



A Brownian dynamics study of liquid–liquid phase separation in multiscale chromatin networks

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Abstract In living cells, proteins involved in specialized biochemical functions are often spatially organized within biomolecular condensates. Increasing evidence suggests that some of these condensates, including DNA repair condensates, emerge through liquid–liquid phase separation (LLPS). In the nucleus, however, condensates form within a highly heterogeneous environment composed of chromatin fibers, RNA, and additional protein scaffolds such as PAR chains, all of which may interact with phase-separating proteins. Moreover, condensate formation is frequently associated with specific chromatin conformations; for instance, loop extrusion has been proposed as a mechanism promoting DNA repair condensates. Here, we investigate how the surrounding fibrous environment controls the morphology and spatial organization of phase-separated condensates. Using Brownian dynamics simulations of minimal models combining Lennard–Jones particles with fixed fibrous substrates, we examine the respective roles of local fiber geometry and large-scale network organization, reflecting the multiscale architecture of chromatin. We show that protein–fiber interactions strongly influence droplet positioning relative to the substrate, in a manner analogous to wetting transitions in soft condensed matter systems. Both local geometric constraints and global network organization markedly affect droplet size, morphology, and multiplicity. In addition, large-scale asymmetries in fiber organization can induce robust spatial localization of the dense phase. Our results thus highlight how multiscale structural heterogeneity of the nuclear environment can regulate the emergence and organization of biomolecular condensates.

1 Introduction

Biomolecular condensates, also referred to as membraneless organelles, are mesoscale structures with radii ranging from about 10 nm to several micrometers [1–8]. These assemblies are found both in the cytoplasm (e.g., stress granules or P-bodies) [1, 2] and in the nucleoplasm of eukaryotic cells, where they include nucleoli, repair foci, and transcription factories [6, 9–12]. Many of these condensates display liquid-like properties and are thought to form via liquid–liquid phase separation (LLPS), a process in which a homogeneous mixture demixes into two coexisting liquid phases [5, 13, 14]. Hallmark features of LLPS include condensate fusion [15], internal rearrangement, and dynamic exchange of components between dilute and dense phase [16–18].

In the nucleus, LLPS of RNA and protein factors underlies the formation of condensates involved in DNA replication and repair [19–21], transcriptional regula-

tion [12], and RNA processing [3, 6]. These processes are tightly coupled to the structural organization of chromatin, a heteropolymer of DNA and histone proteins arranged into epigenetic domains [22–25], characterized by preferential intra-domain contacts [26]. The interplay between chromatin folding and condensate formation is therefore increasingly recognized as a key regulator of nuclear organization and gene expression [6, 27–30].

Recent advances in imaging enable quantitative characterization of condensate geometry and dynamics [1, 18, 31, 32]. A striking observation is the coexistence of many mesoscopic condensates within single cells, pointing to robust mechanisms to control growth mechanisms. While non-equilibrium biochemical reactions have been proposed to arrest Ostwald ripening [5, 33], alternative mechanisms may arise from the nuclear environment itself. In particular, chromatin fibers provide a heterogeneous scaffold that can influence nucleation, wetting, and droplet stability [34]. In this context, LLPS and wetting are intrinsically coupled, as

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both are governed by the balance of interfacial free energies.

Phase separation is primarily characterized by the number, size, and dispersity of droplets. In the presence of fibers or surfaces, the spatial positioning of the dense phase with respect to these interfaces becomes an additional key property. This is particularly relevant for nuclear condensates: For instance, DNA repair condensates are observed to form specifically at damaged sites [19]. We refer here to this phenomenon as localization of the dense phase. Several mechanisms may account for such localization, including local nucleation triggered by a perturbation [19], colocalization of a pre-existing droplet and a specific site [35], or redistribution of material via coarsening dynamics [20]. Disentangling these contributions requires understanding how geometry alone can bias condensate positioning.

The physics of wetting on fibers has been extensively studied at macroscopic scales [36–38], while at smaller scales thermal fluctuations and finite-size effects become important [39–41]. In biological systems, additional complexity arises from the multi-scale organization of chromatin, including its geometry, topology, and biochemical heterogeneity. On the LLPS side, minimal theoretical models such as Flory–Huggins descriptions have provided key insights into condensate formation [33, 42–46]. These approaches capture the essential role of weak multivalent interactions between biomolecules, often modeled as effective isotropic interactions, and highlight the sensitivity of phase behavior to small parameter variations.

While protein–protein interactions have been extensively characterized, the role of substrate-binding interactions and of the underlying geometry remains less understood [34, 47]. In particular, although the effects of network elasticity and concentration on embedded droplets have been studied [39, 45, 47–49], it is still unclear how the geometry of a fibrous scaffold controls condensate size, number, and spatial organization. However, some studies indirectly suggest that geometric changes of chromatin are critical to condensate formation. For instance, some experiments correlate loop extrusion, chromatin domain formation and condensate growth [28].

In this article, we address this question using minimal coarse-grained models. We perform Brownian Dynamics simulations of phase-separating fluids interacting with fixed fibers, focusing on how both local fiber geometry and large-scale network organization affect the macroscopic structure of the dense phase. By neglecting chromatin flexibility, we isolate the role of geometry and interactions, and provide a baseline description of LLPS in the presence of an immobile scaffold.

As a reference, we first consider a Lennard–Jones fluid in bulk, where phase separation leads to the formation of a single droplet at equilibrium. We then progressively introduce chromatin-like fibers with increasing geometric complexity. We analyze single fibers (straight, zigzag, and looped) to probe the role of curvature and intersections, and extend the study to

multi-fiber networks with controlled spatial organization, ranging from regular to disordered configurations.

We show that fiber geometry provides a robust control of condensate organization. First, protein–chromatin interactions induce wetting transitions that modify droplet morphology and shift the effective phase behavior. Second, local geometric features such as loops or intersections act as preferential binding sites, enabling the coexistence of multiple droplets in regimes where bulk systems would coarsen into a single domain. Third, the large-scale organization of the fiber network controls the spatial localization of the dense phase, with structural inhomogeneities driving condensates toward chromatin-specific regions. Together, these results demonstrate that chromatin geometry alone can regulate condensate size, multiplicity, and positioning, providing an equilibrium physical mechanism that complements biochemical and non-equilibrium models of condensate organization.

2 Model

2.1 Model for the proteins condensate in presence of chromatin

As a minimal model of a phase-separating fluid around fibers, we use an effective two-species system, including explicit proteins P and fixed chromatin C into an implicit solvent. As chromatin beads are fixed, there are only two kinds of pair interaction potentials, denoted U_{PP} for the protein–protein interactions and U_{PC} for protein–chromatin interactions. These interaction potentials account for the mean influence of solvent particles. The interaction between two particles m and n depends on their species P or C (hereafter labeled α and β) and on their relative distance $r_{mn} = |\mathbf{r}_m - \mathbf{r}_n|$. The evolution equations of the protein positions obey Brownian dynamics (i.e., overdamped Langevin) [50], which are integrated via the LAMMPS computational package [51]:

$$\frac{d\mathbf{r}_n}{dt} = \sqrt{2D}\boldsymbol{\eta}_n(t) - \frac{D}{k_B T} \sum_{m \neq n} \nabla U_{\alpha\beta}(r_{mn}), \quad (1)$$

where we assume that all the proteins have the same bare diffusion coefficient D , and where $\boldsymbol{\eta}_n(t)$ is a Gaussian white noise of zero mean and unit variance $\langle \eta_{n,i}(t)\eta_{m,j}(t') \rangle = \delta_{ij}\delta_{nm}\delta(t-t')$, with $\eta_{n,i}$ being the i -th component of $\boldsymbol{\eta}_n$. Since the dynamics is overdamped, the velocities of the proteins at a given time are irrelevant, and the state of the system is completely described by the positions of the proteins. The particles interact with each other through a Lennard–Jones (LJ) potential, which is truncated at a distance $r_c = 2.5\sigma_{\alpha\beta}$ ($\sigma_{\alpha\beta}$ being the distance at which $U_{\alpha\beta} = 0$ which is equivalent to the particle diameter for $\alpha = \beta$), and shifted in order to ensure continuity of the potential at $r = r_c$. It reads $U_{\alpha\beta}(r) = [U_{\alpha\beta}^{\text{LJ}}(r) - U_{\alpha\beta}^{\text{LJ}}(r_c)]\theta(r_c - r)$,

where $U_{\alpha\beta}^{\text{LJ}}(r) = 4\varepsilon_{\alpha\beta} \left[\left(\frac{\sigma_{\alpha\beta}}{r} \right)^{12} - \left(\frac{\sigma}{r} \right)^6 \right]$ is the standard LJ potential and $\theta(r)$ denotes the Heaviside function (U_{PP} and U_{PC} shown in Fig. 1a).

The energy parameters of the interaction potentials are ε_{PP} and ε_{PC} . Throughout the paper, the distances will be measured in units of the protein diameter $\sigma = \sigma_{PP}$, the energies in units of $k_B T$ and time in units of σ^2/D .

2.2 Biological length scales

Since thermal fluctuations of chromatin are ignored in our model, the bead size does not need to be directly related to the persistence length of chromatin. In line with minimal models of protein phase separation [52–54], we represent one chromatin bead at the same scale as a typical DNA-binding protein, which naturally leads us to choose the nucleosome as the basic unit of chromatin fiber. The nucleosome is the fundamental building block of chromatin. It consists of 200 ± 40 DNA base pairs wrapped around a histone octamer [55,56]. Its diameter is approximately 11 nm [55], which we set as $\sigma_{PC} = 1.5\sigma_{PP}$. In human interphase cells, the genome spans $\sim 3 \times 10^9$ base pairs, corresponding to roughly 1.5×10^7 nucleosomes per nucleus. In our systems, the number of chromatin beads is referred to as the number of nucleosomes N_{nucle} , and is varied to mimic different conditions.

We do not aim to infer the spatial distribution of nucleosomes from real imaging data of a living cell, nor to choose the potentials between nucleosomes and nuclear proteins as those of a specific DNA-binding protein. Instead, our goal is to systematically vary: (1) chromatin geometry, represented by nucleosome positions, using either biologically realistic concentrations or lower concentrations for isolated fibers as detailed hereafter; and (2) protein–chromatin interactions.

