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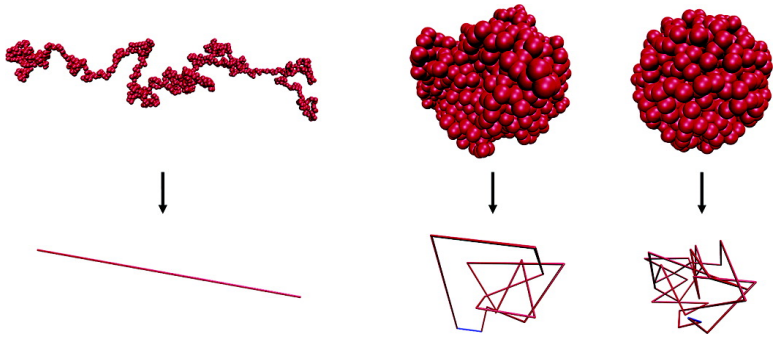

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Knots in Globule and Coil Phases of a Model Polyethylene

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Abstract: We examine the statistics of knots with numerical simulations of a simplified model of polyethylene. We can simulate polymers of up to 1000 monomers (each representing roughly three CH_2 groups), at a range of temperatures spanning coil (good solvent) and globule (bad solvent) phases. We quantify the abundance of knots in the globule phase and in confined polymers, and their rarity in the swollen phase. Since our polymers are open, we consider (and test) various operational definitions for knots, which are rigorously defined only for closed chains. We also associate a typical size with individual knots, which are found to be small (tight and localized) in the swollen phase but large (loose and spread out) in the dense phases.

Introduction

As a topological property of closed strings, knots are primarily a topic of mathematical inquiry, yet they have long fascinated chemists and physicists. Indeed, the classification of knots starts with the work of scientists such as Thompson[1] and Tait,[2] motivated by the ideal of "vortex atoms". Polymers provide a practical testing ground for entanglements, and considerations of their configurations in the early 1960s led to the Frisch−Wasserman−Delbrück conjecture,[3,4] that sufficiently long polymers must be knotted. Unfortunately, the rigorous proof of this conjecture for lattice polygons[5,6] does not provide a means to estimate the typical size at which knots are likely to appear in a particular polymer. This is a relevant question for biological systems whose fundamental constituents are long biopolymers. An early example was provided by the discovery of knots in single-stranded DNA by Liu et al. in 1976.[7] Since then, many knots were created artificially, e.g., by the action of *E. coli* topoisomerase I on circular DNA. In this case, an abundance of the enzyme changes the quality of the solvent and provides internal constraints which favor the formation of complex knots.[8] In the capsid of normal phages (wild type), there is no knot formation in a strict mathematical sense because one end of the linear DNA stays in the loading channel and cannot join the other terminus. Complex knots are, however, frequently observed in mutants in which both ends enter the capsid.[9,10] On the other hand, knots formed by random cyclization of DNA in a good solvent are rare.[11,12] Likewise, there are only few knots in globular protein structures.[13,14]

Does the presence (or the absence) of knots in a polymer (e.g., DNA or protein) provide any clues to its function or origin? The first step toward answering such a question is to compare with the expected number (and variety) of knots in the polymer due to pure chance. Existing numerical results are not entirely satisfactory for such comparison because they are mostly based on somewhat abstract polymer models. The first simulations of knotted states can be traced back to the groundbreaking works of Vologodskii et al. in 1974.[15,16] After some initial interest in random polygons, many groups focused on self-avoiding polymers in the swollen (coil) phase.[17−22] There are relatively few simulations of dense (globular) polymers, mainly involving simplified lattice models such as Hamiltonian walks,[23−25] or self-avoiding polygons in prism and slab geom-

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etries.[26] They confirm the expected increase in the probability of finding knots as the polymer becomes more compact, but are not very suitable for a quantitative comparison with realistic polymers.

