Active Loop Extrusion Guides DNA-Protein Condensation

Ryota Takaki,[1] Yahor Savich,[1,2,3] Jan Brugués,[1,2,3,4,*] and Frank Jülicher[1,3,4,†]
[1]Max Planck Institute for the Physics of Complex Systems, Dresden, Germany
[2]Max Planck Institute of Molecular Cell Biology and Genetics (MPI-CBG), Dresden, Germany
[3]Center for Systems Biology Dresden, Dresden, Germany
[4]Cluster of Excellence Physics of Life, TU Dresden, Dresden, Germany

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The spatial organization of DNA involves DNA loop extrusion and the formation of protein-DNA condensates. While the significance of each process is increasingly recognized, their interplay remains unexplored. Using molecular dynamics simulation and theory we investigate this interplay. Our findings reveal that loop extrusion can enhance the dynamics of condensation and promotes coalescence and ripening of condensates. Further, the DNA loop enables condensate formation under DNA tension and position condensates. The concurrent presence of loop extrusion and condensate formation results in the formation of distinct domains similar to TADs, an outcome not achieved by either process alone.

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How cells read and process genomic information represents a fundamental question that is not fully understood. This process involves physical interactions between DNA and proteins that transduce sequence information on DNA to express genes and to organize chromatin. Loop extrusion by structural maintenance of chromosomes (SMC) complexes have been identified as a primary candidate of genome organization and regulation [1–6]. Loop extrusion has been studied through both *in vitro* experiments [7–18] and theoretical approaches [19–26]. DNA loops are involved in the formation of topologically associating domains (TADs) in chromatin. TAD boundaries are determined by the position of CCCTC-binding factor (CTCF) molecules on the DNA [4,27–32]. Another key process involved in chromatin organization is the formation of biological condensates, a process similar to phase separation [33–41]. Such condensates have been suggested, for example, to play a role in bringing promoters and enhancers into physical proximity [42]. Indeed condensates have been shown to exert capillary forces which could be involved in such processes [43]. These capillary forces are of similar magnitude as forces exerted by SMC molecules during loop extrusion [43]. This raises the question of how loop extrusion and condensate formation synergize to organize chromatin.

*Contact author: jan.brugues@tu-dresden.de
†Contact author: julicher@pks.mpg.de

In this Letter, we use simulation and theory to explore the interplay between loop extrusion and protein condensation in the spatial organization of DNA. We report that DNA loops play a pivotal role in nucleating and positioning protein-DNA co-condensates. The DNA loops not only facilitate the formation of co-condensates but also contribute to their stability under mechanical tension along DNA. We further discuss how loop extrusion and condensation contribute to the emergence of domains in chromatin contact maps, which characterize the DNA spatial organization.

Here we consider a configuration often used in biophysical studies of DNA, where a single DNA molecule is attached at both ends to a surface [8,43] (Fig. 1). We perform Langevin dynamics simulations that incorporate three distinct types of particle representing DNA segments, proteins, and SMC molecules. These particles interact according to Lennard-Jones potentials as well as FENE potentials along the DNA contour [44]. DNA-protein and protein-protein interactions are attractive while the interaction among DNA segments is repulsive. DNA segments are coarse-grained by particles with 10 nm diameter, and all three particle types have the same diameter. SMC molecules can bind to the DNA strand in the region indicated in blue in Fig. 1. Upon binding of an SMC molecule to a DNA segment, a two-sided loop extrusion process is initiated. The loop extrusion process terminates when the extruded DNA reaches a boundary of the blue region, mimicking the role of CTCF molecules [27,45]. We start our simulation from randomized initial positions of proteins and DNA segments, with DNA ends fixed at a prescribed distance L_{end} μm. The contour length of DNA is set to $L_c = 16.5$ μm, corresponding to λ-DNA [43]. See Supplemental Material [46] for simulation details.

