

3D Genomics

Marc A. Marti-Renom CNAG-CRG · ICREA

http://marciuslab.org
http://3DGenomes.org
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Chromosome Conformation Capture

Dekker, J., Rippe, K., Dekker, M., & Kleckner, N. (2002). Science, 295(5558), 1306–1311. Lieberman-Aiden, E., et al. (2009). Science, 326(5950), 289–293.



Hierarchical genome organisation

Lieberman-Aiden, E., et al. (2009). Science, 326(5950), 289–293. Rao, S. S. P., et al. (2014). Cell, 1–29.







Is this organization stable and preserved in ancient samples?



Marcela Sandoval Velasco (ex) Gilbert Lab



Olga Dudchenko Aiden Lab



Juan Antonio Rodríguez (ex) Marti-Renom Lab



Cynthia Perez Estrada (ex) Aiden Lab





Erez Lieberman Aiden



The discovery of ancient chromosome fossils

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Cell. **187** 3541–3562



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



A "whoolly" phenomenal sample



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 beyond the range of radiocarbon dating but older than >45,000 years

Photo credit: Chris Waddle









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



% of Hi-C read pairs aligning to loxAfr3

Distance (bp)

Hi-C assisted assembly

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

Initialize with horse assembly

Final donkey assembly



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

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- Chromosome territories

Facilitates de novo assembly of whole chromosomes

Compartments preserved in a 47K years old sample



Tissue specific compartmentalization chr18 84Mb

chr18 chr18 chr18 chr18 chr18 chr18

0

52 Mammoth Altered Regulation Sequences (MARS)



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- 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



Inactive chromosome X segregates



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Hallmarks of a successful Hi-C experiment

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- 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



How is this possible?

The "chromoglass" hypothesis



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.

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