



HAL
open science

Principles of chromatin organization in yeast: relevance of polymer models to describe nuclear organization and dynamics

Renjie Wang, Julien Mozziconacci, Aurélien Bancaud, Olivier Gadal

► To cite this version:

Renjie Wang, Julien Mozziconacci, Aurélien Bancaud, Olivier Gadal. Principles of chromatin organization in yeast: relevance of polymer models to describe nuclear organization and dynamics. *Current Opinion in Cell Biology*, 2015, 34, pp.54 - 60. 10.1016/j.ceb.2015.04.004 . hal-01682615

HAL Id: hal-01682615

<https://hal.science/hal-01682615>

Submitted on 15 Jan 2018

HAL is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.

Special issue: "Cell Nucleus"

Current Opinion in Cell Biology

Principles of Chromatin Organization in yeast:

Relevance of polymer model to describe nuclear organization and dynamics

Renjie Wang^{1,2}, Julien Mozziconacci^{3,4}, Aurélien Bandaud^{4,5,6} and Olivier Gadal^{1,2,4*}

1: LBME du CNRS; 2: Laboratoire de Biologie Moléculaire Eucaryote, Université de Toulouse, 118 route de Narbonne, F-31000 Toulouse, France.

3: Laboratory for Theoretical Physics of Condensed Matter, UPMC, 75005 Paris, France.

4: Groupement de recherche Architecture et Dynamique Nucléaire (GDR ADN)

5: CNRS, LAAS, 7 avenue du colonel Roche, F-31400 Toulouse, France

6 : Univ de Toulouse, LAAS, F-31400 Toulouse, France

* Corresponding author:

Olivier Gadal

email: gadal@biotoul.fr

Phone: +33(0)5 61 33 59 39; Fax: +33 (0)5 61 33 58 86;

Abstract

Nuclear organization can impact on all aspects of genome life cycle. This organization is thoroughly investigated by advanced imaging and chromosome conformation capture techniques, providing considerable amount of datasets describing the spatial organization of chromosomes. In this review, we will focus on polymer models to describe chromosome statics and dynamics in the yeast *S. cerevisiae*. We suggest that the equilibrium configuration of a polymer chain tethered at both ends and placed in a confined volume is consistent with the current literature, implying that local chromatin interactions play a secondary role in yeast nuclear organization. Future challenges are to reach an integrated multi-scale description of yeast chromosome organization, which is crucially needed to improve our understanding of regulation of genomic transaction.

Running head: Chromatin Organization in yeast

Keywords: Nuclear structure; chromatin dynamics; chromatin organization; *Saccharomyces cerevisiae*

Introduction: the necessary jump toward integrative view of chromatin organization

The driving forces responsible for the establishment and maintenance of high-order chromatin structure remain the subject of intense research. Our understanding of genome organization has always been intimately linked to technical progresses, which fed new insights that confirmed or contradicted working hypotheses [1,2]. From the seminal use of dyes by Flemmings to identify chromatin, microscopy was, and still is, a central tool to study nuclear organization [3]. Carl Rabl suggested that interphase chromosome organization was guided by the tethering of centromeres and telomeres in opposite directions, a folding latter named "Rabl-organisation" [4]. Rabl-like configuration of budding yeast chromosome was established more than 100 year later [5-8]. At smaller length scales, the heterogenous distribution of chromatin in the nucleus was observed in 1928 by Emil Heitz [9] using optical microscopy of Giemsa stained chromosomes. This organization was confirmed by Transmitted Electron Microscopy (TEM) with considerable gain in resolution [10]. Further after extraction of the soluble material, TEM led to the observation of the "nuclear matrix" as a nucleo-skeleton onto which chromatin was attached [11]. Live cell imaging of fluorescently labeled nuclear components were developed, collectively called F-techniques, and showed that a large fraction of nuclear proteins, some of which present in nuclear matrix fraction, were highly dynamic [12]. Techniques to label chromosome loci based on fluorescent operator-repressor system (FROS), which involve LacI-GFP or TetR-GFP binding to array of 256 *lacO* or 112 *tetO*, equivalently ~10 kb of DNA, have also been set up, and time-lapse analysis of chromosome motion revealed the mobility of DNA *in vivo* [13-15]. Over the last decade we witnessed the advent of genomic methods to sense nuclear architecture, such as Chromatin immunoprecipitation (ChIP), DNA adenine methyltransferase identification (DamID), and the most widely used intra-molecular ligation of cross-linked DNA, named chromosome conformation capture (3C), and its genome wide derivatives including Hi-C [16,17]. This booming field calls for new models to integrate datasets of different nature (microscopic distance measurements, ChIP, DamID, contact frequency map from 3C), and coarse-grained polymer physics models met some success in the recapitulation of heterogeneous data with a single and unified representation [18]. Necessary improvements are still needed to enhance the spatial resolution of polymer models so as to recapitulate the folding principle of DNA, chromatin, and chromosomes. Here we wish to discuss the successes of these models in the context of *S. cerevisiae* nuclear architecture, as well as to

