

The three-dimensional folding of the α -globin gene domain reveals formation of chromatin globules.

Davide Baù

Structural Genomics Group

centre nacional d'anàlisi genòmica
centro nacional de análisis genómico

cnag



“Highlight 2011”

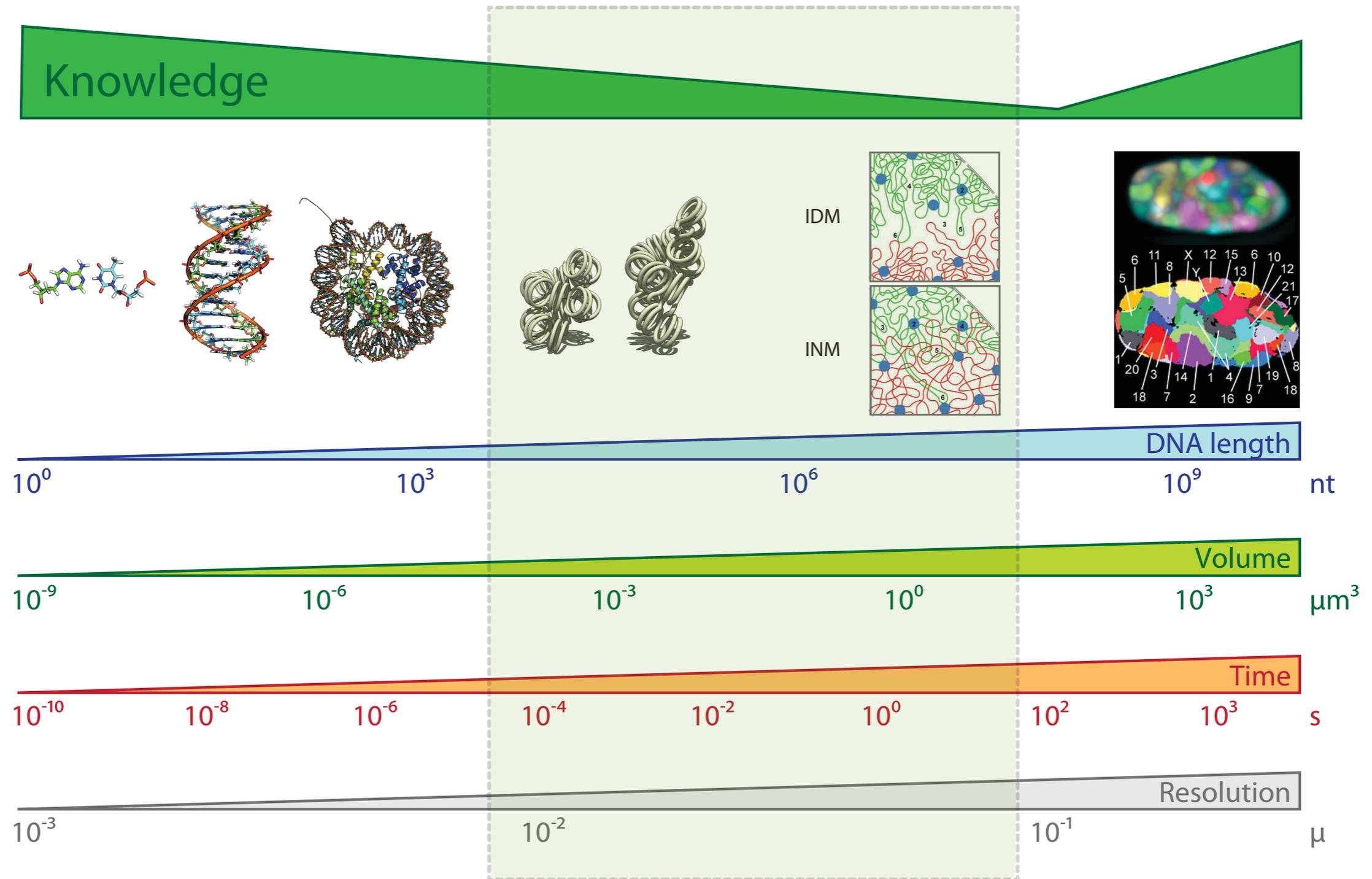
nature
structural &
molecular biology



The three-dimensional folding of the α -globin gene domain reveals formation of chromatin globules

Davide Baù^{1,4}, Amartya Sanyal^{2,4}, Bryan R Lajoie^{2,4}, Emidio Capriotti¹, Meg Byron³, Jeanne B Lawrence³, Job Dekker² & Marc A Marti-Renom¹

Resolution



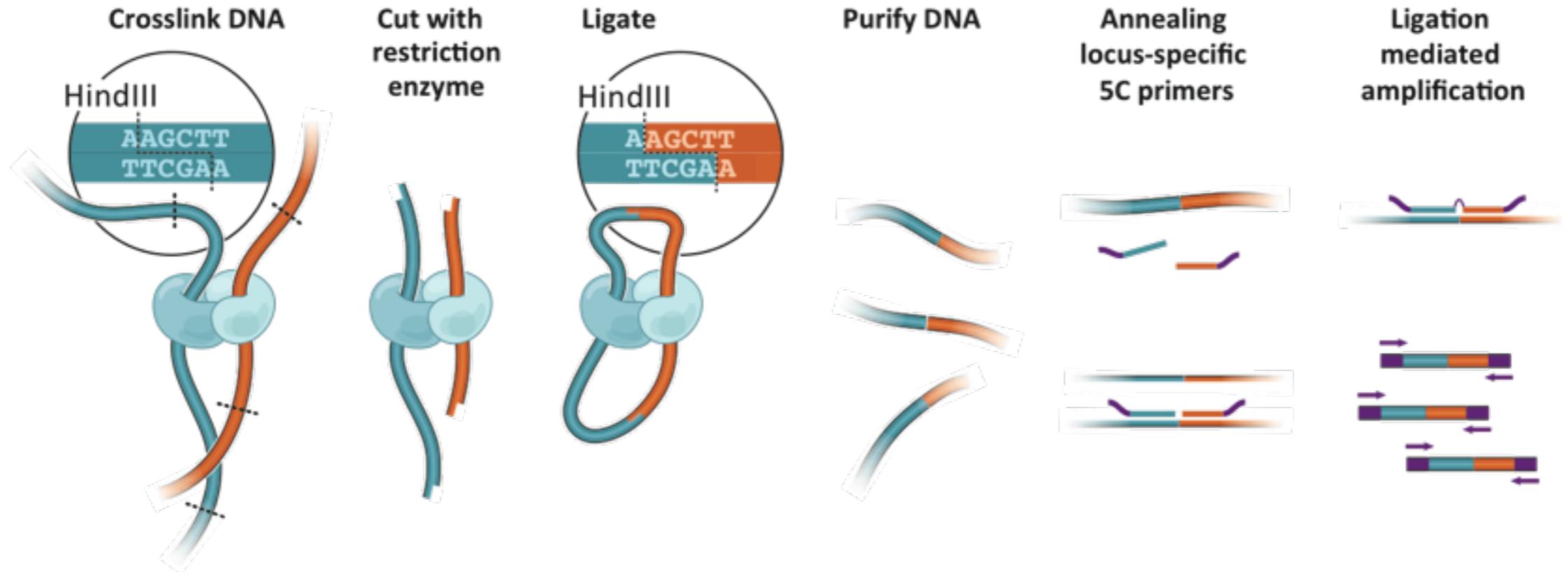
Adapted from:
Langowski and Heermann. *Semin Cell Dev Biol* (2007) vol. 18 (5) pp.

