

Comprehensive Mapping of Long-Range Interactions Reveals Folding Principles of the Human Genome

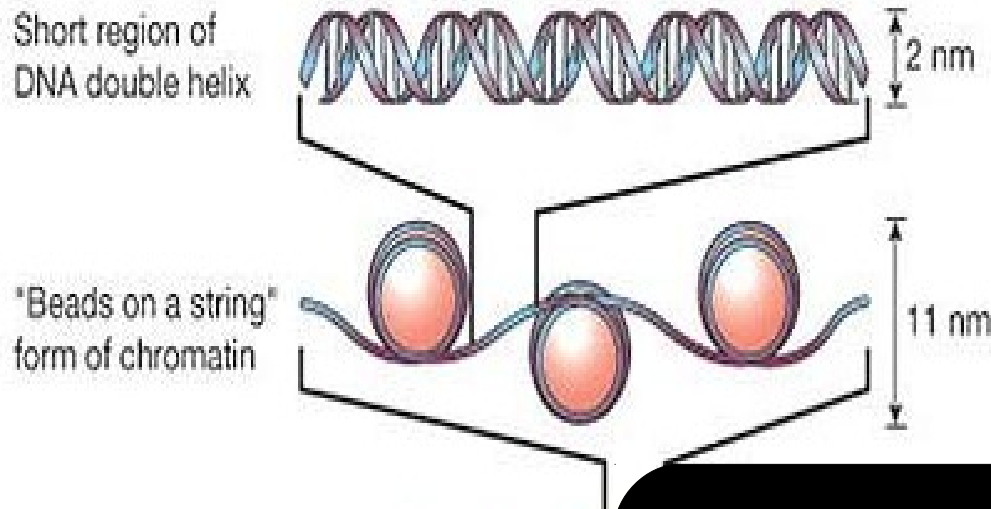
Erez Aiden et al, Science 2009

Song Qiang

Outline

- Introduction to 3D structure of chromosomes
- Describe Hi-C method
- Results
 - Chromosome territories
 - Chromosome compartmentation
 - Fractal globule model
- Summary and opinions

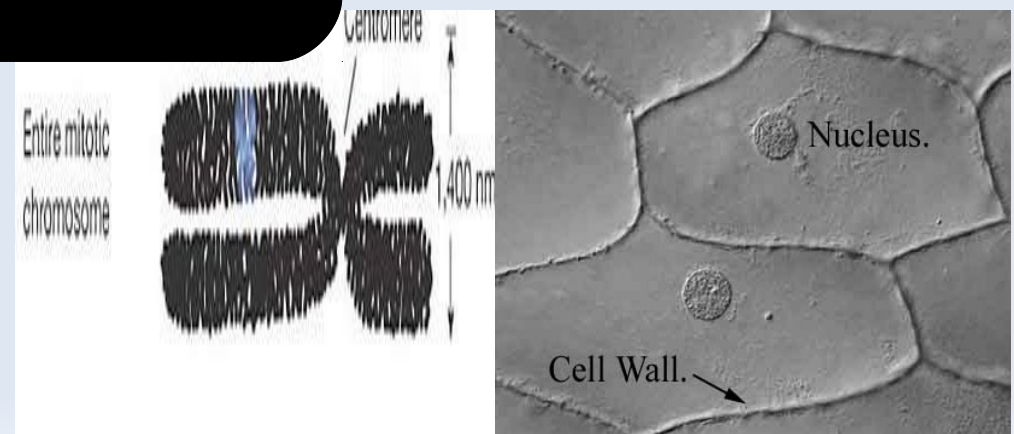
How is a 2-meter long DNA sequence fitted into the tiny space of a nucleus?



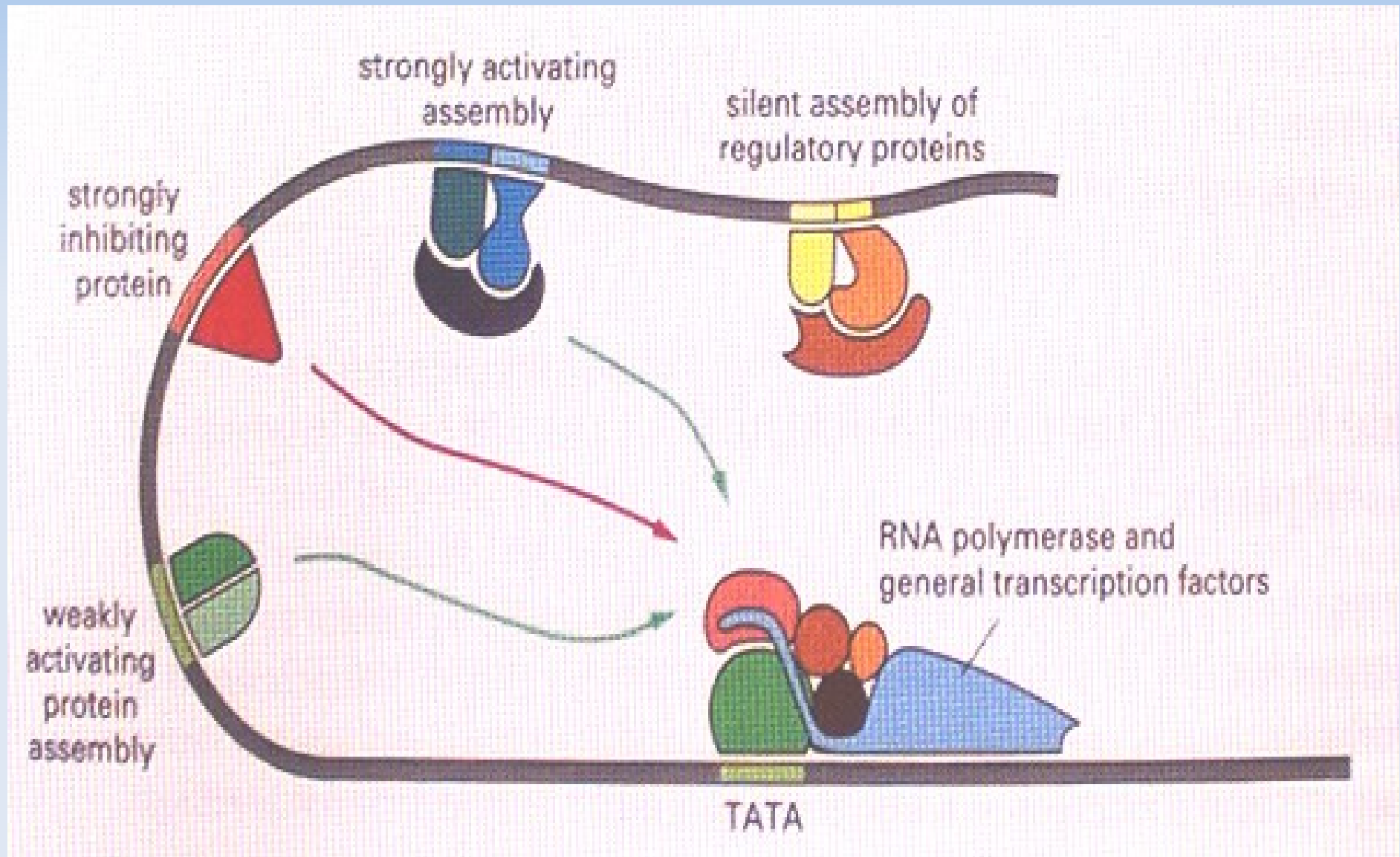
- Sequencing
- X-Ray
- ChIP-Seq
- Electronic microscope



