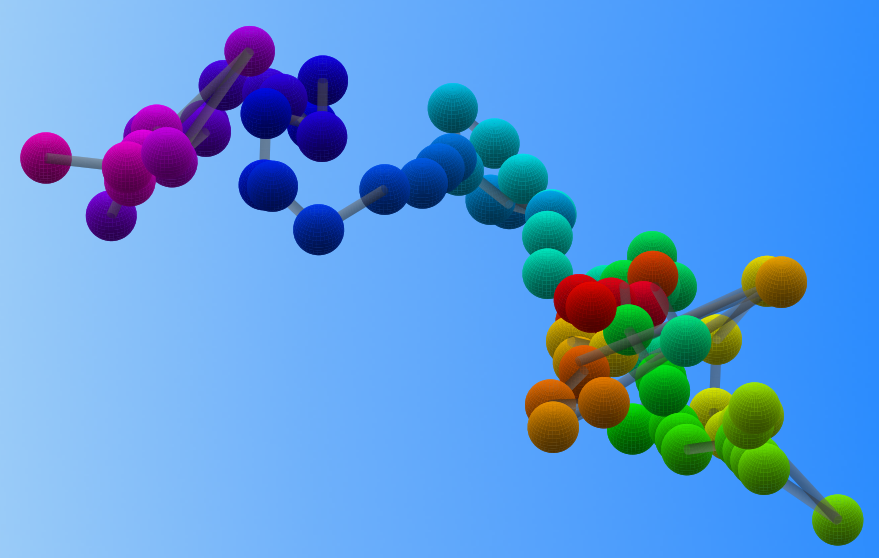




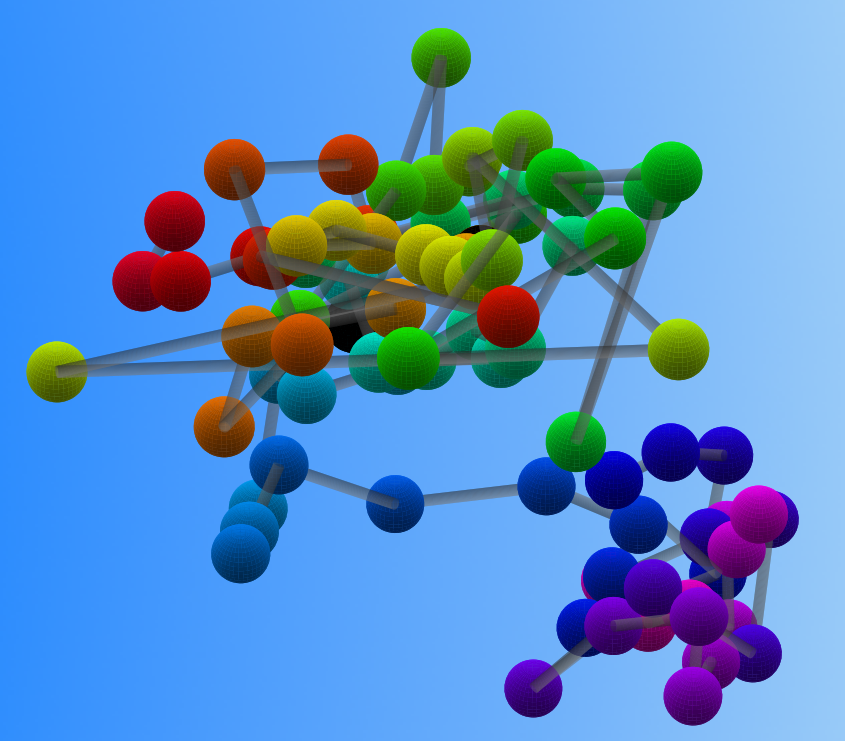
Revealing DNA's topology

A spectral energy approach to loop detection

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Introduction

Loops play a central role in the organisation of chromatin and gene regulation:

- Cohesin and CTCF create loops, forming TADs
- Looping DNA initiates transcription through enhancer-promoter proximity

- By revealing the spatial arrangement of chromatin at the single-cell level, sequential FISH imaging allows the study of conformational fluctuations as never before
- Despite unprecedented access to 3D paths, its application in investigating chromatin loops is yet to be fully realised

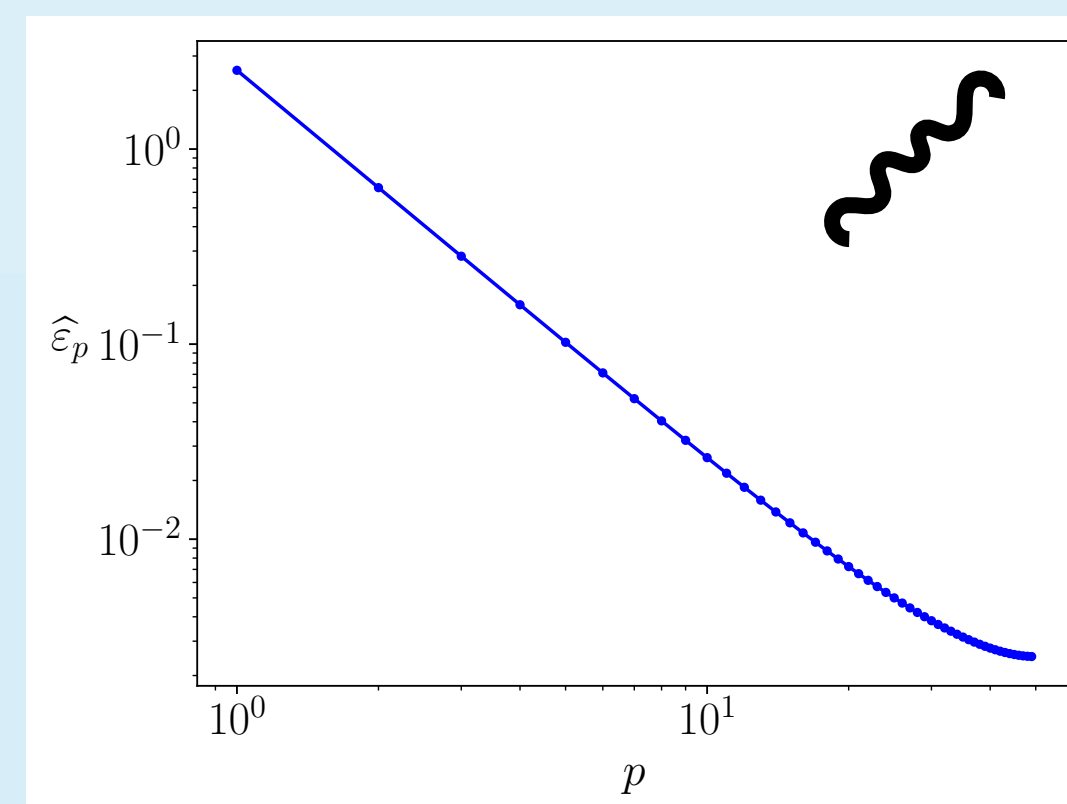
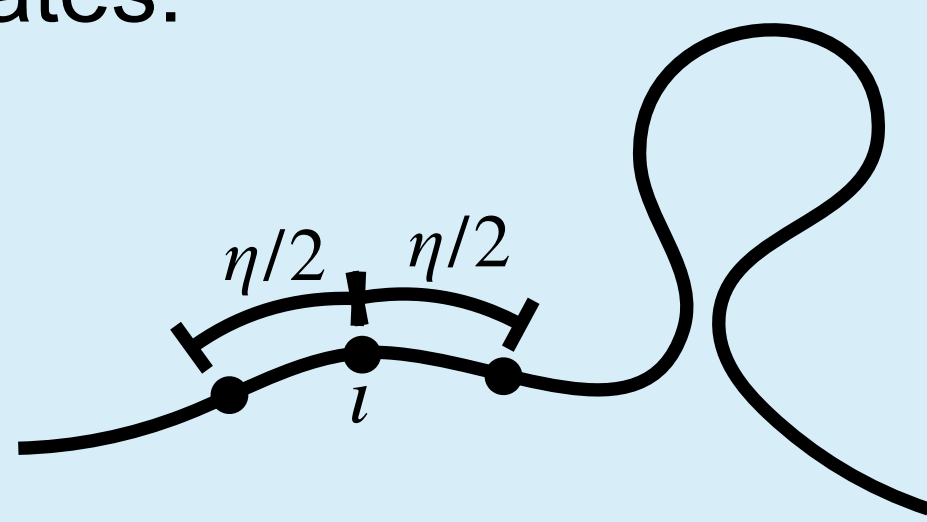
Methods