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

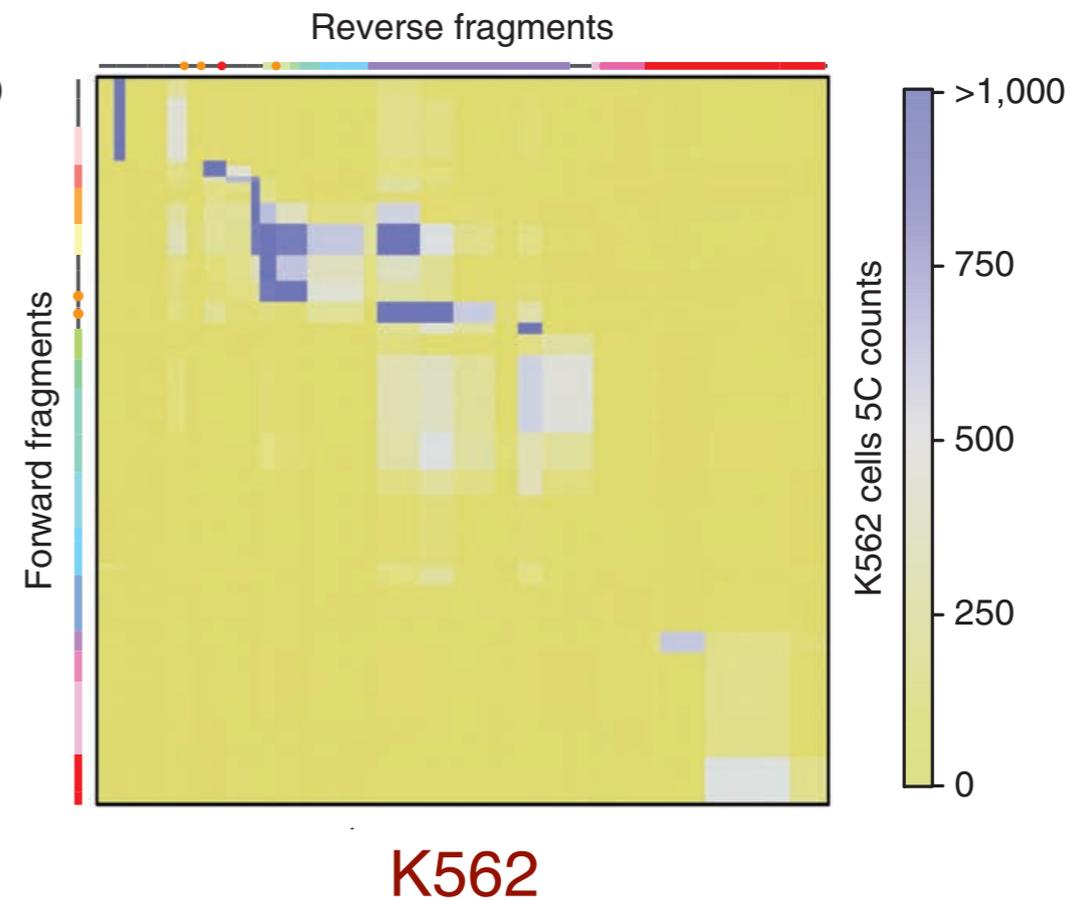
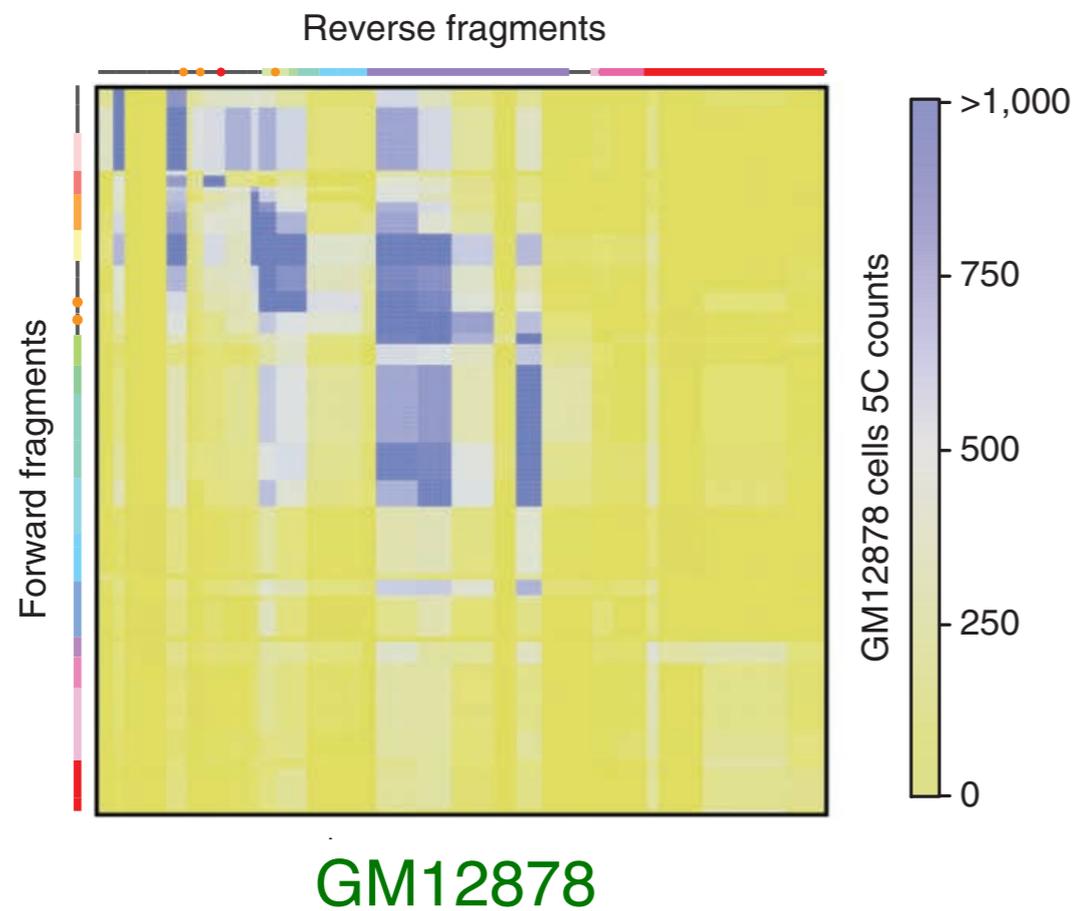
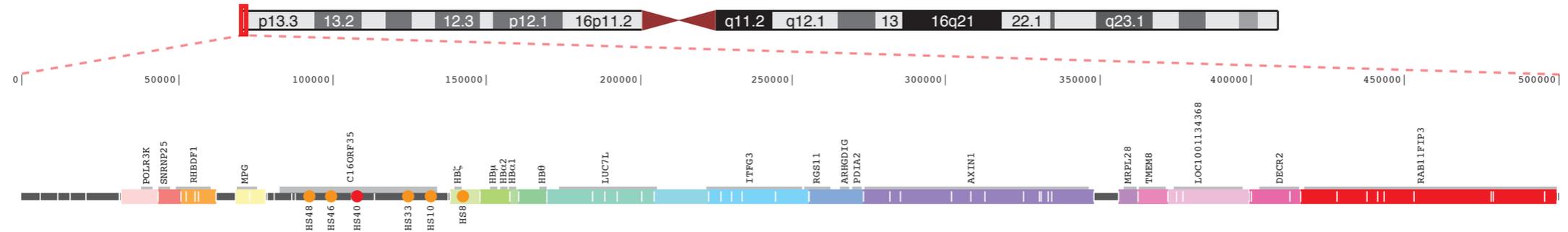


The ENCODE data for ENm008 region was obtained from the UCSC Genome Browser tracks for: RefSeq annotated genes, Affymetrix/CSHL expression data (Gingeras Group at Cold Spring Harbor), Duke/NHGRI DNase I Hypersensitivity data (Crawford Group at Duke University), and Histone Modifications by Broad Institute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

Human α -globin Domain

ENm008 genomic structure and environment

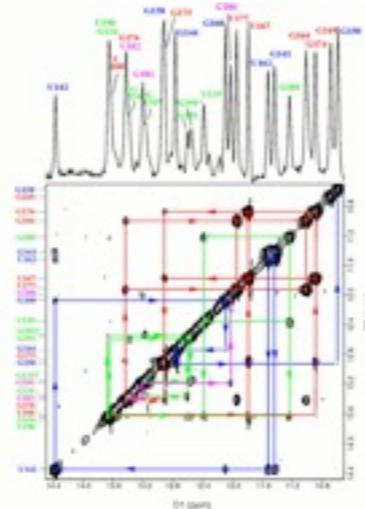
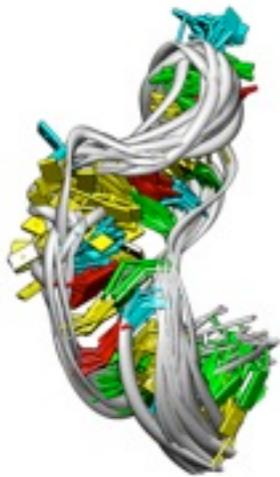
ENCODE Consortium. Nature (2007) vol. 447 (7146) pp. 799-816



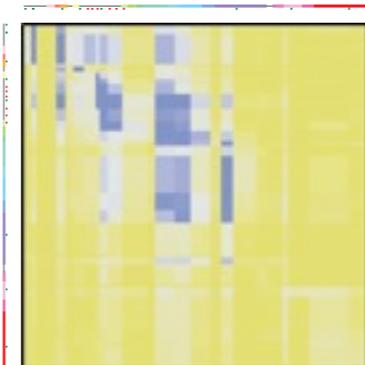
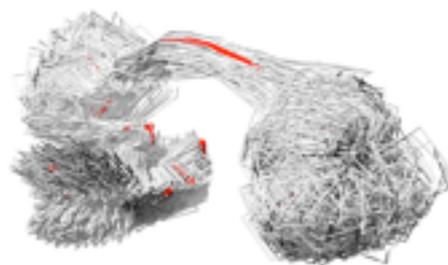
Structure Determination

