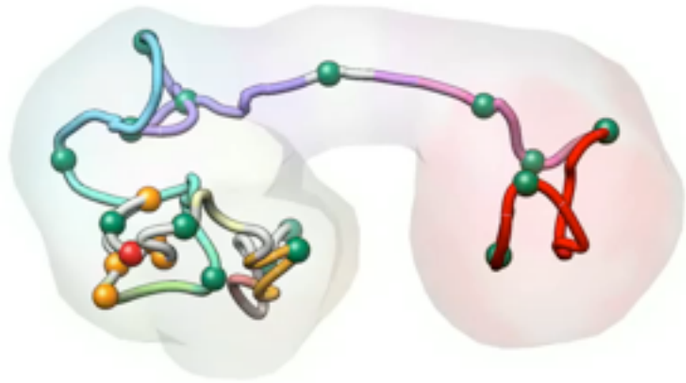
K562
Cluster #2
314 model



Regulatory elements

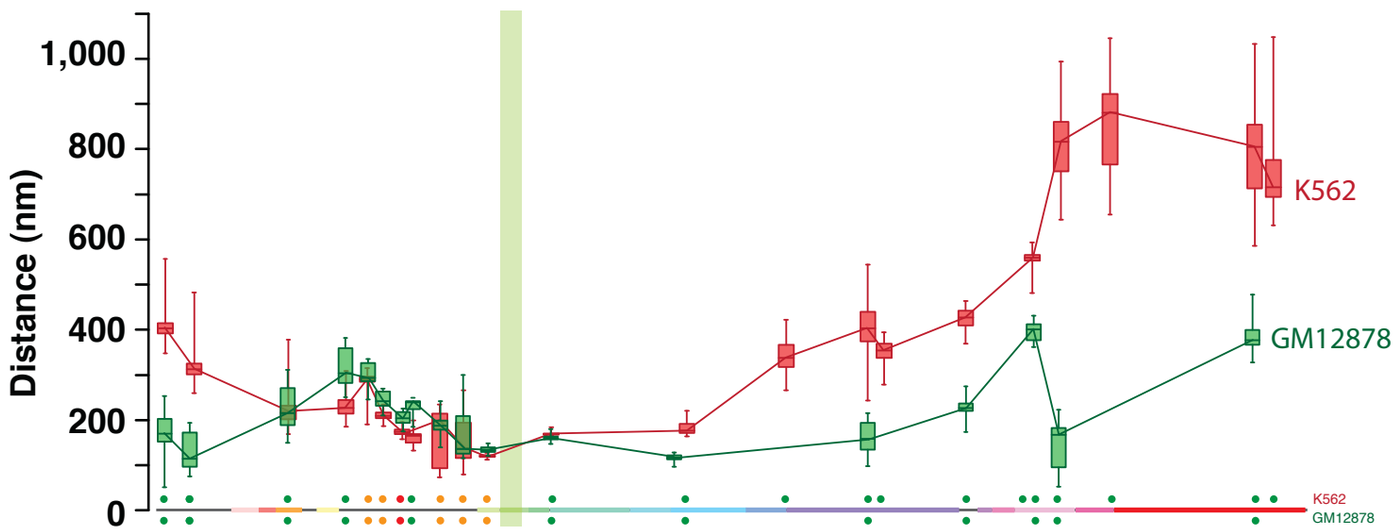
GM12878

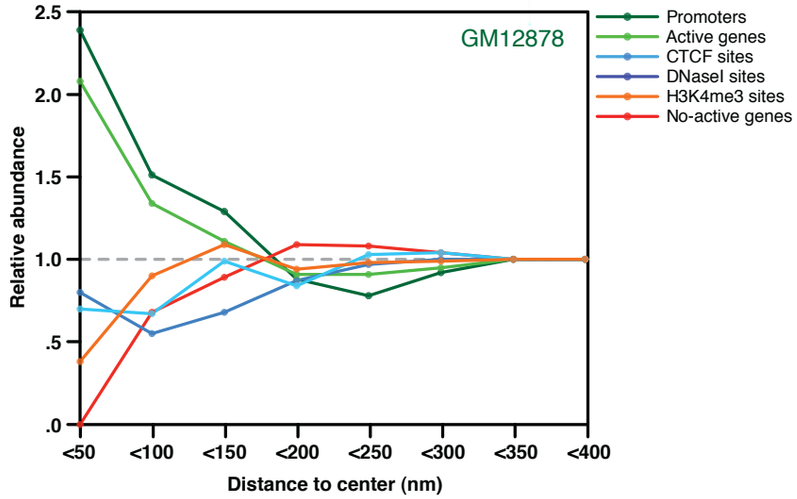
Cluster #1
2780 model

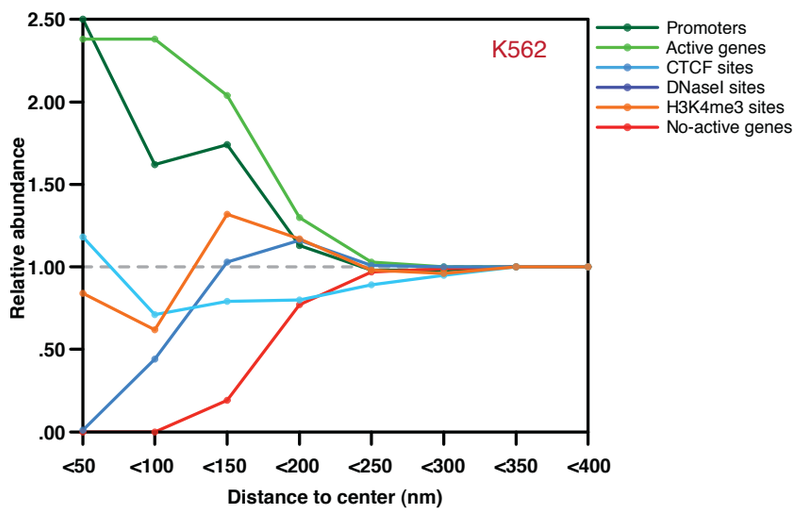


