Massachusetts Institute of Technology

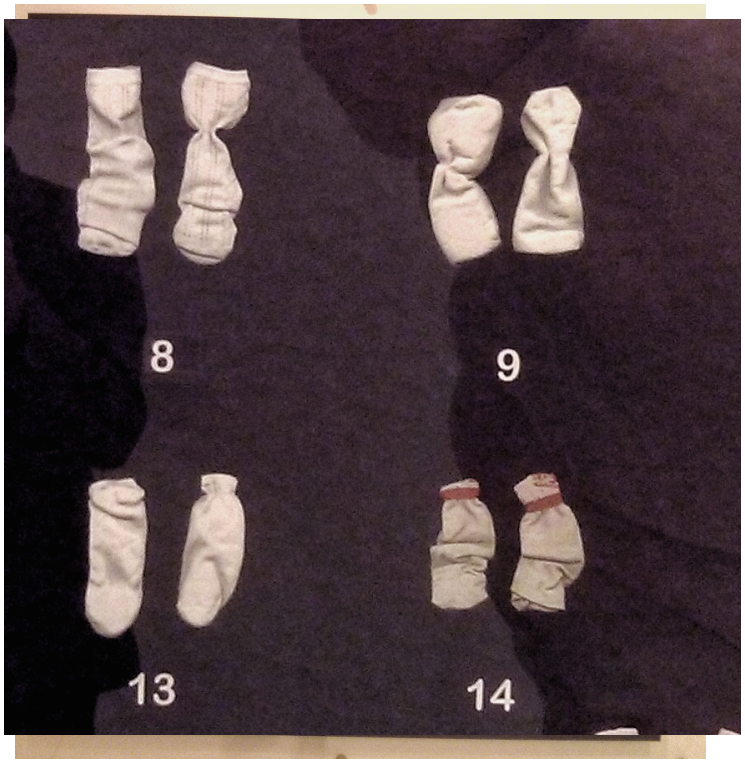
MIT DEPARTMENT OF PHYSICS

imes INSTITUTE FOR MEDICAL ENGINEERING & SCIENCE

Genome in 3D : modeling chromosome organization

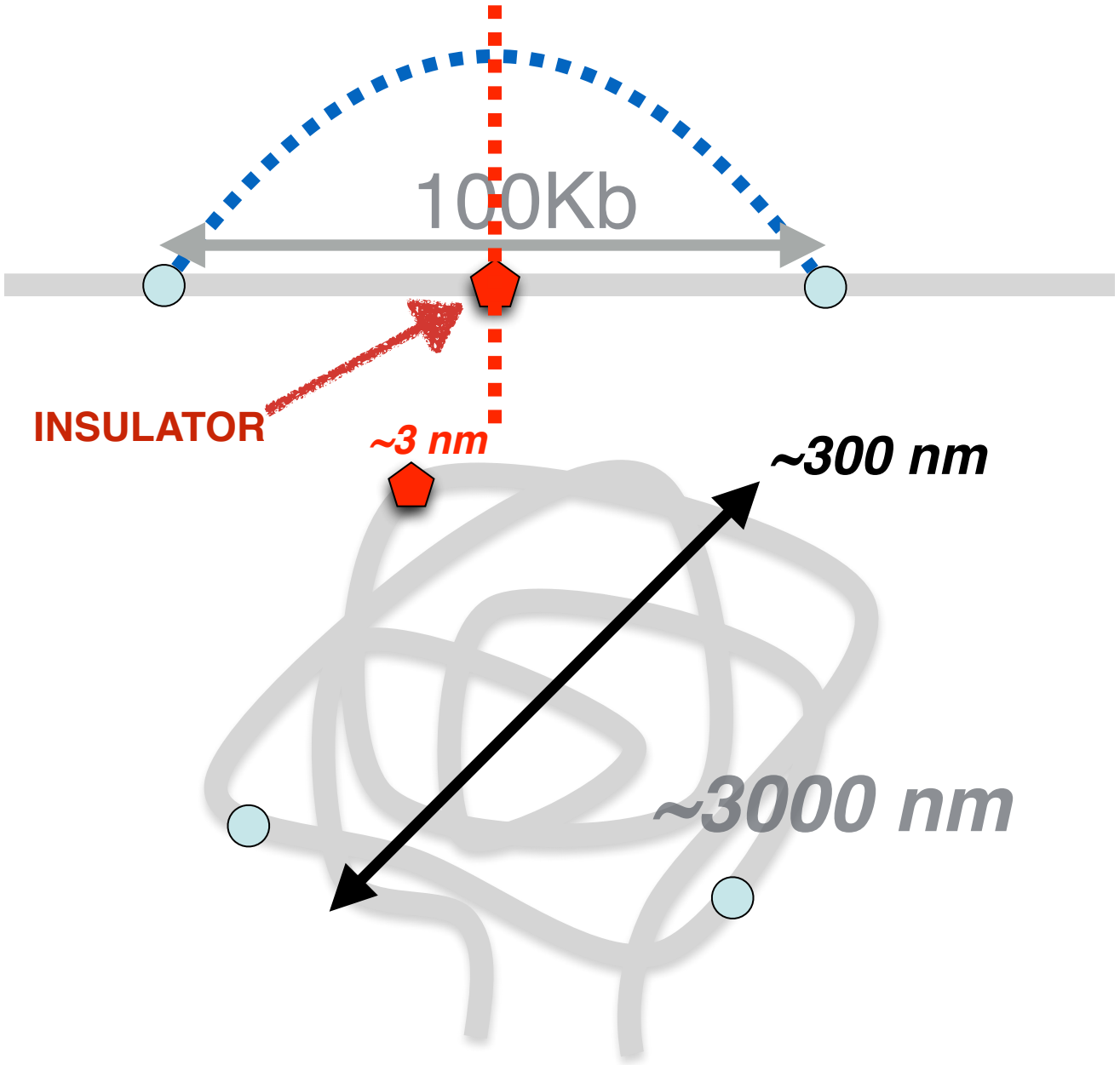
Leonid Mirny

leonid@mit.edu

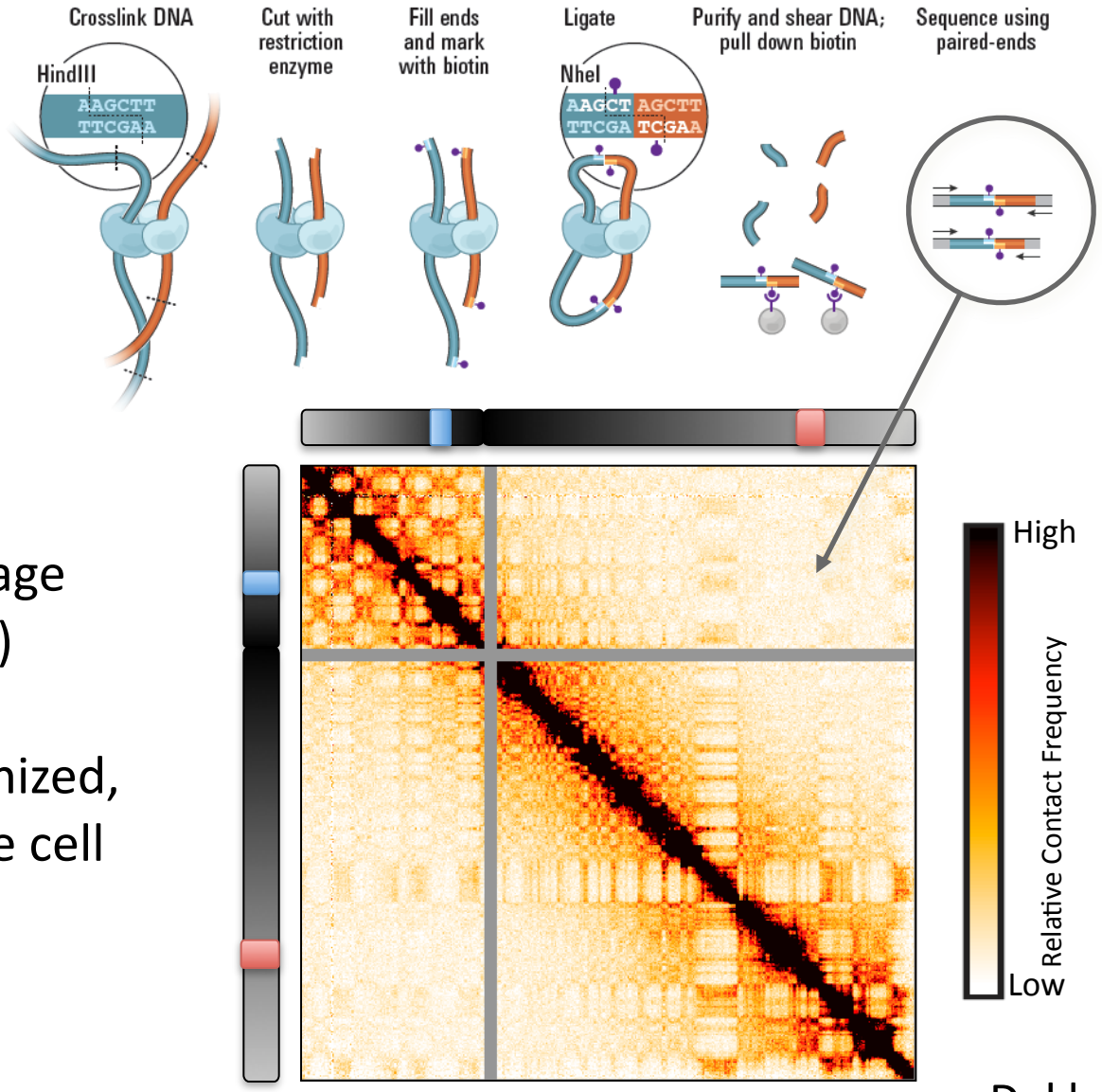


Andrea Duncan (2002)
Wellcome Collection, London

PROBLEM 1: how can a small protein control long-range interactions?



Chromosome Conformation Capture (Hi-C)

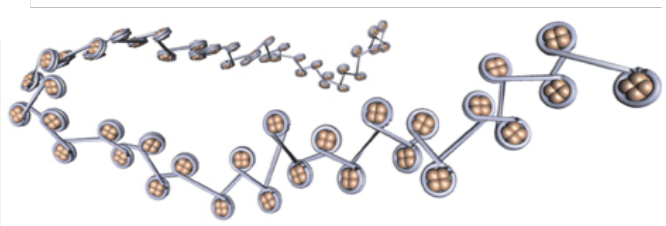


- ensemble average (over 10^7 cells)

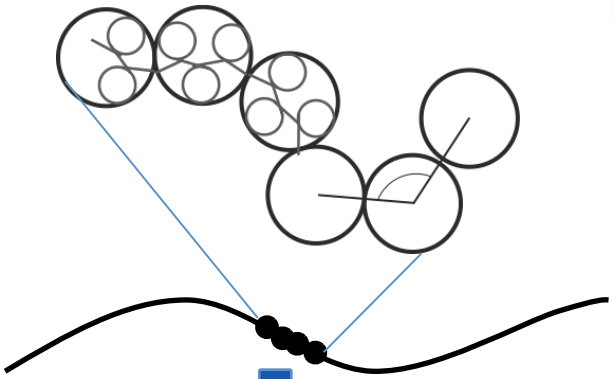
- unless synchronized, averages over the cell cycle as well!