Step 1: Ensemble averages

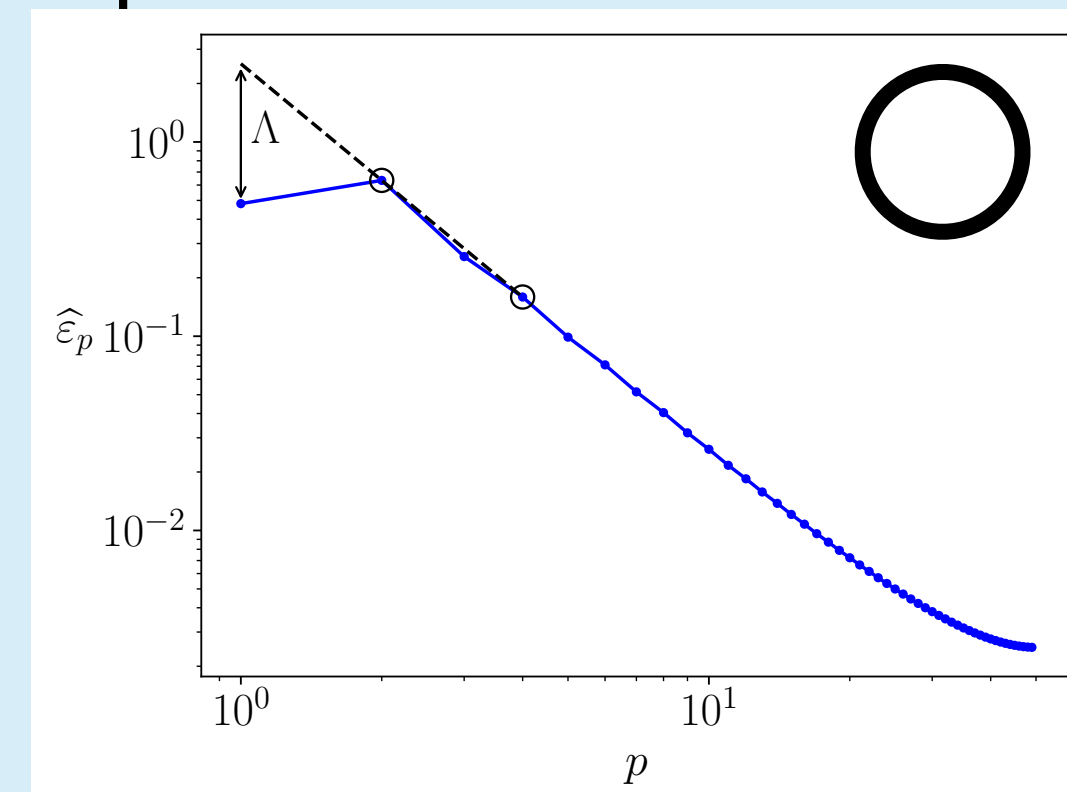
- Start from 3D-configurations and consider the coordinates as signals
- Calculate the Fourier (cosine) modes of the discrete signals
- Square the modes and average: **spectrum**^[2]

- Largest scales (smallest modes) are affected by being looped
- Exploit this: **log-spectral ratio** Λ
- Single number discriminating looped and non-looped
- Apply it to all subchains to get Λ -plot

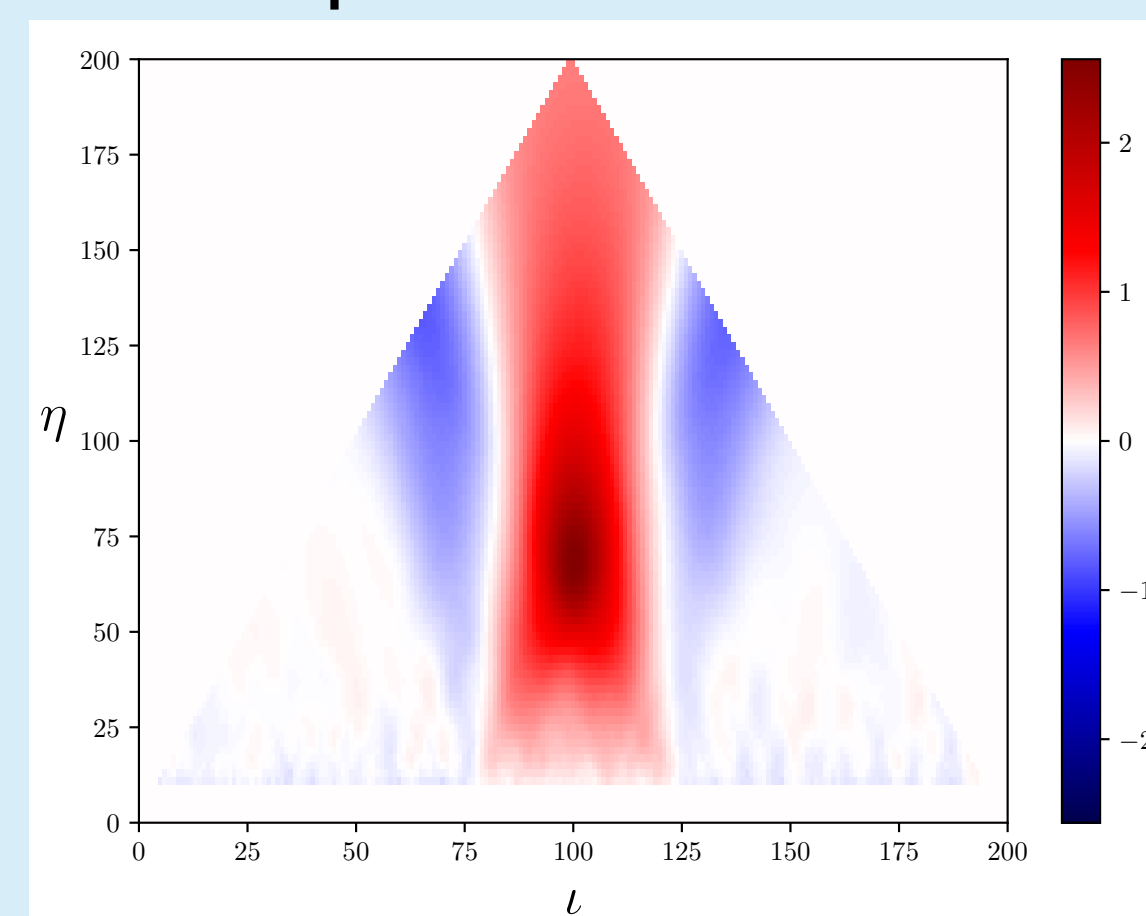
- Coordinates:



