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3D modeling of Hi-C contacts: seeing the spatial organization of fungal chromosomes

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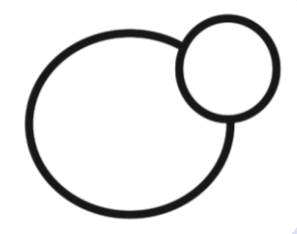
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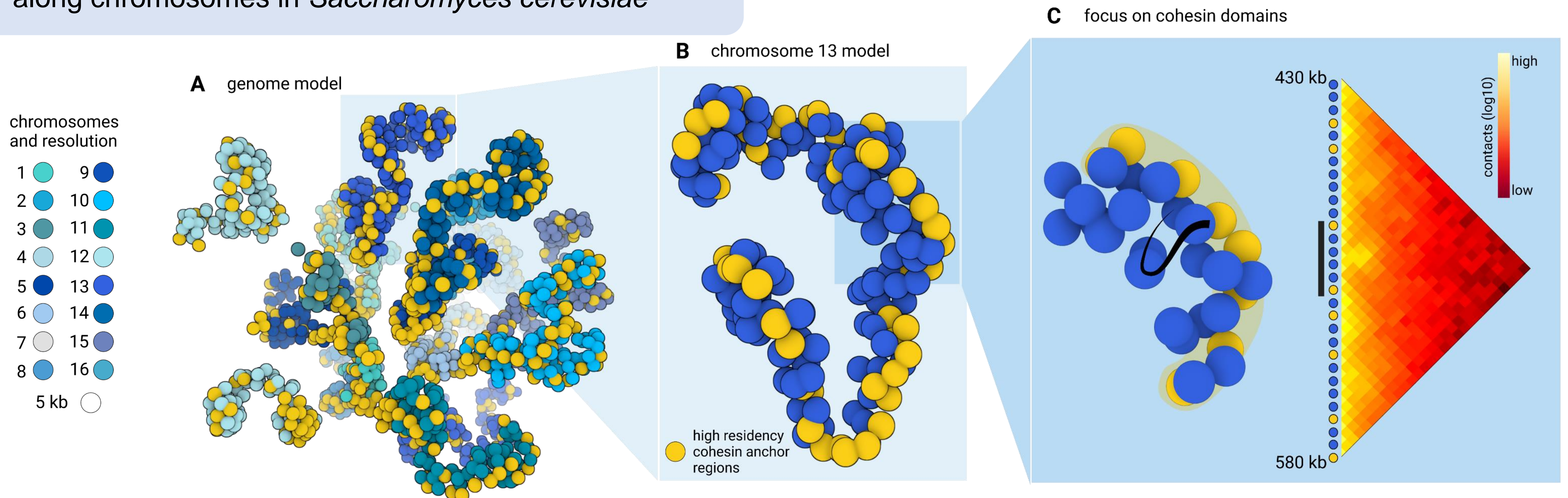
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Thibault Poinsignon, Méline Gallopin, Pierre Grognet, Fabienne Malagnac, Gaëlle Lelandais* and Pierre Poulain*

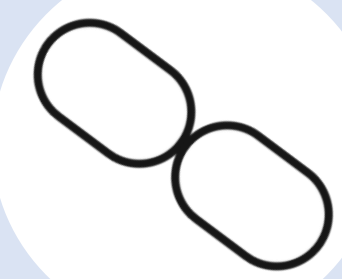
The spatial architecture of genomes in the nuclei is essential to study their function. The number of studies incorporating Hi-C approaches to probe interactions inside the chromatin is growing and, at the same time, the field for developing 3D modeling computational methods offers numerous solutions. However, this opportunity for original and insightful modeling is under exploited, and most fungal Hi-C studies don't propose 3D models of chromatin contact networks. Our aim was thus to further promote the association between 3D modeling of the chromatin along contact maps in fungal Hi-C studies. To do so, we propose here striking and precise examples of 3D modeling of entire genomes and a software tool to share this approach. Our analysis process was assembled into a "one command use" and modular workflow based on state-of-the-art analysis and modeling software that goes from Hi-C raw data to fully annotated 3D models. With this workflow, we re-analysed public Hi-C datasets available in three model species to visualize them in a 3D context. New models of the organization of those three emblematic fungal genomes were generated, summarizing the known features of fungal genomes into rich and integrated illustrations while also offering new insight into *Saccharomyces cerevisiae* cohesin anchor regions organization.



