Contributions of 3D chromatin structure to cell-type specific gene regulation

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Abstract

Eukaryotic genomes are organized in 3D in a multi-scale manner, and different mechanisms acting at each of these scales can contribute to transcriptional regulation. However, the large single-cell variability in 3D chromatin structures represent a challenge to understand how transcription may be differentially regulated between cell types in a robust and efficient manner. Here, we describe the different mechanisms by which 3D chromatin structure was shown to contribute to cell type-specific transcriptional regulation. Excitingly, several novel methodologies able to measure 3D chromatin conformation and transcription in single cells in their native tissue context, or to detect the dynamics of *cis*-regulatory interactions, are starting to allow quantitative dissection of chromatin structure noise and relate it to how transcription may be regulated between different cell types and cell states.

Noise in 3D genome structure

Eukaryotic chromosomes are compacted into several levels, including chromosome territories (Cremer and Cremer 2001), active and repressive (A/B) compartments (Lieberman-Aiden et al. 2009), lamina-associated domains (LADs) (Manzo, Dauban, and van Steensel 2022), topologically associating domains (TADs) (Dixon et al. 2012; Nora et al. 2012; Sexton et al. 2012), and loops formed by CCCTC-binding factor (CTCF) binding sites predominantly located at TAD borders (Rao et al. 2015). This multi-scale organization provides the means to regulate transcription at multiple levels (Zheng and Xie 2019; Nollmann et al. 2022), including by histone modifications, by chromatin opening, by localization to active/repressive compartments or to the nuclear periphery, or by modulation of cis-regulatory (e.g. enhancer, promoter) proximities.

3D chromatin structure is highly variable from cell to cell, which we will call in this review 'chromatin structure noise', and this occurs at all levels of chromatin organization. For instance, imaging and single-cell genomics revealed that many interactions between LADs and the nuclear lamina vary from cell to cell (Hoskins, Smith, and Reddy 2021). Similarly, the arrangement of A and B compartments between individual alleles displays large structural heterogeneities: while segregation between A/B compartments was observed, compartments are often spatially intermixed in single cells (Su et al. 2020). In addition, formation of A-compartments tends, but is not always correlated, with active transcription (Su et al. 2020). This incomplete correlation may be related to other sources of heterogeneity introduced by transcription-independent mechanisms (Xie et al. 2022), or by non-coding RNAs (Creamer, Kolpa, and Lawrence 2021).

Likewise, TAD-like structures were detected in single cells but display a large degree of structural variation between cells (Beliveau et al. 2015; Boettiger et al. 2016; Cattoni et al. 2017; Szabo et al. 2018; Götz et al. 2022; Bintu et al. 2018; Finn et al. 2019). Inter-TAD associations are common (Finn et al. 2019; Cattoni et al. 2017), and uncorrelated between alleles in single nuclei (Finn et al. 2019). Notably, the position of boundaries between TAD-like structures vary from cell to cell, and preferential borders detected by ensemble methods can only be retrieved when insulation profiles from multiple single cells are averaged together (Bintu et al. 2018; Flyamer et al. 2017; Takei, Zheng, et al. 2021; Arrastia et al. 2022). Consistent with these results, dynamic visualization of chromatin looping revealed that intra-TAD loops are rare and dynamic, and only briefly involve TAD boundaries (Gabriele et al. 2022; Mach et al. 2022). All in all, this recent evidence suggests that TADs may represent ensemble averages over large cell populations rather than unique structures present in most single cells (Beagan and Phillips-Cremins 2020).

Finally, physical proximity between cis-regulatory elements such as enhancers and promoters is also highly variable between single cells, as seen by imaging (Mateo et al. 2019; Espinola et al. 2021; Götz et al. 2022) or by single-cell genome-wide approaches (Arrastia et al. 2022). Moreover, the relation between enhancer-promoter proximity and transcriptional activation may not be straightforward (Wurmser and Basu 2022; Lim and Levine 2021; Brandão, Gabriele, and Hansen 2021) (**Figure 1**). Thus, chromatin structure noise is prevalent at all genomic scales, and is likely the reflection of polymer dynamics but also of multiple molecular processes (e.g. loop extrusion, E-P contacts, recruitment to nuclear periphery) acting on chromatin to affect function. This raises the question of whether and how chromatin organization could be fine-tuned to regulate cell-type specific transcriptional programs despite large cell-to-cell variations. This question will be the main topic of the next section.

