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Entropic Competition between Supercoiled and Torsionally Relaxed Fibers Drives Chromatin Loop Extrusion

Insights by molecular dynamics simulation.

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In 1977 Paulson and Laemmli dissolved meiotic chromosome – the X shaped one – and discovered that it consisted of about 100 kilobase DNA loops attached to a protein scaffold. Immediately it came to the question, if these loops have a biological function. If such a biological function should exist, the loops would need to exist also in interphase chromosomes, i.e. during the longest period of the cell cycle when the chromosomes exist in form of globules and perform their basic biological functions. Experimental discovery of the loops in the interphase chromosomes was challenging and became only possible after developing a group of experimental methods for chromosome conformation capture – also named 3C. After improvement of the method's resolution in the new generation called Hi-C, the loops were independently discovered by three teams of authors in 2012.

Next question that naturally occurred was how these loops are created. In our paper, we propose a novel Brownian ratchet mechanism. Our model consists of fibre whose portion is stressed by axial rotations and a torsionally relaxed part. These two parts are separated by position of the SMC sliplink. The axial rotations mimic action of RNA-polymerase that performs transcription. The SMC is thermodynamically coupled with the fibre by exerting friction to axial rotations, thus preventing the supercoiling to escape. The supercoiled fibre can relieve from the increased energy only when the SMC moves further ahead from the transcription site and new portions of relaxed fibre flow into the emerging loop. The decrease in energy is temporary and soon replenished by the ongoing transcription and the SMC has to move again.

Reference Rusková, R.; and Račko, D.; „Entropic Competition between Supercoiled and Torsionally Relaxed Chromatin Fibers Drives Loop Extrusion through Pseudo-Topologically Bound Cohesin“ *Biology*, **2021**, 10(2), 130.

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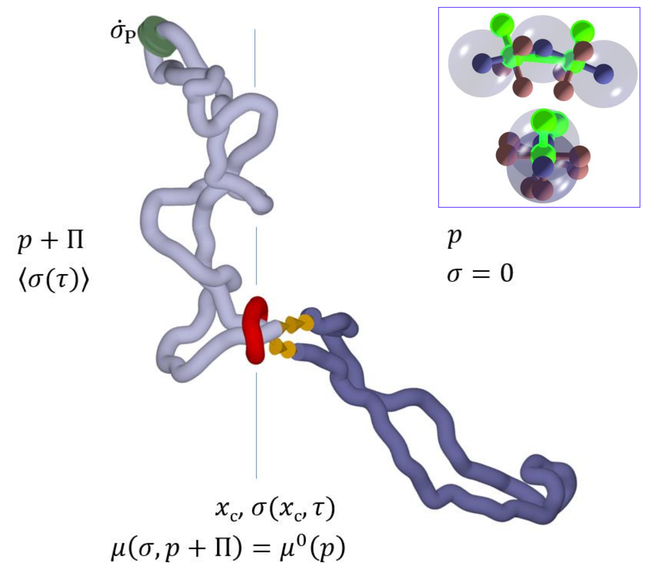

Figure 1 The coarse-grained model for molecular dynamics simulations. The coarse-grained chain consisted of 150 beads each representing 400 bp of DNA with length 10 nm. The beads were bound by bead spring potential $V(r) = k(r - r_0)^2$. Three-body harmonic potential, $V(q) = 0.5k_b(q - q_0)^2$ was employed to impose molecular stiffness of 50 nm. Additionally, torsional stiffness was introduced by the harmonic torsional four-body potential between periaxially placed vectors placed along the chain (inset picture). The equilibrium angle of the torsional potential was gradually changed introducing axial stress, simulating transcription at the position of green element with σ_p = 10 rotations per second. The torsional potential was interrupted at the position of the SMC protein leading to torsional relaxation of the fiber. The rotational drag at the position of the SMC protein was varied to simulate different friction between the fiber and SMC protein (cohesin ring).

$$\frac{\partial\sigma(x,\tau)}{\partial\tau} = D_\sigma(x)\frac{\partial^2\sigma(x,\tau)}{\partial x^2} \qquad (1)$$

$$\frac{\partial x_c}{\partial\tau} = -\frac{1}{\gamma_c}\left(\frac{\partial u}{\partial x_c}\right) \qquad (2)$$

Equations 1 & 2 The proposed mathematical model for entropically driven loop extrusion. The equation (1) describes accumulation of torsional stress from the source of transcription to the position of the SMC protein. At the position of the SMC protein D_σ is increased to simulate modulated friction between the fiber and the protein. Behind the SMC position the axial stress is relaxed σ = 0. Position of the SMC ring protein (cohesin) is pushed by the change of chemical potential defined as the change of the internal energy related to the energy of supercoiling $u = K\sigma^2$.

