Stochastic resonance during a polymer translocation process

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We have studied the occurrence of stochastic resonance when a flexible polymer chain undergoes a single-file translocation through a nano-pore separating two spherical cavities, under a time-periodic external driving force. The translocation of the chain is controlled by a free energy barrier determined by chain length, pore length, pore-polymer interaction, and confinement inside the donor and receiver cavities. The external driving force is characterized by a frequency and amplitude. By combining the Fokker-Planck formalism for polymer translocation and a two-state model for stochastic resonance, we have derived analytical formulas for criteria for emergence of stochastic resonance during polymer translocation. We show that no stochastic resonance is possible if the free energy barrier for polymer translocation is purely entropic in nature. The polymer chain exhibits stochastic resonance only in the presence of an energy threshold in terms of polymer-pore interactions. Once stochastic resonance is feasible, the chain entropy controls the optimal synchronization conditions significantly. © 2016 AIP Publishing LLC. [<http://dx.doi.org/10.1063/1.4945559>]

I. INTRODUCTION

Stochastic resonance (SR) is a noise-induced phenomenon, where background noise plays a constructive role in enhancing the response of a nonlinear system to a weak periodic signal.^{1–4} This phenomenon has been observed in a variety of disciplines including geology, information processing, optics, biology, and medicine.^{5–8} Most of the theoretical work related to SR has focused on a Brownian particle hopping over an *energy barrier* in a bistable potential, in the presence of a weak oscillatory force with frequency ω_s and amplitude F_0 . The power spectrum of such a Brownian particle exhibits an enhanced signal in the linear response regime for an optimum thermal noise strength. The effect of the input signal with frequency ω_s is to transfer power from the background noise into the signal at ω_s . The signal to noise ratio (SNR) is one of the measures of SR and is generally found to be proportional to $F_0^2 T^{-2} r_K$, where T is the temperature and r_K is the Kramers rate⁹ of hopping in the absence of the externally imposed oscillatory force. In general, r_K is proportional to $e^{-U/T}$, with U being proportional to the energy barrier separating the bistable states. Therefore SNR (proportional to $T^{-2} e^{-U/T}$) exhibits an optimal temperature, namely, optimal noise strength, for realizing maximum SNR. Indeed, the precise conditions for SR depend on the specifics of the prefactors pertinent to the specifics of the theoretical model.²

If the Brownian particle is not rigid, as in the case of flexible macromolecules, the particle is endowed with considerable conformational fluctuations. When such a macromolecule confronts a physical barrier, it is subjected to a reduction in its conformational degrees of freedom resulting in an *entropic barrier*.¹⁰ If there is additional energetic interaction between the macromolecule and the

physical barrier, the crossover of the molecule occurs across a *free energy barrier*. Such a basic model has recently played a major role in interpreting many experimental results on single-molecule translocations through nonporous under a constant external force.^{11,12} How an externally imposed oscillatory signal in time couples to the various conformations of the polymer chain and the noise strength as the chain undergoes translocation across a free energy barrier is of increasing interest in view of potential implications in macromolecular transport in biological contexts. The primary objective of the present paper is to address SR arising from the coupling between the externally imposed oscillatory signal and polymer translocation through a free energy barrier.

Before considering the role of chain fluctuations, there is an easier situation where a rigid Brownian particle hops across an entropic barrier instead of an energy barrier, under an externally imposed oscillatory force. The entropic barrier^{13–15} is created by translational entropy associated with confining the particle within uneven boundaries. It has been shown that such entropic barriers can also lead to SR, now called as entropic stochastic resonance (ESR).^{16,17} However, an additional potential energy contribution such as gravity is critically required in order to realize ESR in this system.^{16,17}

Returning to our present objective, there have already been several attempts to investigate SR of a flexible polymer. Using a combination of theory and simulations, the crossing of a flexible chain across an *ad hoc* bistable potential barrier under an oscillatory force field was studied.^{18,19} The polymer chain was characterized by a spring constant for the bond connecting the nearest neighboring beads along the chain contour and the chain length. The system exhibits SR at optimal values of noise strength, bond spring constant, and chain length. Since chain conformations are allowed to fluctuate in addition to the imposition of an energy barrier, the SR here may be called entropic stochastic resonance (ESR). Instead of imposing the *ad hoc* energy barrier, Zhang *et al.*²⁰

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FIG. 1. Model description of two-state translocation process in presence of a finite length pore.

have investigated the plausibility of true ESR by simulating a flexible polymer chain in two dimensions confined in a dumb-bell-shape geometry, with a bottleneck in the middle. In this numerical simulation, ESR was realized where the temporal coherence of the polymer motion occurs maximally at an optimal noise strength, for a certain intermediate values of the bottleneck width.

