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# The self-stirred genome: large-scale chromatin dynamics, its biophysical origins and implications

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## Abstract

The organization and dynamics of human genome govern all cellular processes – directly impacting the central dogma of biology – yet are poorly understood, especially at large length scales. Chromatin, the functional form of DNA in cells, undergoes frequent local remodeling and rearrangements to accommodate processes such as transcription, replication and DNA repair. How these local activities contribute to nucleus-wide coherent chromatin motion, where micron-scale regions of chromatin move together over several seconds, remains unclear. Activity of nuclear enzymes was found to drive the coherent chromatin dynamics, however, its biological nature and physical mechanism remain to be revealed. The coherent dynamics leads to a perpetual stirring of the genome, leading to collective gene dynamics over microns and seconds, thus likely contributing to local and global gene-expression patterns. Hence, a possible biological role of chromatin coherence may involve gene regulation.

### Keywords

chromatin dynamics; genome self-organization; chromatin coherent motions; active nucleoplasm; genome biophysics; gene regulation

## Introduction

The human genome consists of about 2 m of DNA organized into chromosomes, tightly packed inside a cell nucleus barely 10 $\mu$m in diameter [1]. Chromosomes are comprised of linear DNA molecules wrapped around nucleosomes, made of core histone proteins, forming a chromatin fiber [1, 2]. Twenty years ago, the Human Genome Project revealed the sequence of the human genome [3], while in the past decade chromosome conformation capture techniques uncovered its 3D static folded state [4–7]. Such a picture is extraordinarily rich and intricate, elucidating the static structure, architecture, topology and

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organization of the genome inside the nucleus at many length scales: The chromatin fiber is spatially organized into a hierarchy of loops, leading to formation of topologically associated domains, further grouped into A and B compartments, corresponding to transcriptionally active and inactive regions, respectively, and finally, at larger length scales, chromosome territories [4–7].

Although the static folded state of the genome has been described in detail, it remains unclear how to reconcile this picture with its dynamic nature, both biochemical and biophysical. Chromatin serves as a template for number of biological processes such as transcription, replication and DNA repair. Therefore, when needed, DNA has to be accessible to the molecular machinery of these processes, inevitably leading to local chromatin rearrangements and spatial displacements of both DNA and its molecular machinery. Figure 1 illustrates the close interplay between local changes in chromatin structure due to dynamical and ATP-dependent DNA transactions, such as transcription and replication, and chromatin dynamics at different timescales and length scales. The biochemistry of such DNA transactions has been extensively studied over several decades [1, 2], but the mechanistic picture behind their contributions to the physical motion of chromatin remains elusive [6–10]. Recent advances in the microscopy and image processing techniques open new avenues for elucidating the genome's positional fluctuations *in vivo*, illuminating its physical behavior in space and time. These efforts are revealing unusual motion of chromatin, different from free diffusion of small molecules or motor-driven motion of cytoskeletal filaments. In this review, we survey the current knowledge about the large-scale physical movements of the genome in live cells and their possible impact on chromatin physiology.

## Chromatin dynamics: from nucleosomes to genome-wide motions

The human genome undergoes large-scale reorganizations during interphase, the time between two cell divisions: First, highly compact mitotic chromosomes decondense into loosely packed interphase chromosomes, each of which presents a long linear polymer and occupies a well defined region, chromosome territory, in the cell nucleus [1, 11]. Next, the genome is duplicated, followed by chromosome condensation, preparing genome for segregation during mitosis [1]. Notably, nuclear size monotonously increases during interphase [12]. In addition, numerous local chromosome transactions occur at specific DNA sites, such as transcription, DNA replication and DNA repair, contributing to local chromatin dynamics during the cell cycle [Fig. 1].

