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Di usion-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 τ_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 τ_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 [1,2]. Similarly, DNA looping in the 30 nm chromatin fiber may trigger the initiation of DNA replication at di erent sites along the DNA by enabling long-distance interactions [3]. In protein folding, two distant residues start to come into contact via looping [4,5]. Measurements of loop forml?Glzc:[D[EExc?'xginsSqctio]g [DEgvszgsF-race-gtsrandeeinsx5gbs]xDqgy [DMs s th]zc:[a b

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 o the barrier. The resulting e ective 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

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

where the well curvatures $\omega(r) = \frac{1}{\ell_p} \sqrt{\partial_{rr} U(r, \ell)}$ are evaluated at the top and bottom of the e ective potential $U(r, l)$. The exponential factor is

$$\exp\left[-\frac{\Delta U}{k_B T} \right] = \frac{P(r_t, \ell)}{P(r_b, \ell)} \simeq \frac{\alpha^2 G(0, \ell)}{r_b^2}$$

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 e ective potential derived from G is time independent. If the chain relaxation times are too long, the potential e ectively 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 $\tau_{\rm R}(\ell)$ with $\tau_{\rm Kr}(\ell)$ and $\tau_{\rm c}(\ell)$ in both the flexible ($\ell \gg 1$) and sti -chain ($\ell < 1$) limits.

In the flexible limit, we can use the Rouse model to estimate the longest relaxation time, which gives $\tau_{\rm R} \sim \ell^2$, in units of the basic time scale $\ell_{\rm p}^2/D$. By contrast, at large ℓ, eq. (5) gives $\tau_{\rm Kr} \sim \ell^{3/2}/\alpha$. (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 $\tau_{\rm c}$: The closing time is at most a time necessary for the slowest "random walker" to travel, with di usion constant that of the entire chain $D_{\rm chain} \sim D/RRtn$

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 τ_{SSS} and τ_{Doi} are, respectively, lower and upper bounds for τ_c [11]. Similarly, based on their BD simulation results, Podtelezhnikov *et al.* [28] suggested that $\tau_c \simeq \tau_R/\alpha$ near the boundaries.

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[19] For a smooth short-range potential of range α, the curvature at the top must be $1/\alpha$ by dimensional analysis. We note that many simulations assume reaction upon first passage through the distance α. Despite the seeming di erence 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 $\tau_{\rm c}$ $1/\alpha$ for α 1 (cf. eq. (5)). If we had assumed kinetic-limited looping, then the particle would sample most of the reactive region, resulting in $\tau_{\rm c}$ $1/\alpha^2$ [7].
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