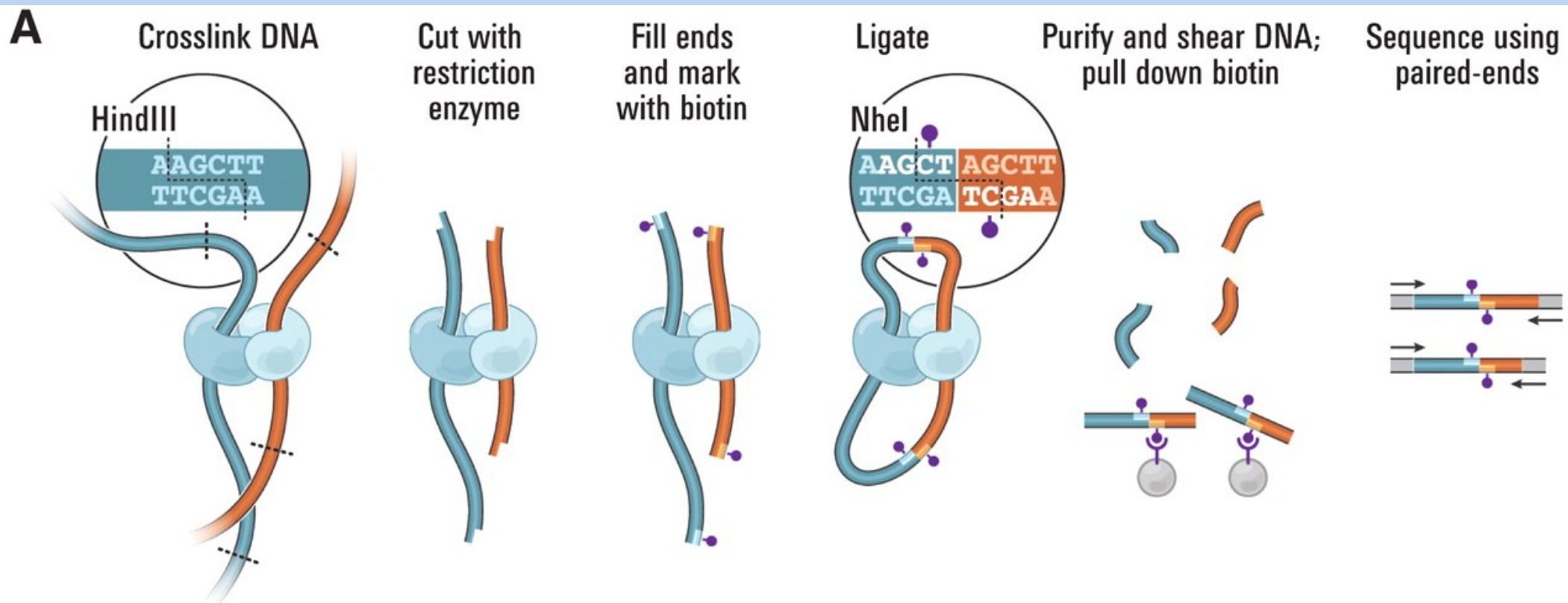
- Light microscope
- Electronic microscope



