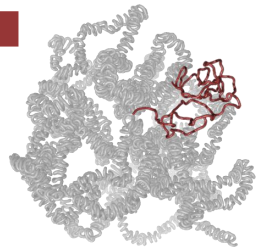
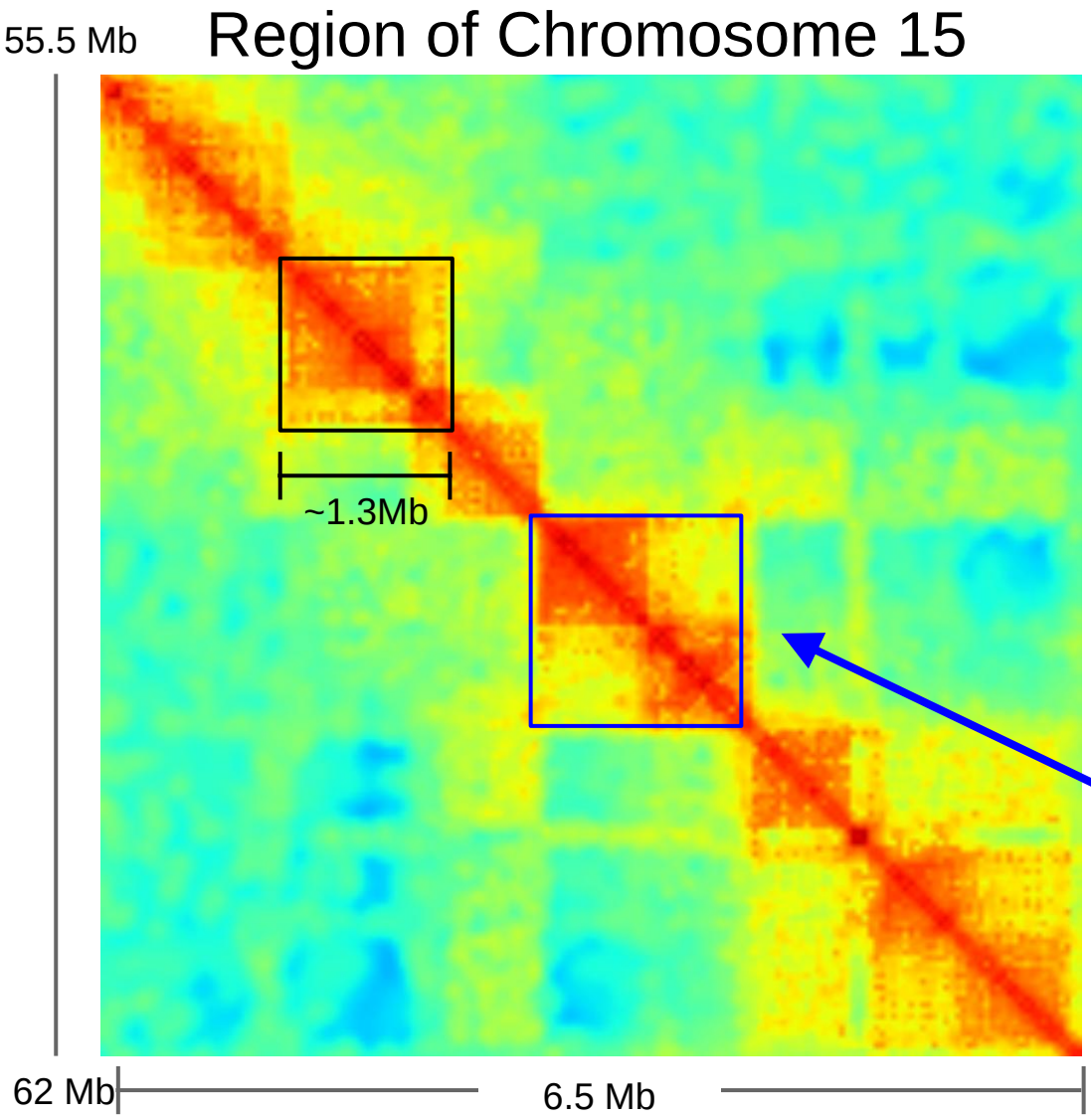


2013

Dynamic Folding of Chromatin Domains by Active SMC-Mediated Loops

Carolyn Lu

TADs: Topologically Associated Domains

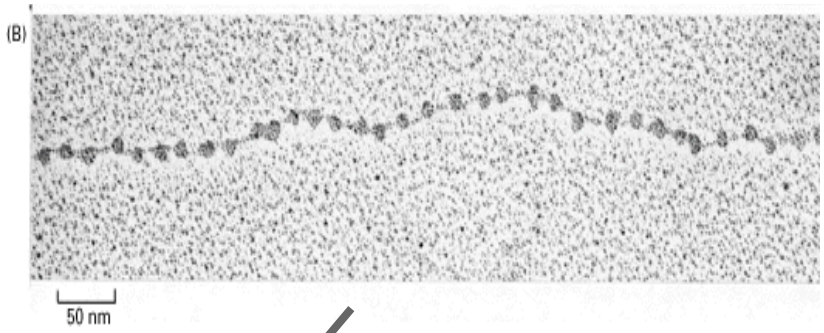


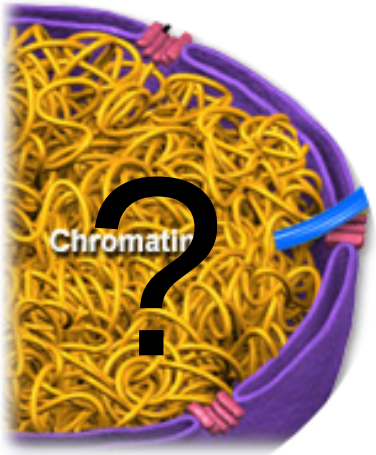
- Regions of increased interaction
- Decreased interaction across boundaries
- TAD-within-a-TAD behavior

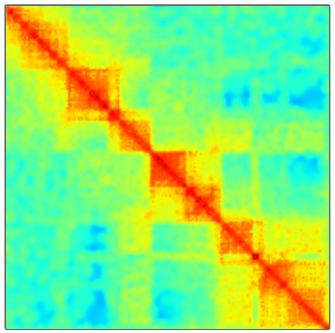
What are possible mechanisms for the formation of TADs?

Methods: Polymer simulations

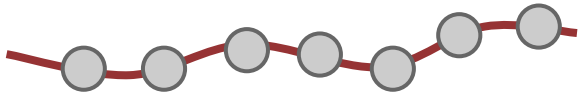
Experimental

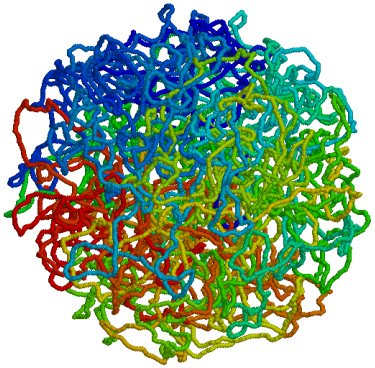






Simulation





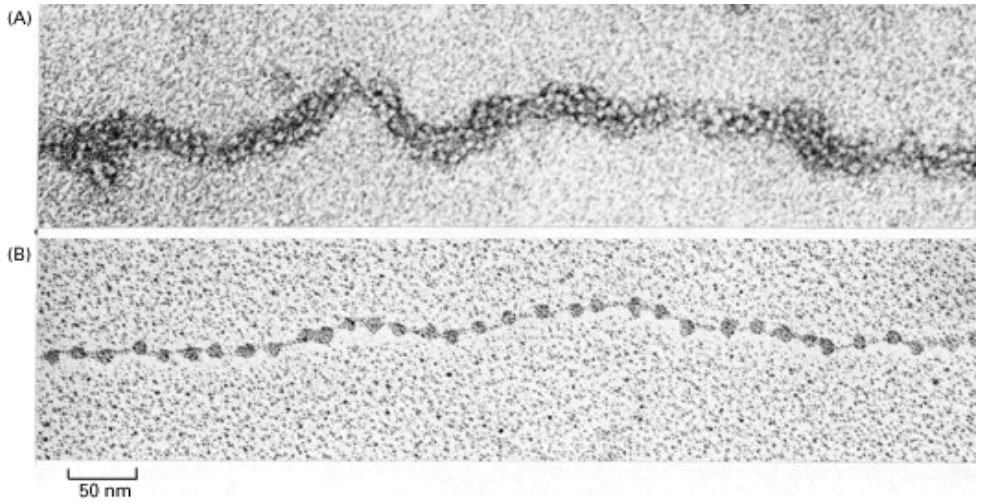
contact map

Can local properties of the chromatin fiber create TADs?