Other studies have focused on mechanical properties of knotted polymers. It was demonstrated that the presence of a knot severely weakens the strand and that under tension the polymer will break at the entrance to the knot.[27−29] Knots may facilitate nucleation processes,[30] and the dynamics of unknotting has also been addressed, both with simulations[31] and experiments.[32]

One of the simplest and best studied polymeric systems is polyethylene, $H-(CH_2)_n-H$, for which a wealth of experimental data is available, including phase diagrams as a function of temperature, density, interfacial tension, and n. It has been shown that for small n much of these data can be reproduced by a simplified polymer model of N interacting beads, each bead corresponding to roughly three CH_2 groups, i.e., $n \approx 3N$.[33,34] Here, we perform simulations of this model, focusing on the propensity for knots as a function of N, and as the polymer is cooled from the coil to the globule state. Knots are indeed rare in the coil phase, with only around one percent of configurations knotted for $N = 1000$, and common in the globule state − roughly half the configurations are knotted for $N \approx 600$. We also find that an externally compacted polymer shows approximately the same number of knots as in the globule phase.

It is important to emphasize that the above results are obtained for *open polymers*, whereas mathematically, knots are only properly defined in *closed loops*. Indeed, almost all investigations of knotted states deal with closed strings, although most polymers and DNA strands are actually open. One way to overcome this difficulty is to join the ends according to a particular scheme, for example as suggested in refs 20,2. By comparing several such schemes we estimate a typical error resulting from artificial closure. Another interesting quantity that is not mathematically well defined is the *size of a knot*: Is the knot confined to a small portion of the chain, or spread out and loose? It can be shown in a few cases that interactions[35] (e.g., Coulomb repulsion) or entropic factors[36,37] (e.g., when adsorbed on a surface) lead to tight (small and localized) knots. We explore this question using operational definitions complimentary to, yet distinct from, those in ref 38. We find that in the coil phase the typical size of an isolated trefoil grows sublinearly as N^t with $t \approx 0.65$. While the entangled region increases with N, it vanishes in proportion to the entire chain. By contrast, knots in globule and confined phases are spread out, and the entangled region grows proportional to N.

Methods

Our model for polyethylene consists of a sequence of beads in continuous three-dimensional space.[33] A pair of monomers at separation r interact by the truncated and shifted Lennard−Jones potential

$$V_{\mathrm{LJ}}(r) = \begin{cases} 4\epsilon\left[\left(\frac{\sigma}{r}\right)^{12} - \left(\frac{\sigma}{r}\right)^{6} + \frac{127}{16384}\right], & \text{if } r < r_c \\ 0, & \text{else} \end{cases} \quad (1)$$

Adjacent beads are connected with FENE (finitely extensible nonlinear elastic) springs

$$V_{\mathrm{FENE}}(r) = -33.75\epsilon \ln\left[1 - \left(\frac{r}{1.5\,\sigma}\right)^2\right] \quad (2)$$

The parameters ϵ and σ define the depth and the width of the potential; r denotes the distance between two beads, and $r_c = 2\sqrt[6]{2}\,\sigma$ is the upper cutoff of the potential.

Equilibrated configurations are generated by a combination of slithering snake and local Monte Carlo moves in the compact phases, and by pivot and local moves in the swollen phase.[39] In general, the polymer faces a competition between two opposing states. On one hand, it would like to have access to many configurations which favors a swollen state (Figure 1 left). On the other hand, it would like to minimize its energy by placing many monomers close to the minimum of the combined pair-potential of eqs 1 and 2. This favors a globular shape (Figure 1 middle). The transition between the two states for a polymer of infinite length occurs at the so-called Θ-point. At high temperatures (which also correspond to good solvent conditions), the free energy is dominated by the entropic contribution. At low temperatures (or in bad solvent conditions) the energetic gain is more important, and a globule is formed. Our simulations of the swollen phase took place at $T = 1.5\ T_\Theta (= 4.98\ \epsilon/k_B)$.[41] The equilibrated globule was obtained at $T = 0.5\ T_\Theta (= 1.66\ \epsilon/k_B)$. We also confined a polymer of chain length $N = 1000$ at $T = 1.5\ T_\Theta$ to a hard spherical cage of radius $R = 7\ \sigma$ (see Figure 1 right). This corresponds to 120% of the radius of gyration of an average globule at $T = 0.5\ T_\Theta$.

