



Dynamic Enhancer–promoter Communication Beyond Loop Extrusion*

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Abstract Enhancer-promoter communication is fundamental to the spatial and temporal control of gene expression. Cohesin-mediated loop extrusion has long been considered a major structural mechanism that brings distal regulatory elements into proximity with their target promoters. Recent findings from Aboreden *et al.* refine this view by showing that depletion of Nipped-B-like protein (NIPBL), a key regulator of cohesin loading and loop extrusion, markedly disrupts architectural chromatin loops, whereas many *cis*-regulatory contacts and broad post-mitotic transcriptional reactivation are only modestly affected. These observations suggest that loop extrusion is important, but not sufficient, for explaining productive regulatory communication. In this Comment, we discuss how transcriptional condensate-like assemblies may provide an additional biochemical and kinetic layer that helps convert regulatory proximity into transcriptional output. By locally enriching transcription factors, coactivators, mediator and RNA polymerase II (Pol II) around active loci, such regulatory hubs may stabilize productive enhancer-promoter encounters and modulate transcriptional activity. We further propose that transcriptional bursting provides a useful framework for understanding this conversion, because gene expression can be decomposed into burst frequency, burst duration and burst size. Integrating chromatin architecture, condensate organization and bursting dynamics may therefore provide a more complete view of how enhancer-promoter communication is re-established after mitosis and how regulatory proximity is converted into transcriptional output through mechanisms beyond loop extrusion.

Key words enhancer-promoter communication, loop extrusion, cohesin, transcriptional condensates, transcriptional bursting

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1 Loop extrusion and enhancer–promoter contacts

The spatial and temporal control of gene expression depends in part on the ability of distal enhancers to communicate with target promoters within the three-dimensional nuclear environment^[1-2]. Because developmental enhancers can act over large genomic distances, understanding how they engage promoters is essential for linking spatial genome organization to transcriptional output^[3-4]. One prominent structural framework for this communication is cohesin-mediated loop extrusion^[5]. In this model, cohesin folds chromatin into loops and contact domains, often constrained by CCCTC-binding factor (CTCF)-bound boundaries. Such folding can increase the spatial proximity between

distal regulatory elements and promoters, thereby creating a permissive context for long-range enhancer action^[3-4] (Figure 1a). Yet proximity alone is not always sufficient to explain transcriptional output. Enhancer-promoter contacts are often dynamic, and their relationship with gene expression can be nonlinear^[4]. Thus, although loop extrusion provides an important structural route for long-range gene

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regulation, it does not fully explain how regulatory contacts are converted into productive transcription^[6].

Recent work by Aboreden *et al.*^[7] refines this proximity-based view. The authors depleted Nipped-B-like protein (NIPBL) during the mitosis-to-G1 transition, a critical window in which chromatin organization is rebuilt after mitosis. This experimental design allowed them to test whether NIPBL-driven loop extrusion is required for the de novo formation of chromatin contacts. NIPBL loss severely disrupted architectural loops, particularly long-range CTCF/cohesin-associated loops. By contrast, many *cis*-regulatory contacts still re-formed, and broad post-mitotic gene activation was only mildly affected. These findings are consistent with RAD21-depletion studies in self-renewing embryonic stem cells, in which much of post-mitotic gene reactivation remained largely cohesin-independent^[8]. Together, these observations do not rule out a role for loop extrusion; rather, they indicate that its role is selective. NIPBL-dependent extrusion is important for rebuilding architectural loops, but many regulatory contacts can recover without efficient extrusion.

