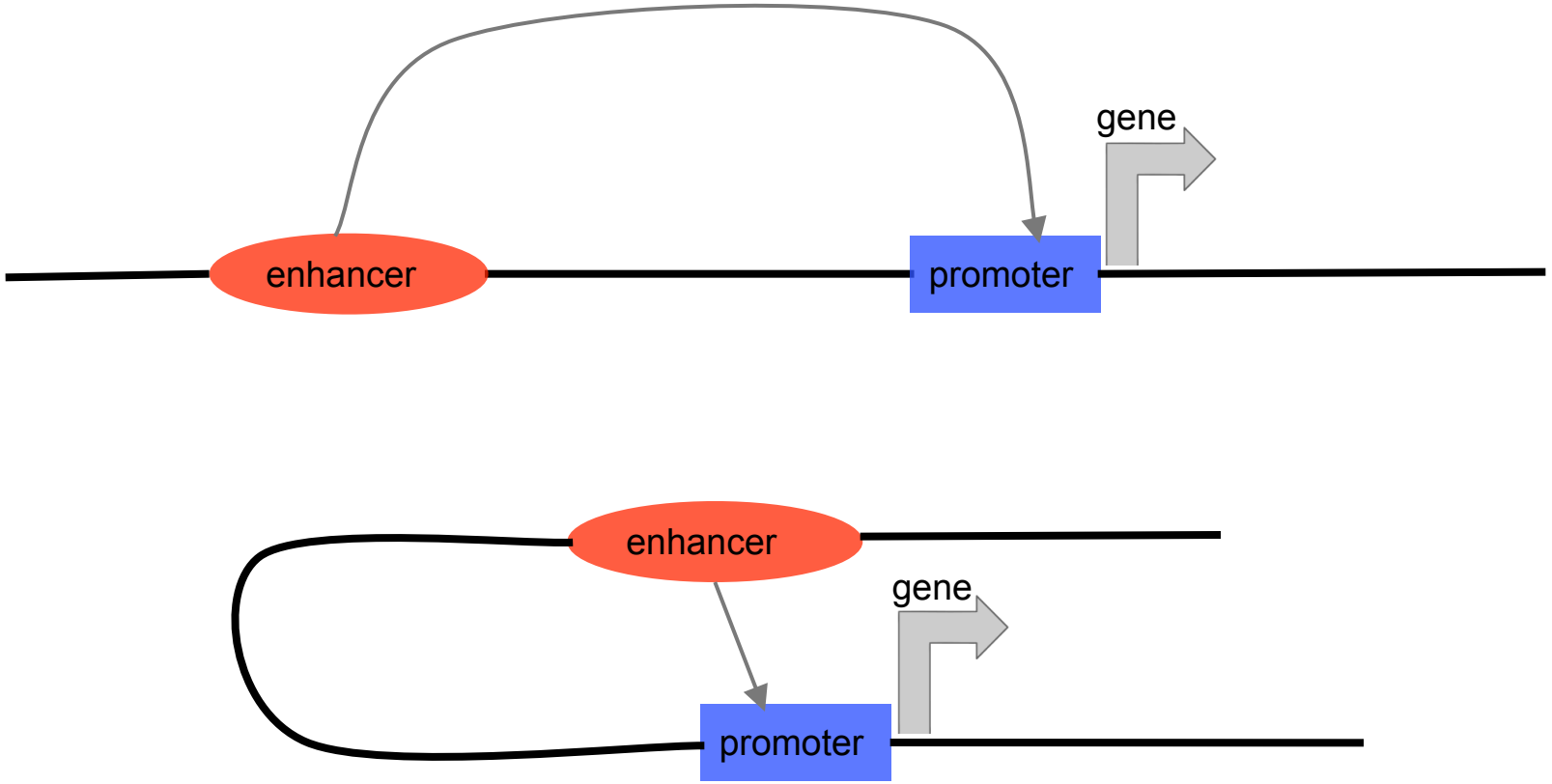
Local Structure of the Chromatin Fiber Arbitrates 3D Chromosomal Interactions

Boryana Doyle and Carolyn Lu

Second Annual MIT PRIMES Conference, May 20, 2012

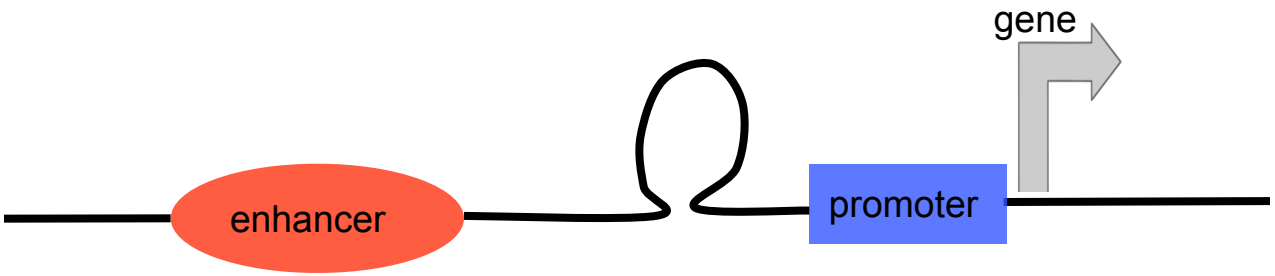
Enhancers, Promoters, and Genes

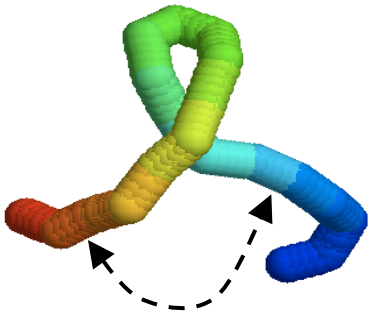
In order for gene expression to occur, an enhancer and a promoter of that gene must come in contact with each other.



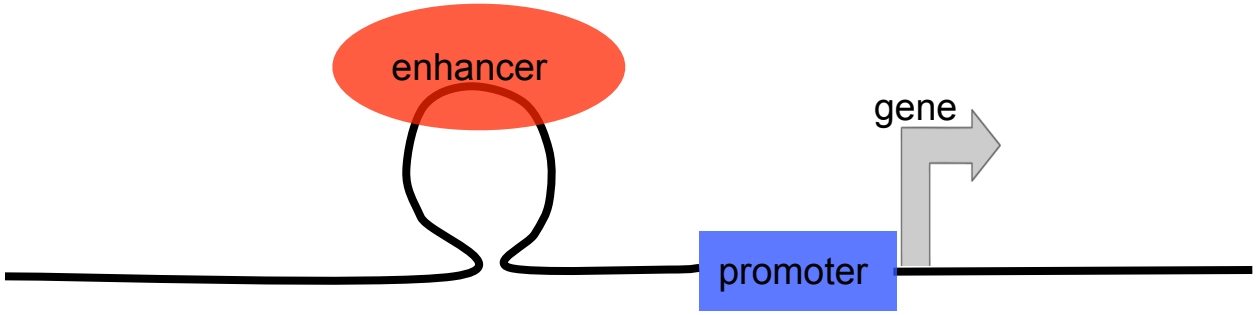
Role of Chromatin Loops in Enhancer-Promoter Interactions

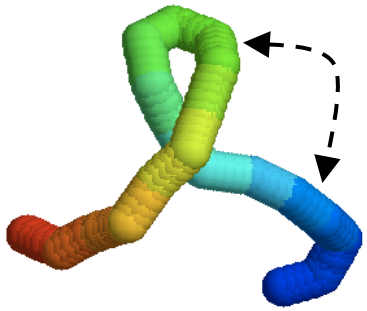
Case 1:





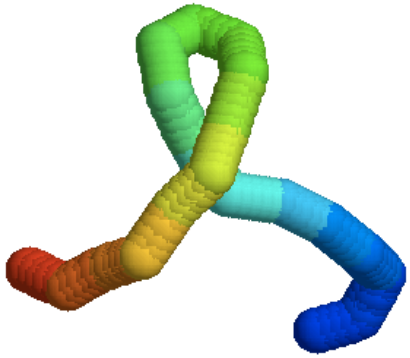
Case 2:





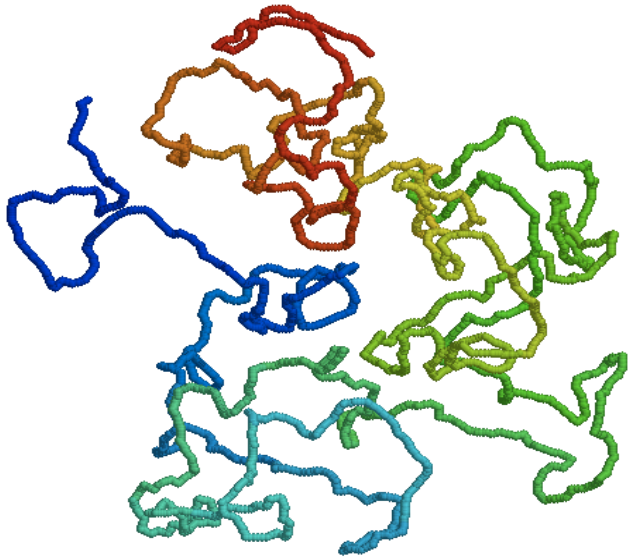
Approach

Connect monomers to form a loop in the polymer.