- Varying fiber thickness

Inactive

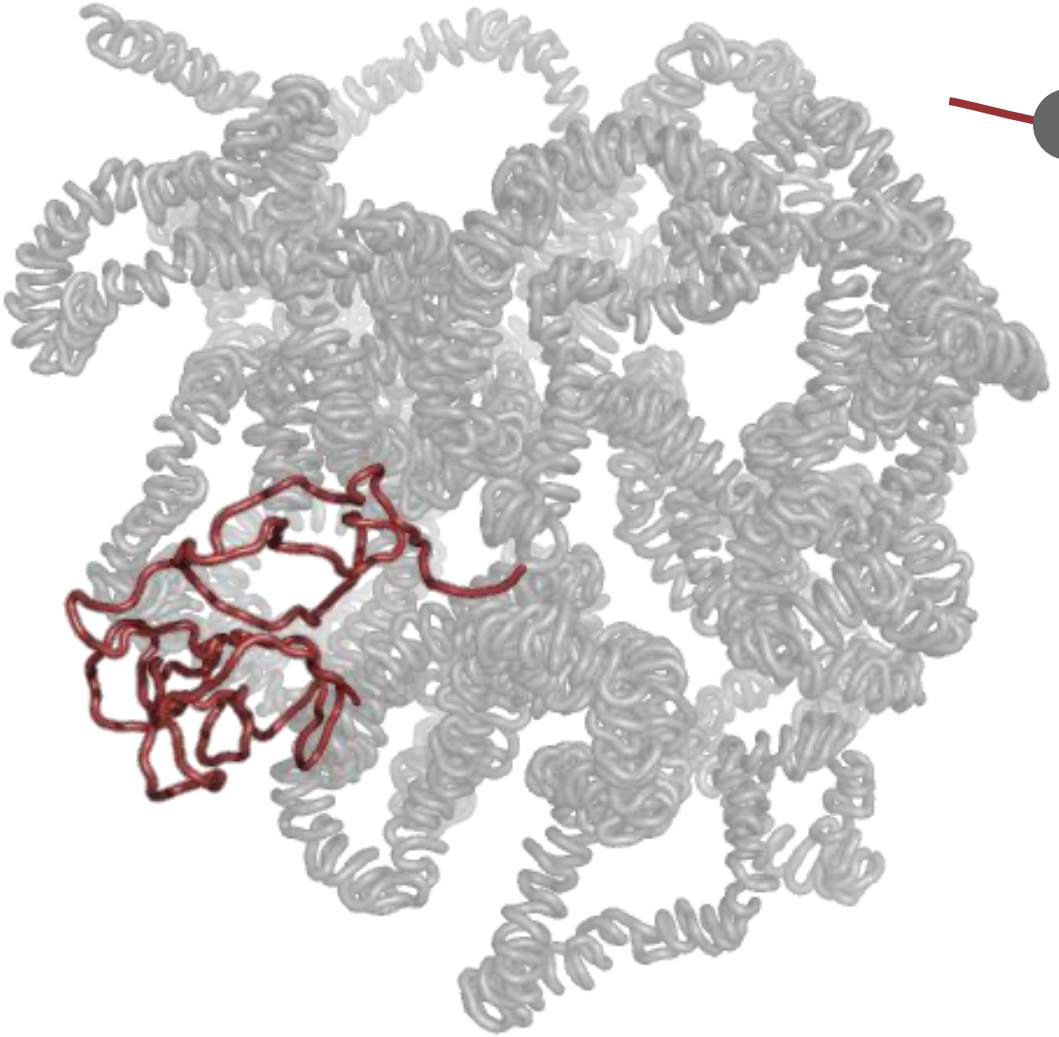
Active

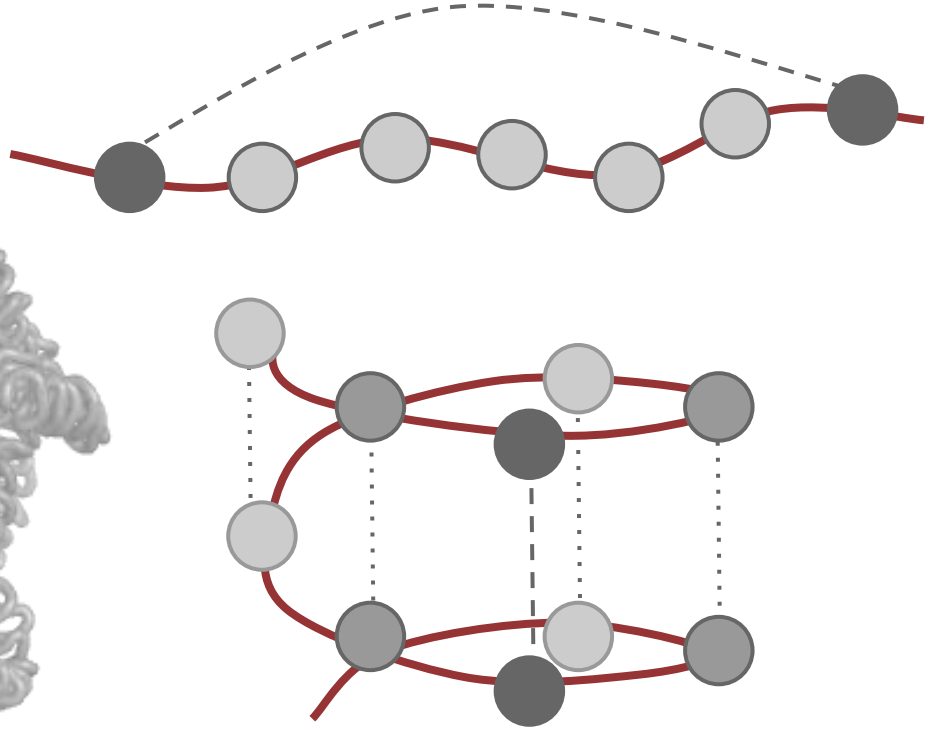


(Alberts, Molecular Biology of the Cell, 2002)

