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Diffusion mechanisms of localised knots along a polymer

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Abstract. – We consider the diffusive motion of a localised knot along a linear polymer chain. In particular, we derive the mean diffusion time of the knot before it escapes from the chain once it gets close to one of the chain ends. Self-reptation of the entire chain between *either* end and the knot position, during which the knot is provided with free volume, leads to an L^3 scaling of diffusion time; for sufficiently long chains, subdiffusion will enhance this time even more. Conversely, we propose local “breathing”, *i.e.*, local conformational rearrangement inside the knot region (KR) and its immediate neighbourhood, as additional mechanism. The contribution of KR-breathing to the diffusion time scales only quadratically, $\sim L^2$, speeding up the knot escape considerably and guaranteeing finite knot mobility even for very long chains.

Introduction. – Double-stranded DNA under standard salt conditions has a persistence length ℓ_p of *circa* 50 nm. Nanochannels can presently be manufactured with widths that are comparable to, or even smaller than, ℓ_p . In such channels, that is, linear DNA is stretched beyond the blob regime, assuming undulations in the bending-affected Odijk regime [1]. This makes it possible to detect and separate individual DNA molecules and characterise, for instance, their length [2, 3]; it even appears feasible in the future to use nanochannels for sequence determination [4]. While being pushed through the nanochannel by an electric field, the DNA chain occasionally collides with local channel defects, bottlenecks created during the manufacturing process. Such collisions often cause a superstructure in the chain, visible in the experiment using stained DNA as a spot of increased fluorescence and concurrent reduction of the end-to-end length of the chain (fig. 1). On switching off the electric field, after a period of immobilisation, these features eventually move toward one of the chain ends and escape [5]. We argue that these intermittent features likely correspond to knots threaded into the DNA

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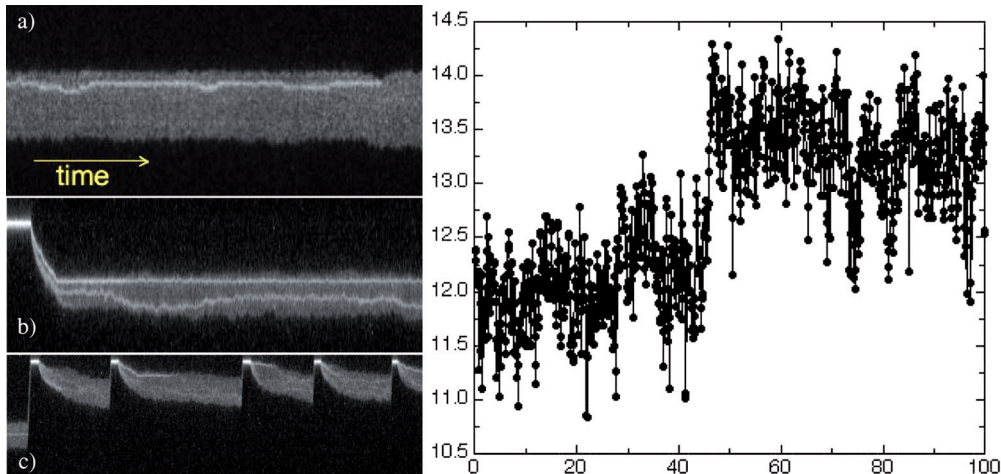


Fig. 1 – Phage λ DNA of contour length $L \approx 16.5 \mu\text{m}$ in a $60 \times 80 \text{ nm}$ channel. Left: three fluorescence time-traces of the DNA. a) The feature is almost immobile before escape; b) two features created by a forced collision; c) repeated collisions producing new features, that escape prior to a new collision. Right: evolution ($[\mu\text{m}]$ vs. $[\text{s}]$) of the end-to-end length corresponding to the trace in a). The jump ($\Delta N \approx 2.3 \mu\text{m}$, or 6.8 kbp) at around 42s corresponds to the escape of the feature [5].

on collision⁽¹⁾. In what follows, we propose a mechanism for the diffusive escape of the knot, obtaining a shorter than previously assumed knot diffusion time.

