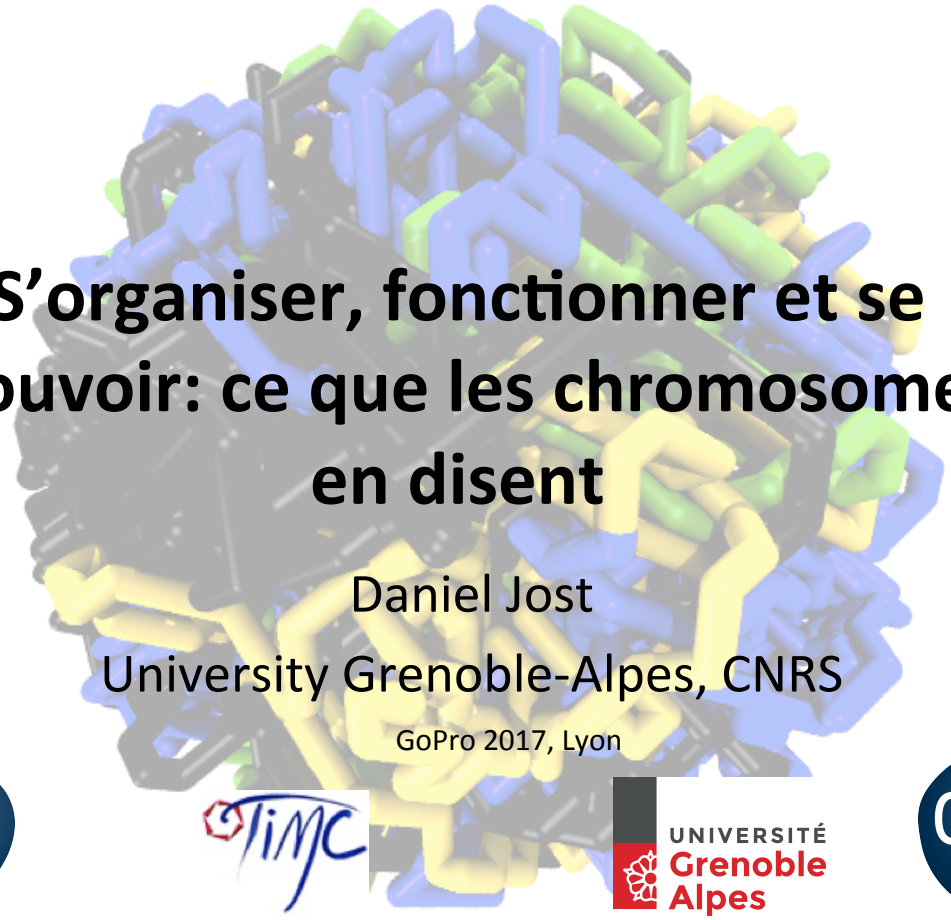


S'organiser, fonctionner et se mouvoir: ce que les chromosomes en disent

Daniel Jost

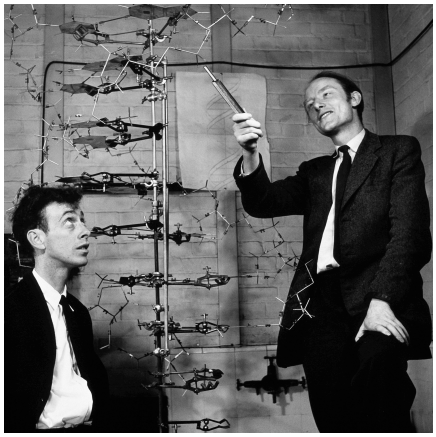
University Grenoble-Alpes, CNRS

GoPro 2017, Lyon

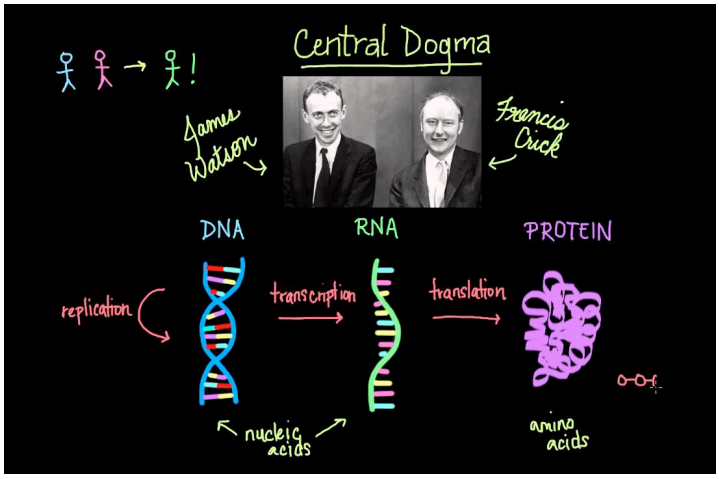
Today's menu

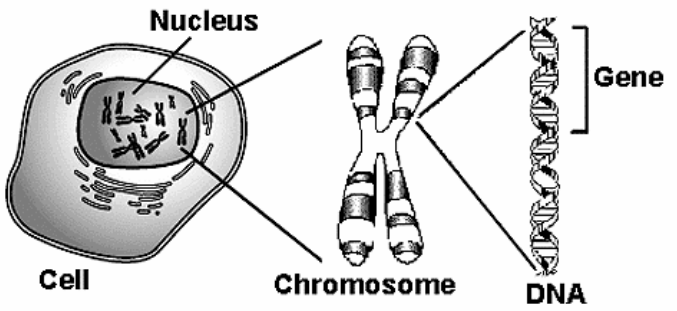
- General introduction on chromatin/chromosome
- How chromosomes are spatially organized?
- How 3D organization impact genome functions?
- How chromosome and factors efficiently move?