Knot invariants, like the Alexander polynomial[42,43] allow us to distinguish between simple knots.[44] The calculation, however, consumes a considerable amount of computer time ($O(N^3)$), and it is necessary to adopt reduction schemes beforehand. In this paper we implement a particularly efficient algorithm suggested by Koniaris and Muthukumar.[17,18] A similar scheme was developed independently by Taylor,[13]

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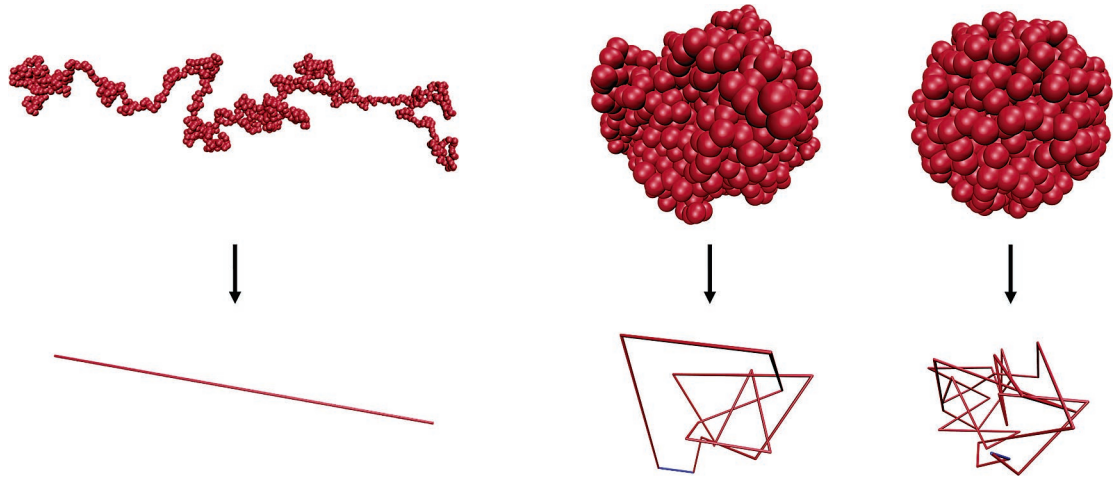

Figure 1. Polymer configurations in the coil phase (left), in the globule phase (middle), and under spherical confinement (right), before (up) and after (down) the application of the KMT algorithm.[18] The coil is most often reduced to its endpoints. The blue line in the reduced compact structures marks the artificial connection between the first and the last particle, which is necessary for calculating Alexander polynomials. Both compact structures contain a trefoil knot. Pictures were rendered with VMD (Visual Molecular Dynamics).[40]

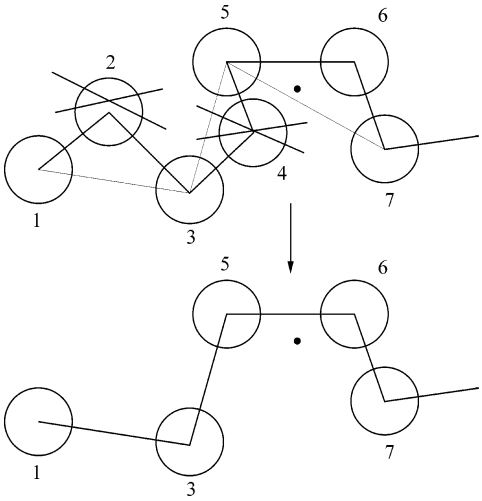

Figure 2. Illustration of the KMT algorithm. Monomers 2 and 4 can be removed in the first iteration step without changing the topology of the chain. The black dot marks a bond which is part of a different section of the polymer. This bond intersects with the triangle formed by monomers 5, 6, and 7. Particle 6 is not removed because by replacing bonds 56 and 67 with 57 we cross the impinging bond and potentially alter the topology.

and we will therefore refer to this method as the KMT reduction. As the knot definition requires closure, we need to join both ends of the polymer before invariants can be calculated. We test four variations: First, we simply join the two termini by a straight line. Second, we connect both ends to infinity by straight lines along the line passing through the end monomers. Both closures are repeated, but this time we apply the KMT reduction beforehand. Each method has its advantages and drawbacks: The reduction does not change topology in closed loops, but if we close before reducing the chain we may create knots simply as a result of the closure. This influence decreases substantially when we reduce the configuration first. In this case, however, the specifics of the reduction procedure also have some potential to alter the outcome as reported in ref 47.

