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Molecular dynamics simulations indicate that DNA bases through graphene nanopores can be identified by their translocation times

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Abstract

The improvement of the resolution of DNA sequencing by nanopore is very important for its real life application. In this paper, we report our work of using molecular dynamics simulation to study the dependence of DNA sequencing on the translocation time of DNA through a graphene nanopore, using the single strand DNA fragment translocation through graphene nanopores with diameters down to ~2 nm as examples. We found that A, T, C, and G could be identified by the difference in the translocation time between different types of nucleotides through 2 nm graphene nanopore. In particular, the recognition of the graphene nanopore to different nucleotides can be greatly enhanced in a low electric field. Our study suggests that the recognition of a graphene nanopore to different nucleotides is the key factor to sequencing DNA by translocation time. Our study also implies that the surface of a graphene nanopore can be modified to increase the recognition to nucleotides and to improve the resolution of DNA sequencing based on the DNA translocation time with a suitable electric field.

Key words: DNA sequencing, Translocation time, Blockade current, Graphene nanopore

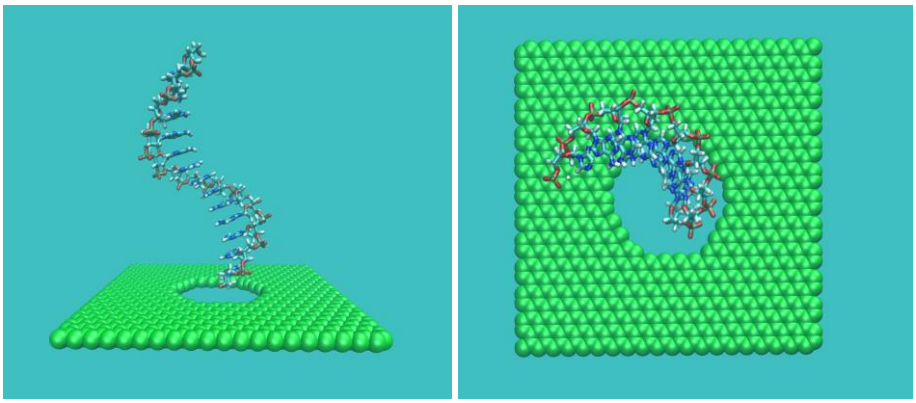
1. Introduction

DNA sequencing with nanopores has attracted much attention since DNA translocation through the biological nanopore α-hemolysin was first demonstrated.[1] In nanopore sequencing, a negatively charged biological molecule such as DNA[2] or RNA[3] is electrophoretically driven through a nanopore and its sequence is read off directly by measuring the reduction of the ion current during its translocation through the pore. This provides a promising technology for low-cost and high-throughput DNA sequencing which is free of fluorescent labeling and enzyme-dependent amplification steps.[4,5]

It has been reported that DNA sequencing with single-nucleotide resolution could be achieved by a mutant MspA nanopore with phi29 DNA polymerase. This represents a great progress in DNA sequencing with nanopores.[6] However, the harsh environment for the lipid membrane used for supporting the biological nanopore has limited its further development. On the other hand, solid-state nanopores offer a number of advantages compared with the biological nanopores, such as superior mechanical properties,[7, 8] multiplex detection,[9] and high stability to complex environments.[10] In recent years, a significant progress has been made in DNA sequencing with solid-state nanopores.[2, 11, 12] However, conventional nanopores made from silicon nitride,[13] aluminum oxide,[14] and silicon oxide,[15] are of several nanometers in thickness. As a result, a nanopore is occupied by many DNA bases at the same time in sequencing, which makes it difficult to detect a single stranded DNA (ssDNA) molecule at single-base resolution. This reflects that the resolution of DNA sequencing with solid state nanopores needs to be improved. A number of experiments and theoretical studies have been carried out to improve the resolution of DNA sequencing.[16-21] For example, a sub-2nm nanopore was used in DNA sequencing by Wu's[22] and Wang's Groups[23], where the force peak was considered as an effective index to distinguish DNA nucleotides by simulating the stretching process of a DNA molecule through the graphene nanopore. Dekker *et. al* pointed out that the resolution of DNA sequencing could be improved and the translocation time will decreased by decreasing the hydrophobicity of graphene nanopores with non-covalently bound hydrophilic functional group on graphene nanopore surface.[24] These studies greatly enhanced our understanding of DNA sequencing and paved a way to improve the resolution of DNA sequencing with solid-state nanopores. However, the error rate of DNA sequencing with solid-state nanopores is still too high for real life applications and other ways for reducing the error rate for DNA sequencing with nanopores need to be developed.

