



REVIEW

Novel insights into mitotic chromosome condensation [version 1; referees: 2 approved]

Ewa Piskadlo, Raquel A. Oliveira

Instituto Gulbenkian de Ciência, Rua da Quinta Grande 6, Oeiras, 2780-156 , Portugal

v1 **First published:** 25 Jul 2016, 5(F1000 Faculty Rev):1807 (doi: [10.12688/f1000research.8727.1](https://doi.org/10.12688/f1000research.8727.1))

Latest published: 25 Jul 2016, 5(F1000 Faculty Rev):1807 (doi: [10.12688/f1000research.8727.1](https://doi.org/10.12688/f1000research.8727.1))

Abstract

The fidelity of mitosis is essential for life, and successful completion of this process relies on drastic changes in chromosome organization at the onset of nuclear division. The mechanisms that govern chromosome compaction at every cell division cycle are still far from full comprehension, yet recent studies provide novel insights into this problem, challenging classical views on mitotic chromosome assembly. Here, we briefly introduce various models for chromosome assembly and known factors involved in the condensation process (e.g. condensin complexes and topoisomerase II). We will then focus on a few selected studies that have recently brought novel insights into the mysterious way chromosomes are condensed during nuclear division.

Open Peer Review

Referee Status:

	Invited Referees	
	1	2
version 1 <small>published 25 Jul 2016</small>		

F1000 Faculty Reviews are commissioned from members of the prestigious F1000 Faculty. In order to make these reviews as comprehensive and accessible as possible, peer review takes place before publication; the referees are listed below, but their reports are not formally published.

- Frank Uhlmann**, The Francis Crick Institute UK
- Yves Barral**, Institute of Biochemistry Switzerland

Discuss this article

Comments (0)

Corresponding author: Raquel A. Oliveira (rcoliveira@igc.gulbenkian.pt)

How to cite this article: Piskadlo E and Oliveira RA. **Novel insights into mitotic chromosome condensation [version 1; referees: 2 approved]** *F1000Research* 2016, 5(F1000 Faculty Rev):1807 (doi: [10.12688/f1000research.8727.1](https://doi.org/10.12688/f1000research.8727.1))

Copyright: © 2016 Piskadlo E and Oliveira RA. This is an open access article distributed under the terms of the [Creative Commons Attribution Licence](#), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

Grant information: The author(s) declared that no grants were involved in supporting this work.

Competing interests: The authors declare that they have no competing interests.

First published: 25 Jul 2016, 5(F1000 Faculty Rev):1807 (doi: [10.12688/f1000research.8727.1](https://doi.org/10.12688/f1000research.8727.1))

Introduction: why do chromosomes condense during mitosis?

Mitosis was first described in the 19th century and has captivated generations of scientists ever since. This fascinating process comprises the assembly of interphase chromatin into individual chromosomes and subsequently the equal separation of the genetic material between two daughter cells. Mitosis is undoubtedly an extremely complex operation that needs to be conducted and controlled precisely under the penalty of dismantling genome integrity. One of the key steps in mitosis is chromosome condensation – the compaction of the chromatin into well-defined rod-shaped structures (for other recent reviews, see 1–3). This process is cytologically very evident, yet both the internal structure of the mitotic chromosomes and the mechanisms by which this transformation is achieved remain quite elusive. To ensure that cell division is feasible within the cell space, vertebrate cells compact their DNA around 2–3 times more than in interphase, as estimated by chromatin volume measurements^{4,5} and Förster resonance energy transfer (FRET)-based assays between histones⁶. Spatial compaction, however, is not the only important outcome of condensation. The structural reorganization during condensation leads to the separation of the identical sister chromatids from each other (known as sister chromatid resolution). Several topological constraints arise throughout interphase (most notably during DNA replication) that result in the entanglement of the two DNA molecules. The resolution of such intertwinings (i.e. individualization) is

crucial for efficient and faithful chromosome segregation during mitosis. Condensation of chromatin into sturdy chromosomes is also necessary to establish proper physical properties. Chromosomes must be stiff, resilient, and elastic enough to withstand forces coming from pulling microtubules and cytoplasmic drags during mitosis to prevent damage and breaks caused by external tensions.

Despite the utmost importance of chromosome condensation for the fidelity of mitosis, the molecular mechanisms that drive this process remain very unclear. Here we highlight recent findings regarding this process, discussed in the context of different models for mitotic chromosome condensation.

Models for mitotic chromosome architecture

Over the past few decades, detailed characterization of metaphase chromosomes, using different cytological approaches, has led to the proposal of several models for mitotic chromosome assembly (Figure 1).

Classical views on chromosome organization postulate that mitotic chromosomes result from chromatin fiber folding. DuPrav suggested that fiber folding occurs randomly, transversely, and longitudinally, with no intermediate levels of compaction⁷. However, mitotic chromosomes fold into a reproducible structure in every mitosis, at least to some extent. Mitotic chromosomes acquire a