In our implementation of the KMT reduction, we start with one end of the chain and consider successively triangles of adjacent monomers (123, 345, 567 in Figure 2). If a triangle (like 123 in Figure 2) is not intersected by any part of the remaining chain, we delete the monomer in the middle (#2). If any bond crosses the triangle (black dot in Figure 2), then we keep the monomer in the middle (#6) because a further reduction (from 56 and 67 to 57) could change the relative position of the chain with respect to the intersecting bond. The first and the last monomer are never deleted. Going back and forth between the termini, we either end up with two particles (the first and the last monomer, see Figure 1 lower left) or with a highly reduced representation of the original chain (Figure 1 lower middle and right). The procedure works surprisingly well and almost always reduces the chain to its termini when no knots are present. In rare cases, however, entangled configurations with no knots remain. As demonstrated in Figure 1, the scheme also provides us with a first impression on the abundance of knots, their sizes and locations.

The size of a simple trefoil knot can be determined by a series of deletions from each side as suggested by Taylor.[13] Throughout the procedure, we keep the termini of the chain. We successively remove all particles between the end-monomers and the knotted region, first from one side, then from the other. After each particle removal, we determine whether the chain is still knotted. We continue along one side until we obtain an unknot. Then, we repeat the procedure for the remaining side of the chain, this time starting with the last configuration which resulted in a trefoil. Again, we proceed until we obtain an unknot. We analyze the last configuration which contained a trefoil, and define the knot size as the difference in monomer numbers of the two particles next to the termini. An alternative definition of knot sizes is implemented in ref 38.

The algorithm for computing the Alexander polynomial $\Delta(t)$ is given elsewhere.[18,43] However, we would like to mention a technical trick which simplifies the procedure: $\Delta(t)$ can only be determined up to a factor of $\pm t^m$ with m being an arbitrary integer. A common solution to this problem is to calculate only $|\Delta(-1)|$. Unfortunately, $|\Delta(-1)|$ is a much weaker invariant than $\Delta(t)$ and even some of the simplest knots cannot be distinguished: Although knots 4_1 and 5_1 have different Alexander polynomials ($-1 + 3t - t^2$ and $1 - t + t^2 - t^3 + t^4$), $|\Delta(-1)| = 5$ in both cases. Some authors calculate additional invariants such as Vassiliev numbers[48,49] to further discriminate knots. Another option is to compute the full polynomial using machine algebra which allows for normalization of the final result.[17,18] In this paper, we would like to propose an alternative solution, which provides full access to the Alexander polynomial and is similar to an approach suggested in ref 23. If one calculates $\Delta_P(t) \equiv |\Delta(t)^*\Delta(1/t)|$, the pre-factors cancel out. The product is also a knot invariant and inherits some properties

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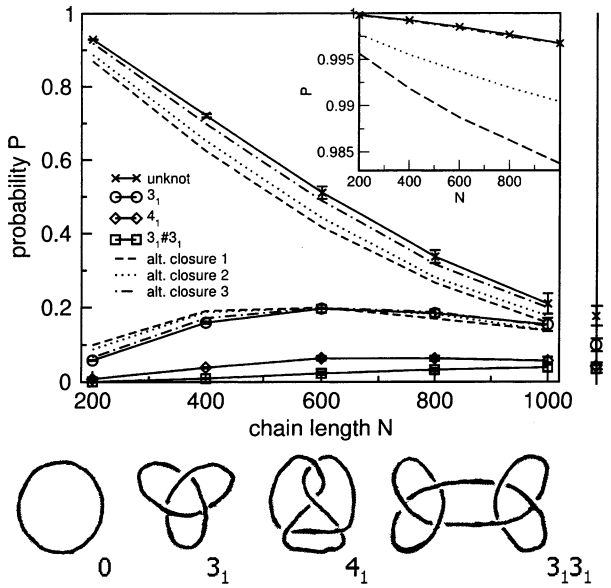

Figure 3. Probability of not having any knots (unknot) in the globule phase (at $T = 0.5T_\Theta$), and of observing a trefoil knot (3_1), a figure-eight knot (4_1) and composite trefoils ($3_1\#3_1$). "Ideal" representations of these knots are depicted below. Inset: The probability of not finding any knots in the swollen phase (at $T = 1.5T_\Theta$). The line to the right of the figure is marked with the knotting probabilities for a polymer of length $N = 1000$ under spherical confinement. All symbols and closed lines refer to a closure, which was obtained by joining the two end monomers by a straight line after the application of the KMT reduction. The errors of the mean values were based on the number of independent configurations estimated by the corresponding autocorrelation times. Error bars for the swollen phase are too small to be visible in the inset. Dashed line: Closure obtained from joining the end monomers before the application of the KMT reduction. Dash−dotted (dotted) line: Closure obtained by connecting end monomers to infinity after (before) the application of the KMT algorithm. Error bars for these alternative closures are not shown but are of comparable size.