Historically, chromatin dynamics has been studied by tracking motions of fluorescently labeled nuclear proteins highlighting chromatin structures of interest; from nucleosomes [13–15], single genes [16–25], nuclear proteins, enzymes and machineries [26–33], subchromosomal foci [34, 35] to entire chromosome territories [36, 37]. In turn, measuring fluorescence recovery after photobleaching [38–41] and photoactivation [42, 43] of nuclear proteins, has illuminated their kinetics. All of these approaches provide an invaluable insight into the timescales and length scales of dynamic processes in the cell nucleus. These studies found chromatin dynamics largely subdiffusive to diffusive, with an occasional directed motion. The dynamical information obtained by single particle tracking reports on local

chromatin dynamics of a tracked entity. How these local motions amount or contribute to the global genome-wide dynamics remains an open question.

Recent progress shedding light on the global genome-wide chromatin dynamics *in vivo* came from a new spectroscopy-based method Displacement Correlation Spectroscopy (DCS) [44]. DCS is a microscopy-based image correlation method, which introduced spatiotemporal spectroscopy analysis into the dynamic image correlation processing. It maps chromatin dynamics over time intervals, while concurrently sampling all time intervals accessible by the experiment. Using transgenic histones H2B-GFP as markers of chromatin position and high-resolution spinning disc confocal microscopy, this noninvasive technique enables measurement of chromatin dynamics in real time across the entire nucleus in live cells [Fig. 2A], while simultaneously probing different timescales and length scales [44]. Using DCS chromatin dynamics was found to be subdiffusive [44]. Strikingly, DCS revealed two distinct timescales and length scales in nucleus-wide chromatin dynamics: (*i*) local, fast movement consistent with single particle tracking studies [Fig. 2B], and (*ii*) a slower, coherent movement – which is new – where chromatin in large regions (~ 3-5 μm) moved in same direction for several seconds [Fig. 2C & D] [44]. Both types of motion occur in the nucleus concurrently and superposed. The discovery of coherent chromatin motion was later corroborated by high-resolution imaging of local motion of single nucleosomes and replication domains [45, 46]. Recently, DCS-like correlative imaging and spectroscopy analysis has reproduced nucleus-wide measurements of the coherent motion in U2OS cells over the same time intervals and length scales as DCS revealed in HeLa cells [44, 47]. This speaks to the reliability and robustness of the correlative spectroscopy analysis introduced in DCS [44] as well as generality of the phenomenon of coherent chromatin motion in the interphase nucleus.

## Micron-scale coherence of chromatin motion

The fact that interphase chromatin moves coherently over microns and seconds, has major implications for organization of nuclei on micron-second scales and collective gene behavior [Fig. 2A–D]. Strikingly, regions of coherent motion were found to extend beyond the boundaries of single chromosome territories suggesting elastic coupling of motion over length scales much larger than genes [44]. It is unclear if the coherence has a biological role or is an epiphenomenon occurring as a result of other biological processes. However, even as an epiphenomenon, coherence allows groups of genes to travel together for several seconds. Such collective gene dynamics might have important implications for the local and global gene expression patterns in both space and time, impacting the spatiotemporal evolution of gene regulation.

To elucidate the biological role of coherent motion, it is critical to understand the biophysical mechanism behind it. Active (ATP-dependent) processes were shown to drive coherent motion without the involvement of cytoplasmic cytoskeletal forces, thus pointing to the activity of nuclear AT-Pases [44, 48]. The list of possible candidates is long. Interestingly, upon inhibiting transcription, replication or topoisomerase activity, coherent motion becomes eliminated [44, 47]. Surprisingly, the local chromatin displacements become uncoupled, yet their amplitude significantly increases [44]. Inducing direct DNA

damage in the form of DNA double stranded breaks, and thus initiating the DNA damage response, led to the same effect [44]. This suggests that DNA damage response activated upon perturbing of DNA-related processes (e.g. transcription, replication) is responsible for the elimination of the chromatin coherence by relaxing the chromatin and preventing the long-distance communication of forces. In other words, a loss of function of a nuclear ATPase leads to a gain in function by activating the DNA damage response [44]. This connection requires that we understand the chromatin dynamics associated with the DNA damage response in order to elucidate the dynamical contribution of nuclear enzymes to the emergence of coherent motion. Moreover, it implies that coherent chromatin motion is a signature of a healthy cell.