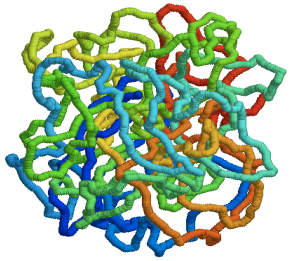


Simulation

Polymer Model Parameters: Density

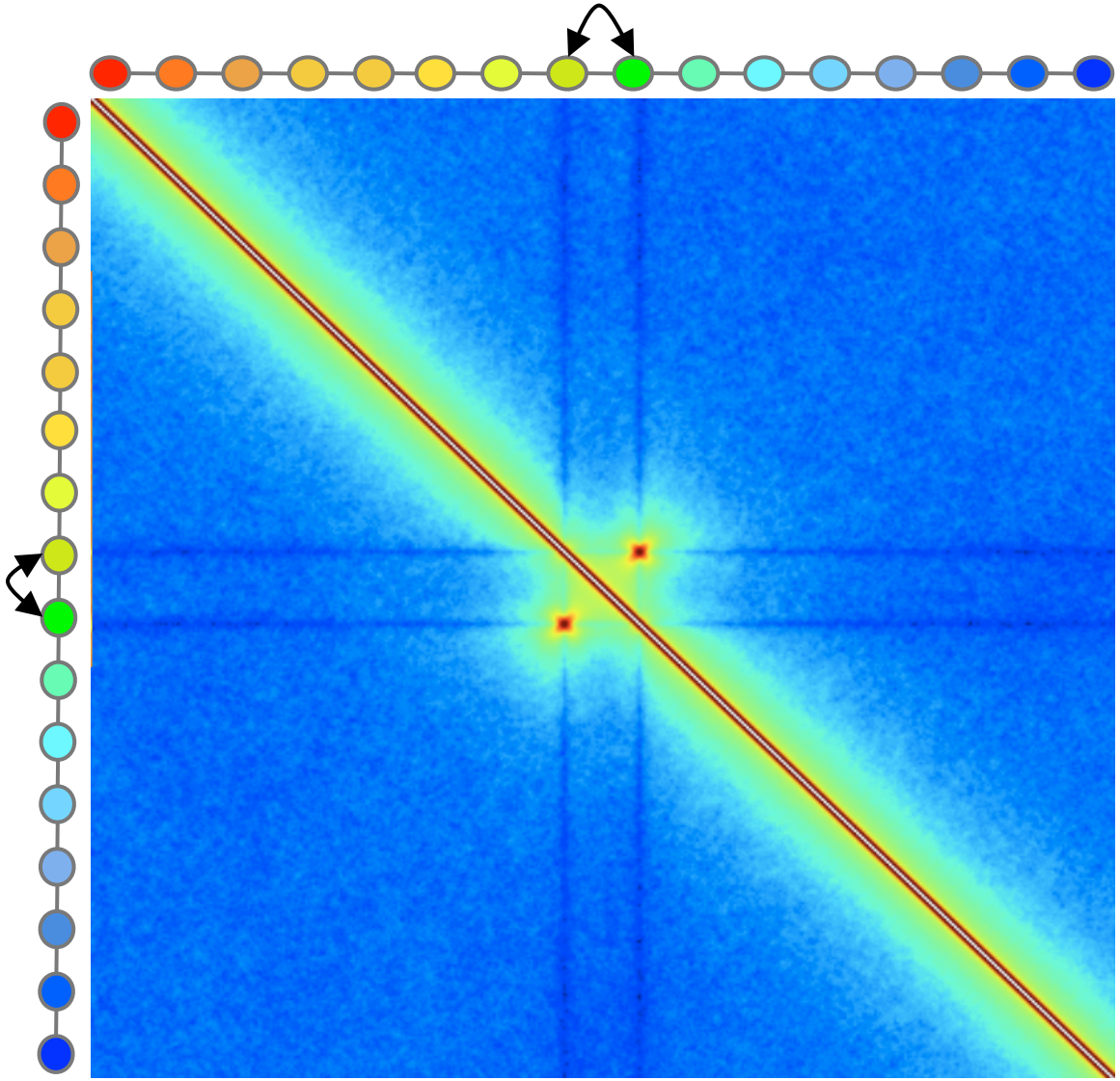


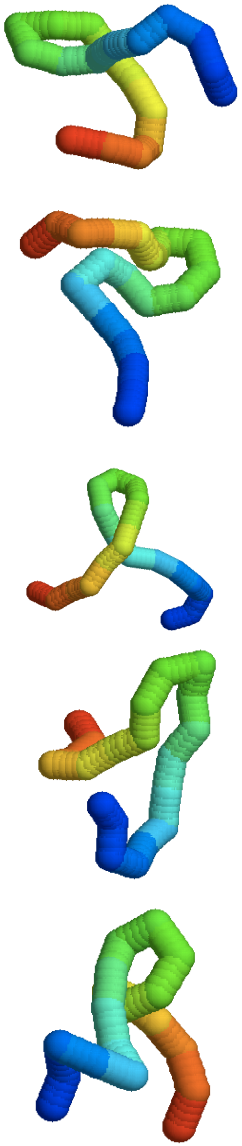
Low Density = Confined in Larger Sphere



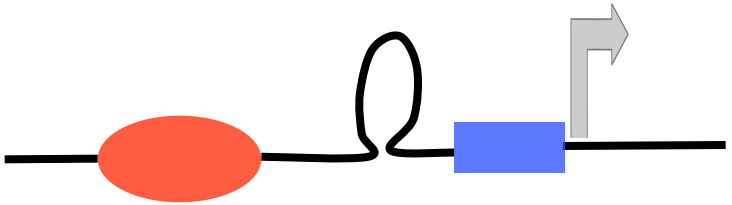
High Density = Confined in Smaller Sphere

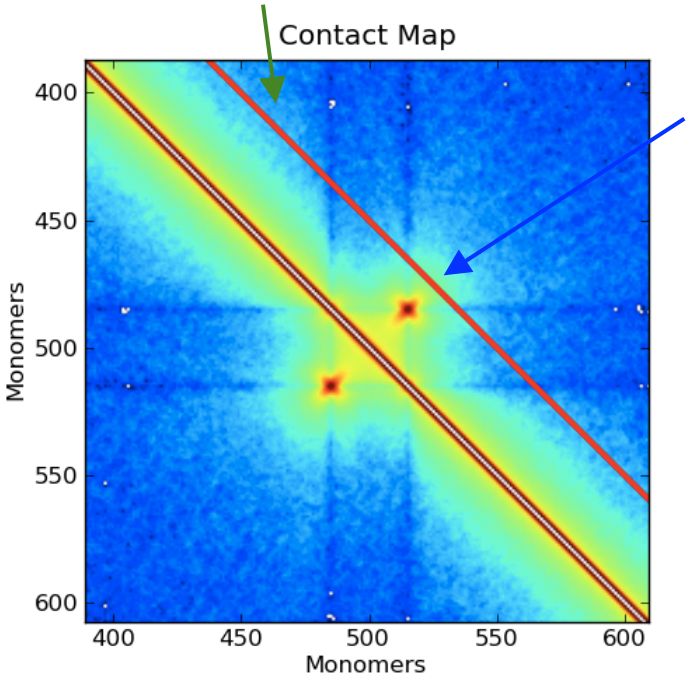
Results: Contact Maps

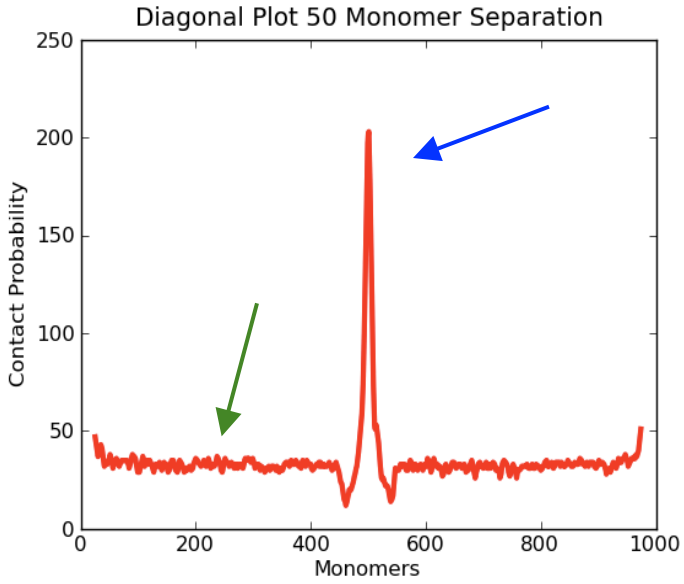


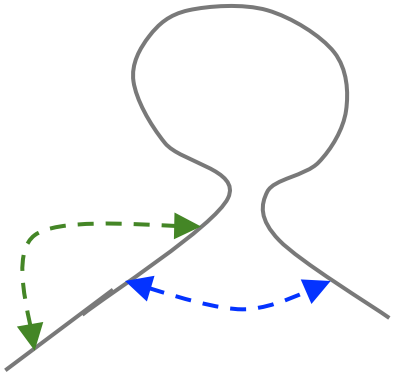


Case 1: Facilitates
Increased Contact Probability between monomers before and after the loop structure.

