Diffusion-limited loop formation of semiflexible polymers: Kramers theory and the intertwined time scales of chain relaxation and closing

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Abstract. – We show that Kramers rate theory gives a straightforward, accurate estimate of the closing time $\tau_c$ of a semiflexible polymer that is valid in cases of physical interest. The calculation also reveals how the time scales of chain relaxation and closing are intertwined, illuminating an apparent conflict between two ways of calculating $\tau_c$ in the flexible limit.

The looping of polymers is a physical process that allows contact and chemical reaction between chain segments that would otherwise be too distant to interact. Polymer loops are particularly important in biology: In gene regulation, looping allows a DNA-bound protein to interact with a distant target site on the DNA, greatly multiplying enzyme reaction rates \cite{1,2}. Similarly, DNA looping in the 30 nm chromatin fiber may trigger the initiation of DNA replication at different sites along the DNA by enabling long-distance interactions \cite{3}. In protein folding, two distant residues start to come into contact via looping \cite{4,5}. Measurements of loop formation in single-stranded DNA segments with complementary ends have also been used to extract elasticity information (\textit{e.g.}, the sequence-dependent stiffness of single-stranded DNA \cite{6}).

Despite its importance and despite considerable theoretical effort, there are relatively few analytical results concerning the dynamics of loop formation. Even for the simplest case of an ideally flexible polymer with no hydrodynamic effects (or simply a Rouse chain), there are two rival theoretical approaches that lead to contradictory results: Szabo, Schulten, and Schulten (SSS) conclude that the time for a loop to form (“closing time” $\tau_c$) should scale for moderately large polymer lengths $L$ as $\tau_c \sim L^{3/2}$ \cite{7}, while Doi, applying Wilemski-Fixmann (WF) theory \cite{8}, finds $\tau_{\text{Doi}} \sim L^2$ \cite{9}. The discrepancy between the two continues to spur debate \cite{10,11}. For the important case of stiff chains \cite{12,13}, where the polymer length $L$ is not too much longer than the persistence length $\ell_p$, only limited numerical results are known (see, for example, \cite{14,15} and references therein). The main difficulty arises from the interplay between two seemingly distinct processes: chain relaxation and chain closure. This interplay is unique to a polymeric system and originates from the chain connectivity of a polymer immersed in a noisy environment.
In this article, we argue that Kramers’ rate theory [16,17] applies to the most physically relevant cases and leads to analytical results for $\tau_c$. We capture, for the first time, that there is a minimum loop-formation time for chain lengths of approximately $3–4\ell_p$. Roughly speaking, shorter chains require too much energy relative to the thermal energy $k_B T$, while longer chains need to search too many conformations for ends to “find” each other. We also show that consideration of the requirements for Kramers theory to apply leads one naturally to identify different regimes governing the closing time $\tau_c$. This classification shows how the physics of chain relaxation is intertwined with that of chain closing and clarifies the above-mentioned controversy between the SSS and Doi approaches to loop-formation dynamics.

Consider a chain of length $\ell \equiv L/\ell_p$ with two ends that react when first brought within a distance $a$ of each other (“diffusion-limited” loop formation dynamics). We apply Kramers rate theory, viewing the process as a noise-assisted “tunneling” over a potential barrier. After first presenting the straightforward calculation, we then consider carefully its domain of applicability, followed by a scaling description of loop formation outside this domain.

The basic idea is to project the internal degrees of freedom of the polymer chain onto a single “reaction coordinate” $r \equiv R/\ell_p$, with $R$ the end-to-end distance of the chain. The reduced, one-dimensional dynamics then obey a Langevin equation of the form

$$\frac{dr}{dt} = -\frac{D}{k_B T} \partial_r U(r, \ell) + \xi(t),$$

where $D = 2D_0$ is twice the diffusion coefficient of a monomer (both ends diffuse [10]) and $\xi(t)$ represents Gaussian white noise: $\langle \xi(t) \rangle = 0$ and $\langle \xi(t)\xi(t') \rangle = 2D\delta(t-t')$, with $\langle \ldots \rangle$ a thermal average. The dynamics are governed by an effective potential $U(r, \ell)$. Strictly speaking, this description is valid for a chain in local equilibrium, for which we can write

$$U(r, \ell) = -k_B T \ln P(r, \ell),$$

where $P(r, \ell) = 4\pi r^2 G(r, \ell)$ is the radial distribution function of end-to-end distances $r$ of a polymer of length $\ell$ and $G(r, \ell) \equiv G(|r_\ell - r_0|; \ell)$, the angle-averaged distribution function for the end-to-end vector $r = r_\ell - r_0$. We assume isotropic chemical interactions between end monomers, so that end binding can be modeled by adding to $U$ a smooth short-range potential $f(r/\alpha)$, with $\alpha \equiv a/\ell_p$ the interaction range. A typical distribution function and resulting effective potentials are shown in fig. 1.

