We consider the generalization of the Kramers escape over a barrier problem to the case of a long chain molecule. The problem involves the motion of a 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 length of the molecule is much larger than the width of the barrier. The width is taken to be sufficiently wide that a continuum description is applicable to even the portion over the barrier. We use the Rouse model and analyse the mechanism of crossing a barrier. There can be two dominant mechanisms. They are: end crossing and hairpin crossing. We find the free energy of activation for the hairpin crossing is two times that 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 non-zero velocity from the lower free energy side to the other, leading to $t_{\text{cross}} \sim N / \sqrt{T}$. 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.

I. INTRODUCTION

The escape of a particle over a one dimensional barrier has been the subject of a large number of investigations. 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 [3]. 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 occurring 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/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 chain or 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 it has to pass through \[7–10\], resulting in an increase in the free energy for the portion of the chain inside the pore. In infection by bacteriophages, conjutive 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). Bezerukov et. al. \[13\] have studied the partitioning of polymer molecule into a nanoscale pore. Chipot and Pohoille \[14\] 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. \[13\] 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 \[16\] 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 exponential slowing down of diffusion with the number of segments \( N \) in the chain. Baumgartner and Skolnick \[7\] studied the movement of polymers through a membrane driven by an external bias and membrane asymmetry. Park and Sung \[8,18\], 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 involve motion of \( N \) segments across the pore, the time taken to cross, \( t_{\text{cross}} \) scales as \( N^3 \). They also show that in cases where there is adsorption on the trans side, translocation is favored and then \( t_{\text{cross}} \) scales as \( N^2 \). In a very recent paper, Park and Sung \[21\] 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 [22] 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 \( t_{\text{cross}} \) proportional to \( N \). Again, they assume diffusive dynamics. In a recent paper, we have suggested [23] 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, \( l << w << Nl \).

For example, in eukaryotic cells [9], the length of the nuclear pore is about 100 Å, while the Kuhn length for a single stranded DNA is perhaps around 15 Å [22]. 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, non-linear term in the model. We refer to this as the non-linear Rouse model. The non-linear 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 non-linear Rouse model, arising because of the non-linearity. 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 \( t_{\text{cross}} \) proportional to \( N \). Traditionally, the non-linear models that one studies (for example, the \( \phi^4 \) or the sine-Gordon model [24–27]) have potentials that are translationally invariant, and hence the kink can migrate freely in space. In comparison, in our problem, the non-linear term is fixed in position space and hence the kink too is fixed in space. However, the chain molecule (modelled as a string [19]) 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 polymer translocation.

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 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 \( N \) and hence for a sufficiently long chain, this 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 principle, in addition to these, it is possible for more than one hairpin to be formed.
However, it is obvious that in passage through a pore, unless the pore is rather wide, only the end-crossing mechanism would operate.

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. \cite{13}, 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 section are quite general and do not depend on the model that one uses to describe the polymer dynamics but involves the assumption 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 figure 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, corresponds to a free energy of zero in the free energy hypersurface shown in figure 2. In crossing over to the trans side, it has to go over a barrier, as in the figure 1. The transition state for the crossing can be easily found, from physical considerations. It is the state shown in figure 3. In it, the configuration of the polymer is such that the end of the polymer on the trans side is located exactly at the point on the trans side at which its free energy per segment is zero, with the other end on the cis side, and the chain is such that the free energy of the whole chain is a minimum. This is so because if one moves the end 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 minimum), then the total free energy of the system would decrease. Hence in the free energy hypersurface figure 2, the configuration shown in the figure 3 corresponds to the maximum (i.e. transition state). 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, with out changing the configuration of the polymer in the barrier region. As there is a free energy difference $\Delta V$ between the two sides, this would lead to a lowering of the free energy by $\Delta V$ 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 figure 3). Such a landscape implies that the translocation process would involve two steps. First step is going through the transition state by the overcoming of the activation barrier. Once the system has done this, it encounters a rather wide region of width proportional to the length of the chain. Crossing this region is the second step. As this region has a constant slope, the motion in this region is driven and it is similar to that of a Brownian particle subject to a constant force. Such a particle would take a time $t_{\text{cross}}$, proportional to $N$ to cross this region.

