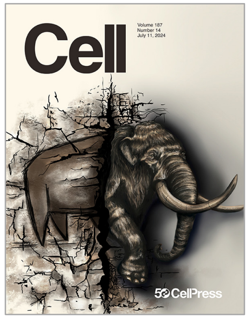
Picture from the book: Castells i Castellers. Una voluntat col·lectiva.

Fossilized chromosomes from woolly mammoth

Marc A. Marti-Renom
CNAG-CRG · ICREA

Cell. Volume 187 (14) July 11, 2024.



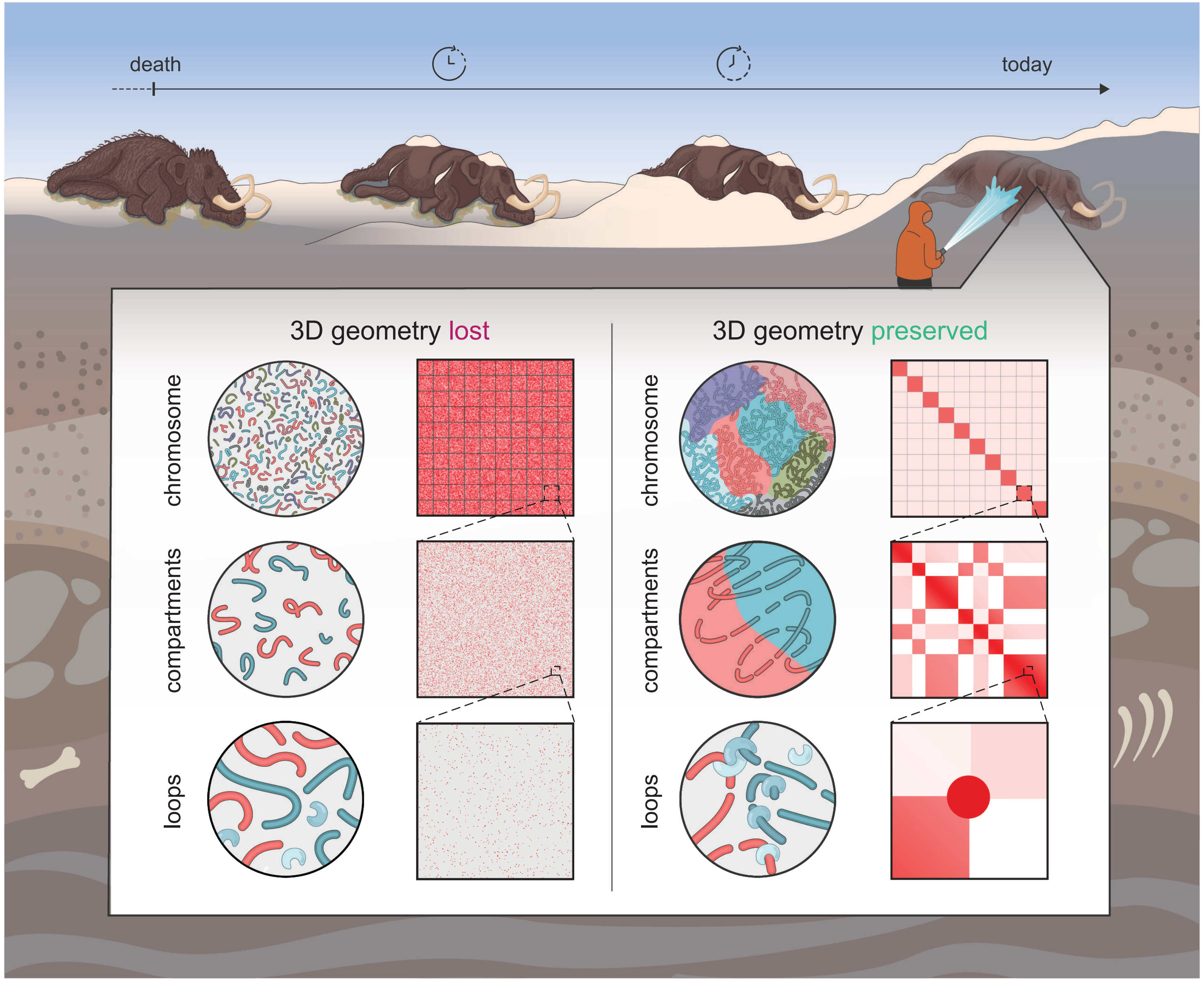
Marcela Sandoval Velasco
(ex) Gilbert Lab

Olga Dudchenko
Aiden Lab

Juan Antonio Rodríguez
(ex) Marti-Renom Lab

Cynthia Perez Estrada
(ex) Aiden Lab

What happens to the nucleus in 10s of thousands of years?



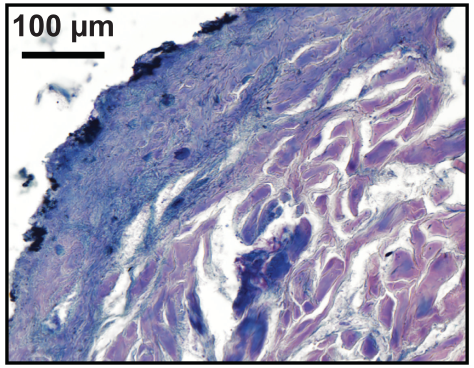
A “whoolly” phenomenal sample

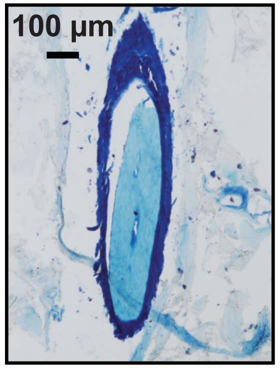
Photo credit: Chris Waddle

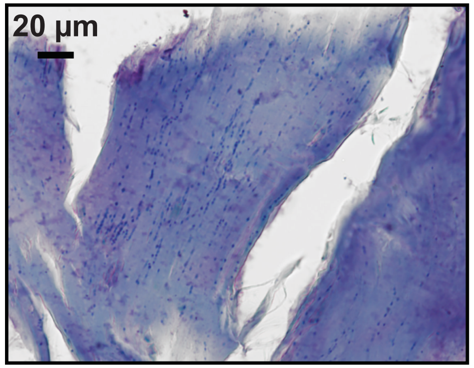
Dan Fisher
UMich, Museum of Paleontology

Valeri Plotnikov
Sakha Academy of Sciences

- Found in permafrost in the summer of 2018
- Belaya Gora in Yakutia, Russia
- Date >45,000 years







Paleo-HiC complements ancient DNA-seq

Limitations of (a)DNA-Seq

What is in the genome?