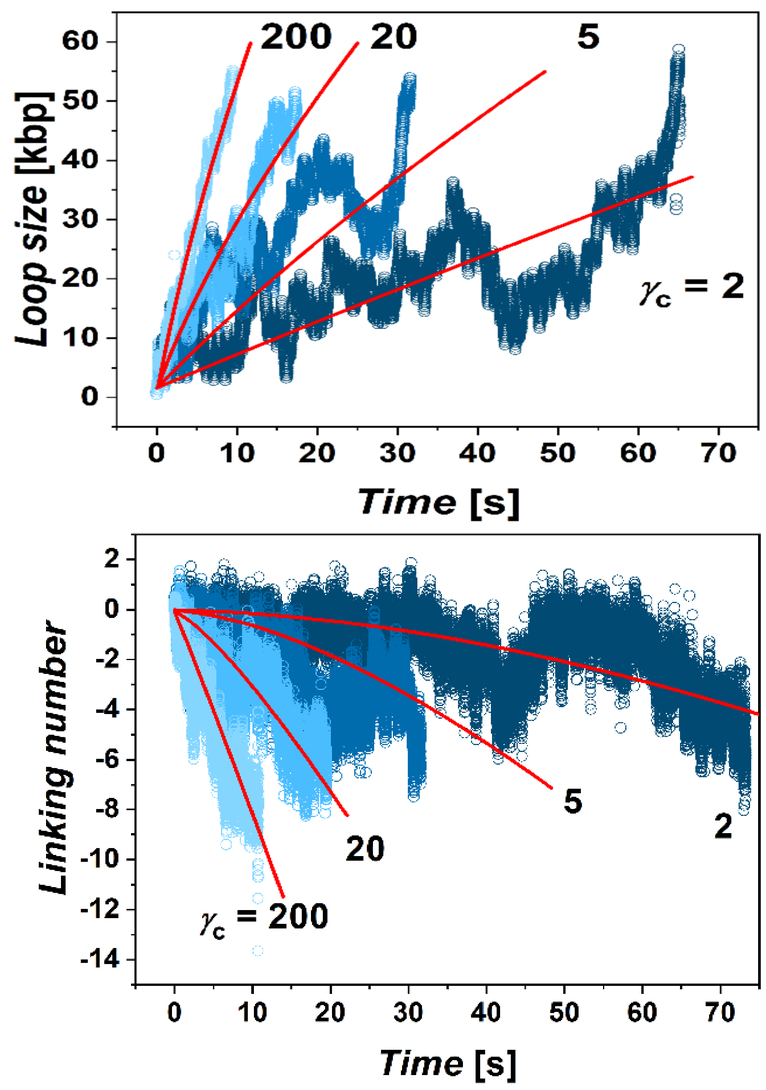

Figure 2 The chromatin loop extrusion from molecular simulations (points) and the proposed mathematical model (lines). The graphs show loop sizes and torsional stress in terms of linking number evolution with time as a function of friction between SMC protein and chromatin fiber.

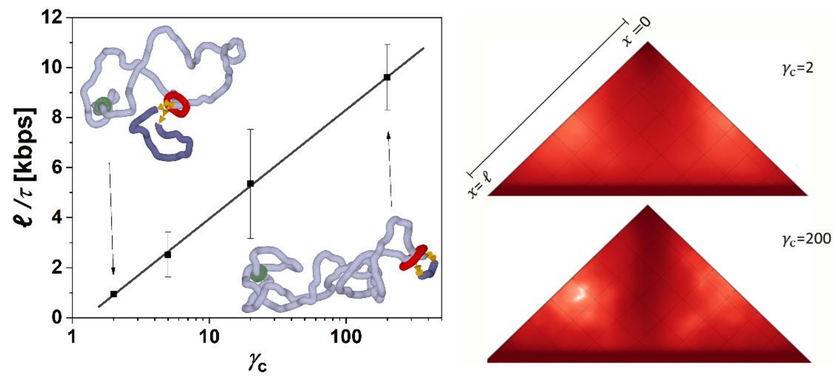

Figure 3 Conclusions The increased friction between chromatin fiber and the SMC protein leads to accumulation of higher levels of axial stress. The larger axial stress results in higher speeds of loop extrusion. The proposed mathematical model indicates that the loop extrusion is driven by the drop of internal energy due to torsional relaxation of the fiber at the interface of the SMC protein. As the change of the internal energy along the fiber is definition of the chemical potential, the difference of the chemical potentials at the SMC interface is definition of osmotic pressure. Here, the relaxed fiber acts like solute flowing into torsionally stressed part of the extruded loop and tries to "dissolve" the torsional stress. The proposed mechanism is so called Brownian ratchet motor. Additionally, the simulations show the intermediate levels of friction would be reasonably reproducing both extrusion speed and contact maps from biological experiments.