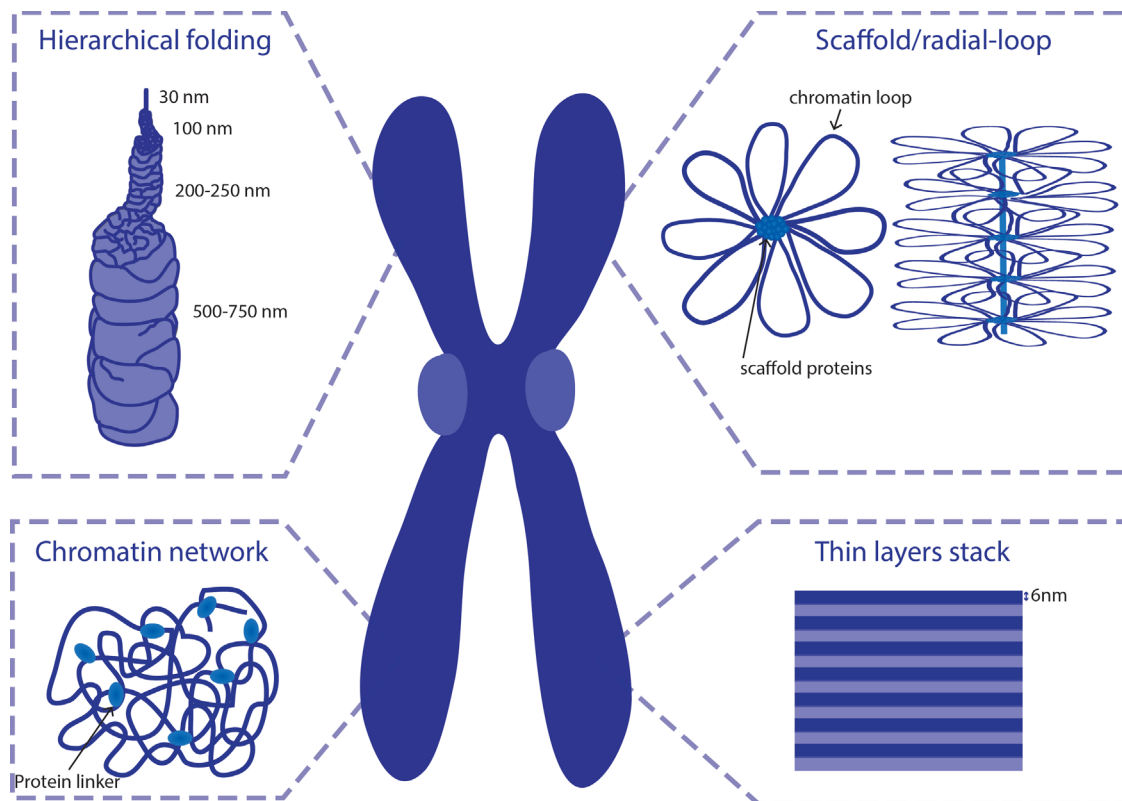


Figure 1. Schematic representation of current models for mitotic chromosome condensation. Adapted from Daban *et al.*²¹

reproducible length and display an invariable signature pattern of bands after staining with specific dyes, such as Giemsa. Moreover, specific DNA sequences occupy a reproducible position along the longitudinal and transverse axes of the chromosome⁸. Although some degree of randomness was observed within chromosomal domains^{9,10}, chromosome assembly cannot be explained as a purely random process.

Alternatively, it has been suggested that metaphase chromosomes result from helical coiling events (helical-coiling model). The nucleo-histone fiber is proposed to be coiled up into a helix, which is hierarchically wound up into larger helices to achieve the compactness of the mitotic chromosome (Figure 1)^{11,12}. This model has been widely accepted, as lower levels of chromatin organization were long postulated to result from hierarchical folding: wrapping of DNA around nucleosomes forms a 11 nm bead-on-a-string structure that coils up into a 30 nm fiber. However, the existence of this 30 nm fiber *in vivo* is yet to be confirmed and has been recently highly debated^{13–15}.

Using electron microscopy (EM) studies, Paulson and Laemmli¹⁶ provided a novel view on chromosome organization. Upon histone removal, chromosomes revealed a scaffold or core that has the shape of intact chromosomes, surrounded by loops of chromatin attached to this central core^{17,18}. These and subsequent studies led to the consolidation of the scaffold/radial-loop model, which argues that radial DNA loops extend out from a protein element or scaffold positioned along the central axis of the chromatid.

In contrast to the scaffold model, analysis of the biophysical properties of mitotic chromosomes has challenged the idea that the continuity of mitotic chromosomes depends on its proteinaceous core. Taking advantage of the highly elastic behavior displayed by mitotic chromosomes, *in vitro* elasticity measurements revealed that the elastic response of mitotic chromosomes is lost after DNA digestion¹⁹. Mild protease treatment, in contrast, does not impair a reversible elastic response despite a progressively reduced force constant^{19,20}. This led to the proposal of the chromatin-network model, in which chromatin itself is proposed to be the mechanical contiguous component of the mitotic chromosome.

More recent ideas for the internal folding of chromosomes suggest that mitotic chromosomes are arranged into stacks of 6 nm layers²¹. Those layers would be perpendicular to the chromosome axis and contain around 1 Mb of consequent DNA. Such arrangement of chromosomes has the advantage of explaining properties of G-bands and the geometry of chromosome translocations in a better way than other models.

Despite the differential contributions for chromatin/protein components within chromosome organization, these models might not be mutually exclusive and stacks, coils, and radial loops may co-exist within a less ordered structure.

Known players of condensation

Despite the several unknowns on the precise molecular details of chromosome assembly, some key components are believed to be crucial for chromosome organization.

Condensins

Condensins are a conserved group of multi-subunit proteins (Figure 2a) fulfilling many roles in chromatin organization throughout the cell cycle, but their most prominent function is to ensure efficient chromosome segregation (reviewed in 22–24). They were first isolated from *Xenopus* egg extract, and immunodepletion studies have suggested that this protein complex is required for proper chromosome condensation *in vitro*^{25,26}. However, subsequent studies have challenged the view for condensin's requirement in chromosome condensation, as chromosomes do condense to a certain degree upon condensin's

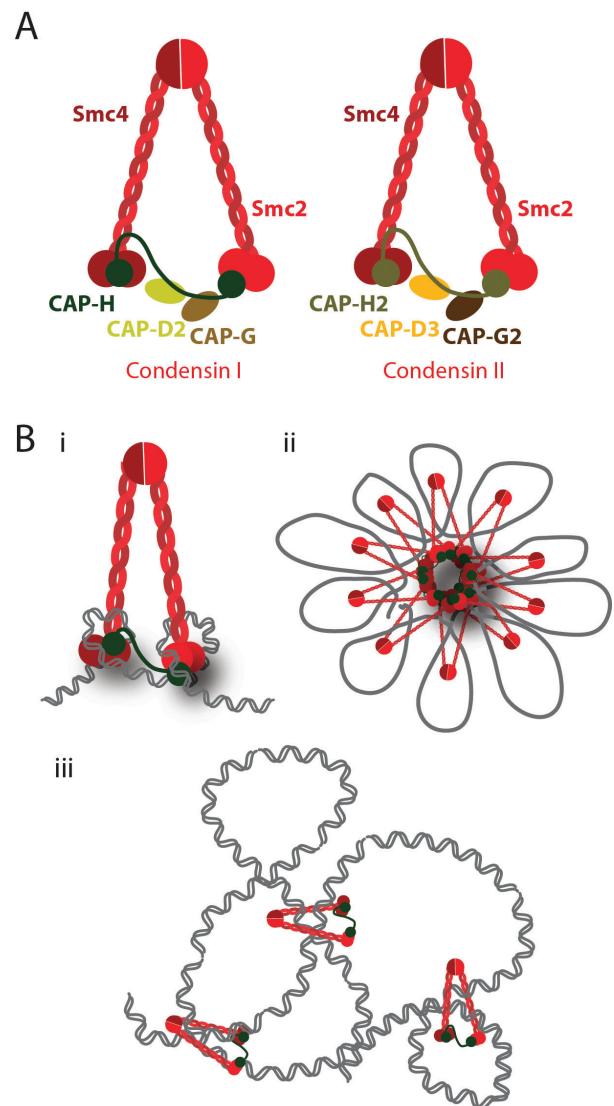


Figure 2. Condensin complexes. **A)** Schematic representation of the structure of condensin complexes. In metazoans, there are two types of condensins, condensin I and condensin II. The SMC2/SMC4 heterodimer is shared by both complexes, while the non-SMC subunits differ: CAP-D2, CAP-G, and CAP-H (Kleisin γ) for condensin I and CAP-D3, CAP-G2, and CAP-H2 (Kleisin β) for condensin II. **B)** Possible models for the condensins' role in DNA compaction include DNA supercoiling, loop-holder, and topological linker.

inactivation in several *in vivo* studies^{27–32}. In addition to chromosome compaction, several studies revealed other roles for condensin in mitotic chromosome organization: maintenance of chromosomal structural integrity^{28,30,33} and resolution of topological DNA entanglements^{27,29–31,33}. Recent studies, using novel protein inactivation tools based on timely proteolytic cleavage of condensin complexes, revealed that condensin complexes (particularly condensin II) are indeed needed to support the structure of assembled meiotic chromosomes³⁴. It should be noted that meiotic chromosomes are very different from their mitotic counterparts, as the mono-orientation of bivalents imposes pulling forces along the entire chromosome length (rather than simply at the pericentromeric regions). Thus, it remains to be addressed if condensins are required for chromosome condensation *per se* or simply to resist mechanical stress.