Need chrom-length de novo assemblies!

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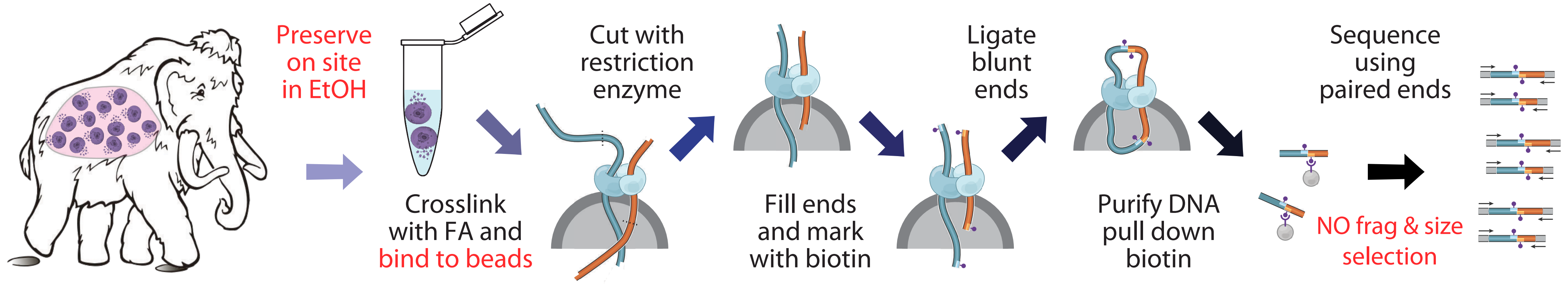
Paleo-HiC improves endogenous long-range contact recovery



