Week 12: Chromosal organization through loop extrusion

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This weeks paper by Fudenberg et al (group of Leonid Mirny) is entitled "Formation of Chromosomal Domains by Loop Extrusion". In addition, I encourage you to look at the review article by Mirny et al "Two major mechanisms of chromosome organization" that discusses the interplay of loop extrusion and phase-separation like mechanisms to organize chromatin. The mechanisms of loop extrusion was one of the major insights into chromatin organization of the last decade and is a beautiful example of how non-equilibrium physics can explain large scale features of biological organization. These insights were made possible by high-throughput sequencing technologies and methods like Hi-C.

- Have a look at higlass.io and explore HiC data at scale
- Physics perspective: Seminar by Leonid Mirny `https://youtu.be/FqoLm7E0mZ4`
- Molecular biology of cohesins by Jan-Michael Pieters `https://youtu.be/ckFS9Wr32Ic`.

Question 1: Chromatin conformation capture techniques

- How do they work in principle?
- What are the data they produce? How are these data represented in the papers?
- On what genomic length scale are the structures of interest?

Question 2: Topologically associated domains (TADs)

- What are TADs? What features do they have in contact maps?
- TADs are traditionally thought of as static? What evidence is presented against that view?

Question 3: Simulation model in one dimension

- Describe the 1D model of loop extrusion.
- How are loops initiated? How do boundary elements define domains?
- What aspects of the problem can be described in 1D, which ones require 3D?

Question 4: Simulations in 3D

- What are the elementary units of the 3D model?
- How do LEF affect the polymer dynamics?
- What are the important parameters of the model?

Question 5: TADs

- How does processivity and separation affect the contact maps and fit to the data?
- How does separation between LEFs affect the result?
- What is the loop coverage and the independent loop size in these regimes?

Question 6: Corner peaks, loops, and TADs

- Corner peaks seem to be an optional feature of TADs. What is their origin and interpretation?
- What parameters tend to produce more pronounced corner peaks?
- What features of TADs are missing in model with permanent loops?

Question 7: The role of boundary elements (BE)

- BEs are not physical boundaries but stopping point for LEFs. How does this result in domains?
- What is the evidence for CTCF as boundary element?
- What evidence for directional BEs do they discuss?

Question 8: Large scale organization

In addition to the megabase scale organization of TADs, chromosomes show order on much larger scales. This is discussed in the review article by Mirny et al.

- What is the interpretation of the characteristic checkerboard pattern?

- What are the proposed mechanisms for this organization?
- How do they differ? Equilibrium/non-equilibrium? ATP-dependent or not?