Graphene nanopores have been investigated in DNA sequencing due to their single-atom thickness and unique mechanic properties. They have been used widely in DNA detection in

recent years.[25-27] In this work, single molecule sequencing with graphene nanopores to identify four bases was investigated by molecular dynamics (MD) simulation. Table 1 lists all the MD simulations we performed in various conditions. As shown in Fig.1, an ssDNA molecule was observed translocating through a graphene nanopore under a certain electric field and the translocation time was calculated to distinguish different types of bases. In this figure, the starting time t_1 is defined as the time when the first atom of the DNA molecule starts to enter into the nanopore and the end time t_2 is defined as the time when the DNA molecule exit the nanopore completely. The time interval between t_1 and t_2 is defined as the DNA translocation time. By characterizing the profile of the translocation time for the DNA passing through graphene nanopores of different diameters under various applied electric fields, we are able to distinguish the nucleotides of the DNA.



(a) (b)

Fig.1. Initial structure of a system with an ssDNA and a graphene nanopore: (a) side view and (b) top view. The water molecules and ions are not shown for clarity.

2. Simulation details

System setup

To construct a graphene nanopore, the graphene sheet was set in the *x*-*y* plane with its center of mass in the origin (0, 0, 0) of the Cartesian coordinate, and the atoms with their coordinates satisfying $x^2 + y^2 < r^2$ were deleted, where r is the radius of the graphene nanopore. ssDNA fragments with different nucleotide compositions (as shown in Table 1) were constructed by using the Hyperchem software (Version 7.0, Hypercube, Inc). Each system, which consists of a nanopore and an ssDNA fragment, was solvated in a box of TIP3P[28] water molecules and underwent a 50000-step energy minimization. 14 K^+ were added into the system as counterions. Then, KCl ions were added into the box to match the same concentration as used in experiment.[29] The DNA and KCl were modeled by the CHARMM27 force field[30] and all carbon atoms in the graphene sheet were set to be neutral. The force field

parameters for graphene were obtained from our previous work, with $\sigma_{CC} = 0.385$ nm and ε_{CC} = -0.439 kcal/mol.[31, 32] All simulations were performed by the GROMACS 4.5.2 program,[33] and all simulations were repeated in 3 times. The periodic boundary condition was applied to model the infinite graphene nanopore and the particle mesh Ewald summation was used to recover the long range electrostatic interaction, with a cutoff of 1.3 nm for the separation of the direct and reciprocal space summations. All atoms including hydrogen atoms were represented explicitly and the lengths of the bonds containing hydrogen atoms were fixed. The cutoff for the non-bonded van der Waals interaction was set by a switching function starting at 1.0 nm and reaching zero at 1.2 nm. The time step is 2 fs. The Langevin method was employed to keep the temperature at 298 K with the pressure set at 101.3 kPa. Different bias voltages were applied in the simulations to drive the ions and ssDNA passing through the nanopores.