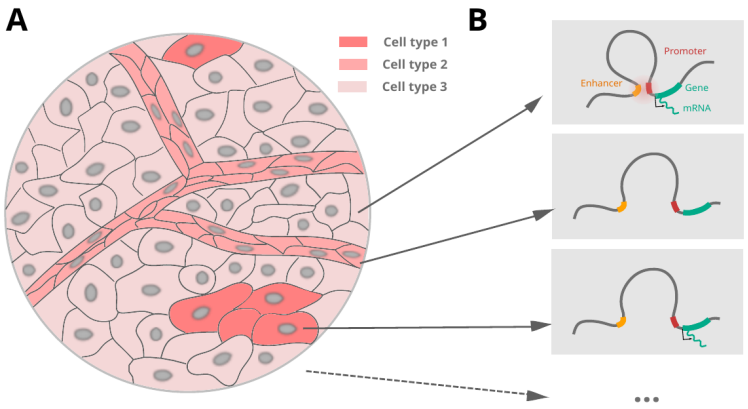

Figure 1. Tracing chromatin structure in single cells with information on cell type identity and spatial localisation. *(**A**) Schematic diagram of a complex tissue composed of three cell types presenting different spatial distributions. (**B**) Different cell types may be identified by differential RNA expression that may or may not be correlated to different 3D chromatin structures, such as E-P interactions at specific loci.*

How does 3D genome structure change between cell types?

Comparative studies of embryonic stem cells (ESC) and ES-derived cell lineages reported extensive changes in A/B compartments (Dixon et al. 2015; Bonev et al. 2017). Earlier studies reported that TADs are conserved between cell types and across species (Dixon et al. 2012), and remain stable during differentiation (Dixon et al. 2015). However, a higher-resolution work showed that TADs can change between mouse ESC and differentiated culture cells (Bonev et al. 2017; Chiariello et al. 2020; Oudelaar et al. 2018). We note that evolutionary conservation of TADs does not necessarily reflect structural stability (see previous section).

TADs tend to contain genes and the fundamental *cis*-regulatory elements that control gene expression: promoters, enhancers and insulators (Oudelaar and Higgs 2021). Importantly, *cis*-regulatory elements control chromatin structure and transcription at multiple levels: by promoting or preventing specific 3D proximity (e.g. enhancer-promoter), by participating in the formation of transcriptional foci (Wagh, Garcia, and Upadhyaya 2021), by regulating loop extrusion, or by recruiting epigenetic writers. Conversely, chromatin structure changes with local gene activity and epigenetic modifications, and therefore can by itself both instruct and reflect transcriptional status (Beagan and Phillips-Cremins 2020; Nollmann et al. 2022). Notably, early gene-editing studies showed that deletion of TAD boundaries can lead to enhancer hijacking and to transcriptional deregulation (Beagan and Phillips-Cremins 2020). More recently, deletion of individual CTCF binding sites at TAD borders was used to suggest that the insulation ability of a border is determined by the number, and specific identity of CTCF sites (Anania et al. 2022; Chang et al. 2021), and that orientation does not seem to be a strict determinant. Other studies, however, have revealed that rewiring of *cis*-regulatory elements within TADs do not always lead to abnormal transcription or disease (Ibrahim and Mundlos 2020; Ghavi-Helm et al. 2019; Kragesteen et al. 2018; Despang et al. 2019; Williamson et al. 2019; Beagan and Phillips-Cremins 2020). A recent review summarizes current thinking on the roles of TADs on enhancer function (Gabriel R Cavalheiro , Tim Pollex, Eileen Em Furlong 2021).

