

Asymmetric Mean First Passage Time for DNA Translocation Through a Nanopore

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We studied the Mean first passage time for the DNA translocation through a narrow pore. We also proved that, for an asymmetric ratchet potential, the mean first passage time for the same DNA to translocate through the membrane can be different when passing from the two different ends, even without external potential. We further extended the situation to a more general case, where a periodic chain with N subunits and m steps in each subunit is studied, and we proved that the difference of the two mean first passage time is of the order linear to the number to periodicity. We also explained the reason for the more distinct difference between MFPT when external potential is present.

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I. INTRODUCTION

Recent experimental achievements have aroused great interest in DNA translocation through a membrane.[1–3] There is also much theoretical work done on the subject of polymer translocation through a narrow pore.[4–8] In these papers, translocation process with an external potential is studied both for the continuous situation and for the discrete situation. A common approach is to focus on the dynamics of a single variable representing the monomer number at the pore, [4, 5, 7, 8] and define an entropic barrier for the system.

However, recent experimental results have reported that, the DNA translocation time through a membrane exhibits two distinct values when there is an external potential[4], and even when there is no external potential. To explain these experimental data, here we set up several models for calculating the Mean First Passage Time(MFPT) for the DNA translocation through a membrane. Assuming Brownian Motion, we found the difference between translocation time can be explained by an asymmetric configuration of the polymer itself due to the different interaction potentials between different monomers and the membrane pore.

We first studied the case for the simplest situation, the two state periodic polymer without external potential. Then we extended the case to the polymer travelling in an external potential, and explained why there are give MFPT difference for travelling in an external potential. Finally, we presented a general model of the polymer travelling without external potential, where each unit is composed of m arbitrary subunits. We showed by the general m -state model the behavior of the general MFPT. We proved it is always to the order of N^2 , and the difference of the MFPT when reversing the travelling direction

of the polymer is always linear to N , and proportional to the interaction differences between subunits.

II. MEAN FIRST PASSAGE TIME

For a one-dimensional potential profile, the mean first-passage time is a very good description of the diffusion dynamics of the system[9, 10]. For a given set of probabilities P_i , the MFPT from 0 to N (in terms of number of steps) can be described as:

$$\overline{t_{0,N}} = N + \sum_{k=0}^{N-1} \omega_k + \sum_{k=0}^{N-2} \sum_{i=k+1}^{N-1} (1 + \omega_k) \prod_{j=k+1}^i \omega_j, \quad (1)$$

here p_i, q_i are position dependent hopping probabilities to the right and to the left, $\omega_i = q_i/p_i$. We assume the particle here either jump forward or back ward, there is no probability for them to stay in the original place, thus they satisfy $p_i + q_i = 1$. According to Michael and Mehran[5], it is most natural to assume that

$$p_i \propto e^{-\beta(U_{i+1}-U_i)}, q_i \propto e^{-\beta(U_{i-1}-U_i)}, \quad (2)$$

where $\beta = (k_B T)^{-1}$, and U_i is the sequence dependent component of the potential energy.

A. MFPT for Two-State Ratchet Potential without External force

For the simplest situation, we assume the polymer chain is periodic, and is only composed of two different units as shown in 1. It is obvious that in this situation one of the two units is easier to travel through the membrane pore than the other. Thus we can assume the ω_i is alternating between two different values, x_1 and x_2 . They satisfy the constraint $x_1 * x_2 = 1$. This is a typical two-state ratchet potential, which is studied in many biological systems for both continuous situation and discrete situation[11–14].

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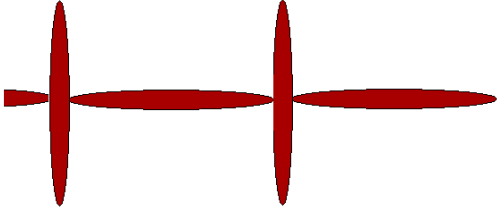


FIG. 1: Model of the DNA configuration for two-state ratchet potential.

