

Modeling translocation of particles on one-dimensional polymer lattices

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We introduce a general random walk model that is an extension of the random walk model proposed by Berg. The model can be used to describe a particle's translocation along a polymeric lattice with a nonuniform distribution of obstacles. These obstacles are representative of DNA-bound proteins, of drugs, and of a DNA packing environment. Using this model in the bacteriophage replication process, we show the effects of random obstacles on an ATP-driven particle's translocation along single-stranded DNA. The principal finding is that the average statistical time of the translocation process decreases with the increase of an obstacle's strength. We also find an interesting relation between the average statistical time and the DNA chain length. Our results can be used to explain some physiological phenomena. They show the usefulness of our model in an analysis of the effect of random obstacles on particles' translocation along one-dimensional polymer lattices.

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I. INTRODUCTION

Many physiological processes require the transport of macromolecules or macromolecular complexes from one position to another within cells. If these movements are directional or vectorial in nature they are also called translocation, and they must (1) involve movement along a polymer, filament, or surface to permit the maintenance of directionality; and (2) be coupled to a source of free energy, which generally involves a chemical energy to mechanical energy transition by the enzymatic hydrolysis of ATP. Examples of such directional ATPase-driven translocation in living systems include the movement of organelles along microtubules [1], the movement of myosin along fibrous actin [2,3], and the unwinding of double-stranded DNA by helicase [4,5]. The translocation of ATPase-bearing molecular motors is characterized by four central features [6]: the characteristic processivity, the directional (vectorial) movement, the role of ATP hydrolysis in producing directional movement, and the characteristic thermodynamic efficiency. Although the processivity and directionality of such translocation processes can be measured in certain systems [7–9], the translocation process itself cannot generally be monitored by chemical means as there is no definite product associated with translocation. Therefore, theoretical models need to be developed so that the translocation process can be described, and so that the observed ATP consumption rates can be interpreted. Porter *et al.* [10] proposed a microtubule model for explaining the movement of organelles in cells. In an attempt to drive the rate constant of ATP-driven translocation process along a DNA chain, a biased random walk model was developed in Ref. [6]. This model was based on Berg's random walk of the diffusion process of a repressor along a strand of DNA chain [11]. A bias is introduced to statistically describe the translocation along a chain with uniformly distributed obstacles. However, in most situations the distribution of obstacles along a DNA chain is nonuniform. For example, histone protein complexes, drugs, and metabolites can all act as obstacles distributed on the DNA chain. These obstacles affect translocation in a nonuniform manner. In order to take

these nonuniform obstacles into consideration, it is necessary to develop a generalized model with a nonuniform biased walk. In this paper we present a model, and apply it to a system that mimics the DNA of bacteriophage. We will calculate different average statistical times in different biological environments, and analyze the effects of random obstacles on the ATP-driven helicase translocation along single-stranded DNA. The behavior of translocation under different obstacle strengths and along different strand lengths is discussed.

II. MODEL

Let us consider a particle translocating along a one-dimensional polymer lattice with length L . We begin by presenting the random walk model proposed by Berg [11]. When a particle is released at position $x=a$, as indicated in Fig. 1(a), how long does it take to blunder into an absorber at

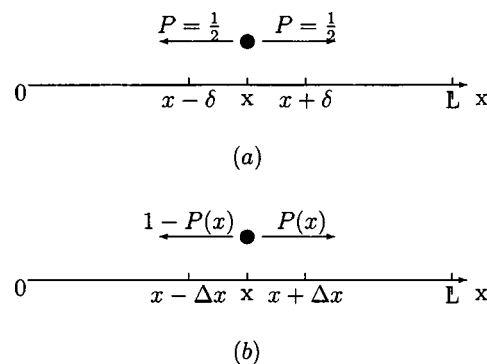


FIG. 1. Models for the translocation of a particle on a one-dimensional polymer lattice. (a) A particle can move to either side along a one-dimensional polymer lattice, and the probabilities of motion to the right or left were both equal to $\frac{1}{2}$. (b) A particle can move to either side along a one-dimensional polymer lattice. The probabilities of translocation in both directions along the one-dimensional polymer lattice are not equal to $\frac{1}{2}$. The particle walk to the right has a probability $P(x)$, and that to the left $1 - P(x)$, where $P(x)$ is position dependent.

