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Titolo	EXPLORING CHANGES IN HIGHER-ORDER GENOME ORGANISATION DURING THE COORDINATED TRANSCRIPTIONAL UP-REGULATION IN DROSOPHILA DOSAGE COMPENSATION [Tesi di dottorato]
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Sommario	Dosage compensation (DC) is a highly plastic process responsible for altering transcriptional regulation, so as to preserve homeostasis in species with different karyotypes in the sexes. Over the past several decades this process has emerged as a robust model for understanding the relationship between transcriptional regulation and higher-order chromatin structure. In Drosophila melanogaster DC, the single male chromosome X undergoes an average two-fold transcriptional up- regulation for balancing the transcriptional output between sexes. Previous literature evidences proposed that a global change in chromosome structure may accompany this process. Recent studies in other model systems suggested that chromosome X in response to dosage compensation shows a highly altered structure. Namely, in mammals it loses all genome compartmentalisation post silencing by Xist, and in C. elegans it shows altered insulation post reduction of gene expression. All of these studies were based on Hi-C. Yet, in case of drosophila, no such structural changes were found using Hi-C. This raises questions regarding the sensitivity of Hi-C in cases where transcription un-regulation is localized, and questions the mounting evidence in literature showing a causal link between transcriptional processes

	and higher-order chromatin structure. Here I show that global conformational differences are indeed present in the male X chromosome and are detectable using Hi-C data on sex-sorted embryos alongside male and female cell lines. This task, was only made possible with the implementation of novel data analyses solutions. I show that the male X chromosome presents a more accessible structure. I identified differences in local genome compartmentalization, with several TAD boundaries disappearing or weakening in male X chromosome. These boundaries co-localize with features related to the binding of the dosage compensation complex. The strongest correlation we observed was in relation to a dosage compensation complex co-factor CLAMP, which shows differential binding pattern between the sexes. This protein was reported to enhance chromatin accessibility. I present conclusive evidence supporting a changing global chromosome structure in response to dosage compensation. I did not observe any differences in insulator binding. This in addition to change in insulation challenges the idea that insulation is a function of insulator binding. In the future, I would like to explore this avenue to understand how different players affecting genome functionality affect insulation as read-out from Hi-C data. In the course of this work, Hi-C data binned at higher resolutions tended to become extremely memory intensive. With this, I identified a need to develop a data handling solution which would allow me to work more efficiently with such high-resolution Hi-C datasets. Although, such solutions have been described for python, no such solution exists for R. I aimed to create an on-disk database which circumvents the problem of loading data into memory, solves its own dependencies and plays well with existing Hi-C formats. To address these aims, I developed HiCLegos, a package built for the R statistical environment. HiCLegos, implements an on-disk HDF data structure for storing and manipulating Hi-C data. HiCLegos is deployed as a Bioconductor package. This ensures better dependency solving and higher visibility from a growing community of biology focused developers. Finally, HiCLegos provides methods for loading 2D matrices and consortium generated sparse matrix files. From a user perspective, HiCLegos offers analysis centred methods for data retrieval, such as retrieving data for genomic loci separated by a certain distance.
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