



The University of Texas at Austin
Department of
Molecular Biosciences
College of Natural Sciences



Cohesin organizes the genome via loop extrusion

Hongshan ZHANG

Ilya Finkelstein Lab

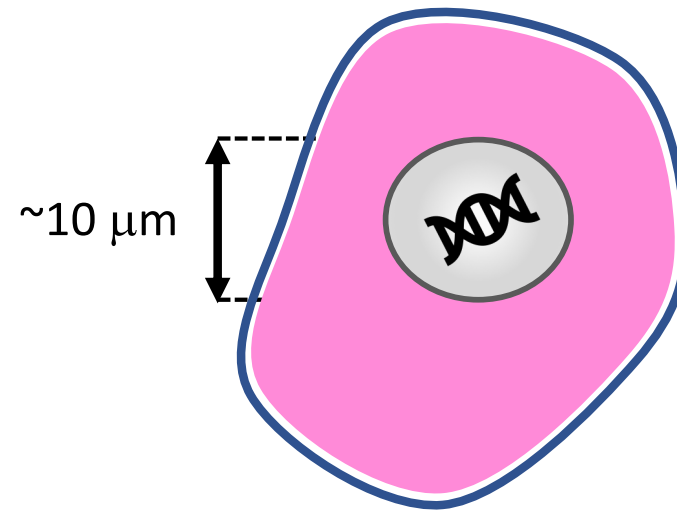
Aug.19th,2020

Genomic DNA organizes in different levels in nucleus

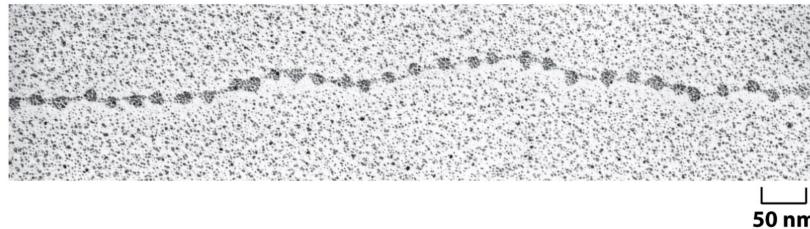
Human DNA

6 billion bases

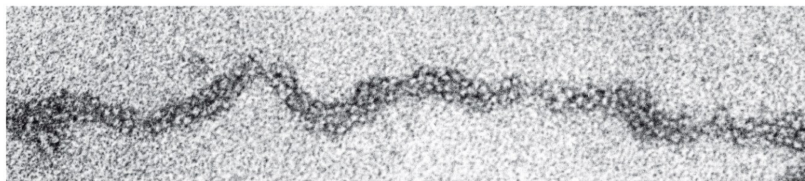
2 meters of DNA



Nucleosomes on DNA

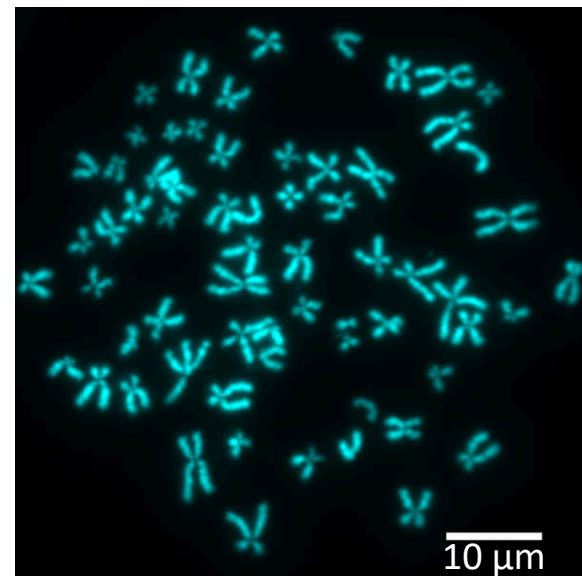


Chromatin fiber



Alberts et al. Molecular Biology of the Cell. 2002

Human Chromosome