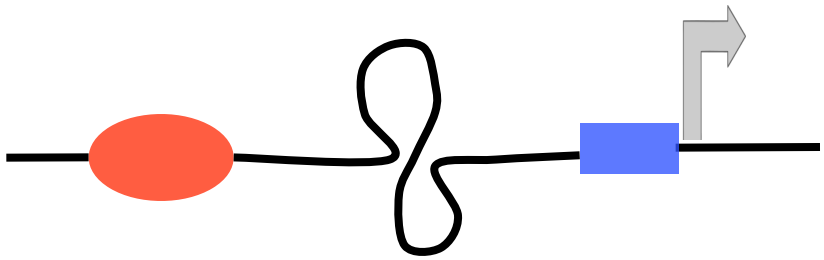


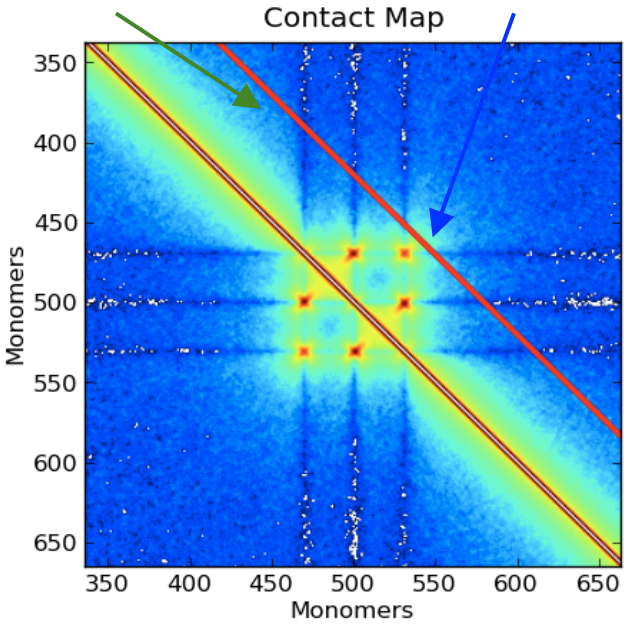


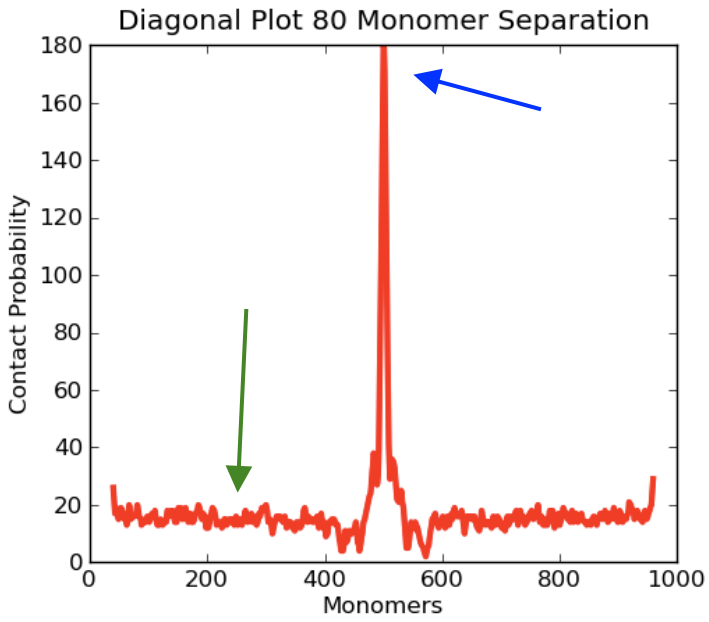


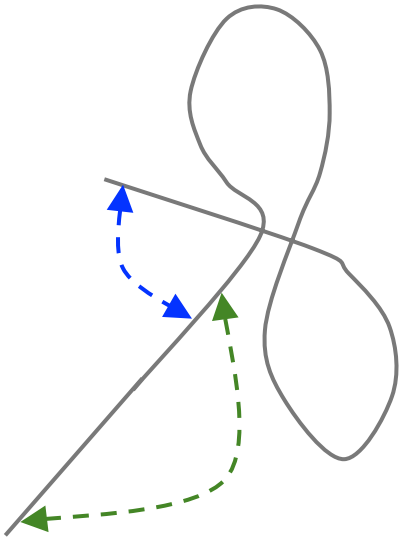


Case 1: Facilitates
Increased Contact Probability between monomers before and after the loop structure.

