

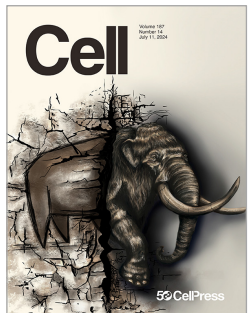


Picture from the book: Castells i Castellers. Una voluntat col·lectiva.

Fossilized chromosomes from woolly mammoth

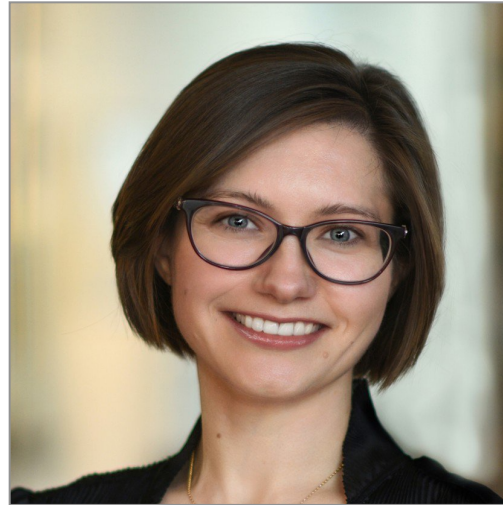
Marc A. Marti-Renom
CNAG-CRG · ICREA

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





Marcela Sandoval Velasco
(ex) Gilbert Lab



Olga Dudchenko
Aiden Lab

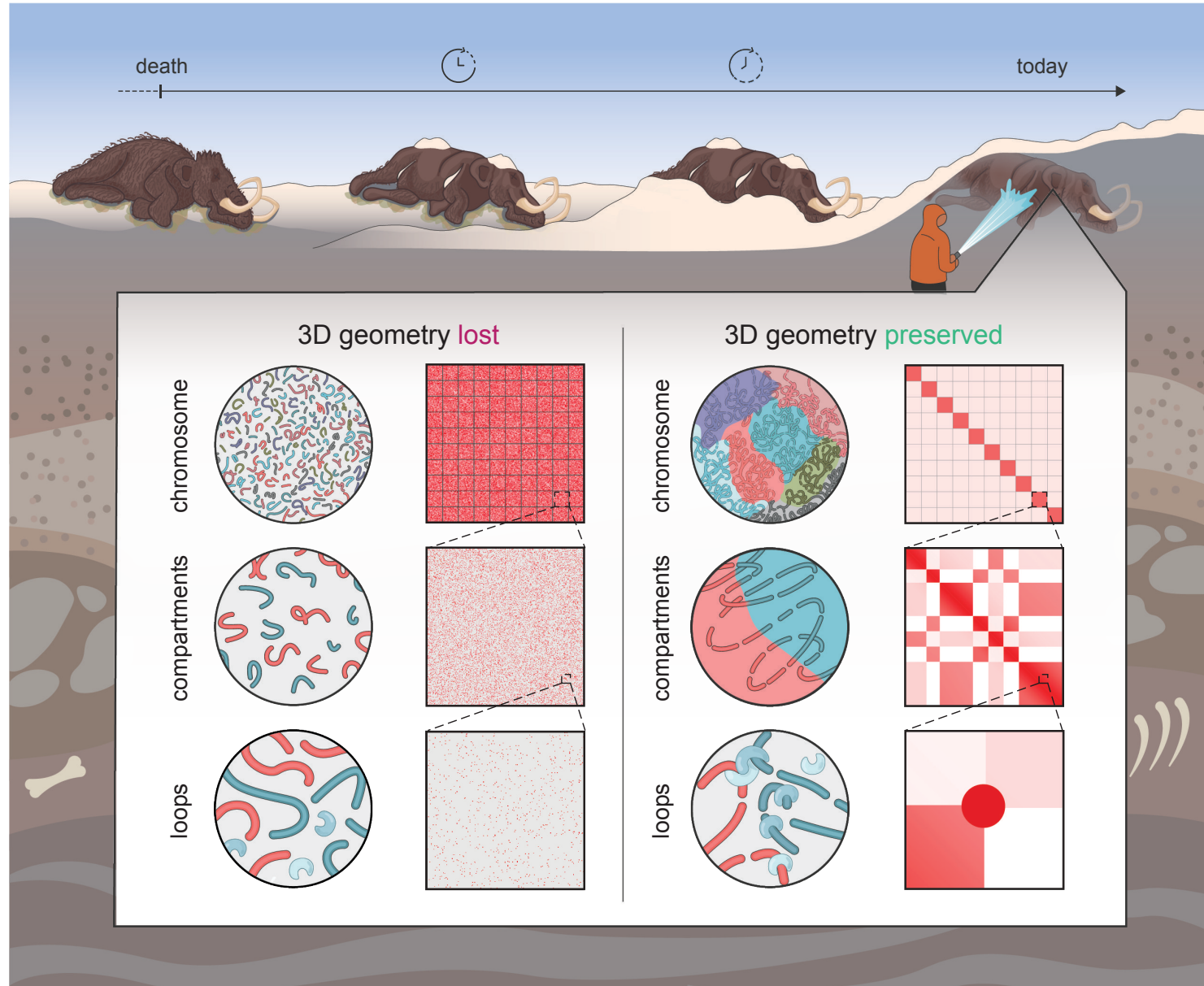


Juan Antonio Rodríguez
(ex) Marti-Renom Lab



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

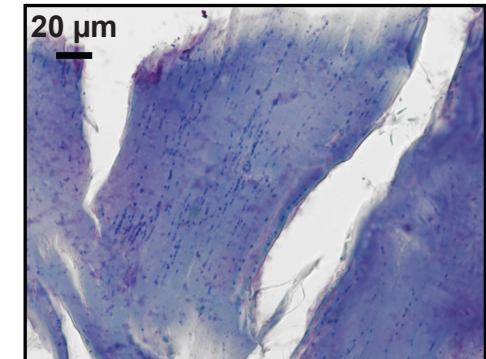
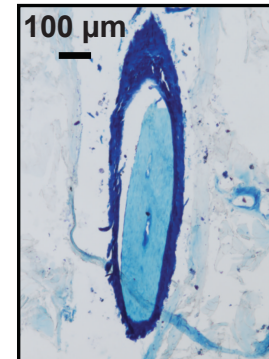