The related phenomenon of resonant activation (RA) of polymer transport has also received attention. In resonant activation,^{21,22} the barrier height is allowed to fluctuate and there is cooperative interplay between the barrier height fluctuation rate and the noise-induced barrier crossing rate. For example, translation of a rigid rod-like polymer in the presence of a fluctuating chemical potential difference has been found to exhibit resonant activation-like phenomenon, where the translocation rate attains a maximum at an optimal fluctuation amplitude.²³ In another example, the mobility of a polymer chain undergoing transport through a micro-channel in the presence of a periodic driving force can have a maximum at an optimal frequency.²⁴ Also, a sinusoidal driving force can induce an oscillatory behavior of the translocation time.²⁵ A recent simulation study reveals that the translocation rate can be significantly faster in the presence of a pore with an oscillatory width.²⁶ Furthermore, it is well known in the literature that the characteristics of polymer translocation through nanopores are dramatically influenced by pore-polymer interactions.^{12,27–35} Using simulations in two dimensions, Ikonen *et al.* have shown that the attractive pore-polymer interactions significantly induce resonant activation.³⁶ Stochastic resonance has been

realized^{37,38} in several practical situations such as electronic circuits, bistable ring-lasers, sensory processes of crayfish, and voltage-dependent ion channels. Few attempts have also been made at a single molecule level.^{39,40} As an example, the transition rate between unfolded and folded single DNA/RNA hairpins under an oscillatory force field has been investigated by experiments³⁹ and simulations.⁴⁰

With the above mentioned background of the literature on stochastic resonance and resonant activation of flexible polymer chains, where simulations in one or two dimensions have been the major tool, we present here analytical results for the occurrence of SR for a flexible polymer chain undergoing translocation through a nano-pore under a weak oscillatory driving force. The polymer translocation is treated as a two-state model, as depicted in Fig. 1, where a chain moves back and forth between state A and state B. In state A, one chain end is at the pore entry and the rest of the chain has restricted conformational degrees of freedom due to confinement in the donor compartment. In state B, the other end of the chain is at the pore exit with the rest of the chain confined in the receiver compartment. As the polymer undergoes translocation, every monomer inside the pore is subjected to pore-polymer interaction energy and the two tails (shown in Fig. 2(a)) have different entropic contributions to the free energy barrier of the system, depending on their lengths. Following our earlier work,²⁷ we have calculated the free energy landscape for the translocation and the intrinsic rate of crossing over the free energy barrier between state A and state B, after validating the used assumptions in deriving the results. We then combine our results for the present model with the calculation of power spectra by McNamara and Wiesenfeld¹ for the two-state model of SR. Based on the derived analytical formulas, we present the criteria for the occurrence of SR in terms of pore-polymer interaction, noise strength, and chain length. The key result for the present model is that a finite energy threshold in terms of polymer-pore interaction is required for SR to occur. Once SR is feasible, the chain entropy significantly controls the synchronization condition

FIG. 2. (a) Schematics of a Gaussian chain with N segments undergoing single-file translocation through a pore of length MI , with $N-m$ segments in the donor compartment and $m-M$ segments in the receiver compartment. Both compartments are spheres of radius RI . (b) Free energy profile $A(m)$ versus the scaled translocation coordinate (m/N) for different values of ϵ . For all four cases, $R = 5.0$, $N = 100$, $\zeta = 1$, $k_B T = 1$, and $M = 10$. Vertical dashed lines are used to depict different stages of chain translocation.

between the rate of translocation and frequency of the driving force.

The rest of the paper is organized as follows: In Sec. II, we provide a description of the free energy barrier and the rate of translocation across the barrier within the Fokker-Planck formalism. This is followed by a brief summary of the two-state model of McNamara and Wiesenfeld¹ to express the effect of an additional external periodic force on the power spectrum of the process. In Sec. III, we discuss the results with particular attention to the role of non-zero polymer-pore interaction energy in order to make SR feasible, and the relative control of the energetic and entropic parts of the total free energy on the predicted SR. The paper is concluded in Sec. IV.

II. THE MODEL

To begin with, we consider a Gaussian polymer chain of N segments each with step length l . The chain is confined among two spheres, 1 and 2, each with radius Rl as shown in Fig. 2(a). The spheres are connected by a cylindrical pore with finite length (ML). We further assume that the diameter of the pore connecting the two spheres is small enough so that the polymer can translocate only as a single file. If m is the number of translocated segments out of the donor compartment, the translocation process can be described in terms of the translocation coordinate (m) by the following Fokker-Planck equation:^{12,27}

$$\frac{\partial P(m,t)}{\partial t} = \frac{\partial}{\partial m} \left[\frac{k_0}{k_B T} \frac{\partial A(m)}{\partial m} P(m,t) + k_0 \frac{\partial}{\partial m} P(m,t) \right], \quad (1)$$

where $P(m,t)$ is the probability of finding the chain with state m at time t and k_0 is the rate constant associated with the dragging of each segment through the pore. We consider $k_0 (=k_B T/l^2 \zeta)$ to be independent of chain size N and the translocation coordinate m . ζ is the monomeric frictional coefficient. k_B and T are the Boltzmann constant and temperature of the system, respectively. If hydrodynamic interaction is present in the system, it is incorporated into the phenomenological parameter k_0 . The associated free-energy ($A(m)$) for m th state, with $N > 0$, can be expressed as^{12,27}

$$\begin{aligned} A(m) &= \epsilon m - k_B T \ln \left[\frac{2a}{R} f(N-m, R) \right] \\ &\quad - (N-m)k_B T \ln z_0, \quad \text{for } 0 < m \leq M, \\ A(m) &= \epsilon M - k_B T \ln \left[\frac{4a^2}{R^2} f(N-m, R) f(m-M, R) \right] \\ &\quad - (N-M)k_B T \ln z_0, \quad \text{for } M < m < N, \\ A(m) &= \epsilon(M-m+N) - k_B T \ln \left[\frac{2a}{R} f(m-M, R) \right] \\ &\quad - (m-M)k_B T \ln z_0, \quad \text{for } N \leq m \leq N+M, \\ f(N, R) &= \sum_{j=1}^{\infty} \exp \left(-\frac{j^2 \pi^2 l^2 N}{6R^2} \right). \end{aligned} \quad (2)$$