K562

Cluster #2
314 model

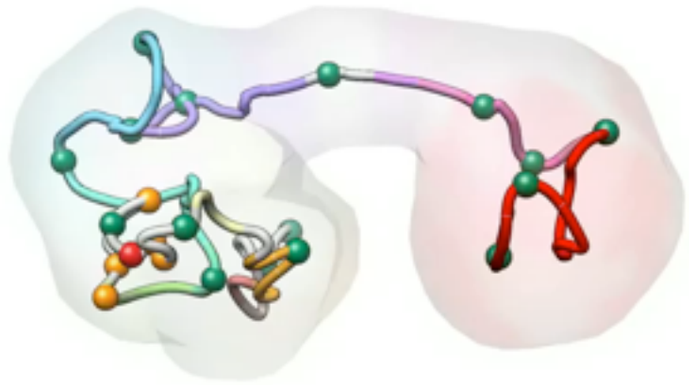




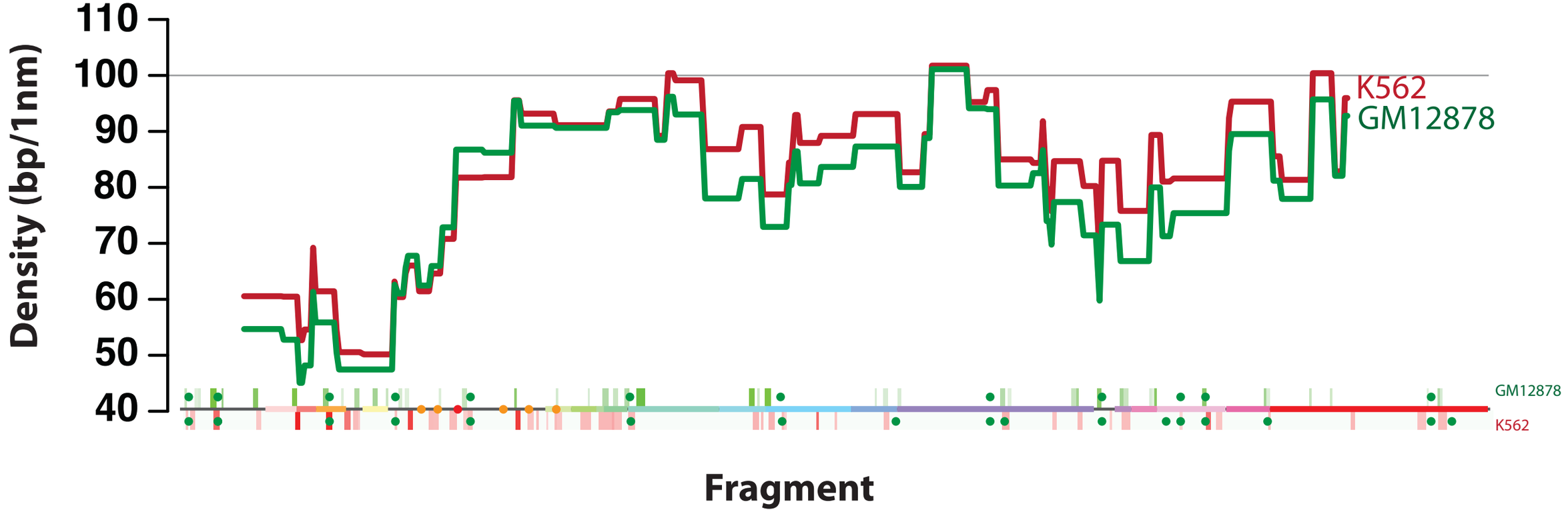


Compactness

GM12878
Cluster #1
2780 model



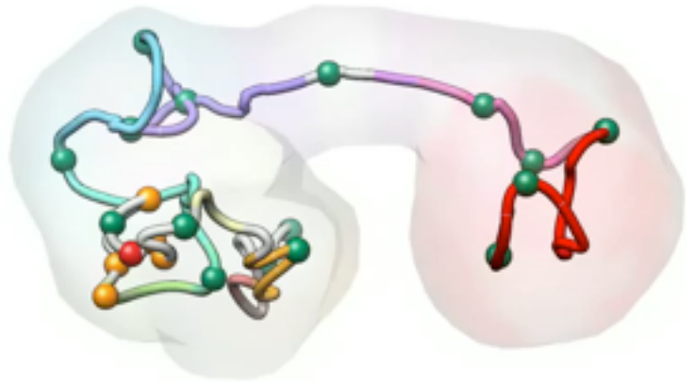
K562
Cluster #2
314 model



Multi-loops