DNA & genes & chromosomes



Watson & Crick, 1953



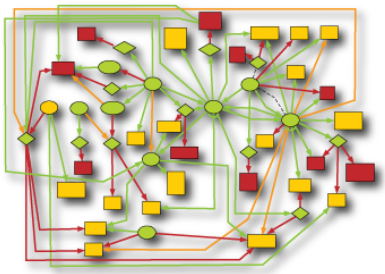


1 genome = many ways of translating it

- Where does species complexity arise from?
  - ➢ Complexity of gene expression patterns,
  - ➢ Complexity of regulatory mechanisms.

Beyond the central dogma: multiplicity of regulatory mechanisms

A cell as a interaction network



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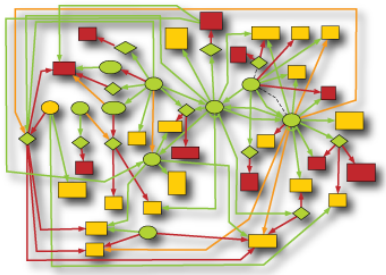

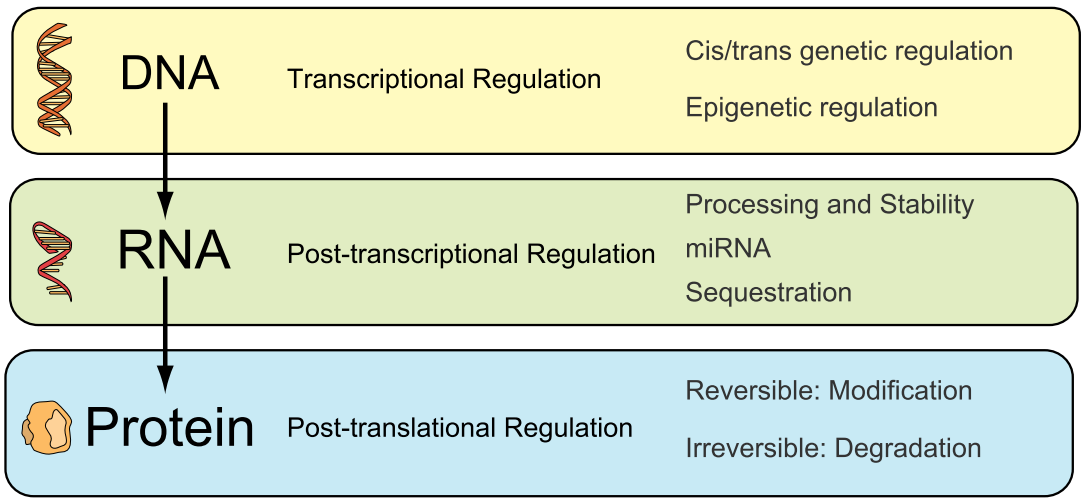

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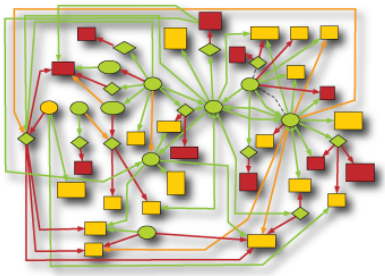