Here, ϵ is the average pore-polymer interaction energy per segment and z_0 is the effective coordination number in the bulk solution if it were to be taken as an effective lattice for the random walk statistics of the chain. Since the bulk solution

is a continuum, the effective coordination number is only a local parameter and we take this to be 4 ($z_0 = 4$). Any value in this neighborhood can be chosen in the calculations below without changing the physical conclusions. Thus the term $k_B T \ln z_0$ is an entropic loss for each segment placed inside the pore, arising from the lack of its ability to explore the three-dimensional space. a is an “anchoring” distance as discussed in Ref. 27. In this article, we set $z_0 = 4$, $a = l/2$, and $l = 1$. In Fig. 2(b), we show the free energy ($A(m)$) variation with scaled translocation coordinate (m/N) for four different values of ϵ and with $R = 5.0$, $N = 100$, $\zeta = 1$, $k_B T = 1$, and $M = 10$. The free energy profiles show that the translocation process is subjected to a free energy barrier. If ϵ is sufficiently attractive ($\epsilon = -1.45$ (black line) or -1.6 (green line)), the chain experiences a downhill free energy stabilization during pore filling stage and an uphill free energy threshold during chain expulsion stage. On the other hand, if ϵ is inert ($\epsilon = 0$ (red line)) or repulsive ($\epsilon = 0.2$ (blue line)), the chain experiences a free energy barrier during the pore filling stage.

The mean translocation time over such a barrier, i.e., the average time required by the chain to translocate from state A ($m = 1$) to state B ($m = N + M - 1$), can be evaluated as^{12,27}

$$\langle \tau_0 \rangle = \frac{1}{k_0} \int_1^{N+M-1} dm_1 \int_1^{m_1} dm_2 \exp \left(\frac{A(m_1) - A(m_2)}{k_B T} \right). \quad (3)$$

Here, we use a reflecting boundary condition with $m = 1$ and an absorbing boundary condition at $m = N + M - 1$. We define the mean translocation rate W_0 for the translocation process as

$$W_0 = \frac{1}{\langle \tau_0 \rangle}. \quad (4)$$

The mean translocation time $\langle \tau_0 \rangle$ is calculated from Eq. (3) by substituting Eq. (2) for $A(m)$. In general, this calculation needs to be done numerically due to the presence of the infinite sum for $f(N, R)$ in Eq. (2). However, for strong confinements, keeping only the leading term, known as the ground state dominance (GSD) approximation, was shown²⁷ to be of sufficient accuracy. The use of GSD approximation enables analytical tractability and transparency of the physical results which are otherwise buried inside numerics. Using GSD approximation, the mean translocation time ($\langle \tau_0 \rangle$) follows from Eqs. (2) and (3) as

$$\begin{aligned} k_0 \langle \tau_0 \rangle &= \frac{(N-M)^2}{2} + \frac{(N-M)}{\mu_1} \left(\frac{2a}{R} + \frac{R}{2a} \exp(\mu_1 M) \right) \\ &\quad \times [1 - \exp(-\mu_1 M)] \\ &\quad + \frac{2}{\mu_1^2} \exp(\mu_1 M) [1 - \exp(-\mu_1 M)]^2, \end{aligned}$$

where

$$\mu_1 = \frac{\epsilon}{k_B T} + \mu_2 \quad \text{and} \quad \mu_2 = -\frac{\pi^2 l^2}{6R^2} + \ln z_0. \quad (5)$$

Eq. (5) describes how the chain length (N), geometric constraints (M , z_0 and R), and the thermal energy ($k_B T$) affect the translocation time. Eq. (5) also suggests that with a finite size of the pore, μ_1 plays a significant role in determining the translocation time $\langle \tau_0 \rangle$. μ_1 essentially consists of two parts,

where μ_2 accounts for the effective entropic loss per chain segment placed inside the pore and $\frac{\epsilon}{k_B T}$ is the energetic change (gain or loss) per segment due to pore-polymer interaction. Thus, the relative contributions of ϵ and μ_2 determine the mean translocation time $\langle \tau_0 \rangle$. For convenience, we denote $\langle \tau_0 \rangle$ as τ_0 for the rest of the paper. To provide a dimensionless description, we henceforth scale all lengths in terms of the characteristic segment length l , taken as 0.34 nm. We have also scaled the energy in terms of the reference energy $k_B T_R$, by taking the reference temperature T_R as 298 K. This gives the scaled temperature $\tilde{T} = T/T_R$ for the present calculation. Similarly, we have scaled the time by $t_R = \sqrt{\frac{m_R l^2}{k_B T_R}}$, where the reference mass m_R is taken as 100 Da. For our choice of l, m_R , and T_R , the reference time unit t_R is 2 ps. This in turn gives a reference friction coefficient $\zeta_R = m_R/t_R$ to scale ζ as $\tilde{\zeta} = \frac{\zeta}{\zeta_R}$. We shall omit the tilde sign in our discussion for convenience.