Analysis method

To describe the blockade current of a DNA molecule passing through a nanopore and to understand the phenomenon, the time-dependent ionic current *I(t)* was calculated as,[17]

$$I(t) = \frac{1}{t_{\text{int}} L_z} \sum_{i=1}^{N} q_i [z_i(t + t_{\text{int}}) - z_i(t)] \quad (1)$$

where L_z is the length of the system in the *z*-direction, t_{int} is set to 10 ps, N is the total number of atoms, including those of the DNA and ions, and q_i is the charge of atom i, respectively. The translocation time Δt_{tl} of a DNA fragment through a nanopore was calculated as

$$\Delta t_{tl} = t_2 - t_1 \quad (2)$$

where t_1 is the time when the first atom of the DNA fragment enters into the nanopore and t_2 is the time when the DNA fragment exits the nanopore completely. All DNA atoms were tracked with their positions; therefore, one could track the first atom that enters into the nanopore as well as the time t_1. Similarly, if all atoms translocate through the position of graphene nanopore, t_2 could be identified. The average blockade current for the DNA fragment to pass through the nanopore was calculated by

$$\langle I \rangle = I_{total} / \Delta t_{tl}, \text{ where } I_{\text{total}} = \sum_{t_1}^{t_2} \mathrm{I}(t) \quad (3)$$

Table 1. Simulated systems*

	Number of atoms	Electric field (mv/nm)	Diameter of the pore (nm)	KCl Concentration (M)	DNA (bp)	Time(ns)
SimIA1	41,564	100	1.6	1.0	$poly(A)_{15}$	50
SimIT1	41,246	100	1.6	1.0	$poly(T)_{15}$	50
SimIC1	41,504	100	1.6	1.0	$poly(C)_{15}$	50
SimIG1	41,335	100	1.6	1.0	$poly(G)_{15}$	50
SimIA2	41,564	200	1.6	1.0	$poly(A)_{15}$	50
SimIT2	41,246	200	1.6	1.0	$poly(T)_{15}$	50
SimIC2	41,504	200	1.6	1.0	$poly(C)_{15}$	50
SimIG2	41,335	200	1.6	1.0	$poly(G)_{15}$	50
SimIA3	41,564	400	1.6	1.0	$poly(A)_{15}$	50
SimIT3	41,246	400	1.6	1.0	$poly(T)_{15}$	50
SimIC3	41,504	400	1.6	1.0	$poly(C)_{15}$	50
SimIG3	41,335	400	1.6	1.0	$poly(G)_{15}$	50
SimIA4	41,564	600	1.6	1.0	$poly(A)_{15}$	50
SimIT4	41,246	600	1.6	1.0	$poly(T)_{15}$	50
SimIC4	41,504	600	1.6	1.0	$poly(C)_{15}$	50
SimIG4	41,335	600	1.6	1.0	$poly(G)_{15}$	50
SimIA5	41,735	100	2.0	1.0	$poly(A)_{15}$	30
SimIT5	42,705	100	2.0	1.0	$poly(T)_{15}$	30
SimIC5	42,713	100	2.0	1.0	$poly(C)_{15}$	30
SimIG5	41,938	100	2.0	1.0	$poly(G)_{15}$	30
SimIA6	41,735	200	2.0	1.0	$poly(A)_{15}$	10
SimIT6	42,705	200	2.0	1.0	$poly(T)_{15}$	10
SimIC6	42,713	200	2.0	1.0	$poly(C)_{15}$	10
SimIG6	41,938	200	2.0	1.0	$poly(G)_{15}$	10
SimIA7	41,735	400	2.0	1.0	$poly(A)_{15}$	10
SimIT7	42,705	400	2.0	1.0	$poly(T)_{15}$	10
SimIC7	42,713	400	2.0	1.0	$poly(C)_{15}$	10
SimIG7	41,938	400	2.0	1.0	$poly(G)_{15}$	10
SimIA8	41,735	600	2.0	1.0	$poly(A)_{15}$	10
SimIT8	42,705	600	2.0	1.0	$poly(T)_{15}$	10
SimIC8	42,713	600	2.0	1.0	$poly(C)_{15}$	10
SimIG8	41,938	600	2.0	1.0	$poly(G)_{15}$	10
SimIA9	41,735	50	2.0	1.0	$poly(A)_{15}$	50
SimIT9	42,705	50	2.0	1.0	$poly(T)_{15}$	50
SimIC9	42,713	50	2.0	1.0	$poly(C)_{15}$	50
SimIG9	41,938	50	2.0	1.0	$poly(G)_{15}$	50
SimA5	42,831	50	2.0	0.0	$poly(A)_{15}$	30
SimT5	43,961	50	2.0	0.0	$poly(T)_{15}$	30
SimC5	43,921	50	2.0	0.0	$poly(C)_{15}$	30
SimG5	43,105	50	2.0	0.0	$poly(G)_{15}$	30

*Sim represents simulation; I means that KCl ions were added to the system in the simulation; A, T, C and G represent the type of nucleotides.