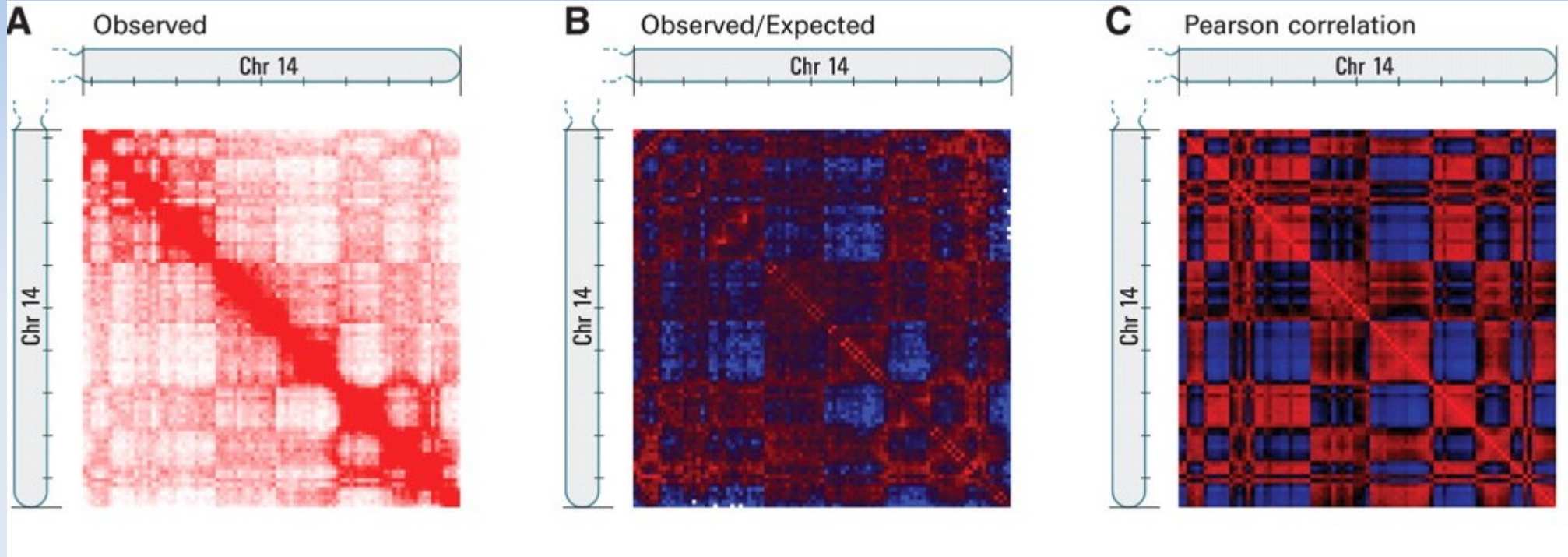
Functionally, chromosome folding are related to long-range interactions between genomic elements, e.g. Enhancers and silencers



Hi-C method combines chromosome conformation capture (3C) and massively parallel sequencing, enabling the study of long distance relationships between loci genome-wide

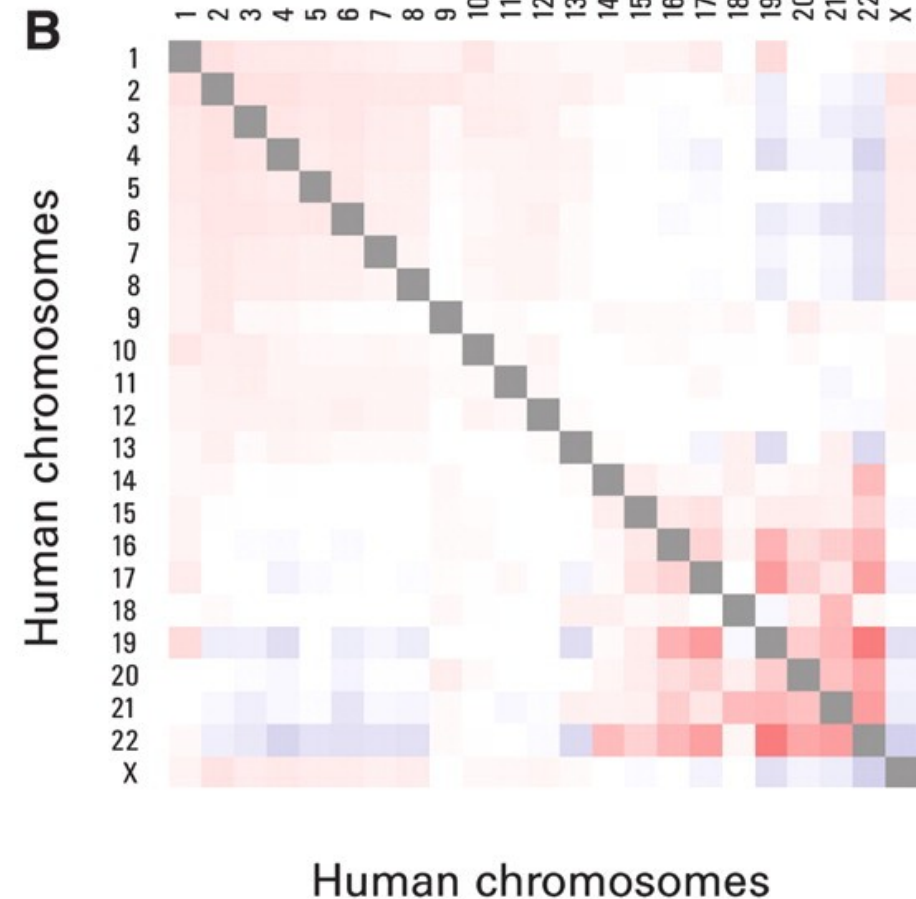
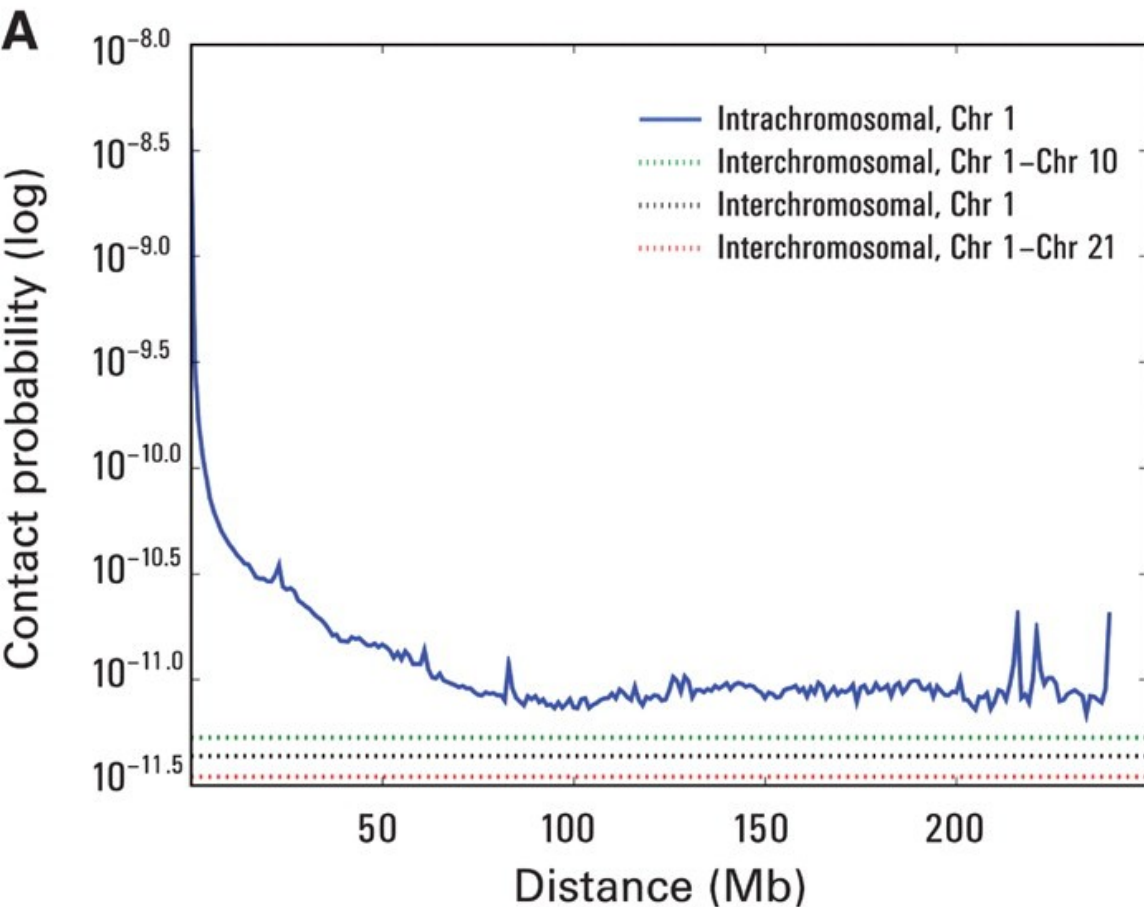