Similarly, the role of 3D *cis*-regulatory conformations in the regulation of cell-type specific transcriptional programs also seems to be context dependent (**Figure 1**). Ensemble sequencing methods, such as Hi-C or promoter-capture Hi-C (pcHi-C), were widely used to study whether interactions between *cis*-regulatory elements change during cell differentiation. First, a pcHi-C study in 17 human primary hematopoietic cell types showed that CRE interactions are highly cell-type

specific and tend to link active promoters and enhancers (Javierre et al. 2016). Later studies used Hi-C and pcHi-C on human and mouse ES and lineage-committed cells to report that rewiring of *cis*-regulatory interactions during lineage commitment are correlated with changes in target gene expression (Bonev et al. 2017; Freire-Pritchett et al. 2017; Rubin et al. 2017). Interestingly, lineage commitment not only involved changes in connectivity between *cis*-regulatory regions, but also in their chromatin state (Freire-Pritchett et al. 2017). More recently, use of enhancer-capture Hi-C during human mesenchymal stem cell differentiation revealed that enhancer interaction networks evolve during differentiation and are positively correlated to enhancer activity (Madsen et al. 2020). Consistently, high-resolution Hi-C maps of multiple mouse embryonic tissues showed that most E-P interactions display tissue-specific contact frequencies that correlate with enhancer activation (Chen et al. 2022). Notably, genetic variations in *cis*-regulatory regions lead to tissue deregulation and disease states (Miguel-Escalada et al. 2019; Beagan et al. 2020). All in all, these studies have clearly established that *cis*-regulatory interactions change between cell types and during cell differentiation.

Other studies, however, have revealed that specific *cis*-regulatory interactions are pre-established and predate the onset of transcription. During early *Drosophila* embryonic development, *cis*-regulatory interactions can be pre-formed before the target genes are activated (Ghavi-Helm et al. 2014; Espinola et al. 2021). Similarly, studies in an *in vitro* human epidermal differentiation system found that a set of *cis*-regulatory contacts are found in both undifferentiated progenitor and differentiated cells (Rubin et al. 2017). Thus, these two classes of *cis*-regulatory contacts likely present distinct mechanisms of formation and regulation (Rubin et al. 2017). We note that observation of pre-established *cis*-regulatory contacts does not provide information on their dynamic stability or on their frequency of formation. In other words, they reflect the ability of *cis*-regulatory regions to interact before gene activation, however, these interactions may be infrequent and short lived.

More recently, several groups focused on understanding whether nuclear structure changes between cell types, specifically focusing on the brain (Harabula and Pombo 2021). Use of diploid chromatin conformation capture (Dip-C), a method that captures chromosome interactions in single cells (Tan et al. 2018), showed that different mouse neural cell types display distinct overall nuclear organizations (Tan et al. 2018, 2019), and multiple genes change A/B compartment between adult neural cell types (Tan et al. 2021). This approach, however, lacked genomic coverage to clearly detect *cis*-regulatory interactions. Genome architecture mapping (GAM), a ligation-free sequencing method, was adapted to build chromatin interaction maps for three distinct neural cell types (Winick-Ng et al. 2021). This study revealed that the most significant differential chromatin contacts between pyramidal glutamatergic and dopaminergic neurons contained putative binding sites for a set of transcription factors differentially expressed in each of these neural cell types (Winick-Ng et al. 2021). These results suggest that binding of tissue-specific transcription factors to enhancers and promoters may be in part responsible for fine-tuning cell-type specificity in transcriptional regulation.