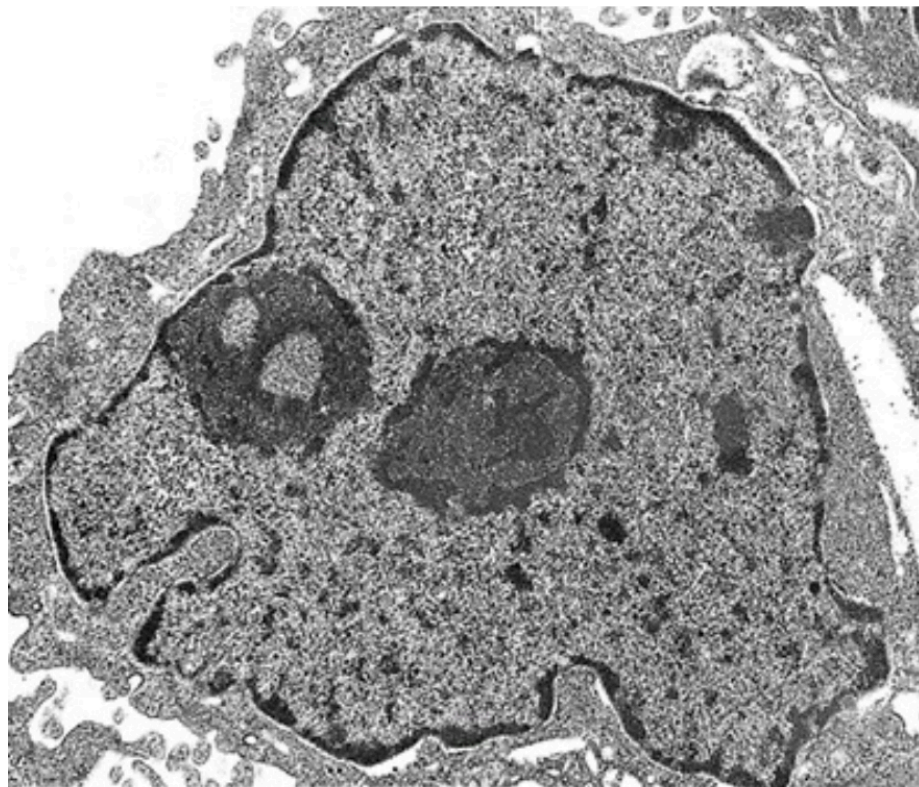
Uhlmann. BMC Biology 2013

Genomic DNA organizes in different levels in nucleus

Interphase Nucleus

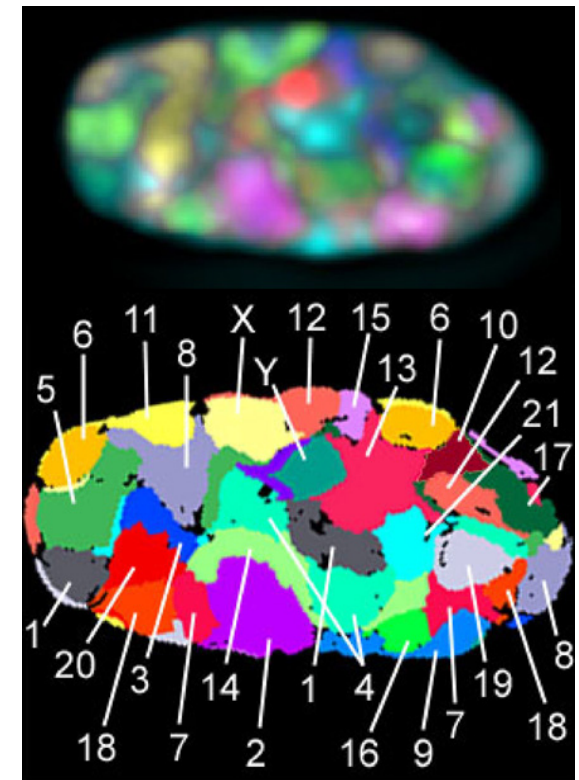
Heterochromatin – Condensed & Inactive

Euchromatin – Less dense & Active



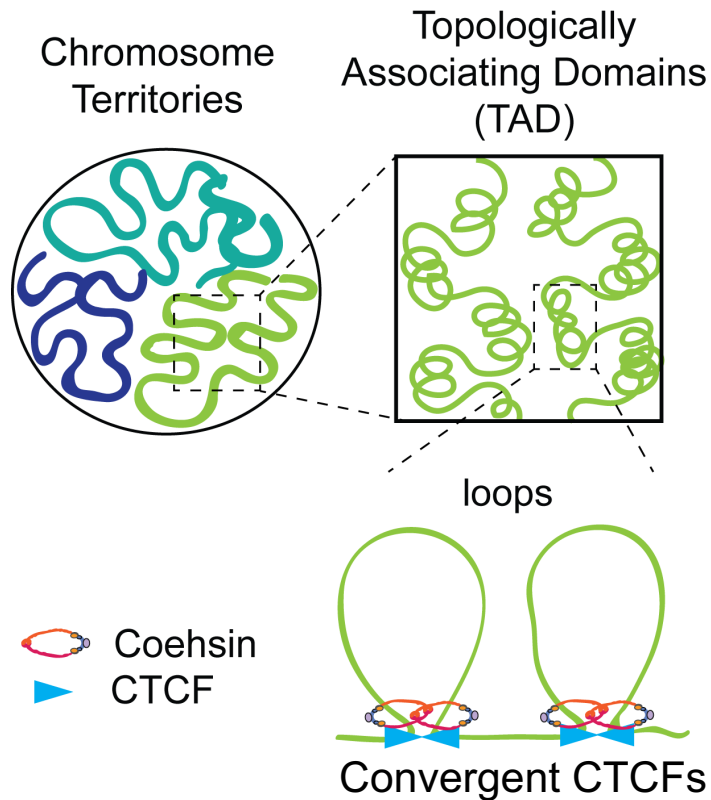
W W Franke. Int Rev Cytol. 1974

human chromosome territories



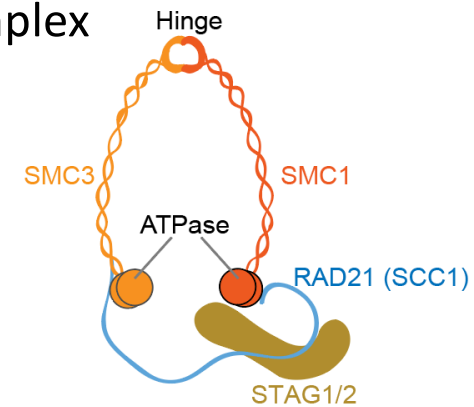
A Bolzer, ...T Cremer. PLoS Biol. 2005

TADs and chromatin loops depend on cohesin and regulated by CTCF

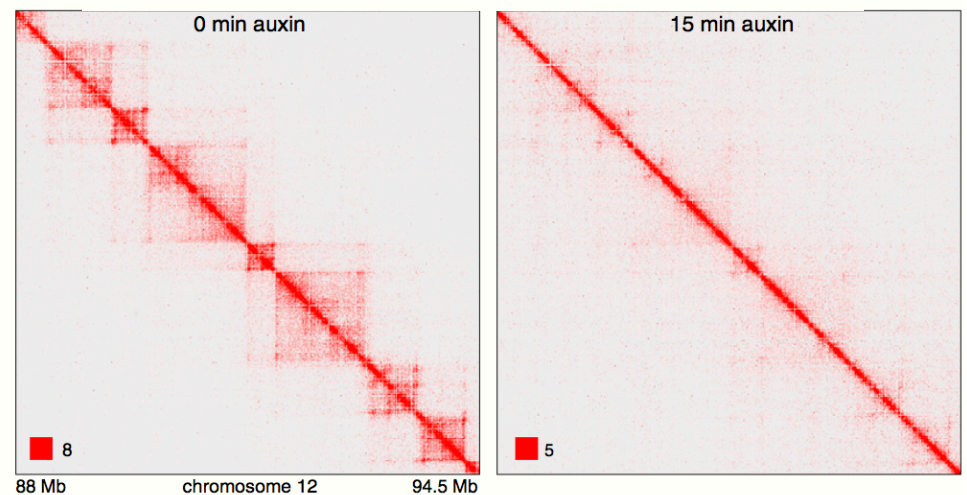
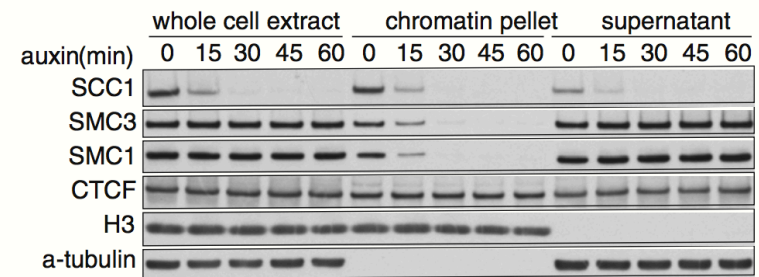