This recovery, however, is not uniform. Contacts among weak *cis*-regulatory elements (CREs) show delayed kinetics after NIPBL depletion, whereas contacts anchored by highly active enhancers can form with similar kinetics despite impaired extrusion. This difference in NIPBL dependency may arise because weak CREs harbor lower local concentrations of transcription factors and cofactors, making them more reliant on loop extrusion to rapidly promote long-range interactions^[7]. Similar results from RAD21 depletion suggest that active regulatory features and strong enhancers can support cohesin-independent contact reassembly^[8]. Other perturbation studies point in the same direction: CTCF loss can disrupt chromatin hubs without proportionally blocking enhancer-mediated gene activation, and enhancer synergy can render selected distal regulatory programs less dependent on cohesin^[5,9]. These findings suggest that loop extrusion contributes to the rebuilding of genome architecture after mitosis, but does not by itself determine whether *cis*-regulatory contacts recover or whether they produce transcriptional output. Instead, contact recovery appears to be shaped by enhancer strength, regulatory activity and the local chromatin environment. Thus, loop extrusion can bring enhancers and promoters into

closer spatial proximity, but additional mechanisms are likely required to convert these contacts into productive transcription.

2 Transcriptional condensates as a biochemical layer in enhancer–promoter communication

Aboreden *et al.* show that many *cis*-regulatory contacts can recover despite impaired NIPBL-driven extrusion, but the mechanisms that support this recovery remain incompletely understood. Related studies point to several possible contributors, including compartmentalized enhancer-promoter interactions^[6], RNA polymerase II (Pol II)-dependent enhancer-promoter contact formation^[10], and local clustering of regulatory factors, such as dynamic transcription factor clusters and Pol II/mediator-enriched assemblies^[11–12]. These observations suggest that enhancer-promoter communication may depend not only on spatial proximity, but also on the local biochemical environment in which regulatory contacts occur.

In this context, transcriptional condensate-like hubs provide a useful framework for considering how re-formed regulatory contacts may be coupled to transcriptional output. Rather than serving merely as passive consequences of enhancer-promoter proximity, these assemblies may create local biochemical environments in which transcription factors, coactivators, mediator and Pol II are enriched around active regulatory loci^[11–12] (Figure 1b). Such enrichment may be supported by intrinsically disordered or low-complexity regions in transcriptional regulators and the Pol II machinery, which can promote weak, multivalent interactions^[12–13]. By increasing the local concentration and residence of transcriptional components, condensate-like hubs may raise the probability that recovered enhancer-promoter contacts become productive.

This view does not imply that transcriptional condensates replace chromatin loops. Rather, condensate-like hubs may complement chromatin folding by providing a biochemical layer that acts on top of spatial proximity. Loop extrusion and other architectural mechanisms can create opportunities for enhancers and promoters to encounter one another, whereas local enrichment of regulatory factors may

help determine whether these encounters become transcriptionally productive. Consistent with this idea, the “golden mean” model proposed by Zhu *et al.*^[14] suggests that enhancer-promoter communication is optimized at an intermediate level of clustering strength. When clustering is too weak, regulatory factors may not be sufficiently enriched to support efficient long-range communication; when clustering is too strong, excessive crowding, sequestration or competition may reduce communication efficiency. Live-cell imaging at the Sox2 locus further supports this concept by showing that condensate position, rather than enhancer distance alone, is closely associated with transcriptional output^[11]. Thus, condensate-like hubs are unlikely to act as simple on/off activators. Instead, they may function as tunable regulatory environments that modulate the productivity of enhancer-promoter contacts.

3 Transcriptional bursting as a kinetic readout of regulatory communication

Enhancer-promoter communication is often evaluated by changes in average gene expression, but this readout alone does not explain how transcriptional output is generated at individual promoters. At the single-locus level, transcription frequently occurs in bursts, with promoters stochastically switching between transcriptionally active states, during which Pol II produces nascent RNA, and inactive states, during which little or no RNA is generated. This discontinuous mode of transcription is commonly described as transcriptional bursting^[15-16]. Bursting provides a kinetic framework for interpreting gene expression output by decomposing average expression into parameters such as burst frequency, burst duration and burst size^[16-17]. Burst frequency describes how often a promoter enters an active state, burst duration describes how long the active episode persists, and burst size describes how much RNA is produced during each active episode. Similar average expression levels can therefore arise from different combinations of bursting parameters. This perspective is particularly relevant here because condensate-like regulatory hubs may tune transcriptional output by altering one or more bursting parameters, rather than simply determining whether transcription occurs^[17-18] (Figure 1c).