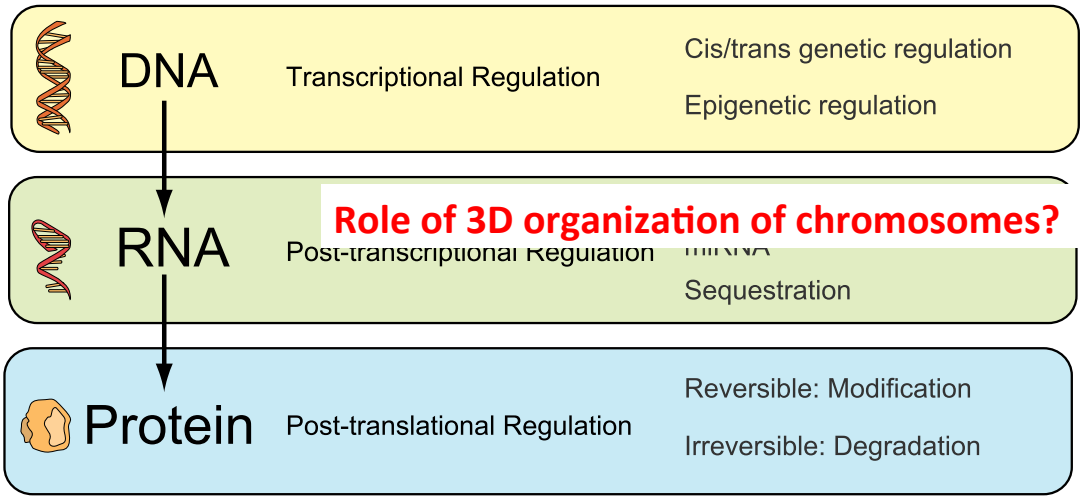

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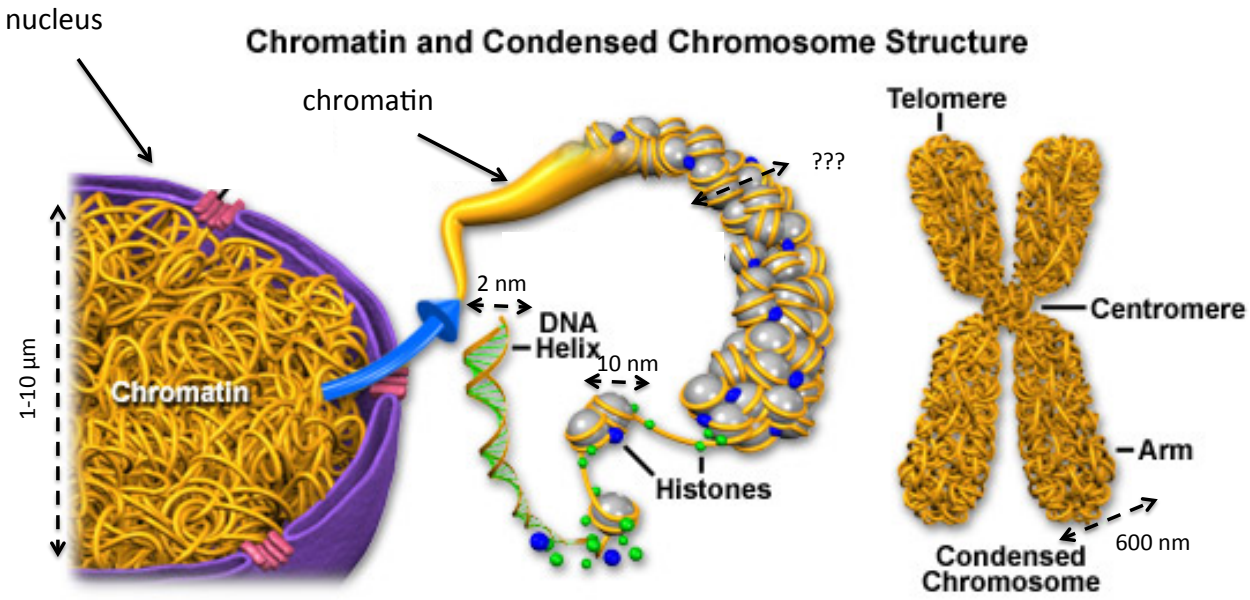
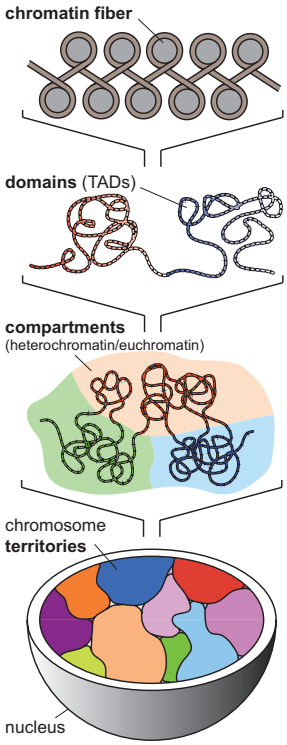
Basics on chromatin/chromosome: a hierarchical folding



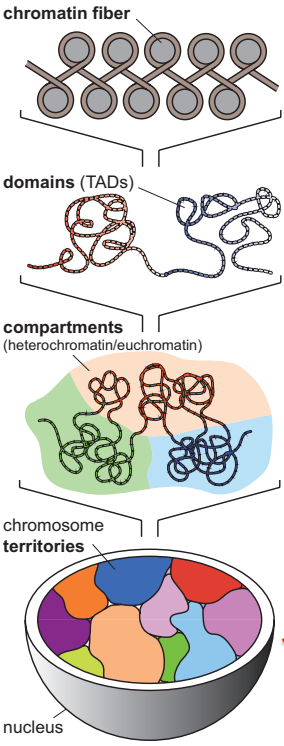
Genomes: 1Mbp – 6 Gbp (few mm to m)

