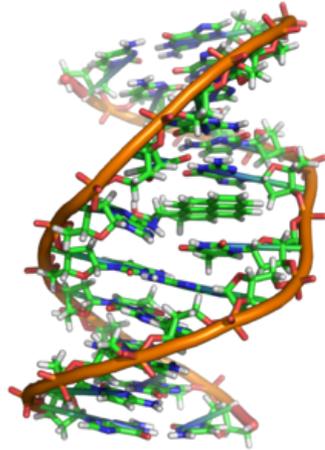


The physics of DNA packing

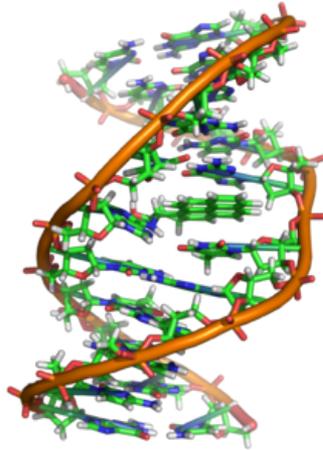
Anton Goloborodko, 8.592,
2013

Human DNA vs artificial data storage



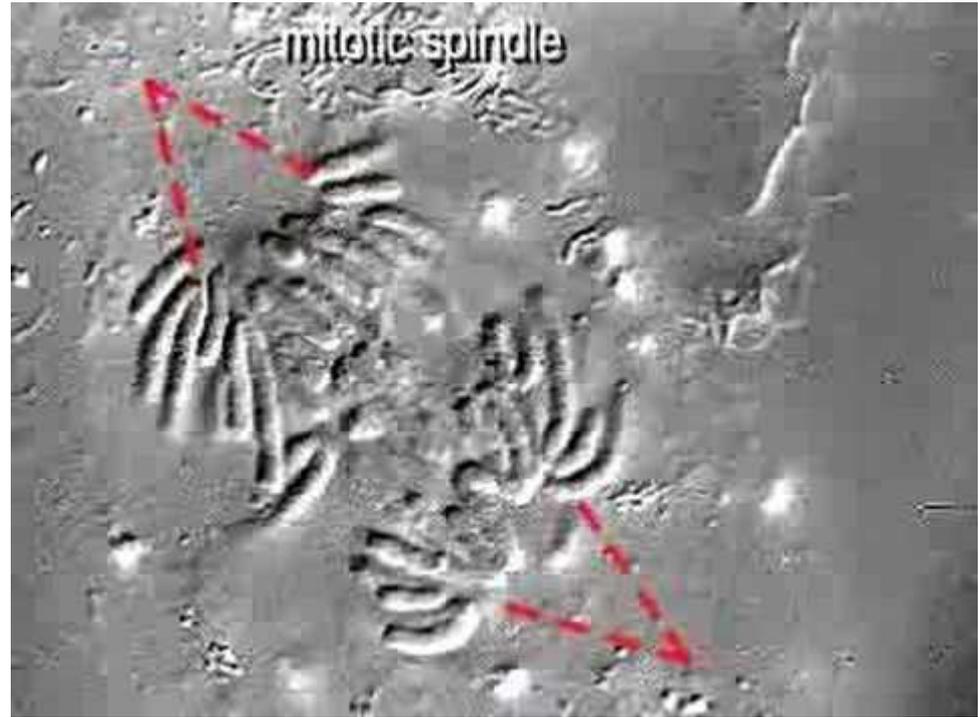
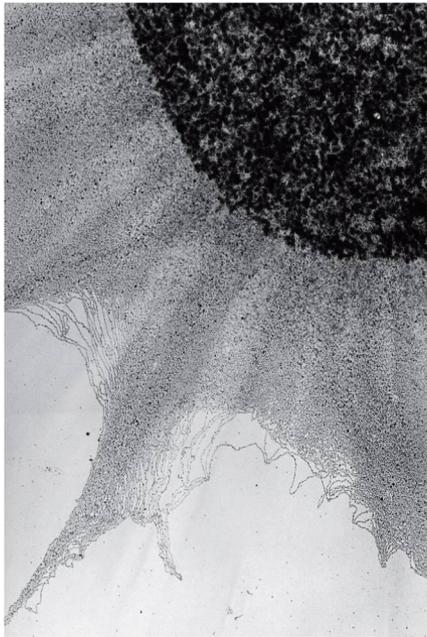
capacity	750 MB	5 TB	25 GB
linear size	~1 m per set, ~5-10 μm nucleus	~1 km with 1152 tracks ~0.1 m cassette	~20-30 km ~0.1 disk
density	~6 bit/nm	~0.005 bit/nm/track	~0.003 bit/nm/track
data rate	varies a lot, for HeLa estimated max is ~0.5 MB/s	240 MB/s	6 MB/s

Human DNA vs artificial data storage

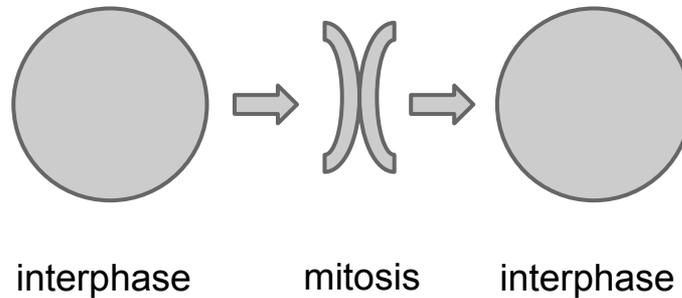


parallel random access	yes	no	no
self-replication	yes	no?	no?
self-repair	yes	no	no
extra compaction (mitosis)	yes	no	no

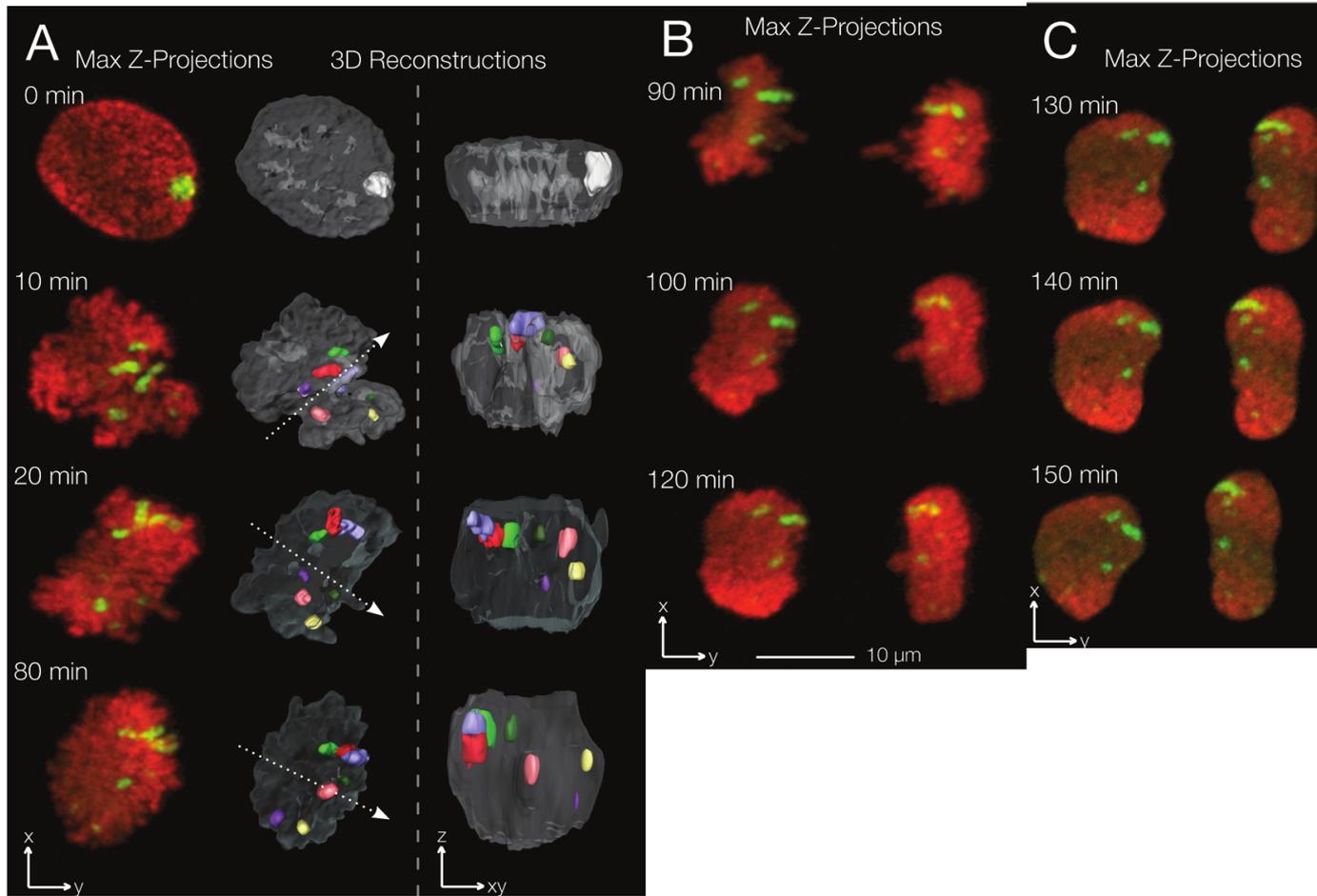
How does DNA look like inside a nucleus?



