Massachusetts Institute of Technology

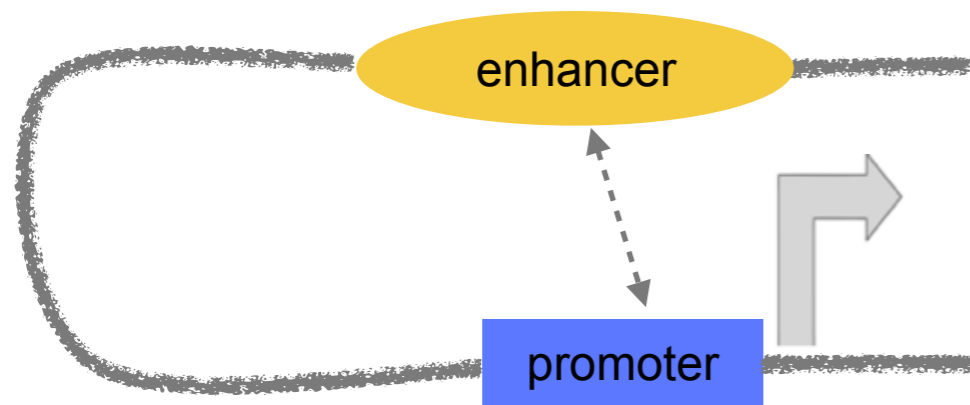Institute for Medical Engineering and Sciences

Chromatin organization: from polymer loops to topological domains

Boryana Doyle

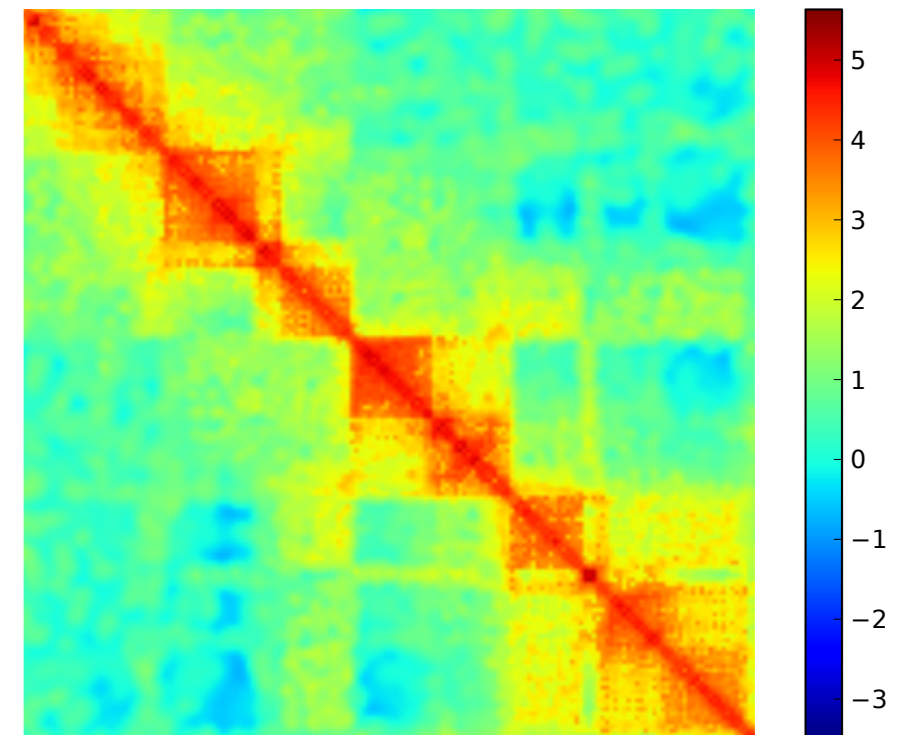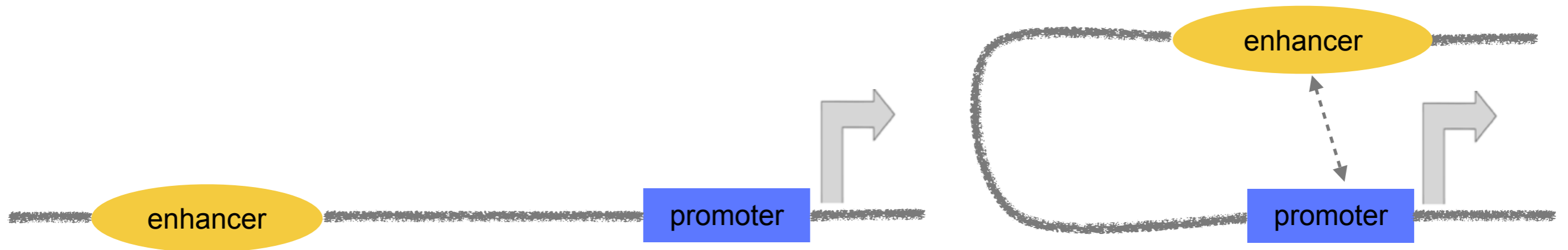Maxim Imakaev, Geoffrey Fudenberg, Leonid Mirny

Outline

Part 1

Enhancer-promoter interactions studied in polymer simulations

Part 2

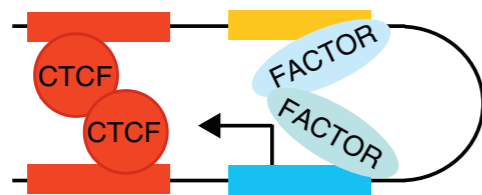Analysis of experimental Hi-C data

Part 1: Introduction

enhancer

promoter

enhancer

promoter

Enhancer and promoter interactions—long distance calls

Ivan Krivega and Ann Dean

(a)

CTCF

CTCF

FACTOR

FACTOR

β-globin and APO

Raab and Kamakaka. Nat Rev Genet. 2010
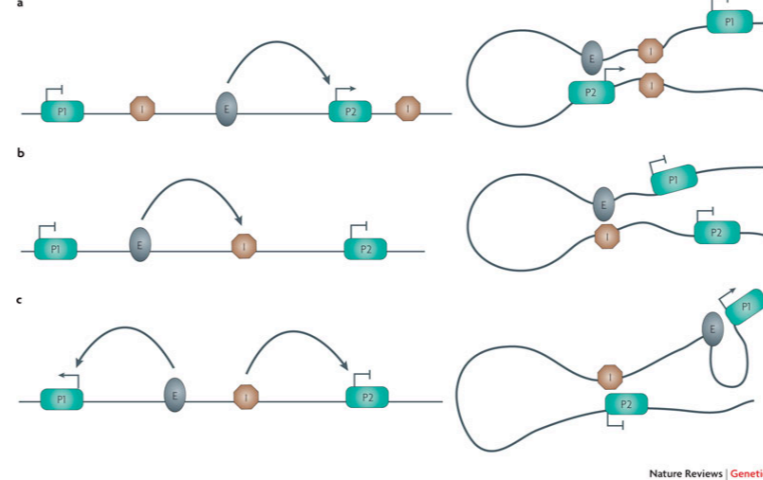
Nature Reviews | Genetics

Theoretical analysis of the role of chromatin interactions in long-range action of enhancers and insulators

agatam Mukhopadhyay[a], Paul Schedl[b], Vasily M. Studitsky[c,d], and Anirvan M. Sengupta[e,1]

Inter-domain Interaction
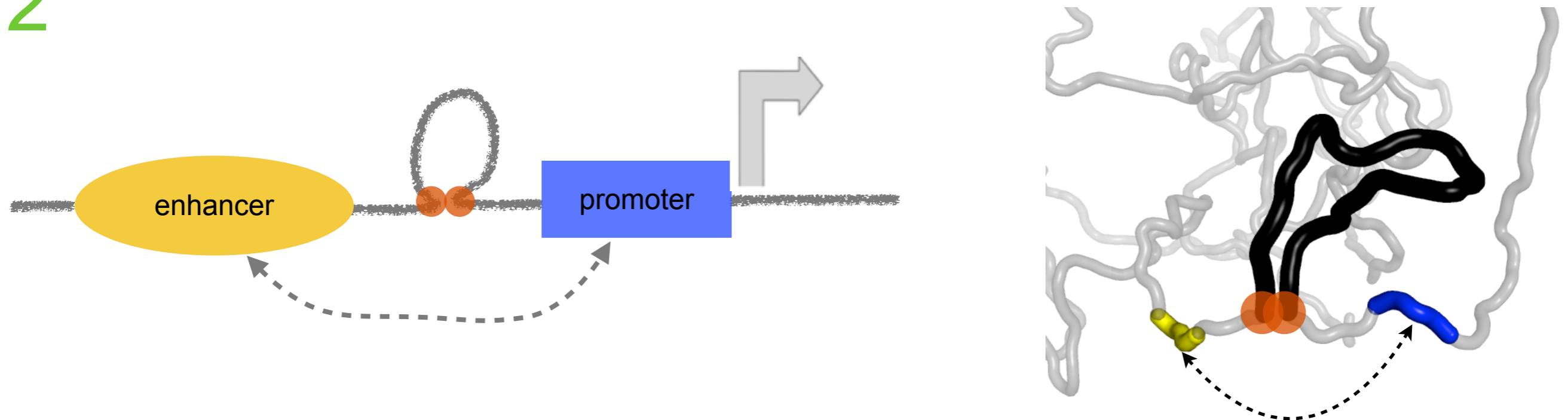
Inter-domain Interaction

Intra-domain Interaction
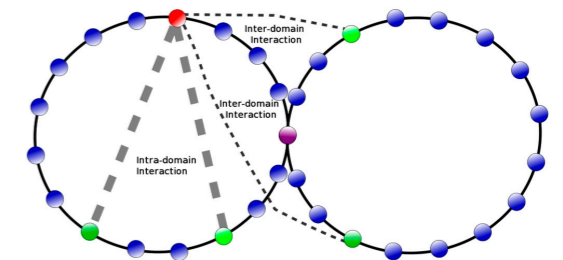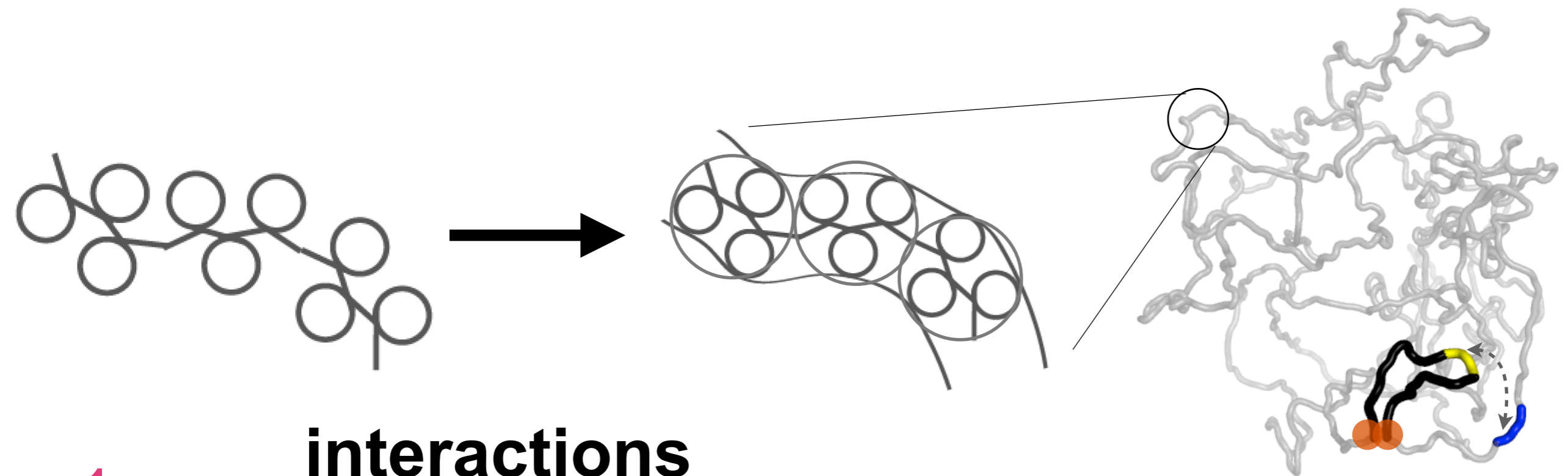
How can enhancer-promoter interactions be affected by local genome folding?
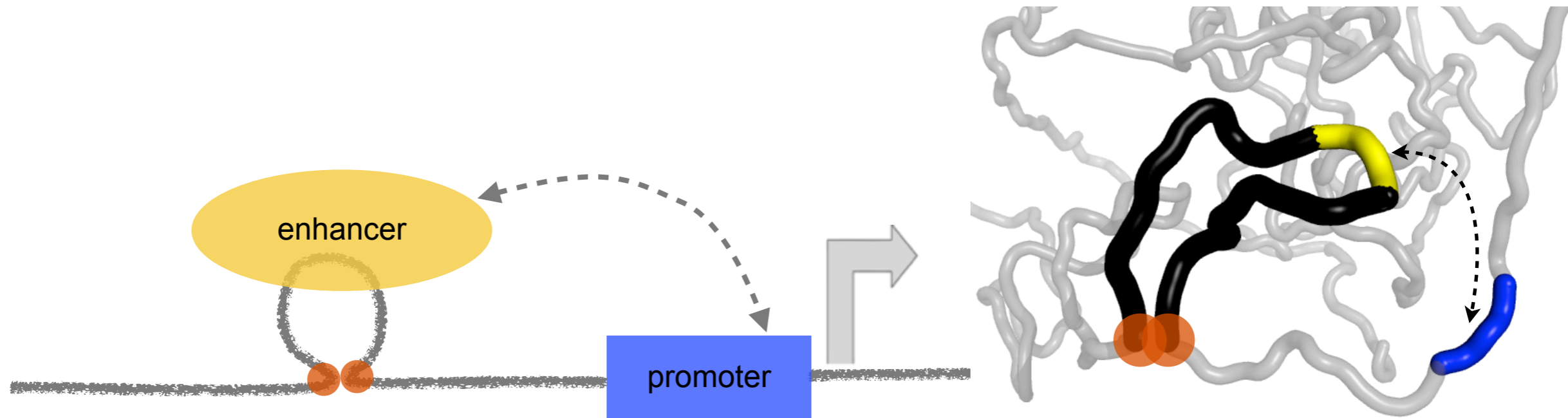
Model: chromatin as a polymer