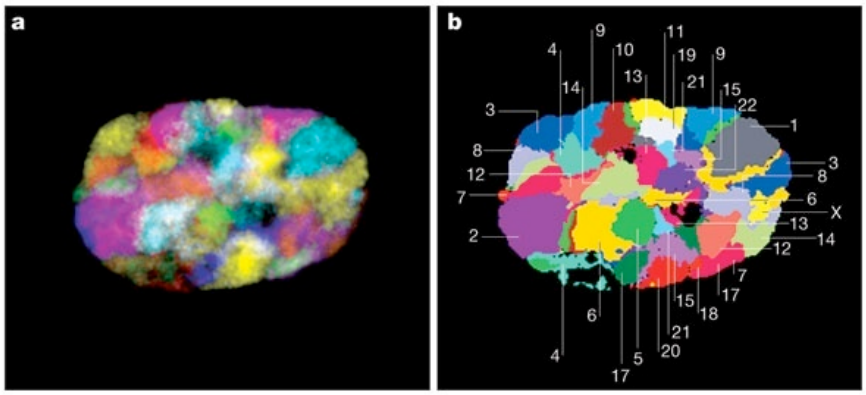
Volumic density: 10^{-2}-10^{-1}

Basics on chromatin/chromosome: a hierarchical folding



Basics on chromatin/chromosome: a hierarchical folding





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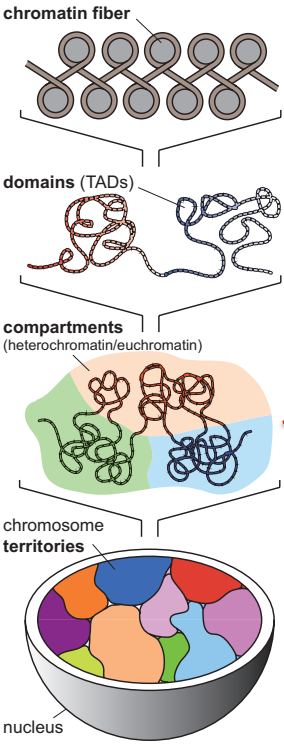
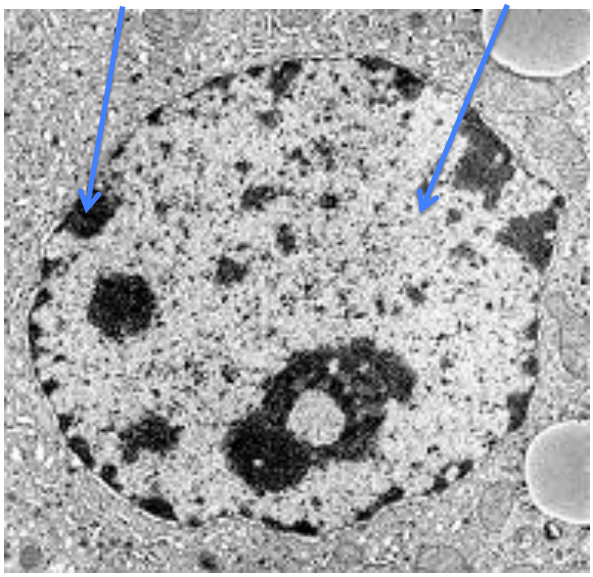


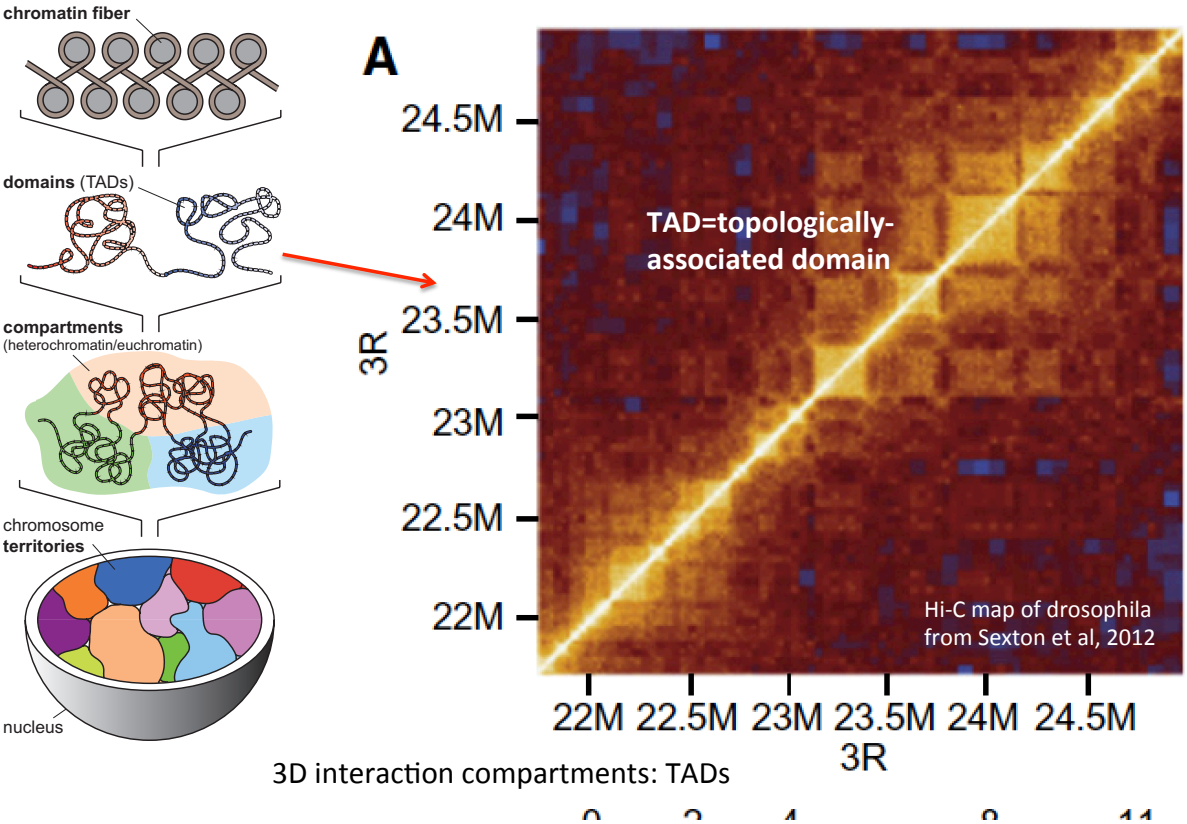
heterochromatin:
inactive genes

euchromatin:
active genes



Electron microscopy of a nucleus

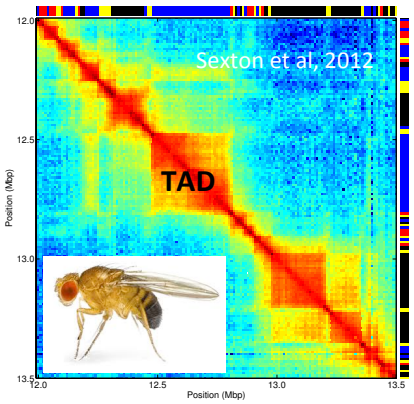
Basics on chromatin/chromosome: a hierarchical folding