Preserve on site in EtOH

Crosslink with FA and bind to beads

Cut with restriction enzyme

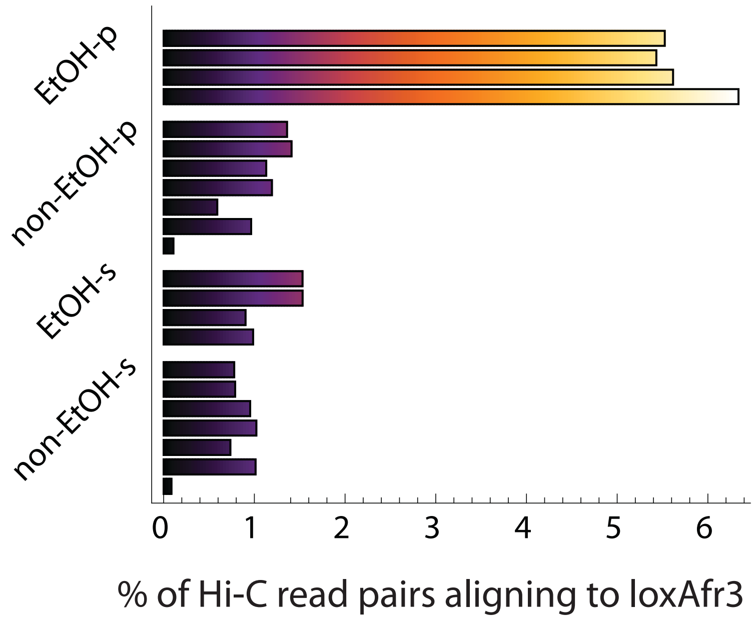
Fill ends and mark with biotin

Ligate blunt ends

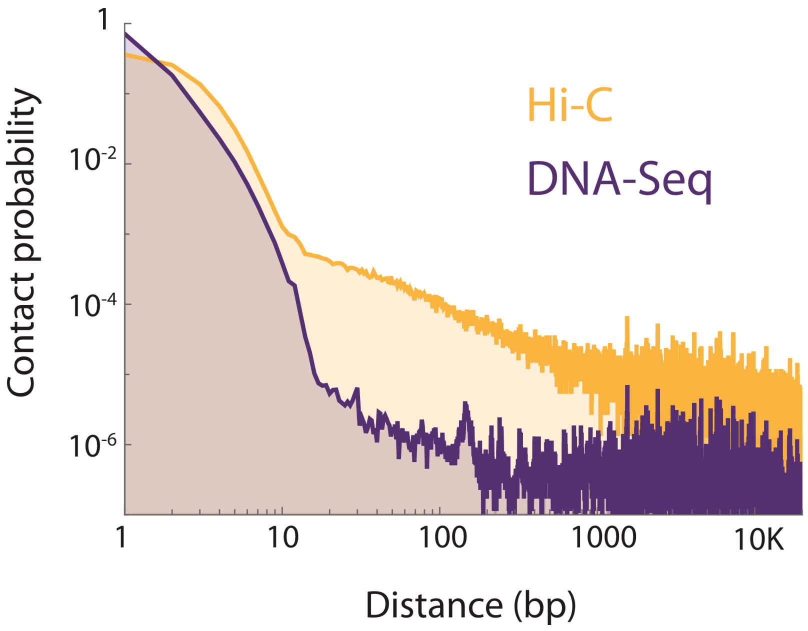
Purify DNA pull down biotin

Sequence using paired ends

NO frag & size selection

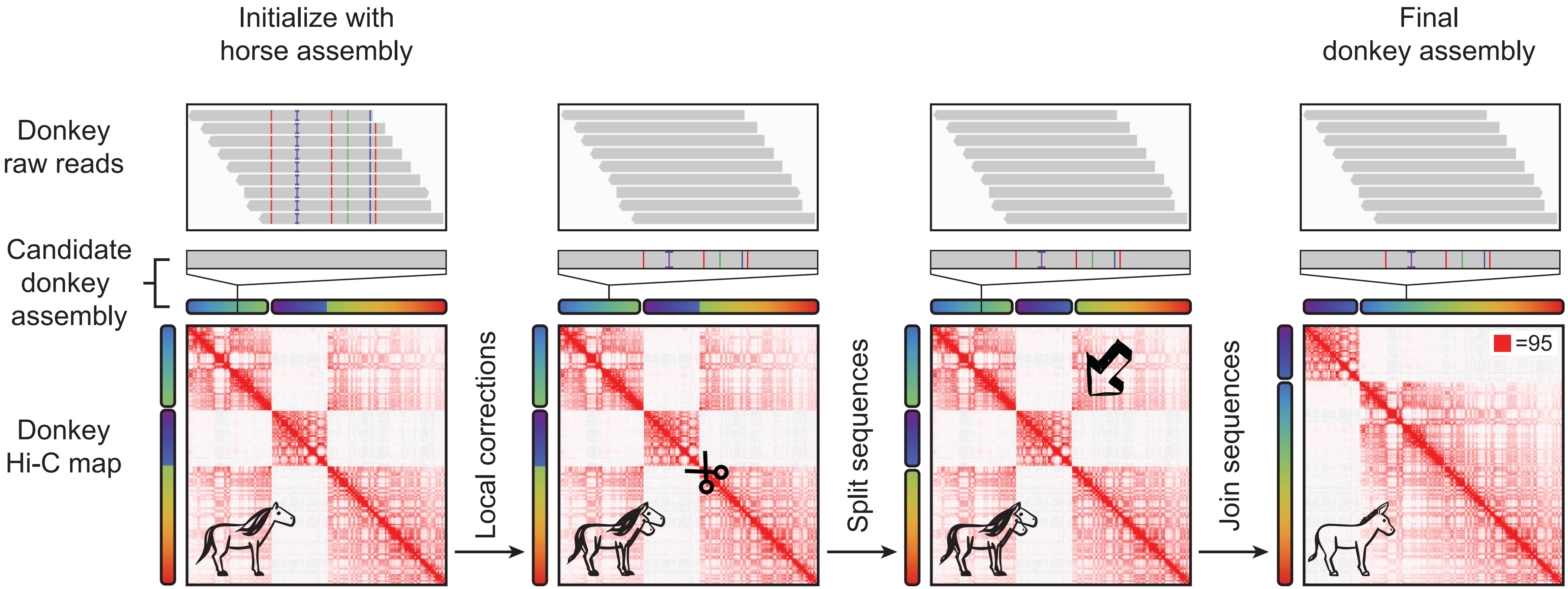


Total read count	4,444,894,354
Unique paired alignments (loxAfr3)	24,415,411
Unique paired (%)	0.55%
Long-range (20kb)	1,763,225
Long-range (%)	0.04%