discuss the clarifications that are needed to reach a better understanding of chromosome organization *in vivo*.

Models of nuclear architecture: Direct vs indirect modeling

In the last 25 years, essentially two classes of models have been proposed to describe genome organization: direct (or data driven) modeling or inverse (or physics driven) modeling (for review, see [19]). In direct modeling, experimental datasets are used as inputs, and modeling is built by minimizing the discrepancy of the model to the data. Therefore, such models are tailored to recapitulate input data but by construction, they have little or no predictive value, and new datasets must be obtained before generating a modified model. They can be however very useful since they recapitulate complex data in a frame which is usually amenable to be visually interpreted directly. The other approach consists to build a model with a set of assumptions involving, among others, the mechanics of chromosomes (rigidity and friction) and the geometry of the nucleus. The output of the model can be compared with experiments [20-22], and its predictive value can be challenged with novel datasets or whenever the set of microscopic parameters that fit experiments appear to be inconsistent with the literature. In fact the consistency of the model with experiments does not imply its validity, especially because the essential parameters to describe large-scale nuclear architecture remain elusive. At this step we propose to highlight some of the main conclusions inferred from modeling of eukaryotic organization with polymer physics.

What do we learn from Chromosome Conformation Capture?

The genome wide implementation of the 3C technique (Hi-C) enables the mapping the self contacts resulting from the DNA molecules being folded in chromosomes within the live nucleus and is therefore reflecting this architecture (See on figure 1a this contact map for the yeast genome, [23]). Direct 3D modeling [24] applied on this contact map leads to a 3D structure which recapitulates known features of yeast chromosomes organization such as strong centromere clustering, weaker telomere co-localization and the spatial segregation of long and short chromosomal arms (Figure 1b). A pending question is whether or not this organization is quantitatively compatible with polymer physics. In the seminal Hi-C paper, the authors compared their data with two polymer models describing chromosomes as

crumple or equilibrium globules [25]. These models differ in their predictions on the decrease of the contact probability p between two loci on the same chromosomes as a function of their genomic distance s (see figure 1c). The finding that $p(s)$ followed a power law decrease with s characterized by an exponent close to -1 ($p(s) \sim s^{-1.08}$) appeared to be in agreement with the crumple globule model. Other results were later published on different organisms, including the yeast *S. cerevisiae* [26]. They seemed to indicate that metazoan genomes shared common folding principles with a similar exponent of -1 whereas the yeast genome, which has shorter chromosomes is organized as an equilibrium globule in agreement with physical models (see figure 1d) [21,22]. This simple view have been however challenged as additional Hi-C data obtained with standardized protocols became available [27], because it was for instance found that the exponent of $p(s)$ somewhat varied in the range of -1.5 to -1 for different human cell lines [28]. The general relevance of the crumpled globule model has therefore been called into question, because $p(s) \sim s^{-1.5}$ is expected to be detected in equilibrium globules. Concerning the yeast *S. cerevisiae*, only two genome-wide datasets are available [23,29], and more data and analysis are needed to confirm or invalidate the actual folding scheme. Notably possible fixation artifacts (some of which can be normalized) in 3C techniques, and the difficulties to convert contact frequency to physical distances should not be ignored [30-33]. It has been suggested that one way around these technical limitations was to combine 3C methods with microscopy observations, which are now combined [17,25]. We thus conclude that the folding principles of chromosomes at the *entire* genome level remain controversial, but the number of contributions in this booming field should rapidly clarify these central questions. Conversely the motion of a chromosome locus is associated to the *local* properties of chromatin, and the main results obtained by physical modeling of spatial fluctuations will be described in the following paragraph.