Interestingly, highly interconnected enhancers exhibit networks of interactions with multiple enhancers and promoters that change during differentiation (Madsen et al. 2020). Analogously, pcHi-C studies reported that enhancers, so-called 'super-enhancers' (Blobel et al. 2021), and promoters display multiple interactions amongst each other that change between cell-types (Miguel-Escalada et al. 2019). More recently, a high-resolution capture micro-C assay was used to detect patterns of highly nested and focal 3D interactions connecting enhancers and promoters in mouse ESCs (Goel, Huseyin, and Hansen 2022). We note, however, that these observations could arise from the formation of 3D *cis*-regulatory hubs in single cells, or alternatively, from an ensemble-averaging effect with different single cells exhibiting distinct *cis*-regulatory interactions. Dissecting between these two models would require use of sequencing methods able to detect multi-way interactions in single cells (Quinodoz et al. 2021; Beagrie et al. 2017; Oudelaar, Downes, and Hughes 2022), or of imaging technologies able to chart the spatial distribution of multiple chromatin targets at once (see section below).

Can cell-type-specific *cis*-regulatory interactions respond to external stimuli in terminally differentiated-cells? Several studies addressed this question using sequencing methods in mice models. Use of Dip-C reported extensive changes in A/B compartments during the first postnatal month in mice, however these global changes in genome structure seem to be unaffected by sensory stimulation (Tan et al. 2021). Interestingly, concurrent studies used high-resolution bulk Hi-C to show that interaction frequencies between *cis*-regulatory elements do in fact change during learning in mice (Yamada et al. 2019; Beagan et al. 2020). All in all, these studies suggest that lineage-specific *cis*-regulatory interactions may be further remodeled after differentiation to respond to external stimuli. In future, use of methods able to resolve chromatin structure in single cells with high-resolution will be required to determine if these changes in *cis*-regulatory interactions are cell-type-specific.

Most of the studies highlighted above relied on the use of chromatin conformation capture methods to map chromatin structures during *in vitro* differentiation, or to detect differences between cell-types dissociated from tissues pooled from different animals and isolated through fluorescence-activated cell sorting. In addition, these approaches did not measure chromatin organization and transcriptional activity in the same single cells, thus only correlations between chromatin structure and transcription measured in bulk in different cells were possible. Concurrent measurement of 3D genome conformation and transcription in tissues while maintaining the spatial relationships of different cell types will be essential to: quantitatively measure variability in *cis*-regulator interactions, investigate the origin of such variability, and relate it to how transcription is regulated between different cell types and cell states. A new family of chromatin conformation capture methods based on imaging was recently developed that addresses many of these limitations.

Visualizing chromatin organization in single cells

Imaging-based methods have been used for many decades to investigate chromosome organization, with fluorescence *in situ* hybridization (FISH) being arguably the most popular. A critical limitation of conventional FISH labeling approaches was uplifted by Oligopaint (Beliveau et al. 2012), which enables flexible, rapid, and efficient design and synthesis of FISH probesets. This technology, combined with microfluidics and with innovative oligonucleotide designs, enabled the simultaneous imaging of multiple genomic loci in single cells at ~100 kb resolution (Wang et al. 2016). Further improvements of this method led to the development of several multiplexed chromatin imaging methods, to visualize TAD structure in culture cells at 25kb (chromatin tracing) (Bintu et al. 2018), combined visualization of chromatin organization and transcription of a single gene in intact *Drosophila* embryos at 3kb (Hi-M) (Cardozo Gizzi et al. 2019), and detection of spatial changes in TAD structure together with the transcription of multiple genes at 2-10kb resolution in *Drosophila* embryo cryo-sections (ORCA) (Mateo et al. 2019). More recently, sequential encoding schemes were used to detect multiple RNA targets and reconstruct chromatin architecture of entire chromosomes at ~50kb resolution (Su et al. 2020). Strikingly, use of combinatorial encoding schemes enabled chromatin imaging genome-wide at 0.5-1Mb resolution and detection of multiple RNA species and nuclear landmarks (DNA-MERFISH and seqFISH+, respectively) (Su et al. 2020; Takei, Yun, et al. 2021). In parallel, combination of Oligopaint with super-resolution imaging methods (oligoSTORM, oligoDNA-PAINT) were used to image 8 chromosomal regions at high-resolution (Nir et al. 2018), while combination of Oligopaint with fluorescence *in situ* sequencing (oligoFISSEQ) was used to super-resolve the structure of multiple chromosomal regions at once (Nguyen et al. 2020). Recent variations of multiplexed chromatin imaging methods were reviewed in more detail elsewhere (Bouwman, Crosetto, and Bienko 2022).