In parallel to the experimental efforts, new theories have been developed to illuminate the physical origin of coherent chromatin motion. Such approaches conceptually and mechanistically account for the non-equilibrium sources of activity without knowing their molecular identity. Motivated by the DCS measurements, a first chromatin hydrodynamics theory was developed [44, 49]. In this theory, *hydrodynamic* (fluid-mediated) interactions between the chromatin and nucleoplasm were considered, while simultaneously accounting for two types of sources of non-equilibrium activity: *scalar* and *vector* events [49]. Scalar events represent the local condensation and decondensation of chromatin that is mostly caused by the chromatin remodelers [49, 50]. In contrast, vector events are generated by nuclear enzymes such as polymerase II, helicase and topoisomerase II, which can be represented by a *force dipole*, thus possessing both a magnitude and direction [49]. A force dipole consists of two equally large, but opposite forces, corresponding to a force that an enzyme applies on the chromatin fiber and an opposite force applied on the surrounding fluid by virtue of Newton's third law [Fig. 2E]. Hence force dipoles induce flows that in turn transmit forces on the chromatin fiber. Such flow-mediated interaction is referred to as hydrodynamic coupling. This theory predicts that the chromatin concentration fluctuations (condensation/decondensation) dominate chromatin dynamics at short length scales, while the force-dipole activity dominates the long length-scales [49].

Notably, the physical size of active nuclear enzymes such as RNA polymerase II, helicase, or topoisomerase is ~ 5 nm and the coherent regions span 3–5 $\mu$m, thus a single force dipole is unlikely to drive the coherent motion. Instead, this suggests that the nucleus-wide coherent motion might be caused by a collective effort of ATP-dependent force-generating nuclear enzymes, as supported by experiments [44]. It could be hypothesized that such an effect can be achieved by a *nematic* (parallel) alignment of force dipoles [Fig. 2E] in the following ways: (*i*) a local transient force applied on the chromatin fiber might align the force dipoles along the chromatin fiber [Fig. 2F], or (*ii*) through hydrodynamic coupling, i.e., fluid-mediated interactions, between force dipoles [Fig. 2G]. In fact, both effects might occur in the nucleus at the same time, with force-induced alignment nucleating a region of coherent motion and hydrodynamic coupling growing the size of the coherent region.

Numerical simulations of hydrodynamic self-interactions of the chromatin fiber with dipolar activity identified the presence of *extensile* force dipoles (outward forces) as required for generation of the coherent chromatin motion [48]. The extensile force dipoles were also shown to generate organized nucleoplasmic flows and lead to a local nematic alignment of

the chromatin fiber. In contrast, *contractile* force dipoles (inward forces) lead to an accelerated Brownian-like chromatin dynamics and no fiber alignment [48].

An alternative approach omits the presence of nucleoplasm and fluid-mediated interactions, instead using a 3D-conformational space of the chromatin fiber emerging from a quasi-equilibrium energy landscape [51]. To generate such an energy landscape, Langevin dynamics at an effective temperature was assumed, which implicitly captures the chromatin activity and its non-equilibrium nature. This model was also able to capture the large-scale coherency of chromatin motion [51]. Another hydrodynamics-free model explores the spatiotemporal dynamics of interphase chromosomes describing chromatin as a heteropolymer directly informed by the HiC data of human chromosomes [52]. To mimic chromatin activity, an isotropic noise was used and the large-scale spatial correlation of local chromatin displacements was again successfully recapitulated [52]. Moreover, chromatin dynamics was found to be *glassy* with a wide range of subdiffusive behavior [53].

In all of these models, activity of nuclear enzymes acting on the chromatin fiber is required to generate coherent chromatin motion, as corroborated by experiments. However, while one group of models finds the chromatin fluid-mediated interactions to be critical for generating the spatial coherence in chromatin dynamics, the other group of models suggests that specific conformations of the fiber, as revealed by HiC or determined by proposed energy landscapes, might be of importance. The former suggests that nucleoplasm plays a major role in large-scale chromatin dynamics, whereas the latter might indirectly imply nucleoplasm in facilitating formation of the preferred chromatin fiber conformations.