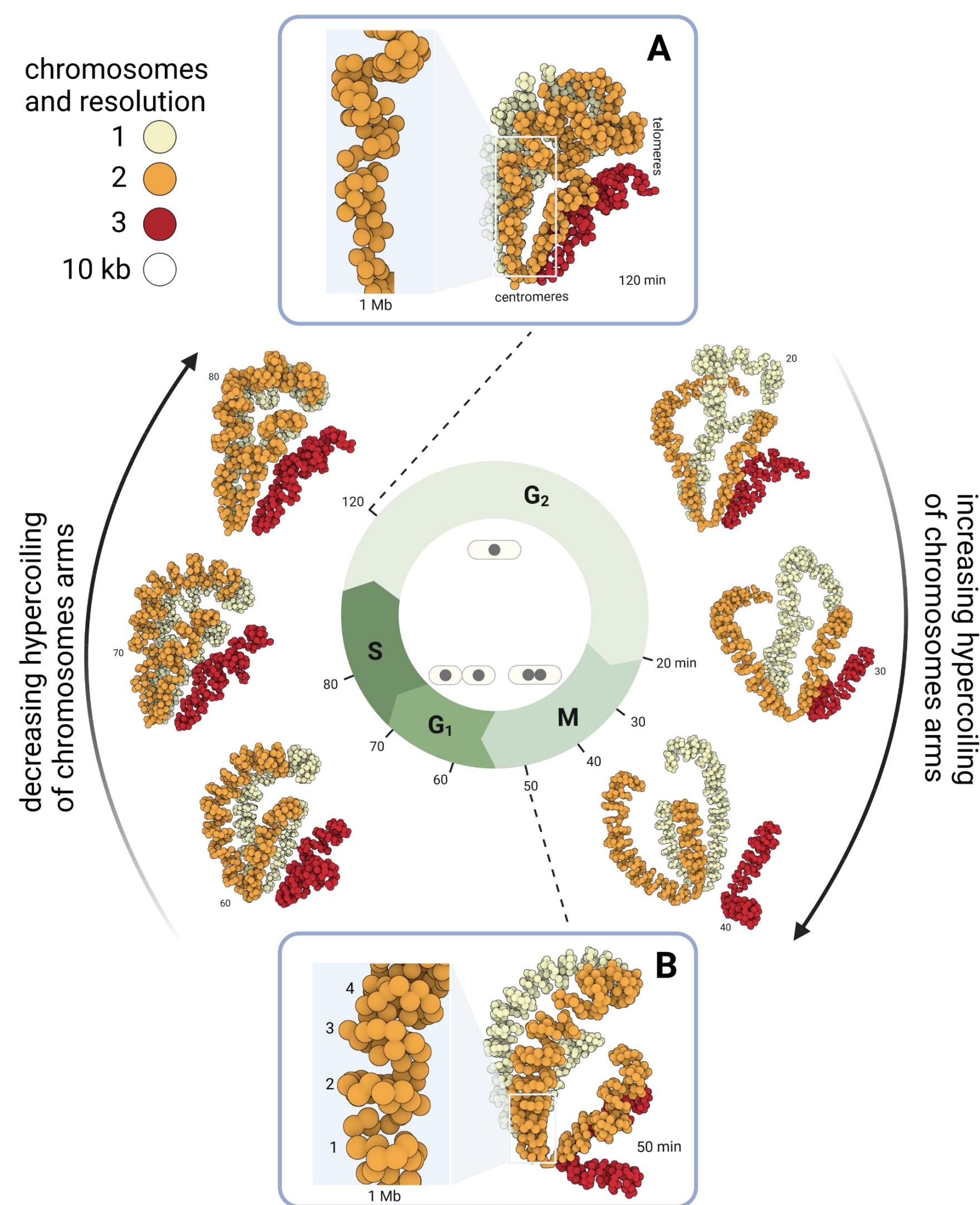
Revealing the spatial alignment of cohesin binding sites along chromosomes in *Saccharomyces cerevisiae*



Revealing the 3D skeleton formed by cohesin in the *Saccharomyces cerevisiae* genome. (A) 3D model of the SCERE genome, obtained with 3DGB, using the Micro-C XL data from Costantino *et al.* 2020. Each bead represents a 5 kb chromosomal region and is colored according to the ChIP-seq signal intensity of the Mcd1p cohesin subunit, in mitotically arrested cells. (B) Isolation of chromosome 13 from the overall structure, allowing to observe the spatial alignment of the DNA binding sites of cohesin. Cohesin structures a chromosomal skeleton on which chromatin loops can form. (C) Juxtaposition of the 3D model and the associated contact map, for the beads which are located between 430 and 580 kb. On the 3D structure, the cohesin backbone is highlighted in yellow. Viewing this spatial alignment of cohesin is complementary to the information contained in the contact card, i.e. the frequencies of contacts are very high inside genomic regions delimited with yellow beads (yellow color on the contact map).