- Varying fiber stiffness

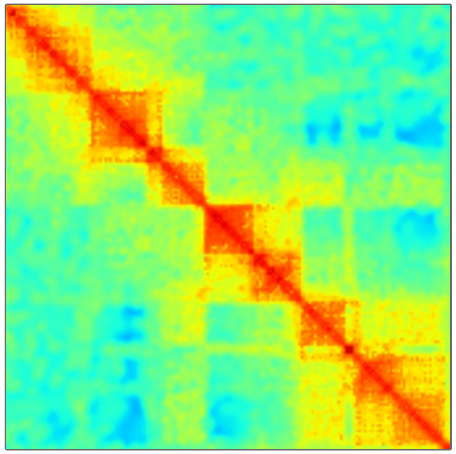
Thick-Thin-Thick model

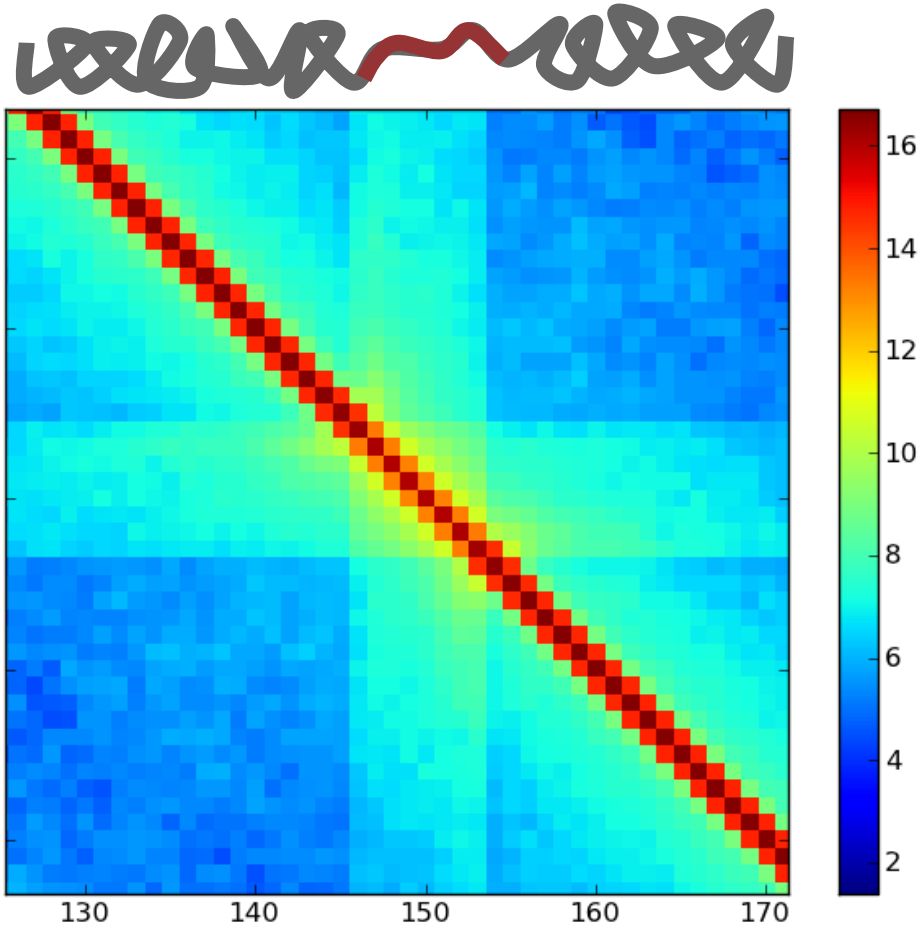




Thick fiber is made by coiling thin fiber.

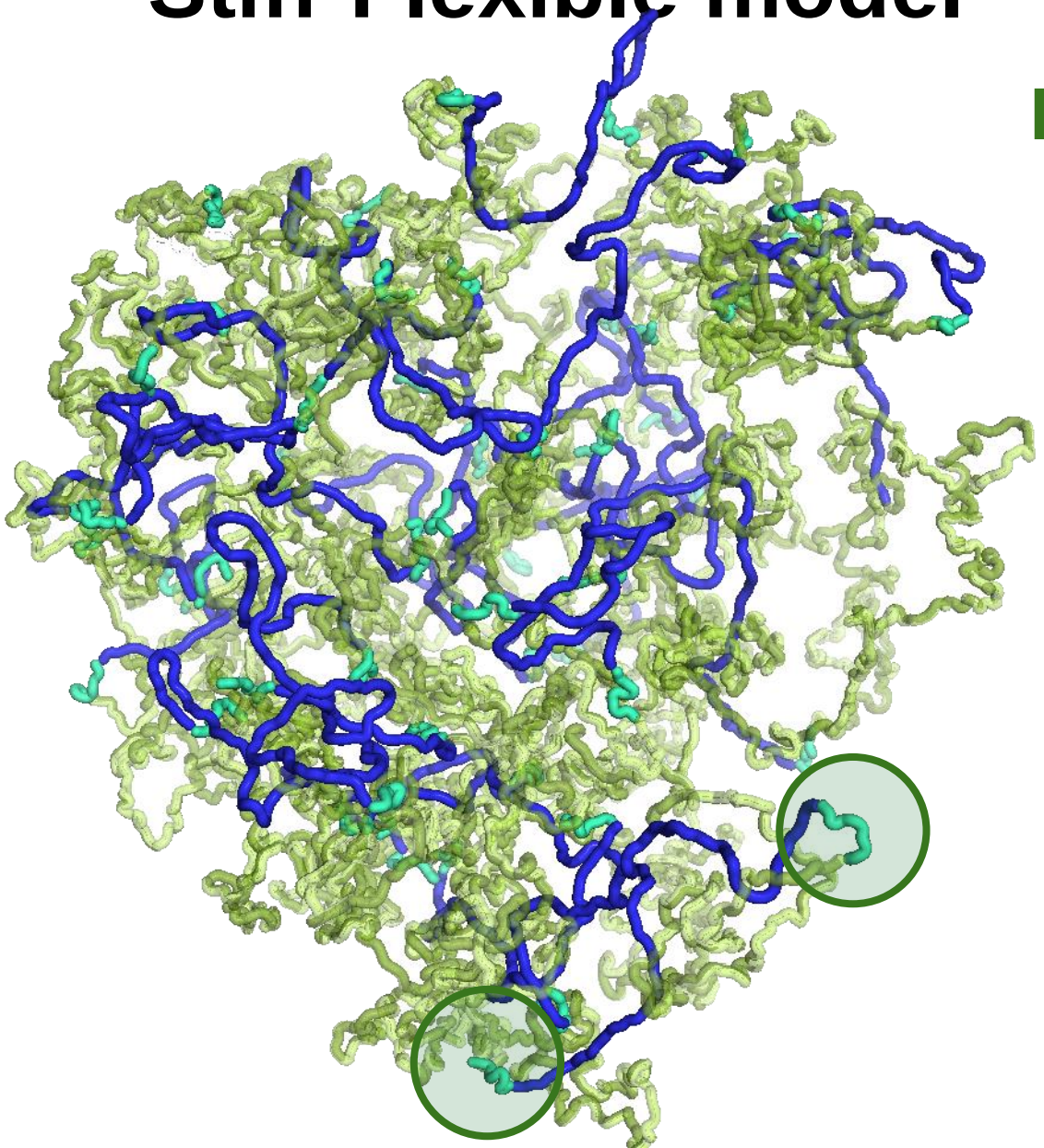
Thin fibers do not create TAD boundaries between thick fibers



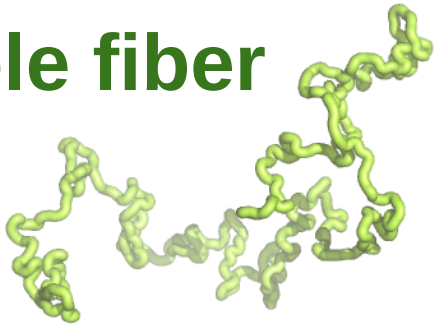


In the thin fiber, a small genomic distance can lead to a comparatively large spatial distance, in turn decreasing contacts between surrounding thick fibers.