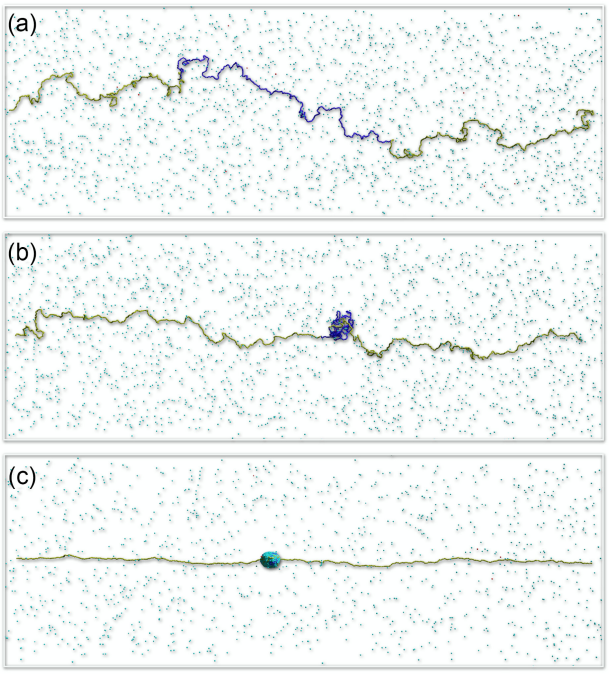

FIG. 1. (a) Initial configuration of the simulation with yellow and blue DNA particles indicating the DNA strand and SMC binding sites on DNA, respectively. Light blue particles represent proteins, and red particles SMC molecules. (b) Example of a DNA loop created by an SMC molecule. (c) Example of a Protein-DNA co-condensate. (a)–(c) Independent simulations for $L_{\mathrm{end}} = 6$ μm.

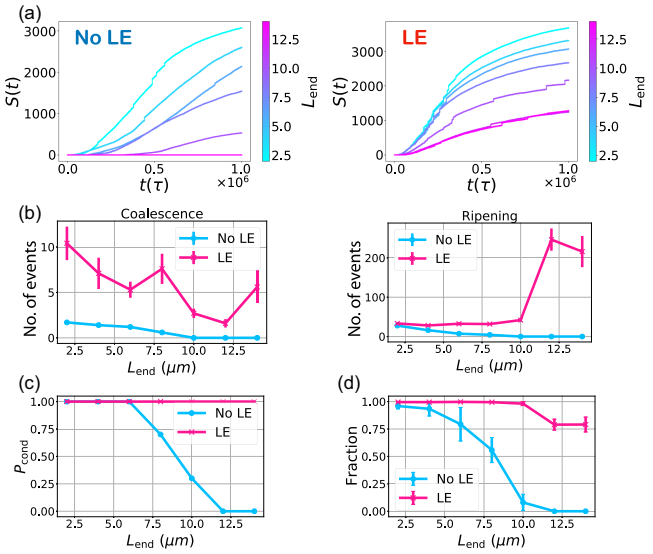

FIG. 2. (a) Size of the largest condensates $S(t)$ as a function of time t. Here τ is the unit time in our simulation (Supplemental Material [46]). The color bars represent the DNA end-to-end distance, L_{end}. Results without loop extrusion (No LE) and with loop extrusion (LE) are shown. (b) Number of condensate disappearance events due to droplet coalescence (left) or disassembly during ripening (right). Lines represent scenarios without loop extrusion (blue) and with loop extrusion (red). (c) Probability of condensate presence in the final frame of the simulation. (d) Fraction of SMC-binding DNA segments (blue in Fig. 1) within the condensate. Error bars indicate the standard error across ten simulations with the same parameter values.

We first focus on the dynamics of condensate growth. Similar to conventional droplet kinetics, DNA-protein condensates grow through coalescence and Ostwald ripening when multiple condensates exist. Figure 2(a) displays the size S of the largest droplet as a function of simulation time t, averaged over ten simulation trajectories. The size S is defined as the number of DNA and protein particles contained in the condensate (Supplemental Material [46], Sec. V.A). Stepwise increases of $S(t)$ indicate coalescence events, while gradual growth corresponds to ripening. We compare simulations without loop extrusion [Fig. 2(a), left)] to simulations with loop extrusion [Fig. 2(a), right] for different L_{end}. This comparison reveals that loop extrusion accelerates ripening but also enhances coalescence.

