



# Motor domain of condensin and step formation in extruding loop of DNA

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## Abstract

During the asymmetric loop extrusion of DNA by a condensin complex, one domain of the complex stably anchors to the DNA molecule, and another domain reels in the DNA strand into a loop. The DNA strand in the loop is fully relaxed, or there is no tension in the loop. Just outside of the loop, there is a tension that resists the extrusion of DNA. To maintain the extrusion of the DNA loop, the condensin complex must have a domain capable of generating a force to overcome the tension outside of the loop. This study proposes that the groove-shaped HEAT repeat domain Ycg1 plays the role of a molecular motor. A DNA molecule may bind to the groove electrostatically, and the weak binding force facilitates the random thermal motion of DNA molecules. A mechanical model that random collisions between DNA and the nonparallel inner surfaces of the groove may generate a directional force which is required for the loop extrusion to sustain. The hinge domain binds to the DNA molecule and acts as an anchor during asymmetric DNA loop extrusion. When the effects of ATP hydrolysis and the viscous drag of the fluid environment are considered, the motor–anchor model for the condensin complex and the mechanical model might explain the asymmetric loop extrusion, the formation of steps, the step size distribution in the loop extrusion, the tension-dependent extrusion speed, the interaction between coexisting loops on the DNA strand, and untying the knots during extrusion. This model can also explain the observed formation of the Z-loop.

**Keywords** Loop extrusion · Condensin · Step formation · Motor domain · Mechanical model

## 1 Introduction

Human genomic DNA, despite being very long, is compactly stored in a cell's nucleus measuring only a few micrometers [1–3]. The linear DNA molecule is wrapped around a string of histone octamers to form a nucleosome, which considerably shortens its length. These nucleosomes are further packaged by the structural maintenance of chromosome (SMC) complexes to form chromosomes. SMC complexes were postulated to compact DNA through loop extrusion [4, 5]. This was confirmed by Ganji et al., who first observed DNA loop extrusion in a

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yeast condensin complex in real-time images in 2018 [6]. In 2019, Davidson et al. [7] and Kim et al. [8] have observed DNA loop extrusion in human cohesin complexes.

Condensin and cohesin, two well-studied SMC complexes, have similar structures consisting of two flexible SMC proteins, a kleisin protein, and HEAT repeat proteins [9–13]. The two SMC coiled-coil proteins are connected at one end by a globular hollow hinge domain. These SMC coiled coils exhibit flexibility and can adopt various folded conformations, as observed through high-speed atomic force microscopy (AFM) in a liquid environment [13–15]. The hinge domain serves as a DNA-strand-binding site [15] and is proposed to function as an anchor in the loop extrusion process in this study. At the opposite end of the SMC proteins are globular head domains that contain binding sites for DNA molecules. These two heads are connected with a kleisin protein (Brr1 in condensin and SCC1 in cohesin), and they interact with each other through the binding of ATP molecules. Additional subunits, namely HEAT repeat proteins, associate with the kleisin protein and complete the configuration of the SMC complex. HEAT repeat proteins play crucial roles in the interaction between SMC proteins and genomic DNA [6–8]. In the case of condensin, the HEAT repeat proteins are Ycg1 and Ycs4. Many researchers have considered HEAT repeats as binding sites for DNA molecules due to their similar groove-like structures and DNA-binding configurations (where a DNA strand passes through the trough of the groove) [11, 12]. In this study, Ycg1 is identified as the molecular motor within condensin complexes because of its structure being similar to those of nonstructured helicases [16, 17]. Thus, in this study, the condensin complex is modeled as a combination of an anchor and a motor.

Condensin can extrude loops in moderately stretched, double-tethered DNA strands [6, 18–20]. However, the tension in the DNA strand may resist DNA extrusion. Thus, the SMC complex may possess molecular motor domains, which generate the necessary force to overcome the tension in the DNA strand. A single condensin complex asymmetrically extrudes a partially relaxed, double-tethered DNA molecule into a loop structure [6, 20]. When the loop is growing, condensin stably anchors itself on one arm of the DNA loop, and the DNA strand is threaded into the loop structure from the other arm. A simple force analysis can be performed to understand the extrusion process. Experimental observations revealed that the DNA strand in the loop is fully relaxed, indicating little to no tension in the looped DNA strand. However, for the doubly tethered DNA molecule, there exists a tension force, denoted as  $F$ , in the direction that tends to pull the DNA strand out of the loop, just outside of the loop. This tension force increases as the extrusion process advances. Thus, a force is required at the boundary of the loop, where the DNA strand interacts with the condensin complex, to overcome the tension and maintain the continuous extrusion of DNA into the loop. Loop extrusion experiments have indicated the necessity of a molecular motor in the SMC complex. The molecular motor must generate a unidirectional force on DNA to reel the DNA strand into the loop. The molecular motor binds to the DNA molecule with moderate strength, ensuring that the generated force is sufficient to overcome the binding force acting on the DNA strand. High-speed AFM studies of loop extrusion events have reported that both the hinge and globular head domains bind to the DNA molecule. One of these binding domains might play a role in the function of the molecular motor, whereas the other domain might serve as the anchor. Such a motor–anchor model for the condensin complex is essential in explaining the loop extrusion process, but it must be complemented with a plausible mechanism for generating the force required by the motor domain.

Various models were proposed to explain the loop-extrusion of DNA by the SMC complexes, for example, the scrunching model [15], the Brownian ratchet model [21], and the hold-and-feed model [22]. All of these models are based on the large conformational

changes of the SMC complex along with interactions between DNA and the SMC complex through the binding sites of DNA on the SMC complex, and ATP binding and hydrolysis. The possible DNA binding sites on the condensin complex are the ATPase head domains, the hinge domain, and the HEAT-repeat subunits associated with the kleisin subunit, which have positively charged surfaces. AFM observations confirmed the binding of SMC complex to DNA through the binding sites. In the scrunching model, when a DNA molecule interacts with an SMC complex, the DNA molecule binds to the hinge and HEAT repeat proteins. Simultaneously, ATP molecules bind to the head domains, causing contact between the two head domains. This action triggers the SMC complex's arms to fold over, and the hinge domain approaches the head domains. Thus, the SMC complex collapses into a scrunching state, with a DNA strand binding to the head domains. The hinge domain is then released from the DNA strand, returning to its extended conformation. The hinge domain may then bind the DNA strand at a new position, allowing the DNA to slide while binding to the HEAT domain. These processes may repeat, propelling the SMC complex to move along the DNA strand.

The Brownian ratchet model [21] involves DNA binding to the SMC complex in a gripping state, SMC head opening after ATP hydrolysis, followed by a stochastic swing of the hinge domain to enlarge the DNA loop, a release and rebounding of DNA by the hinge domain. The cycle of loop extrusion ends by returning to the gripping state.

Shaltiel et al. [22] proposed a similar motor–anchor concept for DNA loop extrusion. In their proposed hold-and-feed model, a motor chamber was formed by the kleisin domain and Ycs4, and another kleisin chamber included the Ycg1 protein, which bound to the DNA strand, and acted as the anchor. Upon ATP binding, the coiled coil arm opens, the hinge domain swings and temporarily binds to DNA at a position. After ATP hydrolysis, the segment of DNA between the hinge and the head domain is pushed into the new enlarged loop between the motor and anchor chambers by the hinge domain along with the folding of the SMC complex's arms.

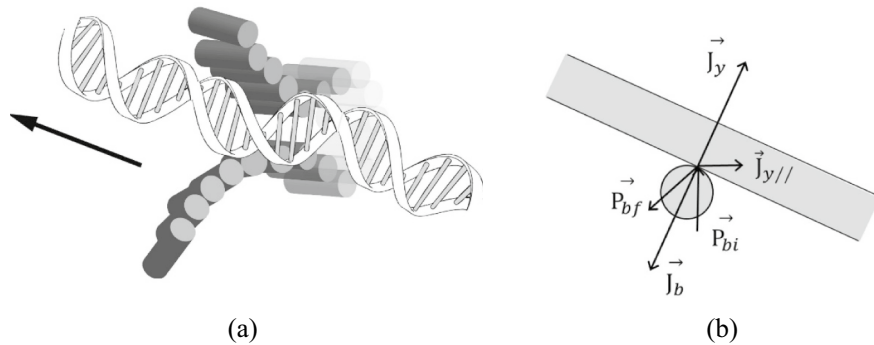
In a newly proposed reel-and-seal model, Dekker et al. [23] adopt the clamping and releasing of DNA by a HEAT repeat and the head domain to serve the function of the motor domain of the hold-and-feed model. The processes of the binding and pushing DNA segment into a loop are similar to the hold-and-feed model.

