Interactions between chromatin states shape the nuclear organization
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Correlation between epigenome and contactome

- Epigenome: 1D compartmentalization of the genome. In eukaryotes, the genome is linearly organized into cell-type-specific epigenomic domains [1,2,3].
- Contactome: 3D compartmentalization of the genome. HiC experiments show the 3D partition of the genome into topologically-associated domains (TADs) (Fig. A) [4,5,6].

Polymer modeling of chromatin with epigenomically-driven interactions

- Working hypothesis: chromatin organization is driven by physical interactions between epigenomic loci mediated by chromatin-associated proteins like Polycomb, HP-1 or CHCF [8].
- Model: heterogeneous self-avoiding chain (Fig. E), each monomer representing 10 kbp and characterized by an epigenomic state [7].
- We consider two types of contact interactions: (i) non-specific interactions to account for compaction due to confinement and crumpling; (ii) specific short-range interactions between monomers of the same epigenomic state.

Bottom-up analysis of the model (Jost et al., Nucleic Acids Res., 2014)

- To simplify we assume that interaction strengths are the same for all the chromatin states
- A Complex phase-diagram made of 4 different regions [7] (Fig. F):
  - Coil phase: extended chain conformations;
  - Globular phase: collapsed chain conformations;
  - Microphase separation phase: packing of all the monomers with the same epigenomic state into distinct 3D domains.
  - Multistability region: TAD formation transient/metastable contacts between domains with the same epigenomic state.

Top-down inference: toward a predictive model of chromatin folding

- Maximum likelihood inference with iterative Boltzmann inversion on the number of contacts between TADs or subTADs using a Gaussian approximation of the model that includes crumpling (Fig.G,H)
- Gaussian formalism: fast generation of 3D structures compatible with the data (Fig.H)
- Perspectives: building statistical model for the epigenetic-dependence of interactions and testing the predictive power of the full model (other drosophila species, mutants, etc.)

Finding TAD boundaries. Development of a constrained hierarchical clustering approach to find boundaries between (sub-)TADs. Application to drosophila (Fig.A): median length of 50 kbp (Fig. C).

Quantifying the correlation between 1D and 3D partitions. TADs are in average composed by 80% of the same chromatin state (Fig. D).

References

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Inference on sliding windows (1.2 Mbp): heterochromatic domains self-interact strongly, euchromatic domains not significantly (Fig.I)