PHYSICAL REVIEW E VOLUME 62, NUMBER 1 JULY 2000

Kramers problem for a polymer in a double well

K. L. Sebastian and Alok K. R. Paul
Department of Inorganic and Physical Chemistry, Indian Institute of Science, Bangalore 560012, India

(Received 1 February 2000)

We consider a long chain molecule, initially confined to the metastable side of a biased double well potential. It can escape from this side to the other by the motion of its N segments across the barrier. We assume that the length of the molecule is much larger than the width w of the barrier. The width w is taken to be sufficiently large that a continuum description is applicable to even the portion over the barrier. We use the Rouse model and analyze the mechanism of crossing the barrier. There can be two dominant mechanisms: end crossing and hairpin crossing. We find the free energy of activation for the hairpin crossing to be two times that for end crossing. The pre-exponential factor for hairpin crossing is proportional to N, while it is independent of N for end crossing. In both cases, the activation energy has a square root dependence on the temperature T, leading to a non-Arrhenius form for the rate. We also show that there is a special time dependent solution of the model, which corresponds to a kink in the chain, confined to the region of the barrier. The movement of the polymer from one side to the other is equivalent to the motion of the kink on the chain in the reverse direction. If there is no free energy difference between the two sides of the barrier, then the kink moves by diffusion and the time of crossing $t_{\text{cross}} \sim N^2/T^{3/2}$. If there is a free energy difference, then the kink moves with a nonzero velocity from the lower free energy side to the other, leading to $t_{\text{cross}} \sim N/\sqrt{T}$. We also discuss the applicability of the mechanism to the recent experiments of Kasianowicz [Proc. Natl. Acad. Sci. USA **93**, 13 770 (1996)], where DNA molecules were driven through a nanopore by the application of an electric field. The prediction that $t_{\text{cross}} \sim N$ is in agreement with these experiments. Our results are in agreement with the recent experimental observations of Han, Turner, and Craighead [Phys. Rev. Lett. **83**, 1688 (1999)]. We also consider the translocation of hydrophilic polypeptides across hydrophobic pores, a process that is quite common in biological systems. Biological systems accomplish this by having a hydrophobic signal sequence at the end that goes in first. We find that for such a molecule, the transition state resembles a hook, and this is in agreement with presently accepted view in cell biology.

PACS number(s): 83.10.Nn

I. INTRODUCTION

The escape of a particle over a one dimensional barrier has been studied in a large number of papers. The problem, often referred to as the Kramers problem [1,2], has been the subject of detailed reviews [3,4]. Kramers found solutions in the limit of weak friction and also in the limit of moderate to strong damping [1,2]. The intermediate regime has been an active area of investigation [3]. The reason for this extensive activity is that this forms a model for a chemical reaction occuring in a condensed medium. Kramers problem for few degrees of freedom has also been the topic of study [3,4]. The quantum problem of escape or tunneling through a barrier too is of considerable interest. In the case where the system has an infinite number of degrees of freedom, this has been referred to as the decay of metastable vacuum, a problem that has attracted quite a bit of attention in field theory, cosmology and mesoscopic quantum phenomena [5,6]. In this paper, we consider a similar situation involving only classical physics. The trapped object has $N(\rightarrow\infty)$ degrees of freedom, and is a polymer (a string). Though there are no quantum effects, the problem is similar, and some experiments are already available, that the results of the theory are easily verified. Further, the mathematics is considerably simpler than in the other cases, being equivalent to that of quantum mechanical tunneling of a single particle in a bistable potential.

The way that the N degrees of freedom are connected (a string) leads to interesting new aspects to the problem that are not present in the case where there are only finite number of degrees of freedom. Also, the problem is of great interest in biology as many biological processes involve the translocation of a chain molecule from one side of a membrane to the other, through a pore in the membrane. The translocation of proteins from the cytosol into the endoplasmic reticulum, or into mitochondria or chloroplasts are processes of great interest and importance. Often, the proteins are hydrophilic and the pore in the membrane forms a hydrophobic region, through which they have to pass[7–10], resulting in an increase in the free energy for the portion of the chain inside the pore. In infection by bacteriophages, conjugative DNA transfer etc, long chain DNA molecules snake through pores in membranes [11,12]. In all these cases, the chain molecule seems to get across the membrane rather easily, contrary to the expectation that one gets from the theoretical analysis available in the literature on the subject (see below). In a very interesting experiment Kasianowicz *et al.* [13] forced a 150 nucleotide long, single stranded DNA to move through a pore in a membrane and studied the time that it takes the molecule to cross the pore, as a function of the length of the molecule. In this experiment, the pH was such that the polynucleotide had a negative charge and the pore itself was charged [13]. The molecule was forced to move through the pore by the application of a potential difference between the two sides of the membrane. Bezerukov *et al.* [16] have studied the partitioning of polymer molecules into a nanoscale

1063-651X/2000/62(1)/927(13)/$15.00

pore. Chipot and Pohoille [15] have carried out a molecular dynamics simulation of a polypeptide, translocating through the interface between hexane and water. They found that the polypeptide (undecamer of poly-L-leucine), initially placed in a random coil conformation on the aqueous side of the interface rapidly translocates to the interfacial region and then folds. In another interesting experiment, Han *et al.* [14] observed the forced movement of long, double stranded DNA molecules through microfabricated channels which have regions that present an entropic barrier for the entry of the molecules.

All these problems involve the passage of a long chain molecule, through a region in space, where the free energy per segment is higher, thus effectively presenting a barrier for the motion of the molecule. This problem forms the generalization that we refer to as the Kramers problem for a chain molecule. On the theoretical side, a variety of studies exist on this kind of problem. Muthukumar and Baumgartner [17] studied the movement of self-avoiding polymer molecules between periodic cubic cavities seperated by bottlenecks. The passage through the bottleneck presents an entropic barrier to the motion, and they show that it leads to an exponetial slowing down of diffusion with the number of segments N in the chain. Baumgartner and Skolnick [18] studied the movement of polymers through a membrane driven by an external bias and membrane asymmetry. Park and Sung [8,19], have studied the translocation through a pore. They analyze the passage through a pore on a flat membrane, with only the effects of entropy included. The resultant entropic barrier is rather broad, its width being proportional to N. Consequently, they consider the translocation process as being equivalent to the motion of the center of mass of the molecule. Using the result of the Rouse model that the diffusion coefficient of the center of mass is proportional to $1/N$, they effectively reduce the problem to the barrier crossing of single particle having a diffusion coefficient proportional to $1/N$. As the translocation involves motion of N segments across the pore, the time taken to cross (t_{cross}) scales as N^3. They also show that in cases where there is adsorption on the trans side, translocation is favored and then t_{cross} scales as N^2. In a very recent paper, Park and Sung [22] have given a detailed investigation of the dynamics of a polymer surmounting a potential barrier. They use multidimensional barrier crossing theory to study the motion of a chain molecule over a barrier, in the limit where the width of the barrier is much larger than the lateral dimension of the molecule. In an interesting recent paper, Lubensky and Nelson [23] study a case where they assume the interaction of the segments of the polymer with the pore to be strong. They argue that effectively, the dynamics of the portion of the chain inside the pore is the one that is important and this, they show, can give rise to t_{cross} proportional to N. Again, they assume diffusive dynamics. In a recent paper, we have suggested [24] a kink mechanism for the motion of the chain across a barrier and it is our aim to give details of this mechanism in this paper.

We consider a polymer undergoing activated crossing over a barrier. This can form a model for a polymer going through a pore too, as the pore can cause an increase in the free energy of the segments inside it, as they would interact with the walls of the pore. The width w of the barrier is assumed to be much larger than the Kuhn length l of the polymer, but small in comparison with the total length Nl of the polymer. That is, $l \ll w \ll Nl$. For example, in the experiments of Kasianowicz *et al.* [13,25], the length of the pore is about 100 Å, while the Kuhn length for a single stranded DNA is perhaps around 15 Å [23]. Therefore, one is justified in using a continuum approach to the dynamics of the long chain. (It is possible to retain the discrete approach, and develop the ideas based on them, but this is more involved mathematically.) Our approach is the following: We describe the motion of the polymer using the Rouse model. The force that the barrier exerts on the chain appears as an additional, nonlinear term in the model. We refer to this as the nonlinear Rouse model. The nonlinear term causes a distortion of the portion of the chain inside the barrier, which we refer to as the kink. Movement of the chain across the barrier is equivalent to the motion of the kink in the reverse direction. The kink is actually a special solution of the nonlinear Rouse model, arising because of the nonlinearity. In the presence of a free energy difference between the two sides, the kink moves with a definite velocity and hence the polymer would cross the barrier with t_{cross} proportional to N. Traditionally, the nonlinear models that one studies (for example, the ϕ^4 or the sine-Gordon model [26,28–30]) have potentials that are translationally invariant, and hence the kink can migrate freely in space. In comparison, in our problem, the nonlinear term is fixed in position space and hence the kink too is fixed in space. However, the chain molecule (modelled as a string [20]) can move in space and hence the kink migrates, not in space, but on the chain. As far as we know, such a suggestion has never been made in the past and we believe that this is a very useful idea in understanding barrier crossing by long polymer molecules.

In general, the polymer can escape by essentially two mechanisms. The first, which we refer to as end crossing, involves the passage of one end of the polymer over the barrier, by thermal activation. This leads to the formation of the kink, which is then driven by the free energy difference between the two sides of the barrier. The second is by the escape of any portion of the polymer over the barrier, in the form of a hairpin. The hairpin is a kink-antikink pair. For a flexible polymer, the hairpin crossing has twice the activation energy for end escape and hence one expects it to be less probable. However, as it can take place anywhere on the chain, the frequency factor for it is proportional to N. Hence, for a sufficiently long chain, hairpin crossing can become the dominant mechanism for the escape. Hairpin crossing leads to the formation of a kink-antikink pair. The pair moves apart on the chain, driven by the free energy gain and hence the time of crossing is still proportional to N, though one expects that it is roughly half the time of crossing in the end crossing case. In addition to these, in principle, it is possible for more than one hairpin to be formed. The formation of a hairpin would require bending the chain. The polymer chain is flexible only over a length larger than the Kuhn length. This means that the curved portion of the hairpin would have a radius of curvature of the order of a few Kuhn lengths. Hence, in passage through a narrow pore, only the end-crossing mechanism can operate. However, if the width of the pore is a few times larger than the Kuhn length, hairpin crossing too can occur.