from Molecular Biology of the Cell,
Alberts et.al.

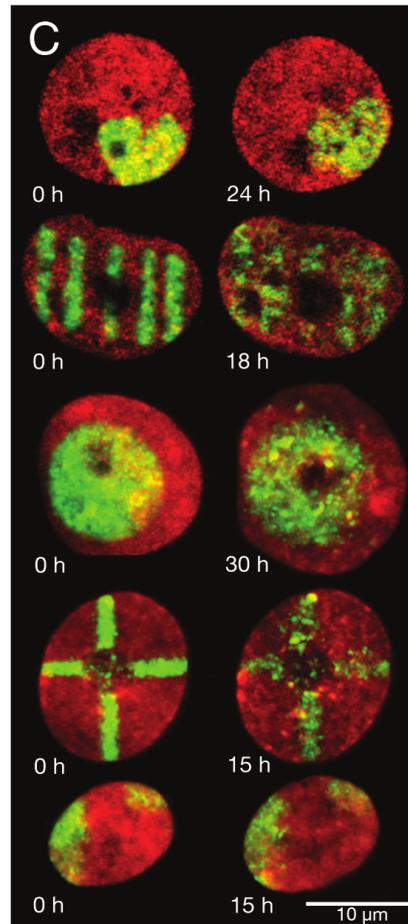


How does DNA look like inside a nucleus?



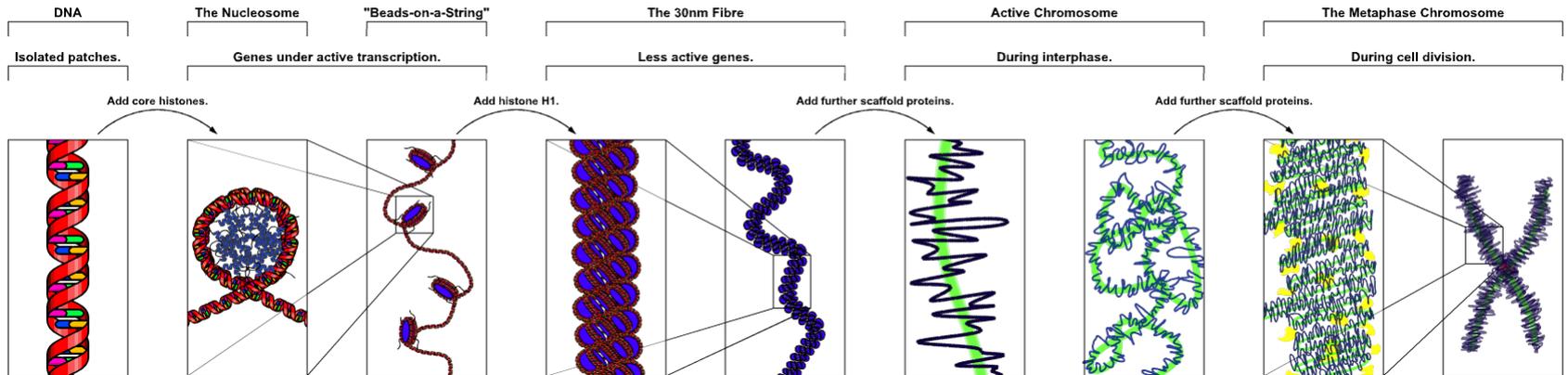
from H. Strickfaden, A. Zunhammer, S. van Koningsbruggen, D. Köhler, and T. Cremer, *Nucleus*, vol. 1, no. 3, pp. 284–97, 2010.

How does DNA look like inside a nucleus?



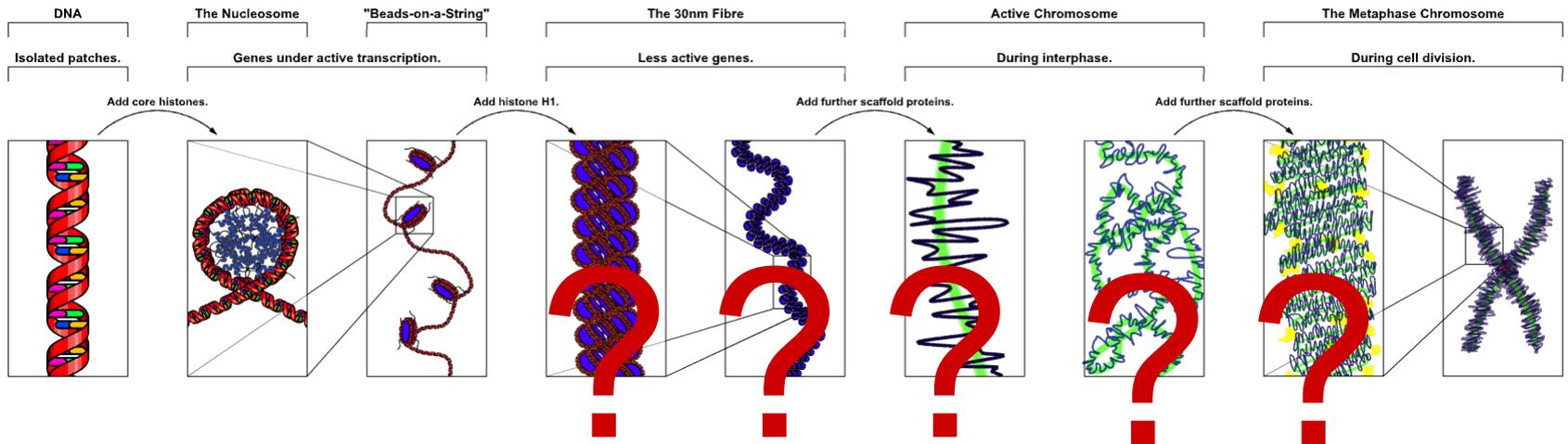
from H. Strickfaden, A. Zunhammer, S. van Koningsbruggen, D. Köhler, and T. Cremer, *Nucleus*, vol. 1, no. 3, pp. 284–97, 2010.