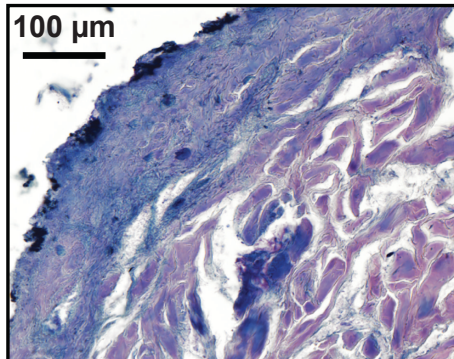
Dan Fisher

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

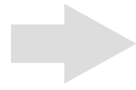


Paleo-HiC complements ancient DNA-seq

Limitations of (a)DNA-Seq

What is in the genome?

Need chrom-length de novo assemblies!
aDNA-Seq relies on modern references



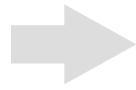
What is expressed in individual tissues?

Need to probe transcriptional activity!

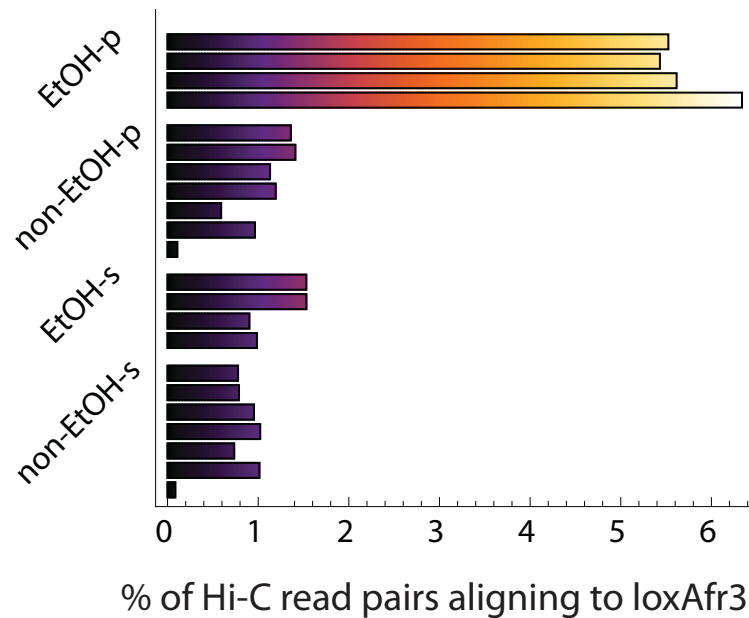
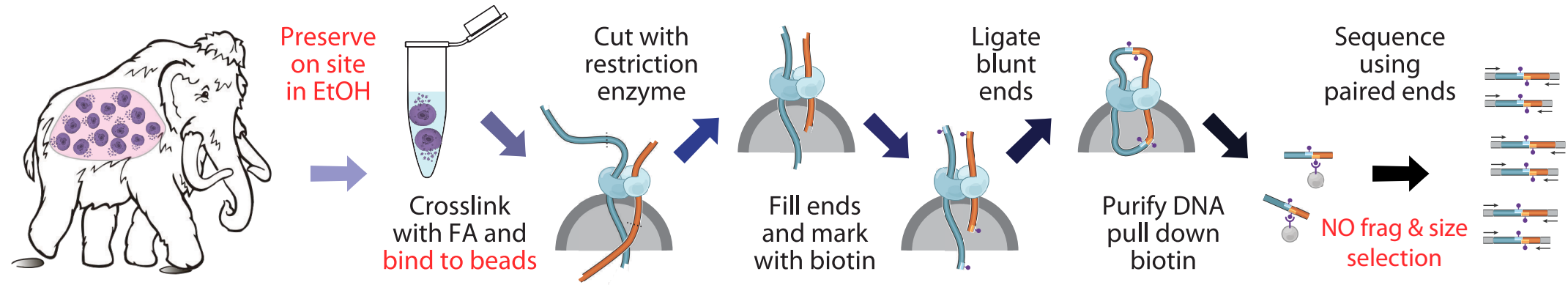


How expression patterns arise?