Before we proceed further, we make a quick survey on (a) how good the ground state dominance (GSD) approximation is and (b) how the different controlling factors influence τ_0 . In this spirit, as an example, we have examined the variation of mean translocation time (τ_0) with pore-length (M) for a fixed thermal energy ($k_B T = 1$), as shown in Fig. 3(a). We show the results for three different values of ϵ (-1.6 (red line and red circular points), -1.3 (black line and black triangular points), and -1.2 (blue line and blue star-like points)) with $\zeta = 1$, $N = 100$ and $R = 5$. In all three cases, the smooth curves are from GSD approximation and the data points are from numerical evaluation of Eq. (3). The results obtained from GSD approximation are consistent with the full numerical integration results. In fact, we have tested the applicability of GSD approximation for a wide range of the parameter space (not shown here) and have found that the approximation is valid within 2-10 percent error.

Fig. 3(a) shows that when μ_1 is positive ($\epsilon = -1.2$), i.e., when the energetic gain due to the pore-polymer attraction ($\epsilon = -1.2$) is less than the entropic loss $\mu_2 = 1.32$, τ_0 increases monotonically with an increase in M . This is because of the fact that in this limit, μ_2 dominates over $\frac{\epsilon}{k_B T}$. Thus, the first term of the right hand side of Eq. (5) $\frac{(N-M)^2}{2}$ and entropic parts of the terms containing $\exp(\pm \mu_1 M)$ dominate over the energy

threshold for the process in determining τ_0 . In this case, the translocation process experiences an *entropy dominated* free energy barrier. In contrast, for a sufficiently strong attractive polymer-pore interaction ($\epsilon = -1.6$), μ_1 is negative. In this limit, τ_0 increases at a nonmonotonic rate with an increase in M . This is because of the fact that in the limit of $M \rightarrow 0$, the first term of right hand side of Eq. (5) $\frac{(N-M)^2}{2}$ dominates over the others to determine τ_0 . On the other hand for higher values of M , terms containing $\exp(\pm \mu_1 M)$ also contribute to τ_0 significantly. Hence, τ_0 increases more steeply with an increase in M in this limit. The latter can be expressed as an *energy dominated regime*. Finally, when μ_1 is very low due to $|\frac{\epsilon}{k_B T}| \sim \mu_2$, both the energetic and entropic contributions are comparable irrespective of the pore length in determining τ_0 (Fig. 3(a) with $\epsilon = -1.3$). This situation corresponds to a crossover case between the *entropy dominated* and *energy dominated* regimes.

In order to visualize the relative dominances of the energy and the entropy contributions to the translocation process, we have calculated the variation of the translocation rate (W_0) with both ϵ and M , as shown in Fig. 3(b). The variation shows that a highly negative μ_1 , i.e., with $\epsilon < -1.3$ and high M , results in a very low W_0 , which corresponds to the *energy dominated regime*. Similarly, in a strongly *entropy dominated situation*, when μ_1 is highly positive ($\epsilon \gg -1.3$ and high M), W_0 is also very low. On the contrary, in the limit of $\mu_1 \rightarrow 0$, there exists a crossover region between two aforesaid regimes with high translocation rate. It must be pointed out that the Fokker-Planck description of the translocation process, as used here, is valid under an adiabatic condition that the translocation time scale (τ_0) is much longer than the longest relaxation time ($\tau_{Rouse} = \frac{\zeta N^2}{12\pi^2 k_B T}$) of the Rouse chain. In the present study, the mean translocation times (τ_0) are always longer than τ_{Rouse} at least by a factor of 60.

Next, we introduce a weak periodic alternating driving force $F(t) = F_0 \cos \omega_s t$ across the cylindrical pore. Here, F_0 and ω_s are the strength and the angular frequency of the driving force ($F(t)$), respectively. To evaluate the effect of this weak periodic alternating force, we map the driven translocation process with a two-state model in the spirit of McNamara and Wiesenfeld.¹ To describe the two extreme

FIG. 3. (a) Variation of mean translocation time (τ_0) with pore length (M) for three values of ϵ ($R = 5.0$, $N = 100$, $\zeta = 1$ and $k_B T = 1$). Points represent the values obtained from numerical integration of Eq. (3) and the smooth curves are obtained from the ground state dominance approximation. (b) A two-parameter variation of scaled translocation rate ($W_0 \times 10^4$) with pore length (M) and pore polymer interaction energy (ϵ). Parameter set chosen: $N = 100$, $R = 5.0$, $\zeta = 1$, and $k_B T = 1$.

states state A and B of Fig. 1, symmetrically, we introduce a scaled state variable in terms of translocation coordinate as $\bar{m} = \frac{2m-(N+M)}{N+M}$. This ensures that the donor state A can be described as $\bar{m} = -m_c \rightarrow -1$ for $m = 1$ and the receiver state B with $\bar{m} = m_c \rightarrow +1$ for $m = N + M - 1$. We express the time-dependent transition rate out of $\pm m_c$ states in the presence of $F(t)$ as $W_{\pm}(t)$ and the corresponding probability densities of the states as $n_{\pm}(t)$. The governing master equation for $n_{\pm}(t)$ reads as

$$\frac{dn_+(t)}{dt} = -\frac{dn_-(t)}{dt} = W_-(t)n_-(t) - W_+(t)n_+(t). \quad (6)$$

Using the normalization condition, $n_+(t) + n_-(t) = 1$, the solution of Eq. (6) is given by

$$n_+(t) = g^{-1}(t) \left[n_+(t_0)g(t_0) + \int_{t_0}^t W_-(t')g(t')dt' \right], \quad (7)$$

$$g(t) = \exp \left[\int_{t_0}^t (W_-(t') + W_+(t')dt') \right],$$

where $n_+(t_0)$ is the probability density of +1 state at $t = 0$.