To calculate the mean first-passage time difference for a polymer's travelling from the plus end and the minus end through the membrane. According to equation 1, suppose the chain is composed with N periods, each period with a x_1 and a $1/x_1$, equation (1) then becomes:

$$\overline{t_{0,2N-1}} = 2N + N(x_1 + 1/x_1) + (2 + 1/x_1 + x_1)N^2 - (1 + x_1)N \quad (3)$$

Hence we can see the first two terms are symmetric to x_i and $1/x_i$, only the last term changes when reversing the DNA travelling direction. Whereas in the last term, the N^2 term is still symmetric to changing the direction of the polymer, but the linear term is not. Thus we can see that the MFPT shows a difference in the polymer's travelling from the two different directions, even without external force. We also see that this difference is:

$$\Delta t = N|(1/x - x)| \quad (4)$$

thus is proportional to the number of periodicities of the polymer chain.

B. MFPT for two-state potential with an external force

In their paper[4], Nelson and Lubensky also reported that there exists distinct difference between the DNA travelling from the 3' end and the 5' end, when there is external force. Here we will give an explanation for the case with an external force, based on our two-state scheme, and show that when external force is exerted, the MFPT difference can be proportional to N^2 , thus is much more distinct than the difference without an external force.

When the external potential is large enough, the polymer will gain a visible velocity towards one direction, thus their original difference generated by the two different configurations can be neglected. If we assume the velocity for the polymer moving forwards is v_1 , and the velocity for the polymer moving backwards is v_2 , and $v_1 > v_2$, and then we can assume the probability for the polymer to jump forward and backward, p, q , has: $p/q = v_1/v_2, p + q = 1$.

Then, following our derivation for the MFPT, let $\alpha = q/p < 1$, we can get:

$$\overline{t_{0,N}} = N(1 + \alpha)/(1 - \alpha), \quad (5)$$

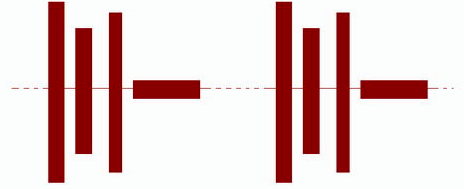


FIG. 2: Model of the DNA configuration for arbitrary number of state periodic ratchet potential.

when changing the direction of polymer travelling, we are getting $\alpha = p/q > 1$, then MFPT behaves like:

$$\overline{t_{0,N}} = \alpha^N(\alpha^2 + \alpha)/(\alpha - 1)^2, \quad (6)$$

Also when travelling from the 3' and 5' end, it is reasonable that the α are different even if the same external potential are exerted. Thus it is also reasonable for the obvious MFPT difference in the situation with external potential as shown in Nelson's paper.

C. MFPT for a general periodic chain

To study the more general mean first-passage time behavior for the polymer translocation, we can further extend our model to a periodic chain with N periods, each period contains m states, as shown in 2. Here, the drifting velocity for each unit can be arbitrary, and thus the ω_i is a periodic function with periodicity m . We name them ω_{ni} , where n ranges from 1 to N and denotes the number of period the monomer belongs to, and i ranges from 0 to $(m - 1)$ and denotes the monomer's position in that particular period. Similar to the two-state situation, as there is no external force in this system, the total velocity for the polymer to travel forward and travel backward should be the same, thus we should have the similar constraint as the two-state situation here:

$$\prod_{i=0}^{m-1} \omega_{ni} = 1 \quad (7)$$

For simplicity, we denote ω_{ni} as x_i , and we know when the polymer travels from the reverse side, all the x_i s will become $1/x_i$, and this still satisfies the constraint as in equation 7.

Thus the equation 1 in this general case becomes:

$$\overline{t_{0,mN-1}} = mN + \sum_{k=0}^{mN-1} \omega_k + \sum_{k=0}^{mN-2} (1 + \omega_k) \sum_{i=k+1}^{mN-1} \prod_{j=k+1}^i \omega_j, \quad (8)$$

Here we want to compare the MFPT difference for the x_i set and the $1/x_i$ set. Obviously, the first term remains the same when all the " x_i "s are reversed. The second term is just $N \sum_{i=0}^{m-1} x_i$, thus the difference is also easy