Contact matrix and correlation matrix



Data from experiment on human lymphoblastoid cells

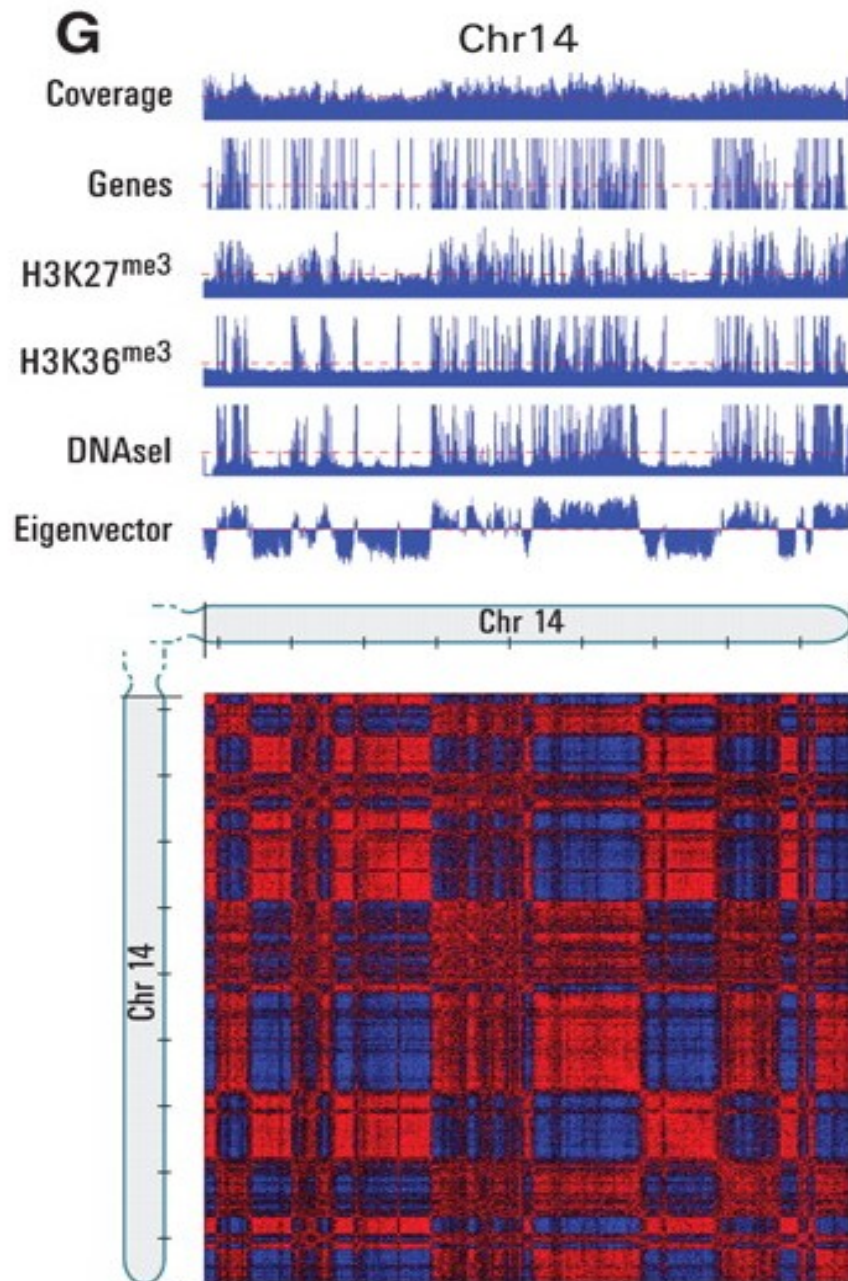
Hi-C data re-confirms the presence of chromosome territories



