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Chromosome dynamics during interphase: a biophysical perspective

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The dynamic nature of chromosome organization plays a central role in the regulation of many crucial processes, such as DNA transcription and replication. However, the molecular bases of the link between genomic function, structure and dynamics remain elusive. In this review, we focus on how biophysical modelling can be instrumentally used to rationalize experimental studies of chromosome dynamics, and to probe the impact of putative mechanisms on genome folding kinetics during interphase. We introduce the general connection between chromatin internal organization and dynamics, and outline the potential effects of passive interactions mediated by architectural proteins and of active, energy-dependent processes on chromatin motion. Finally, we discuss current ambiguities emerging from *in vivo* observations, in particular related to ATP depletion and transcriptional activation, and highlight future perspectives.

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Introduction

Over the last decade, our understanding of chromosome organization and its relation to genome (mis-)function has dramatically improved, thanks to the advent of chromosome conformation capture (Hi-C) combined with rapid progress in genome engineering and microscopy [1]. Chromosomes are hierarchically organized at multiple scales: from the local packaging of nucleosomes into chromatin fiber that subsequently folds into subMbp topologically associating domains (TADs) to the spatial compartmentalization of genomic regions sharing the same epigenomic content and the large-scale positioning of chromosome territories.

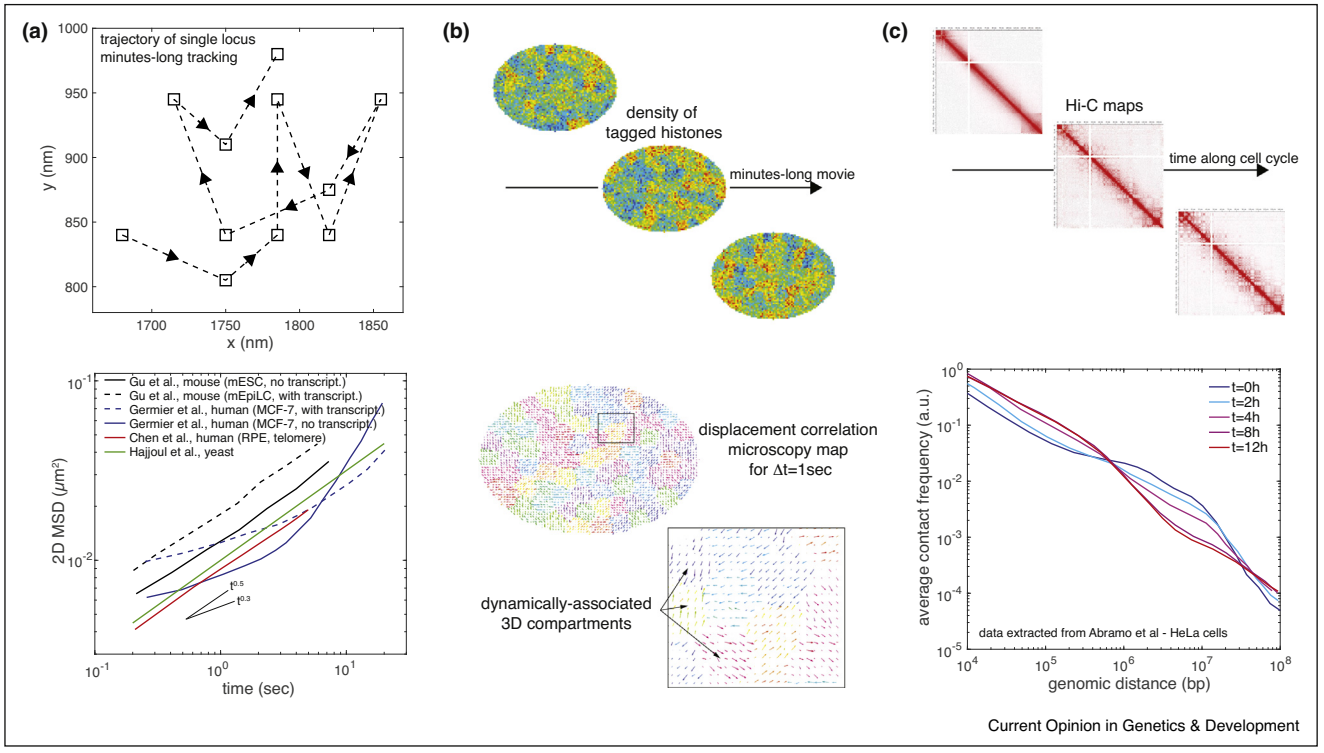
Most current works are structural and focused on the average, 'static' 3D organization of the genome, along with its biological functions. However, many studies have highlighted the importance of chromosome dynamics [2]. Briefly, the live-tracking of fluorescently tagged genomic loci or nucleosomes in living cells has evidenced the subdiffusive, visco-elastic motion of the chromatin fiber (Figure 1a). Chromatin motion may strongly depend on transcriptional status [3–6], nuclear positioning [7–9] or DNA damage [10••,11–13]. Whole genome dynamical studies have further revealed the existence of dynamically associated spatial regions, in which the motions of loci are correlated, and which closely match chromatin-associated nuclear compartments [5,14,15] (Figure 1b). Additionally, the use of 'static' methods like Hi-C at different time points also illustrates the global out-of-equilibrium dynamics of the genome, from the continuous decompaction of chromosomes after mitosis (Figure 1c) to their large-scale nuclear reorganization after hormonal induction [16] or DNA damage [17].