Knots also occur *in vivo*. For instance, in bacteria cells DNA knots are created physiologically [6]; they are implicated to have an active role in gene regulation, separating topologically different parts of the genome [7]. Packaging of mutant DNA into virus capsids turns out to be a highly efficient manner to produce DNA knots *in vitro* [8]. After dissociation of the capsid, the knot needs to be locked by cyclisation of the formerly linear DNA, before it escapes at either chain end. In both cases it is of interest to characterise better the knot motion along the DNA chain. Nanochannel techniques promise to add novel quantitative information to the understanding of knot motion in polymers.

Knot diffusion in stretched, single λ DNA was studied experimentally by Bao *et al.* [9]. In their analysis they argue that the diffusion time of the knot from an initial position inside the chain to one of the ends should scale like L^2/D . Assuming a diffusion coefficient $D \simeq L^{-1}$, the diffusion time τ_D of the knot scales like $\tau_D \simeq L^3$. This scenario implies that the entire chain self-reptates to create the motion of the knot. We here argue that i) this self-reptation is asymmetric in an open knot leading to increased mobility toward the chain ends, and ii) suggest an additional mechanism, namely, breathing of the knot region (KR)⁽²⁾. KR-breathing involves exchange of stored length *locally* with the vicinal chain. This mechanism is expected to dominate in long chains, significantly increasing the knot diffusivity with quadratic scaling of the diffusion time, $\tau_D \simeq L^2$. Even in long chains, KR-breathing causes Brownian diffusion.

Let us first discuss the nature of the observed feature. *A priori*, one might suspect that the feature is a fold⁽³⁾ in the DNA of the shape of a Z or a \mathfrak{S} , or a knot. Both simple knot

⁽¹⁾Repeated collision of the same chain with the defect almost always causes a new superstructure (fig. 1).

⁽²⁾In the case of a localised knot, the volume that contains all non-trivial topological entanglements [10].

⁽³⁾Similar to folds created when trying to push an electric cable in a larger cable canal.

and fold structures carry a bending energy amounting to some $3k_B T^{(4)}$. This is a fairly small energy such that thermal fluctuations would be sufficient to remove the folds. Moreover, the folds are not self-confining so that they should fluctuate significantly in size; on the images, however, the fluorescence spot is strongly localised at all times. In fact, it is known that in nano-confined DNA knotting occurs almost with probability one [8]. We are therefore confident that the observed features correspond to a knotted state of the DNA chain. While the knotting studies in nano-confinement suggest that the created knots are more complex, a defect size of $\approx 2 \mu\text{m}$ indeed suggests a knot with larger number of essential crossings [9, 13].

Immobilisation period. – Once formed while being smashed against the channel defect by the external electric field, the created knot is relatively tight such that, initially, it is immobile. Only when, driven by thermal fluctuations, sufficient contour length is introduced into the KR, it becomes flexible enough to start its diffusion toward a chain end. We pursue a simple energetic argument to quantify the knot immobilisation. In the remainder we assume that chain relaxation is fast compared to the knot immobilisation time.