Hi-C assisted assembly

Dubchenko et al. Science. 2017 Apr 7;356(6333):92-95



Initialize with horse assembly

Final donkey assembly

Donkey raw reads

Candidate donkey assembly

Donkey Hi-C map

Local corrections

Split sequences

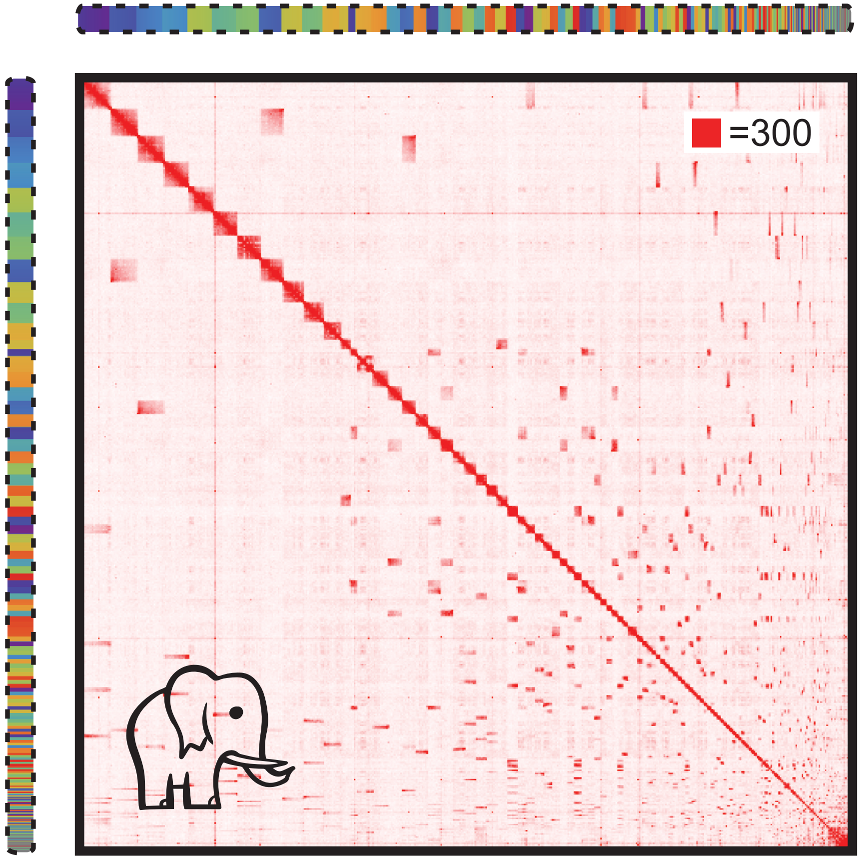
Join sequences

correct · split · orient · order

This is a Hi-C from mammoth

based on Loxafr3.0

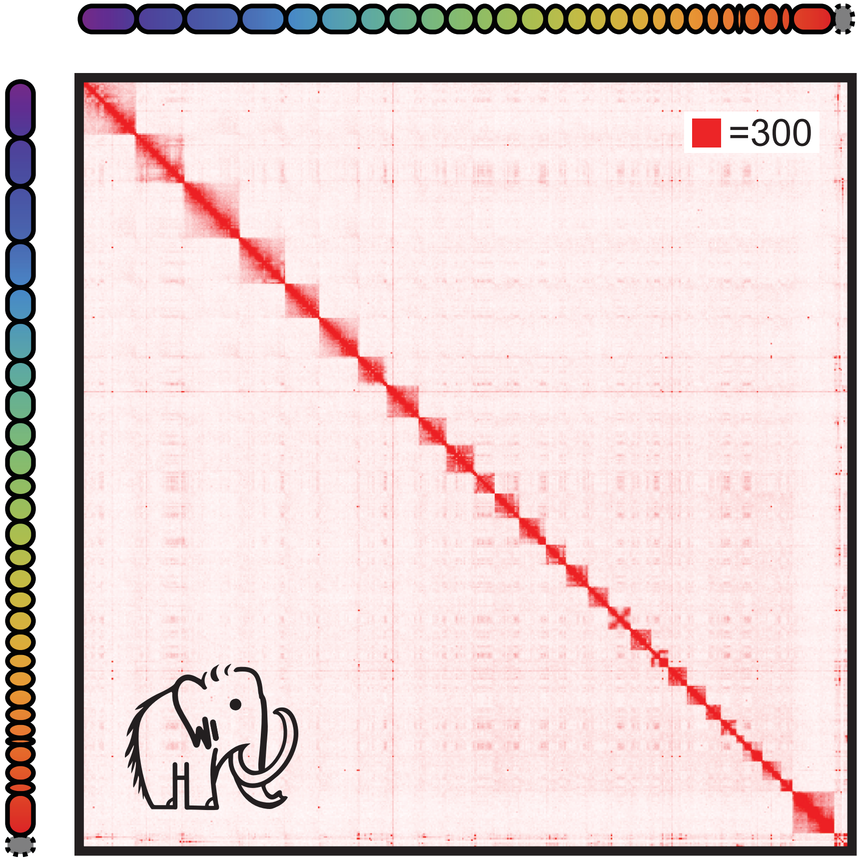
PaleoHi-C vs Loxafr3.0,
fragmentary African elephant assembly