Because polymers — whatever their stiffness — have a most probable end-to-end separation (radius of gyration), there is a local minimum in the effective potential at $r_0$ (bottom), which is $\sim \ell$ in the stiff-chain limit and $\sim \sqrt{\ell}$ in the flexible-chain limit, neglecting self-avoidance effects.
Also notice the barrier to chain closing at \( r_t \approx \alpha \) (top), which is created by the balance of chain entropy and bending energy as implied by \( U(r, \ell) \). The short-range attractive potential then rounds off the barrier. The resulting effective potential has thus the qualitative form often assumed in Kramers-rate calculations.

In the limit of strong damping \([18]\), the time needed to tunnel over the barrier (mean first-passage time), calculated using Kramers rate theory, is

\[
\tau_{Kr} = \left[ \frac{D}{k_B T} \frac{\omega_t \omega_b}{2\pi} \exp \left( -\frac{\Delta U}{k_B T} \right) \right]^{-1}, \tag{3}
\]

where the well curvatures \( \omega(r) = \frac{1}{\ell^2} \sqrt{\partial^2_r U(r, \ell)} \) are evaluated at the top and bottom of the effective potential \( U(r, \ell) \). The exponential factor is

\[
\exp \left[ -\frac{\Delta U}{k_B T} \right] = \frac{P(r_t, \ell)}{P(r_b, \ell)} \approx \frac{\alpha^2 G(0, \ell)}{G(r_b, \ell)} (\alpha \ll 1). \tag{4}
\]

We find the surprisingly simple result \([19]\)

\[
\tau_{Kr}(\ell) = C \frac{1}{\alpha D} \frac{\ell^2}{G_0(\ell)}, \tag{5}
\]

with \( G_0 \equiv G(0, \ell) \) and with \( C(r_b, G(r_b, \ell)) = \sqrt{2\pi}\ell^2G(r_b, \ell)/(6/\pi^2 \ell^4 - G''(r_b, \ell)/G(r_b, \ell))^{1/2} \) a dimensionless prefactor that is practically a constant for all \( \ell \) (see below).

Equation (5) shows that the closing time may be estimated using the static distribution \( G(r, \ell) \). Unfortunately, no analytic expression for \( G(r, \ell) \) has been found that is accurate for all \( r \) and \( \ell \), and one must make a pastiche of approximations. For \( r = 0 \) and \( \ell < 10 \), we use an approximation for a wormlike chain derived by Shimada and Yamakawa \([20, 21]\): \( G_0(\ell) = (896.32/\ell^3) \exp[-14.054/\ell + 0.246\ell] \). Note here that the \( 1/\ell \)-term in the exponent solely arises from bending energy, while the rest comes from chain fluctuations around the lowest-energy conformation. For \( r = 0 \) and large \( \ell \), we use an interpolative formula due to Ringrose et al. that blends SY with the result for a freely jointed chain, \( G_0(\ell) \sim \ell^{-3/2} \) \([22]\).

Near \( r = r_b \), we use an approximation derived by Thirumalai and Ha (TH) \([23]\), valid to 10%:

\[
G(r, \ell) = n(\ell)[1-(\xi)^2]^{-3/2} \exp[-3(1-(\xi)/[1-(\tau/\ell)^2]],
\]

with the normalization factor \( n(\ell) \) fixed by requiring \( \int_0^\ell 4\pi r^2 G(r, \ell) dr = 1 \). Note that a more accurate but more complicated expression recently derived by Winkler \([24]\) gives essentially the same results. Using TH, we find that the dimensionless prefactor \( C(\ell) \) of eq. (5) is \( O(10^{-1}) \), varying less than a factor of 2 over \( 0 < \ell < \infty \).

In fig. 2a, we plot the \( \tau_{Kr}(\ell) \) that results from eq. (5), using the various approximations to \( G(r, \ell) \) discussed above. The solid curve uses the Ringrose expression for all \( \ell \), while the dashed curved uses SY for small \( \ell \). The two curves compare well with recent simulations using parameters appropriate to double-stranded DNA \([14]\). Note that the material parameters of the simulation were used (see caption). Considering the heuristic nature of the arguments, the agreement is excellent.