Integrative Modeling Platform

<http://www.integrativemodeling.org>

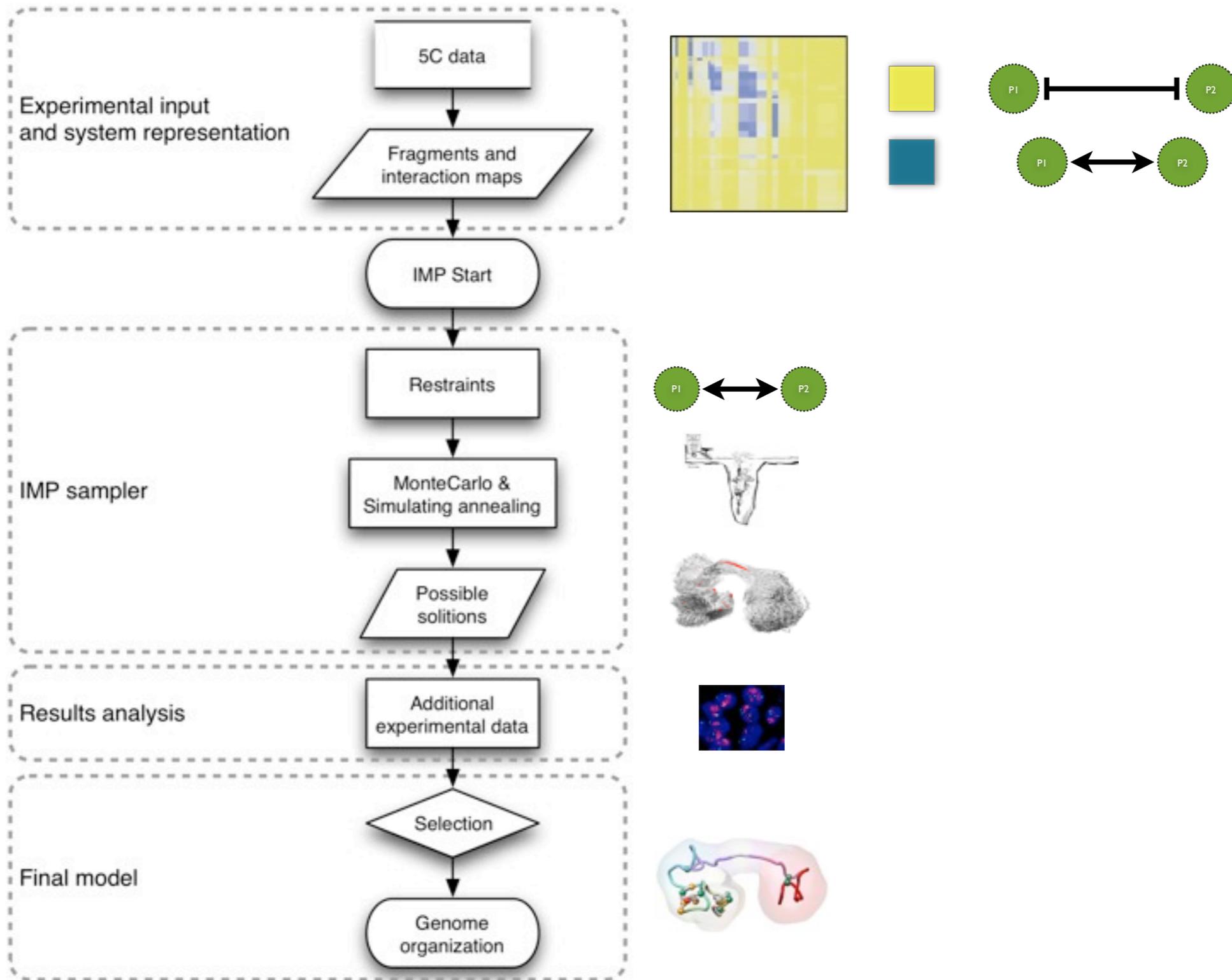


Biomolecular structure determination
2D-NOESY data



Chromosome structure determination
5C data

Integrative modeling



Representation

Harmonic

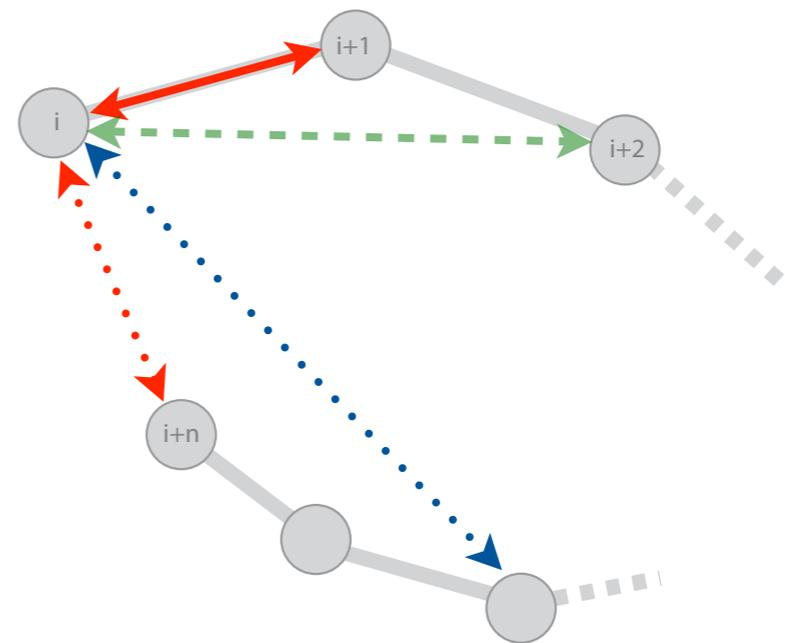
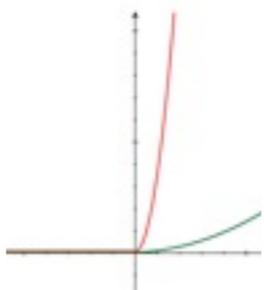
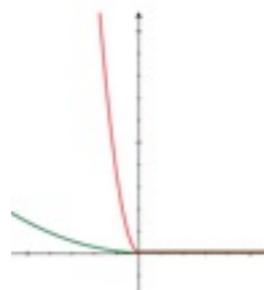
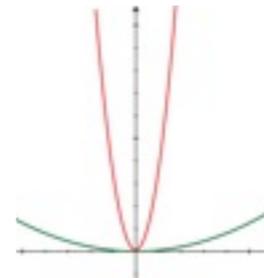
$$H_{i,j} = k(d_{i,j} - d_{i,j}^0)^2$$

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

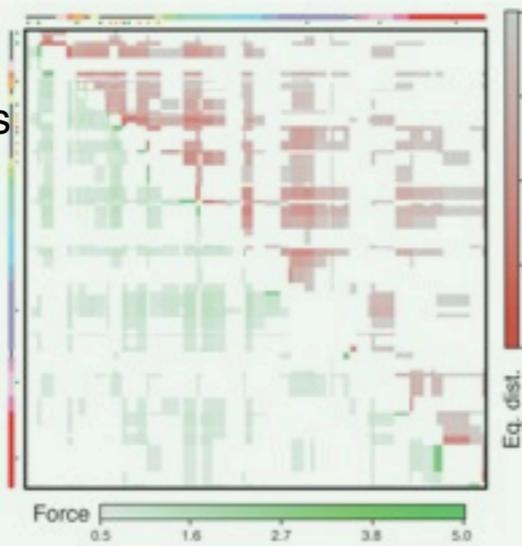
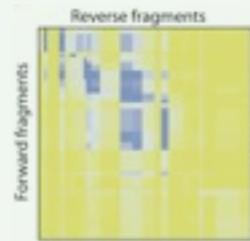
$$\begin{cases} \text{if } d_{i,j} \geq d_{i,j}^0; & ubH_{i,j} = k(d_{i,j} - d_{i,j}^0)^2 \\ \text{if } d_{i,j} < d_{i,j}^0; & ubH_{i,j} = 0 \end{cases}$$



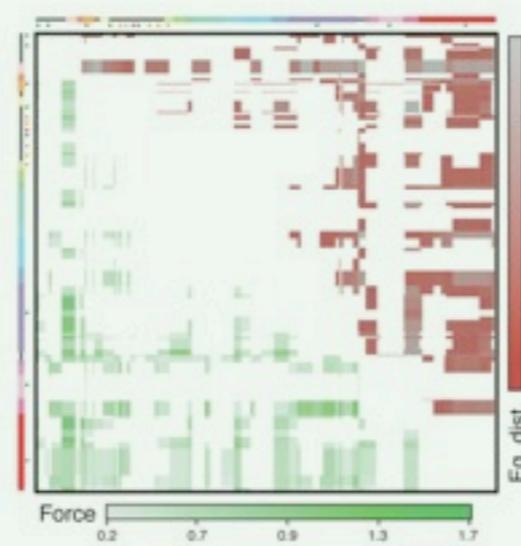
Scoring

GM1287

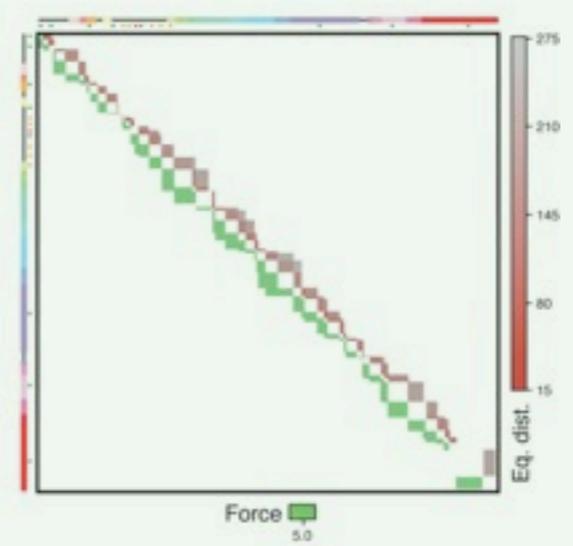
70 fragments
1,520 restraints



Harmonic



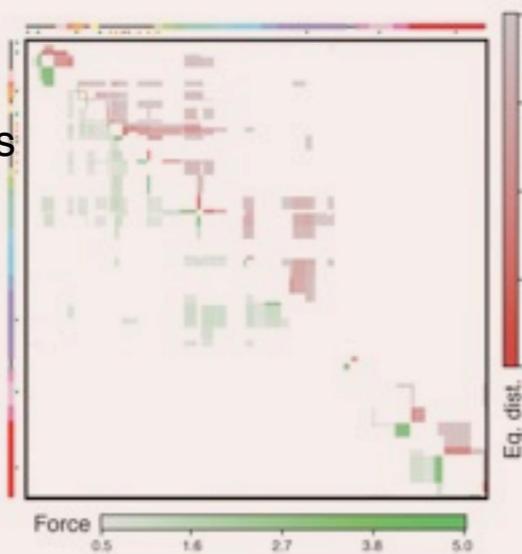
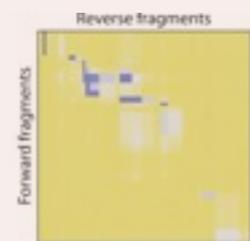
Harmonic Lower Bound