Viewed through this framework, local regulatory organization may shape transcriptional output by influencing distinct features of transcriptional bursting. In the Sox2 super-enhancer system, Du *et al.*^[11] showed that distant condensates were associated with basal bursting, whereas closer condensate-gene proximity increased both burst frequency and burst size. Live-cell imaging further revealed a real-time negative correlation between condensate-gene distance and burst intensity, supporting the idea that condensate proximity can amplify transcriptional output rather than simply switch transcription on or off^[11]. At the Nanog locus, polymer simulations informed by sequential DNA/RNA fluorescence *in situ* hybridization (FISH) and live-cell imaging data estimated longer durations of gene-enhancer proximity in the transcriptionally active state across the proximity thresholds examined^[15], suggesting that sustained regulatory proximity may help maintain productive transcription. Complementary live-imaging studies have also shown that dynamic transcription factor clustering at enhancers can promote burst induction and regulate bursting output^[12,19]. Single-cell nascent RNA sequencing further supports this kinetic view by showing that burst frequency and burst size can be estimated from transcribing polymerases in individual cells, and that super-enhancer bursting can precede bursting of associated genes^[20]. Together, these studies suggest that recovered regulatory contacts may be functionally interpreted through changes in bursting behavior, including how often transcription is initiated, how much RNA is produced during each active episode, and how long productive regulatory states are maintained.

This perspective argues that studies of enhancer-promoter regulation should not stop at loop extrusion alone. Loop extrusion may influence transcription by shaping the spatial opportunity for enhancers and promoters to encounter one another, whereas condensate-like regulatory hubs may provide a biochemical layer that helps determine whether these encounters become productive. At the same time, this relationship is likely to be bidirectional. Live tracking at the Sox2 locus suggests that transcriptional activity can compete with loop extrusion and influence promoter-enhancer dynamics^[21]. Thus, enhancer-promoter communication should be viewed as a dynamic process in which chromatin folding, local

regulator enrichment and transcriptional activity influence one another.

4 Perspectives and concluding remarks

A key future challenge is to determine which recovered enhancer-promoter contacts become transcriptionally productive after loop-extrusion perturbation. Future studies should measure chromatin proximity, condensate-associated factor enrichment and nascent RNA production within the same cellular system, ideally after NIPBL or cohesin depletion. Such experiments could test whether condensate-like hubs still assemble near active loci when extrusion is impaired, whether their position, lifetime, composition or regulatory-factor enrichment changes, and whether these changes alter burst frequency, burst duration or burst size^[2, 11, 15, 20]. Current imaging approaches are often limited by spatial resolution; therefore, single-molecule and super-resolution imaging will be particularly valuable for resolving condensate dynamics and transcriptional activity at the nanoscale. For example, single-molecule

fluorescence resonance energy transfer can report molecular interactions and conformational dynamics, whereas single-particle tracking and super-resolution microscopy can resolve molecular motion, confinement and spatial heterogeneity within condensates^[22]. Combining high-resolution live-cell imaging with single-allele nascent transcription measurements could test whether perturbation-induced changes in condensate position, lifetime or composition precede changes in burst frequency, duration or size, thereby moving from correlation toward causal validation. This integrated approach would help define when loop extrusion is required, when enhancer activity and local regulator enrichment are sufficient, and how three-dimensional genome organization is converted into transcriptional kinetics. Together, these efforts would move the field beyond a proximity-only model toward a more complete view in which chromatin architecture creates regulatory opportunities, condensate-like hubs organize local biochemical competence, and transcriptional bursting reports the kinetic output of productive enhancer-promoter communication.

