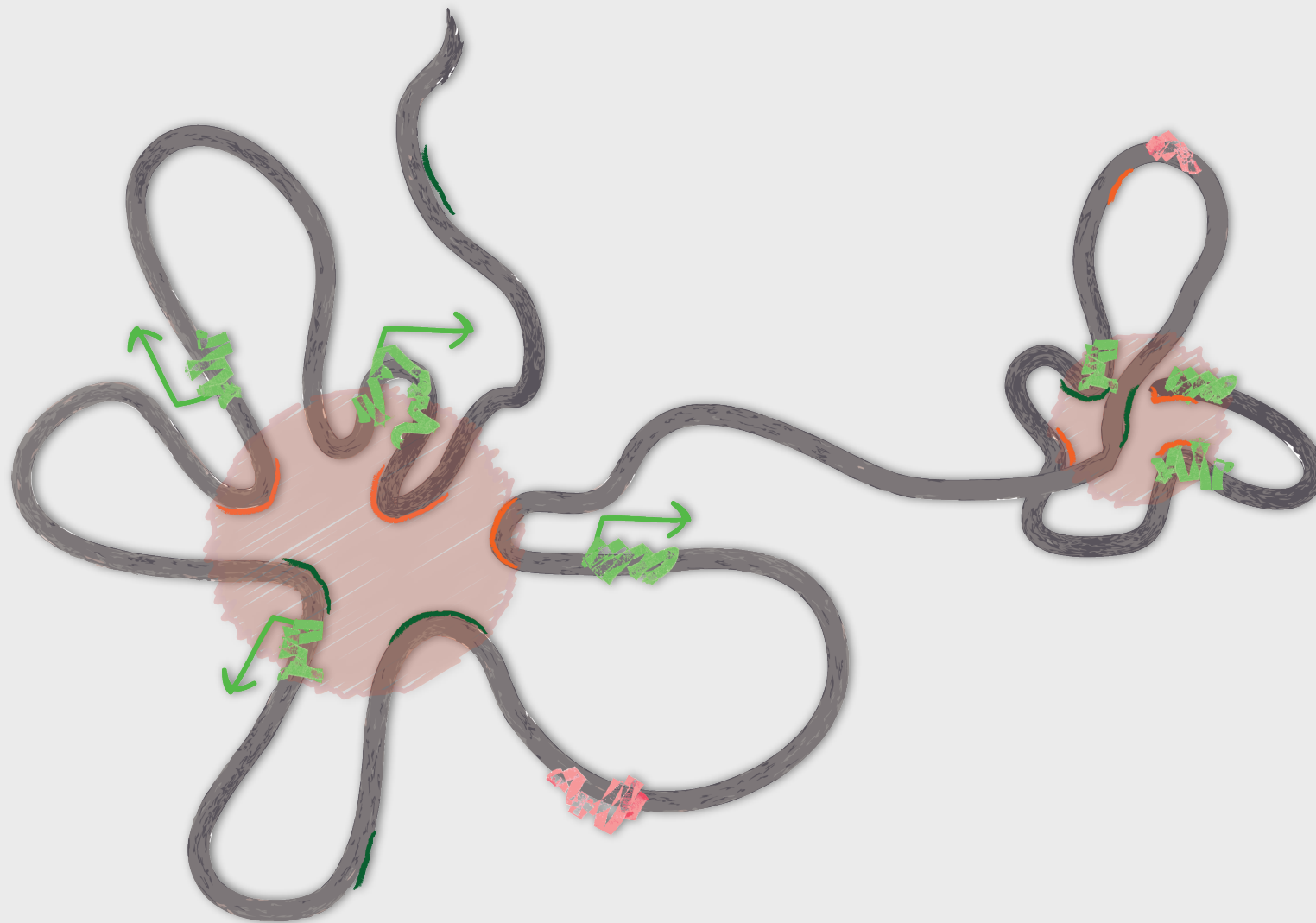


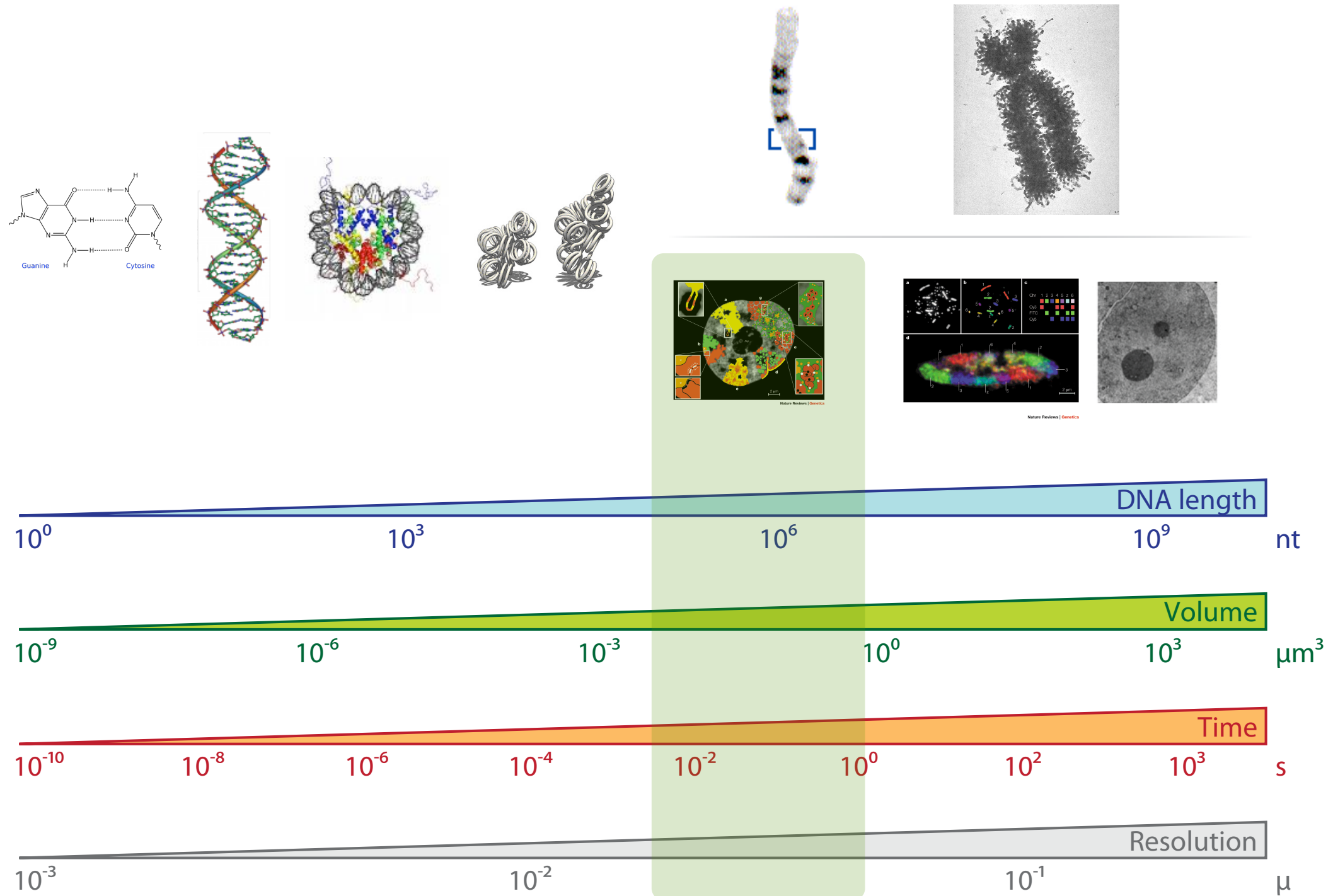
# 3D folding of chromosomal domains in relation to gene expression



# Resolution

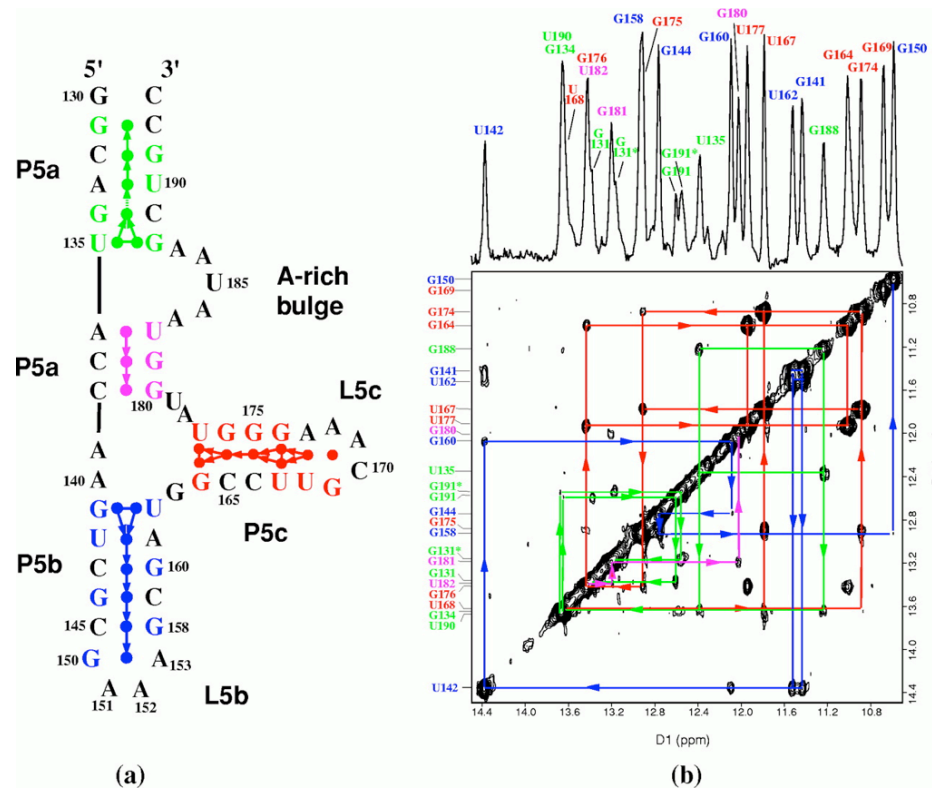
Limited knowledge...