To provide further insight into the condensate growth dynamics, we count the number of events where condensates disappear either by coalescence or by Ostwald ripening, see Fig. 2(b). We find a systematic increase of condensate coalescence events in the presence of loop extrusion as compared to the absence of loop extrusion. Furthermore we observe that droplet disappearance by ripening is strongly enhanced for large L_{end}. The enhancement of Ostwald ripening by loop extrusion can be understood as follows: condensates outside the loop are subjected to the tension of the polymer and therefore disfavored as compared to the condensate inside the loop which is not subject to tension (Supplemental Material [46], Sec. II).

We next calculated the probability of condensate formation (P_{cond}), defined as the probability of condensate formation in the final frame of our simulation trajectories [Fig. 2(c)]. For short L_{end}, a condensate is present irrespective of whether a loop was extruded. For larger L_{end} the probability to find a condensate drops and eventually vanishes if no loop is extruded, similar to previous results [43]. Interestingly, loop extrusion enables condensate formation even at large L_{end}. Loop extrusion can also position condensates. In fact, in our simulations, condensates are often found where the loop is formed. To quantify this colocalization, we compute in Fig. 2(d) the fraction of SMC-binding DNA segments (blue in Fig. 1) within the condensate. With loop extrusion, these segments are largely included inside the condensate, even for larger values of L_{end}. In contrast, without loop extrusion, this fraction decreases with increasing L_{end}.

The positioning of condensates by loop extrusion can be discussed by considering three possible scenarios. In scenario (a), the DNA loop is located outside of the condensate [Fig. 3(a)]. In the scenario (b), the condensate is located at the DNA loop and only the DNA loop is inside

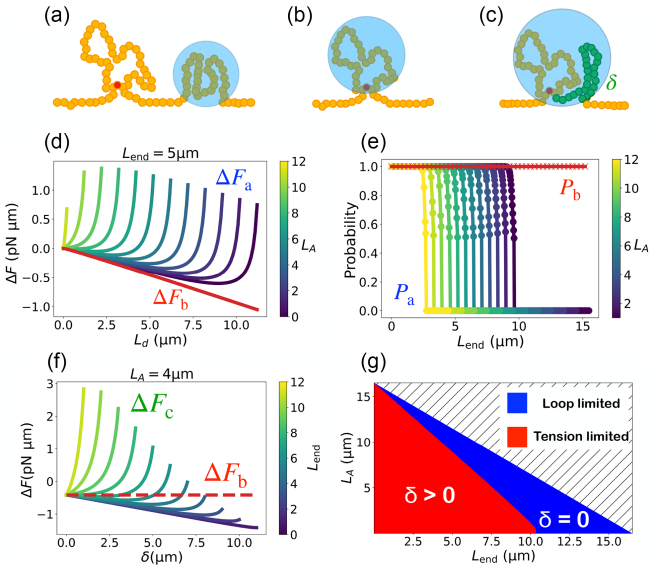

FIG. 3. (a)–(c) Schematic representations of three scenarios of protein-DNA co-condensation. Yellow, blue, and red circle indicates DNA segments, condensate, and SMC protein, respectively. (a) Condensate positioned outside the DNA loop. (b) Condensates at the DNA loop. (c) Condensate at the loop, including extra DNA length δ (green). (d) Free energy, ΔF_a, for scenario (a) compared to ΔF_b corresponding to (b), as a function of the length L_d within the condensate for different loop length L_A. (e) Probability P_a (P_b) of condensation formation for scenario (a) (scenario (b)) as a function of L_{end}. (f) Free energy ΔF_c for scenario (c) as a function of δ compared to ΔF_b for different L_{end}. (g) Phase diagram of condensation in the presence of DNA loop as a function of L_A and L_{end}. The loop limited regime (blue) and the tension limited regime (red) are indicated. The hatched region is physically inaccessible.