One striking feature of the plot of \( \tau_{Kr}(\ell) \) is the existence of a minimum at \( \ell \approx 3.4 \), where

\[
\tau_{Kr}^* = 0.78 \frac{\ell^3}{D_0 a} \tag{6}
\]

In eq. (6), the prefactor 0.78 is calculated by Monte Carlo simulation of \( G(r, \ell) \), in units of seconds, and is about 10% less than the prefactor obtained using the TH approximation. As
Fig. 2 – Closing time $\tau_c$ vs. chain length. (a) BD simulation [14] (empty circles) and Kramers theory (eq. (5)) are shown. For direct comparison, we used the same parameters as in ref. [14] (bead size $= 3.18$ nm for $D = 2D_0 = 1.54 \times 10^{-11}$ m$^2$/s and $\alpha = 0.1$) with $\ell_p = 50$ nm. For $G_0(\ell)$, we used the SY result [20] and an interpolation [22] (see text). Relaxation times $\tau_R$ for these parameters are also shown (triangular symbols), with the $\ell^4$ and $\ell^2$ scaling regimes apparent in the inset. (b) Single-“particle” MC simulations of $\tau_c$ with the potential $U/k_B T = -\log[P(r, \ell)]$ taken from fig. 1b. Here, $\tau_c$ is a first-contact time averaged over about 2000 realizations of the initial position randomly selected from $P(r, \ell)$. We have chosen $\alpha = 0.25, 0.5, 0.75, 1.0$. As expected, $\tau_c \sim \ell^{3/2}$ (inset).

mentioned above, the existence of a minimum in $\tau_{Kr}$ reflects a balance between the energy of bending and the entropy of conformations that must be searched for two ends to meet.

For the above Kramers-rate calculation to hold so that $\tau_{Kr}$ equals $\tau_c$, three conditions must be satisfied: The damping must be sufficiently strong; the barrier height $\Delta U$ must be large compared to $k_B T$; and the global chain relaxation time $\tau_R$, a characteristic time scale for chain deformation, must be much shorter than the Kramers time $\tau_{Kr}$.

The first condition is normally satisfied for molecules in solution [18]. For the second, since there is a minimum in the effective potential at $r_h$, we require that $\alpha$ be sufficiently less than $r_h$ so that the barrier height is large. The condition $\Delta U/k_B T = 1$ is shown in fig. 3 as a dotted line in the $(\ell, \alpha)$-parameter-plane, using a diffusion constant appropriate to double-stranded DNA. To the left of the dashed line, the barrier height is larger than $k_B T$.

The third condition, $\tau_R \ll \tau_{Kr}$, is more subtle and requires discussion. In using a “one-particle” description of chain closing dynamics, we are assuming that all internal degrees of freedom of the polymer chain have relaxed. As a result, the end-to-end distance is the only

Fig. 3 – Scaling regimes in the $(\ell, \alpha)$-plane for DNA (see text). Region I is the Kramers regime, with $\tau_c > \tau_R$; region II is the dynamic-fluctuation regime. In the primed regions to the right of the dashed line, $\Delta U/k_B T < 1$. The black region is unphysical: $\alpha > L$. 
dynamic variable (cf. eq. (1)). This assumption of local equilibrium allows one to apply the equilibrium distribution function $G(r, \ell)$ and implies that the effective potential derived from $G$ is time independent. If the chain relaxation times are too long, the potential effectively becomes time dependent and has to be obtained self-consistently, along with the motion of the internal modes. We thus compare the scaling behavior of $\tau_R(\ell)$ with $\tau_K(\ell)$ and $\tau_c(\ell)$ in both the flexible ($\ell \gg 1$) and stiff-chain ($\ell < 1$) limits.

In the flexible limit, we can use the Rouse model to estimate the longest relaxation time, which gives $\tau_R \sim \ell^2$, in units of the basic time scale $\ell_p^2/D$. By contrast, at large $\ell$, eq. (5) gives $\tau_K \sim \ell^{3/2}/\alpha$. (This is just the result of SSS [7,10] and has been confirmed by single-"particle" simulations — see fig. 2(b) and the caption.) Thus, when $\ell > 1/\alpha^2$, the third condition is violated and the Kramers calculation does not hold. Nonetheless, we can still estimate the upper limit of $\tau_c$: The closing time is at most a time necessary for the slowest "random walker" to travel, with diffusion constant that of the entire chain $D_{\text{chain}} \sim D/l$, the end-to-end distance. Since $r \sim \sqrt{\ell}$, we have $\tau_c \lesssim r^2/D_{\text{chain}} \sim \ell^2/D \sim \tau_R$. In other words, when the third condition does not hold, $\tau_c$ is not $\tau_K$, but is set by the Rouse time $\tau_R$.