3D assisted assembly

→

PaleoHi-C vs MamPri_Loxafr3.0_assisted_HiC,
chromosome-length mammoth assembly



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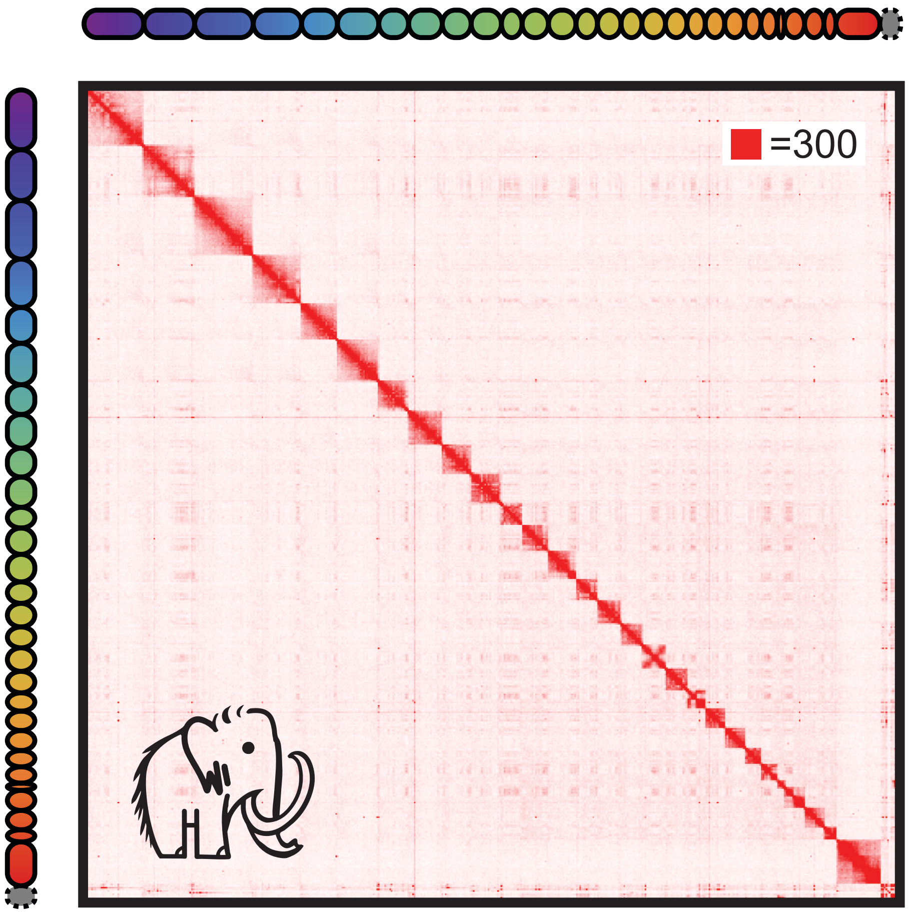
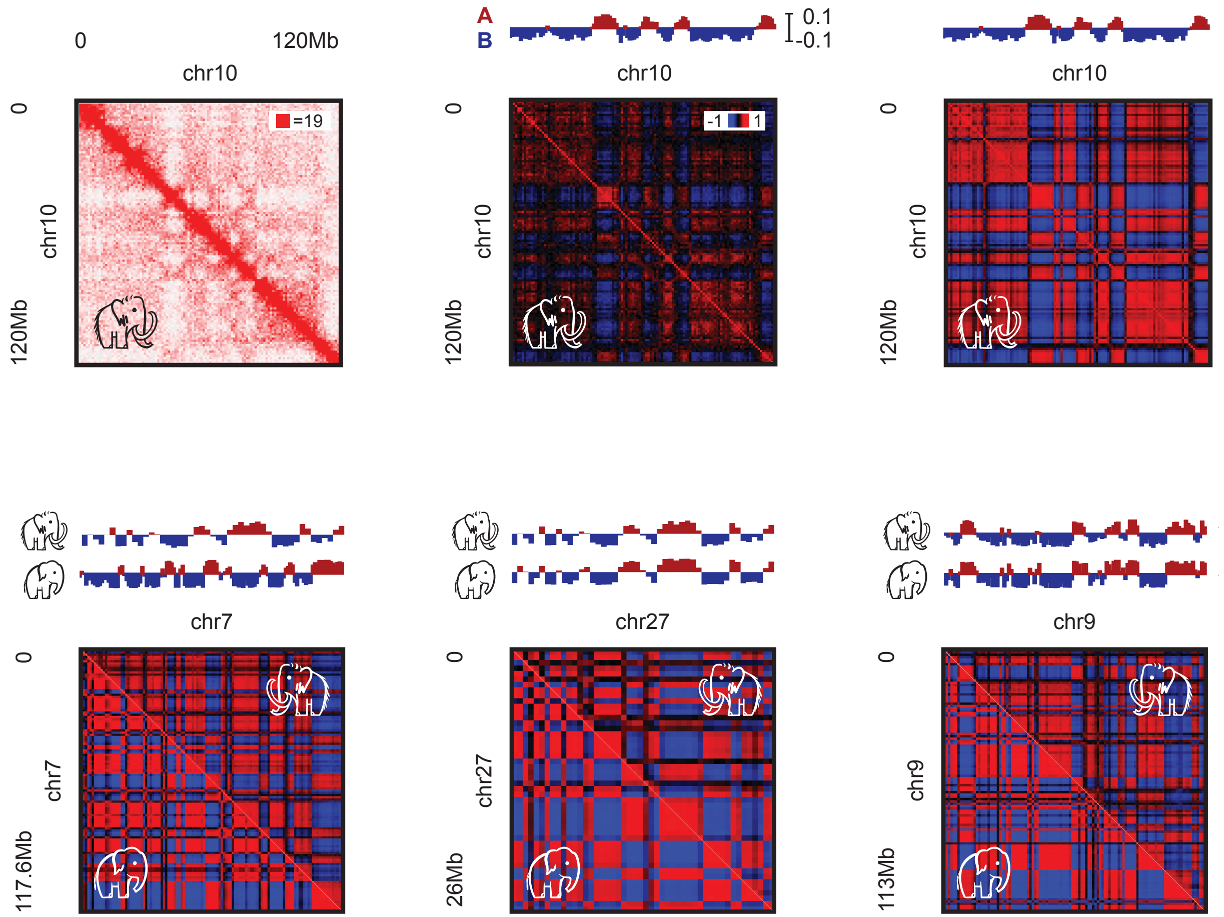
Hallmarks of a successful Hi-C experiment

- Chromosome territories

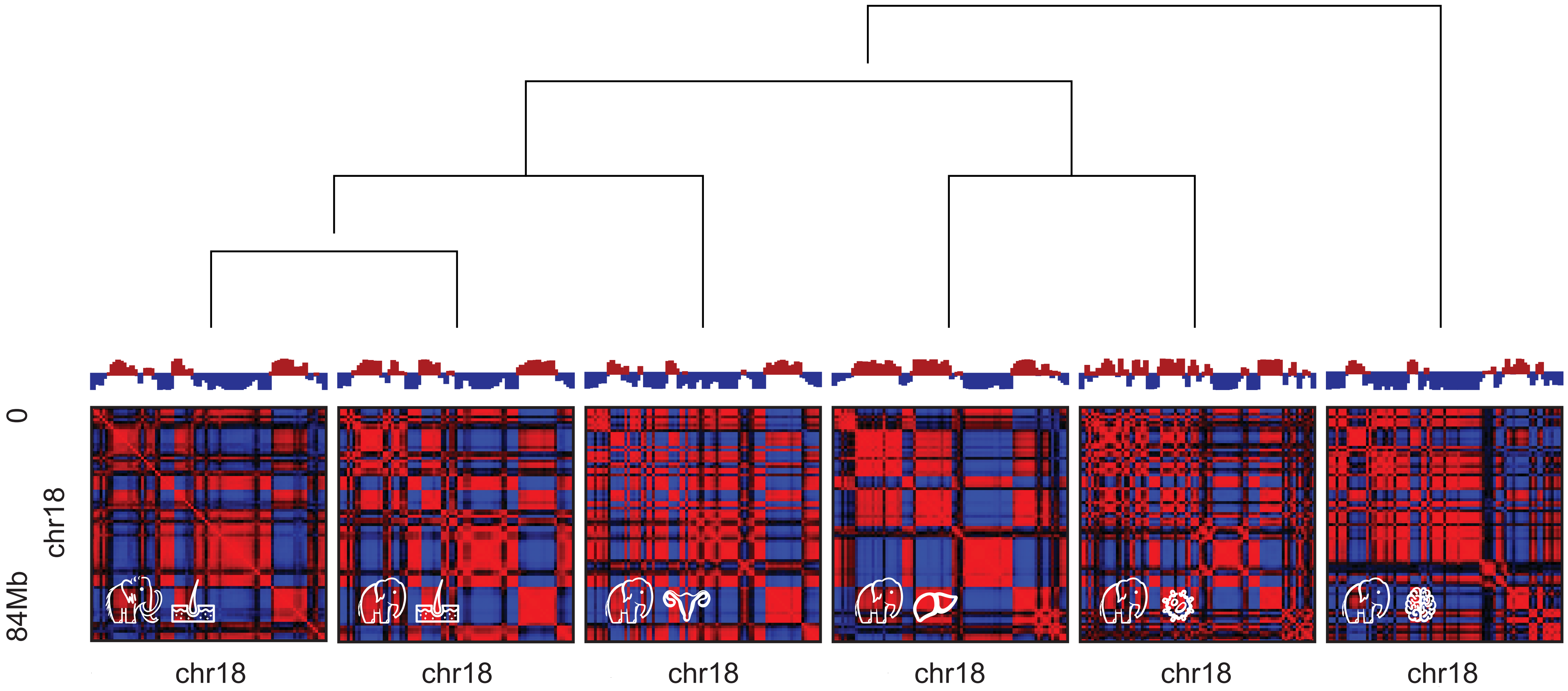
  Facilitates **de novo assembly of whole chromosomes**