3. Results and discussion

3.1 Effect of graphene diameter on DNA translocation

With the graphene nanopore of 1.6nm in diameter, the translocation time for the nucleotides is rather long. Of poly$(A)_{15}$, poly$(T)_{15}$, poly$(C)_{15}$ and poly$(G)_{15}$, none was observed to translocate through the nanopore completely in our simulations carried out for 50 ns under the electric field from 100mv/nm to 600mv/nm (SimIA1-SimIG4 in Table 1). The reason is that the diameter of ssDNA (~ 1.1nm) measured from experiments is almost comparable to that of the nanopore (1.6nm), which makes it difficult for the DNA to pass through completely in the limited simulation time due to the steric effect. Based on our previous work,[21] a large graphene nanopore can facilitate the translocation of ssDNA but decrease the identification at single nucleotide resolution. To achieve a balance between simulation time and resolution, a 2.0nm graphene nanopore was selected for sequencing the DNA in our simulations. We found that poly$(A)_{15}$, poly$(T)_{15}$, poly$(C)_{15}$, and poly$(G)_{15}$ can translocate through the nanopore under the electric field of 100mv/nm (SimIA5-SimIG5 in Table 1) within 30 ns. The averaged blockade currents during the translocation of different nucleotides were calculated from the simulations (SimIA5-SimIG5 in Table 1), as shown in Fig.2. One can see that the order of the averaged blockade currents is T < C < A < G. Compared with the experimental order T < G< C<A, the order of T, C, A is in accordance with the experiment one,[6] with the exception that the blockade of G is much smaller than A in the experiment; however, the error rate in the experiment is always with the high blockade current of G, which means the blockade current for G is not so stable. The reason of blockade of G in our simulation is much bigger than that in experiment is that the applied electric field (100mv/nm) in these simulations is much larger than that in experiments, which makes it difficult to distinguish the blockade currents between A and G. Our results show that T and G can be identified from the blockade current very clearly since the blockade current for T is much smaller than that for G, which has been also observed experimentally.[6, 34] However, the difference in the blockade current between A and C is too small to be distinguishable with the 2.0 nm graphene nanopore. Another interesting phenomenon is that all the nucleotides tend to adsorb on the graphene nanopore surface after translocation. This observation has also been confirmed by the experimental and theoretical works.[17, 24]

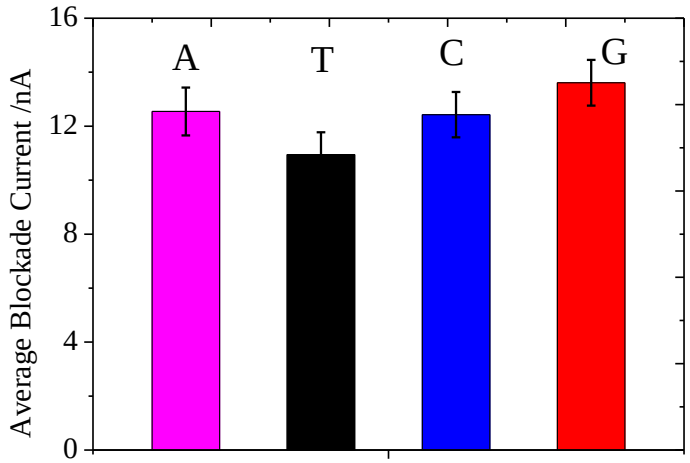


Fig. 2. The averaged blockade currents of different nucleotides poly(A)$_{15}$, poly(T)$_{15}$, poly(C)$_{15}$, and poly(G)$_{15}$ in the 2 nm graphene nanopore under the electric field of 100mv/nm.