To proceed further, we approximately describe the time-dependent translocation rates ($W_{\pm}(t)$) as

$$W_{\mp}(t) = W_0 \exp(\pm \eta_0 \cos \omega_s t),$$

where

$$\eta_0 = \frac{F_0}{k_B T}. \quad (8)$$

Following the treatment by McNamara and Wiesenfeld,¹ we obtain the one sided time-averaged power spectrum ($S(\Omega)$), which is defined for positive Ω only, as

$$S(\Omega) = \langle S(\Omega) \rangle_t + \langle S(-\Omega) \rangle_t$$

$$= \left(1 - \frac{2W_0^2 \eta_0^2}{4W_0^2 + \omega_s^2} \right) \left[\frac{8W_0}{4W_0^2 + \Omega^2} \right]$$

$$+ \frac{4\pi \eta_0^2 W_0^2}{4W_0^2 + \omega_s^2} \delta(\Omega - \omega_s). \quad (9)$$

Eq. (9) is the power spectrum for the translocation process under consideration. Eq. (9) also shows that the power spectrum has two parts: the signal output which is a δ -function at the signal frequency, and the rest of the part is the noise

output. Subsequently, the *Signal* and the signal-to-noise ratio (*SNR*) can be expressed as¹

$$Signal = \frac{4\pi \eta_0^2 W_0^2}{4W_0^2 + \omega_s^2}, \quad (10)$$

$$SNR = \frac{\pi \eta_0^2 W_0}{2 \left(1 - \frac{2W_0^2 \eta_0^2}{4W_0^2 + \omega_s^2} \right)}. \quad (11)$$

It is to be recalled that $\eta_0 \sim F_0/k_B T$, ω_s is the driving frequency, F_0 is the amplitude of the driving force, and W_0 is the translocation rate given by Eq. (5), which in turn depends on T, ϵ, z_0, M, N , and R . In the present context, either *Signal* or *SNR* can be used as a quantifier for stochastic resonance.

Before we proceed to Sec. III, we mention a few pertinent points. First, the value of μ_1 depends on the choice of the bulk coordination number (z_0). We have arbitrarily set $z_0 = 4$ for the rest of the paper, as already mentioned. Second, we have ignored the temperature dependence of the segment length (l) in our calculation. Finally, we have used a temperature independent monomeric frictional coefficient ($\zeta = 1$). The physical conclusions are robust and are insensitive to the particular choices for these local parameters.

III. RESULTS AND DISCUSSIONS

We first consider the situation where the free energy barrier is purely entropic. This corresponds to the pore length being zero with $M\epsilon = 0$. We examine the variation of signal-to-noise ratio (*SNR*) with the scaled temperature (T) for three different values of N ($=75, 100$ and 150) as shown in Fig. 4(a) (for $\omega_s = 10^{-3}$, $F_0 = 0.1$, and $R = 5.0$). Results show that the *SNR* decreases monotonically with increasing temperature and hence no stochastic resonance is present. The corresponding *Signal* given by Eq. (10) is plotted against the reduced temperature in Fig. 4(b) with same parameter set as used in Fig. 4(a). This figure also shows that the signal decays monotonically with the increasing noise strength. Therefore, in absence of any pore-polymer interaction ($M\epsilon = 0$), no stochastic resonance phenomenon is observed for the model described in Fig. 1. The absence of SR for $M = 0$ can be explained as follows. Following Eq. (5),

FIG. 4. (a) Variation of scaled *SNR* ($=SNR \times 10^5$) with scaled temperature (T) for different N . Parameter set chosen: $\omega_s = 10^{-3}$, $F_0 = 0.1$, and $R = 5.0$. (b) Variation of *Signal* with scaled temperature (T) for different N with same parameter set as used in (a). τ_0 has been calculated using GSD approximation (Eq. (5)) for lines and by direct numerical integration (Eq. (3)) for points.

it can be shown that the equilibrium translocation time (τ_0) shows the limiting behavior $k_0\tau_0 \rightarrow \frac{N^2}{2}$ for $M = 0$. Thus, the translocation rate W_0 varies linearly with temperature as $\frac{2T}{N^2}$, because k_0 is proportional to T . Consequently, the $SNR \sim \frac{W_0}{T^2}$ becomes inversely proportional to the thermal noise, $\sim \frac{1}{TN^2}$. By a physical inspection also, one can argue that for $M\epsilon \rightarrow 0$, the free energy expression (Eq. (2)) provides a smooth entropy barrier that the chain experiences during translocation and the exponential terms of the τ_0 expression in Eq. (3), $\exp\left(\frac{A(m)}{k_B T}\right)$, becomes independent of temperature. Therefore, W_0 is proportional to T (from the k_0 factor). Hence, SNR decreases monotonically with an increase in temperature as no energy threshold exists for the barrier crossing event. As a result, no stochastic resonance is seen for a translocation over such purely entropic barriers. The monotonic variation of $Signal$ can also be explained following the same line of argument. Since the $Signal$ varies as $\frac{1}{T^2} \frac{W_0^2}{W_0^2 + \omega_s^2}$, for a moderate to high value of T , $W_0 \gg \omega_s$ and the $Signal$ changes as $\frac{1}{T^2}$. On the other hand, at $T \rightarrow 0$ limit, signal approaches to an asymptotic value proportional to $\frac{1}{\omega_s^2}$. Consequently, the $Signal$ cannot exhibit any nonmonotonicity with T in the absence of an energy threshold.