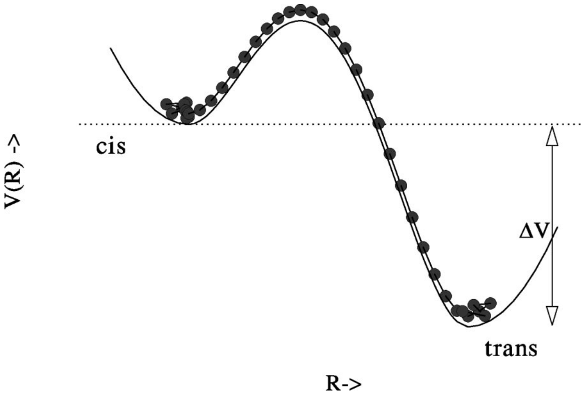

FIG. 1. The potential energy per segment of the chain, plotted as a function of position.

In all our mathematical development, we use the one-dimensional version of the Rouse model. This is no limitation, if one is concerned with translocation across the interface between two immiscible liquids or the experiments of Han *et al.* [14], which involve motion in a channel, whose width is large in comparison with the size of the molecule. On the other hand, if one is interested in translocation through a pore, strictly speaking, one has to consider the full three-dimensional nature of the problem, which at present seems rather involved. However, we believe that the one-dimensional model captures the essential physics of the problem. Our analysis should also be useful in situations where the whole of the polymer is in a pore, so that the dynamics may be taken to be one dimensional, with the chain trying to cross a region of high free energy.

II. THE MODEL

A. The free energy landscape

The considerations in this subsection are quite general and do not depend on the model that one uses to describe the polymer dynamics. We assume only that the polymer is flexible over a length scale comparable to the width of the barrier. We start by considering the free energy landscape for the crossing of the barrier. The barrier and the polymer stretched across it are shown in the Fig. 1. The polymer has initially all its units on the cis side, where its free energy per segment is taken to be zero. So the initial state has a free energy zero in the free energy hypersurface shown in Fig. 2. In crossing over to the trans side, it has to go over a barrier, as in the Fig. 1. The transition state for the crossing can be easily found, from physical considerations, by remembering that the transition state is a saddle point—i.e., it is a maximum on the free energy surface in one direction, while in all the other directions it is a minimum. The transition state is shown in the Fig. 3 (see also Fig. 4). In the transition state, the configuration of the polymer is such that the free energy of the chain is a minimum, subject to the two constraints: (a) the end of the polymer on the trans side is located exactly at the point at which its free energy per segment is zero (b) the other end is on the cis side. This is the transition state, because if one moves the end at the trans side either in the forward or in the backward direction (and the rest of the chain adjusted so that the free energy of the chain as a whole is a minimum), then the total free energy of the chain would decrease. Thus the transition state shown in the free energy hypersurface in the Fig. 2 has the configuration shown in the Fig. 3. Once the system has crossed the transition state, the chain is stretched across the barrier. The path of steepest descent then corresponds to moving segments from the cis side to the trans side, without changing the configuration of the polymer in the barrier region. As there is a free energy difference ΔV between the two sides, this would lead to a lowering of the free energy by ΔV per segment, and this leads to a path on the free energy surface with a constant slope, and of width W proportional to N (see the Fig. 2). Such a landscape implies that the barrier crossing would involve two steps. The first step is going through the transition state by overcoming the activation barrier. Once this is done, there is a rather wide region of width proportional to the length of the chain. Traversing this is the second step. As this region has a constant slope, the motion is driven and it is similar to that of a Brownian particle subject to a constant force. Such a particle would take a time t_{cross}, proportional to N to cross this region.

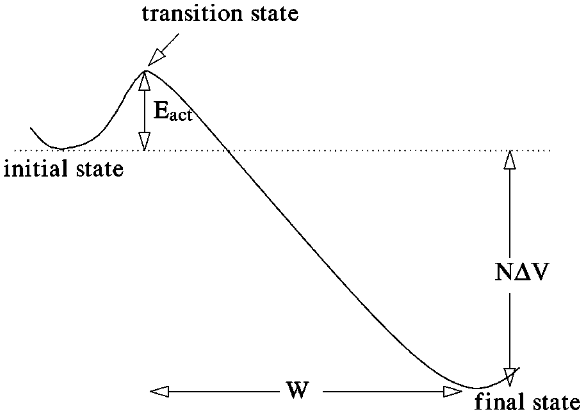

FIG. 2. The total free energy shown as a function of the reaction coordinate. The E_{act} is independent of the length of the chain. After the barrier is crossed, there is a region of width W, with W proportional to N, which is to be crossed. The time required to cross this regions is t_{cross}.

Till now, we considered the case of end crossing. The scenario for hairpin crossing (see Fig. 5) is similar. However, the activation energy is higher for hairpin crossing. In hairpin crossing, the transition state is equivalent to the one end

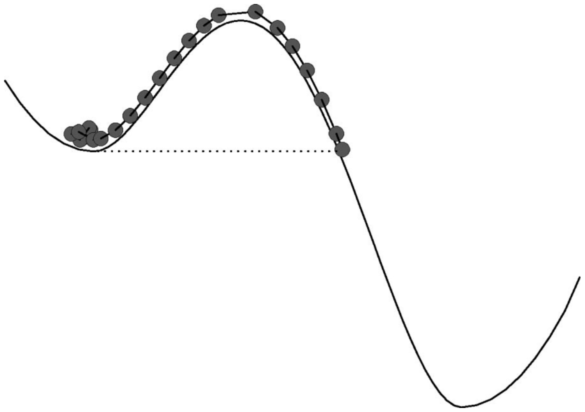

FIG. 3. The transition state.

crossing, repeated two times. Hence the activation energy for the process is two times larger (see Sec. II D). Once a hairpin crossing occurs, a kink-antikink pair is formed and the kink and the antikink separate on the chain, due to the driving force of the free energy gain. Then further crossing occurs by the movement of these two on the chain, and this too leads to a time of crossing proportional to *N*. In the following we make all these considerations quantitative, using the Rouse model to describe the dynamics of the chain.

B. The Dynamics

We consider the continuum limit of the Rouse model, discussed in detail by Doi and Edwards [20]. The chain is approximated as a string, with segments (beads) labeled by their position *n* along the chain. *n* is taken to be a continuous variable, having values ranging from 0 to *N*. The position of the nth segment in space is denoted by $R(n,t)$, where *t* is time. In the Rouse model, the segment undergoes overdamped Brownian motion and its time development is described by the equation

$$\zeta\frac{\partial R(n,t)}{\partial t}=m\frac{\partial^2 R(n,t)}{\partial n^2}-V'[R(n,t)]+f(n,t). \qquad (1)$$

In the above, ζ is a friction coefficient for the nth segment. The term $m[\partial^2 R(n,t)/\partial n^2]$ comes from the fact that stretching the chain can lower its entropy and hence increase its free energy. Consequently, the parameter *m* is temperature dependent and is equal to $3k_BT/l^2$. [See Doi and Edwards [20], Eq. (4.5). They use the symbol *k* for the quantity that we call m.] As the ends of the string are free, the boundary conditions to be satisfied are $\{\partial R(n,t)/\partial n\}_{n=0}=\{\partial R(n,t)/\partial n\}_{n=N}=0$. $V(R)$ is the free energy of a segment of chain, located at the position *R*. $V(R)$ represents a biased double well and has the barrier located near $R=0$. $f(n,t)$ are random forces acting on the nth segment and have the correlation function $\langle f(n,t)f(n_1,t_1)\rangle=2\zeta k_BT\delta(n-n_1)\delta(t-t_1)$ [see Ref. [20], Eq. (4.12)]. The deterministic part of the Eq. (1), which will play a key role in our analysis, is obtained by neglecting the random noise term in (1). It is

$$\zeta\frac{\partial R(n,t)}{\partial t}=m\frac{\partial^2 R(n,t)}{\partial n^2}-V'[R(n,t)]. \qquad (2)$$

This may also be written as

$$\zeta\frac{\partial R(n,t)}{\partial t}=-\frac{\delta E[R(n,t)]}{\delta R(n,t)}, \qquad (3)$$

where $E[R(n,t)]$ is the free energy functional for the chain given by

$$E[R(n,t)]=\int_0^N dn\left[\frac{m}{2}\left(\frac{\partial R(n,t)}{\partial n}\right)^2+V[R(n,t)]\right]. \qquad (4)$$

C. The form of the barrier

The chain is assumed to be subject to a biased double well potential, of the form shown in Fig. 1. The two minima are at $-a_0$ and a_1, with $a_0<a_1$. There is barrier near $R=0$ with its maximum located at $R=0$. All these conditions can be satisfied if one takes $V'(R)=2kR(R+a_0)(R-a_1)$. Here, *k* is a constant and will determine the height of the barrier. Integrating this and taking $V(-a_0)=0$, we get

$$V(R)=\frac{k}{6}(R+a_0)^2(3R^2-2Ra_0-4Ra_1+a_0^2+2a_0a_1). \qquad (5)$$

The barrier height for the forward crossing is $V_f=V(0)-V(-a_0)=1/6ka_0^3(a_0+2a_1)$ and for the reverse process, it is $V_b=V(0)-V(a_1)=1/6ka_1^3(2a_0+a_1)$. On crossing the barrier, a unit of the polymer lowers its free energy by $\Delta V=V(a_1)-V(-a_0)=\frac{1}{6}k(a_0-a_1)(a_0+a_1)^3$. As we assume $a_0<a_1$, ΔV is negative. The form of the potential is shown in Fig. 1.