The ability of multiplexed imaging methods to trace chromatin and detect RNA and proteins in single cells makes them ideally suited to reveal whether and how chromatin organization changes between cell types (**Figure 1**). We recently applied Hi-M to visualize how chromatin structure within a TAD

changes between cell types in *Drosophila* embryos at nuclear cycle 14 (Espinola et al. 2021). Surprisingly, at this stage of development, chromatin organization was virtually identical between the mesoderm, the neuro-ectoderm, and the dorsal ectoderm (**Figures 2A-B**). By detecting active transcriptional hotspots using intron-FISH, we were able to establish that enhancers and promoters come in close physical proximity, however they do so infrequently, and at similar frequencies between expressing and non-expressing cells. Importantly, E-P proximity patterns arose before the establishment of TADs or of transcription. Single-nucleus analysis further showed that the chromatin structure of active and inactive cells were virtually indistinguishable from each other (Götz et al. 2022). Invariant chromatin topologies in this system were also observed by ensemble sequencing methods (Ing-Simmons et al. 2021; Ghavi-Helm et al. 2014).

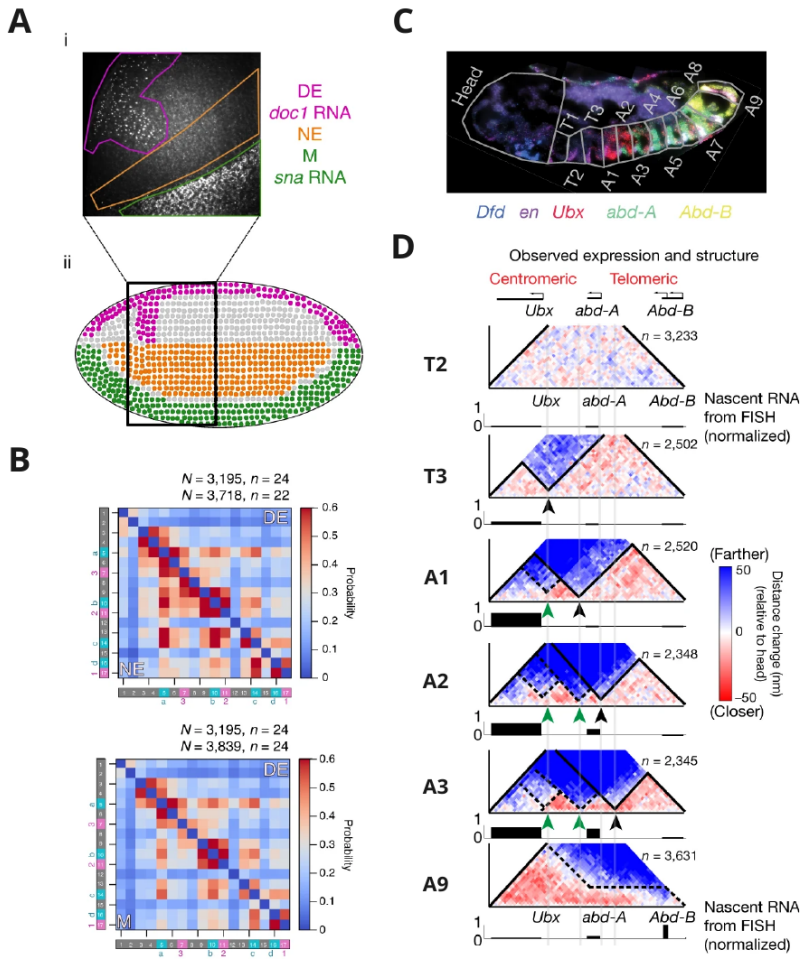

Figure 2. Mapping cis-regulatory interactions in different cell types. *(**A**) Schematic representation of three presumptive tissues in nuclear cycle 14 Drosophila embryos and the respective segmentation of single nuclei based on intron-RNA–FISH (adapted from Espinola et al., 2021). DE: dorsal ectoderm, NE: neuroectoderm, M: mesoderm. (**B**) Contact probability maps for DE and NE (top panel) and for DE and M (bottom panel) (adapted from Espionola et al., 2021). N indicates number of cells, n indicates number of embryos. (**C**) Manual annotation of body segments in a Drosophila embryo. mRNAs are shown for en (purple), Dfd (blue), Ubx (red), abd-A (green) and Abd-B (yellow) (adapted from Mateo et al., 2019). (**D**) TAD organization measured using ORCA in the indicated body segments. Black lines indicate predicted TAD borders, while unexpected TAD borders are indicated by dashed lines. Black arrowheads mark the position of boundaries. Unexpected TAD boundaries are marked by green arrowheads. Vertical gray lines indicate borders of genetic domains. Height of bars below ORCA maps indicate average nascent RNA-FISH intensity, normalized to the segment with the highest expression. Number of cells, n, is indicated for each map (adapted from Mateo et al., 2019).*

ORCA was used to investigate the chromatin organization of a Hox gene cluster in cryo-sectioned *Drosophila* embryos 10-12h post-fertilization (hpf) (Mateo et al. 2019). This study showed that chromatin organization at the TAD-level changes between segments, and correlates with the spatial