In the stiff limit, the physics is dominated by the bending energy $E_b$ of a rod [25], leading simultaneously to faster relaxation times $\tau_R$ and higher-energy barriers, which implies that the Kramers calculation should be valid. To see this, recall that the bending energy of an elastic rod is, by symmetry, proportional to the square of the rod curvature. Since the lowest energy corresponds to a uniform curvature of radius $R$, the bending energy near the rod limit $E_b/k_B T = (1/2)\ell_p L/R^2 \sim 2\ell_p (L - R)/L^2$.

Thus, if we track the relative separation $R$ of the endpoints of a thermally excited rod, it behaves like a particle subject to a constant restoring force $f_c = 2k_B T \ell_p/L^2$. The appropriate Langevin equation for $R$ is then of the form $\dot{R} + \frac{D_{\text{chain}}}{k_B T} f_c \frac{R}{R} = \xi(t)$, with $\xi(t)$ the random force. This implies that the time to relax a distance of order $L$ is $k_B T L / D_{\text{chain}} f_c = L^3/2\ell_p D_{\text{chain}}$. Since the rod moves coherently, the diffusion coefficient of the chain $D_{\text{chain}} \sim D b/L$, leading to $\tau_R \sim L^4 / (2\ell_p T)$, where $b$ is the monomer size. As a result, for $L < \ell_p$, the third condition ($\tau_R \ll \tau_K$) is always satisfied: the lower-limit of $\tau_c$ is given by a time scale for a random walk to travel a distance $R \sim L$, thus $\tau_K \gg \tau_c \gtrsim R^2/D_{\text{chain}} \sim L^3/b D > L^3/\ell_p b D \gtrsim \tau_R$.

To summarize, $\tau_R \sim L^4$ for $\ell < 1$ and $\sim L^2$ for $\ell \gg 1$. Thus, for large enough $\ell$, $\tau_R$ becomes larger than the Kramers estimate [26], as shown in fig. 2a and in the inset. In fig. 3, we plot $\tau_R(\ell) = \tau_K(\ell)$ in the $(\ell, \alpha)$-plane. The white area is region I (Kramers regime), where $\tau_K > \tau_R$, and therefore $\tau_c \sim \tau_K$. The shaded area is region II ("dynamical fluctuation" regime, see below), where $\tau_K < \tau_R$, and therefore $\tau_c \sim \tau_R$. Areas I′ and II′ show where $\Delta U < k_B T$. The black region, defined by $\alpha > \ell$, is unphysical.

In region II, the relaxation and closing processes are coupled. In this case, one may have to solve an $N$-particle diffusion problem, subject to a boundary condition that is difficult to impose [8–10]. Nevertheless, much insight can still be obtained from the simple scaling analysis of random walks given above. In this view, a chain can close because the two ends randomly meet each other while freely relaxing. The existence of such a regime, where $\tau_c \sim \tau_R$, is a unique feature of flexible chains (fig. 3) that we denote the "dynamical fluctuation" regime — the dynamic fluctuation $\delta R(t) \equiv \sqrt{\langle[R(t) - R(0)]^2 \rangle}$ grows up to $R$ as $t \to \tau_R$ and thus can assist chain closing. For a Rouse chain, $\delta R(t)$ can be given as a sum of Rouse modes [27] and, in our simple scaling analysis, $\tau_c$ can be inferred by analyzing this. Short-time behavior of $\delta R(t)$ reflects the internal motion and varies as $\delta R(t) \sim \sqrt{t}$ for $t \ll \tau_R$. We, however, argue that this will not appreciably influence $\tau_c$, as $\delta R(t) \to R$ only when $t \to \tau_R$. In other words, $\tau_c$ is governed by the slowest mode and our assertion of $\tau_c \sim \tau_R$ will not be invalidated by the internal motion, which is important at time scales much smaller than $\tau_c$ (or $\tau_R$). In the stiff-
chain limit, this dynamical fluctuation regime disappears. Note that the boundaries between regions I and II are not sharp but are crossovers. Loop-formation kinetics in the crossover area will likely combine aspects of both regimes, as indicated in recent simulations [10] and by results that show that $\tau_{SSS}$ and $\tau_{Doi}$ are, respectively, lower and upper bounds for $\tau_c$ [11]. Similarly, based on their BD simulation results, Podtelezhnikov et al. [28] suggested that $\tau_c \simeq \tau_R/\alpha$ near the boundaries.