After creation under high confinement, the knot is not molecularly tight in the picture of de Gennes [14]. However, it is small enough such that the self-confined volume of the KR is of a diameter comparable to or smaller than ℓ_p . At several contact points where the topology of the knot prevents expansion the bending stiffness causes that the respective chains lock each other, comparable to static friction effects. Fluctuations now need to simultaneously loosen a number of these locking contacts in order to allow free length to enter the KR. The energy barrier for releasing a contact is of the order of the work necessary to displace one part of the chain from the local potential minimum. To induce a displacement δh , the work $\delta E = F_{\perp} \delta h$ needs to be performed, where F_{\perp} is the force acting on the contact area. To determine how F_{\perp} scales with the size of the KR, R_{Δ} , we note that the typical bending energy of a DNA segment of length ℓ and curvature radius R_{Δ} is $E_b \simeq \pi \kappa \ell / (2R_{\Delta}^2)$, with elastic constant $\kappa = k_B T \ell_p$ [11]. As the KR is not molecularly tight and all segments of the KR tend to assume minimum curvature, the curvature radius is of the order of R_{Δ} . A small normal in-plane displacement δh of a stretch of DNA around the contact point changes the curvature radius approximately by $-\delta h$ (bending reduces R_{Δ} and there are no other parameters of dimension length in this purely geometric argument), so that $F_{\perp} \simeq dE_b/d(\delta h) \simeq -dE_b/dR_{\Delta} \sim R_{\Delta}^{-3}$. Thus, the energy necessary to unlock n contacts is estimated by $\delta E_n \simeq n\pi(\delta h)\kappa\ell_p R_{\Delta}^{-3}$ if we assume ℓ to be of the order of the Kuhn length ξ_K . The sharp R_{Δ}^{-3} -dependence of the potential barrier for loosening the KR suggests that the activation energy becomes unimportant after crossing the first few barriers, and further untightening is controlled by a different mechanism.

The fast tightening of a knot into a locked state by an external force ζ requires the crossing of practically the same potential barrier. If the associated displacement in direction of the force is b , the work necessary is $\delta E_{\zeta} \simeq b\zeta^{(5)}$. The time scale for knot immobilisation according to our barrier crossing argument is therefore (compare [14])

$$\theta \simeq \tau \exp[\delta E_n/k_B T], \quad (1)$$

where τ is a relaxation time, not necessarily of the entire chain. Due to the sharp R_{Δ}^{-3} dependence of the barrier δE_n , it rapidly decays when the size of the KR grows. Therefore the immobilisation time of a knot in an initially tight configuration is large (and proportional to the exponential of the initial tightening force ζ), but the thermally activated untightening process

⁽⁴⁾A trefoil knot in a linear chain as well as the Z or 9 folds correspond to the bending energy of a full circle with a radius equivalent to the channel radius, approx. 50 nm. Using $E \approx k_B T \ell_p \pi / R$ for a radius R , we find the above value [11]. Higher-order knots, that are likely to be created, carry higher bending energy [12].

⁽⁵⁾This relation is analogous to de Gennes' result for a molecularly tight knot [14].

starting after overcoming the initial potential barrier is extremely fast and avalanche-like. After a few thermally activated steps the knot takes its maximally released configuration, with the size restricted only by the external geometric constraints (*i.e.*, channel or tube diameter). The next stage of the process is therefore not activation-dominated, but corresponds to a diffusion of the stored length into the KR. In a control experiment on a linear chain, it should be possible to measure τ independently. Therefore one could obtain the value of the activation energy δE_n as function of the electric field smashing the knot against the channel defect, or, in the case of optical-tweezers experiments, the mechanical tension ζ . Note that for some of the specific knots recorded, the immobilisation period lasts for several tens of seconds. The number of contact points increases with knot complexity, while the curvature radii become somewhat smaller, such that more complex knots are expected to have a drastically enhanced immobilisation time.

Confined knot. – Once unlocked by the provision of sufficient stored length, in the absence of a strong line tension the knot remains in the loose mode until it escapes from the chain. By exchanging stored length between the KR and the rest of the chain, the knot performs a random walk along the polymer. As we will see, the ensuing diffusion process is biased. We distinguish two potential diffusion mechanisms, both providing the fluctuations in additional length, leading to an inchworming of the KR: i) The first diffusive mode is characterised by a strongly disbalanced behaviour, in which length is provided to the KR by motion of the entire chain (from KR to the respective end) to either side of the knot. This “longitudinal” mode is similar to the self-reptation picture of [9]; however, our assumption takes the asymmetry into consideration, that the self-reptative diffusivity should increase when the knot gets closer to one of the chain ends. The efficiency of self-reptation should become reduced under tension (straightening of the chain). ii) The second mode is an autonomous motion of the KR, due to the fact that it is not molecularly tight: local length fluctuations in exchange with the knot’s immediate vicinity slightly change its size, allowing random directional changes. We refer to this “transversal” mode consisting of small variations in the knot size as KR-breathing, causing a sliding motion of the KR along the chain. Once the knot arrives at one chain end, it is released, corresponding to a first exit problem with absorbing boundaries at $x_L = 0$ and $x_R = 0$.