Knowledge

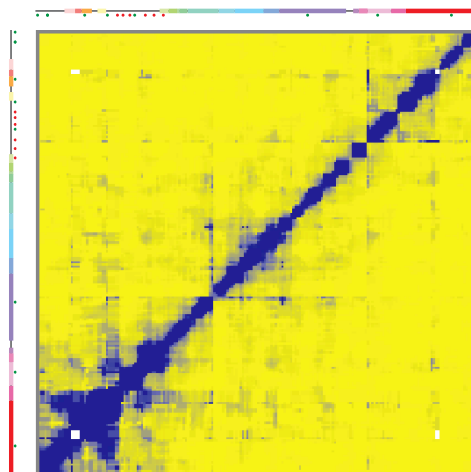
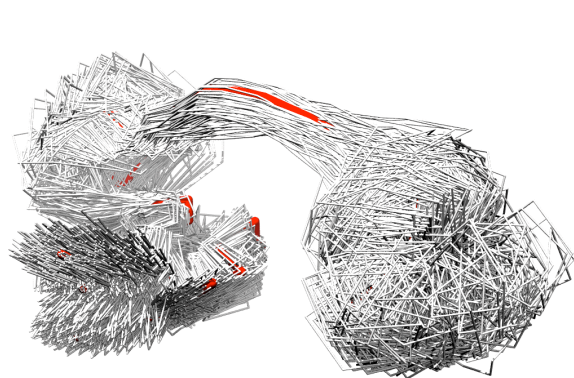


# Structure determination

Integrative Modeling Platform  
<http://www.integrativemodeling.org>



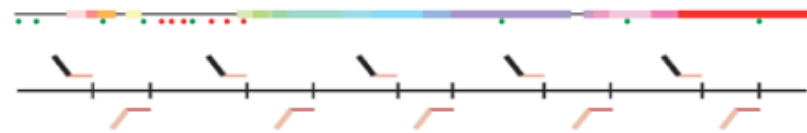
NMR structure determination  
*2D-NOESY data*



Chromosome structure determination  
*5C data*

# Integrative and iterative approach

## Experiments

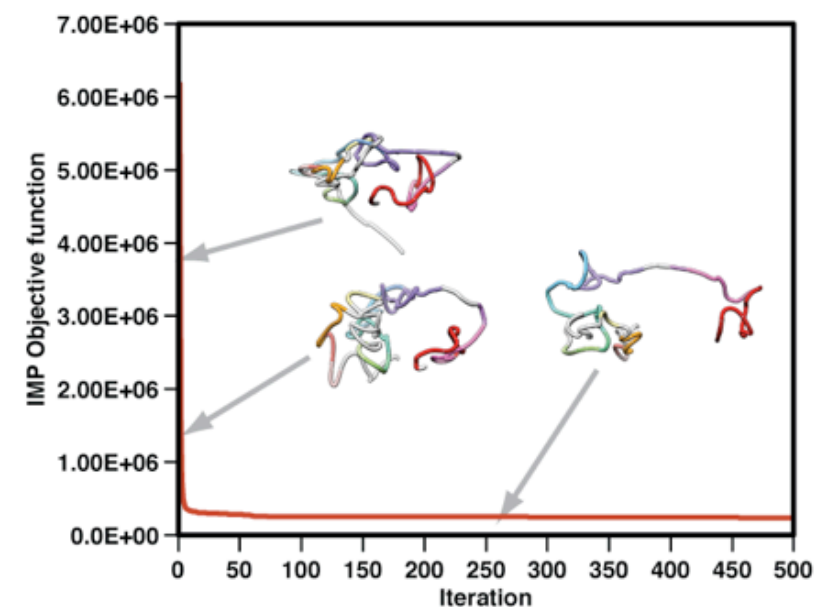
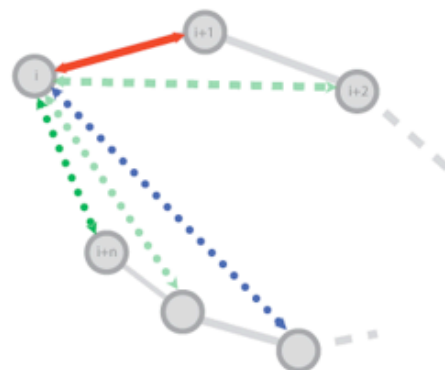
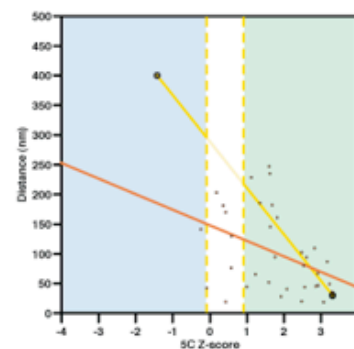
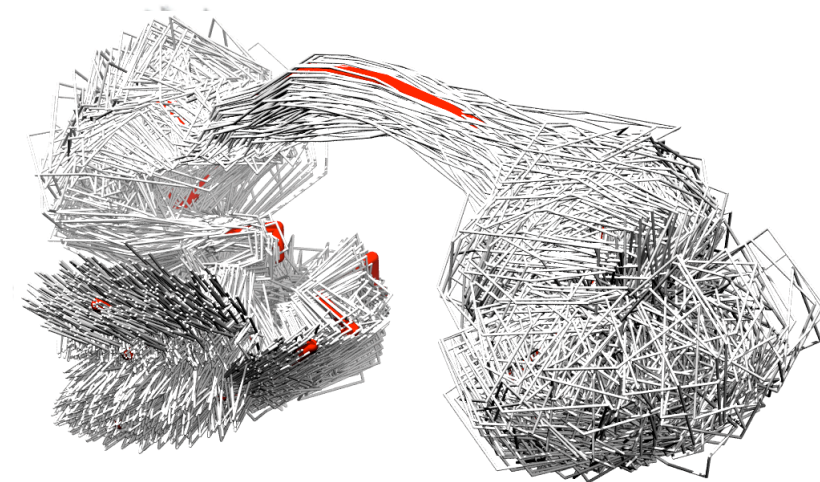


Grow GM12878 and K562 cells

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 



# Human $\alpha$ -globin domain

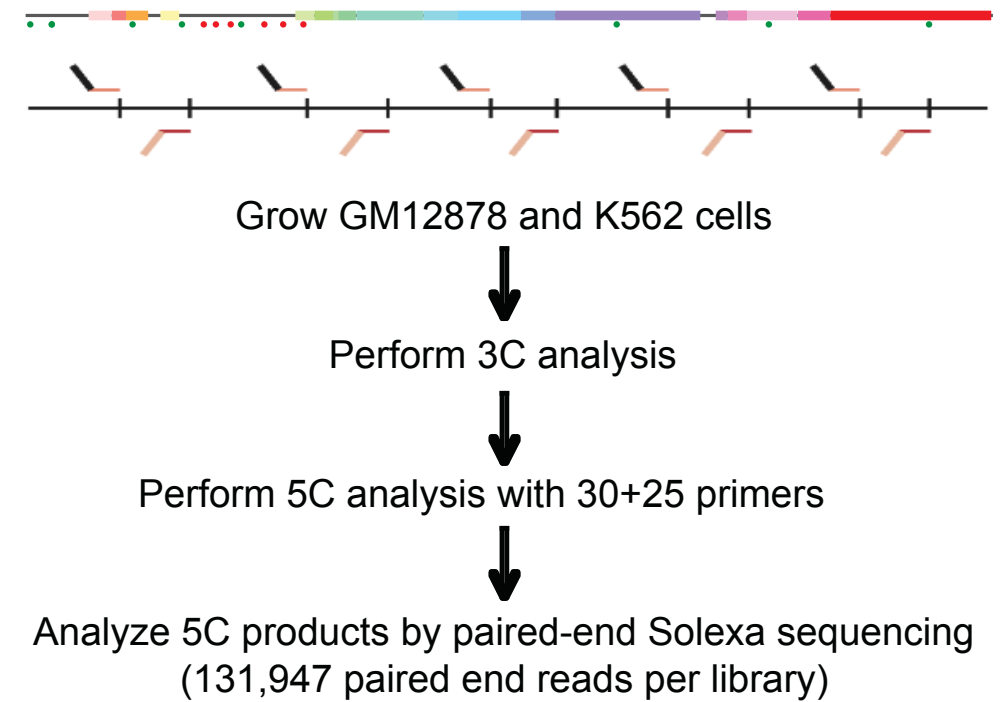
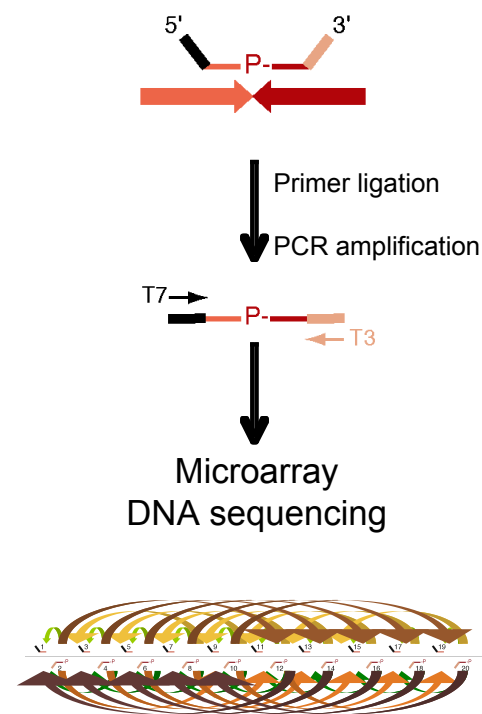
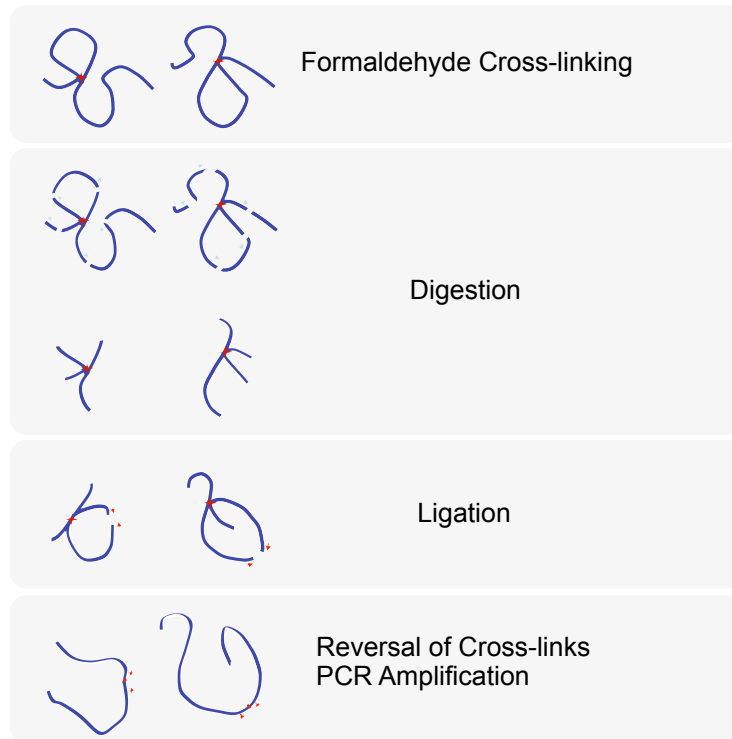
## ENm008 genomic structure and environment