of the Alexander polynomial: First, $\Delta_P(t)$ of the unknot is always one. Second, $\Delta_P(t)$ of a composite knot is the product of $\Delta_P(t)$ of the single knots from which it is derived. For our implementation, we evaluate $\Delta_P(t)$ at $t = -1.1$ and keep the first five decimal places. As a quick check reveals, knots 4_1 and 5_1 can now be distinguished ($\Delta_P(-1.1) \approx 25.09099$ and 25.45745, respectively.) We have tested that $\Delta_P(-1.1)$ discriminates simple knots of up to 10 crossings as does the complete Alexander polynomial. The choice of a t close to -1 further helps us to avoid numerical inaccuracies which occur for larger t.

Results

The resulting knot formation probabilities are plotted in Figure 3. We find that polymers in bad solvent conditions become knotted at rather small chain lengths, whereas knots are rare in good solvent conditions: For $N = 1000$ about 80% of all globular polymers are knotted. By contrast, only about 1% of all polymers are knotted in the swollen phase (inset). The probabilities of finding a specific knot in a polymer confined to a spherical cage (Figure 3, right line) are very similar to those observed in a globule. Consequently, the abundance of knots appears to predominantly depend on the density and not on the means of achieving compactification. Assuming a coarse-graining ratio of roughly 3:1, we expect that a globular or confined polyethylene chain with a few thousand CH_2 groups is already knotted.

Knotting probabilities also depend to some extent on how we connect the two ends, and particularly on whether we apply the reduction process before or after closing the loop. The former

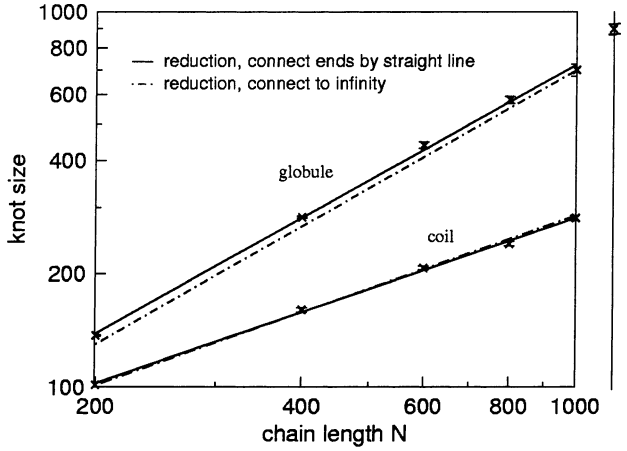

Figure 4. Average size (length of the knotted segment) of a trefoil knot in the globule and in the coil phase. The size appears to grow linearly with N for the globule and sub-linearly for the coil. All straight lines are power-law fits to the data. Crosses and closed line: Closure obtained from connecting the end monomers by a straight line after the application of the KMT reduction. Dash−dotted line: Closure obtained from connecting the end monomers to infinity after the application of the KMT reduction. The respective power-law exponents are 0.63 (coil) and 1.02 (globule) for the closure with the straight line and 0.65 (coil) and 1.04 (globule) for the attachment to infinity. The line on the right is marked with the size of a trefoil knot for a polymer of length $N = 1000$ under spherical confinement.

increases the likelihood of finding an unknotted chain. The discrepancies are, however, rather small and do not affect our qualitative findings: The difference in absolute probabilities is at most 10% for the globule and about 1% for the swollen phase (Figure 3).

Compactness not only increases the likelihood of finding knots, but also their complexity. In the coil phase, the few knots we observe are almost exclusively trefoils, whereas more complicated knots are present in the dense phase: For $N = 1000$, around 60% of all globules contain composite knots or knots with at least 5 crossings. Both frequency and complexity will continue to increase with chain length. However, we will probably need two more orders of magnitude in N to frequently observe single knots in the swollen phase. In globules of such lengths, the knotting complexity will be tremendous. Another gauge for complexity is the probability of observing no knots in the chain which is expected to decay as $\exp(-N/N_0)$.[5] Numerical simulations lead to $N_0 = 241$ for random polygons,[49] and $N_0 = 196$ for Hamiltonian walks.[24,23] A similar fit for the open polymers in our globular phase yields an estimate of 470−535 for N_0 depending on which knot definition we apply. This value should, however, only be considered with caution because it is sensitive to temperature (solvent quality) and finite-size effects.