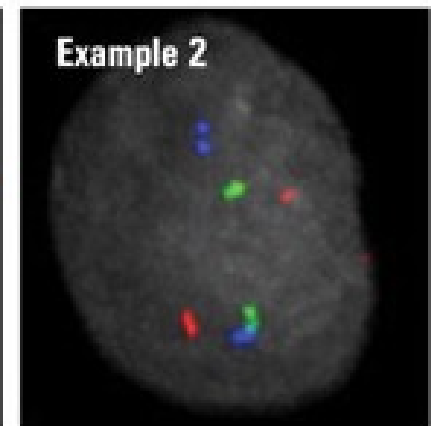
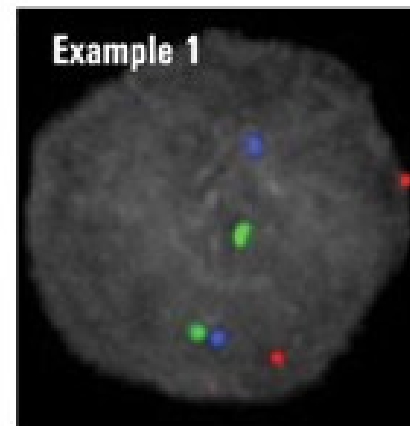
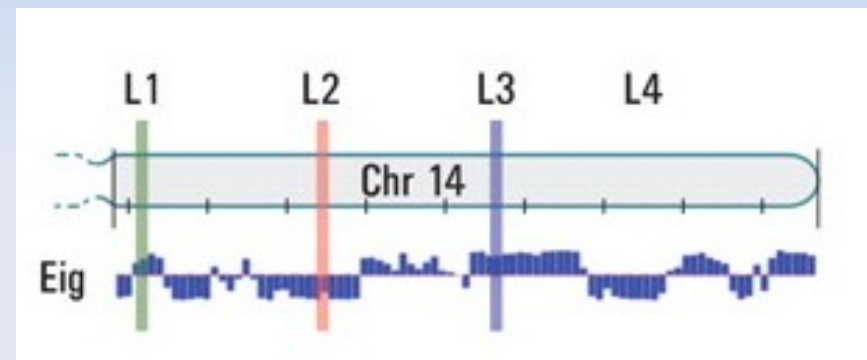
Result 1) Intrachromosomal interactions are stronger than interchromosomal interactions

Result 2) Small, gene-rich chromosomes (16, 17, 19, 21, 22) interact more with each other, suggesting that they cluster together in the nucleus

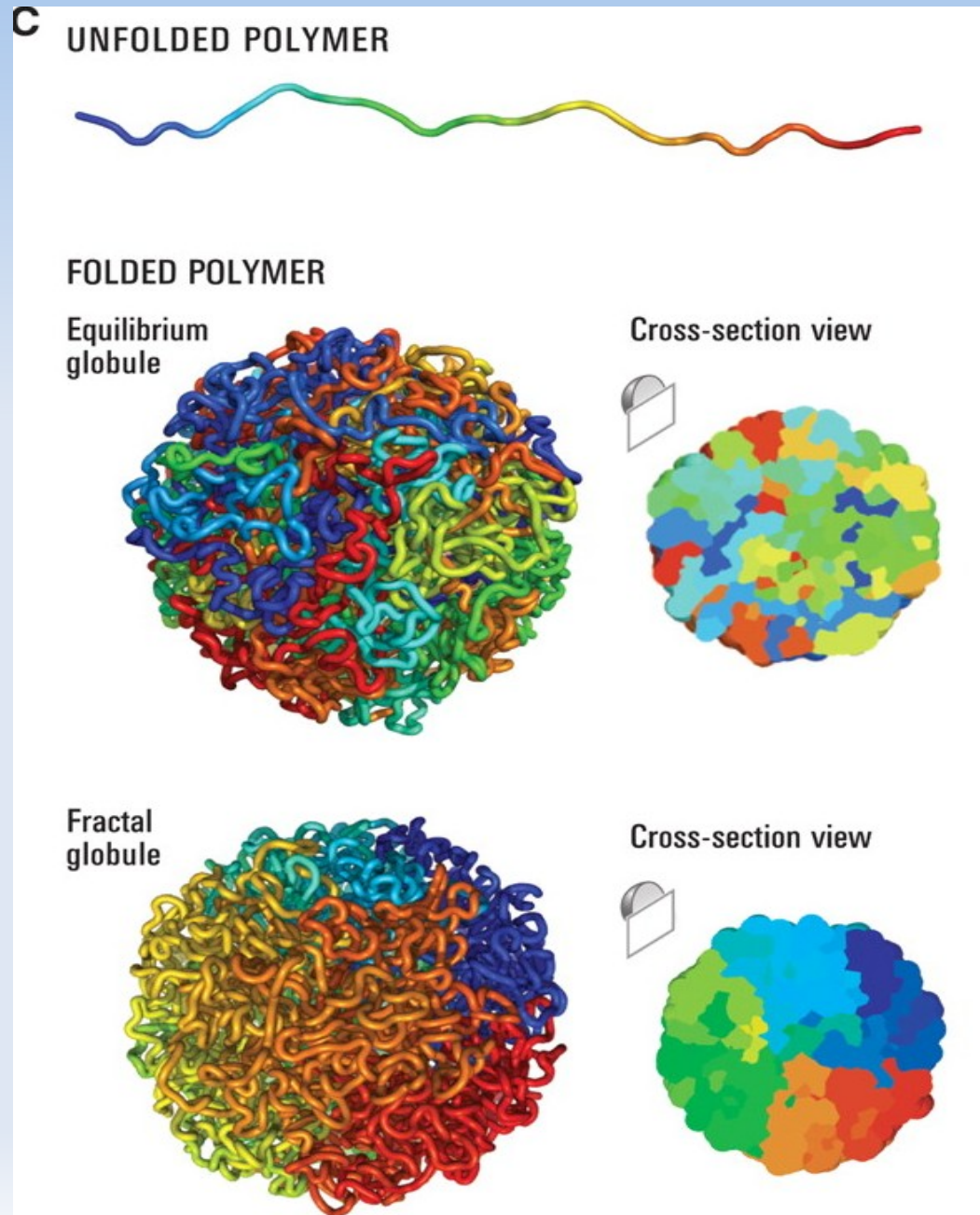
Each chromosome is decomposed into two sets of loci such that interactions within each set are enriched and interactions between sets are depleted