Dekker *et al.* Science 2002
Lieberman-Aiden & van Berkum *et al.* Science 2009

Occam's razor approach

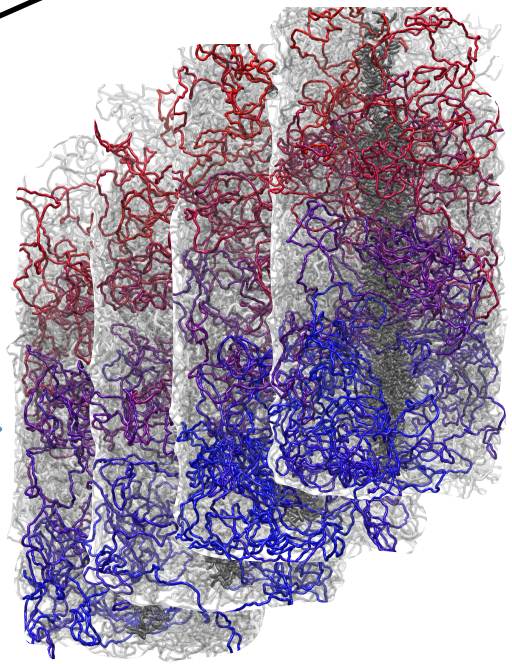


USE PRIOR BIOLOGICAL KNOWLEDGE



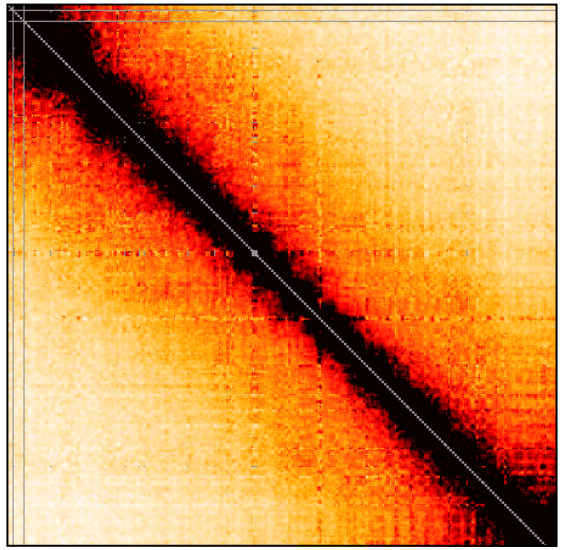
ensemble of conformations

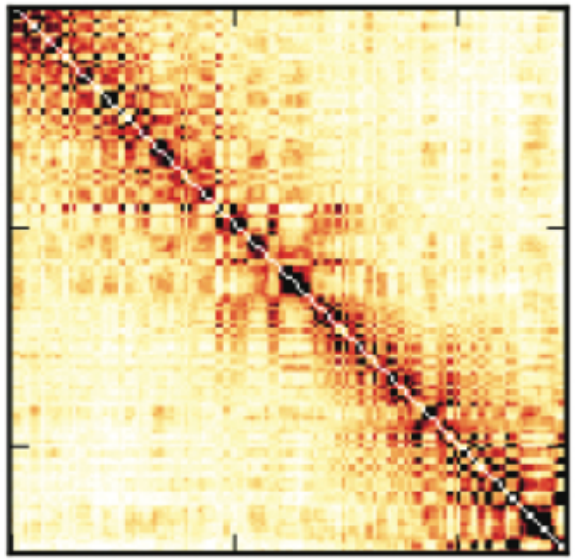
Model-specific constraints



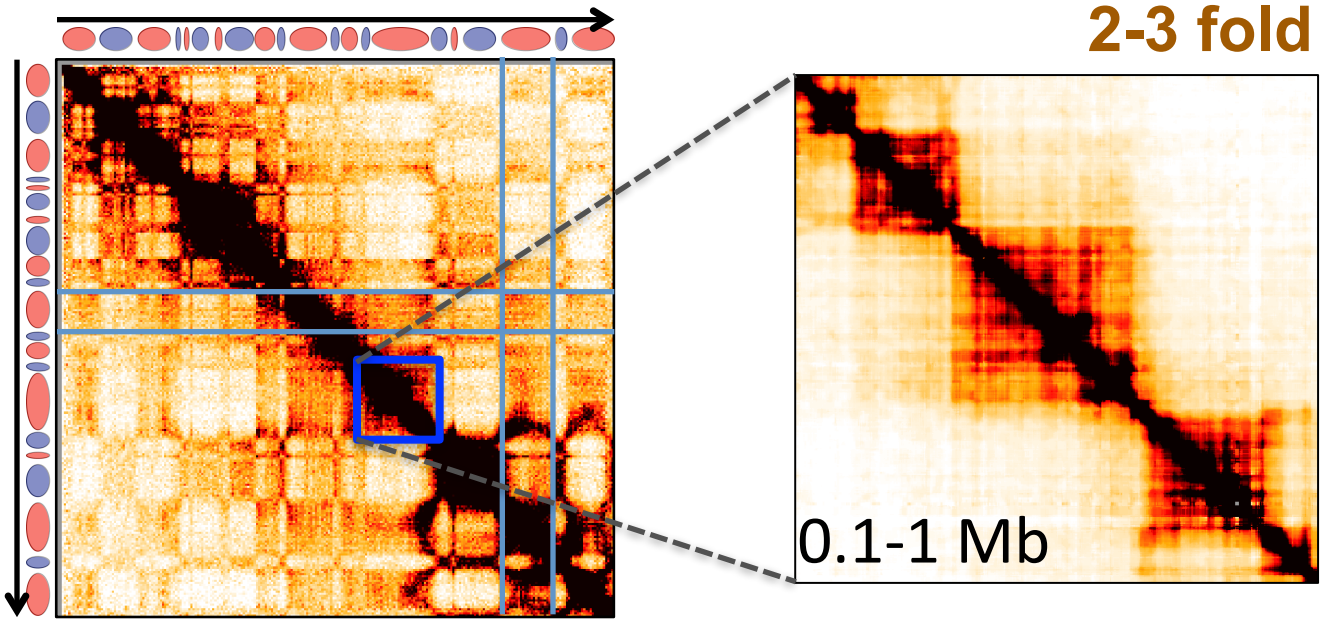
simulate Hi-C experiment

Hi-C data



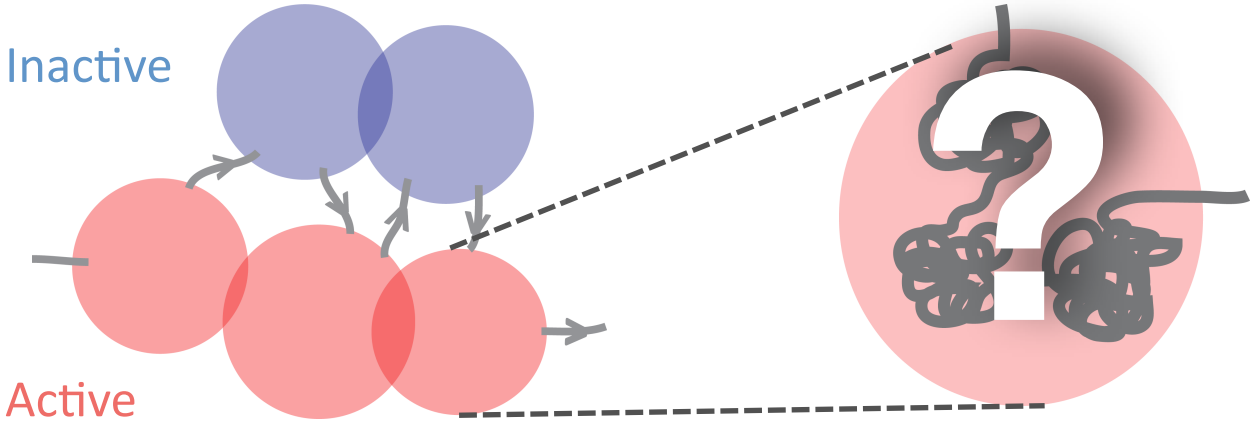


Smaller domains within compartments



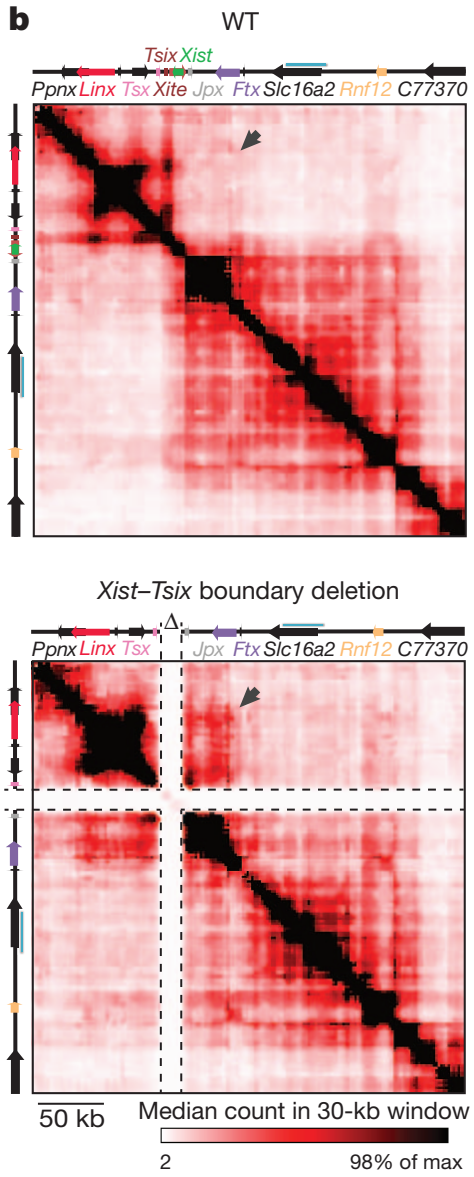
A/B Compartments

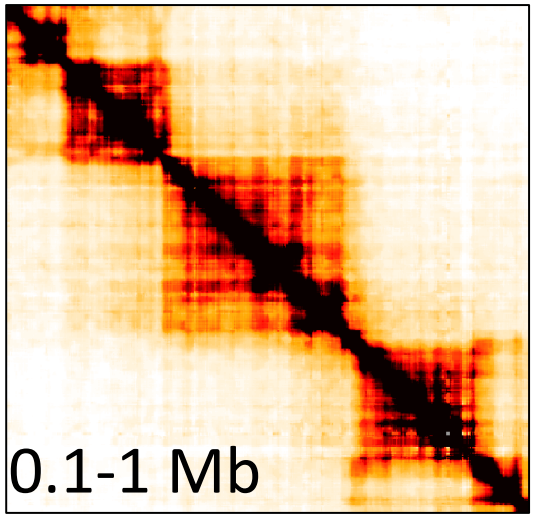
Topological Association Domains (TADs)



Nora et al. Nature 2012; Dixon et al Nature 2012

Domains boundaries are essential for domain formation





Teunissen, H., Splinter, E., Wijchers, P.J., Krijger, P.H., and de Laat, W. (2015). CTCF Binding Polarity Determines Chromatin Looping. Mol Cell *60*, 676-684.

Narendra V, et al. (2015) CTCF establishes discrete functional chromatin domains at the Hox clusters during differentiation. *Science (New York, NY)* 347(6225):1017–1021.

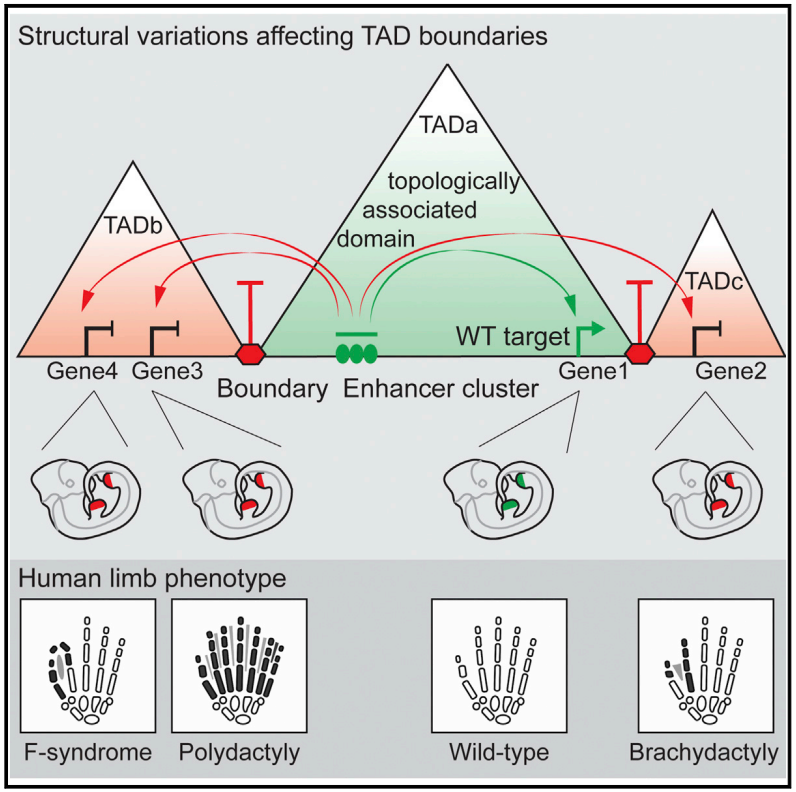
Guo Y, et al. (2015) CRISPR Inversion of CTCF Sites Alters Genome Topology and Enhancer/Promoter Function. *Cell* 162(4):900–910.

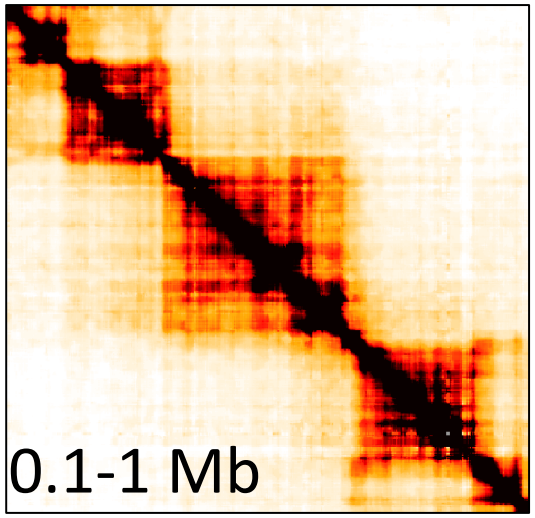
Sanborn AL, et al. (2015) Chromatin extrusion explains key features of loop and domain formation in wild-type and engineered genomes. *Proceedings of the National Academy of Sciences* 112(47):E6456–65.

