

## Cyclization of a Polymer: First-Passage Problem for a Non-Markovian Process

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(Received 8 July 2002; published 26 February 2003)

We discuss a closure of a polymer chain released from a state with given end-to-end distance. Considering the situation as a first passage problem for a non-Markovian process, we express the survival probability through the three-time distribution of the end-to-end distance and evaluate it numerically by solving a Volterra equation. We also show how the Wilemski-Fixmann approximation emerges within this scheme and discuss its geometrical nature.

DOI: 10.1103/PhysRevLett.90.080601

PACS numbers: 05.40.-a, 82.35.-x

Kinetics of reactions involving polymers (especially the luminescent energy transfer) has attracted much theoretical attention in the last decade (see, e.g., [1,2]), due to experimental relevance and to a plenitude of applications. Diffusion-controlled regimes of such reactions differ considerably from diffusion-controlled reactions of small molecules: The reason for this is that the linear memory of a molecule introduces strong temporal correlations in the positions of reacting entities. The approaches used in chemical kinetics for decades neglect important details of such correlations and fail to provide a reasonable description. Cyclization of a single polymer molecule belongs to the most complex problems in the field: In this case the reaction takes place in a system exhibiting non-Markovian behavior on the time scales of interest; the time scale separation, saving the situation in many other cases, does not take place [3–8]. The problem of cyclization equivalently describes luminescence quenching in a system of a donor and acceptor, or fluorescence resonance energy transfer (FRET) between the fluorescence dye molecules attached to the ends of a polymer. The fluorescence self-quenching is a valuable instrument in the studies of single-molecule dynamics, as exemplified by protein folding (see, e.g., [9]). Recent success in micro-manipulation of polymers makes the time-resolved measurements especially interesting and moreover poses a new problem of description of kinetic behavior under given microscopic initial conditions (say a given end-to-end distance).

The strongly non-Markovian nature of the problem involving multiple characteristic time scales mirrors the fact that the reaction takes place in a many-particle system. This makes tempting “reductionist” approaches starting from the full description of the monomers’ motion (at which level the dynamics is Markovian), and then reducing the description to a relevant set of variables [3–8]. However, even for the simplest situation of a Rouse chain, the existing theoretical approaches fail to give an exact description of the situation and rely on additional assumptions. Their domain of applicability is inevitably restricted as proved by direct numerical simulations [7].

The methods of Refs. [3,4,6,8] follow the Smoluchowski approach: The reaction probability is given by the solution of the diffusion equation with a sink term. For reactions taking place with probability 1 on contact, introducing a sink is equivalent to posing an absorbing boundary condition  $P(|\mathbf{r}| - a) = 0$ , where  $\mathbf{r} = \mathbf{R}_0 - \mathbf{R}_N$  gives the relative position of the chain’s ends. Such problem can be reformulated as the first-passage problem from the initial distance  $r = r_0$  between the ends to  $r = a$  [5,7]. In the Markovian case first-passage problems can be solved using an alternative approach [10] based on the renewal property. This approach can be generalized to the non-Markovian situation, and this is the way we proceed.

Since the reaction process depends only on the absolute value  $r = |\mathbf{r}|$ , the problem is essentially one dimensional. Moreover, the trajectories of our process are continuous, just as the trajectories of the usual Wiener process are (*vide infra*). Let us consider the relation between the distribution of the first-passage time to a sphere of the radius  $r = a$  around the origin of the coordinates  $F(a, t | r_0, 0)$  and the conditional probability for the ends to be found at distance  $r$ : If the trajectory starts at point  $r_0$ , and is found at  $r$  at time  $t$ , it may have already visited  $r$  before, at some time  $t' < t$ , departed and returned. Taking the return probability to be independent from initial conditions leads to Markovian approximations (such as the WF one). In general, initial conditions have to be explicitly taken into account. Thus, the conditional probability to be at  $r$  at time  $t$ , provided the particle started at  $r_0$  at time  $t = 0$ ,  $G(r, t | r_0, 0)$ , is given by the following equation:

$$G(r, t | r_0, 0) = \delta(r - r_0)\delta(t) + \int_0^t F(r, t' | r_0, 0)G(r, t | r, t'; r_0, 0)dt', \quad (1)$$

where  $G(r, t | r, t'; r_0, 0)$  is the conditional probability to be at  $r$  at time  $t$ , provided  $r$  was visited earlier at time  $t'$  and that the particle started at  $r_0$  at  $t = 0$ . If  $r_0 \neq r$ , the  $\delta$  term can be omitted. For a Markovian process  $G(r, t | r, t'; r_0, 0) \equiv G(r, t | r, t')$ , so that Eq. (1) reduces to a renewal equation for the first-passage time [10].

Now, according to the Bayes formula,  $G(r, t | r_0, 0) = P(r, t; r_0, 0)/P(r_0, 0)$  and  $G(r, t | r, t'; r_0, 0) = P(r, t; r, t'; r_0, 0)/P(r, t'; r_0, 0)$  where  $P(r_0, 0)$ ,  $P(r, t; r_0, 0)$ , and  $P(r, t; r, t'; r_0, 0)$  are the probability distributions of the end-to-end distances at one-, two- and three different times. The one-dimensional distributions as functions of  $r$  can be expressed as  $P(r, t | r_0, 0) = \int_S ds P(\mathbf{r}, t; \mathbf{r}_0, 0)$  and  $P(r, t; r, t'; r_0, 0) = \int_S \int_S ds ds' P(\mathbf{r}, t; \mathbf{r}, t'; \mathbf{r}_0, 0)$ , where  $S$  is the surface of the sphere of radius  $r$ . The dependence on  $\mathbf{r}_0$  reduces to the dependence on  $r_0$  due to the spherical symmetry. Equation (1) now reads

$$\frac{\int_S ds P(\mathbf{r}, t; \mathbf{r}_0, 0)}{P(r_0, 0)} = \int_0^t F(r, t' | r_0, 0) \times \frac{\int_S \int_S ds ds' P(\mathbf{r}, t; \mathbf{r}, t'; \mathbf{r}_0, 0)}{\int_S ds' P(\mathbf{r}', t'; \mathbf{r}_0, 0)} dt' \quad (2)$$

(where  $|\mathbf{r}_0| > r$ ). We rewrite this equation in the following form:

$$\int_0^t F(r, t' | r_0, 0) Q(t, t', r_0) dt' = 1, \quad (3)$$

with the kernel

$$Q(t, t', r_0) = \frac{\int_S \int_S ds ds' P(\mathbf{r}, t; \mathbf{r}, t'; \mathbf{r}_0, 0) P(\mathbf{r}_0, 0)}{\left[ \int_S ds' P(\mathbf{r}', t'; \mathbf{r}_0, 0) \right] \left[ \int_S ds P(\mathbf{r}, t; \mathbf{r}_0, 0) \right]}. \quad (4)$$

A system we have in mind is a Rouse chain of beads and springs immersed into a viscous fluid. The beads experience friction and random forces due to the thermal motion of the solvent molecules. The positions of beads can be expressed as sums over independent modes of motion (Rouse modes) whose amplitudes are governed by Ornstein-Uhlenbeck processes [11], i.e., correspond to a motion in effective harmonic potentials under the influence of thermal noise. All joint probability distributions for amplitudes of each mode at different times are Gaussian. This is also true for the sums over independent modes entering the end-to-end distance. Thus, all such distributions are (multivariate) Gaussian, a property shared by a large class of so-called generalized Gaussian structures [12].

The one-time density (the equilibrium distribution of the end-to-end distance in a chain) is

$$P(\mathbf{r}, 0) = [2\pi L^2]^{-3/2} \exp[-(r^2/2L^2)], \quad (5)$$

with  $L^2 = \langle x^2 \rangle = \langle y^2 \rangle = \langle z^2 \rangle = b^2 N/3$ , where  $b$  is the effective segment length.