3D-FISH conforms the compartmentment



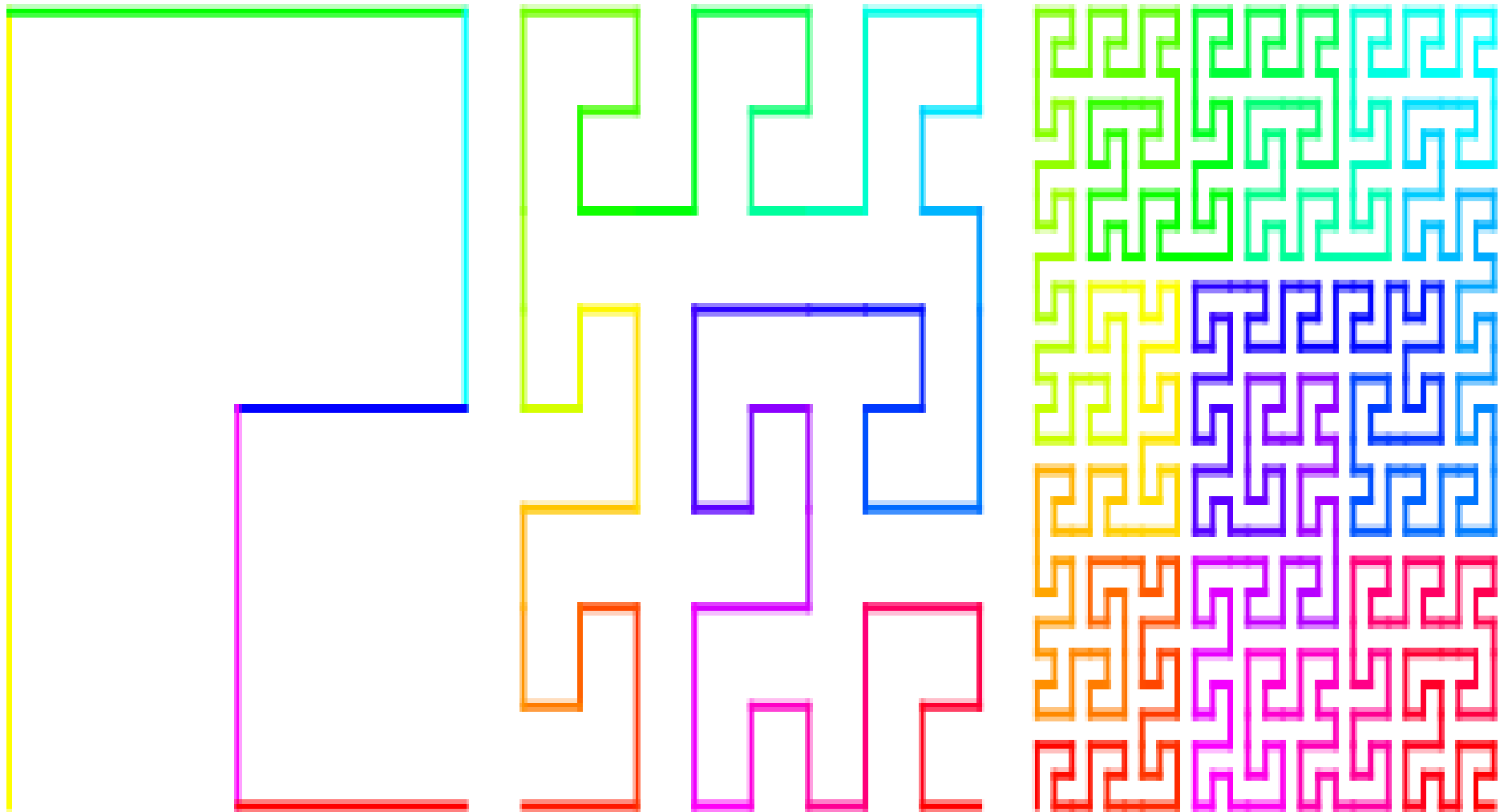
Hi-C data supports that chromosome are folded based on "fractal globule" model instead of "equilibrium globule" model