2.3 Coarse-grained chromatin

2.3.1 Linear fiber

There is a large variety of chromatin geometries within the length scales under study here (nucleosomes to condensates, 10 nm to 1 μm). In order to understand the possible interactions of chromatin with condensate-forming proteins, we choose to concentrate on generic variations of the surface seen by condensate proteins near chromatin. We use both models with single fibers in an elongated simulation box, and models with several fibers in a larger cubic simulation box (Table 1). The reference geometry is an ideal case where proteins only feel chromatin as a single straight alignment of nucleosomes, each placed at a distance $d_{CC} = 1.67\sigma \approx 8.35$ nm of each other (straight fiber in Fig. 1b). In this geometry, the condensate only experiences interactions with one fiber and its periodic images. A first variation to this ideal case consists of adding the typical bending of the chromatin fiber, through a zigzag arrangement [57,58] (shown in Fig. 1c). This adds some rugos-

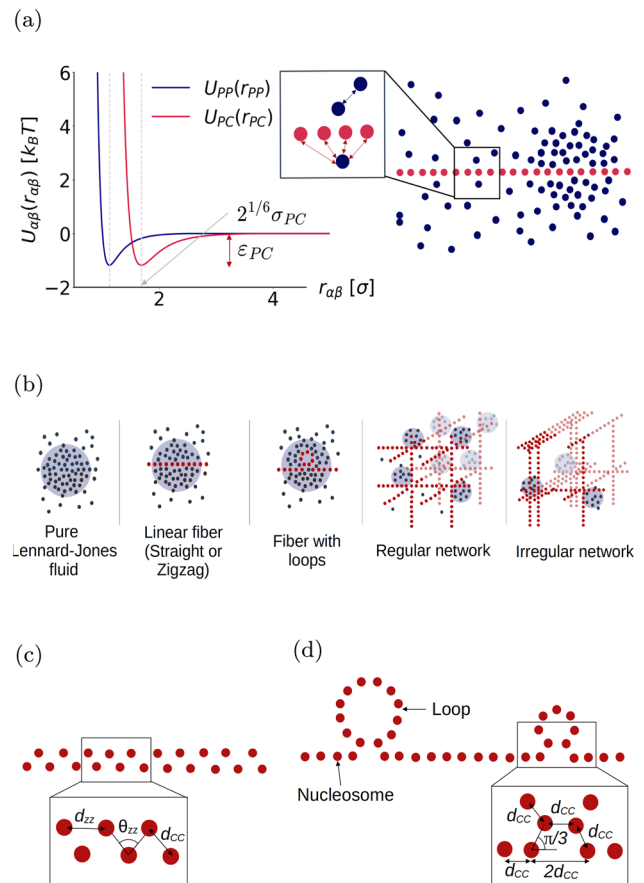


Fig. 1 a. Illustrative sketch of the inter-particle potentials $U_{\alpha\beta}$, for $\varepsilon_{PP} = \varepsilon_{PC} = 1.2$, and $\sigma_{PC} = 1.5\sigma_{PP}$ b. Geometries of the chromatin model. Nucleosomes are represented by red spheres, and free proteins by blue spheres. c. Details of the zigzag geometry. d. Details of the fiber with loops. Note that neighboring loops lie in parallel planes distant of d_{CC} to ensure a minimum distance between nucleosomes of d_{CC}

ity to the fiber at a small length scale compared to that of a typical simulated condensate with a radius of gyration on the order of 80σ (in other words, in our simulations, a droplet wetting the fiber includes several periods of the zigzag pattern). This zigzag geometry allows systematic variation of the total number of nucleosomes N_{nucle} while keeping an effective linear geometry.

2.3.2 Fibers with loops and networks

We then progressively increase the geometrical complexity by adding two related elements: (1) intersections, defined as regions of space where two nucleosomes, which are not neighbors in the chain, come close to each other, and (2) the presence of several fibers in the simulation box. There can be intersections within the same fiber if there is a loop [59,60], or between different fibers. Intersections generically mimic chromatin contacts of various origins, which can be detected by Hi-C experiments [59]. Among models with intersections, we first consider the case of a single fiber with

loops of variable number and size. The loops are constructed as a circular arrangement of nucleosomes, with the same nucleosome-nucleosome distance d_{CC} as the rest of the fiber, as shown in Fig. 1d. The size of the loops are defined by the number of nucleosomes composing them and vary from 4 to 21 nucleosomes. This geometry allows us to study how the presence of intersections can stabilize droplets and localize the droplet material at specific locations along a 1D fiber. We then consider systems with intersections in 3D, belonging to a network of intercrossing fibers in larger simulation boxes ($V = (200\sigma)^3$, around 54 times the box volume used for a single fiber, see details in Table 1). We design systems with multiple fibers arranged either (i) on a regular cubic grid, where intersections contain three orthogonal fibers (regular network in Fig. 1b), or (ii) in a randomized configuration, where the same number of fibers per direction is preserved (the fibers are still parallel to one of the box axes), but their relative positions are randomized, removing systematic intersections (Irregular network in Fig. 1b). In the randomized case, the fiber positions are either all uniformly distributed across the box, or a subset of the fibers (30% or 50%) is confined to a sub-volume ($V_{\text{sub}} = 0.25^3 V_{\text{box}}$), thereby creating a density contrast, while the remaining fibers are still uniformly distributed.

This comparison allows us to disentangle the effects of regularity versus disorder in fiber organization on condensate formation and stability, as well as the role played by network inhomogeneity. Precise values of the system input parameters are given in Table 1.

3 Phase separation in the presence of a linear fiber

In this section, we restrict ourselves to linear fibers, either straight or with a weak zigzag modulation, such that no structural features along the fiber axis can act as a preferred interaction site. The protein-protein interaction is fixed at $\varepsilon_{PP} = 1.2$, a value that leads to the formation of a single spherical droplet (of roughly 2500 proteins) in bulk conditions without chromatin.

Figures 2a and b show the protein content and volume of the denser phase as a function of chromatin-protein attraction strength ε_{PC} , for straight fibers. As ε_{PC} grows, the dense phase expands, with a marked change for $\varepsilon_{PC} > 1.0$. As Brownian Dynamics simulations include thermal fluctuations, the fluctuations of the size of dense phase domains can be quantified. The distributions are shown in Fig. 2c. In all cases, the distribution is divided into two peaks, one representing a large stable domain, and the other peak which is typical of small unstable clusters. As expected, the change of regime around $\varepsilon_{PC} = 1.0$ is reflected in the growth of the largest domains. Interestingly, the regime change also results in strong variations in the distribution of small clusters, with more clusters as ε_{PC} grows to 1.2, in contrast with a sharp decrease of their

probability for larger values of ε_{PC} . The evolution of the dense phase volume is similar for zigzag fibers, but the transition occurs at lower values of ε_{PC} and with a more pronounced effect (shown in Fig. 2a and b in light orange). This difference reflects the higher linear density of nucleosomes in the zigzag configuration, which enhances the effective chromatin-protein attraction.

These results indicate that protein-chromatin interactions shift the local phase boundary and stabilize liquid-like configurations near the surface. Such a substrate-induced modification of the phase behavior is reminiscent of wetting transitions in macroscopic systems, where the onset of complete wetting is described in terms of spreading parameters and interfacial free energies [61,62]. At the microscopic level, the wetting regimes emerge from the balance of pairwise interaction parameters. However, establishing a direct connection with macroscopic theories is not appropriate in our case. Classical wetting descriptions rely on thermodynamic interfaces, continuum density profiles, and diverging film thicknesses [37], whereas our simulations operate in a finite-size molecular regime. In such small systems, film thickness is inherently restricted to only a few particle layers, and the usual distinction between partial and complete wetting therefore loses its physical meaning [63].

While a quantitative connection between our system and classical wetting descriptions is not relevant, qualitative links exist. In addition to the volume of the liquid phase, wetting affects the shape and position of the liquid around the wettable surface. We therefore quantify how increasing ε_{PC} alters droplet morphology (sphericity, size distribution) and positioning relative to the chromatin substrate, for six values of ε_{PP} (1.0, 1.1, 1.2, 1.3, 1.4, $1.5k_B T$) across a range of ten ε_{PC} values (from 0.2 to $2.0k_B T$ in steps of $0.2k_B T$).

In the straight fiber geometry, for a protein-protein interaction strength $\varepsilon_{PP} = 1.2$, we observe the following regimes (representative configurations shown in Fig. 3a):

- For $\varepsilon_{PC} < 1.0$, a droplet forms away from the fiber.
- For $\varepsilon_{PC} \approx 1.0$, the droplet partially wets the fiber, with the contact area increasing with ε_{PC} .
- At sufficiently high ε_{PC} , a protein-rich layer coats the fiber along its entire length.

We will hereafter refer to the change of regime as a wetting transition.

This transition is clearly visible in the number of proteins in contact with the fiber, which exhibits a sharp increase at the wetting transition (Fig. 3b). Notably, in the zigzag geometry, the transition occurs at lower values of ε_{PC} due to the increased nucleosome density.

The values of ε_{PC} at which the change of regime happens increase with ε_{PP} , shown in Fig. 3c. This behavior can again be interpreted as a mesoscale analog of macroscopic wetting phenomena: in macroscopic systems, spreading parameters are governed by differences in surface tensions, whereas mesoscopic wetting

Table 1 Input parameters for the systems in all geometries

	Straight fiber	Zigzag fiber	Fiber with loops	Dilute network	Dense network
Box volume in σ^3	$4 \times (33.44)^3$	$4 \times (33.44)^3$	$4 \times (33.44)^3$	$(200.4)^3$	$(200.4)^3$
Box volume in μm^3	1.87×10^{-2}	1.87×10^{-2}	1.87×10^{-2}	1	1
Nbr. of proteins	7560	7560	7560	48289	48289
Nbr. of proteins per σ^3	0.050	0.050	0,050	0.006	0.006
Nbr. of proteins per μm^3	40.43	40.43	40.43	48289.00	48289.00
Nbr. of fibers	1	1	1	$3 \times 4^2 = 48$	$3 \times 8^2 = 192$
Total nbr. of nucleosome	80	92 to 160	83 to 160	5760	23040
Nucleosome per σ^3	5.3×10^{-4}	6.1×10^{-4} to 1.1×10^{-3}	5.5×10^{-4} to 1.1×10^{-3}	7.2×10^{-4}	2.9×10^{-3}
Nucleosome per μm^3	4.28×10^3	4.92×10^3 to 8.56×10^3	4.44×10^3 to 8.56×10^3	5.76×10^3	2.30×10^4
Nbr. intersections	0	0	1 to 8	64	512
Spacing between fibers	–	–	–	$50\sigma \approx 250 \text{ nm}$	$25\sigma \approx 125 \text{ nm}$

The simulation is set up with periodic boundary conditions to mimic larger volumes. Note that the spacing between fibers is exact only in the case of a regular network, else it is an average. The values given in μm are estimated using $\sigma \approx 5 \text{ nm}$. For the larger systems, the nucleosome concentration corresponds to the average number of nucleosomes per μm^3 in a human nucleus of $1 \mu\text{m}$ of radius and $5 \mu\text{m}$ respectively, taking into account the exact length of the genome and the average distance between nucleosomes in base pairs

is expected to depend on differences between interaction strengths. As the dense phase partially overlaps the fiber, the number of protein–chromatin contacts can be estimated from simple geometrical considerations. Motivated by this observation, we developed a minimal analytical model describing the system energy as a function of the distance between the droplet center of mass and the fiber. The model includes only energetic contributions arising from protein–protein contacts within the droplet and protein–chromatin contacts at the interface (see Appendix B for more details). The model reveals energy minima corresponding to the observed geometries of our systems, from a detached droplet to a centered one when ε_{PC} and ε_{PP} vary. The gray lines in Fig. 3c show the transition limits found with the analytical model (see Appendix B). These transition limits qualitatively correlate with percentage of proteins in contact with the fiber in our simulations, unless ε_{PP} gets lower than 1.2, in which case the system is no longer in the phase-separating region.

Indeed, for values of $\varepsilon_{\text{PP}} \leq 1.1k_B T$ (see Fig. 3c), for which no phase separation is observed in the absence of fibers, only a very thin layer forms around the fiber for large values of ε_{PC} . Such surface condensation has been observed in the case of DNA [64,65] and associated with the prewetting regime. In this regime, a thin layer form near the surface, in the single-phase region of the phase diagram where droplets would dissolve in bulk [61,62].

4 Phase separation in more complex geometries

We next investigate phase separation in systems where the spatial density of fiber elements varies along the fiber axis. In the context of chromatin, such heterogeneity arises from organization at multiple length scales. Here, a local increase in the effective nucleosome

density mimics either higher chromatin compaction or chromatin-associated proteins forming network-like structures (such as PAR chains [66]).

We focus on two classes of systems: (1) Single fibers with loops and (2) Networks of fibers, where both loops and intersections offer a larger contact area than a straight or isolated fiber, hence behaving as preferred binding sites. When several loops or intersections are present, phase separation results from a competition between maximizing contacts with these favorable sites and minimizing the interfacial free energy, which favors the formation of a single large droplet. Geometric details are given in Sect. 2. These two types of fiber models allow us to systematically study differences in local concentration (by varying the loop size), spatial frequency (number of loops or intersections), and spatial regularity (unequal distances between neighboring loops or fibers).

