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Journal:	Nano Letters
Manuscript ID	nl-2024-00403z.R2
Manuscript Type:	Communication
Date Submitted by the Author:	02-Apr-2024
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Electrical transport and dynamics of confined DNA through highly conductive 2D graphene nanochannels

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ABSTRACT

Confining DNA in nanochannels is an important approach to study its structure and transportation dynamics. Graphene nanochannel is particularly attractive for studying DNA confinement due to its atomic flatness, precise height control, and excellent mechanical strength. Here, using femtosecond laser etching and wetting transfer, we fabricate graphene nanochannels down to less than 4.3 nm in height, with the length-to-height ratios up to 10³. These channels exhibit high stability, low noise and self-cleaning ability during the long-term ionic current recording. We report a clear linear relationship between DNA length and the residence time in the channel, and further utilizes this relationship to differentiate DNA fragments based on their lengths, ranging

widely from 200 bps to 48.5 kbps. The graphene nanochannel presented here provides a potential platform to label-free analyses, and reveals fundamental insights of the conformational dynamics of DNA and proteins in confined space.

KEYWORD: graphene nanochannel, DNA transport, highly conductive

Solid-state nanochannels play an important role in detecting biomolecules, such as DNA and proteins¹⁻³. Nanochannels can detect the DNA transportation and conformations by monitoring the ion conductance⁴⁻⁷. When a DNA is confined in the nanochannel, the combination of excluded volume and DNA stiffness stretches DNA to almost its full contour length^{8, 9}. Studying the transport properties of nanoscale-confined DNA is of great interest, and involves many complex physical mechanisms that are still being investigated. To do so, an ideal nanochannel should be slightly larger than the diameter of DNA molecules (~ 2 nm), and long enough to allow DNA chains ($\sim \mu\text{m}$) to be fully stretched within the channel. In addition, to facilitate the passage of DNA, smooth and clean surfaces are essential for nanochannels, especially for those with high length-to-height ratios.

Two-dimensional (2D) materials, such as graphene, molybdenum disulfide (MoS_2) and boron nitride (h-BN), have emerged as the ideal materials for fabricating nanoscale precision channels because of their exceptional flatness, excellent mechanical strength, and the ability to stack many atomic-thick layers to create channels with the desired height, etc¹⁰⁻¹². Cees Dekker *et al.* prepared a single graphene nanochannel and analyzed the ionic signal of different phases of DNA translocation¹³. These channels, however, are too short for DNA to fully stretched, and/or too large compared with DNA diameter. Moreover, such traditional methods to prepare graphene channels, wetting transfer and electron beam lithography, require repeated wetting transfer and chemical cleaning process that introduce surface contamination and defects, which decrease the channels' sensitivity for molecule detection.

Here, we presented a simplified transfer technique, using femtosecond laser etching

and wetting transfer to prepare nanochannel, which minimizes the pollution and defects caused by the transferring and cleaning¹⁴. This technique enables fabricating sub-4.3 nm channels with the length-to-height ratios up to 10^3 while maintaining the intrinsic state of 2D materials. The resulting graphene channels exhibited robust connectivity and long-lasting stability for highly sensitive resistive pulse sensing. The smooth and clean graphene surface effectively prevents the channel being blocked, showing an excellent “self-clean” ability. These channels allow transporting DNA, identifying its conformations, and further demonstrating the DNA stretching mechanism at different voltages, all by monitoring the ionic current. These channels, comparable height as DNA diameter, and enough length to allow DNA chains to be fully stretched within the channel, allow us exploring the full dynamics of DNA in a confined space. In addition to the high sensitivity, the transportation time of DNA through the channel is linearly corresponds to the DNA length, making it possible to discriminate DNA fragments based on their lengths. Finally, we extended this approach to fabricate Z-shape graphene nanochannels, and validated these channels’ ability of to trap DNA without completely blocking the channels. The results presented here highlight the broad application of graphene nanochannels in the fields of fundamental research for DNA and biosensing.