A multivariate Gaussian distribution is fully determined by its covariance matrix. For example, the joint

probability distribution of the relative position of the ends at two times, 0 and  $t$ , is given by

$$P(\mathbf{r}', t; \mathbf{r}, 0) = \frac{(2\pi)^{-3}}{\sqrt{\det \hat{\mathbf{B}}}} \exp\left(-\frac{1}{2} \mathbf{R} \hat{\mathbf{B}}^{-1} \mathbf{R}\right), \quad (6)$$

where  $\mathbf{R} = \{R_i\}$  is a 6-component vector [ $x'(t), y'(t), z'(t), x(0), y(0), z(0)$ ] and the covariance matrix  $\hat{\mathbf{B}}$  has the elements  $B_{ij} = \langle R_i(t) R_j(0) \rangle$ . The diagonal elements of this matrix are all equal:  $B_{ii} = \langle R_i^2 \rangle = L^2$ . For the Rouse chain, the only other nonzero elements correspond to the correlations of the same coordinates at different times  $\langle x(t)x(0) \rangle = \langle y(t)y(0) \rangle = \langle z(t)z(0) \rangle = L^2 \phi(t)$ . The cross correlations of different coordinates vanish. The matrix  $\hat{\mathbf{B}}$  thus has a block-diagonal form

$$\hat{\mathbf{B}} = L^2 \begin{bmatrix} \mathbf{I} & \mathbf{D}(t) \\ \mathbf{D}(t) & \mathbf{I} \end{bmatrix}, \quad (7)$$

where  $\mathbf{I}$  is a  $3 \times 3$  unit matrix and  $\mathbf{D}(t) = \hat{\mathbf{I}} \phi(t)$ . The form of the correlation function  $\phi(t)$  follows from the picture of modes [11]: For a long enough chain ( $N \gg 1$ )

$$\phi(t) = \frac{8}{\pi^2} \sum p^{-2} \exp(-p^2 t / \tau_R), \quad (8)$$

where the summation runs over odd integers  $p$  and  $\tau_R$  is the Rouse time,  $\tau_R = N^2 b^2 / 3\pi^2 D_0$ , with  $D_0$  being a diffusion coefficient of a single monomer. The function  $\phi(t)$  shows how fast the initial positions of the ends are forgotten:  $\langle [x(t) - x(0)]^2 \rangle = 2L^2 [1 - \phi(t)]$  is continuous and tends to zero for  $t \rightarrow 0$  (this fact verifies the continuity of trajectories) and to  $2L^2$  [corresponding to the statistical independence of  $x(t)$  and  $x(0)$ ] for  $t \gg \tau_R$ .

The three-time joint probability distribution is

$$P(\mathbf{r}, t; \mathbf{r}, t'; \mathbf{r}_0, 0) = \frac{(2\pi)^{-9/2}}{\sqrt{\det \hat{\mathbf{A}}}} \exp\left(-\frac{1}{2} \mathbf{R} \hat{\mathbf{A}}^{-1} \mathbf{R}\right), \quad (9)$$

where  $\mathbf{R} = (x, y, z, x', y', z', x_0, y_0, z_0)$  has nine components and the covariance matrix  $\hat{\mathbf{A}}$  consists of nine diagonal blocks:

$$\hat{\mathbf{A}} = L^2 \begin{bmatrix} \mathbf{I} & \mathbf{D}(t-t') & \mathbf{D}(t) \\ \mathbf{D}(t-t') & \mathbf{I} & \mathbf{D}(t') \\ \mathbf{D}(t) & \mathbf{D}(t') & \mathbf{I} \end{bmatrix}. \quad (10)$$

The number of beads  $N$  enters the equations only through  $L^2 \propto N$  and through  $\tau_R \propto N^2$ . Considering chains of different lengths corresponds to rescaling the time and length units. The first-passage time pdf  $F(t, a, r_0, N)$  can thus be expressed through the function of three nondimensional variables:  $F(t, a, r_0, N) = \tau_R^{-1} p(t/\tau_R, a/r_0, r_0/L)$ . In what follows we take  $L$  and  $\tau_R$  as new time and length units.