What do we learn from chromosome motion analysis?

Chromatin loci are in constant random motion within some finite volume of confinement detectable with long time-lapse acquisitions [13,14,34,35]. When locus is release from chromosome (*i.e.* through inducible excision of tagged chromatin rings), chromatin is diffusing in the nucleoplasm, and boundaries are defined by the nuclear envelope [34,36]. Chromosomal loci instead seem to be confined in a "gene territory", as defined by the region of preferential steady-state localization [37]. For shorter time scales, the displacement of

chromosome loci was mainly analyzed based on the mean square displacement (MSD). The MSD was adjusted with models of diffusion or sub-diffusion, meaning that power-law scaling describing its temporal dependence was characterized by an exponent of 1 or lower than 1, respectively. Notably normal diffusion is expected to occur for isolated objects, *i.e.* influenced by thermal fluctuations and viscous friction only. In the case of polymer loci, elastic interactions between neighboring monomers and long-range hydrodynamic interactions associated to solvent flux have to be considered [38]. The nucleus is a concentrated environment composed of DNA, diffusing and bound proteins, as well as RNA, which are expected to screen out hydrodynamic interactions. As was described for the bacterial chromosome [39], the dynamics of chromosomes in yeast was proposed to follow the Rouse model, which assumes that chromatin fiber behaves as a homogeneous series of beads connected by elastic springs, with the notable exception of ribosomal DNA (rDNA) in the nucleolus [40,41]. For an isolated chain and disregarding volume exclusion, the motion of a locus in chain composed of N monomers, of known stiffness characterized by the Kuhn length (Lk) is described by 3 consecutive regimes (Figure 2). For very short time intervals, elastic interactions between neighboring monomers do not restrain motion. This is only valid for small displacements ($MSD \ll Lk$; ~ 30 nm for chromatin), which are difficult to access experimentally (see below). For long displacements larger than the polymer diameter ($MSD \gg Lk \cdot \sqrt{N}$), the entire polymer chain diffuses freely in solvent. In the yeast nucleus, this behavior is not relevant because chromosomes are confined in the nucleus and tethered at their centromere [7,42,43] and telomere [44,45]. Notably this tethering also induces topological constraints that do not allow for reptation, *i.e.* longitudinal diffusion of a monomer along the contour path of the chain. In between those two regimes (for $Lk \ll MSD \ll Lk \cdot \sqrt{N}$), Rouse regime is characterized by $MSD(\tau) = \Gamma \tau^\alpha$, with scaling exponent α of 0.5, which increases to 0.54 whenever volume exclusion is considered. Although this simplistic model overlooks local variations in chromatin structure, it appeared to be consistent with the motion of loci located on chromosome XII, XIV and IV in *S. cerevisiae* [40,41]. These results are further supported by molecular simulations using a polymer model of the entire yeast genome [40,41]. A recent publication however challenged the relevance of the Rouse model by monitoring the motion in 3D of *GAL* genes and control loci in the 0.5-5 s time domain [46]. These authors indeed showed that the exponent of subdiffusion was $\alpha \sim 0.7$, which is apparently not compatible with Rouse regime. The authors suggested that fractional Brownian motion (fBm) could account for this scaling exponent,