Both modes of knot release imply coherent motions of considerable parts of the chain. We assume that such concerted motion of a part of the chain of length l invokes the Rouse-like mobility $\mu(l) \propto l^{-1}$, so that the corresponding diffusion coefficient is $D(l) = \mu(l)k_B T \simeq k_B T/l$. Thus, if $\Delta \ll L$, KR-breathing typically involves the motion of a much shorter segment (of length Δ) than self-reptation, unless the knot travels close to the end of the chain, when the second mode becomes comparable or even more relevant⁽⁶⁾. Let us now discuss the two types of motion in more detail. KR-breathing is characterised by a diffusivity

$$D_{\text{KRB}} \simeq \mu_{\text{KRB}}(\mathcal{K})k_B T \simeq \alpha k_B T/\Delta(\mathcal{K}) \quad (2)$$

involving the motion of a length $\approx \Delta$ of the KR and a small vicinal DNA. The mobility $\mu_{\text{KRB}} \simeq 1/\Delta$ will strongly depend on the knot type \mathcal{K} through its size $\Delta(\mathcal{K})$ [9]. In particular, D_{KRB} is independent of the overall chain length, L . In scaling terms, the diffusion time of the knot on the chain is given by $\tau_{\text{KRB}} \simeq L^2/D \simeq \Delta L^2$, growing slower than the cubic scaling of the reptation time for chain dynamics in a reptation tube [15, 16]. To obtain the dependence of the knot diffusion time on its initial location x_L on the chain, we determine the mean first-passage time $\mathcal{T}(x_L)$ from the diffusion equation $\partial P(x, t)/\partial t = (\partial/\partial x)D(x)(\partial/\partial x)P(x, t)$, with absorbing boundary conditions at both ends. Here, $P(x, t)$ is the probability density to find

⁽⁶⁾In particular, for an unconfined knot as discussed below.

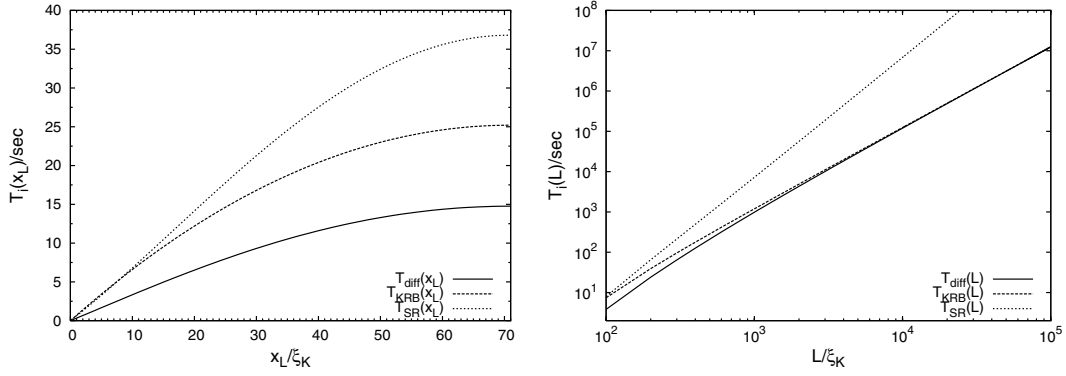


Fig. 2 – Mean first-passage time $\mathcal{T}(x_L)$ vs. initial position x_L of the knot for fixed chain length $L = 165\xi_K$ (left), and vs. chain length L for symmetric initial condition $x_L = L_{\text{red}}/2 = 71\xi_K$ (right). With $\Delta = 23\xi_K$ and $\tau_K = 10^{-2}$ s.