Spectrum: Random walk



Spectrum
Looped random walk

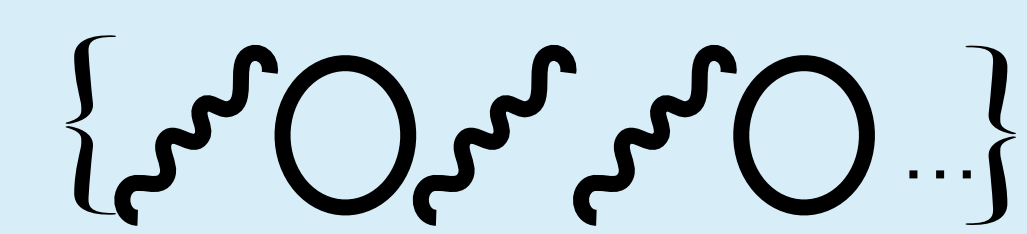


Λ -plot

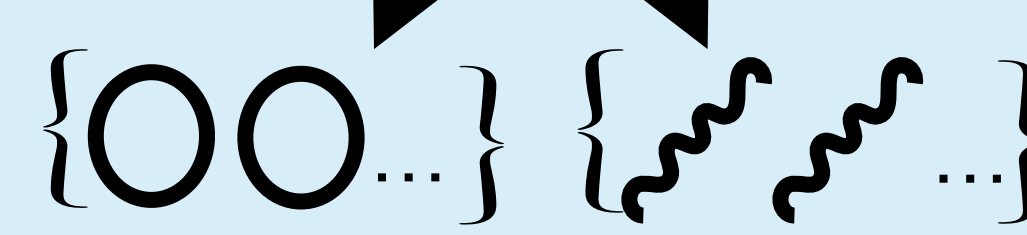
Step 2: Single cell

- From Λ -plot: know where to look
- Apply Neural network to segregate looped and non-looped conformations on a single cell level
- Train neural networks on (looped) random walks
- Thanks to Λ -plot, can avoid exponential complexity in training!

Mix of loops and non-loops



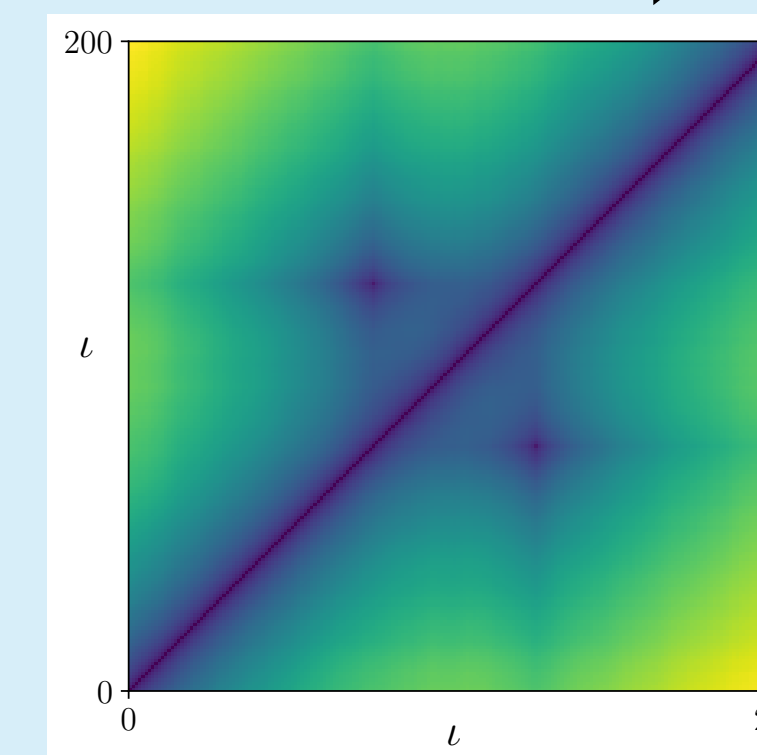
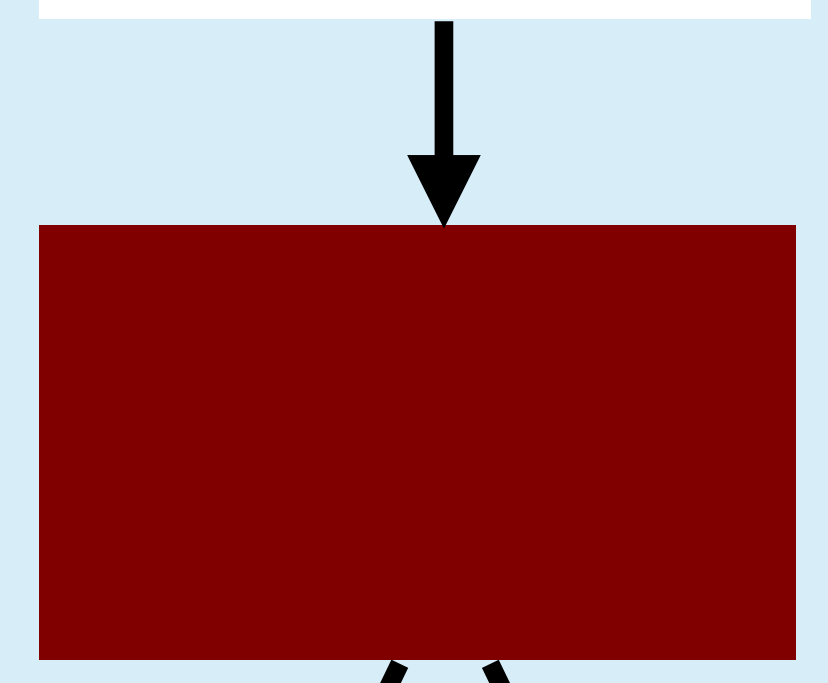
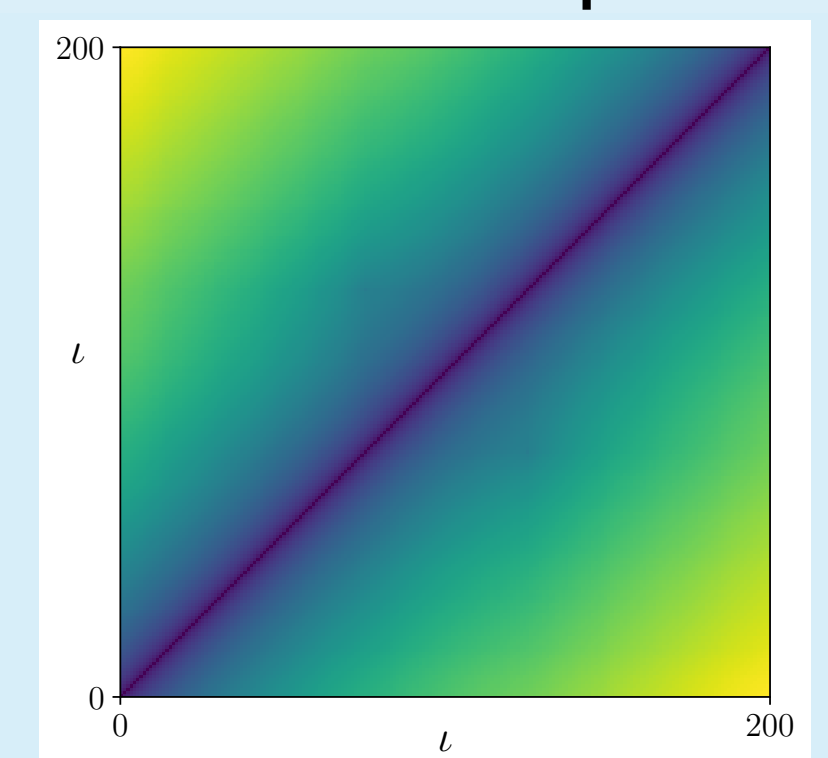
Neural network