DNA has multiple levels of organization



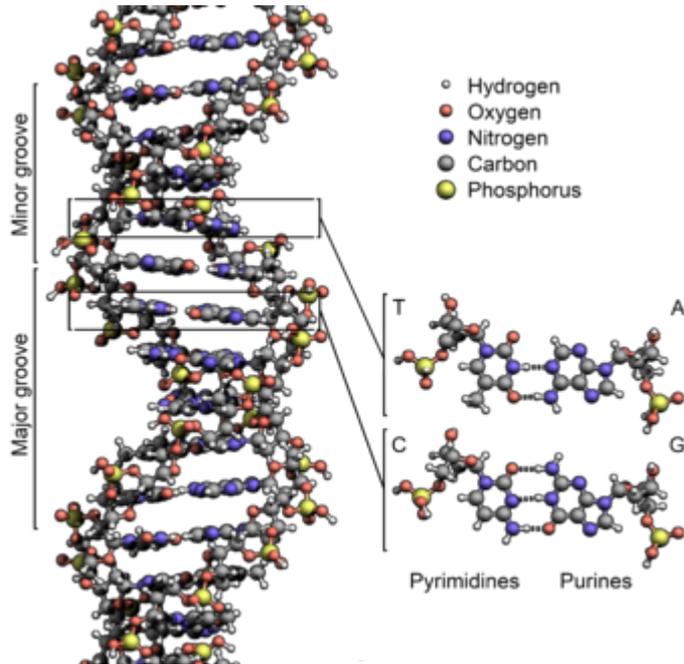
from Wikipedia entry for "Chromatin"

DNA has multiple levels of organization

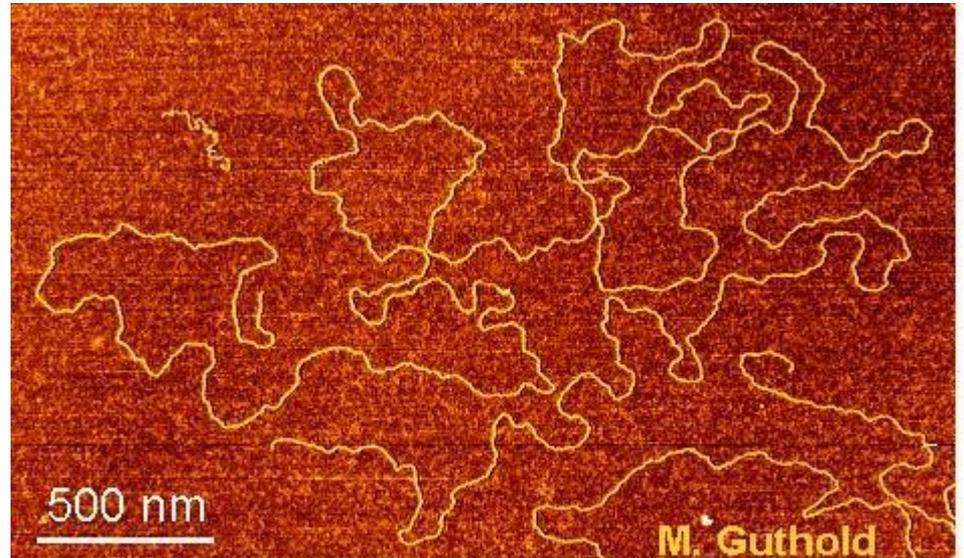


from Wikipedia entry for "Chromatin"

Naked DNA



from Wikipedia entry for DNA

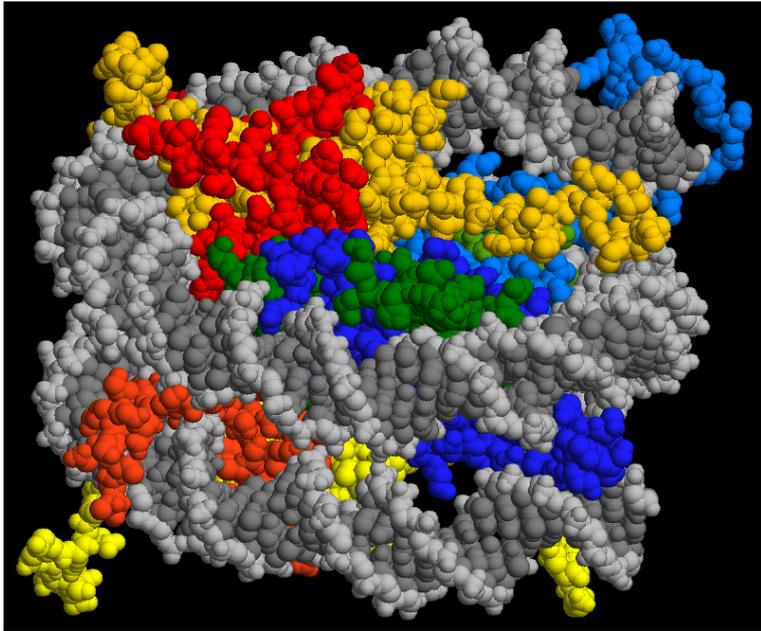


λ -DNA

AFM image of Lambda DNA (~ 16 micrometers long),
from M.Guthold website

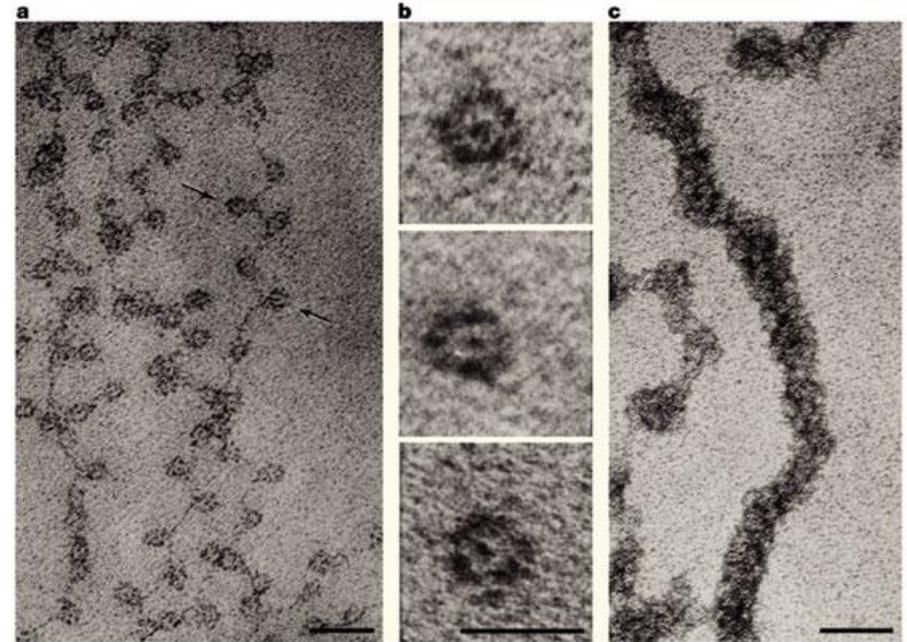
- highly charged ($\sim 1e$ / bp)
- Kuhn length ~ 106 nm or 310 bp
- the largest human chromosome would have gyration radius of ~ 100 micron (SAW)

Nucleosomes provide the second level of DNA organization



from Wikipedia entry for "Nucleosome"

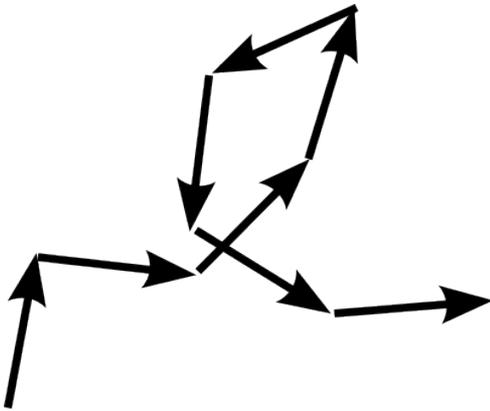
- 146 bp / nucleosome + ~10 bp / linker
- neutralize ~50% of DNA negative charges
- interact with each other to form higher-order fibers (parameters are still discussed)
- provide additional linear compaction of ~5-50, depending on salt conditions and state of nucleosomes
- can have hundreds of different biochemical modifications providing extra informational storage



Nature Reviews | Molecular Cell Biology

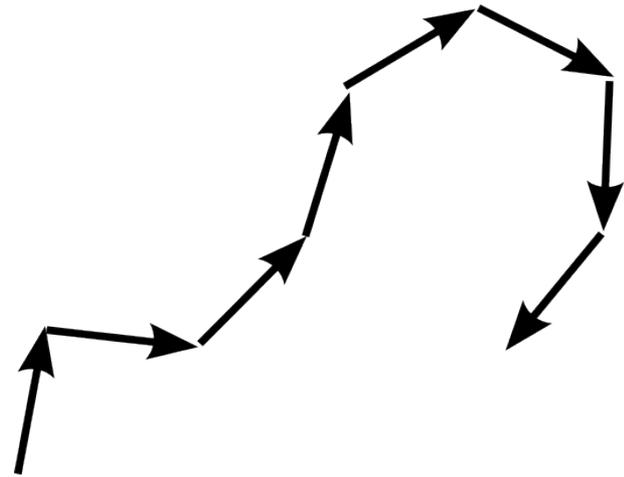
from D.E. Olins and A.L. Olins, *Nature Reviews Molecular Cell Biology* **4**, 809-814 (October 2003)