## Role of nucleoplasm in chromatin dynamics

To date, the observed active motion of interphase chromatin has been attributed purely to the enzymatic activity occurring directly at the chromatin fiber. The presence of nucleoplasm was either neglected or considered to be a passive solvent, in which the chromatin is immersed. However, the nucleoplasm is a complex fluid, and possibly active itself [Fig. 3]. It contains not only RNA and proteins, but also a plethora of subnuclear bodies such as nucleoli, speckles and Cajal bodies [Fig. 3A] [1]. Thus, a next-order description of the nucleoplasm would be a colloidal suspension containing polydisperse colloidal particles (50nm – 3$\mu$m) [Fig. 3B]. These particles, e.g. nucleoli or nucleoplasmic enzymes, might not be only advected by the flows generated by the active chromatin fiber, but also directly contribute to chromatin dynamics by interacting hydrodynamically and/or sterically with the chromatin fiber [Fig. 3C–D]. Moreover, recent observations of nucleolar coalescence in human cells *in vivo* suggest that such a dynamical event in the nucleoplasm might lead to a large-scale chromatin reorganization and dynamics in the nucleus [Fig. 3F] [54, 55]. Intriguingly, velocities measured for the growth of radius of nucleolar neck between two coalescing nucleoli were similar to velocities measured for interphase chromatin [Fig. 3F] [44, 54]. Furthermore, many subnuclear bodies are known to be sites of active processes themselves, e.g., ribosomal synthesis in nucleoli, RNA splicing in speckles [1]. Such internal activity might also in some cases contribute to nucleoplasmic and chromatin motions.

Recently, liquid-liquid phase separation (LLPS) of nucleoplasmic proteins has been implicated in genome organization and function. For example, nucleoli, the largest nuclear

organelles and sites of ribosomal biogenesis, were shown to form via LLPS and behave like liquid droplets [54–57]. Similarly, transcription machinery at actively expressed genes and DNA-repair machinery at double-stranded DNA breaks were found to form liquid-like condensates [58–61]. Moreover, LLPS of heterochromatin HP1 proteins was uncovered to drive the formation of heterochromatin in genome [62, 63]. Indeed, HP1 association with parts of chromatin fiber was found to lead to a microphase separation of heterochromatin and euchromatin [64, 65]. In addition, chromatin fiber itself was suggested to have an intrinsic capacity to undergo local LLPS in the nucleoplasm [66]. It is conceivable that kinetics of such processes could directly impact genome organization as well as its local and large-scale dynamics.

Remarkably, both nucleoplasm and the chromatin fiber are comprised of active (i.e., ATP-driven) and passive (i.e., thermally driven) components. Interestingly, previous studies of colloidal mixtures found that a presence of actively driven particles leads to phase separation of active and passive colloids [67]. Similar behavior has been shown for polymer mixtures containing active and passive polymers, and was in fact proposed to facilitate positioning of chromosomes and formation of transcriptionally active and inactive genomic regions, euchromatin and heterochromatin, respectively [53, 68, 69]. Thus, activity-driven phase separations, where active entities phase separate from passive entities, might also need to be considered in our efforts to elucidate the nucleus-wide motion of genome. Indeed, in non-equilibrium systems such as chromatin and nucleoplasm, combined effects of microphase, activity-driven and liquid-liquid phase separations could occur, leading to new physical phenomena.

