Compression and stretching of a self-avoiding chain in cylindrical nanopores

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Force-induced deformations of a self-avoiding chain confined inside a cylindrical cavity, with diameter $D$, are probed using molecular dynamics simulations, scaling analysis, and analytical calculations. We obtain and confirm a simple scaling relation $-f \cdot D \sim R^{-9/4}$ in the strong-compression regime, while for weak deformations we find $f \cdot D = -A(R/R_0) + B(R/R_0)^{-2}$, where $A$ and $B$ are constants, $f$ the external force, and $R$ the chain extension (with $R_0$ its unperturbed value). For a strong stretch, we present a universal, analytical force-extension relation. Our results can be used to analyze the behavior of biomolecules in confinement.

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Technological advances have made it possible to visualize and manipulate individual polymer molecules that are trapped in nanopores [1, 2, 3, 4]. This enables one to test theoretical predictions on confined polymers, shedding new insights into their static and dynamic properties. Besides their technological importance, confined polymers are relevant in a number of biological processes. In the context of proteins, a newly synthesized protein exits the ribosome through a narrow cylindrical pore [5] assisted, perhaps, by a tensile force [6]. Both chaperone-assisted protein folding and protein degradation by proteosome involve encapsulation of proteins in cylindrical pores, in which they experience compression and stretching forces [7, 8]. Furthermore, many bacterial species are rod-shaped and even filamentous, and their chromosomes are highly compressed inside the cell and yet well-organized [9, 10]. Thus, the study of cylindrically confined polymers is not only of practical importance but also is a first step towards understanding several fundamental biological processes.

Surprisingly, compared to the progress on the experimental side, and despite its fundamental and practical importance, theoretical understanding of force-induced chain deformations in a pore remains behind. In the literature, analysis of force-compression-extension measurements heavily relies on and is often limited to simple scaling arguments [1, 2, 3].

The main purpose of this Letter is to present a quantitative picture of the interplay between confinement and force-induced chain deformations (from strong compression to almost full stretching). To this end, we combine a scaling analysis, molecular dynamics (MD) simulations, and a systematic theoretical approach, and obtain force-compression-extension relations in almost the full range of chain deformations. Our results thus provide a quantitative basis for experiments involving biomolecules (e.g., dsDNA and chromosomes) in strong confinement as in nano- and micro-channels.

Consider a self-avoiding polymer with $N$ monomers in a cylindrical pore with diameter $D$, as illustrated in Fig. 1, with $R$ being the longitudinal end-to-end distance the chain. Owing to the simultaneous presence of self-avoidence and confinement, the chain resembles a linear string of “compression blobs” [11, 12]; inside each blob, the effect of confinement is not significant. Because of the clear separation between two length scales ($> D$ and $< D$), the conventional Flory approach may fail to capture the correct $D$ dependence of relevant quantities (see below). The essential features of the blob-scaling

FIG. 1: Self-avoiding polymer in a nanopore (a). Simulation setting for compression (b) and stretching (c): the two chain ends are confined to, but can freely move within, the confining “piston” walls. By measuring the pressure exerted on the piston walls, we obtain force-compression-stretching relations, for a given chain size $N$ and a pore width $D$. 

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approaches [11, 12] can be reproduced by the following “renormalized” free energy [13],

\[ \beta \mathcal{F}(R, D) = A \frac{R^2}{(N/g)D^2} + B \frac{D(N/g)^2}{R}, \tag{1} \]

where \( g \) is the number of monomers inside a compression blob of diameter \( D \), i.e., \( g \simeq (D/a)^{5/3} \). \( A \) and \( B \) are constants, and \( a \) is the monomer size. (Throughout this paper, \( \beta = 1/k_BT \) with \( k_BT \) being the thermal energy; unless otherwise indicated, \( a \) is the unit of length.) The first term in Eq. 1 describes connectivity of blobs, while the second term, which can be rewritten as \( \sim (N/g) \times \) blob density, represents the mutual repulsion between the blobs, thus ensuring linear ordering. The second term is equivalent to correctly assigning \( k_BT \) to a binary collision of two blobs, independent of their size [11, 14].