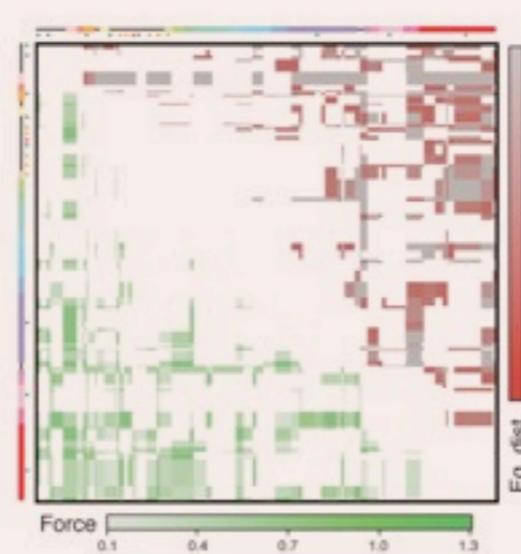
Harmonic Upper Bound

K562

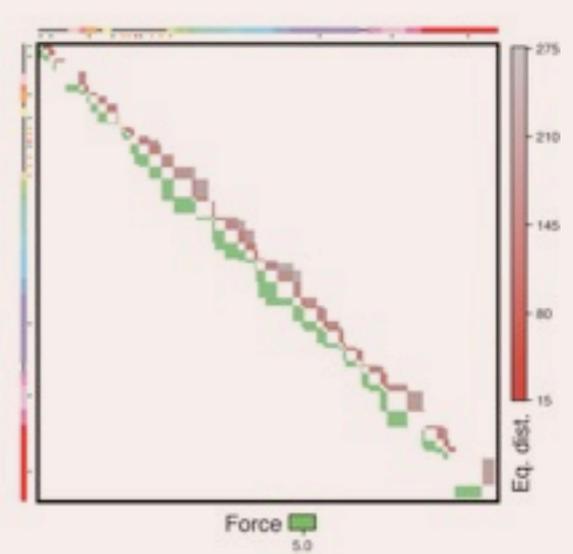
70 fragments
1,049 restraints



Harmonic

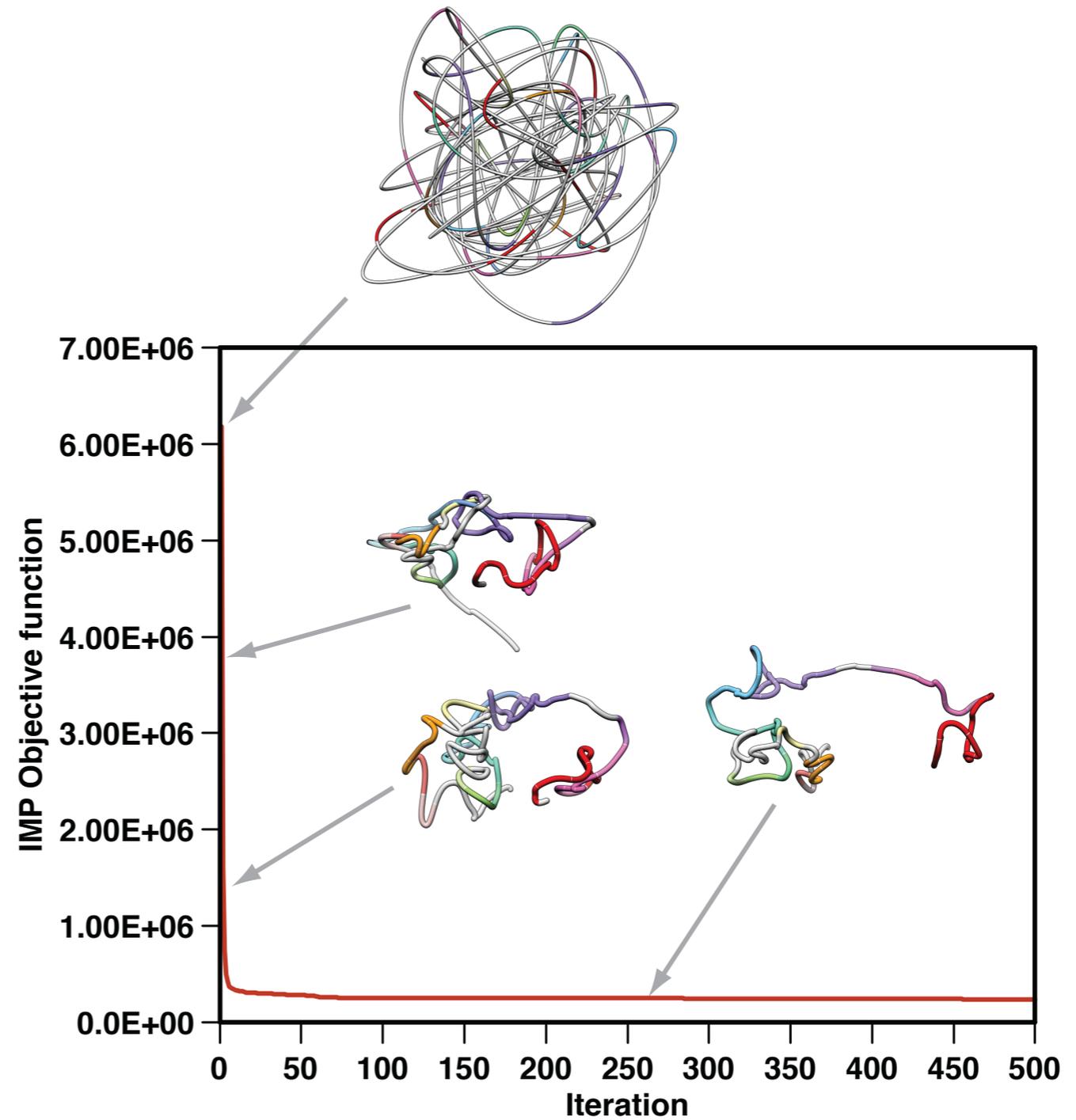
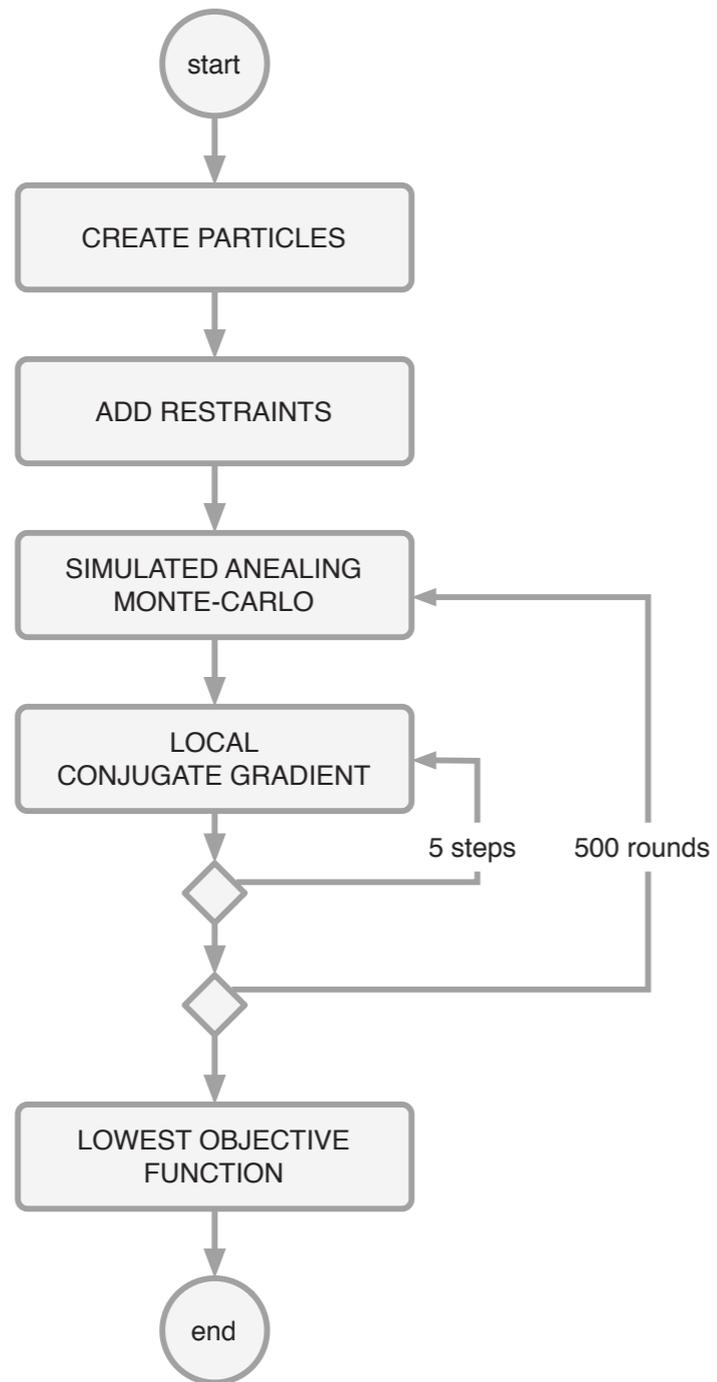