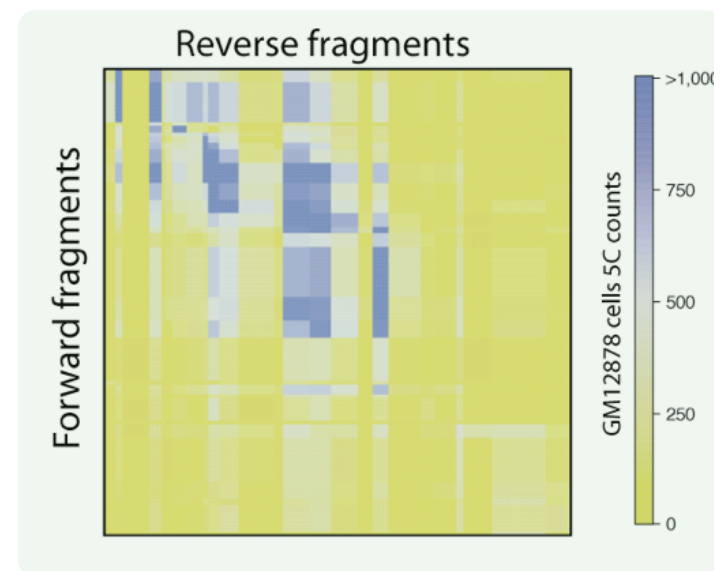
- RNA expression data from the transcriptome group at Affymetrix and Cold Spring Harbor Laboratories.
- CTCF and histone modifications (H3K4me3) from the Broad Institute and the Bradley E. Bernstein Lab at the Massachusetts General Hospital/Harvard Medical School.
- DNaseI data from the Crawford Lab at Duke University and at the Collins Lab at NHGRI.

