

Driven polymer transport through a nanopore controlled by a rotating electric field: Off-lattice computer simulations

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The driven translocation kinetics of a single strand polynucleotide chain through a nanopore is studied using off-lattice Monte Carlo simulations, by which the authors demonstrate a novel method in controlling the driven polymer transport through a nanopore by a rotating electric field. The recorded time series of blockade current from the driven polynucleotide transport are used to determine the sequence of polynucleotides by implementing a modified Monte Carlo algorithm, in which the energy landscape paving technique is incorporated to avoid trapping at deep local minima. It is found that only six-time series of block current are required to completely determine the polynucleotide sequence if the average missing rate (AMR) of current signals in these time series is smaller than 20%. For those time series with AMR greater than 20%, the error rate in sequencing an unknown polynucleotide decreases rapidly by increasing the number of time series. To find the most appropriate experimental conditions, the authors have investigated the dependence of AMR of current signals and qualified rate of measured time series of blockade current on various controllable experimental variables. © 2007 American Institute of Physics. [DOI: 10.1063/1.2717187]

I. INTRODUCTION

The blueprint of all living organisms is encoded in its nucleic acids, which are polymers made from four kinds of nucleotides including adenine (A), guanine (G), cytosine (C), and thymine (T). The order of the nucleotides determines the characteristics of the living organism, much like the order of letters in our alphabet determines the words. The traditional method used to sequence nucleic acids, known as the Sanger method,¹ involves making many copies of a DNA/RNA segment, cutting those strands in many different places, separating the resulting pieces by size, and then reconstructing the original sequence. This method is effective but has a number of limitations on cost, time, and accuracy.²⁻⁴ It is thus desired to develop accurate sequencing methods that are fast and inexpensive.⁵

To overcome the difficulty in combining all sequenced segments with the correct order in the Sanger method, advances in instrumentation have been pursued to permit sequencing of a long DNA chain using single-molecule methods. An interesting idea is to measure the variation of ionic current due to an applied electric field which drives single-stranded polynucleotides through a nanopore in a thin film.⁶⁻¹⁵ In particular, Branton and co-workers have demonstrated the applicability of such a method to distinguish long stretches of the same nucleotides, such as 30 adenines followed by 70 cytosines. In their experiments, ionic currents through the nanopore decrease due to partial blockade of nucleotides whenever single-stranded DNA chains enter the pore. Sequence information of a DNA chain can be obtained by analyzing the time series of current fluctuations during its translocation process. Recent developments in manufactur-

ing processes have made it possible to fabricate robust nanopores on a thin film and provide a new single-molecule-sensing device to characterize polynucleotides.¹⁶⁻²⁰ However, there are still many formidable technical obstacles that must be overcome in order to realize this method for sequencing real DNA at single nucleotide resolution. One major problem in sequencing DNA using nanopores is the thermal fluctuations of the DNA chain during the translocation process, which could vary the translocation time of each nucleotide or even cause the chain to randomly diffuse backward against the applied electric field.⁵ It is also required to slow down DNA translocation speed to improve its time resolution. To reach single nucleotide resolution, the translocation time of each nucleotide should be increased by a factor of 1000, and thermal fluctuations should be suppressed to allow sequence analysis.

In recent years, there are increasing interest in studying the translocation dynamics of a polymer chain through a nanopore in a thin film driven by an external field. This translocation process is also known to link to many fundamental problems in cell biology, such as the movement of RNA molecules across nuclear pores, protein translocation across membrane through channels, and the injection of DNA from a virus into the host cell. Other important applications in biotechnology includes controlled drug delivery and gene therapy. In addition to experimental investigations,^{6-8,21-25} there are numerous theoretical and computational studies of polymer translocation.²⁶⁻³⁷ Most of the theoretical work on the driven polymer translocation are based on the one-dimensional (1D) drift-diffusion model.^{26,30,31} Three-dimensional (3D) computer simulations of driven polymer translocation have been performed to verify results predicted from 1D models and have found good agreement between 1D theory and 3D simulation.³⁴ The dependence of translo-