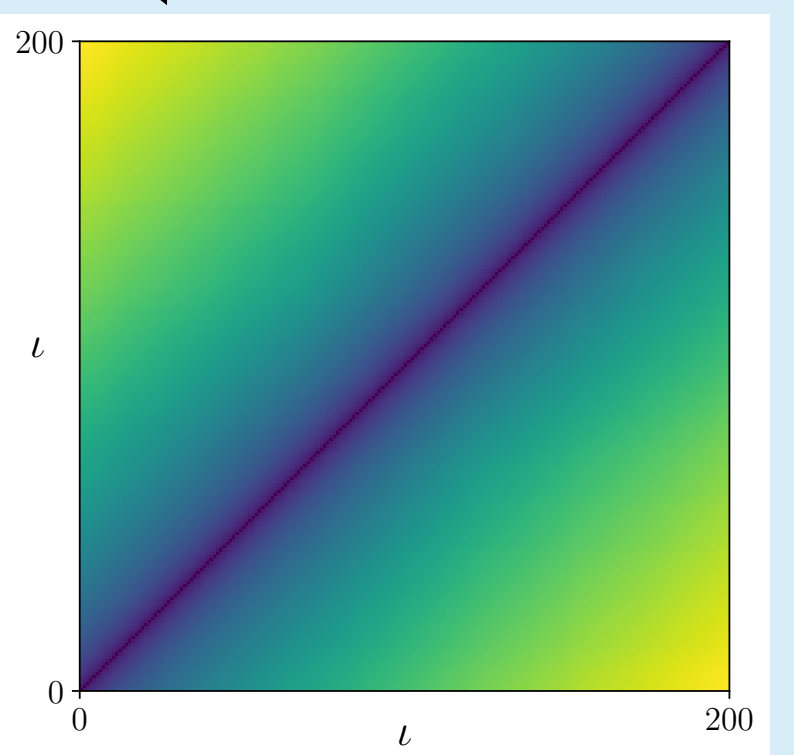
Loops

Non-loops

Mixed population:
20 % loops



Looped
population



Non-looped
population

Experimental results

Experimental data:
Bintu et al. 2018^[1]

Method:
Sequential FISH

N:
83

Resolution:
30 kb

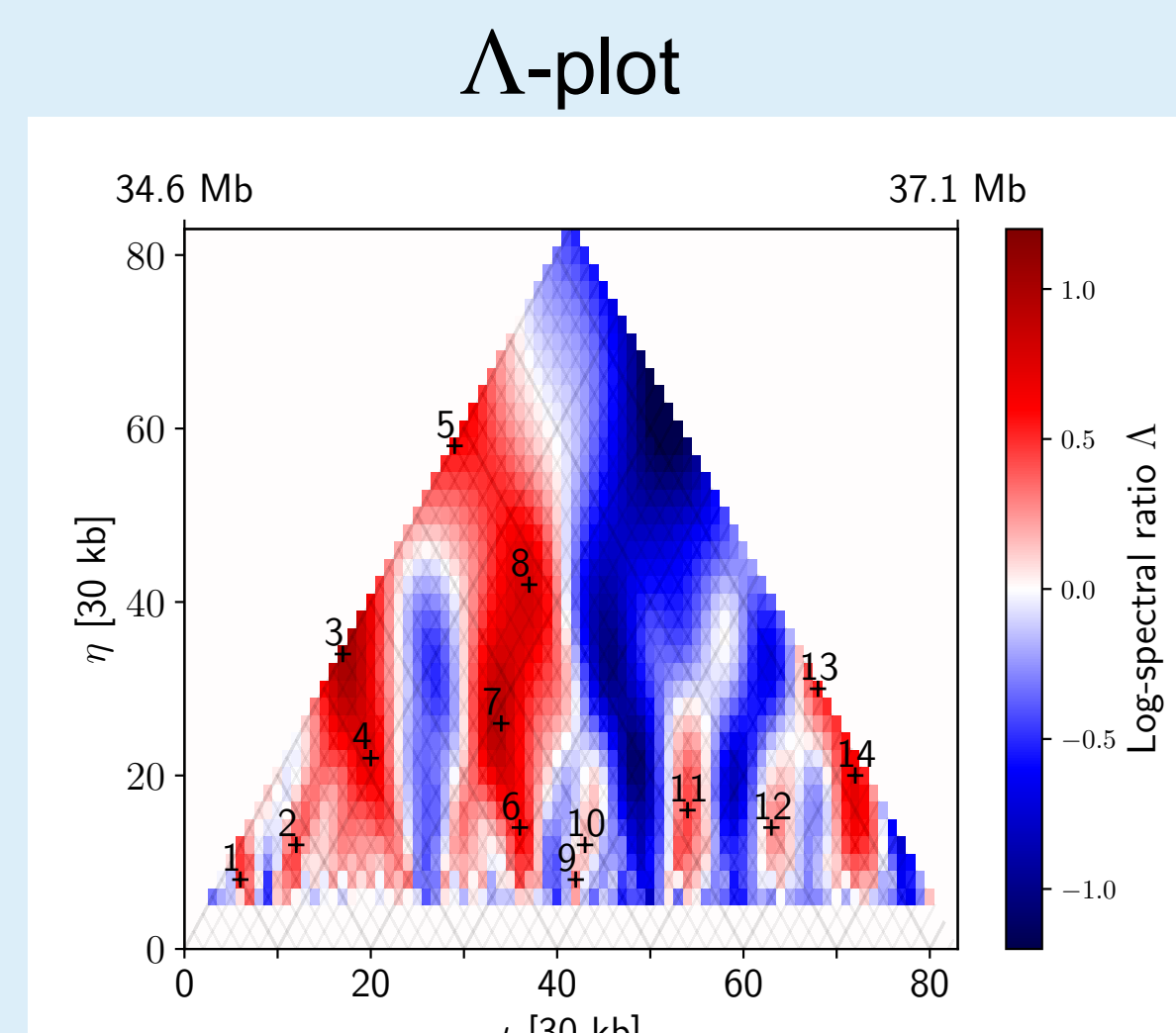
Cell line:
HCT116
Chr. 21

Location:
34.6-37.1 Mb

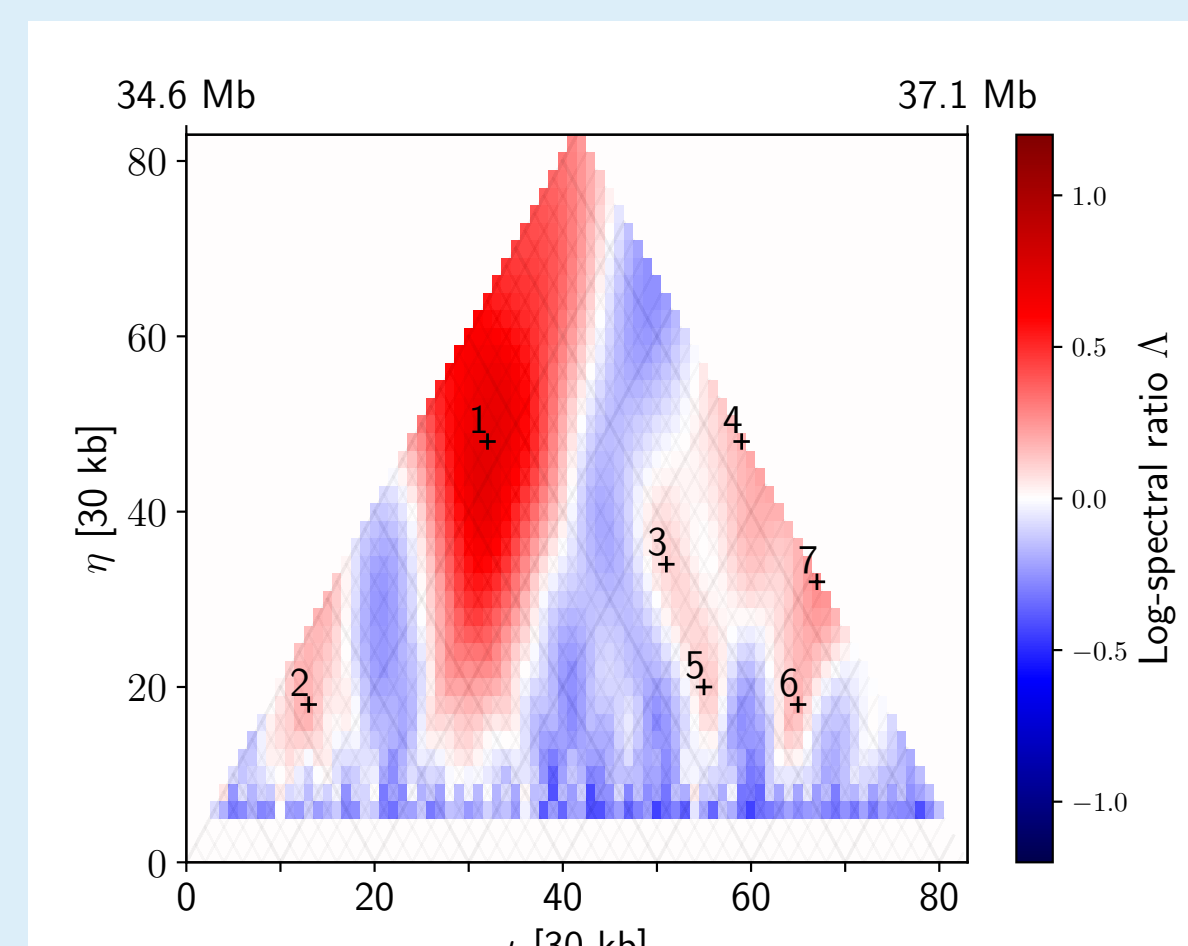
Two variants:
Untreated
(11631 samples)
Auxin-treated*
(9562 samples)

