The physics of the nucleus of cells

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Chromosome organization in the cell nucleus

Organization at the nuclear scale

Cell nucleus by "FISH" microscopy



Chromosomes do not mix like spaghetti jumbled up in a bowl, but form **chromosome territories**.

Chromosome organization in the cell nucleus

Organization at the chromosomal and sub-chromosomal scale

Novel technologies such as **Hi-C** (Leiberman-A. et al. *Science* 2009) or **GAM** (Beagrie, ..., Nicodemi, Pombo *Nature* 2017) return the contact probability between distal chromosome sites:



Chromosome organization in the cell nucleus

Organization at the genes scale and its functional role



Chromosomes 3D architecture influence key cell functions, such as gene regulation. Chromosomes mis-folding can lead to disease (e.g. congenital diseases and cancers).

The String&Binders (SBS) polymer model

Theory: contact patterns emerge by the interactions between chromosomes and particles



A chromosome is modelled as **string** polymer (SAW)

Particles (a gas of **binders**) mediate interactions between the string sites

Hamiltonian of the system:

 $H = H_{string} + H_{free \ particles} + H_{int}$

The String&Binders (SBS) polymer model



Stable architectural classes of the system correspond to its emergent thermodynamics phases.

Conformational changes can be controlled switch-like by, e.g., gene up/down-regulation (acting on c_m) or chemical modifications (acting on E_{int}) with no need of parameter fine-tuning.

SBS reproduce experimental Hi-C patterns

SBS model reproduce general Hi-C features, e.g. TADs

globule phase SAW SBS toy model 2 colors: green/red 0.4 0.8 0.2 0.6 contact probability SBS model reproduce the folding of real genomic regions Hi-C 109 MD 95% Ш corr. 109 111 112 113 115 Mb 110 114 **SBS** Gene 0 chr11 Kcnj2 contact probability

contact matrix

Chiariello A M, Bianco S et al. Sci. Rep. 2016; Barbieri M, Bianco S et al. Nature Struct. Mol. Biol. 2017

Prediction of the determinants of folding

HoxB genes (1Mb region on chr11 in mouse embionic stem cells)

SBS model of the HoxB region



SBS model assuming homotypic contacts between "green" and "red" genes mediated by "green" and "red" particles Microscopy





The model predicted red/green particles have been discovered:



Mediators of interactions ("red" and "green" polymerases) have been detected by triple colocalization experiments.



Barbieri M, Bianco S et al. Nature Struct. Mol. Biol. 2017

Prediction of the effects of genomic mutations



Bianco S, Chiariello A M et al. *Nature Genetics* 2018; Conte M, Fiorillo L, Bianco S et al. *Nature Commun.* 2020 in press

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Summary

- \checkmark Novel experiments have revealed the complex, functional 3D structures of chromosomes.
- ✓ The availability of rich new experimental data today allow to quantitatively study structural features of genomes.
- ✓ Theoretical physics play an important role in this field, as it provides principled models to explain the mechanisms behind data and to make quantitative predictions that can be tested by new experiments.
- ✓ We identified key physical mechanisms that determine genome spatial organization. Some of the molecules that locally drivers chromosomes organization predicted by the SBS model have been experimentally detected. Predictions on pathogenic genomic mutations have been validated by independent experiments.

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