D. The activation free energy for end and hairpin crossings

In this section, we consider the first step and calculate the activation free energy for both end and hairpin crossing. Activation free energy can be obtained from the free energy functional of Eq. (2). This free energy functional implies that at equilibrium, the probability distribution functional is $\exp(-(1/k_BT)\int dn\{\frac{1}{2}m(dR/dn)^2+V[R(n)]\})$. The configurations of the polymer which makes free energy a minimum are found from $\delta E[R(n)]/\delta R(n)=0$, which leads to the equation

$$m\frac{d^2R}{dn^2}=V'(R). \qquad (6)$$

Notice that this is just a Newton's equation for a ficticious particle of mass *m* moving in a potential $-V(R)$ (see Fig. 6). This equation has four solutions that are of relevance for the barrier crossing problem for the polymer. The first two are: (1) $R(n)=-a_0$, (2) $R(n)=a_1$ which are the minima in the free energy hypersurface. The first solution is the initial state, where the polymer is trapped in the vicinity of $-a_0$. This represents the metastable initial state. The second is the most stable minimum and is the final state. In addition to these two solutions, there are two more solutions which are of interest to us. These are *n* dependent and correspond to end and hairpin crossings.

1. End crossing

As we are interested in the case where the polymer is very long, we can imagine *n* to vary from $-\infty$ to 0 and find a saddle point in the free energy surface by searching for a solution of the Eq. (6) satisfying the following conditions: (a) $R(-\infty)=-a_0$, (b) the other end of the polymer has to be at a point with $R>R_{\max}$ [where $R_{\max}$ is the point where $V(R)$ has its maximum value]. The Newton's Eq. (6) implies that $E_c=\frac{1}{2}m(dR/dn)^2-V[R(n)]$ is conserved along the path. For the extremum path that corresponds to the end crossing, $E_c=0$. The ficticious particle starts at $R(-\infty)=-a_0$ with the velocity zero (this follows from the boundary conditons of the Rouse model) and ends up at R_f at the ''time'' $n=0$, again with velocity zero. Here $R_f(>R_{\max})$, is the point such that $V(R_f)=0$. The total free energy of the polymer corre-

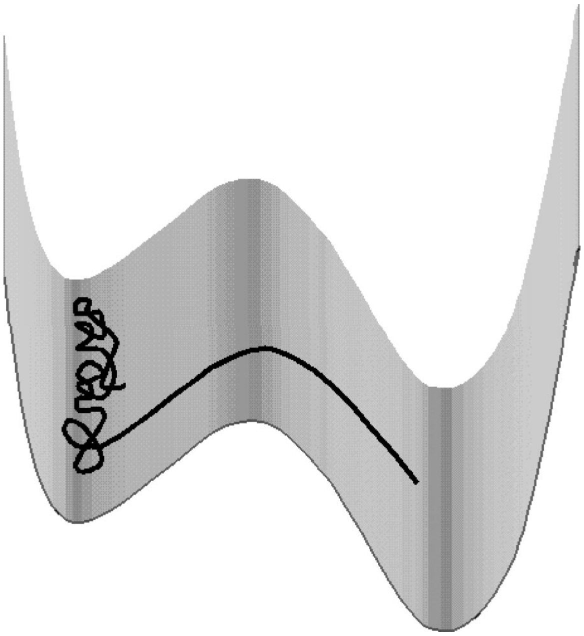

FIG. 4. End crossing.

sponding to this configuration is activation free energy for end crossing. As $E_c=0$, we have $\frac{1}{2}m(dR/dn)^2=V[R(n)]$ and we find the activation free energy to be given by

$$E_{a,\mathrm{end}}=\int_{-a_0}^{R_f}\sqrt{2mV(R)}dR. \tag{7}$$

The end crossing is illustrated in Fig. 4. For the sake of clarity, in Figs. 4 and 5, we have drawn the barrier as a surface by adding one more dimension. For the one-dimensional Rouse model, this extra dimension is not there. However, for polymer motion through channels, discussed in the Sec. IV D, this extra dimension is present. (It is of great interest to note that the formulas of this section are quite analogous to those that result from a semiclassical treatment of quantum tunneling and that $E_{a,\mathrm{end}}$ is just the tunneling exponent.)

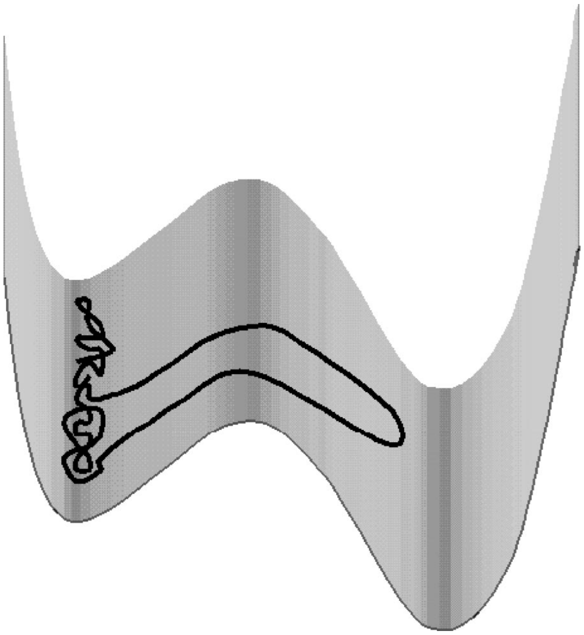

FIG. 5. Hairpin crossing.

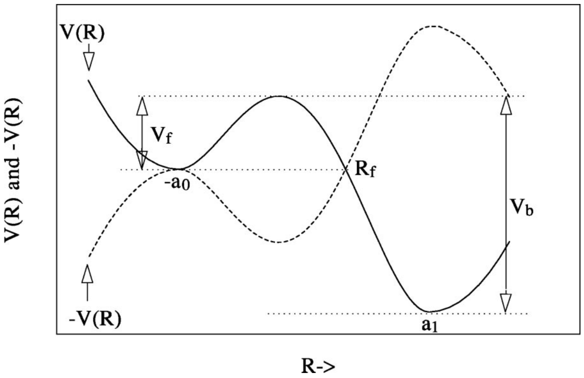

FIG. 6. The barrier and its inverted form. The barrier heights in the forward and backward directions are shown. The dotted line represents the path that determines the activation energy.

2. Hairpin crossing

If one imagines n to vary in the range $(-\infty,\infty)$ a second saddle point may be found by taking $R(-\infty)=-a_0$ and $R(\infty)=-a_0$, so that the Newtonian particle starts at $-a_0$, makes a round trip in the inverted potential $-V(R)$ and gets back to the starting point. This obviously has an activation energy

$$E_{a,hp}=2\int_{-a_0}^{R_f}\sqrt{2mV(R)}dR=2E_{a,\mathrm{end}}. \tag{8}$$

Thus the activation energy is exactly two times that for end crossing [21]. The hairpin crossing is shown in Fig. 5.

3. The temperature dependence

As the parameter m is proportional to the temperature $(=3k_BT/l^2)$, we arrive at the general conclusion that both the activation energies $E_{a,\mathrm{end}}$ and $E_{a,hp}$ are proportional to $\sqrt{T}$. For our model potential of Eq. (5) we find $R_f=a_0(\gamma-\sqrt{\gamma^2-\gamma})$ where $\gamma=[1+2(a_1/a_0)]^{\frac{1}{3}}$ and

$$E_{a,\mathrm{end}}=\frac{\sqrt{mk}a_0^3}{6}\{(3\gamma^2+1)\sqrt{1+3\gamma}-3\gamma(\gamma^2-1)$$
$$\times\ln[\sqrt{\gamma(\gamma-1)}/(1+\gamma-\sqrt{1+3\gamma})]\}. \tag{9}$$

The Boltzmann factor e^{-E_{act}/k_BT} for both end crossing and hairpin crossing over the barrier thus has the form $e^{-\mathrm{const}/\sqrt{T}}$. Further, we find that both are independent of N for large N.

III. THE RATE OF CROSSING

A. Hairpin crossing

We now calculate the rate of crossing in the two cases. We first consider the hairpin crossing, as this has connections with material available in the literature [6]. The methods that we use are quite well known in the soliton literature [26] and hence we give just enough details to make the approach clear. The Rouse model in the Eq. (1) leads to the functional Fokker-Planck equation

$$\frac{\partial P}{\partial t}=\frac{1}{\zeta}\int_0^N dn\,\frac{\delta}{\delta R(n)}\left[k_BT\frac{\delta P}{\delta R(n)}+\frac{\delta E[R(n)]}{\delta R(n)}P\right] \tag{10}$$

for the probability distribution functional P. This equation implies that the flux associated with the coordinate $R(n)$ is [26]

$$j[R(n)]=-\frac{1}{\zeta}\left[k_BT\frac{\delta P}{\delta R(n)}+\frac{\delta E[R(n)]}{\delta R(n)}P\right]. \tag{11}$$

We now consider the initial, metastable state. As the rate of escape is small, we can assume the probability distribution to be the equilibrium one, which is

$$P=\frac{1}{Z_0}\exp\{-E[R(n)]/k_BT\}. \tag{12}$$

To determine Z_0 we use the condition $\int D[R(n)]P=1$, where $\int D[R(n)]$ stands for functional integration. It is convenient to introduce the normal co-ordinates for small amplitude motion around the metastable minimum and do the functional integration using them. For this, we expand $E[R(n)]$ around the metastable minimum, by putting $R(n)=-a_0+\delta R(n)$, and expanding as a functional Taylor series in $\delta R(n)$ and keeping terms up to second order in $\delta R(n)$. Then

$$E[R(n)]=\frac{1}{2}m\int_0^N dn\,\delta R(n)\left(-\frac{\partial^2}{\partial n^2}+\omega_0^2\right)\delta R(n). \tag{13}$$