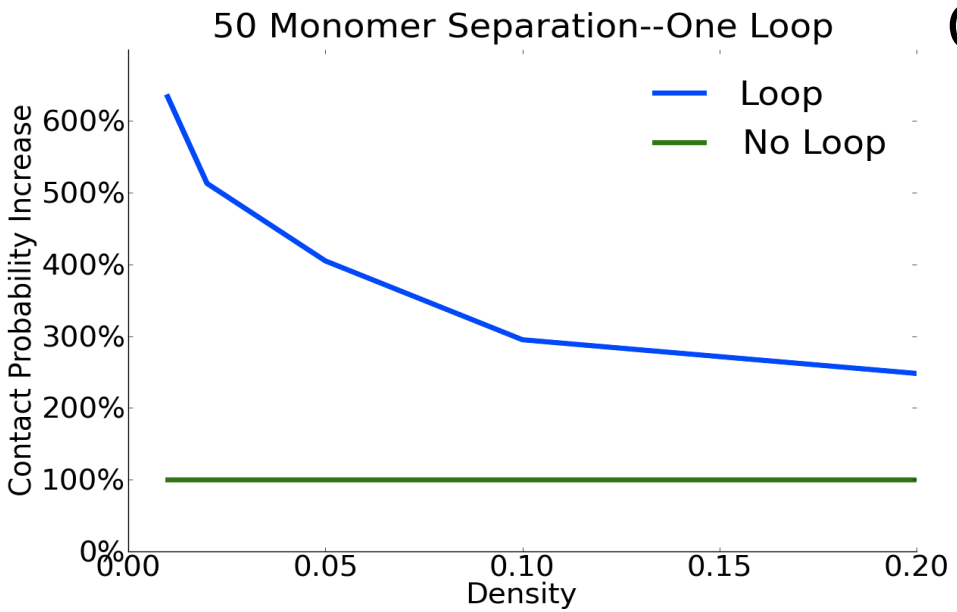




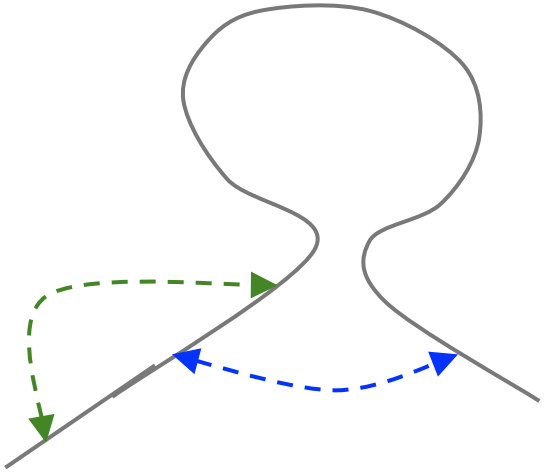


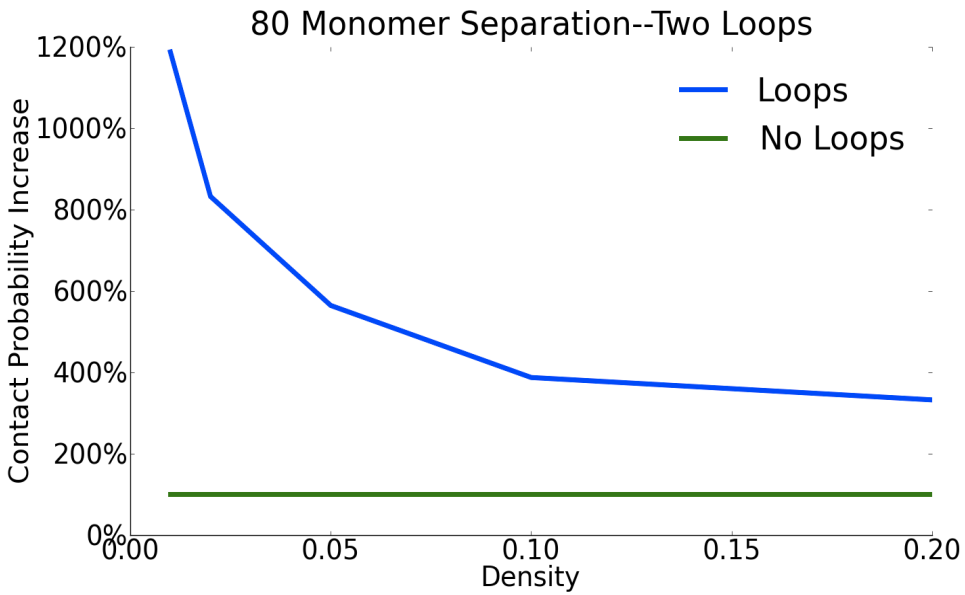


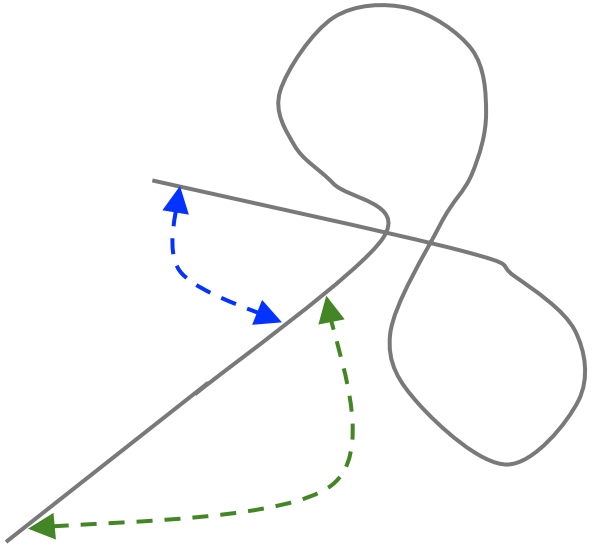
Effect of Density on Facilitation



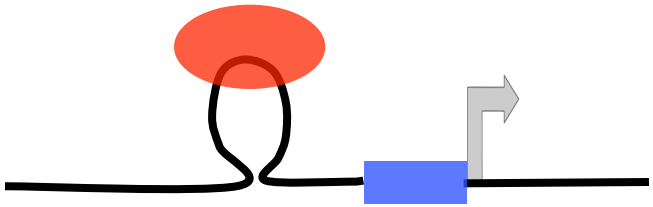
Case 1: Facilitates

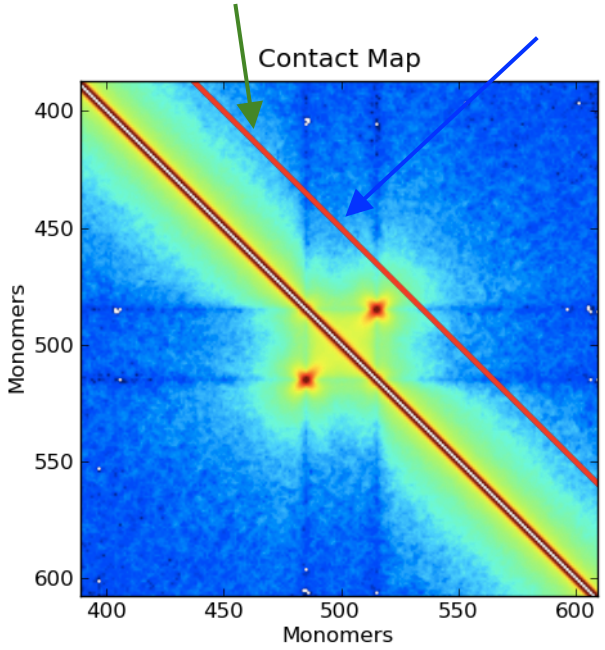


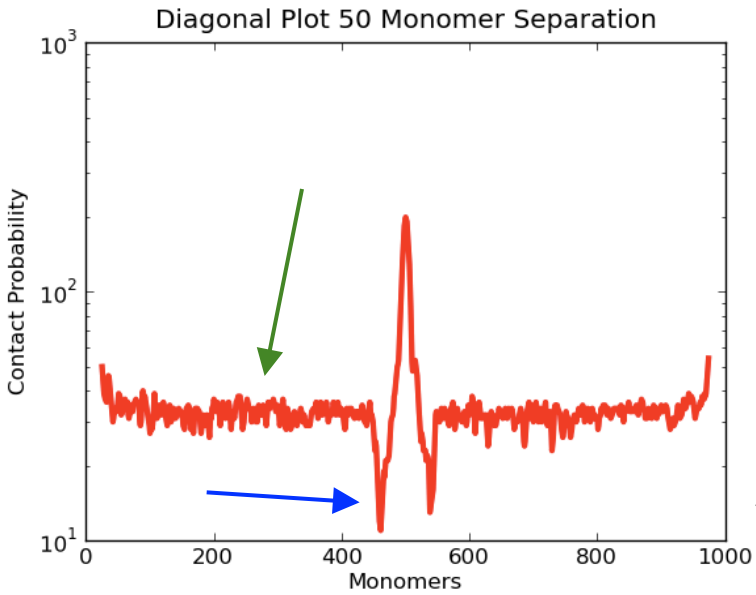


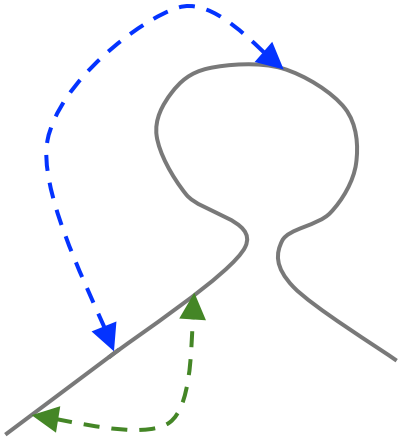


Case 2: Insulates
Decreased Contact Probability between monomers before the loop and within the loop.

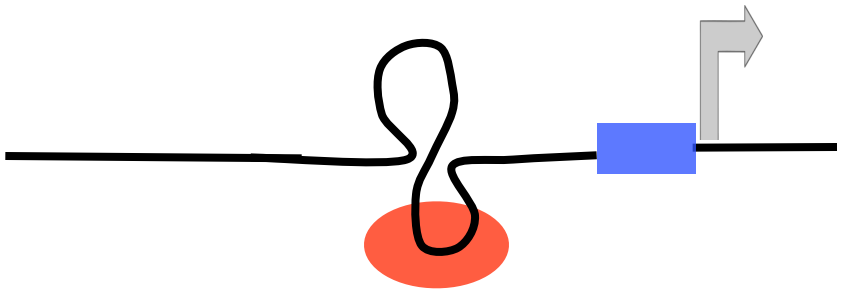


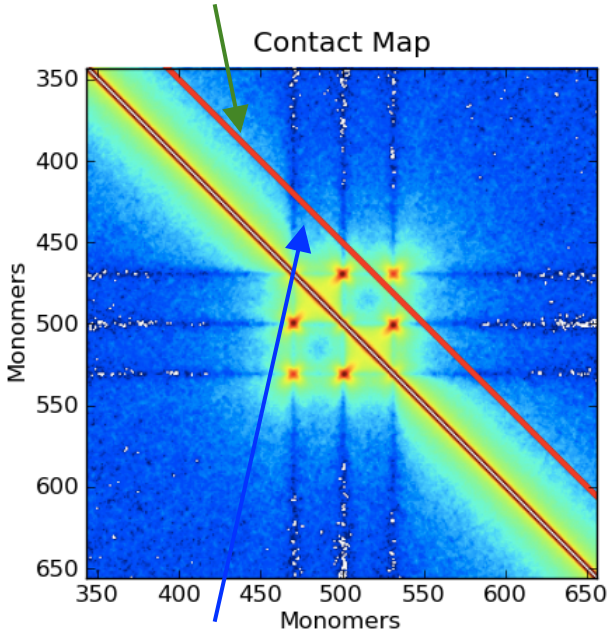


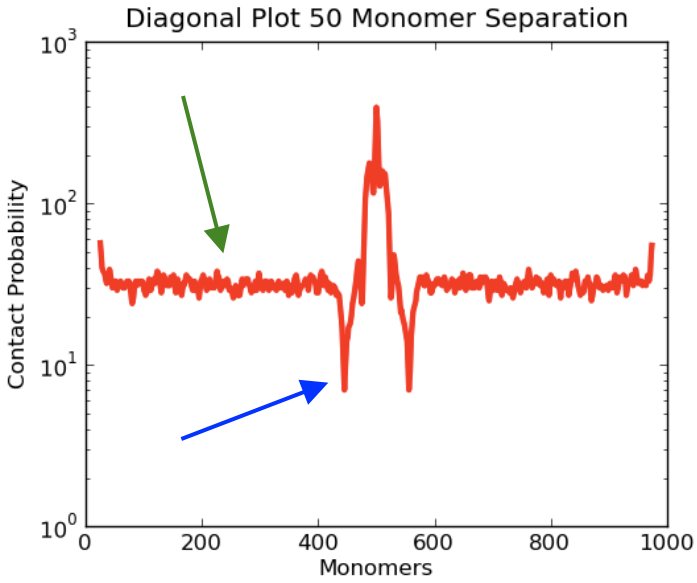


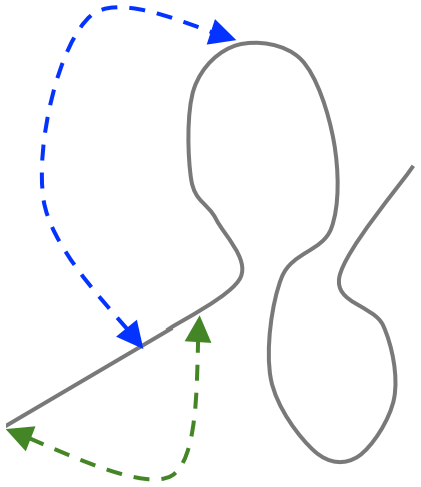


Case 2: Insulates
Decreased Contact Probability between monomers before the loop and within the loop.

