Massachusetts Institute of Technology

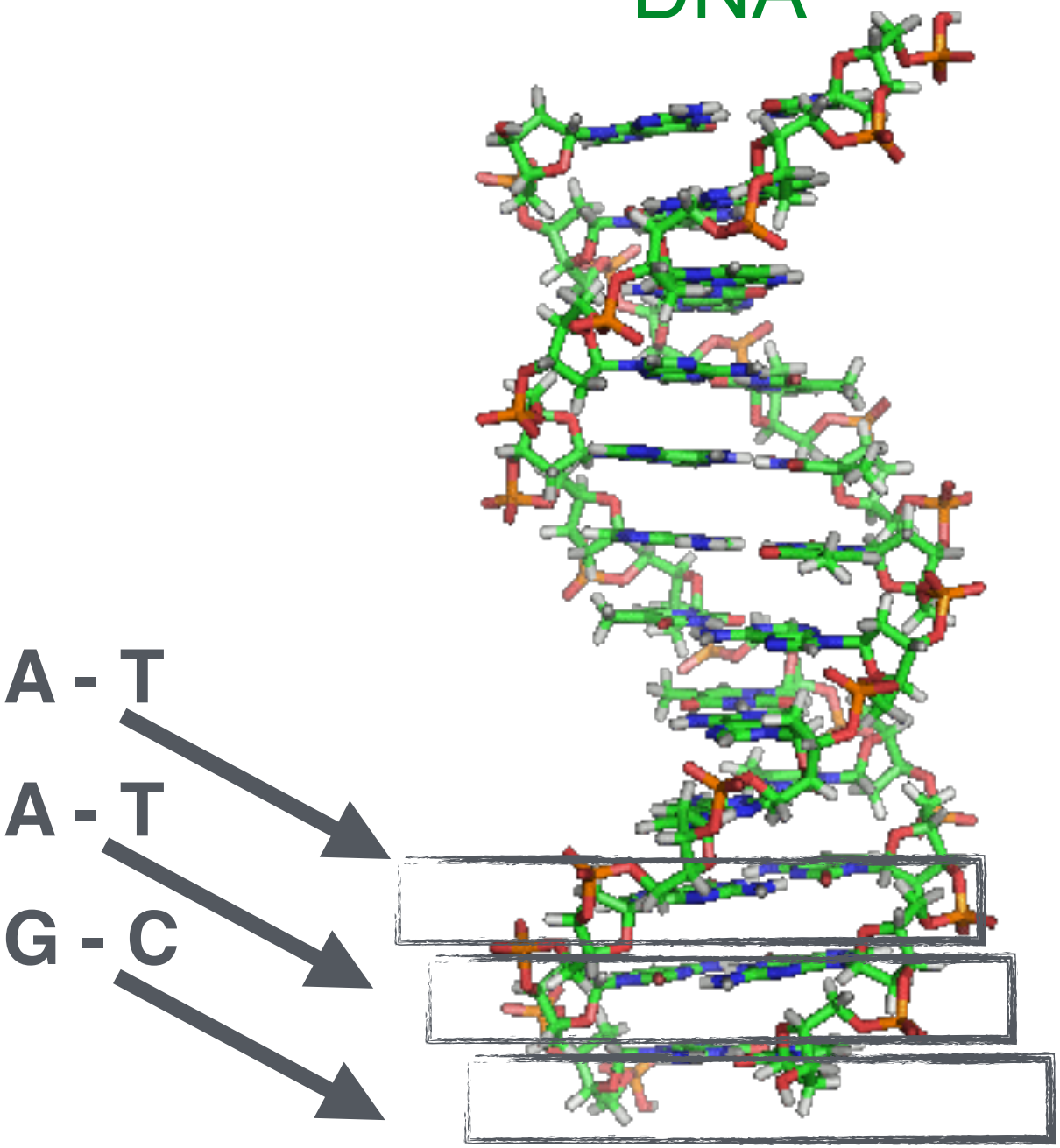
MIT DEPARTMENT OF PHYSICS

INSTITUTE FOR MEDICAL ENGINEERING & SCIENCE

Human Genome
Now in 3D!

Leonid Mirny
leonid@mit.edu

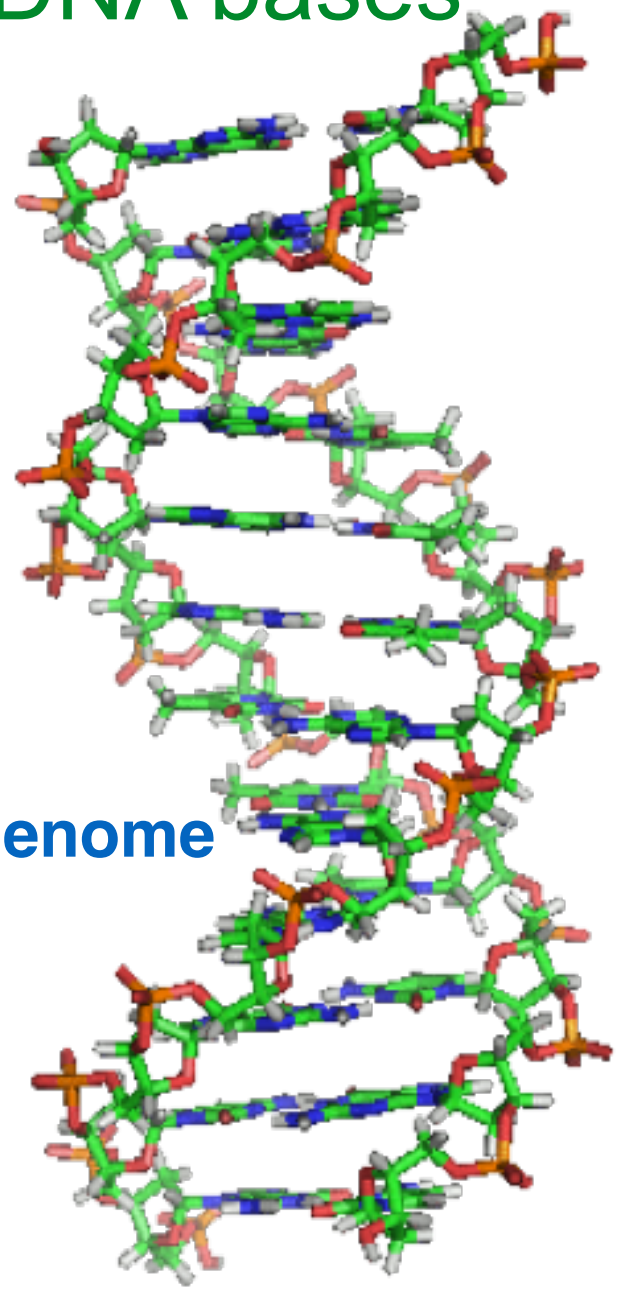
DNA



DNA bases

DNA bases

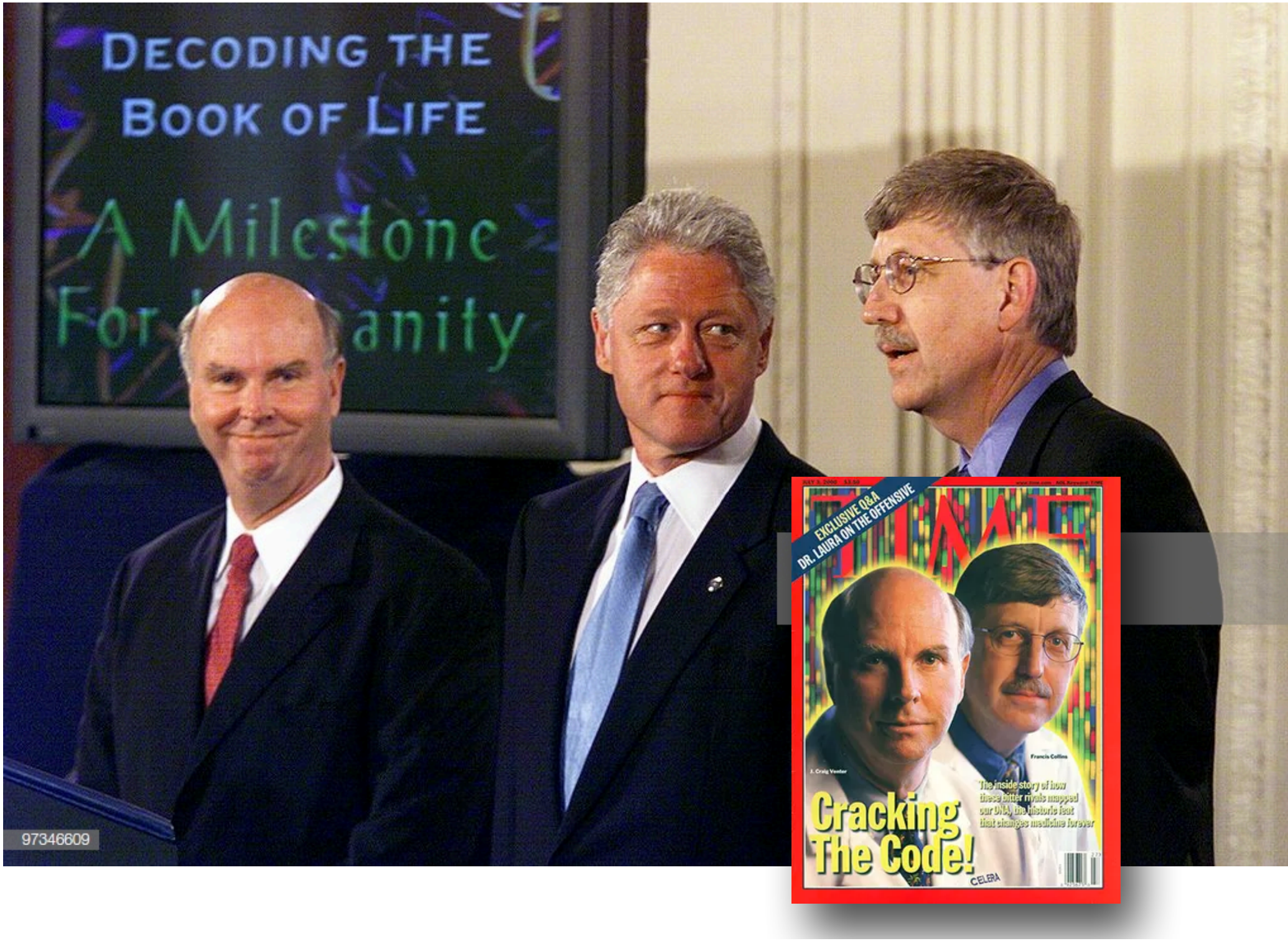
12 bases of DNA



… out of 3,000,000,000 bases of the human genome

The most important technological advancement in biology in 30 years
ability to read DNA

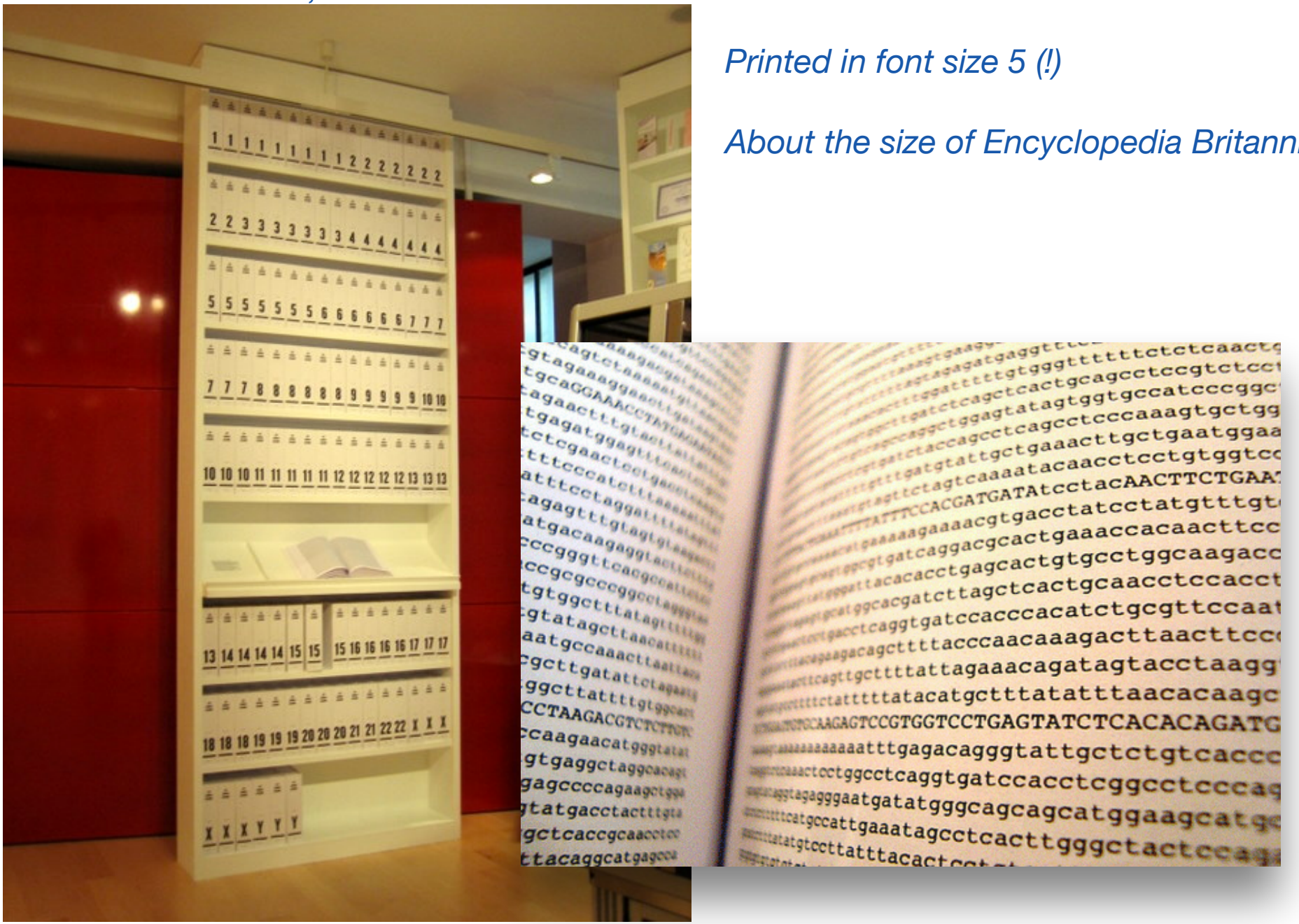
In 2001, most of 3,000,000,000 bases of the Human Genome have been read!


DECODING THE
BOOK OF LIFE
A Milestone
97346609
EXCLUSIVE Q&A
DR. LAURA ON THE OFFENSIVE
J. Craig Venter
Francis Collins
The inside story of how these bitter rivals mapped our DNA, the historic feat that changes medicine forever
Cracking The Code!
CELERA

Genome as we know it in 1D

Genome as we know it in 1D

Wellcome Collection, London



Printed in font size 5 (!)