These observations suggest that a full understanding of the functional role of genomic spatial organization may only be achieved by accounting for its dynamical component. In particular, several mechanisms have been proposed for the regulation of the multi-scale 3D organization of chromosomes [18], from loop extrusion for TAD formation to micro-phase separation of chromatin-binding proteins for nuclear compartmentalization. However, very few studies have precisely quantified these dynamics, leaving a gap between the predicted outcomes of the processes and the experimental observations. Studying the dynamical properties of chromatin through the lens of biophysical modelling may thus provide a powerful tool to complement 'static' experiments, and help elucidate some of these underlying mechanisms.

Generic impact of chromatin structure on chromosome dynamics

Chromosomes consist of a polymeric chain, the chromatin fiber, which is usually modeled as a chain of elastic segments, and whose dynamics can be generically described by polymer physics concepts. In a crowded environment, as encountered in the nucleus, the local motion of genomic loci is mainly dictated by the elastic interactions exerted by neighboring consecutive segments. This is the so-called Rouse model [19], which is characterized by an anomalous subdiffusive regime with $MSD(\tau) = \Gamma\tau^{\alpha}$ and $\alpha < 1$ (Figure 1a), along with a visco-elastic behavior, in good agreement with many

Figure 1

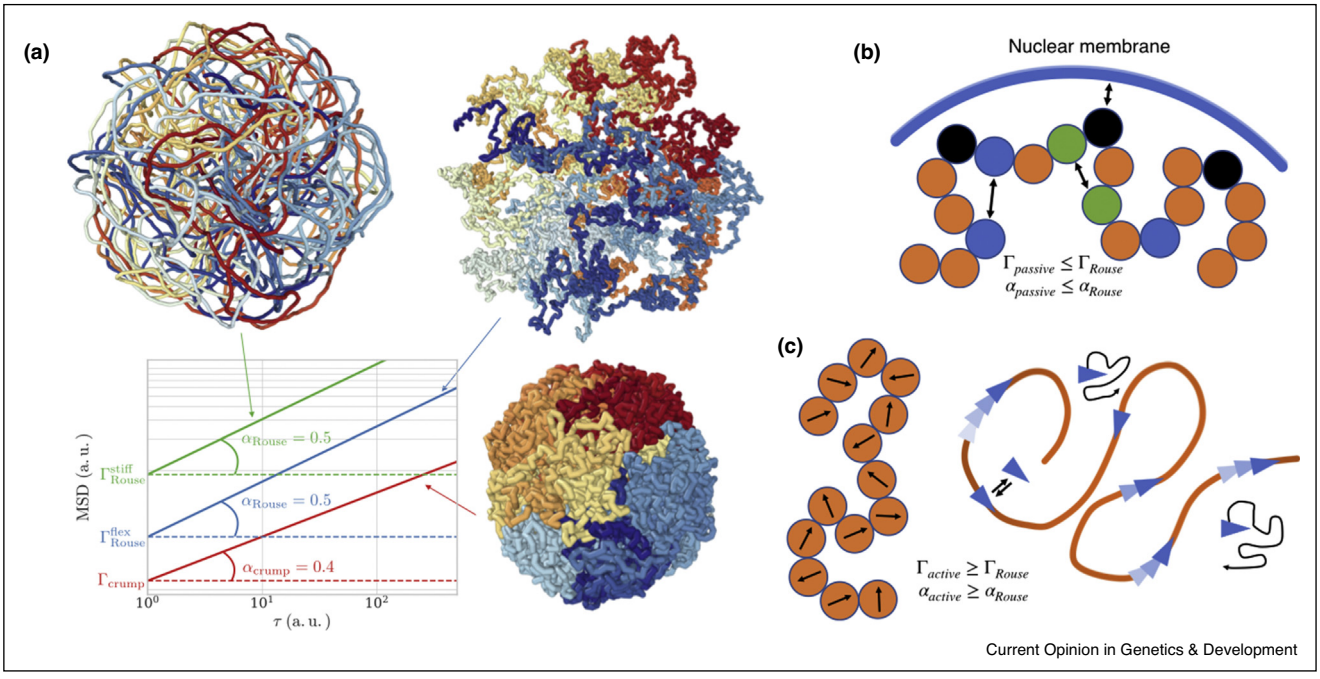


Experimental observations on chromosome dynamics.
(a) (Top) Dynamics of chromosome loci are mainly investigated by tracking in live cells the motion of fluorescently tagged single loci [2] over time ($\sim$ from seconds to minutes) in 2D optical layers. (Down) Statistical quantification is usually performed by computing the temporal variation of the mean squared displacement (MSD) which represents the average displacement after a time lag τ : $MSD(\tau) =< (\boldsymbol{r}(t+\tau) - \boldsymbol{r}(t))^2 >$ with $\boldsymbol{r}(t)$ the position vector and $< . >$ the time-average over one trajectory or the ensemble-average over the many trajectories. Typically, the MSD depends on τ following a power-law: $MSD(\tau) = \Gamma\tau^{\alpha}$ with α the diffusion exponent and Γ the amplitude. For example, for a particle freely diffusing in three dimensions, $\alpha = 1$ and $\Gamma = 6D$ with D the diffusion coefficient. Most of the MSD measurement for chromatin illustrates the subdiffusivity of genomic motion with $\alpha \sim$0.4–0.5 and Γ that may depend on the cell type or transcriptional status. Data