Harmonic Lower Bound



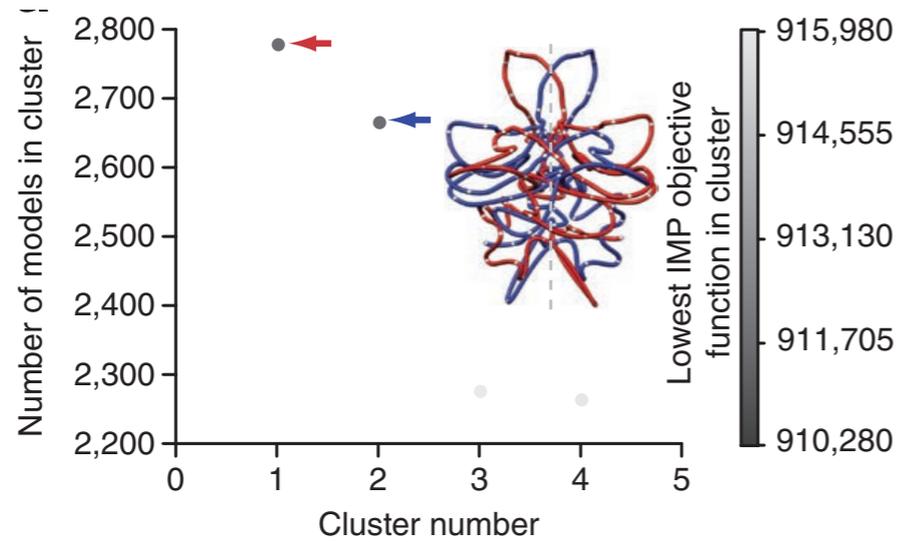
Harmonic Upper Bound

Optimization

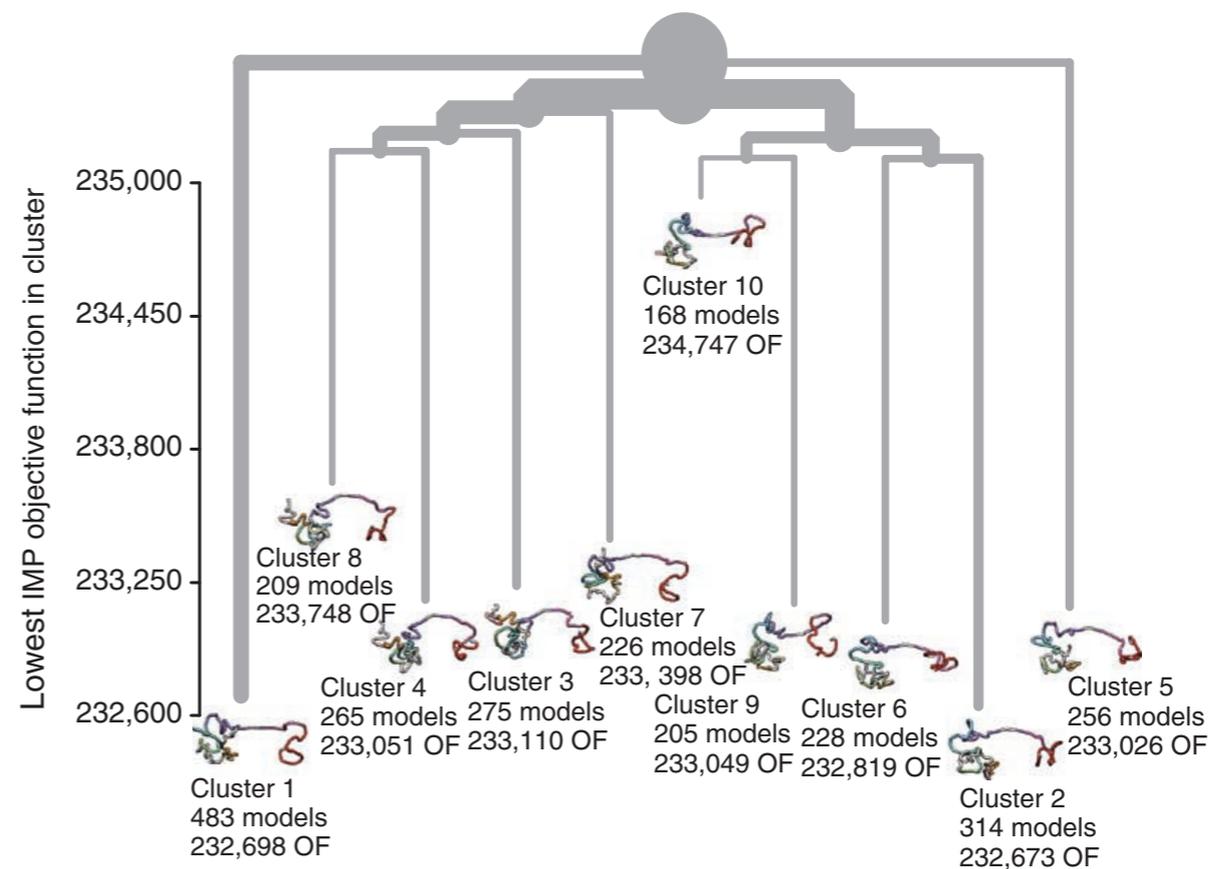
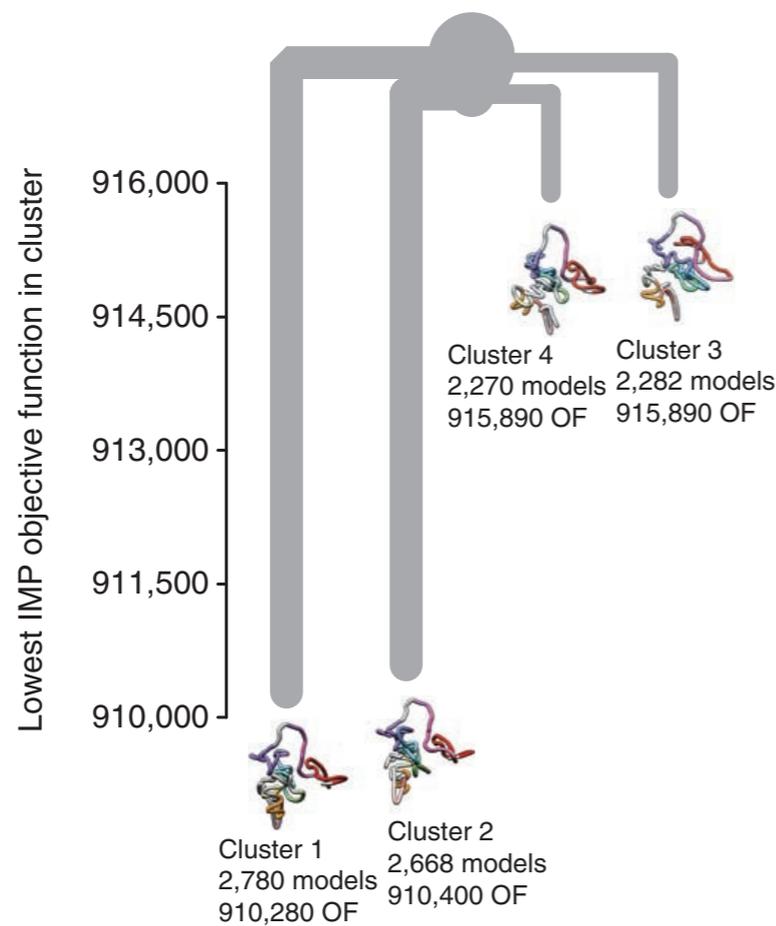
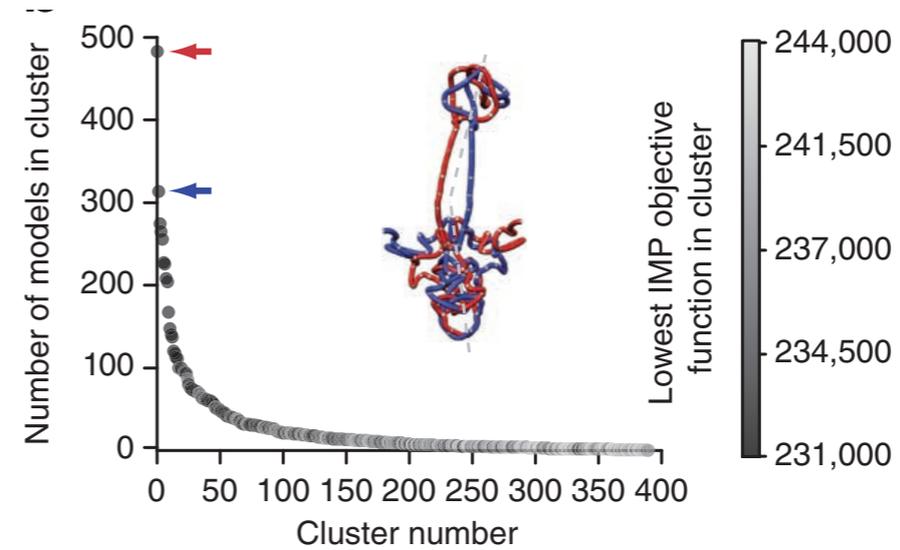