interactions
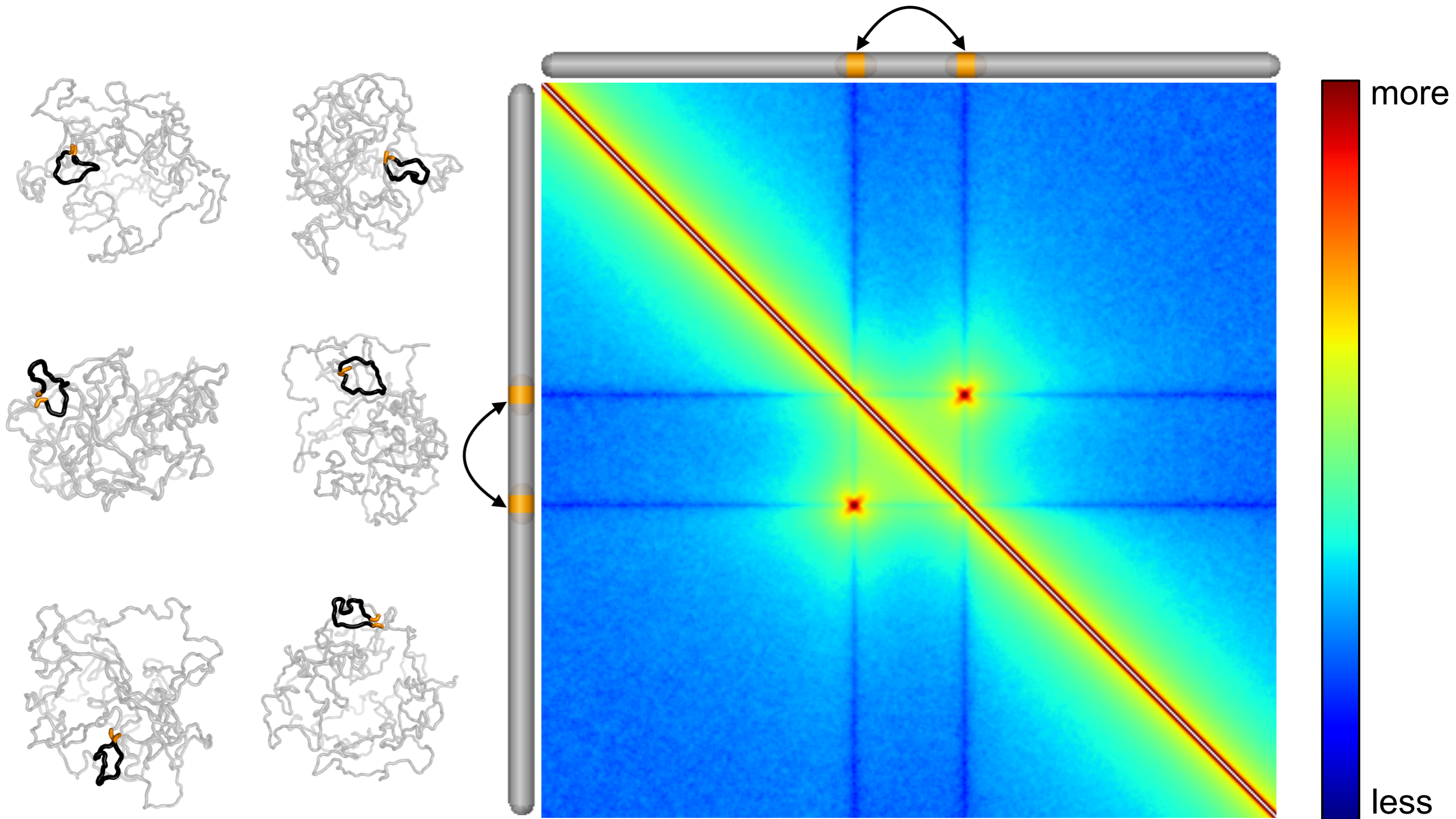
1

50kb

30kb

2

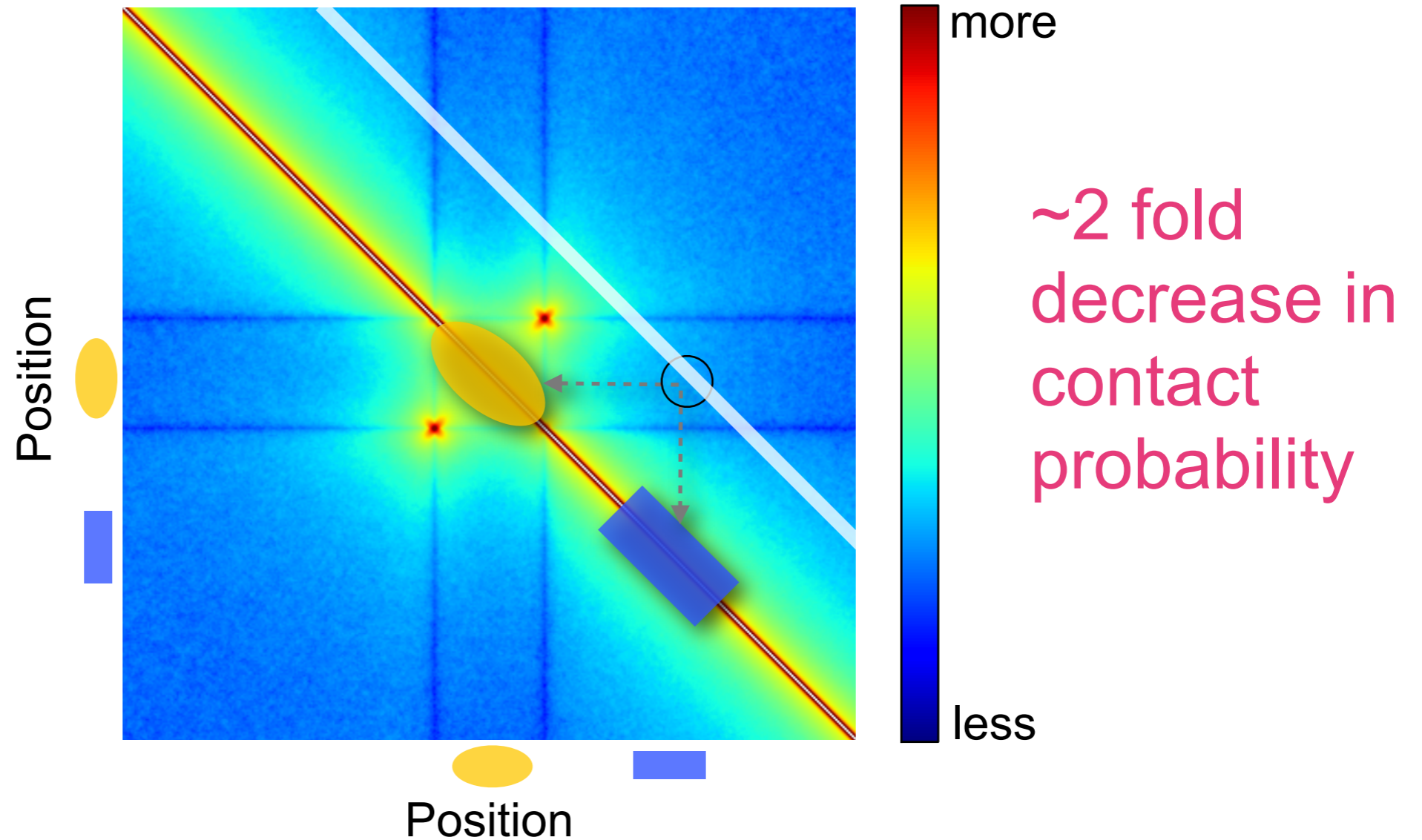50kb

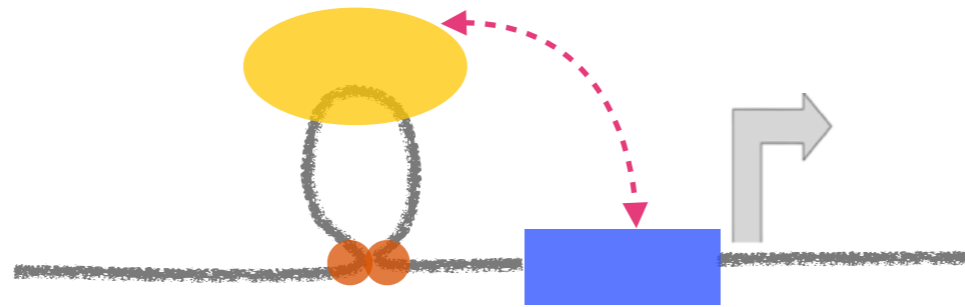30kb
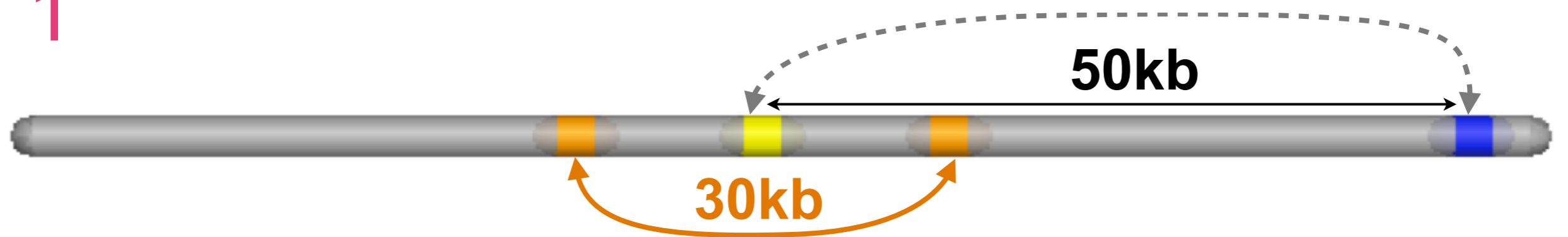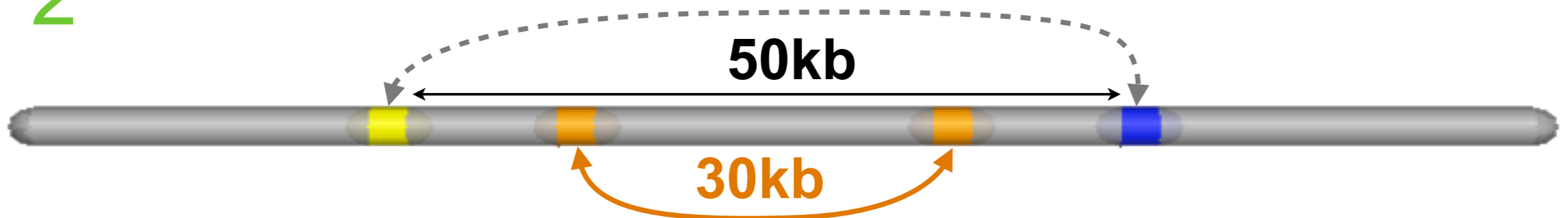
Langevin dynamics simulations