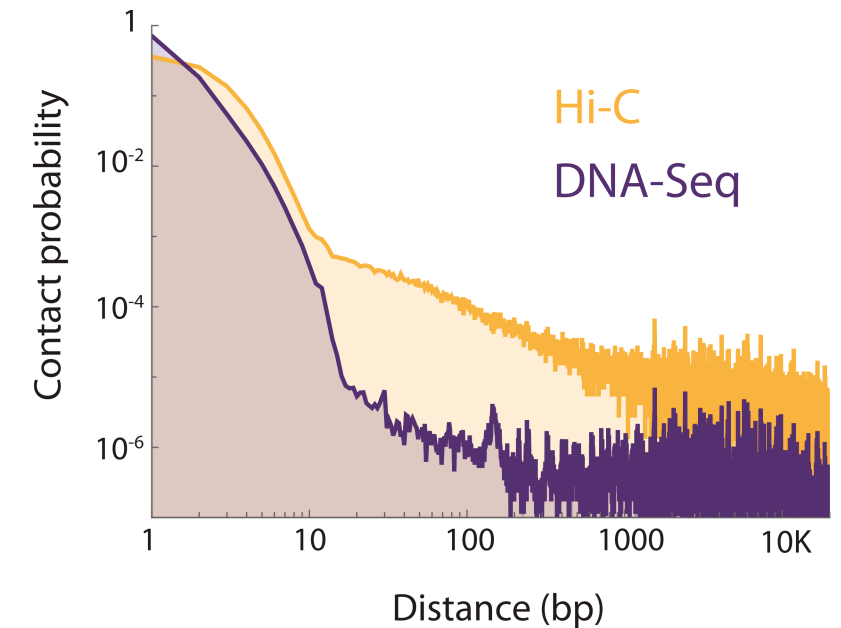
Need to probe genetic regulation!



Paleo-HiC improves endogenous long-range contact recovery



| | |
|------------------------------------|---------------|
| 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% |



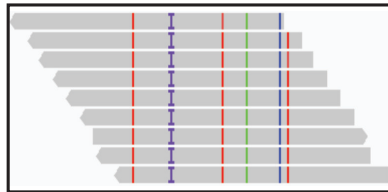
Hi-C assisted assembly

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

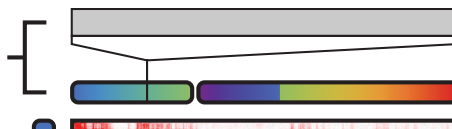
Initialize with
horse assembly

Final
donkey assembly

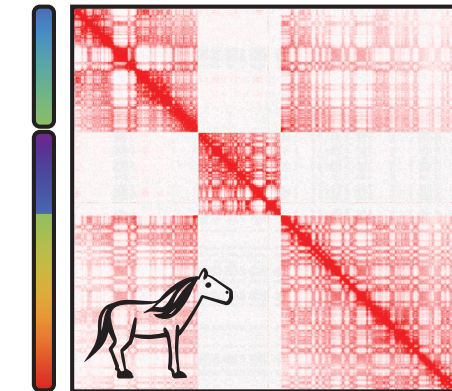
Donkey
raw reads



Candidate
donkey
assembly



Donkey
Hi-C map



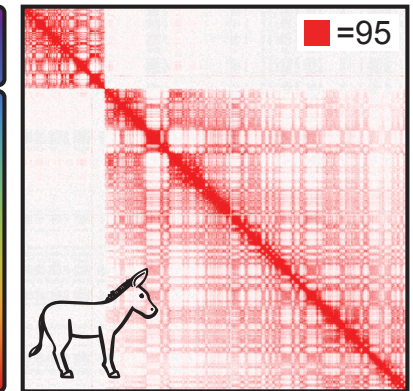
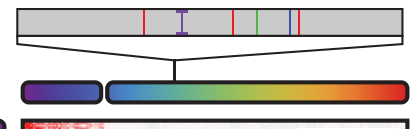
Local corrections