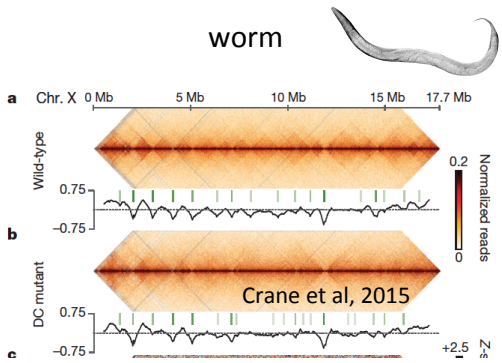
3D interaction compartments: TADs

A conserved feature: nuclear organization is not random

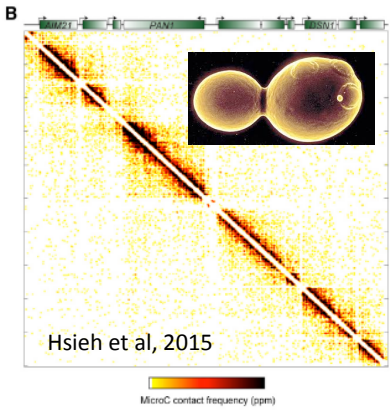
drosophila



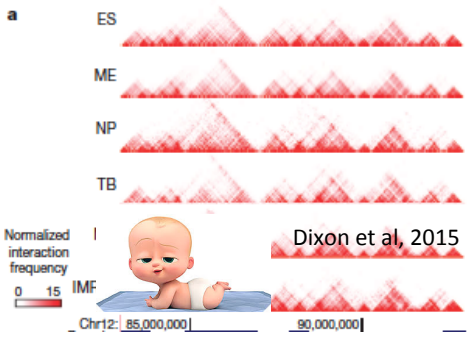
worm



yeast



human



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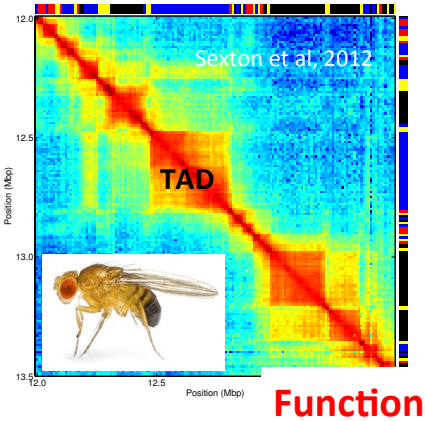
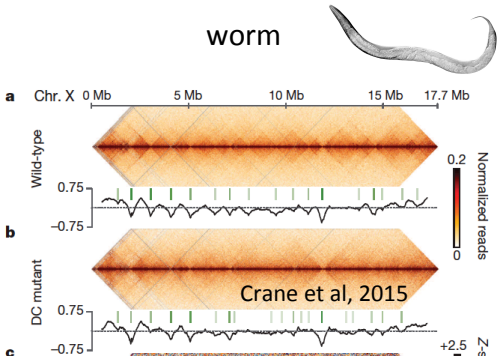
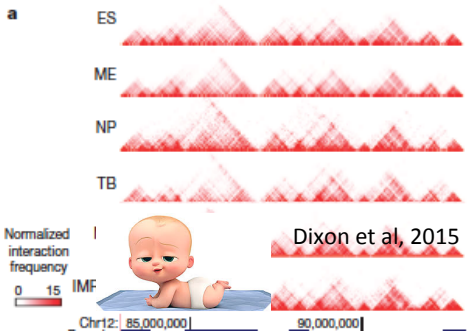


worm

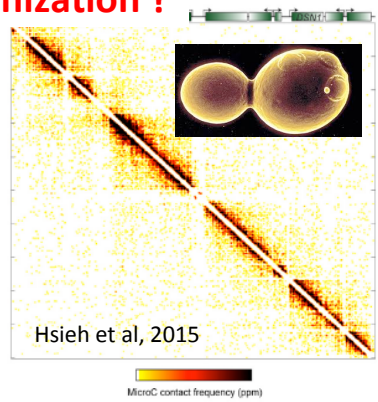


Functional role of 3D organization ?

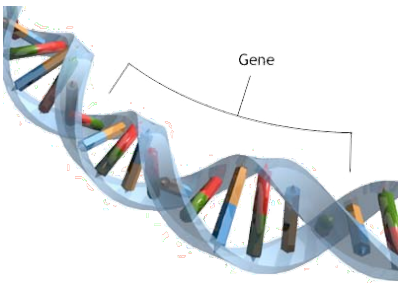
human

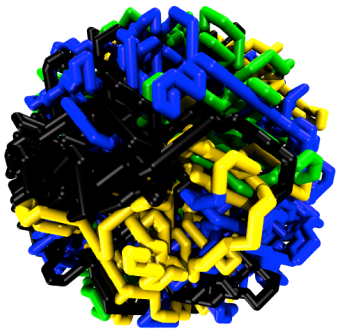


ast



Coupling between 1D and 3D



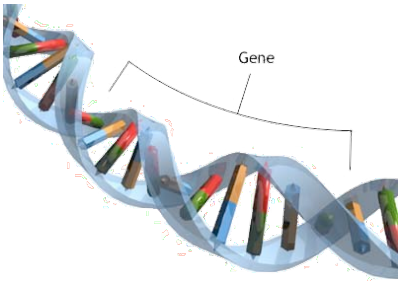


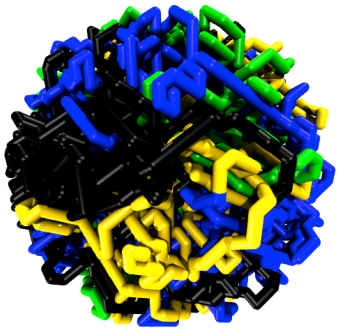
1D = genome & gene activity

3D = chromosome organization

- How 1D control the 3D ?
- How the 3D participates to 1D regulation

Coupling between 1D and 3D





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- **How 1D control the 3D ?**
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Three main independent mechanisms driving chromosome folding