However, three crucial aspects were not considered in the proposed models [15, 21–23]. First, the models do not account for physical forces generated to overcome the dragging force exerted by the fluid environment and the tension existing in the DNA strand during loop extrusion. Second, the temporary release of DNA from the SMC complex is a common process of the above-mentioned models. The tension in the DNA molecule may pull the segment of DNA out of the loop when the binding of DNA to the SMC complex is released. Third, the models do not consider the random motion of the DNA strand, which can lead to movement in a direction that is unfavorable for the feeding of DNA into the loop.

## 1.1 Proposed model of the molecular motor on condensin

### 1.1.1 DNA binding and force generation

DNA binds to the HEAT repeat protein Ycg1 and the kleisin subunit Brn1 of condensin in a safety-belt configuration, forming a wide groove that accommodates the DNA strand [11, 12]. Figure 1a illustrates DNA binding to Ycg1 [11]. The groove-like structure, characterized by two nonparallel side walls, represents the simplest arrangement capable of inducing the



**Fig. 1** Schematic of DNA binding to the Ycg1 groove. The arrow indicates the direction of the motion of DNA relative to Ycg1 according to the mechanical model. **b** Schematic of the generation of impulse  $\vec{J}_{y//}$  required for the translocation of the model groove-like structure of Ycg1 during a single collision event. The shaded area represents the groove wall. The sphere represents the bead in model experiments or the base pair of the DNA molecule colliding with the groove wall, and  $\vec{p}_{bf}$  represent the momenta of the colliding bead before and after collision, respectively.  $\vec{J}_b$  and  $\vec{J}_y$  denote the momentum transfers of the atom of DNA and Ycg1, respectively, during collision.  $\vec{J}_{y//}$  is the horizontal component of  $\vec{J}_y$ . The sum of impulse  $\vec{J}_{y//}$  in the unit of time is the force acting on Ycg1. The base pair of DNA gains  $\vec{J}_b$  and moves toward the large end of the channel.

directional motion of the long DNA strand [16, 17, 24]. This DNA-binding conformation is shared by many translocation-related proteins, including nonstructured helicases. Thus, the HEAT-repeat protein Ycg1 is a promising candidate for a molecular motor in condensin. The positively charged inner surface of the trough provides the electrostatic force necessary to bind the negatively charged DNA strand. Given that long DNA molecules, with a width of approximately 2 nm, exhibit constant random thermal motion at normal body temperature [25], the DNA strand that electrostatically binds to Ycg1 HEAT repeats may move randomly and collide with the inner surface of the Ycg1 HEAT repeat groove. These collisions occur due to the vigorous thermal motion of the DNA molecule and may disrupt the weak electrostatic attraction between Ycg1 and DNA. The weakness of the interaction between Ycg1 and DNA allows DNA to slide along the groove, leading to its continuous binding and release from Ycg1. Therefore, the HEAT-repeat subunit Ycg1 may be driven by impulsive forces generated by the molecular motor, facilitating its translocation along DNA. The safety-belt configuration [11] ensures that Ycg1 remains attached to and moves along the DNA molecule for an extended duration. Moreover, the presence of asymmetric structures in the motor-track system regulates the isotropic random motion of individual entities into directional relative motion [24, 26]. The force required for directional motion may arise from collisions between the DNA molecule and the asymmetric structure.

In the mechanical model, DNA is represented as a string of beads, with each bead corresponding to a single base pair, which is a well-established concept in the literature [26, 27]. Similar to nonstructured helicases, random collisions between the base pairs of DNA (represented by a spherical bead in Fig. 1b) in the groove-like structure and the nonparallel inner side surfaces of the groove can generate impulses  $\vec{J}_{y//}$  on the groove-like structure of Ycg1 according to Newtonian mechanics. The sum of impulses in the unit of time is the force acting on Ycg1. The direction of the force on Ycg1 generated by the mechanical

model is determined by the nonparallel sides of the groove, which is directed toward the smaller opening of the groove structure in Ycg1. As illustrated in Fig. 1a, guided by the small end of the groove structure (on the right of the figure), Ycg1 is translocated along DNA, thus driving the overall movement of the condensin complex. In other words, DNA moves to the left in the figure relative to Ycg1. Ycg1 HEAT repeats associated with flexible kleisin may exhibit different orientations [12], potentially resulting in varying force generation and condensin translocation directions along the stretched DNA strand. Thus, condensins translocate unidirectionally, with an equal probability of moving in either direction along a DNA molecule, as observed in a previous study [18].

## 1.2 Role of ATP hydrolysis in the translocation and loop extrusion of condensin

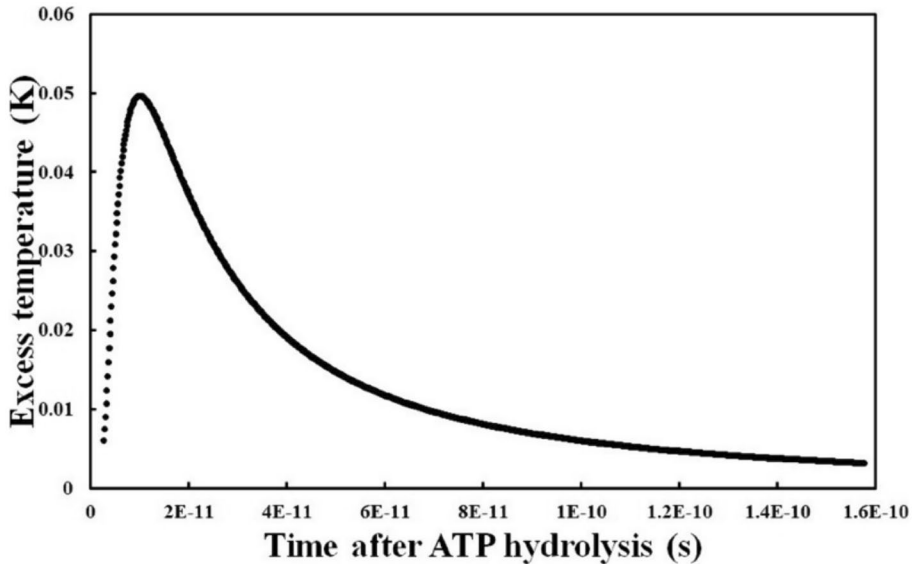
In the absence of ATP hydrolysis, random collisions between DNA and the Ycg1 groove still occur due to the thermal motion of both entities. However, these impulsive forces lead to minimal or no relative motion [6, 28] because the net effects of randomly generated impulsive forces are counteracted by forces arising from random collisions with molecules in the surrounding fluid environment.

The presence of ATPase near or on the molecular motor is crucial for the motor's motion. In the mechanical model, the primary role of ATP hydrolysis is to provide additional energy and increase the local temperature of both the Ycg1 protein and the bound DNA strand in addition to triggering conformational changes in the condensin complex. ATP hydrolysis occurs at an ATPase site in the head domain of the condensin complex as discrete events with a frequency of approximately 2 Hz [6]. The energy released from the ATP hydrolysis event is transmitted into the local environment, including the molecular motor, the track, and nearby molecules, through heat conduction. This temporarily increases the temperature of the local environment [29]. The random movements of the molecular motor and the track become more pronounced, resulting in the generation of an increased directional force by the motor. Thus, the motor moves forward in the direction of the generated force, exhibiting small positional displacement before the excess thermal energy dissipates in the overdamped environment. The relative motion between the molecular motor and DNA strand may continue following subsequent ATP hydrolysis events.