Compartments preserved in a 52K years old sample

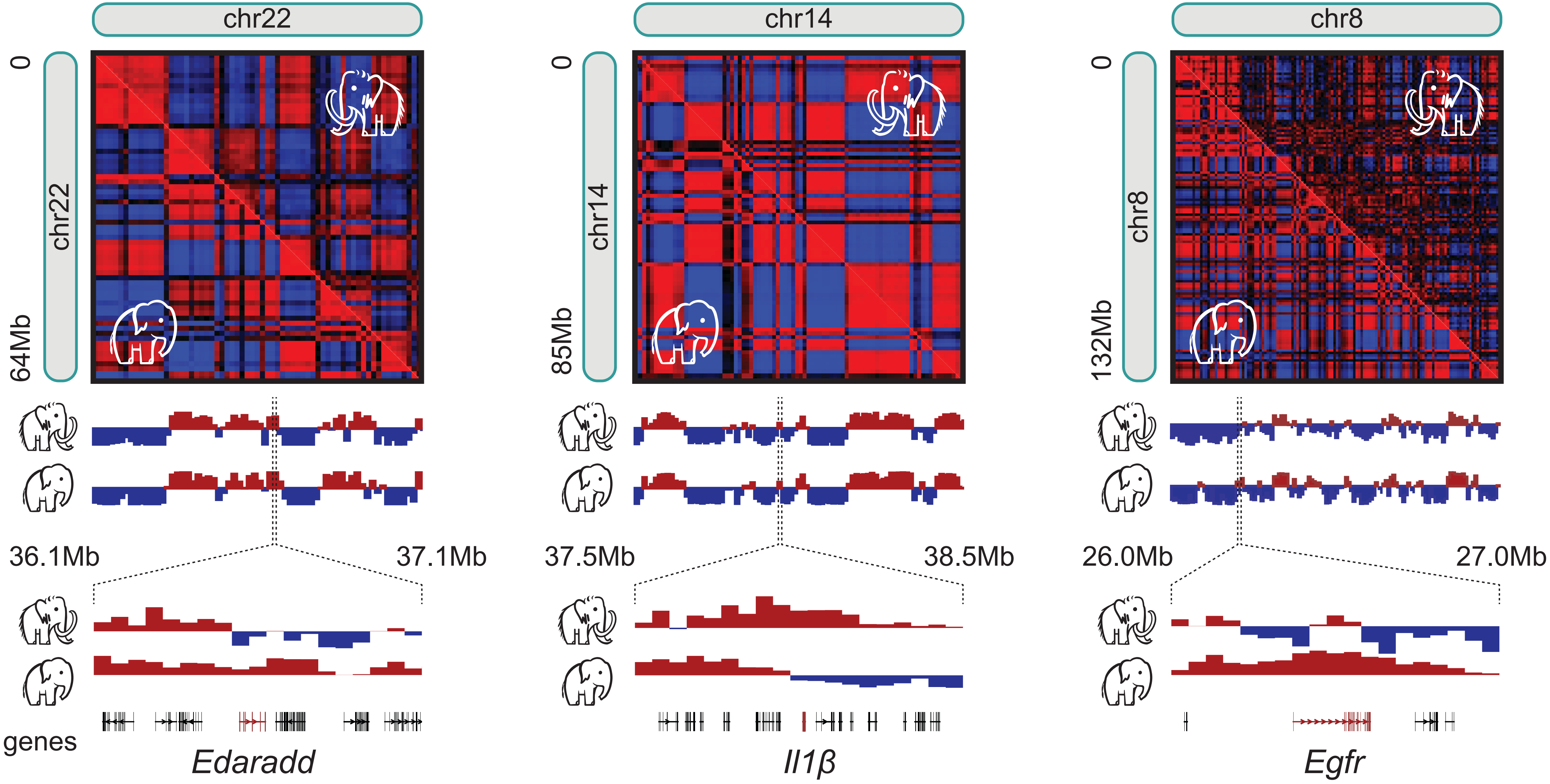




Tissue specific compartmentalization



Mammoth Altered Regulation Sequences (MARS)