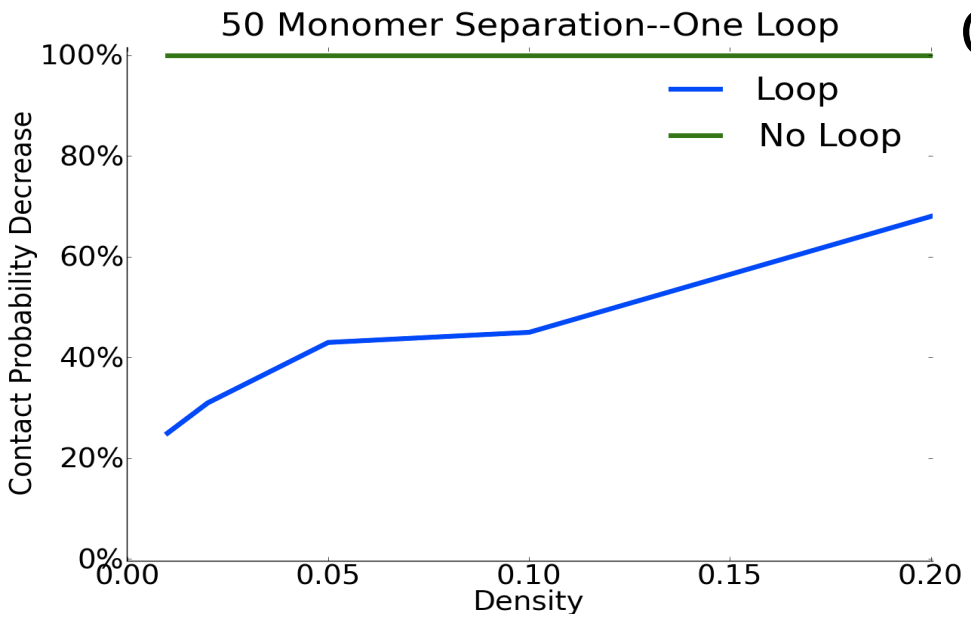


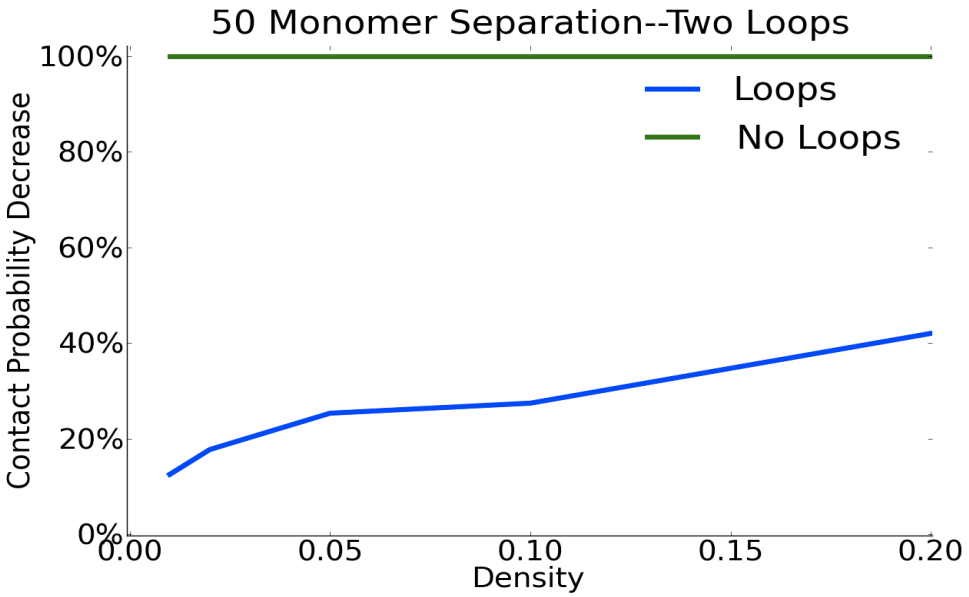




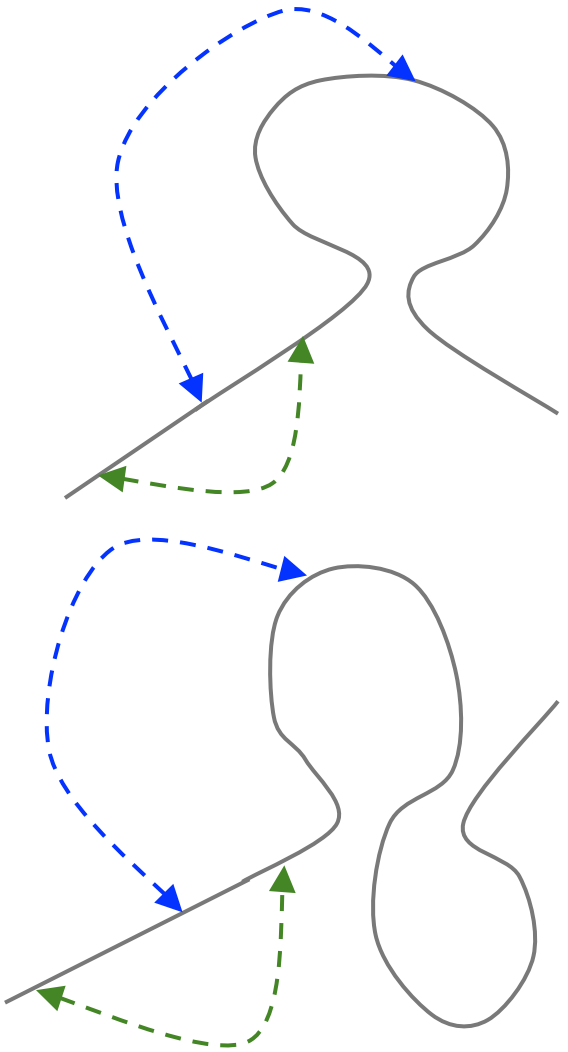


Effect of Density on Insulation





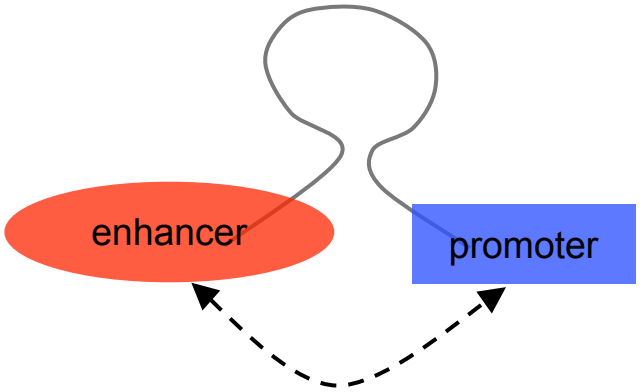
Case 2: Insulates



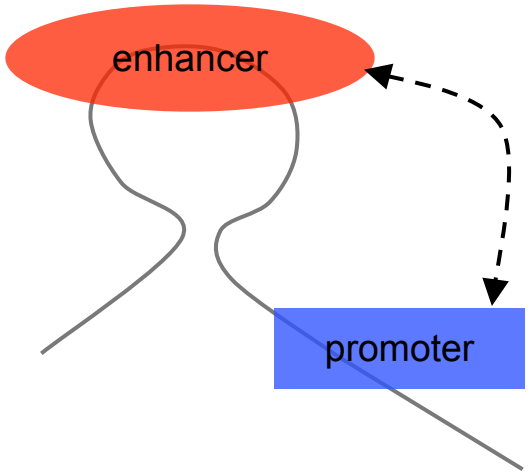
Conclusion

Interactions (such as forming loops) between different genomic regions can modulate enhancer-promoter interactions which regulate gene expression.

Case 1: Facilitates



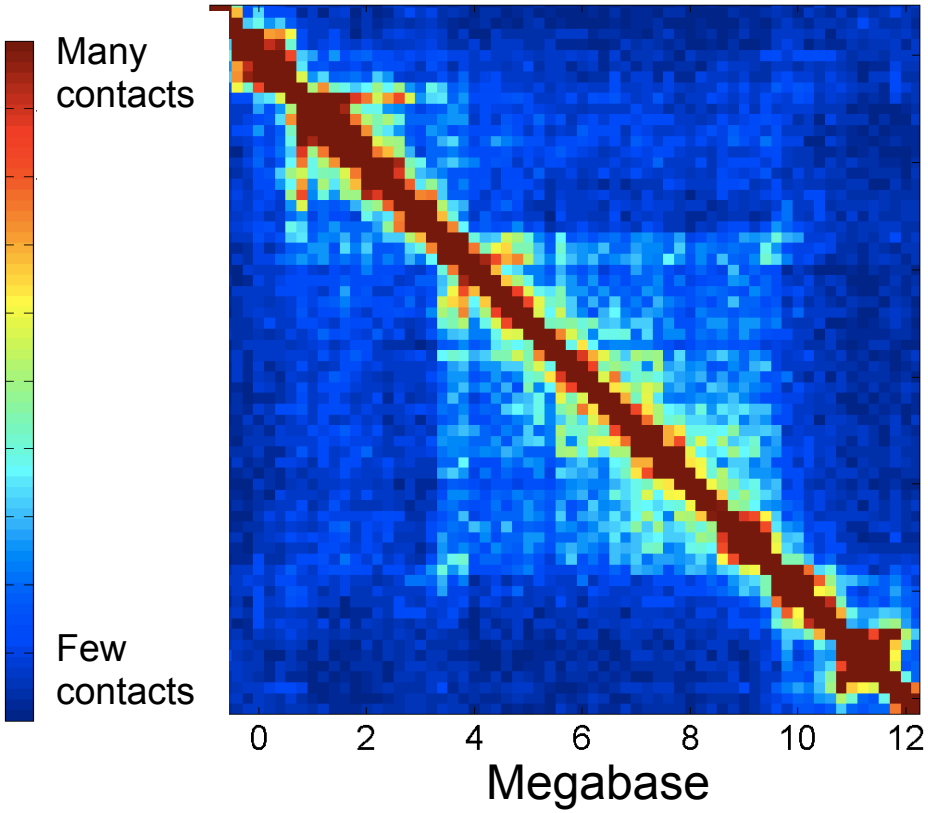
Case 2: Insulates



Similar but more dramatic effects using two loops.

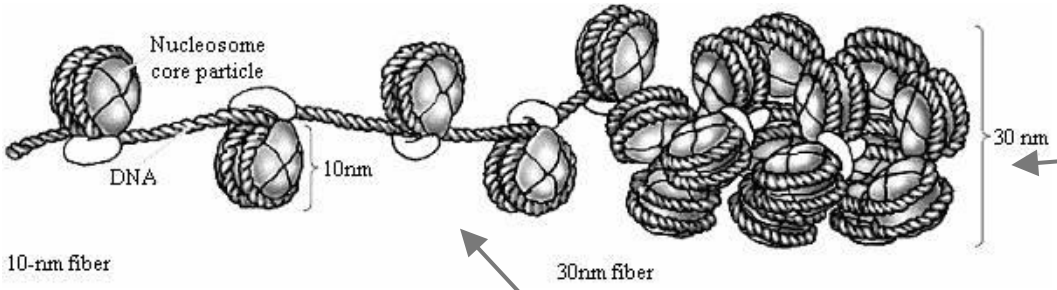
How does local chromatin fiber flexibility affect a chromosomal contact map?

12 Mb Region of Human Chr14



Hypothesis

(Seitz, 2004)