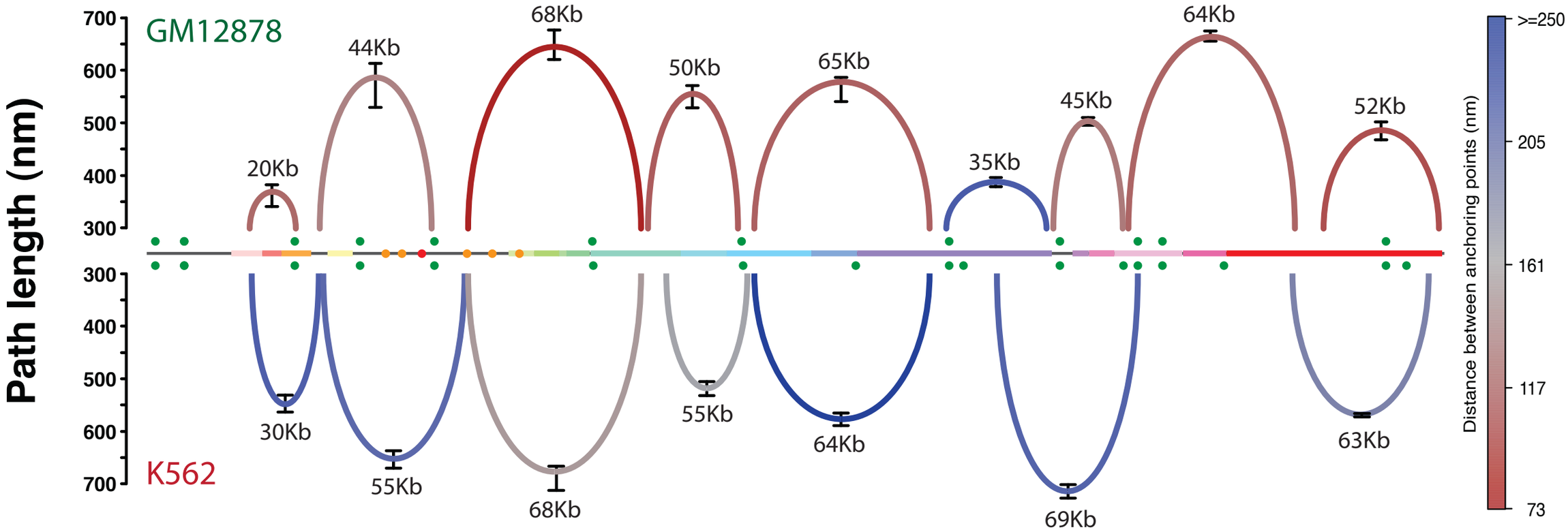
GM12878

Cluster #1
2780 model



K562

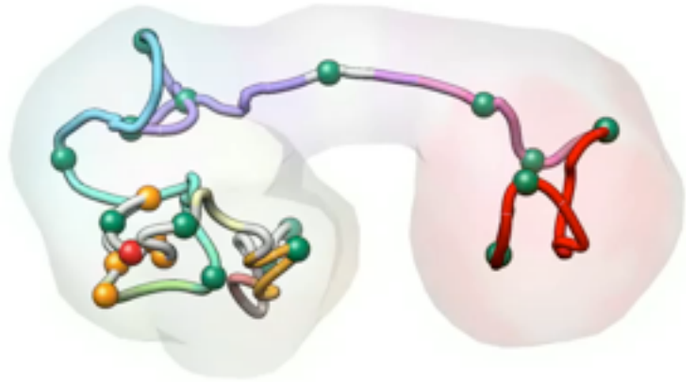
Cluster #2
314 model



Expression

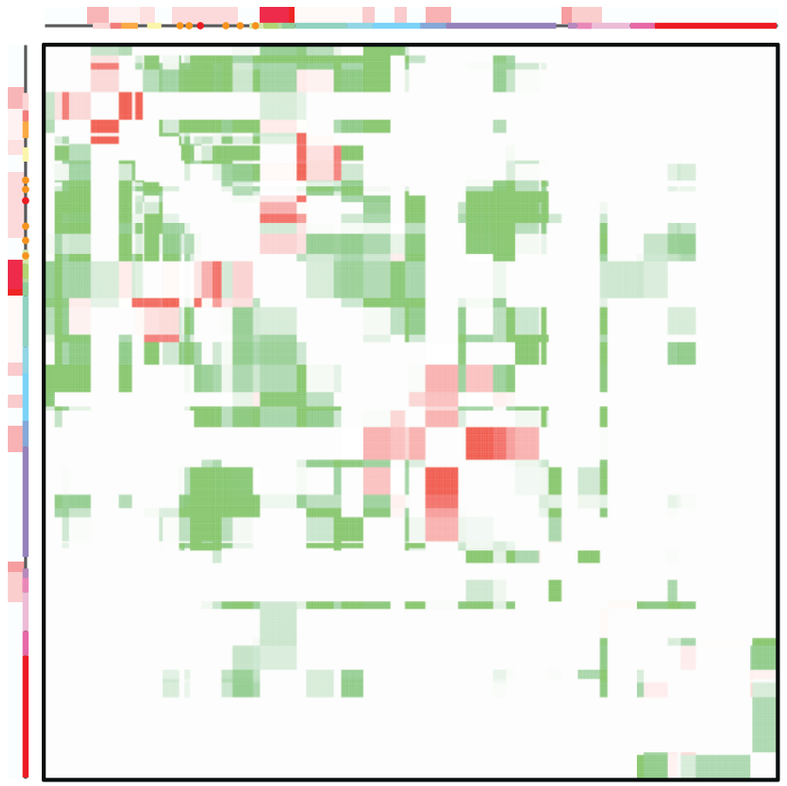
GM12878

Cluster #1
2780 model



K562