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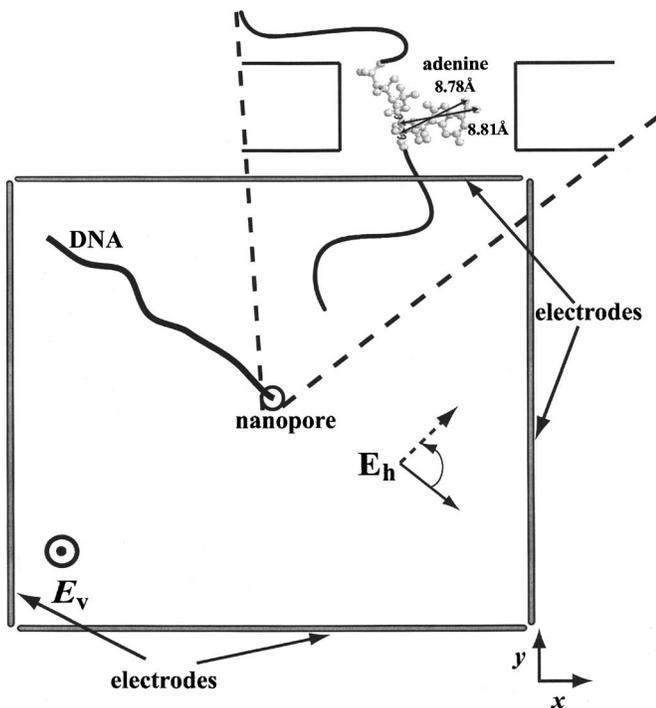


FIG. 1. An illustration of the setup of the rotating field assisted nanopore sequencing experiments. The rotating field is generated by two pairs of electrodes, of which one pair of electrodes are arranged in the x axis and the other pair are arranged in the y axis. On the upper surface of the thin film, there is an electric field E_h rotating counterclockwise at every point within the cell.

cation time on chain length obtained from 3D computer simulations is also found to be consistent with experiment.^{36,37} Given the sensible agreement with theory and experiment, we expect that 3D computer simulations can provide a detailed study of polymer translocation in general and DNA sequencing in particular.

In our previous work,⁹ we have proposed a modification of existing experimental setup by adding two pairs of parallel electrodes on the upper surface of the thin film, as shown in Fig. 1. The electric fields generated by these electrodes are $E_h \cos(\omega t)$ in the x direction and $E_h \sin(\omega t)$ in the y direction. These electrodes will create a rotating electric field for us to control the translocation dynamics of the DNA chain. The transport of the chain is driven by a driving electric field perpendicular to the film (along the z axis). The enlargement of Fig. 1 is a side view of the pore region, which shows the blockade effect of an adenine molecule in the pore. By computer simulations, this rotating electric field has been shown to be able to suppress the thermal fluctuations and to slow down the translocation speed of the DNA chain. More specifically, the translocation time of each nucleotide is nearly quantized, as shown in Fig. 2, which helps us determine the number of repeat nucleotides along the polynucleotide chain. In Fig. 2, quantization of translocation time of each nucleotide, t_n , is observed in a driven polymer transport controlled by a rotating electric field. Such a quantization effect is induced by switching the rotating field between high frequency and low frequency. As demonstrated in the movies of our simulations,³⁸ with a slow rotating field, the electric force acting on the DNA chain by E_h will drag the DNA fragment

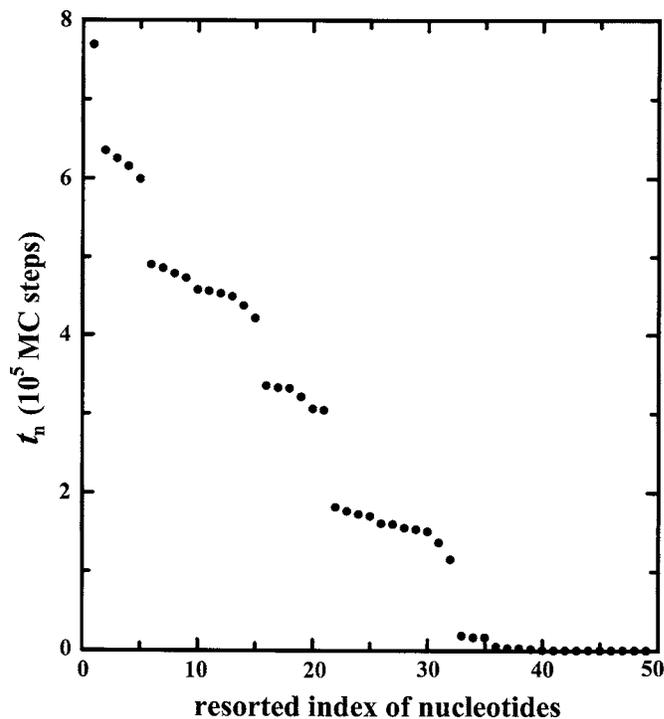


FIG. 2. Quantization of translocation time of each nucleotide for a DNA chain of 50 nucleotides, t_n , in a driven polymer transport controlled by a rotating electric field. Here the x axis shows the index of nucleotides in the chain. To see the quantization effect, we have sorted the index of nucleotides by the value of their translocation time, instead of their position along the chain. In other words, the nucleotide with the longest translocation time will have the smallest index.

