

# Perspectives on Chromosome Organization

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Editorial Overview

# Perspectives on Chromosome Organization

Chromosomes, and their intriguing shapes and behaviors, were first visualized in the late 19th century by pioneers such as W. Flemming, van Beneden, and C. Rabl [1–3]. These early discoveries were enabled by improvements of optical microscopes, new staining procedures, and the choice of excellent experimental models. Ever since, we have wanted to understand how chromosomes are organized in the cell and how this organization relates to their roles as bearers of genetic information and heredity.

This first glimpse into chromosomes was key to define the nucleus of the cell as a compartment enclosing DNA and chromosomes, but with hindsight, also provided a model for the use of disruptive technological breakthroughs to unveil new levels of chromosome organization that was to remain relevant ever since. For instance, X-ray crystallography revealed the atomic structure of DNA [4] and the nucleosome particle 50 years later [5], while electron microscopy revealed the existence of heterochromatin. More recently, the development of fluorescent microscopy provided access to the large scale compartmentalization of chromosomes in eukaryotic interphase nuclei [6,7]. These and subsequent discoveries were critical to establish the organization of DNA at the atomic and micrometer length scales but were not conclusive on intermediate scales where much of the action (i.e. regulation of gene expression, replication, or repair of damages) arguably takes place.

Very recently, the advent of high-throughput sequencing technologies and the development of genome-wide chromosome conformation capture (Hi-C) [8,9] have provided further insights into chromosome structure by revealing the existence of unknown organizational features. Most notably, the observation that the chromosomes of some animals, notably mammals, are subdivided into a variety of sub-Mb domains [10–12]. These domains — originally called topologically associating domains (TADs) — result from the 'self-association of large chromosomal neighbourhoods in the three-dimensional space of the nucleus'[11]. TAD-like and other types of domains have been observed in all kingdoms of life [10–14]. Their biological roles and mechanism of formation will likely differ between species.

TADs often encapsulate genes and their regulatory sequences [15–17]. These observations immediately led to a working model where these domains constituted basic functional units of chromosome organization. This relatively static model is being continuously re(de)fined by new experiments and observations. In this issue of the *Journal of Molecular Biology* (JMB), several reviews describe these observations and provide novel, often disparaging, thoughts on the structural relevance, the biological roles, and the mechanism of formation of TADs.

De Wit provides a historical account of TAD discovery and identification and describes the main mechanisms for TAD formation [18]. He concludes that we need to have a more nuanced view of the role of TADs in transcriptional regulation and proposes that we should define TADs based on the mechanisms that shape them. In a complementary article, Chang et al. [19] review the roles of CCCTC-binding factor (CTCF) and cohesin in inducing TAD borders. TAD borders are prominent in Hi-C data sets, but recent studies report that TADs are only moderately insulated in single cells. Sexton explains that the causal link between TAD organization and transcriptional control is actually complex and context dependent [20]. In fact, convergent CTCF sites explain many of the specific contacts seen in contact matrices but are not sufficient to explain TAD formation. He argues that correlative studies between TAD structures and transcription based on global genome-wide analysis should be complemented with specific case studies to fully understand the functional roles of TADs.

Ghavi-Helm [21] reviews recent evidence from *Drosophila* also arguing for a more nuanced role of TADs in transcriptional regulation [18]. For instance, she reviews recent studies where it is shown that gene expression is only mildly affected by deletion of TAD boundaries or by large chromosomal inversions affecting TAD boundaries. She suggests that TADs are similarly important to provide precision and robustness to gene expression. Jerkovic et al. [22] provide a review of the roles of TADs in defining epigenomic landscapes and in the regulation of transcription [19]. They also discuss the roles of CTCF/cohesin and epigenetics in the formation of TADs in mammals and other species (e.g. *Drosophila*).

While the aforementioned reviews focus mostly on data generated through Hi-C–related techniques, Nollmann et al. [23] review novel optical microscopy

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methods that can now visualize TAD organization in single cells and at the same time transcriptional activity. This approach allows testing the existence of TADs in single cells and their relation to transcriptional regulation. Babokhov et al. [24] also focuses on recent microscopy studies where the dynamics of chromatin and the roles of transcription in these dynamics are addressed.

The data generated in the last ten years has incited theoreticians to develop in silico models to represent and/or understand them. These efforts are reviewed by Bianco and colleagues [25].

At the genesis of the genetic code, Crick [26] introduced an abstract representation based on codes, adapters, and objects, to provide a theoretical framework explaining how the genetic information is converted into proteins. Mozziconacci et al. [27] propose a similar semantic code to understand the roles of transcription factors and 3D TAD folding in the regulation of transcription. In this inspiring analogy, transcription factors represent code words, while the role of adapters is played by the specific set of promoters, enhancers, and insulators that, when occupied by the right set of transcription factors will lead to active transcription.

How do other DNA-related metabolic processes, besides transcription, take place in the context of the higher order folding of chromatin is also discussed in this JMB issue in a review by Arnould and Legube [28], who present how chromosome organization into TADs may contribute to double-strand break (DSB) signaling and post-damage DNA repair responses. Mazur et al. [29] discuss the ability of identical dsDNA molecules to pair *in vivo*, independently of the homologous recombination machinery. Interestingly, fungi have evolved gene silencing mechanisms that can be taken advantage of to study this phenomenon. The potential implications of *in vivo* direct homologous dsDNA-dsDNA pairing will likely impact our understanding of chromosome folding regulation.

Finally, Planchenault et al. [30] discuss the organization of bacterial chromosomes, in particular how this organization changes when multiple chromosomes are present. Interestingly, bacterial chromosomes do not appear to organize in chromosome territories but rather intermingle in the nucleoid space and possess specific systems to ensure their subcellular localization and segregation.

## Conclusions and Perspectives

The first glimpses from Fleming, van Beneden, and Rabl on how chromosomes occupy the intracellular space sparked a myriad of models on chromosome organization and function. Plenty of experiments, combined with the invention and application of new technologies, were necessary to test and refine these models and to understand the underpinning molecular mechanisms. We are lucky to live in an exciting time when the rapid invention of disruptive technologies is likely to continue to revolutionize the study of DNA structure and function.

Since their discovery, TAD-like domains have been observed in many species. It is clear that many mechanisms could account for this level of chromatin organization (e.g. loop extrusion, epigenetics, transcriptional activation, insulators) and that these distinct mechanisms may be simultaneously at play in the same nucleus. Thus, new unbiased and unambiguous nomenclatures should be coined to discriminate between different domain types displaying distinct functions and folding principles.

Single-cell methodologies to monitor genome organization and DNA metabolic functions (e.g. transcription, replication, repair) are still in their infancy. Recent applications of these technologies remind us that chromosome organization, and in particular TAD-like domains and compartments, seem to be structurally very heterogeneous. The reasons and functions of these heterogeneities are still to be unveiled.

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