J R Dixon ... B Ren. Nature 2012
S S Rao ... E L Aiden. Cell 2014
K S Went ... J M Peters. Nature 2008

Cohesin complex



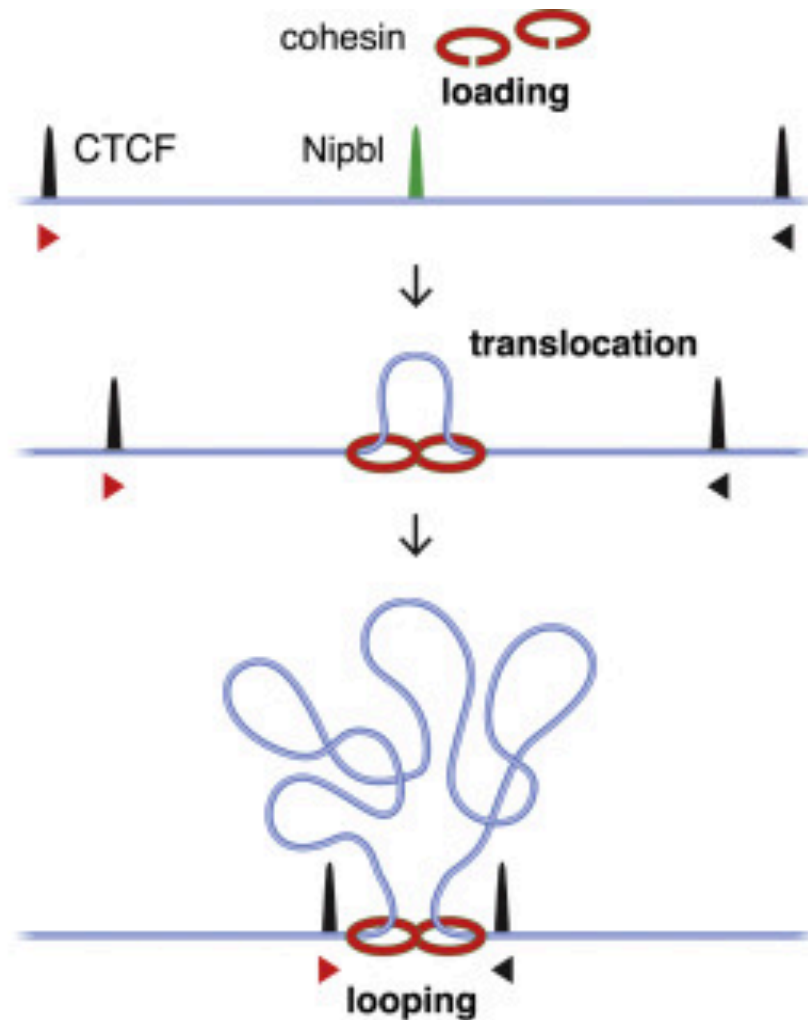
SCC1-mEGFP-AID Hela cells after auxin treatment



G Wutz ... J M Peters. EMBO J 2017
S S Rao ... E L Aiden. Cell 2017

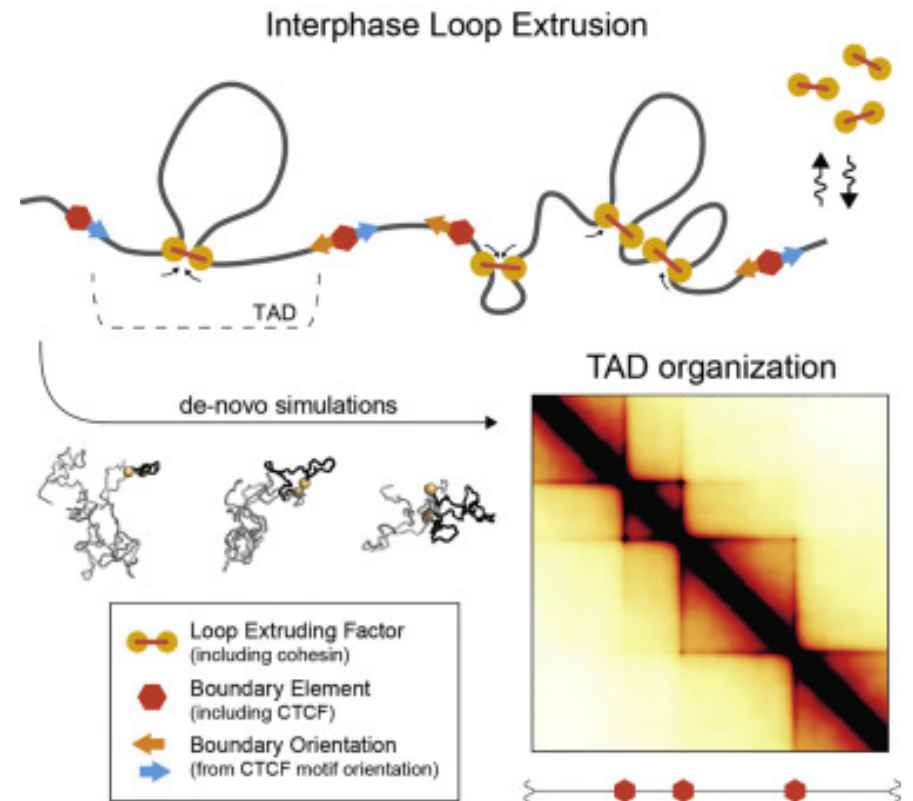
DNA loop extrusion mediated by cohesin and regulated by CTCF