above the thin film to rotate with the electric field, which balances out the driving force acting on the polymer chain by E_v and prevents polymer transport through the nanopore. However, if the rotation of the electric field is much faster than the response of the chain, the average electric force acting on the chain by the rotating field will vanish. A macroscopic analogy to the DNA chain under consideration is a string going through a hole on a table, of which the lower end is attached to a weight and the upper end of the string is attached to a block sitting on the table. If the block is set to undergo a uniform circular motion, the string will be trapped due to two balancing tension forces and cannot translocate through the hole. However, if the circular motion of the block is stopped for a brief time, a small portion of the string will be dragged through the hole by the weight. Therefore, only when the frequency of the rotating field is switched higher than a threshold value will the nucleotide in the nanopore have a chance to translocate through the pore before it is switched back to the slow rotating field. If the period of the slow frequency mode is much longer than that of the fast frequency mode, by switching the rotating field between a slow frequency and a fast frequency, we can control the polymer transport dynamics such that the translocation time of each nucleotide is quantized. The exact sequence of an unknown polynucleotide chain can be determined provided enough sets of time series of blockade current are analyzed.

In this paper, we report a new sequencing algorithm for the rotating electric field assisted nanopore sequencing experiment based on our data from off-lattice computer simu-

lations. The rotating electric field is used to control the translocation of nucleotides through the nanopore in such a way that the translocation time of each nucleotide is approximately T_0 or 0, where T_0 is the period of a switching cycle of the rotating electric field. As shown in Ref. 9, the translocation of polynucleotides can be controlled by the angular frequency of the rotating field, that is, no translocation is allowed if the frequency is lower than a critical value. Therefore, if the rotating field switches between a fast frequency and a slow frequency, the blockade time of each nucleotide in the nanopore can be controlled well by the rotating field. The sequence of an unknown polynucleotide chain can be completely determined by simultaneously comparing several time series of block current using a modified Monte Carlo (MMC) algorithm, in which the energy landscape paving (ELP) technique³⁹ is incorporated to avoid trapping at deep local minima. It is found that only six time series of blockade current are required to completely determine the polynucleotide sequence if the missing rate of these time series is smaller than 20%. The error rate in sequencing an unknown polynucleotide decreases rapidly by increasing the number of time series for those time series with a missing rate greater than 20%. We have carefully investigated the dependence of average missing rate (AMR) of current signals and qualified rate (QR) of measured time series of blockade current for the nanopore translocation processes assisted by a rotating electric field on various controllable experimental variables, such as the amplitude of the driving electric field (E_v) and rotating electric field (E_h), the angular frequency of a fast rotating field (ω_f), the angular frequency of a slow rotating field (ω_s), and the duration of the fast rotating field (t_f). Here AMR refers to the average ratio of undetected nucleotides of the chain during its translocation process through a nanopore, while QR refers to the ratio of qualified time series of blockade current that can be used to determine the complete sequence using our MMC algorithm. An appropriate range of the strength of the two electric fields is between 1.5 and 2.7, under which QR is about 0.8 and AMR is about 0.2. The most appropriate ranges for the two frequencies of the rotating field are $0.002 < \omega_f < 0.01$ and $10^{-5} < \omega_s < 10^{-4}$. The duration of the fast rotating field (t_f) should be controlled within the range between $0.15T_0$ and $0.2T_0$.