the condensate [Fig. 3(b)]. Finally, in scenario (c) the DNA loop is inside the condensate together with additional DNA segments of length δ [Fig. 3(c)]. Our simulations suggest that condensation within the DNA loop is not affected by mechanical tension. Therefore condensates form reliably in the scenario (b) and (c) containing the loop. To understand the effect of DNA loop on the formation of condensates, we use a simple model of co-condensation [43]. In this model, the free energy of the configuration is the sum, $F = F_d + F_p$, where

$$F_d(L_d) = -v\alpha L_d + \gamma 4\pi \left(\frac{3\alpha}{4\pi}\right)^{2/3} L_d^{2/3}, \tag{1}$$

is the free energy of the condensate and

$$F_p(L_d, L_{\mathrm{end}}, L_c) = \frac{k_B T L_{\mathrm{end}}^2}{4 l_p} \left(\frac{1}{L_c - L_d - L_{\mathrm{end}}} + \frac{2}{L_c - L_d}\right) \tag{2}$$

is the free energy of the non-condensed DNA. Here L_d is the length of the DNA segments inside the condensate, k_B is the Boltzmann constant, T represents the temperature, and l_p is the persistence length of DNA. The parameters α, γ, and v are the inverse of the DNA packing density, surface tension of the condensate, and condensation free energy per volume, respectively [43]. We use parameter values obtained for fork head box protein A1 [43]: $\alpha = 0.04\ \mu\mathrm{m}^2$, $\gamma = 0.04\ \mathrm{pN\,\mu m^{-1}}$, $v = 2.6\ \mathrm{pN\,\mu m^{-2}}$ and $l_p = 50$ nm.

We first consider scenario (a) [Fig. 3(a)]. In this case the condensate is located outside the DNA loop of length L_A. We define the energy difference $\Delta F_a = F_d(L_d) + F_p(L_d, L_{\mathrm{end}}, L_c - L_A) - F_p(0, L_{\mathrm{end}}, L_c - L_A)$ as the difference of the free energy before and after condensate formation, where we have taken into account that the DNA contour length L_c is effectively reduced by the loop length L_A. The stable condensate size is then obtained by minimizing ΔF_a with respect to L_d.

In scenario (b), the condensate contains the DNA length $L_d = L_A$ and the free energy change due to condensate formation is simply given by $\Delta F_b = F_d(L_A)$. Correspondingly, in scenario (c), we define $\Delta F_c = F_d(L_A + \delta) + F_p(L_A + \delta, L_{\mathrm{end}}, L_c) - F_p(L_A, L_{\mathrm{end}}, L_c)$. When $\delta = 0$, the DNA length inside the condensate equals to the loop length L_A, reducing this case to scenario (b).

We show ΔF_a in Fig. 3(d), as well as ΔF_b for $L_{\mathrm{end}} = 5$ μm. Increasing the loop length L_A shifts the minimum position of ΔF_a towards smaller values of L_d until the condensate vanishes via a first-order phase transition, similar to the one reported previously [43]. Figure 3(d) reveals that $\Delta F_b < \Delta F_a$, implying that a condensate will always form inside the loop, irrespective of the tension on the DNA. Thus, the DNA loop guides condensate formation. Figure 3(e) shows the conditional probability of generating a condensate outside the loop (P_a) as a function of L_{end}. Increasing L_A shifts the curves for P_a towards smaller L_{end} values: the tension induced by the DNA loop narrows the range where condensation outside the loop is possible. However, condensates in the loop are always favored ($P_b = 1$).

Figure 3(f) shows the free energy profile ΔF_c as a function of δ together with ΔF_b. This shows that for sufficiently large L_{end} the free energy is minimal for $\delta = 0$ and the condensate size is equal to the loop size. We call this loop limited condensate. As L_{end} is decreased below the critical value L_{end}^c, F_c exhibits a minimum at $\delta > 0$ corresponding to a condensate containing a DNA segment that is longer than the loop. In this regime the condensate is tension limited. At $L_{\mathrm{end}} = L_{\mathrm{end}}^c$, where δ vanishes, a continuous second order transition occurs. Figure 3(g) shows the phase diagram for condensates in the presence of a loop. In the blue region, $\delta = 0$ and condensates are loop limited. In the red region, $\delta > 0$ and condensates are tension limited. Both regions meet at a second order transition line.