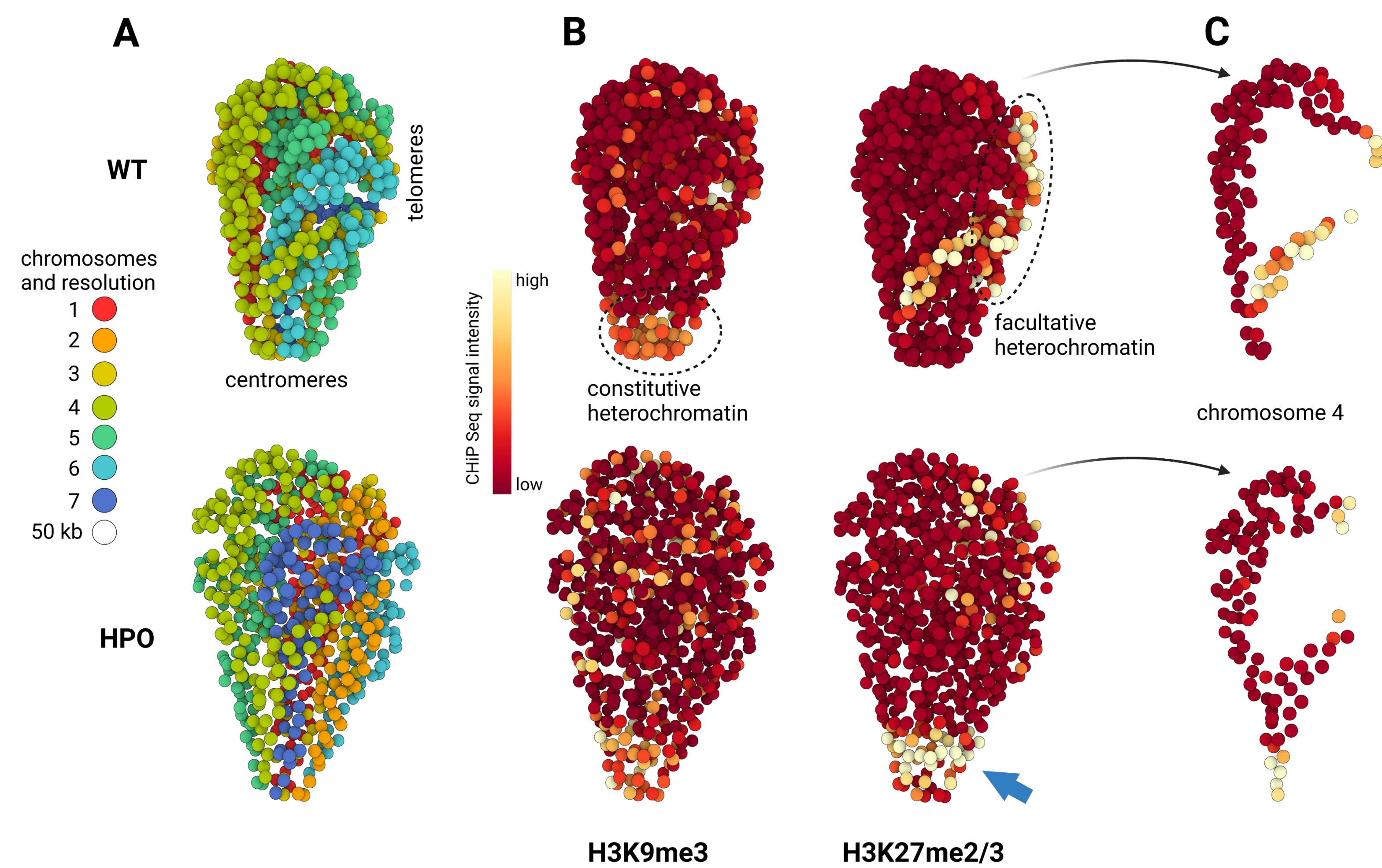
Revealing oscillations in coiling of chromosome arms during cell cycle in *Schizosaccharomyces pombe*



Dynamics of the spatial organization of *Schizosaccharomyces pombe* chromosomes during the cell cycle. Coiling of chromosome arms, as described in the literature, is visible on the 3D models. Zooms are provided in (A) and (B) boxes, which correspond to time points (respectively 120 and 50 minutes) for which the intensity of coiling is minimal and maximal.