# 5C experiments

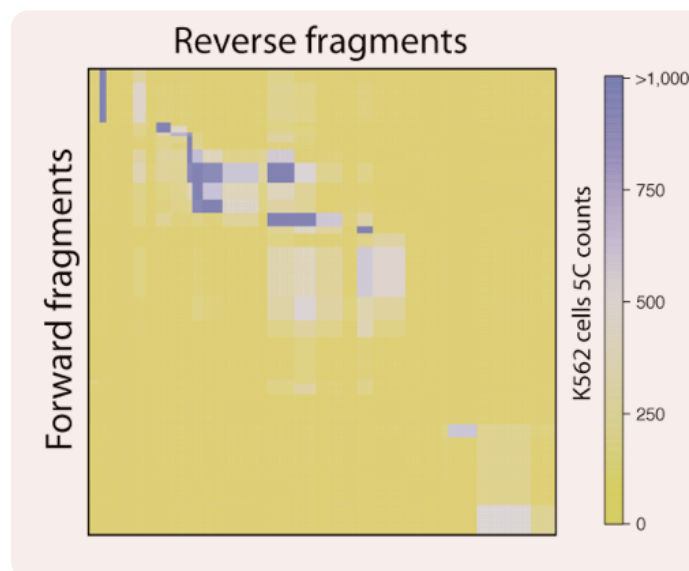
<http://my5c.umassmed.edu>



GM12878

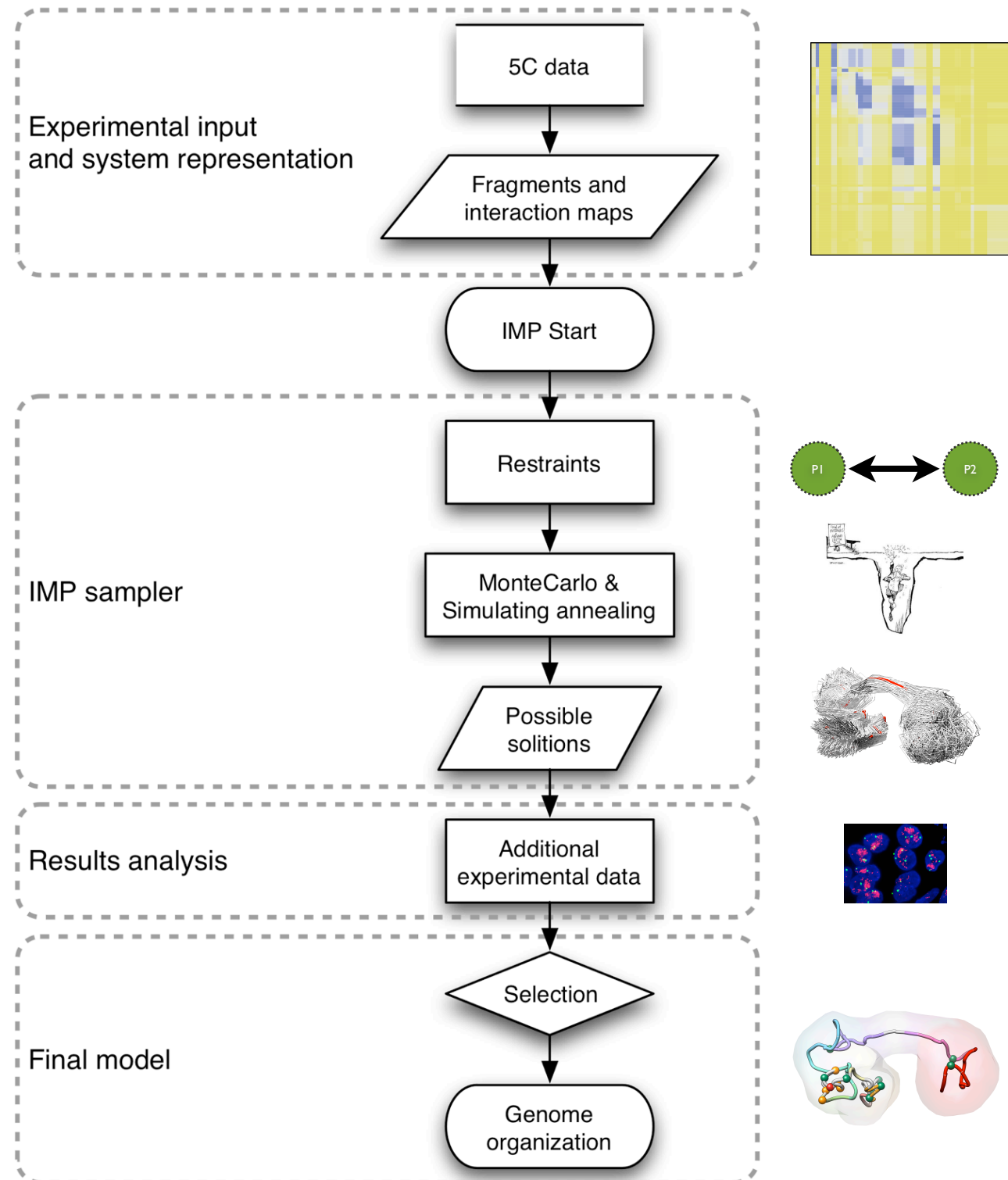


K562



# Integrative Modeling

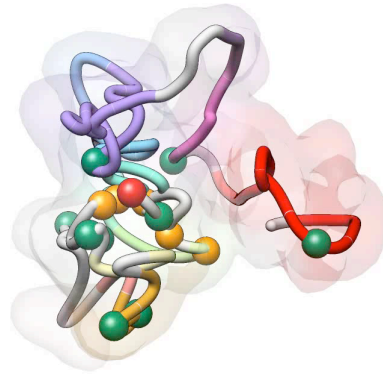
<http://www.integrativemodeling.org>



# Consistency

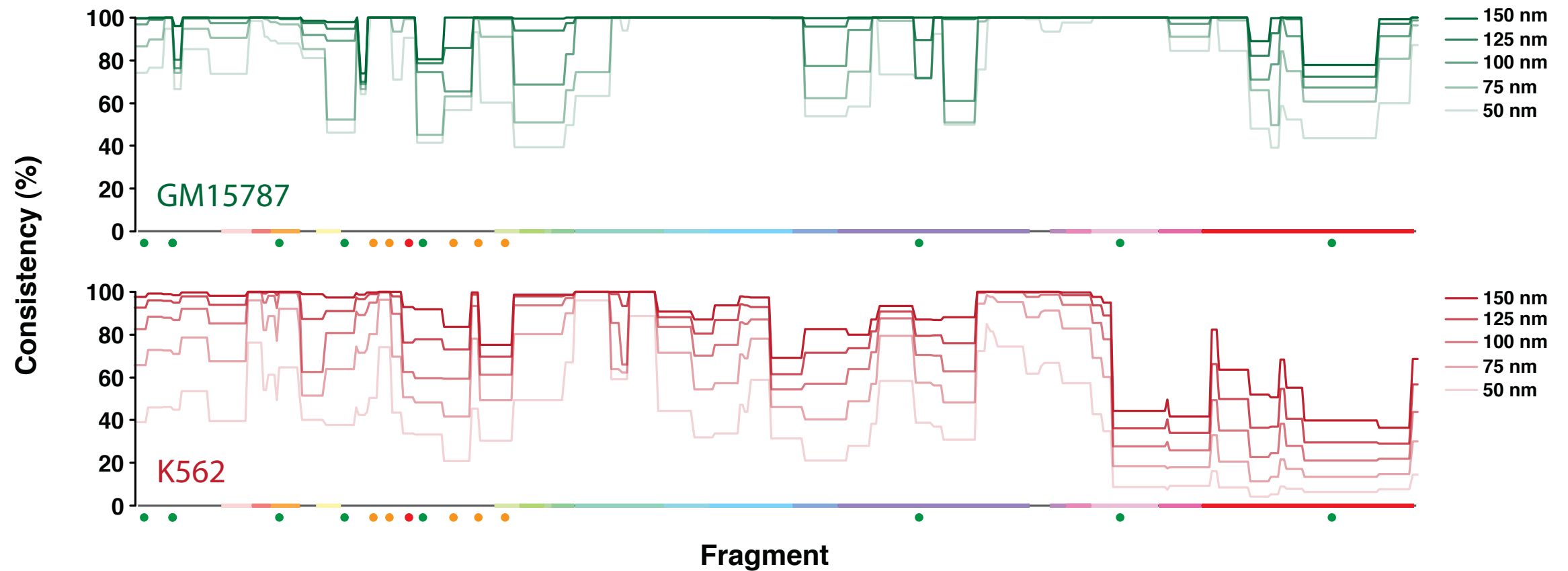
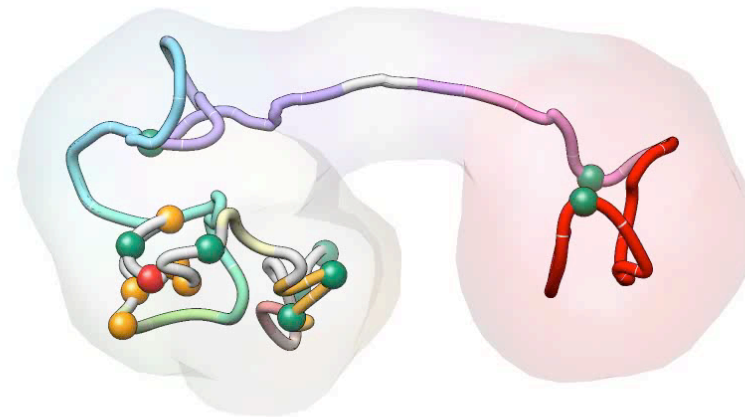
GM12878

Cluster #1  
2780 model  
910,280 IMP OF



K562

Cluster #2  
314 model  
232,673 IMP OF

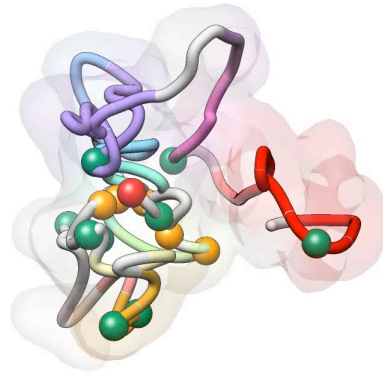




# Compactness

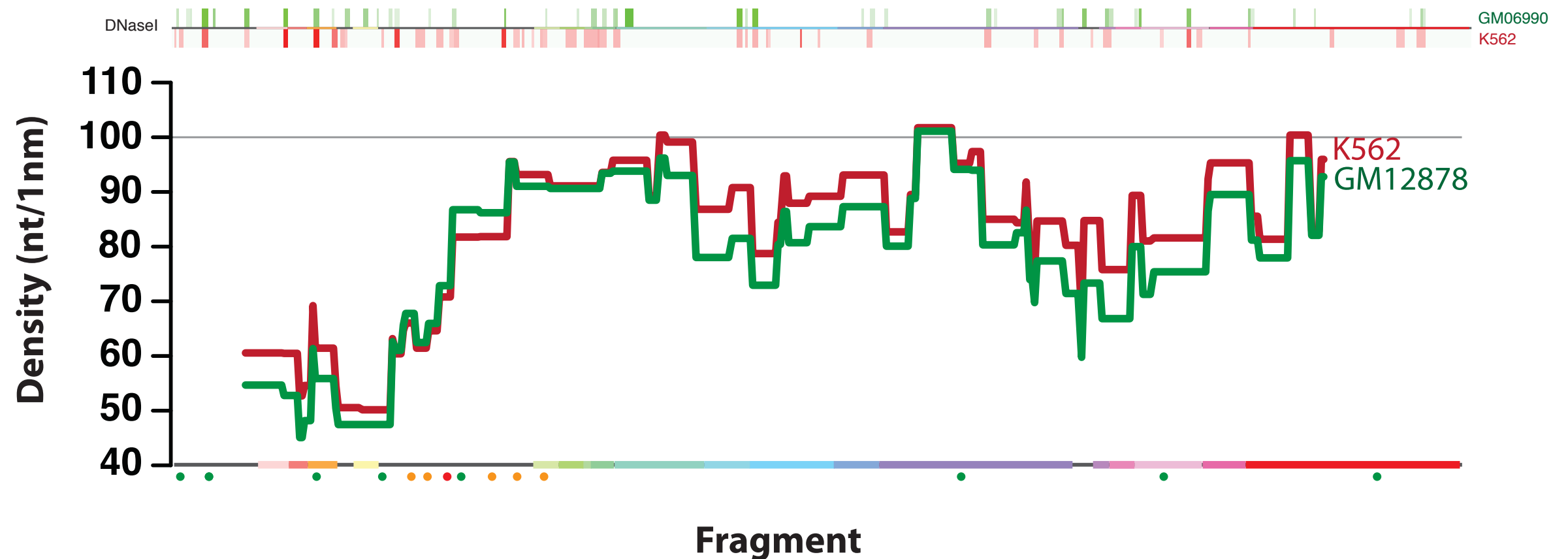
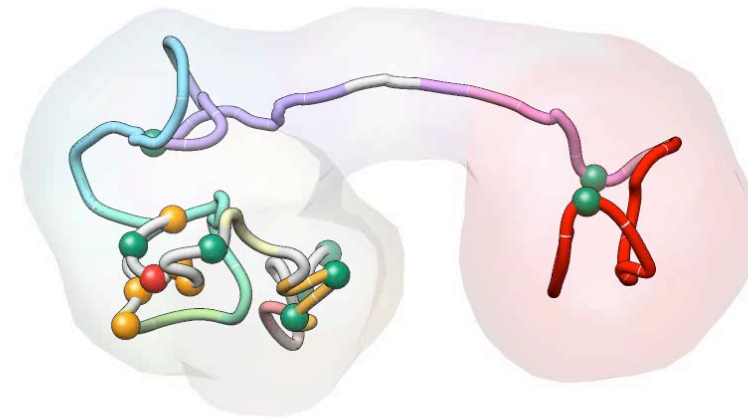
**GM12878**