$x=0$ or $x=L$? If this experiment is repeated many times, what is the mean time to capture $T(a)$? To find the answer, Berg returned to the formalism of a random walk. He considered that particles could move to either side along a one-dimensional polymer lattice, and that the probabilities to the right and to the left were both equal to $\frac{1}{2}$. Release a particle at position x at time $t=0$, and allow it to step to the right or to left a distance δ every t seconds. At a time t , the particle will be at a position $x+\delta$ with a probability of $\frac{1}{2}$ or at position $x-\delta$ with a probability of $\frac{1}{2}$; the mean times to capture from the positions are $T(x+\delta)$ and $T(x-\delta)$, respectively. Thus, the expectation value of $T(x)$ is

$$T(x) = t + \frac{1}{2}[T(x+\delta) + T(x-\delta)]. \quad (1)$$

By adding and subtracting $T(x)/2$, and multiplying through by $2/\delta$, one can obtain

$$\frac{1}{2}[T(x+\delta) - T(x)] - \frac{1}{2}[T(x) - T(x-\delta)] + \frac{2t}{\delta} = 0. \quad (2)$$

When δ is very small, by the definition of a derivative, Eq. (2) can become

$$\left. \frac{dT}{dx} \right|_x - \left. \frac{dT}{dx} \right|_{x-\delta} + \frac{2t}{\delta} = 0. \quad (3)$$

Dividing once more by δ , again appealing to the definition of a derivative, and noting that $2t/\delta^2 = 1/D$, Eq. (3) becomes the following differential equation:

$$\frac{d^2T}{dx^2} + \frac{1}{D} = 0. \quad (4)$$

Given suitable boundary conditions, this differential equation can be solved for T . At an absorbing boundary, the mean time to capture is 0, so $T=0$. At a reflecting boundary the mean time to capture does not vary with x , so $dT/dx=0$. Equation (4) describes a random walk such that there are no obstacles on the polymer lattice. In many real translocation processes, particles are involved in unidirectional ATP-driven translocation with bidirectional ‘‘slipage’’ [6]. Next we introduce our general random walk. It describes biased random walks in translocation processes.

We treat a particle’s translocation as a biased random walk on a one-dimensional polymer lattice with length L . Following Berg [11] and Ref. [6], we believe that particles can move to both sides along a one-dimensional polymer lattice, but we maintain that right and left translocation probabilities are not equal to $\frac{1}{2}$ because of nonuniform obstacles on the lattice. We define a one-dimensional coordinate system along the lattice with its origin at the left end; if a particle is released from position x at $t=0$, as indicated in Fig. 1(b), we assume that it walks to the right with a probability of $P(x)$, and to the left with a probability of $1-P(x)$. $P(x)$ is position dependent because of the nonuniform distribution of obstacles along the lattice. Given that Δt and Δx are the time and distance of each step, we assume them to be position independent. If the translocation is further assumed to be

biased toward the right of the chain [and therefore $\frac{1}{2} < P(x) < 1$], then the mean times $T(x)$, $T(x+\Delta x)$, and $T(x-\Delta x)$ for the particle to walk from position x , $x+\Delta x$, and $x-\Delta x$ to L satisfy the following equation:

$$T(x) = \Delta t + P(x)T(x+\Delta x) + [1-P(x)]T(x-\Delta x). \quad (5)$$

The above equation can be rewritten as follows:

$$P(x)[T(x+\Delta x) - T(x)] + [1-P(x)][T(x-\Delta x) - T(x)] + \Delta t = 0. \quad (6)$$

By adding and subtracting $[1-P(x)][T(x+\Delta x) - T(x)]$, and multiplying through by $1/(\Delta x)^2$, we obtain

$$[1-P(x)] \frac{T(x+\Delta x) - 2T(x) + T(x-\Delta x)}{(\Delta x)^2} + \frac{[2P(x)-1]}{\Delta x} \frac{T(x+\Delta x) - T(x)}{\Delta x} + \frac{\Delta t}{(\Delta x)^2} = 0. \quad (7)$$

