The Role of Cohesin in Chromosome Folding

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Chromosomes contain very long DNA sequences, which are compactly and hierarchically organised in the cell nucleus to ensure genomic stability, effective gene expression, and healthy cellular division. A central component contributing to chromosome organisation is the Structural Maintenance of Chromosomes (SMC) complexes, among which cohesin plays a pivotal role [1]. Cohesin contributes to chromosome organisation by extruding DNA into loops that are anchored at specific binding sites, marked by a DNA-binding protein. At molecular level, cohesin forms a ring-shaped complex that topologically encircles DNA to facilitate loop extrusion (see Figure 1). Abnormal cohesin regulation has been linked to a range of genetic diseases, including cancer [2].

We can visualise cohesin loops and loop binding sites through Hi-C contact maps, which offer a comprehensive view on the total contact frequency distribution $P_c(d)$ across the genome. It has been found experimentally that cohesin depletion reduces both cohesin-mediated loops and the total number of genomic contacts. Most interestingly, a genome fully depleted of cohesin follows a near perfect power law contact distribution, with an exponential factor of $\alpha \approx 1.3$, aligning with the universal scaling behaviour observed in polymers and self-organised systems (Figure 3) [3].

To establish the link between cohesin concentration and genomic interactions, we have recently analysed in vivo yeast Hi-C datasets corresponding to different levels of cohesin concentration (Figure 2). We quantify how the distinctive enhancement of chromosomal interactions at intermediate distances decreases as the cohesin concentration is reduced, as shown in Figure 3. Our methods include data filtering, visualisation, and computational detection of chromatin loops using pattern recognition, ultimately validating loop coordinates against binding site coordinates. We then isolate loop information, and statistically analyse the contact distribution of predicted loops. We use mathematical tools to approach genome organisation as a complex self-organising system. Ultimately, a deeper mathematical understanding of cohesin-mediated interactions will provide novel insights into the biophysical principles underlying genome architecture and its impact in diseases like cancer.

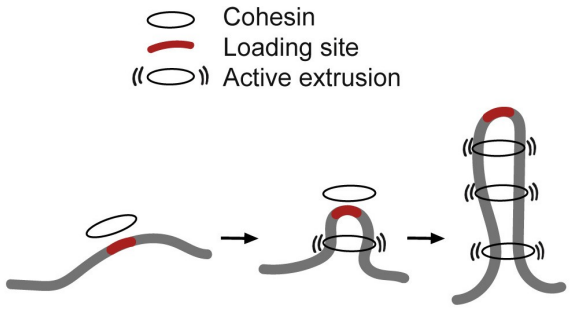

Figure 1: Schematic representation of the ring-like shape of cohesin, and the process of loop extrusion. Diagram taken from Figure 1 (G) of [4].

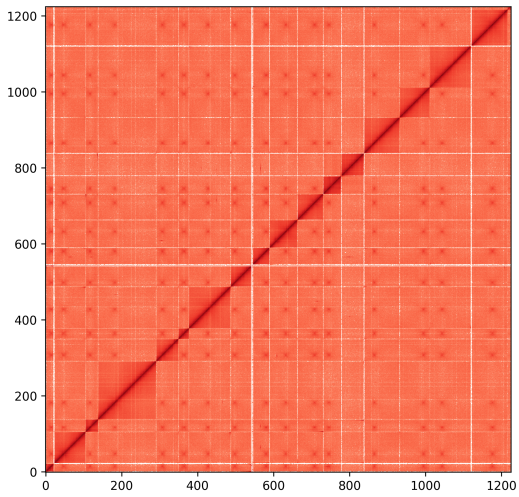

Figure 2: A Hi-C map for the contact distribution of the Wild-Type genome. Darker areas correspond to more frequent interactions, and the axes correspond to genomic coordinates. Genomic coordinates were rescaled to a lower resolution.

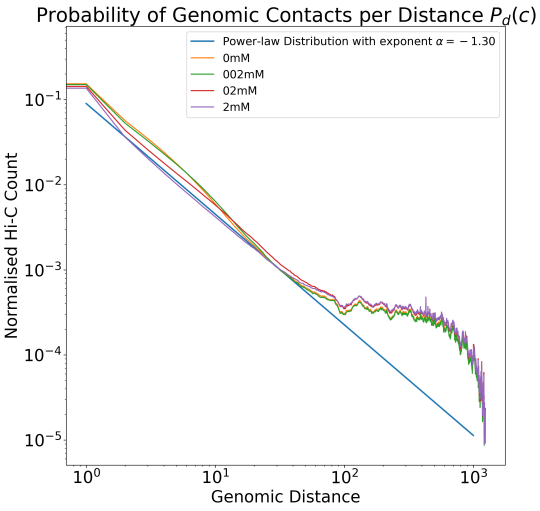

Figure 3: Probability contact distributions at different cohesin depletion levels: 0 mM corresponds to Wild-Type, 2 mM to fully cohesin-depleted genome, and 02 mM and 002 mM represent intermediate states. Genomic distances were rescaled to a lower resolution.

References

[1] Frank Uhlmann. SMC complexes: from DNA to chromosomes. *Nature reviews Molecular cell biology*, 17(7):399–412, 2016.

[2] Todd Waldman. Emerging themes in cohesin cancer biology. *Nature Reviews Cancer*, 20(9):504–515, 2020.

[3] Chaoming Song, Shlomo Havlin, and Hernan A Makse. Self-similarity of complex networks. *Nature*, 433(7024):392–395, 2005.

[4] Ya Guo, Ediem Al-Jibury, Rosalba Garcia-Millan, Konstantinos Ntagiantas, James WD King, Alex J Nash, Niels Galjart, Boris Lenhard, Daniel Rueckert, Amanda G Fisher, et al. Chromatin jets define the properties of cohesin-driven in vivo loop extrusion. *Molecular cell*, 82(20):3769–3780, 2022.