About the size of Encyclopedia Britannica

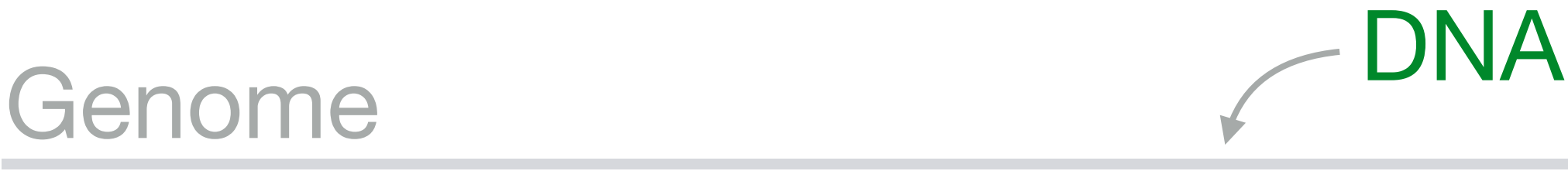
Genome as we know it in 1D

Genome as we know it in 1D

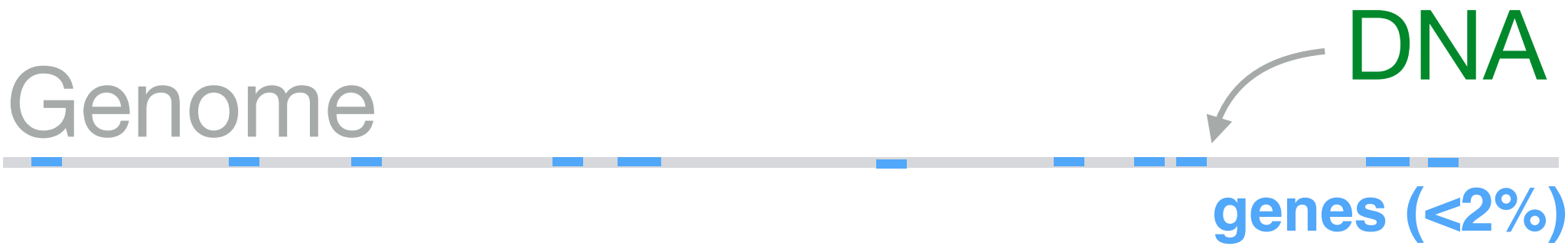
Genes

but only <2%

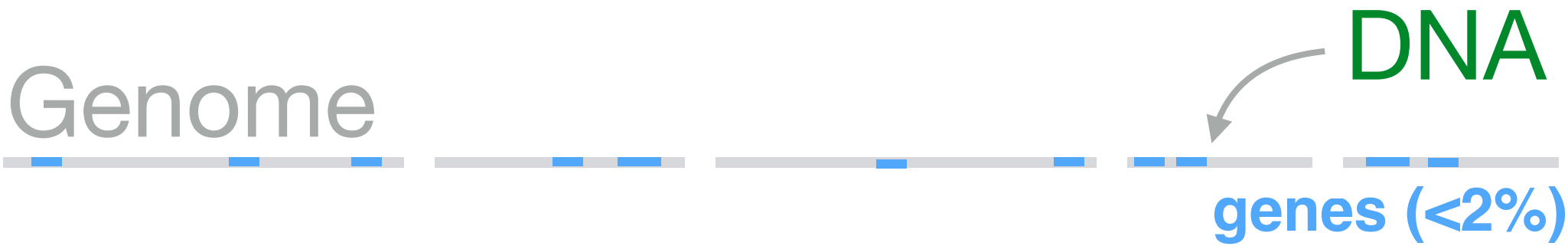
Genome as we know it in 1D



Genome as we know it in 1D



Genome as we know it in 1D



consists of 23 chromosomes

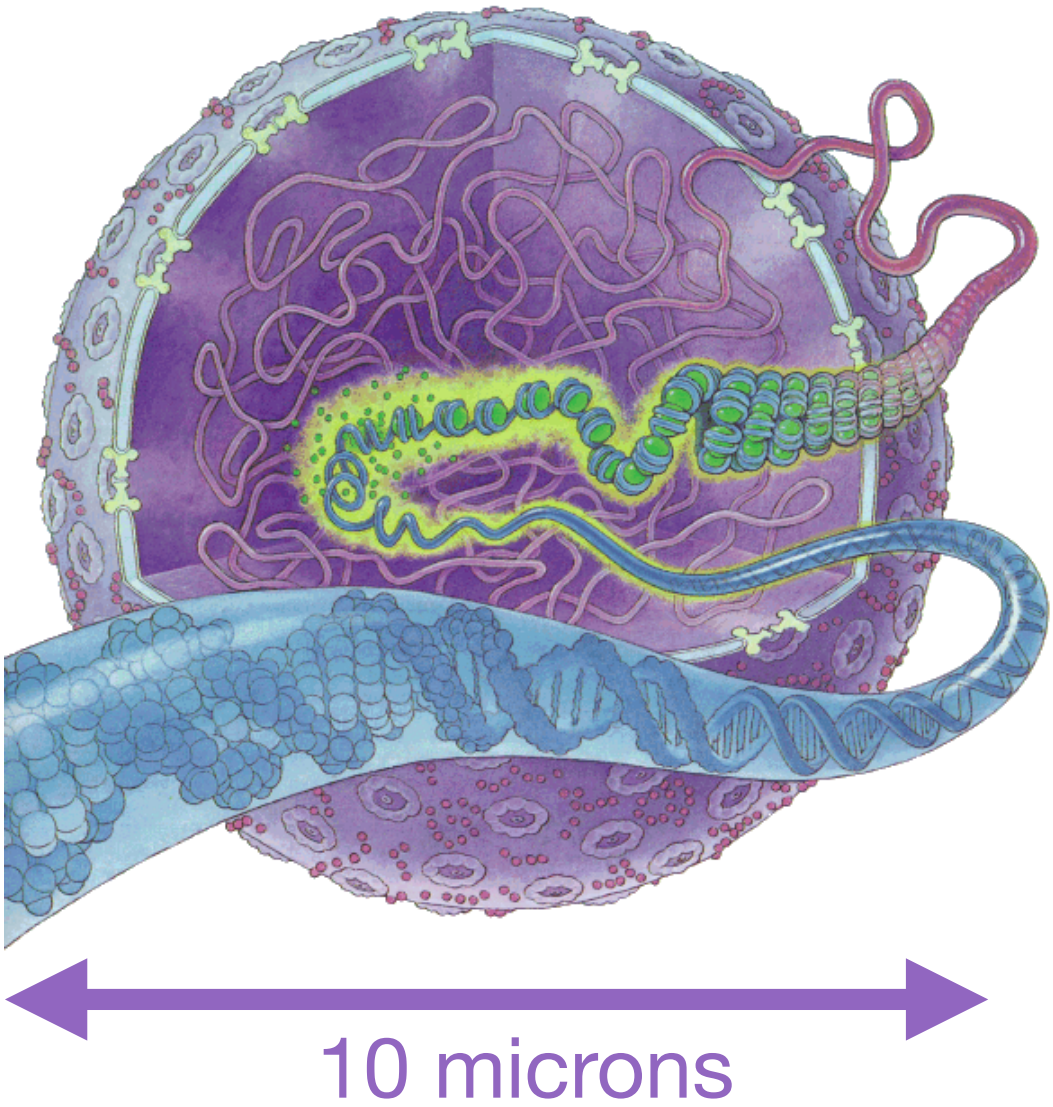
Genome as we know it in 1D

consists of 23 chromosomes

Genome as we know it in 1D

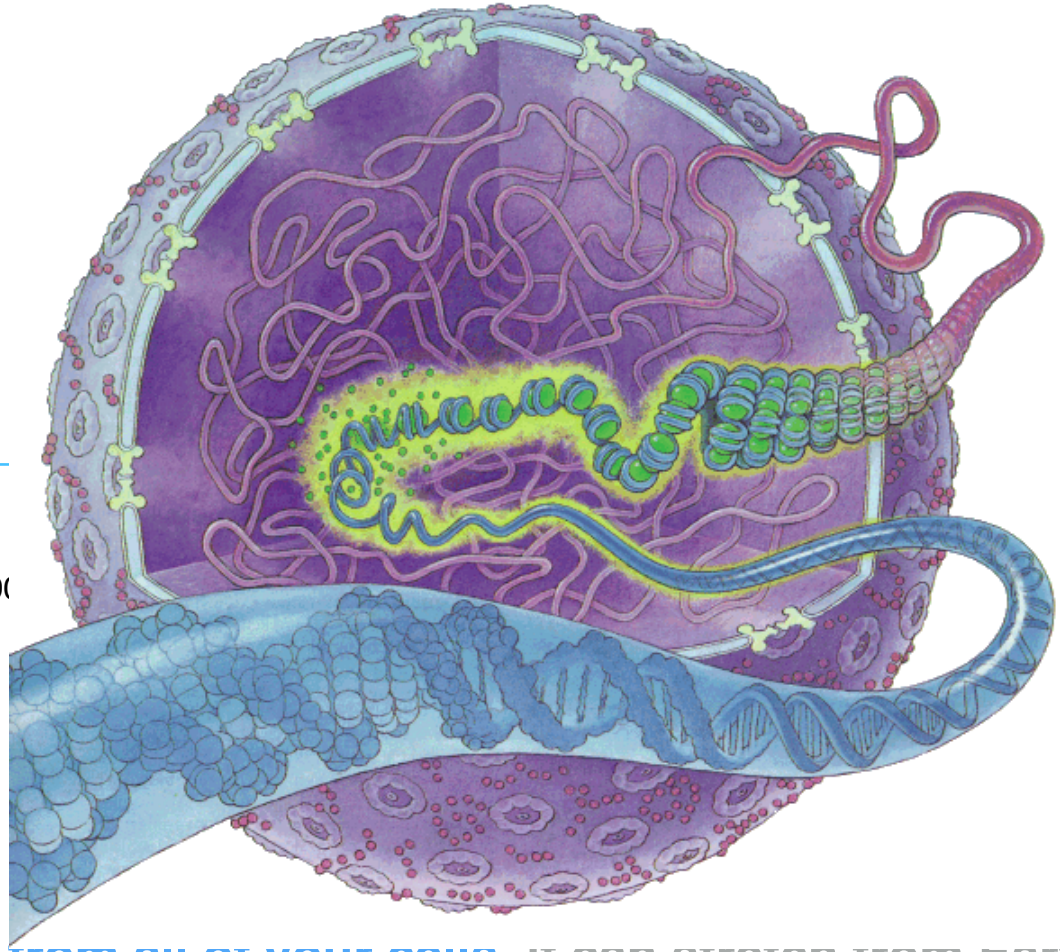
THE PROBLEM

How is 6 ft of DNA packed inside a cell?



THE PROBLEM

How is 6 ft of DNA packed inside a cell nucleus?



DNA

cell nucleus is 200,0(

If cell nucleus = er-to-Aspen)

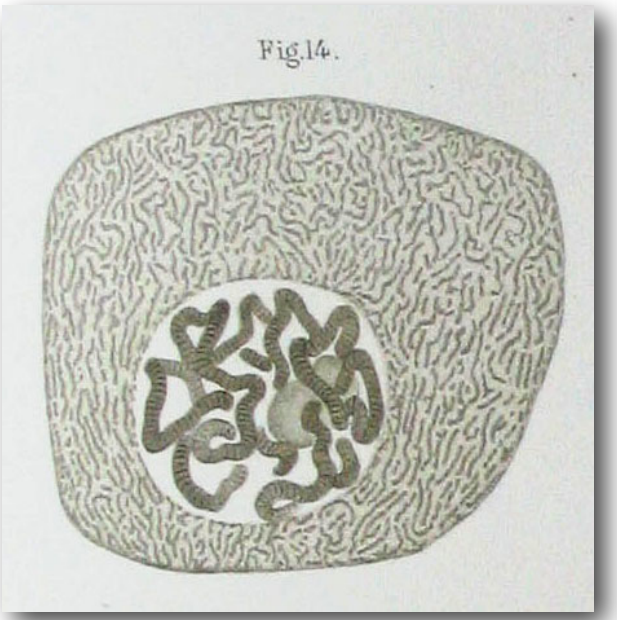
If you take DNA from all of your cells, it can stretch from Earth to Sun and back 500 times!

DNA of people in this room = One Light Year!

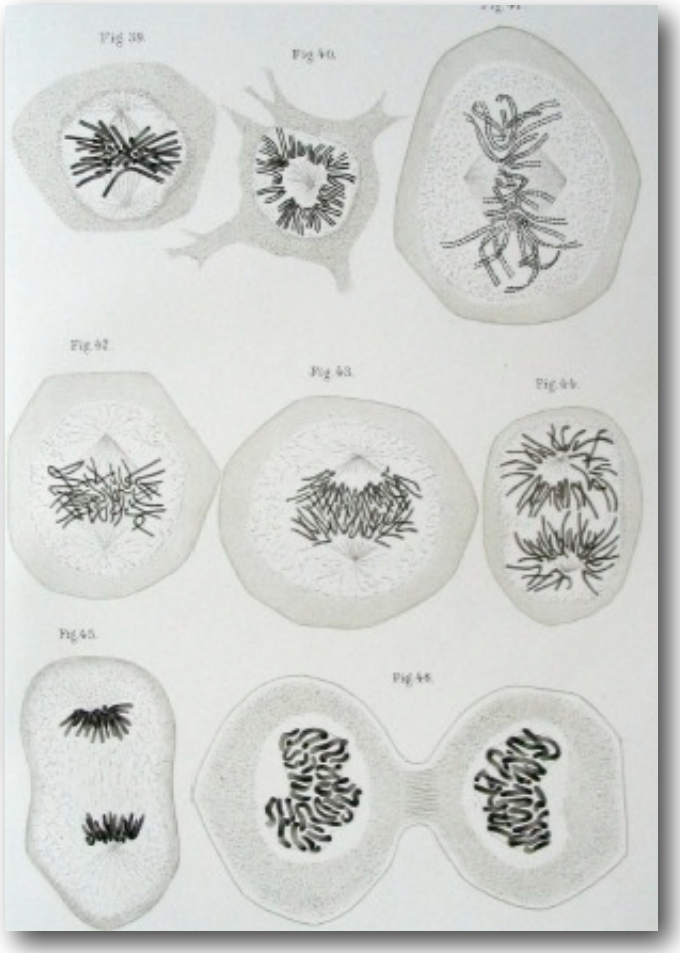
How is human genome
(23 chromosomes)
folded in 3D?

and how is it folded
to allow genome function

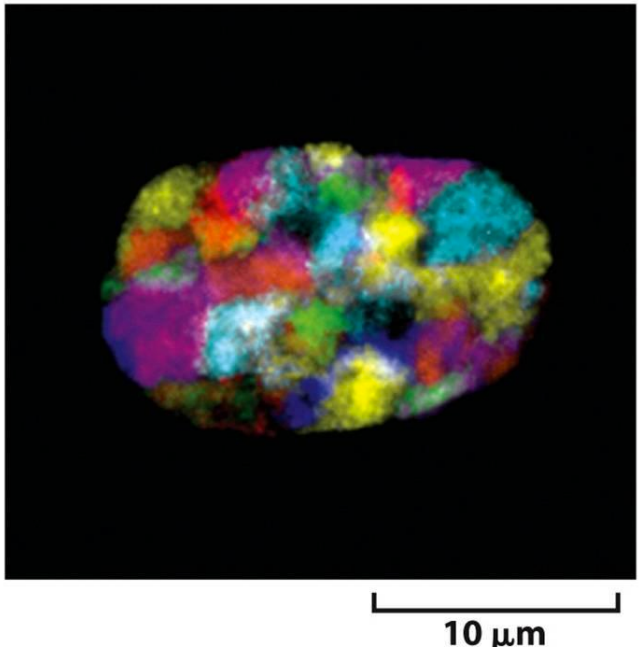
What do we know?



Walther Flemming in 1882



Kern und Zelltheilung (1882) von Walther Flemming



(*2005*)

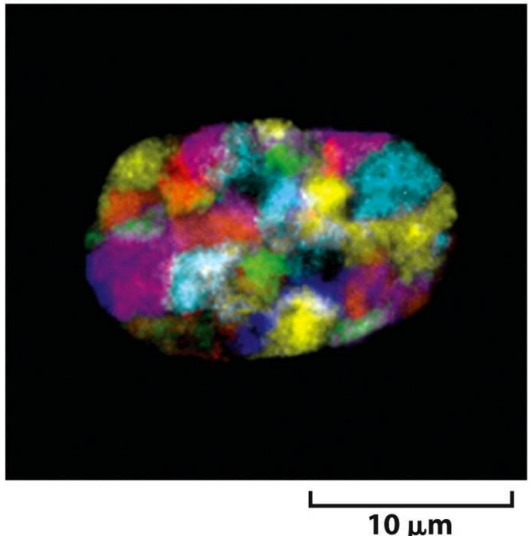
Nelson, Julius

The American Naturalist

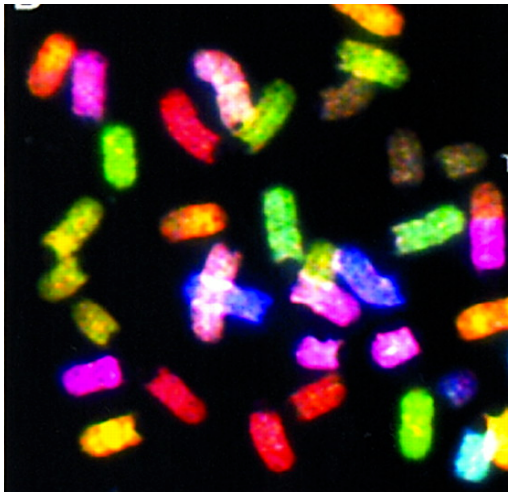
Vol. 21, No. 3, Mar., 1887

What do we know?

During most of cell life chromosomes are unpacked



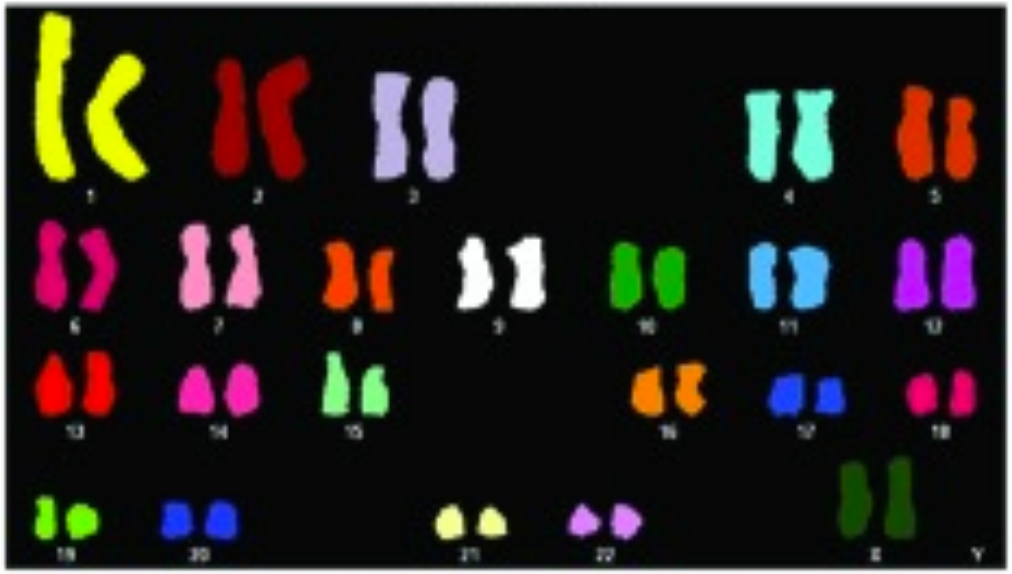
During cell division chromosomes are packed
to be given to two daughter cells



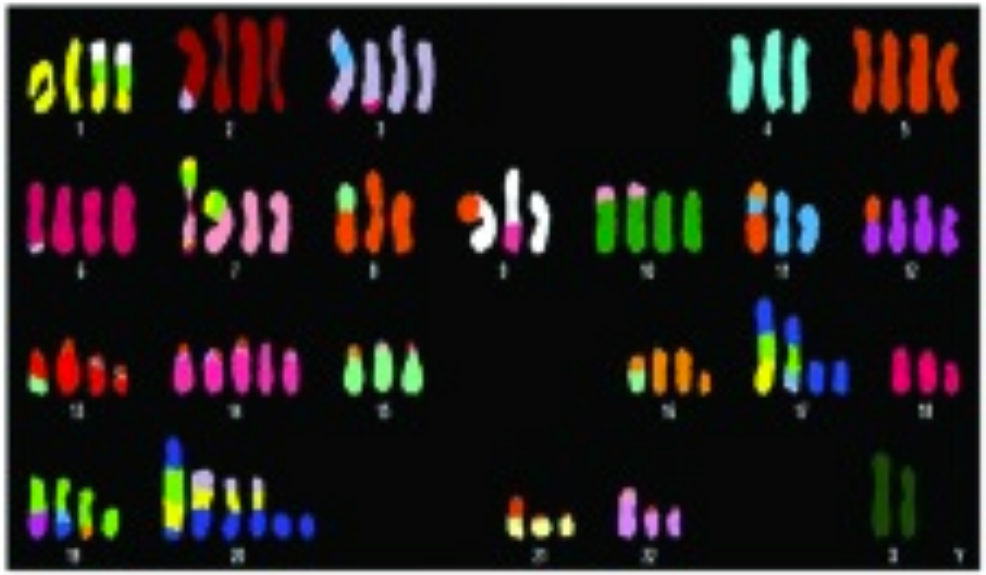
What do we know?

Chromosomes are deformed in cancer !

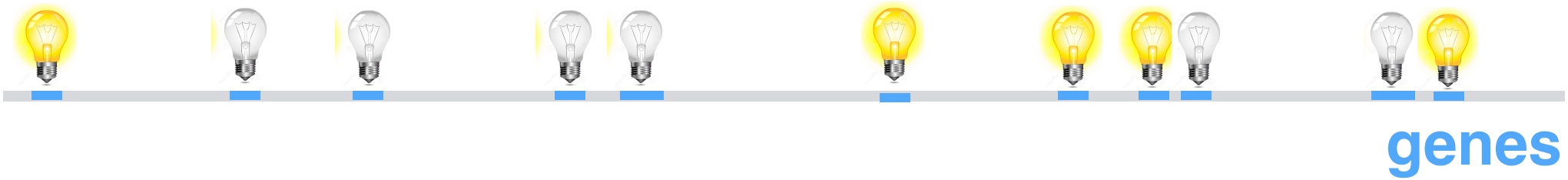
Normal



Breast cancer

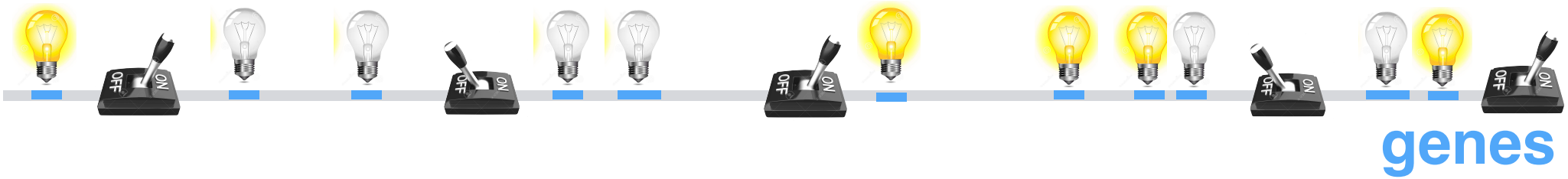


3D folding is important



Genes can be on or off

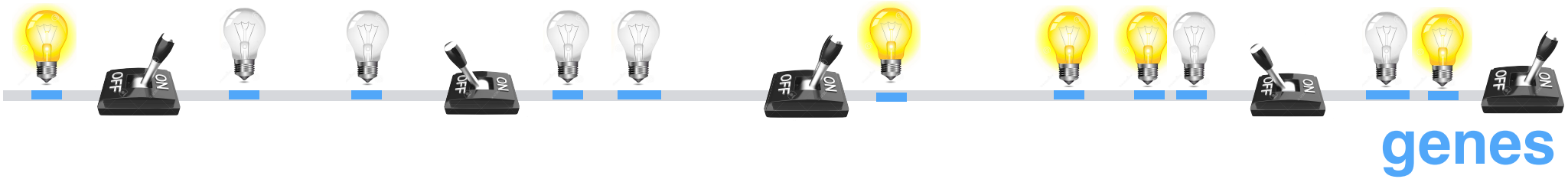
Genes and switches



Genes can be on or off

Genomic switches

Genes and switches

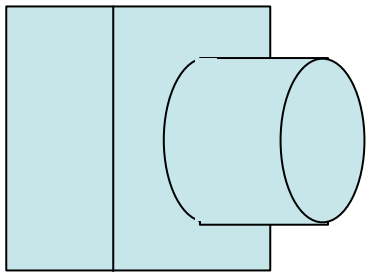


3D folding controls gene activity!