were extracted from [3,4,7,21]. **(b)** (Top) Large-scale, genome-wide information on chromosome dynamics may also be studied by following the minutes-long spatio-temporal evolution of the intensity of stained histones in live cells [5,14,15]. (Down) Time-resolved image correlation analysis during a time interval Δt revealed the existence of micron-scale dynamically associated compartments whose loci have coherent movement during Δt of a few seconds. Schemes were inspired from results in Ref. [14]. **(c)** (Top) Analysis of the slow, large-scale dynamics of genome organization is studied with Hi-C experiments on synchronized cells along the cell cycle [33,34]. After mitosis, the decompaction of chromosomes is gradual: subMbp organization converging rapidly to steady-state while large-scale contacts and compartmentalization remaining out-of-equilibrium. (Down) This can be quantified by estimating the average contact frequency between two loci as a function of their genomic distance at different time points of the cell cycle after mitotic release, that exhibits different dynamics at intermediate or large scales. Data were extracted from Ref. [33].

single-locus tracking studies in different species [3,4,5,20••,21].

More generally, the dynamics of a polymer is intimately connected to its internal organization. Scaling arguments [22–25] provide a relation between the dynamic exponent $\alpha \simeq 2\beta/(2\beta+1)$ and the static Flory exponent β, which quantifies the increase of the average spatial distance $d(s) \sim s^{\beta}$ between two loci with their genomic separation s. For instance, $\beta = 1/2$ for short chains like yeast chromosomes [26], leading to the classical Rouse exponent $\alpha = 1/2$ [19] (Figure 2a) observed for yeast chromatin *in vivo* [7] and *in vitro* [27••]. Interestingly, in this regime, there exists a simple relation between the diffusion amplitude Γ and the local properties of the polymer, such as its local rigidity [27••] (Figure 2a). Socol *et al.* [27••] exploited this property to characterize the native yeast chromatin fiber using detailed Monte-Carlo simulations of nucleosome arrays. The chromatin parameters obtained from the comparison with *in vitro* MSD measurements of yeast-like chromatin (Kuhn length $b \sim 100$ nm; fiber compaction of $\sim$45 bp/nm) were found to be consistent with the values inferred solely from structural data [28]. This relationship between fiber rigidity and dynamics was also invoked to interpret the increase of chromatin motion observed during DNA damage potentially due to changes in fiber properties around double-strand breaks [10••,11,12].