Stiff-Flexible model



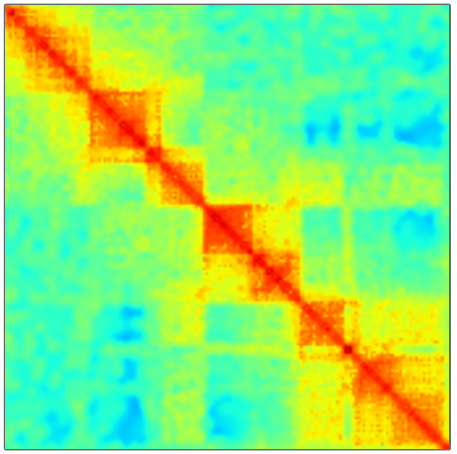
Flexible fiber

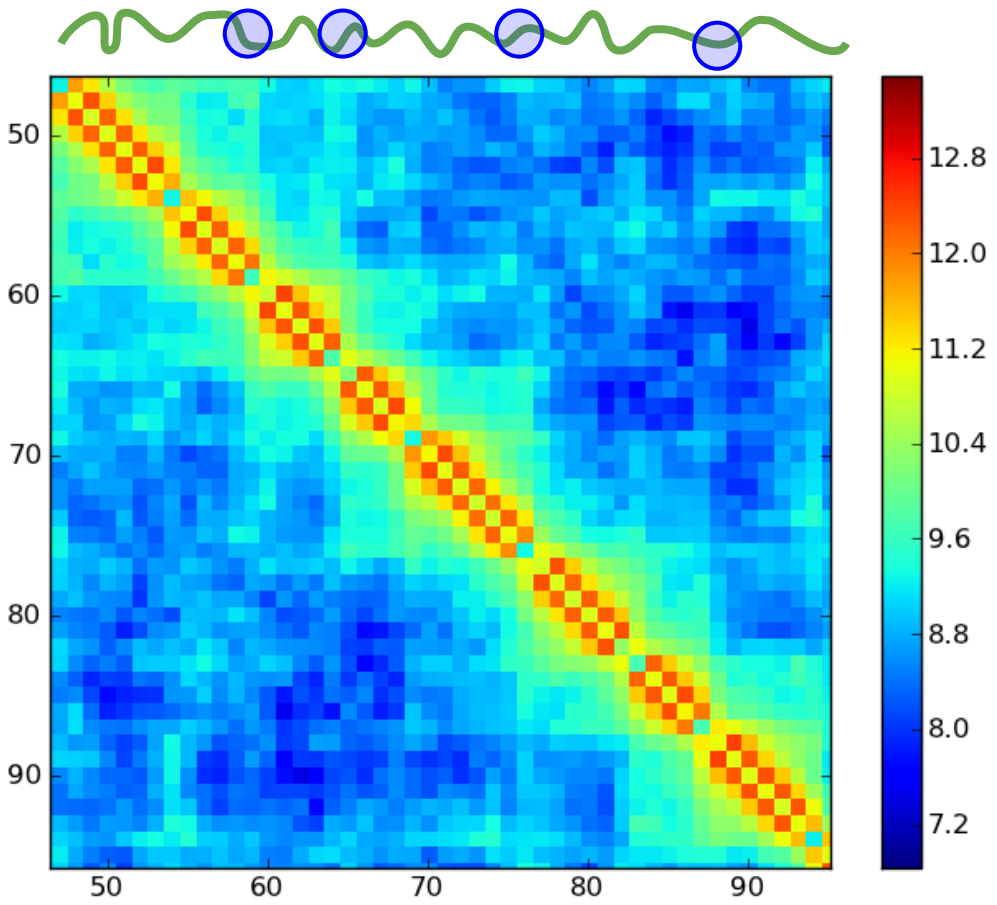


Stiff fiber

Ends of the **stiff fiber** are pushed apart.

Stiff fibers can create TAD-like boundaries but are biologically unrealistic

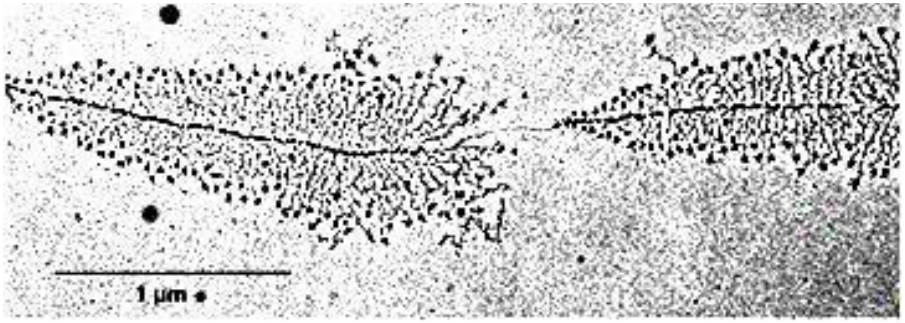


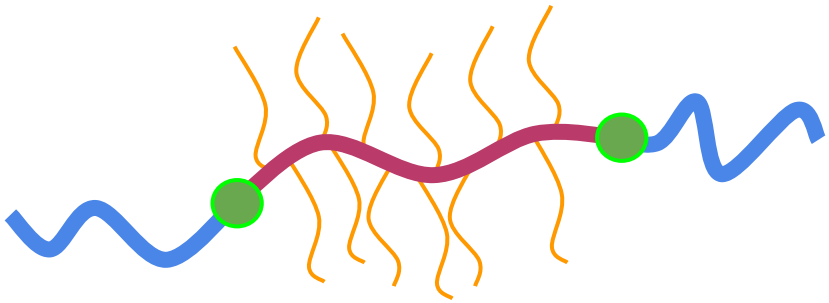


Stiff fibers are extended, decreasing contacts between surrounding flexible fibers.

Can actively transcribed regions create TAD boundaries?

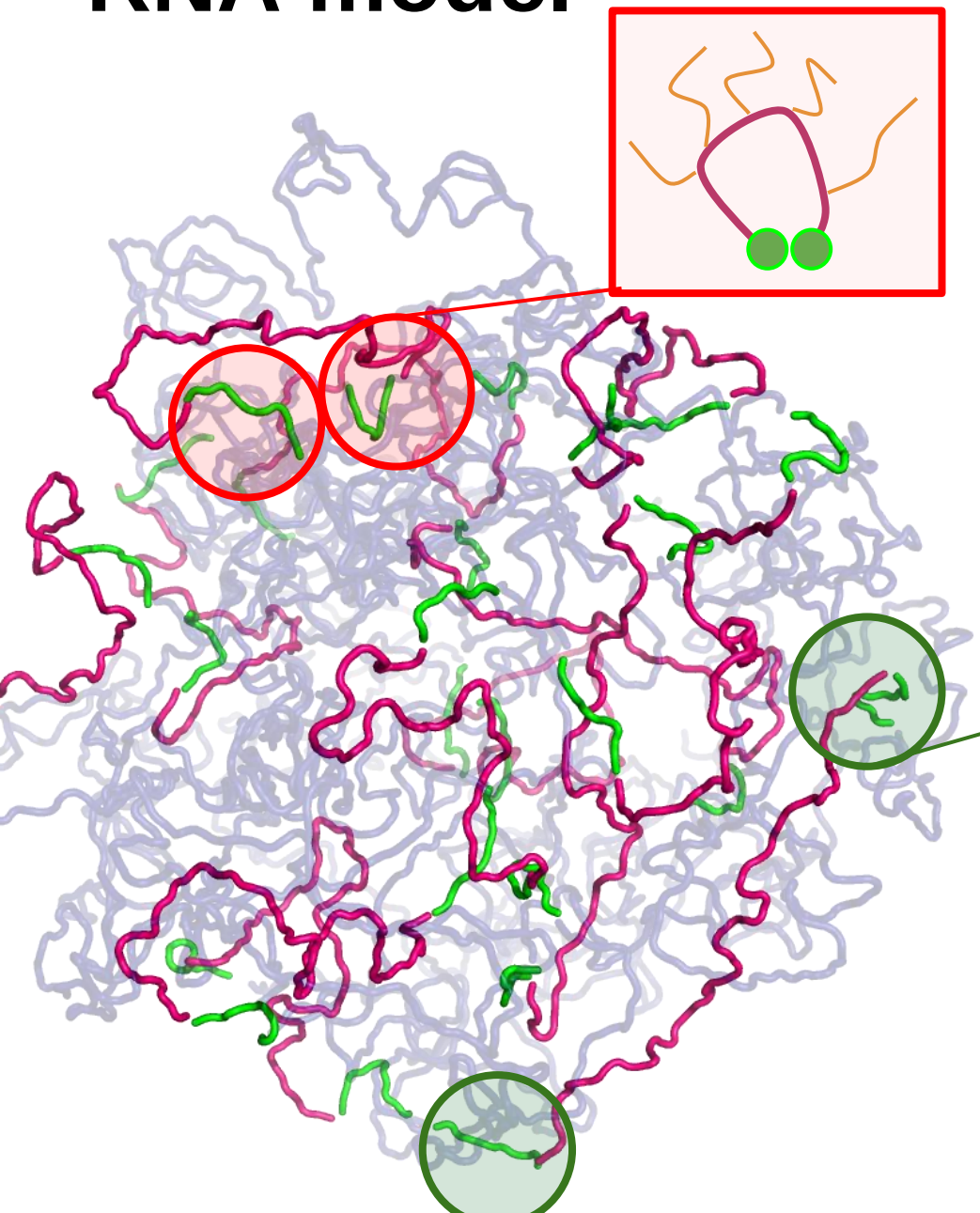
- Genes are known to be localized at edges of TADs
- We simulate highly transcribed genes by grafting a number of short polymers to small regions, creating local "bottle-brushes."