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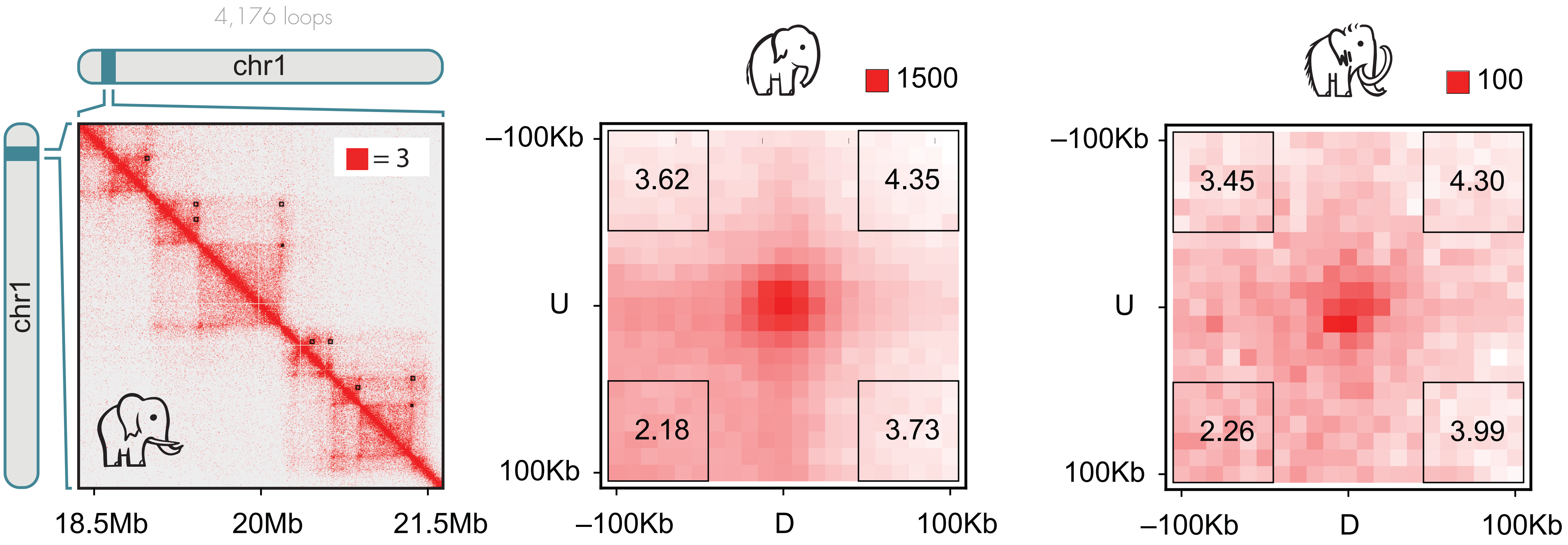
Hallmarks of a successful Hi-C experiment

- Chromosome territories
  Facilitates **de novo assembly of whole chromosomes**

- Active and inactive chromatin compartments
  Probes **Transcriptional activity**

Paleo-hic recovers loop signatures!

Rao, Huntley et al., Cell 2014



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Limitations of (a)DNA-Seq	Hallmarks of a successful Hi-C experiment
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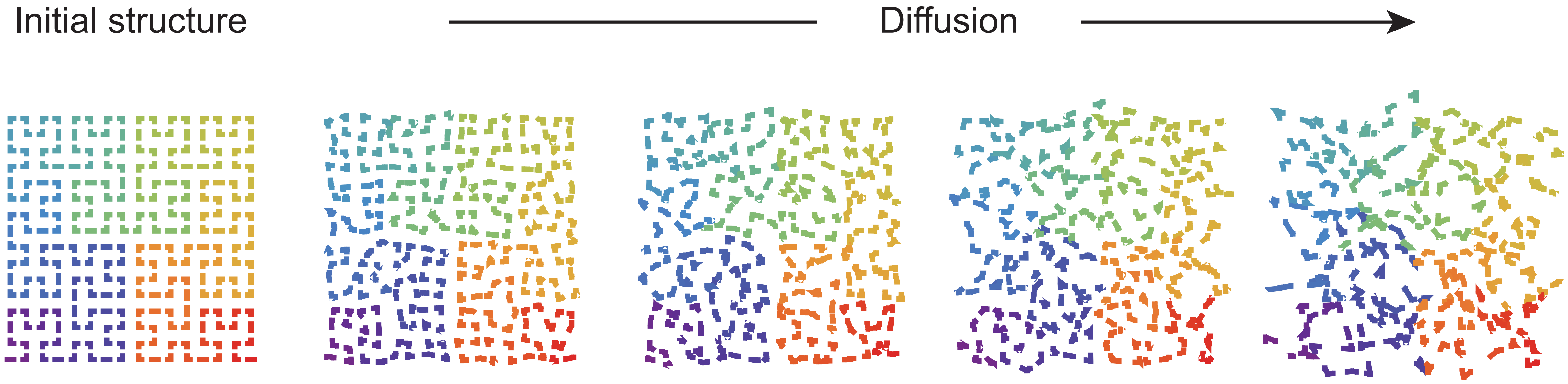
What is expressed in individual tissues? Need to probe transcriptional activity!	- Active and inactive chromatin compartments Probes **Transcriptional activity**
How expression patterns arise? Need to probe genetic regulation!	- Chromatin Loops Reveals **regulation of individual genes**

How is this possible?