## From genome biophysics to gene regulation

The physical characteristics of chromatin and nucleoplasm are inseparable from their biological functions. Their material properties are critical for all cellular processes as they directly impact the central dogma of biology [70, 71]. For example, the viscoelastic nature of the chromatin and the rheological behavior of the nucleoplasm affect the timescales and length scales of local and nucleus-wide chromatin rearrangements, as well as molecular and organelle transport inside the nucleus. Thus, an insight into the physical properties of the cell nucleus and its constituents might prove integral in understanding the genome self-organization and dynamics. This is not trivial considering its non-equilibrium nature. Recent microrheology studies employing artificial as well as naturally occurring cellular probes (e.g., nucleolus) found that nucleoplasm viscosity ranges from 25-3000 Pa·s [54, 72–74]. Such viscosity was proposed to be apparent, i.e. effective, containing viscous effects from chromatin-related and nucleoplasmic enzymatic activity in addition to the viscosity of a passive fluid [54, 55]. In turn, we might speculate that by altering such activity, effective material properties of nuclear constituents could be manipulated locally and globally across the nucleus.

A spatiotemporal modulation of genomic material properties could indeed influence nucleus-wide behavior of many processes such as gene expression or DNA replication. A recent study revealed that kinetics of biomolecular crowding in the cell nucleus directly influences the kinetics and efficiency of the transcriptional machinery [75]. Moreover,

altering the supra-nucleosomal physical structure of chromatin was proposed to allow for the controlled modulation of global patterns in gene expression [76, 77]. Similarly, collective gene dynamics corresponding to the micron-scale coherent motion of chromatin might lead to concerted gene expression, implying that local conformation changes at short timescales could lead to temporal fluctuations in global gene-expression patterns. Hence, a possible biological role of the coherent chromatin motion may involve gene regulation, contributing to transcriptional heterogeneity through local chromatin rearrangements.

## Conclusions and perspective

The genome is a prominent example illustrating the critical interplay between biology, physics and chemistry in a living system. Physical properties of the genome and its nuclear environment are inseparable from chromatin physiology. Hence, insights from biophysics, polymer physics and statistical mechanics are critical to elucidate genome self-organization and non-equilibrium dynamics.

Specifically, elucidating the biophysical mechanism underlying the micron-scale coherent motion of chromatin might provide insight into spatiotemporal organization of the genome at large scales. Moreover, the coherency facilitates collective gene motion, causing groups of genes to travel together for several seconds. This phenomenon might have numerous implications, especially for gene regulation. For example, the constant local stirring of the genome through coherent motion might lead to local changes in the chromatin fiber conformation, accessibility, as well as intragenomic interactions, all of which might play a key role in gene regulation. Furthermore, chromatin motion is closely linked to the motion of nucleoplasm. Thus, nucleoplasmic flows accompanying coherent chromatin motion could contribute to gene regulation by facilitating the distribution of transcription machinery in the cell nucleus. Such local advective flows might accelerate the otherwise diffusion-limited transport. In addition, considering the complex and active nature of the nucleoplasm, we might need to rethink its role in both genome organization and dynamics.

Future studies are needed to connect the detailed picture of static genome folding with its statistics of folding conformations, large-scale dynamics and gene-expression patterns. The biomedical implications of such approaches are far reaching, as they might lead to therapies able to treat complex multi-gene diseases such as cancer.