though the underlying physics accounting for this behavior remains unclear. Another possibility is that the Rouse model remains valid despite the unexpected exponent. High precision 3D microscopy is achieved with strains in which chromosome loci are characterized by high signal-to-noise ratio. These imaging conditions are obtained by increasing the number of bacterial operator binding sites from 56 to 224 *tetO* sequences, equivalently 2.5 to 11 kb of DNA, in order to enhance brightness of the locus. However, due to the increased length of the labeled DNA, the initial free diffusive motion is expected to be slower than for a single monomer (Fig. 2). The transition to the Rouse regime should hence be delayed, leading to an “intermediate” exponent lower than 1 but greater than 0.54 in the short time regime, as was for instance discussed for particle migration in a dense meshwork [47]. In fact we recently observed the same behavior in clones with long FROS labels (Fig. 2). The dynamics of a locus on chromosome XII showed a smooth transition to the Rouse regime after ~5 s. Note that this two-phase response was not detected in our previous report using clones with shorter FROS labels [40,45]. Consequently, the Rouse polymer model does not seem to be invalidated by analyzing the MSD over a limited temporal domain comprised between 0.5-5 s. Nevertheless we suggest that further validations of the Rouse model to describe chromosome motion require additional analyses, including among others step distribution functions, velocity autocorrelation function of locus trajectories [48], or probability of backward motion.

Conclusion: toward an integrated view of nuclear organization and dynamics

This overview suggests that the implementation of a physics model providing an integrated picture of yeast nuclear organization is under rapid and constant improvement. Based on the current literature, we may propose that each chromosome arm extends in the nucleus from its centromere, behaving as a space-filling polymer in a preferential path dictated by the centromere to nucleolus axis (Fig. 3). Volume exclusion in the nuclear volume defines a characteristic tube in which chromosome can be described as a series of polymer beads, called blobs, in which the chain behaves as an ideal constraint-free polymer. In this description, the Rabl-like organization of yeast chromosomes is marginally dictated by polymer-polymer interactions, rather chromosomes behave as extended polymer chains organized by volume exclusion. This description covers the length spectrum from the Kuhn length to the nucleus size, and disregards the folding of chromatin fiber. We argue that the next challenge is to build multi-scale models with improved description at every spatial dimension to explore

gene specific properties: Gene relocalization documented in yeast during gene expression such as tRNA gene preferential interaction with NPC or nucleolus [49,50], peripheral recruitment of SAGA-regulated genes [51-53], the formation of replication factory [54] or increased motility toward DNA damage [55-57]. The benefits of this effort are expected to help clarify how the cells organize its genome for gene expression regulation or efficient repair. Finally, the recent organization of chromosome arm in fission yeast in globule by local cohesin association at specific sites demonstrate that combination of biophysical properties of chromatin and mapping chromatin bound factors will allow tremendous progress in our understanding of chromatin architecture *in vivo* [58].

Figures captions

Figure 1 : 3C insights on the structure of the *S. cerevisiae* chromosomes.

(A) Contact map of the 16 chromosomes as obtained by genome-wide 3C ([23], individual chromosomes are labeled with roman numbering). The map has been normalized so that the sum over each line and column is equal to one [32]. Note that the colorscale is in log 10. (B) Direct 3D modeling from this map [24]. The colorcode for each chromosome on the structure is indicated in (A). Telomeres and centromeres are labeled with respectively purple and black beads. (C) Zoom on the intra chromosomal contact map of chromosome XV, corresponding to the blue box in (A). The value $p(s)$ is obtained for each genomic distance s with averaging the signal in the red box. (D) Plot of the mean number of contacts obtained in the experiment with varying distances (s). Note that these number of contacts were not normalized. Picture adapted from [22].

Figure 2: Rouse model of polymer dynamics.