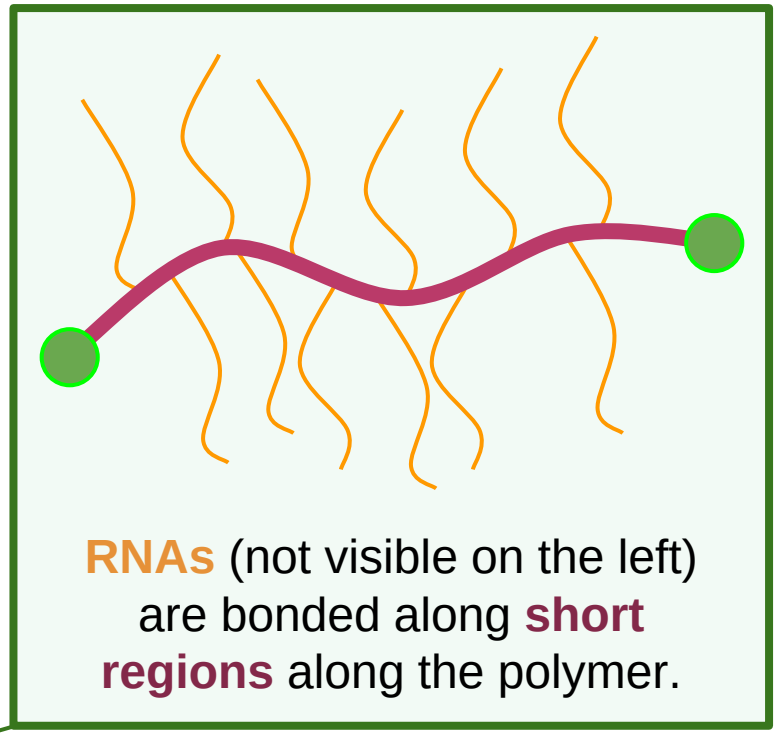




(Alberts, Molecular Biology of the Cell, 2002)

RNA model



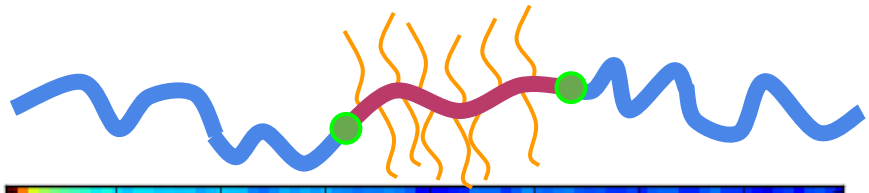


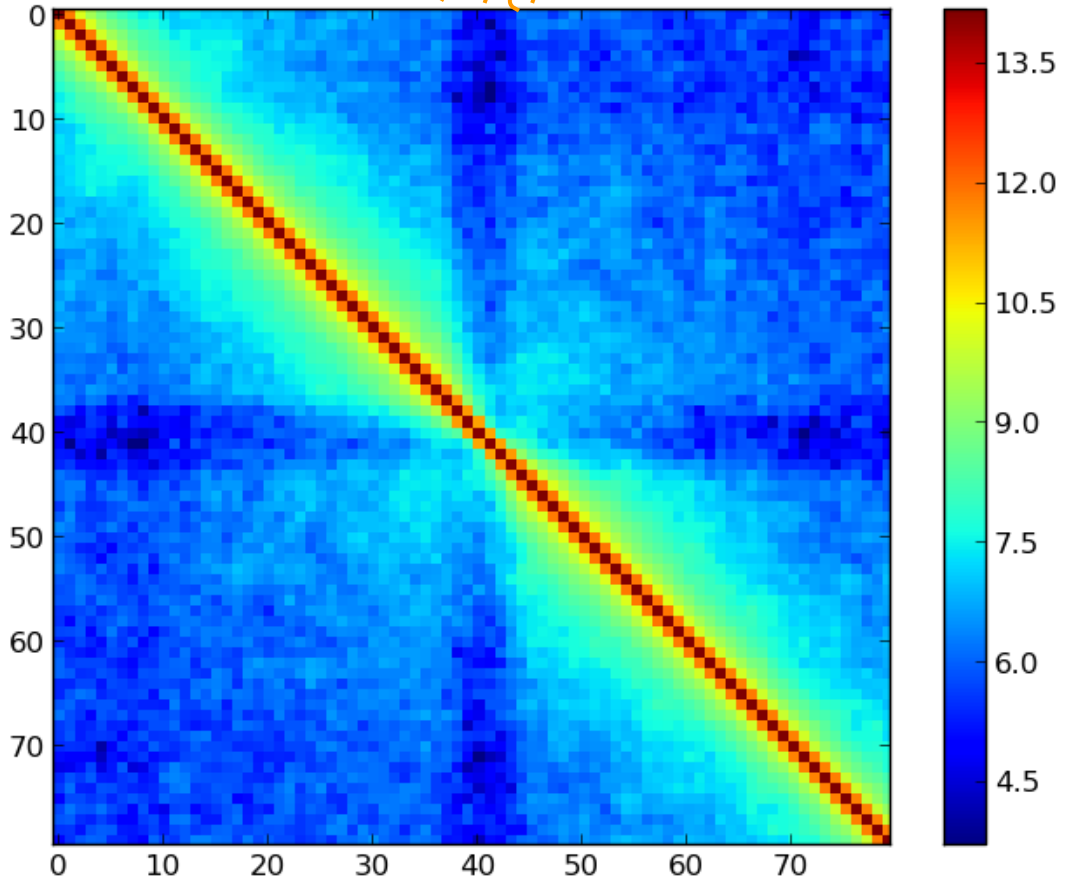
RNAs (not visible on the left) are bonded along **short regions** along the polymer.

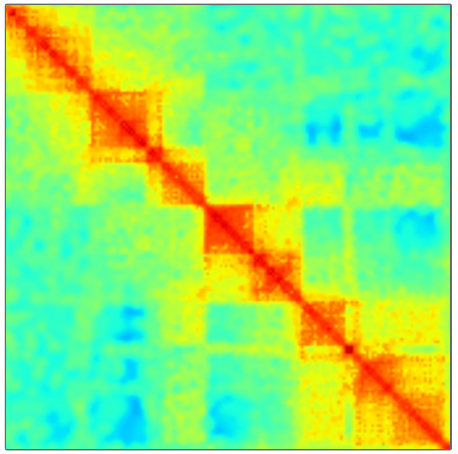
Along the **DNA polymer**, are **regions** where RNAs are attached.

Ends of these **regions** are *sometimes* pushed apart.