We can consider the site of ATP hydrolysis (ATPase) as a point source of energy, namely 30 kJoules/mole. The energy resulting from ATP hydrolysis diffuses into the environment through thermal conduction. The calculation based on the thermal conduction equation yields the excess temperature  $\Delta T(r, t)$  relative to the environmental temperature [29]:

$$\Delta T(r, t) = \frac{Q}{\rho C} (4\pi\alpha t)^{-\frac{3}{2}} \exp\left(-\frac{r^2}{4\alpha t}\right) \quad (1)$$

where  $Q$  is the energy released by a single ATP hydrolysis event,  $\rho$  is the density of water,  $C$  is the heat capacity of water,  $\alpha = 1.5 \times 10^{-7}$  m/s is the thermal diffusivity of water, and  $r$  is the distance between ATPase on the head module of condensin and the bound DNA molecule. As shown in cryo-electron microscopy images [12], the DNA molecule passes through the head module of the condensin complex, and the diameter of the head module is 10 nm. Thus, an estimation of the distance  $r$  at 3 nm between ATPase and DNA appears reasonable. The time dependence of the excess temperature at  $r = 3$  nm is presented in Fig. 2 as an example. The maximum excess temperature of 0.05 K is reached at  $t = 1.1 \times 10^{-11}$  s after the hydrolysis event. The time interval  $\delta t = 3.9 \times 10^{-11}$  s, during which the excess temperature remains above  $1/e$  ( $e = 2.72$  is the exponential constant) times the maximum value, is considered as the effective



**Fig. 2** Excess temperature as a function of time after an ATP hydrolysis event at a distance of 3 nm from the site of the event

duration of the impact of the hydrolysis event on the translocation of condensin. Collisions between the DNA strand and molecular motor within  $\delta t$  may contribute to the relative motion of the two entities. The actual distance  $r$  between ATPase on the head module of condensin and the bound DNA molecule may fluctuate (Fig. 2), and the effects of  $r$  on the step size may be included as an adjustable parameter.

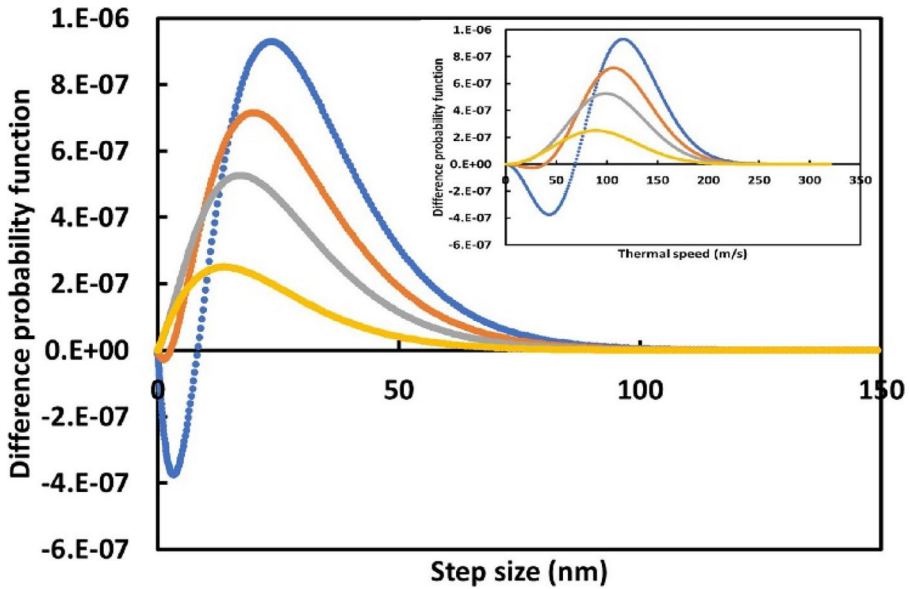
The excess temperature enhances the random motion of both the molecular motor and DNA molecule, which can be observed through changes in the distribution of the thermal speed  $v$  of DNA base pairs in the groove. In addition, the effects of tension  $F$  should be included in the speed distribution function [30]. The total energy of a DNA base pair in the presence of a force field  $F$  is given by  $mv^2/2 + F\xi$ , where  $\xi$  is a fitting parameter with dimensions of length [31, 32]. The speed distribution for  $T + \Delta T$  can be written as

$$f(v, T + \Delta T) = \left( \frac{m}{2\pi k_B(T + \Delta T)} \right)^{\frac{3}{2}} 4\pi v^2 \exp\left( -\frac{\frac{1}{2}mv^2 + F\xi}{k_B(T + \Delta T)} \right) \quad (2)$$

where  $m$  is the mass of the DNA strand, and  $k_B$  is the Boltzmann constant. For small  $\Delta T$ ,  $f(v, T + \Delta T)$  can be approximated as the sum of two components:

$$f(v, T + \Delta T) \approx f(v, T) + f(v, \Delta T) \quad (3)$$

where  $f(v, \Delta T) = \left( 9\sqrt{\frac{3}{2\pi v_0^2}} \right) \left( \frac{v}{v_0} \right)^2 \left( \frac{\Delta T}{T} \right) \left( \frac{v^2}{v_0^2} + \frac{2}{3} \frac{F\xi}{k_B T} - 1 \right) \exp\left( -\frac{3v^2}{2v_0^2} - \frac{F\xi}{k_B T} \right)$ , and  $v_0 = (3k_B T/m)^{1/2}$  is the difference distribution function. The component  $f(v, T)$  corresponds to the equilibrium Boltzmann–Maxwell distribution of speed. Without excess energy from ATP hydrolysis, the force generated by the DNA molecule with speed  $v$  colliding with the Ycg1 of the condensin complex is counteracted by the drag force exerted by the fluid



**Fig. 3** Difference distribution function  $f(v, \Delta T)$  between the Boltzmann–Maxwell distributions at temperatures  $T + \Delta T$  and  $T$ , displayed as a function of the step size for various tensions in the DNA strand. The curves represent tensions of  $F = 0.2, 0.4, 0.6,$  and  $1.0$  pN in descending order. In the inset, the difference distribution function  $f(v, \Delta T)$  is plotted as a function of thermal speed. The parameter  $\xi$  used in the calculation (Eq. 3) is set at 18 nm

environment. In other words,  $f(v, T)$  accounts for the random motion of condensin around the equilibrium position with or without ATP hydrolysis.

After an ATP hydrolysis event, the DNA base pair exhibits an increased probability, denoted as  $f(v, \Delta T)$ , of colliding with Ycg1 at speed  $v$  on the high-speed side. Such collisions are responsible for relative motion between DNA and condensin. Thus,  $f(v, \Delta T)$  may be considered as the probability of the occurrence of relative motion between DNA and condensin. Because of the discrete nature of ATP hydrolysis events (occurring at approximately 2 Hz) on the globular head domain of condensin, relative motion between DNA and condensin occurs in a step-like manner. In the mechanical model, the impulsive force generation and the occurrence of a loop-extrusion step both coincide with the ATP hydrolysis event, which is consistent with a recent observation of twist-inducing events when ATP hydrolyses and steps occur [33]. Figure 3 illustrates the difference probability function  $f(v, \Delta T)$  for different values of tension  $F$ .

The negative values of  $f(v, \Delta T)$  result from a decrease in the number of molecules with low speed at higher temperatures, which is necessary to maintain the normalization condition. The collision of low-speed molecules with Ycg1 might contribute to the motion of DNA in the reverse direction (the reverse steps). The mass of condensin is approximately 700 k Da, which is considerably more than the mass of DNA base pairs colliding with condensin. Thus, condensin can be considered less mobile when subjected to collisions with DNA. In the following analysis, only the motion of DNA base pairs involved in the collision is considered. Compared with  $f(v, T)$ ,  $f(v, \Delta T)$  exhibits smaller values, and the most probable speed decreases as the tension increases. These two characteristics of  $f(v, \Delta T)$  have substantial effects on the speed of translocation and DNA extrusion by condensin

on DNA. For example, they contribute to the rarity of step occurrences as tension increases and may account for the long dwell times observed during the formation of large steps.