II. MODEL

In our simulations,^{9,37} we represent a single strand polynucleotide of length N by the bead-spring model, and simulate its motion by the Metropolis Monte Carlo (MC) algorithm in a continuous space at a constant temperature T . The simulation setup is schematically illustrated in Fig. 1. A driving electric field with a constant amplitude E_v in the z direction is used to drive the polynucleotide chain through a cylindrical nanopore of size D in a thin film of thickness L . Above the thin film, we add a rotating electric field $\mathbf{E}_h = E_h \cos(\omega t)\hat{i} + E_h \sin(\omega t)\hat{j}$ to control the translocation of the polynucleotide, where \hat{i} and \hat{j} are unit vectors in the x and y directions. The enlargement in Fig. 1 illustrates the blockade effect of a nucleotide inside the nanopore. From our previous

study,⁹ it is already known that the polynucleotide chain above the thin film will be straightened in response to the rotating electric field for $\omega < 10^{-4}$. In this case, the two balancing electric forces acting on the chain due to \mathbf{E}_v and \mathbf{E}_h (behave like two tension forces acting on two ends of a string) will trap a nucleotide in the nanopore and stop the translocation process. For higher values of ω , the mobility of nucleotides cannot catch up with the rotating field and the average rotating electric force vanishes. In this case, the polynucleotide chain will be dragged through the nanopore by the driving electric force. Thus, if the rotating electric field switches between a fast frequency ω_f and a slow frequency ω_s , it is then possible to translocate the chain through the nanopore one nucleotide by one nucleotide with a uniform speed. For simplicity, a switching cycle in our simulations consists of a slow frequency period of time t_s and a fast frequency period of time t_f , and we choose $t_s + t_f = \pi / (2\omega_s) \equiv T_0$. By choosing appropriate values of t_f , it is found that the translocation time of each nucleotide is approximately T_0 or 0. In real simulations, we randomly pick up a nucleotide at each instant, and attempt to move it in any direction by one arbitrary step size. If an attempted move of nucleotides satisfies the excluded volume constraint, this move is accepted with probability $p = \min[1, \exp(-\Delta U/kT)]$, where ΔU is the energy change of the chain and kT is thermal energy. The chain's energy in our simulations is expressed as $U = U_{\text{bend}} + U_{\text{electric}}$, where $U_{\text{bend}} = \sum_{i=1}^{N-2} e(1 - \cos \theta_i)$ is the bending energy of the chain with rigidity e and bending angles $\{\theta_i\}$, and U_{electric} is the electric potential energy due to the above two electric fields.^{37,40-42} It is known that a single strand DNA chain is quite flexible; thus the bending energy of the chain should be small compared to thermal energy. In addition, since the dielectric constant of water ($\kappa \approx 80$) is quite different from that of silicon nitride thin film ($\kappa \approx 7.5$), induced charges near the interface between water and thin film due to the driving electric field are expected to change the electric field in our system. A recent study of this electric field effect by molecular dynamics simulations has calculated the averaged electric field along the z axis measured around the nanopore without water and with water.⁴³ It is found that the value of the averaged electric field along the z axis in the presence of water is about half of that in the absence of water. When water is present, there is about 10% variation in the field strength along the z axis, but the field strength is nearly uniform in the pore region. In addition, the typical salt concentration in most translocation experiments is about $1M$.⁶⁻⁸ Such a high salt concentration will effectively screen charge-charge interaction since Debye length is inversely proportional to the square root of salt concentration. Thus we assume a constant driving electric field along the z axis and neglect charge-charge interaction among nucleotides, as proposed in Refs. 9, 34, and 36. Possible hydrogen bonding between nucleotides is also ignored due to high salt concentration. For a chain of 150 nucleotides, we choose the pore diameter $D=4$ (about 1.5 nm), the thickness of thin film $L=2$, temperature $T=1$, and the bending rigidity $e=0.2$. Here thermal energy and electric charge of each nucleotide have been set to unity, and the corresponding electric field is of the order of 10^7 V/m. In other words, in our units, the change in

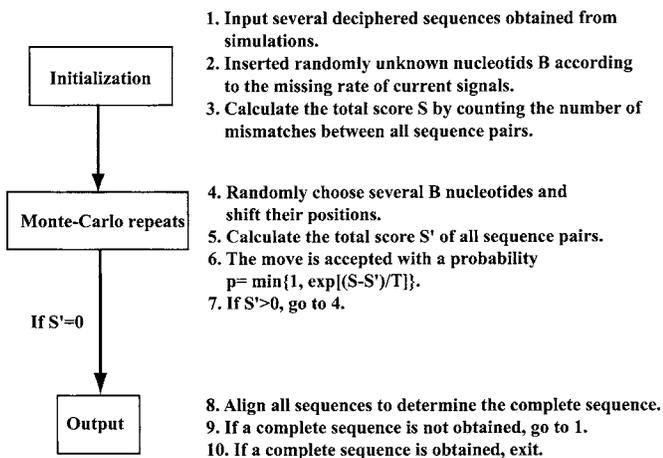


FIG. 4. Flow chart for implementing the Monte Carlo algorithm to determine the complete sequence of an unknown polynucleotide chain by comparing several deciphered sequences obtained from computer simulation or experiment.