Cluster #2
314 model



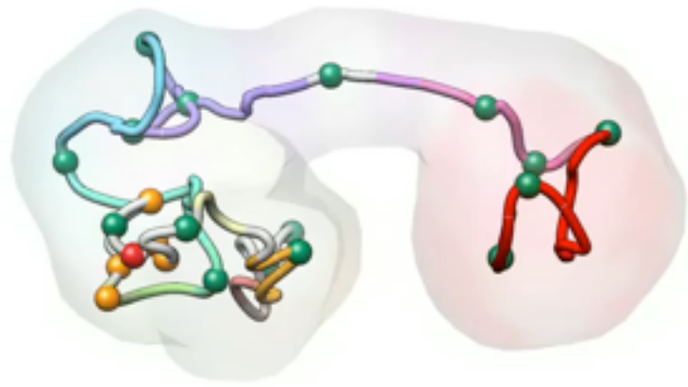
Increased in GM12878

=

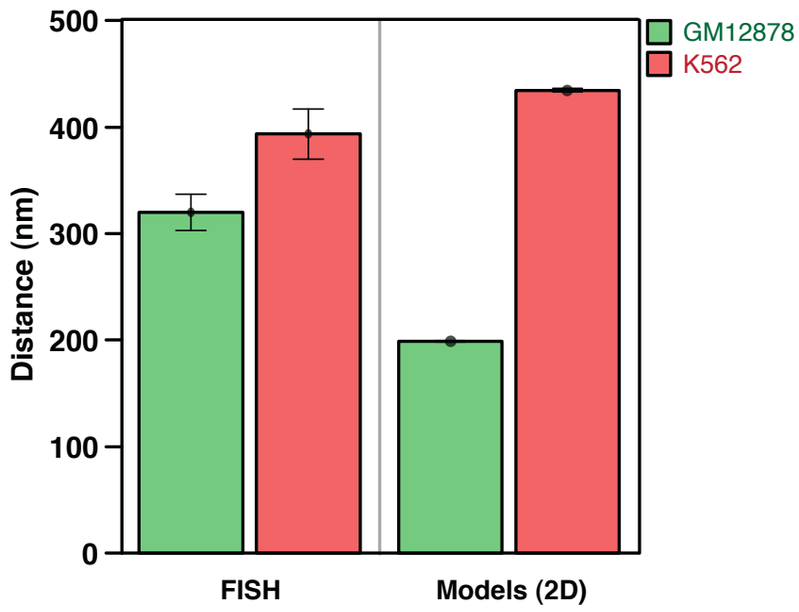
Increased in K562

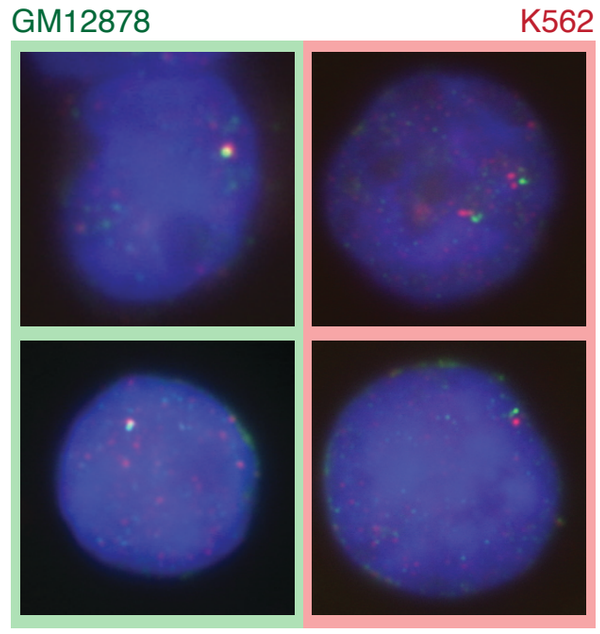
FISH validation

GM12878
Cluster #1
2780 model