Second, we consider the situation with a finite pore length but no pore-polymer interaction ($\epsilon = 0$ and $M \neq 0$). In this situation also translocation progresses over a purely entropic barrier. In this limit, Eq. (5) can be expressed as

$$k_0\tau_0 = \frac{(N-M)^2}{2} + \frac{(N-M)}{\mu_2} \left(\frac{2a}{R} + \frac{R}{2a} \exp(\mu_2 M) \right) \times [1 - \exp(-\mu_2 M)] + \frac{2}{\mu_2^2} \exp(\mu_2 M) [1 - \exp(-\mu_2 M)]^2, \quad (12)$$

$$\mu_2 = -\frac{\pi^2 l^2}{6R^2} + \ln z_0.$$

Eq. (12) suggests that even in the presence of a finite pore length, the exponential terms $\exp(\pm\mu_2 M)$ of τ_0 become independent of temperature. Consequently, the translocation rate W_0 varies linearly with the noise strength as $\frac{2T}{(N-M)^2}$ (the T dependence coming from k_0). Hence, the SNR ($\sim \frac{W_0}{T^2}$) varies inversely proportional to the temperature, $\sim \frac{1}{TN^2}$. This

suggests that no stochastic resonance could be observed if the pore is inert ($\epsilon = 0$). As an illustration of the lack of SR in the present situation, the SNR and $Signal$ are plotted in Figs. 5(a) and 5(b), respectively, against T for different values of N (50, 75, and 100) with $M = 5$, $\omega_s = 10^{-5}$, $F_0 = 0.1$, and $R = 5.0$. Fig. 5(a) shows a monotonic variation of SNR with reduced temperature for different values of N , demonstrating the absence of SR even in the presence of a finite pore if the pore polymer interaction energy is zero. A monotonic decay is observed in $Signal$ variation with T for $\epsilon = 0$ as expected (Fig. 5(b)). Therefore, SR is not feasible in the absence of pore-polymer interaction energy.

Finally, we consider a pore of finite length ($M \neq 0$) with a finite pore-polymer interaction energy, $\epsilon \neq 0$. Now, the free energy barrier consists of both the energetic and entropic contributions. The variations of SNR and $Signal$ with T are plotted in Fig. 6 for different values of ϵ ($N = 100$, $M = 10$, $\omega_s = 10^{-5}$, $F_0 = 0.1$, and $R = 5.0$). While only monotonic decay is observed for $\epsilon = 0$ (as shown in Fig. 5), both SNR and $Signal$ change nonmonotonically with T , passing through a maximum, for an attractive pore ($\epsilon < 0$). Thus SR is feasible when pore-polymer interaction is allowed. To explain the situation, we recall Eq. (5), which suggests that the translocation process experiences an energy threshold as the exponential terms ($\exp(\pm\mu_1 M)$) are now temperature dependent. Consequently, the $SNR \sim \frac{W_0}{T^2}$ changes non-monotonically with increasing temperature as $\sim \exp(\frac{\pm\epsilon M}{T})$ terms are no longer negligible in determining W_0 . Hence, if $\epsilon M/T$ is not too small, the system experiences an efficient energy threshold and an interplay between the exponential term and the prefactor of τ_0 results in a turnover variation of SNR . A similar explanation can be provided for non-monotonic variation of the signal also (Fig. 6(b)). Therefore, the entropic barrier alone is not sufficient to exhibit SR and the presence of a threshold energy is crucial to observe SR during such translocation event. Fig. 6 also shows that with an increase in pore-polymer interaction energy the position of the resonance zone has shifted towards the high temperature regime. The observation is consistent with physical intuition. If pore-polymer interaction is sufficiently attractive, any further increase in $|\epsilon|$ results in a stronger energy threshold which makes τ_0 longer. To compensate this

FIG. 5. (a) Variation of scaled SNR ($=SNR \times 10^5$) with scaled temperature (T) for different N . Parameter set chosen: $M = 5$, $\omega_s = 10^{-5}$, $F_0 = 0.1$, $\epsilon = 0.0$, and $R = 5.0$. (b) Variation of $Signal$ with scaled temperature (T) for different N with the same parameter set as in (a). τ_0 is calculated using GSD approximation (Eq. (5)) for lines and by direct numerical integration (Eq. (3)) for points (for $N = 75$ only).

FIG. 6. (a) Variation of scaled SNR ($=SNR \times 10^5$) with scaled temperature (T) for different ϵ . Parameter set chosen: $N = 100$, $\omega_s = 10^{-5}$, $F_0 = 0.1$, $M = 10$, and $R = 5.0$. (b) Variation of $Signal$ with scaled temperature (T) for different ϵ with the same parameter set as in (a). Curves are obtained using GSD approximation and points are from numerical integration of Eq. (3) for $\epsilon = -1.8$.

slowdown in the translocation time, one can expect the need of a higher thermal energy. Consequently, the resonance zone has shifted towards higher temperature region with an increase in threshold energy. Therefore, the relative contribution of the energetic and entropic parts in the free energy barrier is crucial in determining the position of the resonance zone.