We find that the phase transition line between the loop limited and tension limited regimes lies within the force

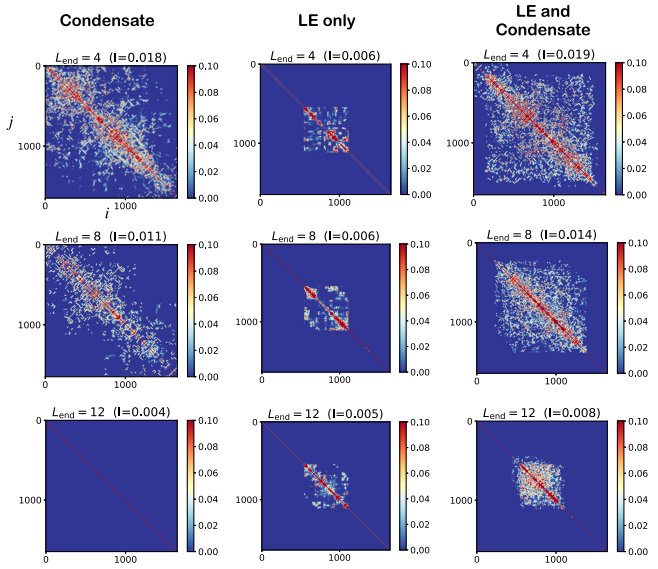

FIG. 4. Contact maps obtained in simulations for only condensation (left), only loop extrusion (middle), and both loop extrusion and condensation (right) as a function of DNA particle indices i and j. Contact maps are presented for $L_{\mathrm{end}} = 4, 8, 12$ μm (top to bottom). The contact probability between particle i and j is shown as a color code. The fraction I of contacts, defined as the sum of the all contact probabilities normalized by the total number of pairs (1650^2), is given.

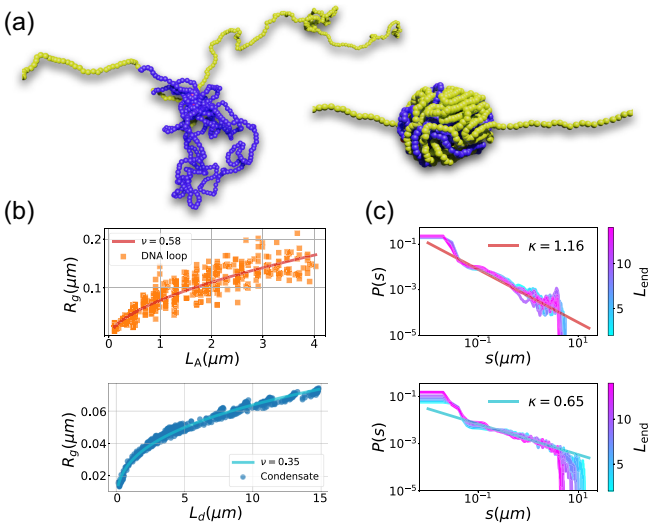

FIG. 5. (a) Representative snapshots showing a DNA loop without condensation (left) and a DNA-protein condensate containing the DNA loop (right). Yellow and blue particles indicate the DNA strand and SMC binding site on DNA, respectively. Protein particles are not shown to emphasize the DNA structure. $L_{\mathrm{end}} = 6$ μm. (b) Radius of gyration R_g of DNA loops without condensation as a function loop length L_A (top, $\nu \simeq 0.58$) and of DNA within a condensate as a function of condensed DNA length L_d (bottom, $\nu \simeq 0.35$). The data is fit using $R_g \sim L^{\nu}$ (solid lines). (c) Probability of contact inside loops and condensates, P, as a function of the DNA length between contacts, s, for different L_{end}. Loop extrusion without condensation (top, $\kappa = 1.16$) and loop extrusion with condensation (bottom, $\kappa = 0.65$). The data are fit using $P \sim s^{-\kappa}$ (solid lines). The reported values of κ are the mean value of the exponents for different L_{end} fit in the range 5×10^{-2} μm $< s < 3$ μm.

range where CTCF molecules efficiently regulate the loop extrusion process of cohesin [27]. This suggests that the loop limited regime may play a role in regulating TAD formation (see Sec. III in Supplemental Material [46] for further analysis).