3.2 Effect of electric fields on DNA translocation

Here, we investigate the effect of electric fields on DNA translocation time. Poly(A)$_{15}$, poly(T)$_{15}$, poly(C)$_{15}$ and poly(D)$_{15}$ were driven to pass through the 2 nm graphene nanopore by a series of electric fields ranging from 50 mv/nm to 600 mv/nm. Under the electric field of 600 mv/nm, the dynamics of poly(A)$_{15}$ is rather different from that under the field of 100mv/nm. The applied electric field of 600 mv/nm is so high that the bases went through the nanopores instantaneously. The reason is that in high electric field like 600 mv/nm, the dynamics of DNA molecule translocating through the nanopore was accelerated due to higher electric field force on DNA molecule. Although the thickness of graphene should be close to the spacing between two bases, the DNA molecule might bend in conformation and has less time to relax during the translocation process in higher electric field (with fast translocation dynamics) and small nanopore. Therefore, the ratio of signal to noise decreased since two or more bases occupied the nanopore at the same time. This observation indicates that a high electric field is not appropriate for DNA sequencing with graphene nanopores because the field can increase the noise and decrease the resolution of DNA detection. To understand the effect of electric fields on the DNA translocation, the translocation time for different polynucleotides to pass through the graphene nanopore under various electric fields was calculated. As shown in Fig. 3, the translocation times for different nucleotides are almost the same when the electric field is higher than 100mv/nm, reflecting that the translocation times of the nucleotides can hardly be distinguished with the 2nm graphene nanopore under a high

electric field. Based on the Newton's equation, the entire movement of the DNA fragment can be calculated as follows:

$$F = \int_{i=1}^{i=n} E\mathrm{dq_i} - \Delta f(t) \tag{4}$$

$$a = \int_{i=1}^{i=n} \frac{E}{\mathrm{m_i}}\mathrm{dq_i} - \Delta f(t)/m_i \tag{5}$$

where $\Delta f(t)$ is the total force on the DNA fragment due to graphene atoms, water molecules and ions, which is time dependent. Under a high electric field, $\Delta f(t)$ can be ignored. The acceleration a can be estimated by Eq. (6) and the translocation time can be expressed by Eq. (7) where L is the length of the DNA fragment. Thus, for a certain DNA fragment, the translocation time is calculated in an ideal case that DNA dose not interact with the ion, water and graphene in the system, which is only related to the electric field as expressed in Eq. (8), where A is the parameter.

$$a = \int_{i=1}^{i=n} \frac{E}{\mathrm{m_i}}\mathrm{dq_i} \tag{6}$$

$$\Delta \mathrm{t_{equ}} = \left(\frac{2L}{\mathrm{a}}\right)^{1/2} \tag{7}$$

$$\Delta \mathrm{t_{equ}} = A(E)^{-1/2} \tag{8}$$

As shown in Fig. 3(b), the curves obtained from fitting to Eq. (8) are in good agreement with the translocation times from the simulations, especially under high electric fields. This verifies that the interactions between the bases and other components, such as ions and the graphene nanopore, can be ignored under a high electric field, which is also the reason why the translocation times for different bases are almost the same under high electric field, therefore, the different type of bases could not be distinguished by translocation time under high electric field.

To distinguish different bases of ssDNA by the translocation time, a lower electric field of 50mv/nm was applied in the simulations with the 2 nm graphene nanopore. The translocation times of poly$(G)_{15}$, poly$(C)_{15}$, poly$(A)_{15}$, and poly$(T)_{15}$ in the nanopore are 13.2 ± 0.8 ns, 10.1 ± 0.6 ns, 4.8 ± 0.2 ns and 3.2 ± 0.1 ns, respectively, as shown in Fig. 4. The translocation time for poly$(G)_{15}$ is ca.13.2ns in the electric field of 50mv/nm, and is ca. 6.4ns in 100mv/nm. With a much lower electric field, the translocation time for all types of nucleotides is extended. This means that the speed of translocation can be decreased with a lower electric field, which is in consistence with the results from our previous work[21] and the experimental work from other groups.[27] In addition, the gaps between the translocation times of four types of nucleotides are much larger in 50mv/nm than those in 100mv/nm. The gap between the translocation times of poly$(G)_{15}$ and poly$(A)_{15}$ is ca. 3.1 ns in the electric field of 50mv/nm,