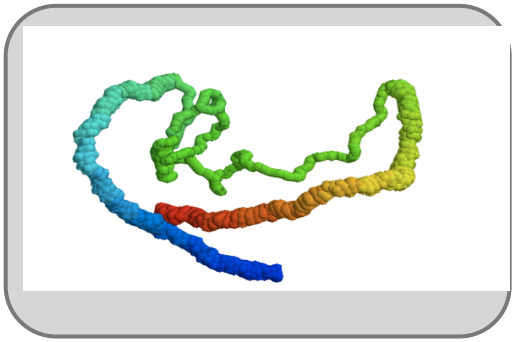


Inactive Genes/
No Genes

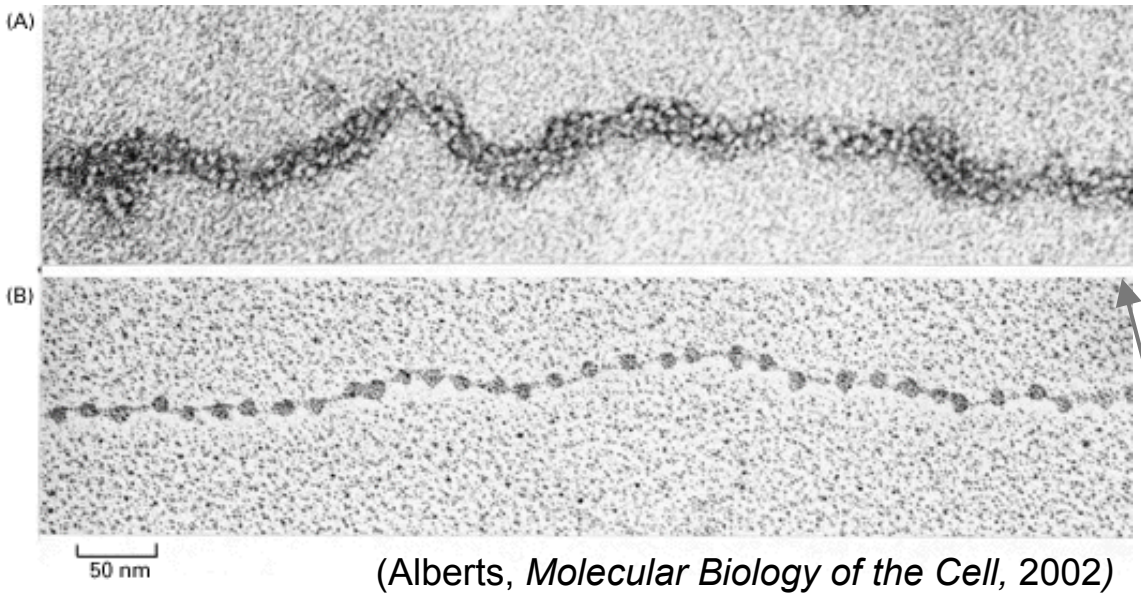
⇩

Thick Stiff
Fiber

Active Genes ⇨ Thin Extended Fiber



Images of Chromatin Fiber

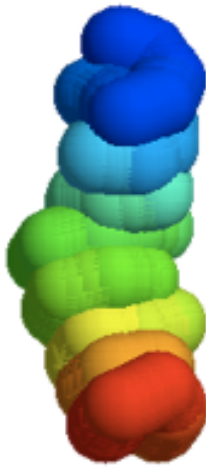


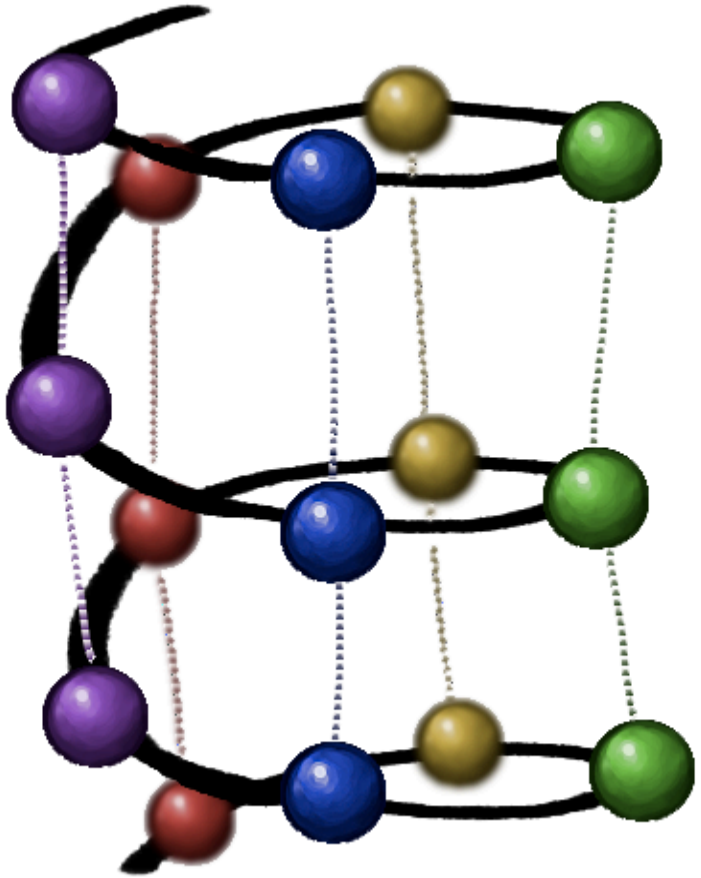
(Alberts, *Molecular Biology of the Cell,* 2002)

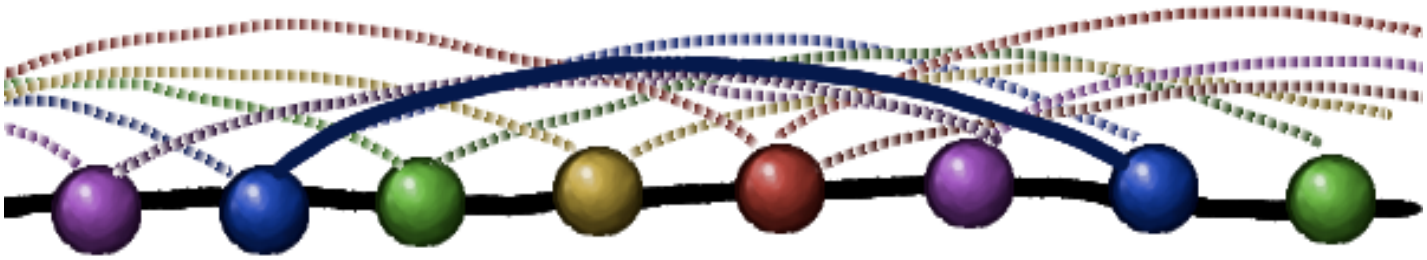
Electron
Microscopy images
of chromatin fiber.

Model for Thick Fiber

Bonds between monomers at intervals form a stiff thick fiber.



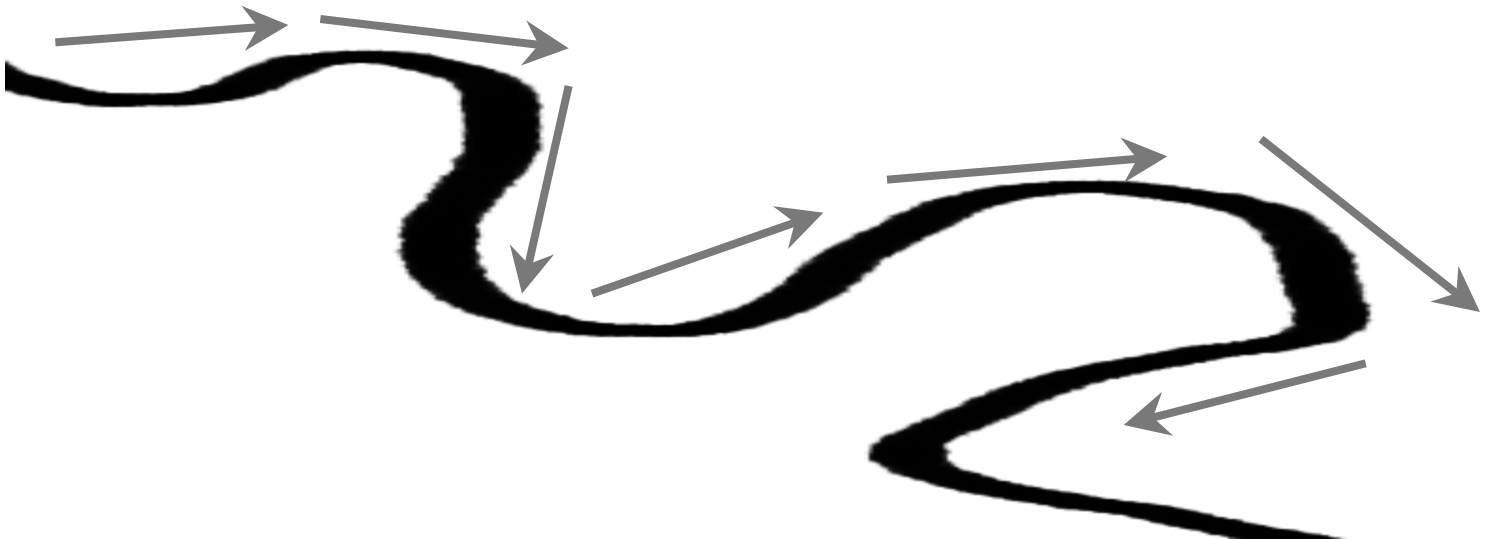




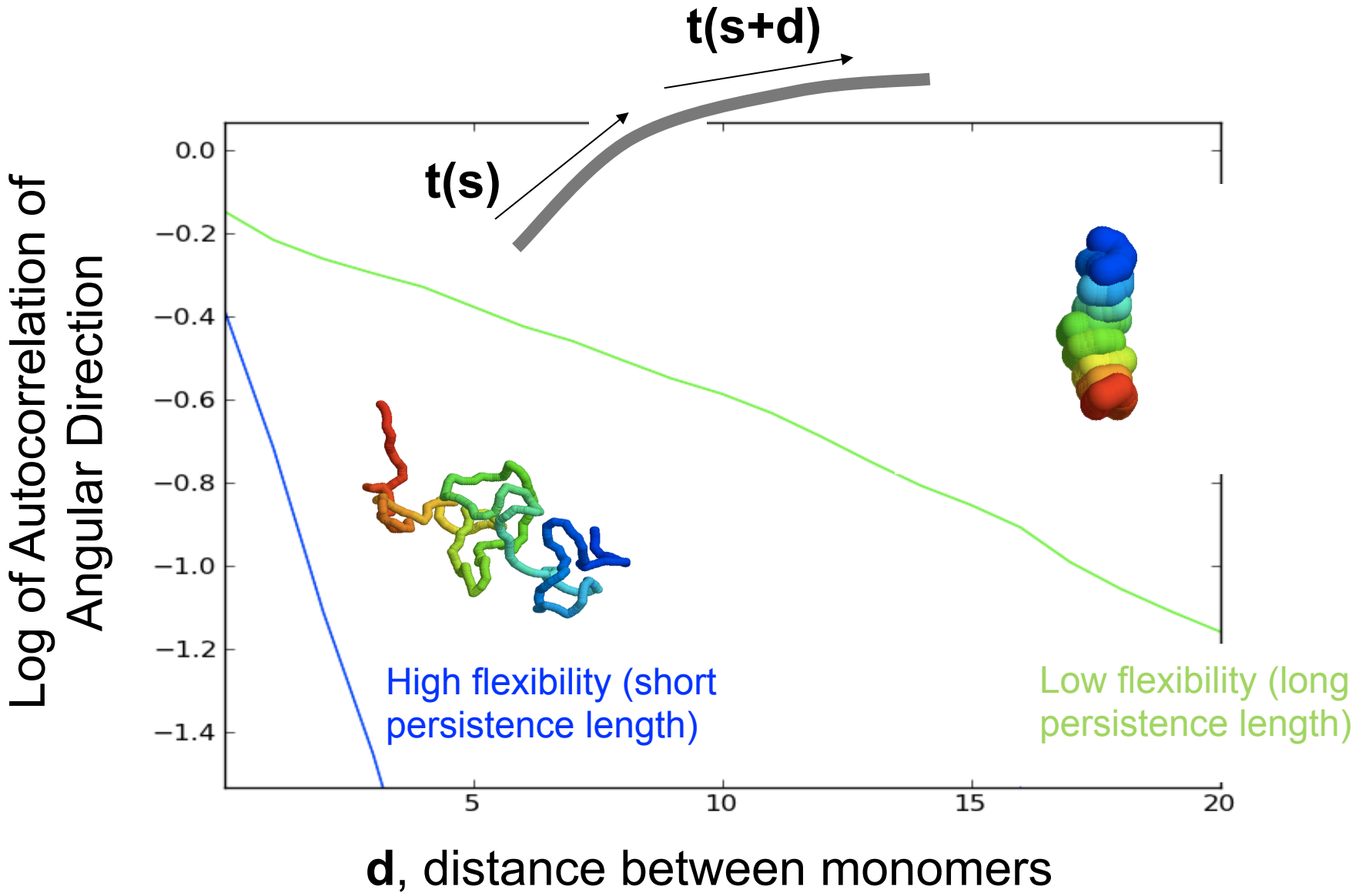
Persistence Length is a measure of Polymer Flexibility

The persistence length = length over which polymer's path is relatively straight.