Random coil and swollen coil are two basic models of local polymer statistics



random walk

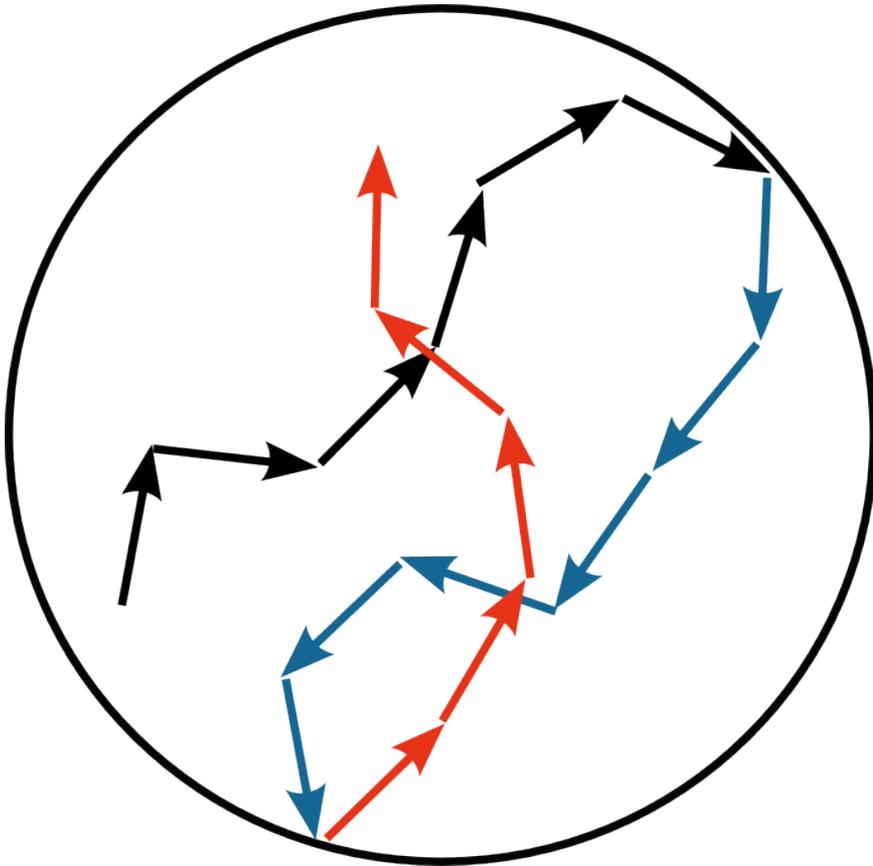
$$R \sim b N^{1/2}$$



self-avoiding walk

$$R \sim b N^{3/5}$$

Equilibrium globule is a conformation of a fully equilibrated confined polymer



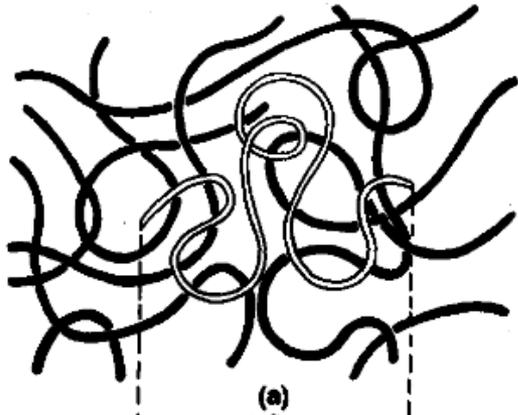
$$R \sim b * s^x, s \ll (R_{\max}/b)^{1/x}$$

$$R \sim R_{\max}, s \gg (R_{\max}/b)^{1/x}$$

$$(R_{\max}/b)^{1/x} \sim 1/100 N$$

for the largest chromosome

Chain in a melt or confinement is ideal (Flory theorem)



the concentration profile is flat across the confining volume

=>

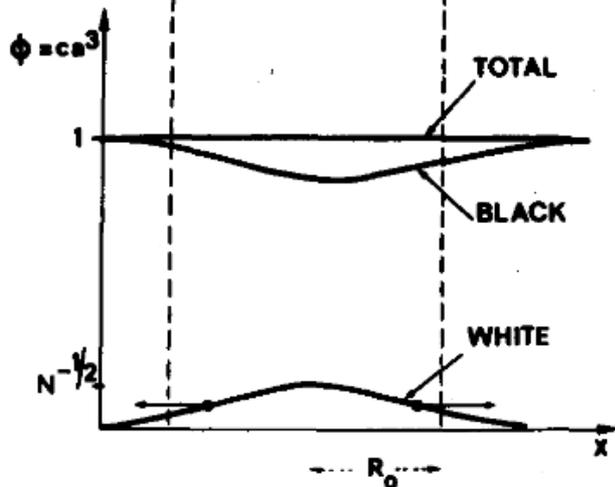
the excess of same-chain monomers is compensated by decreased concentration of monomers from the other chains

=>

chain has the ideal statistics,

$$R \sim b * s^{1/2}, s \ll N^*$$

$$R \sim \text{const}, s \gg N^*$$

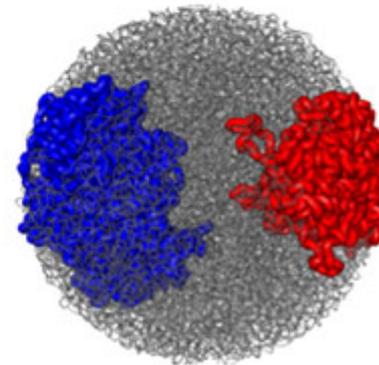
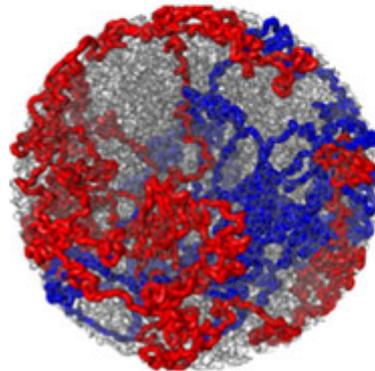
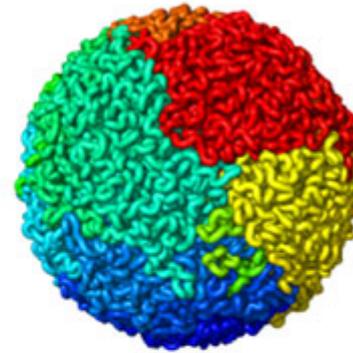
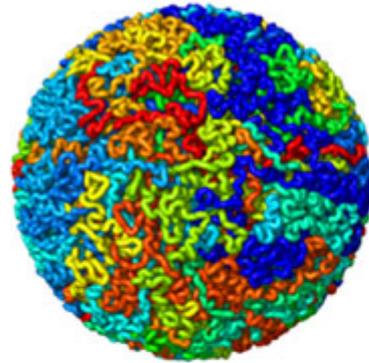