Figure 2



Impact of polymer properties, passive and active forces on chromatin motion.
(a) Effects of local polymer structure and internal organization on chain diffusion. (Top) In the regime of limited chromatin compaction, as in the case of yeast chromosomes, the dynamics of the chain may be well described by the Rouse model, $MSD(\tau) = \Gamma_{Rouse}\tau^{0.5}$. The diffusion amplitude $\Gamma_{Rouse} \sim b/\sqrt{\zeta}$ may then be related to the monomer friction coefficient ζ, which generally depends on the local chain geometry, and to the so-called *Kuhn length* b, defined as the genomic separation distance beyond which the orientations of two distinct chain segments are statistically uncorrelated [27••]. Increasing chromatin rigidity may thus enhance the polymer dynamics in diluted systems, albeit without affecting the long-time diffusion exponent α obtained from the slope of the MSD curve in log-log scale. (Bottom) In higher eukaryotes, the denser organization of chromosomes is generally better captured by the slower *crumpled* polymer dynamics, $MSD(\tau) = \Gamma_{crump}\tau^{0.4}$, with $\Gamma_{crump} < \Gamma_{Rouse}$. **(b)** Schematic representation of a passive polymer with specific attractive interactions. In this model, blue and green monomers may respectively bind to one another, and black particles may bind to the nuclear membrane, further constraining the chain dynamics. Orange monomers are assumed to be inert. Passive forces usually lead to slower dynamics ($\Gamma \leq \Gamma_{Rouse}$; $\alpha \leq \alpha_{Rouse}$). **(c)** (Left) Schematic representation of an active polymer. The chain consists of connected, self-propelled monomers known as *active Brownian particles*, whose velocities bear a constant magnitude and a randomly diffusive direction (black arrows). *Polar* active polymers correspond to the case in which the monomer velocity vector is always borne by the local tangent to the chain backbone. (Right) Schematic representation of translocating motors acting on chromatin. In this model, molecular motors (blue triangles) diffuse in 3D space and may bind/unbind to a passive polymer (orange curve). Actives forces usually lead to faster dynamics ($\Gamma \geq \Gamma_{Rouse}$; $\alpha \geq \alpha_{Rouse}$).

For higher eukaryotes with longer chromosomes (Figure 2a), the generic organization is more compact ($\beta = 1/3$) [29]. This leads to $\alpha = 0.4$, consistent with many experimental measurements obtained in mammalian cells [3,4,5,14,20••,21,22] ($\alpha \sim 0.38 - 0.44$) and with polymer simulations of genome folding [30•,31]. This regime has been associated with the notions of crumpled polymers [32] (or fractal globules) that emerge from the decondensation of unknotted, mitotic-like polymers [29]. In this framework, the presence of topological constraints arising from steric interactions and confinement dramatically slows down the dynamics of large-scale organization. Genome folding thus remains out-of-equilibrium even at long timescales, as observed in Hi-C or MSD studies on synchronized cells at different time points along the cell cycle [33,34] (Figure 1c).

Passive interactions constrain chromatin motion

The organization and dynamics of chromosomes *in vivo* are further impacted by the many mechanical forces that emerge from the various biochemical factors acting on chromatin. In particular, many processes driving small and large-scale genome organization (TAD formation, A/B compartmentalization, nuclear positioning) have been associated with 'passive', ATP-independent mechanisms involving protein–protein and/or protein–DNA interactions [18] (Figure 2b). Polymer models have been instrumental in understanding the role of such interactions.

Generically, the presence of passive (transient or permanent) intra-chain or inter-chain loops constrains the local motion of monomers. This confinement effect inhibits their intrinsic ability to diffuse, leading to a decrease in

the diffusion amplitude Γ, and may potentially induce a global compaction of the chromatin chain, leading to a smaller Flory exponent β, and thus a lower diffusion exponent α [35]. For example, Socol *et al.* [27••] showed that a simple Rouse model decorated with non-specific forces, putatively nucleosome–nucleosome interactions, may explain the difference in chromatin mobilities observed between *in vivo* and *in vitro* yeast chromatin ($\Gamma_{vivo} \sim \Gamma_{vitro}/3$) [27••]. Interestingly, to fit both the experimental Hi-C and MSD data, the lifetime of such transient loops in the model may exceed several seconds, considerably longer than typical timescales of chromatin local fluctuations ($\sim 10^{-2} - 10^{-1}$ s) [30•]. Loops may therefore play the role of momentary anchors for chromatin, perturbing dramatically its dynamics. In a different context, similar conclusions on loop lifetimes were inferred by Khanna *et al.* when studying the constrained relative motion of V and DJ immunoglobulin segments in B-cells [20••]. The MSD data was found to be consistent with a network of long-lived (∼ seconds) transient loops, typical of a gel phase near the sol-gel transition [20••].