Split sequences



Join sequences

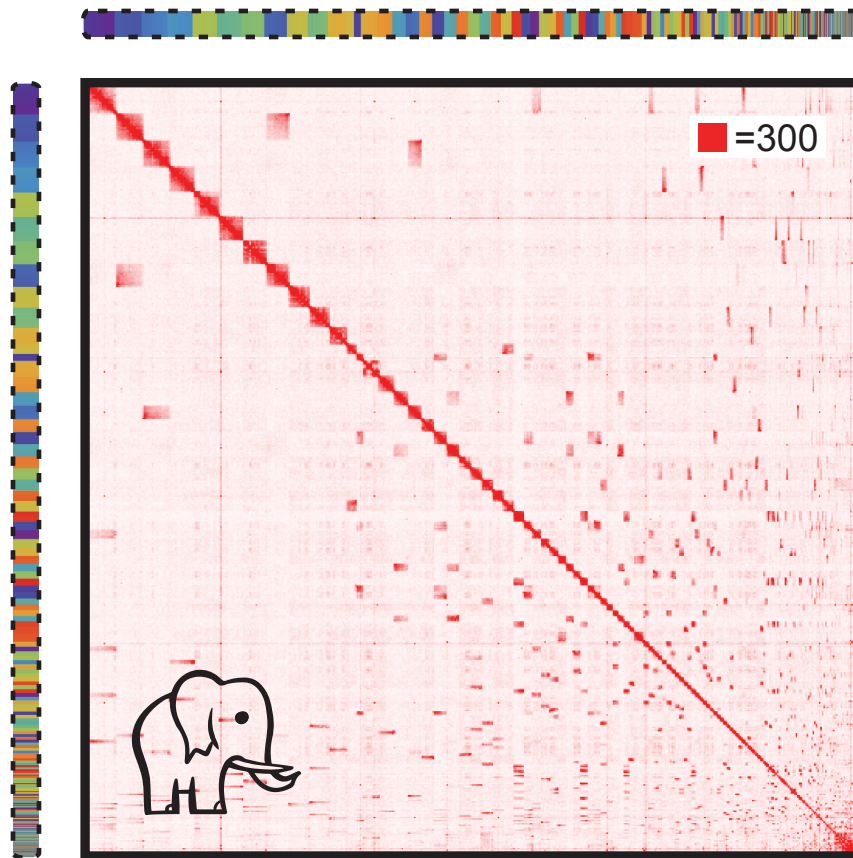


correct · split · orient · order

This is a Hi-C from mammoth

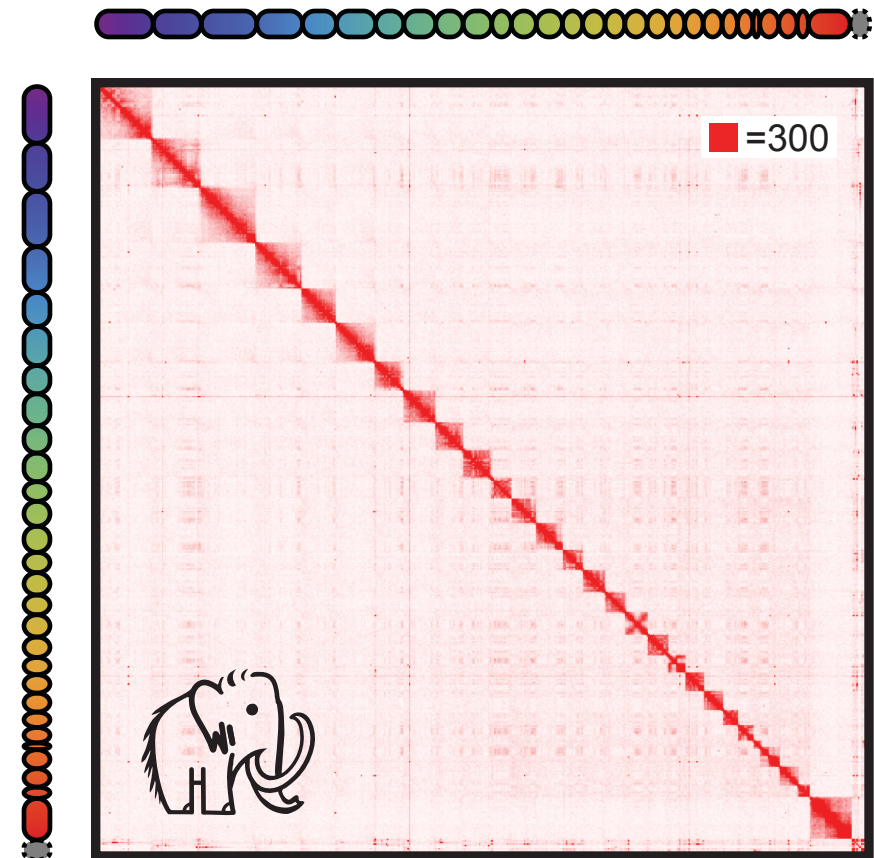
based on Loxafr3.0

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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What is in the genome?

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Hallmarks of a successful Hi-C experiment

- Chromosome territories

Facilitates **de novo assembly of whole chromosomes**

What is expressed in individual tissues?

Need to probe transcriptional activity!

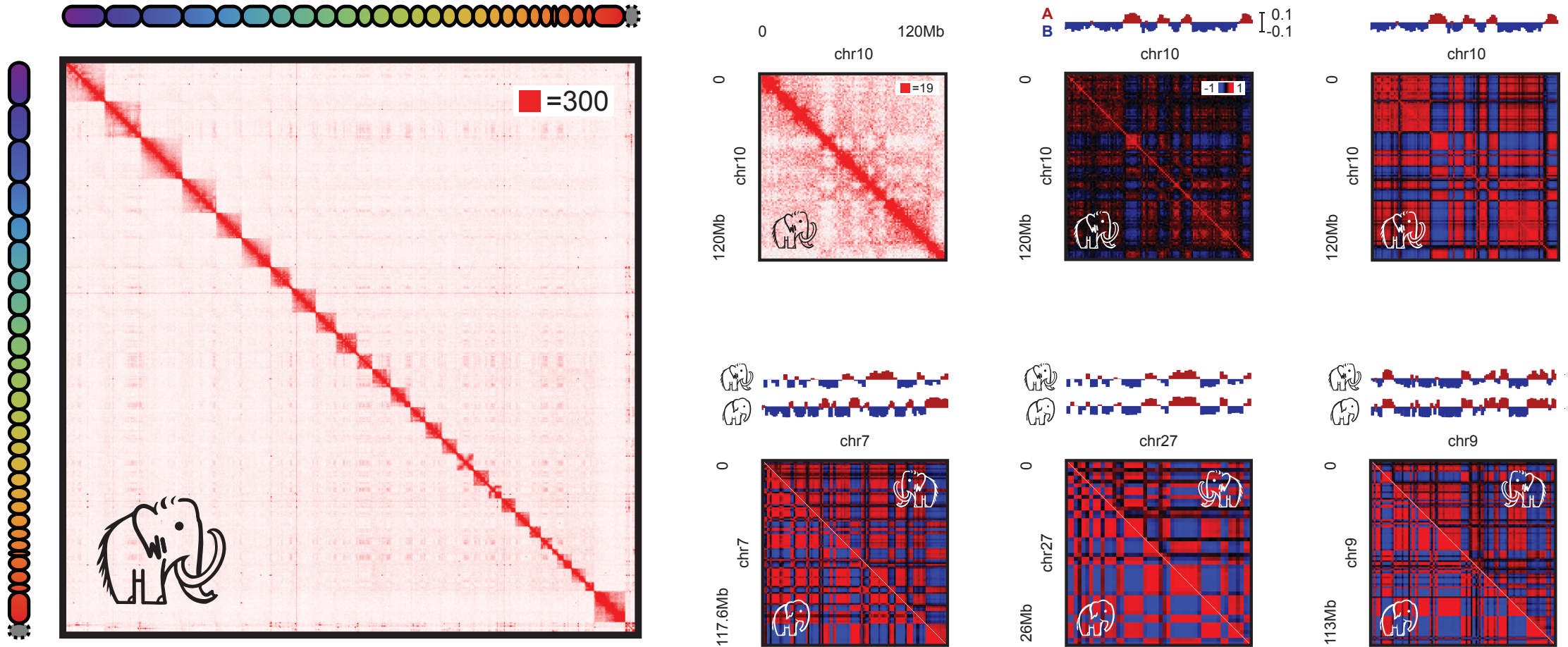


How expression patterns arise?