from de Gennes, Scaling concepts in polymer physics, 1979

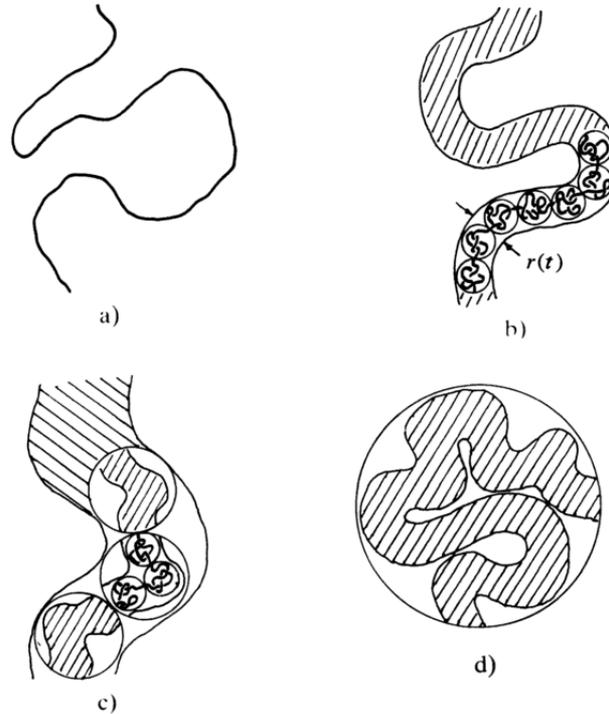
Second possible model of chromatin fiber folding

equilibrium globule

fractal globule

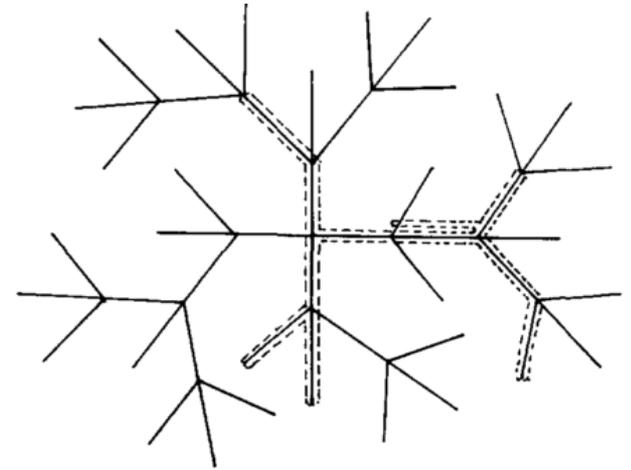
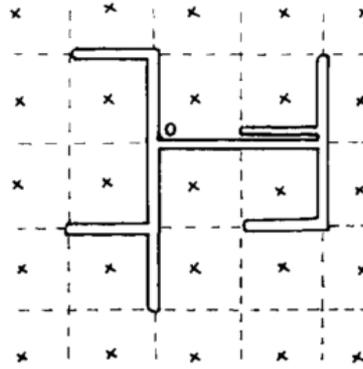
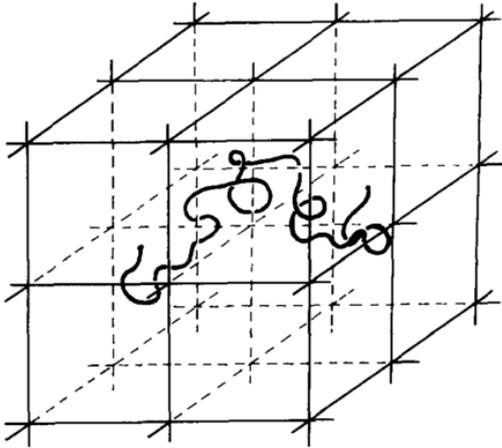


Crumpled (fractal) globule is a long-lived non-equilibrium state of a collapsed polymer



A. Y. Grosberg, S. K. Nechaev, and E. I. Shakhnovich, “The role of topological constraints in the kinetics of collapse of macromolecules,” *Journal de Physique*, vol. 49, no. 12, pp. 2095–2100, 1988.

Crumpled (fractal) globule is a space-filling fractal curve



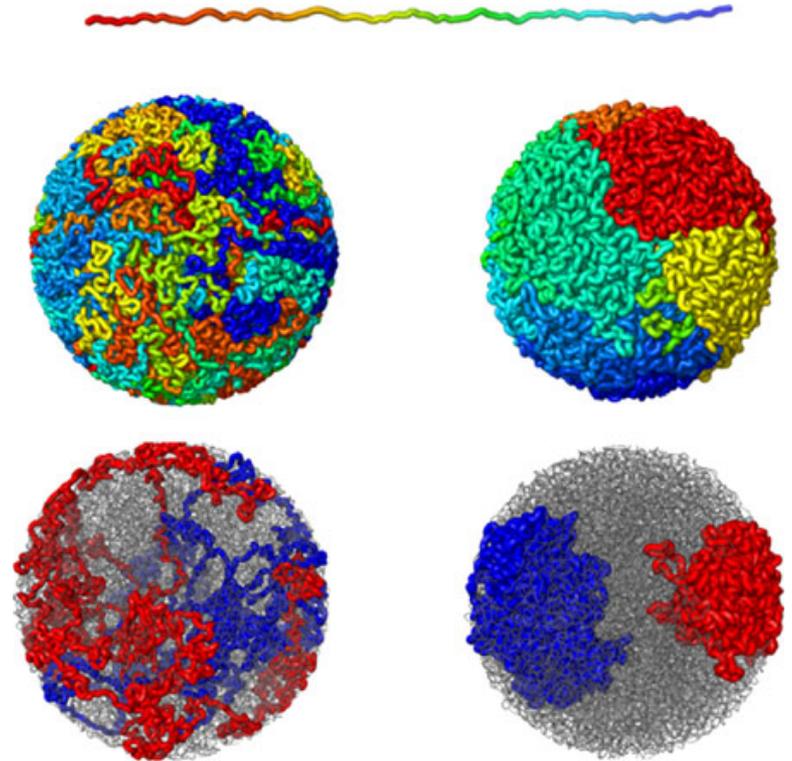
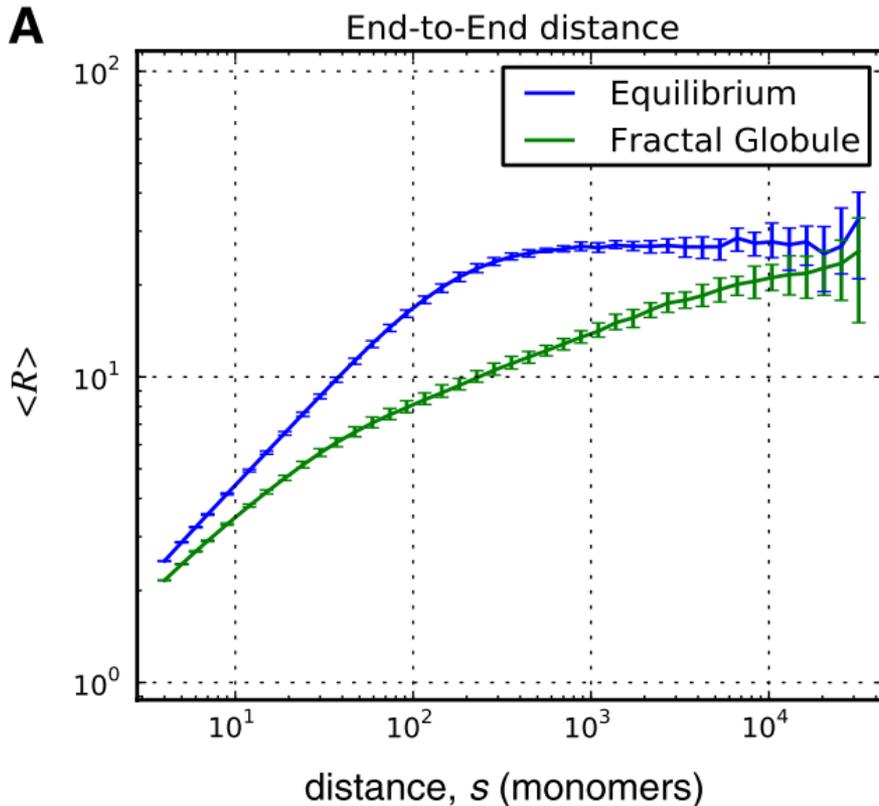
$$R \sim a * i^{1/2}, i \sim s^{1/2}, \Rightarrow R \sim a * s^{1/4},$$