RNAs do not create TAD boundaries



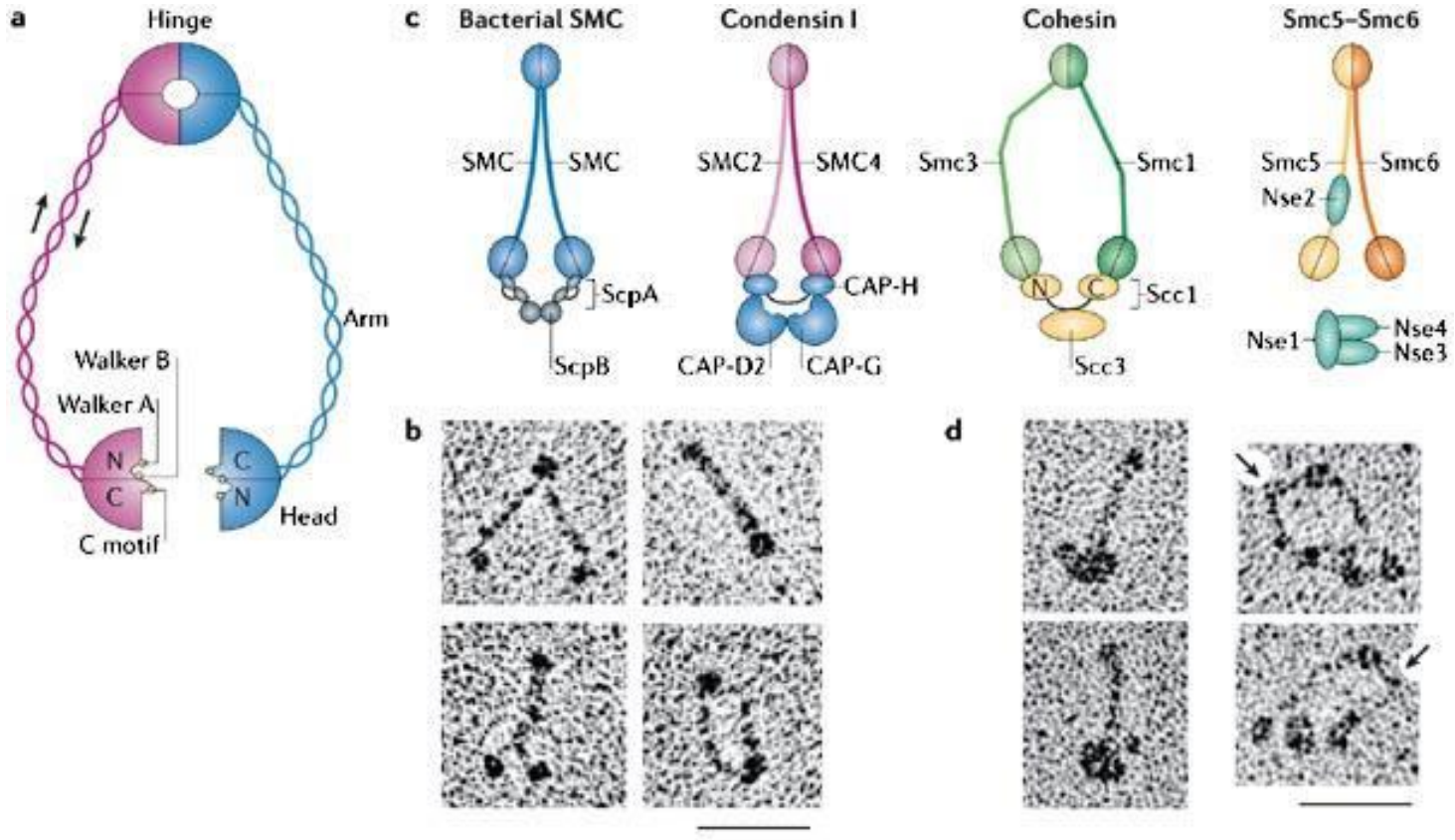




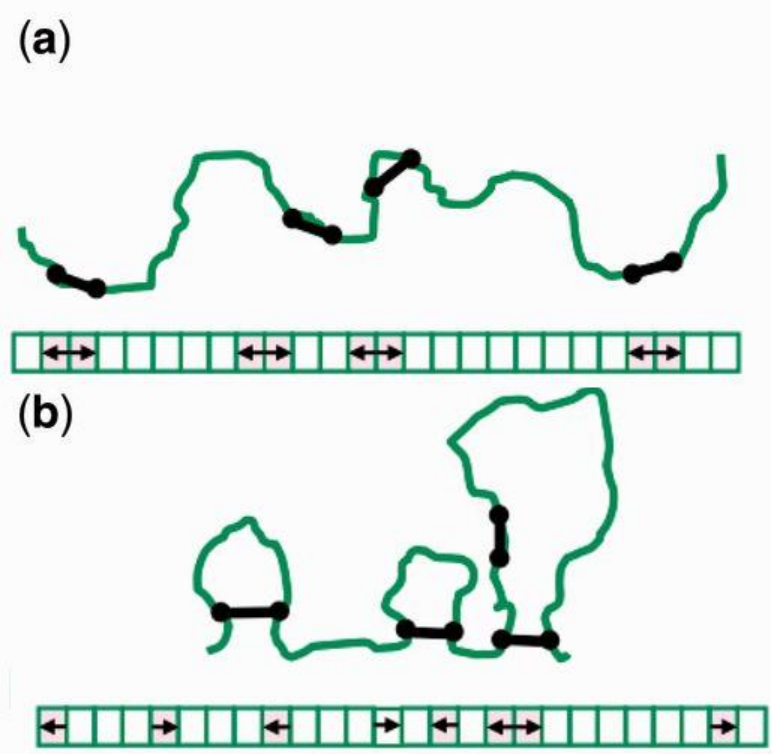
RNAs prevent contacts by RNA spots and stretch out path somewhat (though spots do loop back).

SMCs

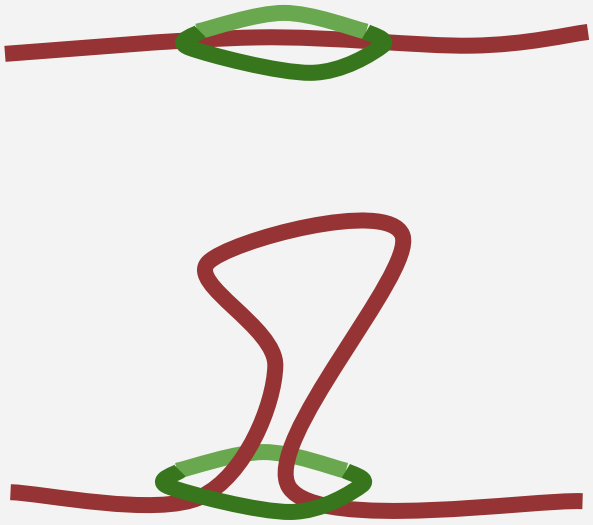
Structural Maintenance of Chromosomes proteins



What can SMCs do?

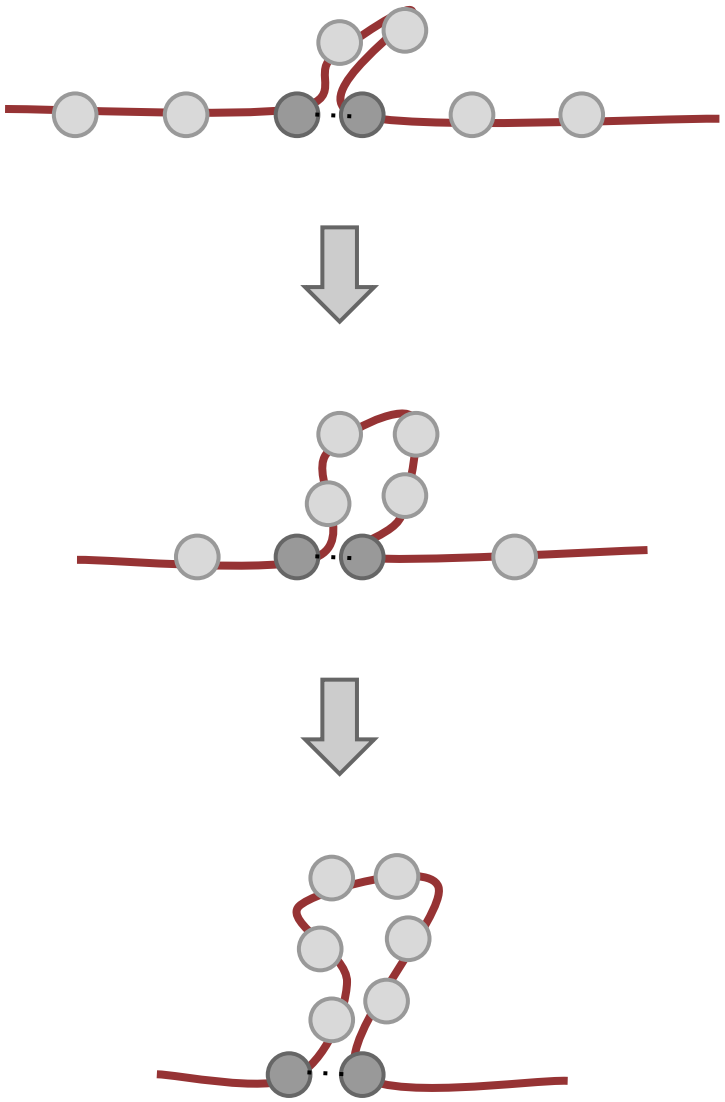


Extrude Loops?