Till now, we considered the case of end-crossing. The scenario for hairpin crossing is similar. However, the activation energy is higher for hairpin crossing. In hairpin crossing,
the transition state is equivalent to the one end crossing, repeated two times. Hence the activation energy for the process is two times larger. Once a hairpin crossing occur, a kink-antikink pair is formed and the kink and the anti-kink separate rapidly, due to the driving force of the free energy gain. Then further crossing occurs by the movement of these two on the chain, which again 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 [19]. The chain is approximated as a string, with segments (beads) labelled 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 $n^{th}$ segment in space is denoted by $R(n,t)$, where $t$ is time. In the Rouse model, this position undergoes overdamped Brownian motion and its time development is described by the equation

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

In the above, $\zeta$ is a friction coefficient for the $n^{th}$ segment. The term $m \frac{\partial^2 R(n,t)}{\partial n^2}$ comes from the fact that stretching the chain can lower its entropy and hence increase its free energy. Consequently, the parameter $m = 3k_BT/l^2$ (see Doi and Edwards [19], equation (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 \( \left\{ \frac{\partial R(n,t)}{\partial n} \right\}_{n=0} = \left\{ \frac{\partial R(n,t)}{\partial n} \right\}_{n=N} = 0 \). $V(R)$ is the free energy of a segment of chain, located at the position $R$. We assume that $V(R)$ leads to a barrier located near $R = 0$. $f(n,t)$ are random forces acting on the $n^{th}$ 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 [19], equation (4.12)). The deterministic part of the equation (1), which will play a key role in our analysis, is obtained by neglecting the random noise term in (1). It is:

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

This may also be written as:

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

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

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

**C. The form of the barrier**

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

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

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

**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 equation (2). This free energy functional implies that at equilibrium, the probability distribution functional is \( \exp \left[ -\frac{1}{k_B T} \int dn \left\{ \frac{1}{2} m \left( \frac{dR}{dn} \right)^2 + V(R(n)) \right\} \right] \). The configurations of the polymer which makes free energy a minimum are found from

\[
\frac{\delta E[R(n)]}{\delta R(n)} = 0,
\]

which leads to the equation

\[
m \frac{d^2 R}{dn^2} = V'(R)
\] (6)

Notice that this is just a Newton’s equation for a particle (fictitious, of course) of mass \( m \) moving in a potential \(-V(R)\). This equation has four solutions that are of interest to us. The first two are: (1) \( R(n) = -a_0 \), (2) \( R(n) = a_1 \) which are the minima of the free energy. The first solution is the initial state, where the polymer is trapped in the vicinity of \(-a_0\).

The second is the most stable minimum, at \( R(n) = a_1 \). In addition to these, 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 satisfying \( R(-\infty) = -a_0 \) and the other end of the polymer to be at a point with \( R > R_{max} \), where \( R_{max} \) is the point where \( V(R) \) has its maximum value. For the Newton’s equation (3), the conserved energy is \( E_c = \frac{1}{2} m \left( \frac{dR}{dn} \right)^2 - V(R(n)) \). For the extremum path, \( E_c = 0 \). Thus, the particle starts at \( R(-\infty) = -a_0 \) with the velocity zero (this follows from the boundary conditions of the Rouse model) and ends up at \( R_f \) at the ”time” \( n = 0 \). Here \( R_f (R_{max}) \), is the point such that \( V(R_f) = 0 \), again with the velocity zero.

Further, free energy of this configuration is activation free energy for end crossing. As for this configuration, \( \frac{1}{2} m \left( \frac{dR}{dn} \right)^2 = V(R(n)) \), we find the activation free energy to be given by

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

The end crossing is illustrated in figure 4.
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 its starting point. This obviously has an activation energy

\[
E_{a,\text{hp}} = 2 \int_{-a_0}^{R_f} \sqrt{2mV(R)}dR = 2E_{a,\text{end}}
\]  

Thus the activation energy is exactly two times for end crossing \([20]\). The hairpin crossing is shown in figure \([5]\).