but $R > a * N^{1/3}$,

=>

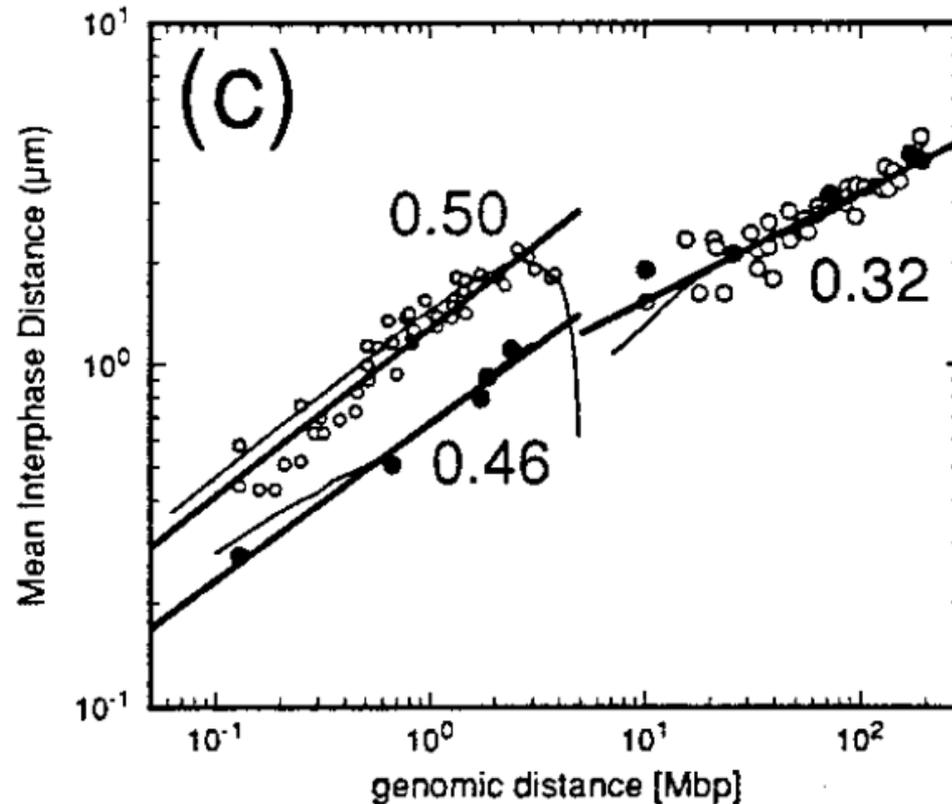
$$R \sim b * N^{1/3}, \text{ does not plateau!}$$

Equilibrium vs fractal globule

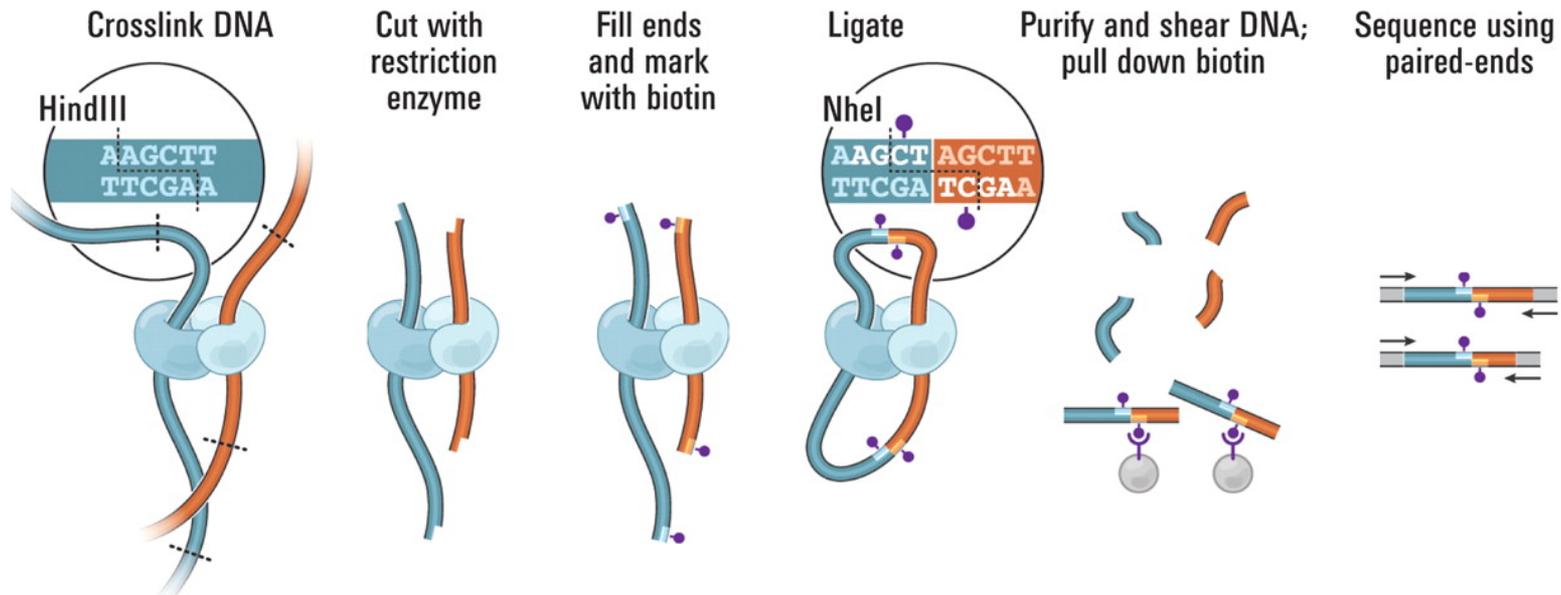


from L. Mirny, *Chromosome research*, vol. 19, no. 1, pp. 37–51, Jan. 2011.

Mean spatial separation measured by optical microscopy is consistent with the fractal globule model