patterns of Hox gene expression (**Figures 2C-D**). In particular, borders between active and repressed Polycomb genes were cell-type specific, and deletion of Polycomb-independent borders led to ectopic E-P proximities and aberrant gene expression. To note, the correlation between E-P proximity and transcriptional activation was weak, and many inactive promoters were proximal to known enhancers, similar to what was observed in early embryos. This lack of direct correlation between E-P proximity and gene expression was further explored using deep-learning approaches to dissect which changes in single-cell chromatin structure were most important to predict transcriptional state (Rajpurkar et al. 2021). This method outperformed conventional approaches based purely on the quantification of E-P proximity. Notably, prediction of transcriptional output depends on multiple structural parameters, with binary E-P interactions providing only a minor contribution to the overall predictive power of this method. Analogously, multiple structural parameters, including chromatin condensation and TAD borders, contribute to shaping the 3D chromatin structure of single-nuclei during early *Drosophila* embryogenesis (Götz et al. 2022).

A putative role of TADs in transcriptional regulation is to facilitate E-P communication within TADs and to prevent enhancers from activating genes in neighboring TADs. However, this model is puzzling when considering that promoters interact only two-fold more frequently with enhancers within their TAD than with enhancers in neighboring TADs. Two independent imaging-based studies have recently addressed this question. ORCA imaging data in *Drosophila* embryos 10-12 hpf was combined with modeling approaches to show that a futile cycle mechanism in which E-P proximity occurs but does not display strong correlation with transcriptional output (Xiao, Hafner, and Boettiger 2021). Concomitantly, a second study investigated this issue by detecting how the genomic distance between enhancer and promoter influenced transcriptional output (Zuin et al. 2022). Remarkably, transcriptional output scaled non-linearly with the frequency of E-P contacts, and increased with enhancer strength. Mathematical modeling suggests a mechanism whereby multiple E-P contact events are required for promoter activation, and predict that these contacts may be short-lived (i.e. second time-scale). Overall, these results are in line with earlier ensemble experiments where it was shown that E-P contact frequency scaled with mRNA expression following a power-law (Tsujimura et al. 2020). All in all, these observations and predictions are consistent with the infrequent E-P proximities observed by multiplexed imaging methods.

Two recent studies applied multiplexed chromatin imaging methods to mouse tissues. Multiplexed imaging of nucleome architecture (MINA) was used to visualize chromatin architecture in E14.5 mouse fetal liver, revealing changes in A/B compartments between cell-types and increased frequency of a E-P contact in hepatocyte versus non-hepatocyte cells (Liu et al. 2020). SeqFISH+ was used to retrieve chromatin organization in the adult mouse cerebral cortex, revealing that the association of some loci to nuclear bodies (e.g. speckles, nucleolus) is cell-type specific, and affects inter-chromosomal interactions and nuclear positioning (Takei, Zheng, et al. 2021).