Results: Contact Maps

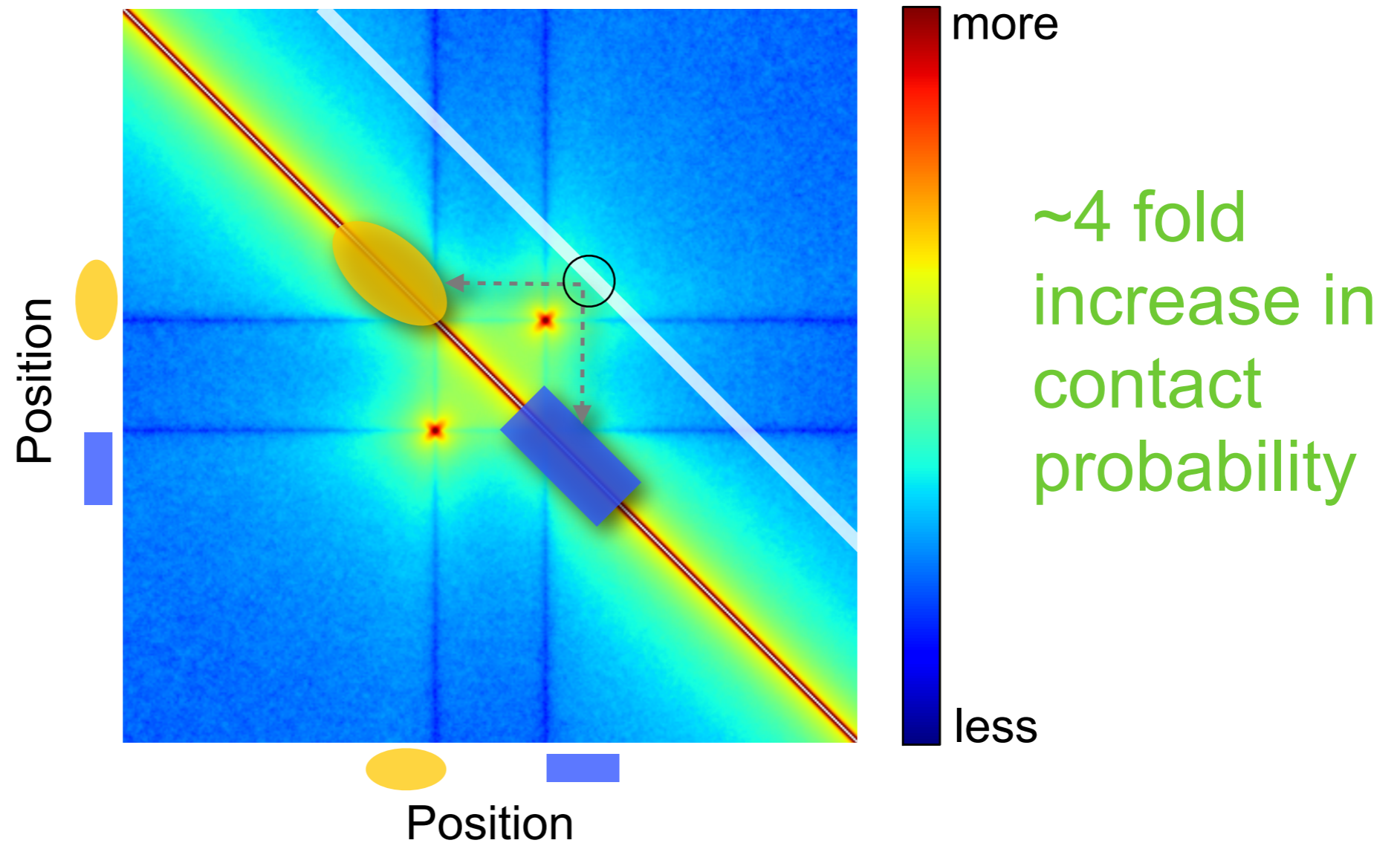average over 10^5 conformations $\longrightarrow$ 1 contact map

more

less

Case 1: Insulates
Enhancer inside loop. Promoter outside loop.

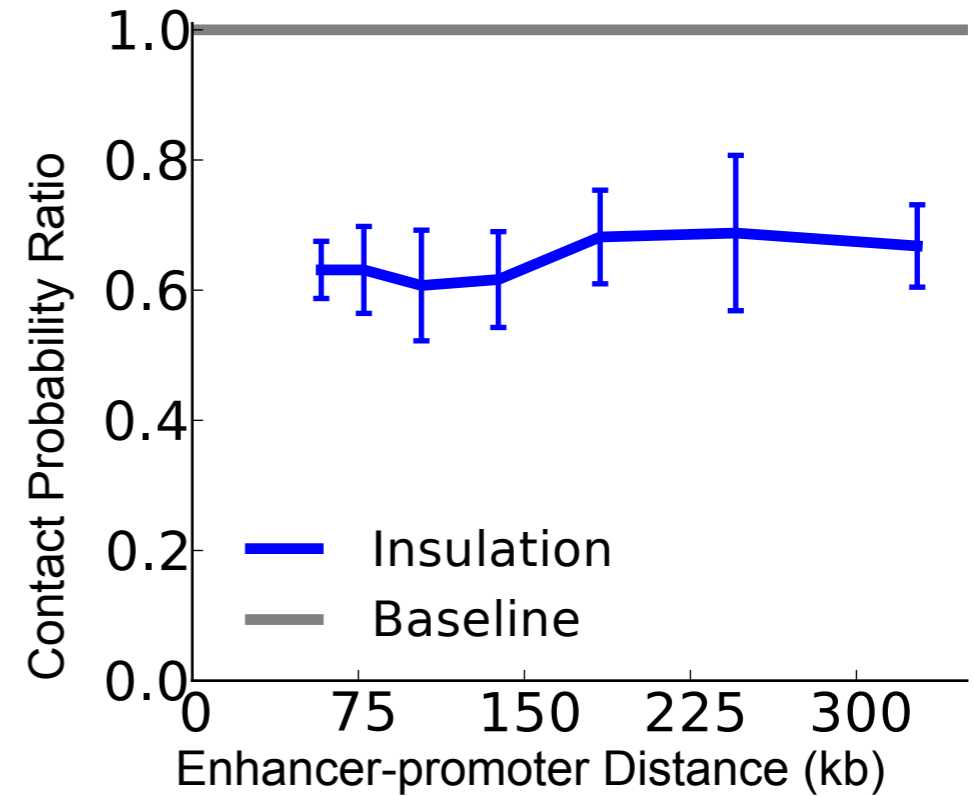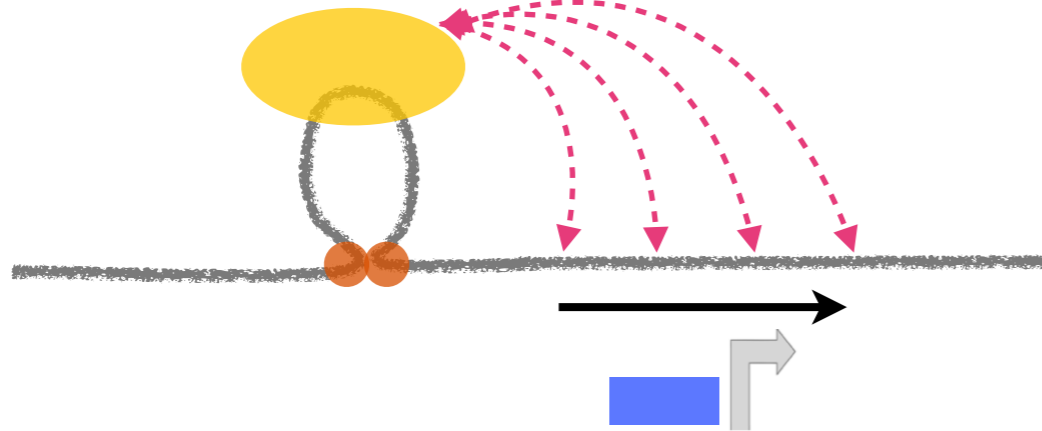~2 fold decrease in contact probability

Case 2: Facilitates
Enhancer before loop. Promoter after loop.
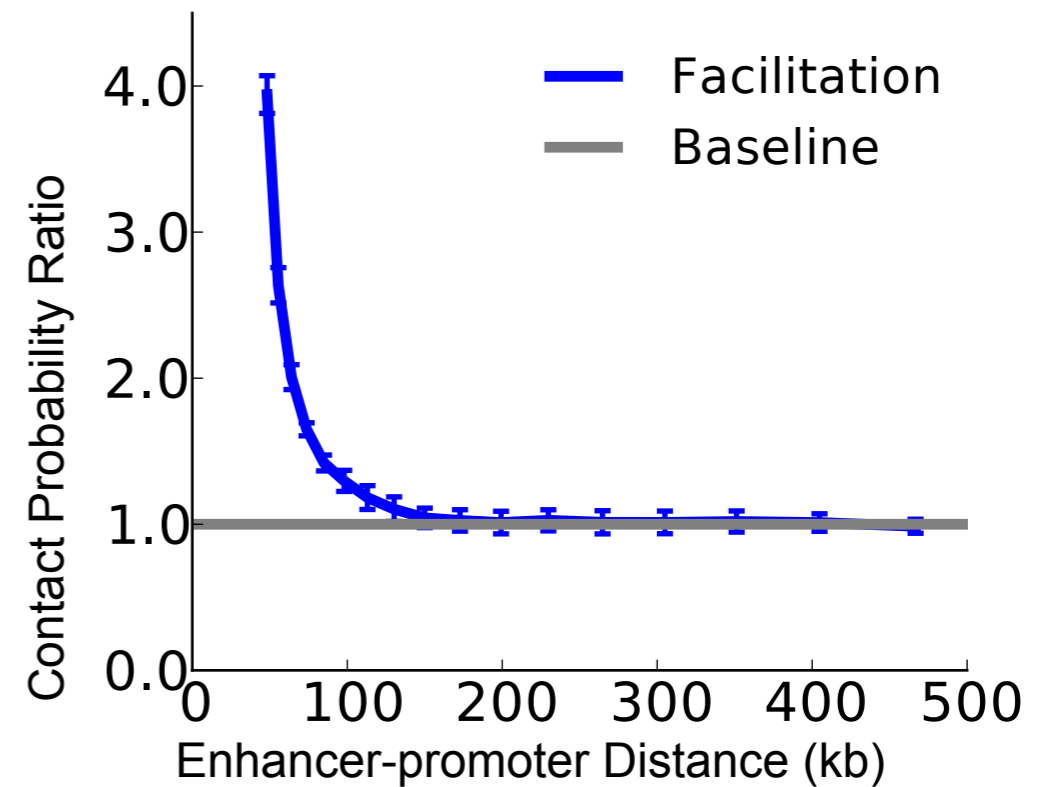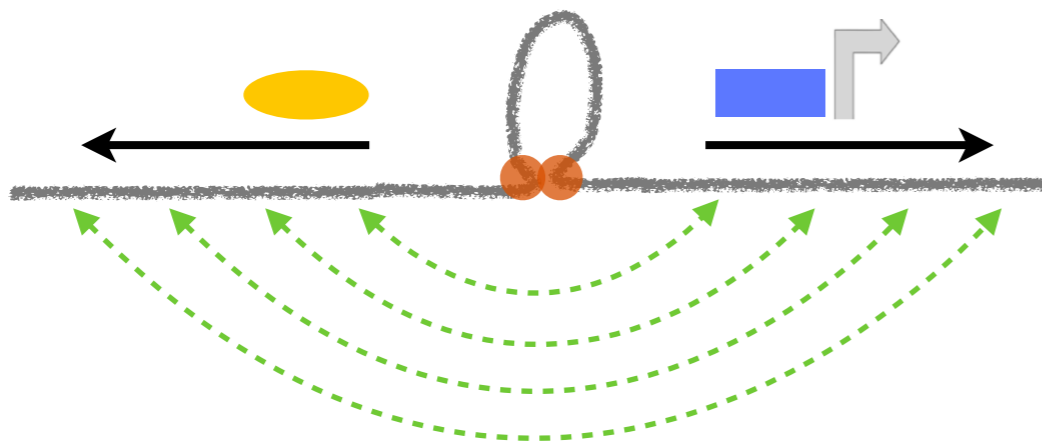

~4 fold increase in contact probability
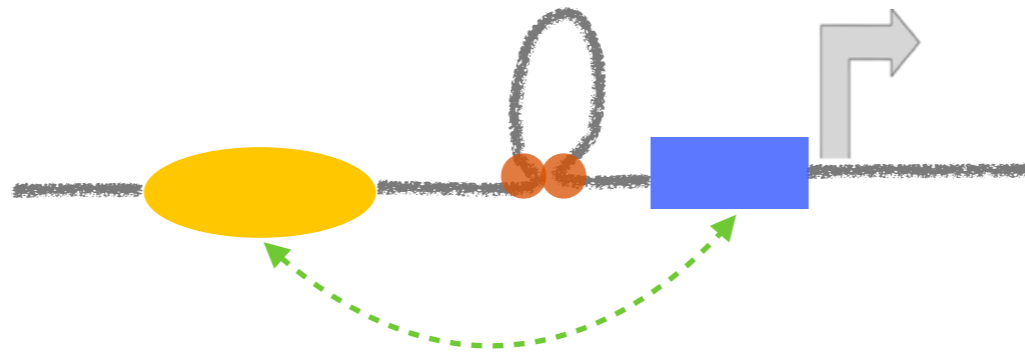
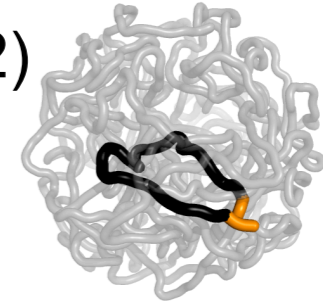# **Insulation** is global, while **facilitation** is local