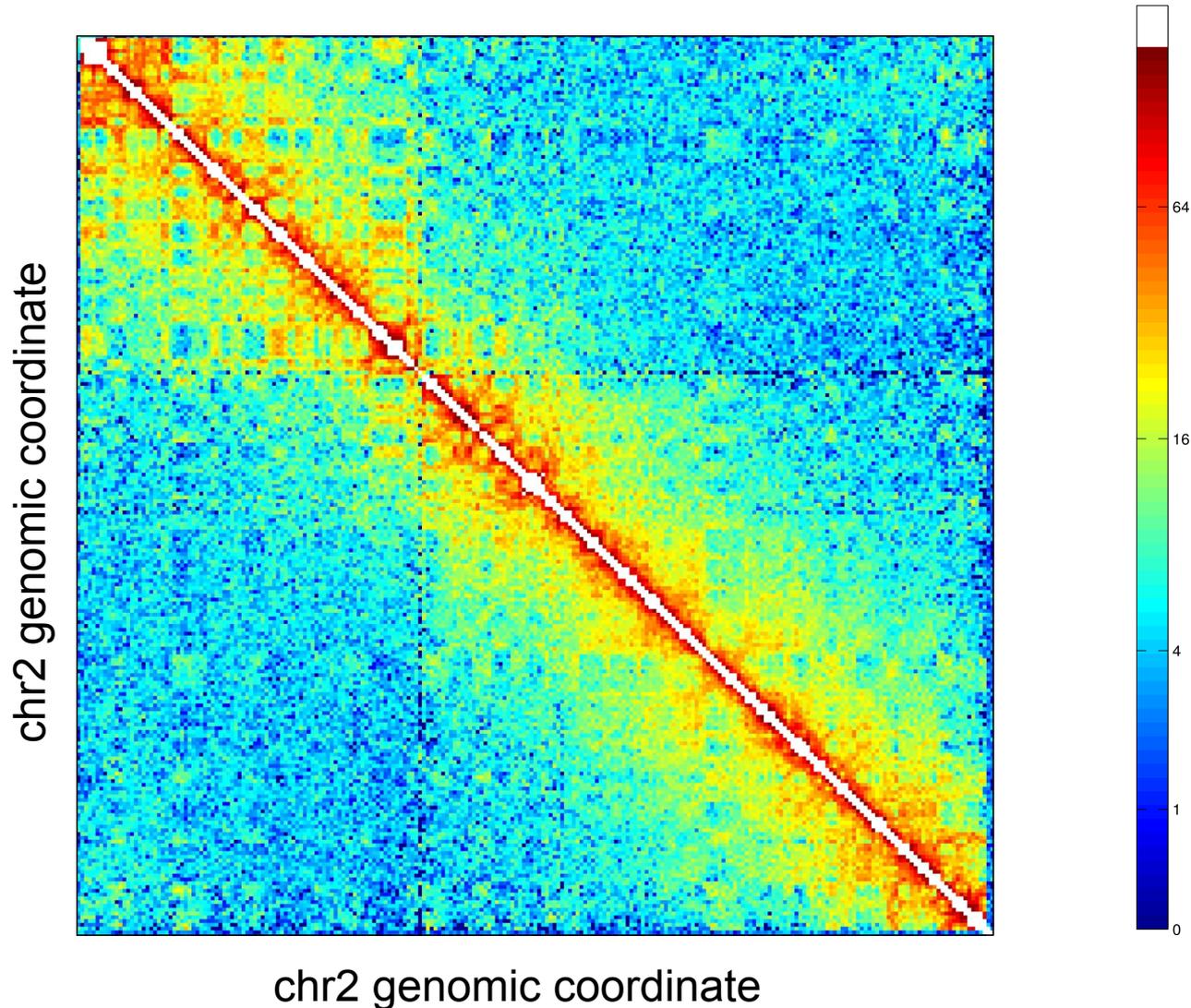


Principles of chromatin fiber folding were revealed by Hi-C

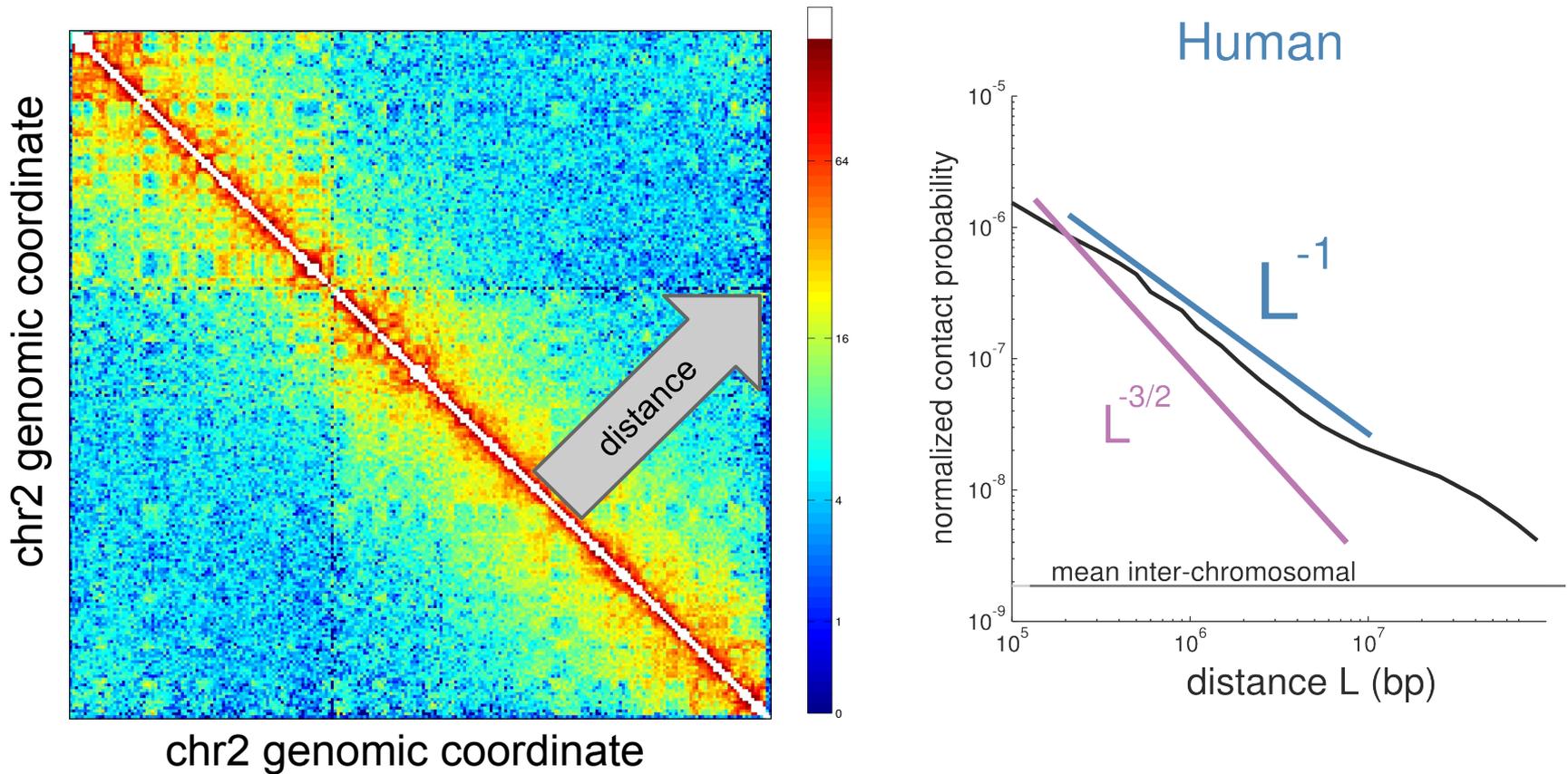


E. Lieberman-Aiden, et.al, "Comprehensive mapping of long-range interactions reveals folding principles of the human genome.," *Science (New York, N.Y.)*, vol. 326, no. 5950, pp. 289–93, Oct. 2009.

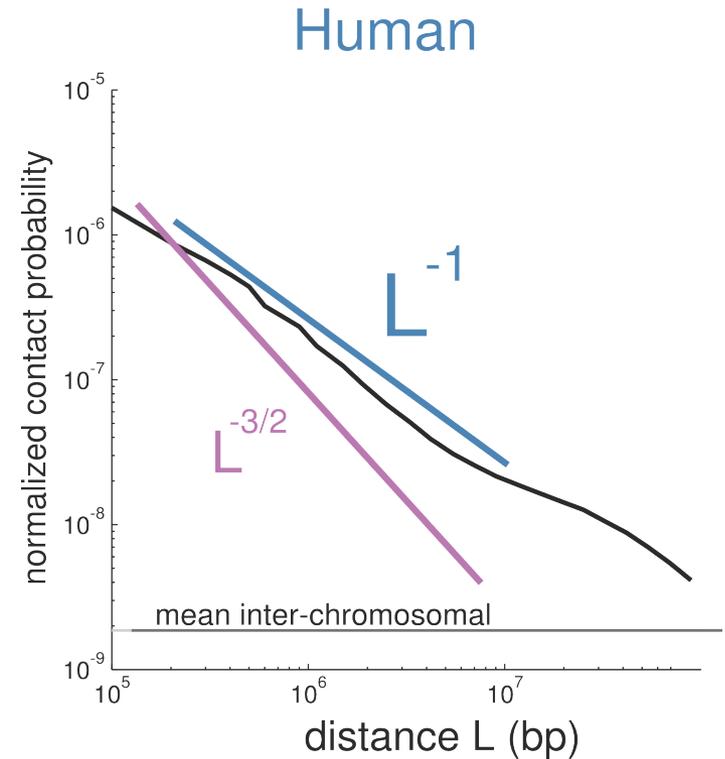
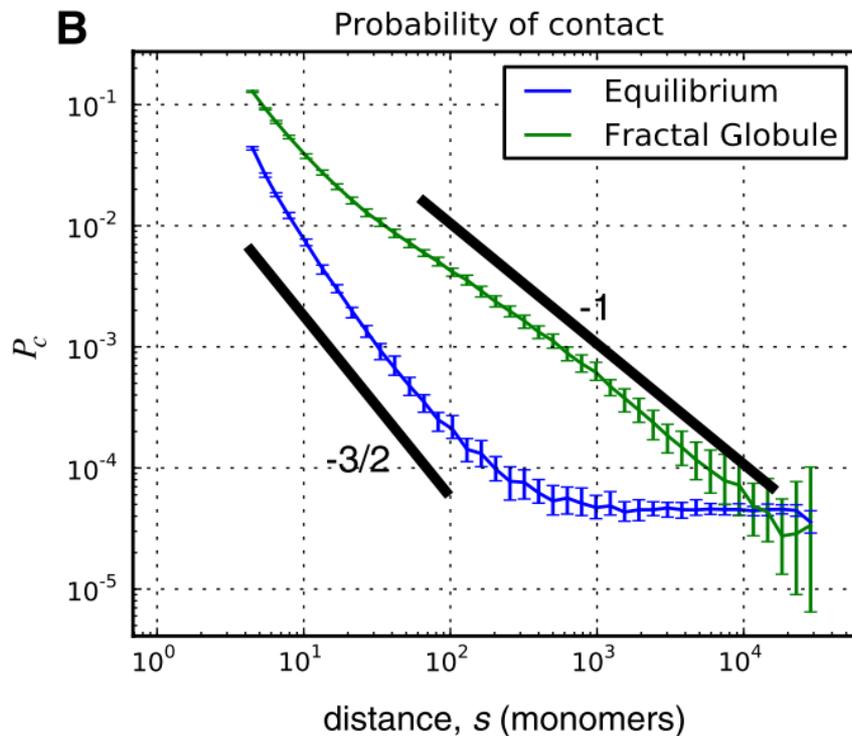
Hi-C measures frequency of contacts between regions of DNA