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 \( E_{a,\text{end}} \) and \( E_{a,\text{hp}} \) are proportional to \( \sqrt{T} \).

For our model potential of equation \( (3) \) we find \( R_f = a_0(\gamma - \sqrt{\gamma^2 - \gamma}) \) where \( \gamma = (1 + 2\frac{a_1}{a_0})\frac{1}{3} \) and

\[
E_{a,\text{end}} = \frac{\sqrt{mk_0^2}}{6} \left[ (3\gamma^2 + 1)\sqrt{1 + 3\gamma} - 3\gamma(\gamma^2 - 1) \ln \left( \sqrt{\gamma} / \left( 1 + \gamma - \sqrt{1 + 3\gamma} \right) \right) \right].
\]  

The Boltzmann factor \( e^{\frac{E_{\text{act}}}{k_BT}} \) for the crossing of one end of the polymer over the barrier thus has the form \( e^{\text{constant}/\sqrt{T}} \). Further, we find that it is 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 \([24]\) and hence we give just enough details to make the approach clear. The Rouse model in the equation \( (1) \) leads to the functional Fokker Planck equation

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

for the probability distribution functional \( P \). This equation implies that the flux associated with the co-ordinate \( R(n) \) is \([24]\)

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

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
We now do the functional integration using the variables \( c \) and the eigenfunctions \( \psi \) satisfying the Rouse boundary conditions \( \partial \psi = 0 \) at the two ends of the string. (The superscript "ms" in \( \hat{H}^{ms} \) stands for metastable). Now we can expand \( \delta R(n) \) as \( \delta R(n) = \sum_k c_k \psi_k(n) \) so that the expression for energy (13) becomes

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

We have defined \( \omega_0 \) by putting \( m \omega_0^2 = \left[ \frac{\partial^2 V(R)}{\partial R^2} \right]_{R=-a_0} \). The normal (Rouse) modes are just the eigenfunctions \( \psi_k(n) \) of the operator \( \hat{H}^{ms} = \left( -\frac{\partial^2}{\partial n^2} + \omega_0^2 \right) \), having the eigenvalue \( \varepsilon_k \) and satisfying the Rouse boundary conditions \( \frac{\partial \psi_k(n)}{\partial n} = 0 \) at the two ends of the string. In determining the crossing of the barrier, the key role is played by the quantities \( \omega_0 \) and \( \varepsilon_k \), having the eigenvalue \( \varepsilon_k \) and satisfying the Rouse boundary conditions \( \frac{\partial \psi_k(n)}{\partial n} = 0 \) at the two ends of the string. (The superscript "ms" in \( \hat{H}^{ms} \) stands for metastable). Now we can expand \( \delta R(n) \) as \( \delta R(n) = \sum_k c_k \psi_k(n) \) so that the expression for energy (13) becomes

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We now do the functional integration using the variables \( c_k \). Then the normalization condition \( \int D[R(n)] P = 1 \) becomes

\[
\frac{1}{Z_0} \prod_k \int \delta c_k \exp \left[ -\frac{1}{2} m \beta \varepsilon_k c_k^2 \right] = 1.
\]

This leads to

\[
Z_0 = \left( \frac{2\pi}{m \beta \varepsilon_k} \right)^{1/2}.
\]

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 the equation (10) is rather difficult to handle as we have not been able to obtain analytic solutions to the Newton’s equation (10). In determining the crossing of the barrier, the key role is played by the quantities \( \omega_0 \) and \( \varepsilon_k \), having the eigenvalue \( \varepsilon_k \) and satisfying the Rouse boundary conditions \( \frac{\partial \psi_k(n)}{\partial n} = 0 \) at the two ends of the string. (The superscript "ms" in \( \hat{H}^{ms} \) stands for metastable). Now we can expand \( \delta R(n) \) as \( \delta R(n) = \sum_k c_k \psi_k(n) \) so that the expression for energy (13) becomes

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We now do the functional integration using the variables \( c_k \). Then the normalization condition \( \int D[R(n)] P = 1 \) becomes

\[
\frac{1}{Z_0} \prod_k \int \delta c_k \exp \left[ -\frac{1}{2} m \beta \varepsilon_k c_k^2 \right] = 1.
\]