the number of deciphered sequences required to determine the complete sequence as a function of the missing rate. It is found that four deciphered sequences are required to determine the complete sequence for a missing rate of 5% or 8%, while six deciphered sequences are required for a missing rate between 10% and 20%. For larger values of missing rate, more deciphered sequences are required to determine the complete sequence. Error in prediction could occur for insufficient number of deciphered sequences, as shown in Fig. 6. In general, the prediction error decreases rapidly as the number of deciphered sequences increases, and a small prediction error is expected with ten deciphered sequences if the missing rate is less than 40%. However, for a missing rate greater than 40%, considerably more deciphered sequences than ten would be required to get an accurate prediction. Therefore, it is important to find appropriate experimental conditions through computer simulations in order to reduce the missing rate. Particularly, a missing rate less than 40% is desired. In addition, due to thermal fluctuations, it is also found that nucleotides can occasionally be trapped at the

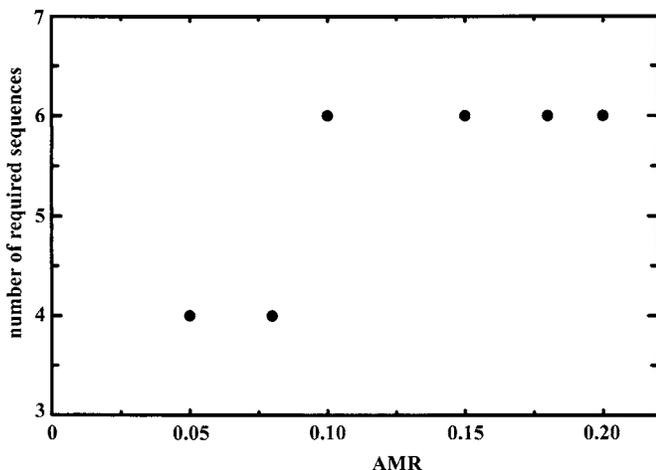


FIG. 5. Number of required deciphered sequences to determine the complete sequence of an unknown polynucleotide chain by using the Monte Carlo algorithm as a function of average missing rate of current signals.

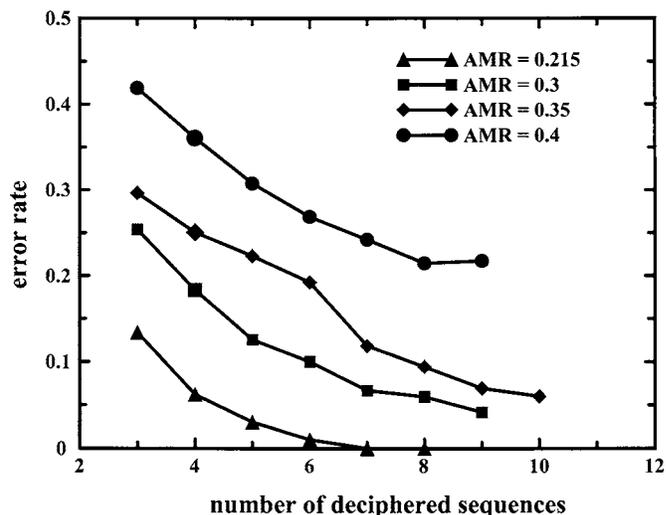


FIG. 6. Error rate in predicting the sequence of an unknown polynucleotide chain as a function of the number of deciphered sequences for AMR = 0.215, 0.3, 0.35, and 0.4.

nanopore for more than 1 μ time. In this case, these unqualified deciphered sequences will jeopardize our algorithm to find the complete sequence. Although these unqualified deciphered sequences can be detected in running our modified MC algorithm, it is also desired to suppress the number of unqualified sequences by choosing appropriate experimental conditions. In the next section, we will investigate the effect of E_h/E_v , ω_f , ω_s , and t_f/T_0 on the QR and the AMR of qualified translocation processes.