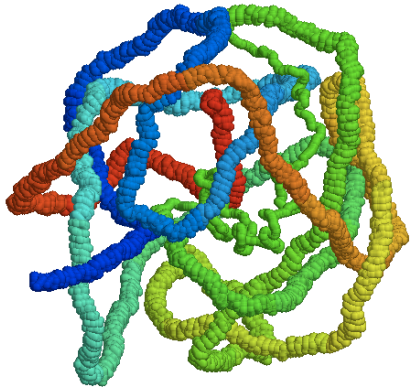
Lower persistence length = more flexible
Higher persistence length = stiffer



Thick and Thin Fibers Have Differing Flexibilities



Model

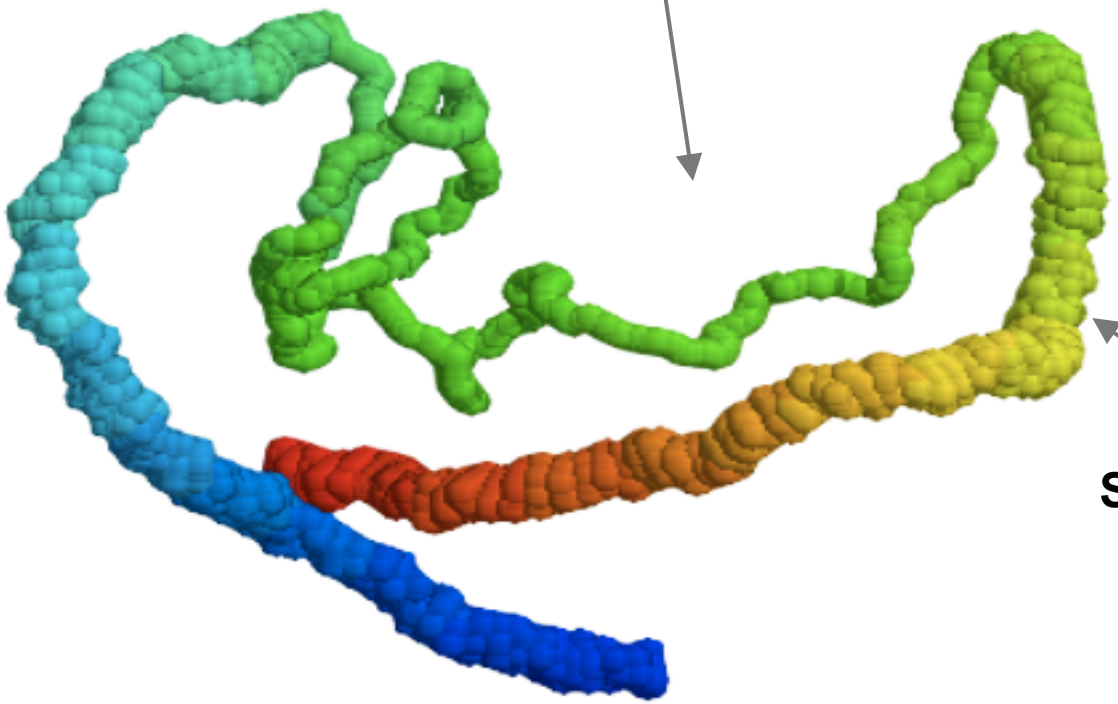


Contact map

?

Stiff Thick Fiber

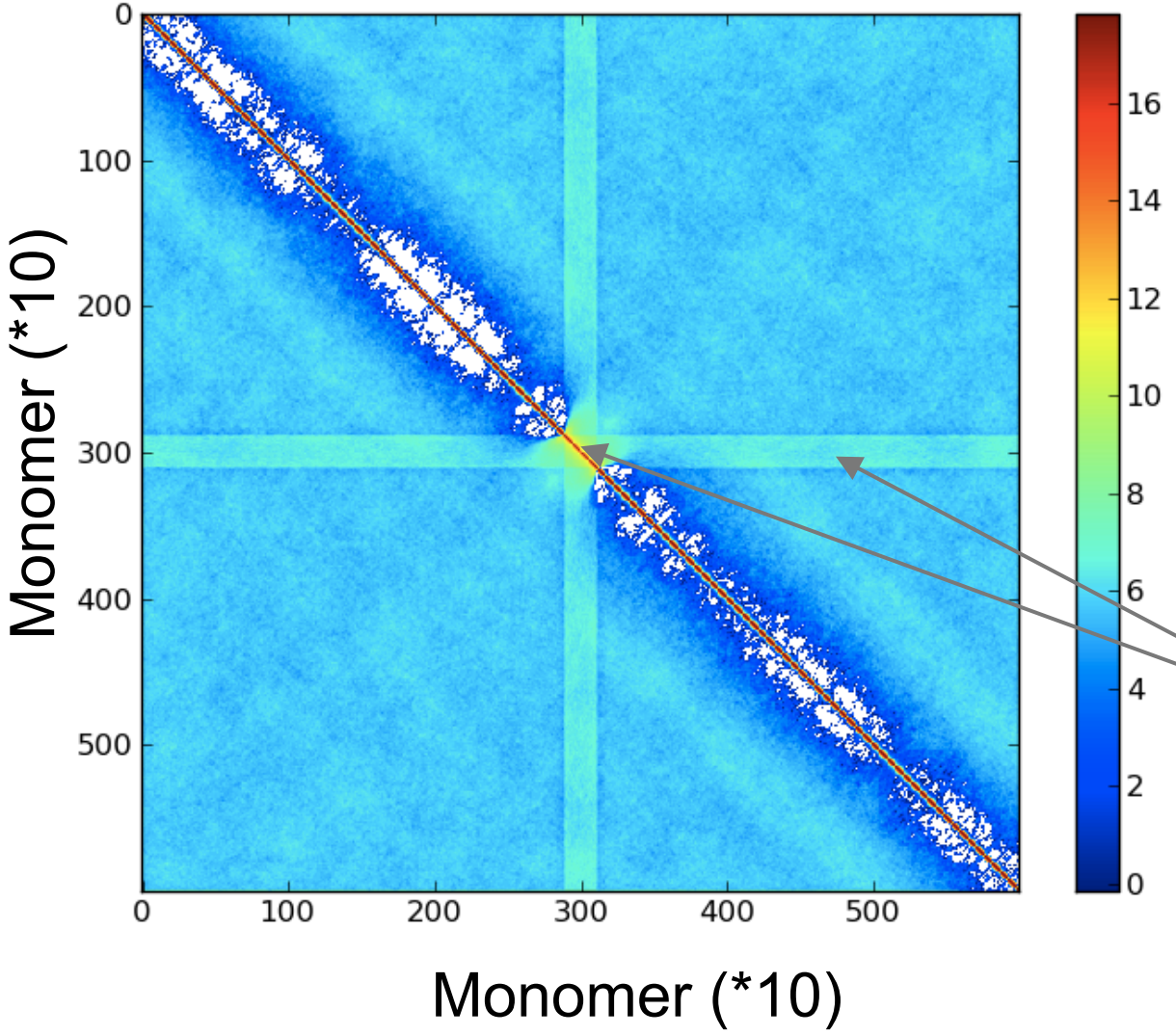
Flexible Thin Fiber



Stiff Thick Fiber

Thin Fiber Makes More Contacts

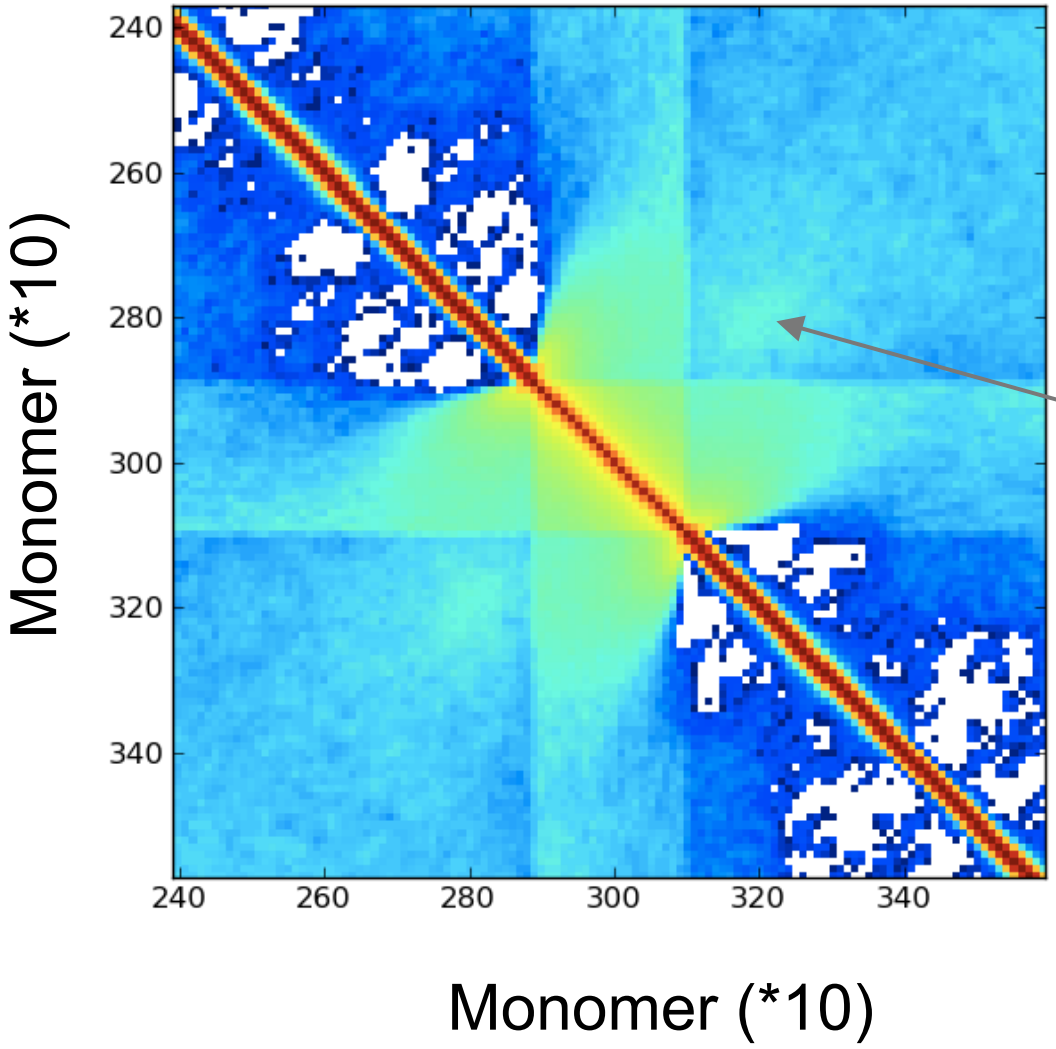
Average Contact Map for 6000 monomer long fiber