Not just one solution

GM12878

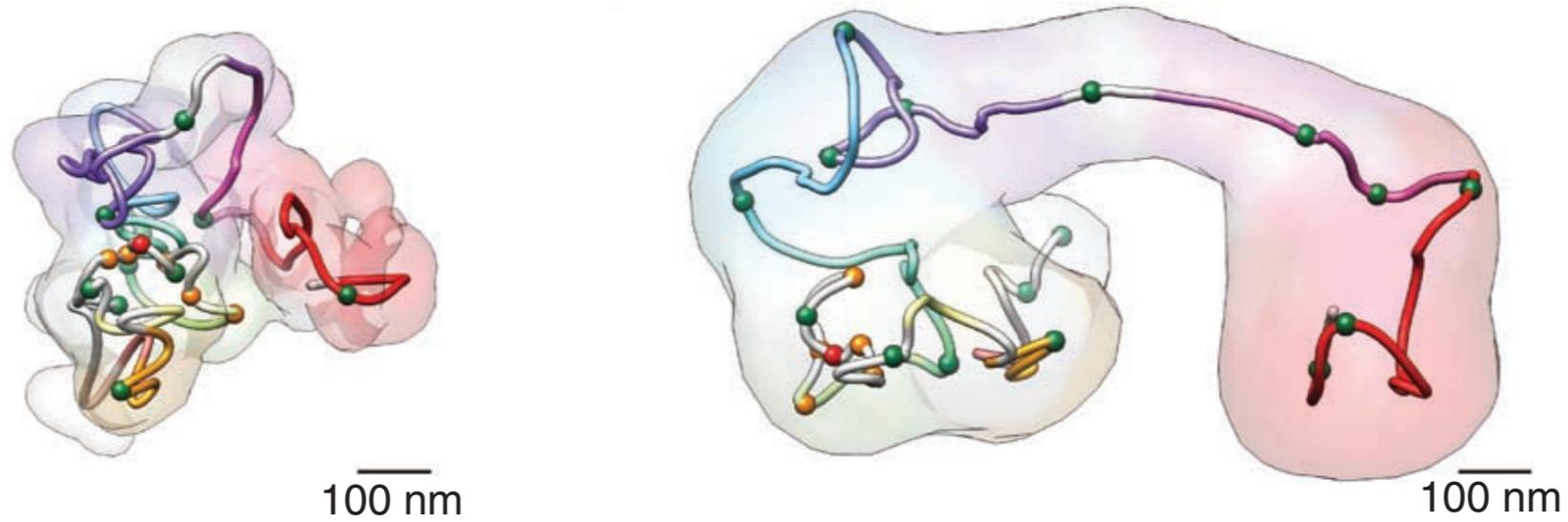


K562

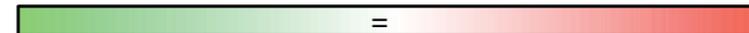


Chromatin globules

Frequency contact map differences

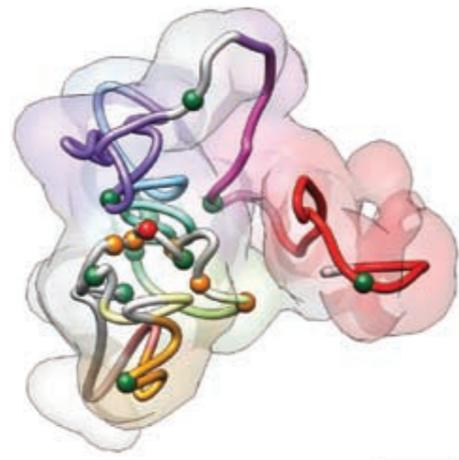


Increased in GM12878

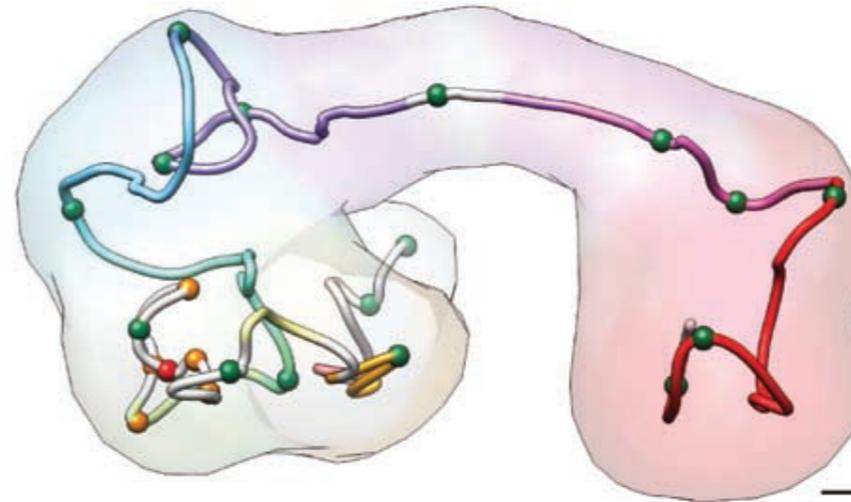


Increased in K562

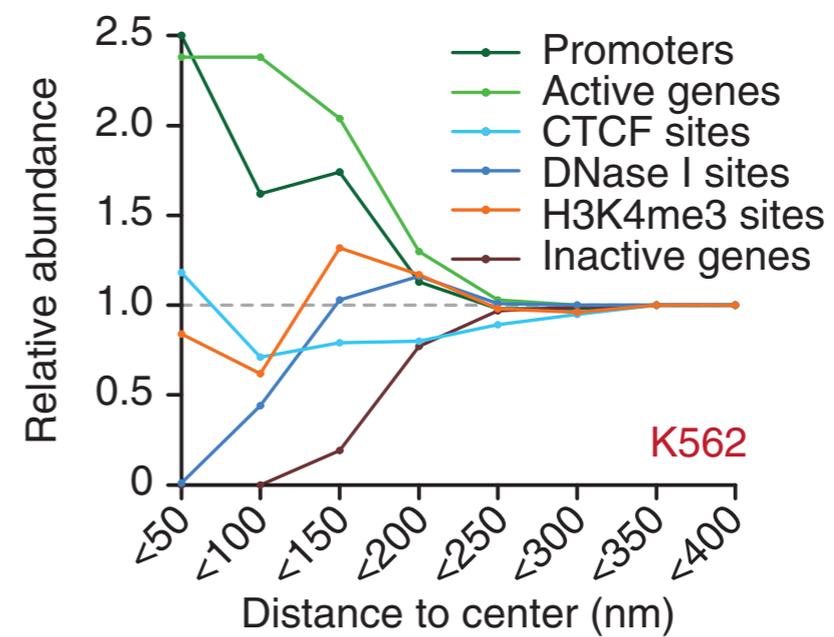
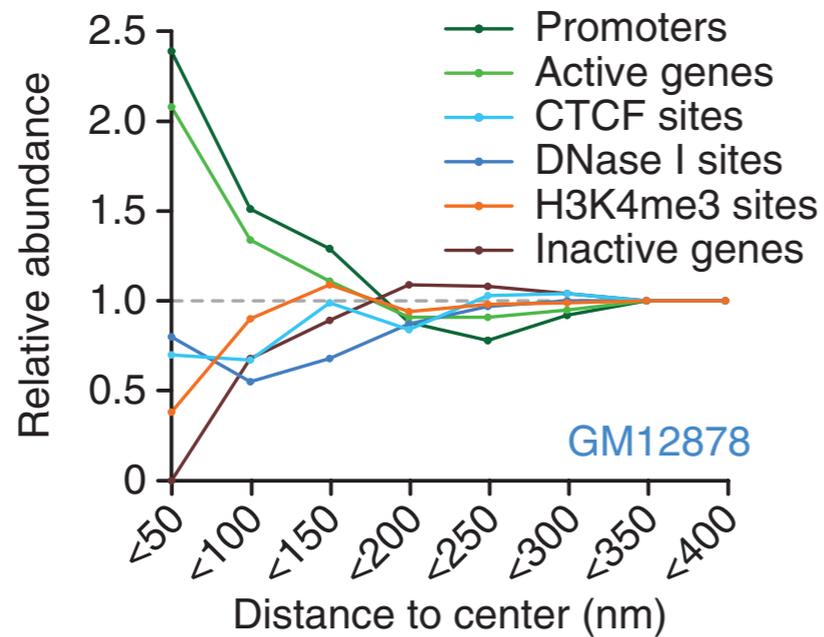
Genes location within the globules