(A) This figure describes the difference in segmental dynamics of one monomer or a fragment with n monomers (color-coded in green or blue, respectively). In the short time limit, the motion of the locus is not restricted by elastic interactions with its neighboring polymer segments, leading to a regime of free diffusion. The larger dimension of a fragment with n monomers is associated to a slow down in diffusion (the blue curve is below the green one). This second regime corresponds to Rouse model of polymer dynamics, in which the MSD increases with time with a power-law scaling of 0.54. The red rectangle represents the observation window in a real experiment with finite temporal and spatial resolutions. (B) The blue dataset represents the average MSD over 45 trajectories for a selected bright locus located at position 380 kb on chromosome XII (room temperature). Note that standard errors are indicated as vertical caps. Two regimes can be distinguished with a sharp increase of the MSD at short time scales (scaling exponent of 0.75) followed by a behavior consistent with the Rouse regime (scaling exponent of 0.54). Respective trend lines are shown in black and red.

Figure 3 : Two schematic representation of yeast nucleus.

(A) Schematic representation of yeast nucleus for biology point of view. Chromosome arms are depicted in color lines. Centromeres (CEN; yellow circle) are attached to spindle pole body (SPB; black circle) by microtubules (red lines). Telomeres (TEL) (green circle) are distributed near nuclear envelope (NE) (double-black-lines circle). Nucleolus (red crescent abutting NE) contains rDNA (bold purple line). Blue and brown crosses depicts respectively nuclear and nucleolar center (B) Schematic representation of yeast nucleus for polymer physics point of view. The color circles represent polymer blobs, containing Rouse chain (lines within blob). Each chains represent one chromosome arms anchored at both end (yellow circle and green circle). Blobs are fulfilling nucleoplasm (gray circle). Nuclear and nucleolar center are forming a central axis around which chromosome are organized. Note that rDNA in the nucleolus has property distinct from nucleoplasm.

Acknowledgements

O.G. was supported by an ATIP-plus grant from CNRS, by the Agence Nationale de la Recherche (programme JCJC). JM, AB and OG are supported by Agence Nationale de la Recherche (ANDY).

References

1. Olins DE, Olins AL: Chromatin history: our view from the bridge. *Nat Rev Mol Cell Biol* 2003, 4:809-814.
2. Cremer T, Cremer C, Lichter P: Recollections of a scientific journey published in
•• human genetics: from chromosome territories to interphase cytogenetics and comparative genome hybridization. *Hum Genet* 2014, 133:403-416.

An excellent, historical perspective of chromatin structure in cell nucleus.

3. Flemming W: *Zellsubstanz, Kern und Zelltheilung* Edited by Leipzig FCWV; 1882.
4. Rabl C: Über Zelltheilung. *Morphol. Jahrbuch* 1885:214-330.
5. Guacci V, Hogan E, Koshland D: Centromere position in budding yeast: evidence for anaphase A. *Mol Biol Cell* 1997, 8:957-972.
6. Jin Q, Trelles-Sticken E, Scherthan H, Loidl J: Yeast nuclei display prominent centromere clustering that is reduced in nondividing cells and in meiotic prophase. *J Cell Biol* 1998, 141:21-29.
7. Jin QW, Fuchs J, Loidl J: Centromere clustering is a major determinant of yeast interphase nuclear organization. *J Cell Sci* 2000, 113:1903-1912.
8. Bystricky K, Heun P, Gehlen L, Langowski J, Gasser SM: Long-range compaction and flexibility of interphase chromatin in budding yeast analyzed by high-resolution imaging techniques. *Proc Natl Acad Sci U S A* 2004, 101:16495-16500.
9. Heitz E: Das Heterochromatin der Moose. *Jahrb. Wiss. Botanik* 1928:762–818.
10. Tooze J, Davies HG: Light- and electron- microscope studies on the spleen of the newt *Triturus cristatus*: the fine structure of erythropoietic cells. *J Cell Sci* 1967, 2:617-640.