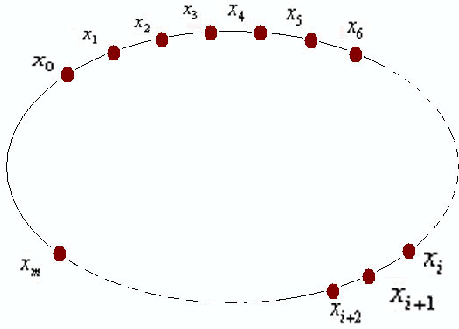


FIG. 3: the DNA model with periodic ratchet potential can be visualized as a chain like this.

to calculate, simply as

$$\Delta t_{2nd} = N \left(\sum_{i=0}^{m-1} (x_i - 1/x_i) \right), \quad (9)$$

The third term in equation(8) is more complicated, and here we shall study it in more detail. When $k = 0$, the last term contributes:

$$t_{3rd0} = (1 + x_0)(x_1 + x_1x_2 + x_1x_2x_3 + \dots + x_1 \dots x_{m-1} + x_1 \dots x_m), \quad (10)$$

Using the periodicity property that $x_m = x_0$, also for all x_i , we have $x_i = x_{i+m}$ (this can be seen more explicitly as in Fig. 3), we can write the entire contribution of the third term as:

$$\begin{aligned} t_{3rd} = & (N^2 + N)[m + (x_0 + x_1 + \dots + x_{m-1}) \\ & + (x_0x_1 + x_1x_2 + \dots + x_{m-1}x_0) \\ & + (x_0x_1x_2 + \dots + x_{m-1}x_0x_1) + \dots \\ & + (x_0 \dots x_{m-2} + x_1 \dots x_{m-1} + \dots + x_{m-1} \dots x_{m-3})] \\ & - N[(1 + x_0) * 0 + (1 + x_1)(x_2 \dots x_{m-1}x_0) \\ & + (1 + x_2)(x_3 \dots x_m + x_3 \dots x_{m+1}) \\ & + (1 + x_3)(x_4 \dots x_m + x_4 \dots x_{m+1} + x_4 \dots x_{m+2}) \\ & + \dots \\ & + (1 + x_{m-1})(x_m + x_mx_{m+1} + \dots + x_m \dots x_{2m-1})], \quad (11) \end{aligned}$$

From this equation, we can see that, as all the " x_i "s satisfy the condition that $\prod_{i=0}^{m-1} x_i = 1$, when reversing the travelling direction of the polymer, the first term in t_{3rd} remains the same. This term is proportional to $N^2 + N$, and is thus determined by N^2 . On the other hand, the second term on t_{3rd} , which is proportional to N , will change when all the x_i become $1/x_i$. Thus combining Δt_{2nd} and Δt_{3rd} , we can draw the conclusion that for a periodic chain with arbitrary potential configuration, the difference of the MFPT is always linear to N , which is the number of periods.

III. CONCLUSION AND DISCUSSION

In this paper, by setting up an asymmetric potential, we gave an explanation for the difference of the DNA translocation through a narrow pore. We argued that it is because this is only a dynamic process, not a system at equilibrium, and also because that we are only measuring the mean first-passage time here, which is a statistical parameter for non-equilibrium situation, that we are getting different values for DNA translocation from the two different ends. By using the simplified two state ratchet potential and the generalized m-state potential, we further calculated the difference between the two mean first-passage time. We see that for the situation without external potential, the mean first-passage time is always to the N^2 order, and is not sensitive to the travelling direction of the polymer to the N^2 term. However, the MFPT without an external potential always differ to an order proportional to N . Thus the MFPT difference can be relatively important when N is small. Also, we can increase the MFPT difference by making the drifting velocity of each unit change drastically. In experiments where N is between 20 and 30, distinct MFPT have been reported. We also showed here, when an external force is exerted, the difference between the two MFPT can vary greatly, which means to the leading order of the travelling time. This is observed in many experiments, and our result give a good description of this phenomenon. We could further extend our work to the continuum limit and solve it for the diffusion equation, however, the continuum limit is only an extreme situation of the m-state case discussed above, and we already can see the behavior of the MFPT for the general situation in the m-state model, thus we believe it is a sufficient description here.

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