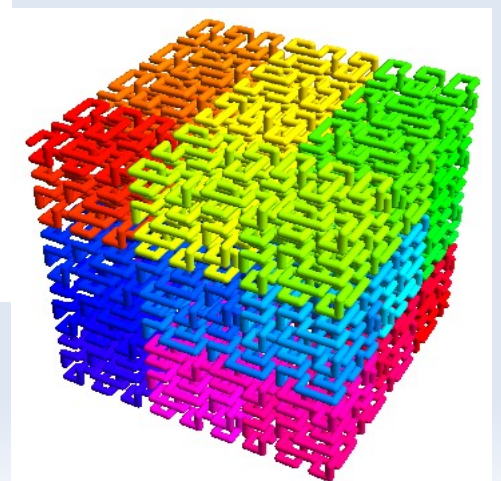
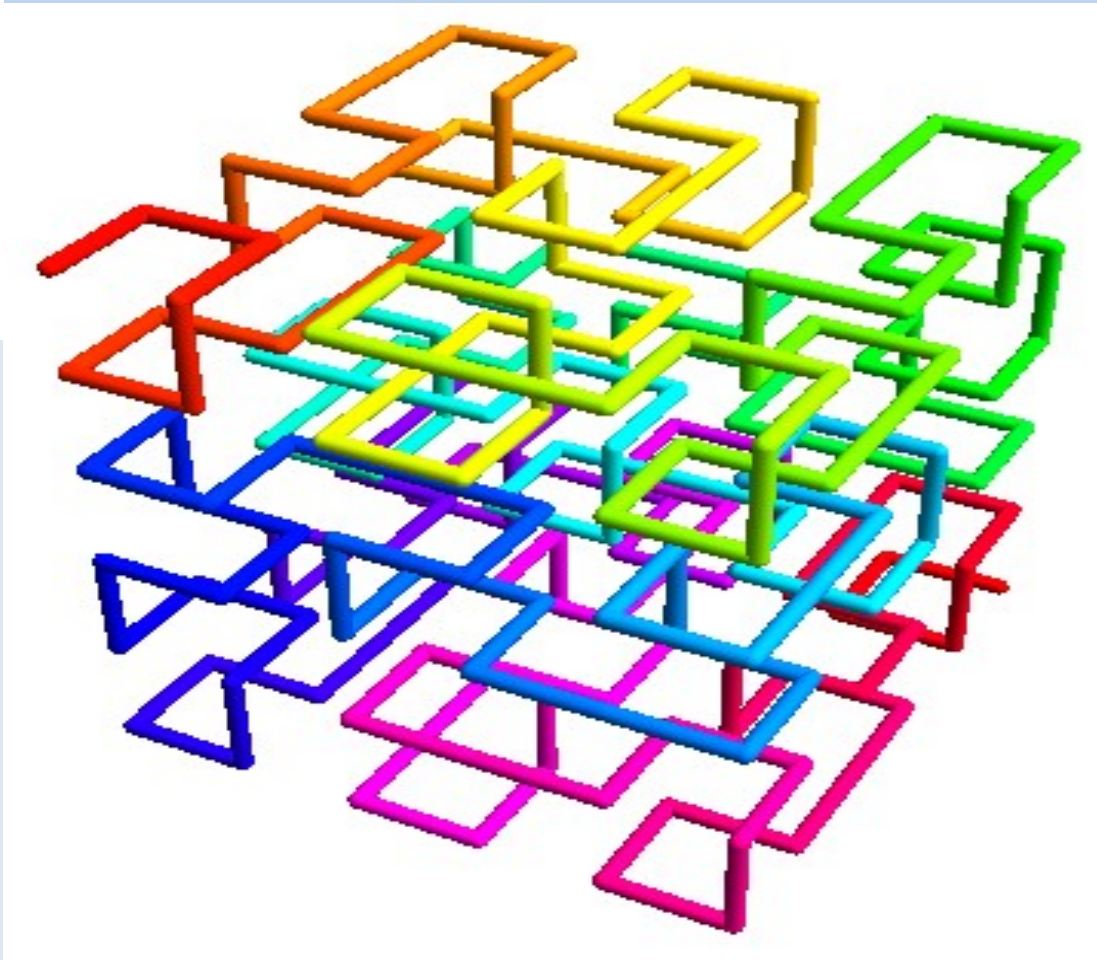
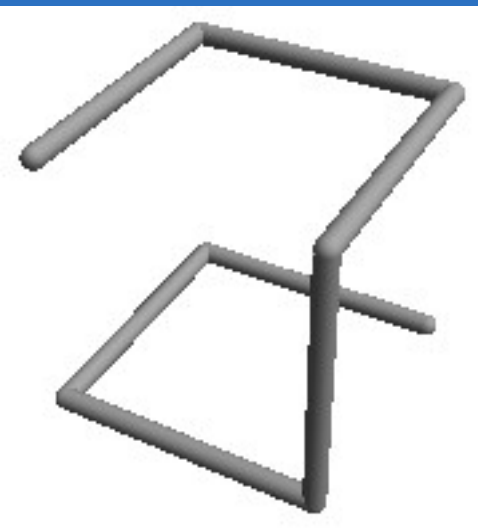
Fractals

- Definition
 - A fractal is "a rough or fragmented geometric shape that can be split into parts, each of which is (at least approximately) a reduced-size copy of the whole,"
- Properties
 - Self-similarity
 - Simple and recursive generating rules