4.1 Single fiber with loops

We first examine this interplay using fibers containing several equivalent loops, i.e., loops of identical size and regularly spaced along the fiber. Specifically, we study fibers with four loops of equal size (either 9 or 21 nucleosomes) while varying the protein–chromatin attraction strength ε_{PC} . We then fix the interaction parameters ($\varepsilon_{\text{PP}} = \varepsilon_{\text{PC}} = 1.2$) and investigate how the morphology of the dense phase depends on the loop size, which is varied from 4 to 21 nucleosomes.

Within the explored parameter range, the fiber geometry has little influence on the total number of particles in the dense phase or on its volume; instead, the total number of nucleosomes is the dominant control parameter. As shown in Fig. 4, systems with linear fibers and fibers with loops exhibit a similar dependence on ε_{PC} for the same number of nucleosomes N_{nucle} . A notable deviation is observed for fibers with four large loops (21 nucleosomes) at high ε_{PC} . In this regime, the dense

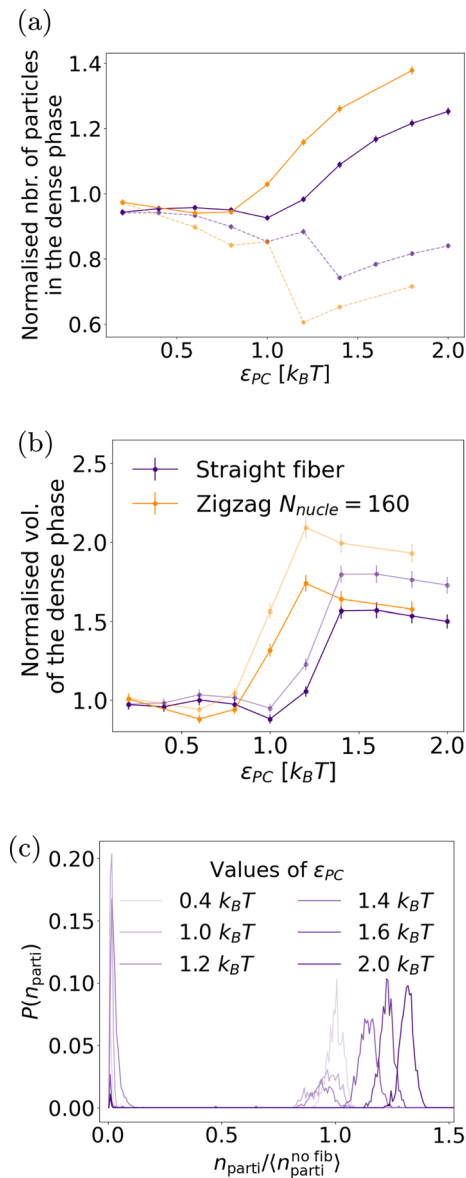


Fig. 2 a. Number of particles in the dense phase for various protein-chromatin attraction strength (ϵ_{PC}) and chromatin linear densities. The counting method is described in Appendix A 1. This number is normalized by the number of particles in the dense phase in the absence of fiber. The light dashed line corresponds to the number of particles in the dense phase that are not in contact with the fiber. b. Volume of the dense phase as a function of ϵ_{PC} , normalized by the volume of the dense phase in the absence of fiber. The lighter lines correspond to the droplet volume V . The darker lines represent the droplet volume excluding the volume occupied by the fiber, i.e., $V - V_{fib}^{drop}$. Calculation details of V and V_{fib}^{drop} are given Eq. (A2) and Eq. (A3) respectively, in Appendix A 2. c. Distribution of the number of particles per droplet n_{parti} for the straight fiber system ($N_{nucle} = 80$), where n_{parti} is normalized by the average number of particles in the droplet in the absence of fibers, $n_{parti}^{no\ fib}$

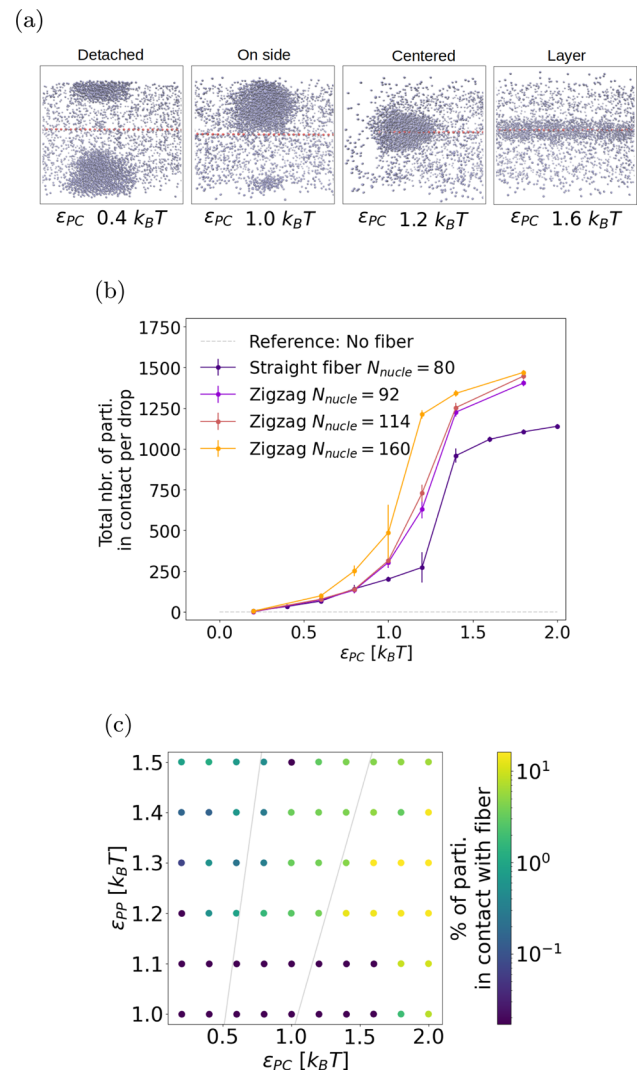


Fig. 3 a. Snapshots of typical system configurations with a linear fiber. b. Number of particles in contact with the fiber as a function of the protein-chromatin attraction strength ϵ_{PC} . c. Percentage of particles in the droplet being in contact with the fiber as a function of ϵ_{PC} for the system with a straight fiber. The gray lines correspond to the transition from detached to side and side to centered found with the analytical model with $n_{parti} = 2600$. This number of particles corresponds to the droplet size in the absence of fiber with $\epsilon_{PP} = 1.2 k_B T$ (details in Appendix B)

phase fully coats the fiber surface (Fig. 5a), leading to non-ellipsoidal droplet shapes and a consequent overestimation of the dense phase volume.

Representative configurations are shown in Fig. 5a. As for straight fibers, the system undergoes a wetting transition upon increasing ϵ_{PC} : droplets move far from the fiber at low ϵ_{PC} and are localized on the fiber at stronger ϵ_{PC} . For $\epsilon_{PC} \gg \epsilon_{PP}$, strong wetting leads to the formation of a continuous dense phase coating the whole fiber. In contrast to the linear case, droplets are also localized along the direction of the fiber axis, preferentially forming around the loops. In

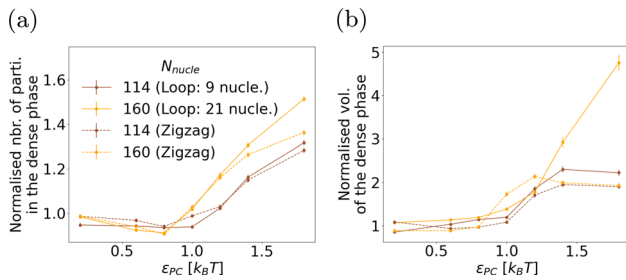


Fig. 4 a. Number of particles in the dense phase and b. volume of the dense phase, for 4 different chromatin geometries. Both quantities are normalized by the reference values in the absence of fibers. The data are shown for systems containing fibers with four loops of 9 nucleosomes or 21 nucleosomes. These results are compared with zigzag fibers (without loops) containing the same total number of nucleosomes

addition, stronger protein-chromatin attractions and larger loop sizes both reduce droplet size fluctuations, as reflected by the narrowing of the droplet size distributions (Fig. 5b).

Compared to linear fibers, the key qualitative difference introduced by loops is the emergence of preferred nucleation sites, which can stabilize the coexistence of several droplets. This contrasts with bulk systems or straight fibers (for intermediate ϵ_{PC}), where Ostwald ripening and coalescence typically lead to a single dominant droplet for the system sizes considered here. This behavior is apparent both in the simulation snapshots and in the droplet size distributions, where droplet sizes fluctuate around a fraction of the size of a whole dense phase (Fig. 5b).

For fibers containing multiple loops, three distinct regimes can be identified:

- *Single-droplet regime*: a single loop nucleates and stabilizes a droplet, while the other loops remain uncoated.
- *Multi-droplet regime*: droplets are stabilized at several or all loops, leading to droplet coexistence.
- *Coating regime*: a single droplet spreads over and coats the entire fiber surface.

The stability of loop-associated droplets depends sensitively on both loop size and loop number (Fig. 5c). Larger loops provide an increased contact area, enhancing droplet stabilization, whereas smaller loops typically support only a small droplet. Increasing the number of loops introduces an additional competition: Although each loop can act as a potential nucleation site, the finite amount of dense phase material limits the number of stable droplets.

Droplets form with a higher probability at loop regions than along other parts of the fiber. This effect is quantified using pair correlation functions $g(r)$ between the droplet center of mass (D) and nucleosomes. We compute these correlations both with respect to all nucleosomes, $g_{DN}(r)$, and by restricting the analysis

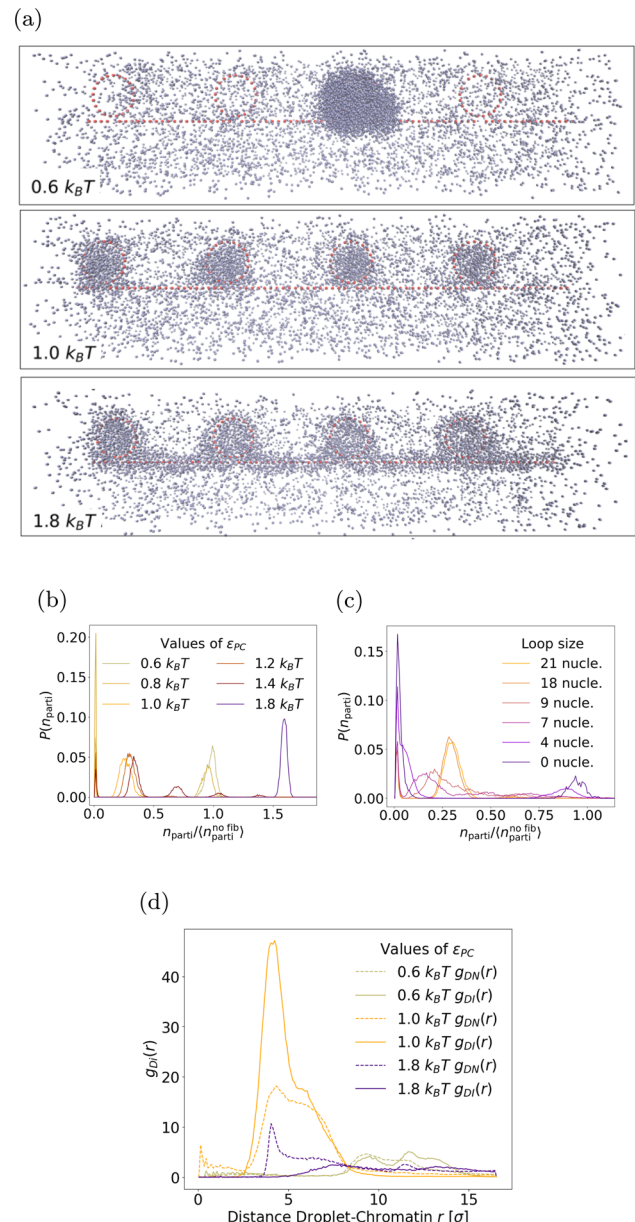


Fig. 5 Impact of the attraction strength ϵ_{PC} , loop size, and loop number on the morphology of the dense phase. a. Representative snapshots for fibers with loops for $\epsilon_{PC} = 0.6; 0.8$ or $1.8 k_B T$. b. Effect of ϵ_{PC} on the droplet size distribution for a fiber with four loops of 21 nucleosomes. c. Effect of loop size on the droplet size distribution for fibers with four loops at $\epsilon_{PP} = \epsilon_{PC} = 1.2 k_B T$. d. Quantification of droplet localization for a system with four regularly spaced loops of 21 nucleosomes. $g_{DN}(r)$ and $g_{DI}(r)$ are the pair correlation functions between the droplet centers of mass (D) and nucleosomes, considering either all nucleosomes ($g_{DN}(r)$) or only nucleosomes near fiber intersections ($g_{DI}(r)$)

to nucleosomes belonging to loop regions, $g_{DI}(r)$ (see Sect. A 3). The results are shown in Fig. 5d for systems with regularly spaced loops. For parameter values at which several droplets are stabilized (illustrated here for $\varepsilon_{PC} = 1.0$), droplets are significantly more likely to be located near loop regions than near randomly selected nucleosomes. By contrast, this preferential localization is not observed for detached droplets or for droplets that coat the entire fiber.