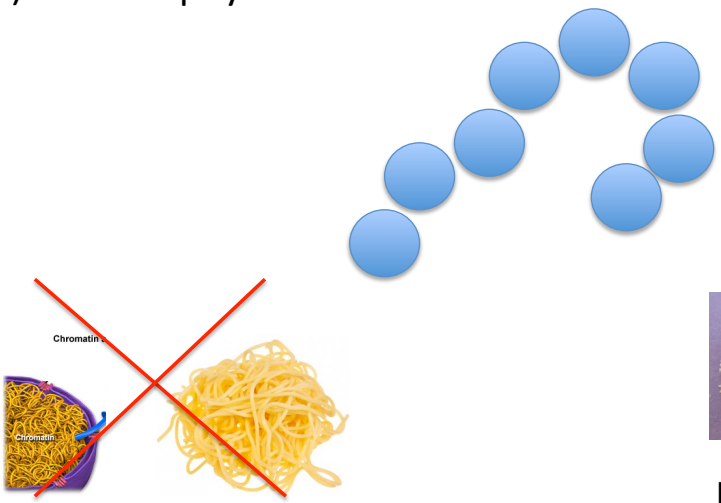
1) Intrinsic physics of long polymers

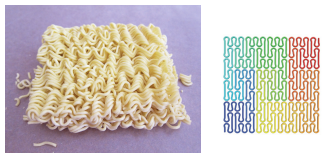
2) Gene-activity-dependent phase-separation

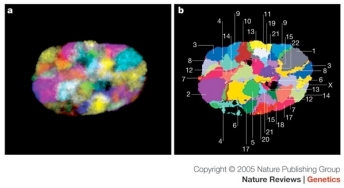
3) Local domains formation by loop extrusion

Three main independent mechanisms driving chromosome folding

1) Intrinsic physics of confined – unknotted- long polymers



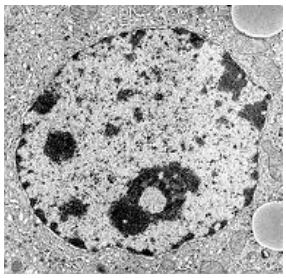


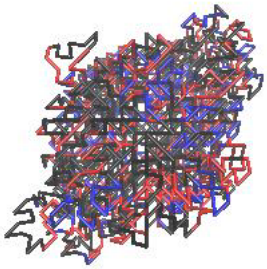


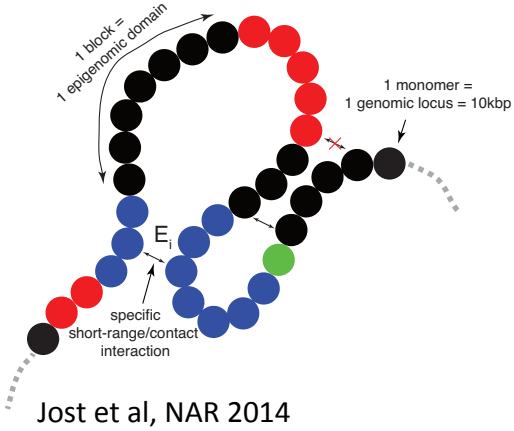
Rosa & Everaers, PLoS CB 2008

Three main independent mechanisms driving chromosome folding

2) Gene-activity-dependent phase-separation



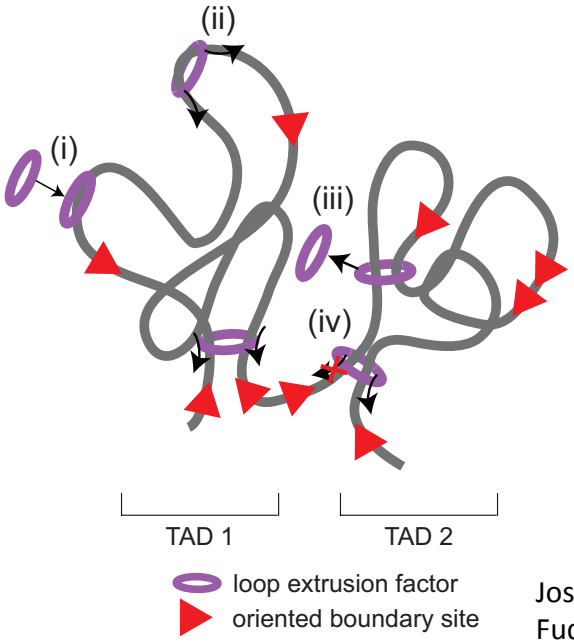


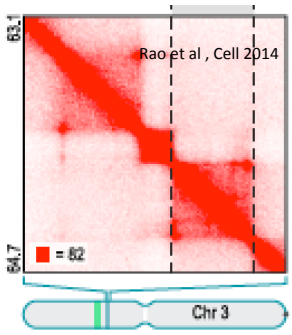


Jost et al, NAR 2014
Ghosh & Jost, 2017

Three main independent mechanisms driving chromosome folding

3) Local domains formation by loop extrusion





Jost et al, COCB, 2017
Fudenberg et al, Cell Report, 2016

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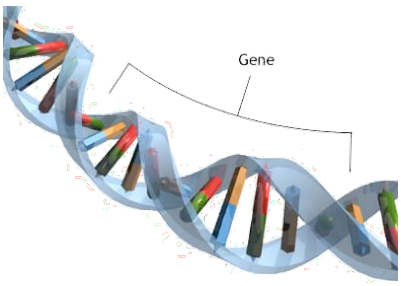