Importantly, it is yet to be determined how these different functions on chromosome organization are brought about, if they result from differential activities of condensins on mitotic chromatin, or, alternatively, if a single condensin-driven reaction may account for all the reported phenotypes. *In vitro* studies revealed that condensins are able to introduce positive supercoils on circular DNAs^{35,36}, which could account for chromosome compaction. Yet it is not clear if (and how) condensin supercoiling activity is required for *in vivo* chromosome condensation. Condensin subunits are also the major components of the chromosome scaffold^{18,37}, and it has thus been proposed to hold chromatin loops at the central axial core of chromosomes. However, condensin I (but not condensin II) displays a highly dynamic association with mitotic chromosomes^{28,38}, questioning the hypothesis that this complex is statically holding chromatin loops. Recent studies in budding yeast revealed that condensin complexes topologically embrace DNA molecules *in vivo*³⁹, providing strong evidence that condensins may work as an intra-chromosomal linker that brings together two distant segments of one sister chromatid and thereby promotes compaction. Further understanding on how condensin works on mitotic chromosomes is pivotal, not only to uncover the molecular mechanisms of these complexes but also to elucidate chromosome architecture itself.

Topoisomerase II

Topoisomerase II can introduce several changes in the topology of DNA molecules by driving both supercoiling and relaxing of the supercoils, and also the catenation and decatenation of DNA molecules⁴⁰. Although some of these reactions can be brought about by topoisomerase I, only topoisomerase II can promote the resolution of catenated sister-DNA molecules. Topoisomerase II is able to decatenate intertwined DNAs by transiently cutting both strands of a DNA molecule, which are then resealed after passage through another DNA duplex (Figure 3). It is therefore essential for sister chromatid resolution and their efficient separation at the end of mitosis. Topoisomerase II is also a major component of the chromosome scaffold⁴¹, and it has long been debatable whether or not this enzyme promotes chromosome compaction in addition (or in parallel) to sister chromatid resolution.

Topoisomerase II was reported to be dispensable for chromosome condensation in some model organisms (*Saccharomyces cerevisiae*³², *Xenopus laevis*⁴², and human cells⁴³). Nevertheless,

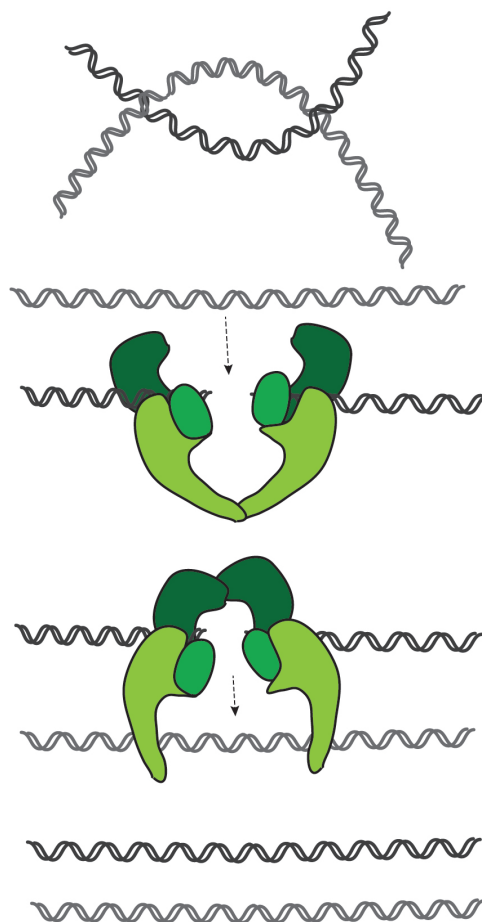


Figure 3. Topoisomerase II: DNA decatenation reaction driven by topoisomerase II. This enzyme cuts both strands of a DNA duplex and allows strand passage of a second duplex through the break. After strand passage, topoisomerase seals the break and releases both strands. It can thus promote the resolution of intertwines (catenations) between sister DNA molecules.

other studies provide evidence that topoisomerase II is necessary or at least contributes to establishing proper condensation and chromosome structure in *Schizosaccharomyces pombe*^{44,45}, *S. cerevisiae*⁴⁶, *X. laevis*^{47,48}, *Drosophila melanogaster*⁴⁹, chicken⁵⁰, hamster⁵¹, or human^{52,53} cells. How exactly topoisomerase II could facilitate condensation, however, remains unclear.

Interplay between condensin I and topoisomerase II

Both condensin I and topoisomerase II localize to the central axis of mitotic chromosomes^{54,55} and both complexes have the ability to alter DNA topology. Thus, it has been speculated that these proteins may cooperate (directly or indirectly) in establishing chromosome compaction and organization. Condensin I was initially proposed to directly interact with topoisomerase II²⁶, but later studies failed to provide evidence for a physical interaction between these proteins^{26,47,57}. Nonetheless, depletion of condensins causes delocalization of topoisomerase II from the chromosome axis and decreases its decatenation activity⁵⁴. Recent evidence further

supports the notion that during anaphase, topoisomerase is recruited to chromosome arms in a condensin-dependent manner⁵⁸.

Importantly, topoisomerase II was shown to be particularly efficient in decatenating (unlinking) supercoiled DNA molecules⁵⁹. Given the condensins' ability to introduce positive supercoiling, it has been proposed that the topology generated by condensin I could be attracting topoisomerase II in order to drive global decatenation⁵⁹. This notion is further supported by studies that measure the efficiency of decatenation of circular mini-chromosomes *in vivo*, revealing that condensin promotes DNA decatenation⁵⁷.

In contrast to the cooperation model, other studies support the idea that condensins and topoisomerase II may have antagonistic roles in chromosome assembly. Condensins were proposed to drive lateral compaction, while topoisomerase II was suggested to induce axial compaction^{50,60}. The question of how condensins and topoisomerase II are able to cause directional compaction within separate sister chromatids without creating new links within individual sister chromatids and tangling them together remains.