Although the product of the pore length M and the average pore-polymer interaction energy ϵ controls the energy threshold ($\frac{M\epsilon}{k_B T}$), M and ϵ are independent contributors to the total free-energy of the system. This is because of the fact that any change in M modifies both the energy and the entropy, whereas ϵ only affects the energetic part of the total free energy. In this spirit, we first study a two-parameter variation of SNR with both the pore length (M) and the temperature for $\epsilon = -1.0$ (attractive), as shown in Fig. 7(a) (with $R = 5.0$, $\omega_s = 10^{-5}$, $N = 100$ and $F_0 = 0.1$). The variation shows that for a very short pore-length ($M \sim 1$), the SNR decays monotonically with temperature and only after a threshold $|M\epsilon|$, the non-monotonic variation of SNR is feasible. In a similar two parameter variation of SNR with $\epsilon = 0$ (Fig. 7(b)), one can notice that the SNR always decreases monotonically with temperature regardless of the length of the pore (M). The latter case represents a translocation over a purely entropic barrier.

Next, the simultaneous variation of SNR with temperature and average polymer-pore interaction energy (ϵ) is shown in Fig. 8(a) for a fixed pore length $M = 5$ ($N = 100$, $\omega_s = 10^{-5}$, $F_0 = 0.1$ and $R = 5.0$). Fig. 8(a) shows that in the limit of

$\epsilon \rightarrow 0$, the SNR does not show any resonance behavior and it increases monotonically with decreasing temperature. On the other hand, a clear turn-over occurs when the pore-polymer interaction energy is either attractive ($\epsilon < 0$) or repulsive ($\epsilon > 0$) and above a threshold value. Therefore, SR occurs for both repulsive and attractive pore-polymer interaction energies. However, the variation of SNR is not symmetric between $+\epsilon$ and $-\epsilon$. One can explain this asymmetry by scrutinizing the expression for τ_0 . From Eq. (5), in the limit of high pore-polymer interaction $|\mu_1| \gg 1$, we have

$$k_0\tau_0 = \frac{(N-M)^2}{2} + \left[\frac{2}{\mu_1^2} - \frac{(N-M)}{\mu_1} \left(\frac{2a}{R} \right) \right] \exp(-\mu_1 M), \quad (13)$$

for large and negative ϵ , and

$$k_0\tau_0 = \frac{(N-M)^2}{2} + \left[\frac{2}{\mu_1^2} + \frac{(N-M)}{\mu_1} \left(\frac{R}{2a} \right) \right] \exp(\mu_1 M), \quad (14)$$

for large and positive ϵ .

Therefore, $\tau_0(\epsilon) \neq \tau_0(-\epsilon)$ and consequently, the translocation rate $W_0 = \frac{1}{\tau_0}$ is not symmetric when the sign of the interaction is reversed. As a result, SNR ($\sim W_0$) does not exhibit symmetry between attraction and repulsion for the pore-polymer interaction. One can also expect this behavior as a consequence of a pathway effect by examining the free energy profile. Fig. 2(b) depicts that the chain experiences an energy barrier during the chain expulsion stage ($m \geq M$)

FIG. 7. A two-parameter variation of scaled SNR ($=SNR \times 10^5$) with scaled temperature (T) and pore length (M) with (a) $\epsilon = -1.0$ and (b) $\epsilon = 0.0$. In both cases, the color bars represent the values of the scaled SNR . Parameter set chosen: $R = 5.0$, $\omega_s = 10^{-5}$, $N = 100$ and $F_0 = 0.1$.

FIG. 8. (a) A two-parameter variation of scaled SNR ($=SNR \times 10^5$) with scaled temperature (T) and ϵ for $N = 100$, $M = 5$, $\omega_s = 10^{-5}$ and $F_0 = 0.1$. (b) A two-parameter variation of scaled SNR ($=SNR \times 10^5$) with pore length (M) and ϵ for $N = 100$. Parameter set chosen: $T = 1$, $\omega_s = 10^{-5}$, and $F_0 = 0.1$. In both cases, the color bars represent the values of the scaled SNR .

for a sufficiently strong attractive case ($\epsilon = -1.45$ or -1.6). In contrast, the chain is subjected to a free energy threshold during the pore filling stage ($m \leq M$) when pore-polymer interaction is zero or repulsive in nature. Thus, for a repulsive $\epsilon (\geq 0)$, the chain experiences the energy barrier during pore filling stage. The trend in Fig. 8(a) also suggests that in the high temperature limit, SNR becomes independent of the sign of ϵ . This is because of the fact that the system does not have any energy threshold and SNR becomes inversely proportional to the temperature in this limit. In principle, this argument can be readily generalized to more complicated pore-polymer interactions, such as those among patterned pore,⁴¹ patterned cavities, and patterned polymers.⁴²