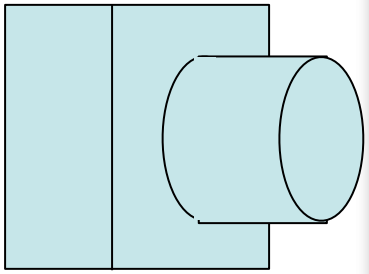
New techniques
allow us to examine chromosome
folding inside the cell!

Chromosome Conformation Capture

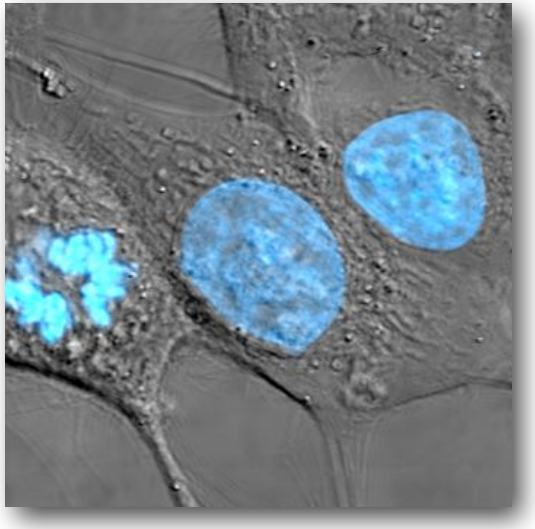
“paparazzi” technology

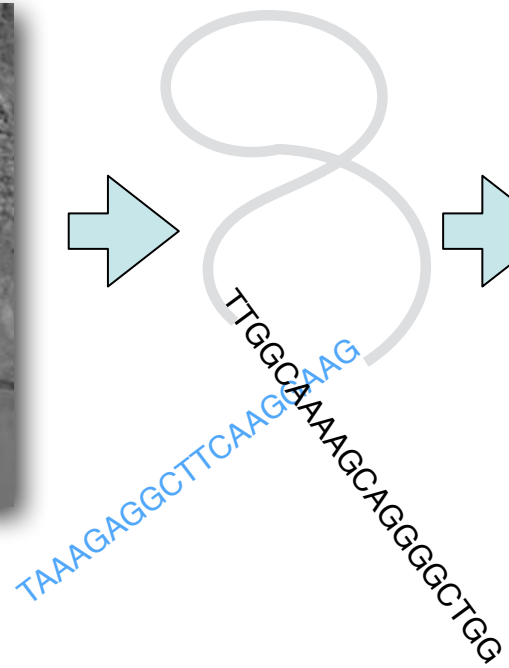


First — Capture a photo
then — Identify who were together in the shot



Hi-C
“chemical microscope”

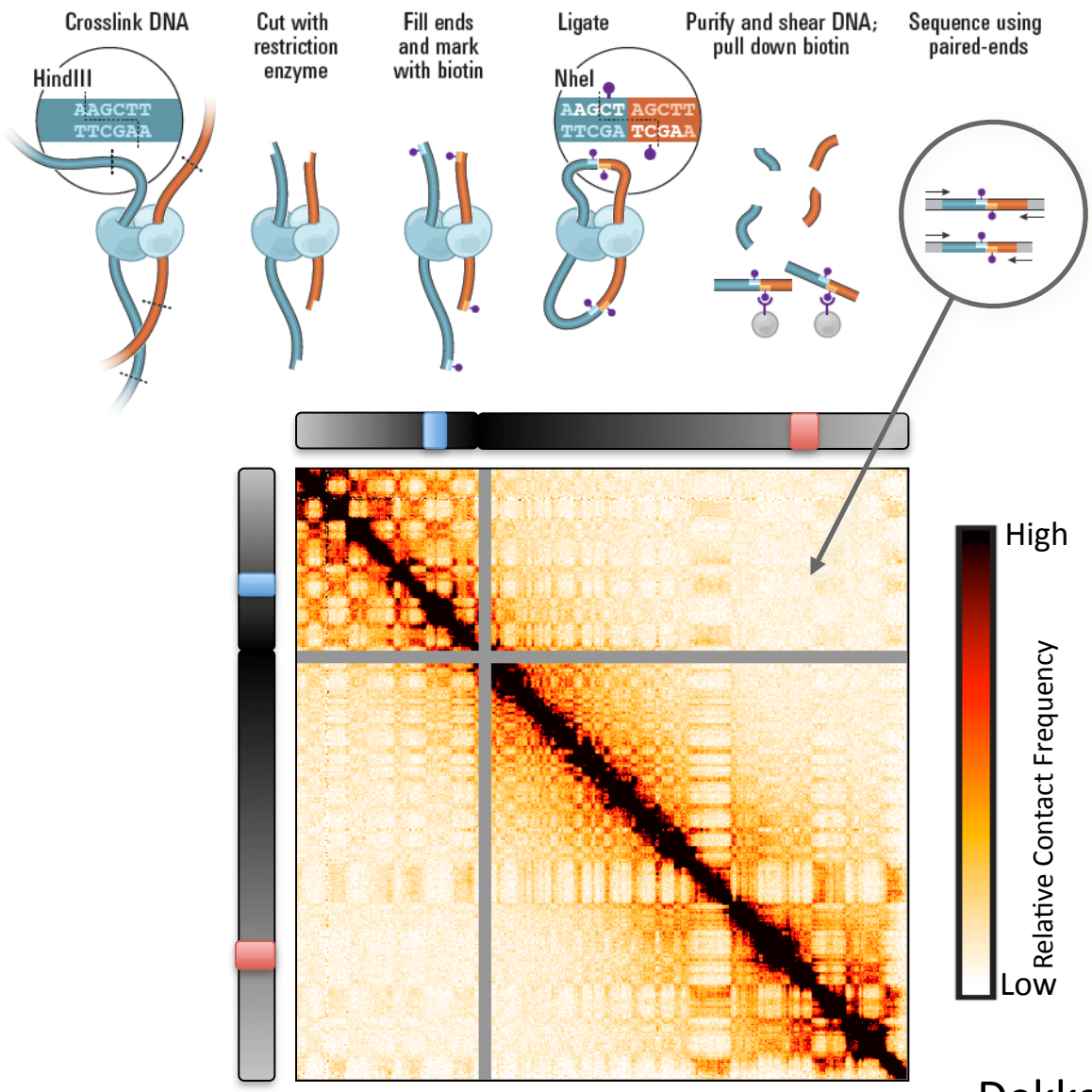




Read DNA to identify regions that were together

Do this billions of times in one experiment!

Chromosome Conformation Capture (Hi-C)

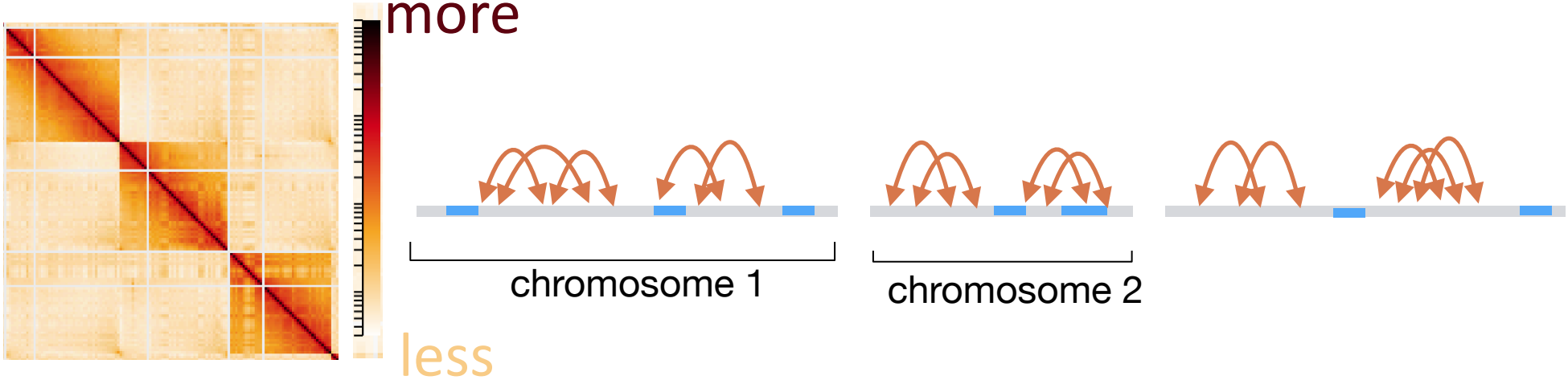


Job Dekker
UMass Medical School

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

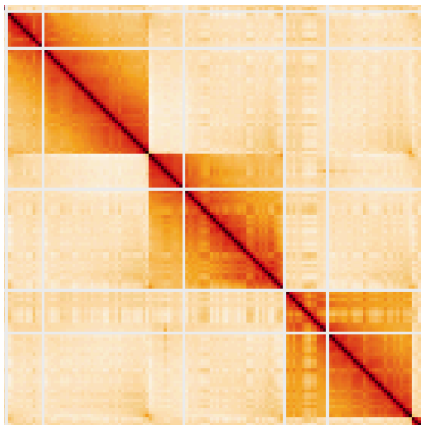
Genomic interactions

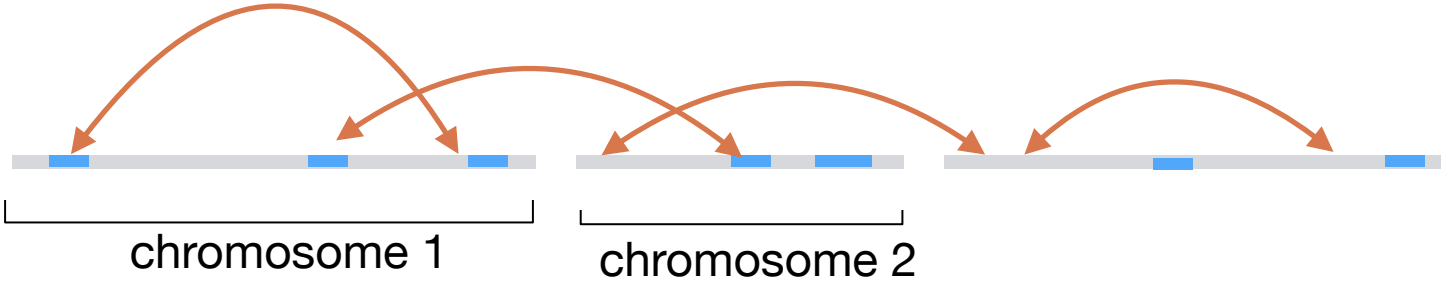
- **Lots** of interactions between genomic neighbors



Genomic interactions

- **Rare** interactions between regions that are far apart on the genome (strangers)

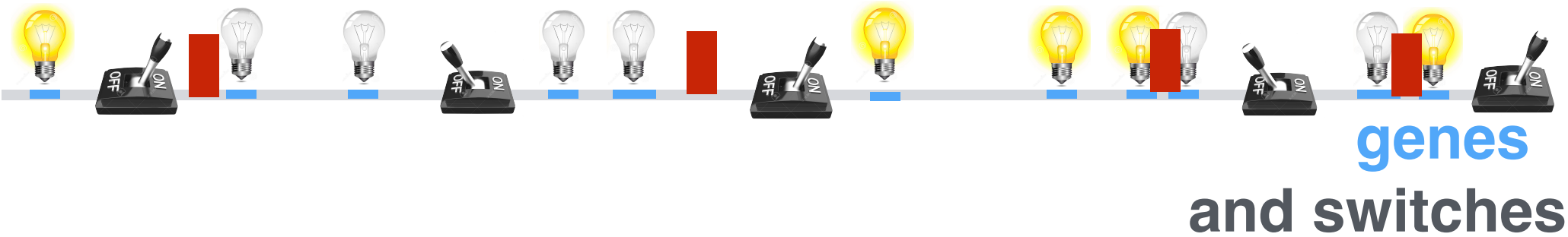




Why is this important?

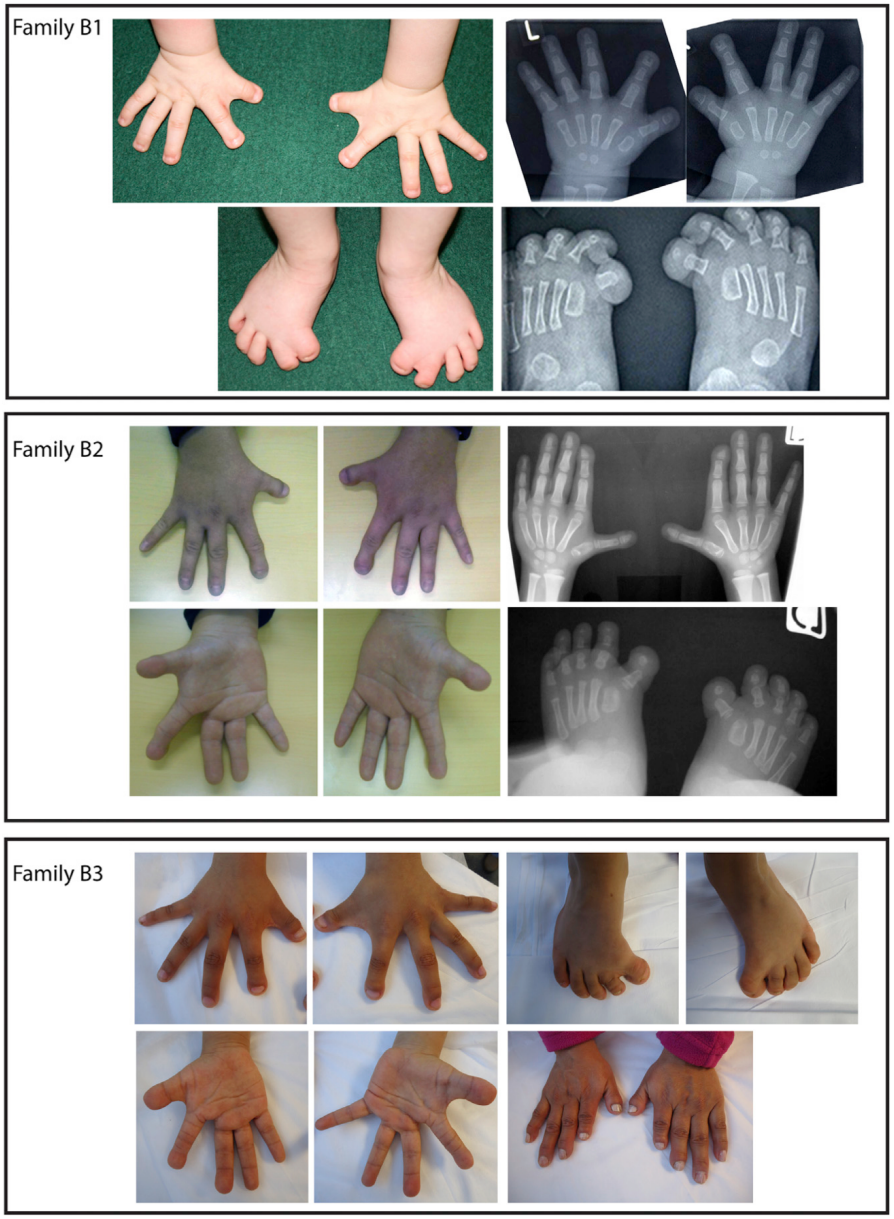
Genomic interactions

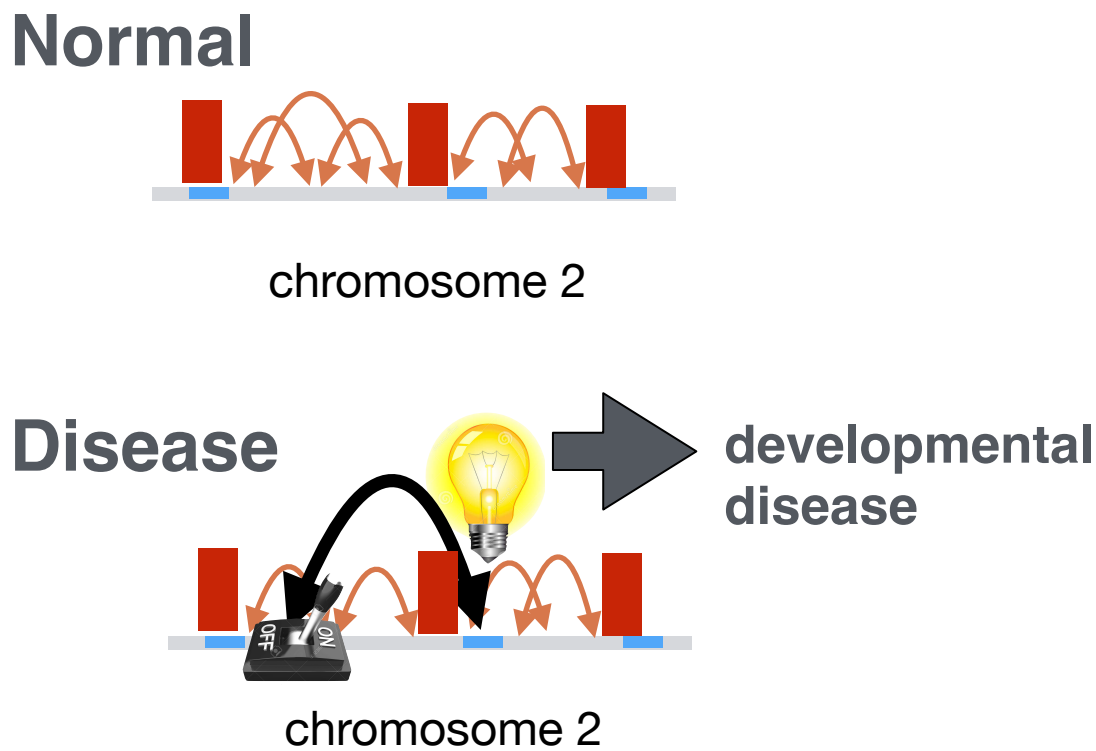
- **Fences** control how **switches** act on **genes**



How does it all work and look in 3D?