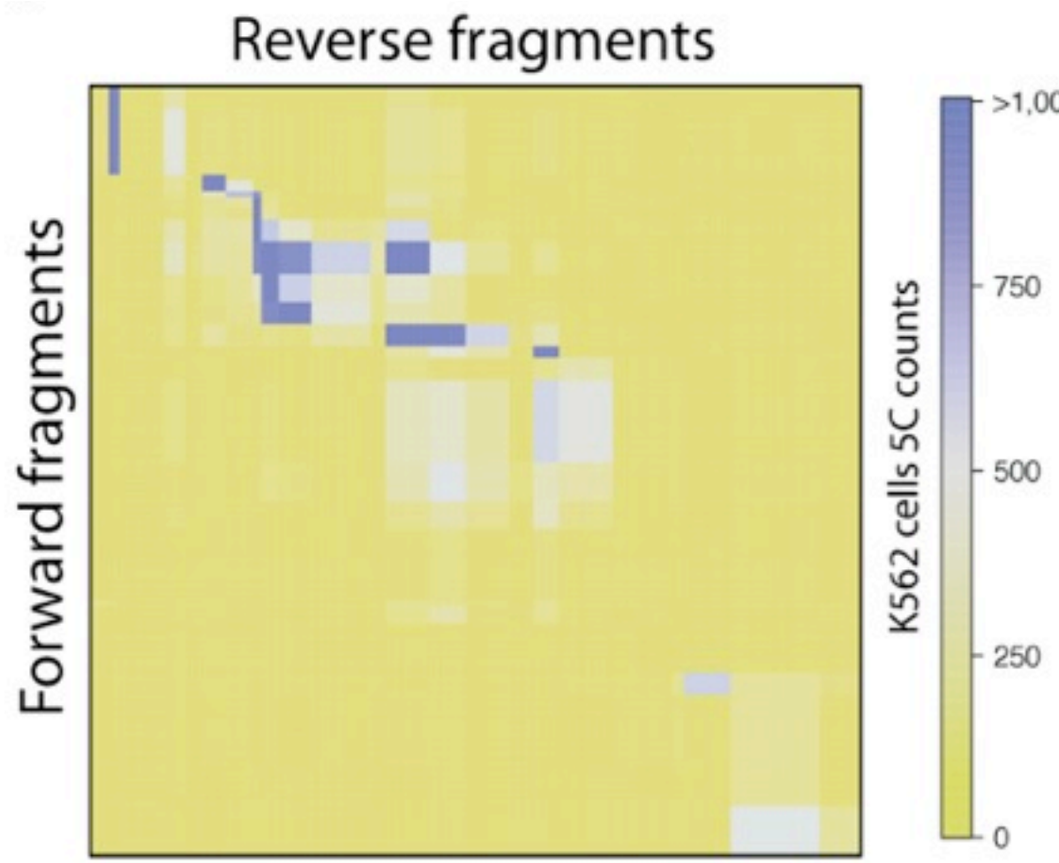
K562
Cluster #2
314 model

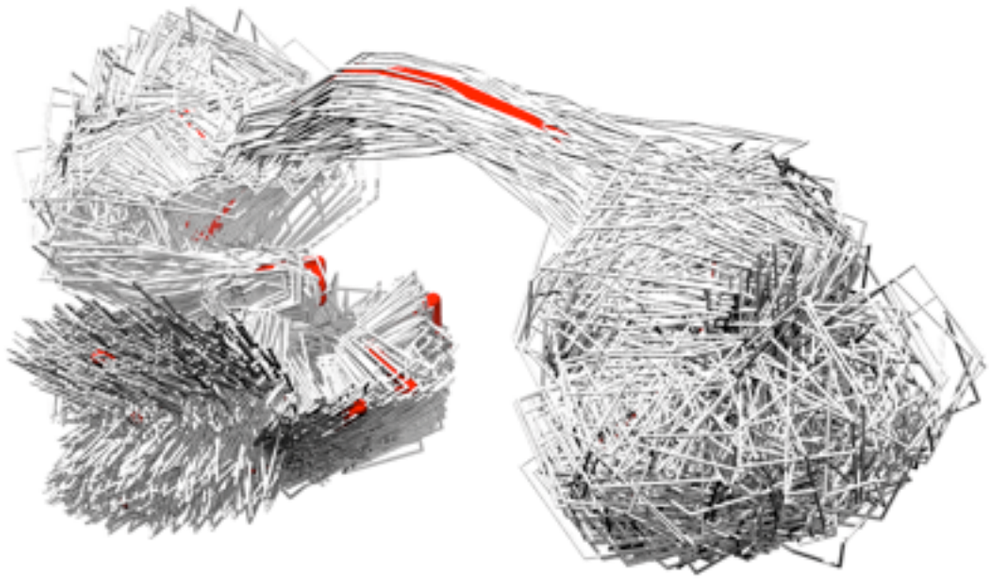


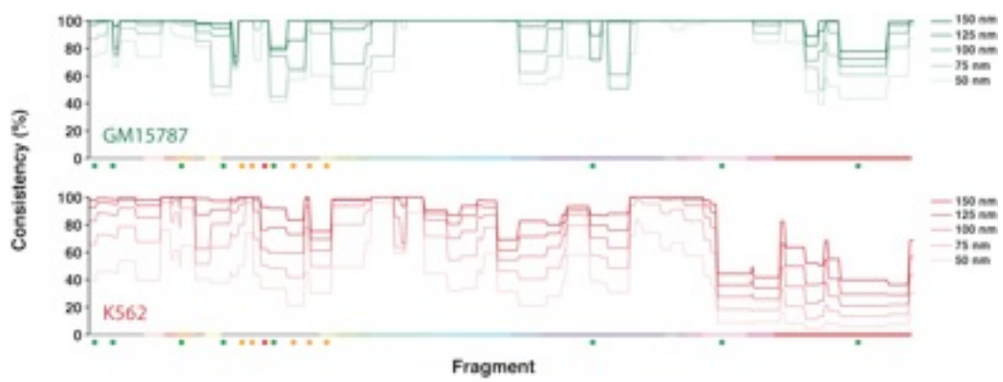


Summary

5C data results in comprehensive interaction matrices to build a consistent 3D model