When loop sites are no longer equivalent, droplet localization can extend to the scale of the entire system, thereby mimicking a biological situation in which a condensate forms at a specific chromatin location. To illustrate this effect, we consider fibers containing four loops, in which the two central loops are displaced, breaking the regular spacing while keeping the total fiber length and the positions of the outer loops fixed. In this context, localization refers to the preferential formation of droplets at specific positions along the fiber (here, between the two central loops), rather than to the formation of a single droplet at an arbitrary position within the simulation box. These specific positions are defined as those of the nucleosomes with the highest local nucleosome density (see Sect. A 3 for details). Hereafter, we refer to this region as the specific site. This localization effect is quantified using the pair correlation function between the droplet center of mass and the positions of nucleosomes within the specific site, $g_{DS}(r)$.

We observe that for irregularly spaced loops, most of the matter gathers around the two central loops, while small droplets form around the outer loops. This is shown for a system with loops of size 21 nucleosomes in Fig. 6a. The presence of asymmetry leads to droplet size polydispersity (Fig. 6b), and a localization of the droplets around the specific site (Fig. 6c). Interestingly, when the central loops get closer to each other, there is a maximum in the size of the central droplet at intermediate distances between loops (this can be seen in the snapshots, and in the peak on the size distribution corresponding to the largest droplet). This simple example shows how the geometry of chromatin domains attracting condensate proteins may finely control the extent of the condensate. In next section, we shall get further insight into such control mechanism with multi-fiber models.

4.2 Fiber networks

We then focus on networks of fibers, where intersections mimic regions where chromatin elements come close together in trans configurations. In regular networks, analogous to fibers with regularly spaced loops, droplets preferentially form near intersections (Figs. 7a–7d), and show smaller size fluctuations for stronger protein-chromatin attraction (Fig. 7e). As with loops, the systems evolve toward two types of geometries for the dense phase: (i) one droplet per intersection (numerous small droplets, e.g., Fig. 7a and b) and (ii) fewer, larger droplets (e.g., Fig. 7c and d). This crossover is

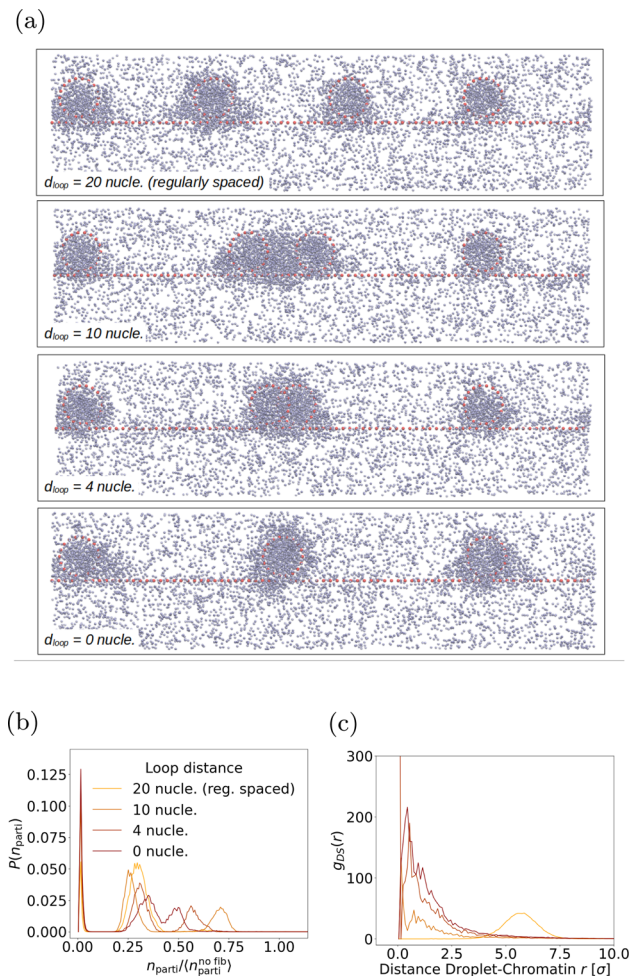


Fig. 6 a. Representative snapshots of the system configurations, for systems with 4 loops of size 21 nucleosomes with irregular spacing. Selected distance between the two central loops $d_{loop} = [20$ (regular case) 10; 4; 0] nucleosomes. b. Droplet size distribution: number of particles per droplet normalized by the number of particles in a single droplet in the absence of fibers. c. Pair correlation function $g_{DS}(r)$ between the center of mass of the droplets and the nucleosomes from the specific site. This site is fixed and located at the center of mass of the densest chromatin region

controlled by the balance between the energy gain from favorable protein-chromatin contacts at intersections and the energy cost of creating additional interfaces.

The first case (i), where droplets are stabilized at each intersection, is observed for sufficiently large values of ε_{PC} . For instance, at $\varepsilon_{PP} = 2.0$ and $\varepsilon_{PC} = 3.0$, all 64 intersections of a sparse network can host droplets, shown in Fig. 7a, where the number of proteins per droplet fluctuates around 1/64 times the number of proteins in the dense phase in the absence of fibers (Fig. 7e). In contrast, for a weaker protein-chromatin attraction $\varepsilon_{PC} \leq 2.0$, only a fraction of the intersections are coated by proteins (case ii), resulting in a larger number of proteins per droplet. Please note that, in systems with networks, the time required to reach

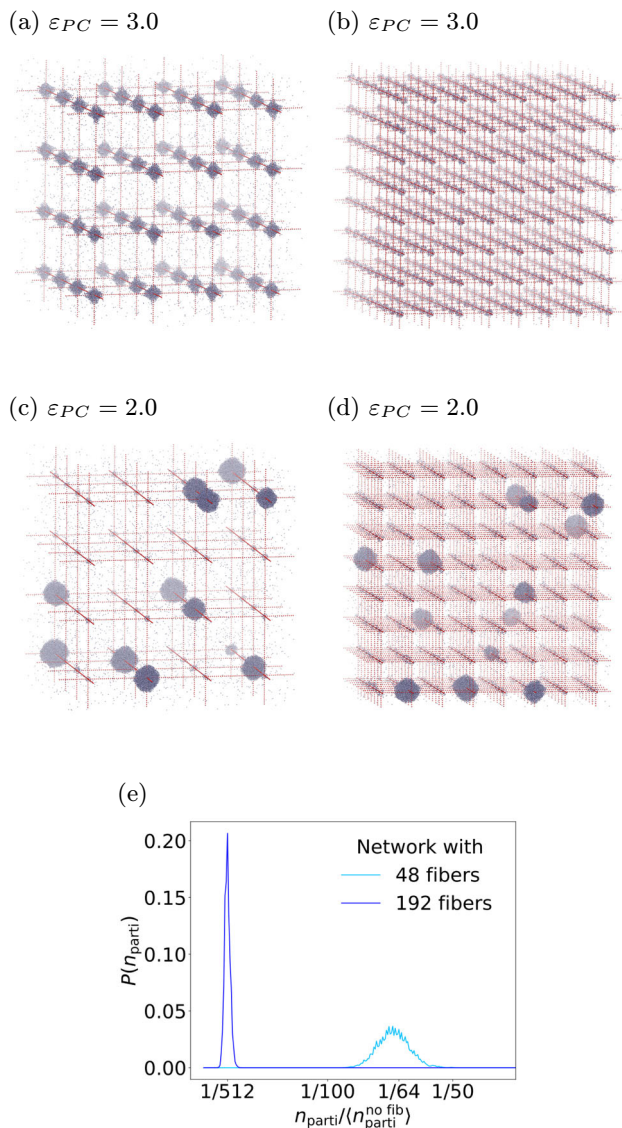


Fig. 7 a-d. Representative snapshots of simulations after 15×10^7 time steps, for a regular network of 48 fibers with 64 intersections (a, c), or a regular network of 192 fibers with 512 intersections (b, d). In all cases, the protein-protein interaction parameter is $\varepsilon_{PP} = 2.0$. e. Droplet size distribution for regular networks with $\varepsilon_{PP} = 2.0$ and $\varepsilon_{PC} = 3.0$. The droplet size is the number of proteins per droplet. It is normalized by the total number of proteins in the dense phase in the absence of fibers $n_{\text{parti}}^{\text{no fib}}$

steady state increases significantly, as some droplets may remain temporarily trapped in metastable positions within the network. Consequently, a fraction of the systems analyzed below may still contain such metastable droplets. Nevertheless, the simulation times considered here are substantially longer than those used for all previously studied systems, which were unambiguously found to be at steady state.

Both the volume and the protein content of the dense phase are poorly impacted by the number of fibers in the system and ε_{PC} (Fig. 7e). Therefore, in the case

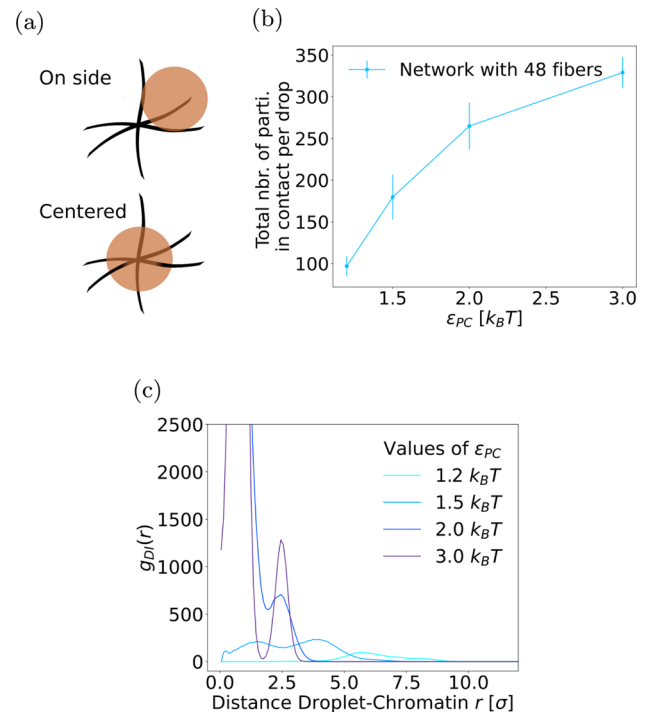


Fig. 8 a. Illustrative sketch of the transition between different wetting states of the droplets. b. Number of particles in contact with fibers as a function of ε_{PC} . c. $g_{DI}(r)$ pair correlation function between the droplet center of mass (D) and the network intersections (I). The results are given for systems with a regular network of 48 fibers, in which one droplet per intersection is observed in the simulations

where droplets are stabilized at all intersections, the number of preferred binding sites provided by the network determines the droplet size.