*Auxin causes CTCF depletion

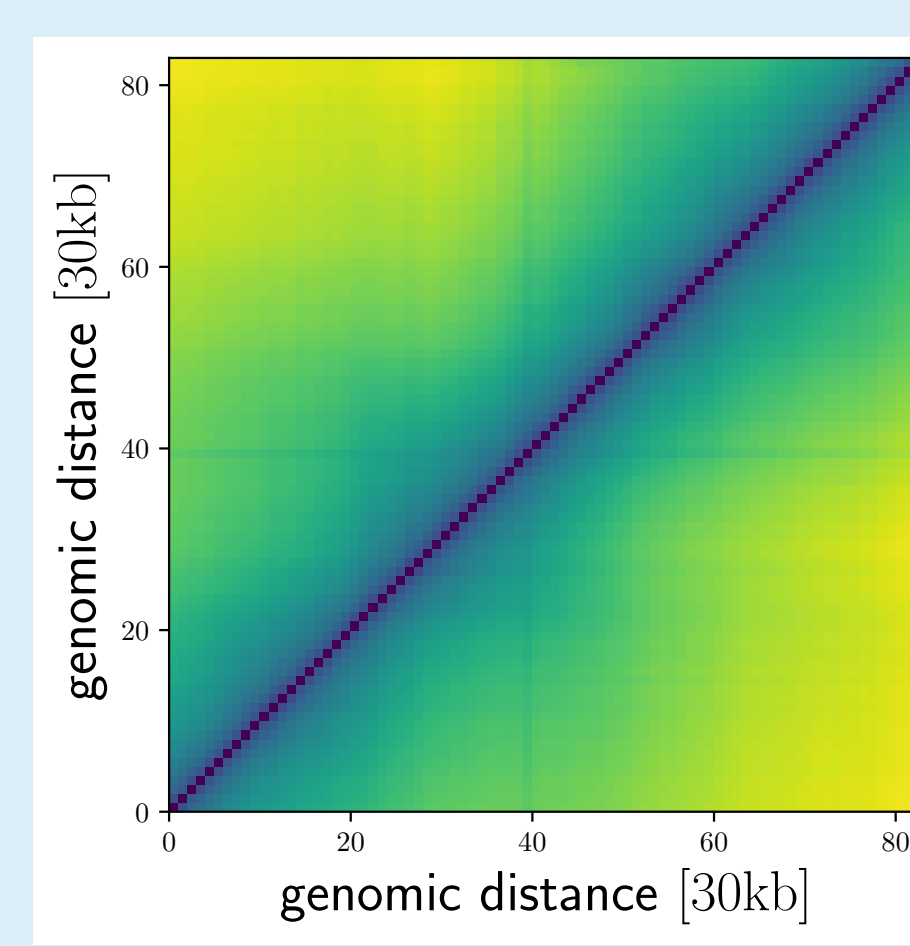
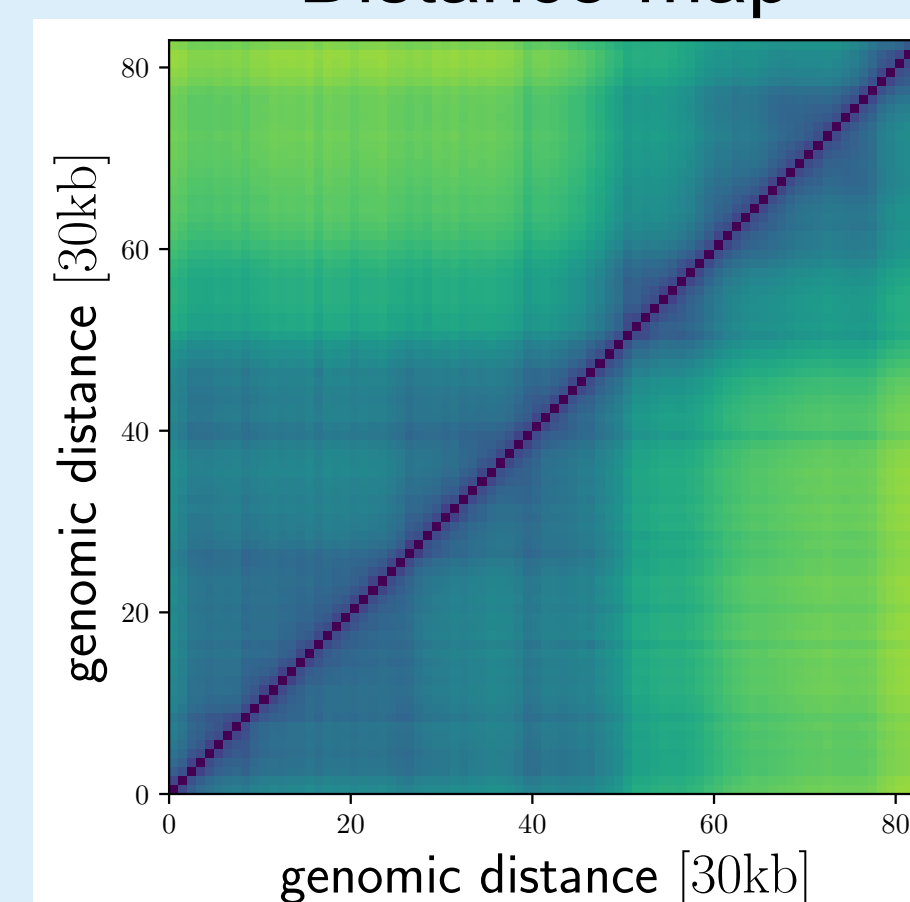
Untreated