Our discussion has neglected hydrodynamic effects and excluded-volume interactions. Both can influence chain relaxation and closing simultaneously. The hydrodynamic effect will not change $\tau_{Kr}$, since it is a function of the equilibrium distribution $G(r,l)$. However, the hydrodynamic interaction tends to promote chain relaxation (e.g., in the Zimm model, $\tau_R \sim l^{3/2}$, in contrast to $\tau_R \sim l^2$ in the Rouse model considered here [27]) by increasing the mobility of the chain, resulting in a wider Kramers regime than implied by fig. 3. On the other hand, the excluded-volume interaction both decreases $D_{\text{chain}}$ and reduces $G_0$ [27, 29]. But for loops of just a few persistence lengths, which are the most physically relevant (see below), both effects are expected to be minor. A final caveat is that we have assumed isotropic binding interactions. While mathematically simpler and relevant to simulations [14], most real polymers have directional bonding. In the Kramers calculation, this would modify $G_0(l)$.

The Kramers calculation holds in region I of the $(l, \alpha)$-parameter-space shown in fig. 3. What are the physically relevant values of $\alpha$ and $l$? The interaction distance $a = \alpha l_p$ will be the thickness of the polymer, or less. For polymers of biological interest, the persistence length will be typically at least this size and often much larger. For example, for double-stranded DNA, the monomer size is 0.34 nm, while the persistence length is 50 nm. For chromatin, the thickness is 30 nm, comparable to its persistence length [30]. Thus, we generally expect $\alpha < 1$ and sometimes $\alpha \ll 1$.

What are the relevant values of $l$? Although polymers in principle may have any length, the existence of a minimum closing time $\tau^*_Kr$ (eq. (6)) leads one to speculate that where looping is biologically relevant, polymer lengths near $l \approx 3–4$ might be favored because they minimize $\tau_c$. In this regime, the Kramers calculation will be valid, for small $\alpha$. Thus, biological selectivity may arise from a physical mechanism. For example, a recent study of Jun et al. [3] on DNA replication noted that the typical spacings between replication origins in early embryo Xenopus are 3–4 times the $l_p$ of chromatin, the DNA-protein complex present during replication. It is then natural to speculate that origins are related by looping and that the spacing may be selected to maximize the contact rate of origins, optimizing replication efficiency.

In conclusion, we have shown that Kramers rate theory gives a straightforward estimate of the closing time of a semiflexible polymer. Although phenomenological, the calculation explains the existence of a minimum closing time and accurately reproduces numerical simulations. Moreover, considering the requirements for the calculation to hold shows how the intertwining of the relaxation time with the closing time explains the apparently conflicting results for $\tau_c$ (SSS and Doi). Fortunately, the physically relevant cases are precisely the ones where the Kramers calculation is expected to hold and may even be selected biologically through evolution.

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\[
\tau_K = \frac{D}{k_BT} \frac{\alpha}{\pi} e^{-\frac{\Delta A}{k_BT}} \left( 1 + \sqrt{1 + \frac{4mD^2\omega^2}{(k_BT)^2}} \right).
\]

The correction term \( \frac{4mD^2\omega^2}{(k_BT)^2} \) is \( \approx 10^{-7} \) for DNA monomers and can be neglected, justifying our use of the strong-damping limit (eq. (3)).

For a smooth short-range potential of range \( \alpha \), the curvature at the top must be \( \sim 1/\alpha \) by dimensional analysis. We note that many simulations assume reaction upon first passage through the distance \( \alpha \). Despite the seeming difference between our Kramers' approach and simulations that track the time for particle ends to first pass through the \( r = \alpha \) sphere, the “particle” (in a single-particle picture) in both cases is not allowed to equilibrate within the reactive region \( r \approx \alpha \). Thus, in each case, one expects \( \tau_c \sim 1/\alpha \) for \( \alpha \ll 1 \) (cf. eq. (5)). If we had assumed kinetic-limited looping, then the particle would sample most of the reactive region, resulting in \( \tau_c \sim 1/\alpha^2 \) [7].

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