17 MAY 2012 | VOL 485 | NATURE |

Elphège P. Nora[1,2,3], Bryan R. Lajoie[4]*, Edda G. Schulz[1,2,3]*, Luca Giorgetti[1,2,3]*, Ikuhiro Okamoto[1,2,3], Nicolas Servant[1,5,6], Tristan Piolot[1,2,3], Nynke L. van Berkum[4], Johannes Meisig[7], John Sedat[8], Joost Gribnau[9], Emmanuel Barillot[1,5,6], Nils Blüthgen[7], Job Dekker[4] & Edith Heard[1,2,3]

Domains boundaries controls functional interactions



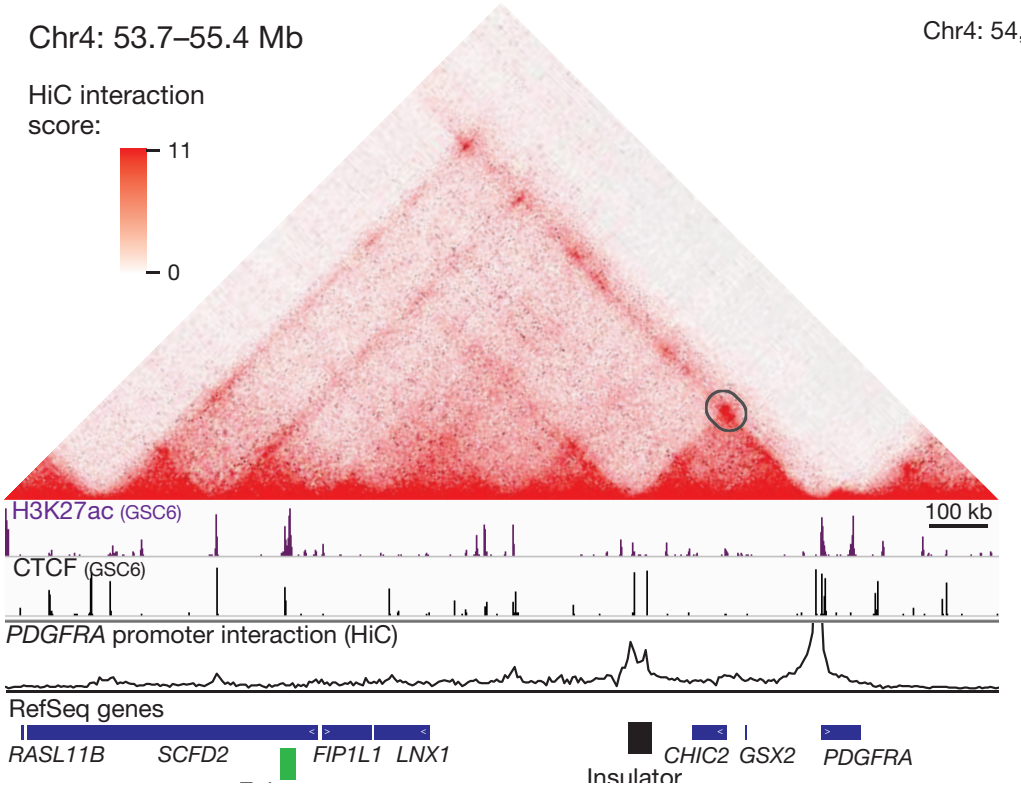


Disruptions of Topological Chromatin Domains Cause Pathogenic Rewiring of Gene-Enhancer Interactions

Darío G. Lupiáñez,[1,2] Katerina Kraft,[1,2] Verena Heinrich,[2] Peter Krawitz,[1,2] Francesco Brancati,[3] Eva Klopocki,[4] Denise Horn,[2] Hülya Kayserili,[5] John M. Opitz,[6] Renata Laxova,[6] Fernando Santos-Simarro,[7,8] Brigitte Gilbert-Dussardier,[9] Lars Wittler,[10] Marina Borschiwer,[1] Stefan A. Haas,[11] Marco Osterwalder,[12] Martin Franke,[1,2] Bernd Timmermann,[13] Jochen Hecht,[1,14] Malte Spielmann,[1,2,14] Axel Visel,[12,15,16] and Stefan Mundlos[1,2,14,*]

Lupiáñez et al., 2015, Cell *161*, 1–14
May 21, 2015
http://dx.doi.org/10.1016/j.cell.2015.04.004

Domains of controls functional interactions in cancer



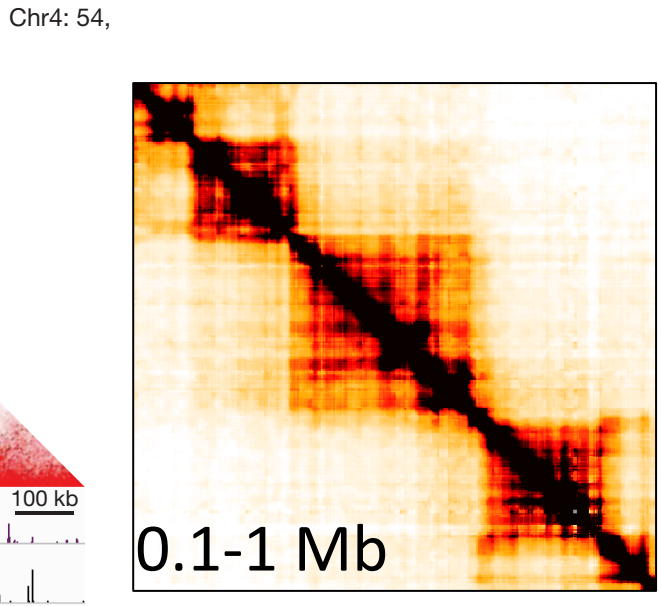
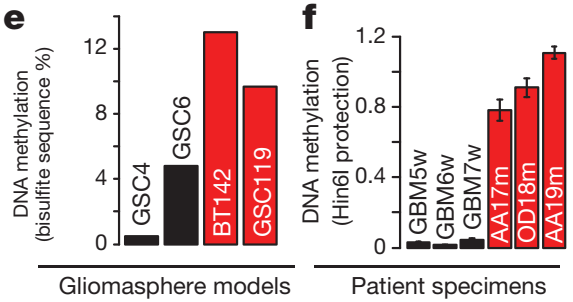


Figure 3 | Insulator loss allows *PDGFRA* to interact with a constitutive enhancer. a, Contact domain structure shown for a 1.7-Mb region



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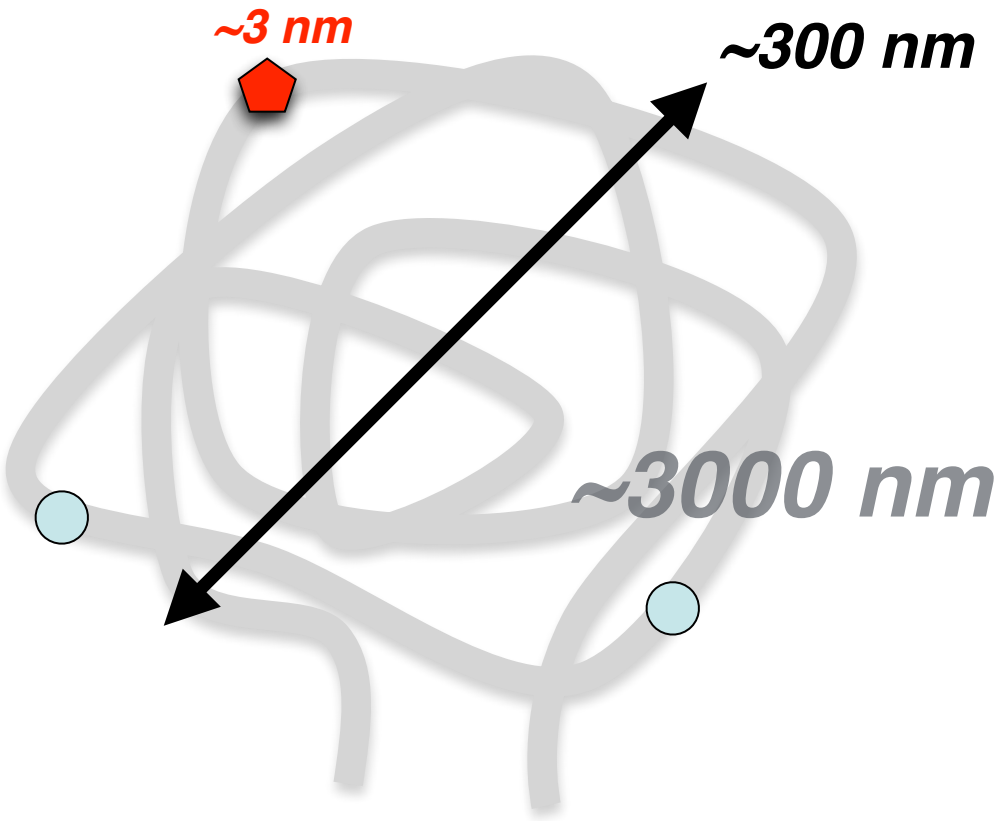
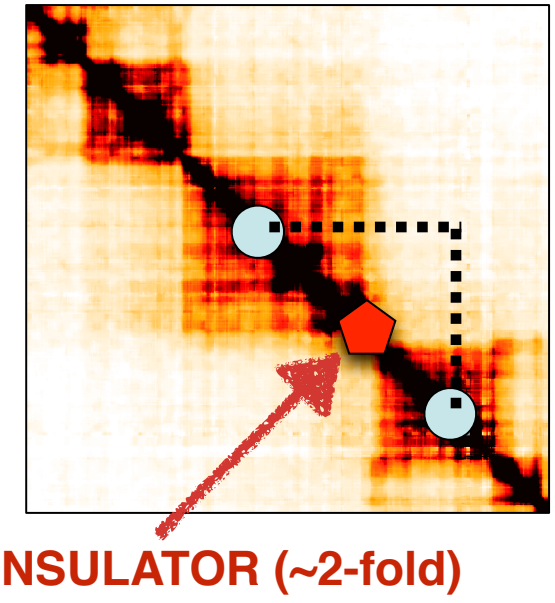
Insulator dysfunction and oncogene activation in *IDH* mutant gliomas

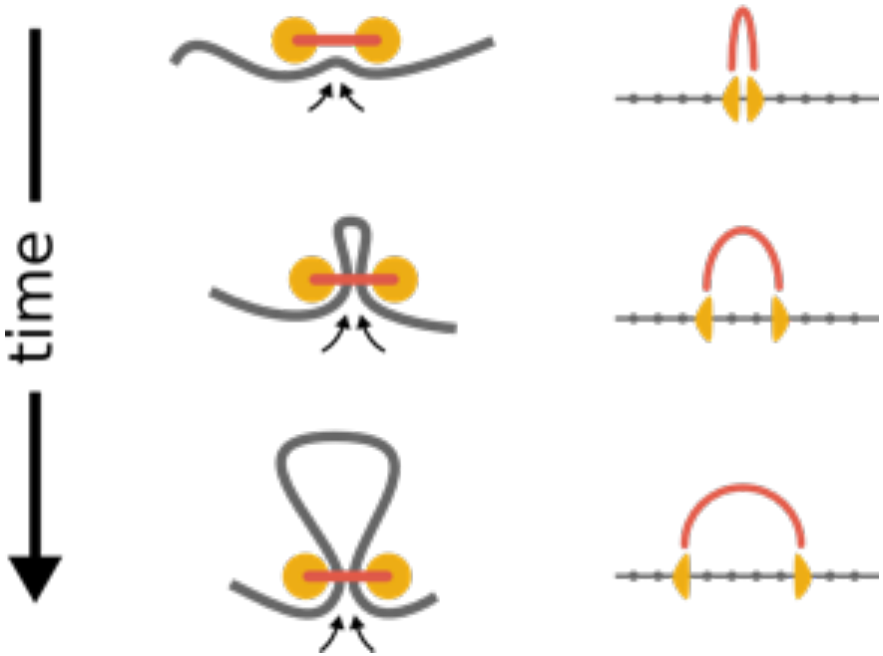
William A. Flavahan[1,2,3]*, Yotam Drier[1,2,3]*, Brian B. Liau[1,2,3], Shawn M. Gillespie[1,2,3], Andrew S. Venteicher[1,2,4], Anat O. Stemmer-Rachamimov[1], Mario L. Suvà[1,2] & Bradley E. Bernstein[1,2,3]

What mechanism can lead to domain formation?





Mechanism of loop extrusion



Formation of Chromosomal Domains by Loop Extrusion
bioRxiv Aug 14 (2015)
Fudenberg, Imakaev et al.
DOI: 10.1101/024620

bioRxiv beta
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Loop extrusion proposed for chromosome condensation

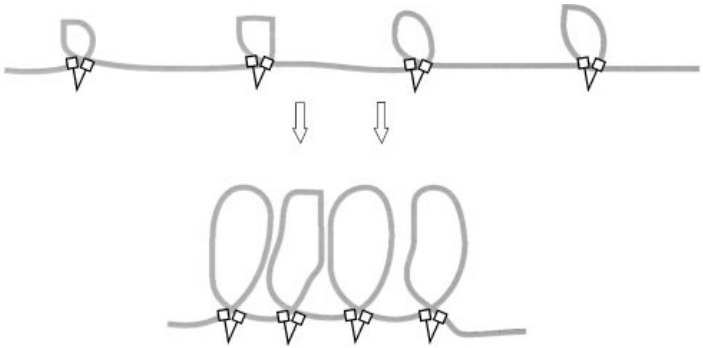
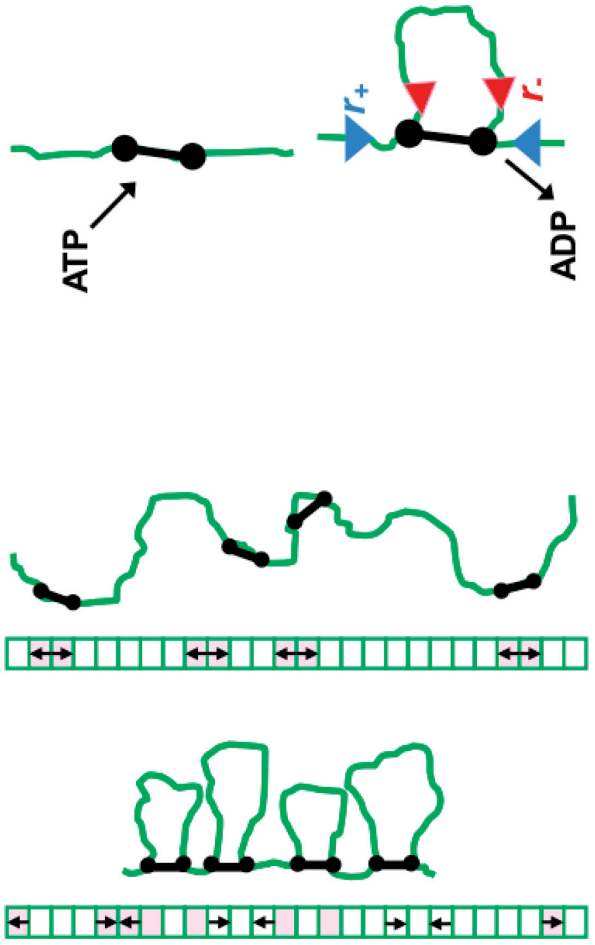


Figure 5 A model for how condensin could form axial cores and thereby help to resolve sister chromatids from each other.