Similarly to systems containing a single fiber, we observe distinct regimes analogous to a macroscopic wetting transition, as illustrated in Fig. 8a. Upon varying the interaction parameters ε_{PC} or ε_{PP} , droplets either form at the periphery of the intersections or become centered on them. This transition is characterized by an increase in the total number of proteins in contact with the fiber (Fig. 8b). It is further quantified using the pair correlation function $g_{DI}(r)$ between the droplet centers of mass and the intersections. For $\varepsilon_{PC} \geq 2.0, k_B T$, $g_{DI}(r)$ is maximized at $r = 0$ (Fig. 8c), corresponding to droplets centered on the fibers. In contrast, for weaker protein-chromatin interactions, $\varepsilon_{PC} < 2.0, k_B T$, the first peak of $g_{DI}(r)$ occurs at $r > 0$.

For regular networks, as all the intersections are equivalent, the dense phase is not expected to be localized at a specific location in the system. On the other hand, in the case of disordered networks, and more specifically when there is a region of higher chromatin density, the dense phase can be spatially localized. In order to study the localization of the dense phase, we investigate phase separation in the presence of irregular networks, with and without a specific site where a

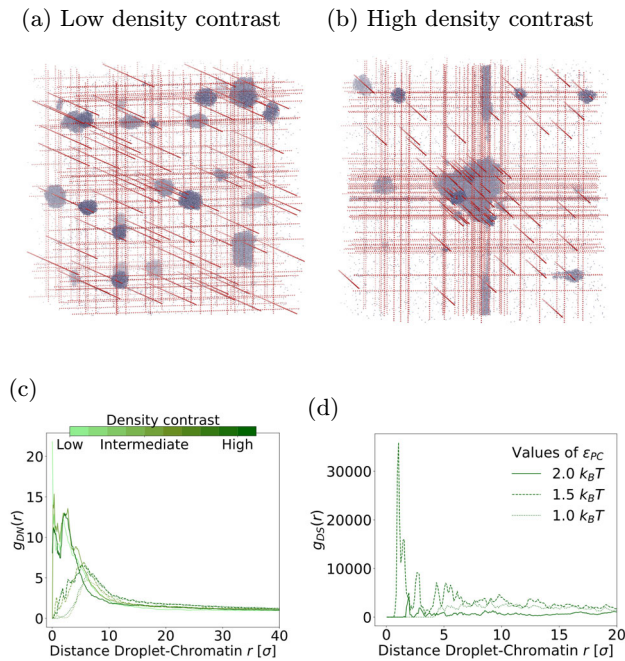


Fig. 9 a-b. Representative snapshots of disordered networks for $\varepsilon_{PC} = 2.0$. In the case of a low density contrast, the fiber positions are randomly chosen in two directions from a uniform probability distribution (a). In the case of a high density contrast, the probability distribution is biased so that 50% of the fibers are located in the central sub-volume (b). c. $g_{DN}(r)$ for irregular networks of 192 fibers. Three chromatin density contrasts are considered. In the case of low contrast, all the fibers are uniformly placed in the box. In the intermediate case, 30% are constrained in the sub-volume. In the High contrast case, 50% of the fibers are concentrated in the sub-volume. The 3 cases correspond to light green, medium green and dark green, respectively. d. $g_{DS}(r)$ for irregular networks of 192 fibers with 50% of the fibers concentrated in the sub-volume

bias is introduced to favor a high fiber concentration in a specific area of the simulation box (see details in Sect. 2).

The asymmetry of the network strongly influences the size distribution and number of droplets in the system. In the studied parameter range, the number of droplets at steady state is considerably reduced in comparison to regular networks with identical parameters (Fig. 9a and b). The localization of droplets is studied through the pair correlation function $g_{DN}(r)$ between droplet centers of mass and nucleosomes, shown in Fig. 9c. Droplets are more localized with respect to chromatin (shorter typical distance between droplet center of mass and chromatin) for stronger protein-chromatin attraction ε_{PC} , while keeping $\varepsilon_{PP} = 2.0$ constant. Visualizing the system shows configurations with a large droplet coating the fibers around the specific site (chromatin dense region). A typical configuration is shown in Fig. 9b for $\varepsilon_{PP} = \varepsilon_{PC} = 2.0$. Note that in the range of parameters studied, density contrast does not

seem to strongly affect the typical droplet-nucleosome distance (Fig. 9c).

To confirm that the positions of droplets are correlated with the location of the specific site, and not only with respect to generic nucleosomes, we studied the pair correlation function $g_{DS}(r)$ between the center of mass of droplets and the nucleosomes within the specific site. This confirms the localization of droplets around the specific site for large values of ε_{PC} (Fig. 9d), with the first peaks of $g_{DS}(r)$ located at $r < 4$ for $\varepsilon_{PC} \geq 1.5k_B T$. Figure 9d also shows a very low probability of finding a droplet at short distances around the specific site for $\varepsilon_{PC} = 1.0$. This points toward the fact that the protein-chromatin interactions can play an important role in droplet localization in a fibrous environment.

In the context of chromatin and protein condensates, there are only a few experimental studies characterizing at the same time the density of chromatin (e.g., of histone proteins), and the density of condensate-forming proteins. In a recent study, Mazzocca and coworkers [67] have shown that depending on protein-protein interactions within condensates and on protein-chromatin interactions, some condensates localize far from chromatin dense regions, while the opposite may also be found. In particular, when protein-protein interactions lead to solid-like properties of the condensates, proteins are more concentrated in less compact chromatin areas, which is consistent with the regime we observe when ε_{PP} is larger than ε_{PC} .

5 Conclusion

The mechanisms governing condensate size selection and spatial localization in cells are numerous and strongly interdependent. In this work, we focused on the role of the surrounding environment in these processes, and in particular on how fibrous structures such as chromatin influence the organization of phase-separated condensates. These results corroborate and extend experimental observations on various condensates forming on fibers.

Condensates and fibers can mutually affect one another through a coupling between wetting and phase separation. To isolate the contribution of fiber geometry and concentration to condensate properties, we employed minimal coarse-grained models combining phase-separating Lennard-Jones particles with fixed fibrous substrates. By keeping the fibers immobile, we decoupled geometric effects from scaffold rearrangements and focused on the equilibrium organization of the dense phase. This is partly motivated by the fact that chromatin dynamics is typically slower than that of diffusing proteins on the timescales relevant for condensate assembly. Nevertheless, our claim here is not to assume chromatin mobility is unimportant, but our works starts from the necessity of understanding the coupling of wetting and condensate formation for fixed fibers, before tackling the more complex case of a deformable substrate.

We found that when protein-chromatin interactions are sufficiently strong for condensates to wet fibers, both local geometric features and large-scale network organization strongly influence droplet size, morphology, and number. In most of the parameter space explored, the presence of fibers only moderately affects the total volume and protein content of the dense phase, with more pronounced shifts observed at higher protein-chromatin affinity. These changes are associated with a wetting-like transition, in which droplets evolve from detached configurations at low protein-chromatin interaction strength to partially wetted states, and eventually to complete coating of the fibers. Similar wetting transitions of chromatin-associated condensates have been reported experimentally for transcription factors Klf4 and BRD4 [34, 68].

Local variations in fiber geometry, such as loops along a single fiber or intersections within a network, create regions of enhanced nucleosome density and increased available contact area. These sites act as preferential binding and nucleation points for the dense phase, as it was suggested from experimental observations of loop extrusions [27, 28]. As a result, condensate organization reflects a competition between interfacial tension, which favors coarsening into a single droplet via Ostwald ripening, and the energetic gain associated with maximizing protein-chromatin contacts at these geometrically favorable locations. This competition enables the coexistence of multiple droplets when preferred sites are equivalent, providing an equilibrium mechanism for droplet size regulation that complements previously proposed non-equilibrium models based on biochemical turnover [5, 33].

Beyond local effects, we showed that asymmetries in fiber organization at the system scale, such as uneven loop spacing or inhomogeneous fiber networks, can drive robust spatial localization of condensates. This behavior is consistent with recent experimental observations of DNA repair condensates that nucleate reproducibly at specific loci following local damage and consequent chromatin reorganization [19, 20, 69] and with observations of nuclear condensates whose locations are chromatin-concentration dependent [67]. Within such model, wetting on chromatin suggests the multiple droplets of water dispersed on a spider web, where droplets of various sizes coexist on several favorable locations of the web, or at some point may all fuse to the same region, such as the denser center of the spider web.

In vivo, many nuclear condensates perform specialized functions at well-defined locations, including transcriptional regulation [12, 70, 71] and DNA repair [72, 73]. Our results indicate that the interplay between protein-chromatin affinity and chromatin network organization can contribute significantly to the spatial control of such condensates. In particular, our findings are consistent with recent studies showing that condensate localization can correlate either positively or negatively with chromatin density depending on the relative strengths of protein-protein and protein-chromatin interactions [3, 67]. While additional lay-

ers of regulation—such as chromatin dynamics, active processes [33, 74, 75], and sequence-specific interactions—are undoubtedly important in living cells, our study demonstrates that geometric and energetic constraints imposed by chromatin architecture alone can already shape condensate size, coexistence, and localization.

Author contribution statement

All authors contributed to the study conception and design. Simulations were prepared and analyzed by Léa Beaulès, under the supervision of Pierre Illien and Vincent Dahirel. The first draft of the manuscript was written by Vincent Dahirel and Léa Beaulès and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

Data Availability Statement Data are stored in a repository. The link will be made available on reasonable request to vincent.dahirel@sorbonne-universite.fr.

Appendix A Methods

1 Droplet identification

Two proteins are considered as part of the same droplet if they are closer than a threshold distance r_{cut} of each other. The value of r_{cut} is chosen as the distance at the first minimum in the protein-protein pair correlation function ($r_{\text{cut}} = 1.65\sigma$ for the small systems with a single fiber and $r_{\text{cut}} = 1.55\sigma$ for the large systems with several fibers). In the presented data, a cluster of proteins is considered as a droplet if it is composed of more than 30 proteins.

2 Estimating the droplet volume

Quantifying the volume of the distinct phases within a microscopic system presents significant challenges due to the absence of clearly defined phase boundaries. It is estimated from the positions $\mathbf{r}_i = (r_{ix}, r_{iy}, r_{iz})$ of the n_{parti} proteins in each droplet. The center of mass of their positions along the m coordinate is calculated as $\mathcal{R}_m = \frac{1}{n_{\text{parti}}} \sum_{i=1}^{n_{\text{parti}}} r_{im}$, with $m, n \in \{x, y, z\}$. We then define the gyration tensor S_{mn} as:

$$S_{mn} = \frac{1}{n_{\text{parti}}} \sum_{i=1}^{n_{\text{parti}}} (r_{im} - \mathcal{R}_m)(r_{in} - \mathcal{R}_n). \quad (\text{A1})$$

For spherical droplets, S_{mn} is diagonal with eigenvalues $\lambda_1 = \lambda_2 = \lambda_3$, and the gyration radius is given by: $R_g^2 = \lambda_1 + \lambda_2 + \lambda_3$. To include the case of ellipsoidal droplets, the droplet volume V is estimated from the eigenvalues λ_1, λ_2 and λ_3 of S_{mn} , as:

$$V \approx 4\pi\sqrt{3\lambda_1\lambda_2\lambda_3} \quad (\text{A2})$$

If the droplet coats the fiber, the volume is slightly overestimated. In order to estimate the contribution from the fiber to the droplet volume, the contact length between the

fiber and the droplet ($l_{\text{fib}}^{\text{drop}}$) is measured. The volume occupied by the fiber is then estimated as that of a cylinder of radius $r_{\text{fib}} = (\sigma_{\text{PC}} - \sigma_{\text{PP}})2^{1/6} = 2^{1/6}$:

$$V_{\text{fib}}^{\text{drop}} \approx \pi(r_{\text{fib}})^2 l_{\text{fib}}^{\text{drop}}. \quad (\text{A3})$$

3 Droplet localization

To quantify the localization of the droplets with respect to the fibers, we calculate the pair correlation function $g_{\text{DN}}(r)$ between the center of mass of a droplet and the positions of all nucleosomes as:

$$g_{\text{DN}}(r) = \left\langle \frac{1}{N_{\text{drop}} N_{\text{nucle}}} \sum_i^{N_{\text{drop}}} \sum_j^{N_{\text{nucle}}} \delta(d_{ij} - r) \right\rangle_t, \quad (\text{A4})$$

d_{ij} being the distance between the i_{th} droplet center of mass and the j_{th} nucleosome and N_{drop} and N_{nucle} being the number of droplets identified at time t and the total number of nucleosomes in the system, respectively.