For one-dimensional polymer lattices the step Δx is very small, and no less than the distance between neighboring base pairs (3.4 Å), so we may think that $\Delta x \rightarrow 0$. Appealing to the definition of a derivative, we substitute $d^2T(x)/dx^2$ and $dT(x)/dx$ for $[T(x+\Delta x) - 2T(x) + T(x-\Delta x)]/(\Delta x)^2$ and $[T(x+\Delta x) - T(x)]/\Delta x$, respectively; therefore, Eq. (7) becomes the following differential equation:

$$[1-P(x)] \frac{d^2T(x)}{dx^2} + \frac{[2P(x)-1]}{\Delta x} \frac{dT(x)}{dx} + \frac{1}{D} = 0. \quad (8)$$

Here $1/D = \Delta t/(\Delta x)^2$.

This differential equation is our general random walk model equation, and it can be solved given a specific set of boundary conditions. Different physiological processes have different boundary conditions. If there are two absorbing points at both boundaries, the corresponding boundary conditions are $T(0) = T(L) = 0$. If there is a reflecting boundary at $x=0$, the mean time to capture a particle does not vary with x [11], so the boundary condition is $dT(0)/dx=0$; on the other boundary at $x=L$, there exists an absorbing point, and $T(L)$ is 0. In this work, we chose the latter set of boundary conditions, since they correspond with the real physiological environment.

Given the solution of Eq. (7) or (8). One can determine the average statistical time \bar{T} and the rate constant k_t of a particle along a polymer lattice of length L by the following formulas:

$$\bar{T} = \frac{1}{L} \int_0^L T(x) dx, \quad (9)$$

$$k_t = \frac{1}{\bar{T}} = \frac{L}{\int_0^L T(x) dx}. \quad (10)$$

If several special constants are chosen for $P(x)$, Eq. (8) has analytical solutions. For instance, when $P(x)=1$, and a particle moves unidirectionally, Eq. (8) becomes.

$$\frac{dT(x)}{dx} + \frac{\Delta t}{\Delta x} = 0, \quad (11)$$

which has the solution

$$T(x) = \frac{\Delta t}{\Delta x} (L - x). \quad (12)$$

The average statistical time \bar{T} and the rate constant k_t of a particle translocation along a chain of length L can be shown to be

$$\bar{T} = \frac{L\Delta t}{2\Delta x}, \quad (13)$$

$$k_t = \frac{2\Delta x}{L\Delta t}. \quad (14)$$

Both are dependent on the chain length. In this case our model can be used to describe the unidirectional movement of myosin along fibrous actin, and of some organelles along microtubules.

If $P(x) = \frac{1}{2}$, the particle walk to both sides is equally probable. Equation (8) then become

$$\frac{d^2T}{dx^2} + \frac{2}{D} = 0. \quad (15)$$

This is the equation derived by Berg [11]. Under our boundary conditions, it has the following solution:

$$T(x) = \frac{1}{D} (L^2 - x^2). \quad (16)$$

From this, one can derive the average statistical translocation time \bar{T} and rate constant k_t :

$$\bar{T} = \frac{D}{L} \ln 2, \quad (17)$$

$$k_t = \frac{L \ln 2}{D}. \quad (18)$$

Both are dependent on the lattice length. In this case, our model can be used to describe the translocation of particles along a polymer lattice with free obstacles.

In another case, in which $P(x) = \text{const}$ and yet $P(x) \neq \frac{1}{2}$ and $P(x) \neq 1$, Eq. (8) was expressed in Ref. [6] as

$$\frac{d^2T(x)}{dx^2} - 4\beta \frac{dT(x)}{dx} + \frac{2}{k_r + k_f} = 0, \quad (19)$$

where

$$\beta = \frac{k_r - k_f}{2(k_r + k_f)} = \frac{2P - 1}{(1 - P)\Delta x}, \quad (20)$$

$$k_r + k_f = D(1 - P). \quad (21)$$

The constant β defines the degree of bias of the walk. k_f and k_r represent the rate constants for movement in the forward step and reverse direction, respectively. In this case β , k_f , and k_r can be determined by the constant P , and our model can be used to describe the translocation of particles along uniformly distributed obstacle lattices.