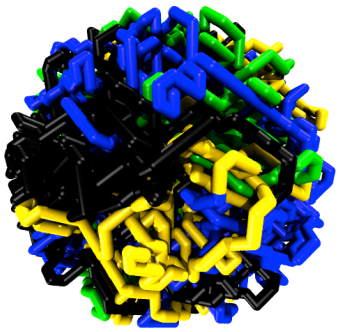

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Functional role of 3D organization

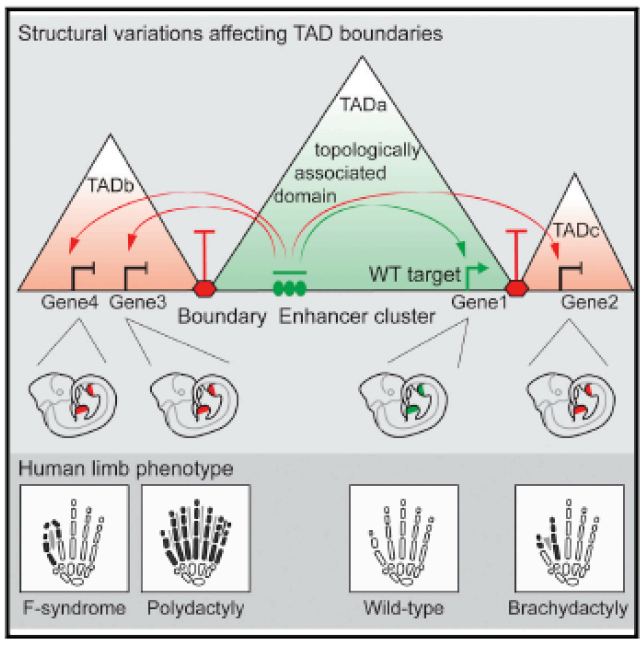
1) Control promoter-enhancer interactions

2) Efficient co-regulation

3) Facilitate the maintenance of active/inactive states

Functional role of 3D organization

1) Control promoter-enhancer interactions



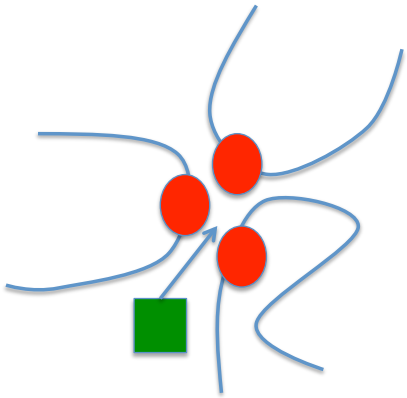
Lupianez et al, Cell 2015

+ onset of cancer
Hnisz et al , Science 2016

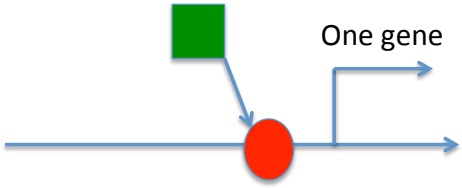
Functional role of 3D organization

2) & 3) Efficient co-regulation and maintenance of gene activity:
Sharing resources: efficiency, robustness, stability

No knots : easy access or colocalization



Transcription factor



promoter

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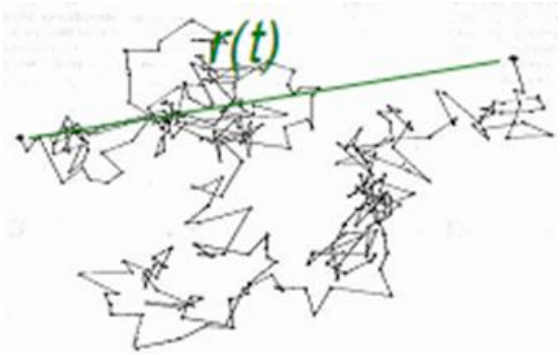
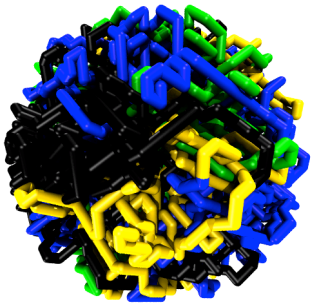
Chromosome organization is dynamical and stochastic

How to move in a crowded, confined environment for a polymer?