III. RESULTS AND DISCUSSION

One of the great advantages of computer simulations is that virtual experiments can be conducted to investigate the detailed properties of a physical process by changing all related parameters independently before these experiments are realized. With the advancement in information technology, in silicon analysis it is now much more efficient and inexpensive to simulate various physical processes. Here we study how to control the driven translocation dynamics of polynucleotides through a nanopore to obtain events of high QR and low AMR by changing the value of E_h/E_v , ω_f , ω_s , and t_f/T_0 . Each data point in our analysis is an average of 20 independent simulations of the driven translocation process. Note that, in all of our simulations, we have assumed that the active range of E_v (below the thin film) is greater than 100 nm, in which case both QR and AMR are independent of the range of E_v . The values of QR and AMR decrease if the range of E_v is smaller than 100 nm.

To investigate how the value of E_h/E_v affect QR and AMR, we have chosen the following set of parameters: $N = 150$, $\omega_s = 0.00005$, $\omega_f = 0.004$, and $t_f/T_0 = 0.15$. As shown in Fig. 7, we have calculated QR and AMR as a function of E_h/E_v for $E_v = 1.5, 2.5, \text{ and } 3.5$. For these three cases, it is found that both QR and AMR decrease drastically at large values of E_h/E_v due to the stretching of the polynucleotide chain by the rotating electric field. When the chain is more stretched, it becomes more difficult for the translocation of nucleotides through the nanopore after the switching of ro-

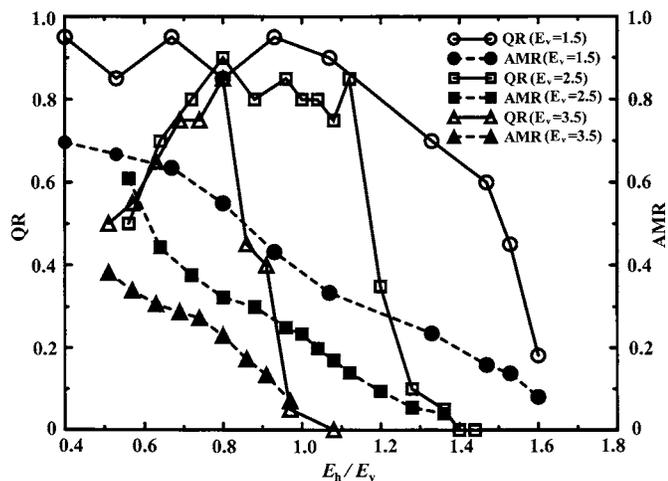


FIG. 7. The value of QR and AMR as a function of E_h/E_v for $E_v=1.5$, 2.5, and 3.5.

tating field from low frequency to high frequency. An appropriate range of the strength of these two electric fields is between 1.5 and 2.7, under which QR is about 0.8 and AMR is about 0.2. Note that QR also decreases at small values of E_h/E_v for $E_v=2.5$ and 3.5, which is due to the entanglement of the chain around the nanopore. In these simulations, only a small segment of the chain above the thin film is stretched due to a weak rotating field. Entanglement occurs when the unstretched segment of the chain is trapped at the nanopore due to a strong vertical electric field.

Further, we discuss the effects on QR and AMR by changing ω_f or ω_s . The set of parameters is chosen to be $N=150$, $E_v=2.5$, $E_h=2.4$, and $t_f/T_0=0.15$. As shown in Fig. 8, we have calculated QR and AMR as a function of ω_f , where ω_s is set to be 0.000 05. It is found that QR is zero for $\omega_f < 0.001$ and about 0.8 for $\omega_f > 0.004$. Moreover, an oscillation of the value of QR is also observed by changing ω_f . The minima of oscillation occur at $\omega_f=0.003$, 0.0048, 0.006, 0.0075, and 0.009. We have investigated the translocation processes of the chain at these frequencies and found that the chain is not completely relaxed during the fast frequency period. By investigating those unqualified translocation pro-

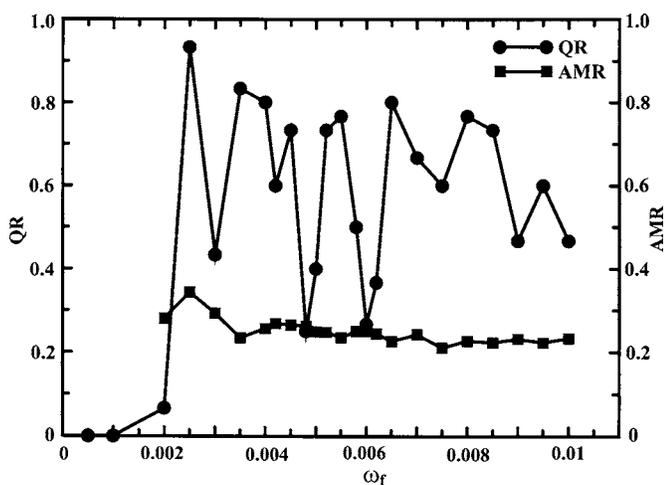


FIG. 8. The value of QR and AMR as a function of ω_f .