### 1.3 Estimation of speed

As presented in Fig. 1a, DNA base pairs may move toward the large end of the groove-like structure of Ycg1 with a speed of  $v_t = 2v_{bi}\sin\theta \sim v_{bi} = v$  after each collision, where  $v_{bi} = p_{bi}/m$  is the initial speed of the collision,  $m$  is the mass, and  $v$  is the thermal speed of DNA base pairs. The other force acting on the DNA base pair is the drag force  $f_\eta$  of the fluid. For slowly moving molecules, the drag force may be proportional to their speed. The motion of DNA decays with a time constant  $\tau$  of viscous drag force [25]. However, the drag force depends on the actual shape of DNA molecules and has not been measured. Thus, the time constant  $\tau$  is treated as a fitting parameter in this study. During the effective time  $\delta t$  required for the energy of ATP hydrolysis to dissipate through heat conduction, multiple collisions can occur between DNA and condensin. The time interval between two consecutive collisions may be estimated using  $d/v$ , where  $d$  is the gap between the inner wall of the groove-like Ycg1 and the bound DNA. Considering the electrostatic interaction between Ycg1 and DNA, a gap  $d$  of 0.5 nm might be a reasonable estimate [11] and can be treated as another fitting parameter. Thus, the number of collisions within the effective time  $\delta t$  is estimated to be  $v\delta t/d$ . The DNA base pairs may travel a distance

$$L = A (v\delta t/d) * v * \tau \quad (4)$$

after each ATP hydrolysis event. The distance  $L$  is the step size observed in previous studies [28, 34].  $A$  is a constant of the order of unity depending on the strength of the molecular motor.

Two ATP hydrolysis events occur every second. Thus, the speed of the relative motion of DNA to the condensin complex without considering the drag effect of the anchor can be estimated as

$$v_{dna} = 2L = 2Av^2\delta t\tau/d \quad (5)$$

Comprehensive measurements of the distribution of step sizes were obtained from a previous study [34], especially for tension  $F=0.4$  pN. The parameter  $\tau$  was adjusted to match the peak values of the distributions of the step size between the calculated and measured values. The peak of the distribution of the measured step size occurred at  $L=20$  nm [34]. With a  $v$ , the most common speed of the distribution function  $f(v, \Delta T)$ , of 123 m/s (Fig. 3) for tension  $F=0.4$  pN,  $\delta t$  was calculated to be  $3.9 \times 10^{-11}$  s (Fig. 2). When  $d=0.5$  nm, the adjustable parameter  $\tau$  was  $1.7 \times 10^{-11}$  s. The mean free time for the water molecule was in the order of  $1 \times 10^{-13}$  s [35]. Tens of collisions of water with DNA molecules would be required to significantly change the speed of DNA. Thus, a value of the viscous damping time constant ( $\tau$ ) of  $1.7 \times 10^{-11}$  s is reasonable. The same value of  $\tau$  was used in the fitting of the observed and expected functional form of the dependence of the probability of the occurrence of steps on the step size. The distance  $r$  between ATPase on the head module of condensin and the bound DNA molecule may affect the maximum value  $\Delta T$  and the width  $\delta t$  of the time-dependence of  $\Delta T$ . The estimated step size and  $v_{dna}$  are linearly dependent on  $\delta t$ . Moreover,  $\Delta T$  has little effect on the thermal speed, as indicated in Eq. 4. Thus, the effects of  $r$  may be compensated by the adjustable parameter  $\tau$  when comparing between the estimated and measured step sizes.



The result in Eq. 4 indicates the extrusion effects for a single ATP hydrolysis event. In actual cases, steps with various sizes are possible. When comparing the experimental and calculated results, only the comparison between the average of an ensemble of measurements and the expected value of the calculated step size is meaningful. The expected value of the step size may be evaluated from

$$L_{ave} = C \int L df(v, \Delta T) dv$$

$$v_{dna} = C \int 2Ldf(v, \Delta T)dv \quad (6)$$

where  $C$  is a normalization constant and can be evaluated by comparing between the average value of the measured step size distribution [34] and the calculated one from Eq. 6. The dependence of the constant  $C$  on the tension in the DNA strand remains unclear because of the presence of only one set of comprehensive measurement for the distribution of step sizes. In this study,  $C$  was treated as a constant of the tension.

Keenholz et al. observed that in single-molecule magnetic tweezer experiments, DNA could be extruded slowly by the condensin complex into a loop structure even without ATP [28]. Although the slow extrusion observed might originate from the drift of the experimental apparatus, transient asymmetric forces may always be generated due to ever-existing random collisions between Ycg1 and the bound DNA strand. Occasionally, forces may not be balanced out by the viscous damping force, resulting in slow directional motion in the isothermal overdamped environment without ATP.

## 2 Results

### 2.1 Translocation

Identifying the location and mechanism of the molecular motor on SMC complexes is the initial step to understand SMC complex translocation and loop extrusion processes. For the asymmetric growth of a DNA loop, it is likely that a DNA-binding site, separate from the site for molecular motor binding, exists on the SMC complex. In their AFM study [15], Ryu et al. observed that DNA binds to the hinge subunit and HEAT repeats. Furthermore, a DNA loop forms with its base bound to the hinge and molecular motor. The hinge domain is another binding site apart from the Ycg1 HEAT repeats, and given its simple structure, this domain may function as an anchor in loop extrusion of the DNA strand. For the hinge domain to serve as the anchor for loop formation, the binding strength of DNA to the hinge domain should be strong. However, the binding strength must be weaker than the force generated by the motor, which enables the entire SMC complex to be translocated on the stretched double-tethered DNA strands [6, 18, 19]. Thus, in the mechanical model, the molecular motor is predicted to lead to the translocation of the SMC complex along DNA strands.

The orientation of condensin complex is defined by the arrow pointing from the hinge domain to the motor domain, as depicted in the first image of Fig. S1(a). The translocation of condensin on a stretched DNA strand is uni-directional for each condensin complex; however, translocation can occur in either direction with the same probability [18]. This

symmetry in translocation direction may be attributed to variations in the orientation of the groove structure of Ycg1, which is associated with the flexible kleisin.

Two speeds are associated with the motion of the DNA strand bound to Ycg1. One is  $v_{\text{dna}}$  in Eq. 5, which represents the speed at which the DNA strand moves through the Ycg1 groove, and it is closely related to the speed of loop extrusion. The other speed pertains to the translocation of condensin on the stretched double-tethered DNA strand. The binding force between the hinge domain and DNA provides a drag force on the motion of condensin. Thus, condensin translocates on the stretched tethered DNA at a speed much lower than  $v_{\text{dna}}$  and the speed of ordinary molecular motors [18, 19]. In this study, the translocation speed of condensin on the stretched tethered DNA could not be calculated without the knowledge of the binding force between the hinge domain and DNA strand. The existence of these two speeds may be observed in a single experiment of loop extrusion by condensin [6, 18, 34]. As depicted in Fig. S2, the condensin complex binds to a DNA strand and rapidly reels it into a loop at a high speed (Eq. 5). Subsequently, after the loop is fully developed, the condensin and entire loop are slowly translocated over a long distance with negligible changes in the size of the loop [6]. The translocation speed of the loop is comparable to that of the condensin complex on the stretched tethered DNA molecule. In the mechanical model, the translocation of the condensin complex and the loop is primarily led by the head domain where the motor Ycg1 is located.

## 2.2 Loop extrusion

Loop extrusion by condensin and cohesin complexes differ fundamentally. In the case of condensin complexes, DNA is extruded asymmetrically, wherein the condensin complex is anchored on the DNA strand, and only one arm of the DNA loop undergoes elongation. The molecular motor is located on the growing arm, and the hinge domain is anchored on the DNA strand, as observed through AFM [15]. Initially, the DNA strand located between two binding sites (one is Ycg1 in the head domain and the other is the hinge domain) serves as the seed for loop formation. As the DNA strand is pulled toward the anchor by the motor domain, the excess DNA strand bends between the motor and anchor. Thus, the soft DNA strand is extruded into a loop. The growth of the loop does not require the DNA strand to pass through the interior of the ring of the SMC complex. Hence, as observed, the loop does not extrude topologically. The speed of loop growth depends on the power of the molecular motor (Eq. 5) and the tension in the DNA strand. Once the loop is fully developed on a long double-tethered DNA molecule, the entire loop may be slowly translocated on the DNA strand along the direction of the orientation of the condensin complex [6].