Kif4

Kif4 is a motor protein able to bind to mitotic chromosomes. Studies in vertebrate cells reveal that Kif4 contributes to the establishment of a correct morphology and structure of chromosomes^{50,61}. It is proposed to cooperate or work alongside condensin in shortening the lateral axis of chromosomes, possibly by creating loops of chromatin⁵⁰, although little is known about the molecular mechanisms in this process.

Histone modifications

During mitosis and concomitantly with chromosome condensation, the landscape of histone modifications is altered. Histone H1, the linker histone, is hyper-phosphorylated during mitosis^{62,63}, and it was initially thought to directly participate in condensation. However, subsequent studies suggest that histone H1 phosphorylation is not necessary for condensation^{64,65} but nevertheless changes the overall chromatin structure^{66,67}. Another key mitotic histone modification is the phosphorylation of serine 10 residue of histone 3 (H3 S10) by the mitotic kinase Aurora B⁶⁸. The role for this modification in chromosome condensation has also been controversial⁶⁹⁻⁷¹, although recent evidence proposes that it drives the recruitment of deacetylase Hst2, which, in turn, induces deacetylation of lysine 16 of histone 4. This change in the properties of the histone 4 tail promotes interaction with histones H2A and H2B from other nucleosomes⁷², thereby shortening the distance between neighboring nucleosomes. This would thus support the notion that histone modifications alone can promote the condensation of chromosomes. It should be noted that several histones and histone modifications were also described to be a chromosomal "receptor" for condensin binding⁷³⁻⁷⁶. Thus, some histone modifications may not be a direct contributor for chromosome compaction but rather a facilitator by promoting the binding of specialized proteins that model DNA topology.

New insights from novel approaches

Chromosome condensation revealed by high-resolution imaging and novel quantification methods

The chromosome condensation field has been largely dominated by cytological analysis. Yet, only recently, and with the advances in imaging and imaging analysis techniques, the field has started to adopt sophisticated quantification methods to estimate changes in chromosome structure during mitosis, revealing not only the compaction state but also the kinetics of the process.

Although chromosome condensation was often thought of as a linear and gradual process, a new study suggests that in the early mitosis stages, chromosomes undergo a series of subtle compaction and expansion steps⁷⁷. The authors applied a series of sophisticated imaging and image analysis methods to describe changes in condensation throughout mitosis. Until mid-prophase chromosomes compact, but at late prophase stages their morphology changes and they expand at the same time sister chromatids are being individualized. This is followed by another compaction phase during prometaphase and metaphase. These observations were anticipated by a theoretical model of condensation that predicted this compaction-expansion cycle⁷⁸. This hypothesis assumes that compaction is causing more "stress" to chromatin, as tethering segments together induces constraints and accumulates higher potential energy. The expansion stage, therefore, releases such stress and lowers the potential energy of chromosomes. The mentioned tethers causing physical constraints could be of various natures, such as protein linkers (cohesin, condensins) or DNA catenations. The authors propose that the stress cycle is ensuring the usage of the energy stored during the early compaction events for the energy-consuming drastic changes in chromosome structure, such as individualization of sister chromatids in late prophase. A recent study, however, revealed that the resolution of sister chromatids starts early during prophase, concomitantly with chromosome compaction⁷⁹. The authors used sequential replication labeling with two distinct nucleotide derivatives to differentially label each DNA strand, which combined with quantitative advanced imaging allowed the assessment of the resolution process with unprecedented temporal resolution. Thus, the aforementioned compaction-expansion cycles may not necessarily correlate with differential processes throughout prophase.

In addition to the estimation of global compaction on entire chromosomes, recent quantitative microscopic assays were developed to assess local compaction⁸⁰. Using a fluorescent reporter to target specific loci, this study reveals that the fluorescence intensity of the reporter varies depending on the compaction stage of chromosomes – the fluorescence is 2–2.5 times higher when chromatin is less compacted (interphase) than in mitotic, condensed chromosomes. This intensity variation was caused by quenching of bound fluorophore due to changes in the local environment created by packed chromosomes. The drop in fluorescence of reporters disappears if interactions between H2A and H4 histones are abolished, suggesting that the assay is primarily sensitive to

compaction at the level of neighboring nucleosomes. Therefore, it provides a convenient tool to study short-range condensation. Combining two different reporter genes along arms of a chromosome, it was possible to trace at the same time the axial (long-range) contraction of chromosomes along their longitudinal axis (distance between the reporter loci) and the short-range compaction of the marked regions. Remarkably, short-range and axial compaction have different kinetics during mitosis. In anaphase, short-range nucleosome-nucleosome compaction is happening before the axial decrease of chromosome length. Moreover, condensin depletion does not affect short-range compaction and, conversely, disturbing nucleosome-nucleosome interaction does not affect axial contraction. This led to the conclusion that short-range compaction and axial contraction are probably mostly independent and governed by different mechanisms. A common factor in both pathways is Hst2 deacetylase. By regulating H2A–H4 interaction, Hst2 promotes short-range nucleosome-nucleosome interactions and compaction. Additionally, Hst2 was shown to contribute to axial contraction by promoting condensin activity. This study proves that obtaining accurate quantification of microscopic data is very often challenging but can lead to novel discoveries.

The minimal chromosome assembly system revealed by *in vitro* approaches

In vitro studies have brought major insights into many fields of biology. Separation of biological components into a controlled artificial environment with less complexity allows simpler and more precise interpretation of data. It is undeniably true that the *in vitro* results cannot be always directly translated back to the *in vivo* situation. Nevertheless, once the component or process (like chromosome condensation) is studied in the *in vitro* environment, it is easier to understand it in the *in vivo* context.

A breakthrough towards this idea was the identification of the minimal set of components that allows *in vitro* formation of a mitotic structure from uncondensed DNA in *Xenopus* egg extracts⁴⁸. This reductionist approach demonstrated that out of thousands of possible proteins present in metaphase extract, only six factors, when combined, are sufficient to drive effective condensation. In addition to the “usual suspects” condensins and topoisomerase II, painstaking selection of other critical components further reveals the requirement of four other factors: nucleoplasmin, Nap1, and FACT (all of them are histone chaperone proteins) and embryonic core histones. In addition, the process was shown to be ATP dependent, which is necessary for enzymatic actions of condensins and topoisomerase II. This unique approach holds the promise of providing important insights into chromosome condensation by *in vitro* perturbations.

Lessons from studies on isolated chromosomes

Isolated entire chromosomes can be micromanipulated and subjected to measurements of their mechanical properties. This approach, pioneered using large newt chromosomes^{19,20,81,82}, allows a direct measurement of the physical characteristics of chromosomes. Chromosomes can be assessed for their elastic properties in various conditions by stretching them and determining the force needed to double the chromosomal length. A major recent advance was the ability to perform similar studies on much smaller human

chromosomes⁸³. Importantly, most of the prior observations were confirmed in human chromosomes, further supporting the idea that a scaffold of protein crosslinkers is not necessary to keep chromosome structure together, which is instead sustained by a network of intertwined DNA. Yet the absence of these “modulating proteins” leads to significant changes in the properties and morphology of this chromosome network.