The "chromoglass" hypothesis



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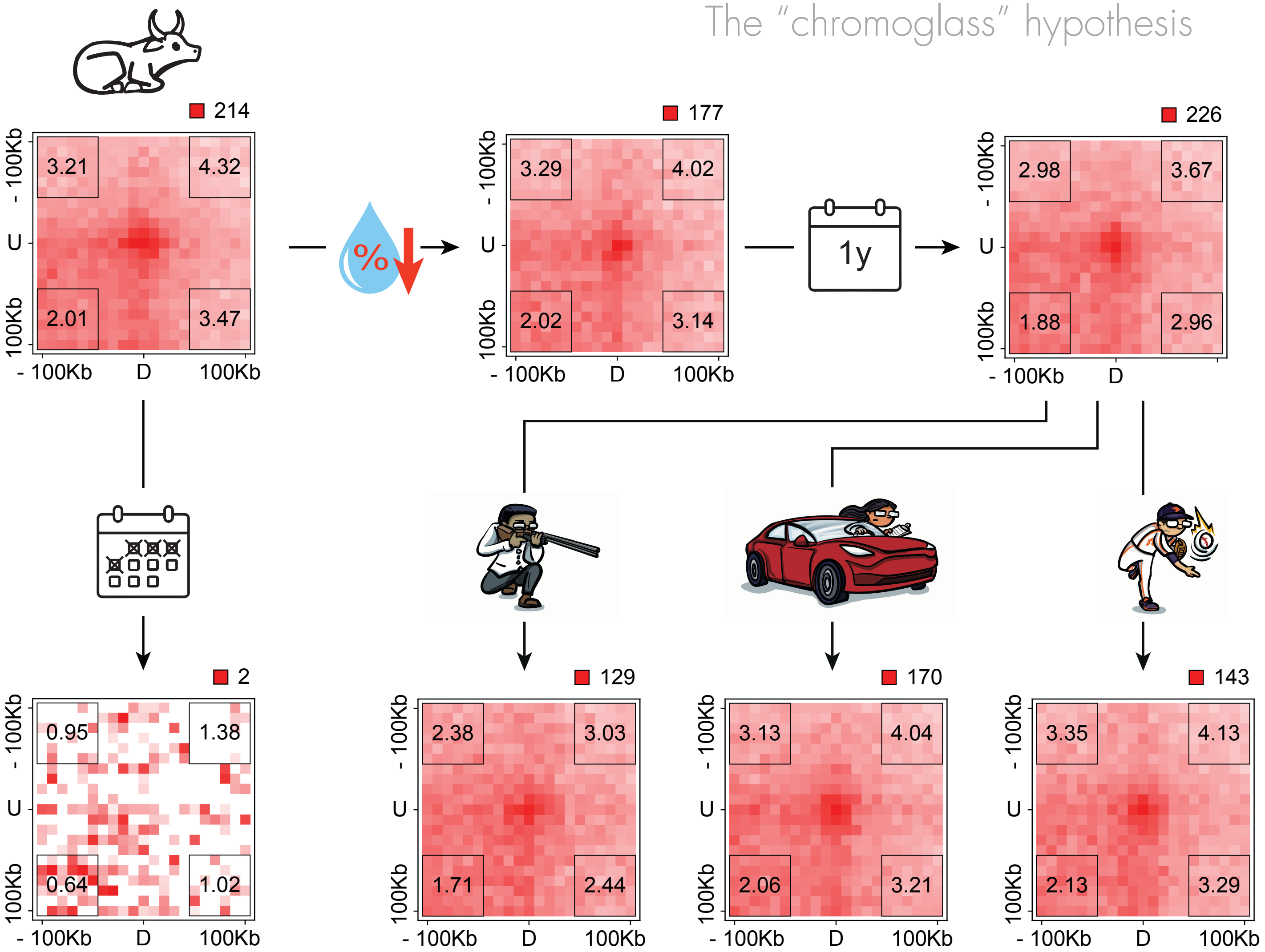

THREE-DIMENSIONAL GENOME ARCHITECTURE PERSISTS IN A 52,000-YEAR-OLD WOOLLY MAMMOTH SKIN SAMPLE

Marcela Sandoval-Velasco[#], Olga Dudchenko[#,†], Juan Antonio Rodríguez[#], Cynthia Pérez Estrada[#], Marianne Dehasque, Claudia Fontsere, Sarah S.T. Mak, Ruqayya Khan, Vinícius G. Contessoto, Antonio B. Oliveira Junior, Achyuth Kalluchi, Bernardo J. Zubillaga Herrera, Jiyun Jeong, Renata P. Roy, Ishawnia Christopher, David Weisz, Arina D. Omer, Sanjit S. Batra, Muhammad S. Shamim, Neva C. Durand, Brendan O'Connell, Alfred L. Roca, Maksim V. Plikus, Mariya A. Kusliy, Svetlana A. Romanenko, Natalya A. Lemskaya, Natalya A. Serdyukova, Svetlana A. Modina, Polina L. Perelman, Elena A. Kizilova, Sergei I. Baiborodin, Nikolai B. Rubtsov, Gur Machol, Krisha Rath, Ragini Mahajan, Parwinder Kaur, Andreas Gnirke, Isabel Garcia-Treviño, Rob Coke, Joseph P. Flanagan, Kelcie Pletch, Aurora Ruiz-Herrera, Valerii Plotnikov, Innokentiy S. Pavlov, Naryya I. Pavlova, Albert V. Protopopov, Michele Di Pierro, Alexander S. Graphodatsky, Eric S. Lander, M. Jordan Rowley, Peter G. Wolynes, José N. Onuchic, Love Dalén, Marc A. Marti-Renom[†], M. Thomas P. Gilbert[†], Erez Lieberman Aiden[†]

Cell 2024

Take home messages:

Mammoth foot
Photo credit: Love Dalén

- Hi-C was done in a 52,000-year-old well conserved sample.
- Chromosome fossils also enable to assemble the entire genome of extinct species.
- Chromosome fossils help to interpret how the genomes of those species were organized in space as well as its functional activity.
- Key mammoth genes associated with hair follicle development were active in mammoth compared to modern elephants.
- Specific loop interactions in the genome regulating gene expression were also visible and conserved in the mammoth sample.
- Chromoglass (a glass-like-state of the chromosomes) allowed the genome structure to be physically conserved over such long period of time.

https://tinyurl.com/MammothPaper

http://marciuslab.org
http://3DGenomes.org

@mamartirenom

cnag CRG Centre for Genomic Regulation ICREA

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Federica Di Palma et al.

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