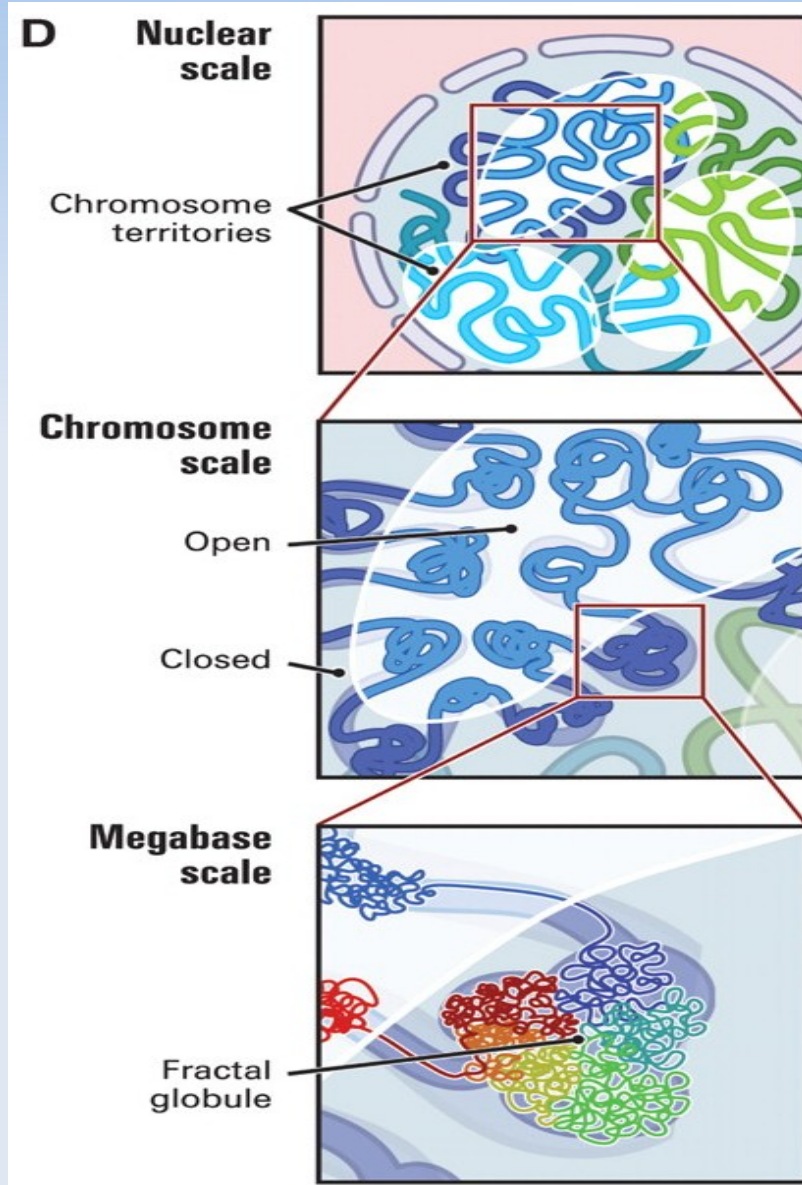
Wunderlich curve fill a plane



Wunderlich curves fill a cubic



The "fractal globule" model has some advantages and important implications



- Highly densed
- Knot-free
- Spacital sectors
- Simple recursive folding rule in different scales
- 3D structures are replicable features of chromosomes

Summary

- Hi-C combines proximity-based ligation with massively parallel sequencing, enabling the study of long distance interactions between genomic loci
- Experimental data are in favor of fractal globule model of genome folding
- Intrachromosomal interactions are stronger than interchromosomal interactions, confirming "chromosome territories"
-

Opinions

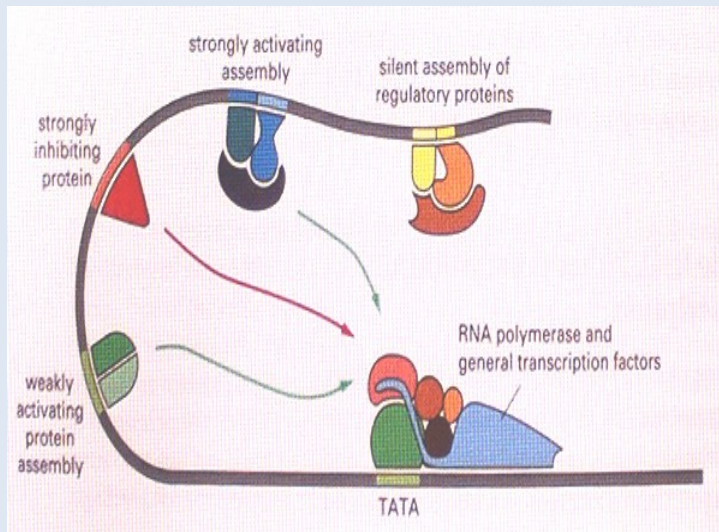
- Hi-C needs to improve resolution
 - Current resolution is 1M bp, but studying interactions between genomic elements requires 10K bp resolution. Resolution increases by n , reads counts increases by n^2
- Computational Issues
 - Stastical inference of significant interactions;
 - Compare interaction maps of different cell types
 - Advanced data structure. Contact matrix become impractical in high resolution
 - Use interaction map to predict functions of genomic elements

The Long Distance Relationships

A poetic conclusion



Though miles may lie between us,
We're never far apart,
For friendship doesn't count the miles
It's measured by the heart.



Though millions of basepairs may lie
between us,
We're never far apart,
For genomic interaction doesn't count
the basepairs,
It's measured by the 3D structure.