Cluster #1  
2780 model  
910,280 IMP OF



**K562**

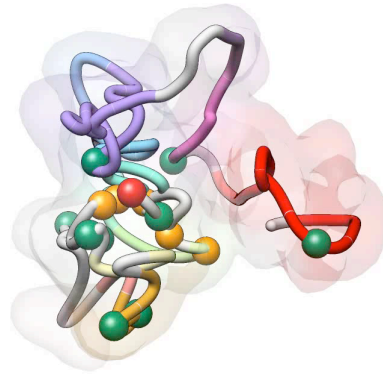
Cluster #2  
314 model  
232,673 IMP OF



# Regulatory elements

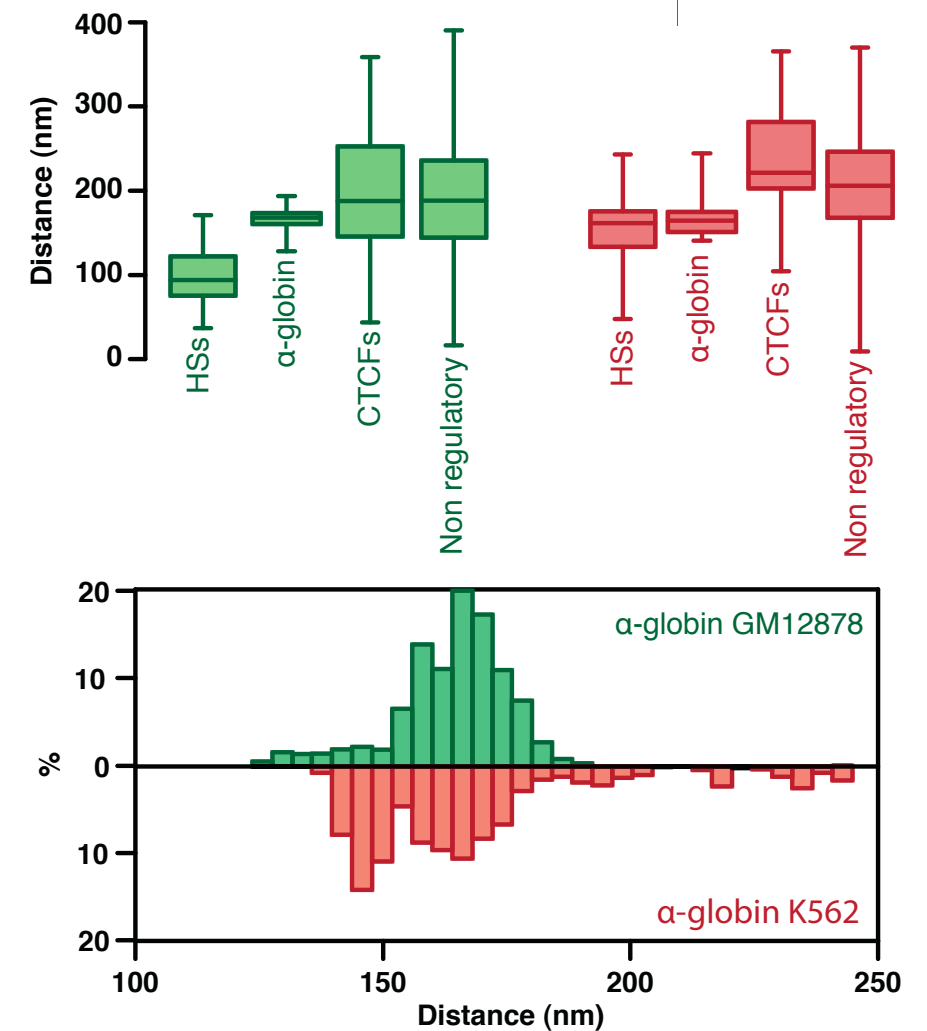
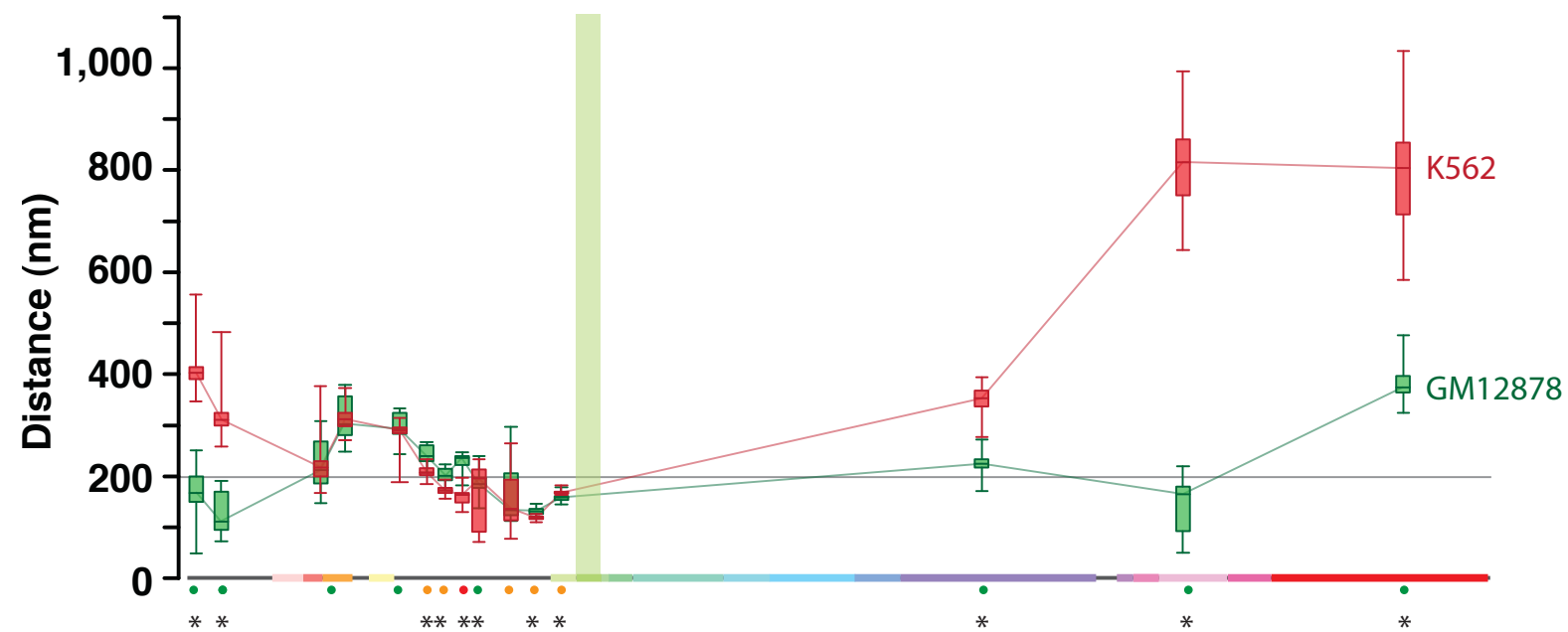
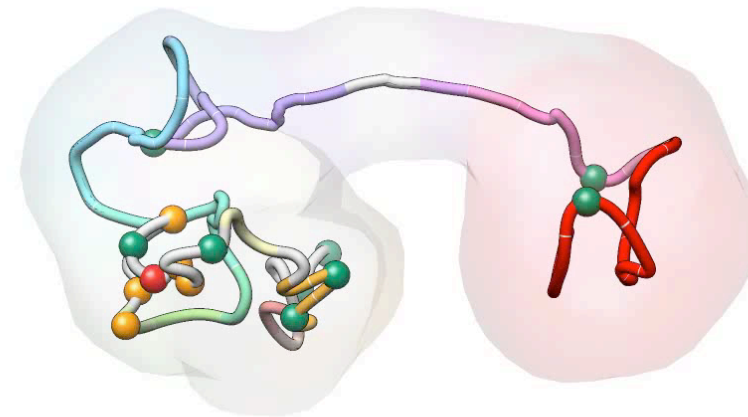
GM12878

Cluster #1  
2780 model  
910,280 IMP OF



K562

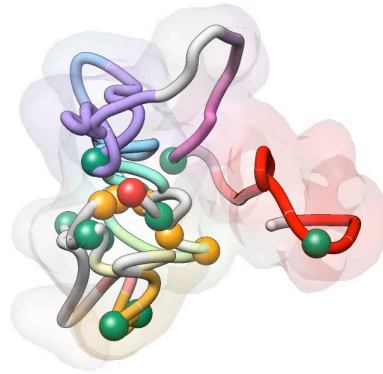
Cluster #2  
314 model  
232,673 IMP OF



# Multi-loops

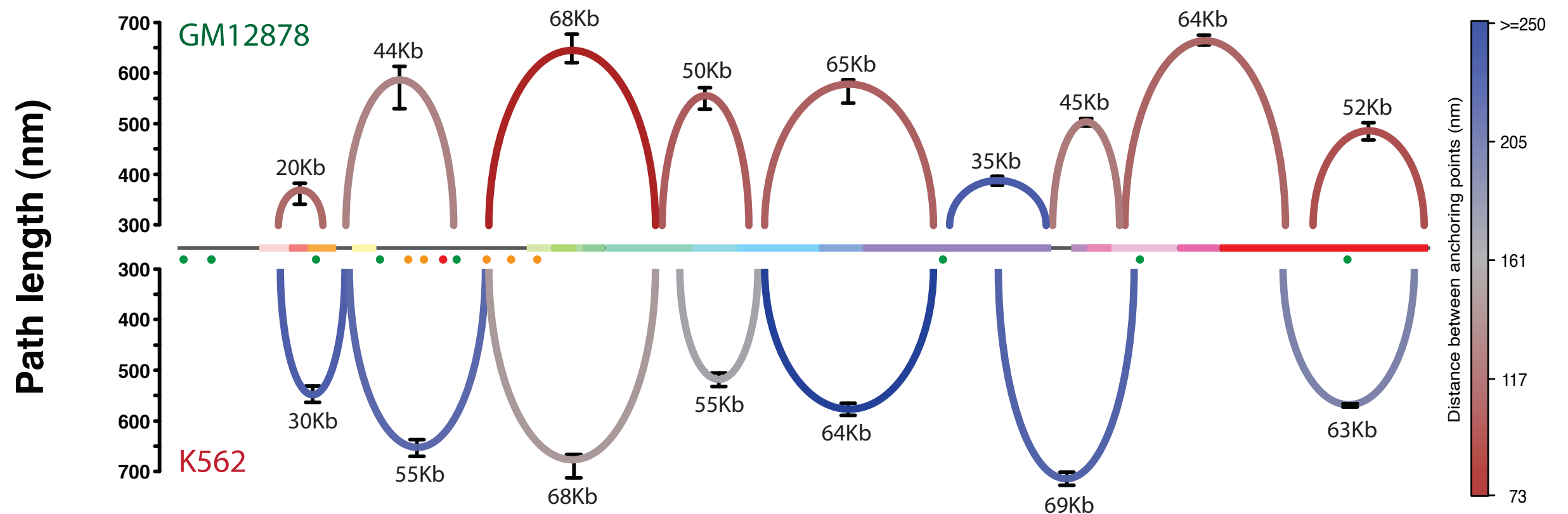
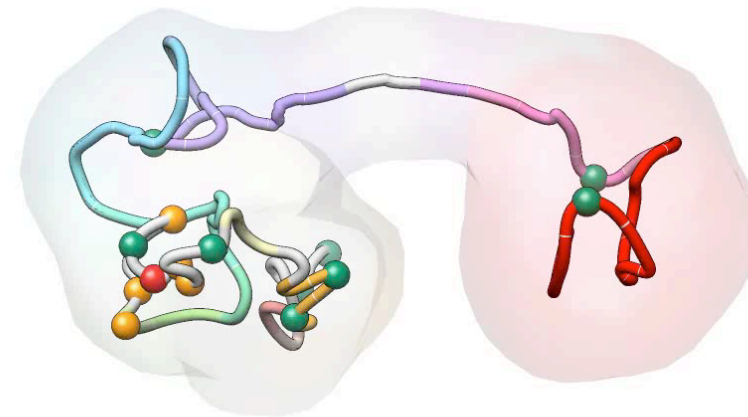
GM12878