Summary

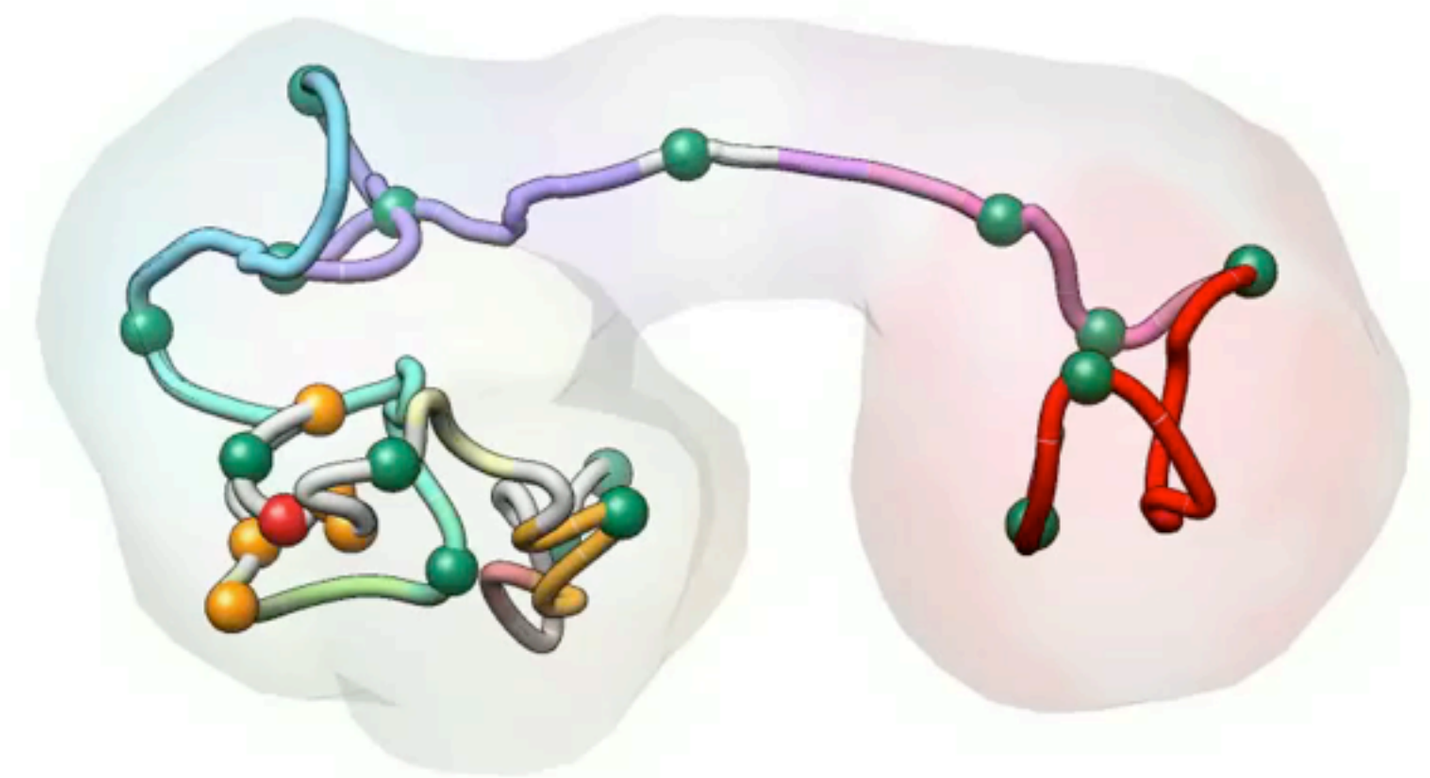
Models allow for 5C data de-convolution

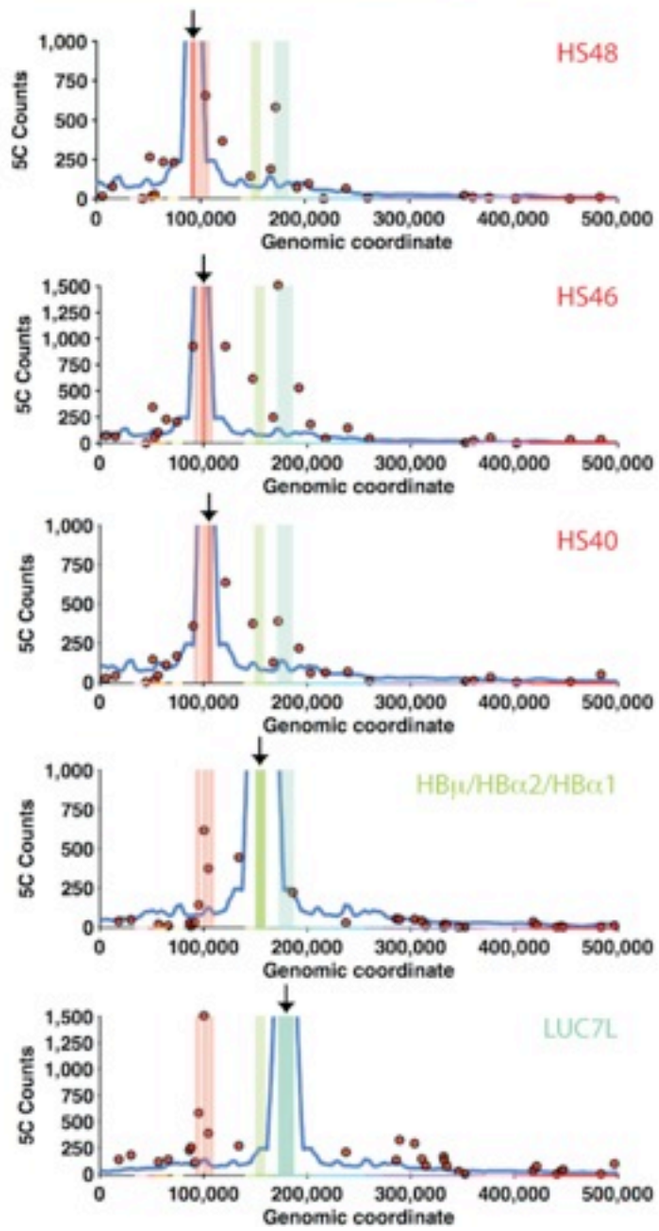
Summary

Models allow for 5C data de-convolution

Summary

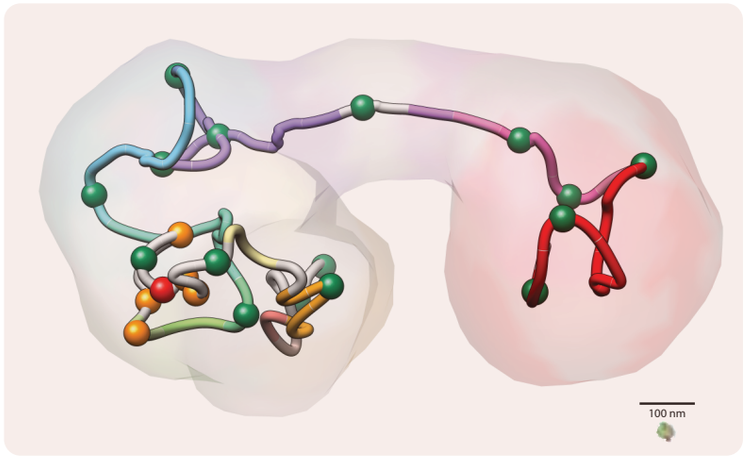
Selected models reproduce known (**and new**) interactions

