Chromatin 3D organization principles revealed by network theory: gene-regulation, replication, and beyond

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Recent technological advances have allowed us to map chromatin conformation and uncover the spatial organization of the genome inside the nucleus. These experiments have revealed the complexities of genome folding, characterized by the presence of loops and domains at different scales which can change across development and cell types.
Many approaches have been employed to describe 3D genome organization, which can be broadly divided into polymer physics models, constraint based models and statistical approaches.

An increasingly popular representation of chromatin is given by networks, in which genomic fragments are the nodes and connections represent experimentally observed spatial proximity of two genomically distant regions. This formalism, applied to promoter centred chromatin interaction networks generated by promoter capture HiC, has allowed us to consider a variety of chromatin features in association with the 3D structure. In particular, we exploited a known popular network metric to define Chromatin Assortativity: the tendency for regions of chromatin with similar properties to preferentially interact with each other. In addition to recapitulating known results, measuring chromatin assortativity of tens of features in mouse embryonic stem cells led us to novel biological insight on gene regulation [1].

Moreover, we have characterized DNA replication in a 3D chromatin context, generating novel maps of replication origins in mouse embryonic stem cells under normal conditions and during DNA replication stress. These origins were then contextualized by projection on a promoter-centred chromatin contact network defined at a few kb resolution. We found that replication origins with similar efficiency and genomic regions of similar replication timing interact with each other preferentially [2]. These findings suggest that DNA replication takes place in the context of hierarchical multi-scale structures spanning tens of megabases and even bridging chromosomes. More specifically, origins that interact with others tend to replicate earlier and with higher efficiency. The changes of origin activation patterns in normal and stressed conditions support a stochastic model of activation in which both local and global chromatin properties modulate efficiency.

Finally, we propose tools to investigate chromatin organization at different scales using networks, in particular an R package and an online chromatin network interaction viewer building on this framework. The ChAseR package allows users to efficiently integrate genome-wide datasets or lists of genomic regions with 3D chromatin interaction networks. It then efficiently computes Chromatin Assortativity of these features, highlighting the ones that are most strongly associated with genome architecture and performing different kinds of randomizations to assess the significance of these associations. Furthermore, we have developed GARDE-NET (https://pancaldi.bsc.es/garden-net), a web-portal where users can visualize multiple chromatin networks (>10 human PCHiC datasets and mouse embryonic

stem cell PCHiC so far) in combination with pre-loaded chromatin features (histone modification peaks etc.) and with a chance to upload their own chromatin features of interest [3].

We will conclude by reflecting on general organization principles in genome architecture that can be revealed by applying this formalism.

[1] Pancaldi et al. Genome Biology 17 (1), 152 2016
[2] Jodkowska, Pancaldi et al. bioRxiv 644971 2019
[3] Madrid-Mencia, Raineri and Pancaldi, bioRxiv 717298 2019