This leads to

\[
Z_0 = \left( \frac{2\pi}{m \beta \varepsilon_k} \right)^{1/2}.
\]

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 the equation (10) is rather difficult to handle as we have not been able to obtain analytic solutions to the Newton’s equation (10). In determining the crossing of the barrier, the key role is played by the quantities \( \omega_0 \) and \( \varepsilon_k \), having the eigenvalue \( \varepsilon_k \) and satisfying the Rouse boundary conditions \( \frac{\partial \psi_k(n)}{\partial n} = 0 \) at the two ends of the string. (The superscript "ms" in \( \hat{H}^{ms} \) stands for metastable). Now we can expand \( \delta R(n) \) as \( \delta R(n) = \sum_k c_k \psi_k(n) \) so that the expression for energy (13) becomes

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

We now do the functional integration using the variables \( c_k \). Then the normalization condition \( \int D[R(n)] P = 1 \) becomes

\[
\frac{1}{Z_0} \prod_k \int \delta c_k \exp \left[ -\frac{1}{2} m \beta \varepsilon_k c_k^2 \right] = 1.
\]

This leads to

\[
Z_0 = \left( \frac{2\pi}{m \beta \varepsilon_k} \right)^{1/2}.
\]
\[ E[R(n)] = E_{a, hp} + \frac{1}{2} m \int dn \delta R(n) \left[ -\frac{\partial^2}{\partial n^2} + \omega_0^2 \left\{ 1 - 3 \sec h^2 \left( \omega_0(n - n_0)/2 \right) \right\} \right] \delta R(n) \]  

For the potential of equation (13) \( E_{a, hp} = (8R_0/15) \sqrt{2m_v_0} \). The normal modes for fluctuations around the saddle are determined by the eigenfunctions of the operator \( \hat{H}^t = -\frac{\partial^2}{\partial n^2} + \omega_0^2 \left\{ 1 - 3 \sec h^2 \left( \omega_0(n - n_0)/2 \right) \right\} \). (\( \hat{t} \) is used to denote the saddle point). The eigenfunctions are: (a) the discrete states \( \psi_0^\dagger, \psi_1^\dagger \) and \( \psi_2^\dagger \) having the eigenvalues \( \varepsilon_0^\dagger = -5\omega_0^2/4, \varepsilon_1^\dagger = 0 \) and \( \varepsilon_2^\dagger = 3\omega_0^2/4 \) and (b) the continuum of eigenstates with eigenvalues of the form \( \varepsilon_k^\dagger = \omega_0^2 + k^2 \) (more details are given in appendix A). We denote the eigenfunctions by \( \psi_k^\dagger \). The existence of the eigenvalue \( \varepsilon_1^\dagger = 0 \) comes from the freedom of the kink-antikink pair to have its center anywhere on the chain (the hairpin can be formed anywhere). In the following, \( \sum_k \) would stand for summation over all the eigenstates, including both the discrete and continuum states while a symbol like \( \sum_{k \neq 1} \) means that the bound state \( \psi_1^\dagger \) is to be excluded from the sum. Now writing \( \delta R(n) = \sum_{k \neq 1} c_k^\dagger \psi_k^\dagger \), we get

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

We write the probability density near the saddle as

\[ P = \frac{\theta(c_0^\dagger, c_1^\dagger \ldots)}{Z_0} \exp \left\{ -\frac{E[R(n)]}{k_B T} \right\} \]

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

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

Using the equations (17) and (18) we get

\[ j_k^\dagger = -\frac{k_B T}{Z_0 \zeta} \frac{\partial \theta(c_0^\dagger, c_1^\dagger \ldots)}{\partial c_k^\dagger} \exp \left\{ -\frac{1}{k_B T} \left( E_{a, hp} + \frac{1}{2} m \sum_{k \neq 1} \varepsilon_k^\dagger \left( c_k^\dagger \right)^2 \right) \right\} \]  

(19)