To quantify whether proteins localize around preferred sites, as in particular in regions where chromatin is more packed, the same correlation function is calculated, but this time considering only a subset of nucleosomes. Two types of sites are considered:

- The intersections, with the associated pair correlation function denoted as $g_{\text{DI}}(r)$. This is the set of nucleosomes that are in close proximity (less than two typical nucleosome-nucleosome distances) from an intersecting fiber.
- The specific site, with the corresponding pair correlation function $g_{\text{DS}}(r)$. This corresponds to the nucleosomes within the densest chromatin regions, which can be unambiguously defined in the case of irregular networks with a biased fiber distribution as explained hereafter.

The local nucleosome density is used as a criterion to identify nucleosomes belonging to these preferred sites. For each nucleosome, the local nucleosome density is calculated as the number of neighboring nucleosomes within a given radius divided by the volume considered. With this criterion, intersections correspond to a local increase in the nucleosome density compared to an isolated straight fiber (within a radius of $2.25d_{\text{CC}} \approx 3.76\sigma$). In practice, a regular intersection of three fibers corresponds to 12 selected nucleosomes. The specific site corresponds to nucleosomes with the 5% highest large-scale nucleosome density, within a radius of $20.25d_{\text{CC}} \approx 33.82\sigma$. As a reference, the size of the cubic sub-volume used to bias the fiber distribution in the irregular networks is $0.25 \times 200\sigma = 50\sigma$. The radius is then chosen to be around the specific site length scale in order to select the nucleosomes at the center of the densest area.

For disordered networks the density contrast is quantified as the variance of the distribution of the local nucleosome density (considering a radius of $20.25d_{\text{CC}} \approx 33.82\sigma$).

Appendix B Analytical model

From simple energy estimation one can show that the energy of a two-phase Lennard–Jones fluid is minimized by the for-

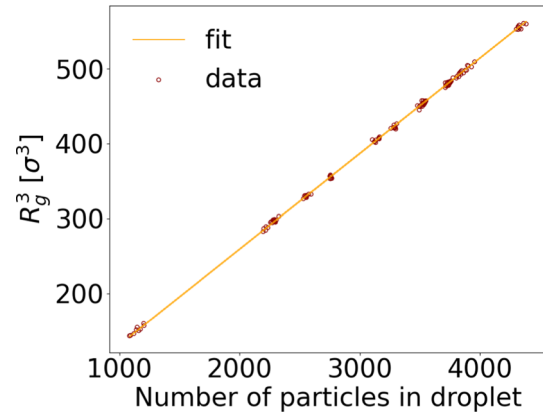


Fig. 10 Cube radius of the droplets as a functions of the number of particles per droplet

mation of a single spherical droplet. The energy is estimated from the number of particles on the droplet surface and the number of inter-particle interactions. We consider a fixed total number of particles in the dense phase N_{parti} , and the number of interactions within the dilute phase as negligible. If all droplets have the same size (N_{drop} droplets of radius R) the number of particles in a droplet is estimated as $n_{\text{parti}} = N_{\text{parti}}/N_{\text{drop}}$. Only the number of droplets N_{drop} and the interaction potentials ε_{PP} and ε_{PC} vary.

The energy $E_{\text{no fib}}$ of the N_{drop} droplets in the absence of fibers can be estimated as:

$$E_{\text{no fib}} = N_{\text{drop}} \left[-n_{\text{parti}} n_{\text{neib}} \varepsilon_{\text{PP}} + \frac{n_{\text{neib}} \varepsilon_{\text{PP}}}{2} \frac{S_{\text{drop}}}{s_{\text{prot}}} \right] \quad (\text{B1})$$

with $S_{\text{drop}} = 4\pi R^2$ being the surface of the droplet, n_{neib} the average number neighbors around a protein when it is inside the droplet and s_{prot} the effective surface occupied by a protein. The surface tension created by the energy cost of forming a surface leads to the minimization of $E_{\text{no fib}}$ for $N_{\text{drop}} = 1$.

The main geometrical assumption is that the radius of the droplet scales linearly with the cube root of the number of particles in the droplets such that:

$$R^3(n_{\text{parti}}) = n_{\text{parti}} A + B, \quad (\text{B2})$$

where A and B are inferred from fitting simulations data. Using simulation results, we have found this assumption to be valid in the limit of large enough droplets (more than a thousand particles per droplet), as shown in Fig. 10.

We here extend the calculations to the case where the droplets form at a certain distance d from an intersection of n_{fib} fibers of radius r_{fib} , where d is the distance between the center of the spherical droplet and the fibers. Two cases are studied:

- Case in which a single droplet forms on a single fiber. ($n_{\text{fib}} = 1$)
- Case in which N_{drop} droplets form around or near an intersection of a regular network ($n_{\text{fib}} = 3$). An illustrative sketch of an intersection is shown in Fig. 8a.

The presence of fibers is included as an additional surface S_{fib} , which is the surface of contact between the droplet and the fiber:

$$S_{\text{fib}}(R, d) = n_{\text{fib}} \left[2\pi r_{\text{fib}} l_{\text{fib}}^{\text{drop}}(R, d) \right] \alpha(R, d); \quad (\text{B3})$$

with $l_{\text{fib}}^{\text{drop}}$ being the total fiber length in contact with the droplet, and $\alpha(R, d)$ being the proportion of the fiber coated by the droplet. $\alpha(R, d)$ equals 1 if the droplet is centered around the fiber ($d = 0$) and to 0 if the droplet is detached from the fiber and is defined as:

$$\alpha(R, d) = \begin{cases} 1 & \text{if } d - R < -r_{\text{fib}} \\ \frac{1}{2\pi} 2 \arccos \frac{d-R}{r_{\text{fib}}}, & \text{if } |d - R| \leq r_{\text{fib}} \\ 0 & \text{otherwise,} \end{cases} \quad (\text{B4})$$

To account for the portion of the droplet surface taken up by the fiber, S_{drop} becomes:

$$S_{\text{drop}}(R, d) \approx 4\pi R^2 - \alpha(R, d) 2n_{\text{fib}} \times \pi r_{\text{fib}}^2. \quad (\text{B5})$$

The energy E_{wetting} of the N_{drop} droplets is calculated as:

$$E_{\text{wetting}} = N_{\text{drop}} \left[-n_{\text{parti}} n_{\text{neib}} \varepsilon_{PP} + n_{\text{neib}} \frac{\varepsilon_{PP}}{2} \frac{S_{\text{drop}}}{s_{\text{prot}}} + \left(n_{\text{neib}} \frac{\varepsilon_{PP}}{2} - n_{\text{neib}}^{PC} \varepsilon_{PC} \right) \frac{S_{\text{fib}}}{s_{\text{prot}}} \right] \quad (\text{B6})$$

with n_{neib}^{PC} being the average number of nucleosomes a protein in contact with the fiber interacts with.

For comparison with the simulations, one can extract from this analytical description the number of proteins in contact with the fiber at the energy minima. This leads to a sharp transition similar to the one shown in Fig. 3b. From there, the transition from detached to on the side of the fiber is located where the number of particles in contact becomes greater than 1. The transition from on the side to the centered state corresponds to the values of ε_{PC} where the number of particles in contact reaches the plateau. Both transitions are shown in Fig. 3c.

Although the model does not explicitly represent intersections, comparing the optimal number of droplets with the number of intersections may also help interpret our findings in networks. We have identified two regimes in regular fiber networks: one droplet per intersection (many small droplets) and fewer, larger droplets occupying only a fraction of the available intersections. We therefore use our model to express E_{wetting} as a function of the number of droplets N_{drop} for droplets centered around the intersections ($d = 0$).

For $d = 0$, we get $\alpha(R, d) = 1$ and $l_{\text{fib}}^{\text{drop}} = 2R$. Replacing $S_{\text{drop}}(R, d = 0)$ (Eq. B5) and $S_{\text{fib}}(R, d = 0)$ (Eq. B3) into Eq. B6, yields an expression for E_{wetting} of the form:

$$E_{\text{wetting}} = N_{\text{drop}} \left[-\frac{N_{\text{parti}}}{N_{\text{drop}}} n_{\text{neib}} \varepsilon_{PP} + k_1 R^2 + k_2 R + k_3 \right], \quad (\text{B7})$$

where

$$\begin{aligned} k_1 &= \frac{n_{\text{neib}} \varepsilon_{PP}}{2s_{\text{prot}}} 4\pi, \\ k_2 &= \left(\frac{n_{\text{neib}} \varepsilon_{PP}}{2s_{\text{prot}}} - \frac{n_{\text{neib}}^{PC} \varepsilon_{PC}}{s_{\text{prot}}} \right) n_{\text{fib}} 4\pi r_{\text{fib}}, \text{ and} \\ k_3 &= -\frac{n_{\text{neib}} \varepsilon_{PP}}{2s_{\text{prot}}} 2n_{\text{fib}} \pi r_{\text{fib}}^2. \end{aligned}$$

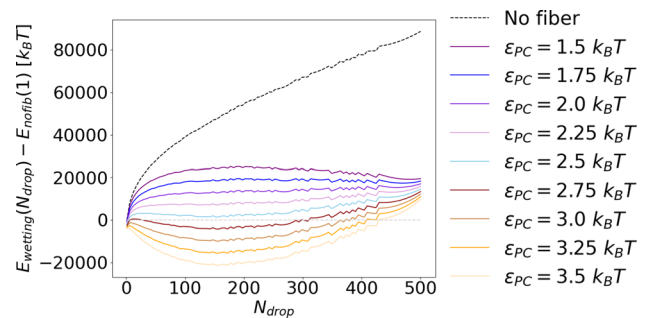


Fig. 11 Results from our analytical model for $\varepsilon_{PP} = 1.2k_B T$ with droplets centered around intersections composed of 3 fibers

To express E_{wetting} solely as a function of N_{drop} , R is replaced by $\left(\frac{N_{\text{parti}}}{N_{\text{drop}}} A + B \right)^{1/3}$ (see Eq. B2) which gives

$$\begin{aligned} E_{\text{wetting}}(N_{\text{drop}}) &= -N_{\text{parti}} n_{\text{neib}} \varepsilon_{PP} \\ &+ k_1 (N_{\text{parti}} A)^{2/3} N_{\text{drop}}^{1/3} \\ &+ k_2 (N_{\text{parti}} A)^{1/3} N_{\text{drop}}^{2/3} \\ &+ \left(k_1 B^{2/3} + k_2 B^{1/3} + k_3 \right) N_{\text{drop}}. \end{aligned} \quad (\text{B8})$$

The energy in the absence of fibers, $E_{\text{no fib}}(N_{\text{drop}})$, follows the same form as $E_{\text{wetting}}(N_{\text{drop}})$, except that $k_2 = k_3 = 0$.