More specifically, the spatial partitioning of chromosomes into active/inactive (A/B) compartments emerges from the ability of architectural proteins like HP1 and PRC1 to oligomerize and/or form liquid-like condensates [36]. Polymer models [37] have suggested that such epigenetically driven interactions may drive a (micro)-phase separation of chromatin states consistent with Hi-C data and the formation of H3K9me3/HP1 intra-nuclear droplets [38]. The dynamical consequences of these interactions are numerous. Strongly interacting regions will exhibit low mobility due to interactions with other monomers sharing the same chromatin state [30•]. As hetero-heterochromatin interactions were suggested to be stronger than their euchromatic counterparts based on polymer-physics interpretations of Hi-C data [37,39], this implies that heterochromatic loci may generally exhibit slower dynamics [23,31,40•] ($\Gamma_{hetero.} \leq \Gamma_{eu.}$; $\alpha_{hetero.} \leq \alpha_{eu.}$), as observed experimentally [5,22]. Interestingly, polymer models also predict that monomers inside a given compartment move collectively over second-long periods [23,40•], thus providing for a mechanistic interpretation of the micron-size dynamic compartments observed in mammalian nuclei [5,14,15] (Figure 1b).

Passive interactions may also play an important role in the spatial positioning of the genome, notably at the nuclear periphery, although the microscopic origins of membrane–chromatin interactions remain unclear. The localization of genomic regions at the membrane leads to the reduction of their available diffusion space, and may hence result in smaller diffusion amplitudes Γ for perinuclear loci [7,41]. MSD experiments have indeed shown a decrease in mobility of about 30–40% for regions preferentially interacting with the nuclear envelope like telomeres in yeast via SIR4 [7] or heterochromatin and lamina-associated domains in higher eukaryotes [22], potentially mediated by Lamin B1 [8]. Interestingly, another major component of the nuclear lamina, Lamin A, was shown to greatly influence chromosome dynamics throughout the nuclear interior [42,43], suggesting that the presence of interactions between chromatin and the nucleoplasmic lamina network may help regulate gene mobility.

Active processes enhance chromatin mobility

Chromatin is also subjected to many energy-fueled processes, including nucleosome positioning, transcription, replication, loop extrusion or DNA repair. These active processes are intrinsically out-of-equilibrium and are expected to significantly affect the local and global dynamics of chromosomes. Although very few experiments have directly addressed the role of active processes on chromosome dynamics, many polymer models have been introduced to hypothesize their dynamical consequences.

At a coarse-grained level, an intuitive way of introducing the impact of active processes is via an increased, effective temperature acting on monomer diffusibility. 'Hot', fast particles correspond to highly active, euchromatic regions while 'cold', slow particles refer to more passive, heterochromatic loci. Polymer models accounting for such epigenetic-related heterogeneities in the local thermal fluctuations allowed to recapitulate structural effects like the A/B-type compartmentalization [23,44].

At a finer scale, active processes may be accounted for via an 'active noise' that also enhances the local fluctuations of monomers. In this framework, genomic loci are considered as connected self-propelled particles moving in random directions [45], as connected extensile dipoles [46•], or as passive monomers in an active viscous medium [47] (Figure 2c). Theoretical analysis of such models has shown that the diffusivity of the polymer is significantly increased compared to standard Rouse model ($\Gamma_{active} > \Gamma_{Rouse}$), and that the MSD may exhibit a superRousean regime ($\alpha > 0.5$) at short time-scales, while remaining Rousean or subRousean ($\alpha \leq 0.5$) at longer time-scales. Interestingly, these predictions are consistent with experiments probing the dynamical effect of ATP where lower MSDs and weaker spatially correlated motions were observed in yeast or mammalian cells following ATP depletion [14,46•,48]. Furthermore, they provide a rationale for the *in vivo* observations of super-Rousean dynamics in various contexts [3,42,43].

However, the exact nature of this active noise is still unclear. One potential contribution may arise from the intense traffic of active motors like chromatin remodeling factors or RNA and DNA polymerases on chromatin: according to Newton's third law, the directional

displacement of molecular motors along the chromatin fiber may generate significant forces on the substrate [49]. For example, response to DNA damage is associated with an increased chromatin mobility that can be related to ATP-dependent processes [13], putatively via the motor activity of the ATPase Rad54 that can actively translocate along chromatin [50]. Another contribution may lie in nuclear myosin activity. Recent evidence in yeast suggests that nuclear myosins can bind to some transcription factors attached to chromatin, and hence propel the underlying genomic locus through the actin nuclear matrix, potentially over large (micron-scale) distances [51].