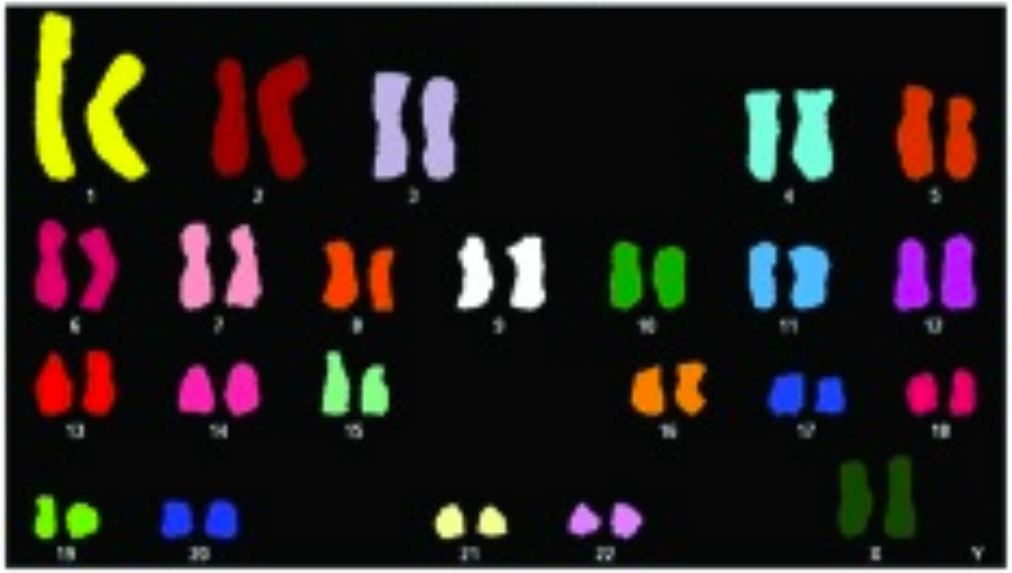
If some fences are broken…



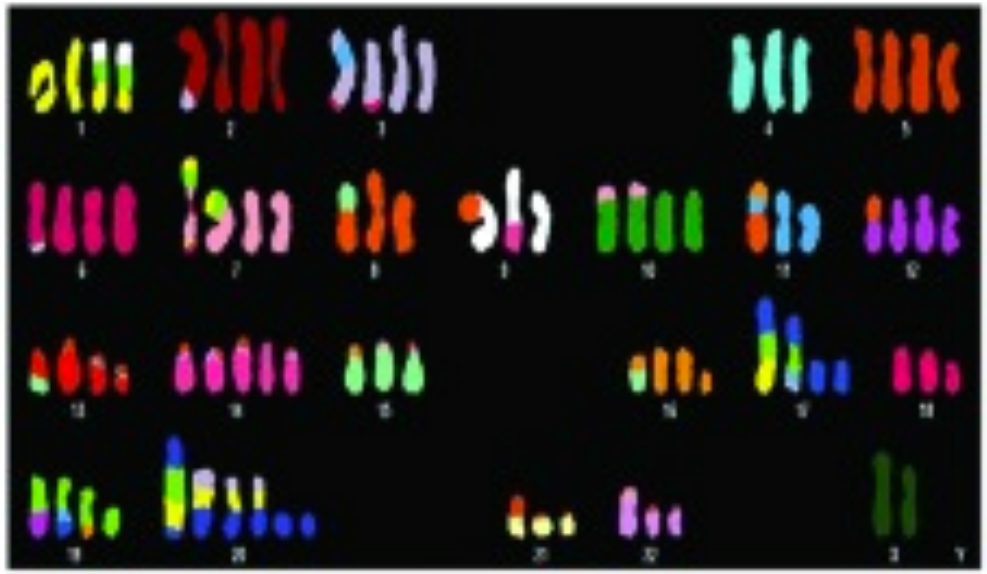


Cancer: many broken fences and misplaces switches

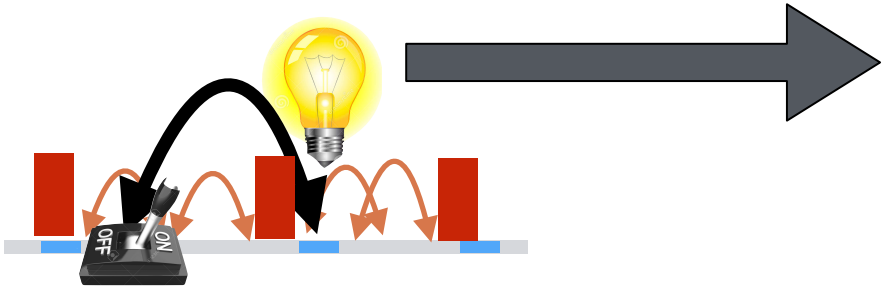
Normal



Breast cancer



Glioma

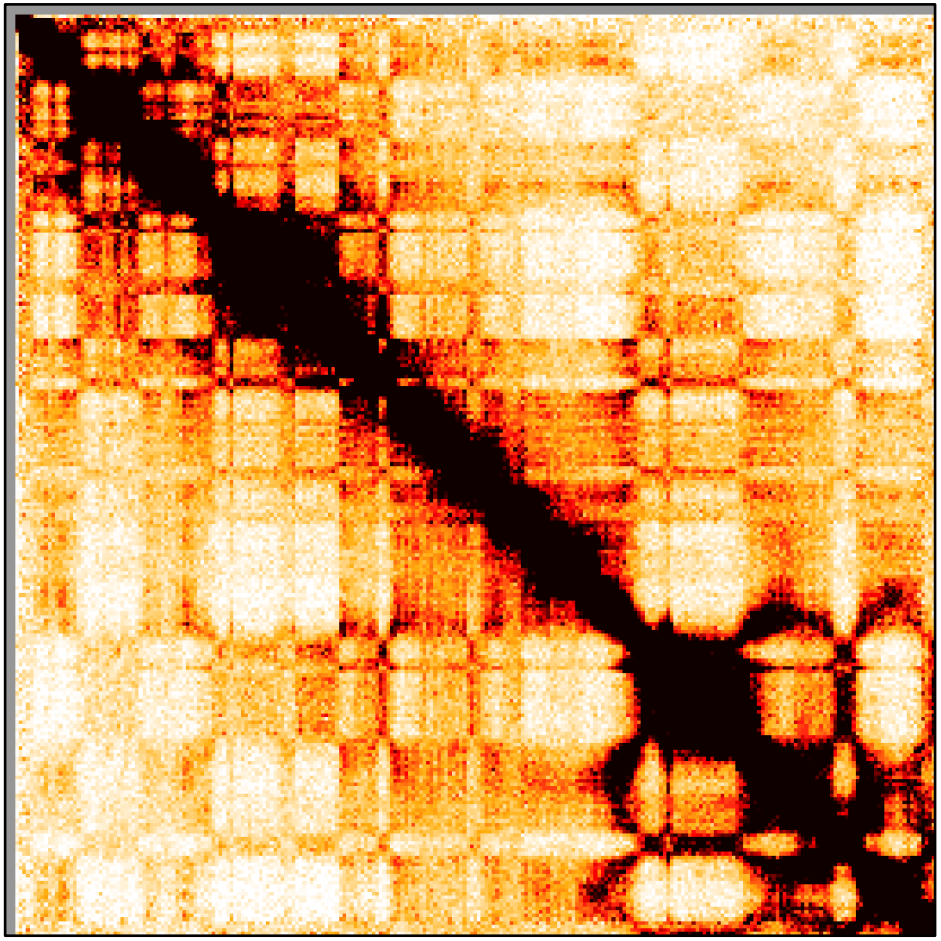


chromosome 4

cancer development

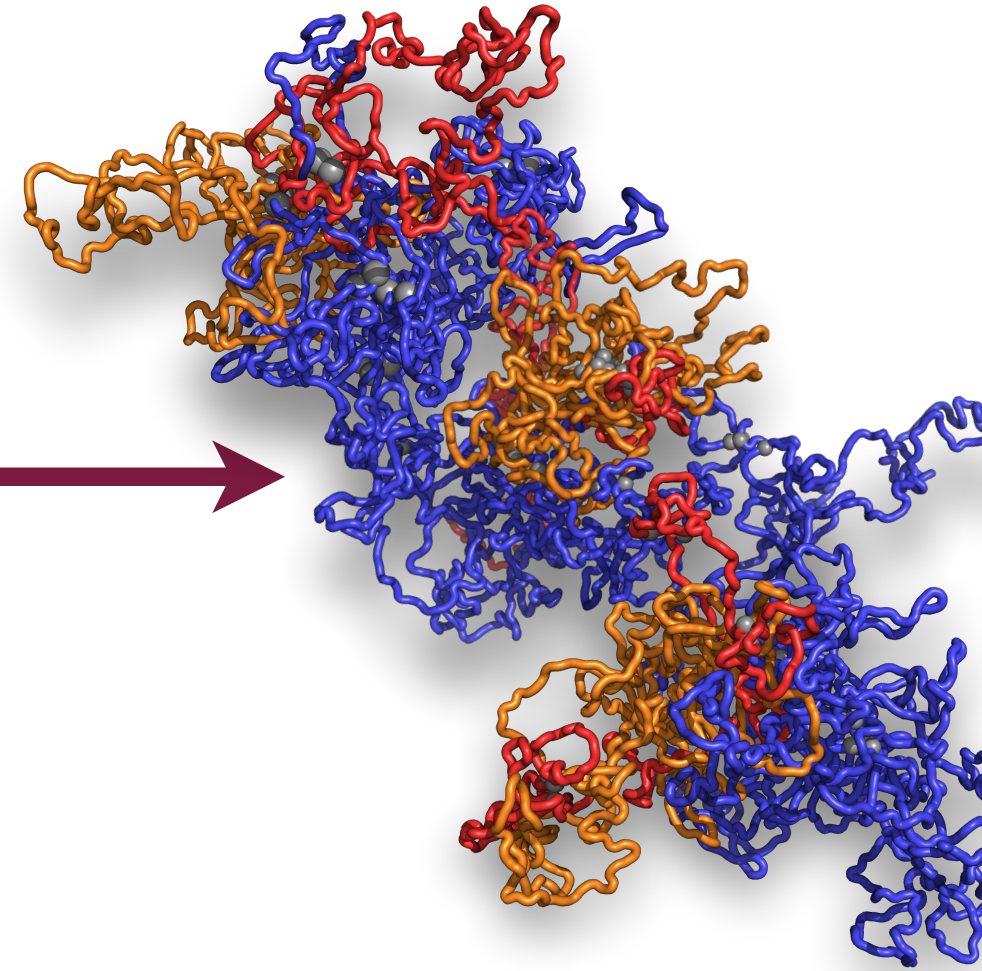
Genome in 3D

Hi-C data

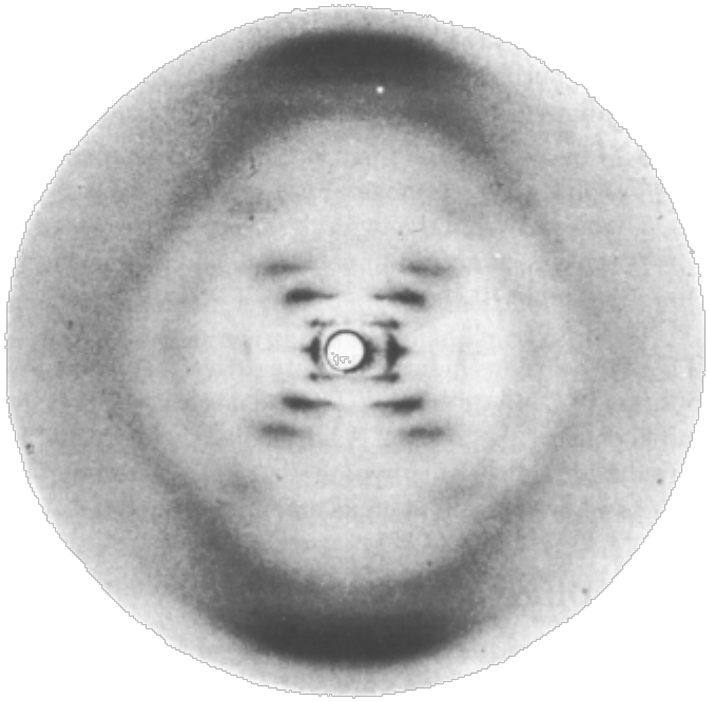


Chr 14 - 106 Mb

Genome in 3D

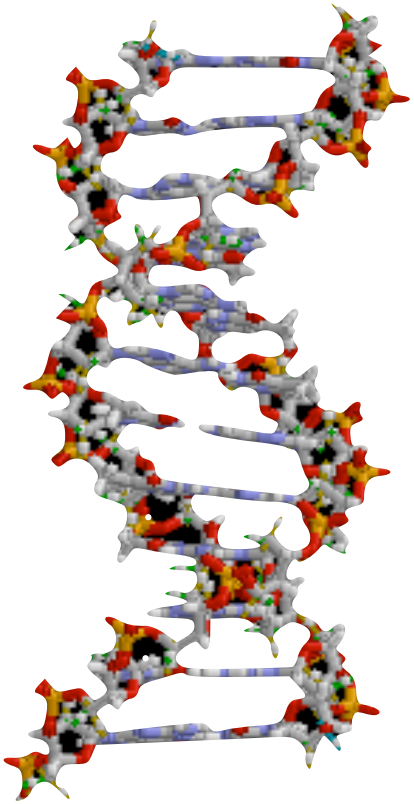


X-ray data



Photograph 51 Rosalind Franklin in 1952

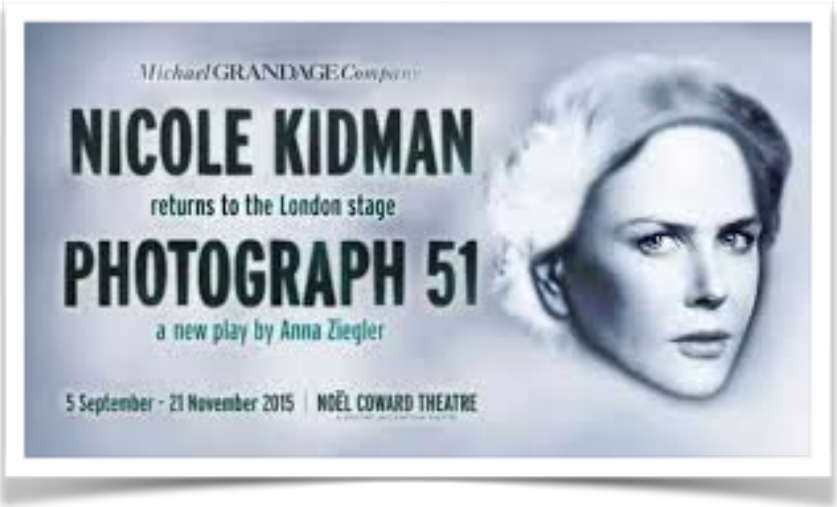
3D model



12 bases of DNA

easy

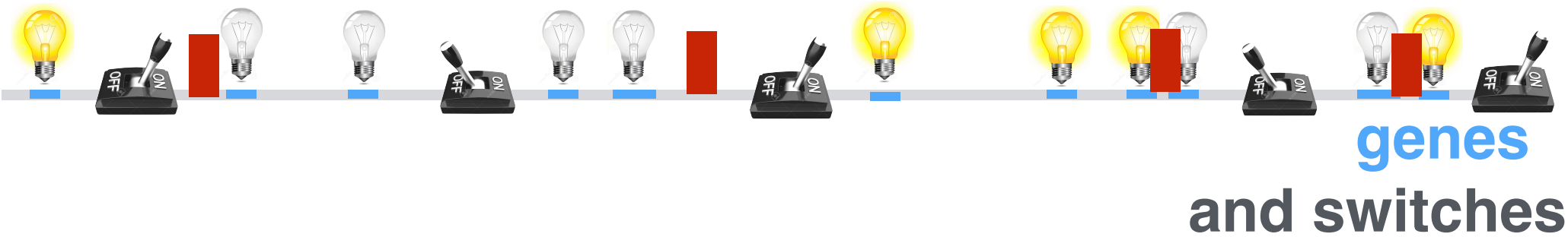
HARD



We would like to find out how the whole human genome of 3,000,000,000 bases is folded!

Genomic interactions

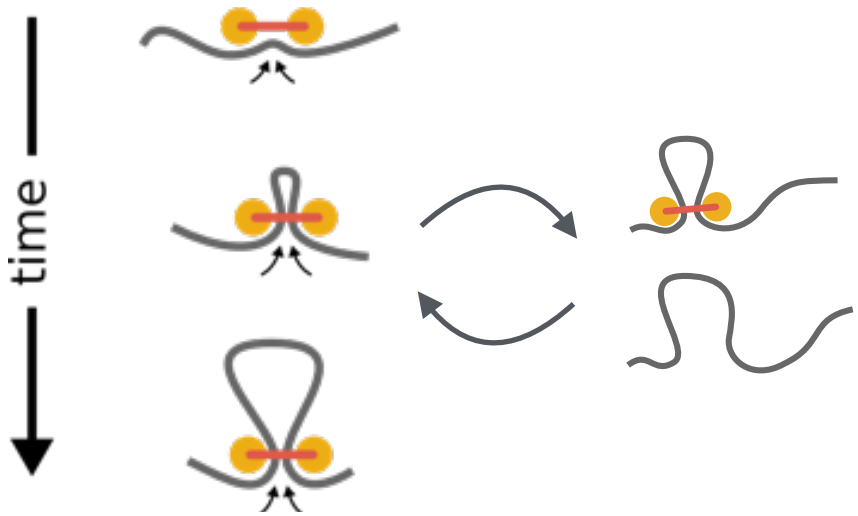
- **Fences** control how **switches** act on **genes**

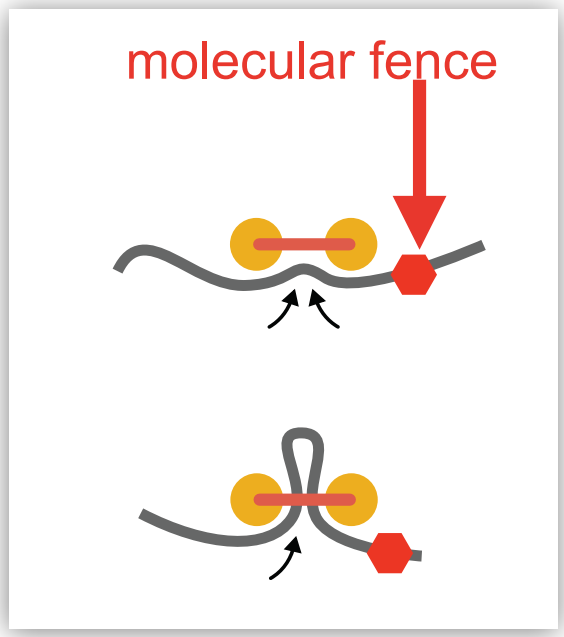


How does it all work and look in 3D?

Hypothesis: **Loop extrusion** with **fences**

John Marko
Northwestern U.