In a steady state, there is flux only in the unstable direction. That is, only \( j_0^\dagger \) is non-zero. This means that \( \theta \) can depend only on \( c_0^\dagger \), which implies that \( j_0^\dagger \) must have the form

\[ j_0^\dagger = A \exp \left\{ -\frac{1}{k_B T} \left( \frac{1}{2} m \sum_{k \neq 1} \varepsilon_k^\dagger \left( c_k^\dagger \right)^2 \right) \right\} \]

(20)

where \( A \) is a constant, to be determined. Using the equation (20) in (19) we get

\[ \frac{\partial \theta(c_0^\dagger)}{\partial c_0^\dagger} = -A \exp \left\{ -\frac{m}{2k_B T} \varepsilon_0^\dagger \left( c_0^\dagger \right)^2 \right\} \]  

The fact that \( \theta(c_0^\dagger) \) must approach unity as \( c_0^\dagger \to -\infty \), enables one to get

\[ A = \left( \frac{m|c_0^\dagger|}{2\pi k_B T} \right)^{1/2} \]  

Hence \( \theta(c_0^\dagger) = \left( \frac{m|c_0^\dagger|}{2\pi k_B T} \right)^{1/2} J_{1/2} \int_{c_0^\dagger}^\infty \exp \left\{ -\frac{1}{2k_B T} m |c_0^\dagger| z^2 \right\} \]  

Now
the net flux crossing the barrier is found by integrating \( j_0^\pm \) over all directions other than \( c_0^\pm \). The integrals over all \( c_k^\pm \), except \( c_1^\pm \) is straightforward. As \( \epsilon_1^\pm = 0 \), \( f \, dc_1^\pm \) 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, \( f \, dc_1^\pm = \alpha \, dn_0 \), where \( \alpha^2 = f_{-\infty}^{\infty} \, dn \left( \frac{\partial R_{hp}(n)}{\partial n} \right)^2 = \frac{E_{a, hp}}{m} \).

Hence the rate becomes

\[
k_{hp} = \frac{k_B T}{Z_0 \zeta} \left( \frac{m |\epsilon_0^\pm|}{2 \pi k_B T} \right)^{1/2} \prod_{k>1} \left( \frac{2\pi k_B T}{m |\epsilon_k^\pm|} \right)^{1/2} \left( \frac{E_{a, hp}}{m} \right)^{1/2} N \exp \left( -\frac{E_{a, hp}}{k_B T} \right) \tag{21}\]

The notation \( \prod \) is used to indicate product over all eigenvalues of \( \tilde{H}^\dagger \), except the first two. On using the expression for \( Z_0 \),

\[
k_{hp} = \frac{k_B T}{\zeta} \left( \frac{m |\epsilon_0^\pm|}{2 \pi k_B T} \right)^{3/2} I_{hp} \left( \frac{|\epsilon_0^\pm| E_{a, hp}}{|\epsilon_2^\pm| m} \right)^{1/2} N \exp \left( -\frac{E_{a, hp}}{k_B T} \right) \tag{22}\]

where \( I_{hp} = \left( \prod_{k \geq 2} \frac{\epsilon_k}{\epsilon_0} \right)^{1/2} \). This infinite product is evaluated in the appendix B and is found to be \( I_{hp} = \frac{15}{2} \omega_0^3 / \zeta \). This leads to

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

**B. End Crossing**

In this case, the analysis is similar to the above. The operator \( \tilde{H}^\dagger \) is the same as earlier. However, there is an interesting difference. In the hairpin case, the boundary conditions on \( \psi_k^\dagger \) (\( \frac{d \psi_k^\dagger}{dn} = 0 \), 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 \( \psi_k^\dagger \) that exists in the hairpin case as they do not satisfy the Rouse boundary condition \( \frac{d \psi_k^\dagger}{dn} = 0 \) 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 the two ends). The discrete spectrum now has only the eigenvalues \( \epsilon_0^\pm = -5 \omega_0^2 / 4 \), and \( \epsilon_2^\pm = 3 \omega_0^2 / 4 \). The expression for the rate is