Conclusions and future perspectives

Over the last two decades, multiple lines of evidence independently established that 3D chromatin organization can drastically change between single cells of the same specimen (chromatin structure noise). In the last few years, the advent of multiplexed imaging, time-lapse microscopy, and single-cell sequencing methods has enabled the dissection of single-cell variability in genome organization at multiple genomic and physical scales, and showed that this noise is present at all levels of chromatin organization: from A/B compartments to LADs and TADs, in the nuclear positioning of chromatin and its association to a variety of nuclear bodies, and most notably in the interactions between *cis*-regulatory elements. Thus, in part, this noise reflects the action of molecular processes with a functional role in transcriptional regulation. Most of these multi-scale studies have relied on cultured cells, where these variations may be exacerbated by changes in cell cycle, gene expression, or cellular micro-environment. A more limited number of studies in tissues, however, still supports the idea that 3D genome structure considerably changes between single-cells of the same cell-type (Xiao, Hafner, and Boettiger 2021; Götz et al. 2022; Takei, Zheng, et al. 2021).

An important challenge for future experiments will be to characterize intrinsic and extrinsic chromatin structure noise (Finn et al. 2019) within and between cell-types in tissues, dissect the relative contribution of the different mechanisms participating in these variations, and investigate their possible biological function.

Multiple factors likely contribute to chromatin structure noise, therefore dissection of their role and function will require the further deployment of methods able to map changes in chromatin organization in single cells simultaneously with other readouts, such as transcription, nuclear localization, protein levels, post-translational modifications, metabolomes, etc. Combination of these multiple biochemical readouts and understanding of their contributions to chromatin structure noise will require considerable developments in novel analysis (e.g. machine learning, graph analysis) (Amitay et al. 2022; Atak et al. 2021; Coullomb and Pancaldi 2021) and modeling methods (e.g. kinetic modeling, polymer physics) (Das, Shen, and McCord 2022; Zuin et al. 2022; Di Stefano et al. 2021; Gabriele et al. 2022; Rajpurkar et al. 2021; Xiao, Hafner, and Boettiger 2021). In this context, use of synthetic approaches will become essential to experimentally test predictions from models (Zhang, Lam, and Blobel 2021).

Noise in chromatin structure also reflects its dynamics, originating from the intrinsic polymer nature of chromatin, as well as from the direct action of molecular motors (e.g. cohesin) and of DNA-binding proteins (e.g. transcription factors) (Nollmann et al. 2022). Considerable progress has been made in monitoring transcription factor binding dynamics (Lu and Lionnet 2021), progression of loop extrusion (Gabriele et al. 2022; Mach et al. 2022), or the dynamics of RNA synthesis (Pichon et al. 2020), one at a time. However, a full understanding of the role of chromatin structure dynamics in transcription will be considerably accelerated by single-cell measurements of the multi-factorial occupancy of *cis*-regulatory elements, their 3D interactions, and transcriptional dynamics. These simultaneous dynamic measurements are currently out of reach, but may hopefully become possible in the future.

At this stage, it should be apparent that the question of whether and how chromatin structure contributes to transcriptional regulation of cell-type specific transcription is difficult to address, in part because the many actors and processes concurrently acting on chromatin to introduce structural noise are cell-type specific and can change during development and differentiation. In addition, the specific action of motors, DNA-binding proteins, and histone modifiers is differentially encoded between genomic loci, for instance through the differential recruitment of co-activator or co-repressor sub-complexes by specific combinations of transcription factors. Thus, a single size does not fit all: 3D chromatin structure likely regulates transcription by multiple, distinct mechanisms, that can be deployed on different organisms and at different loci, and fine-tuned between cell-types and during development. Ultimately, this highlights the importance of continuing to study different model organisms, and of decorticating the specific mechanisms at play at multiple, specific genomic loci with single-cell resolution and with multiple read-outs.

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