Revealing relocalisations of histone marks in *Neurospora crassa* mutants for heterochromatin regulators



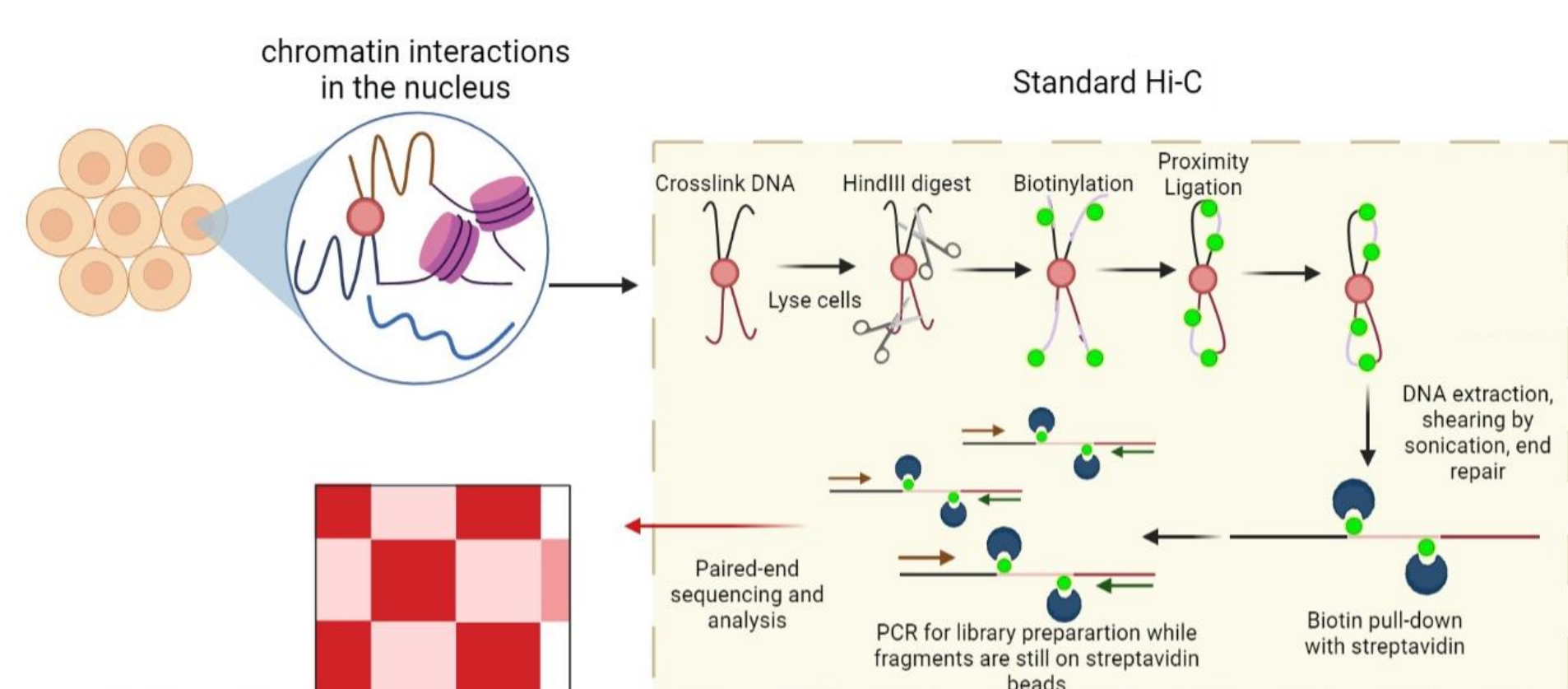
Visual integration of ChIP Seq data using 3D models of the *Neurospora crassa* genome. (A) 3D models respectively in the wild type (WT) and HP1-deficient (*hpo*) strains. (B) Same models as shown in (A), using the ChIP-seq signal intensity as a color code for beads. In the *hpo* strain, important changes in the intensities of ChIP-seq signals are observed, with notably, a massive relocalization of H3K27me3 high intensity signal to the centromeres (blue arrow). (C) Isolation of chromosome 4, better highlighting the changes in H3K27me2/3 ChIP-seq signal intensity between WT and *hpo* strains.