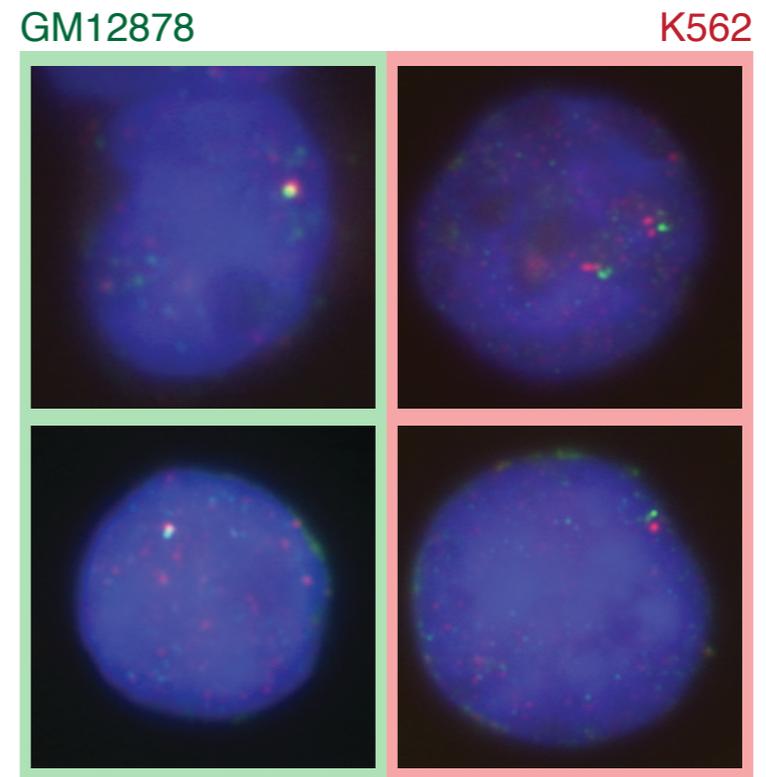
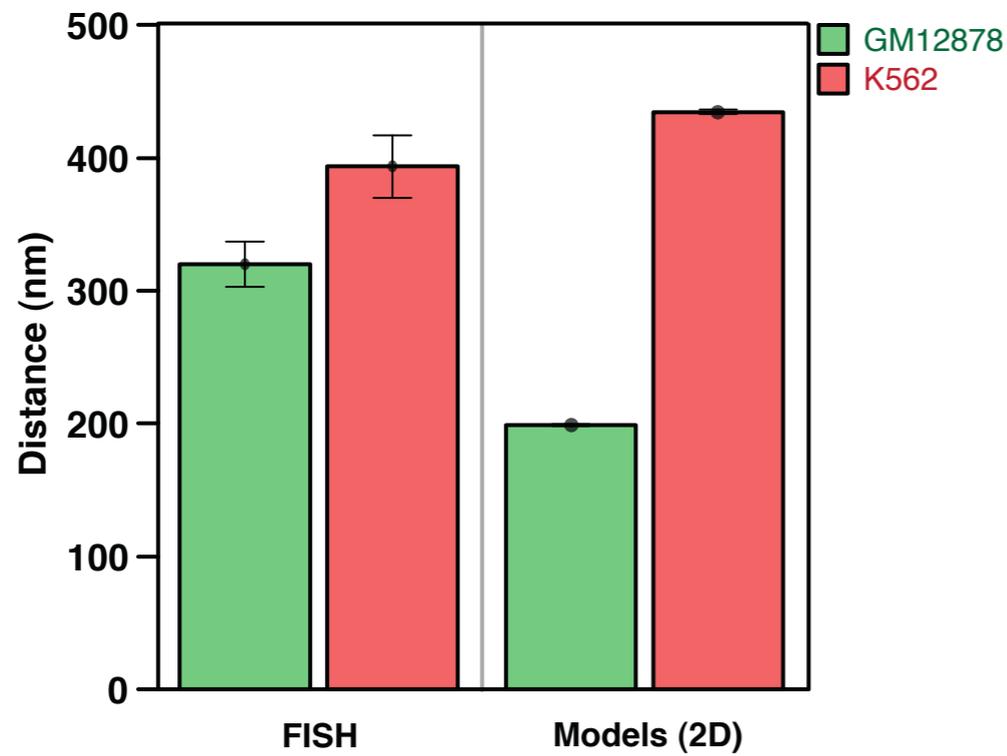
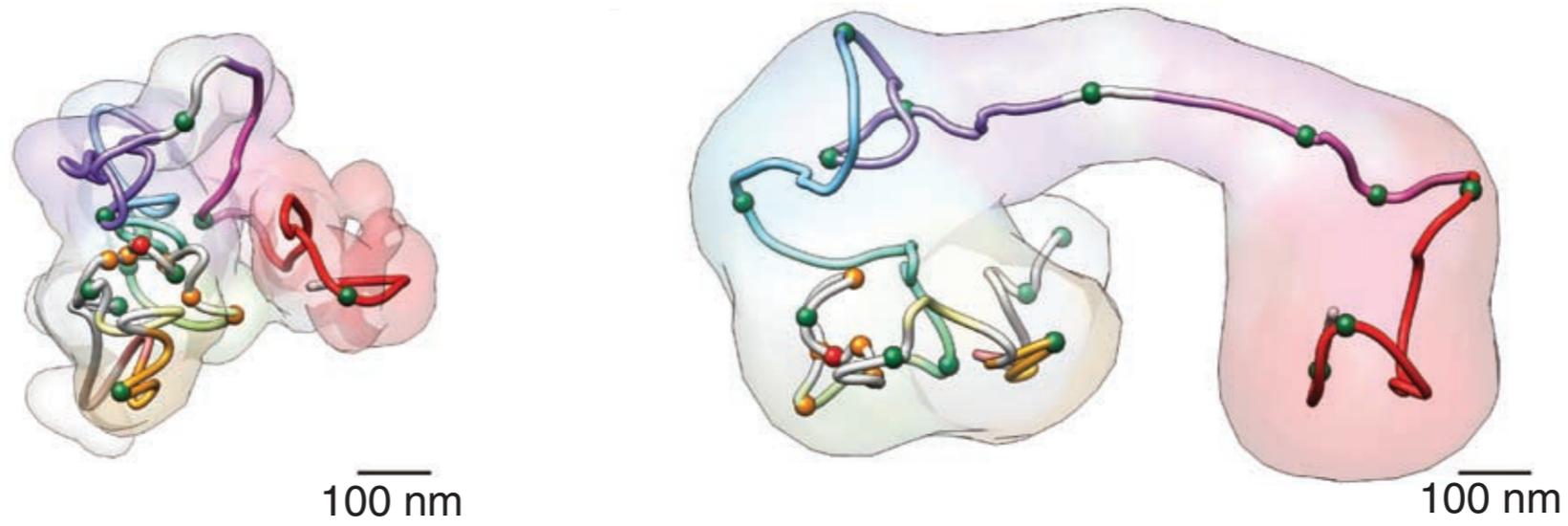
100 nm