Some polymer models have also explicitly described the impact of specific active mechanisms on chromosome dynamics. Foglino *et al.* showed that the translocation of multiple fast motors (e.g. RNA polymerases) can exert large-enough mechanical forces on the chromatin fiber to enhance its overall mobility [49]. This is compatible with the higher diffusion amplitude Γ observed by Gu *et al.* upon gene transcriptional activation in mouse ES and epiblast-like cells [4], but contradicts other experiments showing opposite effects in two human cell lines [3,6]. For the loop extrusion mechanism by SMCs involved in TAD formation and mitotic condensation [18], Nuebler *et al.* predicted that the passage of loop extruding factors will slightly increase the chromatin mobility, but only on a short time-scale representing the residence time of the loop extruding factor at a given locus [52]. However, this cannot explain the role of condensins in constraining local chromatin motion during mitosis as observed by MSD measurements in fission yeast [53].

Significant challenges nonetheless remain to fully characterize the role of ATP and energy-consuming processes in the regulation of chromosome dynamics. For example, global depletion of nuclear ATP has been associated with lower mobilities [14,46•,48]. Is it mainly caused by a general reduction of molecular motor activity affecting the 'active noise' contribution of local fluctuations or by the expected increase of the nuclear concentration of Mg^{2+} cations normally chelated to ATP [54], that may lead to chromatin condensation [5,54], and thus to slower dynamics via passive (electrostatic) interactions [5]?

Similarly, how to interpret that inducing some active processes like transcription may inhibit chromatin mobility [3,6,14]? Clearly, an increase in active noise would enhance dynamics and cannot explain this phenomenon. Possibly, reduced dynamics may arise from passive interactions between active motors [6,13] via the formation of transcription or replication factories, from the relocalization at the nuclear periphery [9] or from local changes in the chromatin fiber structure due to differential histone/epigenetic-marks turnover [10••].

Discussion

Nuclear genome organization is driven by numerous passive and active processes that may have very different signatures on chromosome dynamics, but not necessarily on chromosome structure: the presence of passive interactions generally slows down the dynamics and constrains the motion of genomic loci, while active mechanisms are associated with an increase in chromatin mobility (Figure 2). The recent combination of structural and dynamical experiments with biophysical modeling has demonstrated the power of dynamical studies to assess quantitatively the basic mechanistic properties of chromatin. The future development of these approaches would be essential to rationalize novel experimental observations and disentangle current ambiguities. For example, they might be used to clarify whether the increased dynamics observed during DNA damage is due to a stiffening of the fiber [12], to local chromatin decompaction, which might result from changes in histone degradation [10••,11], and/or to the higher activity of some molecular motors [13] like Rad54 trafficking on chromatin.

In this context, probing chromosome dynamics using biophysical models may provide a significant contribution to our understanding of its functional roles, and may shed new light on how chromatin fiber properties, passive and active forces impact the dynamical communication between distal loci. These considerations are especially relevant for promoter–enhancer interactions [55]. Indeed, the molecular mechanisms behind the transcriptional control by enhancers remain largely unknown. Current views propose an activity-by-contact model where activation is related to spatial proximity [56,57]. The analysis of the dynamical aspects of such models by studying the first-encounter and residence times between promoters and enhancers [30•,58] could provide one of the keys to gain new insights into this crucial regulatory process.

Finally, the link between nuclear ATP, active processes and chromatin mobility would deserve further scrutiny. The direct correlation between nuclear ATP levels and ionic content [5,54] suggests that ATP depletion experiments alone are not sufficient to disentangle the respective roles of electrostatic condensation and of ATP-dependent activity in the observed alterations of chromatin dynamics [14,46•,48]. Further experimental studies based on the precise joint-measurement of nuclear ATP and free Mg^{2+} concentrations [54] as well as on the systematic inhibition of chromatin-binding ATPases [5] would be highly desirable to resolve these important ambiguities. Similarly, perturbation experiments decoupling the motor activity of key complexes like RNA polymerases from their intrinsic capacity to self-interact or phase separate [59] would allow for a rigorous assessment of the relevance of the different proposed mechanisms on chromatin activity.

Conflict of interest statement

Nothing declared.

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