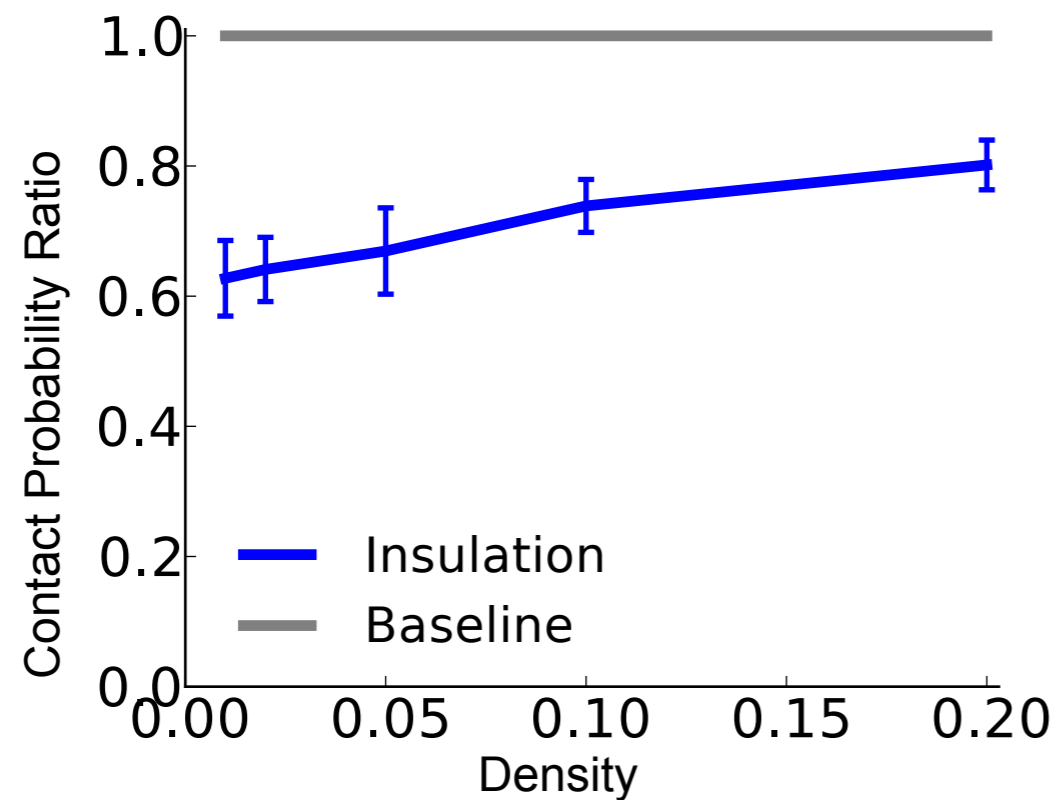# Weaker insulation and facilitation in compact chromatin
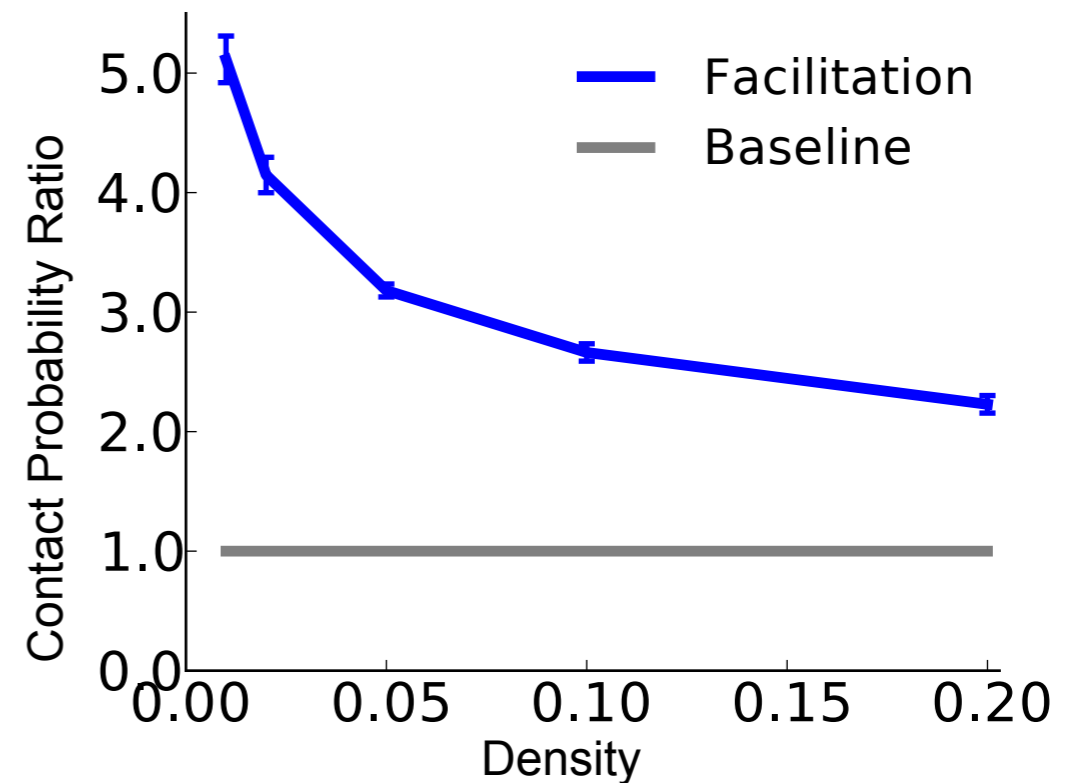
low density (0.01)

high density (0.2)

1

2

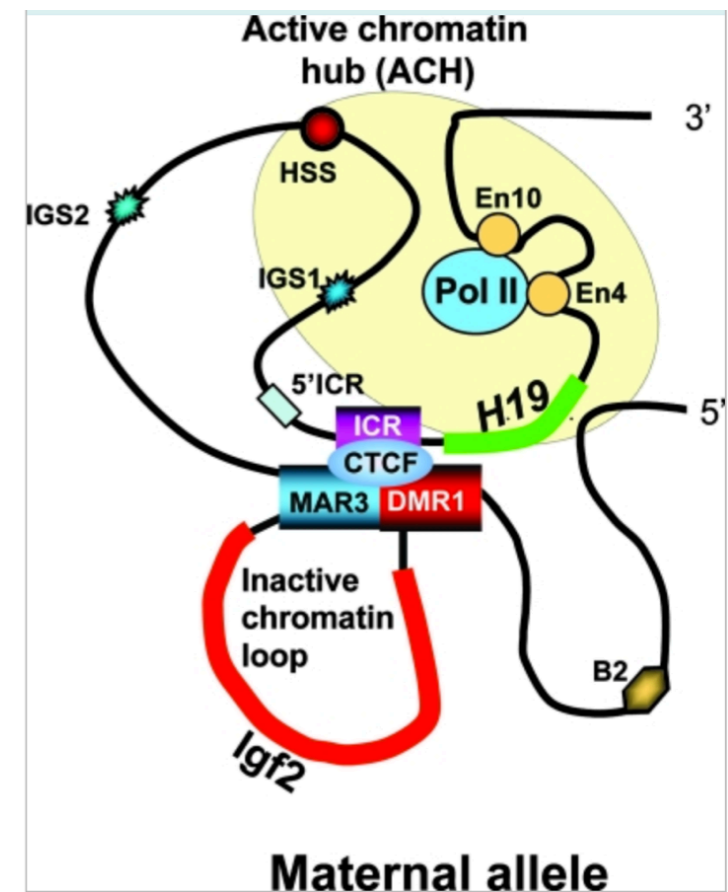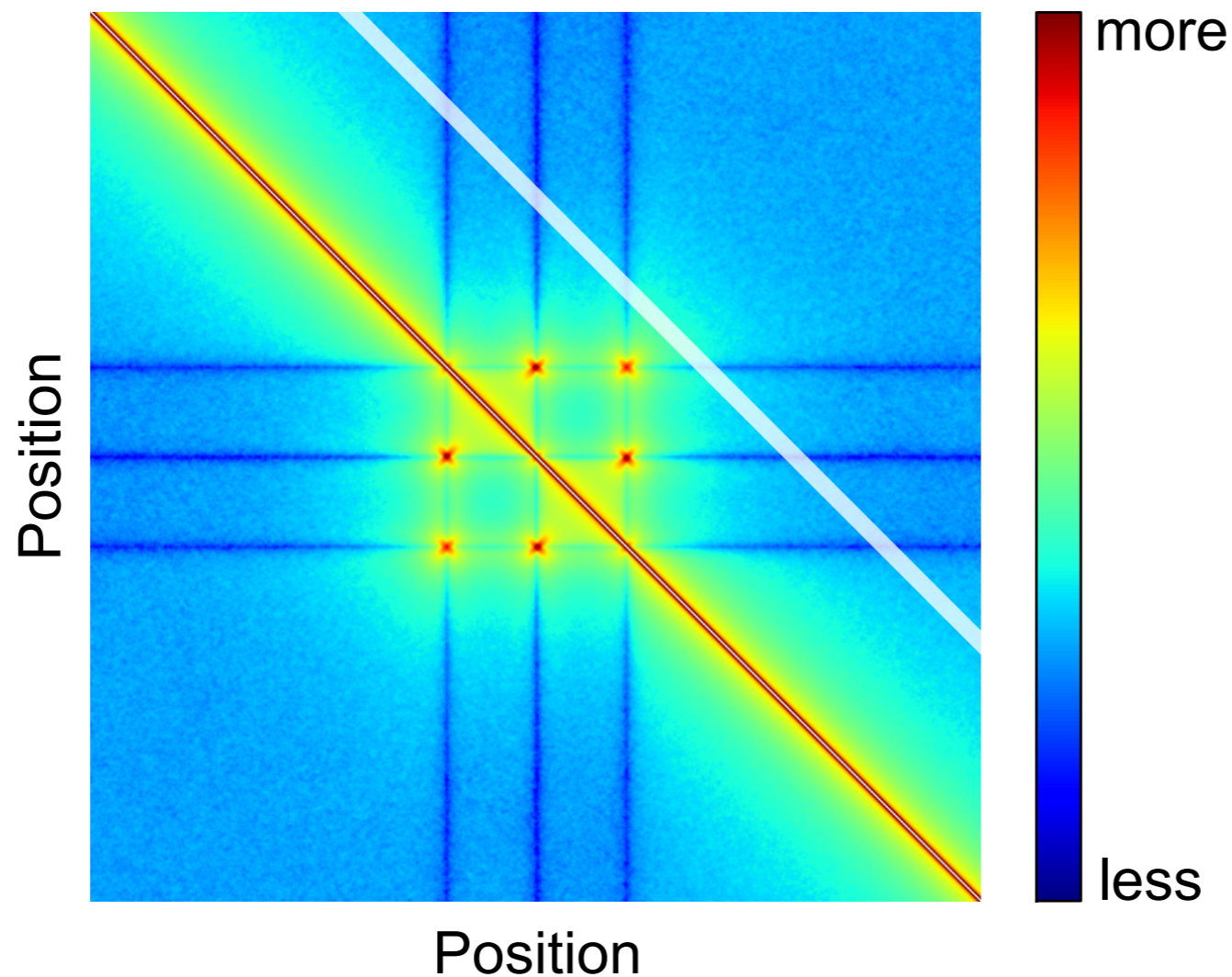# Similar insulation and facilitation regardless of topological constraints
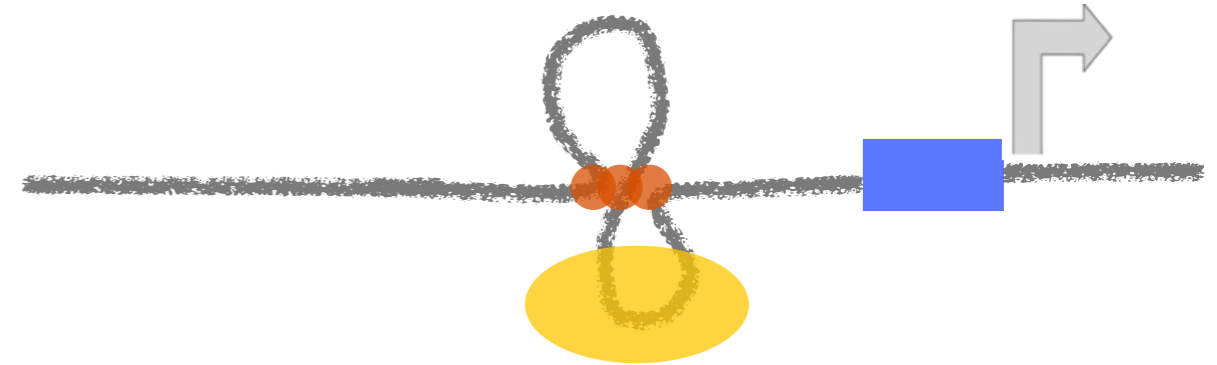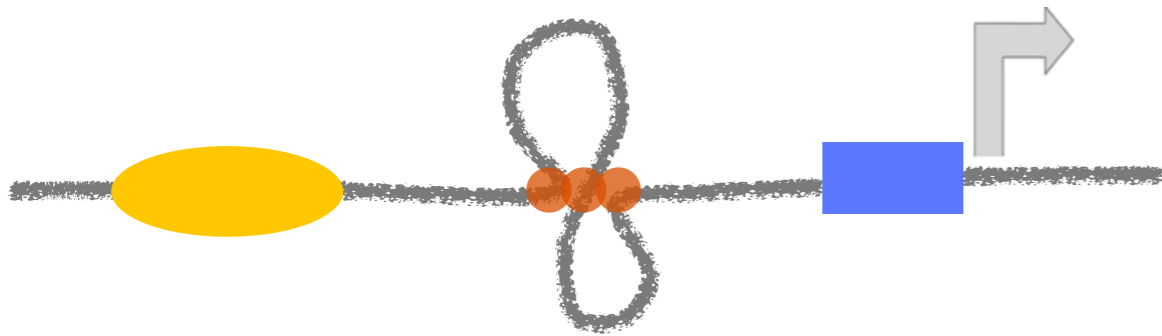
Without topological constraints = chain passing allowed
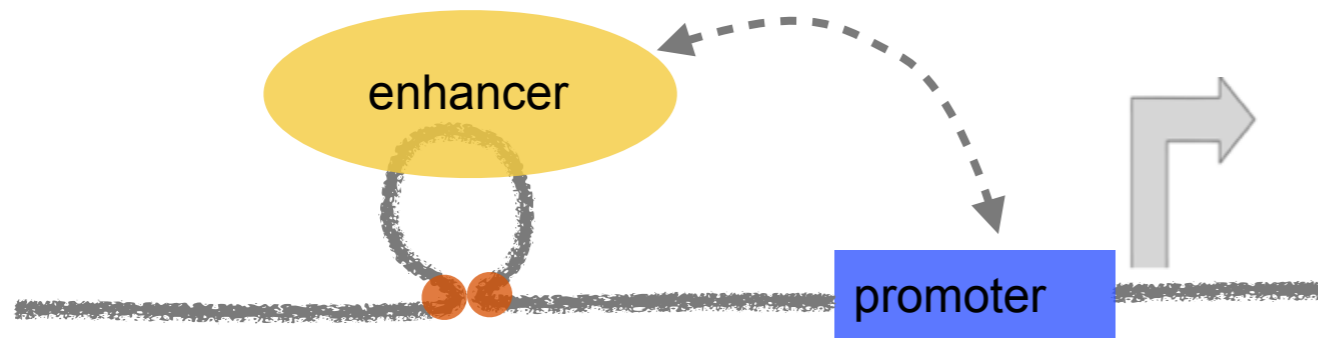
With topological constraints = chain passing not allowed