Hi-C provides the scaling of contact probability with distance

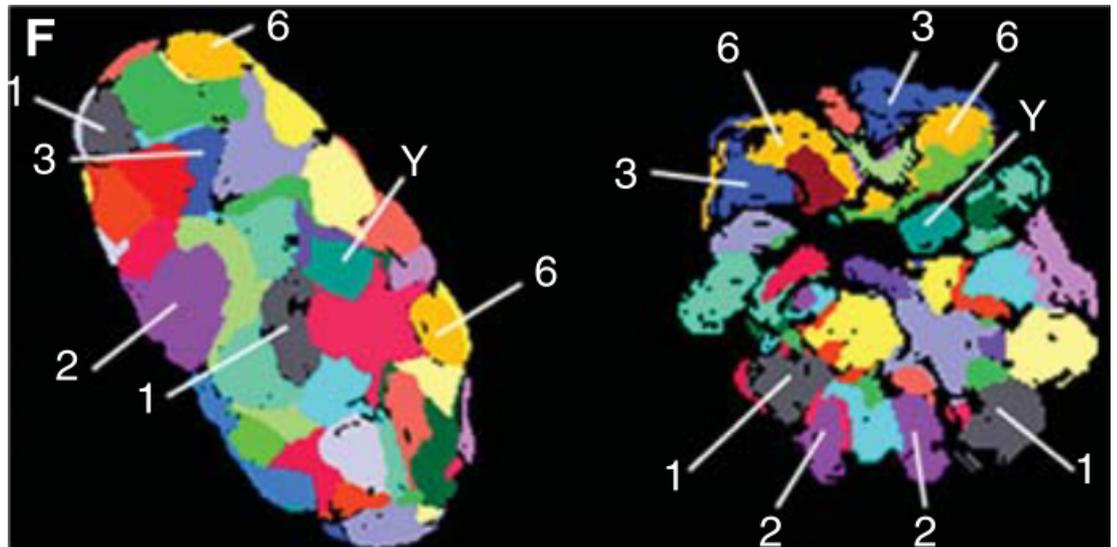
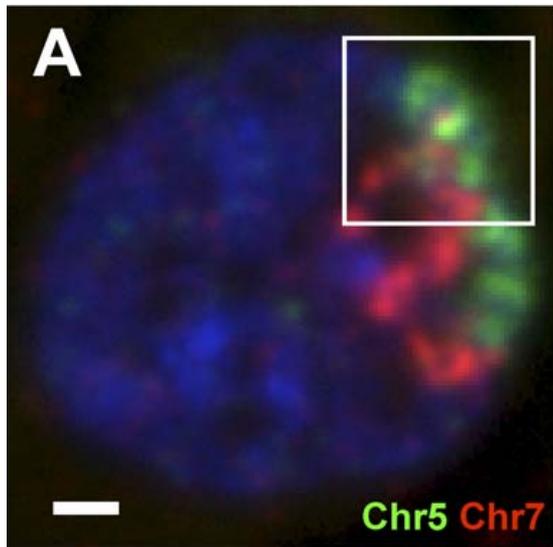


Hi-C contact probability scaling is consistent with the fractal globule



from L. Mirny, *Chromosome research*, vol. 19, no. 1, pp. 37–51, Jan. 2011.

Human chromosomes form separate "territories"



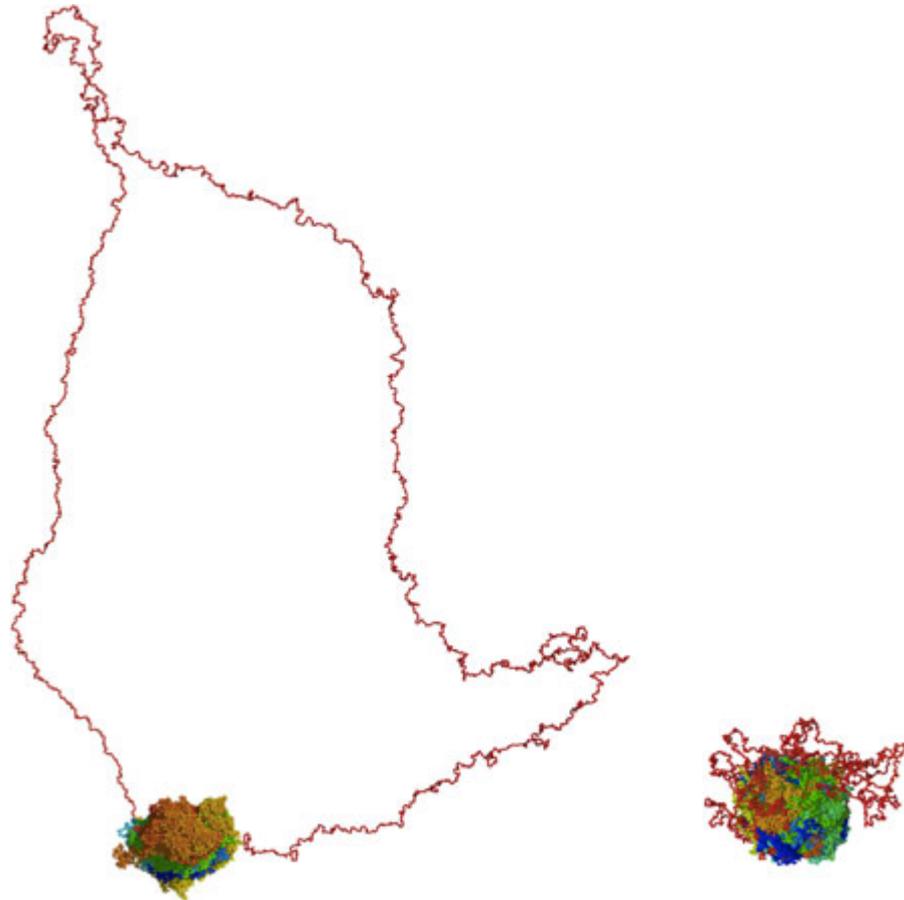
[1] M. R. Branco and A. Pombo, "Intermingling of chromosome territories in interphase suggests role in translocations and transcription-dependent associations.," *PLoS biology*, vol. 4, no. 5, p. e138, May 2006.

[2] from T. Cremer and M. Cremer, "Chromosome territories.," *Cold Spring Harbor perspectives in biology*, vol. 2, no. 3, p. a003889, Mar. 2010.

Biological implications of fractal globule

- gene colocalization
- DNA search / repair
- frequency of genomic alterations (e.g. cancer)
- mechanism of mitotic condensation

Biological implications of fractal globule: chromatin decondensation



from L. Mirny, *Chromosome research*, vol. 19, no. 1, pp. 37–51, Jan. 2011.

Other organisms with the fractal structure of genome

- mouse
- fruit fly

Not applicable to:

- bacteria
- yeast
- plants (?)