With Eq. B8, the model allows us to explore the transition between two regimes: (i) a single-droplet state, in which the energy is minimized for $N_{\text{drop}} = 1$, and (ii) a multidroplet state, in which the global minimum of E_{wetting} occurs at a finite number of droplets, $N_{\text{drop}}^{\text{min}} > 1$. At fixed protein-protein interaction strength ε_{PP} , the system crosses over from the single-droplet regime to the multidroplet regime when the protein-chromatin interaction strength ε_{PC} exceeds a crossover value. This is shown in Fig. 11, where the crossover value is approximately $\varepsilon_{PC} = 2\varepsilon_{PP}$. Interestingly, the value of $N_{\text{drop}}^{\text{min}}$ in the multidroplet regime does not depend on ε_{PC} within the model: increasing ε_{PC} changes the energy of the minimum but not its position.

An important distinction between the analytical model and the simulations is that the model does not constrain the number of droplets to the number of available sites on the chromatin substrate. In contrast, in the simulations, droplets preferentially localize at fiber intersections, and their number is therefore constrained by the total number of intersections, N_{inter} .

This constraint modifies the interpretation of the energy profiles predicted by the analytical model. When the unconstrained minimum $N_{\text{drop}}^{\text{min}}$ exceeds the number of available intersections, the system cannot reach this minimum. Instead, the minimum accessible with the simulations is determined by the constraint $N_{\text{drop}} \leq N_{\text{inter}}$. For values of ε_{PC} near the crossover, this constrained minimum may correspond to a single droplet, $N_{\text{drop}} = 1$. In contrast, for $\varepsilon_{PC} \gg \varepsilon_{PP}$, the energetic preference for localization at the chromatin sites becomes stronger, and the energy is minimized by forming $N_{\text{drop}} = N_{\text{inter}}$ droplets, corresponding to a state in which all available intersections host a droplet.

References

1. C.P. Brangwynne, C.R. Eckmann, D.S. Courson, A. Rybarska, C. Hoege, J. Gharakhani, F. Jülicher, A.A. Hyman, Germline P Granules Are Liquid Droplets That Localize by Controlled Dissolution/Condensation. *Science* **324**, 1729 (2009). <https://doi.org/10.1126/science.1172046>
2. Y. Shin, C.P. Brangwynne, Liquid phase condensation in cell physiology and disease. *Science* (2017). <https://doi.org/10.1126/science.aaf4382>
3. Y. Shin, Y.-C. Chang, D.S. Lee, J. Berry, D.W. Sanders, P. Ronceray, N.S. Wingreen, M. Haataja, C.P. Brangwynne, Liquid Nuclear Condensates Mechanically Sense and Restructure the Genome. *Cell* **175**, 1481 (2018). <https://doi.org/10.1016/j.cell.2018.10.057>
4. B.A. Gibson, L.K. Doolittle, M.W. Schneider, L.E. Jensen, N. Gamarra, L. Henry, D.W. Gerlich, S. Redding, M.K. Rosen, Organization of Chromatin by Intrinsic and Regulated Phase Separation. *Cell* **179**, 470 (2019). <https://doi.org/10.1016/j.cell.2019.08.037>
5. C.A. Weber, D. Zwicker, F. Jülicher, C.F. Lee, Physics of active emulsions. *Rep. Prog. Phys.* **82**, 064601 (2019). <https://doi.org/10.1088/1361-6633/ab052b>
6. B.R. Sabari, A. Dall'Agness, R.A. Young, Biomolecular Condensates in the Nucleus. *Trends Biochem. Sci.* **45**, 961 (2020). <https://doi.org/10.1016/j.tibs.2020.06.007>
7. B. Gouveia, Y. Kim, J.W. Shaevitz, S. Petry, H.A. Stone, C.P. Brangwynne, Capillary forces generated by biomolecular condensates. *Nature* **609**, 255 (2022). <https://doi.org/10.1038/s41586-022-05138-6>
8. M.N. Rouches, B.B. Machta, Polymer Collapse & Liquid-Liquid Phase-Separation are Coupled in a Generalized Prewetting. *Transition* (2024). <https://doi.org/10.1101/2024.04.29.591767>
9. D. Hnisz, K. Shrinivas, R.A. Young, A.K. Chakraborty, P.A. Sharp, A Phase Separation Model for Transcriptional Control. *Cell* **169**, 13 (2017). <https://doi.org/10.1016/j.cell.2017.02.007>
10. K. Rippe, Liquid-Liquid Phase Separation in Chromatin. *Cold Spring Harb. Perspect. Biol.* **14**, a040683 (2022). <https://doi.org/10.1101/cshperspect.a040683>
11. J. Wu, B. Chen, Y. Liu, L. Ma, W. Huang, Y. Lin, Modulating gene regulation function by chemically controlled transcription factor clustering. *Nat. Commun.* **13**, 2663 (2022). <https://doi.org/10.1038/s41467-022-30397-2>
12. R. Mann, D. Notani, Transcription factor condensates and signaling driven transcription. *Nucleus* **14**, 2205758 (2023). <https://doi.org/10.1080/19491034.2023.2205758>
13. C. Brangwynne, P. Tompa, R. Pappu, Polymer physics of intracellular phase transitions. *Nat. Phys.* **11**, 899 (2015). <https://doi.org/10.1038/nphys3532>
14. S.F. Banani, H.O. Lee, A.A. Hyman, M.K. Rosen, Biomolecular condensates: organizers of cellular biochemistry. *Nat. Rev. Mol. Cell Biol.* **18**, 285 (2017). <https://doi.org/10.1038/nrm.2017.7>
15. S. Kilic, A. Lezaja, M. Gatti, E. Bianco, J. Michelena, R. Imhof, M. Altmeyer, Phase separation of 53BP1 determines liquid-like behavior of DNA repair compartments. *EMBO J.* **38**, e101379 (2019). <https://doi.org/10.15252/embj.2018101379>
16. A.A. Hyman, C.A. Weber, F. Jülicher, Liquid-Liquid Phase Separation in Biology. *Annu. Rev. Cell Dev. Biol.* **30**, 39 (2014). <https://doi.org/10.1146/annurev-cellbio-100913-013325>
17. S. Alberti, A. Gladfelter, T. Mittag, Considerations and Challenges in Studying Liquid-Liquid Phase Separation and Biomolecular Condensates. *Cell* **176**, 419 (2019). <https://doi.org/10.1016/j.cell.2018.12.035>
18. M.L. Heltberg, J. Miné-Hattab, A. Taddei, A.M. Walczak, T. Mora, Physical observables to determine the nature of membrane-less cellular sub-compartments. *Elife* **10**, e69181 (2021). <https://doi.org/10.7554/eLife.69181>
19. J. Miné-Hattab, M. Heltberg, M. Villemeur, C. Guedj, T. Mora, A.M. Walczak, M. Dahan, A. Taddei, Single molecule microscopy reveals key physical features of repair foci in living cells. *Elife* **10**, e60577 (2021). <https://doi.org/10.7554/eLife.60577>
20. M.S. Heltberg, A. Lucchetti, F.-S. Hsieh, D.P. Minh Nguyen, S.-H. Chen, M.H. Jensen, Enhanced DNA repair through droplet formation and p53 oscillations. *Cell* **185**, 4394 (2022). <https://doi.org/10.1016/j.cell.2022.10.004>
21. F. García Fernández, S. Huet, J. Miné-Hattab, Multi-Scale Imaging of the Dynamic Organization of Chromatin. *Int. J. Mol. Sci.* **24**, 15975 (2023). <https://doi.org/10.3390/ijms242115975>
22. G.J. Filion, J.G. Van Bommel, U. Braunschweig, W. Talhout, J. Kind, L.D. Ward, W. Brugman, I.J. De Castro, R.M. Kerkhoven, H.J. Bussemaker, B. van Steensel, Systematic Protein Location Mapping Reveals Five Principal Chromatin Types in Drosophila Cells. *Cell* **143**, 212 (2010). <https://doi.org/10.1016/j.cell.2010.09.009>
23. A.N. Boettiger, B. Bintu, J.R. Moffitt, S. Wang, B.J. Beliveau, G. Fudenberg, M. Imakaev, L.A. Mirny, C.-T. Wu, X. Zhuang, Super-resolution imaging reveals distinct chromatin folding for different epigenetic states. *Nature* **529**, 418 (2016). <https://doi.org/10.1038/nature16496>
24. D.I. Cattoni, A.M. Cardozo Gizzi, M. Georgieva, M.D. Stefano, A. Valeri, D. Chamousset, C. Houbbron, S. Déjardin, J.-B. Fiche, I. González, J.-M. Chang, T. Sexton, M.A. Marti-Renom, F. Bantignies, G. Cavalli, M. Nollmann, Single-cell absolute contact probability detection reveals chromosomes are organized by multiple low-frequency yet specific interactions. *Nat. Commun.* **8**, 1753 (2017). <https://doi.org/10.1038/s41467-017-01962-x>
25. Q. Szabo, D. Jost, J.-M. Chang, D.I. Cattoni, G.L. Papadopoulos, B. Bonev, T. Sexton, J. Gurgo, C. Jacquier, M. Nollmann, F. Bantignies, G. Cavalli, TADs are 3D structural units of higher-order chromosome organization in Drosophila. *Sci. Adv.* **4**, eaar8082 (2018). <https://doi.org/10.1126/sciadv.aar8082>
26. T. Sexton, E. Yaffe, E. Kenigsberg, F. Bantignies, B. Leblanc, M. Hoichman, H. Parrinello, A. Tanay, G. Cavalli, Three-Dimensional Folding and Functional Organization Principles of the Drosophila Genome. *Cell* **148**, 458 (2012). <https://doi.org/10.1016/j.cell.2012.01.010>