Insulation and facilitation are stronger for two loops elements

Kurukuti et al. PNAS. 2006

Part 1: Summary

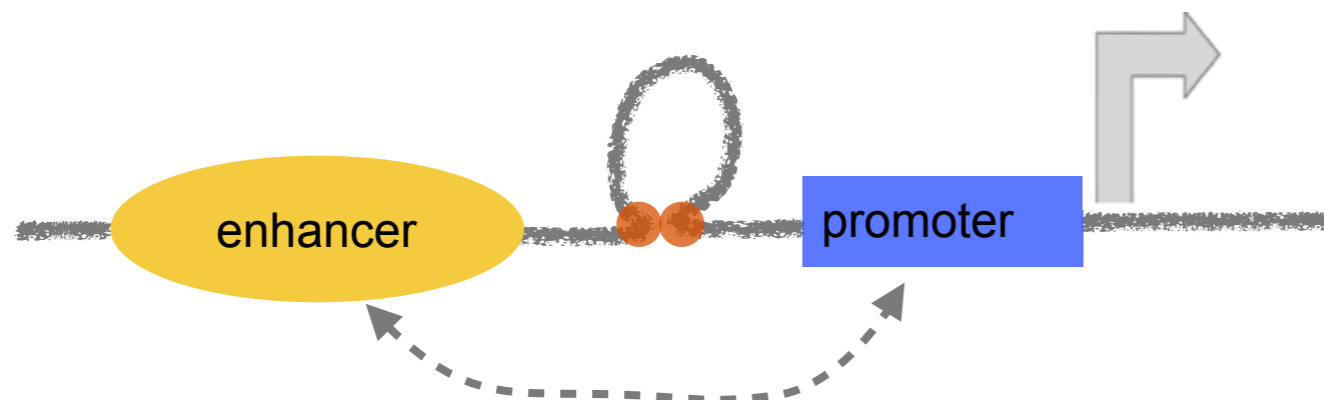## 1: Insulates: ~2 fold effect

Insulation is constant as enhancer-promoter genomic distance increases.

Facilitation diminishes as enhancer-promoter genomic distance increases.

Weaker insulation and facilitation in compact chromatin.

2: Facilitates: ~4 fold effect

Similar insulation and facilitation with and without topological constraints.

Stronger insulation and facilitation with two consecutive loops.

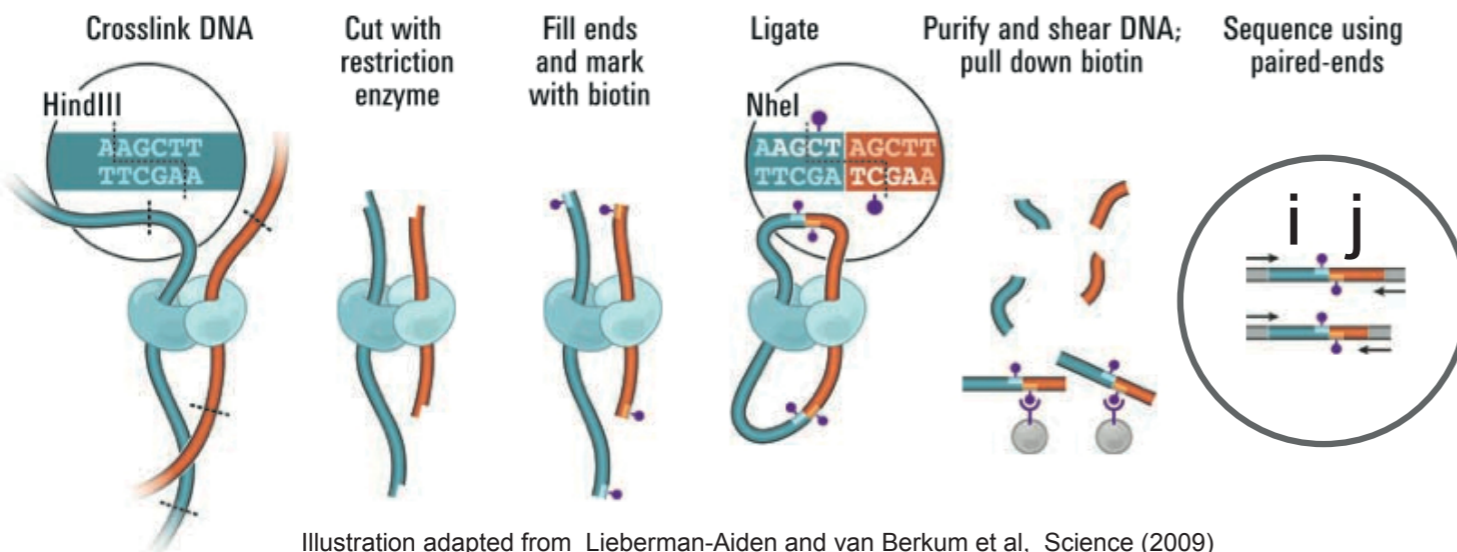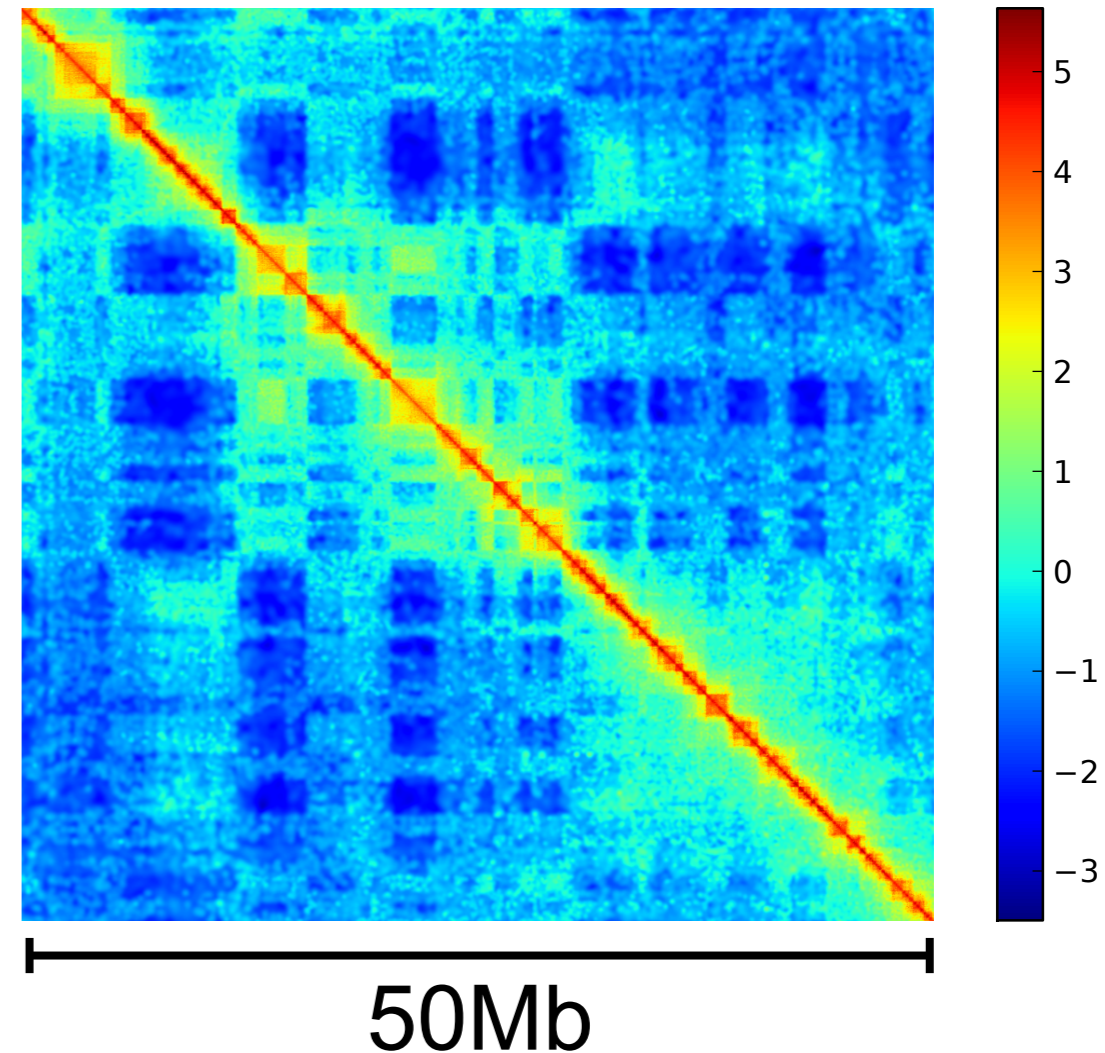# Part 2: Fine scale analysis of experimental Hi-C contact maps

Illustration adapted from Lieberman-Aiden and van Berkum et al, Science (2009)
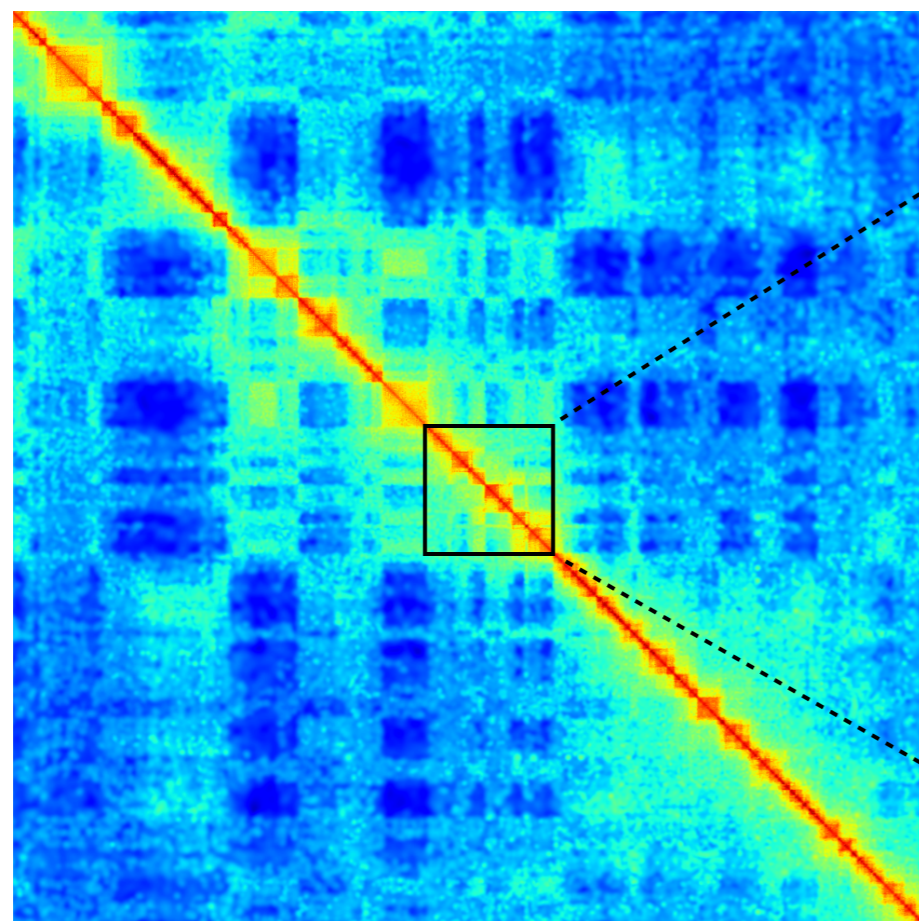
Hi-C experimentally measures spatial contacts in 3D