We have defined ω_0 by putting $m\omega_0^2=[\partial^2V(R)/\partial R^2]_{R=-a_0}$. The normal (Rouse) modes are just the eigenfunctions $\psi_k(n)$ of the operator $\hat{H}^{ms}=(-\partial^2/\partial n^2+\omega_0^2)$, having the eigenvalue ε_k and satisfying the Rouse boundary conditions $\partial\psi_k(n)/\partial n=0$ at the two ends of the string. We assume $\psi_k(n)$ to be normalized. The superscript "ms" in $\hat{H}^{ms}$ stands for metastable. Now we can expand $\delta R(n)$ as $\delta R(n)=\Sigma_k c_k\psi_k(n)$ so that the expression for energy (13) becomes

$$E[R(n)]=\frac{1}{2}m\sum_k \varepsilon_k c_k^2. \tag{14}$$

We now do the functional integration using the variables c_k. Then the normalization condition $\int D[R(n)]P=1$ becomes $(1/Z_0)\Pi_k\int dc_k\exp[-\frac{1}{2}m\beta\varepsilon_k c_k^2]=1$. Evaluation of the Gaussian integrals in this expression gives $Z_0=\Pi_k(2\pi/m\beta\varepsilon_k)^{1/2}$. Now we consider the vicinity of a saddle point, where the probability distribution deviates from the equilibrium one. We first consider the saddle point which corresponds to hairpin crossing. The potential of Eq. (5) is rather difficult to handle as we have not been able to obtain analytic solutions to the Newton's equation (6). In determining the crossing of the barrier, the key role is played by the quantities ω_0 and the height of the barrier for crossing in the forward direction V_f. The quantities that we calculate in this section have no dependence of the behavior of the potential near the stable minimum. So, instead of using the quartic potential of Eq. (5), we use the simpler cubic potential of Eq. (15). This has no stable minimum (corresponding to the final state), but that does not matter, because the quantities that we calculate do not depend on its existence. Thus we use the potential

$$V_c(R)=V_0\left(\frac{R+a_0}{R_0}\right)^2\left(1-\frac{R+a_0}{R_0}\right), \tag{15}$$

where we adjust V_0 and R_0 to reproduce the values for ω_0 and the barrier height V_f [27]. Solving Eq. (6) for this potential, in the limit of an infinitely long chain and taking it to extend from $n=-\infty$ to $+\infty$, the saddle point that corresponds to hairpin crossing is easily found to be given by the equation

$$R_{hp}(n)=-a_0+R_0\left\{\operatorname{sech}\left(\sqrt{\frac{V_0}{2m}}n\right)\right\}^2. \tag{16}$$

In fact one has a continuous family of solutions of the form $R_{hp}(n-n_0)$, where $n_0\in(-\infty,\infty)$ is arbitrary and determines center of the kink-antikink pair. Now expanding the energy $E[R(n)]$ about this saddle, by writing $R(n)=R_{hp}(n-n_0)+\delta R(n)$ we get

$$E[R(n)]=E_{a,hp}+\frac{1}{2}m\int dn\,\delta R(n)\bigg[-\frac{\partial^2}{\partial n^2}+\omega_0^2\{1-3\operatorname{sech}^2[\omega_0(n-n_0)/2]\}\bigg]\delta R(n). \tag{17}$$

For the potential of Eq. (15) $E_{a,hp}=(8R_0/15)\sqrt{2mV_0}$. The normal modes for fluctuations around the saddle are determined by the eigenfunctions of the operator $\hat{H}^{\ddagger}=-\partial^2/\partial n^2+\omega_0^2\{1-3\operatorname{sech}^2[\omega_0(n-n_0)/2]\}$ (‡ is used to denote the saddle point). The eigenfunctions are (a) the discrete states $\psi_0^{\ddagger}$, $\psi_1^{\ddagger}$, and $\psi_2^{\ddagger}$ having the eigenvalues $\varepsilon_0^{\ddagger}=-5\omega_0^2/4$, $\varepsilon_1^{\ddagger}=0$, and $\varepsilon_2^{\ddagger}=3\omega_0^2/4$ and (b) the continuum of eigenstates $\psi_k^{\ddagger}$ with eigenvalues of the form $\varepsilon_k^{\ddagger}=\omega_0^2+k^2$ (more details are given in the Appendix). The existence of the eigenvalue $\varepsilon_1^{\ddagger}=0$ comes from the freedom of the kink-antikink pair to have its center anywhere on the chain. (In the polymer problem, this just means that the hairpin can be formed anywhere along the chain.) In the following, Σ_k would stand for summation over all the eigenstates, including both the discrete and continuum states while a symbol such as $\Sigma_{k\neq 1}$ means that the bound state $\psi_1^{\ddagger}$ is to be excluded from the sum. Now writing $\delta R(n)=\Sigma_{k\neq 1}c_k^{\ddagger}\psi_k^{\ddagger}$, we get

$$E[R(n)]=E_{a,hp}+\frac{1}{2}m\sum_{k\neq 1}\varepsilon_k^{\ddagger}(c_k^{\ddagger})^2.$$

We write the probability density near the saddle as [26]

$$P=\frac{\theta(c_0^{\ddagger},c_1^{\ddagger},\dots)}{Z_0}\exp\left\{-\frac{E[R(n)]}{k_BT}\right\}, \tag{18}$$

where $\theta(c_0^\ddagger, c_1^\ddagger, \ldots)$, is a function that must approach unity in the vicinity of the metastable minimum. Near the saddle, one can calculate the flux $j_k^\ddagger$ in the direction of $c_k^\ddagger$ using the analog of Eq. (11):

$$j_k^\ddagger = -\frac{1}{\zeta}\left[k_B T \frac{\partial P}{\partial c_k^\ddagger} + \frac{\partial E[R(n)]}{\partial c_k^\ddagger} P\right].$$

Using Eqs. (17) and (18) we get

$$j_k^\ddagger = -\frac{k_B T}{Z_0 \zeta} \frac{\partial \theta(c_0^\ddagger, c_1^\ddagger, \ldots)}{\partial c_k^\ddagger} \times \exp\left\{-\frac{1}{k_B T}\left(E_{a,hp} + \frac{1}{2} m \sum_{k \neq 1} \varepsilon_k^\ddagger (c_k^\ddagger)^2\right)\right\}. \tag{19}$$

In a steady state, there is flux only in the unstable direction. That is, only $j_0^\ddagger$ is nonzero. This means that θ can depend only on $c_0^\ddagger$, which implies that $j_0^\ddagger$ must have the form

$$j_0^\ddagger = A \exp\left\{-\frac{1}{k_B T}\left(\frac{1}{2} m \sum_{k>1} \varepsilon_k^\ddagger (c_k^\ddagger)^2\right)\right\}, \tag{20}$$

where A is a constant, to be determined. Using the Eq. (20) in (19) we get $\partial\theta(c_0^\ddagger)/\partial c_0^\ddagger = -A \exp\{-(m/2k_B T)|\varepsilon_0^\ddagger|(c_0^\ddagger)^2\}$. The fact that $\theta(c_0^\ddagger)$ must approach unity as $c_0^\ddagger \to -\infty$, enables one to get $A = (m|\varepsilon_0^\ddagger|/2\pi k_B T)^{1/2}$. Hence $\theta(c_0^\ddagger) = (m|\varepsilon_0^\ddagger|/2\pi k_B T)^{1/2} \int_{c_0^\ddagger}^{\infty} dz \exp\{-(1/2k_B T) m |\varepsilon_0^\ddagger| z^2\}$. Now the net flux crossing the barrier is found by integrating $j_0^\ddagger$ over all directions other than $c_0^\ddagger$. The integrals over all $c_k^\ddagger$, except $c_1^\ddagger$ is straight forward. As $\varepsilon_1^\ddagger = 0$, $\int dc_1^\ddagger$ needs special handling. The integral, as is well known, is performed by converting it to an integral over the kink-antikink position, n_0. That is, $\int dc_1^\ddagger = \alpha \int dn_0$, where $\alpha^2 = \int_{-\infty}^{\infty} dn [\partial R_{hp}(n)/\partial n]^2 = E_{a,hp}/m$. Hence the rate becomes

$$k_{hp} = \frac{k_B T}{Z_0 \zeta}\left(\frac{m|\varepsilon_0^\ddagger|}{2\pi k_B T}\right)^{1/2} \prod_{k>1}\left(\frac{2\pi k_B T}{m|\varepsilon_k^\ddagger|}\right)^{1/2}\left(\frac{E_{a,hp}}{m}\right)^{1/2} N \times \exp(-E_{a,hp}/k_B T). \tag{21}$$

The notation $\Pi_{k>1}$ is used to indicate product over all eigenvalues of $\hat{H}^\ddagger$, except the first two. On using the expression for Z_0,

$$k_{hp} = \frac{k_B T}{\zeta}\left(\frac{m}{2\pi k_B T}\right)^{3/2} I_{hp}\left(\frac{|\varepsilon_0^\ddagger| E_{a,hp}}{|\varepsilon_2^\ddagger| m}\right)^{1/2} N \times \exp(-E_{a,hp}/k_B T), \tag{22}$$

where $I_{hp} = (\Pi_k \varepsilon_k / \Pi_{k>2} \varepsilon_k^\ddagger)^{1/2}$. This infinite product is evaluated in the Appendix and is found to be $I_{hp} = \frac{15}{2}\omega_0^3$. This leads to

$$k_{hp} = \frac{5 N m \omega_0^3}{4\pi\zeta}\left(\frac{15 E_{a,hp}}{2\pi k_B T}\right)^{1/2} \exp(-E_{a,hp}/k_B T). \tag{23}$$