and is ca. 1.9 ns in 100mv/nm. This means that a single nucleotide can be identified easily in the electric field of 50mv/nm. As displayed in Fig. 4, the order of the translocation times for four nucleotides is poly(G)$_{15}$ > poly(C)$_{15}$ > poly(T)$_{15}$ > poly(A)$_{15}$, which is in accordance with the results from Derrington's experiments with the biological MspA nanopore.[35] These results clearly show that under a low electric field it is possible to distinguish four bases from the translocation times with a 2 nm graphene nanopore. However, it is also very important that the applied electric field should not be too low for a DNA fragment to pass through the nanopore since the interaction between the DNA fragment and graphene nanopore is very strong.[17,36] For example, as we shown in our previous work, the fluctuation of translocation time is relatively large under the electric field of 30mv/nm since the DNA fragment could strongly stick on the graphene nanopore.[37] Therefore, to select a suitable electric field with the best balance between the fluctuation of translocation time and the resolution of the DNA sequencing is very important.

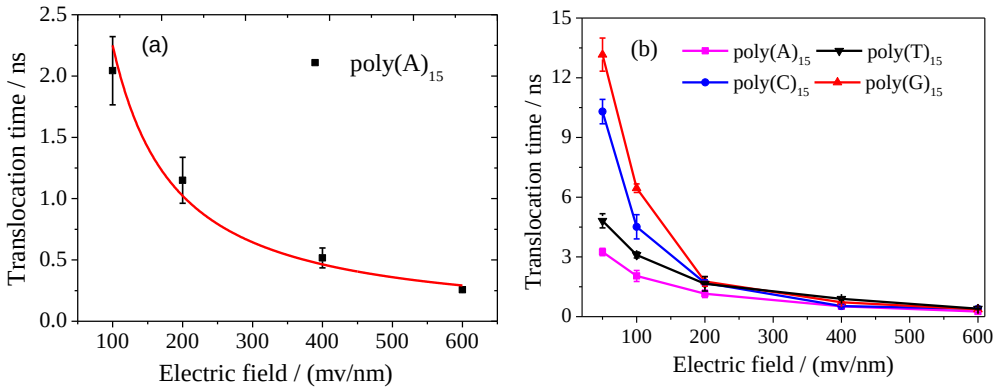


Fig.3. (a) Change of the translocation time of poly(A)$_{15}$ with the electric field (black square) in the 2 nm graphene nanopore. The red line is the fitted curve; (b) Change of the translocation times of different polynucleotides with different electric field in the 2 nm graphene nanopore.

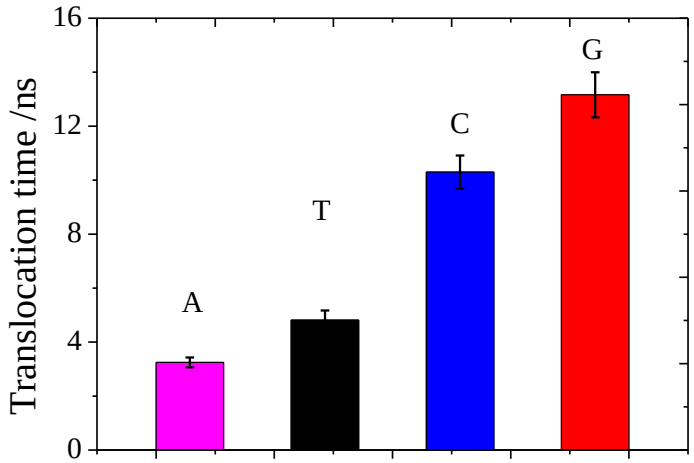


Fig. 4 The translocation times of poly(G)$_{15}$, poly(C)$_{15}$, poly(A)$_{15}$, and poly(T)$_{15}$ through 2 nm graphene nanopore with 1M KCl. The applied electric field is 50 mv/nm.