Hypothesis: Loop Extrusion Model



L Vian ... R Casellas. Cell 2018

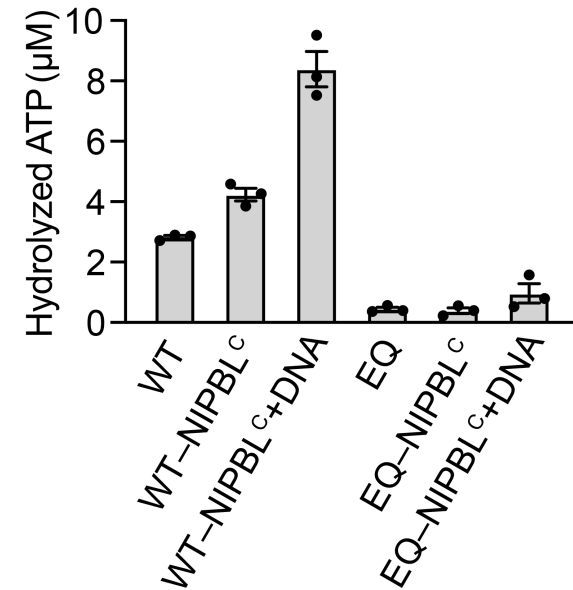
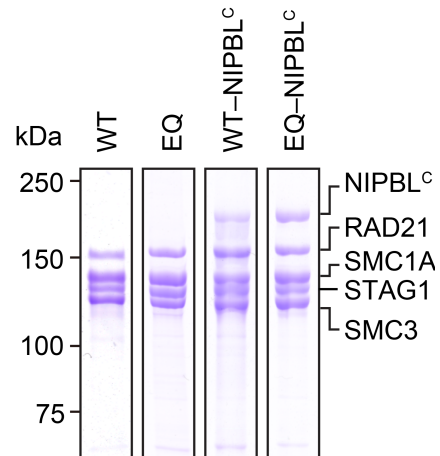
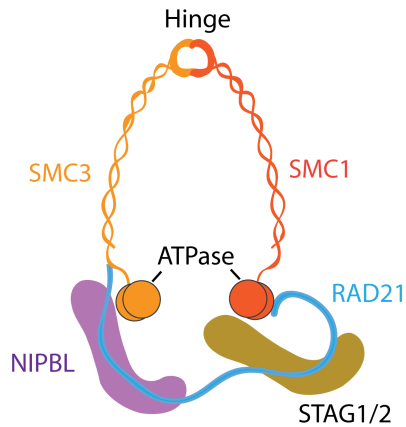
Computational analysis



G Fudenberg ... L.A. Mirny. Cell Rep 2016

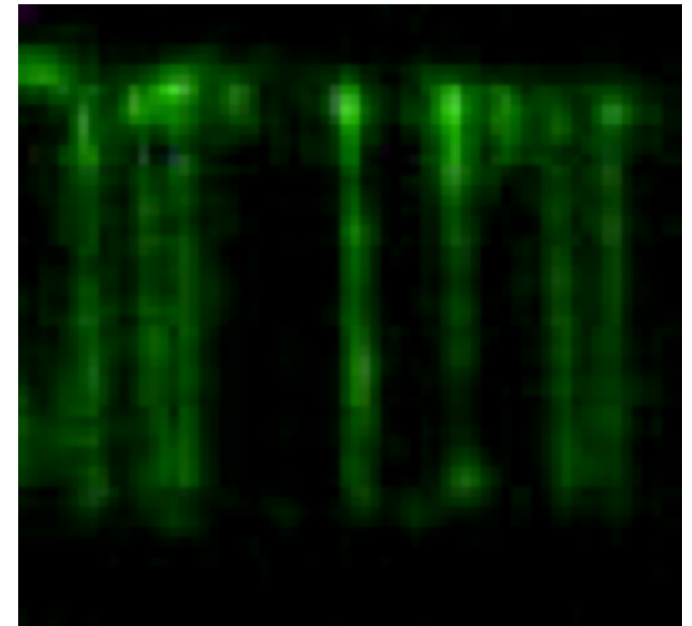
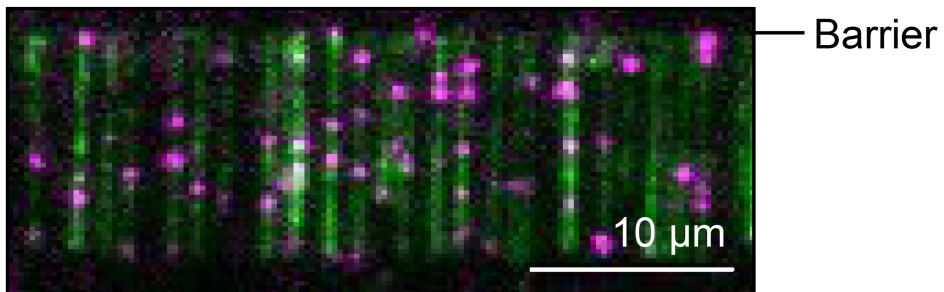
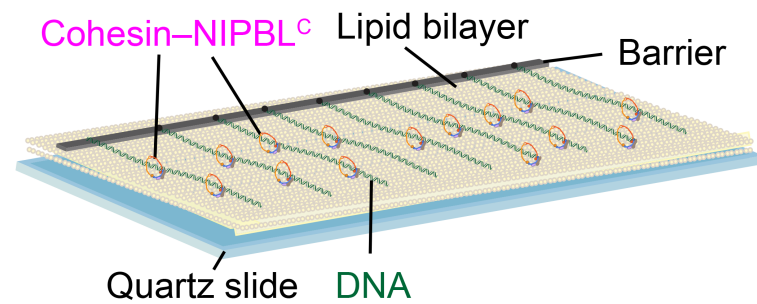
Recombinant human Cohesin complex