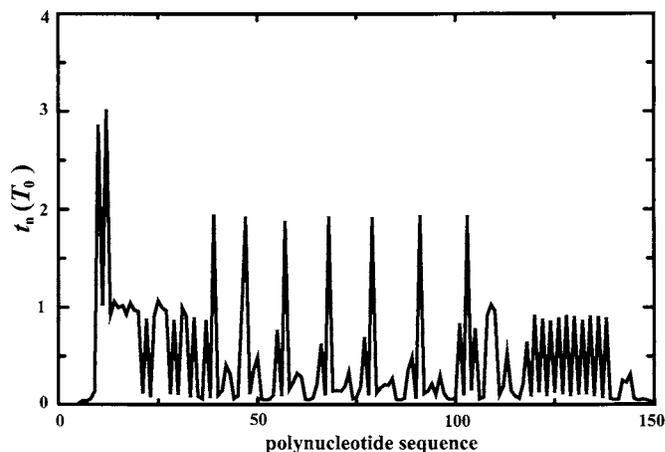


FIG. 9. The translocation time of each nucleotide, t_n , during an unqualified nanopore translocation process of a polynucleotide chain. In this case, $\omega_f=0.0048$.

cesses, we find that, due to the matching of nucleotide mobility and the rotation of electric field, the polynucleotide chain is completely stretched and the nucleotide in the nanopore will be trapped for longer than T_0 . A typical unqualified sequence occurring at $\omega_f=0.0048$ is demonstrated in Fig. 9, in which the chain has been fully stretched seven times for nucleotides between 39 and 103 in the polynucleotide sequence. When the chain is fully stretched, the nucleotide in nanopore usually takes more than 1 μ time to translocate through the pore. Since the time series of blockade current in the above translocation process is not qualified for our MMC algorithm to determine the complete sequence of the chain ($t_n > 1$), the value of QR decreases considerably for $\omega_f=0.003$, 0.0048, 0.006, 0.0075, and 0.009. There is no effect on AMR when changing ω_f . Figure 10 shows the value of QR and AMR as a function of ω_s , where ω_f is set to be 0.004. Qualified translocation processes of polynucleotide chains are observed only in the range of $10^{-5} < \omega_s < 10^{-4}$ in our simulations. For $\omega_s < 10^{-5}$, the polynucleotide chain is almost completely stretched and the relaxation time of the chain would be much longer than t_f . In this case, qualified translocation of the chain is not observed in our simulations.

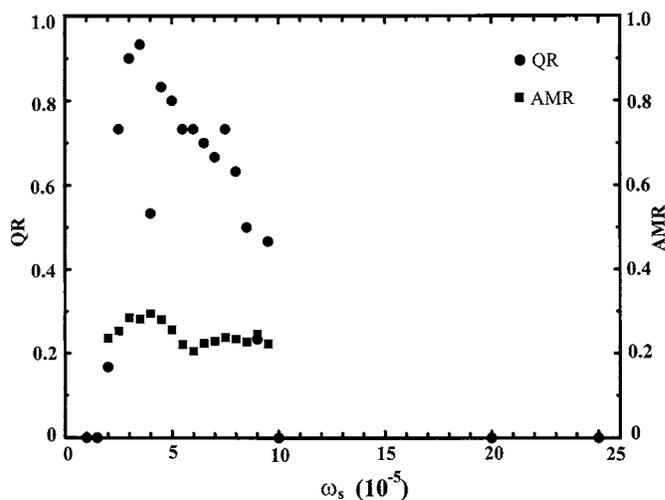


FIG. 10. The value of QR and AMR as a function of ω_s .