If $P(x)$ is a complicated function of x , it is difficult to find analytical solution for Eq. (8). The mean time $T(x)$ of a particle's movement from x to L can be derived by solving Eq. (7) or (8) numerically.

To study the effects of obstacles on particles' translocation, we apply our general random walk model to the bacteriophage T4 DNA replication process, and carry out a calculation to determine the average statistical time \bar{T} using a distribution of obstacles that mimics a single-standard DNA of bacteriophage. For purposes of comparison, a calculation on an obstacle free DNA chain is also carried out.

In real instances of the bacteriophage T4 DNA replication process, a DNA polymerase complex translocates, and pushes the replication fork along a double DNA chain [12]. A class of DNA unwinding enzymes, DNA helicases, is involved in base pair separation at the fork [13]. This unwinding process is driven by the hydrolysis of ATP [14]. According to this physiological process we regard the replication complex [15] as a particle biased toward the replication fork along the single-stranded DNA on the lagging [15] strand. The parameters for our model are chosen as follows: a Okazaki [12] fragment consists of several hundred base pairs, so in this work we first choose 500 base pairs, which typically describe the replication of the lagging [15]. Such a single-stranded DNA has a length L of 1700 Å. The step of walk Δx is the distance between neighboring DNA base pairs $\Delta x = 3.4$ Å. The observed replication rate for bacteria is used to determine Δt tentatively. In real bacteria replication processes, the observed speed of the replication fork is 50 000 base pairs per minute. This gives a Δt of 1.2×10^{-3} s, so $1/D = \Delta t / (\Delta x)^2$ is 1.0×10^{16} s/m². We can solve Eq. (8) with the above parameters.

If a particle moves unidirectionally along an obstacle free DNA chain, the probability P is 1, and the calculated average statistical time \bar{T} and rate constant k_t of finishing the translocating process are 30 s and 0.033, respectively. If a particle moves on an obstacle free DNA chain, such movement can be considered as a completely random walk, and the probability that P is $\frac{1}{2}$. The calculated result is shown in Fig. 2. We can see that the particle being set free at the left end will need the longest time to move to the absorber—the right end of the DNA strand. The average statistical time \bar{T} of the particle's translocation is 3350 s, the rate constant k_t is 0.0003 s⁻¹. In another case there are many obstacles on a single-stranded DNA, we chose to follow Chen *et al.* [16], and maintain that a sine periodic functions describe the effects of obstacles on the translocation process. The distribution probability of a particle's movement can be shown as

$$P(x) = \frac{1}{2} + \frac{1}{2} \varepsilon \sin^2 \alpha x, \quad (22)$$

where $\alpha = 3.8 \times 10^{-3}$ Å⁻¹, and ε describes the level of obstacle resistance and must be $0 < \varepsilon < 1$. For different values

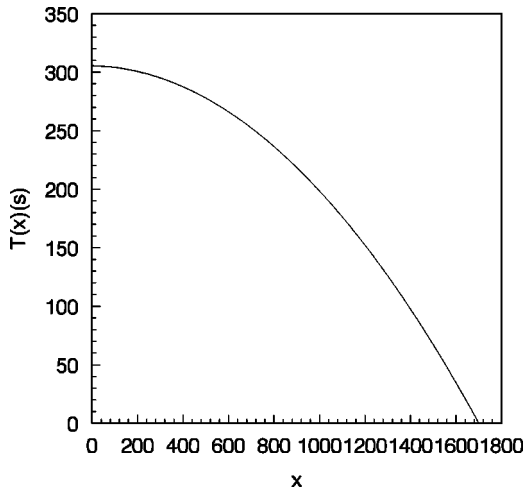


FIG. 2. The calculated mean time $T(x)$ of a particle translocating from position x to position L on a single-stranded DNA with a free obstacle $P = \frac{1}{2}$. The length of the single-stranded DNA is $L = 1700 \text{ \AA}$.