The free energy in Eq. 1 produces not only the expected equilibrium chain size \( R_0 \sim ND^{-2/3} \) [15], when \( \mathcal{F} \) is minimized, but also the correct confinement free energy \( 3\mathcal{F}_{\text{conf}} = \beta \mathcal{F}(R = R_0, D) \sim N/g \sim ND^{-5/3} \), which is linear in \( N \) [11, 12]. The free energy cost for linear ordering is correctly counted as \( \sim k_BT \) per blob (\( D \)-independent). Also, the resulting effective Hookean spring constant of the chain, \( k_{\text{eff}} = (\partial^2\mathcal{F}/\partial R^2)_{R_0} \sim N^{-1}D^{-1/3} \) is consistent with the previous scaling result [1, 12]. Note that, without the renormalization trick in Eq. 1, Flory theory (as employed in [3]; see also [13]) will lead to a \( D \)-independent (thus qualitatively inaccurate) spring constant \( k_{\text{eff}} \).

An important consequence of Eq. 1 is that it predicts a universal scaling relation for (external) force-compression-extension \( (R) \) relation,

\[ D\beta f = D\frac{\partial}{\partial R}(\beta \mathcal{F}) = 2A \left( \frac{R}{R_0} \right) - B \left( \frac{R}{R_0} \right)^{-2}. \tag{2} \]

To test the validity of Eq. 2 (thus Eq. 1 as well), we have carried out molecular dynamics simulations using ESPResSo [16] for a wide range of parameters: \( D = 4.5, \ldots, 15 \) and \( N = 128, 256, 512 \) (see Fig. 1). In ESPResSo, monomers (or beads) are connected by finite extensible nonlinear elastic (FENE) (spring) bonds with a Weeks-Chandler-Andersen (WCA) potential for excluded-volume interactions (monomer-monomer as well as monomer-wall). We confined the two end beads of the chain by “piston” walls at the cylinder ends (Fig. 1(b)&(c)), while allowing the ends to move freely in the plane of the piston wall. By varying the wall-to-wall distance (thus \( R \)), we obtained the longitudinal force \( f(R) \) to keep \( R \) fixed.

Figure 2(a) summarizes our simulation results, where all 24 curves have been rescaled according to Eq. 2. The data perfectly collapse onto a single master curve (the solid line) for \( R < R_0 \). Moreover, in the range of \( 0.5 < R/R_0 < 1.2 \), Eq. 2 fits the rescaled data very well, thus confirming the scaling prediction of Eq. 1 [see the lower-left inset in Fig. 2(a)]. However, as the compression becomes strong \( (R/R_0 \ll 1) \), the blobs break into smaller ones [see Fig. 1(b)], and the correct form of free energy is \( 3\mathcal{F} \sim (R^3/V)^{1/(3\nu-1)} \), where \( R \sim N^\nu \) is the radius of gyration of a corresponding unconfinced chain (with \( \nu \approx 3/5 \) the Flory exponent) and \( V \sim D^2R \) the confining volume [14]. From this, we obtain

\[ -f \cdot D \sim \left( \frac{R_0}{R} \right)^{3\nu} \sim \left( \frac{R_0}{R} \right)^9 \tag{3} \]

[see the upper-right inset in Fig. 2(a)].

Importantly, Fig. 2 shows the limitations of Eq. 2: when the chain is stretched appreciably from its equilibrium length \( (R \gtrsim 1.2R_0) \), the force-extension curves (FECs) do not collapse onto a single universal plot. This is not unexpected since an additional length scale,
namely the tensile blob size $\xi (< D)$ [11], is relevant at high $f$, as indicated in Fig. 1(c). This also signals the onset of a $D$-independent regime at large $f$, as the interactions between the chain and the wall are negligible [see Fig. 2(b) and Fig. 3].