Another *in vitro* approach has also been recently used to understand the roles of DNA catenation in human mitotic chromosomes⁸⁴. DNA catenations have long been speculated to be critical in mitotic chromosome structure, yet measuring DNA catenation *in vivo* has been a virtually impossible task. To test this, the authors used metaphase chromosomes isolated from human cells placed in a microfluidics lab-on-chip system, which allowed simultaneous imaging and environment control. When native metaphase chromosomes were treated with proteinase to remove all proteins, the resulting digested chromosomes were then challenged with various physical obstacles. The chromosomes preserved their canonical X-like shape and sister chromatids are kept together by thin DNA fibers in the centromeric region. Importantly, disrupting catenations, by chemical inhibition of topoisomerase II, caused drastic morphological changes along the entire length of the chromosome. Without functional topoisomerase II, the chromosomes become decondensed (elongated and rounded) and with less-defined axes along the arms. This led to the proposal that DNA catenation networks provided by topoisomerase II activity are crucial to maintain chromosome structure not only at the centromeres but also along the entire length of chromosome arms. It nevertheless remains to be determined if the same holds true *in vivo*, as it is possible that the *in vitro* manipulations may alone contribute to the observed phenotype.

Internal chromosomal linkages revealed by Chromosome Conformation Capture methods

During interphase, chromosomes have their characteristic patterns of physical interactions of distinct regions within a single chromosome. It was recently shown in an elegant way that for the mitotic chromosome it does not really matter how it was previously folded during interphase⁸⁵. When cells enter mitosis, each chromosome is somehow stripped of its interphase physical contact frequency pattern and acquires a homologous physical interaction pattern throughout its entire length (no compartmentalization of interaction within itself, meaning that only short-distance interactions occur). This absence of compartmentalization in mitotic chromosomes seems to be similar in all chromosomes, regardless of the chromosome identity or the cell type. The observed interaction map was confronted with models describing the folding, dynamics, and internal organization of mitotic chromosomes. Among others, it tackles the hierarchical model of packing DNA into chromosome structure and also a long-debated existence of internal scaffold in mitotic chromosomes. The authors argue that their experimental data do not fit with hierarchical folding models while models based on the existence of 80–120 kb long loops stay with the agreement with experimental work. Unfortunately, the authors were not able to anticipate whether or not chromosome structure contains a stiff scaffold around which chromatin is organized. A model in which the folding of interphase chromatin occurs in a two-step process, nevertheless, better explains their

findings. First, linear compaction occurs by creating loops of consecutive regions of the DNA of length 80–120 kb, possibly with the help of SMC complexes. The second step would be consequent axial compaction achieved by interactions of neighboring loops. It needs to be further supplemented with more detailed description of how this transition from interphase to mitotic chromosomes could be conducted inside living cells.

Biophysical modeling combined with interaction mapping has also been recently applied to study chromosome condensation in budding yeast⁸⁶. A computational model was built to simulate the behavior of a large DNA piece (300 kb). The chromatin was modeled as a bead-spring polymer, in which beads (nucleosome) are connected by springs (the DNA linkers between nucleosomes). Such a defined nucleosome chain was subjected to basic physics laws (Hooke's law, Brownian movements, and others) without any additional *a priori* constraints. Simulations, further validated by *in vivo* measurements of loci proximity, indicate that yeast interphase chromatin behaves as an unconstrained nucleosome polymer. Addition of condensins (as stochastic intra-chromosomal linkers) promotes compaction of this array. Importantly, by modeling different modes for condensin binding, either connecting only two chromosomal regions or allowing interactions of two or three condensin-binding sites, the authors found that the binding of two (and no more) chromosomal regions reproduces the interaction maps found experimentally in mitotic cells. Moreover, these dynamic pair-wise interactions, in contrast to the attachment of more than two binding sites, were capable of promoting individualization of two separate DNA molecules by favoring intra-chromosomal interactions. Thus, this study further supports the notion that chromosomes may be assembled through a chromatin self-organization process,

constrained by condensin interactions, rather than organized by higher order assemblies of condensin complexes within chromosomes.

Conclusions and future perspectives

Mitotic chromosome condensation remains one of the greatest mysteries in cell biology. Recent advances in the field start to shed light onto this problem, although it is fair to assume that we are still far from understanding the rules that govern mitotic chromosome assembly. Nevertheless, recent advances to dissect metaphase chromosome compaction fail to provide solid evidence for classical models of hierarchical folding or rigid protein scaffolds at the core of chromosome assembly. A multidisciplinary perspective of the problem, combining advanced imaging with *in vivo* and *in vitro* controlled manipulations, along with biophysical studies and modeling may in the future provide an integrative view to understand how chromosomes fold at the onset of every cell division process.

Competing interests

The authors declare that they have no competing interests.


Grant information

The author(s) declared that no grants were involved in supporting this work.

Acknowledgements

We would like to thank all the members of the Oliveira lab for constructive comments on this review. We apologize to those whose work we have not cited here, owing to space constraints.