Cluster #1  
2780 model  
910,280 IMP OF



K562

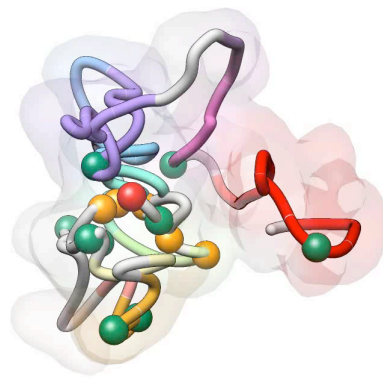
Cluster #2  
314 model  
232,673 IMP OF



# Expression

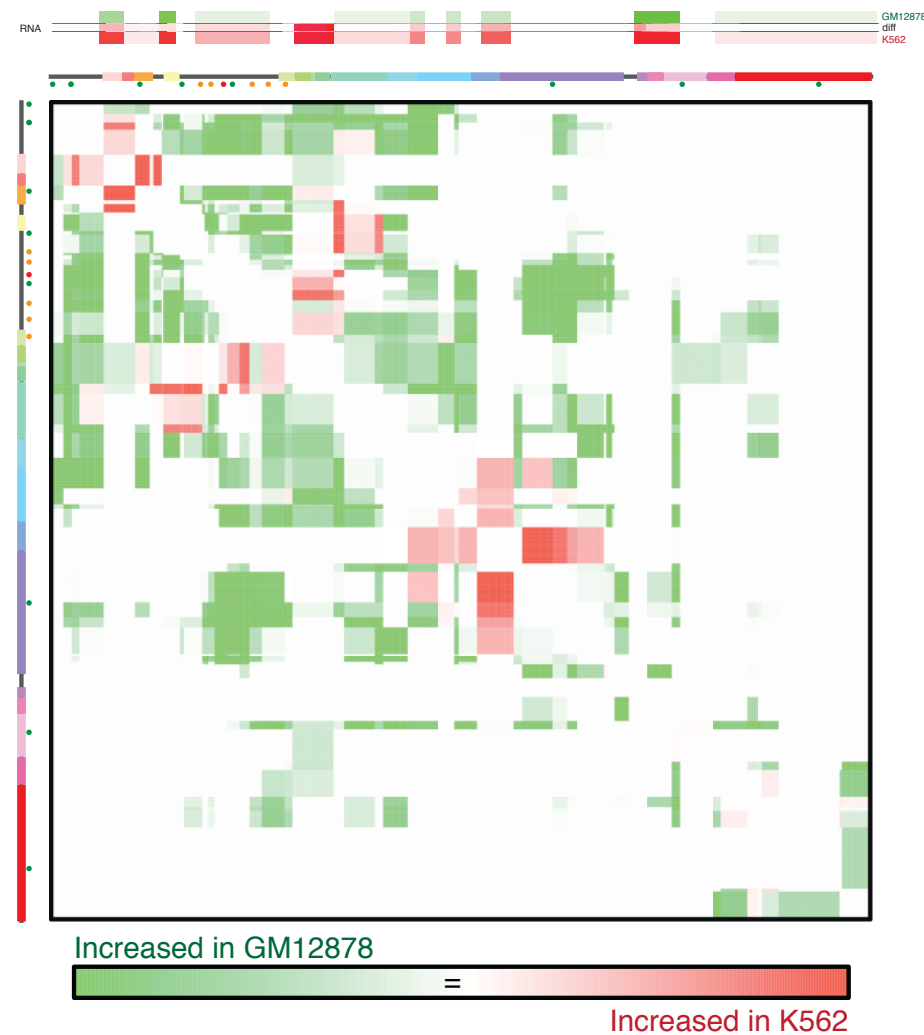
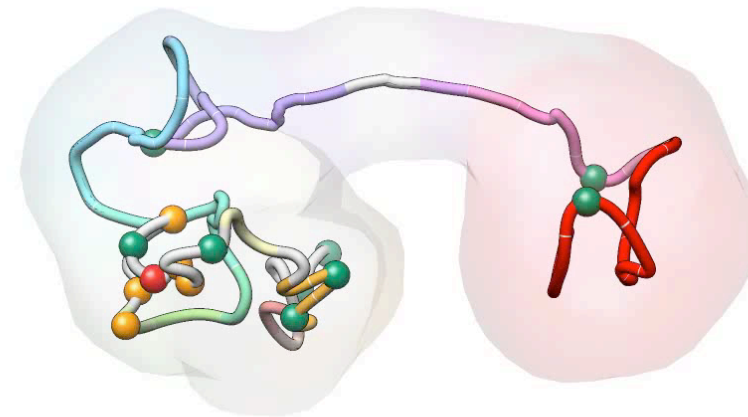
## GM12878

