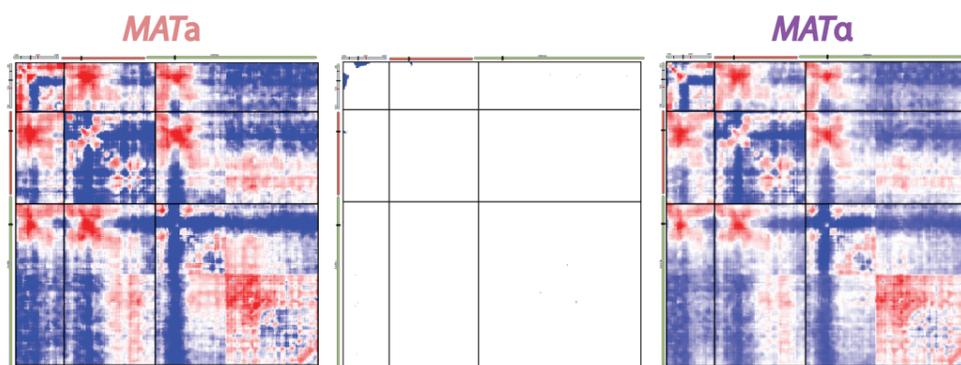
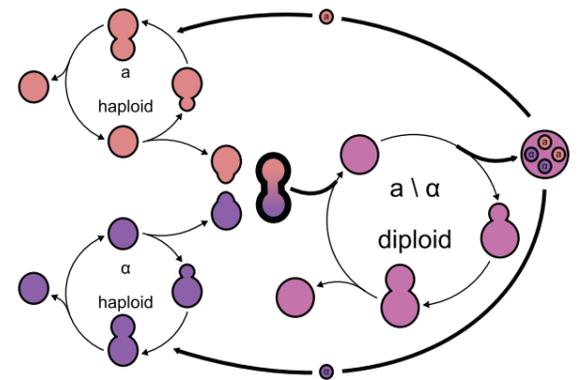


MATING TYPE SPECIFIC FOLDING OF YEAST CHR-III REVEALED BY THREE-DIMENSIONAL MODELING

Davide Bau^{1,2}, Jon-Matthew Belton³, Imen Lassardi^{4,5}, Kerstin Bystricky^{4,5}, Job Dekker³ and Marc A. Marti-Renom^{1,2}

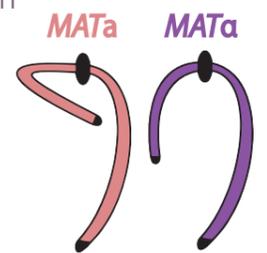
¹Genome Biology Group, National Center for Genomic Analysis (CNAG), Barcelona, Spain. ²Gene Regulation, Stem Cells and Cancer Program, Centre de Regulació Genòmica (CRG), Barcelona, Spain. ³Program in Systems Biology, Department of Biochemistry and Molecular Pharmacology, University of Massachusetts Medical School, Worcester, MA, USA. ⁴University of Toulouse; UPS; Toulouse, France. ⁵Laboratoire de Biologie Moléculaire Eucaryote; CNRS; UMR5099; Toulouse, France.

Introduction: The genome three-dimensional (3D) organization plays important, yet poorly understood roles in gene regulation. Chromosomes assume multiple distinct conformations and undergo dramatic alterations in higher order structure through the cell cycle. Despite advances in microscopy, a general technique to determine the 3D conformation of chromatin has been lacking. We developed a new method for the determination of the 3D conformation of chromatin in the interphase nucleus, which combines 5C experiments with the TADBit library. We used our approach to study the structure of the yeast chromosome III. Our 3D models show that the folding of the chromosome is mating type specific and that the mating type conversion could be related to its intrinsic folding and conformational exploration of the chromosome.