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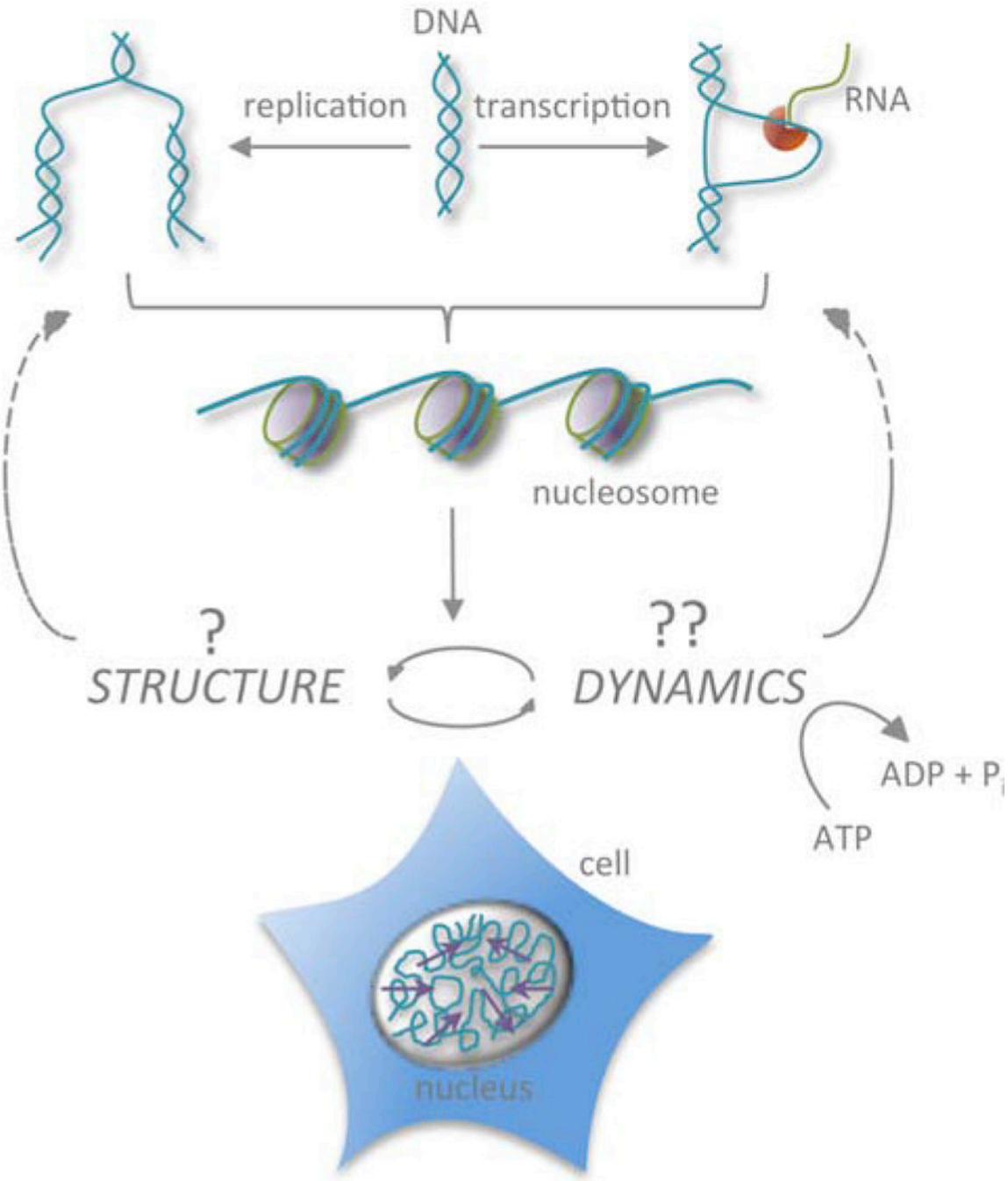


**Figure 1:**
Chromatin structure versus dynamics. Cartoon illustrating a close interplay between local changes in chromatin structure due to dynamical and ATP-dependent DNA transactions, such as transcription and replication, and chromatin dynamics at different length scales and timescales.