The results for the size (length of the knotted segment) of the *trefoil knot* as defined by operations described in the previous section are depicted in Figure 4. We find that the knots are smaller in the coil than in the globule, the ratio getting smaller with increasing N. In the swollen phase, it is entropically favorable to restrict the knot to a limited region of the polymer. In the globule, there is no such gain as the whole structure is compact. Characterizing the size of the knot has garnered serious attention only in the past few years. The knot size can be rigorously defined for polymers absorbed on a two-dimensional surface, where exact scaling results are available. In this case, the distribution of knot sizes follows a power-law with an

universal exponent[36] that depends only on the phase of the polymer:[50] In the swollen (coil) phase, knots are small.[36] In the compact (globule) phase, typical knots are loose and spread out over the entire polymer.[50] The results in Figure 4 indicate similar trends in three dimensions. In the globule phase the average length of the knotted segment scales linearly with the chain length N, which is in qualitative agreement with recent studies on self-avoiding polygons.[51]

In the swollen phase knots are neither maximally tight (of the order of a few monomers), nor spread out, and the most frequent size is around seventy monomers. (There is another spike for sizes close to the polymer length which can be attributed to the closure procedure.) The value for the most likely size appears to be similar for all chain lengths, although statistics are somewhat poor. This is in qualitative agreement with results from a study on knot sizes in random loops.[38] However, without excluded volume the typical length of a knotted segment is considerably smaller (6−8 bonds).

A natural description for the average knot size in good solution is given by a power law increase with N. This is justified by the exact results in two dimensions,[36,50] and by a previous numerical study in three dimensions[52] employing an indirect measure of the knot size. The best fit to the data in Figure 4 indicates a sub-linear growth with an exponent of approximately 0.65. This lies between the previously reported values of 0.75 (for self-avoiding polygons[51]) and 0.4 (for a bead-tether model[52]). The simulations in Figure 4 only depict cases in which we reduce the configurations before joining the ends. As indicated, statistical errors are small (± 0.05), and the two closures yield similar results. However, if we close first, the exponent increases considerably, and the most likely size of a knot in the swollen phase becomes very small. A visual inspection reveals that these small knots exclusively depend on the connection of the end points and disappear without it. We therefore believe that the results reported in Figure 4 give a more faithful representation of typical trefoil sizes. Clearly, more work is needed to establish the universality and the exact value of this exponent. The qualitative statement, however, stands: While the size of the knotted region in good solution grows with increasing chain length, it occupies a progressively smaller fraction of the polymer.

Discussion

In summary, we suggest that all chainlike molecules with similar repetitive units become highly knotted in compact phases in agreement with refs 23, 24, and 26. On the basis of our model, we estimate that a single globular polyethylene molecule with a few thousand CH_2 groups is already knotted. Knots disappear once the polymer is allowed to expand due to a change in solvent conditions or a release from confinement (compare with refs 17 and 20). The time scale involved in the disentanglement is essentially the equilibration time, and it would be interesting to study the dynamics of this process. We have also attempted to characterize the number of monomers that form the knotted portion of the chain. For the trefoil, we find that the size is large (the knot is loose) in compact phases, and relatively small in good solvent conditions.

It is intriguing to consider the role of knots in entangled biological systems. In some cases, nature appears to have developed mechanisms to avoid knots altogether: Globular proteins are mostly unknotted,[13] although it is not entirely clear why. Human DNA is wrapped around histone proteins and phage DNA is usually coiled in its capsid. It was also argued that confined DNA has to be unknotted to preserve its function and can therefore be described as a "crumpled globule".[53] On the other hand, recent experiments suggest that the rather short (unanchored) DNA (10 kB pairs) strand in the P4 deletion mutants is highly knotted. Even in healthy phages some degree of entanglement exists, potentially forming knots if the ends were to be connected.[9] Otherwise, chances of finding a knot in a 10 kB DNA molecule which undergoes random cyclization in good solvent conditions are only a few percent.[11] Do entanglements and knots play any role in the ejection process? If so, to what extent are simple equilibration processes involved in the disentanglement afterward? Why have only few knots been found in globular proteins? These are just a few examples of questions which arise in the context of entangled biopolymers.

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