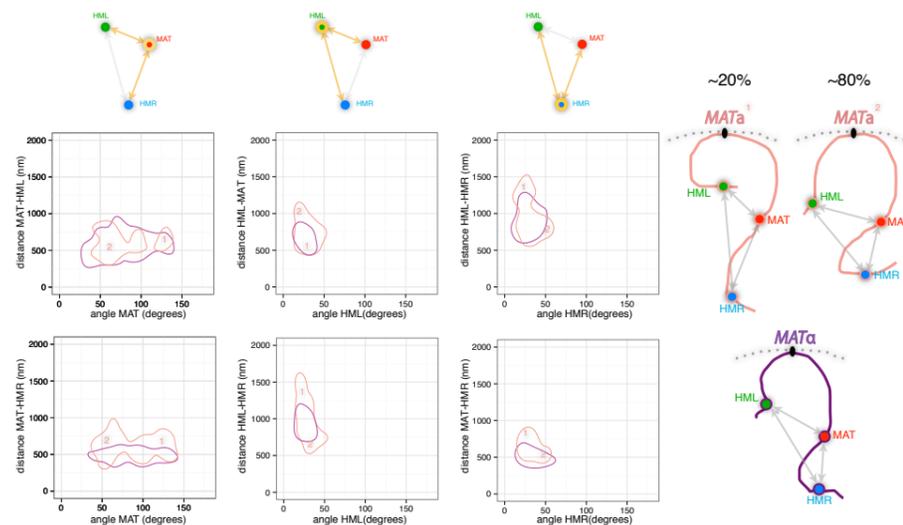
5C experiments show mating type chromosomal changes

Comprehensive 5C experiments performed on chromosomes III, V, and XII indicate that the major interaction differences between mating type reside in the left arm of Chromosome III. In particular, there is an increase of interactions between the right arm of ChrIII and the centromer in MAT-a cells compared to MAT-alpha cells.



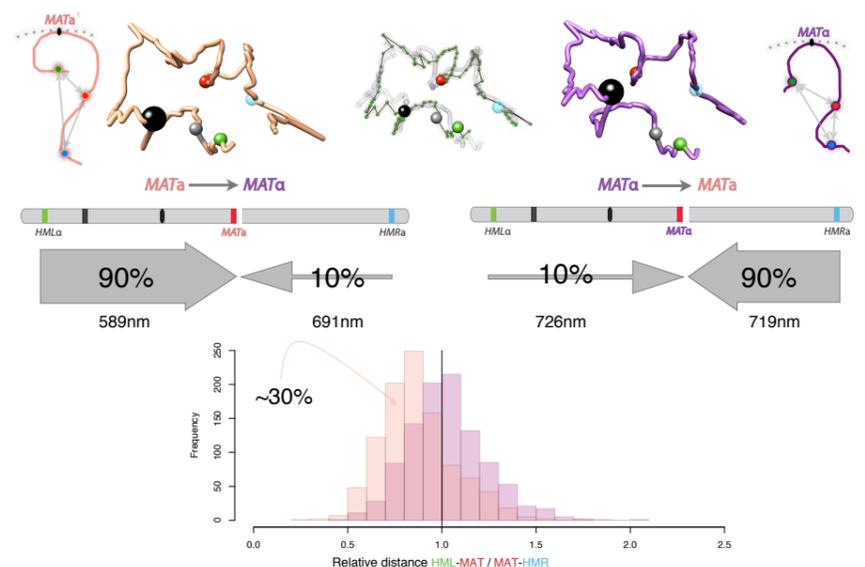
FISH imaging experiments shows two MAT-a populations

Live cell imaging using three colors ratified that the right arm of ChrIII is crumpled are closer to the centromer in MAT-a compared to MAT-alpha. However, the results also show that there is likely to be two different populations of conformations where a closed right arm occurs only about 20% of the time. The second population would result in conformations similar to that of MAT-alpha



3D modeling confirms predicted structures

Finally, integrating 5C data with FISH imaging within TADBit resulted in two differential conformations of the ChrIII, which capture the structural differences between the two mating types. Indeed, the right arm of ChrIII is crumpled towards the centromer of the chromosome resulting in a sub-population (~30%) of models in shorter distances between HML-MAT locus compared to MAT-HMR.



Summary: We generated comprehensive 3D models of the Chromosome III in yeast by integrating 5C interaction matrices, 3D FISH imaging and the TADBit computational library. The models reconstructed all known features of the mating specific folding for ChrIII in yeast and showed the existence of a sub-population of cells where the right arm of the chromosome is folded towards its centromer (likely thanks to the Recombinant Element).

The 3D models are currently being further analyzed to further improve our understanding of the influence of chromosome structure in the decision of mating switch in yeast.