Cohesin-NIPBL complex

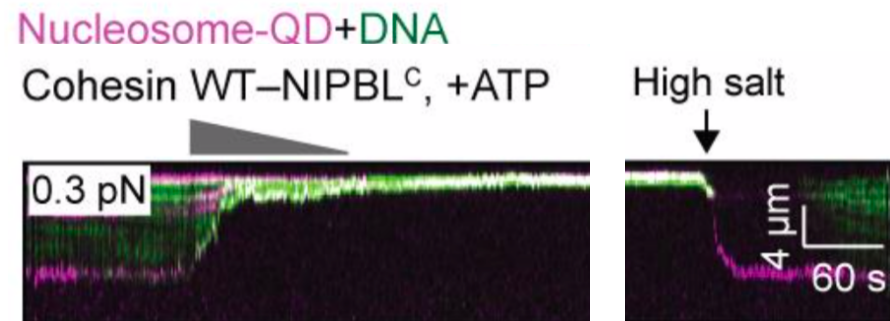
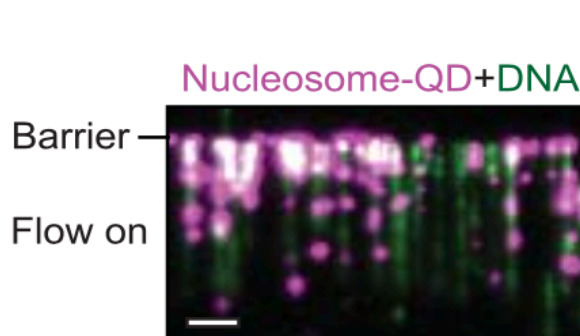
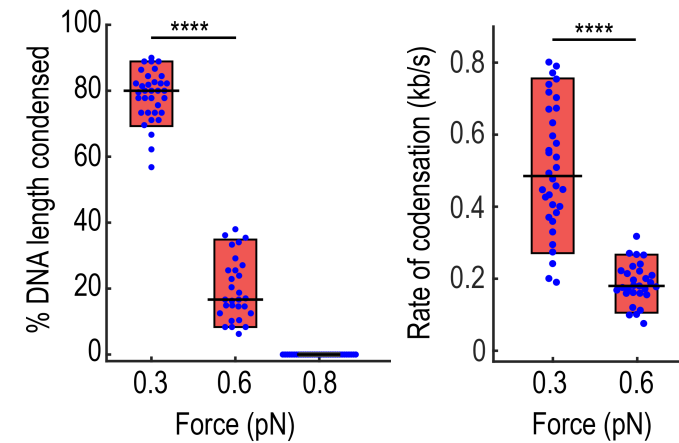
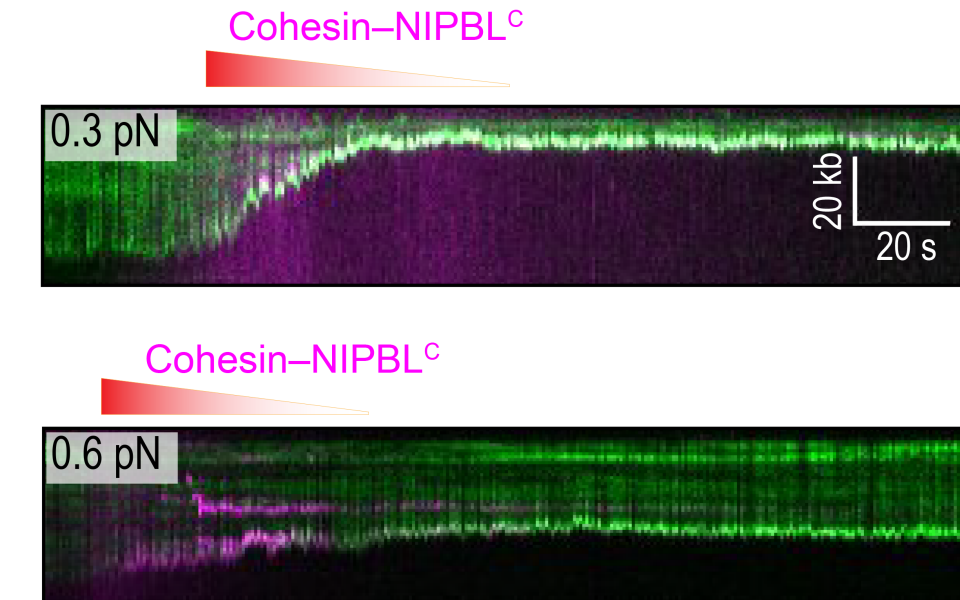


Direct observation of DNA compaction by Cohesin-NIPBL^c

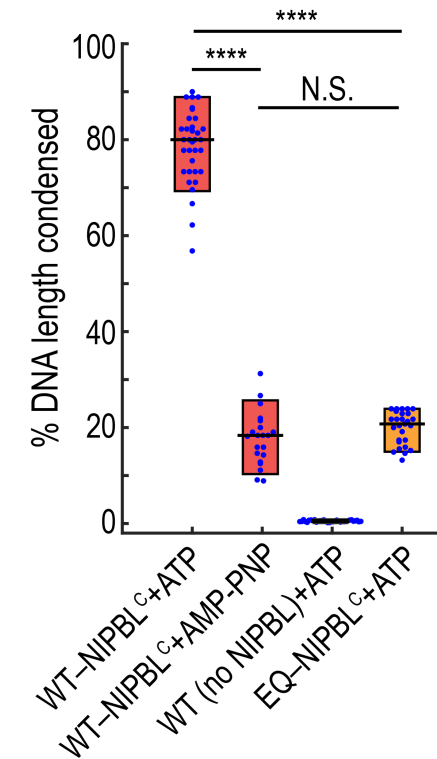
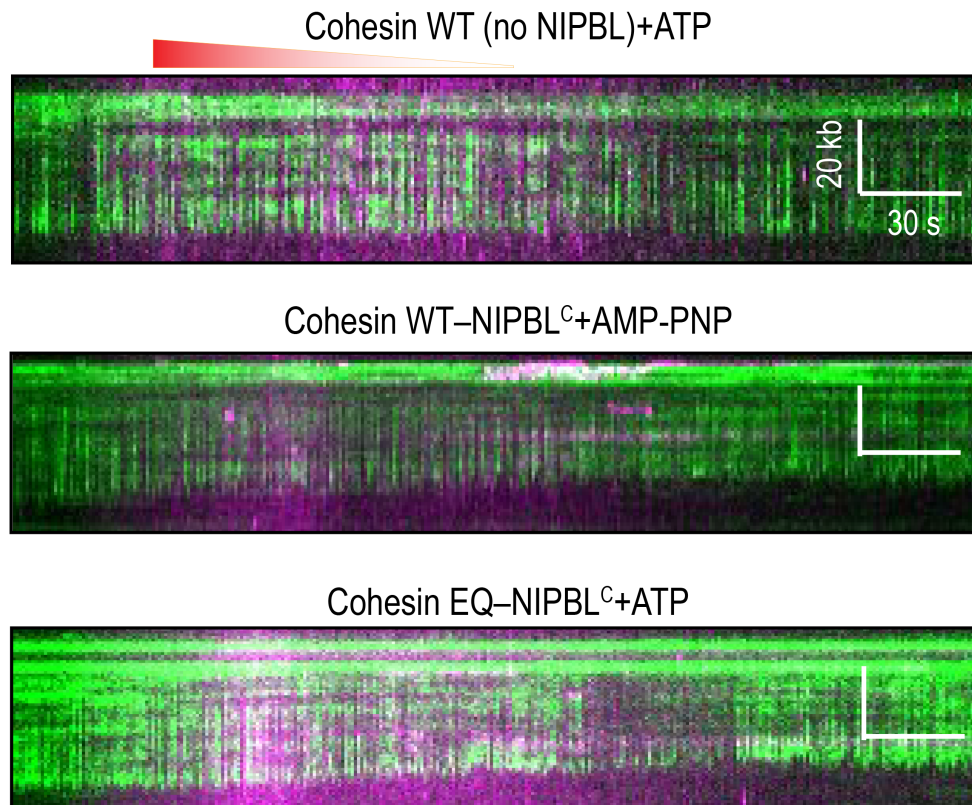
DNA curtain