the defect at position x . Following Gardiner [17], $\mathcal{T}(x_L)$ is given by

$$\mathcal{T}(x_L) = \int_0^{x_L} \frac{L_{\text{red}}/2 - x'}{D(x')} dx', \quad (3)$$

where $L_{\text{red}} = L - \Delta$ is the reduced length of the two linear segments of the chain. With the expression for D_{KRB} , the diffusion time for KR-breathing yields

$$\mathcal{T}_{\text{KRB}}(x_L) = \frac{\Delta L_{\text{red}}^2}{2\alpha k_B T} \left[(x_L/L_{\text{red}}) - (x_L/L_{\text{red}})^2 \right]. \quad (4)$$

In the self-reptation picture, the second diffusion mode, KR motion requires rearrangement of either the left or the right chain respective to the knot location plus the KR itself. Thus,

$$D_{\text{SR}} \simeq \frac{\alpha k_B T}{x_L + \Delta} + \frac{\alpha k_B T}{x_R + \Delta} = \frac{\alpha k_B T(L + \Delta)}{(x_L + \Delta)(L - x_L)}, \quad (5)$$

that quickly increases toward either chain end. From expression (3), there follows:

$$\mathcal{T}_{\text{SR}}(x_L) = \frac{1}{12\alpha k_B T(L + \Delta)} \left[x_L \left\{ x_L(3LL_{\text{red}} - 4Lx_L - 2L_{\text{red}}x_L + 3x_L^3) + \Delta(6L[L_{\text{red}} - x_L] + x_L[4x_L - 3L_{\text{red}}]) \right\} \right] \quad (6)$$

plotted in fig. 2. If $\Delta \ll L$, we have $L \approx L_{\text{red}}$, and we find the simplified expression

$$\mathcal{T}_{\text{SR}}(x_L) \approx \frac{L^3}{4\alpha k_B T} \left[(x_L/L)^2 - 2(x_L/L)^3 + (x_L/L)^4 \right]. \quad (7)$$

Self-reptation, that is, leads to the L^3 scaling of $\mathcal{T}_{\text{SR}}(x_L)$ in analogy to regular reptation [15,16].

Combining both effects to the total diffusivity $D_{\text{diff}}(x_L) = D_{\text{KRB}}(x_L) + D_{\text{SR}}(x_L)$, we cannot obtain an analytic result for the knot diffusion time and resort to numerical evaluation⁽⁷⁾. Rewriting $D_{\text{diff}} = \xi_K^2/\tau_K$ in terms of the Kuhn length as assumed unit for stored length and

⁽⁷⁾Noting that in ref. [9], for a slightly pulled chain the diffusivity $D_{\text{diff}} \approx 1.2 \mu\text{m}^2/\text{s}$ was measured.

therefore the fundamental random-walk step size, for $D_{\text{diff}} \sim 1 \mu\text{m}^2/\text{s}$, we find the associated step time $\tau_K \sim 10^{-2}$ s. From the above relations we obtain the graphs in fig. 2. For initial positions of the KR close to a chain end, the mean first-passage times for both diffusion mechanisms become identical, as it should. For a chain of the size of the λ DNA ($L = 165\xi_K$), the individual modes are both relevant. The scaling of $\mathcal{T}_{\text{diff}}$ with the chain length for the symmetric initial condition $x_L = L_{\text{red}}/2$ is shown in fig. 2, demonstrating that for longer chain lengths, KR-breathing dominates. The scaling dependence of the overall knot diffusion time provides a direct way to test our model experimentally. It will be interesting to monitor the time series of knot defects in a large ensemble of realisations to obtain statistically relevant results for the two contributions θ and $\mathcal{T}_{\text{diff}}$, *i.e.*, immobilisation and diffusion times.