DISSEMINATING THE GENOME: Joining, Resolving, and Separating Sister Chromatids During Mitosis and Meiosis

Kim Nasmyth Annu. Rev. Genet. 2001. 35:673–745

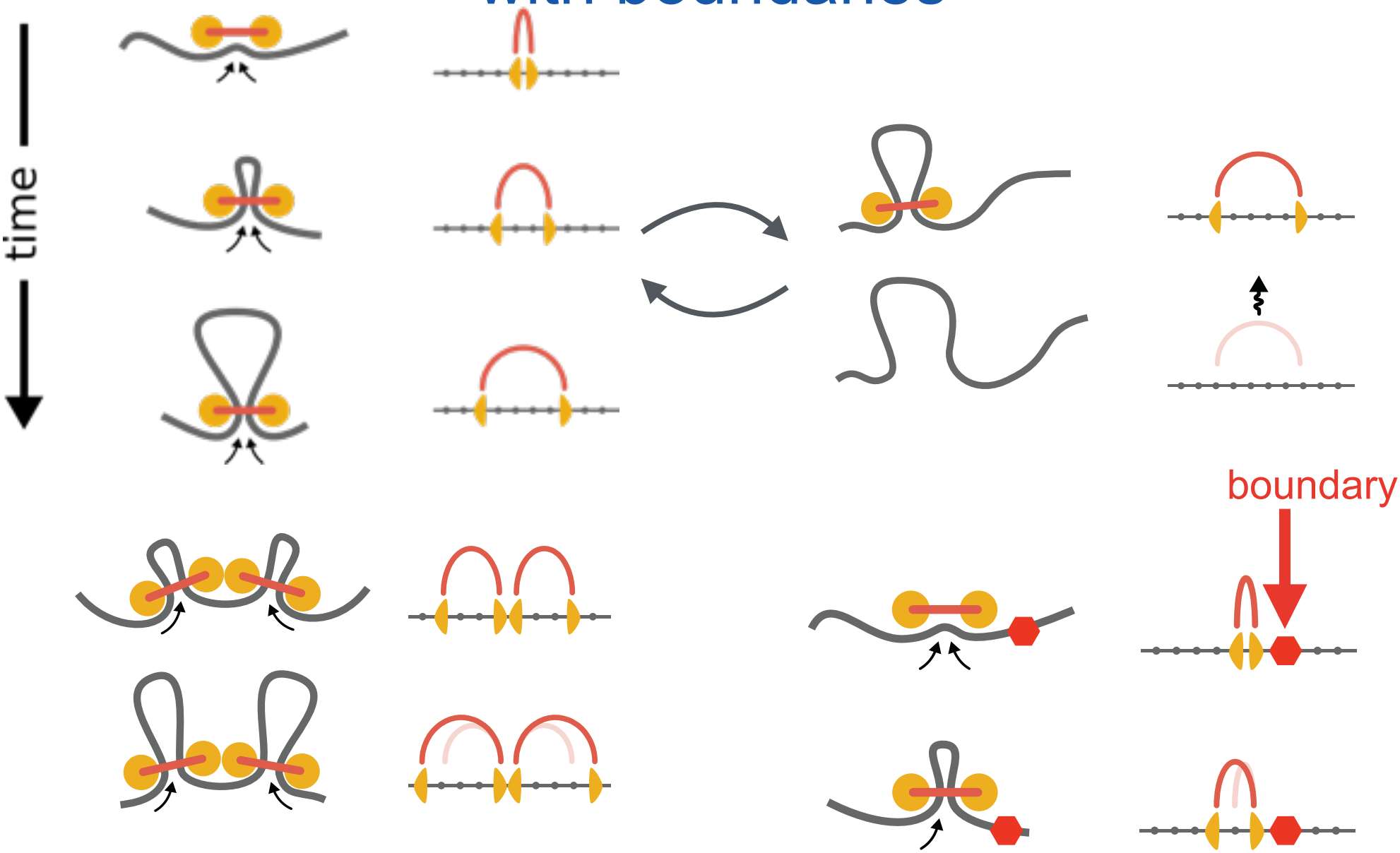


Nucleic Acids Research, 2012, 1–11
doi:10.1093/nar/gks925

Self-organization of domain structures by DNA-loop-extruding enzymes

Elnaz Alipour[1,*] and John F. Marko[2,*]

Loop extrusion during interphase and with boundaries



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doi:10.1093/nar/gks925

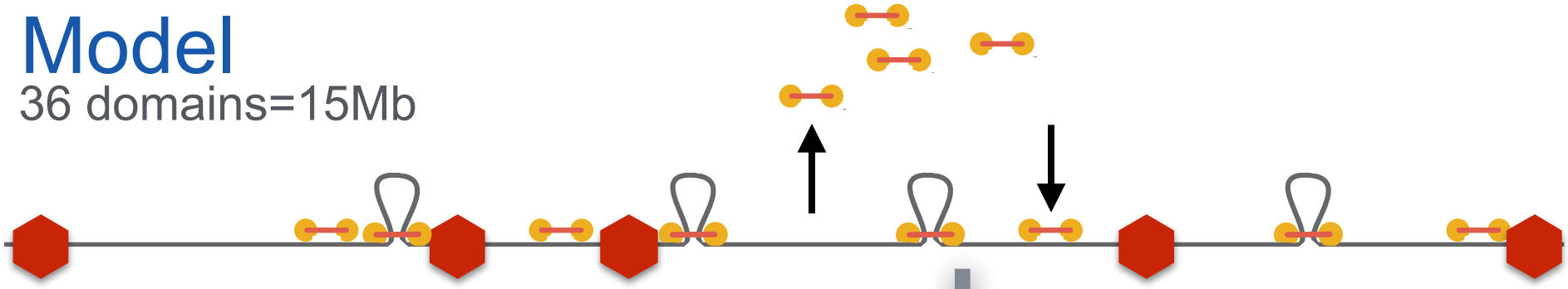
Self-organization of domain structures by DNA-loop-extruding enzymes

Elnaz Alipour[1,*] and John F. Marko[2,*]