Finally, we comment on the observation seen in Fig. 6 and Fig. 8(a) that for an increasing energy dominance ($|\frac{\epsilon}{T}M| \gg \mu_2 M$), the magnitude of the SNR at the maximum position decreases significantly with the noise strength. A low value of W_0 for energy dominated situation compared to that of the crossover zone ($\mu_1 M \sim 0$) is responsible for this effect. In Fig. 8(b), we present a two-parameter variation of SNR simultaneously with ϵ and M for a fixed scaled temperature ($T = 1$). One can compare the values of SNR with W_0 values as shown in Fig. 3(b) at different dominance regimes. The comparison suggests that the relative values obtained from the isothermal variation of SNR and W_0 are consistent with

FIG. 9. Variation of signal with scaled temperature T for $\epsilon = -2.0$ (green), -2.0 (red), -2.5 (blue). $\omega_s = 10^{-7}$ (blue and green) and $\omega_s = 10^{-6}$ (red). Parameter set chosen: $M = 10.0$, $N = 100$, $R = 5.0$, and $F_0 = 0.1$. τ_0 is calculated by direct numerical integration of Eq. (3).

each other in terms of the dominance zones. For example, Fig. 3(b) suggests that W_0 is quite high for crossover zone ($\mu_1 M \sim 0$) and consequently, $SNR \sim W_0$ also possesses a high value in this limit compared to that of a energy dominated case $\mu_1 M \ll 0$ (Fig. 8(a)).

Before we conclude, we provide estimates for the values of the various parameters of the present model in order to observe the SR effect experimentally. To achieve this, we scale the length (l), mass, and energy ($k_B T$) by 0.34 nm, 100 Da (1.66×10^{-25} kg), and 4.11×10^{-21} J, respectively. The energy 4.11×10^{-21} J is the thermal energy at 298 K temperature. This gives the scaling unit for time (t) as 2 ps, as already pointed out. The viscosity of water (η_w) follows the relation $2.414 \times 10^{-5} \times 10^{247.8/(T-140)}$ kg m⁻¹ s⁻¹ within the range of 273 to 640 K.⁴³ We scale η_w within our reference scaling framework and the scaling unit of viscosity coefficient $\eta_R = m_R/(l t_R)$ becomes 2.44×10^{-4} kg m⁻¹ s⁻¹ at 298 K. We now substitute the temperature dependence of k_0 as $\frac{k_B T}{6\pi\eta_w l^3}$ in Eq. (3) to calculate equilibrium translocation time. The variation of signal with reduced temperature for different parameter set is displayed in Fig. 9 with $M = 10.0$, $N = 100$, $R = 5.0$, and $F_0 = 0.1$. The green line in Fig. 9 shows that the signal exhibits a resonance peak around a reduced temperature $T = 0.9939$ (296 K) with $|\epsilon M| = 20$ and $\omega_s = 10^{-7}$. In this case, the equilibrium translocation time in real units is ~ 0.01 ms at 296 K and the time period of the applied external periodic force ($\frac{2\pi}{\omega_s}$) is 0.12 ms. Thus, we have a peak around room temperature ($T = 296$ K) with a driving frequency of about 10 kHz for this parameter set. Fig. 9 also suggests that the resonance temperature greatly depends on ϵ and the forcing frequency (ω_s). For example, if one increases the pore-polymer attraction strength to -2.5 keeping ω_s unaltered (blue line), the resonance zone shifts to a higher temperature region as expected. Also, if one increases the forcing frequency to $\omega_s = 10^{-6}$ (or equivalently 1 kHz) with $\epsilon = -2.0$ (red curve), the signal maximization occurs at a higher temperature, in comparison to $\omega_s = 10^{-7}$.

IV. CONCLUSIONS

We have explored the occurrence of stochastic resonance during polymer translocation as a consequence of the interplay between thermal noise, external periodic driving force, and the free energy barrier of the process. The free

energy barrier associated with a single-file translocation is governed by the conformational entropy of the chain and pore-polymer interactions. By combining our earlier model for polymer translocation as a Fokker-Planck process²⁷ with the two-state model of stochastic resonance,¹ we have derived explicit formulas for the occurrence of stochastic resonance. Implementation of the ground state dominance approximation in the calculation of barrier crossing rate allows analytical results without compromising the accuracy of physical conclusions.

We show that the presence of a finite threshold energy in the free energy barrier is a necessary condition for stochastic resonance to occur. With a purely entropic contribution to the free energy, no stochastic resonance is possible. Once stochastic resonance is feasible due to the pore-polymer interaction being above a threshold value, the resonance condition is influenced by both the entropic and energy contributions to the free energy barrier. We also show that both attractive and repulsive pores allow stochastic resonance as long as the magnitude of the pore-polymer interaction is above a threshold value. However, the synchronization condition is not symmetric with the sign of the pore-polymer interaction energy. We also show that the region of stochastic resonance shifts to higher temperatures as the pore-polymer interaction strength increases. In addition, the magnitude of the signal-to-noise ratio at the maximum signal frequency decreases with an increase in temperature. In addition, we propose suitable conditions to observe stochastic resonance in polymer translocation experiments.

The approximate analytical method presented here can readily be adopted to other models of polymer translocation by simply importing the already derived translocation rates¹² into the expressions for the two-state model of stochastic resonance.¹ This approach is likely to be sufficient to gain insight into stochastic resonance during polymer translocation under diverse conditions, instead of addressing each situation separately. Detailed simulations and the proposed experiments might be worthwhile to determine the quantitative accuracy of the conclusions and assumptions presented here.

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