11. Berezney R, Coffey DS: Identification of a nuclear protein matrix. *Biochem Biophys Res Commun* 1974, 60:1410-1417.
12. Misteli T: Protein dynamics: implications for nuclear architecture and gene expression. *Science* 2001, 291:843-847.
13. Marshall WF, Straight A, Marko JF, Swedlow J, Dernburg A, Belmont A, Murray AW, Agard DA, Sedat JW: Interphase chromosomes undergo constrained diffusional motion in living cells. *Curr Biol* 1997, 7:930-939.
14. Heun P, Laroche T, Shimada K, Furrer P, Gasser SM: Chromosome dynamics in the yeast interphase nucleus. *Science* 2001, 294:2181-2186.
15. Michaelis C, Ciosk R, Nasmyth K: Cohesins: chromosomal proteins that prevent premature separation of sister chromatids. *Cell* 1997, 91:35-45.
16. van Steensel B, Dekker J: Genomics tools for unraveling chromosome architecture. *Nat Biotechnol* 2010, 28:1089-1095.
17. Dekker J, Rippe K, Dekker M, Kleckner N: Capturing chromosome conformation. *Science* 2002, 295:1306-1311.
18. Bau D, Marti-Renom MA: Genome structure determination via 3C-based data integration by the Integrative Modeling Platform. *Methods* 2012, 58:300-306.
19. Rosa A, Zimmer C: Computational models of large-scale genome architecture. *Int Rev Cell Mol Biol* 2014, 307:275-349.

A comprehensive overview of computational model of genome architecture of the last 25 years.

20. Tokuda N, Terada TP, Sasai M: Dynamical modeling of three-dimensional genome organization in interphase budding yeast. *Biophys J* 2012, 102:296-304.

This paper describes a model of yeast chromosome as chains moving under the constraints of nuclear structure and chromatin-chromatin interactions

21. Tjong H, Gong K, Chen L, Alber F: Physical tethering and volume exclusion determine higher-order genome organization in budding yeast. *Genome Res* 2012, 22:1295-1305.

Model supported the view that volume exclusion and physical tethering was sufficient to recapitulate most of yeast genome contact map

22. Wong H, Marie-Nelly H, Herbert S, Carrivain P, Blanc H, Koszul R, Fabre E, Zimmer C: A predictive computational model of the dynamic 3D interphase yeast nucleus. *Curr Biol* 2012, 22:1881-1890.

Computational model reaching similar conclusion with 21, but with the additional notion of heteropolymer model to explain spatial segregation and shape of nucleolus.

23. Duan Z, Andronescu M, Schutz K, McIlwain S, Kim YJ, Lee C, Shendure J, Fields S, Blau CA, Noble WS: A three-dimensional model of the yeast genome. *Nature* 2010, 465:363-367.

24. Lesne A, Riposo J, Roger P, Cournac A, Mozziconacci J: 3D genome reconstruction from chromosomal contacts. *Nat Methods* 2014, 11:1141-1143.

25. Lieberman-Aiden E, van Berkum NL, Williams L, Imakaev M, Ragoczy T, Telling A, Amit I, Lajoie BR, Sabo PJ, Dorschner MO, et al.: Comprehensive mapping of long-range interactions reveals folding principles of the human genome. *Science* 2009, 326:289-293.

26. Halverson JD, Smrek J, Kremer K, Grosberg AY: From a melt of rings to chromosome territories: the role of topological constraints in genome folding. *Rep Prog Phys* 2014, 77:022601.

27. Dixon JR, Selvaraj S, Yue F, Kim A, Li Y, Shen Y, Hu M, Liu JS, Ren B: Topological domains in mammalian genomes identified by analysis of chromatin interactions. *Nature* 2012, 485:376-380.

Identification of topological domains as large, megabase-sized local chromatin interaction domains, as structural constituent of the genome organization

28. Barbieri M, Chotalia M, Fraser J, Lavitas LM, Dostie J, Pombo A, Nicodemi M: Complexity of chromatin folding is captured by the strings and binders switch model. *Proc Natl Acad Sci U S A* 2012, 109:16173-16178.
29. Marie-Nelly H, Marbouty M, Cournac A, Liti G, Fischer G, Zimmer C, Koszul R: Filling annotation gaps in yeast genomes using genome-wide contact maps. *Bioinformatics* 2014, 30:2105-2113.
30. Williamson I, Berlivet S, Eskeland R, Boyle S, Illingworth RS, Paquette D, Dostie J, Bickmore WA: Spatial genome organization: contrasting views from chromosome conformation capture and fluorescence in situ hybridization. *Genes Dev* 2014, 28:2778-2791.