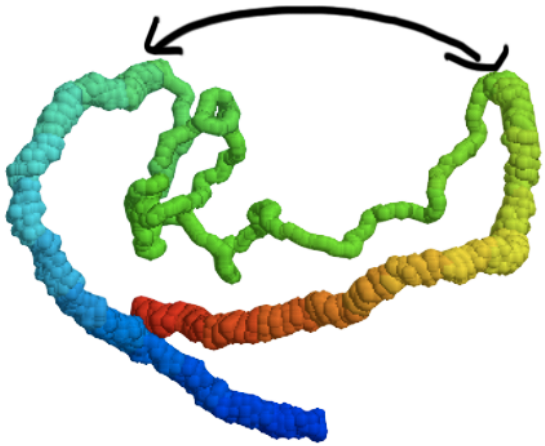


Thin fiber experiences increased contact probability with both itself and thick fibers

Folding of Thin Fiber Increases Contacts Between Thick Fibers Near Boundaries

Zoomed Contact Map (Monomers 240-360)

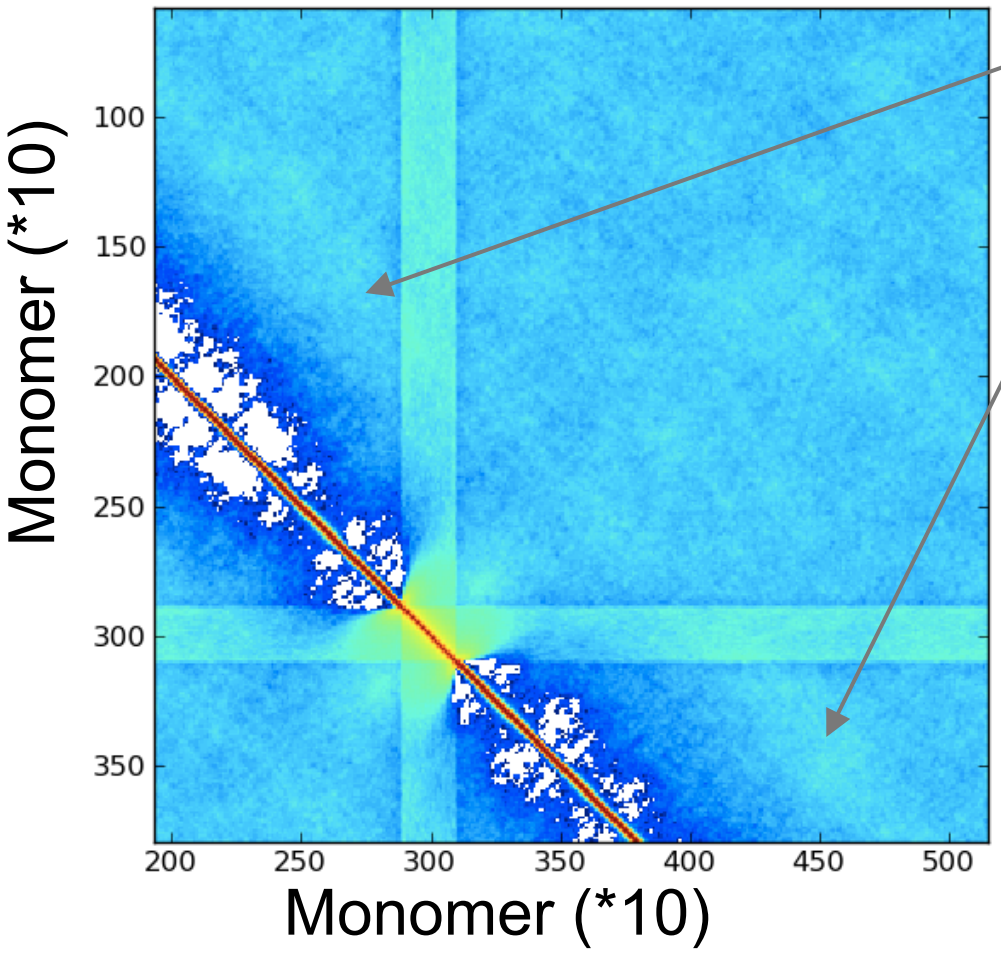




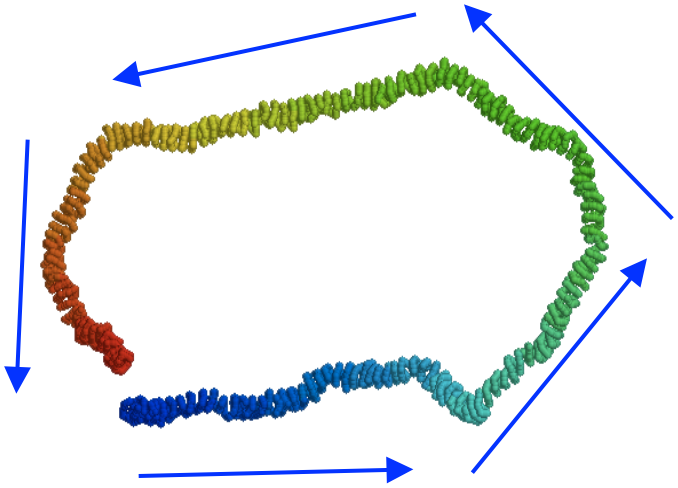
Because of the thin fiber's flexibility, certain monomers in the thick fiber (very close to the thin fiber) fold over and have an increased contact probability.

Thin Fiber Changes Peak Contact Distance for Thick Fiber

Zoomed Contact Map (Diagonal for separation of 100)



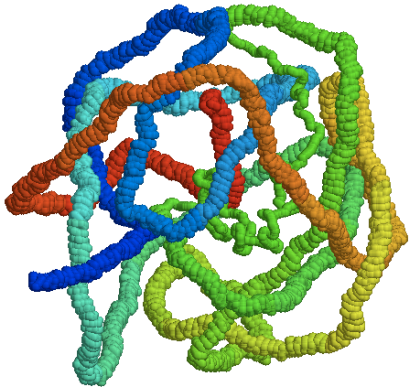
Monomers in thick fiber around 4-5 persistence lengths away have increased contact probability. Thin fiber's low persistence length changes peak contact distance.

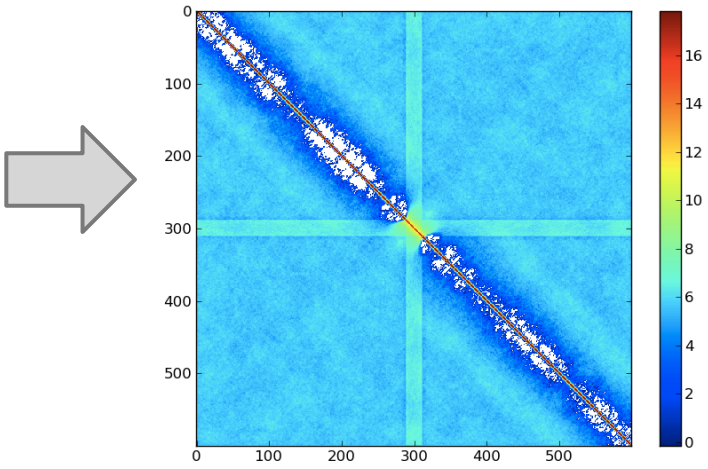


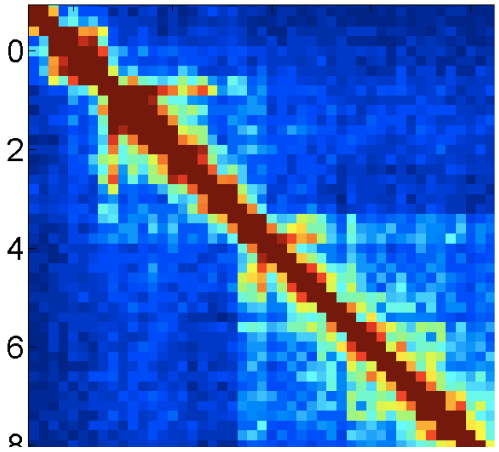
Conclusions

-Model of thick and thin fibers shows the effects of flexibility and compaction in a simulated contact map.

-Variation in fiber flexibility and compaction is a possible explanation for patterns observed in experimental contact maps at short distances.







Many thanks to our mentors Geoffrey Fudenberg and Maxim Imakaev, Prof. Leonid Mirny, and MIT PRIMES.