3D Genome Builder workflow, an intuitive solution for 3D modeling of Hi-C data



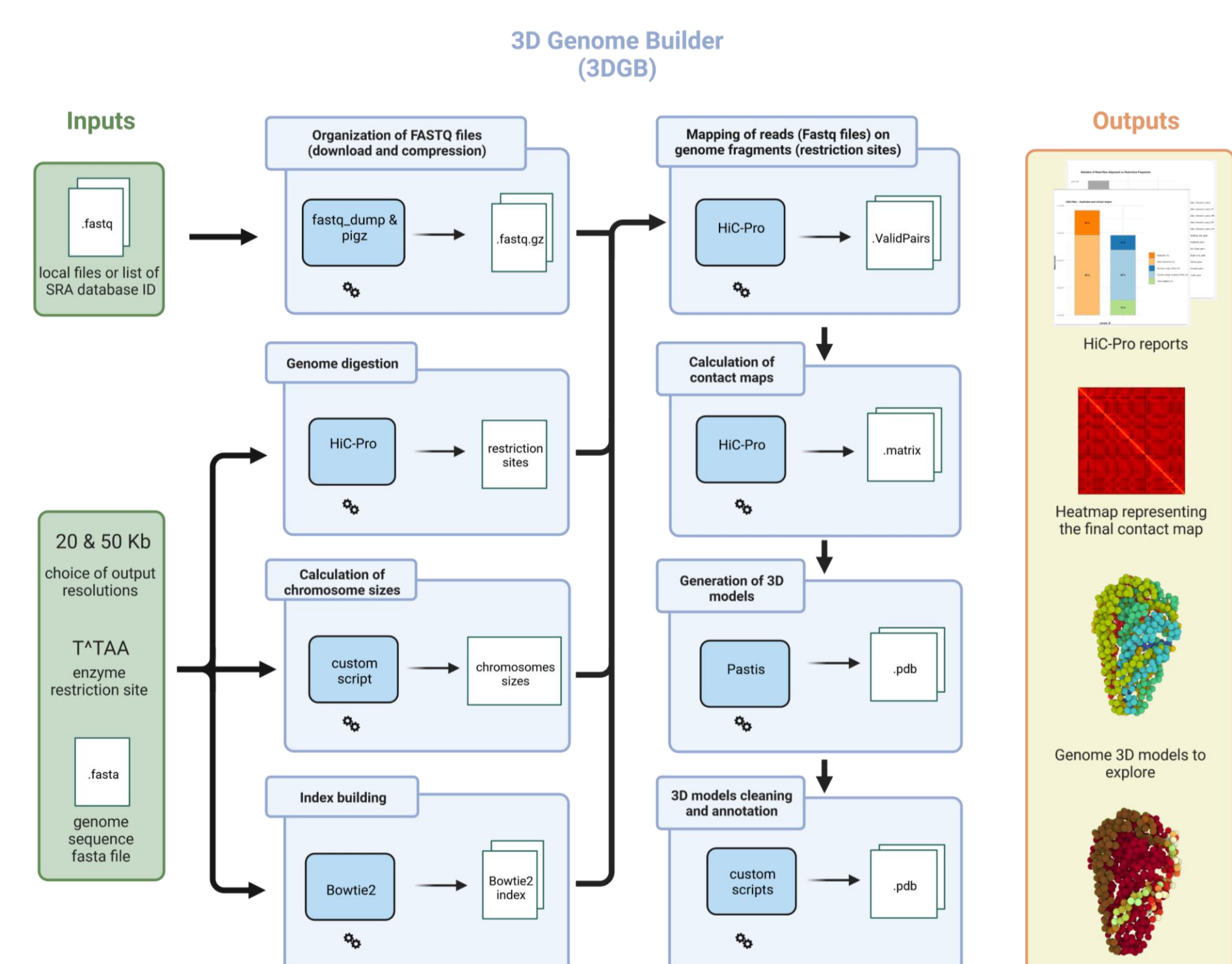
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Hi-C protocol main steps

Species	Genome Size	Chromosomes	Data Source
<i>Saccharomyces cerevisiae</i>	12.2 Mb	16 chromosomes	Micro-C XL data from Costantino <i>et al.</i> 2020 10.7554/eLife.59889
<i>Schizosaccharomyces pombe</i>	12.6 Mb	3 chromosomes	Hi-C data from Tanizawa <i>et al.</i> 2017 10.1038/nsmb.3482
<i>Neurospora crassa</i>	41 Mb	7 chromosomes	Hi-C data from Galazka <i>et al.</i> 2016 10.1101/gr.203182.115

Model species genome features and data sources



3D Genome Builder inputs, outputs and main steps