A simulation of loop extrusion by the condensin complex with the anchor–motor model is depicted in Fig. S2 in supplementary materials. The speed of reeling in the bead chain during loop extrusion decreased with the tension in the bead chain, which counteracted the molecular motor-generated force exerted on the DNA chain (Fig. S2(b) and (c)). After the loop grew fully (Fig. S2(b) at  $t=82$  s), the effect of tension in the long chain became equal to the force generated by the motor, terminating the growth of the loop. The tension in the DNA was transmitted through the condensin complex, straightening or stretching the DNA strands on both sides of the loop; this observation indicated that the loop was fully developed. The condensin complex and the entire loop still translocated on the model DNA chain slowly along the orientation of condensin (Figs. S2(a) and (b)). This slow translocation of the fully developed loop, as evidenced by changes in the anchor position after

the completion of the loop extrusion in Fig. S2(b), was observed in experiments involving actual condensin [6, 19, 20].

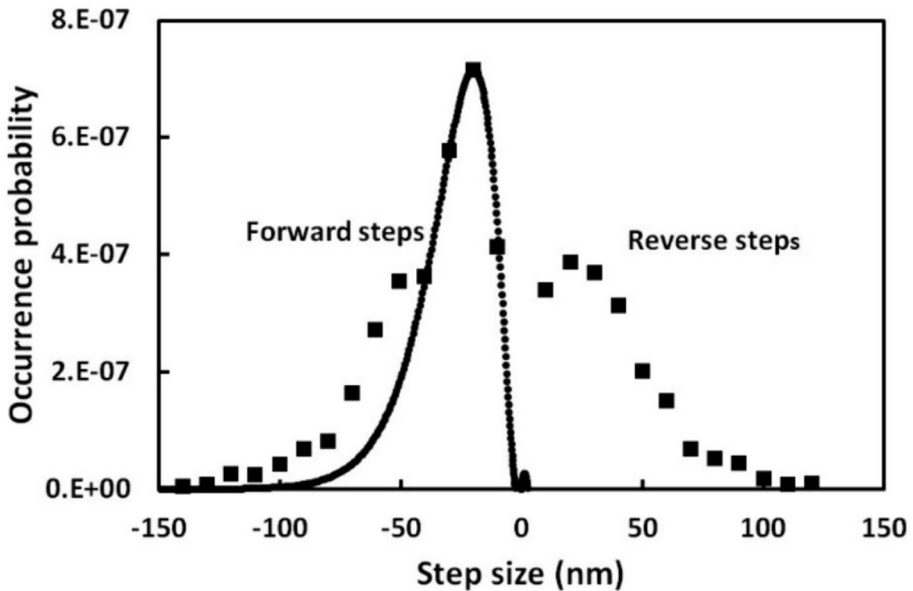
### 2.3 Step formation

The formation of steps and their characteristics are critical for examining the mechanisms underlying loop extrusion. In single-molecule magnetic tweezer (MT) studies of condensin-mediated DNA extrusion [28, 34], various step sizes and dwell times were observed. The presence of ATP greatly enhanced the speed of extrusion. In MT experiments, the DNA molecule was tethered at both ends, one end to a glass coverslip and the other end to a magnetic bead. The end-to-end distance of the DNA could be adjusted using an external magnetic field, placing the DNA molecule under tension during loop extrusion [6, 34]. Upon closer examination of the time traces of DNA loop extrusion in MT experiments [34], it becomes evident that the traces contained an early stage where the steps were not resolved clearly, a medium stage where discrete steps were resolved, and a late stage where steps were well separated. For experiments with high initial tension, the early stage appeared to be absent. In addition, the tension-dependent distribution of step sizes was observed in MT experiments. These observations can be explained by the mechanical model proposed in this study.

The formation of a step requires a sharp, transient force that reels the outside DNA strand into the extruded loop. Once this  $\delta$ -function-like force disappears, the speed of the extruding DNA rapidly decreases to zero due to the viscous drag force in the overdamped environment. The step size corresponds to the length of DNA extruded during the decay time of the extrusion speed (Eq. 4). In the presence of DNA, the ATP hydrolysis rate of condensin is approximately 2 Hz, which ensures that extrusion occurs in a stepwise manner due to the overdamped environment or the smallness of the damping time constant ( $\tau$ ) associated with the drag effect. The energy required for each step might result from one effective ATP hydrolysis event. In MT experiments on extrusion, in the early stage, many small steps might occur at a repetition rate close to 2 Hz, which were not resolved in the experiments [6, 34].

Stepwise extrusion is closely related to the build-up of tension in the DNA strand. During the actual extrusion process in cells, small steps in DNA extrusion, occurring at a frequency identical to that of ATP hydrolysis, might occur in the early stage when the tension in the DNA strand was low as shown in the initial stage of the loop extrusion in Fig. 1B of Ref. [34], where no steps were resolved. As extrusion progresses due to subsequent ATP hydrolysis events, the tension in the DNA strand gradually increased. In the medium stage, collisions between the Ycg1 groove and the slowly moving DNA strand could not generate a force large enough to overcome the rising tension. Thus, the loop temporarily ceased to grow, and extrusion could only occur with the occurrence of a rare high-speed DNA collision with the Ycg1 groove. When a high-speed collision occurs, a step with a larger size in the time trace was formed. The probability of the high-speed collision decreased with speed (in the inset of Fig. 3), indicating an increase in waiting time between steps. Thus, the dwell time increases for each next step. The occurrence of large steps with extended dwell times, as observed in single-molecule MT studies [34], might occur in the late stage of extrusion when the tension in the DNA strand outside of the loop built up.

The average step size  $L_{\text{ave}}$  can be evaluated using the thermal speed  $v$  (Eq. 4); for each  $v$ , the step size and the probability of the occurrence of a step with size  $L$  can be calculated using  $f(v, \Delta T)$ . The step size distribution can be calculated according to the mechanical



**Fig. 4** Calculated (full circles) and measured (full squares, reproduced from Fig. 3B of Ref. [34]) step size distributions of DNA loop extrusion by condensin for tension  $F=0.4$  pN

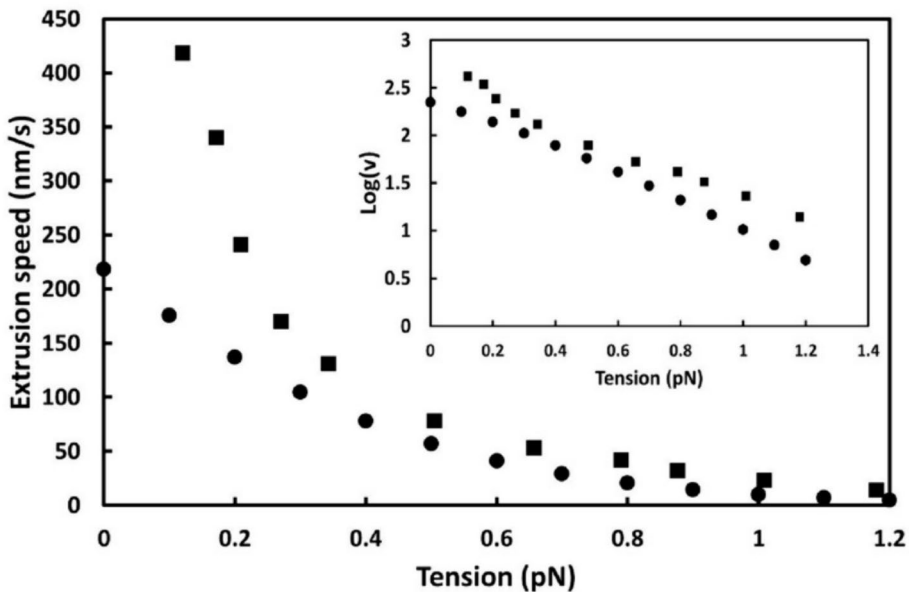
model outlined in Eq. 6. Figure 4 presents a comparison between the measured [34] and calculated step size distribution for tension  $F=0.4$  pN, where the measured and calculated distributions are normalized at their highest occurrence at  $L=20$  nm, assuming a viscous damping time constant ( $\tau$ ) of  $1.7 \times 10^{-11}$  s. The qualitative characteristics of the size distribution of forward steps, such as (a) the low probability of small steps (less than 10 nm) and (b) the sharp rise and the rapid decrease after the maximum of the distribution is reached, are consistent with the published observations.