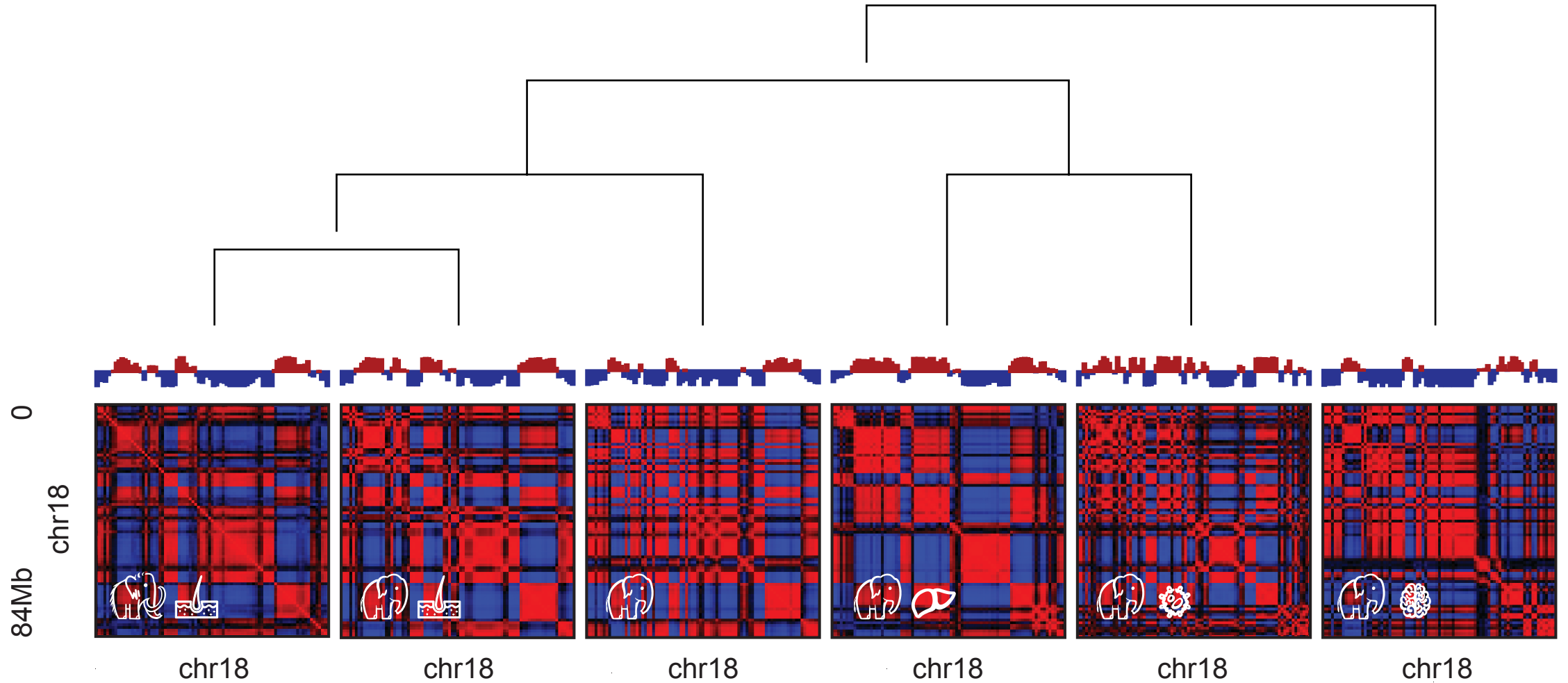
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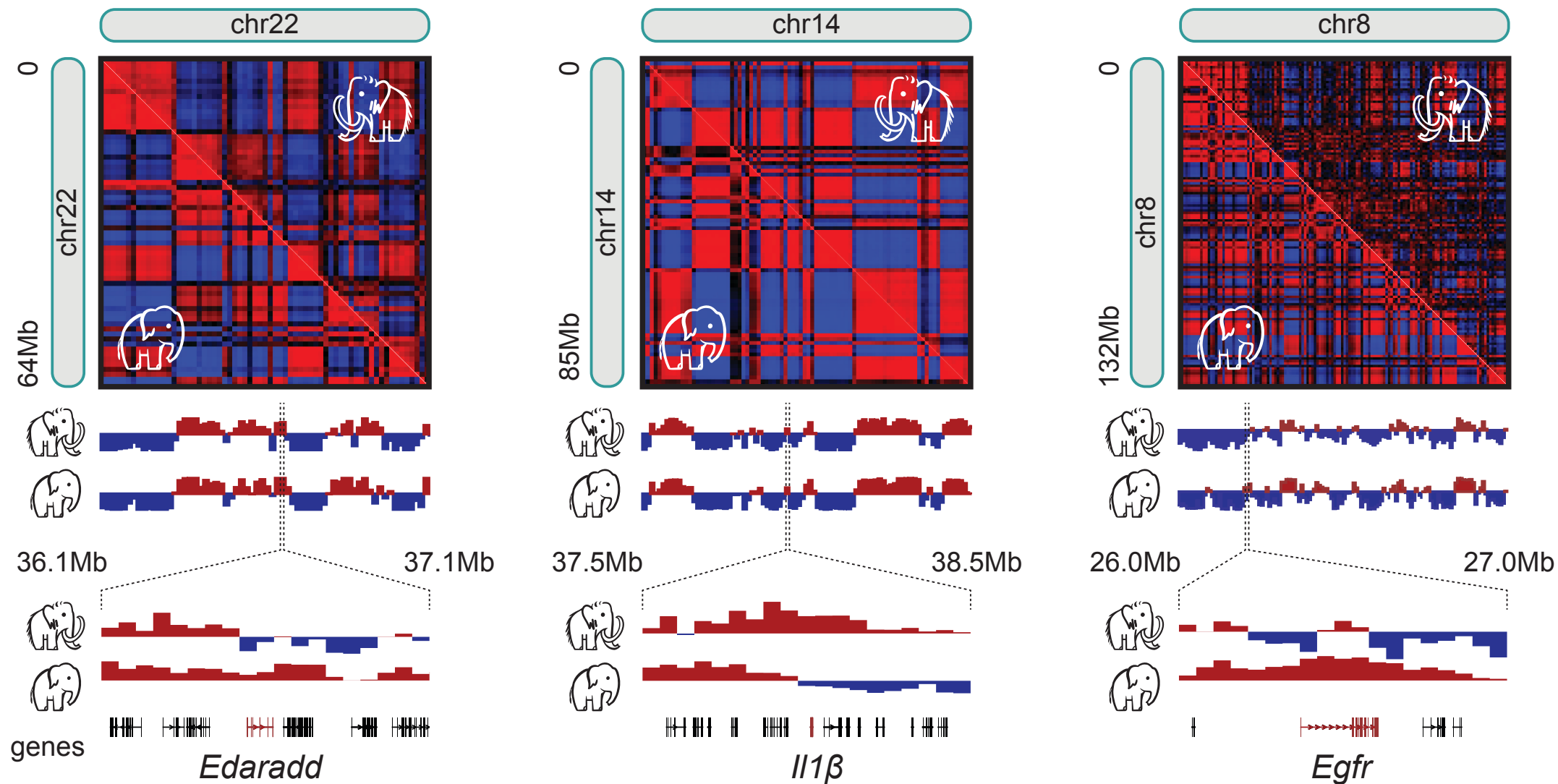
Compartments preserved in a 47K years old sample