of ε , the calculated mean times $T(x)$ for a particle to travel from position x to position L are shown in Fig. 3. All of the $T(x)$ are found to follow an approximately linear relationship with $L - x$. We can also see that, for a given ε , the mean time $T(x)$ to travel from x to L is very small when x is near L , and increases as x approaches 0, the increase is more rapid than in the case of $P = \frac{1}{2}$. The particle being set free at the left end will also need the longest time to move to the absorber—the right end of the DNA strand. That is to say, a particle that is set free closer to the left end will require a longer travel time. We concentrate on the relation between the average statistical time \bar{T} and the obstacle's strength ε . Our findings are shown in Fig. 4. We observe that the average statistical time \bar{T} decreases with an increase of ε , that this decrease becomes more rapid at smaller values of ε , and that it is most

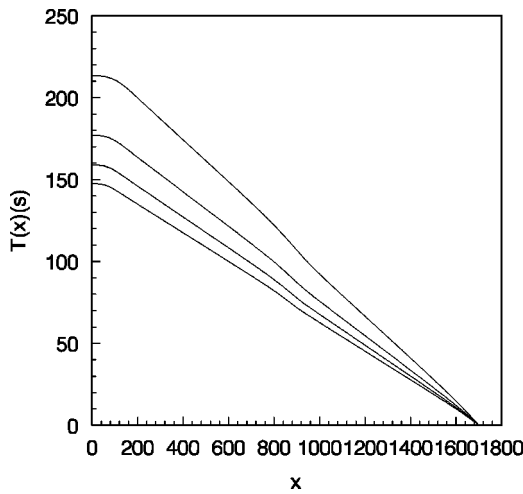


FIG. 3. The calculated mean time $T(x)$ of a particle translocating from position x to position L on a single-stranded DNA with an obstacle distribution $P(x) = \frac{1}{2} + \frac{1}{2}\varepsilon \sin^2(\alpha x)$. The length of the single-stranded DNA is $L = 1700 \text{ \AA}$. The lines from the bottom to the top correspond to $\varepsilon = 1, 0.8, 0.6, 0.4,$ and 0.2 , respectively.

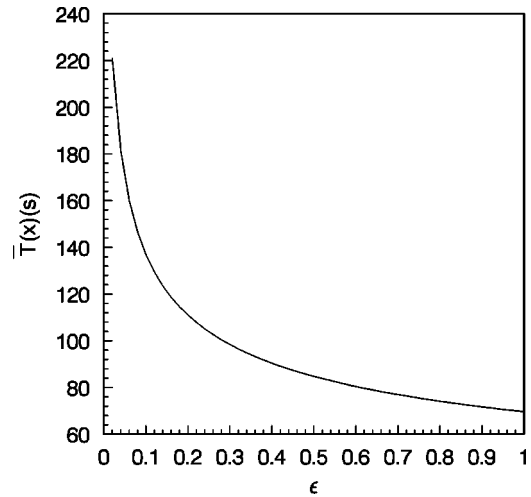


FIG. 4. The calculated average statistical time \bar{T} of a particle translocating on a single-stranded DNA as a function of the obstacle strength ε . The obstacle distribution and chain length are the same as in Fig. 3.

prominent in the region $0 < \varepsilon < 0.2$. On the other hand, at $\varepsilon > 0.2$, the decrease is relatively insensitive to ε . The relation between the rate constant k_t and obstacle's strength ε is shown in Fig. 5. From this, we can see that the rate constant k_t maintains an approximately linear relationship with ε , and that the statistical value is about 10^{-2} s^{-1} which is consistent with existing experiments and relevant theoretical considerations [15].

We have also examined the effects of the DNA chain length on average statistical time \bar{T} . Figure 6 gives the average statistical time \bar{T} as a function of the chain length. We can see that for a given ε the average statistical time \bar{T} forms stairs as a function of L . That is to say, for some lengths the average statistical time is very sensitive to L , but for other lengths it becomes insensitive to L . We find that the behavior is due to such periodic distribution of obstacles on DNA chains.