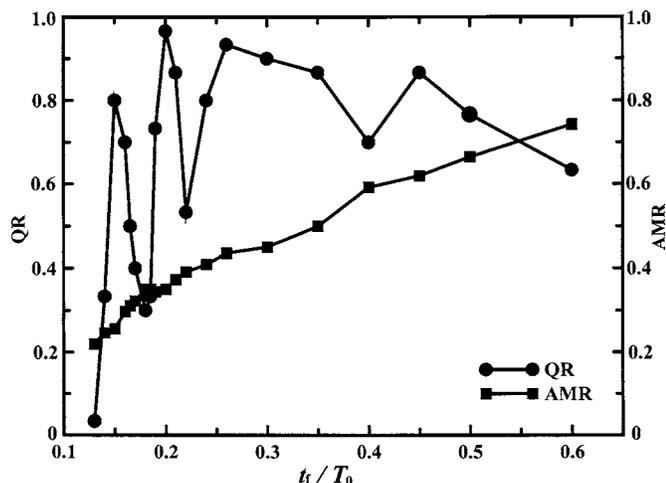


FIG. 11. The value of QR and AMR as a function of t_f/T_0 .

For $\omega_s > 10^{-4}$, although only a short segment of the chain near the nanopore is stretched, $t_f = 0.075\pi/\omega_s$ is too short for a nucleotide to translocate through the nanopore during the fast frequency period. As a result, qualified translocation processes are not observed at large ω_s . The value of AMR is about 20% if the slow frequency is in the range of $10^{-5} < \omega_s < 10^{-4}$.

Finally, we investigate the effect of increasing t_f on QR and AMR by fixing all other parameters ($N=150$, $E_v=2.5$, $E_h=2.4$, $\omega_s=0.00005$, and $\omega_f=0.004$). When t_f increases, one would expect that AMR should also monotonically increase because nucleotides near the nanopore can go through the pore during the relaxed period, as shown in Fig. 11. However, the dependence of QR on t_f is nontrivial. For small values of $t_f (< 0.13)$, the relaxed period is too short and no qualified translocation of the chain is observed. The value of QR increases with t_f and reaches the maximum of 97% at $t_f=0.2T_0$. After the maximum, the value of QR decreases as t_f increases. In this case, the polynucleotide chain cannot be properly stretched in a shorter stretched period ($t_s+t_f=T_0$), which leads to a high density of nucleotides near the nanopore. The translocation process becomes unqualified if the pore is jammed with more than one nucleotide. In addition, we observe the oscillation of QR with t_f for $t_f > 0.15$, which is also due to fully stretching a polymer chain as explained in Fig. 9. We note that, for the range of our parameters, we have observed the oscillation of QR (but not AMR) by changing various parameters. Since QR is defined to be the ratio of qualified time series of blockade current that can be used to determine the complete sequence using our MMC algorithm, its value drops drastically when the chain remains to be stretched in the fast frequency period. We expect that this problem will become less serious in the long chain limit. In this case, it is less possible for a long chain to be fully stretched. In addition, we expect the oscillation of QR will also be suppressed if we allow collective motion of the chain in our simulation model.

IV. CONCLUSIONS

In this paper, we have demonstrated a simple and powerful method to control the translocation processes of poly-

nucleotides through a nanopore assisted by a rotating electric field. Our method can be easily implemented in a nanopore sequencing experiment by adding two pairs of parallel electrodes above the thin film. The recorded time series of blockade current from the nanopore translocation processes of polynucleotides have been used to determine the sequence of a polynucleotide chain by implementing a modified Monte Carlo algorithm, in which the ELP technique is incorporated to avoid the trapping at deep local minima. It is found that only six time series of block current are required to completely determine the polynucleotide sequence if the missing rate of these time series is smaller than 20%. The error rate in sequencing an unknown polynucleotide decreases rapidly by increasing the number of time series for those time series with a missing rate greater than 20%. It is found that, in order to efficiently obtain the complete sequence, the value of AMR should be less than 40%. We have carefully investigated the dependence of AMR and QR for the nanopore translocation processes assisted by a rotating electric field on various controllable experimental variables, such as the value of E_h/E_v , ω_f , ω_s , and t_f/T_0 . An appropriate range of the strength of the two electric fields is between 1.5 and 2.7, under which QR is about 0.8 and AMR is about 0.2. The most appropriate ranges for the two frequencies of the rotating field are $0.002 < \omega_f < 0.01$ and $10^{-5} < \omega_s < 10^{-4}$. The duration of the fast rotating field (t_f) should be controlled within the range between $0.15T_0$ and $0.2T_0$.

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