27. C. Arnould, G. Legube, The Secret Life of Chromosome Loops upon DNA Double-Strand Break. *J. Mol. Biol.* **432**, 724 (2020). <https://doi.org/10.1016/j.jmb.2019.07.036>
28. C. Arnould, V. Rocher, A.-L. Finoux, T. Clouaire, K. Li, F. Zhou, P. Caron, P.E. Mangeot, E.P. Ricci, R. Mourad, J.E. Haber, D. Noordermeer, G. Legube, Loop extrusion as a mechanism for formation of DNA damage repair foci. *Nature* **590**, 660 (2021). <https://doi.org/10.1038/s41586-021-03193-z>
29. C. Arnould, V. Rocher, F. Saur, A.S. Bader, F. Muzopappa, S. Collins, E. Lesage, B. Le Bozec, N. Puget, T. Clouaire, T. Mangeat, R. Mourad, N. Ahituv, D. Noordermeer, F. Erdel, M. Bushell, A. Marnef, G. Legube, Chromatin compartmentalization regulates the response to DNA damage. *Nature* **623**, 183 (2023). <https://doi.org/10.1038/s41586-023-06635-y>
30. J. Shin, A.B. Kolomeisky, Facilitation of DNA loop formation by protein-DNA non-specific interactions. *Soft Matter* **15**, 5255 (2019). <https://doi.org/10.1039/C9SM00671K>
31. F.C. Keber, T. Nguyen, A. Mariossi, C.P. Brangwynne, M. Wühr, Evidence for widespread cytoplasmic structuring into mesoscale condensates. *Nat. Cell Biol.* **26**, 346 (2024). <https://doi.org/10.1038/s41556-024-01363-5>
32. C.P. Broedersz, X. Wang, Y. Meir, J.J. Loparo, D.Z. Rudner, N.S. Wingreen, Condensation and localization of the partitioning protein ParB on the bacterial chromosome. *Proc. Natl. Acad. Sci.* **111**, 8809 (2014). <https://doi.org/10.1073/pnas.1402529111>
33. D. Zwicker, The intertwined physics of active chemical reactions and phase separation. *Current Opinion in Colloid & Interface Science* **61**, 101606 (2022). <https://doi.org/10.1016/j.cocis.2022.101606>
34. A.R. Strom, J.M. Eeftens, Y. Polyachenko, C.J. Weaver, H.-F. Watanabe, D. Bracha, N.D. Orlovsky, C.C. Jumper, W.M. Jacobs, C.P. Brangwynne, Interplay of condensation and chromatin binding underlies BRD4 targeting. *Mol. Biol. Cell* **35**, ar88 (2024). <https://doi.org/10.1091/mbc.E24-01-0046>
35. M. Du, S.H. Stitzinger, J.-H. Spille, W.-K. Cho, C. Lee, M. Hijaz, A. Quintana, I.I. Cissé, Direct observation of a condensate effect on super-enhancer controlled gene bursting. *Cell* **187**, 331 (2024). <https://doi.org/10.1016/j.cell.2023.12.005>
36. L. Rayleigh, On The Instability Of Jets. *Proc. Lond. Math. Soc.* **s1-10**, 4 (1878). <https://doi.org/10.1112/plms/s1-10.1.4>
37. P.-G. De Gennes, F. Brochard-Wyart, D. Quéré, *Capillarity and Wetting Phenomena* (Springer, New York, New York, NY, 2004). <https://doi.org/10.1007/978-0-387-21656-0>
38. J. Eggers, E. Villermaux, Physics of liquid jets. *Rep. Prog. Phys.* **71**, 036601 (2008). <https://doi.org/10.1088/0034-4885/71/3/036601>
39. Y. Zhang, J. Sprittles, D. Lockerby, Thermal capillary wave growth and surface roughening of nanoscale liquid films. *J. Fluid Mech.* **915**, A135 (2021). <https://doi.org/10.1017/jfm.2021.164>
40. N. Gopan, S.P. Sathian, Rayleigh instability at small length scales. *Phys. Rev. E* **90**, 033001 (2014). <https://doi.org/10.1103/PhysRevE.90.033001>
41. Y. Zhang, J.E. Sprittles, D.A. Lockerby, Nanoscale thin-film flows with thermal fluctuations and slip. *Phys. Rev. E* **102**, 053105 (2020). <https://doi.org/10.1103/PhysRevE.102.053105>
42. P.J. Flory, Thermodynamics of High Polymer Solutions. *J. Chem. Phys.* **10**, 51 (1942). <https://doi.org/10.1063/1.1723621>
43. M.L. Huggins, Some Properties of Solutions of Long-chain Compounds. *J. Phys. Chem.* **46**, 151 (1942). <https://doi.org/10.1021/j150415a018>
44. R. Tiani, M. Jardat, V. Dahirel, Phase transitions in chromatin: Mesoscopic and mean-field approaches, *The Journal* (2025)
45. P. Ronceray, S. Mao, A. Košmrlj, M.P. Haataja, Liquid demixing in elastic networks: Cavitation, permeation, or size selection? *Europhys. Lett.* **137**, 67001 (2022). <https://doi.org/10.1209/0295-5075/ac56ac>
46. K.A. Rosowski, T. Sai, E. Vidal-Henriquez, D. Zwicker, R.W. Style, E.R. Dufresne, Elastic ripening and inhibition of liquid-liquid phase separation. *Nat. Phys.* **16**, 422 (2020). <https://doi.org/10.1038/s41567-019-0767-2>
47. R.W. Style, T. Sai, N. Fanelli, M. Ijavi, K. Smith-Mannschott, Q. Xu, L.A. Wilen, E.R. Dufresne, Liquid-Liquid Phase Separation in an Elastic Network. *Phys. Rev. X* **8**, 011028 (2018). <https://doi.org/10.1103/PhysRevX.8.011028>
48. D.S.W. Lee, N.S. Wingreen, C.P. Brangwynne, Chromatin mechanics dictates subdiffusion and coarsening dynamics of embedded condensates. *Nat. Phys.* **17**, 531 (2021). <https://doi.org/10.1038/s41567-020-01125-8>
49. Y. Qi, B. Zhang, Chromatin network retards nucleoli coalescence. *Nat. Commun.* **12**, 6824 (2021). <https://doi.org/10.1038/s41467-021-27123-9>
50. M.P. Allen, D.J. Tildesley, *Computer simulation of liquids*, 2nd edn. (Oxford University Press, Oxford, 2017)
51. A.P. Thompson, H.M. Aktulga, R. Berger, D.S. Bolintineanu, W.M. Brown, P.S. Crozier, P.J. In 'T Veld, A. Kohlmeyer, S.G. Moore, T.D. Nguyen, R. Shan, M.J. Stevens, J. Tranchida, C. Trott, S.J. Plimpton, LAMMPS - a flexible simulation tool for particle-based materials modeling at the atomic, meso, and continuum scales. *Comput. Phys. Commun.* **271**, 108171 (2022). <https://doi.org/10.1016/j.cpc.2021.108171>
52. C.A. Brackley, D. Michieletto, F. Mouvet, J. Johnson, S. Kelly, P.R. Cook, D. Marenduzzo, Simulating topological domains in human chromosomes with a fitting-free model. *Nucleus* **7**, 453 (2016). <https://doi.org/10.1080/19491034.2016.1239684>
53. Y. Zhang, D.S. Lee, Y. Meir, C.P. Brangwynne, N.S. Wingreen, Mechanical Frustration of Phase Separation in the Cell Nucleus by Chromatin. *Phys. Rev. Lett.* **126**, 258102 (2021). <https://doi.org/10.1103/PhysRevLett.126.258102>
54. M.M.C. Tortora, L.D. Brennan, G. Karpen, D. Jost, HP1-driven phase separation recapitulates the thermodynamics and kinetics of heterochromatin condensate formation. *Proc. Natl. Acad. Sci.* **120**, e2211855120 (2023). <https://doi.org/10.1073/pnas.2211855120>
55. J.D. McGhee, G. Felsenfeld, Nucleosome Structure. *Annu. Rev. Biochem.* **49**, 1115 (1980). <https://doi.org/10.1146/annurev.bi.49.070180.005343>

56. D.E. Olins, A.L. Olins, Chromatin history: our view from the bridge. *Nat. Rev. Mol. Cell Biol.* **4**, 809 (2003). <https://doi.org/10.1038/nrm1225>
57. J. Widom, A relationship between the helical twist of DNA and the ordered positioning of nucleosomes in all eukaryotic cells. *Proc. Natl. Acad. Sci.* **89**, 1095 (1992). <https://doi.org/10.1073/pnas.89.3.1095>
58. T. Schalch, S. Duda, D.F. Sargent, T.J. Richmond, X-ray structure of a tetranucleosome and its implications for the chromatin fibre. *Nature* **436**, 138 (2005). <https://doi.org/10.1038/nature03686>
59. E. Lieberman-Aiden, N.L. Van Berkum, L. Williams, M. Imakaev, T. Ragoczy, A. Telling, I. Amit, B.R. Lajoie, P.J. Sabo, M.O. Dorschner, R. Sandstrom, B. Bernstein, M.A. Bender, M. Groudine, A. Gnirke, J. Stamatoyannopoulos, L.A. Mirny, E.S. Lander, J. Dekker, Comprehensive Mapping of Long-Range Interactions Reveals Folding Principles of the Human Genome. *Science* **326**, 289 (2009). <https://doi.org/10.1126/science.1181369>
60. G. Fudenberg, M. Imakaev, C. Lu, A. Goloborodko, N. Abdennur, L. Mirny, Formation of Chromosomal Domains by Loop Extrusion. *Cell Rep.* **15**, 2038 (2016). <https://doi.org/10.1016/j.celrep.2016.04.085>
61. J.W. Cahn, Critical point wetting. *J. Chem. Phys.* **66**, 3667 (1977). <https://doi.org/10.1063/1.434402>
62. P.G. De Gennes, Wetting: statics and dynamics. *Rev. Mod. Phys.* **57**, 827 (1985). <https://doi.org/10.1103/RevModPhys.57.827>
63. K. Binder, D. Landau, M. Müller, Monte Carlo Studies of Wetting, Interface Localization and Capillary Condensation. *J. Stat. Phys.* **110**, 1411 (2003). <https://doi.org/10.1023/A:1022173600263>
64. J.A. Morin, S. Wittmann, S. Choubey, A. Klosin, S. Golfier, A.A. Hyman, F. Jülicher, S.W. Grill, Surface condensation of a pioneer transcription factor on DNA (2020). <https://doi.org/10.1101/2020.09.24.311712>
65. T. Quail, S. Golfier, M. Elsner, K. Ishihara, V. Murugesan, R. Renger, F. Jülicher, J. Brugués, Force generation by protein-DNA co-condensation (2020). <https://doi.org/10.1101/2020.09.17.302299>
66. E.E. Alemasova, O.I. Lavrik, Poly(ADP-ribose) in Condensates: The PARTnership of Phase Separation and Site-Specific Interactions. *Int. J. Mol. Sci.* **23**, 14075 (2022). <https://doi.org/10.3390/ijms232214075>
67. M. Mazzocca, A. Loffreda, E. Colombo, T. Fillot, D. Gnani, P. Falletta, E. Monteleone, S. Capozzi, E. Bertrand, G. Legube, Z. Lavagnino, C. Tacchetti, D. Mazza, Chromatin organization drives the search mechanism of nuclear factors. *Nat. Commun.* **14**, 6433 (2023). <https://doi.org/10.1038/s41467-023-42133-5>
68. J.A. Morin, S. Wittmann, S. Choubey, A. Klosin, S. Golfier, A.A. Hyman, F. Jülicher, S.W. Grill, Sequence-dependent surface condensation of a pioneer transcription factor on DNA. *Nat. Phys.* **18**, 271 (2022). <https://doi.org/10.1038/s41567-021-01462-2>
69. F. García Fernández, J. Park, C. Chapuis, E. Pinto Jurado, V. Imburchia, R. Smith, E. José Longarini, A. Taddei, C. Hubert, N. Sokolovska, I. Matić, S. Huet, J. Miné-Hattab, Single nucleosome imaging reveals principles of transient multiscale chromatin reorganization triggered by histone ADP-ribosylation at DNA lesions. *Nat. Commun.* **16**, 6652 (2025). <https://doi.org/10.1038/s41467-025-61834-7>
70. B.R. Sabari, A. Dall'Agnese, A. Boija, I.A. Klein, E.L. Coffey, K. Shrinivas, B.J. Abraham, N.M. Hannett, A.V. Zamudio, J.C. Manteiga, C.H. Li, Y.E. Guo, D.S. Day, J. Schuijers, E. Vasile, S. Malik, D. Hnisz, T.I. Lee, I.I. Cisse, R.G. Roeder, P.A. Sharp, A.K. Chakraborty, R.A. Young, Coactivator condensation at super-enhancers links phase separation and gene control. *Science* **361**, eaar3958 (2018). <https://doi.org/10.1126/science.aar3958>
71. W.-K. Cho, J.-H. Spille, M. Hecht, C. Lee, C. Li, V. Grube, I.I. Cisse, Mediator and RNA polymerase II clusters associate in transcription-dependent condensates. *Science* **361**, 412 (2018). <https://doi.org/10.1126/science.aar4199>
72. T. Lindahl, D. Barnes, Repair of Endogenous DNA Damage. *Cold Spring Harb. Symp. Quant. Biol.* **65**, 127 (2000). <https://doi.org/10.1101/sqb.2000.65.127>
73. J. Miné-Hattab, S. Liu, A. Taddei, Repair Foci as Liquid Phase Separation: Evidence and Limitations. *Genes* **13**, 1846 (2022). <https://doi.org/10.3390/genes13101846>
74. J. Fries, J. Diaz, M. Jardat, I. Pagonabarraga, P. Illien, V. Dahirel, Active droplets controlled by enzymatic reactions. *J. R. Soc. Interface* **22**, 20240803 (2025). <https://doi.org/10.1098/rsif.2024.0803>
75. R. Berthoin, J.D. Fries, M. Jardat, V. Dahirel, P. Illien, Microscopic and stochastic simulations of chemically active droplets. *Phys. Rev. E* **111**, L023403 (2025). <https://doi.org/10.1103/PhysRevE.111.L023403>

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