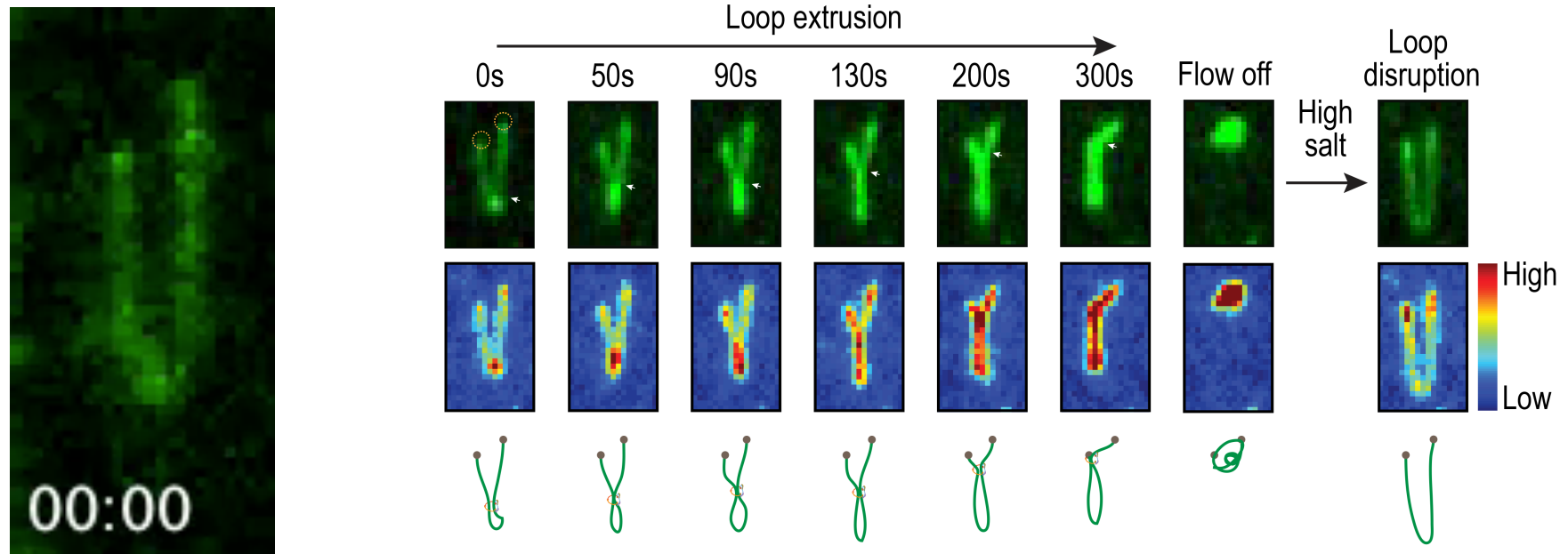
DNA compaction by Cohesin-NIPBL^c is force sensitive



DNA compaction by Cohesin is NIPBL and ATP-dependent

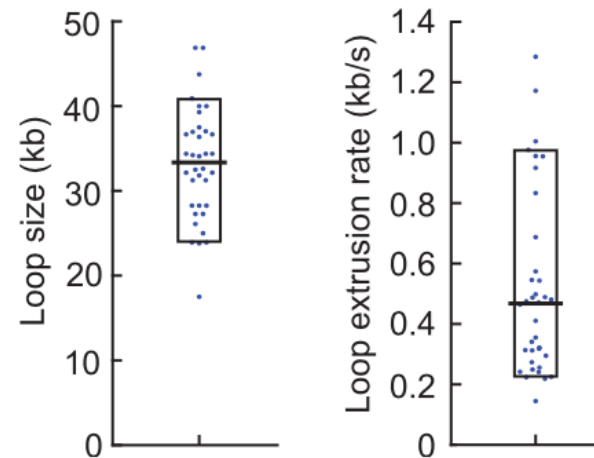
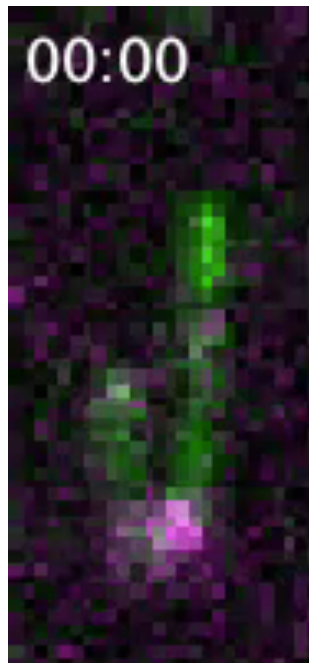


