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

![Image](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

Ends of the stiff fiber are pushed apart.
Stiff fibers are extended, decreasing contacts between surrounding flexible fibers.

Stiff fibers can create TAD-like boundaries but are biologically unrealistic.
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)
Along the DNA polymer, are regions where RNAs are attached. Ends of these regions are sometimes pushed apart.

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

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

Boundary

OR

Stick 

OR

Release
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
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