Region of chromosome 15
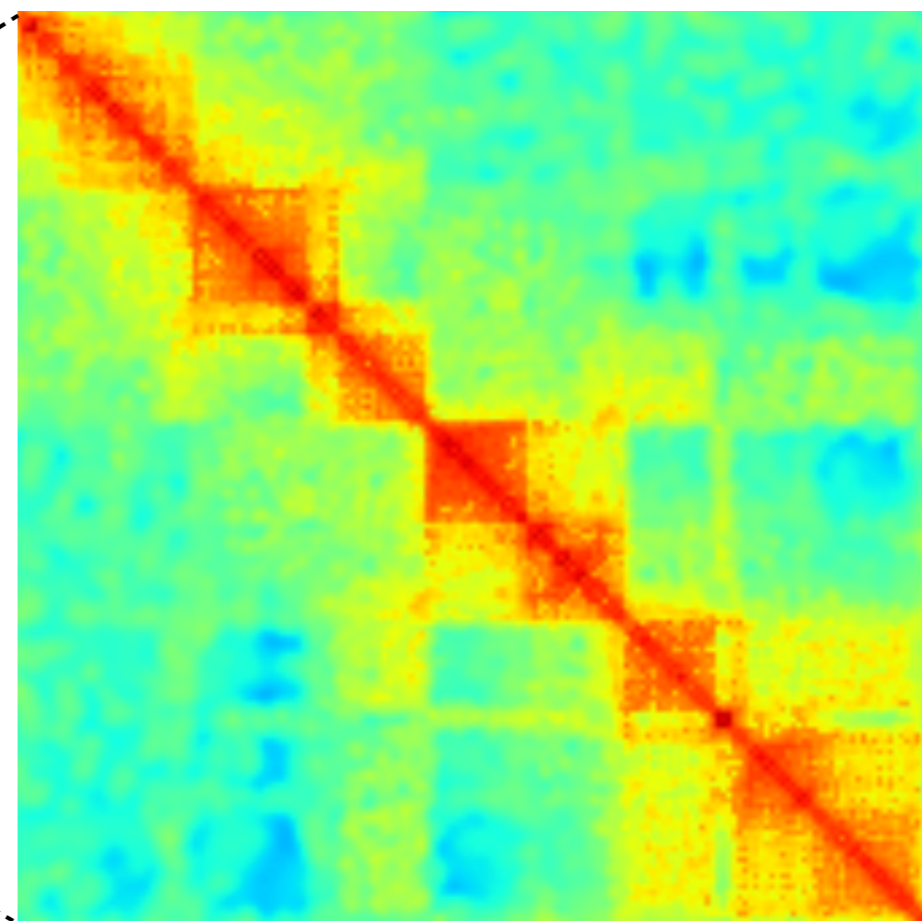

50Mb

Topologically Associated Domains (TADs)