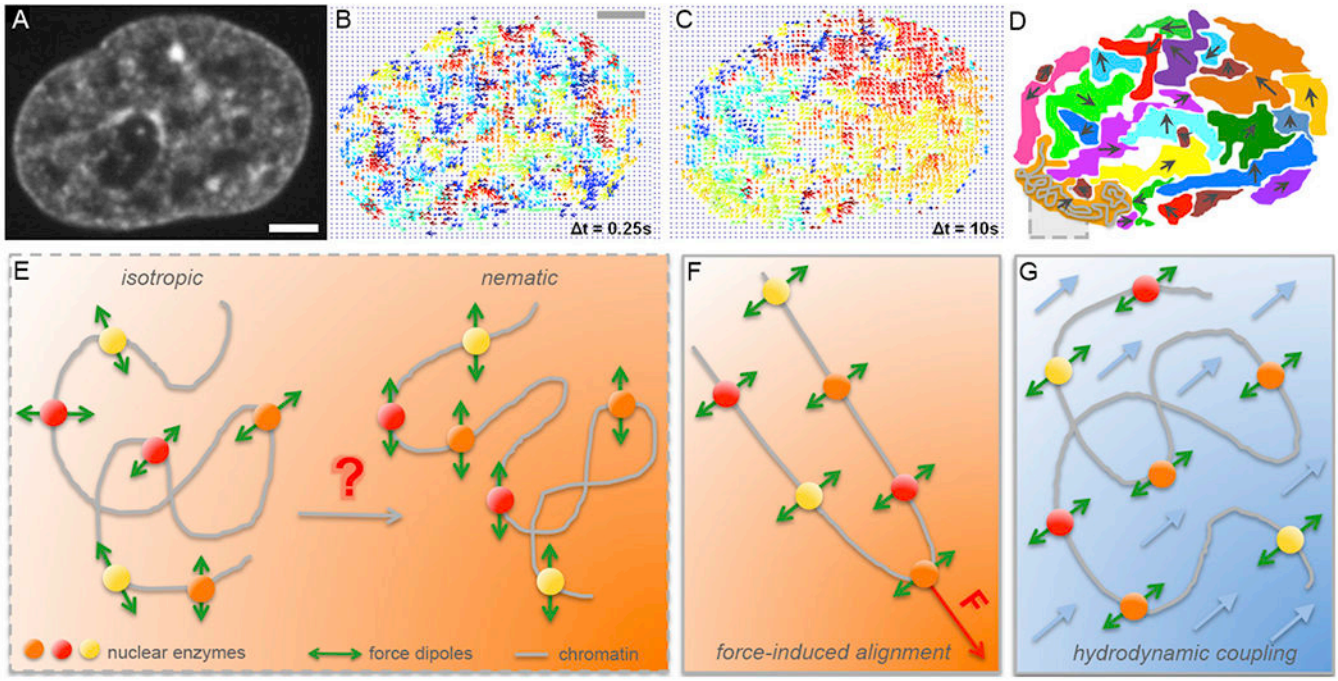


**Figure 2:**

Micron-scale coherence of interphase chromatin. (**A-D**) Mapping of interphase chromatin dynamics using Displacement Correlation Spectroscopy (DCS) [44]: (**A**) A fluorescent micrograph of chromatin visualized by histones H2B-GFP in a live HeLa cell nucleus. (**B**) DCS map of chromatin displacements displayed as vectors (arrows) for $\Delta t = 0.25$ s. The displacement vectors are color-coded by their direction, i.e., the vectors of the same color correspond to a motion in the same direction. Note, chromatin motion at timescale of $\Delta t = 0.25$ s is uncorrelated. (**C**) DCS map of chromatin displacements for $\Delta t = 10$ s. Chromatin motion shows regions, where chromatin displacement vectors are correlated, i.e., chromatin motion is coherent in those regions at timescale of $\Delta t = 10$ s. (**D**) Cartoon highlighting the observed regions of coherency in (C). A grey box highlighting a chromatin fiber (*grey*) inside a coherent region (*orange*). (**E**) Schematics illustrating nuclear enzymes acting on chromatin fiber as force dipoles. In an isotropic state force dipoles are pointing into random directions, whereas in a nematic state force dipoles are ordered in parallel and can lead to coherent chromatin motion over large length scales. (**F-G**) Two hypotheses of inducing a local nematic order of force dipoles: (**F**) force-induced alignment by a local action of a transient force, and (**G**) hydrodynamic coupling, i.e. fluid-mediated interactions between force dipoles (fluid in *blue*, fluid flows indicated by *blue arrows*). (A-C) Adapted from [44]. Scale bar, 2 $\mu$m.