B. End crossing

In this case, the analysis is similar to the above. The operator $\hat{H}^\ddagger$ is the same as earlier. However, there is an interesting difference. In the hairpin case, the boundary conditions on $\psi_k^\ddagger$ ($d\psi_k^\ddagger/dn = 0$, at the two ends) were at $n = \pm\infty$, while in this case, they are at $n = 0$ and at $n = \infty$ (i.e., the boundary value problem is now on the half-line). Due to this, one has to rule out the odd $\psi_k^\ddagger$ that exists in the hairpin case as they do not satisfy the Rouse boundary condition $d\psi_k^\ddagger/dn = 0$ at $n = 0$. So we consider only the even solutions. Thus the eigenvalue at zero is ruled out (which is quite alright as end crossing can occur only at the end and not anywhere else, but we will put in additional factor of 2 as it can occur at any of the two ends). The discrete spectrum now has only the eigenvalues $\varepsilon_0^\ddagger = -5\omega_0^2/4$ and $\varepsilon_2^\ddagger = 3\omega_0^2/4$. The expression for the rate is

$$k_{\text{end}} = \frac{k_B T}{\zeta}\left(\frac{m|\varepsilon_0^\ddagger|}{2\pi k_B T}\right)^{1/2} \tilde{I}_{\text{end}} \exp(-E_{a,\text{end}}/k_B T), \tag{24}$$

where

$$\tilde{I}_{\text{end}} = \frac{\prod_{k \neq 0} (2\pi k_B T / m \varepsilon_k^\ddagger)^{1/2}}{\prod_k (2\pi k_B T / m \varepsilon_k)^{1/2}}.$$

In this product, there are $N-1$ terms in the numerator and N terms in the denominator. One of the $N-1$ terms is the bound state with an eigenvalue $\varepsilon_2^\ddagger = 3\omega_0^2/4$. Separating this out from the product, one can write $\tilde{I}_{\text{end}} = (2m/3\pi k_B T \omega_0^2)^{1/2} I_{\text{end}}$, where $I_{\text{end}} = (\Pi_k \varepsilon_k / \Pi_{k>2} \varepsilon_k^\ddagger)^{1/2}$. The evaluation of this product involves some subtlety and is done in the Appendix. The result is

$$k_{\text{end}} = \frac{5 m \omega_0^2}{2\sqrt{2}\pi\zeta} \exp(-E_{a,\text{end}}/k_B T).$$

Accounting for the existence of two ends leads to

$$k_{\text{two ends}} = \frac{5 m \omega_0^2}{\sqrt{2}\pi\zeta} \exp(-E_{a,\text{end}}/k_B T). \tag{25}$$

IV. THE KINK AND ITS MOTION

A. The kink solution and its velocity

Having overcome the activation barrier, how much time would the polymer take to cross it? We denote this time by t_{cross}. To calculate this, we first look at the mathematical solutions of the deterministic Eq. (2). The simplest solutions of this equation are $R(n,t) = -a_0$ and $R(n,t) = a_1$. As we saw earlier, these correspond to the polymer being on either side of the barrier and these are just mean values of the position on the two sides. Thermal noise makes $R(n,t)$ fluctuate about these mean positions which may be analyzed using the normal coordinates for fluctuations about this mean position. Each normal mode obeys a Langevin equation similar to that for a harmonic oscillator, executing Brownian motion. In addition to these two time independent solutions, Eq. (2) has a time-dependent solution (a kink) too, which corresponds to the polymer crossing the barrier. We analyze the dynamics of the chain, with the kink in it, using the normal modes for fluctuations about this kink configuration. Our analysis makes use of the techniques that have been used to study the diffusion of solitons [26].

As is usual in the theory of nonlinear wave equations, a kink solution moving with a velocity v may be found using the ansatz $R(n,t)=R_s(\tau)$ where $\tau=n-vt$ [26]. Then Eq. (2) reduces to

$$m\frac{d^2R_s}{d\tau^2}+v\zeta\frac{dR_s}{d\tau}=V'(R_s). \tag{26}$$

If one imagines τ as time, then this too is a simple Newtonian equation for the motion of particle of mass m, moving in the upside down potential $-V(R)$. However, in this case, there is a frictional term too, and $v\zeta/m$ is the coefficient of friction. This term makes it possible for us to find a solution for quite general forms of potential. For the potential of Eq. (6), we can easily find a solution of this equation, obeying the conditions $R_s(\tau)=-a_0$ for $\tau\to-\infty$ and $R_s(\tau)=a_1$ for $\tau\to\infty$. The solution is

$$R_s(\tau)=(-a_0+e^{\tau\omega(a_0+a_1)}a_1)(1+e^{\tau\omega(a_0+a_1)})^{-1}, \tag{27}$$

with $\omega=\sqrt{k/m}$. The solution exists only if the velocity has the value $v=(\sqrt{mk}/\zeta))(a_0-a_1)$. This solution is a kink, occurring in the portion of the chain inside the barrier. We shall refer to the point with $\tau=0$ as the center of the kink. [Actually one has a one-parameter family of solutions of the form $R_s(\tau+\tau_0)$, where τ_0 is any arbitrary constant.] As $\tau=n-vt$, the center of the kink moves with a constant velocity v. Note that this velocity depends on the shape of the barrier. Thus for our model potential with $a_0<a_1$, having $\Delta V<0$, this velocity is negative. This implies that the kink is moving in the negative direction, which corresponds to the chain moving in the positive direction. That is, the chain moves to the lower free energy region, with this velocity. If the barrier is symmetric, then $a_0=a_1(V_f=V_b)$ and the velocity of the kink is zero.

B. Fluctuations about the kink

We now analyze the effect of the noise term present in Eq. (1). The center of the kink can be anywhere on the chain—which means that the kink is free to move on the chain. Actually, as the position of the kink is fixed in space, this means that the polymer is moving across the barrier. The kink would also execute Brownian motion, due to the noise term. The motion of the kink caused by the noise terms is a well studied problem in the literature [26] and one can make use of these methods. Following ‘‘instanton methods’’ of field theory [28], we write

$$R(n,t)=R_s(n-a(t))+\sum_{p=1}^{\infty}X_p(t)\phi_p(n-a(t),t). \tag{28}$$

We have allowed for the motion of the kink by taking the kink center to be at $a(t)$. $a(t)$ is a random function of time which is to be determined. ϕ_p are a set of functions (the Rouse modes) to be defined below and $X_p(t)$ are the expansion coefficients. This may be put into Eq. (1) to derive an equation of motion for $a(t)$. Neglecting kink-phonon scattering leads to [24]

$$\dot{a}(t)=v+\xi_0(t)/C. \tag{29}$$

We introduce a new variable $\overline{n}$ by $\overline{n}=n-a(t)$, and define $\psi_0(\overline{n})$ by $\partial_{\overline{n}}R_s(\overline{n})=C\psi_0(\overline{n})$ with

$$\begin{aligned}C^2&=\langle\partial_{\overline{n}}R_s(\overline{n})|e^{v\zeta\overline{n}/m}|\partial_{\overline{n}}R_s(\overline{n})\rangle\\&=\frac{2}{3}\pi\omega\csc\left(2\pi\frac{a_1-a_0}{a_0+a_1}\right)(a_1-a_0)a_0a_1\end{aligned} \tag{30}$$

and

$$\xi_0(t)=\frac{1}{\zeta}\int_{\text{over the chain}}d\overline{n}\psi_0^*(\overline{n})e^{v\zeta\overline{n}/(2m)}f[\overline{n}+a(t),t]. \tag{31}$$

$\xi_0(t)$ is a random function of time, having the correlation function

$$\begin{aligned}\langle\xi_0(t)\xi_0(t_1)\rangle&=\delta(t-t_1)(2k_BT/\zeta)\\&\quad\times\int_{\text{over the chain}}d\overline{n}e^{v\overline{n}\zeta/m}[\psi_0(\overline{n})]^2.\end{aligned} \tag{32}$$

For the potential given by the Eq. (5) one gets

$$\begin{aligned}\langle\xi_0(t)\xi_0(t_1)\rangle&=\delta(t-t_1)k_BT/(2\zeta a_0a_1)\sec\left(2\pi\frac{a_1-a_0}{a_0+a_1}\right)\\&\quad\times(3a_1-a_0)(3a_0-a_1).\end{aligned} \tag{33}$$

Equations (29) and (30) imply that the kink position $a(t)$ executes Brownian motion with drift. As v is negative, the drift is in the negative direction.