Extensive high resolution study of the murin HoxD with 3C methods and FISH products revealed that product captured by 3C do not always reflect spatial proximity, and must be interpreted with caution.

31. Belmont AS: Large-scale chromatin organization: the good, the surprising, and the still perplexing. *Curr Opin Cell Biol* 2014, 26:69-78.
32. Yaffe E, Tanay A: Probabilistic modeling of Hi-C contact maps eliminates systematic biases to characterize global chromosomal architecture. *Nat Genet* 2011, 43:1059-1065.
33. Cournac A, Marie-Nelly H, Marbouty M, Koszul R, Mozziconacci J: Normalization of a chromosomal contact map. *BMC Genomics* 2012, 13:436.

Normalisation of contact map is instrumental to prevent artefacts in contact map. Procedure of normalization is described in detail in this work.

34. Neumann FR, Dion V, Gehlen LR, Tsai-Pflugfelder M, Schmid R, Taddei A, Gasser SM: Targeted INO80 enhances subnuclear chromatin movement and ectopic homologous recombination. *Genes Dev* 2012, 26:369-383.

35. Drubin DA, Garakani AM, Silver PA: Motion as a phenotype: the use of live-cell imaging and machine visual screening to characterize transcription-dependent chromosome dynamics. *BMC Cell Biol* 2006, 7:19.
36. Gartenberg MR, Neumann FR, Laroche T, Blaszczyk M, Gasser SM: Sir-mediated repression can occur independently of chromosomal and subnuclear contexts. *Cell* 2004, 119:955-967.
37. Berger AB, Cabal GG, Fabre E, Duong T, Buc H, Nehrbass U, Olivo-Marin JC, Gadal O, Zimmer C: High-resolution statistical mapping reveals gene territories in live yeast. *Nat Methods* 2008, 5:1031-1037.
38. Teraoka I: *Polymer Solutions: An Introduction to Physical Properties*. In *Polymer Solutions*. Edited by: John Wiley & Sons, Inc.; 2002:i-xv.
39. Weber SC, Spakowitz AJ, Theriot JA: Bacterial chromosomal loci move subdiffusively through a viscoelastic cytoplasm. *Phys Rev Lett* 2010, 104:238102.
40. Hajjoul H, Mathon J, Ranchon H, Goiffon I, Mozziconacci J, Albert B, Carrivain P,
 - Victor JM, Gadal O, Bystricky K, et al.: High-throughput chromatin motion tracking in living yeast reveals the flexibility of the fiber throughout the genome. *Genome Res* 2013, 23:1829-1838.

Analysis of chromatin motion of multiple loci supported subdiffusive behavior of chromatin. Rouse polymer model was used to extract some biophysical properties of chromatin.

41. Verdaasdonk JS, Vasquez PA, Barry RM, Barry T, Goodwin S, Forest MG, Bloom K:
 - Centromere tethering confines chromosome domains. *Mol Cell* 2013, 52:819-831.

Chromosome motion strongly depends on tethering at the centromere. Detachment of centromere increased mobility, and modeling was used to evaluate forces dictating chromosome territorial organization.

42. O'Toole ET, Winey M, McIntosh JR: High-voltage electron tomography of spindle pole bodies and early mitotic spindles in the yeast *Saccharomyces cerevisiae*. *Mol Biol Cell* 1999, 10:2017-2031.