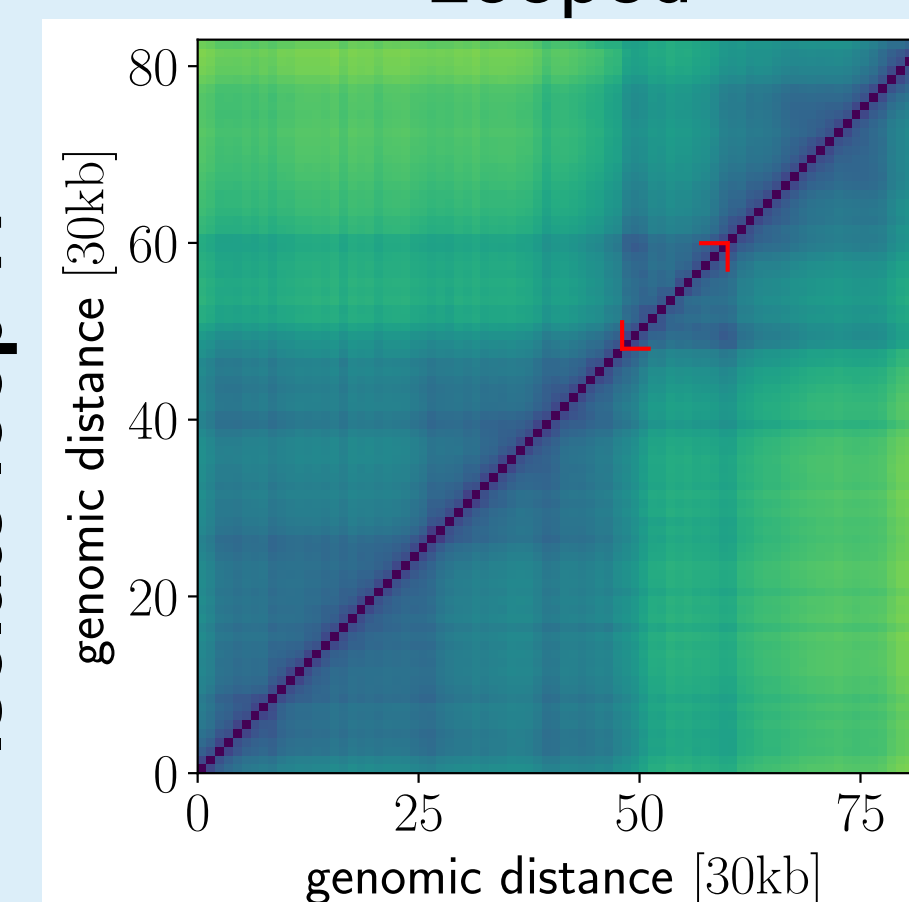
Auxin-treated



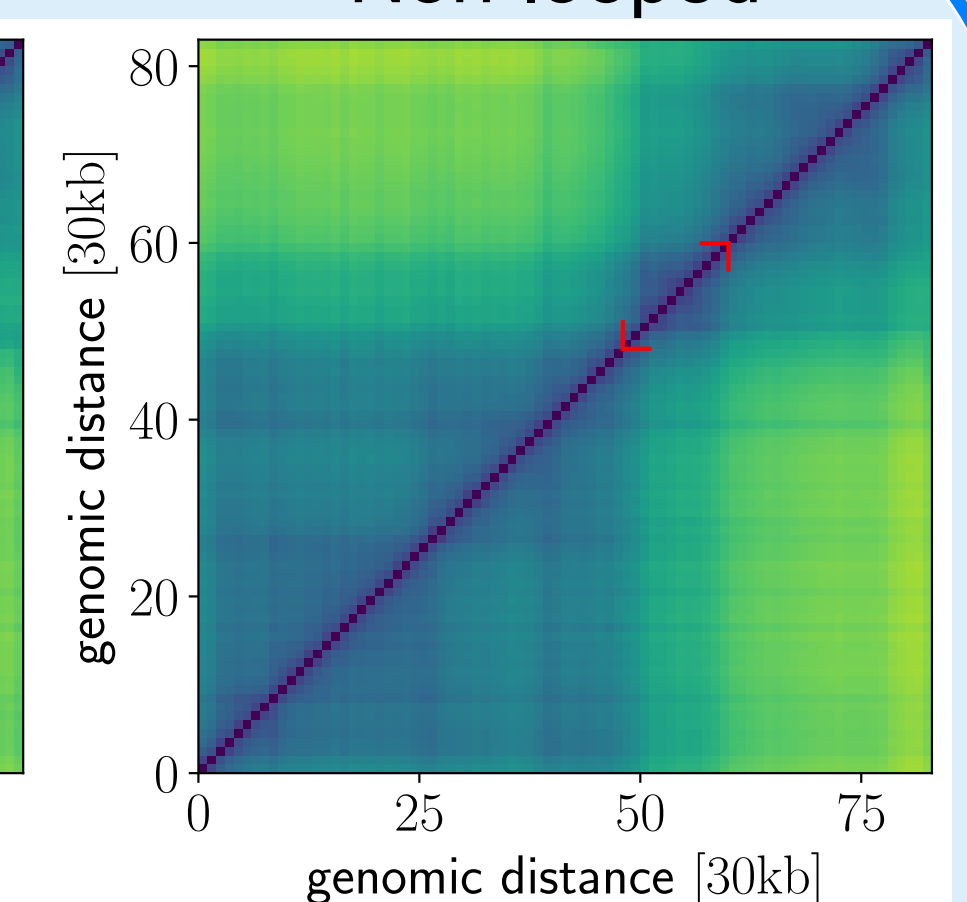
Distance-map



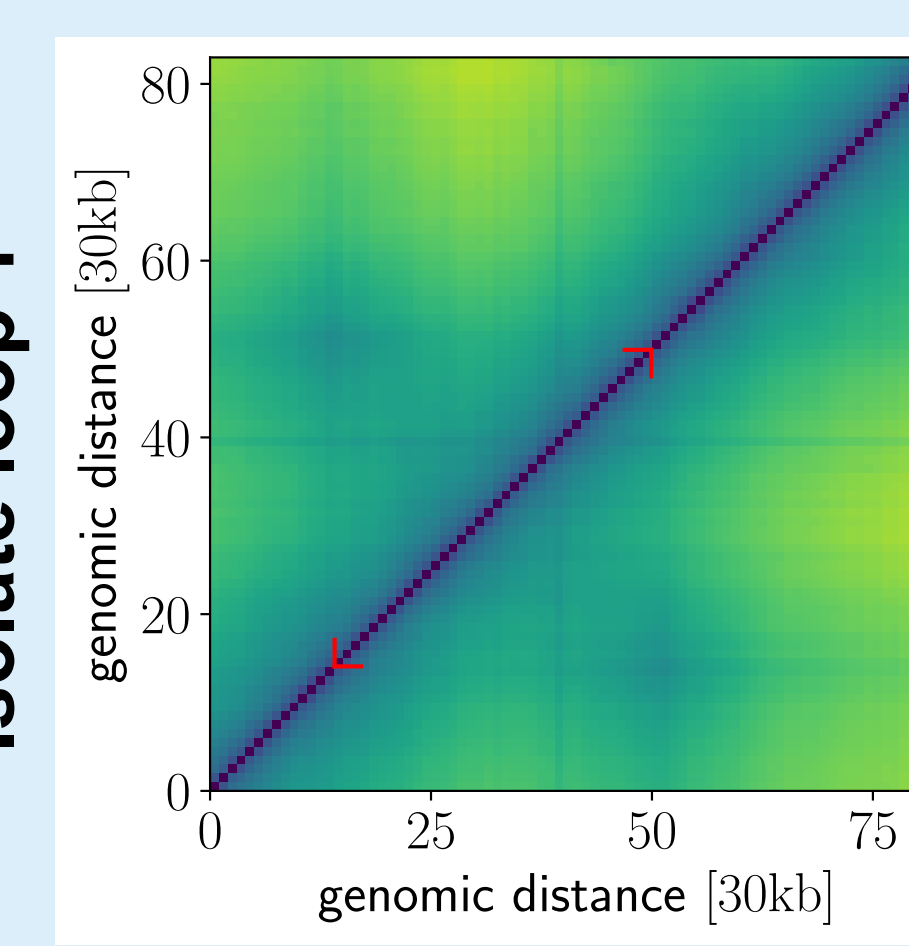
Looped



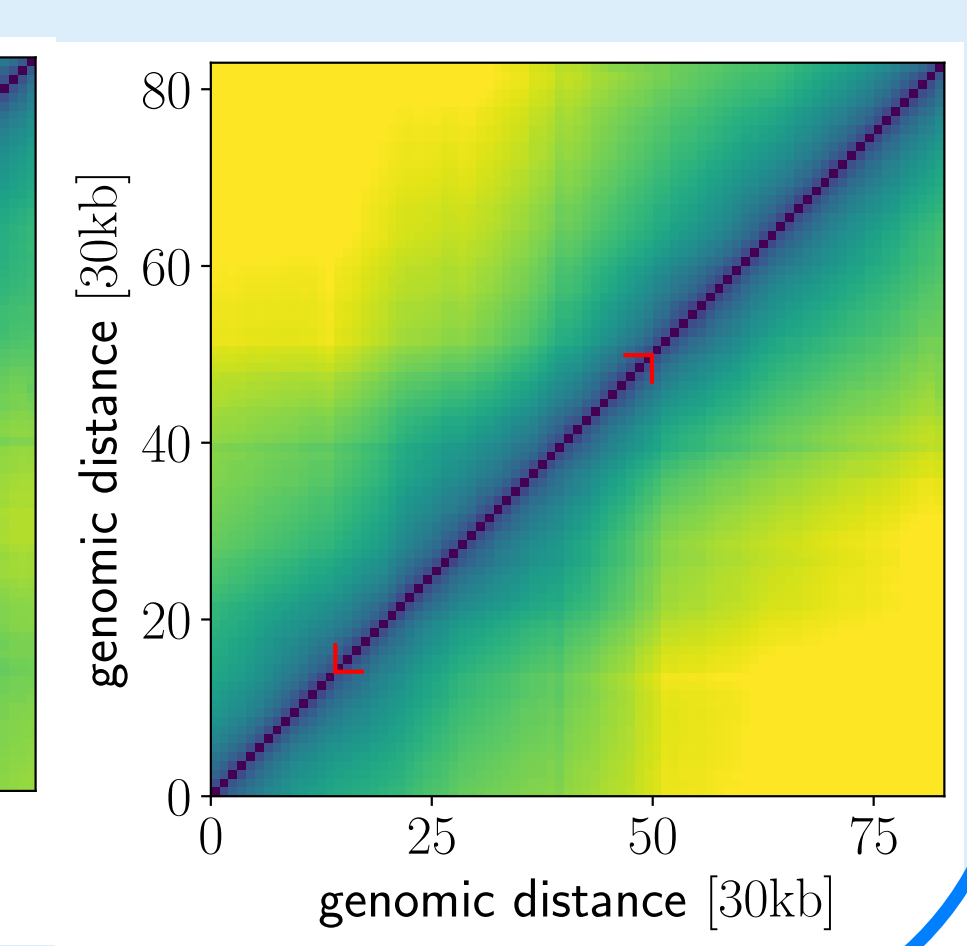
Non-looped



Isolate loop 11

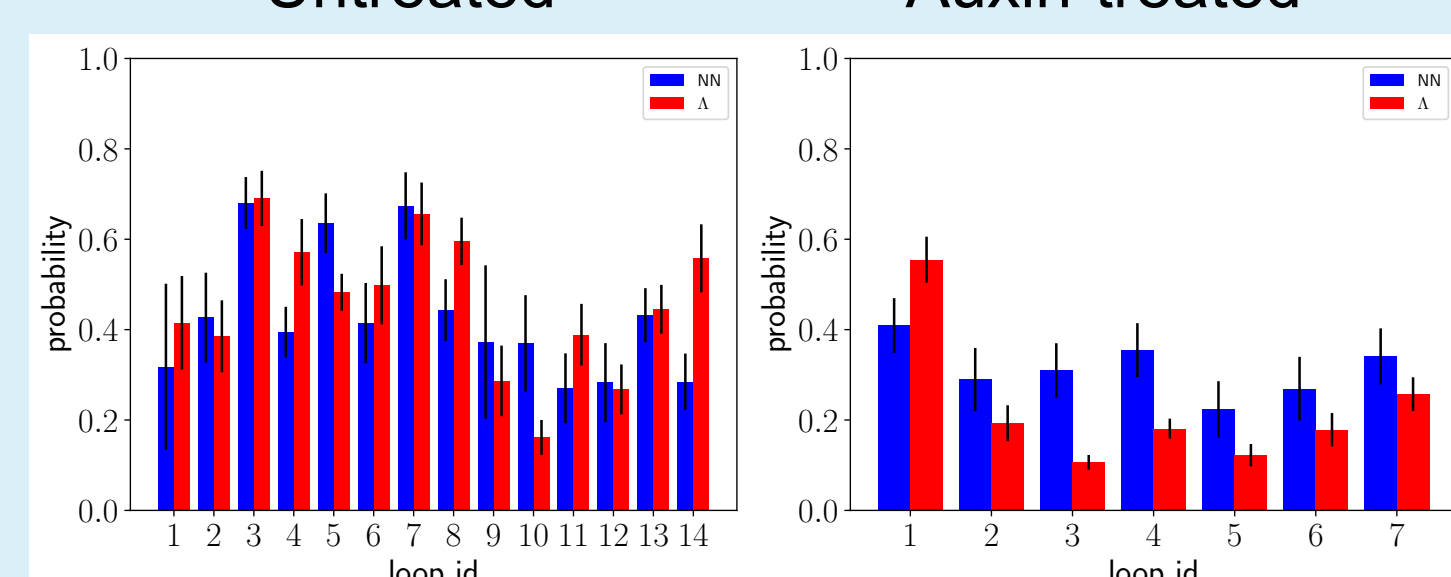


Isolate loop 1



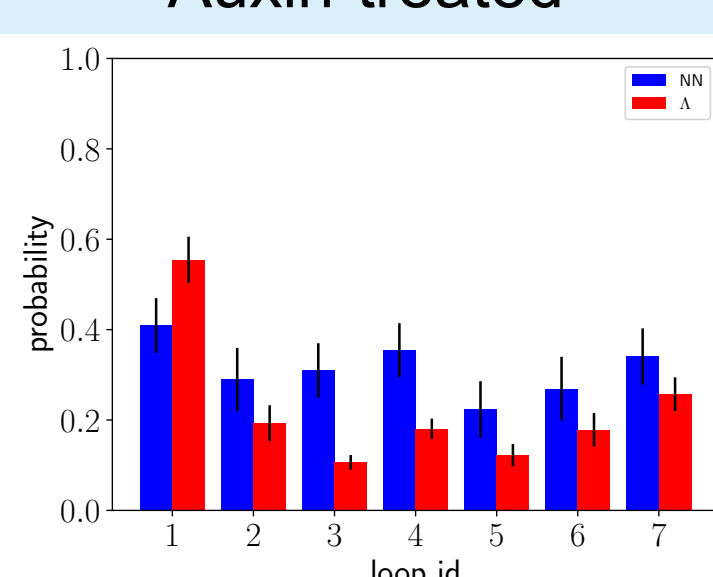
