Exploring the dimensions of the genome organization: 1D chromatin tracks and 2D interaction maps for generating 4D models.

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The characterization of the genome structure and functional state has been boosted by the concomitant development of different genomic techniques. Each of these experiments gives a different layer of information from the localization along the (1D) genome sequence of histone epigenetic modifications to the frequency of interactions in the 3D space of specific loci. The interpretation and integration of these layers have been facilitated by complementary computational techniques. We contributed mostly to the computational efforts and, during my talk, I will discuss the latest developments.

Firstly, I will cover our attempts to reconstruct 3D models of the entire *A. thaliana* genome. The characterization of the genome organization in this plant is challenging because it presents specific features that still lack a seamless interpretation in terms of biophysical mechanisms. These include preferential positioning of various structural futures as the nucleolus in the nuclear centre, and the telomeres and the centromeres at the nucleolar periphery. The 2D Hi-C interaction maps unveiled also specific contact patterns, such as stripes and strongly interacting intra- and inter-chromosome (IHIs) regions. We tested whether the integration of 1D epigenetic tracks in physical-models of chromosomes can unveil basic physical principles that recapitulate all these structural features. We partitioned the genome in epigenetic states and applied simple short-range interactions them in molecular dynamics simulations in 3D chromosome models. Interestingly, we found that by applying attractions within the eu- and the heterochromatic regions, and repulsions between heterochromatin and the other chromatin states (euchromatin and polycomb-like) can produce 3D models, which account for almost all the genomic structural features showing an intrinsic interplay between epigenetic states and 3D genome structure in *A. thaliana*.

Then, I will present TADdyn our novel computational tool to characterise the genome structural organization in 4D. Indeed, TADdyn, combining polymer-based chromatin representation and time-series 2D Hi-C datasets, allows to study how chromosomes regions rearrange over time. We implemented and used several measures to characterize the structure and the dynamics of modelled chromatin *loci*, providing valuable insight on the 3D and 4D chromatin organization that goes beyond the *static* picture characterized by the 2D Hi-C interaction maps. For example, we used TADdyn to study the *Sox2* activation dynamics during cell reprogramming of mouse B cells to Pluripotent cells. We found that during activation *Sox2* is embedded inside a structural domain (*cage*) that constraints within a confined space the dynamics of the *Sox2* transcription starting site (TSS). The *caging* maximizes the contacts between the TSS and the annotated *Sox2* super-enhancer region and, more in general, forms a spatial neighbourhood of open and active regions around the TSS. These results point to a strong interplay between genomic structure and function that can be further investigated and unravelled for different loci and other biological processes by using TADdyn.