C. The crossing time t_{cross}

For the polymer to cross the barrier, the kink has to go in the reverse direction, by a distance equal to N. As the Eq. (29) is just that for a particle executing Brownian motion with drift, we can estimate the time of crossing as a first passage time. As the kink starts at one end, we take the initial position of the particle, a to be N and calculate the average time required for it to attain the value 0, which would correspond to the polymer crossing the barrier fully. Writing the diffusion equation for the survival probability $P(a,t)$ for a Brownian particle starting at $a=N$ at the time $t=0$ and being absorbed at $a=0$, we get

$$\frac{\partial P(a,t)}{\partial t}=D\frac{\partial^2P(a,t)}{\partial a^2}-v\frac{\partial P(a,t)}{\partial a}. \tag{34}$$

Here, the diffusion coefficient

$$D=\frac{1}{2tC^2}\int_0^t dt_1\int_0^t dt_2\langle \xi_0(t_1)\xi_0(t_2)\rangle$$
$$=\frac{3k_BT}{8\pi\zeta}\sqrt{\frac{m}{k}}\frac{(3a_1-a_0)(3a_0-a_1)}{a_0^2a_1^2(a_1-a_0)}\tan\left(2\pi\frac{a_1-a_0}{a_0+a_1}\right). \tag{35}$$

Equation (34) is to be solved, subject to the initial condition $P(a,0)=\delta(a-N)$ and with absorbing boundary condition at $a=0$ [i.e., $P(0,t)=0$] and $P(\infty,t)=0$. It is easy to solve the above equation in the Laplace domain. The result for the Laplace transform $\overline{P}(a,s)=\int_0^\infty dt P(a,t)\exp(-st)$ is

$$\overline{P}(a,s)=\frac{1}{\sqrt{4Ds+v^2}}\left[e^{\frac{(a-N)v-\sqrt{4Ds+v^2}|a-N|}{2D}}\right.$$
$$\left.-e^{\frac{(a-N)v-\sqrt{4Ds+v^2}|a|-\sqrt{4Ds+v^2}N}{2D}}\right]. \tag{36}$$

The Laplace transform of the survival probability is given by $\overline{P}(s)=\int_{-\infty}^{\infty}da\overline{P}(a,s)$ and is found to be

$$\overline{P}(s)=\frac{1}{s}\left[1-e^{\frac{-Nv-\sqrt{4Ds+v^2}N}{2D}}\right]. \tag{37}$$

The average crossing time is given by $t_{\mathrm{cross}}=\mathrm{limit}_{s->0}\overline{P}(s)=N/(-v)$, if $v<0$. As v is proportional $\sqrt{mk}$, assuming $V(R)$ to be temperature independent we find $t_{\mathrm{cross}}\sim N/\sqrt{T}$. This is a general conclusion, independent of the model that we assume for the potential. If the barrier is symmetric, the kink moves with an average velocity $v=0$. Taking the $v\rightarrow 0$ limit of $\overline{P}(s)$, we get

$$\overline{P}(s)=\frac{1}{s}(1-e^{-\sqrt{s}N/\sqrt{D}}) \tag{38}$$

so that the survival probability becomes

$$P(t)=\mathrm{Erf}\left(\frac{N}{2\sqrt{Dt}}\right). \tag{39}$$

This expression for the survival probability implies that the average time that the particle survives is $t_{\mathrm{cross}}\sim N^2/D$. For the symmetric barrier, the value of D may be obtained by taking the limit $a_1\rightarrow a_0$, and one finds $D=(3k_BT/4\zeta a_0^3)\sqrt{m/k}$ and thus $t_{\mathrm{cross}}\sim N^2/T^{3/2}$.

In their analysis, Park and Sung [19] considered the passage of a polymer through a pore for which the barrier is entropic in origin. Consequently, it is very broad, the width being of the order of N. Hence they consider the movement as effectively that of the center of mass of the polymer which diffuses with a coefficient proportional to $1/N$. As the center of mass has to cover a distance N, the time that it takes is proportional to N^3. If there is a free energy difference driving the chain from one side to the other, then the time is proportional to N^2. In comparison, we take the barrier to be extrinsic in origin and assume its width to be small in comparison with the length of the chain. The crossing occurs by the motion of the kink, which is a localized nonlinear object in the chain whose width is of the same order as that of the barrier. As the polymer is intially in a (metastable) potential well, the entropic contribution to the barrier that Park and Sung [19] consider does not exist in our case. Such a potential is realistic, in cases where the polymer is subjected to a driving force (for example, an electric field). As the kink is a localized object, its diffusion coefficient has no N dependence and our results are different from those of Park and Sung [19]. In the case where there is no free energy difference between the two wells, our crossing time is proportional to N^2 (in contrast to N^3 of Park and Sung), while if there is a free energy difference, our crossing time is proportional to N (in contrast to N^2 of Park and Sung). In a very recent paper [22], Park and Sung have considered the Rouse dynamics of a short polymer surmounting a barrier. The size of the polymer is assumed to be small in comparison with the width of the potential barrier. Consequently, the transition state has almost all the segments of the polymer sitting at the top of the barrier, leading to the prediction that the activation energy is proportional to N. This leads to a crossing probability that decreases exponentially with N. In comparison, as found in Sec. II D, the free energy of activation for the kink mechnism does not depend on the length of the chain. Hence, the mechanism is the favored one for long chains.

D. The net rate

As the actual crossing is a two step process, with activation as the first step and kink motion as the second step, the net rate of the two has to be a harmonic mean of the two rates. For a very long chain, the motion of the kink has to become rate determining. In the experiments of Kasianowicz [13] (see Sec. V), one is directly observing t_{cross} and hence our considerations on kink motion must be directly applicable. Also, in the case of translocation of biological macromolecules, considered in Sec. VI there does not seem to be any free energy of activation and then the rate is determined by t_{cross} alone. Recently, the motion of long chains in microfabricated channels has been investigated by Han *et al.* [14]. In contrast to the situtation for a pore, there is an additional dimension available for the molecule to form a hairpin, viz. perpendicular to the direction of movement of the molecule. Consequently, in overcoming the barrier, both end crossing and hairpin crossing can occur (see Figs. 4 and 5). They found the activation energy to be independent of N, in agreement with our analysis. They also found the activation energy to be inversely proportional to the electric field $\mathcal{E}$. Assuming the barrier to be given by $V(R)=0$ for $R<0$ and

$$V(R)=AT-B\mathcal{E}R \tag{40}$$

for $R>0$, (A,B are constants—the barrier is similar to the one in field emission) with AT representing the entropic contribution to the barrier height and $B\mathcal{E}R$ the lowering of the potential due to the electric field $\mathcal{E}$, one easily gets $E_{\mathrm{end}}=4\sqrt{m(AT)^3}/(3B\mathcal{E})\sim T^2/\mathcal{E}$. The inverse dependence on $\mathcal{E}$ is in agreement with the experimental observations. Note that with the potential of Eq. (40), the problem becomes analogous to field emission from a metal, with AT being the work function. Also, $E_{hp}=2E_{\mathrm{end}}$. Experimental results show that the longer molecule crosses the barrier faster. This means

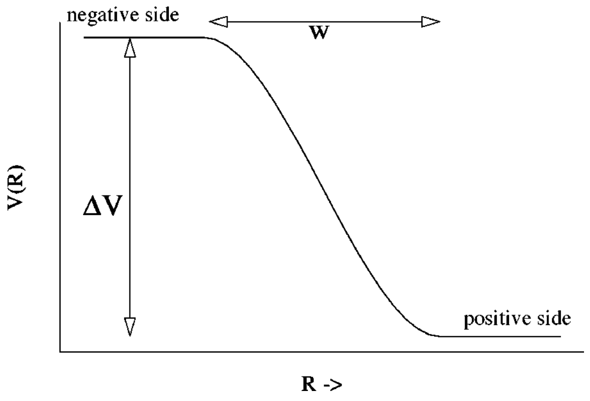

FIG. 7. The free energy per segment of the polymer, shown as a function of the position of the segment (for the case where DNA is drawn through a pore). As the segment goes from the left ($-ve$) to right ($+ve$), the free energy changes by $-\Delta V$.

that the N dependence of k_{hp} causes the hairpin crossing to be the dominant mechanism of crossing in these experiments.

V. DNA DRIVEN THROUGH A PORE

We now discuss a model for the potential which hopefully can mimic the experiments of Kasianowicz *et al.* [13,25]. Under the conditions of the experiment, the DNA strand is negatively charged, and under the influence of a potential difference, it migrates from the side where the potential is negative (cis), to the side where the potential is positive (trans). We shall assume that the charge on the DNA is spread uniformly over all its segments. Then, a segment of DNA on the cis side has a higher free energy than on the trans side. As the segment passes through the pore, it would interact with the walls of the pore, which too are charged. So one expects the free energy per segment of the chain to change as shown in Fig. 7. It is possible that the pore could represent a region where the free energy is larger and hence the translocation process is activated. The pore is about 10 nm wide, and therefore, at any time, there should be more than 10 nucleotides in it. As this number is not small, our continuum approach should be a good approximation. We take the pore width to be w and model the potential inside the pore by $V(R)=\Delta V(R/w)^2(2R/w-3)$ for $0<R<w$ while $V(R)=0$ for $R<0$ and $V(R)=-\Delta V$ for $R>w$. This particular functional form was chosen so that the potential and its derivatives are continuous everywhere in space. For this model potential, the equation for the kink is

$$m\frac{d^2R_s(\tau)}{d\tau^2}+\zeta v\,\frac{dR_s(\tau)}{d\tau}-6\Delta V(R_s/w^2)(R_s/w-1)=0. \tag{41}$$

The kink solution is $R_s(\tau)=w(1+e^{-\sqrt{\Delta V/m}(\tau-\tau_0)/w})^{-2}$ where τ_0 is an arbitrary constant. This solution exists with $\zeta v=-5\sqrt{m\Delta V}/w$. Thus, we find t_{cross} to be proportional to $Nw/(\zeta\sqrt{m\Delta V})$, i.e., the traversal time is directly proportional to the number of units in the polymer, in agreement with the experiments of Kasianowicz *et al.* [13]. Further, our analysis predicts that t_{cross} is inversely proportional to the square root of the applied potential difference.

VI. HOW DO BIOLOGICAL SYSTEMS LOWER THE ACTIVATION ENERGY?

If there was a high activation energy ($\gg k_BT$) for the translocation of biological molecules across membranes, the process would be unlikely and hence, biological systems would not be able to function, if they depended crucially on such transfers. As translocation seem to be very efficient in biological systems, one needs to look at the mechanism that evolution has designed to reduce the barrier. The destination (referred to as sorting) of a biological long chain molecule is determined by a sequence of units at the beginning of the chain, referred to as the signal sequence. For example, proteins destined to the endoplasmic reticulum possess an amino terminal signal sequence, while those destined to remain in the cytosol do not have this. If one attaches this sequence to a cytosolic protein, then the protein is found to end up in the endoplasmic reticulum (see Ref. [9], Fig. 14.6). The way the sequence works is simple. If the pore is hydrophobic and the chain hydrophilic, then the signal sequence is hydrophobic, so that the signal sequence has a low free energy inside the pore.