Figure 1a depicts the schematic of the channel structure and experimental setup. When a worm-like polymer, such as DNA, is confined within a nanochannel that is smaller than the radius of gyration of the polymer in free solution - Odijk model (S2, Supporting Information), the interactions between polymer and the channel walls stretch the polymer along the channel axis (Figure 1b). DNA molecules transport through the nanochannel electrokinetically, resulting in changes of ionic current, which is recorded by using a patch clamp amplifier.

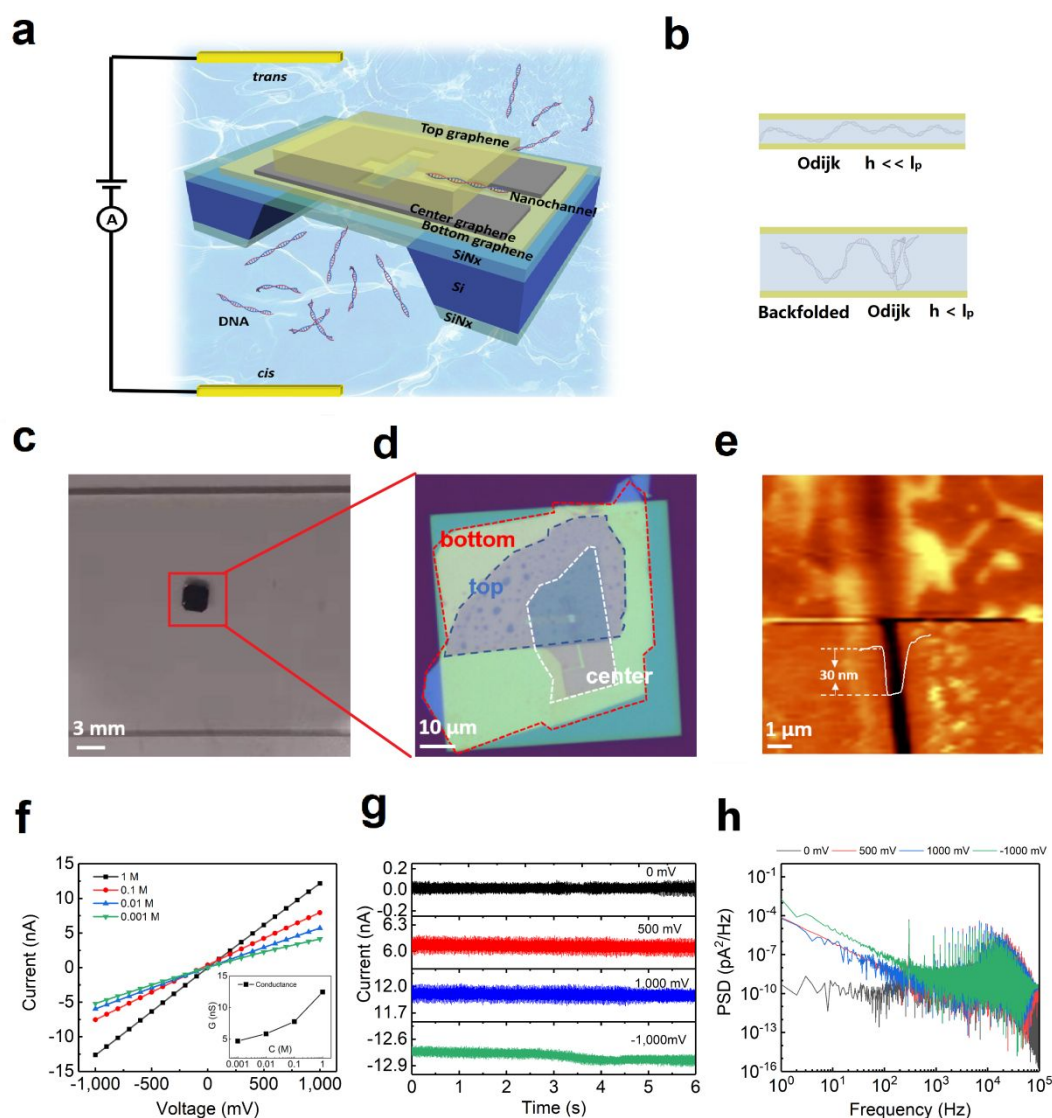


Figure 1. Structure and characterization of graphene nanochannels. (a) Schematic diagram illustrating the transportation of DNA through a graphene nanochannel. (b) Schematic diagram illustrating the transportation of DNA through channels of different heights. (c) Photograph of a silicon chip with a free-standing SiN_x membrane highlighted in the red box. (d) Photograph of a graphene nanochannel on the SiN_x membrane. The red, white, and blue dashed lines indicate the bottom, center, and top layer of the channel. (e) AFM image of the graphene nanochannel. (f) I – V curves of graphene nanochannel measured at KCl concentrations of 0.001, 0.01, 0.1, and 1 M. Inset: The ionic conductance as a function of KCl concentration. (g) Current traces of the graphene nanochannel in 1 M KCl solution acquired at different voltages. (h) Power spectrum density (PSD) of four traces presented in panel g.

The graphene nanochannel on the SiN_x chip consists of three thin graphene layers held together by van der Waals force, as shown in Figure 1c and 1d. The graphene layers were prepared by mechanical exfoliation (see details in Figure S3). The atomic force microscope (AFM) image in Figure 1e reveals the dimensions of one of the fabricated graphene nanochannels, which are 30 nm in height (h), 500 nm in width (w) and 10 μ m in length (L). We validated the conductivity and stability of the graphene nanochannel by measuring I - V curves at different KCl concentrations (Figure 1f and Figure S4). The current trajectory of this nanochannel remains highly stable at different applied voltages (Figure 1g). Even at a high voltage of 1,000 mV, we observed no significant