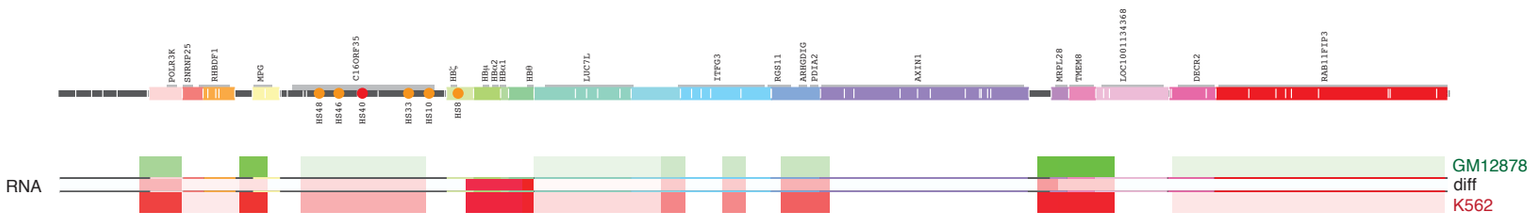


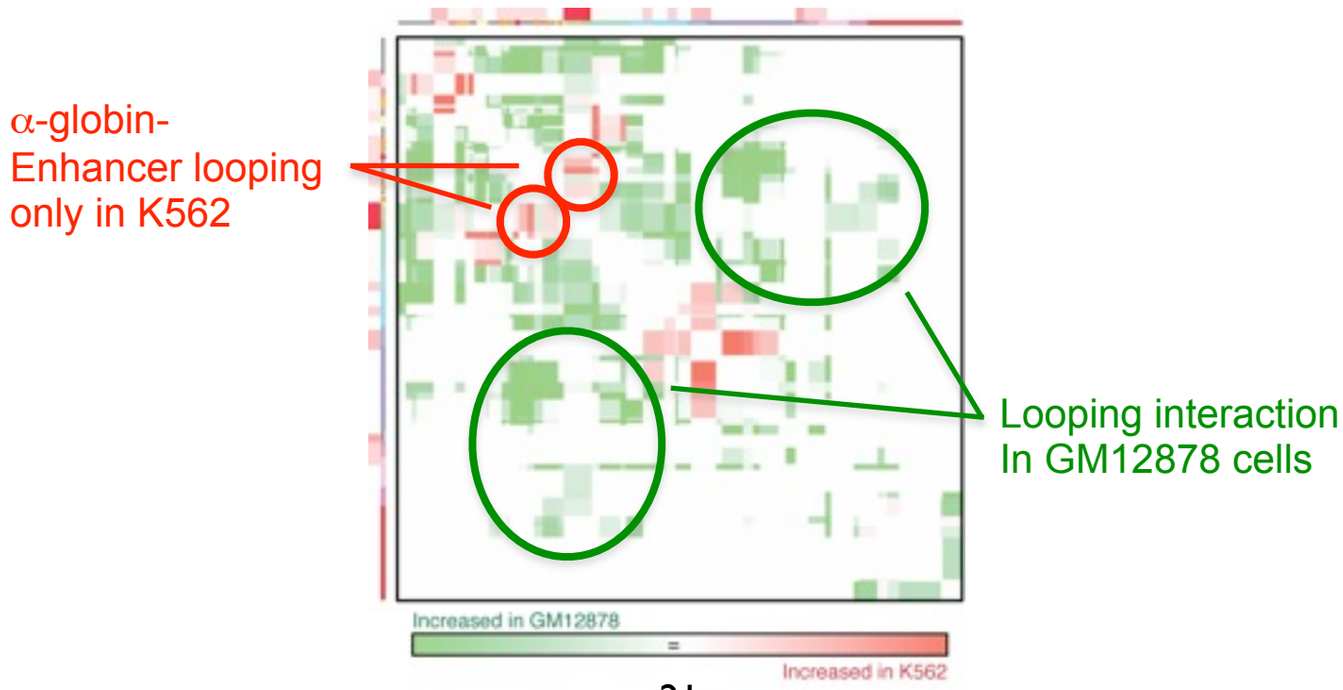


Summary

Large-scale changes in conformation correlate with gene expression of resident genes