In the large step regions of both the forward (positive) and reverse (negative) step sides, the measured occurrences [34] are significantly higher than the calculated ones. It is considered that the consecutive occurrence of a forward step and a reverse step of the comparable size in the late stage (interlocking step) might not be true loop extrusion events for the following reasons: (a) The interlocking steps had virtually no net extrusion effects. (b) They occurred after the major loop-extrusion events (within 50 s after the beginning of loop-extrusion) being completed. (c) The condensin and DNA loop might have collided with the substrate at the late stage of the loop extrusion experiments. The extension of the DNA molecule for the externally applied force of 0.4 pN is 78% of the total length of the DNA molecule; that for a force of 0.2 pN is 70% [36]. For the 1.5 kbp DNA molecule (510 nm in length) used in Ref. [34], the initial extension would be 400 nm for 0.4 pN and 360 nm for 0.2 pN. As observed in Fig. 1 of Ref. [34], the total length of the extruded DNA loop was 350 nm for 0.2 pN. From Fig. 3 of Ref. [34], the total extruded length was 310 nm. If the size of the condensin complex (50 nm) and fluctuations were included, then the sizes of the condensin complex and the DNA loop would exceed the initial extension of the DNA molecule and frequently collide with the base of the glass surface of the flow cell in both of the experiments. And (d), the fluctuations in the polystyrene-bead position were largely

reduced in the late-stage data shown in Fig. 1B of Ref. [34], which is an evidence that the condensin complex might interact with the glass surface of the flow cell used in the experiment. Thus, the interlocking steps may not originate from the genuine DNA loop extrusion. Whether such pairs might be included in the analysis of the statistics of loop extrusion is in doubt. Including the interlocking steps in the statistical analysis would distort the distribution function in the large-step sides of both forward and reverse steps (Fig. 4). If only the steps observed in the medium stage ( $< 50$  s) of the loop extrusion were analyzed in the step-size distribution, the occurrence of reverse steps was rare, and the consistence between the experimental and the calculated results might be improved (Fig. 4).

For quantitative comparison with experimental measurements, the parameter  $C$  can be determined by comparing  $L_{\text{ave}}$  values obtained from Eq. 6 for  $F=0.4$  pN with the measured step size distribution for the same tension [34]. The measured average step size was 39 nm, as extracted from data shown in Fig. 3B of Ref. [34]. Thus, the constant  $C$  was  $7.4 \times 10^4$ . With the measured rate of ATP hydrolysis of 2 Hz, the calculated average extrusion speed  $v_{\text{dna}}$  for  $F=0$  pN was approximately 220 nm/s. This calculated average extrusion speed closely matched the measured value, which was approximately 200 nm/s or 600 bp/s [6], indicating good agreement.

From the force-extension relation for DNA, Ganji et al. [6] deduced the functional dependence of the extrusion speed on the tension in the DNA strand outside of the DNA loop. Some of their data were reproduced as full squares in Fig. 5 and in the semi-logarithmic plot in the inset. The best fit of a straight line of the semi-logarithmic plot of the measured data shown in the inset had a slope of 1.3. From Eq. 6, the exponential dependence of  $df(v, \Delta T)$  on tension  $F$  (Eq. 3) indicated the exponential dependence of the extrusion speed on tension. From the calculated average extrusion speed, we observed that the



**Fig. 5** Calculated (full circles, with  $\xi=18$  nm) and deduced (full squares, reproduced from Fig. 3J replotted from Ref. [6]) extrusion speeds as a function of tension  $F$  in the DNA strand. The semi-logarithmic plots are shown in the inset

exponent is dependent on the parameter  $\xi$ . Thus, a  $\xi$  value of 18 nm was chosen in this study, which resulted in a slope of 1.4 for the calculated data (full circles) shown in the inset. Although there is nearly a factor of 2 difference between the experimental and calculated results, such differences might exist between single-run observations and averaged calculated results.

## 2.4 Loop interaction

Occasionally, two condensins may bind to the same section of the DNA strand, resulting in the extrusion of two loops. These loops may interact in different ways. Kim et. al. [20] reported that the two loops could exchange DNA strands in various ways. One loop might grow in size at the expense of the preexisting loop, regardless of the distance between them or regardless of whether the loops were in contact with each other at the tethering end. When a new loop is formed in the preexisting loop, a complex loop structure (termed as the Z-loop) is formed.

In the following paragraphs, I present the results of simulation experiments based on the mechanical model and the motor–anchor model of the condensin complex. The details of the methods and materials are provided in the supplementary materials. The simulation experiments revealed that many of the interactions between loops are mediated by the tension in the DNA strand.

For two condensins moving in the same direction, (a) when a loop catches up with the other loop at the tether end, the two condensins come into contact. The motor of the trailing condensin continuously collides with the hinge domain of the leading condensin. Thus, the motor may occasionally disrupt the binding between the hinge domain and the leading condensin. Furthermore, the motor of the trailing condensin may reel in the loosened DNA strand. Thus, the back loop will be growing slowly at the expense of the front loop until the front loop disappears, as shown in Fig. S3(a). (b) If the strength of the two motors is different and the strong one is located in the front, the DNA strand of the trailing condensin may be pulled out by the leading condensin through the tension in the DNA strand, as shown in Fig. S4(a).

For two condensins moving in opposite directions and when the simulated DNA strand is initially relaxed, both condensins reel the DNA strand into individual loops. As the tension in the DNA strand increases, the DNA strand is stretched, with both condensins competitively forming DNA loops. The DNA strand bound by the weak condensin is pulled out by the strong condensin through the tension in the DNA strand. Thus, the loop formed by the strong condensin keeps growing, and the loop of the weak condensin finally diminishes. This type of interaction between the two loops does not require physical contact between the condensins, and such interaction can be observed whether the two motors are moving in the same direction or in opposite directions. Fig. S5(a) and (c) presents the images and analysis of the results of the simulation experiments. The interactions between loops observed in the simulation experiments may have corresponding counterparts in actual experiments [20].

When a new condensin is bound to a preexisting loop, the new condensin may extrude the DNA strand to form a new loop with the preexisting loop. The new condensin may traverse the preexisting condensin and form a new complex loop, which contains three DNA strands in parallel with two condensins situated at the ends of the complex loop, and this structure is referred to as the Z-loop [20, 37]. The findings of the simulation experiments revealed that the traversing process can be divided into four steps: (a) The motor domain of one condensin approaches the anchor domain or the motor domain of another condensin.

(b) The approaching motor domain disrupts binding between the anchor domain and the DNA strand of the latter condensin, releasing the trapped condensin. (c) During the traversing process, the freed anchor or motor stochastically binds to a nearby DNA strand. (d) The Z-loop forms after the DNA strand is stretched due to the motion of the motor domain. Figure S6 presents a series of images of the traversing and formation processes of the Z-loop with two condensins translocating in different directions.

## 2.5 Compaction

Many SMC complexes may be involved in DNA compaction through loop extrusion. Figure S7 presents a series of pictures of the compaction process. The large circular chain eventually condensed into a stable compact state by six model SMCs.