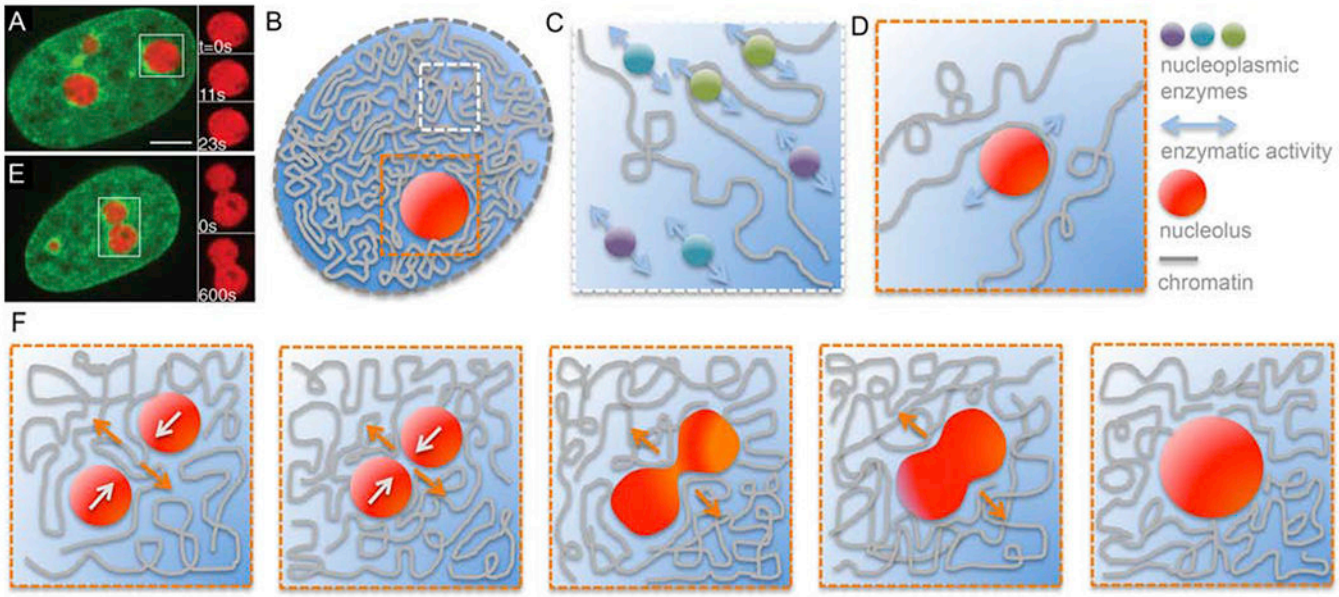


**Figure 3:**

Role of nucleoplasm in chromatin dynamics. (**A**) Micrograph of a HeLa cell nucleus with fluorescently labeled chromatin (*green*, H2B-GFP) and nucleoli (*red*, NPM-mApple). Inset shows an enlarged boxed nucleolus at times $t = 0$, 11 and 23 s [54]. (B) Cartoon of a cell nucleus containing chromatin (*grey*), subnucleolar bodies such as nucleolus (*red*), and nucleoplasm (*blue*). White box highlights a region containing chromatin and nucleoplasm, orange box shows a region around a nucleolus. (**C**) Enlarged view of the white boxed region from (B) showing a schematics of free nucleoplasmic enzymes interacting hydrodynamically with each other leading to a nematic (parallel) alignment of their force dipoles. This could lead to a generation of local nucleoplasmic flows contributing to local chromatin dynamics. (**D**) Enlarged view of the orange boxed region from (B) showing a schematics of a moving nucleolus sterically interacting with chromatin fiber and thus leading to local rearrangement and motion of chromatin. This might occur also for nucleoplasmic enzymes or other subnuclear bodies. (**E**) Micrograph of a HeLa cell nucleus with fluorescently labeled chromatin (*green*, H2B-GFP) and two coalescing nucleoli (*red*, NPM-mApple). Inset shows an enlarged view of the boxed nucleolar coalescenc at times $t = 0$ and 11 s [54]. (**F**) Schematics of nucleolar coalescence leading to large-scale chromatin reorganization and dynamics inside the nucleus. Orange and white arrows indicate the local motion of chromatin and nucleoli, respectively. (A) and (E) adapted from [54]. Scale bar, 5 $\mu$m.