Loop extrusion + polymer model

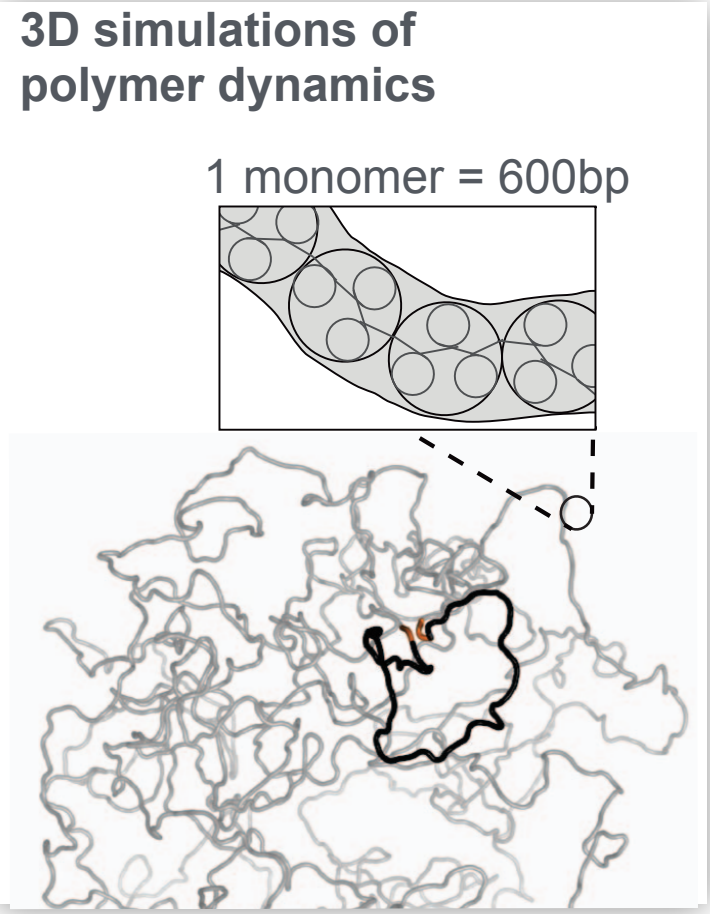
Model

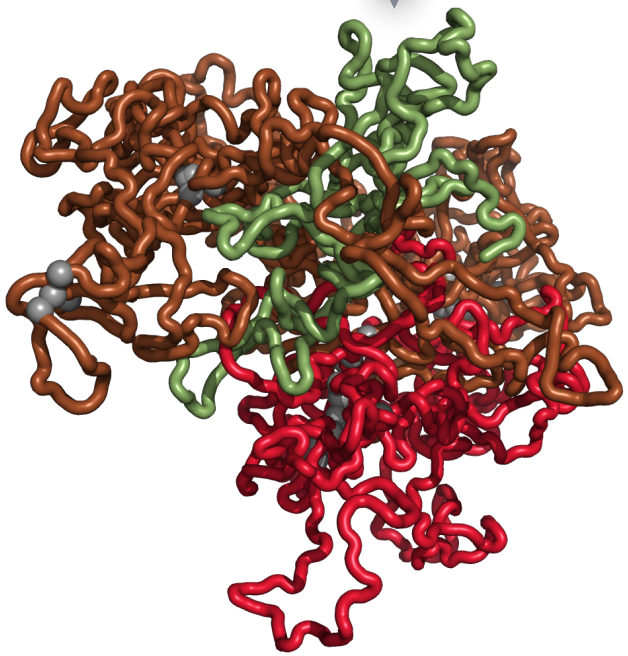
36 domains=15Mb



3D simulations of polymer dynamics

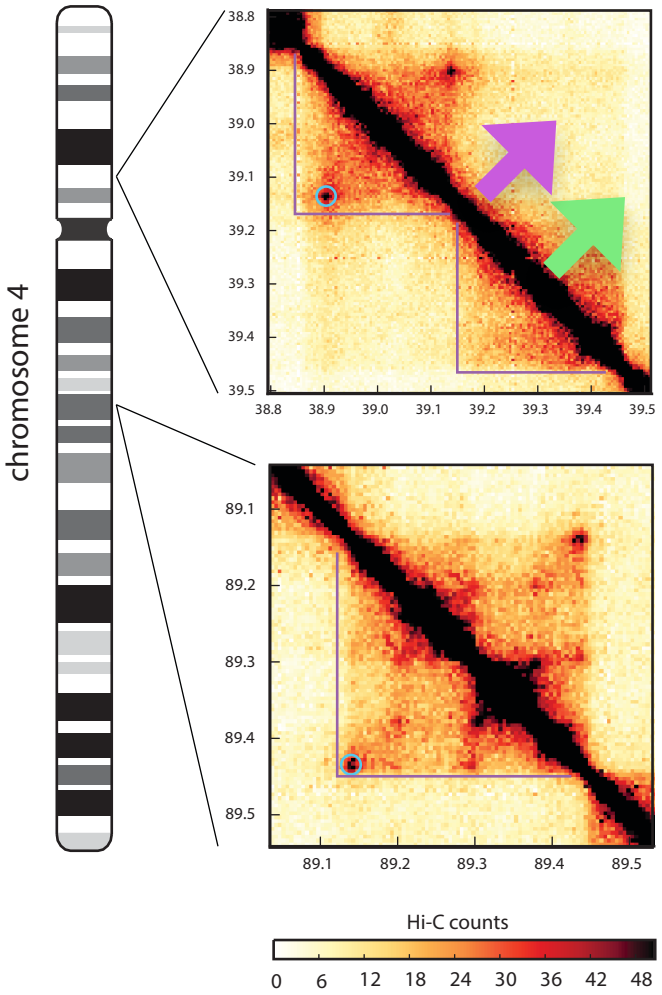
1 monomer = 600bp

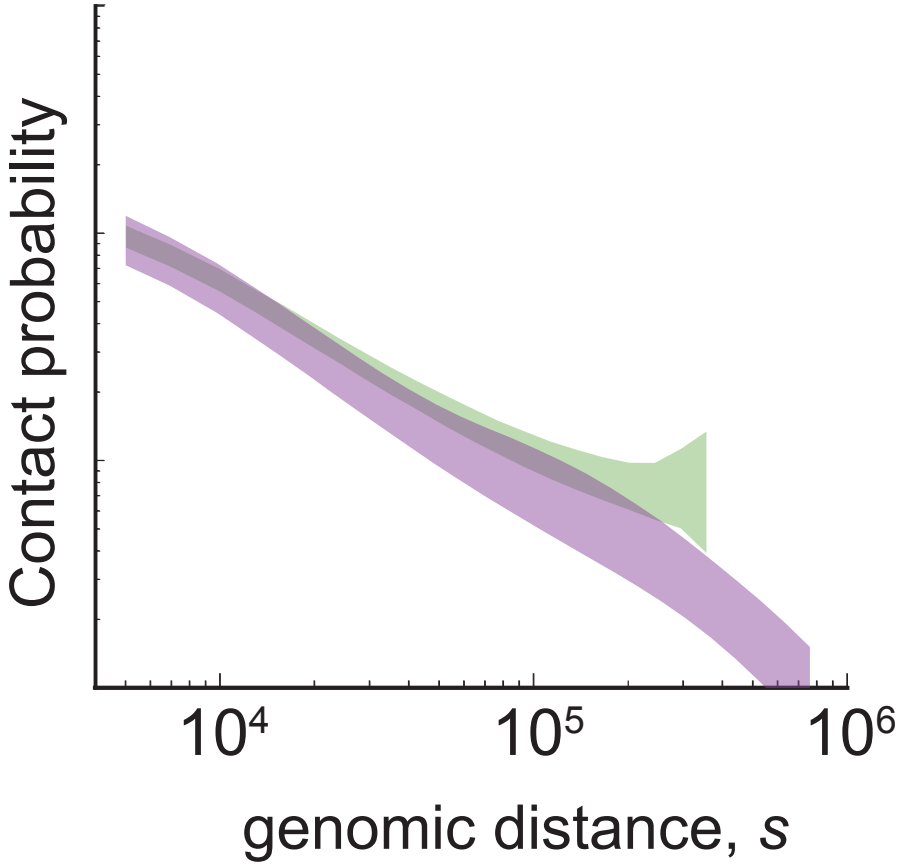




30,000 monomers

Quantitative characteristics

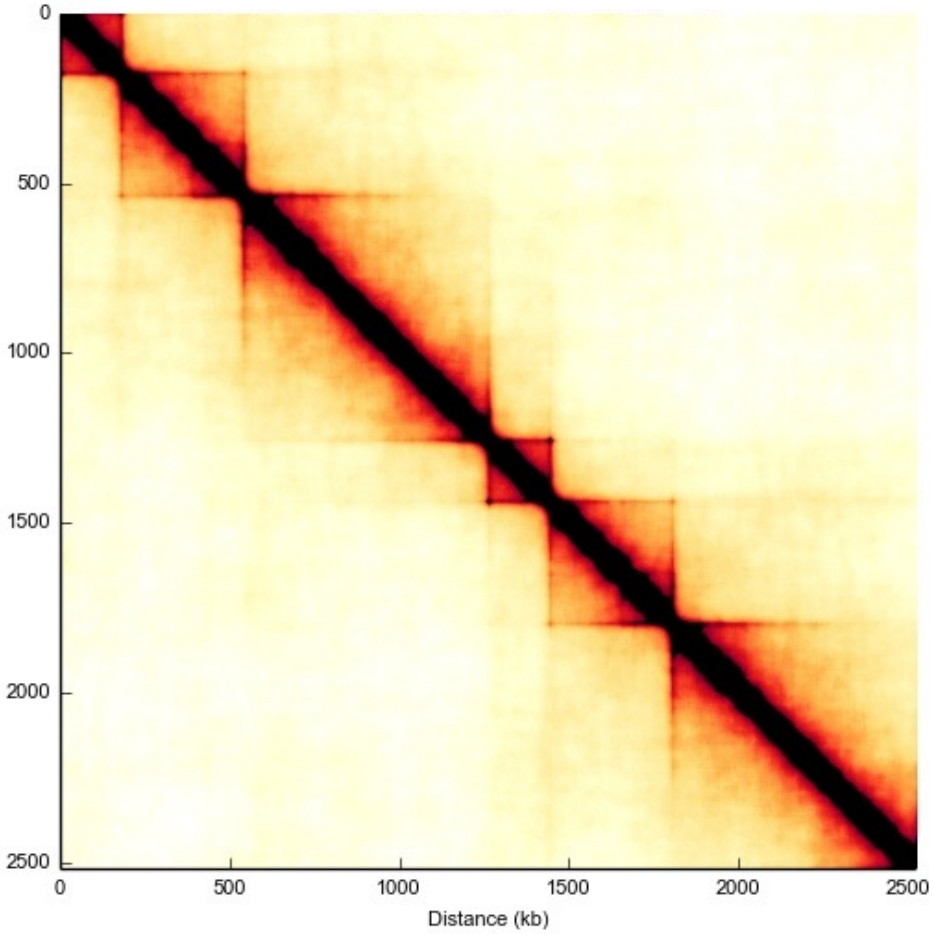


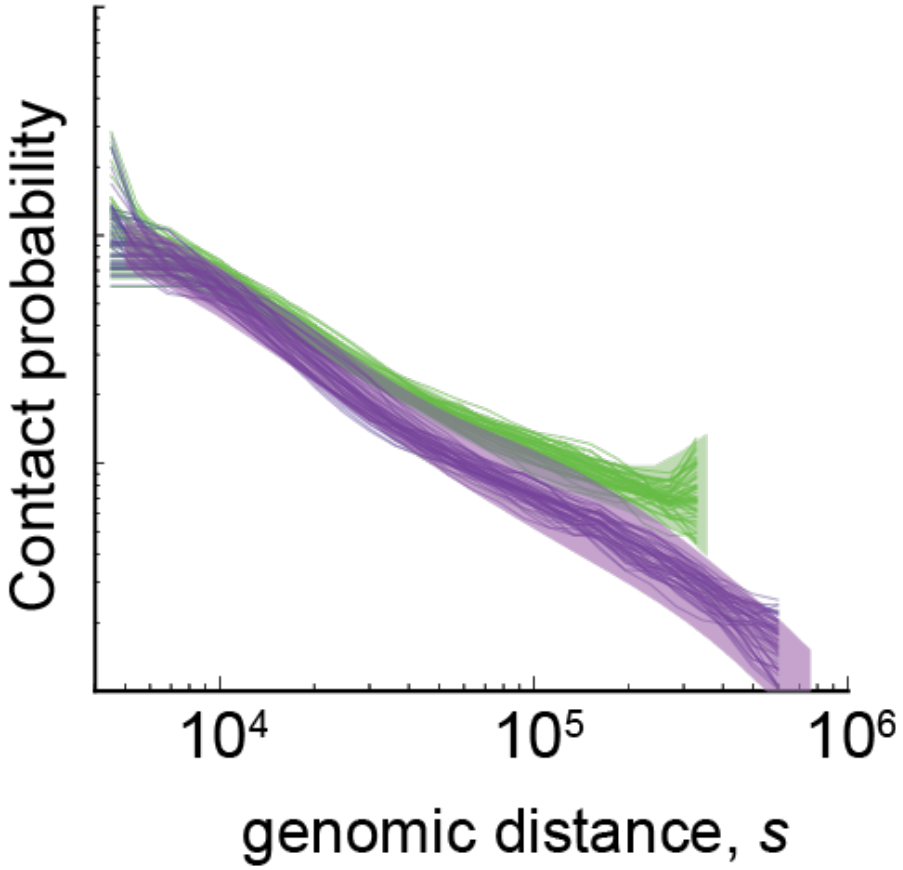


data: GM12878 Rao et.al *Cell* 2014

Loop extrusion can lead to enriched interactions between boundaries

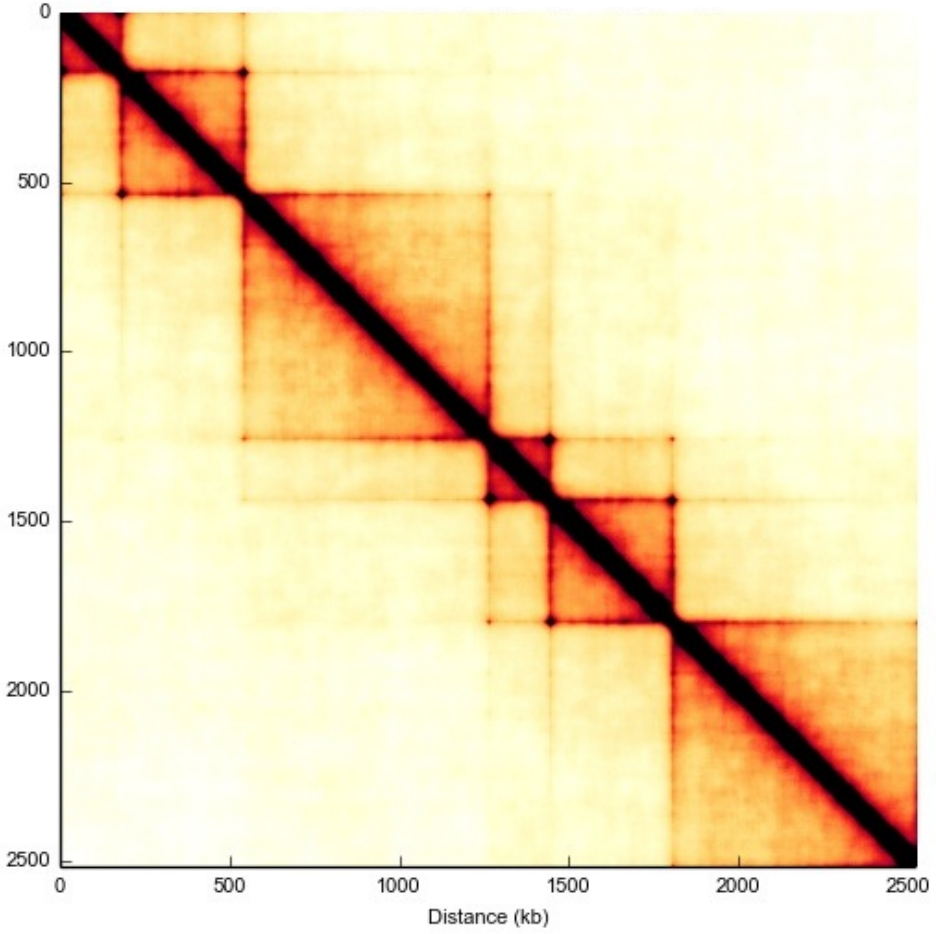
processivity = 100Kb

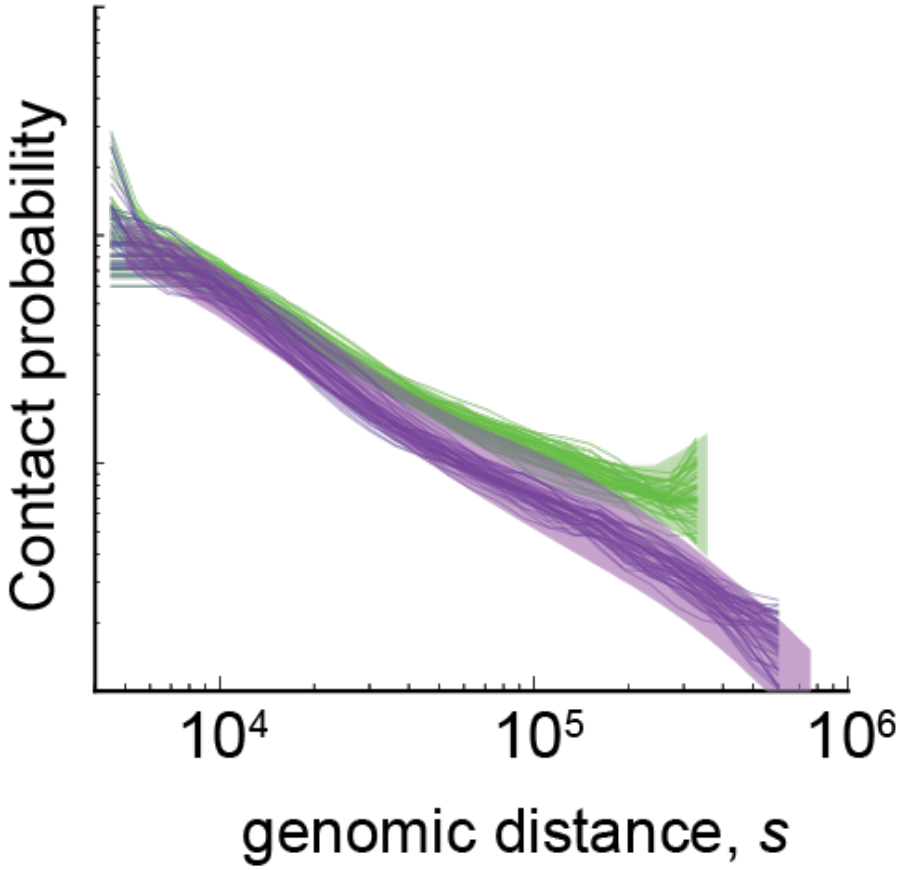




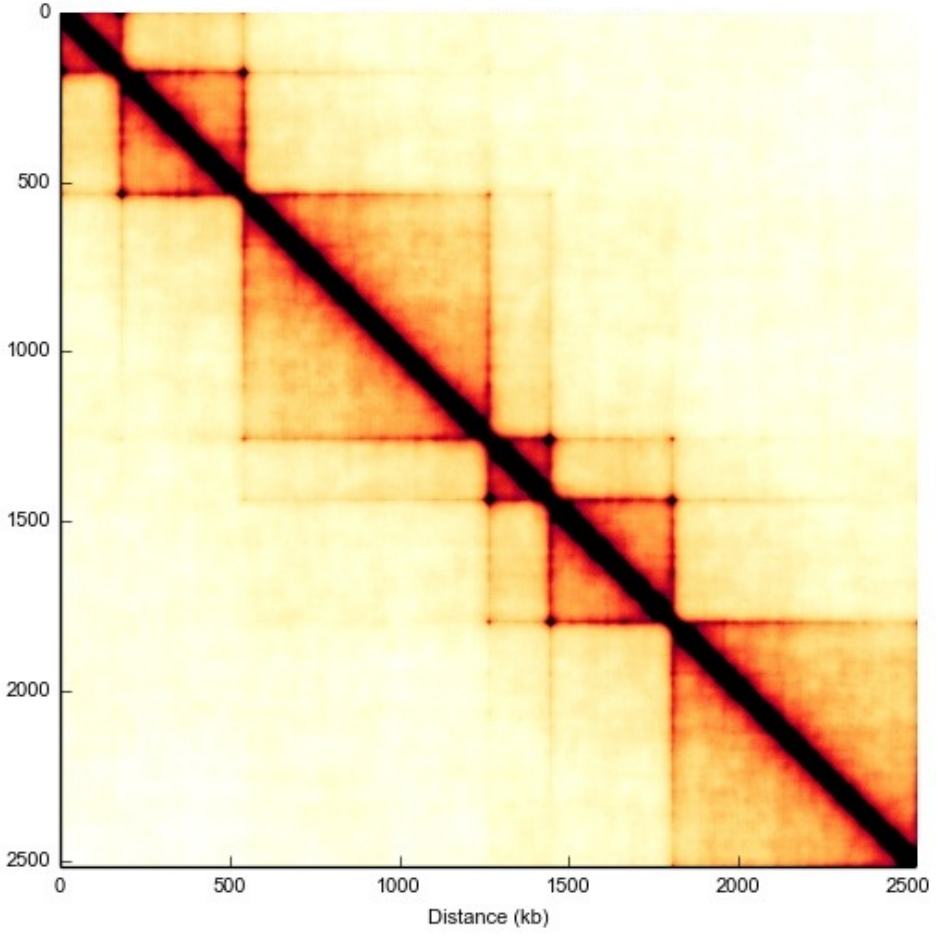
Loop extrusion can lead to enriched interactions between boundaries