3.3 Effect of ions

The radial distribution functions (RDF) in this section was defined as a distribution of K^+ ions around the center of mass of each polynucleotide in the sequencing with 2 nm graphene nanopore and 50mv/nm electric field. It was calculated from the last 10ns trajectory to investigate the effect of ions on the ssDNA translocation. As shown in Fig. 5(a), the first three peaks in the K^+-poly(G)$_{15}$ RDF are much higher than those in the RDFs of K^+-poly(A)$_{15}$, K^+-poly(C)$_{15}$ and K^+-poly(T)$_{15}$. Meanwhile, the second peak of the K^+-poly(A)$_{15}$ RDF is much higher than that in the K^+-poly(C)$_{15}$ and K^+-poly(T)$_{15}$ RDFs. Therefore, the coordination number of K^+ ions around poly(G)$_{15}$ is always larger than that around the other three polynucleotides. The more K^+ ions close to poly(G)$_{15}$, the larger the hydration of the base, making dehydration of the base difficult. This could extend the translocation time of the polynucleotide.

Meanwhile, increase in the hydration of the polynucleotide poly(G)$_{15}$ can decrease the hydrophobic interaction between the base and the graphene nanopore and facilitate the desorption process of the polynucleotide from the nanopore. The translocation time of the polynucleotide will decrease with the acceleration of its desorption process. Therefore, the translocation time of the polynucleotide is the resultant of the dehydration effect and the desorption process, which can be affected by the hydration of ions. To study in detail the effect of K^+ ions on the DNA translocation, systems (SimA5-SimG5) without KCl ions but only with 14 K^+ ions as counterions were simulated under the same condition as for SimIA5-

SimG5. Fig. 6 shows that without KCl, the translocation times for poly(A)$_{15}$, poly(T)$_{15}$, poly(C)$_{15}$, and poly(G)$_{15}$ are 12.1 ± 1.2 ns, 10.1 ± 0.9 ns, 10.5 ± 0.8 ns, and 12.5 ± 1.1 ns respectively. We note that with 1M KCl, the corresponding values are 4.8 ± 0.2 ns, 3.2 ± 0.1 ns, 10.1 ± 0.6 ns, and 13.2 ± 0.8 ns. This indicates that in the absence of KCl, the difference in the translocation time between different polynucleotides is much smaller than that in the presence of 1M KCl ions. Without KCl, the translocation times of poly(A)$_{15}$ and poly(T)$_{15}$ are much longer than those with 1M KCl. In accordance with Luo's results[38], the translocation time of poly(A)$_{15}$ is greatly prolonged in the absence of KCl ions. The reason is probably that the hydration of the ssDNA in the absence of K^+ is much weaker than that in the presence of K^+ ions, thus the hydrophobic graphene nanopore has a much stronger interaction with the ssDNA in the solution.

In a relatively low electric field like 50 mv/nm, the factors such as DNA-graphene interaction and effect of ions is comparable to the electric field force, and they are the main reason that polynucleotide could be identified by translocation time of passing through graphene nanopore. Compared with the dehydration effect of the polynucleotide poly(G)$_{15}$, increase in the interaction between the polynucleotide and nanopore may have a much larger influence on the translocation time and thus likely prolong greatly the translocation times of poly(A)$_{15}$ and poly(T)$_{15}$. However, the translocation time of poly(C)$_{15}$ through the graphene nanopore in the absence of KCl ions is almost as same as that in the presence of 1M KCl. In the absence of KCl, the translocation time of poly(G)$_{15}$ changes a little. For these two polynucleotides, the dehydration and desorption effects may cancel each other in the solution without KCl ions. Thus, our studies indicate that in the absence of KCl, the difference in the translocation time between different polynucleotides is much smaller than that in 1M KCl solution, meaning that under a given electric field, the resolution of ssDNA sequencing decreases greatly in the solution without KCl ions.