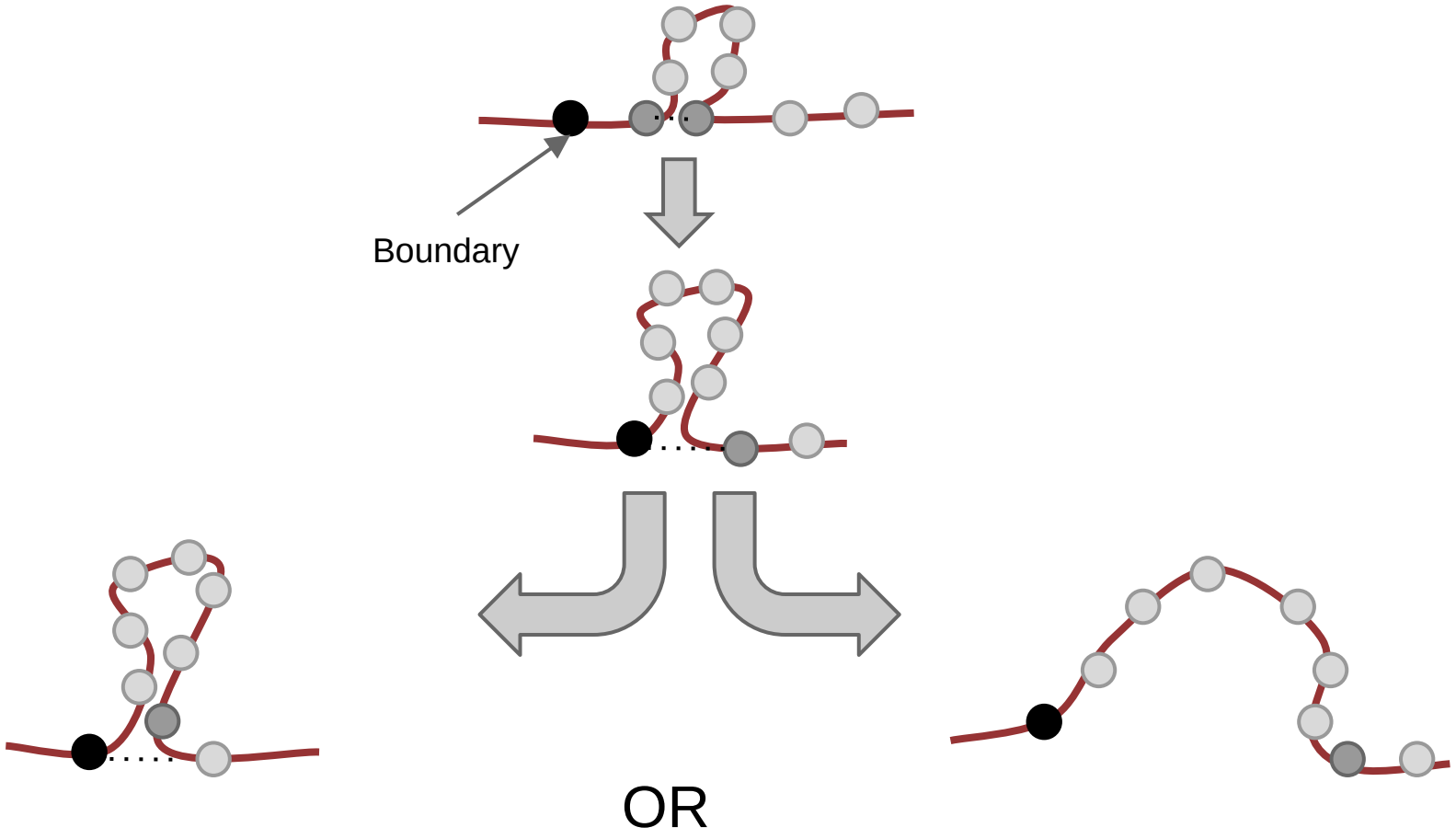
Alipour, Elnaz, and John F. Marko. "Self-organization of domain structures by DNA-loop-extruding enzymes." *Nucleic acids research* 40.22 (2012): 11202-11212.

Simulated SMC Loop Extrusion



Every step, the bonded ends of the loop walk one monomer outwards, extruding a loop.

Simulated SMCs extrude loops until encountering a boundary



Parameters of Simulated SMC Loops

- **"Lifespan"**

  How many steps, on average, a loop will exist. At each step, there is a $\frac{1}{\text{lifespan}}$ chance of a given loop's "death" and subsequent replacement.

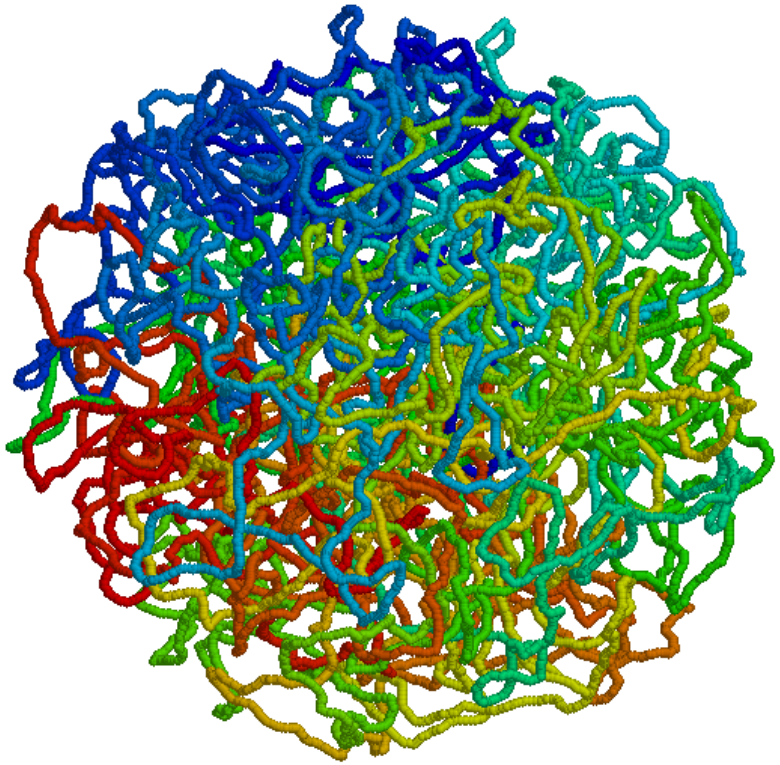
- **Boundary behavior**

  Release, stick, or chance.