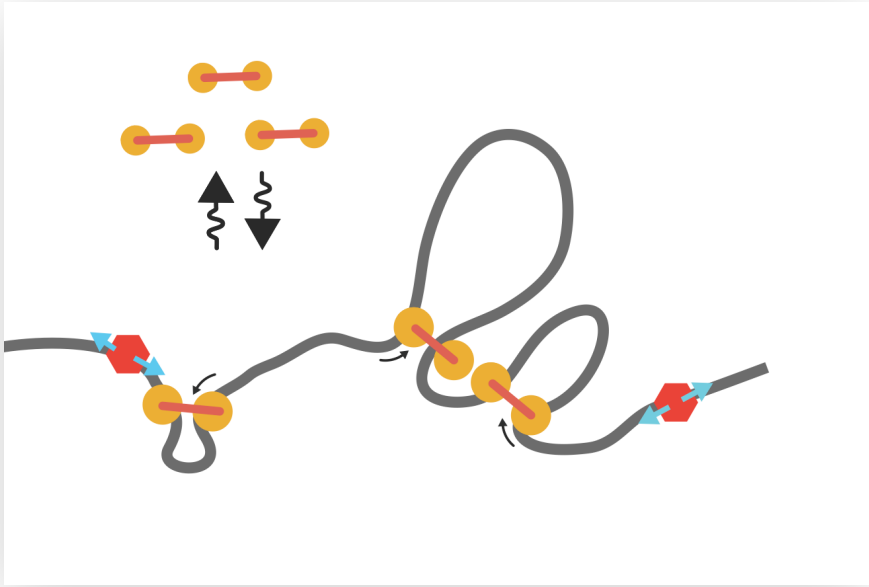
processivity = 200Kb



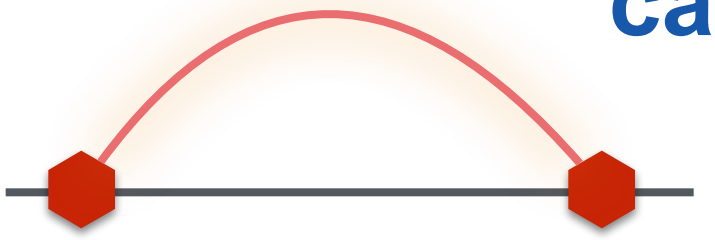


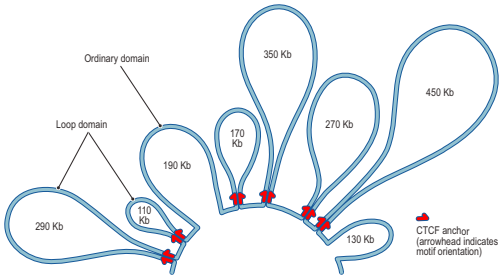
Domains are dynamic systems of extruded loops