Tissue specific compartmentalization



52 Mammoth Altered Regulation Sequences (MARS)



Paleo-HiC complements ancient DNA-seq

Limitations of (a)DNA-Seq

What is in the genome?

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- Chromosome territories
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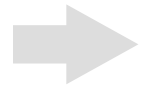
Need to probe transcriptional activity!



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

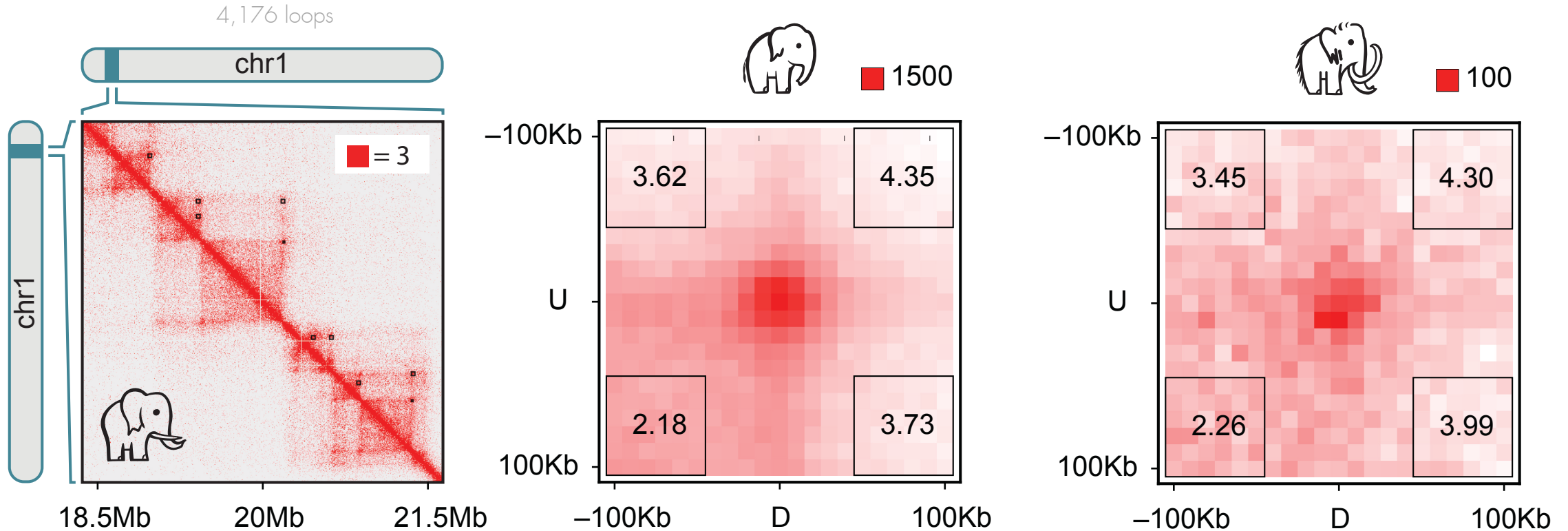
How expression patterns arise?

Need to probe genetic regulation!