Flexible chain. – For flexible chains with persistence lengths much smaller than the channel diameter, the KR is allowed to expand. The size of (at least, simpler) knots in the absence of tension, or under moderate tension scales like a power law of the chain length, $\ell_k \simeq a^{1-c}L^c$, with $c \approx 0.7$ [18, 19]. The *modus operandi* of knot escape from the chain can now follow two different tracks: i) First, the knot can diffuse out while being localised at all times, corresponding to the scenario developed above. As ξ_K is much smaller and therefore L much larger in units of ξ_K , KR-breathing dominates, and the first-passage time scales like $\mathcal{T}_{\text{diff}} \simeq L^2/D_{\text{KRB}}$. Without effective confinement by the channel walls, the KR grows with L , entering the diffusivity $D_{\text{KBR}} = D_{\text{KBR}}(L)$, *i.e.*, the diffusive component with fractal scaling $\mathcal{T}_{\text{KRB}} \simeq L^{2+\alpha}$ yields. For knots dominated by finite-size effects (or complex knots that might tend to delocalisation) [20], or under dense or θ conditions [21], the KR scales like the overall chain length, and we would obtain the reptation scaling $\mathcal{T}_{\text{KRB}} \sim \mathcal{T}_{\text{diff}} \simeq L^3$. Conversely, when confined to two dimensions by adhesion to a surface or by sandwiching between two parallel walls, the knot localises tightly and $\alpha = 0$ [10]. ii) Second, in the absence of external tension the knot can be undone by swelling of the KR until it is of the size L of the chain, and the chain ends are inside the KR. This mode is expected to scale like the all-chain Rouse time $\simeq L^3$.

Discussion. – The possibility to devise nanochannels of a width comparable to the persistence length of polymers, and to monitor the end-to-end distance of a single polymer is a fine example of how new experimental techniques can probe mechanically domains of fundamental behaviour of single polymers. We presented a simple scaling model of both the immobilisation and the diffusion of knots in DNA confined in nanochannels, identifying two different reptation modes. While self-reptation has been considered earlier, we propose a modified self-reptation picture that is, in fact, asymmetric. We also suggest a new mode, namely, KR-breathing, that is expected to dominate the knot diffusion in longer chains. By varying chain length L and the channel diameter-to-persistence length ratio, we expect future experiments to provide new insight in the reptation of single chains that self-confine themselves.

It appears obvious that when the knot gets close to one of the chain ends, the close end can easily reptate into the KR and subsequently release the knot, without the far end being involved. In this picture, it is not necessary to have full chain equilibration on time scales slower than the diffusion time. The connected asymmetry of the diffusion coefficient with respect to the knot position along the chain is indeed corroborated by recent simulations results of a trefoil knot diffusing on a linear chain under moderate tension [22]. The existence of two diffusion modes makes sure that the knot mobility is finite even for very long chains, $L \rightarrow \infty$. In other pictures assuming relaxation of the whole chain as relevant diffusion time scale, in a very long polymer the knot would become effectively immobile.

We note that small external stretching forces should not affect the knot diffusion modes. Moderate forces are expected to reduce self-reptation; as long as the blob size remains larger than the KR, KR-breathing should not be disturbed. For high forces, eventually the system

will be immobilised according to the above picture. We also note that we assumed that the diffusion of the knot modes is Brownian. While this is always true for the KR-breathing mode, for long chains self-reptation should become subdiffusive according to arguments brought forth in the discussion of nanopore translocation [23,24]. In that case, KR-breathing becomes even more dominant. It would be very interesting to directly observe subdiffusion in experiments.

Lastly, from the experimental side, it appears that the de Gennes hypothesis regarding knot immobilisation time (eq. (1)) could be tested by varying the field strength used to compress the DNA, as the tightening force should be related to the compression field. The de Gennes hypothesis would suggest that the knot immobilisation time is a strongly increasing function of the compression field. Also, it would be interesting to study how the generated knot spectrum depends on compression field strength and duration. This could easily be accomplished by compressing DNA at varying field strengths.

* * *

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