In Fig. 2(b), we show FECs for $R > R_0$ by rescaling $R$ by $N$. Since $R/N$ denotes the extension per chain segment, for the same pore diameter $D$, the force extension curves tend to collapse onto one another, as expected. In a recent simulation study [17], the effective spring constant $k_{\text{eff}}$ was shown to vary from $k_{\text{eff}} \sim 1/N^{0.9}$ to $1/N^{1.3}$ for the intermediate chain length (up to $N = 2000$). This differs from the scaling result $k_{\text{eff}} \sim 1/N^{1.3/3}$ [12], which could be reached only when $N \sim 10^4$ [17]. Our results are also in good agreement with Arnold et al. and we find the linear Hookean collapse for $k_{\text{eff}} \sim 1/N^{0.9 \pm 0.2}$ [$f \sim k_{\text{eff}}(R - R_0)$; inset of Fig. 2(b)]. The data cannot be fit using the large $N$ result, $k_{\text{eff}} \sim 1/N^{1.3/3}$ [18].

To further elucidate the subtleties of the FECs in the presence of confinement, we have also performed analytical, self-consistent calculations following the theoretical methods described in [19, 20]. Our motivation is to derive the FEC relation in the large-$N$ limit, which can be reached experimentally (if not computationally; see above). In the continuum limit, the distribution of monomers at $\mathbf{r}(s)$ can be represented by the following Hamiltonian

$$
\beta \mathcal{H} = \frac{3}{2a} \int_0^L \dot{\mathbf{r}}^2(s) ds + \frac{v}{2} \int_0^L ds \delta(\mathbf{r}(s') - \mathbf{r}(s)) - \beta f \int_0^L \dot{s}(s) ds,
$$

where $s$ is the contour length ($0 \leq s \leq L = Na$), $[\ldots] = \partial[\ldots]/\partial s$, and $v$ the excluded volume parameter. Confinement effects will be taken into account through the boundary condition that the probability of finding any monomer on the wall is zero.

We replace $\mathcal{H}$ by the simpler reference $\mathcal{H}_1$ given by $\beta \mathcal{H}_1 = \frac{3}{2a} \int_0^L \dot{\mathbf{r}}^2(s) ds - \beta f \int_0^L \dot{s}(s) ds$ and choose an optimal value of $a_1$ instead of minimizing the free energy as in the Flory approach—so that $R$ obtained using $\mathcal{H}_1$, i.e., $R \equiv (z_L - z_0) = \beta La_1 f/3$, coincides with $R$ calculated using $\mathcal{H}$ to first order in $v$ [19, 20]. Additionally, we use the “ground-state dominance” approximation, which is valid in the large $N$ limit [11]. The optimal $a_1$ satisfies the self-consistent equation (SCE):

$$
La_1^{3/2} \left( \frac{1}{a} - \frac{1}{a_1} \right) = \sqrt{\frac{6}{\pi}} \frac{1.76}{\alpha_0^6 D^2} v \int_0^L ds (L - s) s \exp \left[ -\frac{1}{6} \alpha_1 (\beta f)^2 \right] = 0.4 \frac{v}{D^2} \frac{18e^{-\beta f^2 L a_1}}{L^{1/2} \beta f^2 a_1^3} + \frac{\sqrt{6\pi}(-9 + L \beta^2 f^2 a_1)}{\beta^3 f^5 a_1^{5/2}} \text{erf}(f L a_1/6),
$$

where $\alpha_0 \approx 2.40$ is the smallest (first) zero of the zeroth-order Bessel function of the first kind $J_0(x)$, and erf$(x)$ is the error function. When combined with $R = \beta La_1 f/3$, the solution of the SCE determines the equilibrium chain length along the pore axis.