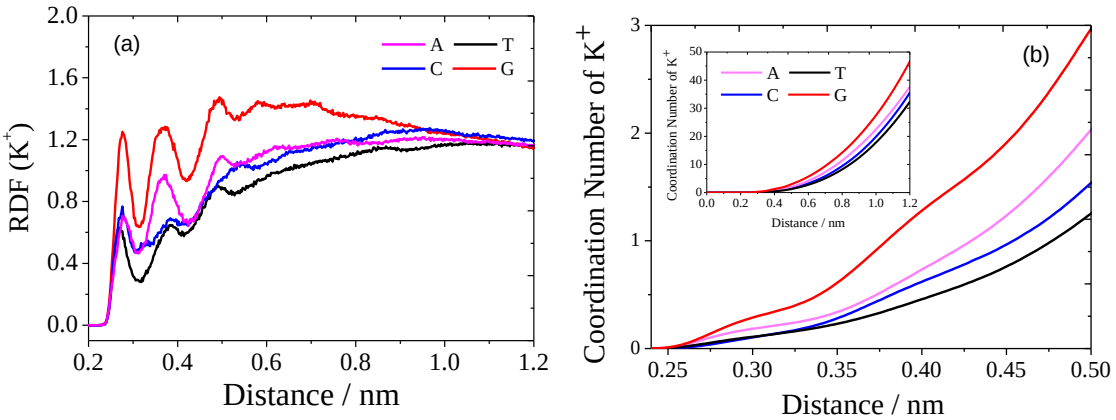


Fig.5 (a). RDFs between K^+ and the polynucleotides. (b) The coordination number of K^+ around each polynucleotide.

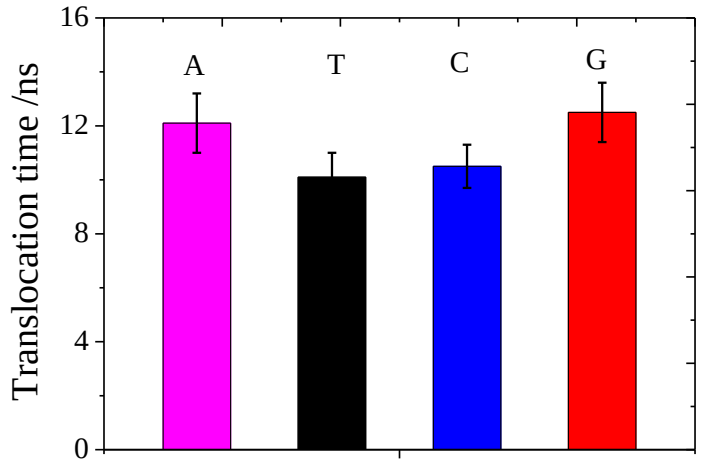


Fig.6 The translocation times of poly(G)$_{15}$, poly(C)$_{15}$, poly(A)$_{15}$, and poly(T)$_{15}$ through the 2 nm graphene nanopore in the absence of KCl. The applied electric field was 50mv/nm.

4. Conclusion

In this work, the translocation time of ssDNA through graphene nanopores was investigated by MD simulations. We found that with a graphene nanopore of appropriate diameter, such as 2 nm, the resolution of DNA sequencing by translocation time could be improved greatly compare with the case of using a larger nanopore as we discussed in previous work.[21] Different nucleotides including A, T, C, and G can be identified by their characteristic translocation times. The recognition of a graphene nanopore to different nucleotides can be improved significantly by applying a low electric field. Since the applied field in experiment is much lower than that in our simulations, our results provide a possible way to increase the resolution of DNA sequencing, which is based on the translocation time of DNA. Moreover, ion effects were found to be very important to the resolution of DNA detection. As the interaction between a graphene nanopore and a polynucleotide can affect the translocation time of the polynucleotide through the nanopore, it is possible to adjust the translocation time by chemical decoration of the nanopore surface. Our future work will focus on the influence of graphene nanopore modification on the resolution of DNA sequencing.

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