\[
k_{end} = \frac{k_B T}{\zeta} \left( \frac{m |\epsilon_0^\pm|}{2 \pi k_B T} \right)^{1/2} \tilde{I}_{end} \exp \left( -\frac{E_{a, end}}{k_B T} \right) \tag{24}\]

where \( \tilde{I}_{end} = \prod_{k \geq 0} \left( \frac{2 \pi k_B T}{m \omega_0} \right)^{1/2} \). 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 \( \epsilon_2^\pm = 3 \omega_0^2 / 4 \). Separating this out from the product, one can write \( \tilde{I}_{end} = \left( \frac{2m}{3\pi k_B T \omega_0} \right)^{1/2} I_{end} \),
where $I_{\text{end}} = \left( \prod_{k} \epsilon_k \right)^{1/2}$. The evaluation of this product involves some subtlety and is done in the Appendix B. The result is

$$k_{\text{end}} = \frac{5m\omega_0^2}{2\sqrt{2}\pi\zeta} \exp \left( -\frac{E_{a,\text{end}}}{k_BT} \right)$$

Accounting for the existence of two ends leads to

$$k_{\text{two-ends}} = \frac{5m\omega_0^2}{\sqrt{2}\pi\zeta} \exp \left( -\frac{E_{a,\text{end}}}{k_BT} \right)$$

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 $t_{\text{cross}}$. To calculate this, we first look at the mathematical solutions of the deterministic equation (2). The simplest solutions of this equation are: $R(n,t) = -a_0$ and $R(n,t) = a_1$. 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 the mean position which may be analyzed using the normal co-ordinates 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, the above equation 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 [24].

As is usual in the theory of non-linear wave equations, a kink solution moving with a velocity $v$ may be found using the ansatz $R(n,t) = R_s(\tau)$ where $\tau = n - vt$ [24]. Then the equation (2) reduces to

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

(26)

If one imagines $\tau$ 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, with $V'(R) \to 0$ as $R \to \pm \infty$. For the potential of the equation (3), 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

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

(27)

with $\omega = \sqrt{k/m}$. The solution exists only if the velocity $v = \frac{\sqrt{mk}}{\zeta} (a_0 - a_1)$. 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 \( \tau_0 \) 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, if \( a_0 < a_1 \), then \( V_f < V_b \), and 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 \( a_0 = a_1( V_f = V_b) \) the velocity of the kink is zero.

B. Fluctuations about the kink

We now analyze the effect of the noise term present in the equation (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 and one can make use of these methods. Following ‘Instanton methods’ of field theory, 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 \( a(t) \), where \( a(t) \) is a random function of time which is to be determined. \( \phi_p \) are a set of functions (the Rouse modes) below and \( X_p(t) \) are expansion coefficients. This may be put into the equation (1) to derive an equation of motion for \( a(t) \). Neglecting kink-phonon scattering leads to

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

where we define \( \psi_0(n) \) by \( \partial_n R_s(n) = C \psi_0^*(n) \) with

\[
C^2 = \left\langle \partial_n R_s(n) \left| e^{v\sqrt{\pi}m} \right| \partial_n R_s(n) \right\rangle = \frac{2}{3} \pi \omega \csc(2\pi \frac{a_1 - a_0}{a_0 + a_1}) (a_1 - a_0) a_0 a_1. \tag{30}
\]

and

\[
\xi_0(t) = \frac{1}{\xi} \int_{-N/2}^{N/2} dn \psi_0^*(n) e^{v\sqrt{\pi}/(2m)} f(n + a(t),t). \tag{31}
\]

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

\[
\langle \xi_0(t) \xi_0(t_1) \rangle = \delta(t - t_1)(2k_B T/\xi) \int_{\text{over the kink}} dn e^{v\sqrt{\pi}/m} [\psi_0(n)]^2 \tag{32}
\]

For the potential given by the equation (5) one gets

\[
\langle \xi_0(t) \xi_0(t_1) \rangle = \delta(t - t_1)k_B T/(2\xi a_0 a_1) \sec(2\pi \frac{a_1 - a_0}{a_0 + a_1}) (3a_1 - a_0) (3a_0 - a_1). \tag{33}
\]