The integrals over the two-point functions can be evaluated analytically:

$$\int_S ds P(\mathbf{r}, t; \mathbf{r}_0, 0) = \frac{2a^2 \exp\left[-\frac{\phi(0)(a^2+r_0^2)}{2[\phi^2(0)-\phi^2(t)]}\right] \sinh\left[\frac{ar_0\phi(t)}{[\phi^2(0)-\phi^2(t)]}\right]}{\pi a r_0 \phi(t) \sqrt{\phi^2(0) - \phi^2(t)}}. \quad (11)$$

Calculating  $\int_S \int_S ds ds' P(\mathbf{r}, t; \mathbf{r}, t'; \mathbf{r}_0, 0)$  we can analytically perform integration over the azimuthal angles so that the corresponding distribution reduces to

$$P(r, t; r, t'; r_0, 0) = \frac{a^4}{(2\pi)^{5/2} A^{3/2} \{\phi\}} \exp\left[-\frac{a^2(2\phi_0^2 - \phi_2 - \phi_3) + r_0^2(\phi_0^2 - \phi_1^2)}{2A\{\phi\}}\right] \\ \times \int_0^\pi \int_0^\pi I_0\left[\frac{a^2 \sin\psi \sin\vartheta(\phi_0\phi_1 - \phi_2\phi_3)}{A\{\phi\}}\right] \exp[f(a, r_0, \{\phi\})] \sin\psi \sin\vartheta d\psi d\vartheta, \quad (12)$$

where  $\vartheta$  and  $\psi$  are the polar angles and  $I_0$  denotes a modified Bessel function. Here  $A\{\phi\} = \phi_0^3 + 2\phi_1\phi_2\phi_3 - \phi_0(\phi_1^2 + \phi_2^2 + \phi_3^2)$  and  $f(a, r_0, \{\phi\}) = \{a^2 \cos\psi \cos\vartheta(\phi_2\phi_3 - \phi_0\phi_1) + ar_0[(\phi_1\phi_2 - \phi_0\phi_3) \times \cos\vartheta + (\phi_1\phi_3 - \phi_0\phi_2) \cos\psi]\}/A\{\phi\}$ , where  $\phi_0 = \phi(0)$ ,  $\phi_1 = \phi(t - t')$ ,  $\phi_2 = \phi(t)$ , and  $\phi_3 = \phi(t')$ .

We note that the forms, Eqs. (5), (11), and (12), are universal and apply to any Gaussian model, whether linear or branched chain, or a network; only the particular forms of the correlation function  $\phi(t)$  differ.

Equation (3) can be solved numerically by approximating the integral by a finite sum. The corresponding first-passage time distributions are shown in Fig. 1 for the initial distances  $r_0 = 1, 2, 4$ , and 8 and for  $a = 0.1$ . The numerical accuracy of the results is around 1%. With a decrease in the initial distance, the typical mean first-passage time decreases very fast; the maximum of the curve corresponding to  $r_0 = 1$  lies around  $t_{\max} \simeq 0.01$ , and is not resolved on the scales of Fig. 1. This effect is due to the fast small-scale motion corresponding to higher modes [4,6] and mirrors the compact exploration of space by the chain's end. On the other hand, the large-scale relaxation is mostly connected with the lowest mode, which is slow.