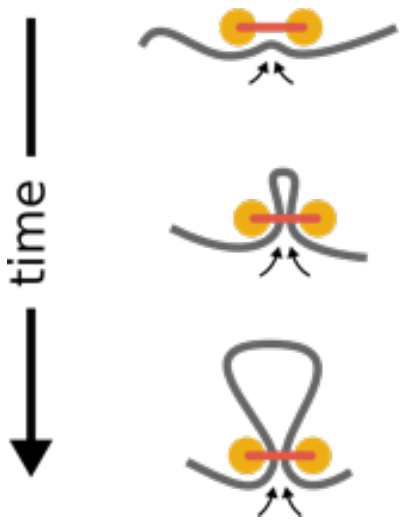
Formation of Chromosomal Domains by Loop Extrusion
Fudenberg, Imakaev et al. Cell Reports (2016)

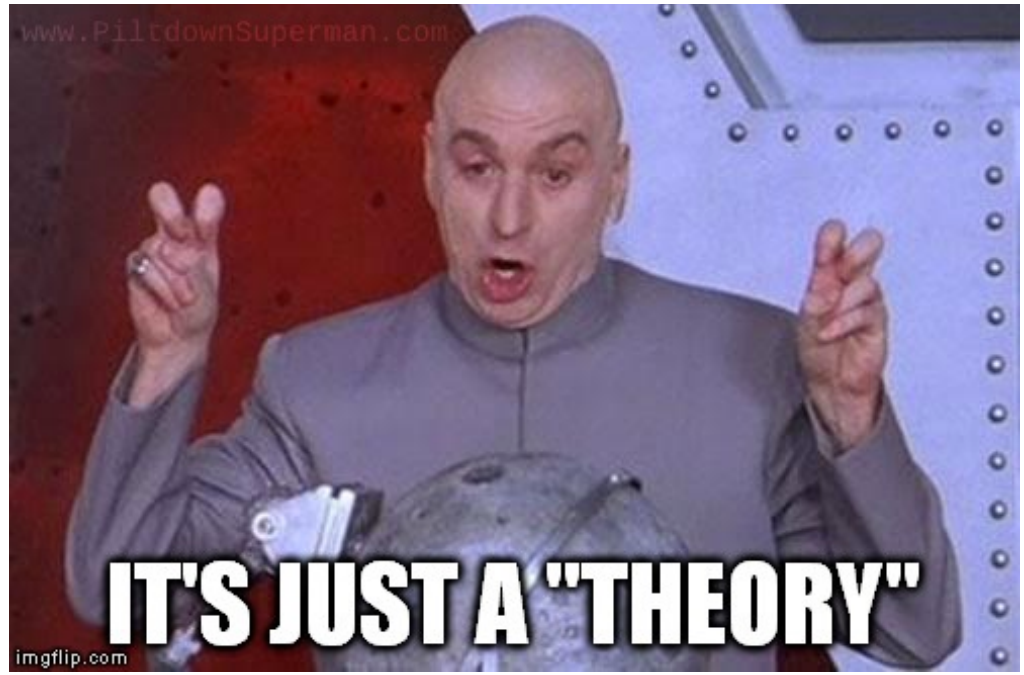
Computer simulations of loop extrusion with fences

YouTube Search youtube mirnylab

https://www.youtube.com/watch?v=8FW6gOx5IPI

It’s just a theory!





… 3 years later

Cees Dekker
UT Delft

Single-molecule experiments

Real-time imaging of DNA loop extrusion by condensin

Science

Mahipal Ganji,[1] Indra A. Shaltiel,[2*] Shveta Bisht,[2*] Eugene Kim,[1] Ana Kalichava,[1] Christian H. Haering,[2†] Cees Dekker[1†]

REPORTS

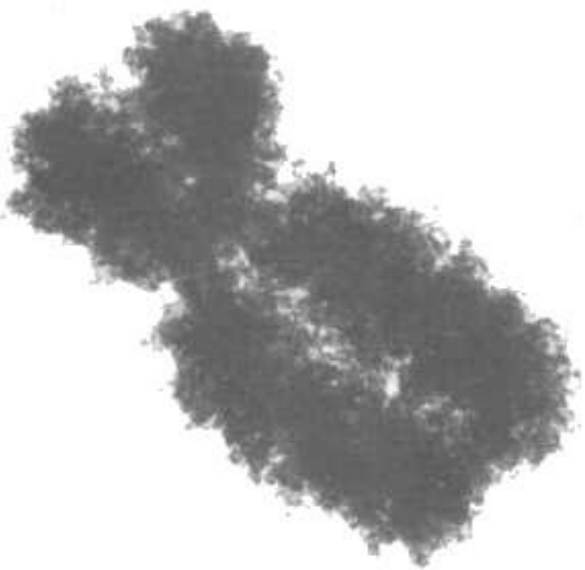
Cite as: M. Ganji *et al.*, *Science* 10.1126/science.aar7831 (2018).

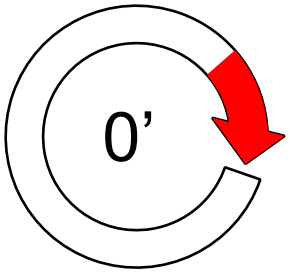
This video shows how a condensin protein gradually causes DNA to extrude a DNA loop over time.

Cees Dekker lab, Kavli Institute of Nanoscience
Delft University of Technology
www.ceesdekkerlab.nl

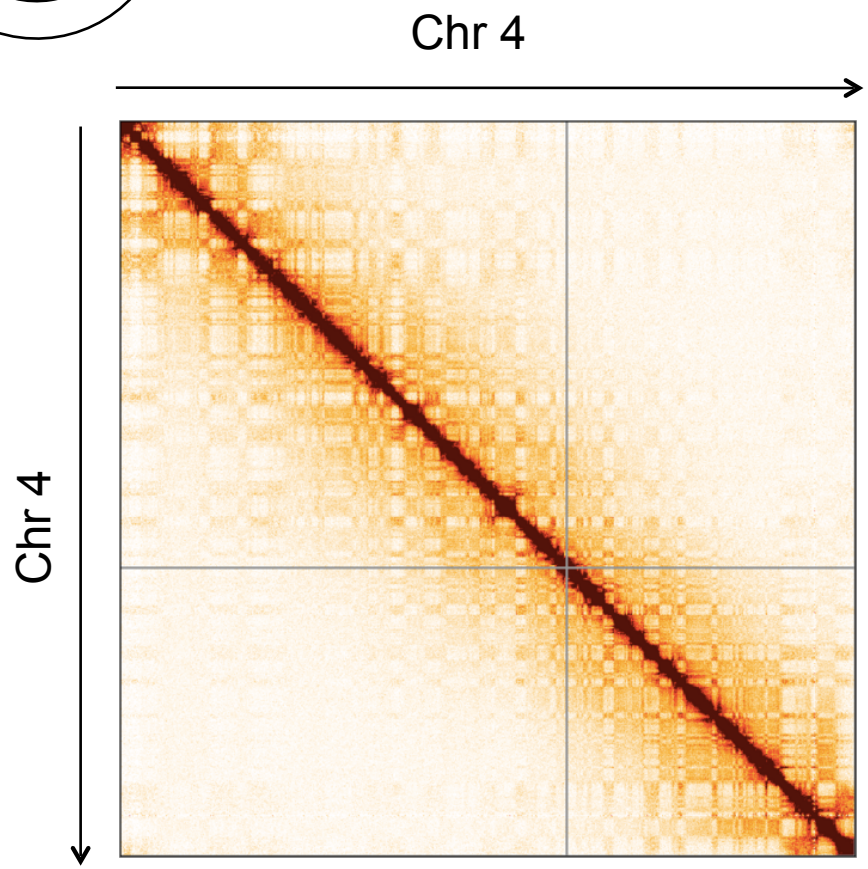
This result is reported in Science (online, Febr.15, 2018)
Paper title: Real-time imaging of DNA loop extrusion by condensin
Authors: Mahipal Ganji (1), Indra A. Shaltiel (2), Shveta Bisht (2), Eugene Kim (1), Ana Kalichava (1), Christian H. Haering (2), Cees Dekker (1)
Affiliations: 1 Department of Bionanoscience, Kavli Institute of Nanoscience Delft, Delft University of Technology, Delft, Netherlands.
2 Cell Biology and Biophysics Unit, Structural and Computational Biology Unit, European Molecular Biology Laboratory (EMBL), Heidelberg, Germany.

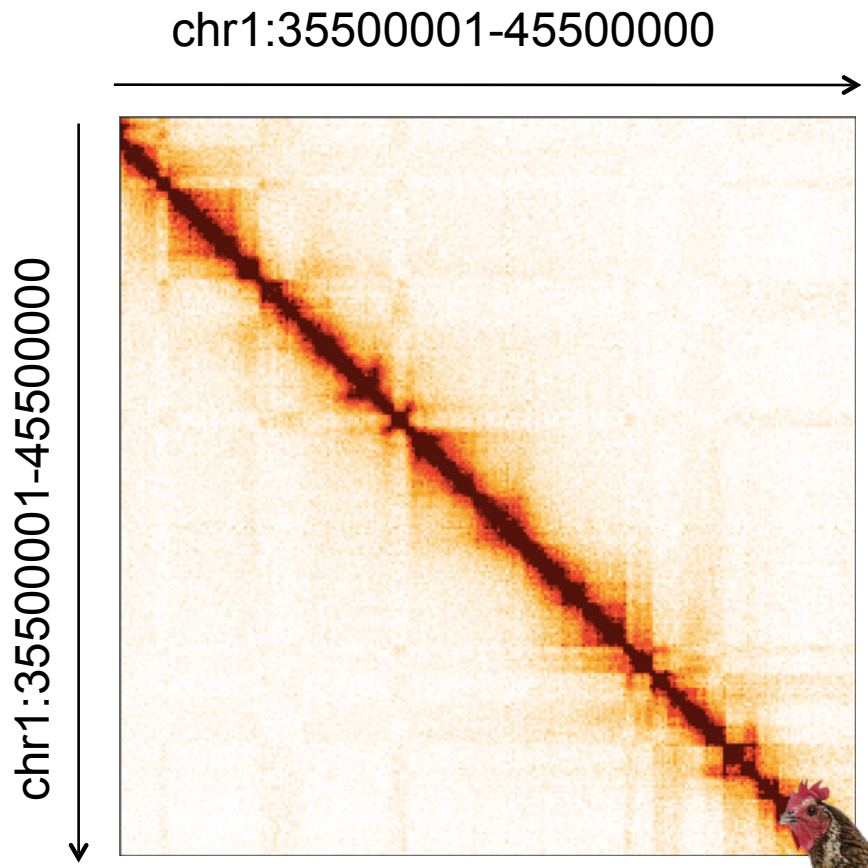
How is DNA packed inside such chromosome?