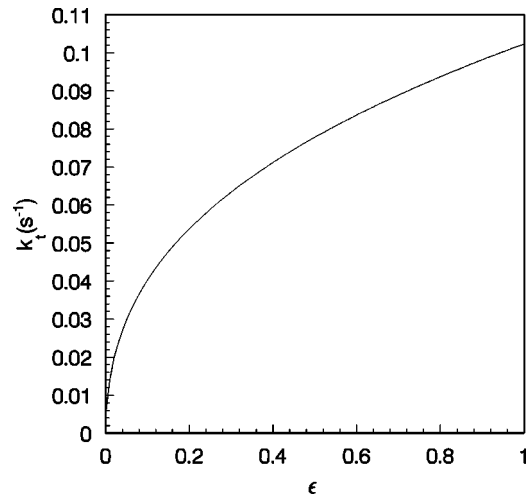


FIG. 5. The calculated translocation rate constant k_t as a function of the obstacle strength ε . The obstacle distribution and chain length are the same as in Fig. 3.

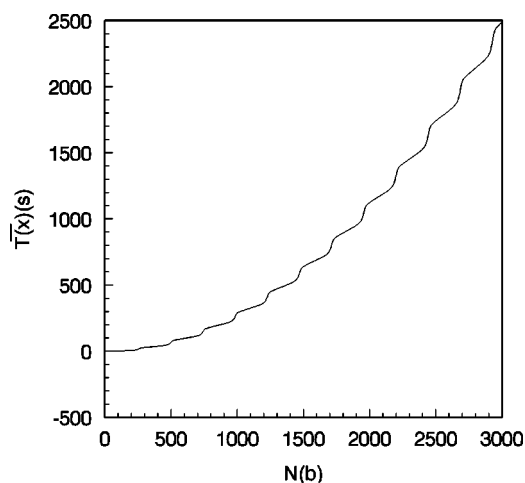


FIG. 6. The calculated average statistical time \bar{T} of a particle translocating on a single-stranded DNA as a function of the number of base pairs N in the DNA chain. N is in units of base pairs (b). The obstacle distribution is $P(x) = \frac{1}{2} + \frac{1}{2}\varepsilon \sin^2(\alpha x)$, where the ε is 1.

III. CONCLUSION

In summary, a general random walk model has been presented. It can be used to study the effects of random obstacles on a particle's translocation along one-dimensional polymer lattices. Our results can provide a way to understand the relationship between the physical nature of one-dimensional translocation on a single-stranded DNA and the physiology of obstacles in such environments. Comparing the general random walks of particles along one-dimensional DNA strands with distributed obstacles and those that are obstacle free, we find that the average statistical time of translocation is much shorter in an obstacle-laden biological

environment than in an obstacle-free biological environment. On the other hand, when comparing general random walks with unidirectional movement, we found the average statistical time of the translocation to be longer in obstacle-laden biological environments than in those that are obstacle free. That is to say, in real instances of lagging strand replication processes the obstacles' biological environments are necessary; therefore, there are some kinds of proteins bound to DNA strands such as *gp32*. These bound proteins can act as obstacles to increase the bidirectional efficient and to reduce the unidirectional efficient. From the relation between the rate constant of a particle's translocation and the obstacle strength, and from the relation between average statistical times and the length of a DNA chain, we can see different obstacle strengths corresponding to different translocation rate constants. The rate constant governs a particle (ATPase) active lattice-bound state. In real physiological processes this lattice-bound state determines the lifetime of translocases [6]. Thus our results can be used to explain some physiological phenomena: for example, the ways in which different enzymes have different lifetimes. This example illustrates that show our model has potential application to all translocation processes, including the movement of RNA polymerase along DNA in transcription, and the diffusion process of protein and drugs along DNA. Our model can also be used to predict the rate of ATP hydrolysis. Corresponding work in this area is currently underway.

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