The 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 $t_{\text{cross}}$

For the polymer to cross the barrier, the kink has to go in the reverse direction, by a distance equal to $N$. As the equation (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 particle starting at $a = N$ at the time $t = 0$ and being absorbed at $a = 0$, we get

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

(34)

Here, the diffusion coefficient

$$D = \frac{1}{2tC^2} \int_0^t dt_1 \int_0^t dt_2 \langle \xi_0(t_1) \xi_0(t_2) \rangle$$

$$= \frac{3k_B T}{8\pi \zeta} \frac{m}{k} \frac{(a_1 - a_0)(3a_0 - a_1)}{(a_1 - a_0)^2(a_1 - a_0)} \tan(2\pi \frac{a_1 - a_0}{a_0 + a_1}).$$

(35)

The 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:

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

(36)

The Laplace transform of the survival probability is given by $\overline{P}(s) = \int_0^\infty da \overline{P}(a, s)$ and is found to be

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

(37)

The average crossing time is given by $t_{\text{cross}} = \text{Limit}_{s \to 0} \overline{P}(s) = N/(-v)$, if $v < 0$. As $v$ is proportional $\sqrt{mk}$, assuming $V(R)$ to be temperature independent we find $t_{\text{cross}} \sim N/\sqrt{T}$. 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 $v \to 0$ limit of $\overline{P}(s)$, we get

$$\overline{P}(s) = \frac{1}{s} \left( 1 - e^{-\frac{\sqrt{N^2}}{2s}} \right)$$

(38)

so that the survival probability becomes

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

(39)

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

13
In their analysis, Park and Sung [18] 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 non-linear object in the chain whose width is of the same order as that of the barrier. As the polymer is initially subject to a potential well, the entropic contribution to the barrier that Park and Sung [18] 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 [18]. In the case where there is no free energy difference, 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 [21], 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 units 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 section II D, the free energy of activation does not depend on the length of the chain. Hence, the mechanism is the favoured 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 case of translocation of biological macromolecules, considered in section V 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 have been investigated by Han et al [13]. In contrast to the situation for a pore, there is an additional direction is 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 figures 4 and 5). Experimental results show that the longer molecule crosses the barrier faster. This means that the $N$-dependence of $k_{hp}$ causes the hairpin crossing to be the dominant mechanism of crossing in these experiments.

### V. HOW DO BIOLOGICAL SYSTEMS LOWER THE ACTIVATION ENERGY?

If there was a high activation energy ($>> k_B T$) for the translocation, 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 begining 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 reference [4], figure 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 the Newton-like equation

\[
m \frac{d^2 R}{dn^2} = V'_{\text{new}}(n, R),
\]

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

\[
V_{\text{new}}(n, R) = -V(R) \text{ if } 0 < n < s \quad \text{and} \quad V(R) \text{ if } s < n < N
\]

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 the figure 3. The boundary conditions \( \left\{ \frac{dR}{dn} \right\}_{n=0} = \left\{ \frac{dR}{dn} \right\}_{n=N} = 0 \) 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 figure 3). 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:

\[
\frac{1}{2} m \left( \frac{dR(n)}{dn} \right)^2 + V(R) = V(R_0).
\]

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:

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

This is the equation of motion of the particle for \( s < n < N \). We are interested in \( N \to \infty \) limit and we have to satisfy the boundary condition \( \left\{ \frac{dR}{dn} \right\}_{n=N} = 0 \) at the end of the chain. In the particle picture, this is equivalent to the condition that the total energy of the particle obeying the equation 10 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 like a hook and the hydrophobic part of the chain is completely in the short arm of the hook (see figure 3). A configuration like the one in the figure 10 where the whole of the hook is formed by the hydrophobic part is not a transition state. The transition state in figure 3, 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. Inspite of these, nature does seem to use this as an inspection of the figure 14-14 of reference [9] shows.

VI. 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 \( Nl << w \) has been considered in a recent paper by Park and Sung [21]. We use the Rouse model and find there are two possible mechanism 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. [13]. The width of the barrier in these experiments is rather large in comparison with the length of the polymer so that the kink mechanism of crossing seems to be unlikely in this case.