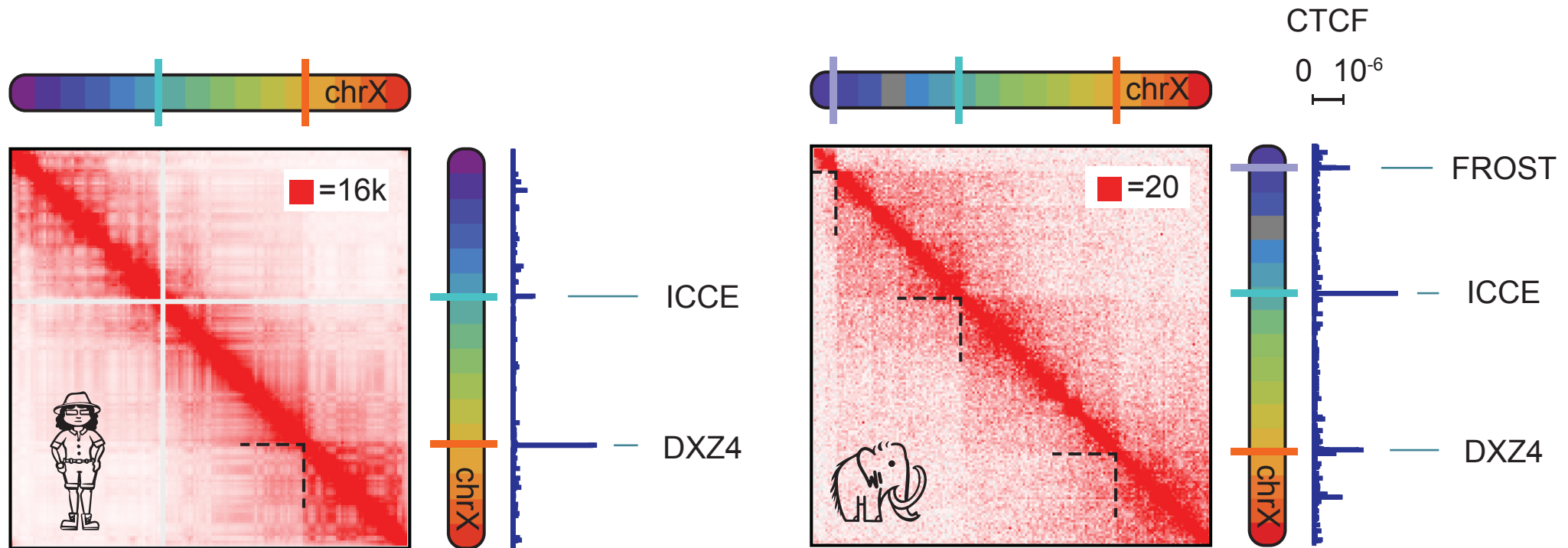


Paleo-hic recovers loop signatures!

Rao, Huntley et al., Cell 2014



Inactive chromosome X segregates



Paleo-HiC complements ancient DNA-seq

Limitations of (a)DNA-Seq

What is in the genome?

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How expression patterns arise?

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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**

- Chromatin Loops

Reveals **regulation of individual genes**

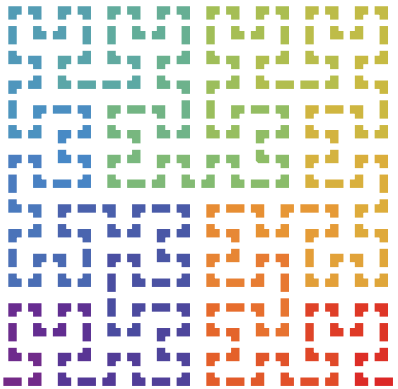
- Barr body of the inactive X

Reflects **chromosome-scale dosage compensation**

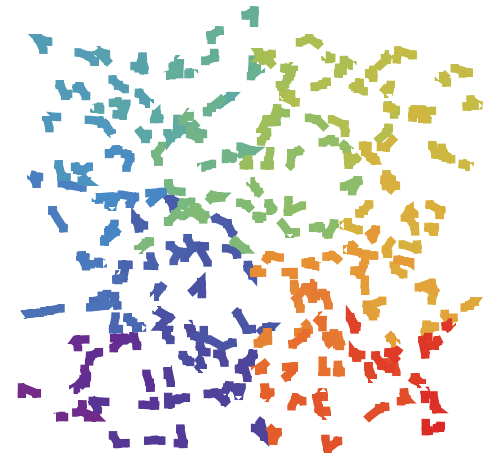
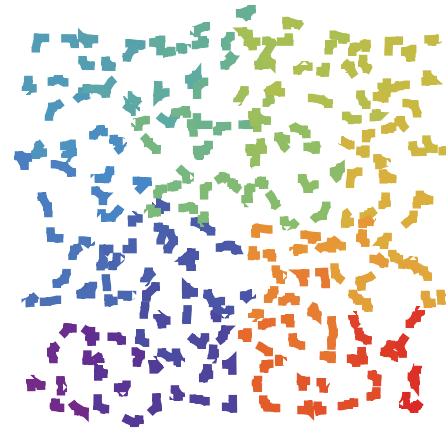
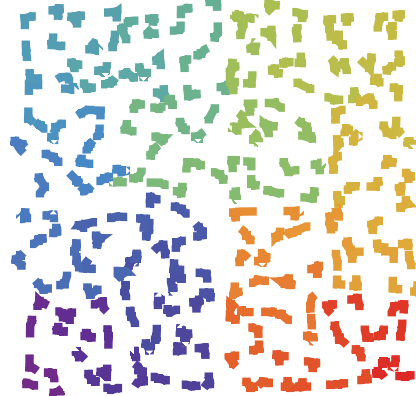
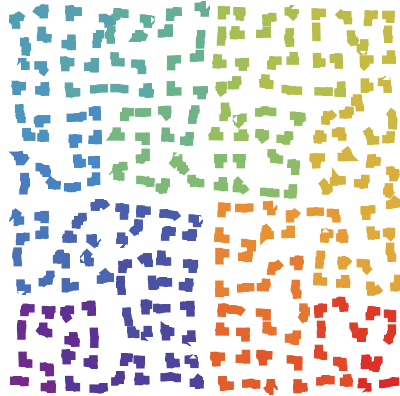
How is this possible?