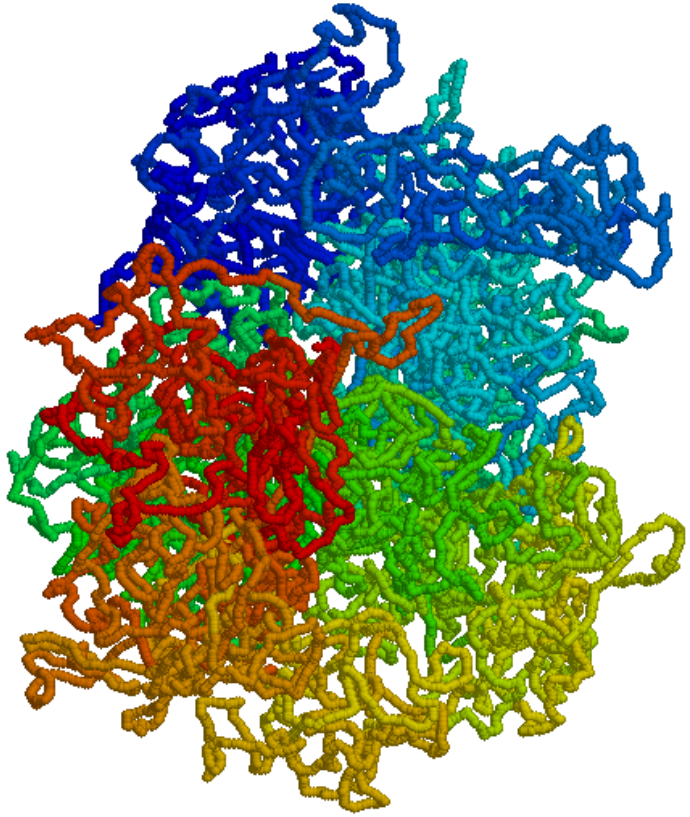
Polymer with SMCs and SMC Boundaries

Polymer with SMCs and SMC Boundaries

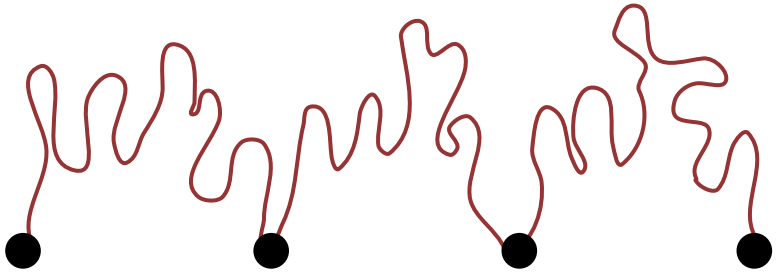
Normal Polymer

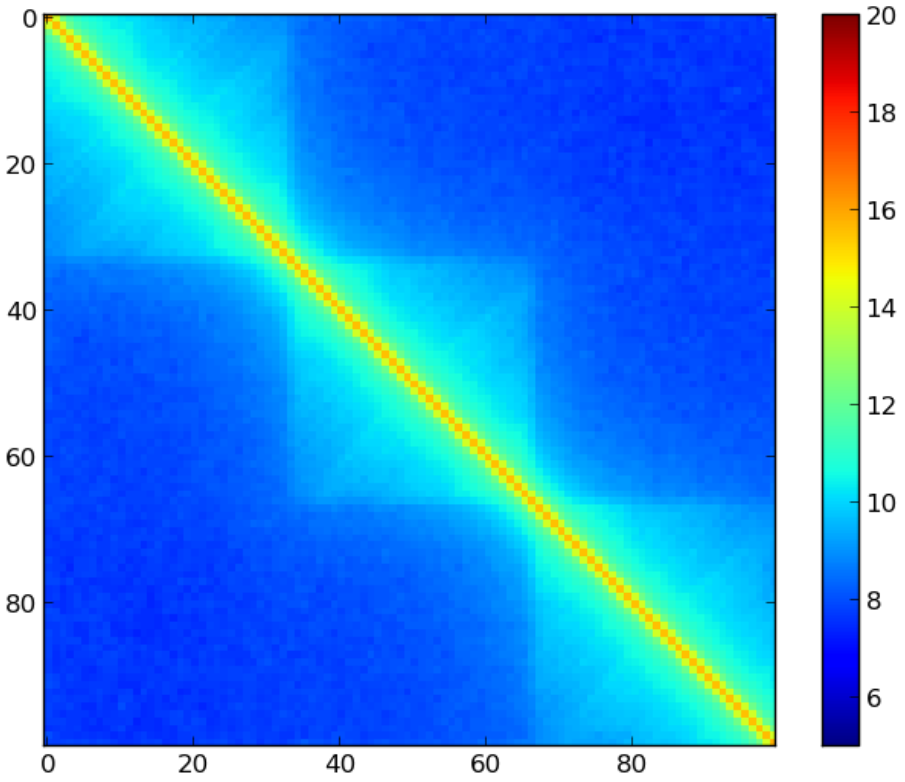


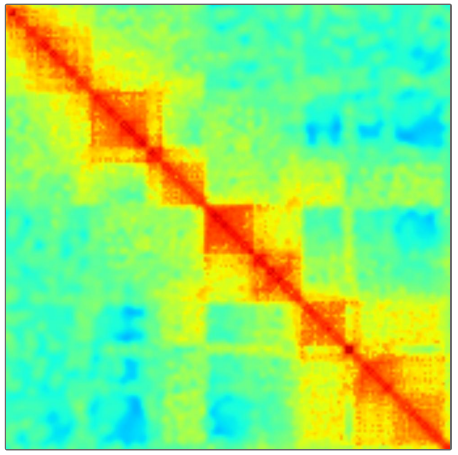
Polymer with SMCs and SMC boundaries



SMC Boundaries create TAD boundaries





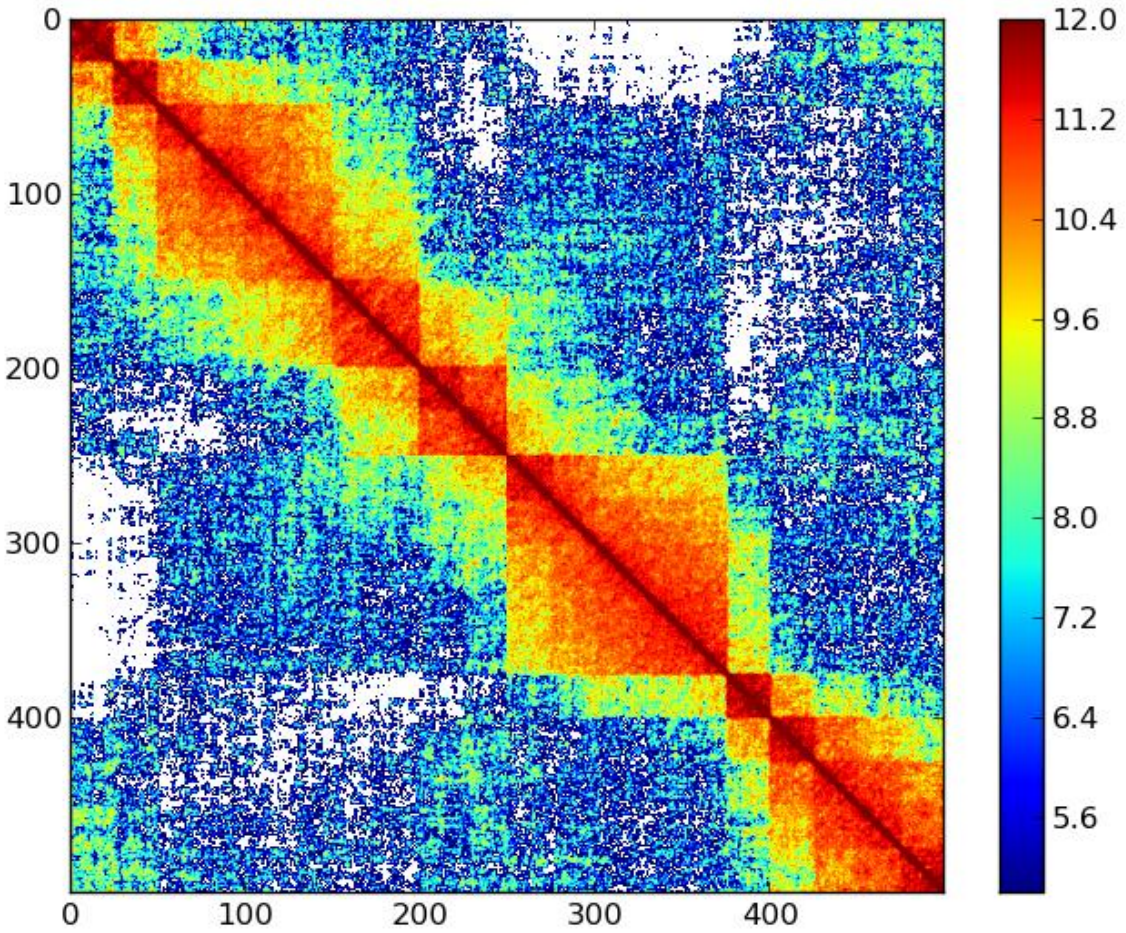


Simulated SMC loop boundaries behave like observed TAD boundaries.

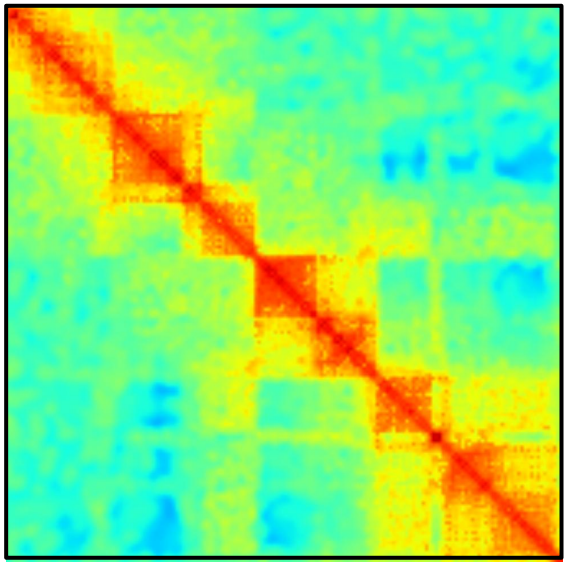
Loops cannot form across boundaries.

SMCs and TAD-within-a-TAD behavior.

TADs with varying boundaries. Lifespan 400.



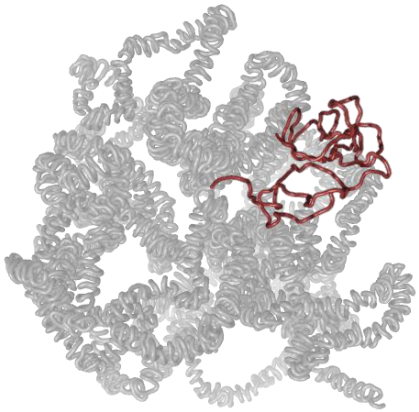
Simulated TADs



Experimentally observed TADs

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

MIT



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