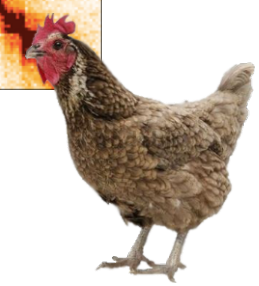


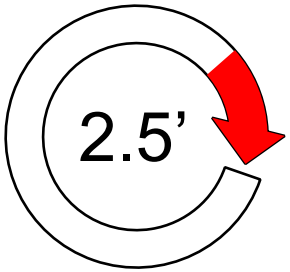


Hi-C on Synchronized DT-40

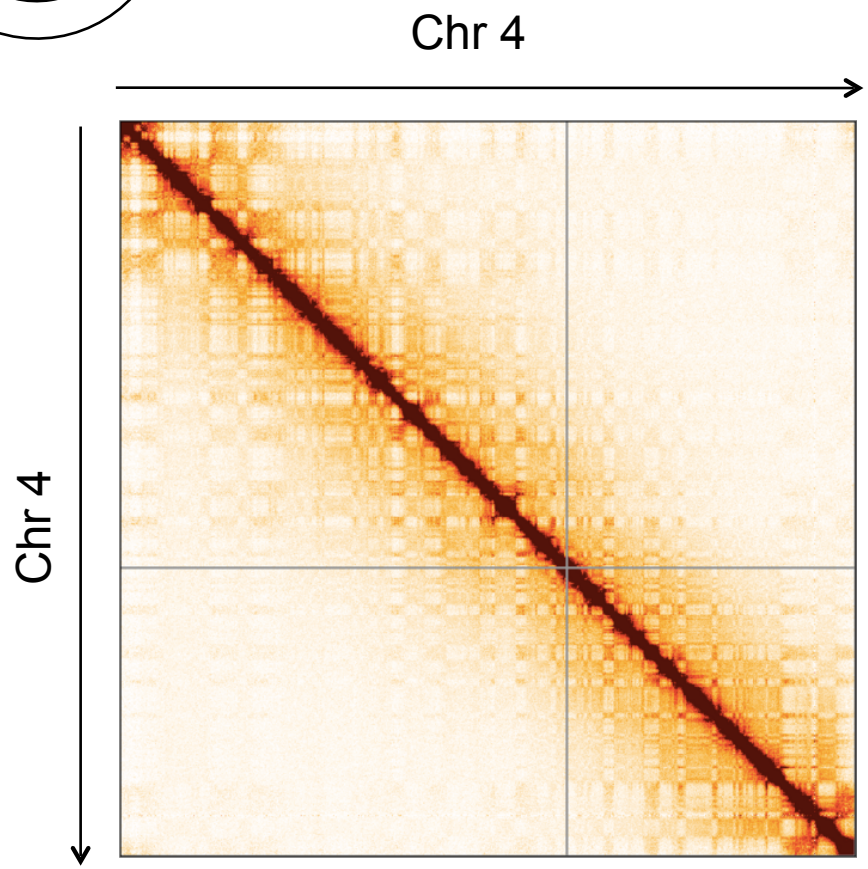


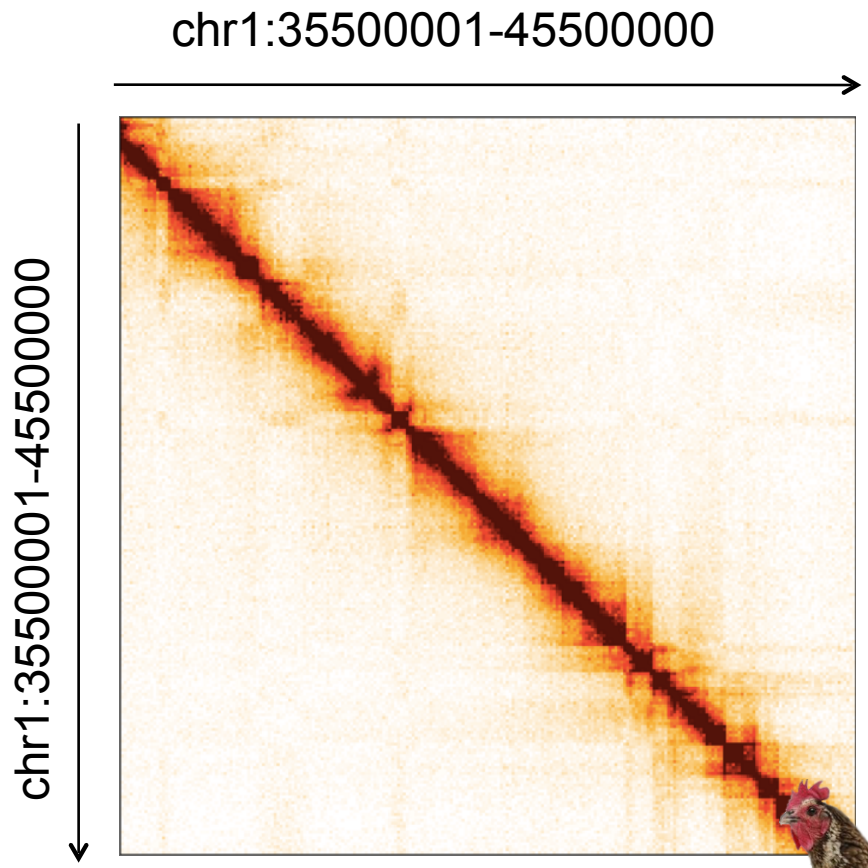


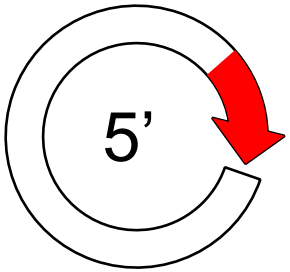




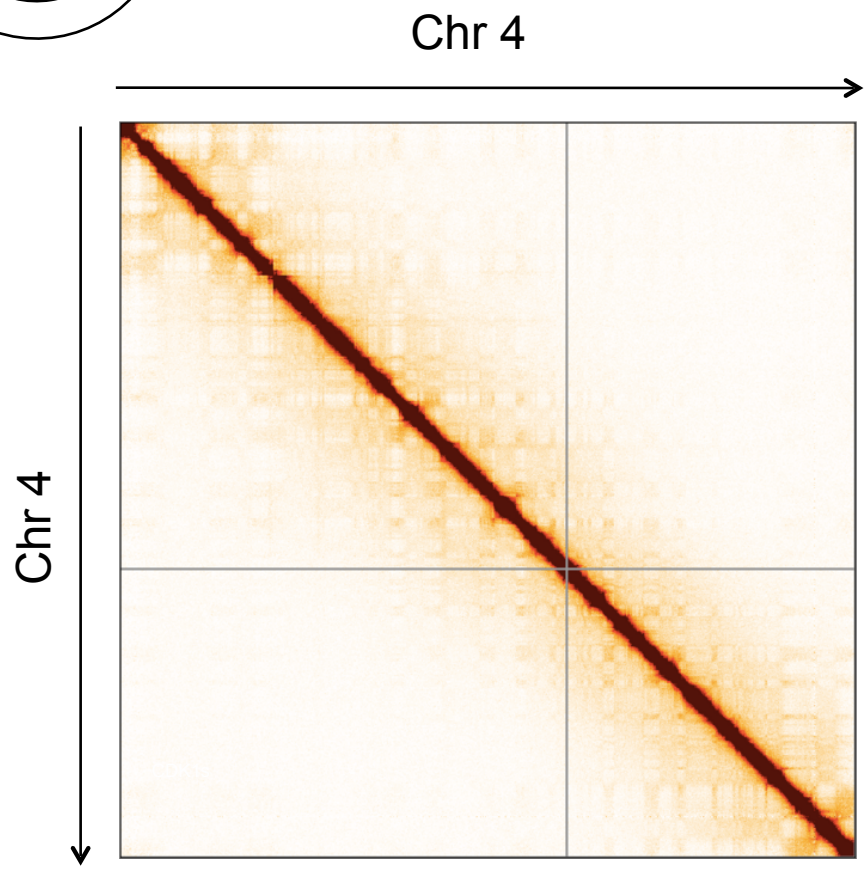
Hi-C on Synchronized DT-40

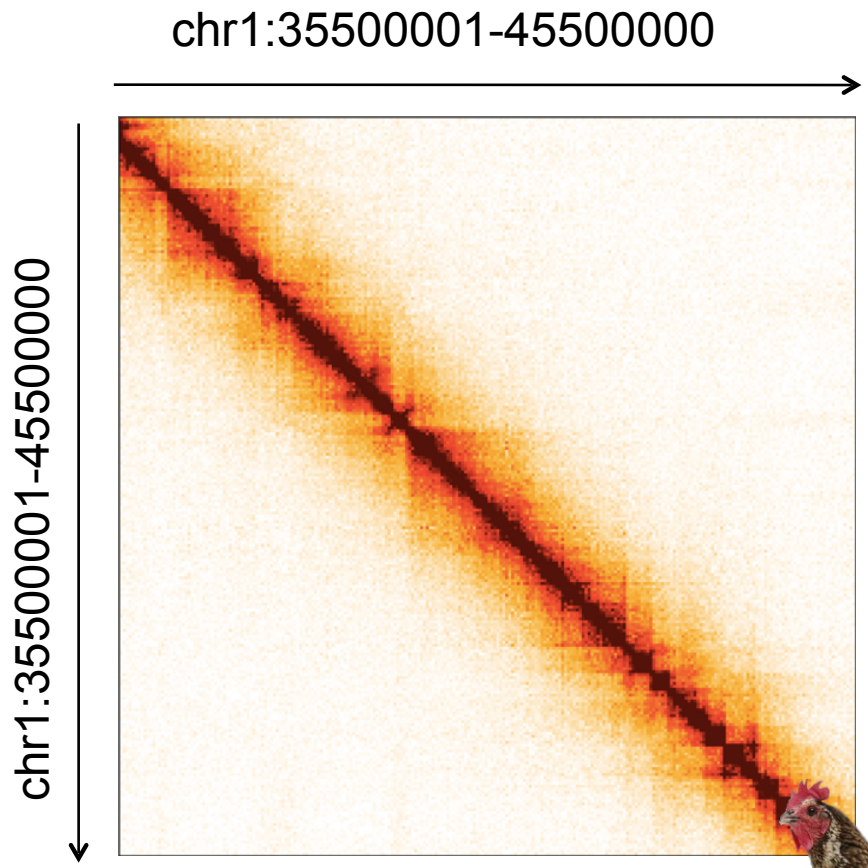


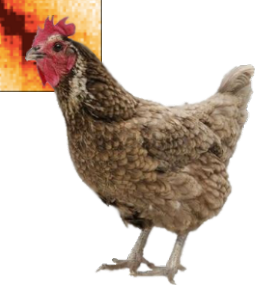


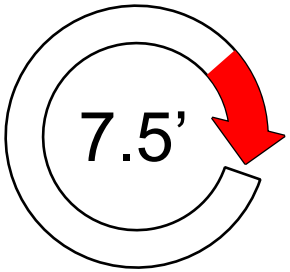


Hi-C on Synchronized DT-40

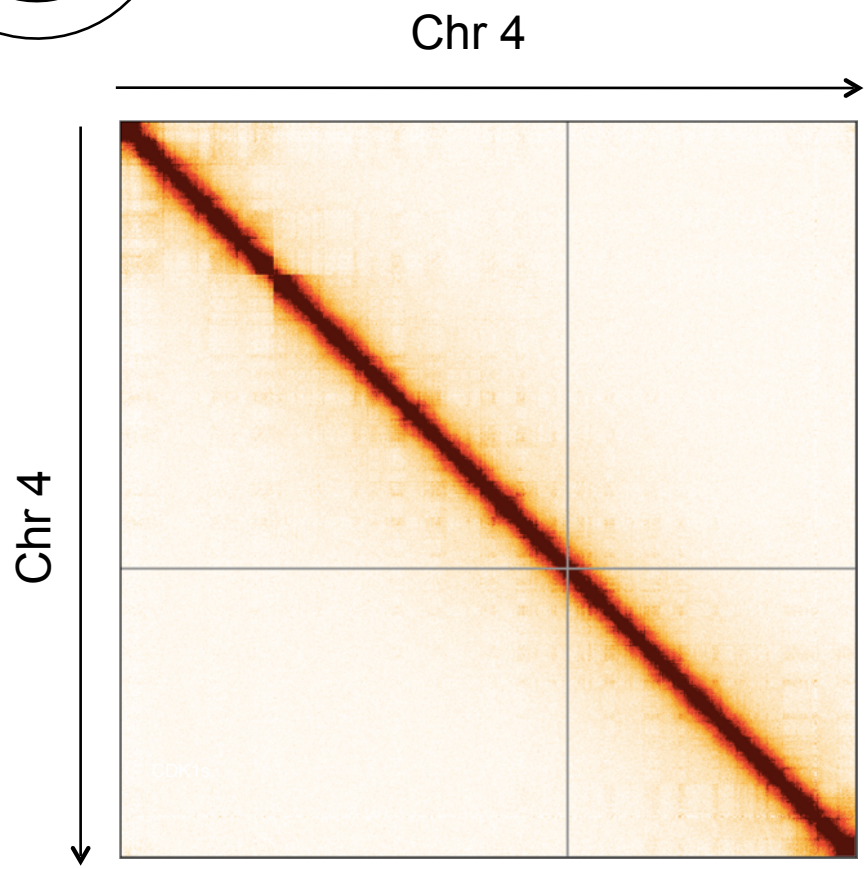


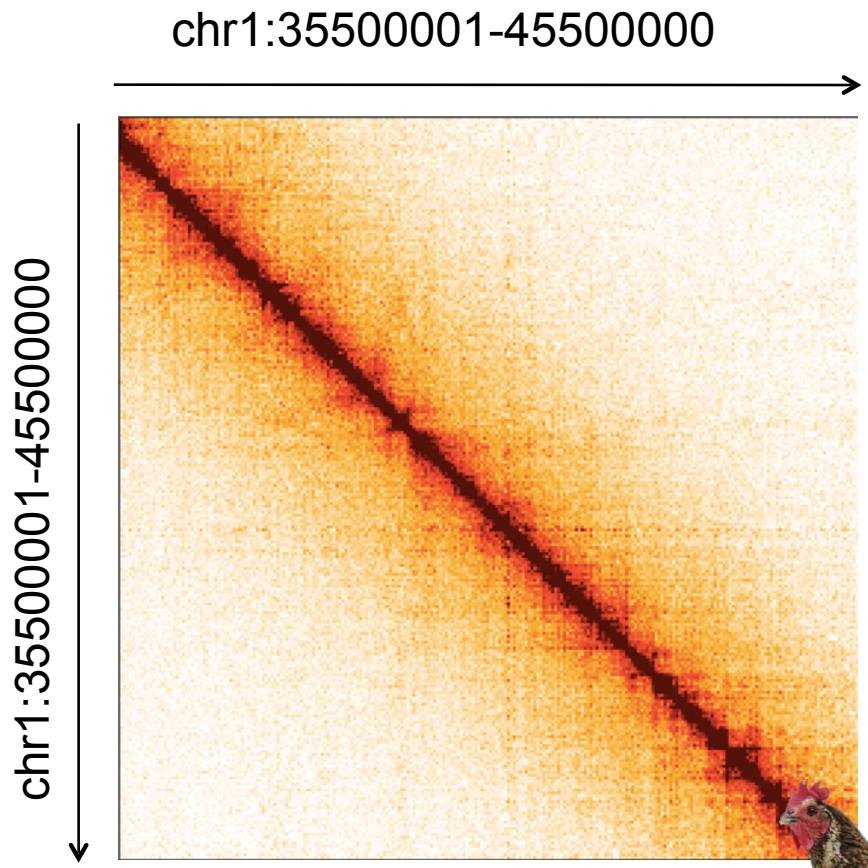


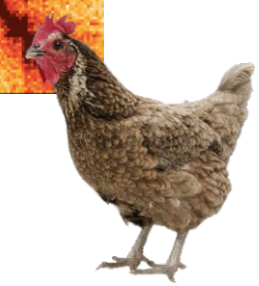


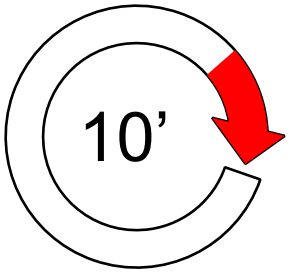


Hi-C on Synchronized DT-40

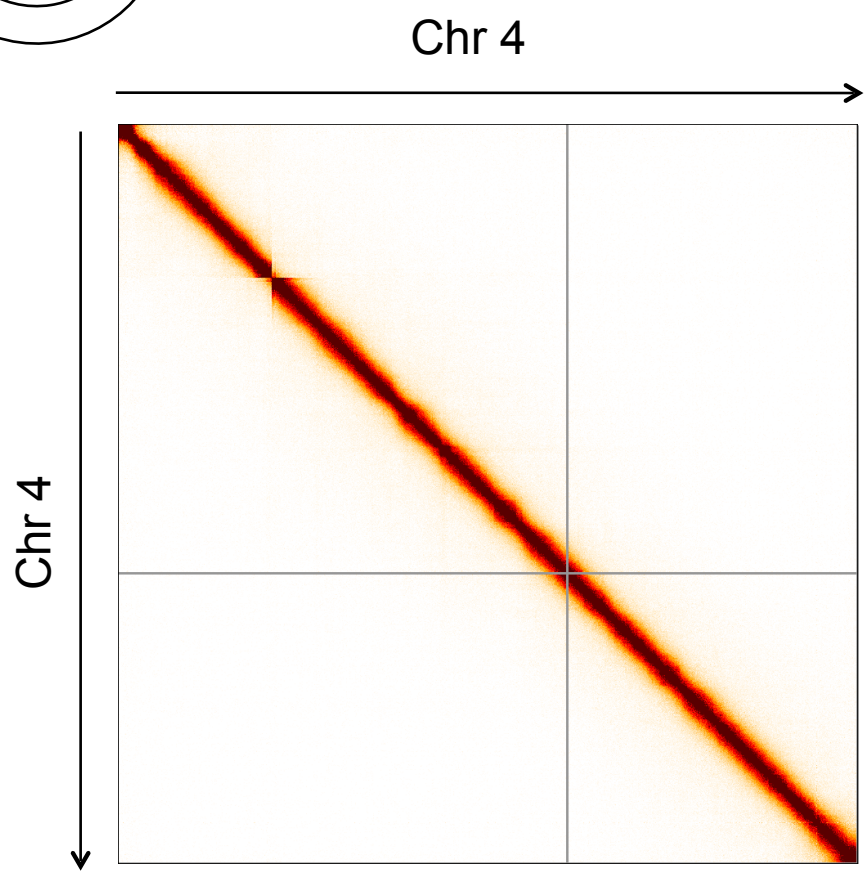


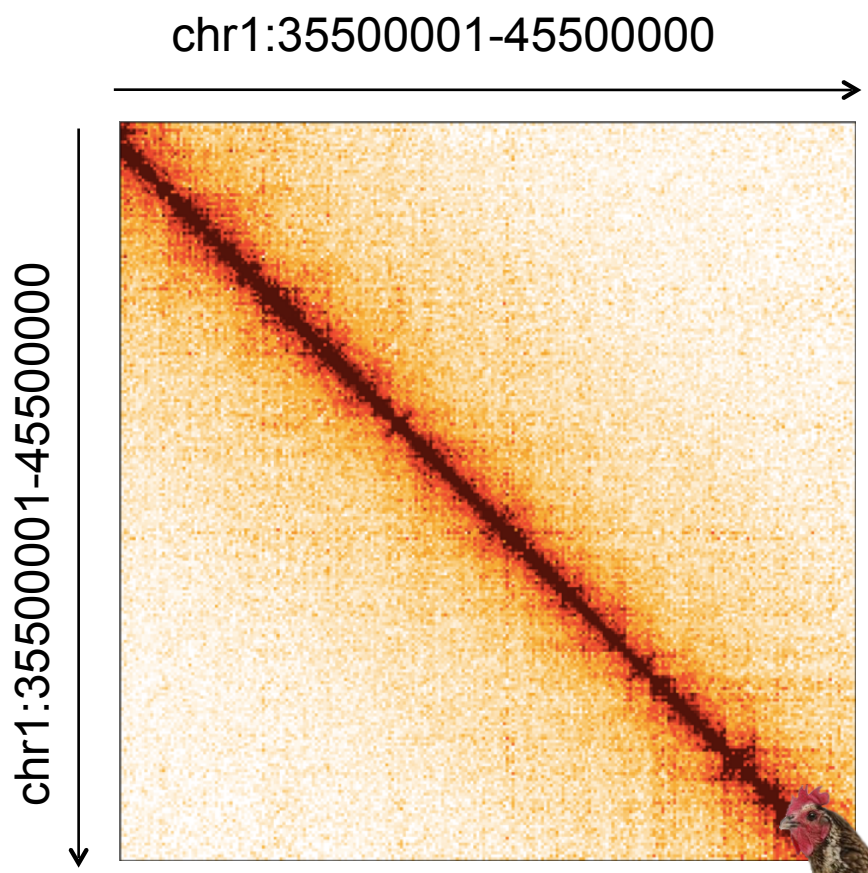


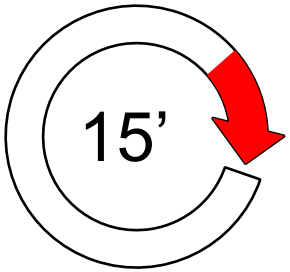




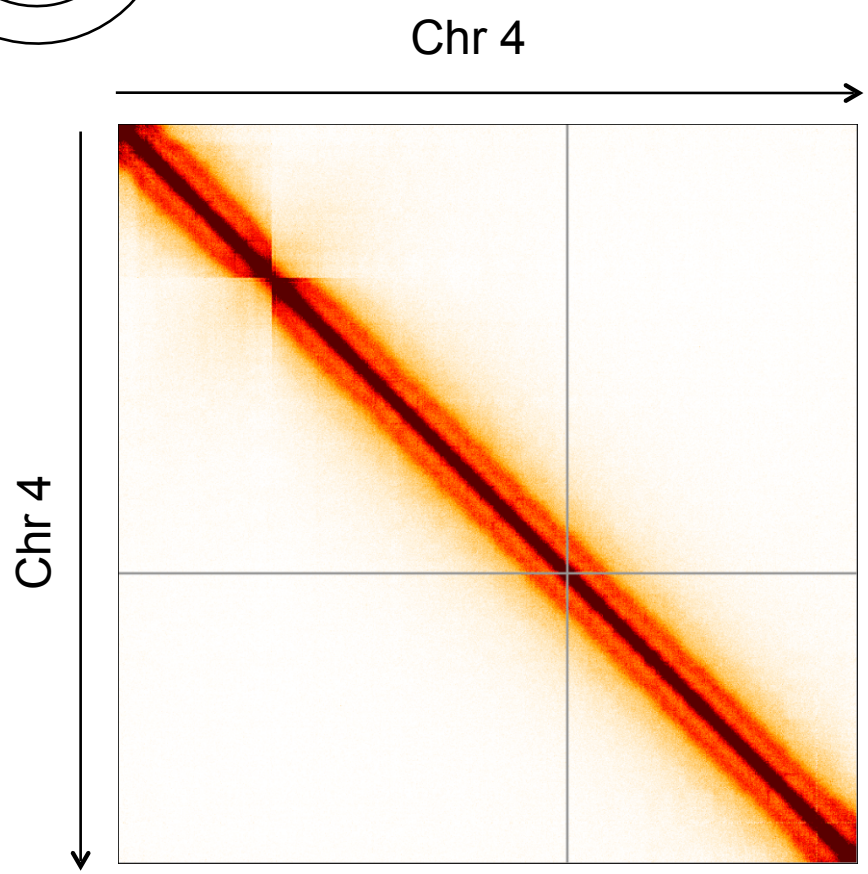
Hi-C on Synchronized DT-40

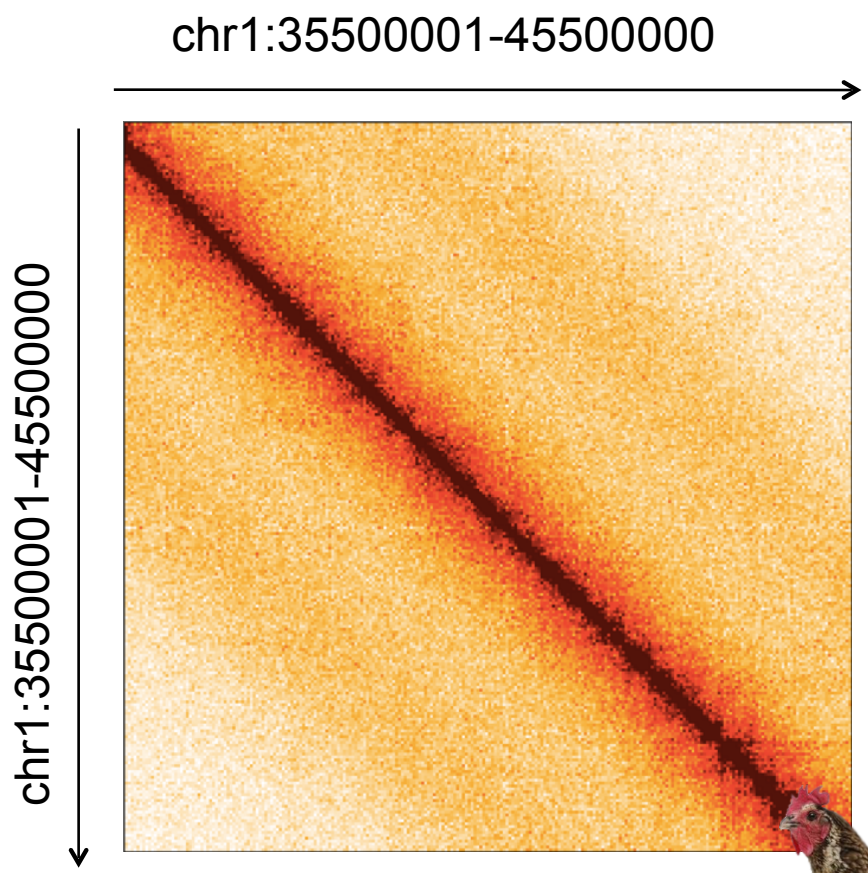