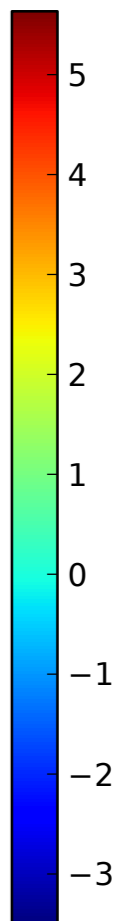## TAD size = 300 kb to 1Mb

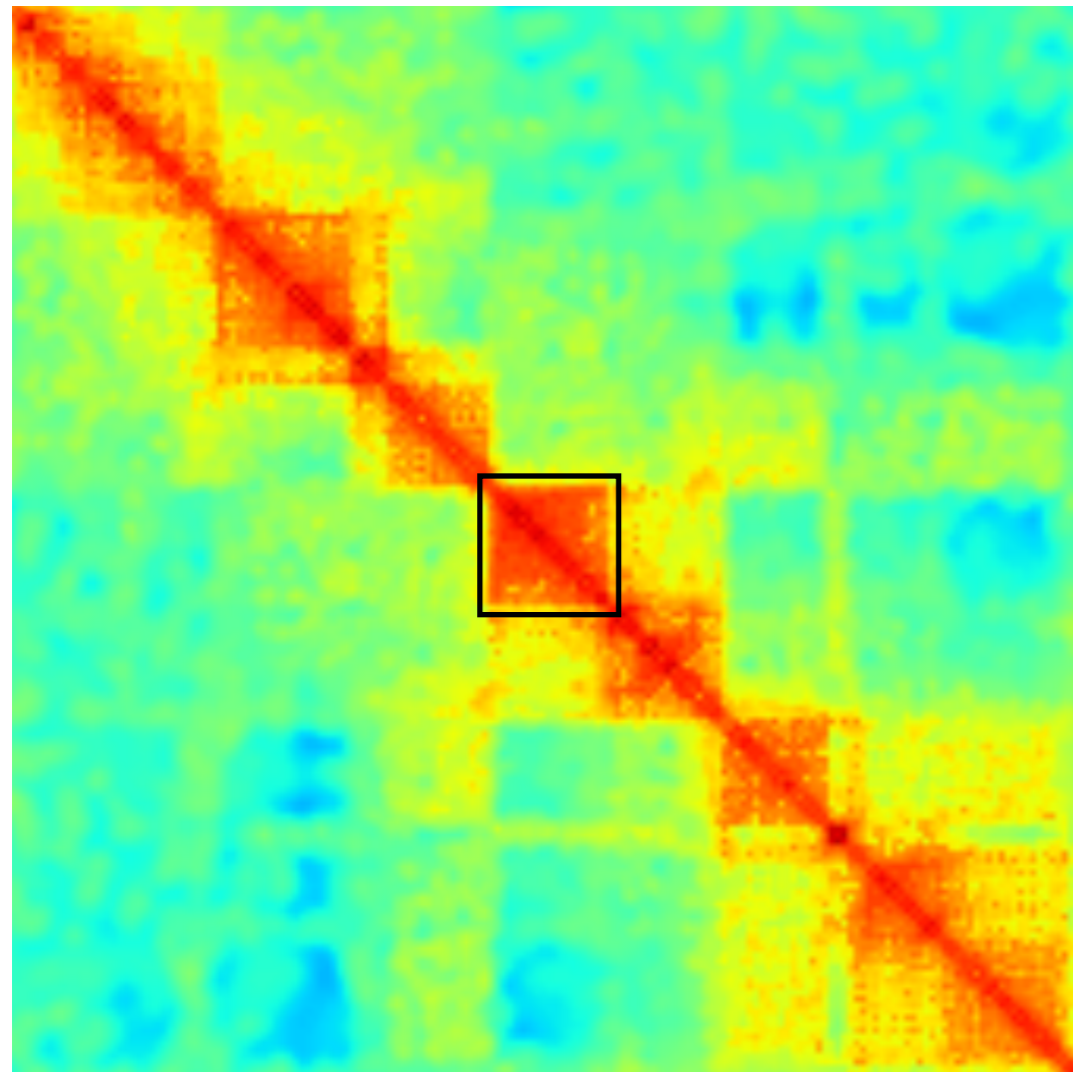Region of chromosome 15

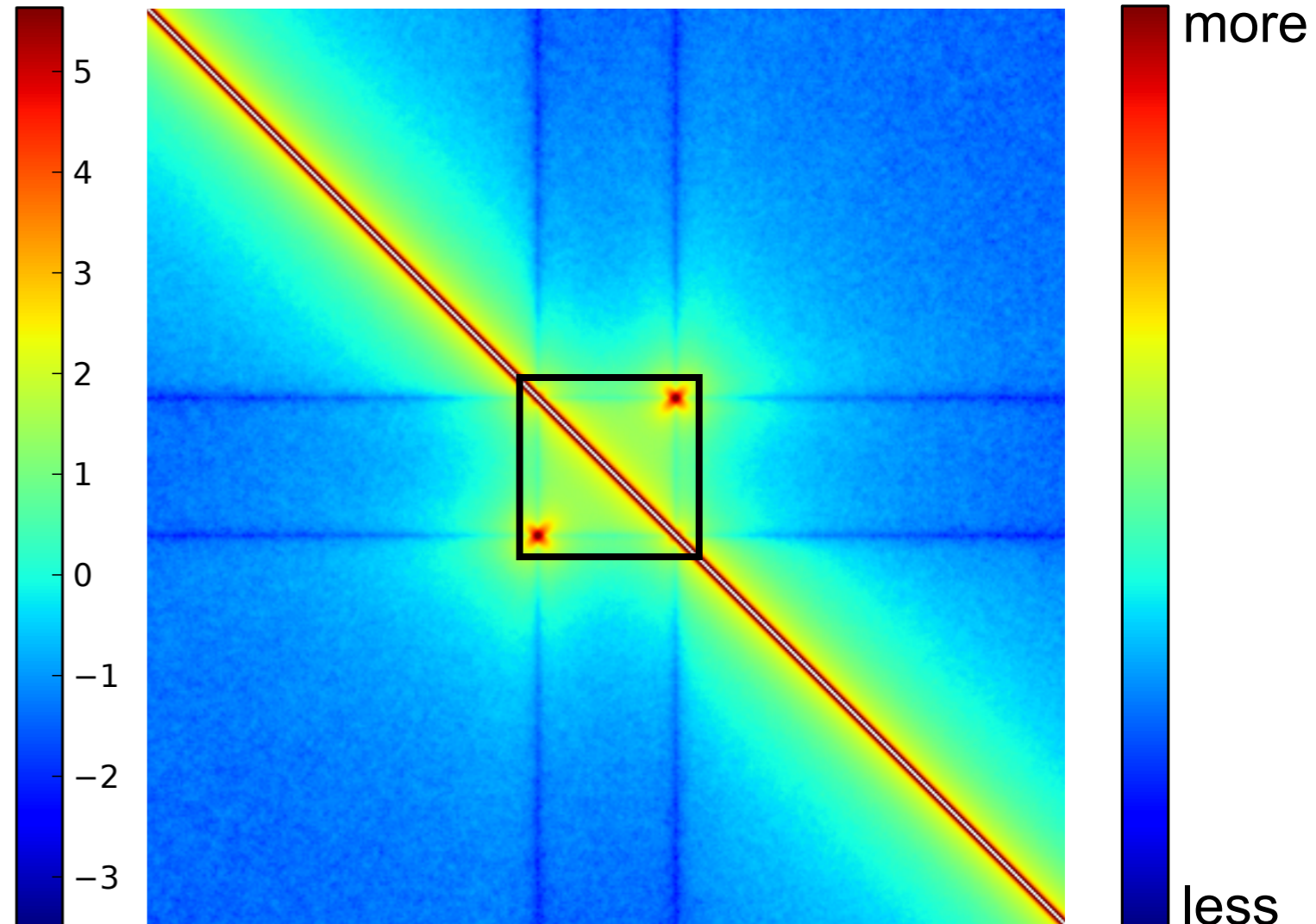Zoom in of chromosome 15

50Mb

6.5Mb

TADs are not single, static loops
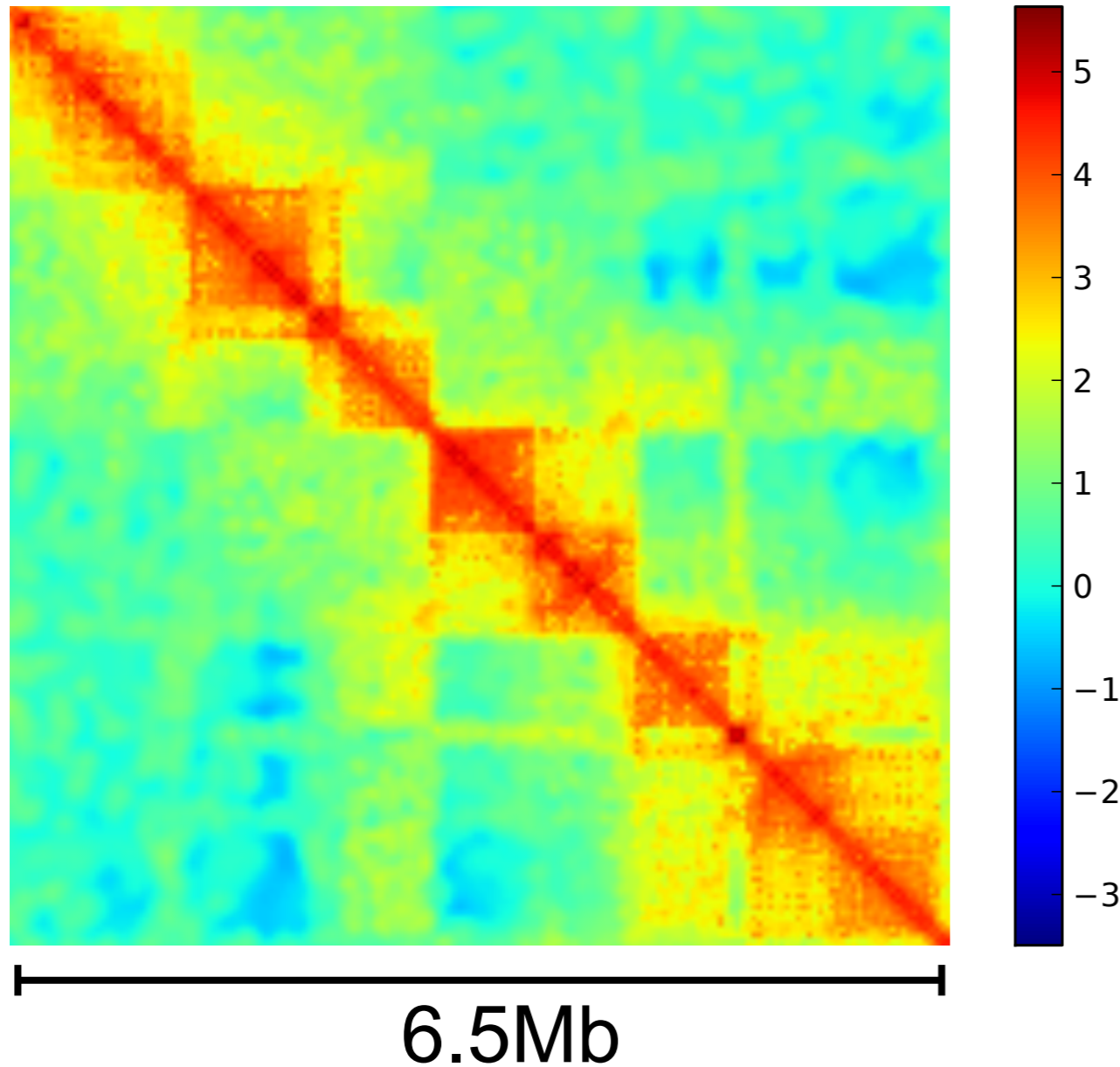
Zoom in of chromosome 15

Simulated polymer with loop

6.5Mb

Before analyzing TADs, we need to find them: Automated TAD detection

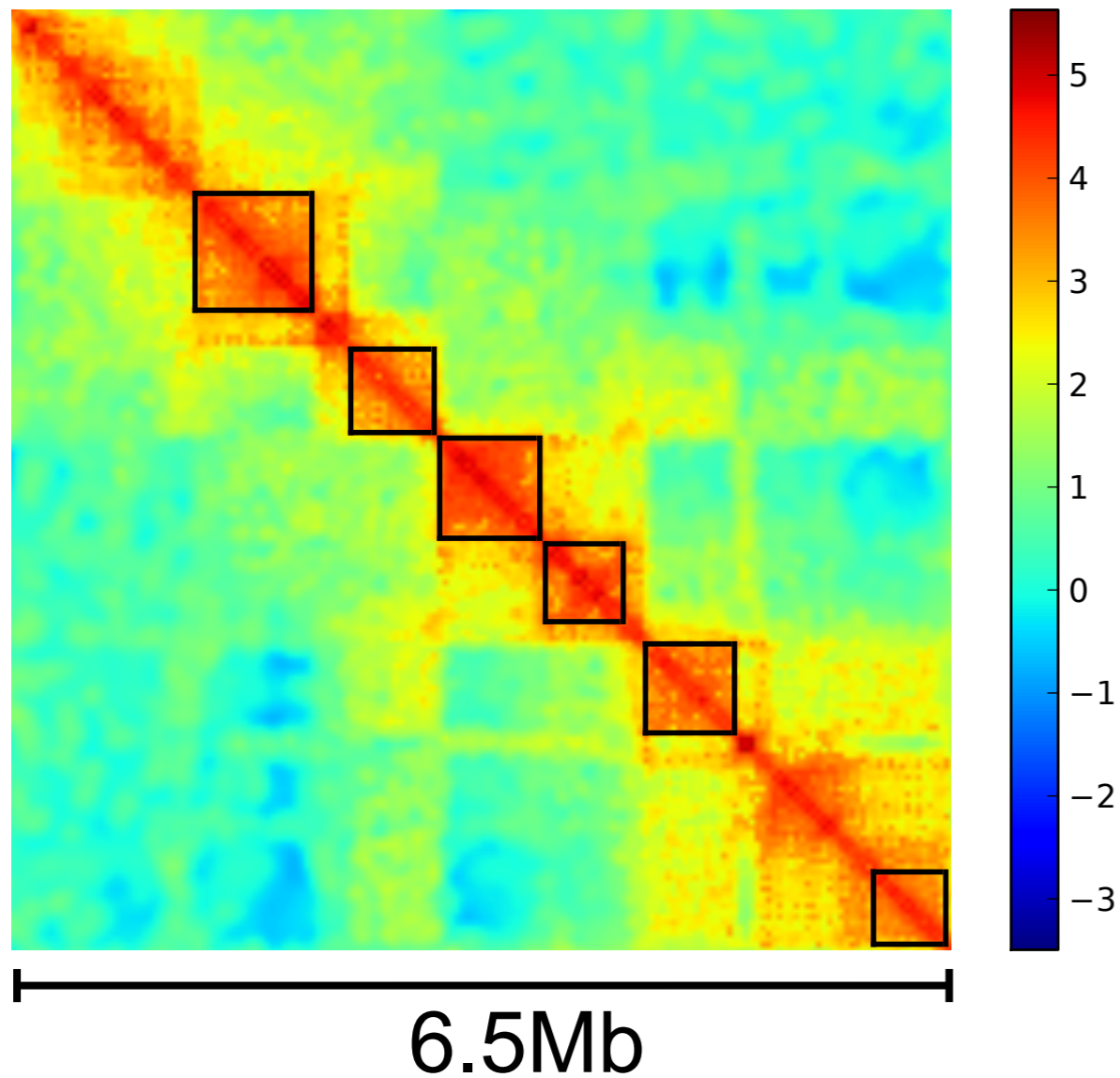Zoom in of chromosome 15

6.5Mb

rather than detecting TAD boundaries, we detect enriched TAD regions.
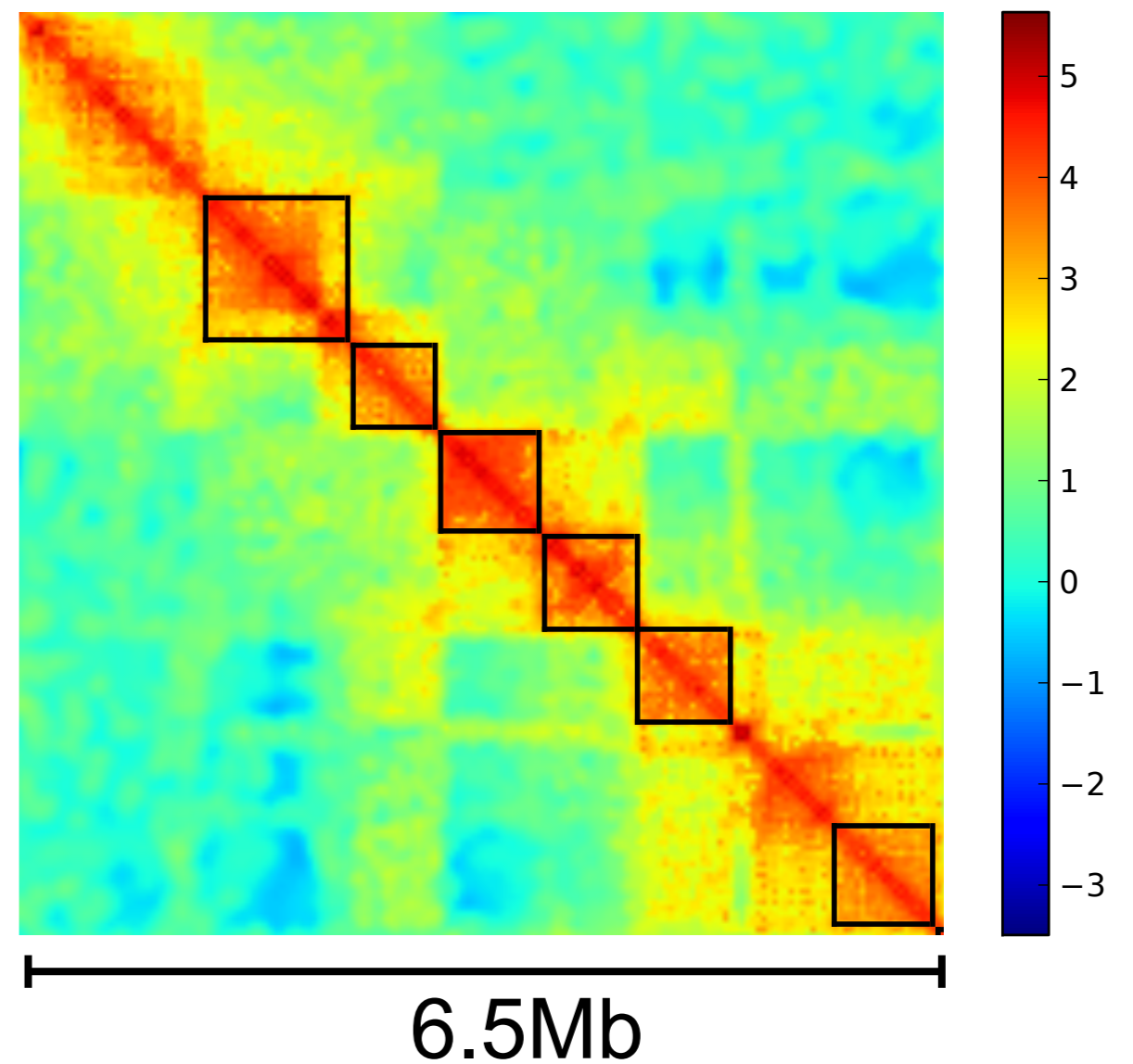
edge detection
    sharp boundaries