## 2.6 The role of loop extrusion in untying knots in DNA

Knots may be formed in the crowded DNA molecules in cells are known to affect the physical and chemical properties of DNA [38] and may cause DNA damage when tightened. It was well known that knots may be formed or untied with type II DNA topoisomerases [39]. Racko et. al. [40] and Orlandini et al. [41] proposed that the SMC loop extrusion working together with type II topoisomerases may facilitate DNA to untie. In a previous publication, Chou found in a simulation experiment that a knot could be pushed to move along a DNA molecule in a forced-reptation manner by a translocase [42]. Consequently, knots can be pushed to the end of a linear DNA molecule and untied or be pushed around and tightened up in a circular DNA molecule. During loop extrusion, SMC complexes can be viewed as translocating along DNA molecule and may have the similar effects of a translocase on the existing knot. Figure S8 shows a series of images of the interactions between the model condensin and a preexisted knot. The force generated from the model condensin extrudes the loop at the same time pushes the knot toward the far end of the bead chain. When the knot reaches the end of the chain, it is untied immediately and leaves a small cross on the chain. Finally, the cross is resolved. Figure S9 shows the tightening of a de-localized trefoil knot with a randomized initial configuration with a fixed anchor on the experimental platform. The knot gradually takes its ordinary shape when the loop is growing. The model experiment finishes when the entire chain is extruded into the unknotted loop. For the actual situation in the cell, the localized knot and SMC facilitate the recruitment of a type II DNA topoisomerase [40, 41]. The type II DNA topoisomerase may induce a strand crossing at the localized knot and resolve the knot. (The experiments were suggested by the reviewer.)

## 3 Discussion and summary

This study proposes a motor–anchor model for the condensin complex, in which the condensin complex can be viewed as a combination of a motor and an anchor connected by two flexible SMC proteins. Based on its structure, Ycg1 serves as the molecular motor, and the hinge domain serves as the anchor site of DNA molecules. At normal body temperature, a section of a DNA molecule moderately binds to Ycg1 and moves randomly relative to the protein. Random collisions between the internal wall of the groove-shaped Ycg1 and

DNA may occur and generate directional impulsive forces on colliding entities, resulting in relative motion between Ycg1 and DNA base pairs. This mechanical model, based on the random thermal motion of nanometer-scaled DNA molecules and the asymmetric structure of Ycg1, explains the translocation of the condensin complex on stretched DNA, the extrusion of loops in the relaxed DNA strand, the formation of steps during DNA extrusion, and the interactions between coexisting loops.

From the images published in Ref. [22], deleting Ycg1 ( $\Delta Ycg1$ ) from the condensin complex turned the translocation and the DNA extrusion by the condensin complex into an irregular way, which confirms the important role of Ycg1 in the regular loop extrusion. However, the fact that the  $\Delta Ycg1$  condensin could extrude DNA is interesting. In order for the  $\Delta Ycg1$  condensin to extrude DNA into a loop structure, there must be two binding sites to the DNA chain. One might be the hinge domain. The other was still unknown. More information about the interaction between the  $\Delta Ycg1$  condensin and DNA is needed to clarify their relative motion and the irregular DNA loop extrusion by the  $\Delta Ycg1$  condensin.

Condensin complexes translocate unidirectionally on stretched DNA strands, with equal probabilities for either direction, indicating that motor domains on the complexes generate unidirectional forces whose direction cannot be specified. These observations may be attributed to DNA molecules binding to condensin complexes at two sites: the hinge domain and the HEAT repeat protein Ycg1, which, in turn, binds to the kleisin domain of the complex. The Ycg1–kleisin domain binding configuration can occur in either of the two directions, leading to the orientations of the groove structure and the generated force being fixed in either direction. This allows the condensin complex to translocate along the stretched DNA molecule in either direction. Based on these findings, we predict that the translocation of condensin along a stretched DNA strand is driven and led by the motor domain (i.e., Ycg1). The binding force of the hinge domain serves as the frictional force for condensin translocation, resulting in slow translocation compared with the extrusion speed.

During loop extrusion, the hinge and motor domains stably bind to a relaxed DNA strand, with the DNA strand between the hinge and motor serving as the seed of the loop. The seed of the loop grows only on one arm of the loop, which is known as asymmetrical extrusion. The hinge domain anchors to the DNA strand during extrusion. The DNA strand in front of the motor domain experiences a tension pointing away from the loop. Thus, the motor domain must generate a physical force that is larger than the tension to reel the DNA strand into the loop.

Energy released from ATP hydrolysis increases the temperature of the local environment of condensin by a small fraction of 1 K, to which the DNA strand is bound to. The excess temperature increases the high-speed side of the Boltzmann-Maxwell distribution function  $f(v, \Delta T)$ . The high-speed DNA base pairs collide with the groove-shaped Ycg1, and both DNA and the condensin complex gain speed along the DNA strand, resulting in the relative motion of condensin and the DNA strand. The low rate of ATP hydrolysis ensures the step-like advances of the DNA strand during extrusion. During the initial stage of extrusion, the tension in the DNA strand was low, resulting in the occurrence of rapid and small steps, which were not resolved in Ref. [34]. In the medium stage, the tension in the DNA strand increases with the number of steps and impairs small steps. Only collisions of high-speed DNA base pairs with Ycg1 cause the advances of the DNA strand. Thus, a step begins with the temperature pulse originating from the energy output of an ATP hydrolysis event. The speed of the DNA strand is dissipated fast by the viscous drag of the fluid environment, which ends the step of extrusion. The scarcity of high-speed base pairs, according to  $f(v, \Delta T)$ , leads to the rarity of large-sized steps.



There is a large discrepancy between the step-size distribution calculated with the distribution function  $f(v, \Delta T)$  and the published experimental observation [34], especially for the reverse steps (Fig. 4). It is argued that the interlocking steps in the late stage of loop extrusion might not be genuine steps and might be originated from the interaction between the condensing complex, DNA, and the substrate which tethered DNA at one end. From the measured DNA loop-extrusion trajectories, there were virtually no observable reverse steps within 50 s after the start of the DNA loop-extrusion. It is expected that omitting the interlocking steps might improve the agreement between the calculated and the measured step-size distribution.

The agreement between the values, as well as the dependence on tension, of the calculated extrusion speed from the mechanical model and published data is reasonably good [6].

The loops on the same DNA strand may simultaneously interact with each other through the tension in the DNA molecule when they are far apart or through physical collisions between condensins when they come in contact with each other. Interactions between loops may result in one of the loops increasing and the other decreasing in size. Many of the results observed in actual condensin–DNA systems [20] corroborate the current model experiment results, including the traversing of loops (Fig. S6 in supplementary materials), compaction of DNA (Fig. S7), and unknotting DNA.

**Supplementary Information** The online version contains supplementary material available at <https://doi.org/10.1007/s10867-024-09661-7>.

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**Data availability** The data that support the findings of this study are available upon request.

## Declarations

**Conflict of interest** The author declares no conflict of interests.

## References

1. Yatskevich, S., Rhodes, J., Nasmyth, K.: Organization of chromosomal DNA by SMC complexes. *Annu. Rev. Genet.* **53**, 445–482 (2019)
2. Kim, E., Barth, R., Dekker, C.: Looping the genome with SMC complexes. *Annu. Rev. Biochem.* **92**, 15–41 (2023)
3. Maeshima, K., Eltsov, M.: Functional dynamics of the nucleus packaging the genome: the structure of mitotic chromosomes. *J. Biochem.* **143**, 145–153 (2008)
4. Uhlmann, F.: SMC complexes: from DNA to chromosomes. *Nat. Rev. Mol. Cell Biol.* **17**, 399–412 (2016)
5. Davidson, I.F., Peters, J.-M.: Genome folding through loop extrusion by SMC complexes. *Nat. Rev. Mol. Cell Biol.* **22**, 445–464 (2021)
6. Ganji, M., Shaltiel, I.A., Bisht, S., Kim, E., Kalichava, A., Haering, C.H., Dekker, C.: Real-time imaging of DNA loop extrusion by condensin. *Science* **360**, 102–105 (2018)
7. Davidson, I.F., Bauer, B., Goetz, D., Tang, W., Wutz, G., Peters, J.-M.: DNA loop extrusion by human cohesin. *Science* **366**, 1338–1345 (2019)
8. Kim, Y., Shi, Z., Zhang, H., Finkelstein, I.J., Yu, H.: Human cohesin compacts DNA by loop extrusion. *Science* **366**, 1345–1349 (2019)
9. Haering, C.H., Löwe, J., Hochwagen, A., Nasmyth, K.: Molecular architecture of SMC proteins and the yeast cohesin complex. *Mol. Cell* **9**, 773–788 (2002)
10. Schleiffer, A., Kaitna, S., Maurer-Stroh, S., Glotzer, M., Nasmyth, K., Eisenhaber, F.: Kleisins: a superfamily of bacterial and eukaryotic SMC protein partners. *Mol. Cell* **11**, 571–575 (2003)