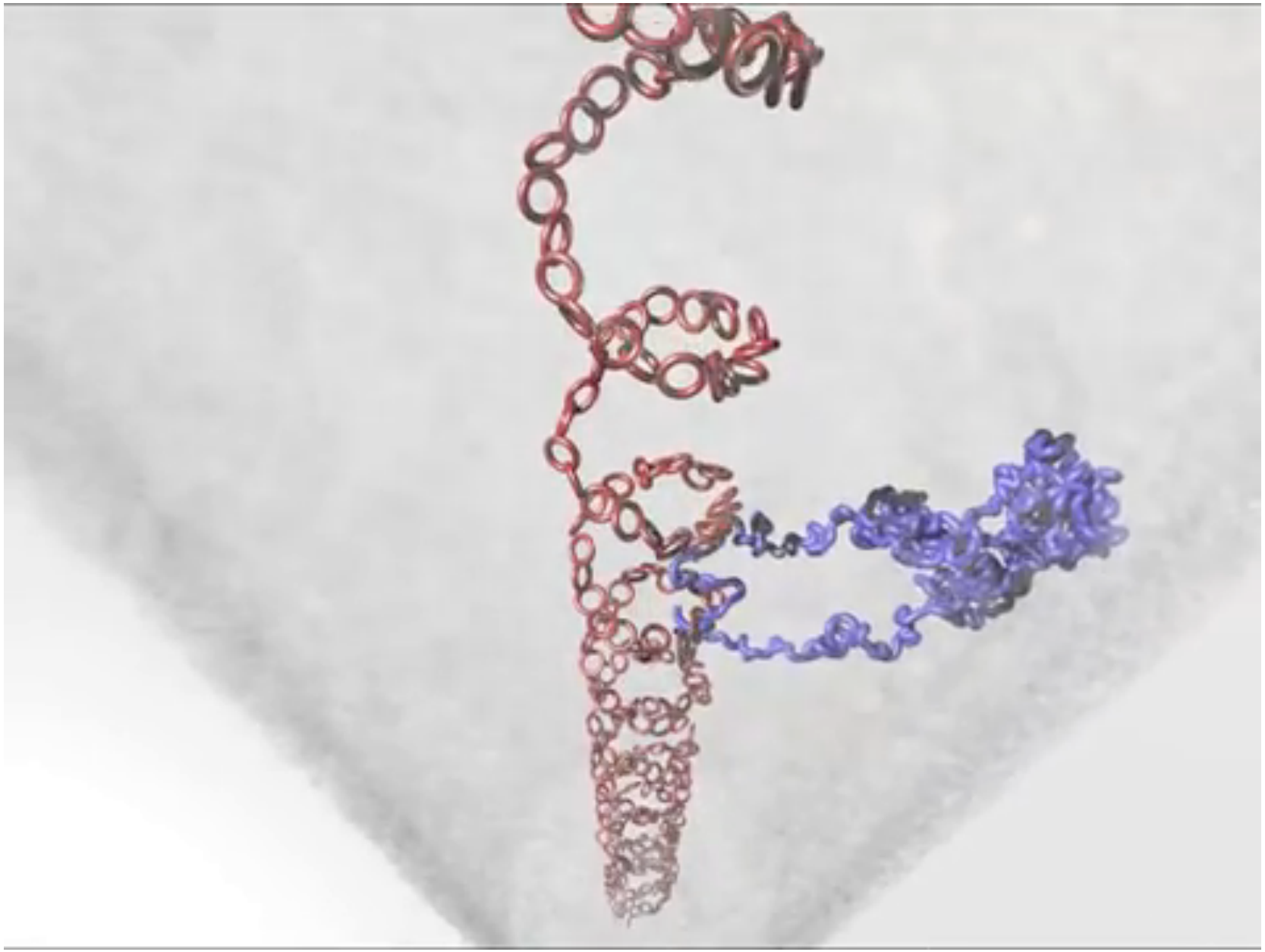


Hi-C on Synchronized DT-40





Model of mitotic chromosome

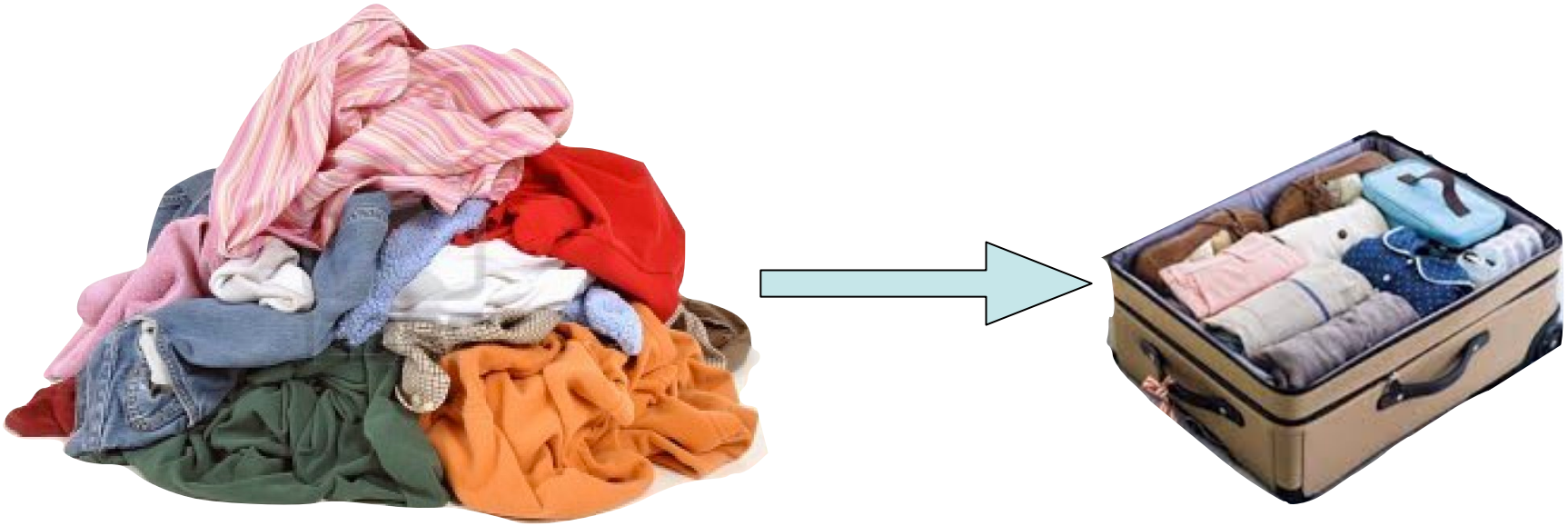


https://www.youtube.com/watch?v=cJSpWCIqb7k

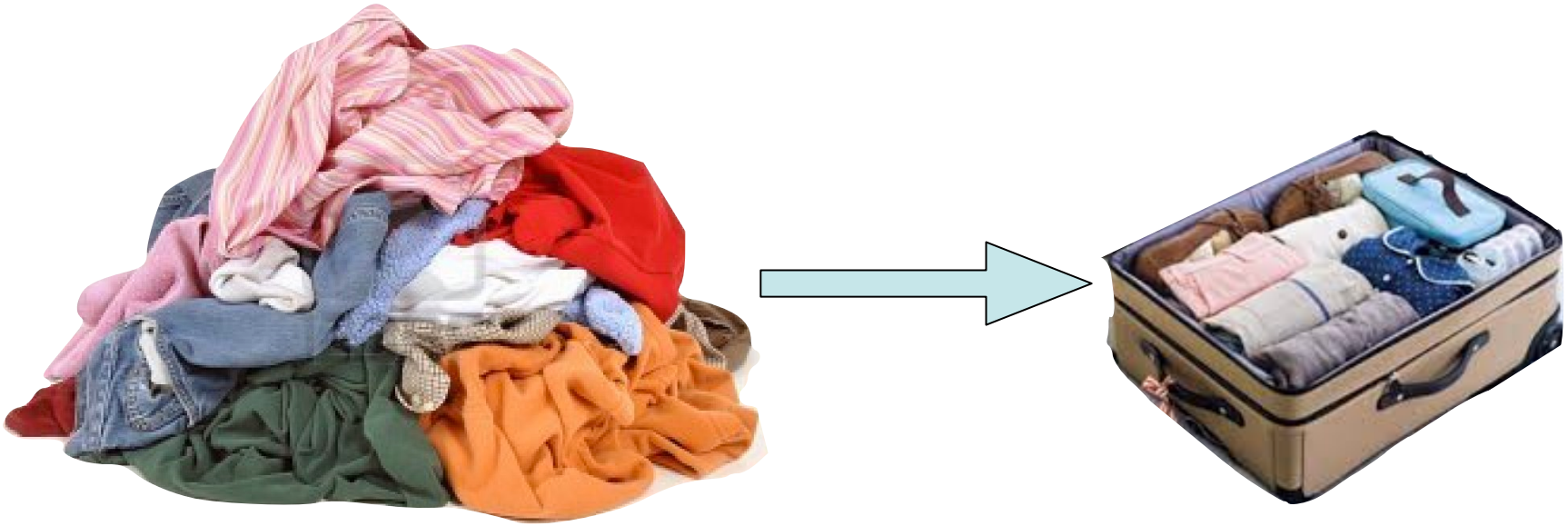
Model of mitotic chromosome

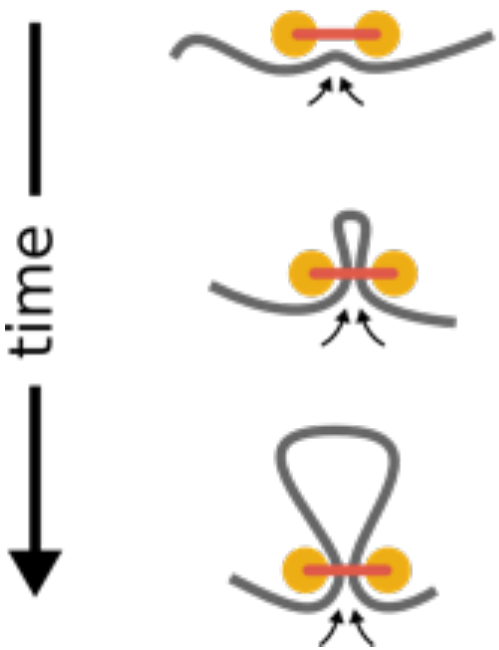
Leonardo da Vinci's Spiral Staircase in Château de Chambord

How can chromosomes fold this way?

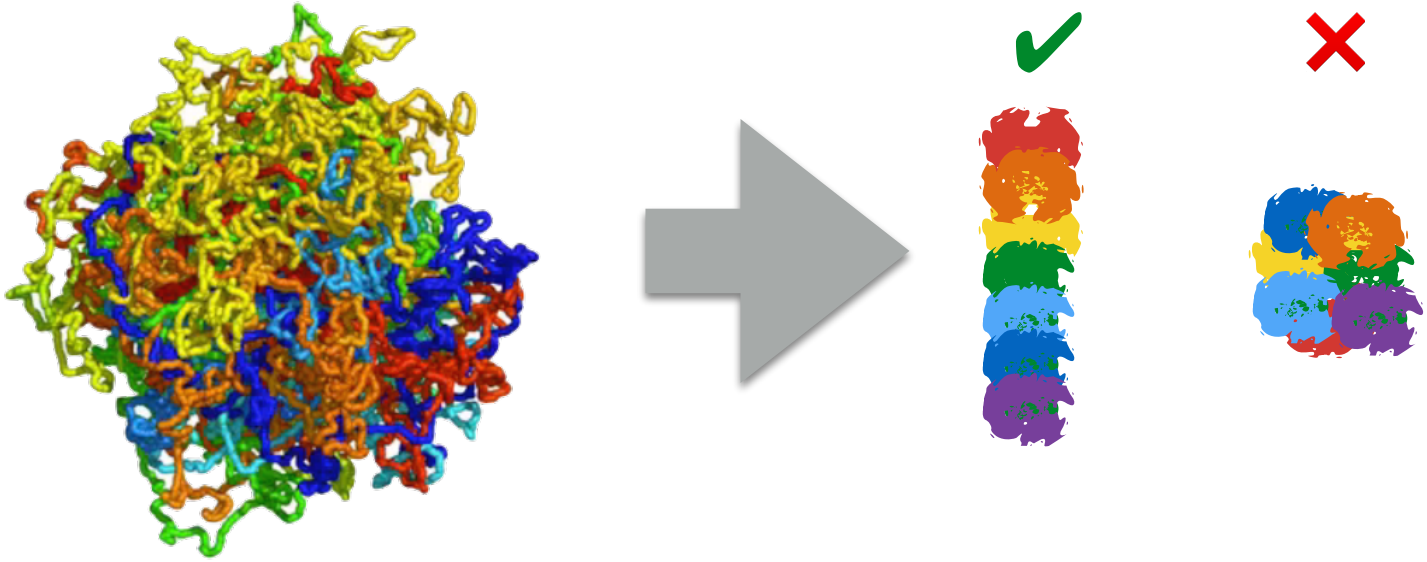


How can chromosomes fold this way?

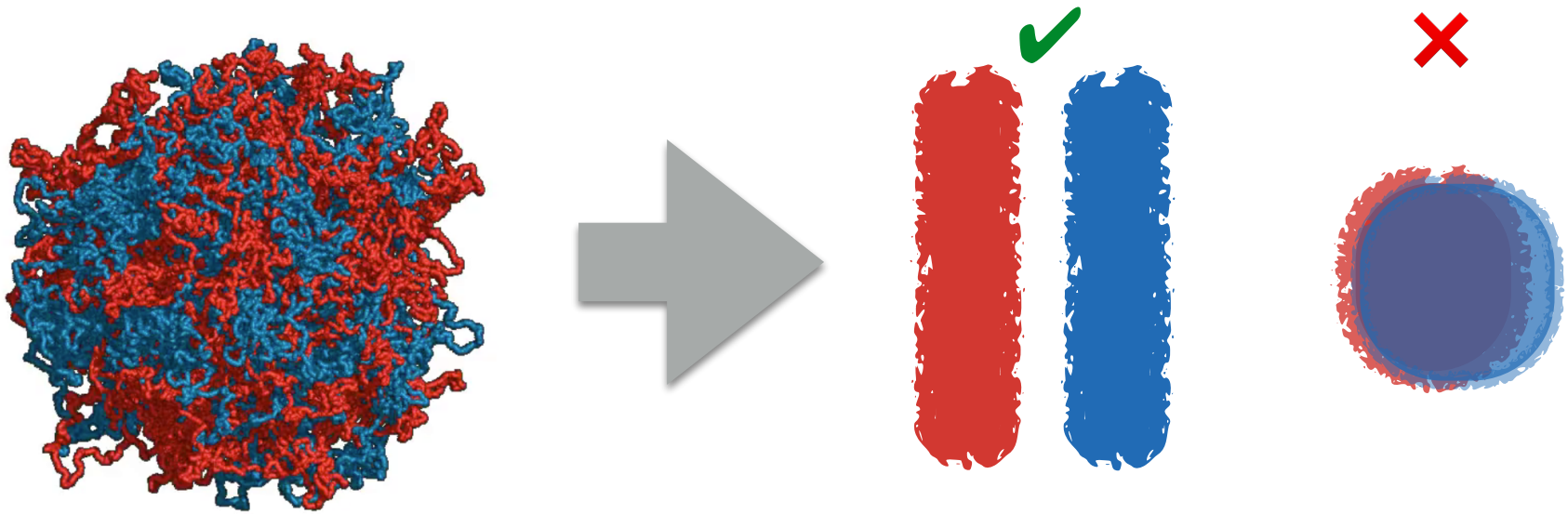




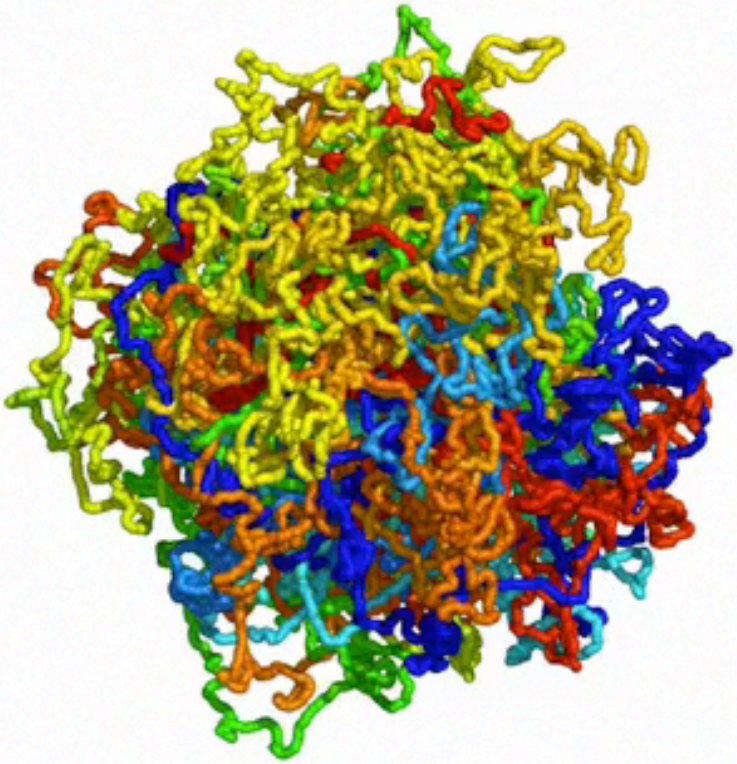
PROBLEM 1:

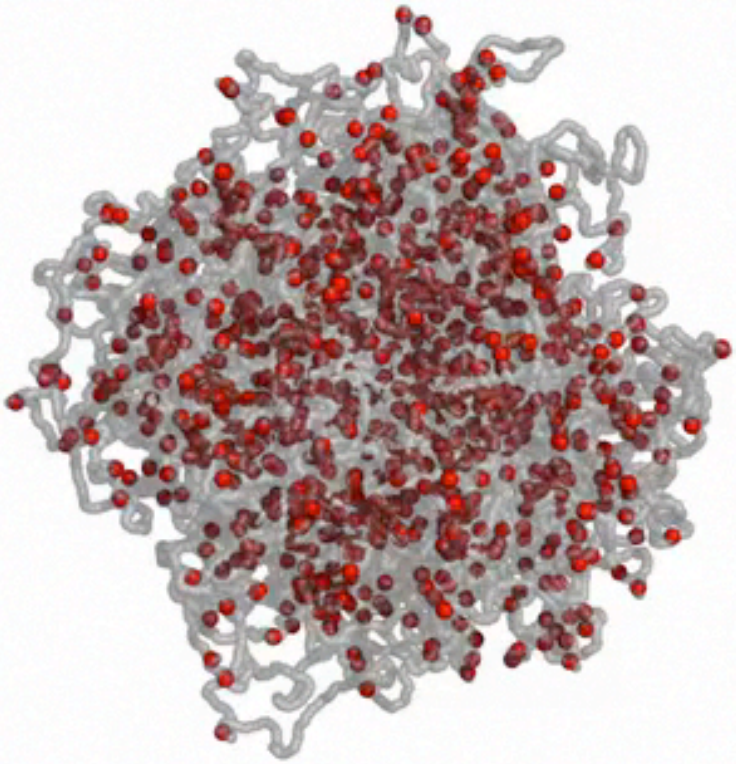


PROBLEM 2: separate two sister chromatids



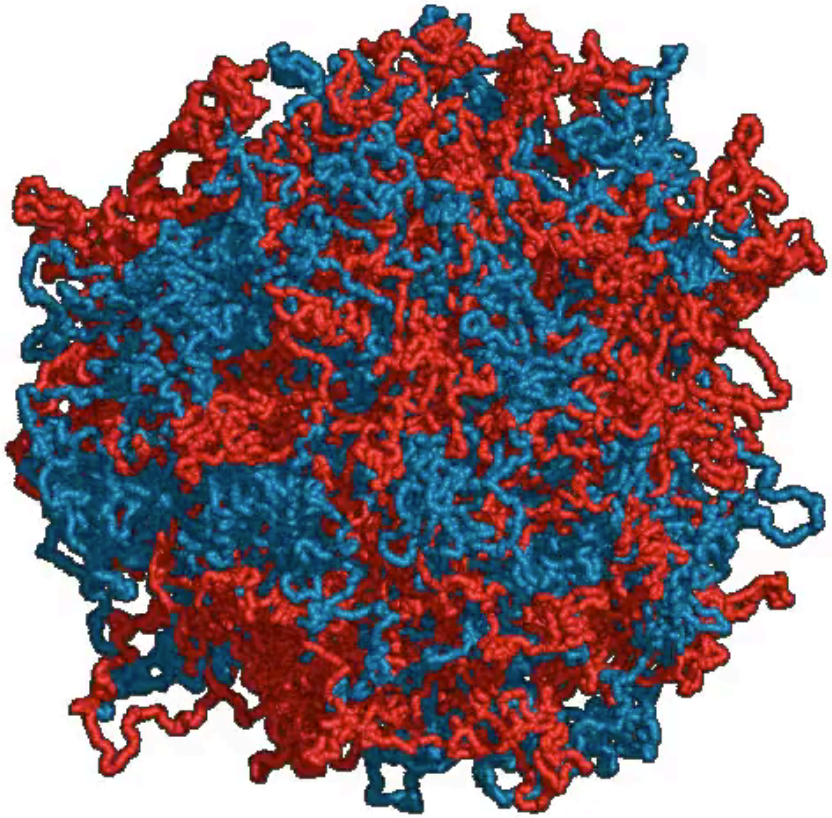
Model of chromosome condensation





https://www.youtube.com/watch?v=_Vc7__xfnfc

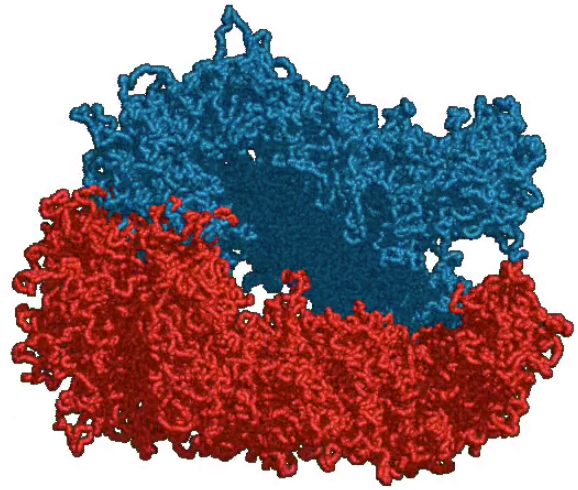
Model of chromosome segregations



https://www.youtube.com/watch?v=stZR5s9n32s

What did we learn?