enriched mean

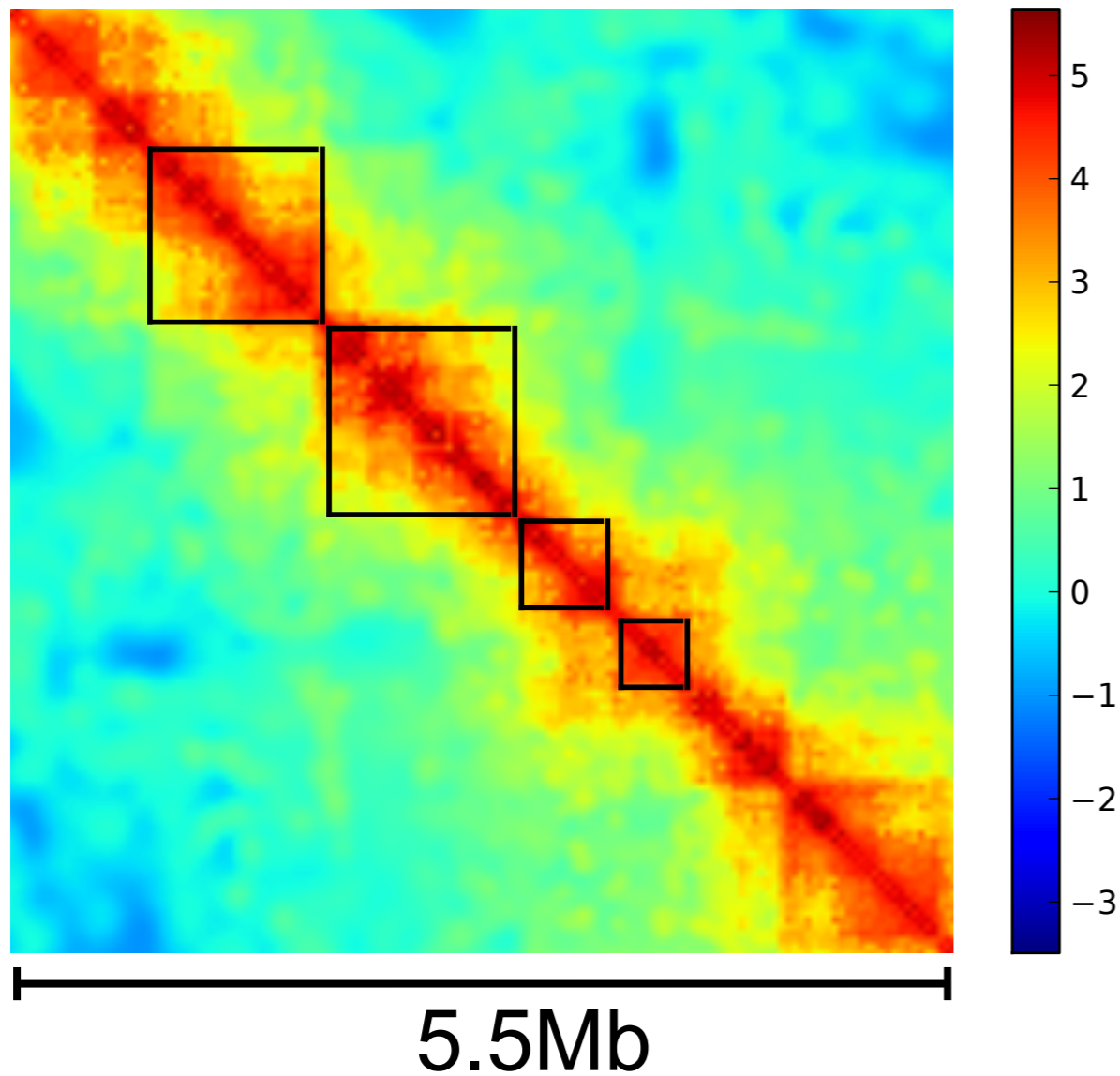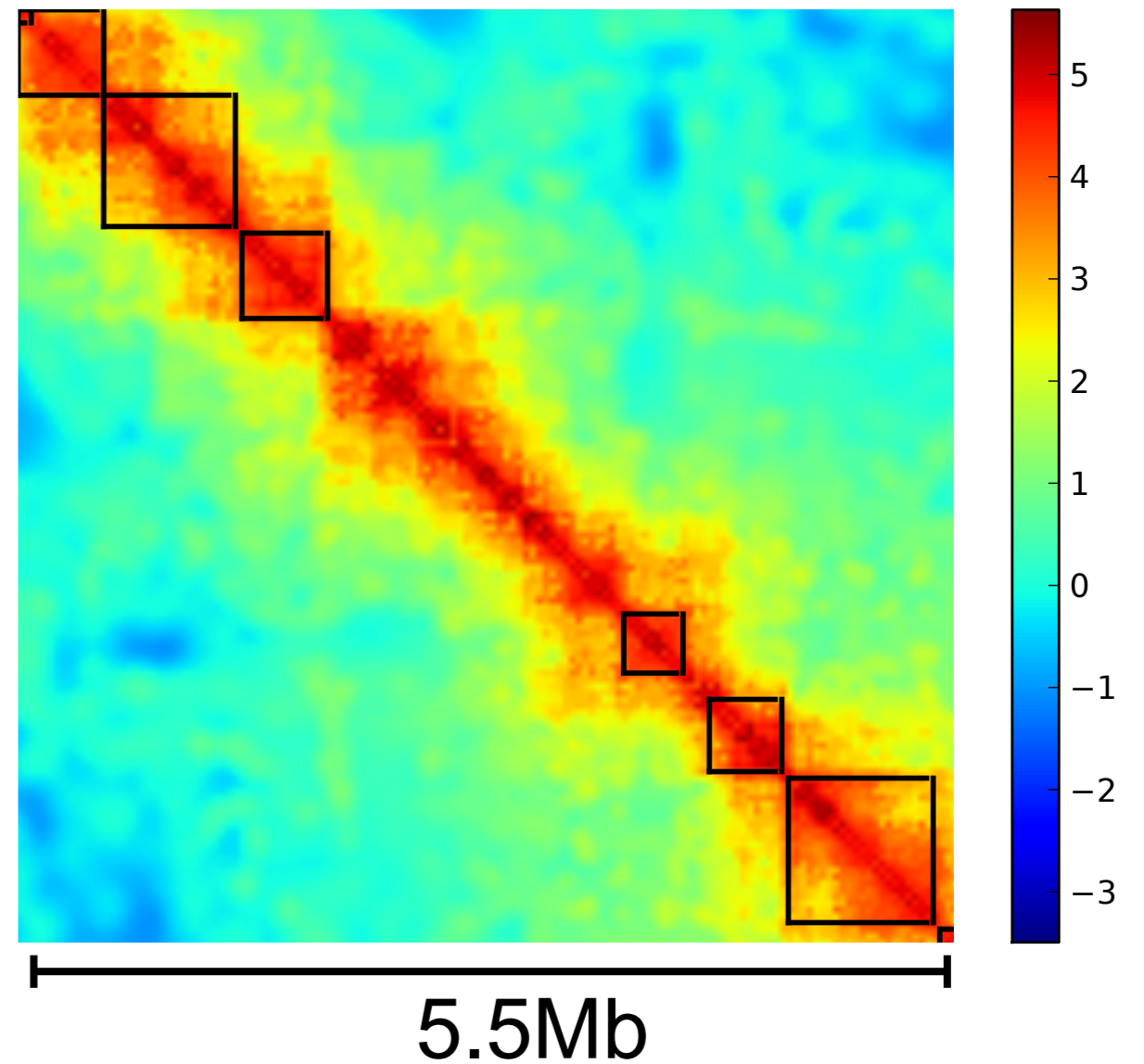# Automated TAD selection vs. manual TAD selection

Automated TAD selection vs. manual TAD selection

Automated

Manual

5.5Mb

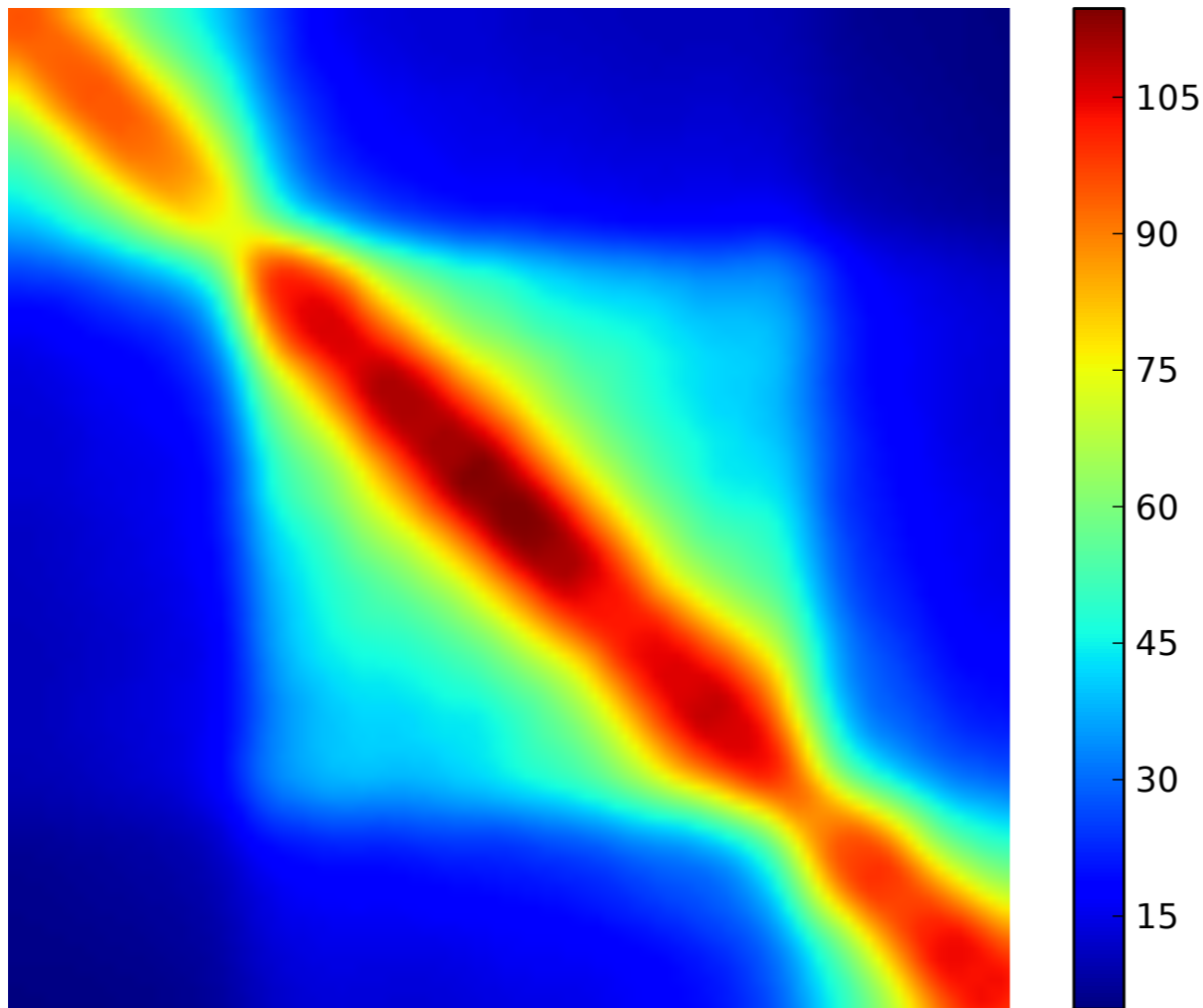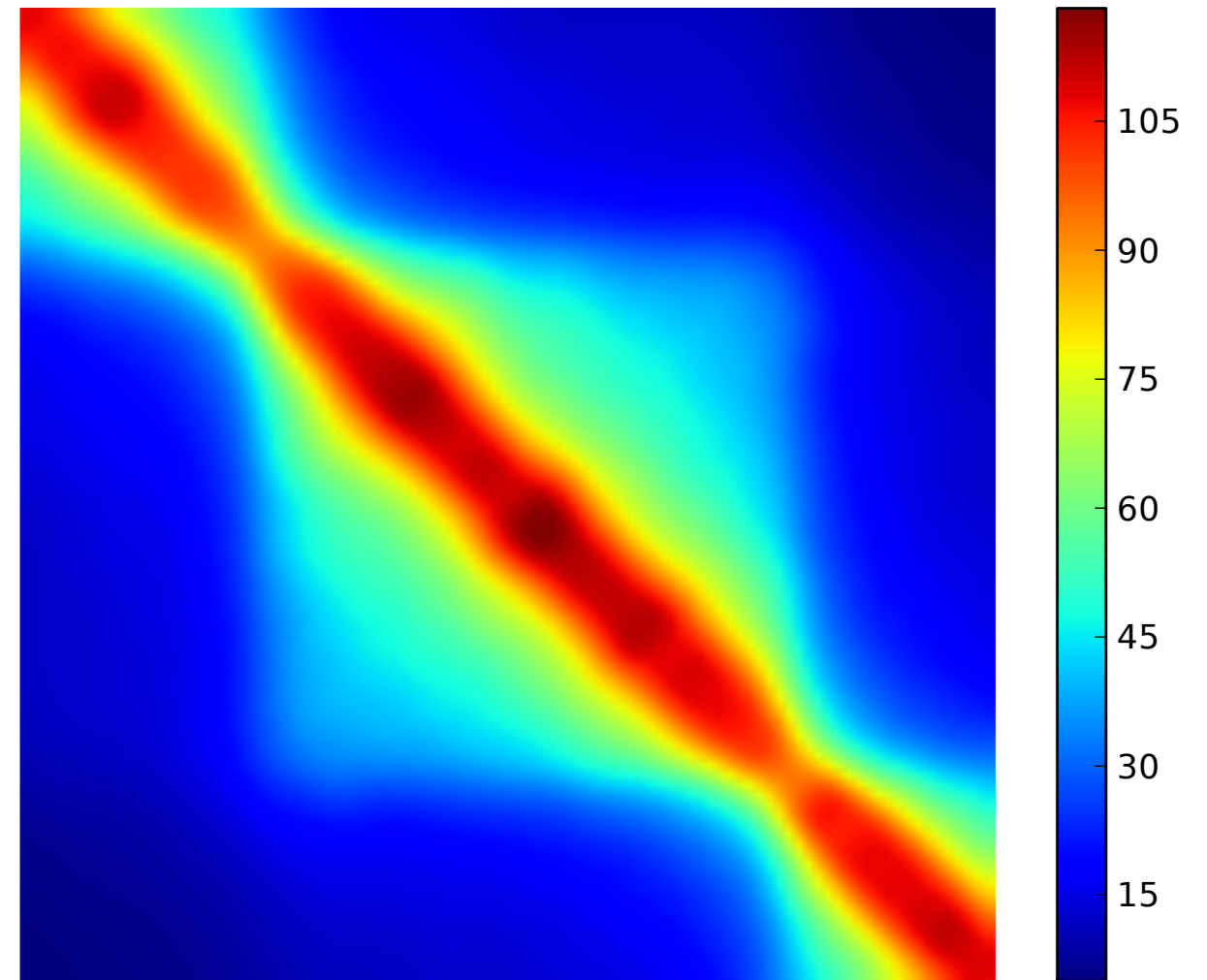5.5Mb

Average TAD for Chromosome 15

Acknowledgements

MIT PRIMES

PRIMES: Program for Research in Mathematics, Engineering and Science for High School Students

In mathematics you don't understand things, you just get used to them.
- John von Neumann

Leonid Mirny lab:
Geoffrey Fudenberg
Maxim Imakaev

Pande lab: OpenMM Molecular dynamics software