Let us now discuss the emergence of the WF approximation within our scheme and estimate the accuracy of this approximation. The WF approximation corresponds to taking  $G(r, t | r, t'; r_0, 0) \simeq G(r, t | r, t')$  in Eq. (1),

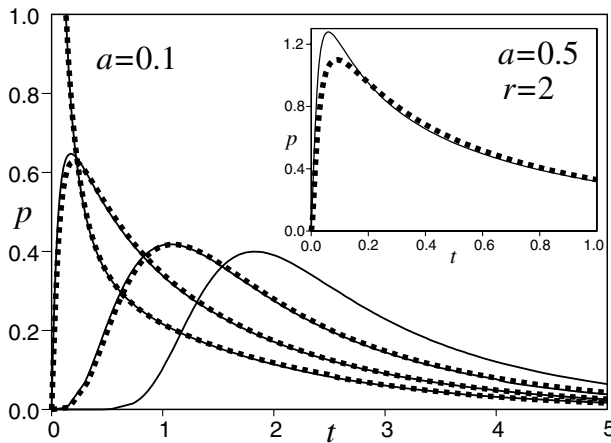


FIG. 1. The first passage time pdf's for  $a = 0.1$  and  $r_0 = 1, 2, 4$ , and 8 (from left to right). The solid curves correspond to the solution of Eq. (3) with the exact kernel, Eq. (4). The dotted lines (shown for  $r_0 = 1, 2, 4$ ) correspond to the WF approximation, Eq. (13). The inset shows the case  $a = 0.5$  and  $r_0 = 2$ .

which, in the language of  $P$  is  $P(\mathbf{r}, t; \mathbf{r}, t'; \mathbf{r}_0, 0) \simeq P(\mathbf{r}, t; \mathbf{r}, t')P(\mathbf{r}_0, 0)$  and  $P(\mathbf{r}', t'; \mathbf{r}_0, 0) \simeq P(\mathbf{r}', t')P(\mathbf{r}_0, 0)$ , i.e., to the approximation of the kernel  $Q$  by

$$Q_{WF}(t, t', r_0) = \frac{\int_S \int_S ds ds' P(\mathbf{r}, t; \mathbf{r}, t') P(\mathbf{r}_0, 0)}{\left[ \int_S ds' P(\mathbf{r}', t') \right] \left[ \int_S ds P(\mathbf{r}, t; \mathbf{r}_0, 0) \right]}. \quad (13)$$

Note that this approximation has a purely geometrical nature, it assumes that the distance from  $\mathbf{r}_0$  to all points on  $S$  is approximately the same and uses the mean value theorem in evaluating the two of the integrals in Eq. (4). The assumption is asymptotically exact for  $r_0 \rightarrow \infty$  and delivers a low-order expression in  $\alpha = a/r_0$ . One can thus suppose that its accuracy will be good for  $\alpha$  small and will decrease for large  $\alpha$ .

The solutions of Eq. (3) with the kernel  $Q_{WF}$  are shown in Fig. 1 for  $r_0 = 1, 2$ , and 4 with dashed lines. These results show that the approximation performs excellently up to  $\alpha = 0.1$ . However, the discrepancies grow when  $\alpha$  gets larger: In an example shown in the inset ( $\alpha = 0.25$ ) we find that the height of the maximum is underestimated by 15% on the cost of the somewhat fatter tail of the distribution; for  $a = 0.75$  ( $\alpha = 0.375$ , not shown) the height of the maximum is underestimated by almost 1/4. Thus, the WF approximation fails to reproduce the exact kinetic curves when  $\alpha$  get large. However, the mean first-passage times  $\tau$  are still given with high accuracy: the value of  $\tau$  is overestimated only by around 3% for  $\alpha = 0.25$  and by around 5% for  $\alpha = 0.375$ .