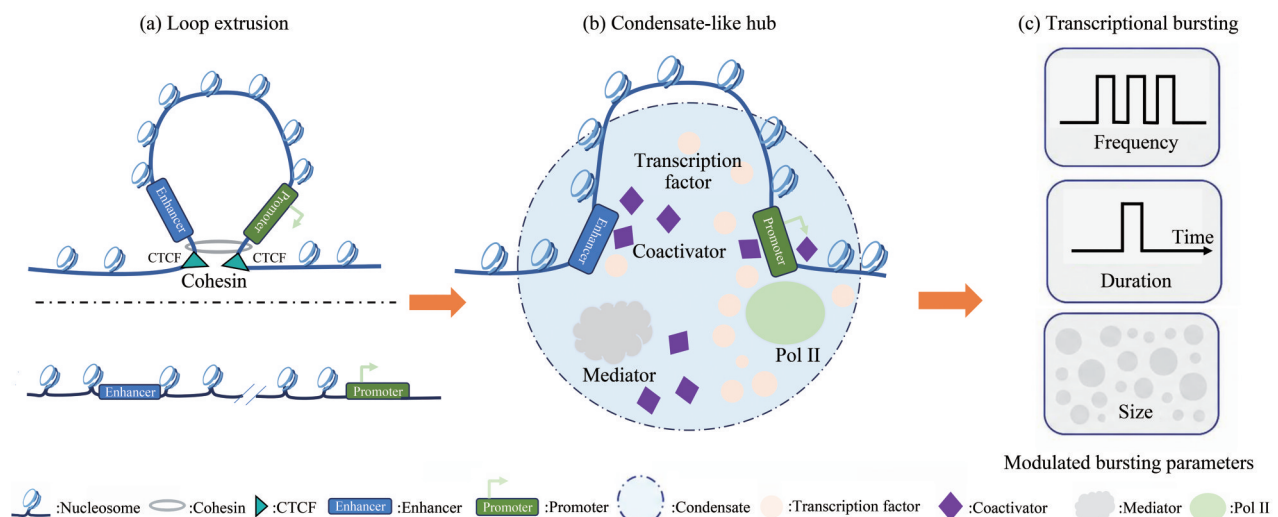


Fig. 1 Conceptual model linking loop extrusion, condensate-like regulatory hubs and transcriptional bursting

(a) Cohesin-mediated loop extrusion can create structural opportunities for enhancer-promoter proximity. (b) Condensate-like hubs enriched in transcription factors, coactivators, Mediator and Pol II may then provide a local biochemical environment that increases the productivity of these contacts. (c) Productive enhancer-promoter communication can be reflected in altered transcriptional bursting parameters, including burst frequency, burst duration and burst size.

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环挤压之外的增强子-启动子动态通讯*

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摘要 增强子-启动子通讯是基因表达时空调控的基础。长期以来, 黏连蛋白介导的环挤压被视为促进远端调控元件与靶启动子接近的重要结构机制。Aboreden等近期研究表明, 在有丝分裂向G1期过渡过程中耗竭黏连蛋白加载与环挤压的关键调控因子NIPBL, 会显著削弱结构性染色质环; 然而, 许多顺式调控接触及广泛的有丝分裂后转录再激活仅受到有限影响。该结果提示, 环挤压是调控通讯的重要组成部分, 但不足以单独解释增强子-启动子接触如何产生有效转录输出。本文探讨了转录凝聚体样组装如何作为额外的生化和动力学调控层, 将调控元件之间的空间接近转化为功能性转录输出。通过在活跃基因位点附近局部富集转录因子、共激活因子、中介因子(mediator)和RNA聚合酶II, 这类调控枢纽可能稳定有效的增强子-启动子相遇, 并调节转录活性。基因表达输出可被分解为爆发频率、持续时间和大小等参数, 基于此, 转录爆发可为理解这一转化过程提供一个有用的动力学框架。因此, 整合染色质结构、凝聚体组织与转录爆发动力学, 有助于更全面地理解有丝分裂后增强子-启动子通讯如何重建, 以及调控元件的空间接近如何通过环挤压之外的机制转化为转录输出。

关键词 增强子-启动子通讯, 环挤压, 黏连蛋白, 转录凝聚体, 转录爆发

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