References

- Kschonsak M, Haering CH: **Shaping mitotic chromosomes: From classical concepts to molecular mechanisms.** *Bioessays*. 2015; **37**(7): 755–66.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
- Vagnarelli P: **Mitotic chromosome condensation in vertebrates.** *Exp Cell Res*. 2012; **318**(12): 1435–41.
[PubMed Abstract](#) | [Publisher Full Text](#)
- Antonin W, Neumann H: **Chromosome condensation and decondensation during mitosis.** *Curr Opin Cell Biol*. 2016; **40**: 15–22.
[PubMed Abstract](#) | [Publisher Full Text](#)
- Martin RM, Cardoso MC: **Chromatin condensation modulates access and binding of nuclear proteins.** *FASEB J*. 2010; **24**(4): 1066–72.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
- Mora-Bermúdez F, Gerlich D, Ellenberg J: **Maximal chromosome compaction occurs by axial shortening in anaphase and depends on Aurora kinase.** *Nat Cell Biol*. 2007; **9**(7): 822–31.
[PubMed Abstract](#) | [Publisher Full Text](#)
-  Lières D, James J, Swift S, *et al.*: **Quantitative analysis of chromatin compaction in living cells using FLIM-FRET.** *J Cell Biol*. 2009; **187**(4): 481–96.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | **F1000 Recommendation**
- DuPraw EJ: **Evidence for a 'folded-fibre' organization in human chromosomes.** *Nature*. 1966; **209**(5023): 577–81.
[PubMed Abstract](#) | [Publisher Full Text](#)
- Baumgartner M, Dutrillaux B, Lemieux N, *et al.*: **Genes occupy a fixed and symmetrical position on sister chromatids.** *Cell*. 1991; **64**(4): 761–6.
[PubMed Abstract](#) | [Publisher Full Text](#)
- Dietzel S, Belmont AS: **Reproducible but dynamic positioning of DNA in chromosomes during mitosis.** *Nat Cell Biol*. 2001; **3**(8): 767–70.
[PubMed Abstract](#) | [Publisher Full Text](#)
- Strukov YG, Belmont AS: **Mitotic chromosome structure: reproducibility of folding and symmetry between sister chromatids.** *Biophys J*. 2009; **96**(4): 1617–28.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
- Sedat J, Manuelidis L: **A direct approach to the structure of eukaryotic chromosomes.** *Cold Spring Harb Symp Quant Biol*. 1978; **42**(Pt 1): 331–50.
[PubMed Abstract](#) | [Publisher Full Text](#)
- Belmont AS, Sedat JW, Agard DA: **A three-dimensional approach to mitotic chromosome structure: evidence for a complex hierarchical organization.** *J Cell Biol*. 1987; **105**(1): 77–92.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
- Maeshima K, Hihara S, Takata H: **New insight into the mitotic chromosome structure: irregular folding of nucleosome fibers without 30-nm chromatin structure.** *Cold Spring Harb Symp Quant Biol*. 2010; **75**: 439–44.
[PubMed Abstract](#) | [Publisher Full Text](#)
- Joti Y, Hikima T, Nishino Y, *et al.*: **Chromosomes without a 30-nm chromatin fiber.** *Nucleus*. 2012; **3**(5): 404–10.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
- Razin SV, Gavrilov AA: **Chromatin without the 30-nm fiber: constrained disorder instead of hierarchical folding.** *Epigenetics*. 2014; **9**(5): 653–7.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
- Paulson JR, Laemmli UK: **The structure of histone-depleted metaphase chromosomes.** *Cell*. 1977; **12**(3): 817–28.
[PubMed Abstract](#) | [Publisher Full Text](#)
- Adolph KW, Cheng SM, Laemmli UK: **Role of nonhistone proteins in metaphase**