We now show how the usual equations of the Wilemski-Fixmann theory (ones averaged over the distribution of the starting points) appear from the decoupling approximation. To do this we return to Eq. (2), now reading as

$$\frac{\int_S ds P(\mathbf{r}, t; \mathbf{r}_0, 0)}{P(\mathbf{r}_0, 0)} = \int_0^t F(r, t' | r_0, 0) \\ \times \frac{\int_S \int_S ds ds' P(\mathbf{r}, t; \mathbf{r}, t')}{\int_S ds' P(\mathbf{r}', t')} dt', \quad (14)$$

and average both sides over the equilibrium distribution of  $r_0$ ,  $P(r_0, 0)$ . Since the function multiplying  $F$  under the integral in the right-hand side does not depend on  $r_0$ , only  $F$  is averaged, giving the averaged first-passage distribution  $\bar{F}$ . The average in the left-hand side is a one-time marginal distribution, i.e.,  $\int_S ds P(\mathbf{r}, t)$ . Thus, the equation for  $\bar{F}$  reads as follows:

$$\int_0^t \bar{F}(r, t' | r_0, 0) \frac{\int_S \int_S ds ds' P(\mathbf{r}, t; \mathbf{r}', t')}{\int_S ds P(\mathbf{r}, t) \int_S ds' P(\mathbf{r}', t')} dt' = 1. \quad (15)$$

Assuming the process  $\mathbf{r}(t)$  to be stationary we denote  $\int_S \int_S ds ds' P(\mathbf{r}, t; \mathbf{r}', t') = C(t - t')$ . Because of correlation decoupling at long time,  $\int_S ds P(\mathbf{r}, t) \int_S ds' P(\mathbf{r}', t')$  is exactly  $C(\infty) = C_\infty$ . Thus, we can rewrite Eq. (15) as  $\int_0^t \bar{F}(r, t' | r_0, 0) C(t - t') / C_\infty dt' = 1$ . Applying the Laplace transform to the both sides of the equation, we get  $\tilde{F}(u) \tilde{C}(u) / C_\infty = 1/u$ , so that  $\tilde{F}(u) = C_\infty / [u \tilde{C}(u)]$ . Moreover, since  $C_\infty = \lim_{t \rightarrow \infty} C(t)$ , for  $u$  small one has  $\tilde{C}(u) = C_\infty / u + A + \dots$ , with  $A = \lim_{u \rightarrow 0} [C(u) - C_\infty / u]$ . Since the mean first-passage time is given by  $\tau = \int_0^\infty t F(t) dt = -\frac{d}{du} \tilde{F}(u) |_{u=0}$ , one obtains

$$\tau = \frac{A}{C_\infty} = \int_0^\infty \left[ \frac{C(t)}{C_\infty} - 1 \right] dt, \quad (16)$$

which is exactly Eq. (12) of Ref. [7]. The approach of Ref. [5] is an approximation of the same nature as the WF one: It assumes that the random process  $r(t)$  is an Ornstein-Uhlenbeck process (the only one Gaussian Markovian process, the one with  $\phi(t) \simeq \exp(-\gamma t)$ , with  $\gamma = 2/\tau_R$  [7]), for which Eq. (14) is exact. Compared to the WF-theory it contains an additional assumption, namely, one of the exponential relaxation.

Compared to the general case, our solution applies to a rather special sink function (a  $\delta$  sink). Let us say a few words on general sink functions. In the WF-theory one has  $C(t - t') = \int_V \int_V d\mathbf{r} d\mathbf{r}' S(\mathbf{r}) S(\mathbf{r}') P(\mathbf{r}, t; \mathbf{r}', t')$ , where  $S(\mathbf{r})$  characterizes the sink strength. Although such expressions have no immediate counterparts within the first-passage time formalism, they can be obtained as mean-field approximations when one associates  $S(\mathbf{r})$  with the density of absorbing regions. In this case, the corresponding surface integrals in Eq. (15) are changed for the volume integrals weighted with the sink function. The same approximation can be done also in a general non-Markovian form, Eq. (4).

Let us summarize our findings. The cyclization of a polymer, or the luminescence quenching in a system of a donor and acceptor attached to the ends of a polymer

molecule is an example of a diffusion-controlled reaction in a system exhibiting strongly non-Markovian behavior on the time scales of interest. Considering the situation as the first passage problem we provide kinetic curves for such a process under different initial conditions. We also discuss the emergence of some known approximations.

The partial financial support by the Fonds der Chemical Industrie is gratefully acknowledged.

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