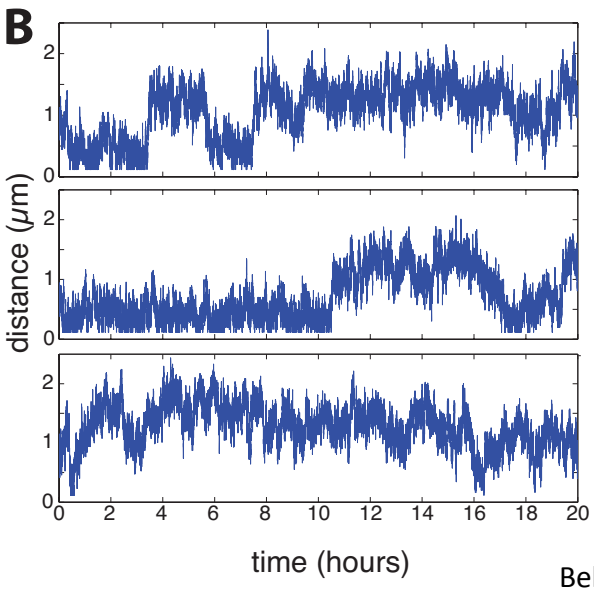


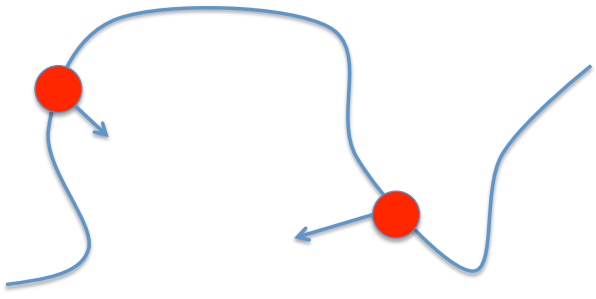
Random (Brownian) motion

Subdiffusive movement, but no knots « accelerate » dynamics

$R(t) \sim t^{1/4}$ → **~1 micron in 10 hours**

Chromosome organization is dynamical and stochastic

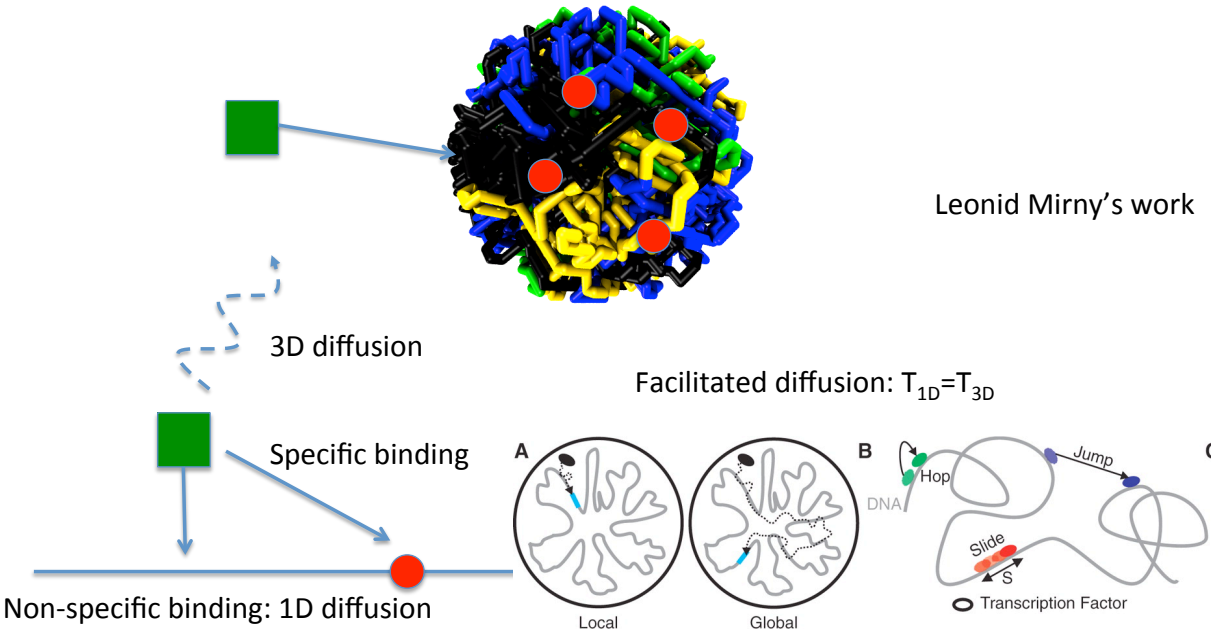




Below 1 Mbp < meet almost every time during 1 cell cycle
Largest scale: may not meet

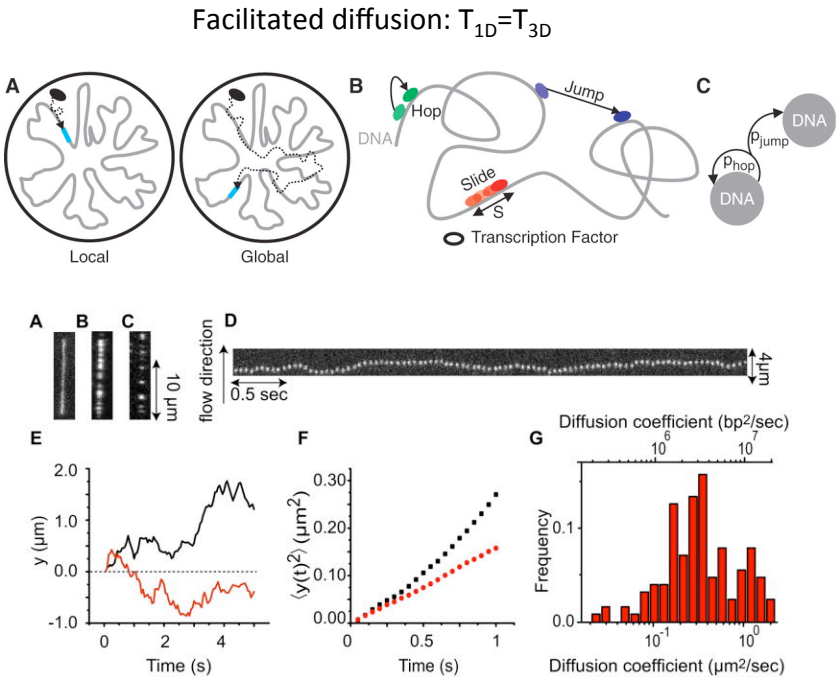
Target finding: 1D/3D travelling problem

How to find a target in a crowded, confined environment for a TF ?



Leonid Mirny's work

Target finding: 1D/3D travelling problem



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Computational and Physical Biology:

TIMC-IMAG, Grenoble:
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Surya Ghosh
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Giacomo Cavalli

University of Bern:
Peter Meister

IAB, Grenoble:
Saadi Khochbin
Elisabeth Brambilla