For $f = 0$, the SCE leads to the equilibrium chain size $R_0 = \sqrt{\langle (z_L - z_0)^2 \rangle_f} \sim L(\frac{v a_1^3}{D})^{1/3}$, which is consistent with the previous result [12, 20]. For $f > 0$, the SCE can be solved numerically. A few comments are in order: First, the excluded volume parameter $v$ in the SCE can be considered as a fitting parameter (see Ref. [19]). The value of $v$ can be adjusted to ensure the best global fit to simulations or experimental data. Second, our SCE does not reflect the kinetic aspects of force-extensions; chain reorientation, allowed in our SCE, is kinetically suppressed for strong confinement (It is strictly forbidden in our simulations.) Finally, because of the ground-state-domiance approximation, the SCE becomes more accurate for large $L$. In the limit $L \to \infty$, chain reorientation becomes irrelevant in that chain alignment in the force-direction is ensured for $f \gtrsim k_B T/R_0$ ($\rightarrow 0$ as $L \to \infty$). In this case, $v$ dependence enters the FEC only via the combination $D^2 v$ and, thus, can be absorbed into an effective $D$ (see below). Our focus below is thus the large $L$ behavior of our SCE.

In the large $L$ limit, the SCE in Eq. 5 reduces to $a_1^3 \left( \frac{1}{a} - \frac{1}{a_1} \right) \approx 0.44 \frac{v}{D^2} \left( \frac{1}{a_1} \right)^{3/2}$. This equation implies that $a_1$ is a function of $\int D^2/\nu^{1/3}$: $a_1 = a_1(\int D^2/\nu^{1/3})$. As a result, $(\Delta R/N) D^2/\nu^{1/3} = (\beta a_1 f/3) D^2/\nu^{1/3}$ is a function of $\int D^2/\nu^{1/3}$, where $\Delta R = R - R_0$. Thus, the FECs collapse onto each other in a $\int D^2/\nu^{1/3}$- $(\Delta R/N) D^2/\nu^{1/3}$ plot. The analytic results justify the scaling plot in Fig. 2, where the renormalized $D_R \sim D\nu^{1/2}$. In Fig. 3, we plot $\Delta R D^2/\nu^{1/3}$ as a function of $\int D^2/\nu^{1/3}$ in the limit $N \to \infty$. All the curves for different values of $D$ collapse onto each other (as found in the simulations) for the reason described above. (Also see the inset in Fig. 3 obtained without $D$ rescaling. This suggests that a more strongly confined chain behaves as a stronger spring.)

Three different force-extension regimes are identified in Fig. 3: linear (green dotted), power-law (red) and linear (cyan). The good linear fit to the very narrow lin-
ear regime indicates a weak $D$-dependence of the force-extension relation [21]. For the power-law fit in the second regime, we have chosen $RD^{2/3}/v \propto \text{const} + (FD^{2/3}/v)^\alpha$ with $\alpha \approx 1.5$. From this, $k_{\text{eff}}$ has been estimated to vary as $D^{-2(1-\alpha)/3} \approx D^{-1/3}$. The seemingly-perfect fit to the force-extension in this regime justifies the scaling result $k_{\text{eff}} \sim 1/D^{1/3}N$. However, the force-extension in this regime is nonlinear, in contrast to what one may expect from the scaling approach [12]. Only over a narrow parameter range can the linearity be recovered. We note, however, that this power-law regime represents a much wider parameter space than the initial linear regime. The large-$f$ linear regime is where the force-extension becomes $D$-independent is due to almost full stretching of chain by large force.

Our results suggest that relaxation dynamics of a chain confined in a narrow channel will show several distinct relaxation rates ($\propto k_{\text{eff}}$) with different $D$ dependence. This explains the limitations of existing scaling arguments based on a single-time scale [1, 2, 3]. The predictions based on a scaling approach are reached only when $N$ is very large. Thus simulations or experiments on short chains need to be interpreted with caution. Our approach can be extended to incorporate other non-trivial but important effects such as chain topology (e.g., branched polymers), electrostatics, molecular crowding, and chain stiffness [22]. Most importantly, the force-compression-extension relations presented above can be used to understand the elastic response of chromosomes confined in microfluidic devices, as well as the fate of proteins in nanopores.

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