The "chromoglass" hypothesis

Initial structure

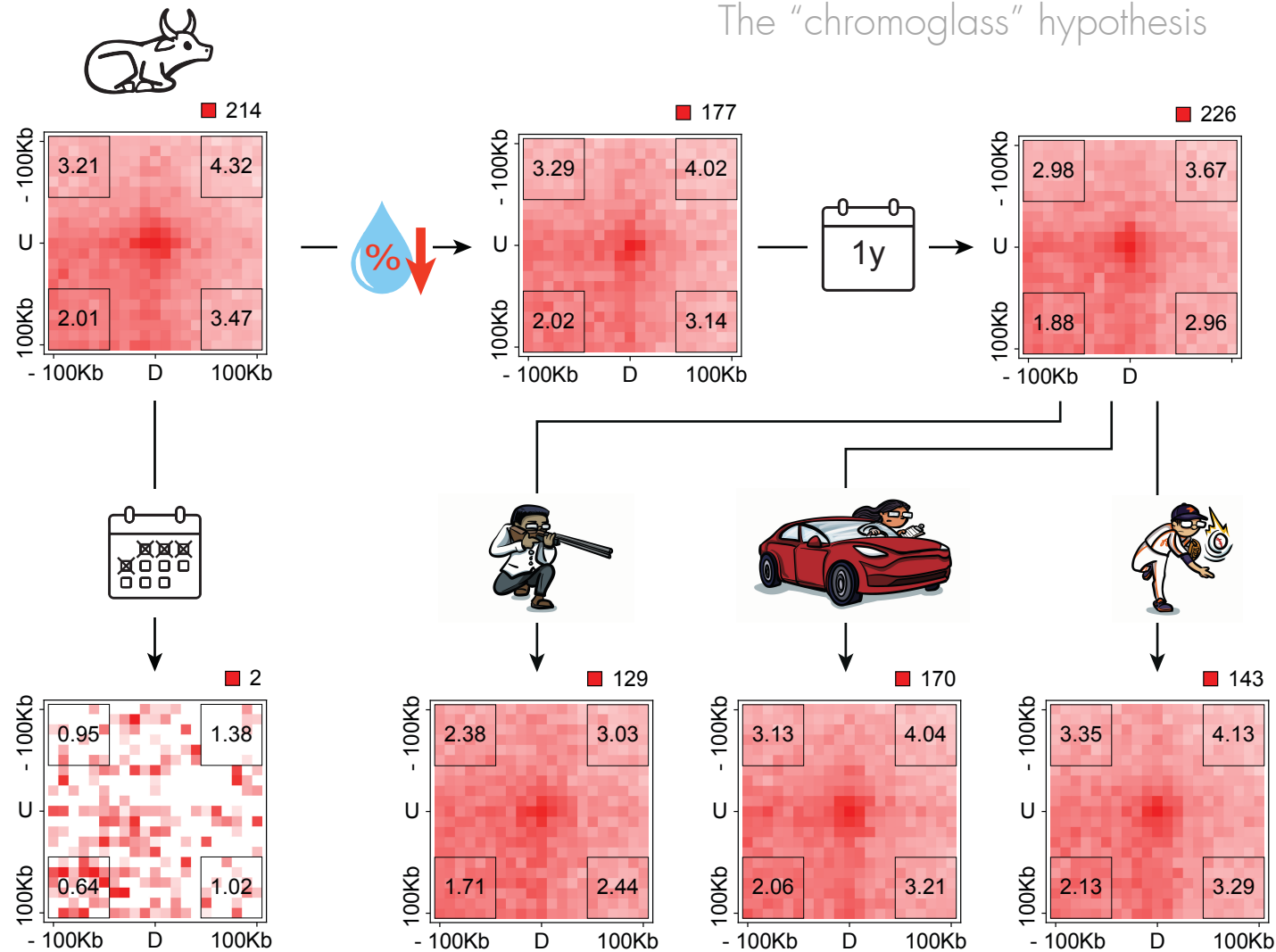


Diffusion



How is this possible?

The “chromoglass” hypothesis



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 Fontseré, 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, Krishna 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

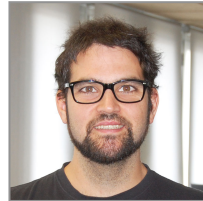
- Hi-C was done in a 52,000-year-old well conserved sample.
- Chromosome fossils also enable to assemble the entire genome of extinct species.
- Chromosome fossils help to interpret how the genomes of those species were organized in space as well as its functional activity.
- Key mammoth genes associated 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



Juan Antonio Rodríguez



Marcela Sandoval Velasco
Tom Gilbert

Olga Dudchenko
Cynthia Perez Estrada
Erez Lieberman Aiden



Love Dalén



Jordan Rowley



Aurora Ruiz-Herrera



Kerstin Lidblad-Toh,
Federica Di Palma et al.



The DNA Zoo

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