- chromosome structure. *Cell*. 1977; 12(3): 805–16.
[PubMed Abstract](#) | [Publisher Full Text](#)
18. Earnshaw WC, Laemmli UK: **Architecture of metaphase chromosomes and chromosome scaffolds.** *J Cell Biol*. 1983; 96(1): 84–93.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
 19. **F** Poirier MG, Marko JF: **Mitotic chromosomes are chromatin networks without a mechanically contiguous protein scaffold.** *Proc Natl Acad Sci U S A*. 2002; 99(24): 15393–7.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
 20. Pope LH, Xiong C, Marko JF: **Proteolysis of mitotic chromosomes induces gradual and anisotropic decondensation correlated with a reduction of elastic modulus and structural sensitivity to rarely cutting restriction enzymes.** *Mol Biol Cell*. 2006; 17(1): 104–13.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
 21. **F** Daban JR: **Stacked thin layers of metaphase chromatin explain the geometry of chromosome rearrangements and banding.** *Sci Rep*. 2015; 5: 14891.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
 22. Hirano T: **Condensins: universal organizers of chromosomes with diverse functions.** *Genes Dev*. 2012; 26(15): 1659–78.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
 23. Piazza I, Haering CH, Rutkowska A: **Condensin: crafting the chromosome landscape.** *Chromosoma*. 2013; 122(3): 175–90.
[PubMed Abstract](#) | [Publisher Full Text](#)
 24. Hirano T: **Condensin-Based Chromosome Organization from Bacteria to Vertebrates.** *Cell*. 2016; 164(5): 847–57.
[PubMed Abstract](#) | [Publisher Full Text](#)
 25. Hirano T, Mitchison TJ: **A heterodimeric coiled-coil protein required for mitotic chromosome condensation *in vitro*.** *Cell*. 1994; 79(3): 449–58.
[PubMed Abstract](#) | [Publisher Full Text](#)
 26. Hirano T, Kobayashi R, Hirano M: **Condensins, chromosome condensation protein complexes containing XCAP-C, XCAP-E and a Xenopus homolog of the Drosophila Barren protein.** *Cell*. 1997; 89(4): 511–21.
[PubMed Abstract](#) | [Publisher Full Text](#)
 27. **F** Hudson DF, Vagnarelli P, Gassmann R, *et al.*: **Condensin is required for nonhistone protein assembly and structural integrity of vertebrate mitotic chromosomes.** *Dev Cell*. 2003; 5(2): 323–36.
[PubMed Abstract](#) | [Publisher Full Text](#) | [F1000 Recommendation](#)
 28. Gerlich D, Hirota T, Koch B, *et al.*: **Condensin I stabilizes chromosomes mechanically through a dynamic interaction in live cells.** *Curr Biol*. 2006; 16(4): 333–44.
[PubMed Abstract](#) | [Publisher Full Text](#)
 29. Steffensen S, Coelho PA, Cobbe N, *et al.*: **A role for Drosophila SMC4 in the resolution of sister chromatids in mitosis.** *Curr Biol*. 2001; 11(5): 295–307.
[PubMed Abstract](#) | [Publisher Full Text](#)
 30. Oliveira RA, Coelho PA, Sunkel CE: **The condensin I subunit Barren/CAP-H is essential for the structural integrity of centromeric heterochromatin during mitosis.** *Mol Cell Biol*. 2005; 25(20): 8971–84.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
 31. **F** Hagstrom KA, Holmes VF, Cozzarelli NR, *et al.*: **C. elegans condensin promotes mitotic chromosome architecture, centromere organization, and sister chromatid segregation during mitosis and meiosis.** *Genes Dev*. 2002; 16(6): 729–42.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
 32. Lavoie BD, Hogan E, Koshland D: ***In vivo* dissection of the chromosome condensation machinery: reversibility of condensation distinguishes contributions of condensin and cohesin.** *J Cell Biol*. 2002; 156(5): 805–15.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
 33. Ribeiro SA, Gatlin JC, Dong Y, *et al.*: **Condensin regulates the stiffness of vertebrate centromeres.** *Mol Biol Cell*. 2009; 20(9): 2371–80.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
 34. **F** Houlard M, Godwin J, Metson J, *et al.*: **Condensin confers the longitudinal rigidity of chromosomes.** *Nat Cell Biol*. 2015; 17(6): 771–81.
[PubMed Abstract](#) | [Publisher Full Text](#) | [F1000 Recommendation](#)
 35. Kimura K, Hirano T: **ATP-dependent positive supercoiling of DNA by 13S condensin: a biochemical implication for chromosome condensation.** *Cell*. 1997; 90(4): 625–34.
[PubMed Abstract](#) | [Publisher Full Text](#)
 36. Kimura K, Hirano T: **Dual roles of the 11S regulatory subcomplex in condensin functions.** *Proc Natl Acad Sci U S A*. 2000; 97(22): 11972–7.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
 37. Lewis CD, Laemmli UK: **Higher order metaphase chromosome structure: evidence for metalloprotein interactions.** *Cell*. 1982; 29(1): 171–81.
[PubMed Abstract](#) | [Publisher Full Text](#)
 38. Oliveira RA, Heidmann S, Sunkel CE: **Condensin I binds chromatin early in prophase and displays a highly dynamic association with Drosophila mitotic chromosomes.** *Chromosoma*. 2007; 116(3): 259–74.
[PubMed Abstract](#) | [Publisher Full Text](#)
 39. **F** Cuylen S, Metz J, Haering CH: **Condensin structures chromosomal DNA through topological links.** *Nat Struct Mol Biol*. 2011; 18(8): 894–901.
[PubMed Abstract](#) | [Publisher Full Text](#) | [F1000 Recommendation](#)
 40. Schoeffler AJ, Berger JM: **Recent advances in understanding structure-function relationships in the type II topoisomerase mechanism.** *Biochem Soc Trans*. 2005; 33(Pt 6): 1465–70.
[PubMed Abstract](#) | [Publisher Full Text](#)
 41. Earnshaw WC, Halligan B, Cooke CA, *et al.*: **Topoisomerase II is a structural component of mitotic chromosome scaffolds.** *J Cell Biol*. 1985; 100(5): 1706–15.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
 42. Wood ER, Earnshaw WC: **Mitotic chromatin condensation *in vitro* using somatic cell extracts and nuclei with variable levels of endogenous topoisomerase II.** *J Cell Biol*. 1990; 111(6 Pt 2): 2839–50.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
 43. Carpenter AJ, Porter AC: **Construction, characterization, and complementation of a conditional-lethal DNA topoisomerase IIalpha mutant human cell line.** *Mol Biol Cell*. 2004; 15(12): 5700–11.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
 44. Uemura T, Ohkura H, Adachi Y, *et al.*: **DNA topoisomerase II is required for condensation and separation of mitotic chromosomes in *S. pombe*.** *Cell*. 1987; 50(6): 917–25.
[PubMed Abstract](#) | [Publisher Full Text](#)
 45. **F** Petrova B, Dehler S, Kruitwagen T, *et al.*: **Quantitative analysis of chromosome condensation in fission yeast.** *Mol Cell Biol*. 2013; 33(5): 984–98.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
 46. Vas AC, Andrews CA, Kirkland Matesky K, *et al.*: ***In vivo* analysis of chromosome condensation in Saccharomyces cerevisiae.** *Mol Biol Cell*. 2007; 18(2): 557–68.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
 47. Cuvier O, Hirano T: **A role of topoisomerase II in linking DNA replication to chromosome condensation.** *J Cell Biol*. 2003; 160(5): 645–55.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
 48. **F** Shintomi K, Takahashi TS, Hirano T: **Reconstitution of mitotic chromatids with a minimum set of purified factors.** *Nat Cell Biol*. 2015; 17(8): 1014–23.
[PubMed Abstract](#) | [Publisher Full Text](#) | [F1000 Recommendation](#)
 49. Buchenau P, Saumweber H, Arndt-Jovin DJ: **Consequences of topoisomerase II inhibition in early embryogenesis of Drosophila revealed by *in vivo* confocal laser scanning microscopy.** *J Cell Sci*. 1993; 104(Pt 4): 1175–85.
[PubMed Abstract](#)
 50. **F** Samejima K, Samejima I, Vagnarelli P, *et al.*: **Mitotic chromosomes are compacted laterally by KIF4 and condensin and axially by topoisomerase IIa.** *J Cell Biol*. 2012; 199(5): 755–70.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
 51. Anderson H, Roberge M: **Topoisomerase II inhibitors affect entry into mitosis and chromosome condensation in BHK cells.** *Cell Growth Differ*. 1996; 7(1): 83–90.
[PubMed Abstract](#)
 52. Sakaguchi A, Kikuchi A: **Functional compatibility between isoform alpha and beta of type II DNA topoisomerase.** *J Cell Sci*. 2004; 117(Pt 7): 1047–54.
[PubMed Abstract](#) | [Publisher Full Text](#)
 53. Gonzalez RE, Lim CU, Cole K, *et al.*: **Effects of conditional depletion of topoisomerase II on cell cycle progression in mammalian cells.** *Cell Cycle*. 2011; 10(20): 3505–14.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
 54. **F** Coelho PA, Queiroz-Machado J, Sunkel CE: **Condensin-dependent localisation of topoisomerase II to an axial chromosomal structure is required for sister chromatid resolution during mitosis.** *J Cell Sci*. 2003; 116(Pt 23): 4763–76.
[PubMed Abstract](#) | [Publisher Full Text](#) | [F1000 Recommendation](#)
 55. **F** Maeshima K, Laemmli UK: **A two-step scaffolding model for mitotic chromosome assembly.** *Dev Cell*. 2003; 4(4): 467–80.
[PubMed Abstract](#) | [Publisher Full Text](#) | [F1000 Recommendation](#)
 56. Bhat MA, Philp AV, Glover DM, *et al.*: **Chromatid segregation at anaphase requires the barren product, a novel chromosome-associated protein that interacts with Topoisomerase II.** *Cell*. 1996; 87(6): 1103–14.
[PubMed Abstract](#) | [Publisher Full Text](#)
 57. **F** Charbin A, Bouchoux C, Uhlmann F: **Condensin aids sister chromatid decatenation by topoisomerase II.** *Nucleic Acids Res*. 2014; 42(1): 340–8.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
 58. Leonard J, Sen N, Torres R, *et al.*: **Condensin Relocalization from Centromeres to Chromosome Arms Promotes Top2 Recruitment during Anaphase.** *Cell Rep*. 2015; 13(11): 2336–44.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
 59. **F** Baxter J, Sen N, Martinez VL, *et al.*: **Positive supercoiling of mitotic DNA drives decatenation by topoisomerase II in eukaryotes.** *Science*. 2011; 331(6022): 1328–32.
[PubMed Abstract](#) | [Publisher Full Text](#) | [F1000 Recommendation](#)
 60. Shintomi K, Hirano T: **The relative ratio of condensin I to II determines chromosome shapes.** *Genes Dev*. 2011; 25(14): 1464–9.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
 61. **F** Mazumdar M, Sundareshan S, Misteli T: **Human chromokinesin KIF4A functions in chromosome condensation and segregation.** *J Cell Biol*. 2004; 166(5): 613–20.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
 62. Fischer SG, Laemmli UK: **Cell cycle changes in Physarum polycephalum histone H1 phosphate: relationship to deoxyribonucleic acid binding and**