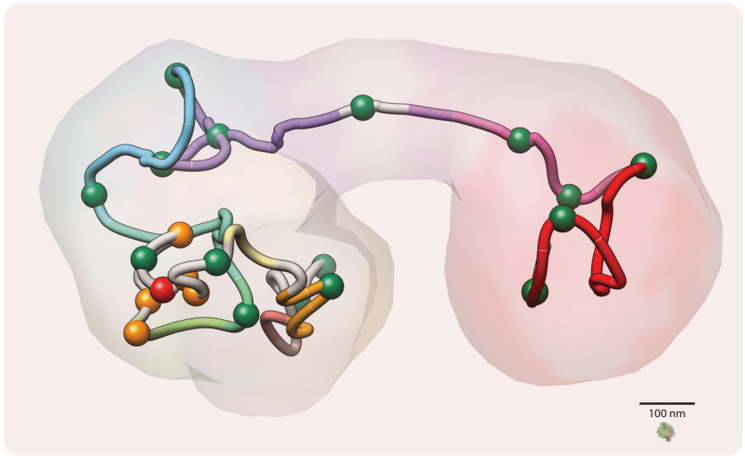


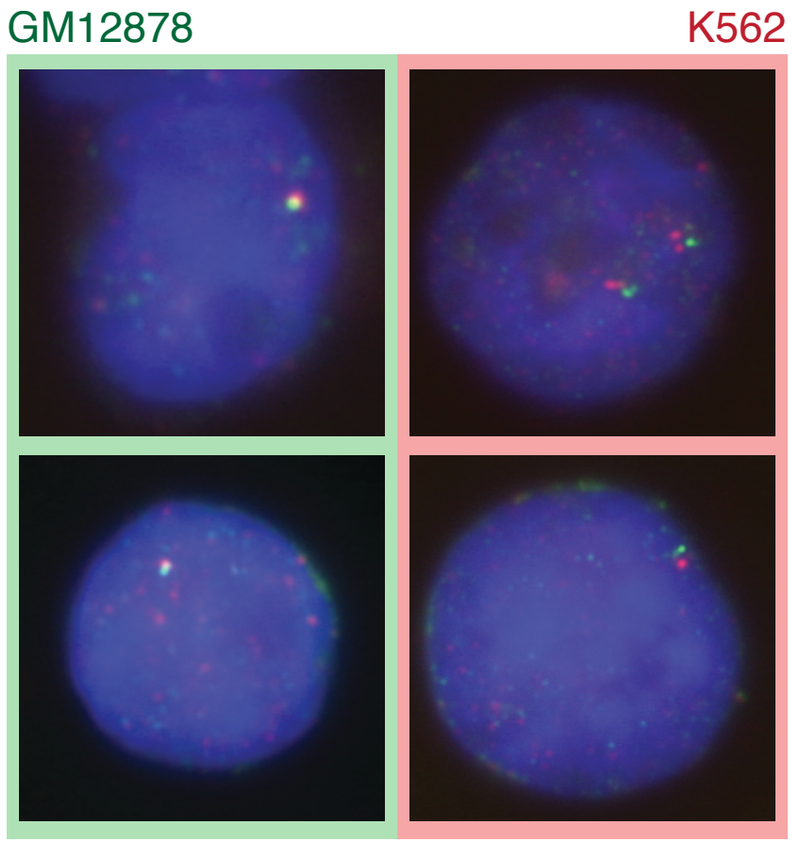




Summary

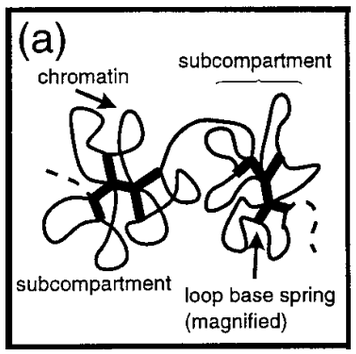
The models have been partially validated by FISH



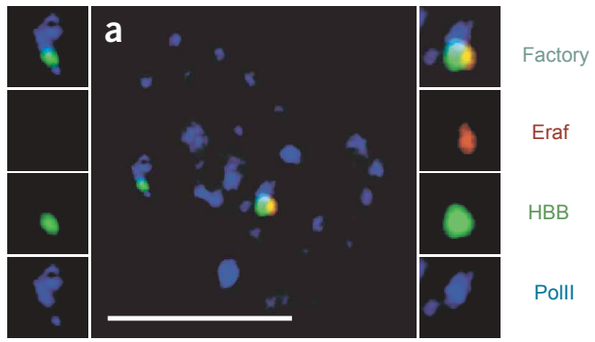


Summary

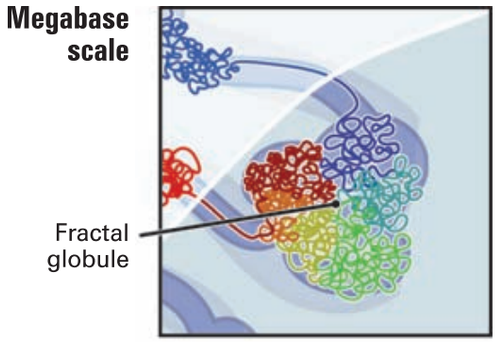
"**Chromatin Globule**" model



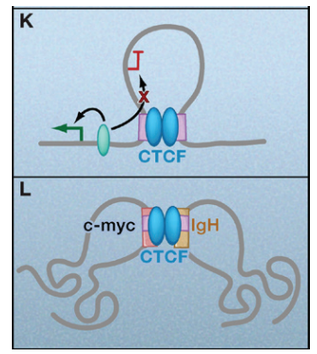
Münkel et al. JMB (1999)



Osborne et al. Nat Genet (2004)



Lieberman-Aiden et al. Science (2009)



Phillips and Corces. Cell (2009)

OPEN POST-DOC POSITION IN THE LAB
Starting sometime 2011

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D. Baù, A. Sanyal, B. Lajoie, E. Capriotti, M. Byron, J. Lawrence, J. Dekker, and M.A. Marti-Renom.
Nature Structural & Molecular Biology (2010) *in press*.

http://sgu.bioinfo.cipf.es
http://integrativemodeling.org