Real time detection of DNA loop extrusion by Cohesin-NIPBL^c

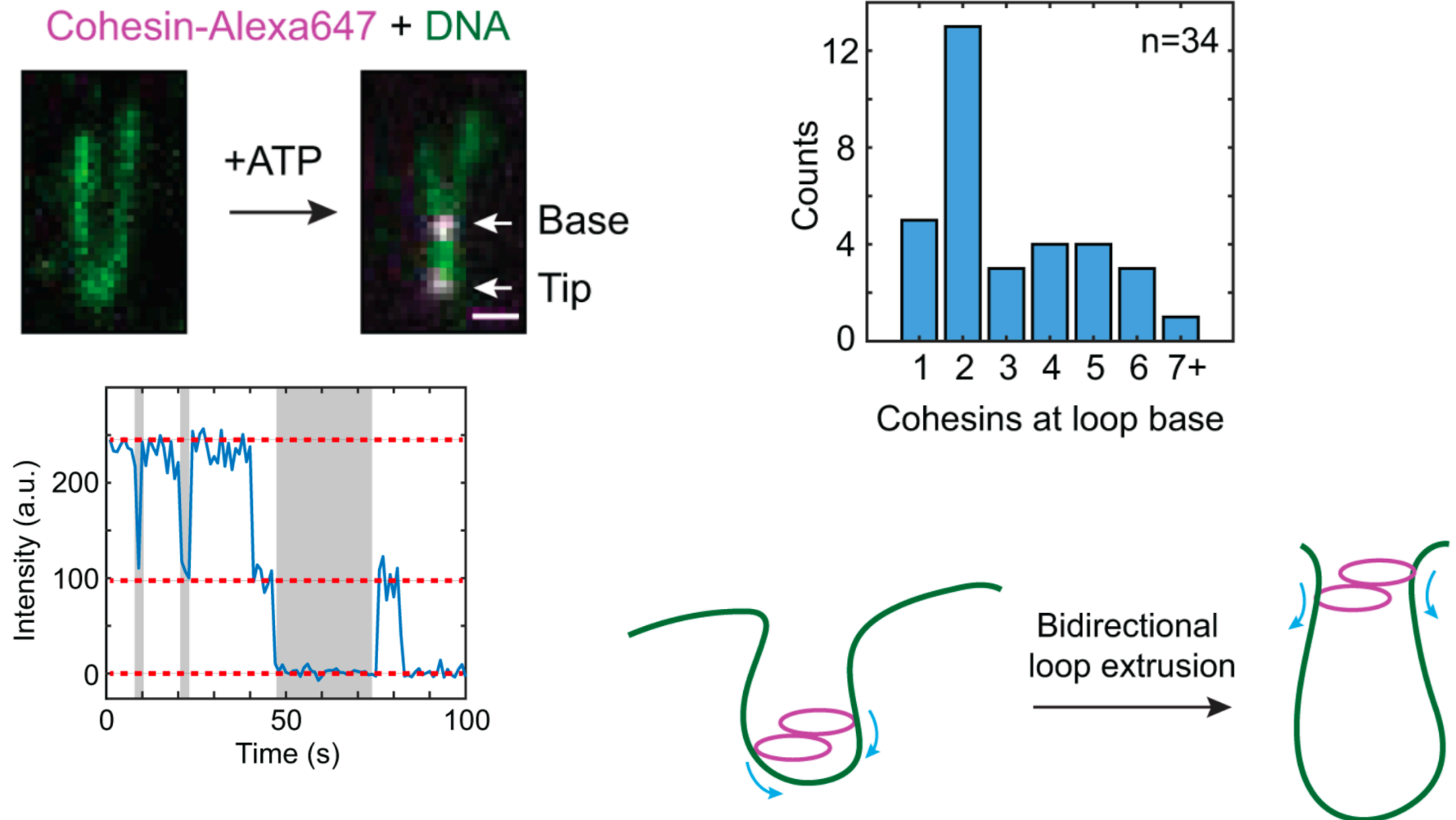


Cohesin extrudes loops in a non-topologically associated state

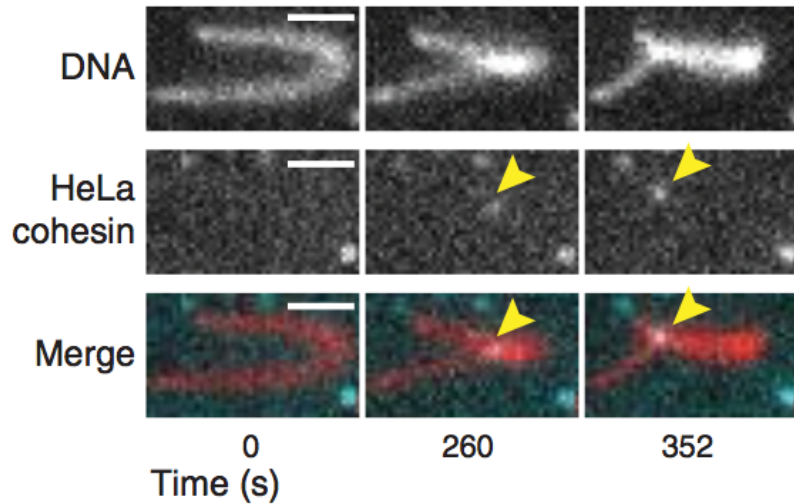
Real time detection of DNA loop extrusion by Cohesin-NIPBL^c



Cohesin-NIPBL^c extrudes DNA as a dimer



Dimer or Monomer?

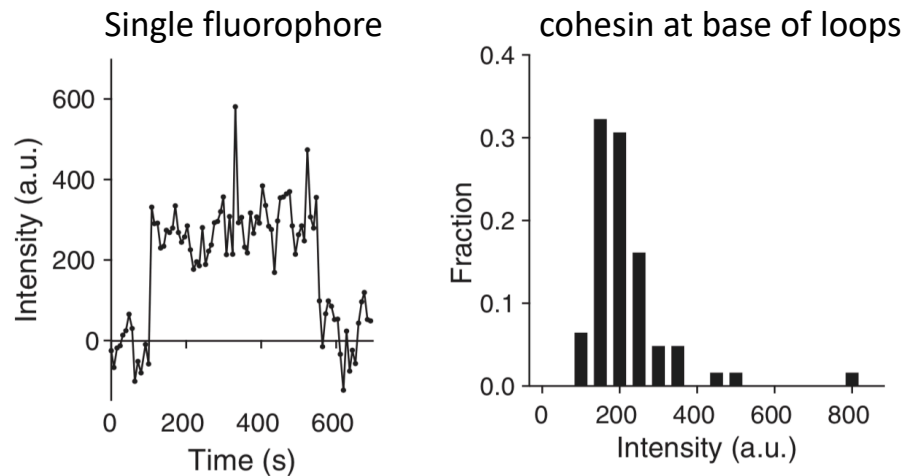


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Cohesin in space and time: architecture and oligomerization *in vivo*.