- chromosome condensation.** *Biochemistry*. 1980; **19**(10): 2240–6.
[PubMed Abstract](#) | [Publisher Full Text](#)
63. Boggs BA, Allis CD, Chinault AC: **Immunofluorescent studies of human chromosomes with antibodies against phosphorylated H1 histone.** *Chromosoma*. 2000; **108**(8): 485–90.
[PubMed Abstract](#) | [Publisher Full Text](#)
64. Guo XW, Th'ng JP, Swank RA, *et al.*: **Chromosome condensation induced by fostriecin does not require p34cdc2 kinase activity and histone H1 hyperphosphorylation, but is associated with enhanced histone H2A and H3 phosphorylation.** *EMBO J*. 1995; **14**(5): 976–85.
[PubMed Abstract](#) | [Free Full Text](#)
65. Shen X, Yu L, Weir JW, *et al.*: **Linker histones are not essential and affect chromatin condensation *in vivo*.** *Cell*. 1995; **82**(1): 47–56.
[PubMed Abstract](#) | [Publisher Full Text](#)
66. Maresca TJ, Freedman BS, Heald R: **Histone H1 is essential for mitotic chromosome architecture and segregation in *Xenopus laevis* egg extracts.** *J Cell Biol*. 2005; **169**(6): 859–69.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
67. **F** Fan Y, Nikitina T, Zhao J, *et al.*: **Histone H1 depletion in mammals alters global chromatin structure but causes specific changes in gene regulation.** *Cell*. 2005; **123**(7): 1199–212.
[PubMed Abstract](#) | [Publisher Full Text](#) | [F1000 Recommendation](#)
68. Hendzel MJ, Wei Y, Mancini MA, *et al.*: **Mitosis-specific phosphorylation of histone H3 initiates primarily within pericentromeric heterochromatin during G2 and spreads in an ordered fashion coincident with mitotic chromosome condensation.** *Chromosoma*. 1997; **106**(6): 348–60.
[PubMed Abstract](#) | [Publisher Full Text](#)
69. van Hooser A, Goodrich DW, Allis CD, *et al.*: **Histone H3 phosphorylation is required for the initiation, but not maintenance, of mammalian chromosome condensation.** *J Cell Sci*. 1998; **111**(Pt 23): 3497–506.
[PubMed Abstract](#)
70. Wei Y, Yu L, Bowen J, *et al.*: **Phosphorylation of histone H3 is required for proper chromosome condensation and segregation.** *Cell*. 1999; **97**(1): 99–109.
[PubMed Abstract](#) | [Publisher Full Text](#)
71. Hsu JY, Sun ZW, Li X, *et al.*: **Mitotic phosphorylation of histone H3 is governed by Ipl1/aurora kinase and Glc7/PP1 phosphatase in budding yeast and nematodes.** *Cell*. 2000; **102**(3): 279–91.
[PubMed Abstract](#) | [Publisher Full Text](#)
72. **F** Wilkins BJ, Rall NA, Ostwal Y, *et al.*: **A cascade of histone modifications induces chromatin condensation in mitosis.** *Science*. 2014; **343**(6166): 77–80.
[PubMed Abstract](#) | [Publisher Full Text](#) | [F1000 Recommendation](#)
73. Ball AR Jr, Schmiesing JA, Zhou C, *et al.*: **Identification of a chromosome-targeting domain in the human condensin subunit CNAP1/hCAP-D2/Eg7.** *Mol Cell Biol*. 2002; **22**(16): 5769–81.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
74. Kim H, Vanoosthuysen V, Fillingham J, *et al.*: **An acetylated form of histone H2A. Z regulates chromosome architecture in *Schizosaccharomyces pombe*.** *Nat Struct Mol Biol*. 2009; **16**(12): 1286–93.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
75. Liu W, Tanasa B, Tyurina OV, *et al.*: **PHF8 mediates histone H4 lysine 20 demethylation events involved in cell cycle progression.** *Nature*. 2010; **466**(7305): 508–12.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
76. Tada K, Susumu H, Sakuno T, *et al.*: **Condensin association with histone H2A shapes mitotic chromosomes.** *Nature*. 2011; **474**(7352): 477–83.
[PubMed Abstract](#) | [Publisher Full Text](#)
77. **F** Liang Z, Zickler D, Prentiss M, *et al.*: **Chromosomes Progress to Metaphase in Multiple Discrete Steps via Global Compaction/Expansion Cycles.** *Cell*. 2015; **161**(5): 1124–37.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
78. Kleckner N, Zickler D, Jones GH, *et al.*: **A mechanical basis for chromosome function.** *Proc Natl Acad Sci U S A*. 2004; **101**(34): 12592–7.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
79. **F** Nagasaka K, Hossain MJ, Roberti MJ, *et al.*: **Sister chromatid resolution is an intrinsic part of chromosome organization in prophase.** *Nat Cell Biol*. 2016; **18**(6): 692–9.
[PubMed Abstract](#) | [Publisher Full Text](#) | [F1000 Recommendation](#)
80. **F** Kruitwagen T, Denoth-Lippuner A, Wilkins BJ, *et al.*: **Axial contraction and short-range compaction of chromatin synergistically promote mitotic chromosome condensation.** *eLife*. 2015; **4**: e10396.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
81. Poirier M, Eroglu S, Chatenay D, *et al.*: **Reversible and irreversible unfolding of mitotic newt chromosomes by applied force.** *Mol Biol Cell*. 2000; **11**(1): 269–76.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
82. Poirier MG, Eroglu S, Marko JF: **The bending rigidity of mitotic chromosomes.** *Mol Biol Cell*. 2002; **13**(6): 2170–9.
[PubMed Abstract](#) | [Free Full Text](#)
83. Sun M, Kawamura R, Marko JF: **Micromechanics of human mitotic chromosomes.** *Phys Biol*. 2011; **8**(1): 15003.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
84. Bauer DL, Marie R, Rasmussen KH, *et al.*: **DNA catenation maintains structure of human metaphase chromosomes.** *Nucleic Acids Res*. 2012; **40**(22): 11428–34.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
85. **F** Naumova N, Imakaev M, Fudenberg G, *et al.*: **Organization of the mitotic chromosome.** *Science*. 2013; **342**(6161): 948–53.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
86. **F** Cheng TM, Heeger S, Chaleil RA, *et al.*: **A simple biophysical model emulates budding yeast chromosome condensation.** *eLife*. 2015; **4**: e05565.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)

Open Peer Review

Current Referee Status:



Editorial Note on the Review Process

F1000 Faculty Reviews are commissioned from members of the prestigious F1000 Faculty and are edited as a service to readers. In order to make these reviews as comprehensive and accessible as possible, the referees provide input before publication and only the final, revised version is published. The referees who approved the final version are listed with their names and affiliations but without their reports on earlier versions (any comments will already have been addressed in the published version).

The referees who approved this article are:

Version 1

- 1 **Yves Barral**, Institute of Biochemistry , Zurich, Switzerland
Competing Interests: No competing interests were disclosed.
- 2 **Frank Uhlmann**, The Francis Crick Institute, London, UK
Competing Interests: No competing interests were disclosed.