43. Gotta M, Laroche T, Formenton A, Maillet L, Scherthan H, Gasser SM: The clustering of telomeres and colocalization with Rap1, Sir3, and Sir4 proteins in wild-type *Saccharomyces cerevisiae*. *J Cell Biol* 1996, 134:1349-1363.
44. Bystricky K, Laroche T, van Houwe G, Blaszczyk M, Gasser SM: Chromosome looping in yeast: telomere pairing and coordinated movement reflect anchoring efficiency and territorial organization. *J Cell Biol* 2005, 168:375-387.
45. Albert B, Mathon J, Shukla A, Saad H, Normand C, Leger-Silvestre I, Villa D, Kamgoue A, Mozziconacci J, Wong H, et al.: Systematic characterization of the conformation and dynamics of budding yeast chromosome XII. *J Cell Biol* 2013, 202:201-210.

46. Backlund MP, Joyner R, Weis K, Moerner WE: Correlations of three-dimensional
 - motion of chromosomal loci in yeast revealed by the double-helix point spread function microscope. *Mol Biol Cell* 2014, 25:3619-3629.

Novel type of fluorescent microscopy to analyse in 3D tracking loci was used, and confirmed sub-diffusive behavior of chromatin in vivo

47. Cai LH, Panyukov S, Rubinstein M: Mobility of Spherical Probe Objects in Polymer Liquids. *Macromolecules* 2011, 44:7853-7863.
48. Weber SC, Thompson MA, Moerner WE, Spakowitz AJ, Theriot JA: Analytical tools to
 - distinguish the effects of localization error, confinement, and medium elasticity on the velocity autocorrelation function. *Biophys J* 2012, 102:2443-2450.

Analysis of loci trajectories are classically analyzed using mean-square displacement (MSD). Other type of analysis were used to explore chromatin motion in vivo

49. Thompson M, Haeusler RA, Good PD, Engelke DR: Nucleolar clustering of dispersed tRNA genes. *Science* 2003, 302:1399-1401.
50. Chen M, Gartenberg MR: Coordination of tRNA transcription with export at nuclear pore complexes in budding yeast. *Genes Dev* 2014, 28:959-970.

51. Brickner JH, Walter P: Gene recruitment of the activated INO1 locus to the nuclear membrane. *PLoS Biol* 2004, 2:e342.
52. Ahmed S, Brickner DG, Light WH, Cajigas I, McDonough M, Froyshteter AB, Volpe T, Brickner JH: DNA zip codes control an ancient mechanism for gene targeting to the nuclear periphery. *Nat Cell Biol* 2010, 12:111-118.
53. Casolari JM, Brown CR, Komili S, West J, Hieronymus H, Silver PA: Genome-wide localization of the nuclear transport machinery couples transcriptional status and nuclear organization. *Cell* 2004, 117:427-439.
54. Saner N, Karschau J, Natsume T, Gierlinski M, Retkute R, Hawkins M, Nieduszynski CA, Blow JJ, de Moura AP, Tanaka TU: Stochastic association of neighboring replicons creates replication factories in budding yeast. *J Cell Biol* 2013, 202:1001-1012.

Super-resolution microscopy was used to investigate spatial organization of individual replicon. Model was used to quantitate replication factories formation.

55. Mine-Hattab J, Rothstein R: Increased chromosome mobility facilitates homology search during recombination. *Nat Cell Biol* 2012, 14:510-517.
56. Dion V, Kalck V, Horigome C, Towbin BD, Gasser SM: Increased mobility of double-strand breaks requires Mec1, Rad9 and the homologous recombination machinery. *Nat Cell Biol* 2012, 14:502-509.
57. Seeber A, Dion V, Gasser SM: Checkpoint kinases and the INO80 nucleosome remodeling complex enhance global chromatin mobility in response to DNA damage. *Genes Dev* 2013, 27:1999-2008.
58. Mizuguchi T, Fudenberg G, Mehta S, Belton JM, Taneja N, Folco HD, FitzGerald P, Dekker J, Mirny L, Barrowman J, et al.: Cohesin-dependent globules and heterochromatin shape 3D genome architecture in *S. pombe*. *Nature* 2014.

High resolution contact map (10kb) in *S. pombe* revealed role of cohesin complex in boundaries of 'globule', a small region of chromatin locally interacting. Cohesin loss disrupt globule, except in heterochromatin domains of the genome.