Interaction between epigenomic states shape the 3D organization of chromatin

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Basics on Epigenomics: Modification of gene expression without altering genetic information
Epigenomics is encoded by biochemical tags

- **Emerging field with lots of implications:**
  - development, stem cells, cancer, environmental adaptation, etc.

- **Lots of high-resolution data.**
From many chromatin tags to few chromatin states

- Genome-wide characterization of epigenome (drosophila, human, mouse, plants, yeast, etc.)

Drosophila (Filion et al., 2010)
Modeling the epigenome regulation

Relation between epigenomics and chromatin organization

Regulation of the histone marks at the gene scale

Coupling
Modeling the epigenome regulation

Relation between epigenomics and chromatin organization

Regulation of the histone marks at the gene scale

Coupling
The 3D organization of epigenome is not random

Electron microscopy of a nucleus

heterochromatin: inactive genes

euchromatin: active genes
High-throughput Chromosome Conformation Capture techniques (Hi-C)

Sexton et al, 2012
Correlation between epigenome and contactome

Sexton et al, 2012; Ho et al, 2014; Filipova et al. 2014, etc.

**Fly:**

- Epigenome:
  - Polycomb
  - HP-1
  - Ultra-repressive

**Human:**

Ho et al., 2014
How the 1D (the epigenome) shapes the 3D (the contactome)?
Epigenomic-associated proteins can oligomerize and make physical bridges

HP1/Swi6 (Canzio et al, 2013)

PRC1 (Isono et al, 2013)

And certainly CTCF, cohesin, condensin, lamin, etc.
The chromatin as a block copolymer

$H_{\text{chain}} = \frac{3k_B T}{2l^2} \sum_n (X_n - X_{n-1})^2 + \sum_{n<m} U_{hc}(r_{nm})$

- Model predictions using self-consistent Gaussian approximation

$$\xi \frac{dD_{mn}}{dt} = 4k_B T - \sum_k \left( \langle J_{m,k} \rangle - \langle J_{n,k} \rangle \right) (D_{m,k} - D_{n,k})$$
Other self-interacting polymer models

Loops (Heermann’s work)

Binders (Nicodemi’s and Marenduzzo’s works)

and so on…

Attractive potentials (Cosentino Lagomarsino’s work)
Experimental maps are compatible with multistable conformations

Consistent with single-cell HiC experiments (Nagano et al, 2013)
Capturing the complexity of contactome: towards a predictive model

- Working at the compartment level
- Learning the compartment-compartment interactions
- Building a statistical model to relate interaction strength to epigenome
- Making quantitative predictions of contactome based on epigenome
Capturing the complexity of contactome: towards a predictive model

Working at the compartment level

Learning the compartment-compartment interactions

Building a statistical model to relate interaction strength to epigenome

Making quantitative predictions of contactome based on epigenome
Detecting 3D compartments

- Original map
- Correlation map
- Constrained hierarchical clustering
- Cutting the tree

A hierarchical folding:

Score = intra-domain variability + #domain penalty
Capturing the complexity of contactome: towards a predictive model

Working at the compartment level

Learning the compartment-compartment interactions

Building a statistical model to relate interaction strength to epigenome

Making quantitative predictions of contactome based on epigenome
Inferring the physical interactions between domains

Specific interactions

Target map

Likelihood maximization

Gaussian approximation

Predicted map

Inferred map

Likelihood: Chi2-based

Optimization algorithm: Inverse Boltzmann

\[ u_{ij}^{(n)} = u_{ij}^{(o)} - \alpha \log \left( \frac{P_{ij}^{\text{target}}}{P_{ij}^{\text{predicted}}} \right) \]
Capturing the complexity of contactome: towards a predictive model

Building a statistical model to relate interaction strength to epigenome

Making quantitative predictions of contactome based on epigenome
Take home & perspectives

- Epigenomics information is a main driver of chromatin folding
- Copolymer physics can explain a significant part of HiC maps
- Detecting the 3D compartments and inferring the interactions
- Building a epigenomic-based predictive model of contactome
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A small message from CID 51

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Demander un co-évaluation par la CID 51 pour les chercheurs CNRS

Vous devez adresser une demande motivée, et visée par votre directeur d’unité, de co-évaluation par la CID51 au service des ressources humaines de votre délégation.

Michael Blum
« Secrétaire scientifique » de la 51