New molecular motor that **packs genome!**



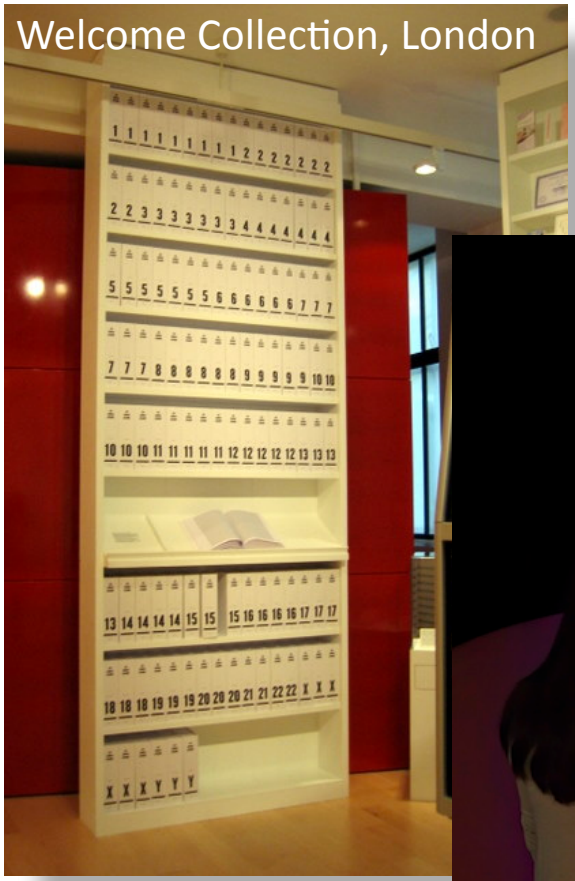
New molecular motor that **organizes genome in 3D**

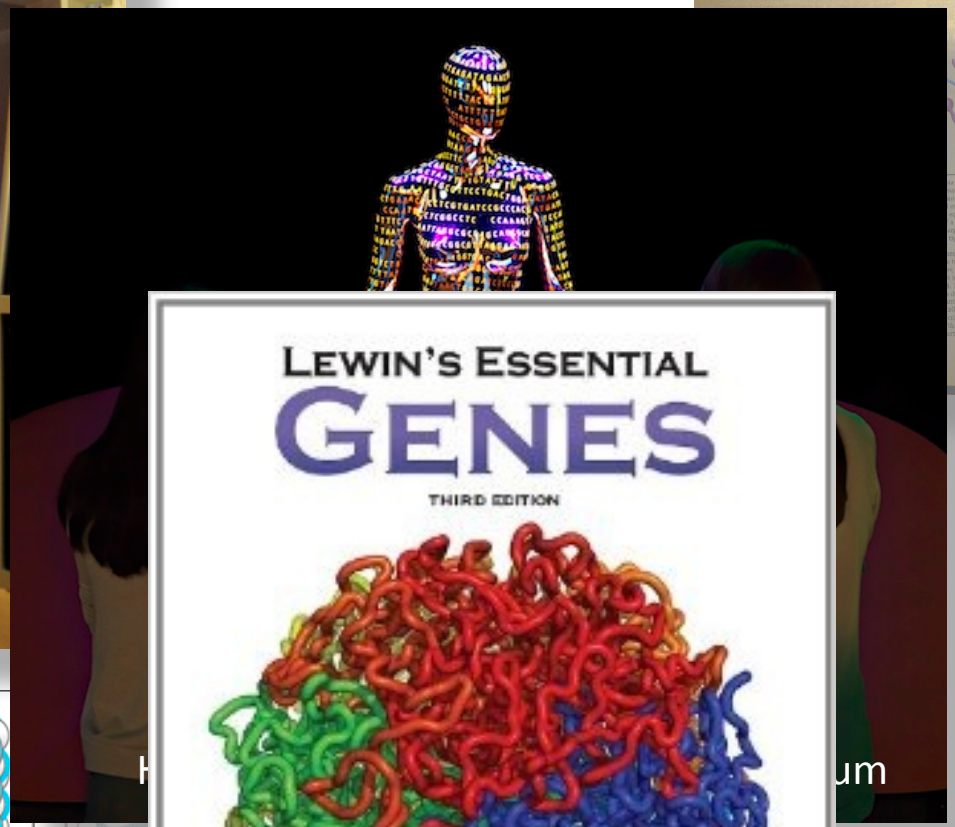
genes

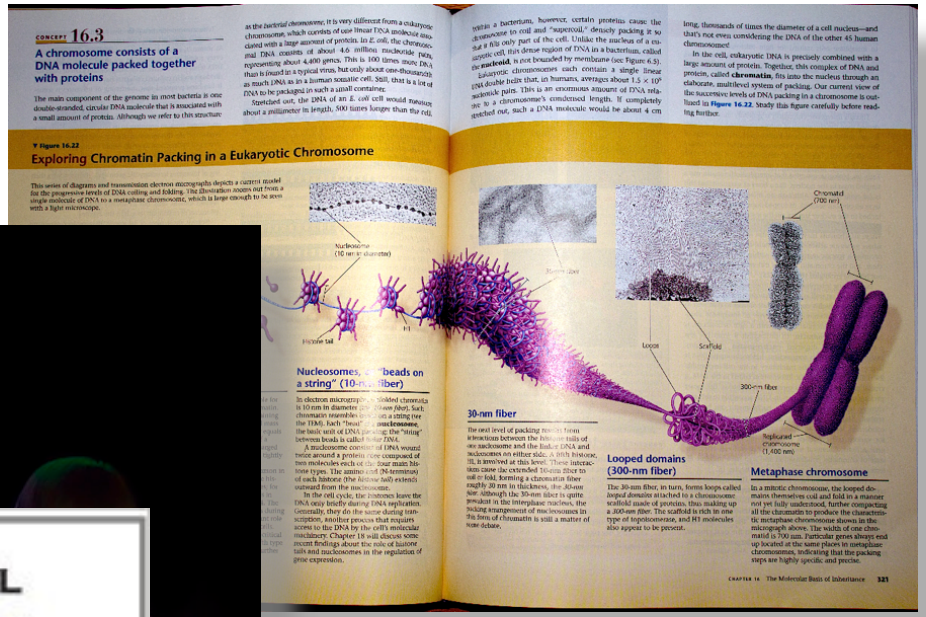
and switches

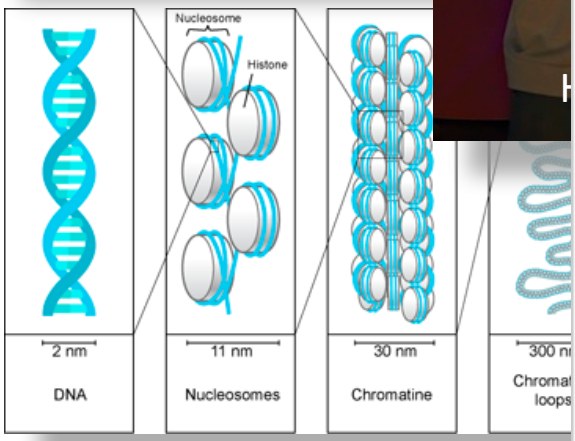
Why is this important?

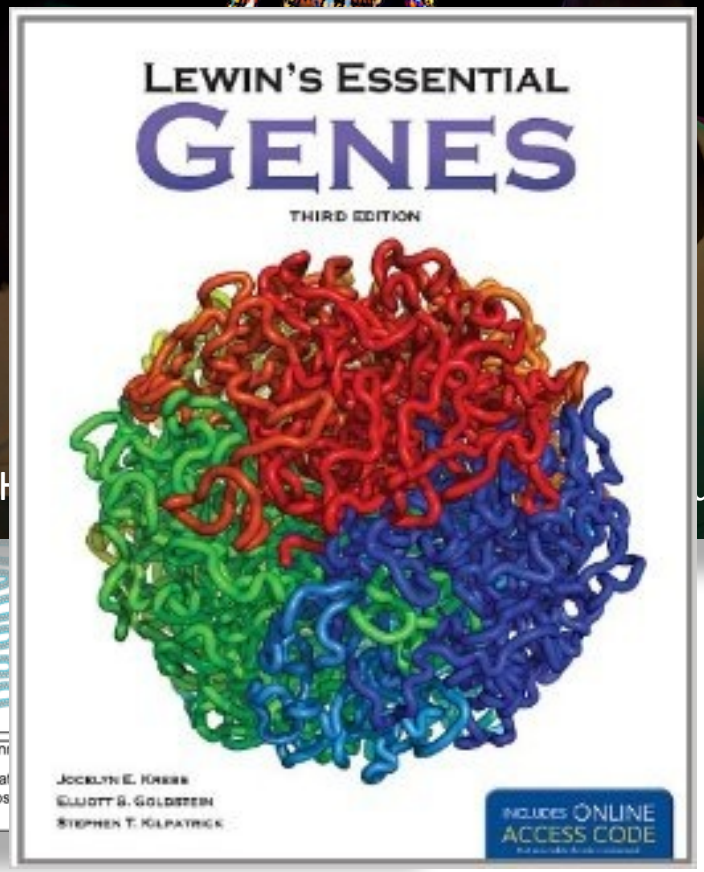
General knowledge

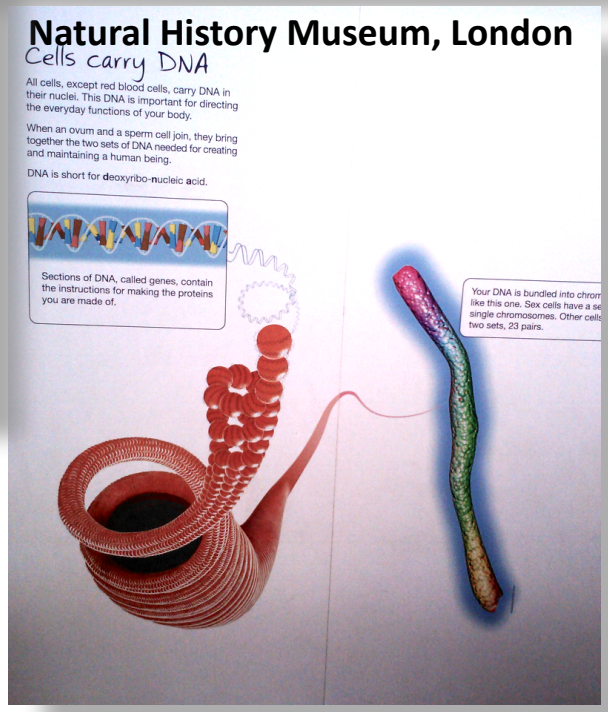




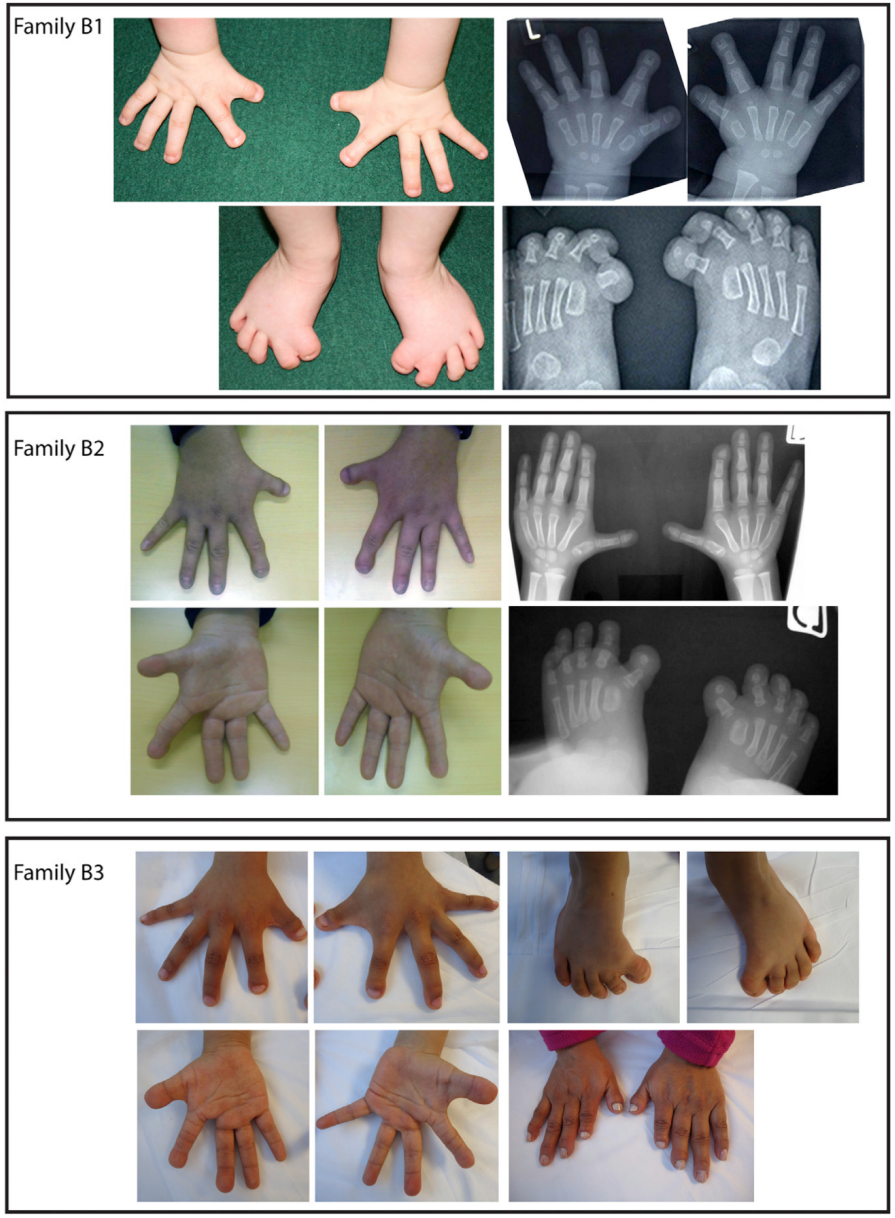


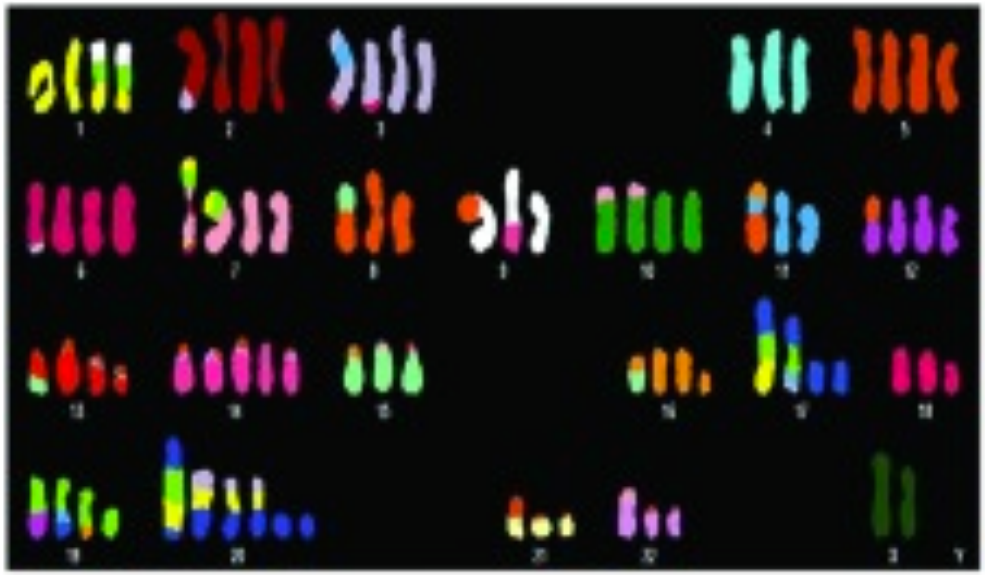




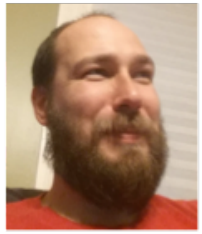


Understand how diseases develop





Thank you!

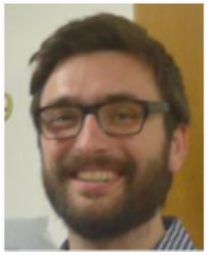


Anton Goloborodko
MIT Physics

Nezar Abdennur
MIT Comp/Sys Biology

Hugo Brandao
Harvard Biophysics

Martin Falk
MIT



Geoff Fudenberg
UCSF

Maxim Imakaev
MIT

Johannes Nübler
MIT

Sameer Abraham
MIT

Carolyn Lu
MIT senior

Aafke Van den Berg
MIT

Ed Banigan
MIT

Simon Grosse-Holz
MIT

NSF, **NIH**: Center of Structure and Physics of the Genome

Job Dekker
UMass Medical

Francois Spitz
Institut Pasteur

Irina Solovei,
LMU

Kick Tachibana-Konwalski
IBMA, Vienna

John Marko
Northwestern U.

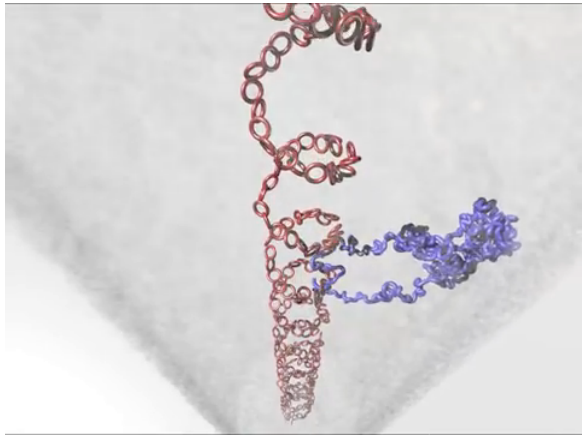
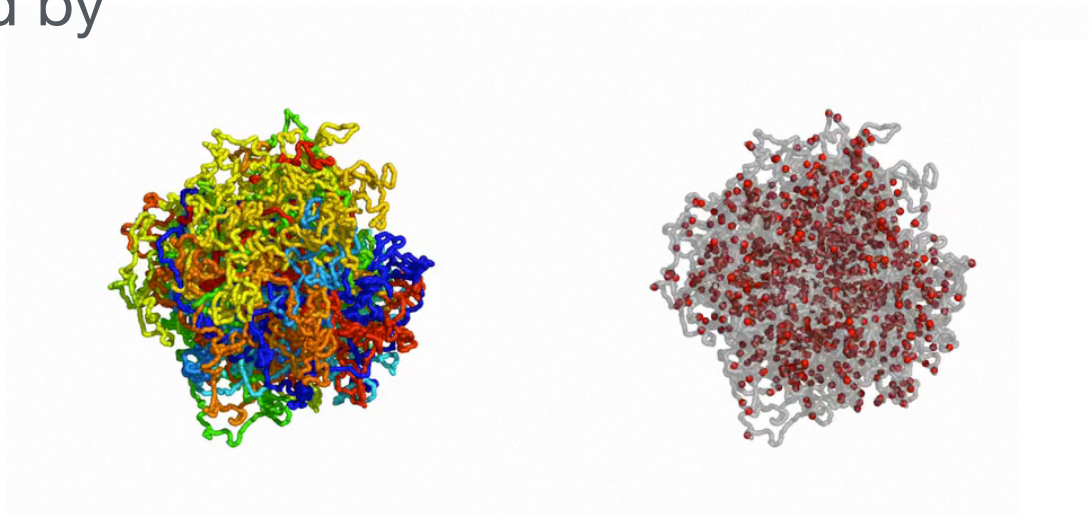
Elphege Nora
Benoit G. Bruneau
UCSF

Bill Earnshaw
U of Edinburgh

Summary

1. Genome is very long (6 feet) and its 3D folding is important in health and disease

2. We start understanding of **Genome in 3D**



3. The genome can be folded by **molecular machines!**