Siheng Xiang and Douglas E. Koshland*
Department of Molecular and Cell Biology, University of California, Berkeley

*For correspondence: koshland@berkeley.edu



Report

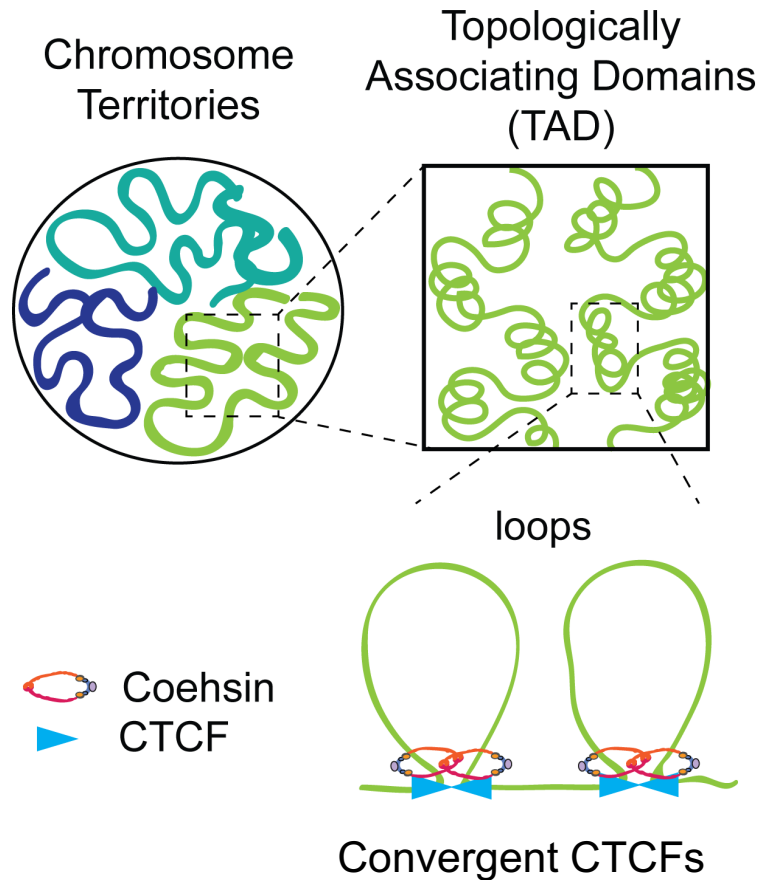


Monomeric cohesin state revealed by live-cell single-molecule spectroscopy

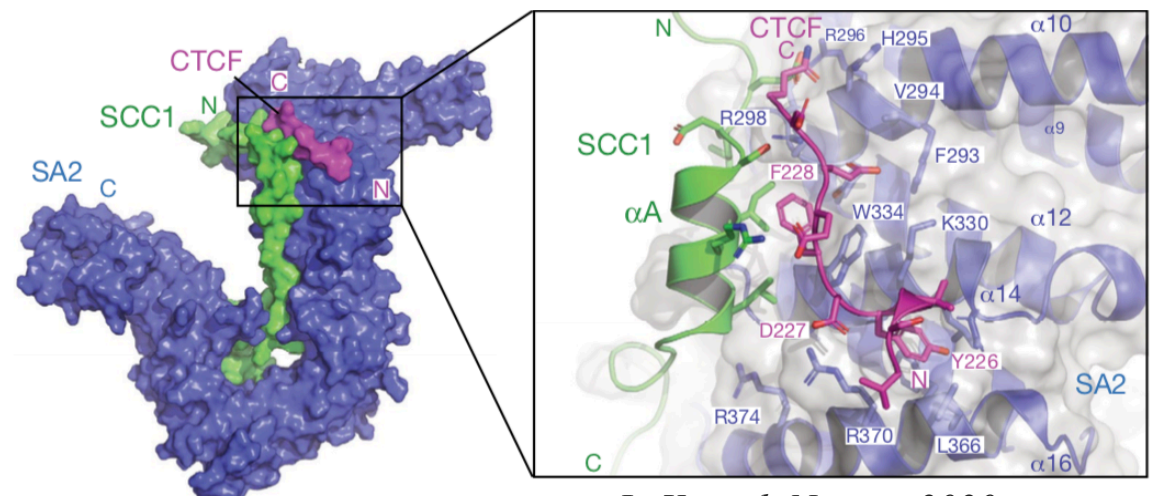
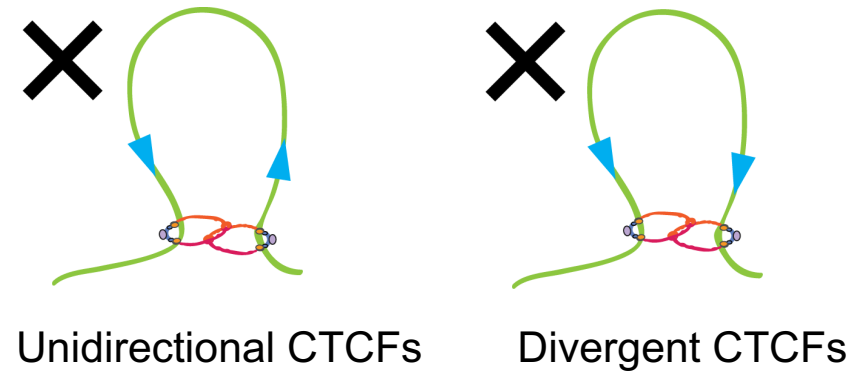
Wenjie Liu^{1,2,†}, Elisheva Biton^{3,†}, Anjali Pathania³, Avi Matityahu³, Joseph Irudayaraj^{1,2,*} & Itay Onn^{3,**}

primarily observe monomeric cohesin with a small population (~10%) of putative dimers.

IF Davidson ... J M Peters. Science. 2019.



- CTCF localizes with cohesin genome wide.
- CTCF binding polarity determines chromatin looping.



S S Rao ... E L Aiden. Cell 2014
E D Wit ... W D Laat. Mol. Cell 2015
K S Went ... J M Peters. Nature 2008

Li Y, et al. *Nature*. 2020

Future questions

- How does cohesin interact with different-oriented CTCF?
- How does CTCF block cohesin translocation?
- What is the mechanism of CTCF-dependent loop extrusion?

Acknowledgements



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Jim Rybarski



Hongtao Yu Lab

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Zhubing Shi



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