While in the short chain limit Park and Sung 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 non-linear 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 \( t_{cross} \sim N^2/T^{3/2} \). If there is a free energy difference, then the kink moves with a non-zero velocity from the lower free energy side to the other, leading to \( t_{cross} \sim N/\sqrt{T} \). 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 [1]. It is also possible that a kink movement mechanism might operate in other biological phenomena, like protein folding [28].

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A. APPENDIX

I. The eigenfunctions of the Hamiltonian $\hat{H}^\dagger$

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

1. Discrete States

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

2. Continuum States

The continuous part of the spectrum starts at $\omega_0^2$. 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:

1) $\psi_{even}(n) = 8k (k^2 + \omega_0^2) \cos(kn) - 3\omega_0 (8k^2 + 3\omega_0^2) \sin(kn) \tanh(\omega_0 n)/2$

2) $\psi_{odd}(n) = -8k (k^2 + \omega_0^2) \sin(kn) - 3\omega_0 (8k^2 + 3\omega_0^2) \cos(kn) \tanh(\omega_0 n)/2$

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

$\psi_{even}(n) = 2k (4k^2 - 11\omega_0^2) \cos(kx) \pm 6\omega_0 (-4k^2 + \omega_0^2) \sin(kx)$, which may be written as $(\text{Constant}) \cos(kx \mp \delta(k))$, so that the phase shift $\delta(k) = \arctan(-3\omega_0 (\omega_0^2 - 4k^2)/k (-11\omega_0^2 + 4k^2))$. 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 $\hat{H}^\dagger$.

II. Evaluation of the Infinite Products

1. Hairpin Crossing

The infinite product is:

$$I_{hp} = \left( \prod_{k} \varepsilon_k \right) \left( \prod_{k>2} \varepsilon_k \right)^{1/2} \tag{A-1}$$

where $\varepsilon_k$ represent the eigenvalues of the continuum states of the hamiltonian $\hat{H}^{ms} = (-\frac{\partial^2}{\partial n^2} + \omega_0^2)$ and $\varepsilon_k^\dagger$ are the eigenvalues of $\hat{H}^\dagger$, satisfying the boundary conditions at $n = \pm\infty$.

The above product involves only the continuum eigenvalues of the two Hamiltonians. Now,
\[
\ln I_{hp} = \frac{1}{2} \left( \sum_k \ln \varepsilon_k - \sum_{k>2} \ln \varepsilon_k^+ \right)
\]

\[
= \frac{1}{2} \int_0^\infty dk \ln \left( \omega_0^2 + k^2 \right) \left( n(k) - n_{hp}^+(k) \right)
\]

where the \( n(k) \) stands for the density of states in the continuum, for the Hamiltonian \( \hat{H}^s \) and \( n_{hp}^+(k) \) for the Hamiltonian \( \hat{H}^\dagger \). The change in the density of states is \( \Delta n_{hp}(k) = -n(k) + n_{hp}^+(k) \) and is easily evaluated from the information given in subsection A1. It is \( \Delta n_{hp}(k) = -\left( \frac{\omega_0}{\omega_0^2 + k^2} + \frac{2\omega_0}{9\omega_0^2 + 4k^2} \right) \frac{2}{\pi} \). Using this, we get

\[
I_{hp} = \frac{15}{2} \omega_0^3 \quad \text{(A-2)}
\]

2. End Crossing

The product that we wish to evaluate is

\[
I_{end} = \left( \prod_k \varepsilon_k \right)^{1/2} \left( \prod_{k>2} \varepsilon_k^+ \right)
\]

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

Hence we find

\[
I_{end} = \left( \frac{15}{2} \right)^{1/2} \omega_0^2 \quad \text{(A-4)}
\]

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

FIG. 2. The potential energy along the reaction co-ordinate. 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 $t_{cross}$

FIG. 3. The transition state

FIG. 4. End Crossing

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.

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 $-\Delta V$.

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 direction in which it moves is shown by the arrows.

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

FIG. 10. This is not a possible transition state.
V(R) & -V(R) ->

path of the particle

R_0 R_s

R->