Cluster #1  
2780 model  
910,280 IMP OF



## K562

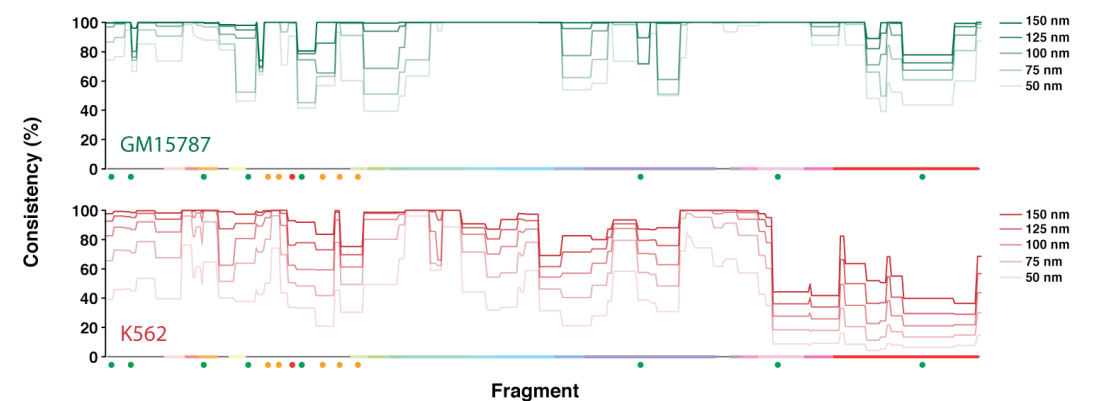
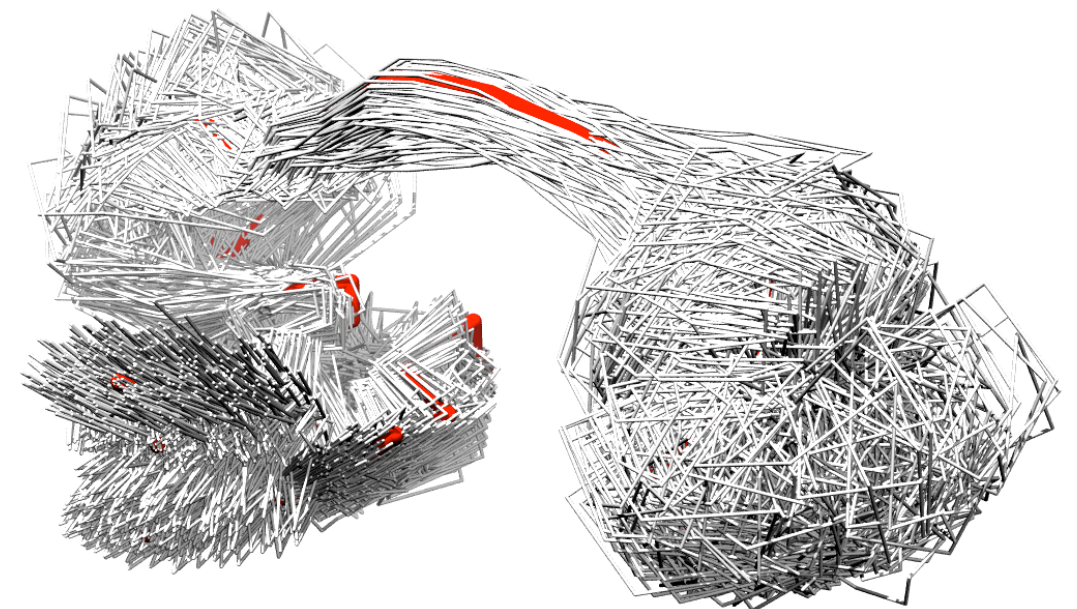
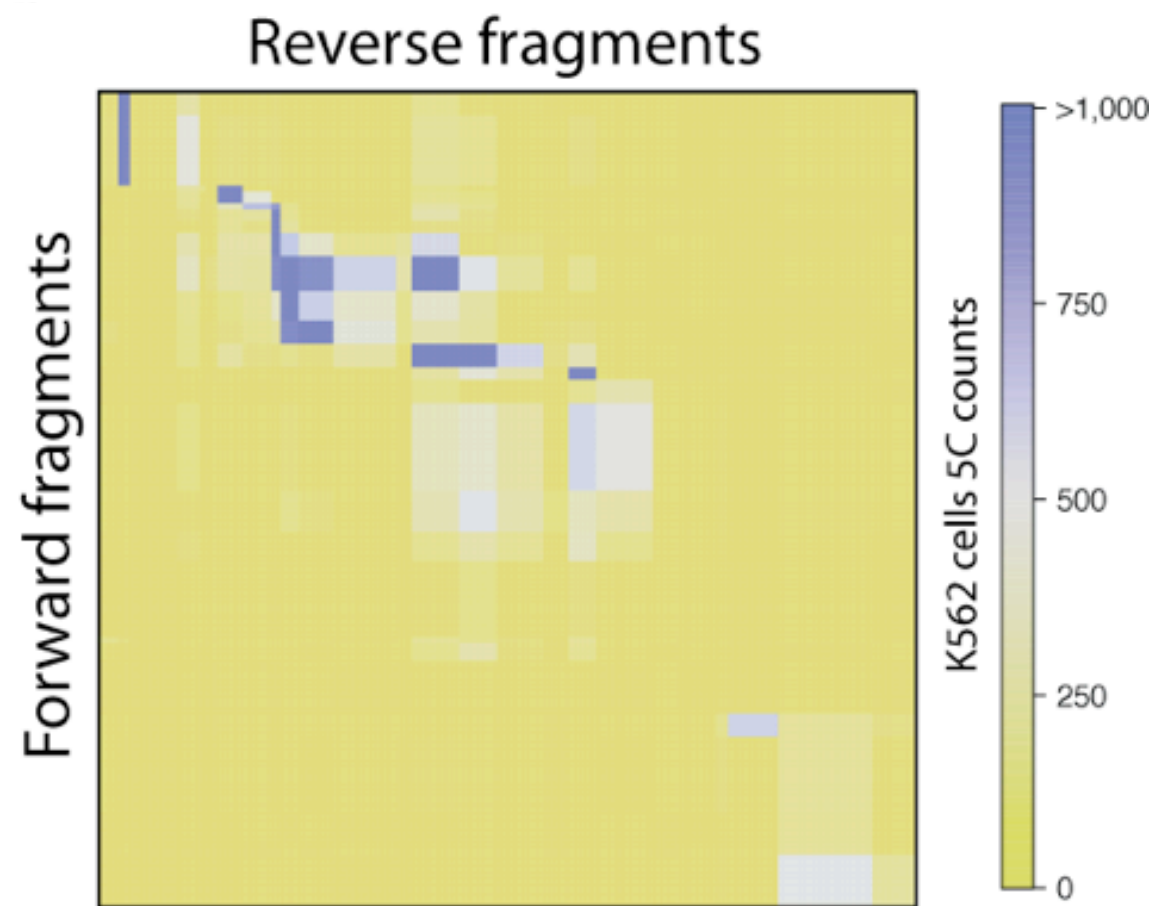
Cluster #2  
314 model  
232,673 IMP OF





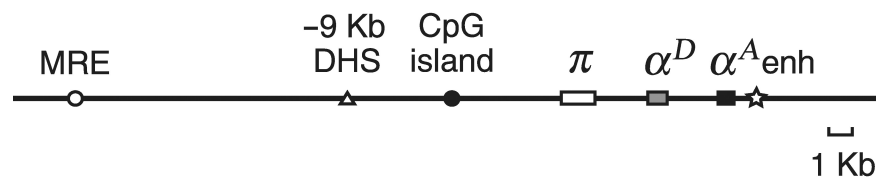
# Summary

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

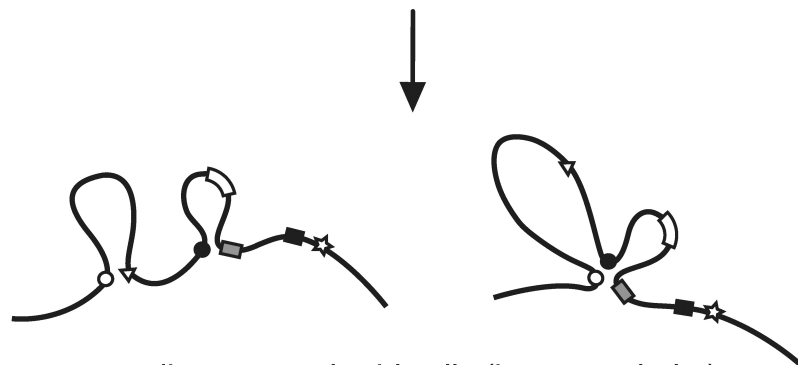


# Summary

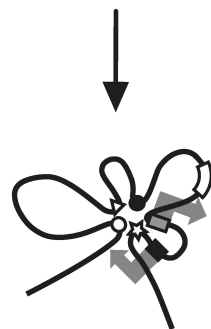
Selected models reproduce known (**and new**) interactions



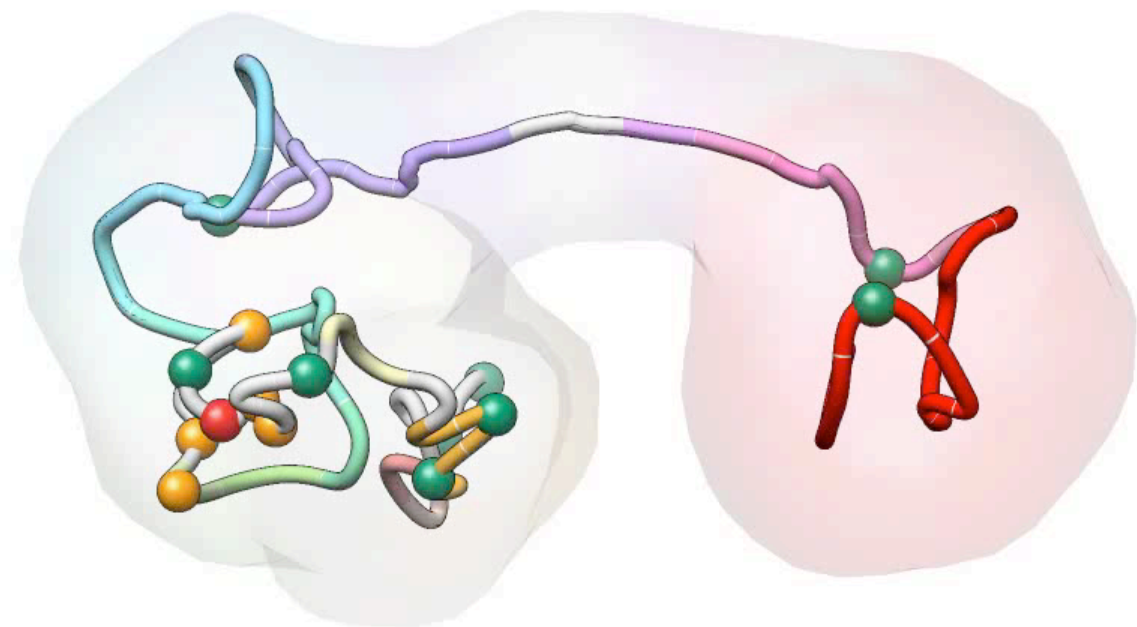
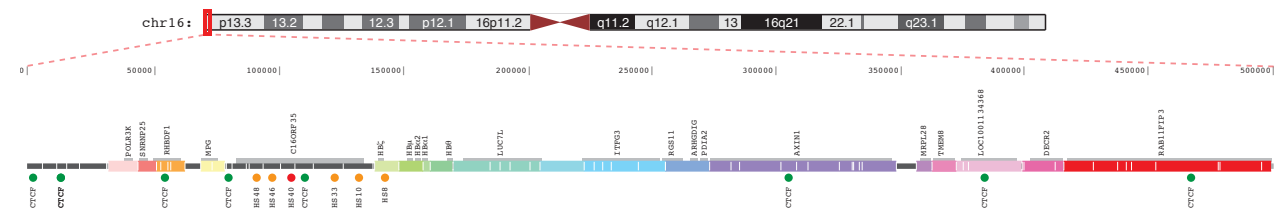
non-erythroid cells (relatively extended configuration)



cycling pre-erythroid cells (immature hubs)