11. Kschonsak, M., Merkel, F., Bisht, S., Metz, J., Rybin, V., Hassler, M., Haering, C.H.: Structural basis for a safety-belt mechanism that anchors condensin to chromosomes. *Cell* **171**, 588–600 (2017)
12. Lee, B.-G., Rhode, J., Löwe, J.: Clamping of DNA shuts the condensin neck gate. *Proc. Natl. Acad. Sci. U.S.A.* **119**, e2120006119 (2022)
13. Bürmann, F., Lee, B.G., Thane, T., Sinn, L., O'Reilly, F.J., Yatskevich, S., Rappsilber, J., Hu, B., Nasmyth, K., Löwe, J.: A folded conformation of MukBEF and cohesin. *Nat. Struct. Mol. Biol.* **26**, 227–236 (2019)
14. Eeftens, J.M., Katan, A.J., Kschonsak, M., Hassler, M., de Wilde, L., Dief, E.M., Haering, C.H., Dekker, C.: Condensin Smc2-Smc4 dimers are flexible and dynamic. *Cell Rep.* **14**, 1813–1818 (2016)
15. Ryu, J.-K., Katan, A.J., van der Sluis, E.O., Wisse, T., de Groot, R., Haering, C.H., Dekker, C.: The condensin holocomplex cycles dynamically between open and collapsed states. *Nat. Struct. Mol. Biol.* **27**, 1134–1141 (2020)
16. Kim, J.L., Morgenstern, K.A., Griffith, J.P., Dwyer, M.D., Thomson, J.A., Murcko, M.A., Lin, C., Caron, P.R.: Hepatitis C virus NS3 RNA helicase domain with a bound oligonucleotide: the crystal structure provides insights into the mode of unwinding. *Structure* **6**, 89–100 (1998)
17. Lin, C.-T., Tritschler, F., Lee, K.S., Gu, M., Rice, C.M., Ha, T.: Single-molecule imaging reveals the translocation and DNA looping dynamics of hepatitis C virus NS3 helicase. *Protein Sci.* **26**, 1391–1403 (2017)
18. Terakawa, T., Bisht, S., Eeftens, J.M., Dekker, C., Haering, C.H., Greene, E.C.: The condensin complex is a mechanochemical motor that translocates along DNA. *Science* **358**, 672–676 (2017)
19. Golfier, S., Quail, T., Kimura, H., Brugués, J.: Cohesin and condensin extrude DNA loops in a cell cycle-dependent manner. *eLife* **9**, e53885 (2020)
20. Kim, E., Kerssemakers, J., Shaltiel, I.A., Haering, C.H., Dekker, C.: DNA-loop extruding condensin complexes can traverse one another. *Nature* **579**, 438–442 (2020)
21. Higashi, T.L., Pobegalov, G., Tang, M., Molodtsov, M.I., Uhlmann, F.: A Brownian ratchet model for DNA loop extrusion by the cohesin complex. *eLife* **10**, e67530 (2021)
22. Shaltiel, I.A., Datta, S., Lecomte, L., Hassler, M., Kschonsak, M., Bravo, S., Stober, C., Ormanns, J., Eustermann, S., Haering, C.H.: A hold-and-feed mechanism drives directional DNA loop extrusion by condensin. *Science* **376**, 1087–1094 (2022)
23. Dekker, C., Haering, C.H., Peters, J.-M., Rowland, B.D.: How do molecular motors fold the genome? *Science* **382**, 646–648 (2023)
24. Chou, Y.C.: Mechanical mechanism for the translocation of hexameric and nonstructural helicases: dependence on physical parameters. *Eur. Phys. J. E* **43**, 21 (2020)
25. Pathria R. K.: *Statistical Mechanics*, Chap. **13**, 441, Pergamon Press, Oxford (1977)
26. Chou, Y.C.: A mechanical mechanism for translocation of ring-shaped helicases on DNA and its demonstration in a macroscopic simulation system. *J. Phys. D Appl. Phys.* **51**, 135401 (2018)
27. de Gennes, P.G.: *Scaling Concepts in Polymer Physics*, p. 32. Cornell Univ, Press, Ithaca, New York, USA (1979)
28. Keenholtz, R.A., Dhanaraman, T., Palou, R., Yu, J., D'Amours, D., Marko, J.F.: Oligomerization and ATP stimulate condensin-mediated DNA compaction. *Sci. Rep.* **7**, 14279 (2017)
29. Beck, J.V., Cole, K.D., Haji-Sheikh, A., Litkouhi, B.: *Heat Conduction Using Green's Function*. Hemisphere Publishing Co., USA (1992)
30. Nomidis, S.K., Carlton, E., Gruber, S., Marko, J.F.: DNA tension-modulated translocation and loop extrusion by SMC complexes revealed by molecular dynamics simulations. *Nucl. Acids Res.* **50**, 4974–4987 (2022)
31. Eddington, A.S.: *Internal Constitution of the Stars*, pp. 260–269. Cambridge University Press, Cambridge, UK (1926)
32. Takaki, R., Dey, A., Shi, G., Thirumalai, D.: Theory and simulations of condensin mediated loop extrusion in DNA. *Nat. Commun.* **12**, 5865 (2021)
33. Janissen, R., Barth, R., Davidson, I. F., Taschner, M., Gruber, S., Peters, J.-M., Dekker, C.: All eukaryotic SMC proteins induce a twist of -0.6 at each DNA-loop-extrusion step. *bioRxiv*: **2024.03.22.586328** (2024)
34. Ryu, J.-K., Rah, S.-H., Janissen, R., Kerssemakers, J.W.J., Bonato, A., Michieletto, D., Dekker, C.: Condensin extrudes DNA loops in steps up to hundreds of base pairs that are generated by ATP binding events. *Nucl. Acids Res.* **50**, 820–832 (2022)
35. Young, H.D., Freedman, R.A.: *University physics* (vol. 18, 12th edn., p. 625). Pearson Education Inc., USA (2007)
36. Marko, J.F., Siggia, E.D.: Stretching DNA. *Macromolecules* **28**, 8759 (1995)
37. Bonato, A., Michieletto, D.: Three-dimensional loop extrusion. *Biophys. J.* **120**, 5544–5552 (2021)

38. Wasserman, S.A., Cozzarelli, N.R.: Biochemical topology: applications to DNA recombination and replication. *Science* **232**, 951–960 (1986)
39. Rybenkov, V.V., Ullsperger, C., Vologodski, A.V., Cozzarelli, N.R.: Simplification of DNA topology below equilibrium values by type II topoisomerases. *Science* **277**, 690–693 (1997)
40. Racko, D., Benedetti, F., Goundaroulis, D., Stasiak, A.: Chromatin loop extrusion and chromatin unknotting. *Polymers* **10**, 1126 (2018)
41. Orlandini, E., Marenduzzo, D., Michieletto, D.: Synergy of topoisomerase and structural-maintenance-of-chromosomes proteins creates a universal pathway to simplify genome topology. *Proc. Natl. Acad. Sci. U.S.A.* **116**, 8149–8154 (2019)
42. Chou, Y.C.: Observations of metastable states of free swelling knots and directional motion of tensioned knots in vibrated bead chains. *Eur. Phys. J. E* **42**, 79 (2019)

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