New possibilities

Untreated

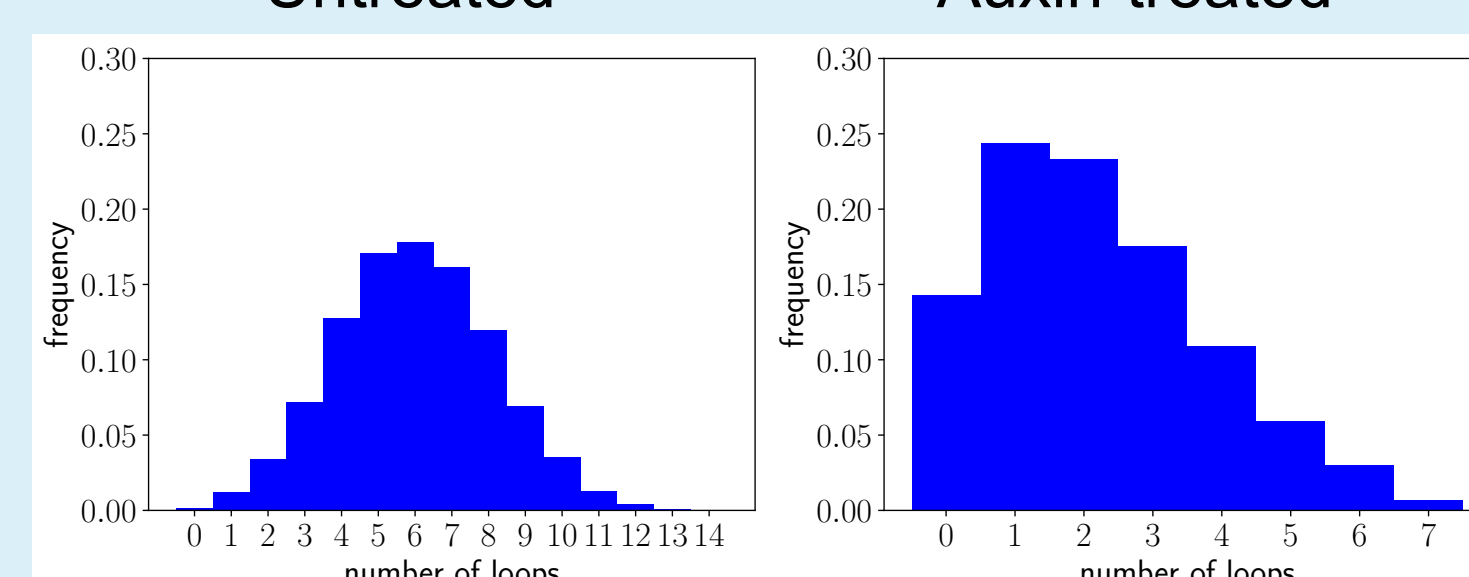


Population percentages of loops

Auxin-treated

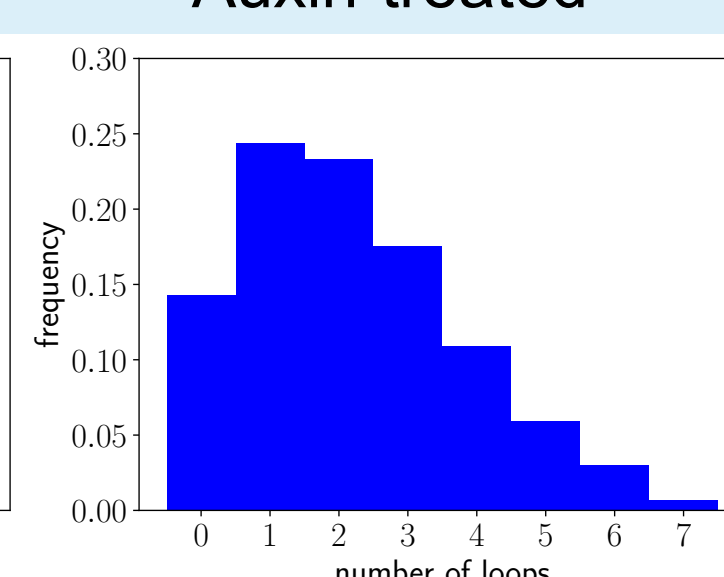


Untreated

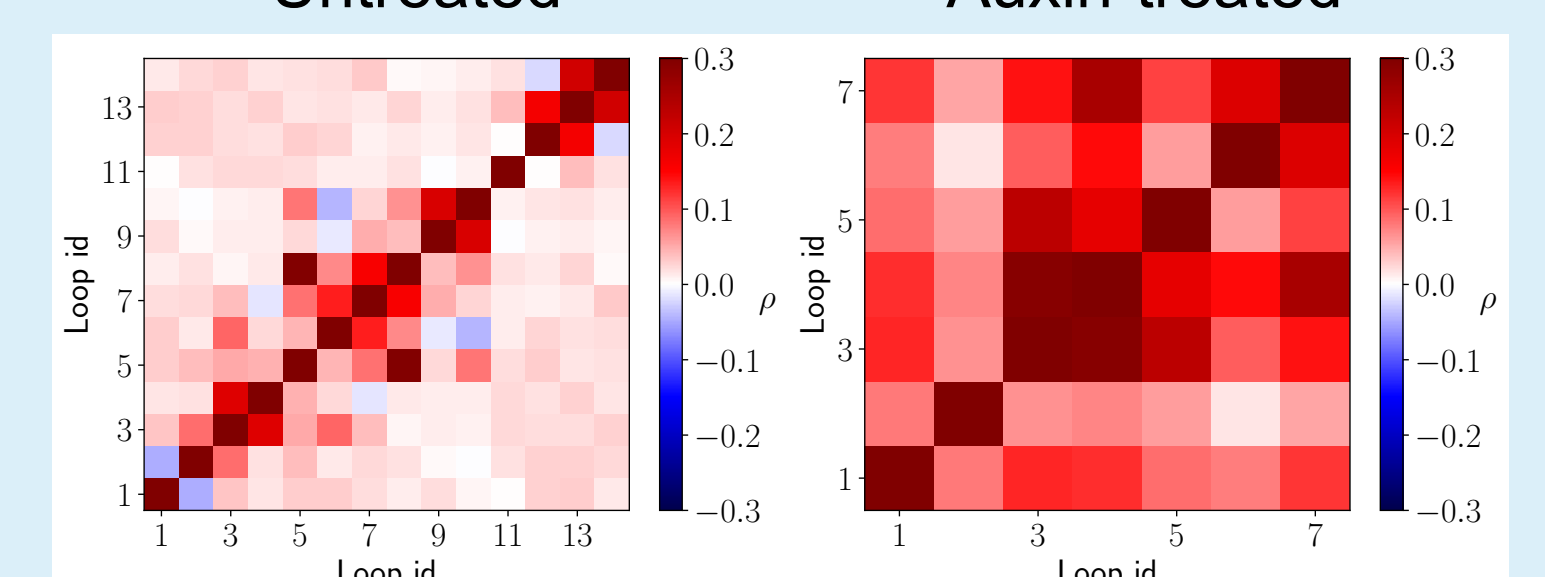


Loops occurring together in one conformation

Auxin-treated

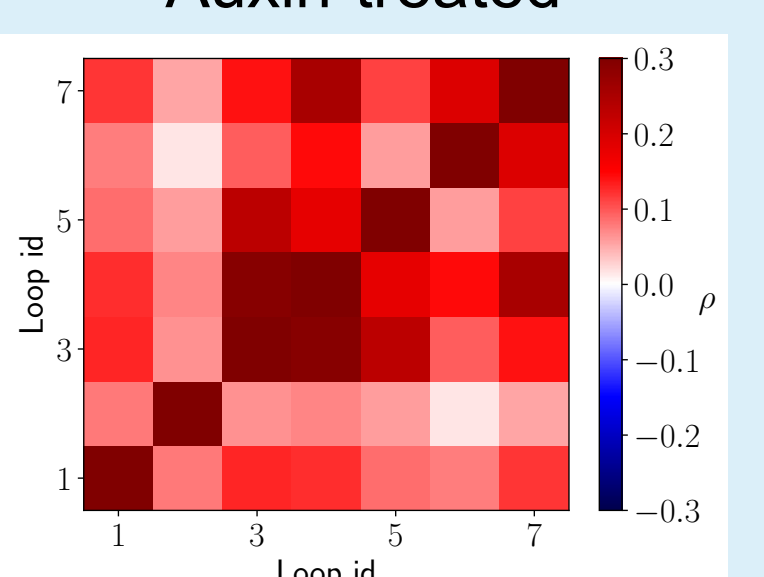


Untreated



Correlation between loops

Auxin-treated



References

- [1] Bintu, B. *et al.* Super-resolution chromatin tracing reveals domains and cooperative interactions in single cells. *Science* **362** (2018).
[2] Földes, T., Lesage, A. & Barbi, M. Assessing the Polymer Coil-Globule State from the Very First Spectral Modes. *Phys. Rev. Lett.* **127**, 277801 (2021).