We now discuss the effects of loops on DNA conformations inside the condensates. Both condensation and loop extrusion lead to a local accumulation of DNA segments, see Fig. 1. Such accumulation fosters contacts between DNA segments, even when they are at a distance along the sequence. The probabilities of such contacts are characterized by a contact map, a key tool to understand chromatin organization [50–54]. We determine contact maps for different end-to-end distance in our simulations. Figure 4 presents examples of contact maps with contact probability between two segments i and j, where i and j are the DNA particle indices of two DNA segments. In Fig. 4, contact maps are shown for DNA-protein co-condensation without loop extrusion (left column), for loop extrusion without condensation (middle column), and for both condensation and loop extrusion (right column), for different values of L_{end}. We find that if only condensation happens, contact maps show many but irregularly positioned disordered contacts for short L_{end}. These contacts disappear as L_{end} is increased and condensates dissolve. For only loop extrusion, contacts occur within the loop and are dominated by short-ranged contacts. When condensation and loop extrusion are combined, square patterns of contacts resembling TADs emerge. These square patterns imply that contacts over longer distances along the chain are prominent.

To further characterize the structures generated by condensation and loop extrusion, we consider the polymeric configuration of loops and condensates. Figure 5(a) shows example configurations obtained in simulations: a DNA loop without condensation (left) and a DNA loop within a condensate (right). This reveals a coil-like structure of the DNA loop and a densely packed DNA within the condensate. Figure 5(b) shows the radius of gyration (R_g) of the DNA loop as a function of loop length, exhibiting a scaling behavior with an exponent $\nu = 0.58$, similar to the Flory exponent $\nu = 3/5$ of a polymer in a good solvent [44]. In contrast, R_g of the DNA inside a condensate exhibits different scaling behavior with $\nu = 0.35$, which is close to the exponent $\nu = 1/3$ of a collapsed polymer in a poor solvent [44]. Using these results, we can explain the difference between the contact maps shown in Fig. 4. In the absence of condensation, the looped polymer behaves as a random coil favoring short range contacts. Indeed, the contact probability decreases for increasing distance along

the polymer, giving rise to the short ranged contact maps shown in Fig. 4, middle. For a loop inside the condensate, the contact probability remains high, giving rise to the longer ranged contact map.

In Fig. 5(c), we plot the contact probability density $P(s)$ as a function of the DNA length s between contact points. We find that the probability density follows a power law, $P \sim s^{-\kappa}$. In the scenario with only loop extrusion, we observe $\kappa \simeq 1.16$ [Fig. 5(c), top]. However, when condensate formation occurs in addition to loop extrusion, the exponent decreases significantly to $\kappa = 0.65$ [Fig. 5(c), bottom]. This result is surprising, as the commonly used mean-field argument, $\kappa = 3\nu$ [55], suggests $\kappa \geq 1$ for $\nu \geq 1/3$. Interestingly, an exponent $\kappa \sim 0.7$ has been observed in experiments [29,56], which is attributed to the scaling regime related to TADs. Such an exponent has been suggested to rise because of a nonequilibrated structure of extruded loops [26] and exponentially distributed loops [6,57]. Our findings show that long-range DNA contacts mediated by protein-DNA co-condensation could also yield an exponent smaller than 1.

In summary, we investigated the interplay between DNA loop extrusion and DNA-protein co-condensation. We found that loop extrusion stabilizes DNA-protein co-condensation under tension and positions the condensate on DNA. We identified a regime of loop limited condensates, where condensate size is set by the DNA loop size. Our work shows that by combining loop extrusion and condensation, a DNA organization with the characteristics of TADs can naturally emerge. In the absence of condensation, the resulting contact maps remain short ranged. The condensation facilitates close contacts of distant DNA segments within the TAD. In our work, we use a simple simulation assay that allows us to control tension along DNA. While we do not recapitulate the complexities of chromatin in the cell nucleus, we think that this assay reveals physical principles that could play a key role for genome organization in the cell. Our work therefore underscores that chromatin organization in TADs may emerge from the interplay between loop extrusion and protein-DNA co-condensation.

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