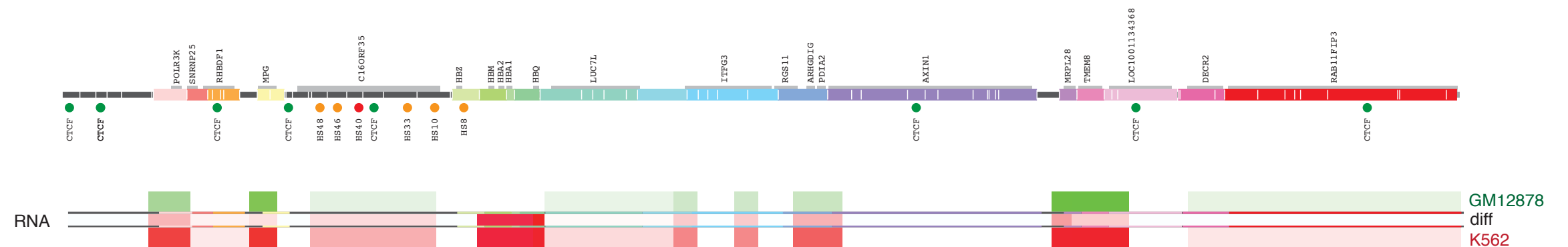
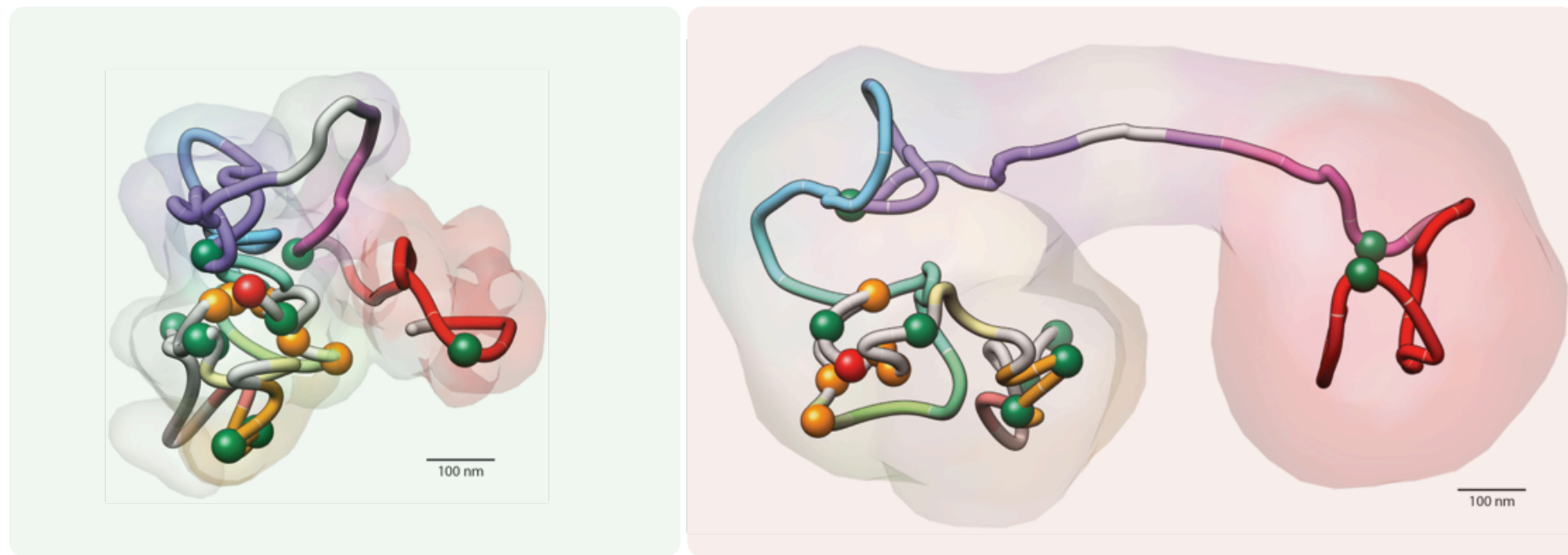


differentiated erythroid cells (active hub)



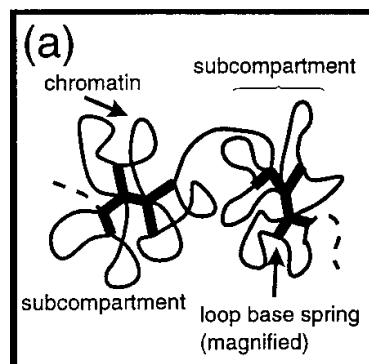
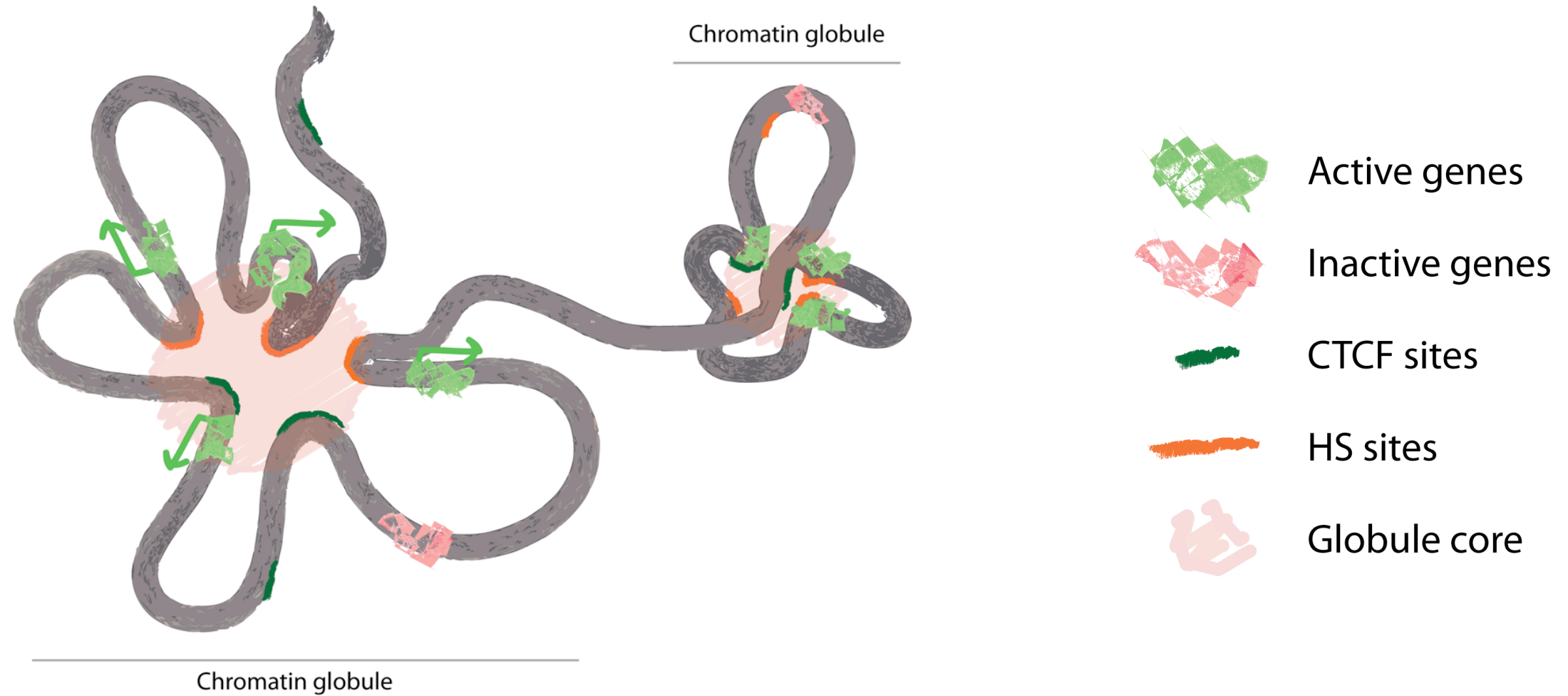
# Summary

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

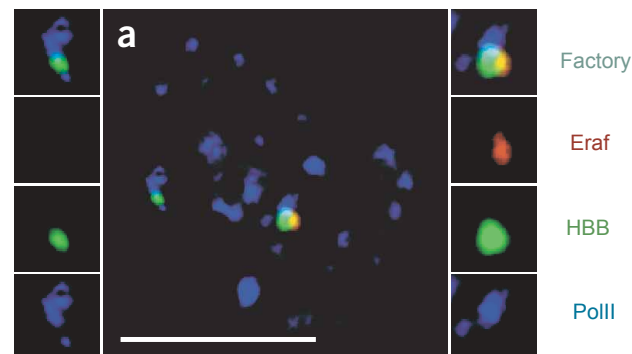


# Summary

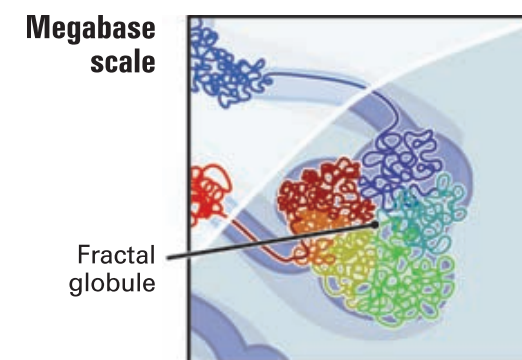
## “Chromatin Globule” model



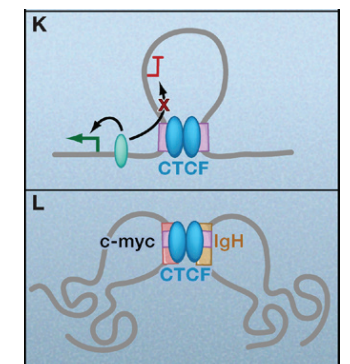
Münkel et al. JMB (1999)



Osborne et al. Nat Genet (2004)



Lieberman-Aiden et al. Science (2009)



Phillips and Corces. Cell (2009)



# Acknowledgments

## Job Dekker

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Worcester, MA, USA



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Structural Genomics Unit