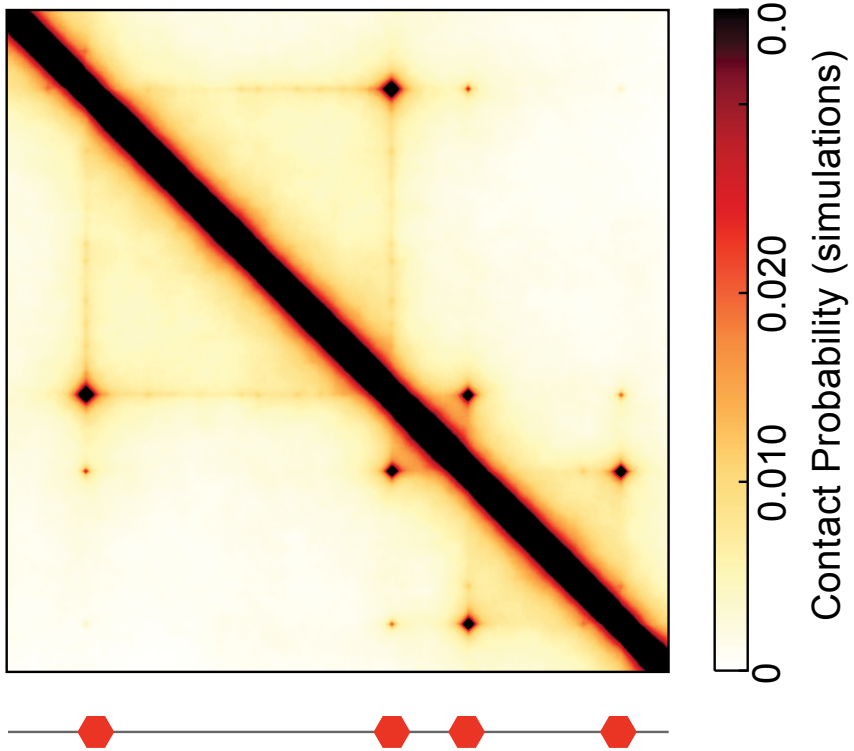


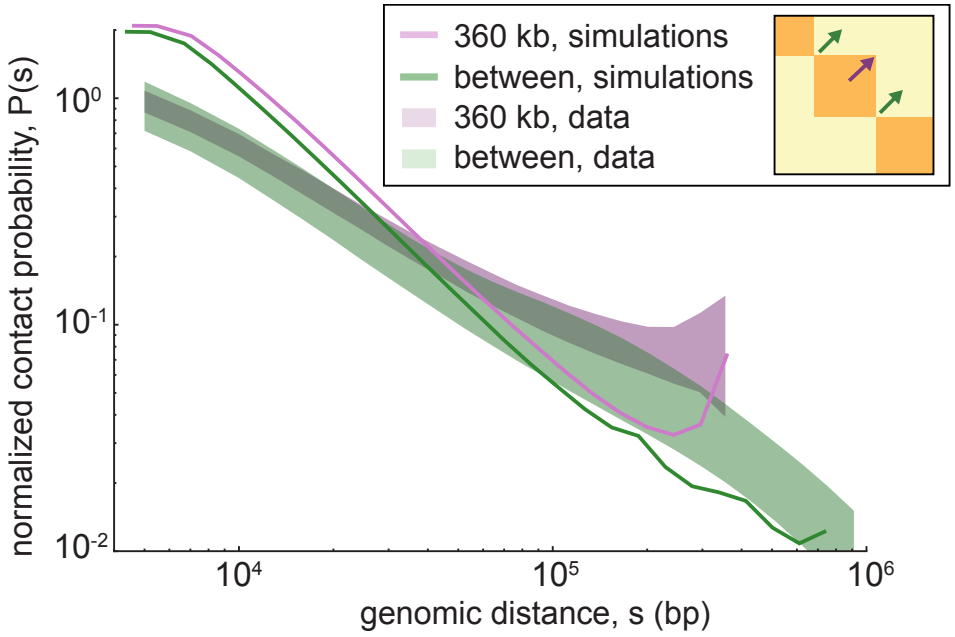


Border-to-border loops **cannot** reproduce Hi-C data



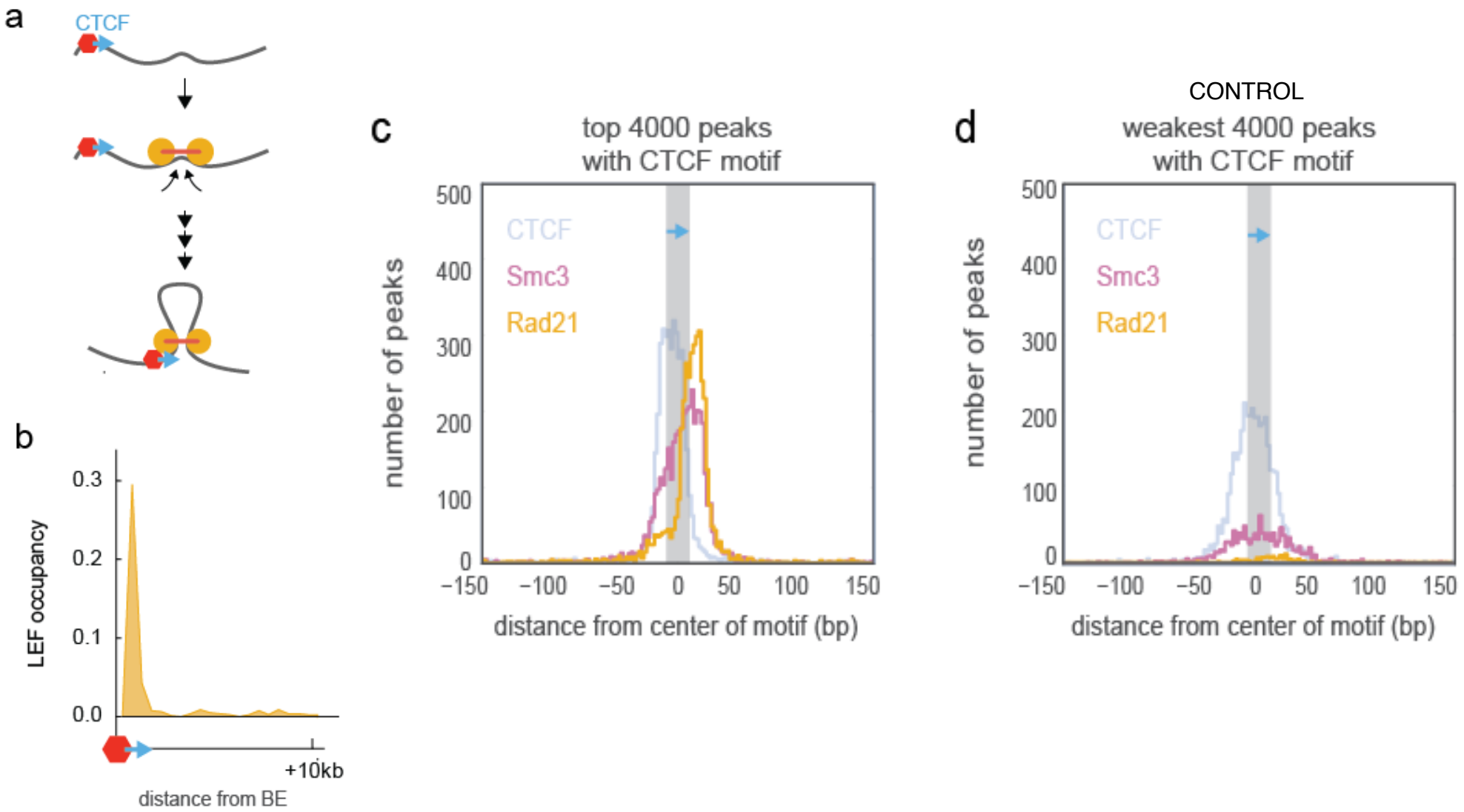




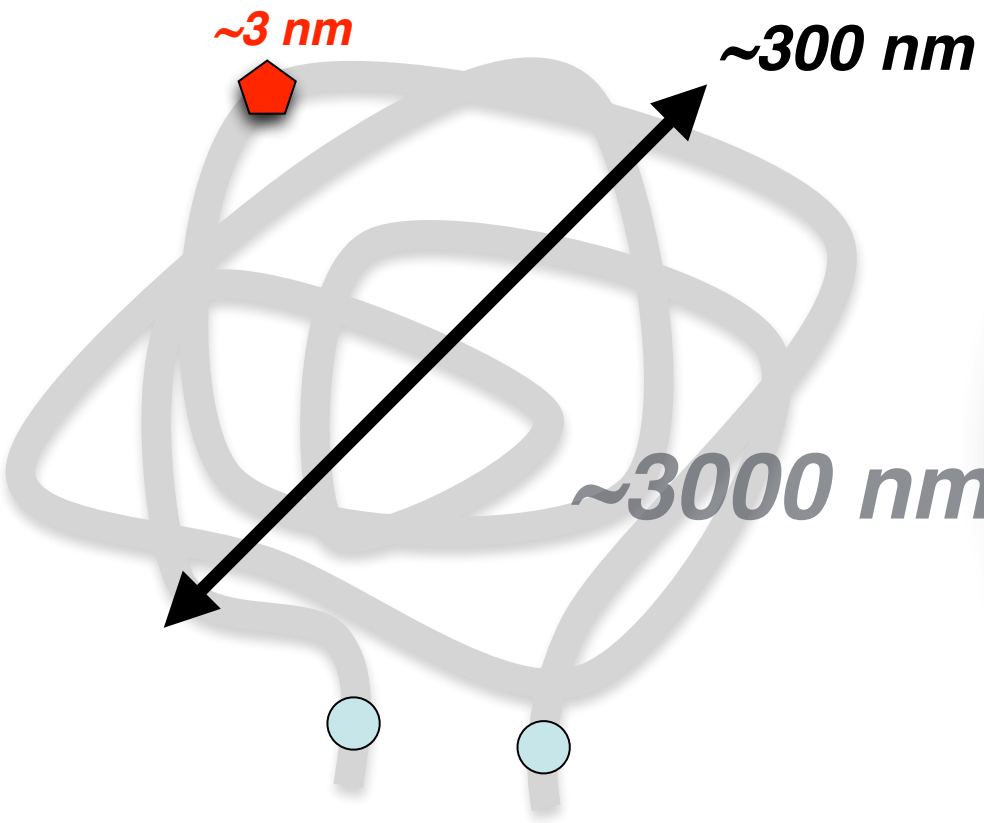


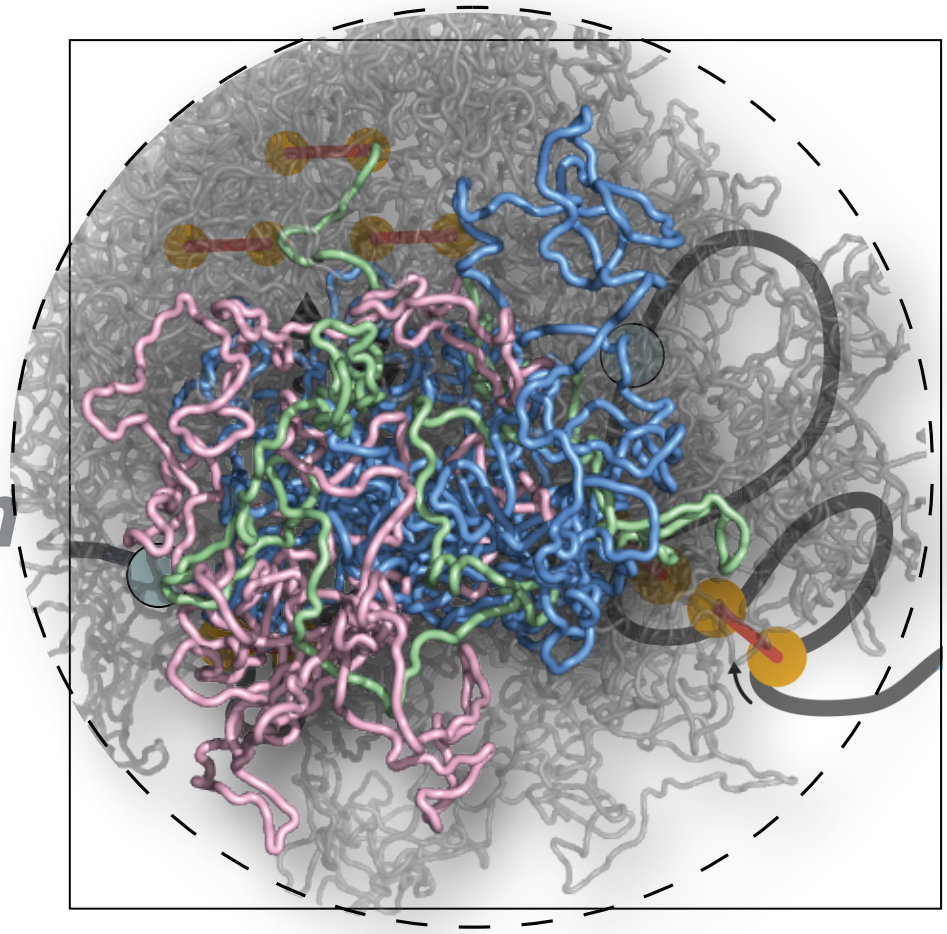
domains ≠ border-to-border loops

CTCF is an orientation-dependent boundary element



SOLVES THE SCALE PROBLEM





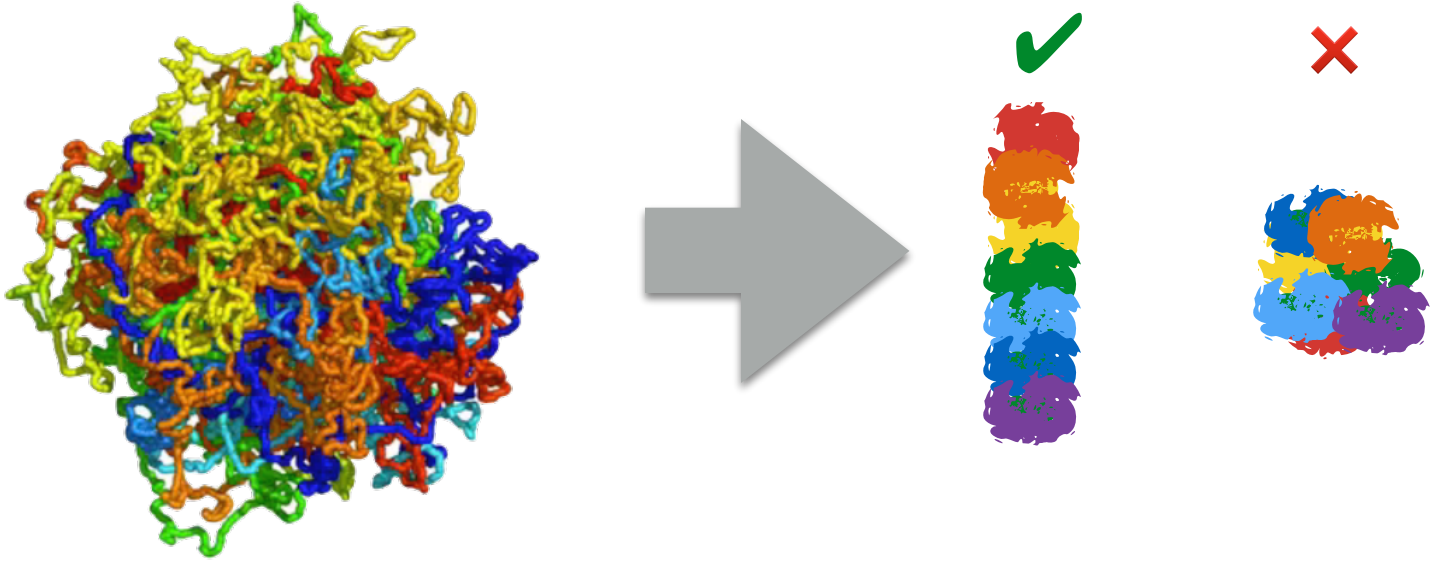
insulates cross-domain loops, but does not prevent 3D contacts

G2 -> M

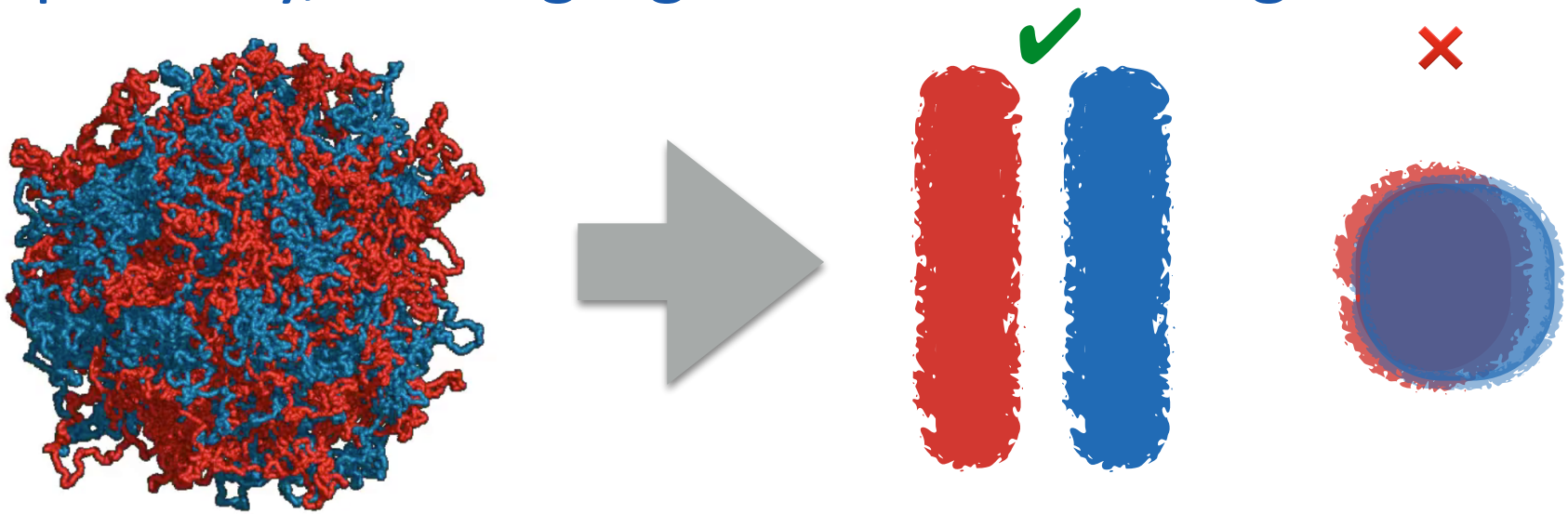
Compaction and segregation of sister chromatids via active loop extrusion
Goloborodko, Marko, Mirny
bioRxiv Jan (2016)

Mitotic chromosome compaction via active loop extrusion
Goloborodko, Marko, Mirny
bioRxiv June (2015)

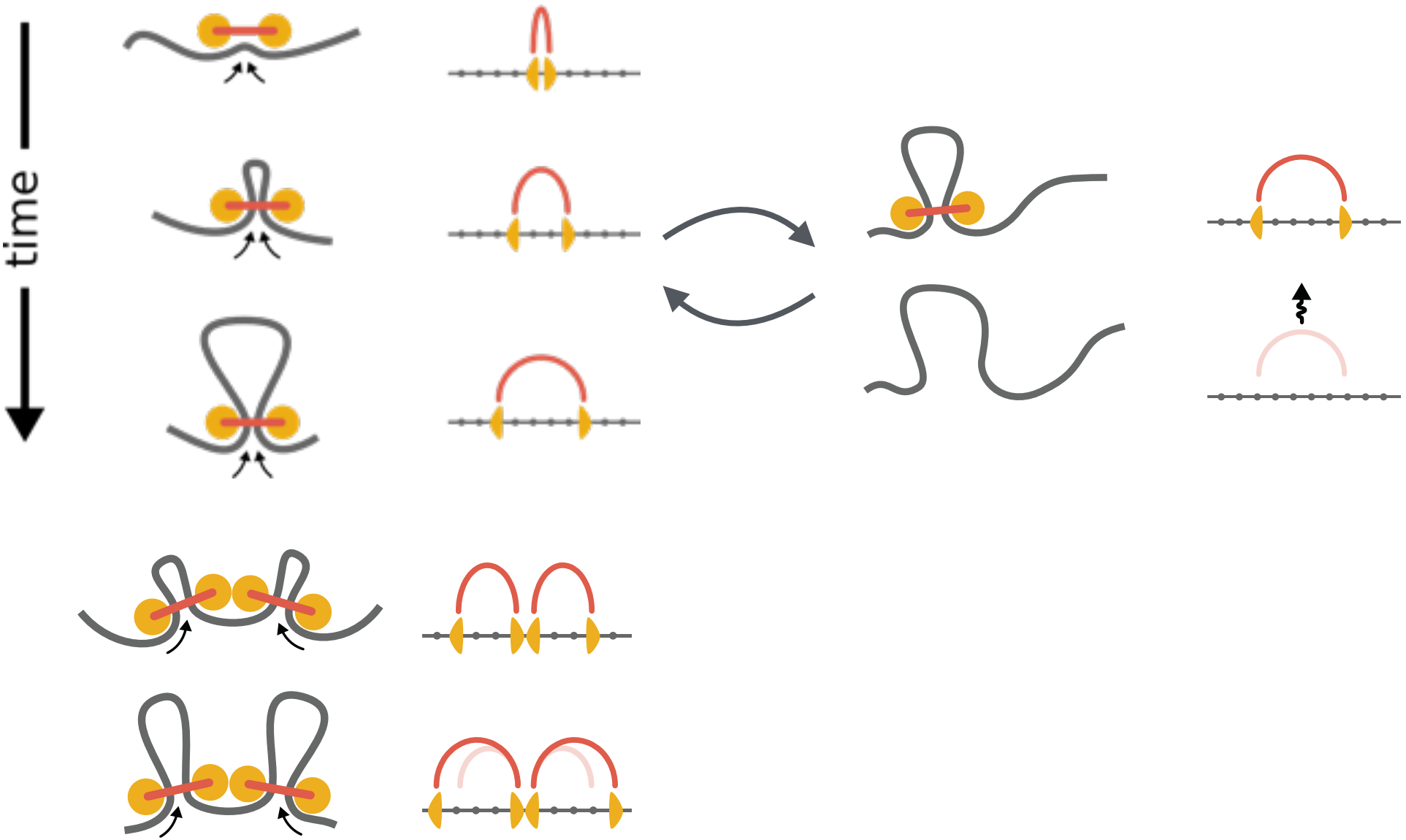
PROBLEM 2: how can chromosome condense while acquiring elongated morphology and linear order?