100 nm

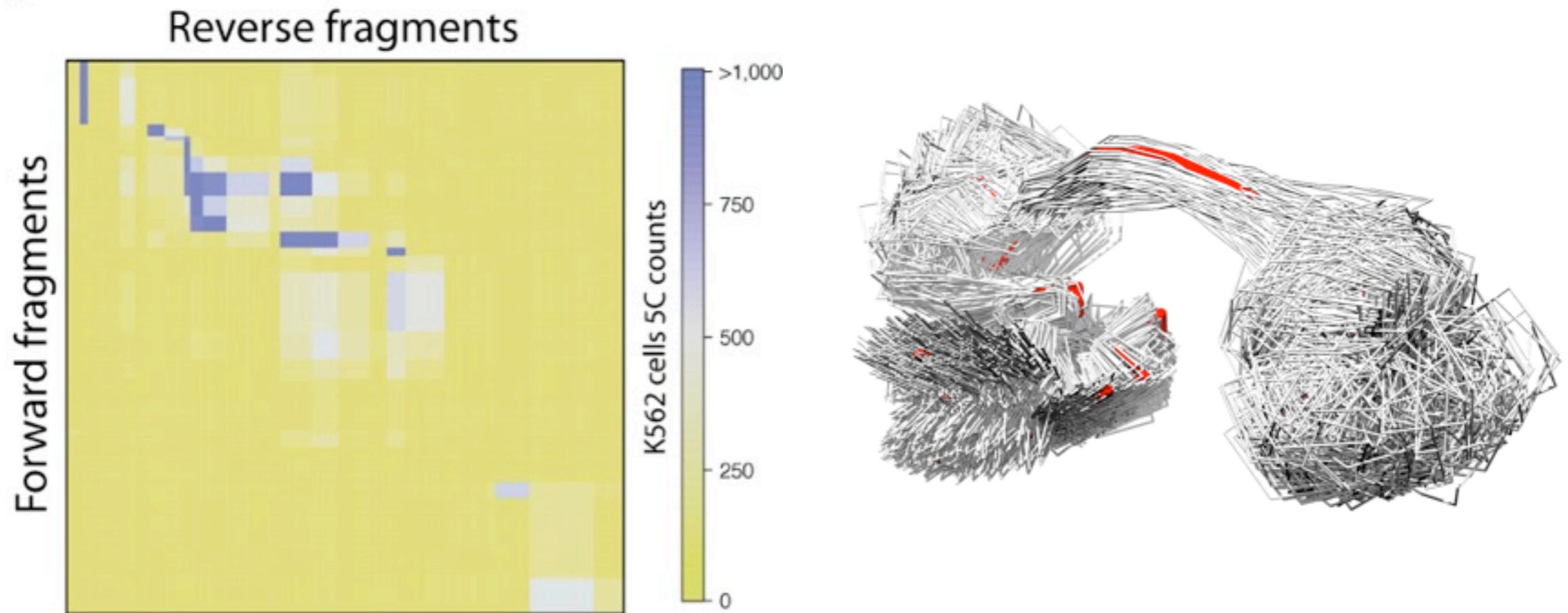


Model validation



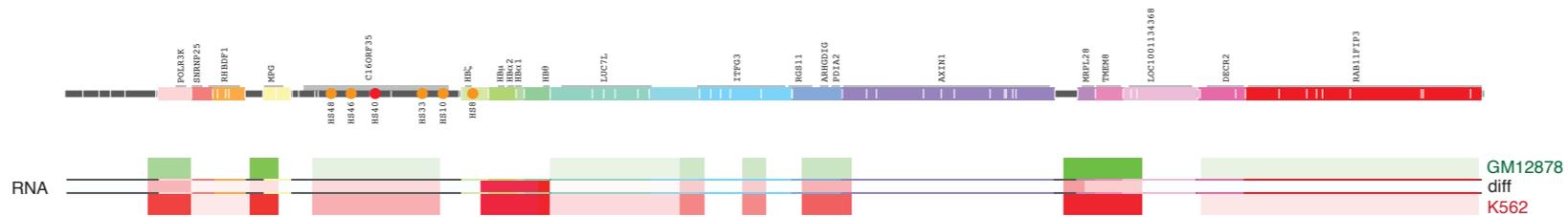
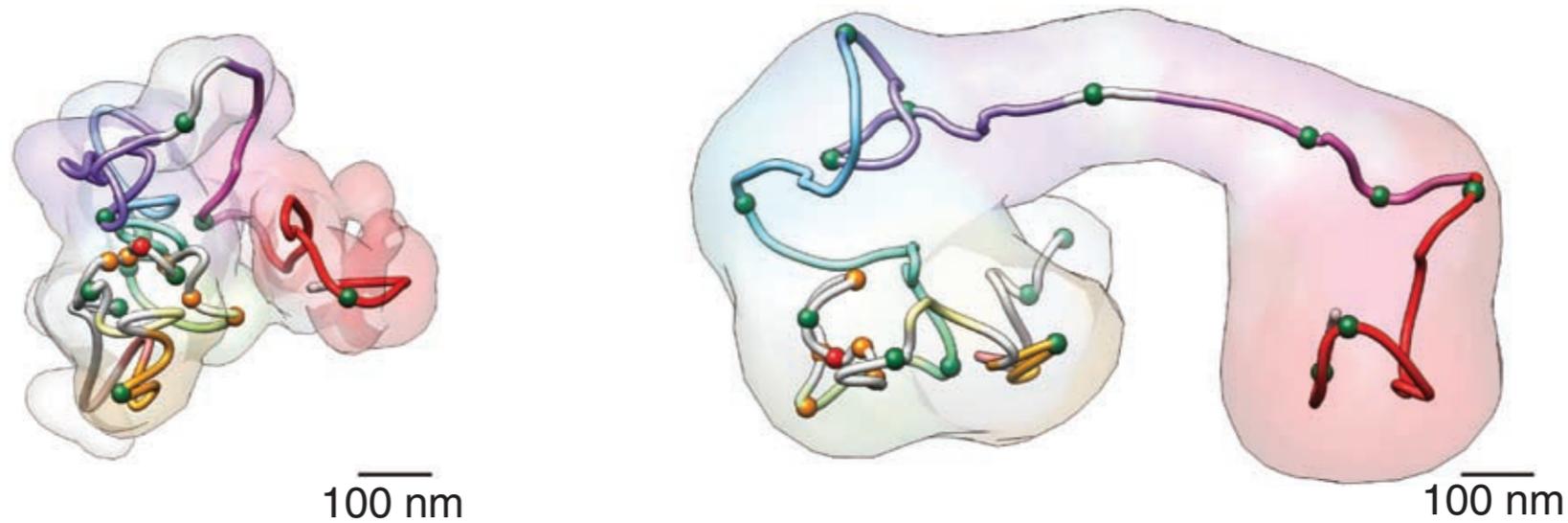
Summary

5C data results in consistent 3D models

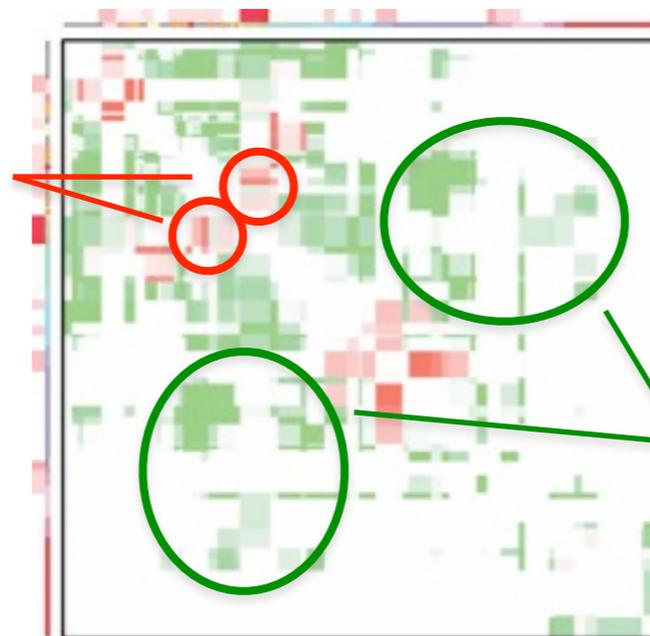


Summary

Conformational changes correlate with gene expression

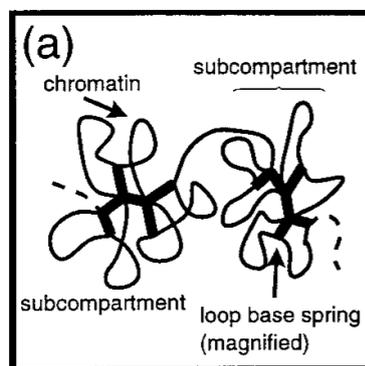


α -globin-
Enhancer looping
only in K562

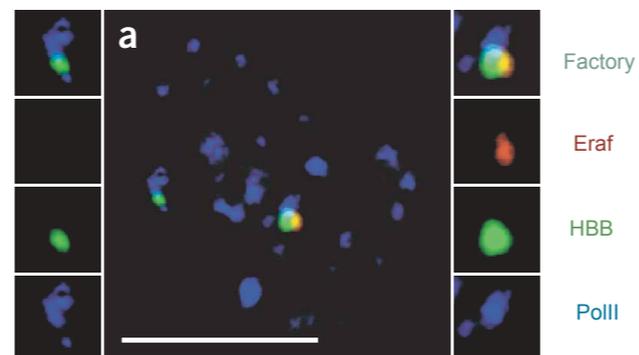


Looping interaction
In GM12878 cells

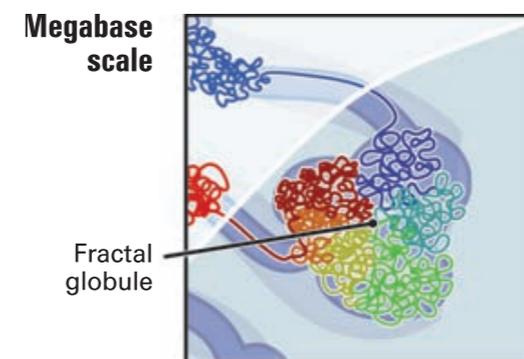
The “chromatin globule” model



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.



OPEN POSITIONS IN THE LAB
Starting early 2012

Acknowledgments



Amartya Sanyal
Bryan R Lajoie
Job Dekker

Meg Byron
Jeanne Lawrence

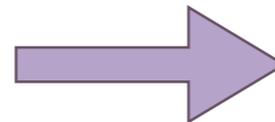


PRINCIPE FELIPE
CENTRO DE INVESTIGACION

Emidio Capriotti
Marc A. Marti-Renom



PRINCIPE FELIPE
CENTRO DE INVESTIGACION



cnag