We qualitatively analyze this type of problem in the following, using the Rouse model. The way to model the situation would be to have a potential that is dependent upon the segment number n in the chain. Hence, in the equations of the Rouse model the potential term would have an explicit dependence on n. Let us denote the length of the signal sequence by s. The simplest model would be to have a potential which is attractive, for $0<n<s$ and which has the shape of a barrier for $s<n<N$. The transition state is determined by the Newton-like equation

$$m\frac{d^2R}{dn^2}=V'_{\mathrm{new}}(n,R), \tag{42}$$

with n playing the role of time (in the following we shall refer to n as the time for the motion of this ficticious particle). We take the potential to be such that

$$\begin{aligned}V_{\mathrm{new}}(n,R)&=-V(R)\quad\text{if}\quad 0<n<s\quad\text{and}\\&=V(R)\quad\text{if}\quad s<n<N.\end{aligned}$$

This corresponds to a particle moving in a time dependent potential, which switches from being repulsive to attractive at the time s. The shape of this time-dependent potential is shown in Fig. 8. The boundary conditions $\{dR(n)/dn\}_{n=0}=\{dR(n)/dn\}_{n=N}=0$ imply that the particle has to start and end with zero velocity. Let us imagine that the particle starts at the point R_0 (see Fig. 8). As the potential that it feels up to the time s is repulsive, it follows the path indicated by the dashed line in the figure, and the conservation of energy may be written as $\frac{1}{2}m(dR(n)/dn)^2+V(R)=V(R_0)$. Let it reach the point R_s after a time s. At this time, the potential is switched from $V(R)$ to $-V(R)$. From this time on, the equation of conservation of energy would be

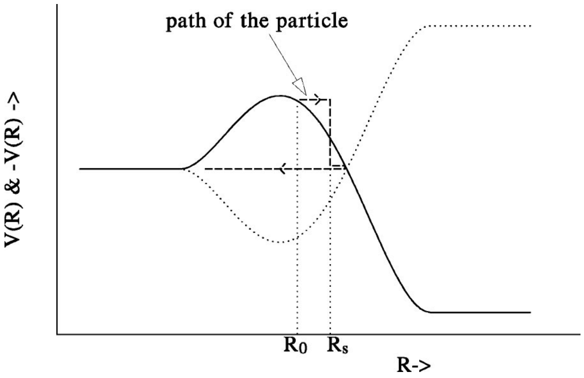

FIG. 8. The full curve is the plot of the potential for the motion of the particle for $0<n<s$, while the dotted curve is the potential for $s<n<N$. The particle starts at R_0 at the time $t=0$, moves on the full curve and reaches R_s at the time $n=s$. At this time, the potential suddenly switches to its negative. The particle then moves on this potential (dotted curve). The path of the particle is drawn with dashes and the direction in which it moves is shown by the arrows.

$$\frac{1}{2}m\left(\frac{dR(n)}{dn}\right)^2-V(R)=V(R_0)-2V(R_s). \tag{43}$$

This is the equation of motion of the particle for $s<n<N$. We are interested in $N\rightarrow\infty$ limit and we have to satisfy the boundary condition $\{dR(n)/dn\}_{n=N}=0$ at the end of the chain. In the particle picture, this is equivalent to the condition that the total energy of the particle obeying Eq. (42) must be zero. This implies that $V(R_0)=2V(R_s)$. For a given s, this uniquely fixes the values of the two variables R_0 and R_s.

The net transition state is shaped as a hook and the hydrophobic part of the chain is completely in the short arm of the hook (see Fig. 9). A configuration like the one in Fig. 10 where the whole of the hook is formed by the hydrophobic part is not a transition state. The transition state in Fig. 9, though it seems likely to occur in crossing between liquid liquid interfaces, it seems rather difficult to form in the case of passage through a pore as there are two difficulties: (1) the chain has to bend to form the hook, (2) the pore has to be wide enough to accommodate the two strands of the hook simultaneously. In spite of these, nature does seem to use this as an inspection of Fig. 14-14 of Ref. [9] shows.

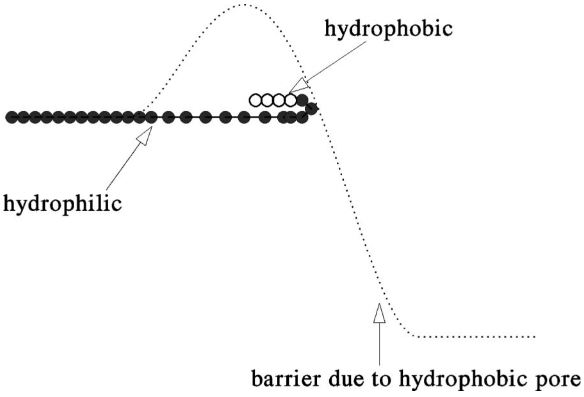

FIG. 9. The transition state for a hydrophilic chain with a hydrophobic signal sequence, passing through a hydrophobic pore. Compare with Fig. 14-14 of the book by Alberts *et al.*

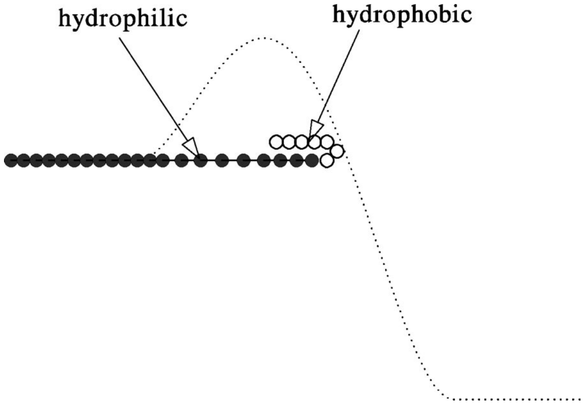

FIG. 10. This is not a possible transition state.

VII. CONCLUSIONS

We have considered the generalization of the Kramers escape over a barrier problem to the case of a long chain molecule. It involves the motion of chain molecule of N segments across a region where the free energy per segment is higher, so that it has to cross a barrier. We consider the limit where the width of the barrier w is large in comparison with the Kuhn length l, but small in comparison with the total length Nl of the molecule. The limit where $Nl\ll w$ has been considered in a recent paper by Park and Sung [22]. We use the Rouse model and find there are two possible mechanisms that can be important—end crossing and hairpin crossing. We calculate the free energy of activation for both and show that both have a square root dependence on the temperature T, leading to a non-Arrhenius form for the rate. We also find that the activation energy for hairpin crossing is two times the activation energy for end crossing. Inspite of this, for long enough chains, where the geometry of the systems permits, hairpin formation can be the dominant mode of escape as seen in the experiments of Han *et al.* [14].

While in the short chain limit Park and Sung [22] find the activation energy to be linearly dependent on N, we find that for long chains, the activation energy is independent of N. We also show that there is a special time-dependent solution of the model, which corresponds to a kink in the chain, confined to the region of the barrier. In usual nonlinear problems with a kink solution, the problem has translational invariance and the soliton/kink can therefore migrate. In our problem, the translational invariance is not there, due to the presence of the barrier and the kink solution is not free to move in space. However, the polymer on which the kink exists, can move, though the kink is fixed in space. Thus, the polymer goes from one side to the other by the motion of the kink in the reverse direction on the chain. If there is no free energy difference between the two sides of the barrier, then the kink moves by diffusion and the time of crossing $t_{\mathrm{cross}}\sim N^2/T^{3/2}$. If there is a free energy difference, then the kink moves with a nonzero velocity from the lower free energy side to the other, leading to $t_{\mathrm{cross}}\sim N/\sqrt{T}$. We also discuss the applicability of the mechanism to the recent experiments of Kasianowicz *et al.* [13], where DNA molecules were drawn through a nanopore by the application of a potential difference. Our result that $t_{\mathrm{cross}} \sim N$ is in agreement with these experiments. We also consider the translocation of hydrophilic polypeptides across hydrophobic pores. Biological systems accomplish this by having a hydrophobic signal sequence at the end that goes in first. Our analysis leads to the conclusion that for such a molecule, the configuration of the molecule in the transition state is similar to a hook, and this is in agreement with presently accepted view in cell biology [9].

ACKNOWLEDGMENTS

K.L. Sebastian is deeply indebted to Professor K. Kishore for the encouragement that he has given over the years. He thanks Professor S. Vasudevan and Professor Diptiman Sen for discussions and Professors B. Cherayil and Indrani Bose for their comments. We also thank Professor M. Büttiker for pointing out some of the references in Ref. [26].