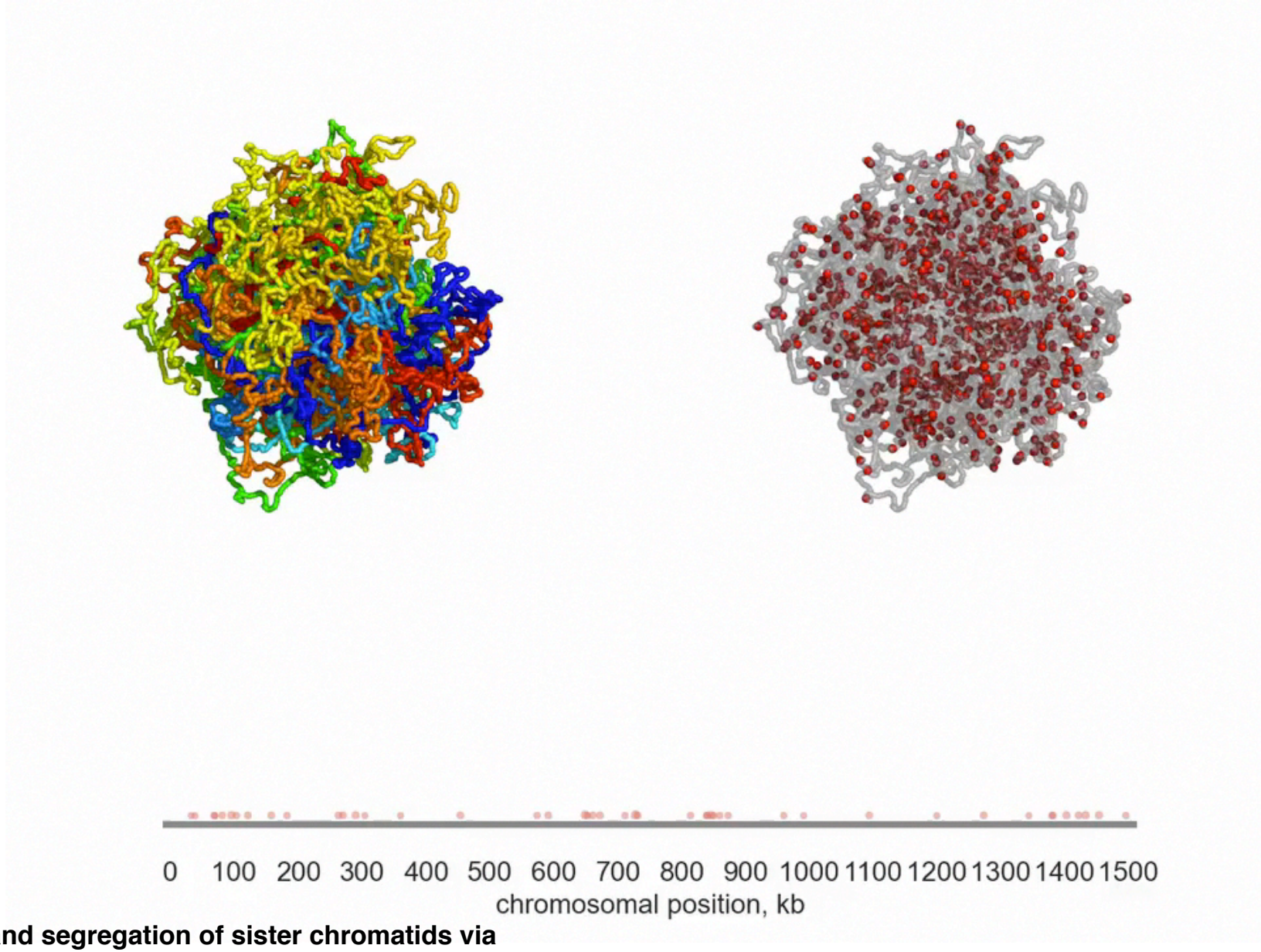
PROBLEM 3: how can two sister chromatids condense separately, i.e. segregate and disentangle



Loop extrusion



Loop extrusion is sufficient for prophase condensation



Compaction and segregation of sister chromatids via active loop extrusion
Goloborodko, Marko, Mirny
bioRxiv Jan (2016)

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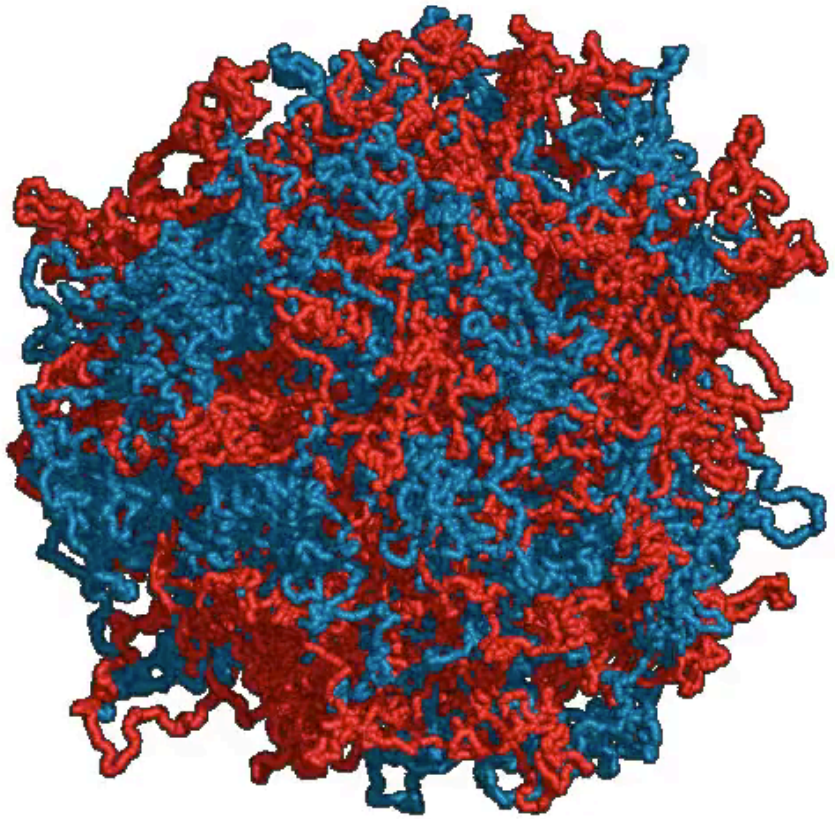
Loop extrusion is sufficient for sister segregation



Compaction and segregation of sister chromatids via active loop extrusion
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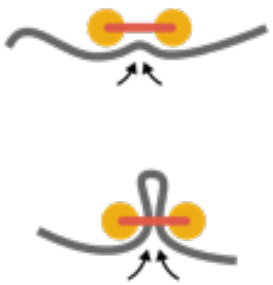
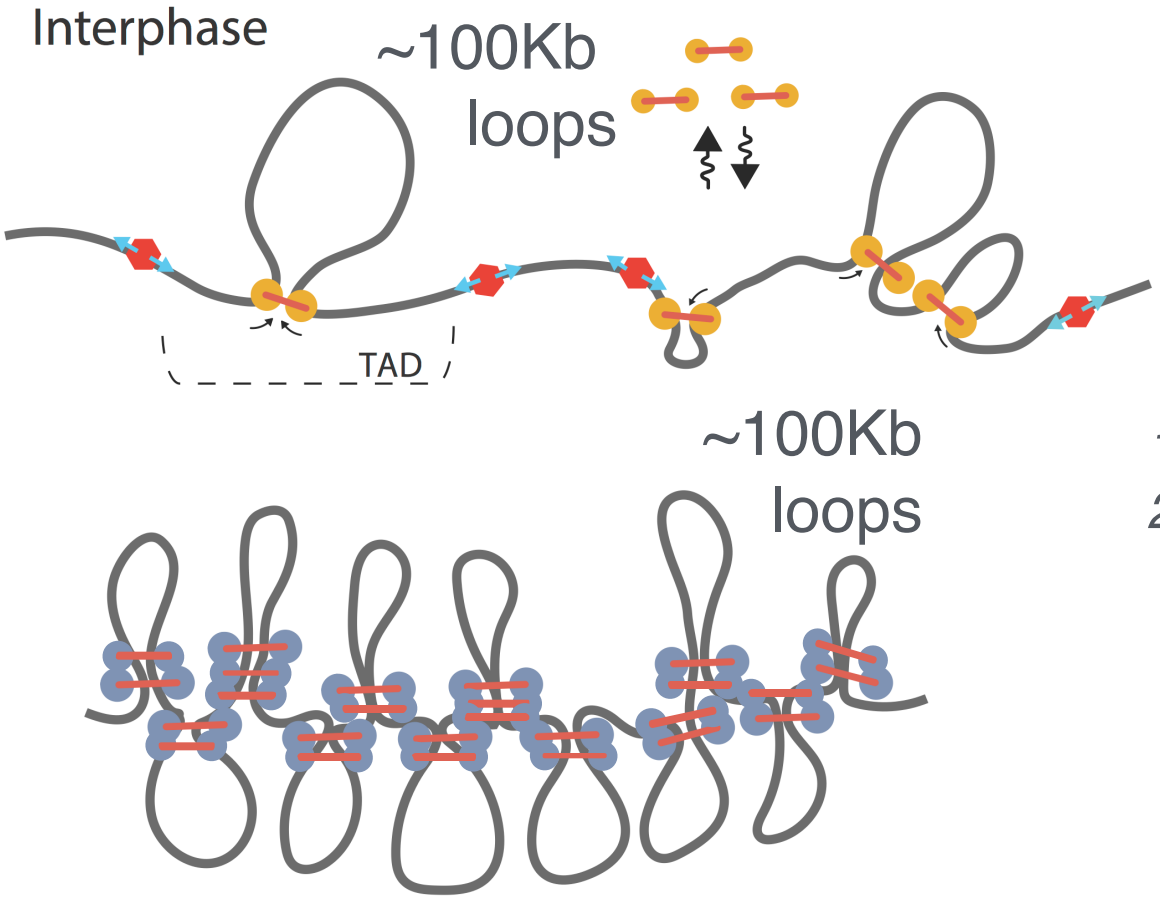
Summary

Active loop extrusion



- *Universal mechanism*

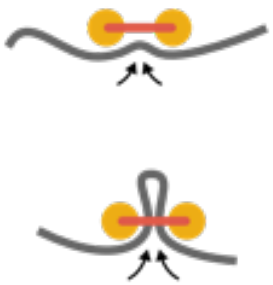
- *Chromosomes are active media*



1. *Remove boundaries*
2. *More (x5-10) loop extruding factors*
   cohesin** is replaced by **condensins

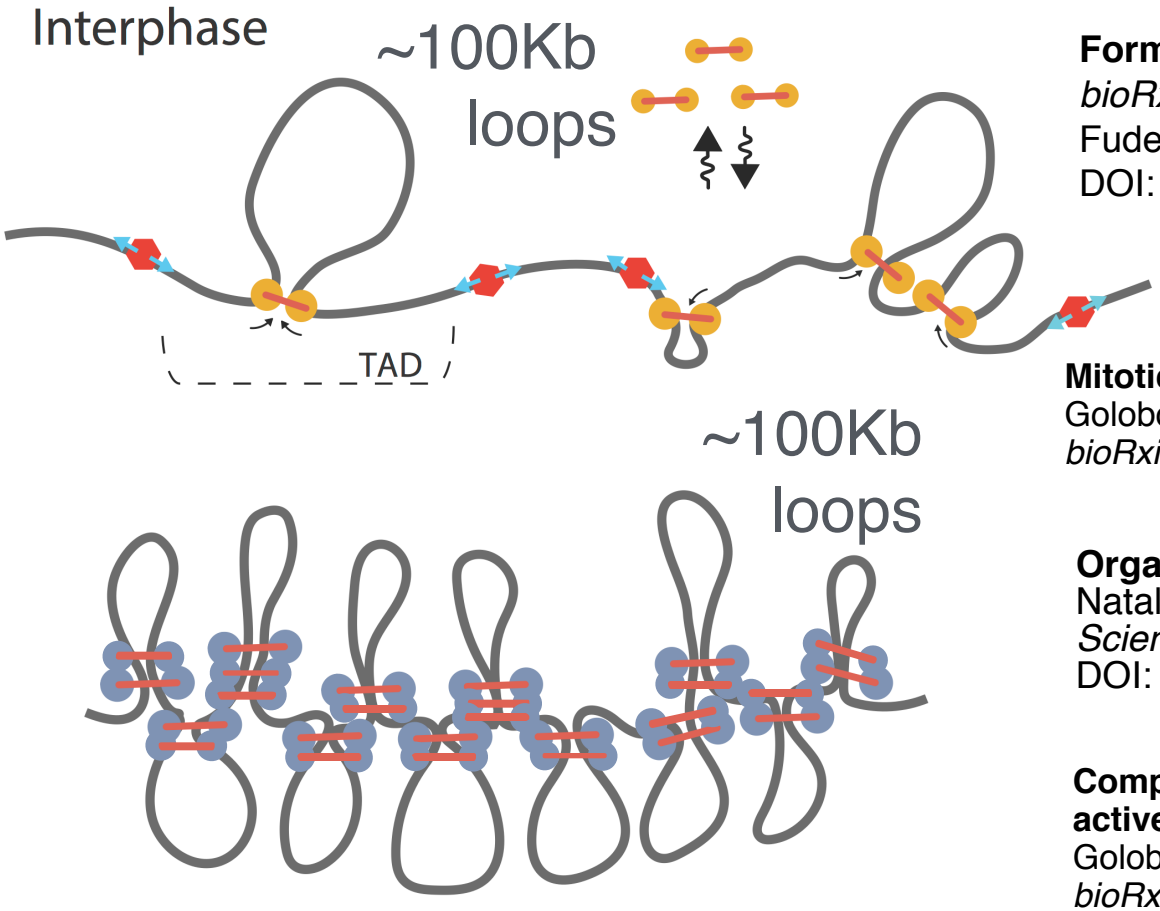
Summary

Active loop extrusion



- *Universal mechanism*

- *Chromosomes are active media*



Formation of Chromosomal Domains by Loop Extrusion
bioRxiv Aug 14 (2015)
Fudenberg, Imakaev et al.
DOI: 10.1101/024620

Mitotic chromosome compaction via active loop extrusion
Goloborodko, Marko, Mirny
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Organization of the Mitotic Chromosome
Natalia Naumova *et al.*
Science **342**, 948 (2013);
DOI: 10.1126/science.1236083

Compaction and segregation of sister chromatids via active loop extrusion
Goloborodko, Marko, Mirny
bioRxiv Jan (2016)

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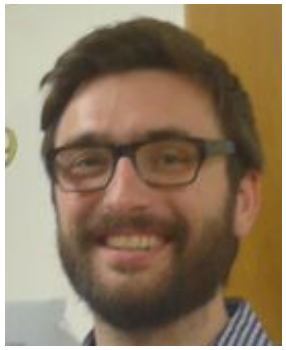

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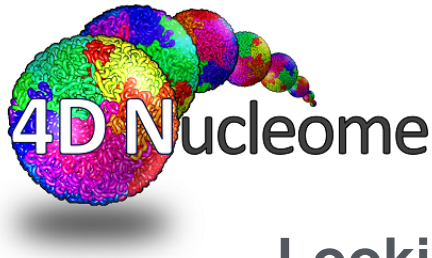

Looking for postdocs!