APPENDIX

1. The eigenfunctions of the Hamiltonian $\hat{H}^{\ddagger}$

The Hamiltonian $\hat{H}^{\ddagger} = -\partial^2/\partial n^2 + \omega_0^2\{1 - 3\,\mathrm{sech}^2(\omega_0 n/2)\}$ has the following eigenfunctions (functions are not normalized) and eigenvalues, if n allowed to be in the range $(-\infty,\infty)$.

a. Discrete states

(1) $\psi_0(n) = \mathrm{sech}^3(\omega_0 n/2)$; $\varepsilon_0 = -5\omega_0^2/4$,
(2) $\psi_1(n) = \mathrm{sech}^2(\omega_0 n/2)\tanh(\omega_0 n/2)$; $\varepsilon_1 = 0$,
(3) $\psi_2(n) = \{-3 + 2\cosh(\omega_0 n)\}\,\mathrm{sech}^3(\omega_0 n/2)$; $\varepsilon_2 = 3\omega_0^2/4$.

b. Continuum states

The continuous part of the spectrum starts at ω_0^2. The potential is reflectionless. Corresponding to an eigenvalue $\omega_0^2 + k^2$, there are two eigenfunctions, which we write as an odd function and an even function. They are

$$\begin{aligned}(1)\quad \psi_{\mathrm{even}}(n) = {} & 8k(k^2+\omega_0^2)\cos(kn) - 3\omega_0(8k^2 \\ & + 3\omega_0^2)\sin(kn)\tanh(\omega_0 n/2) \\ & - 30k\omega_0^2\cos(kn)\tanh^2(\omega_0 n/2) \\ & + 15\omega_0^3\sin(kn)\tanh^3(\omega_0 n/2),\end{aligned}$$

$$\begin{aligned}(2)\quad \psi_{\mathrm{odd}}(n) = {} & -8k(k^2+\omega_0^2)\sin(kn) - 3\omega_0(8k^2 \\ & + 3\omega_0^2)\cos(kn)\tanh(\omega_0 n/2) \\ & + 30k\omega_0^2\sin(kn)\tanh^2(\omega_0 n/2) \\ & + 15\omega_0^3\cos(kn)\tanh^3(\omega_0 n/2).\end{aligned}$$

In the limit $n \to \pm\infty$, the even function becomes

$$\begin{aligned}\psi_{\mathrm{even}}(n) = {} & 2k(4k^2 - 11\omega_0^2)\cos(kx) \\ & \pm 6\omega_0(-4k^2 + \omega_0^2)\sin(kx)\end{aligned}$$

which may be written as $(\mathrm{const})\cos[kx \mp \delta(k)]$, so that the phase shift

$$\delta(k) = \arctan\left(\frac{-3\omega_0(\omega_0^2 - 4k^2)}{k(-11\omega_0^2 + 4k^2)}\right).$$

The phase shift for the odd solution is just the same. Hence the total change in the density of states is given by

$$\Delta n(k) = \frac{2}{\pi}\frac{d\delta(k)}{dk} = -\frac{2}{\pi}\left(\frac{\omega_0}{k^2+\omega_0^2} + \frac{2\omega_0}{4k^2+\omega_0^2} + \frac{6\omega_0}{4k^2+9\omega_0^2}\right).$$

On integration, $\int_0^\infty dk\,\Delta n(k) = -3$, as it should be, as there are three bound states for $\hat{H}^{\ddagger}$.

2. Evaluation of the infinite products

a. Hairpin crossing

The infinite product that is to be evaluated is

$$I_{hp} = \left(\frac{\prod_k \varepsilon_k}{\prod_{k>2} \varepsilon_k^{\ddagger}}\right)^{1/2}, \tag{A1}$$

where ε_k represent the eigenvalues of the continuum states of the Hamiltonian $\hat{H}^{ms} = (-\partial^2/\partial n^2 + \omega_0^2)$ and $\varepsilon_k^{\ddagger}$ are the eigenvalues of $\hat{H}^{\ddagger}$, satisfying the boundary conditions at $n = \pm\infty$. The above product involves only the continuum eigenvalues of the two Hamiltonians. Now,

$$\begin{aligned}\ln I_{hp} &= \frac{1}{2}\left(\sum_k \ln\varepsilon_k - \sum_{k>2}\ln\varepsilon_k^{\ddagger}\right) \\ &= \frac{1}{2}\int_0^\infty dk\,\ln(\omega_0^2 + k^2)[n(k) - n_{hp}^{\ddagger}(k)],\end{aligned} \tag{A2}$$

where the $n(k)$ stands for the density of states in the continuum, for the Hamiltonian $\hat{H}^s$ and $n_{hp}^{\ddagger}(k)$ for the Hamiltonian $\hat{H}^{\ddagger}$. The change in the density of states is $\Delta n_{hp}(k) = -n(k) + n_{hp}^{\ddagger}(k)$ and is easily evaluated from the information given in Sec. 1 of this Appendix. It is

$$\Delta n_{hp}(k) = -\left(\frac{\omega_0}{\omega_0^2+k^2} + \frac{2\omega_0}{\omega_0^2+4k^2} + \frac{6\omega_0}{9\omega_0^2+4k^2}\right)\frac{2}{\pi}.$$

Using this to evaluate the integral in the Eq. (A2) we get

$$I_{hp} = \frac{15}{2}\omega_0^3. \tag{A3}$$

b. End crossing

The product that we wish to evaluate is

$$I_{\mathrm{end}} = \left(\frac{\prod_k \varepsilon_k}{\prod_{k>2} \varepsilon_k^{\ddagger}}\right)^{1/2}. \tag{A4}$$

This infinite product in the above equation is over the continuous spectra of the two Hamiltonians. The change in the density of states is now just half of the density of states for the hairpin case. That is, $\Delta n_{\mathrm{end}}(k)=\frac{1}{2}\Delta n_{hp}(k)$. At first sight, this leads to a problem, such as $\int_0^\infty dk\Delta n_{\mathrm{end}}(k)=-3/2$, instead of the expected 2 (as $\hat{H}^{\ddagger}$ has two bound states while $\hat{H}^{ms}$ has none). The solution to ths is quite well known—$\hat{H}^{ms}$ has a state with eigenvalue ω_0^2 where its continuous spectrum starts, and half of this state is to be considered as a bound state. Then, we can write the above as

$$I_{\mathrm{end}}=\exp\left(-\frac{1}{2}\int_0^\infty dk\Delta n_{\mathrm{end}}(k)\ln(\omega_0^2+k^2)\right)\sqrt{\omega_0}.$$

Hence we find

$$I_{\mathrm{end}}=\left(\frac{15}{2}\right)^{1/2}\omega_0^2. \tag{A5}$$

---

[1] H. A. Kramers, Physica (Utrecht) **7**, 284 (1940).
[2] S. Chandrasekhar, Rev. Mod. Phys. **15**, 1 (1943).
[3] P. Hänggi, P. Talkner, and M. Borkovec, Rev. Mod. Phys. **62**, 251 (1990).
[4] V. I. Mel'nikov, Phys. Rep. **209**, 1 (1991).
[5] S. Coleman, in *The Whys of Subnuclear Physics, 1977*, Erice Lectures, 1977, edited by A. Zichichi (Plenum, New York, 1979).
[6] H. Kleinert, *Path Integrals* (World Scientific, Singapore, 1990).
[7] H. Riezman, Science **278**, 1728 (1997).
[8] P. J. Park and W. Sung, Phys. Rev. Lett. **77**, 783 (1996).
[9] B. Alberts, D. Bray, A. Johnson, J. Lewis, M. Raff, K. Roberts, and P. Walker, *Essential Cell Biology* (Garland, New York, 1998).
[10] S. M. Simon and G. Blobel, Cell **65**, 371 (1991).
[11] B. Dreiseikelmann, Microbiol. Rev. **58**, 293 (1994).
[12] V. Citovsky and P. Zambryski, Annu. Rev. Microbiol. **47**, 167 (1993).
[13] J. J. Kasianowicz, E. Brandin, D. Branton, and D. W. Deamer, Proc. Natl. Acad. Sci. USA **93**, 13 770 (1996).
[14] J. Han, S. W. Turner, and H. G. Craighead, Phys. Rev. Lett. **83**, 1688 (1999).
[15] C. Chipot and A. Pohoille, J. Am. Chem. Soc. **120**, 11 912 (1998).
[16] S. M. Bezrukov, I. Vodyanoy, R. A. Brutyan, and J. J. Kasianowicz, Mater. Charact. **29**, 8517 (1996).
[17] M. Muthukumar and A. Baumgartner, Macromolecules **22**, 1937 (1989); M. Muthukumar and A. Baumgartner, *ibid.* **22**, 1941 (1989).
[18] A. Baumgartner and J. Skolnick, Phys. Rev. Lett. **74**, 2142 (1995).
[19] W. Sung and P. J. Park, Phys. Rev. Lett. **77**, 783 (1996); see also, P. J. Park and W. Sung, J. Chem. Phys. **108**, 3013 (1998); Phys. Rev. E **57**, 730 (1998).
[20] M. Doi and S. F. Edwards, *The Theory of Polymer Dynamics*, (Clarendon, Oxford, 1986). The model has the defect of not taking excluded volume interactions into account.
[21] This is a consequence of assuming a completely flexible model for the polymer. This result is not true for a semiflexible polymer.
[22] P. J. Park and W. Sung, J. Chem. Phys. **111**, 5259 (1999).
[23] D. K. Lubensky and D. R. Nelson, Biophys. J. **77**, 99 005 (1999).
[24] K. L. Sebastian, Phys. Rev. E **61**, 3245 (2000).
[25] K. L. Sebastian, J. Am. Chem. Soc. **122**, 2972 (2000).
[26] There is an extensive literature on this topic. The most relevant to our discussion are M. Büttiker and R. Landauer, Phys. Rev. A **23**, 1397 (1981); M. Büttiker and H. Thomas, *ibid.* **37**, 235 (1988), P. Hanggi, F. Marchesoni, and P. Sodano, Phys. Rev. Lett. **60**, 2563 (1988); F. Marchesoni, *ibid.* **73**, 2394 (1994). For more recent work and the settling of a controversy involving these authors see M. Büttiker and T. Christen, *ibid.* **75**, 1895 (1995); T. Christen and M. Büttiker, Phys. Rev. E **58**, 1533 (1998). S. Habib and G. Lythe, e-print cond-mat/9911228.
[27] The cubic potential of Eq. (15) has a barrier height of $4V_0/27$ and an $\omega_0=\sqrt{2V_0/m}/R_0$. The values of V_0 and R_0 are to be taken so that these match with those for the quartic potential of the Eq. (5).
[28] R. Rajaraman, *Instantons and Solitons* (North Holland, Amsterdam, 1982).
[29] A. Scott, *Nonlinear Science* (Oxford University, Oxford, 1999).
[30] P. M. Chaikin and T. C. Lubensky, *Principles of Condensed Matter Physics* (Cambridge University Press, Cambridge, 1998).