fluctuation for a long duration (i.e. 300 s, Figure S7). This structural stability is crucial for long-term monitoring of the ionic current signal, especially at high voltages. And the structure can be stored for a long time, so multiple test analyses can be performed with the same sample over a long period of time (Figure S4c). The power spectral density (PSD) in Figure 1h further confirms the low noise characteristics of the nanochannel across a wide frequency range of 1 to 10⁵ Hz. This low-noise nanochannel enables us to identify weak ionic signals generated by nanoparticles as they transit through the channel.

To verify the effectiveness of the nanochannels in detecting structures of confined DNA, we compared the transportation of λ -DNA through two different channels, with height of 30 nm and 5 nm, respectively. We added λ -DNA to the *cis* side (negative-voltage-biased) of the fluid cell, which contained 1 M KCl on both sides of the chambers. The λ -DNA transport electrokinetically through the nanochannel from the *cis* side to the *trans* side, resulting in changes in electrical signals in the time domain. We analyzed the ionic current traces of λ -DNA transporting through these two graphene nanochannels at voltages of 800, 900 and 1,000 mV (Figure 2a and 2e, Supplementary Video 1).

For the channel with a height of 30 nm, both the pulse amplitudes $\Delta I/I_0$ and durations of pulses gradually reduce with increasing voltage (Figure 2b). Since the current pulses are, associated with the effective charge on the DNA molecule per unit length (Eq. s4

in S5, supplementary information), a folded DNA generates a higher current pulse than a linear stretched DNA. At 800 mV, the peak distribution of $\Delta I/I_0$ is approximately 0.02 (black circles). This value shifts to 0.015 at 900 mV (red circles) and 0.01 (blue circles) at 1,000 mV. The decreased channel blocking efficiency at high voltage indicates that DNA is gradually elongated as the voltage increases, as conceptionally illustrated by Figure 2d. At the same time, the increasing voltage significantly speeds up DNA transportation - the highest probable dwell time decreased from 55 ms to 15 ms as the voltage increased from 800 mV to 1,000 mV.

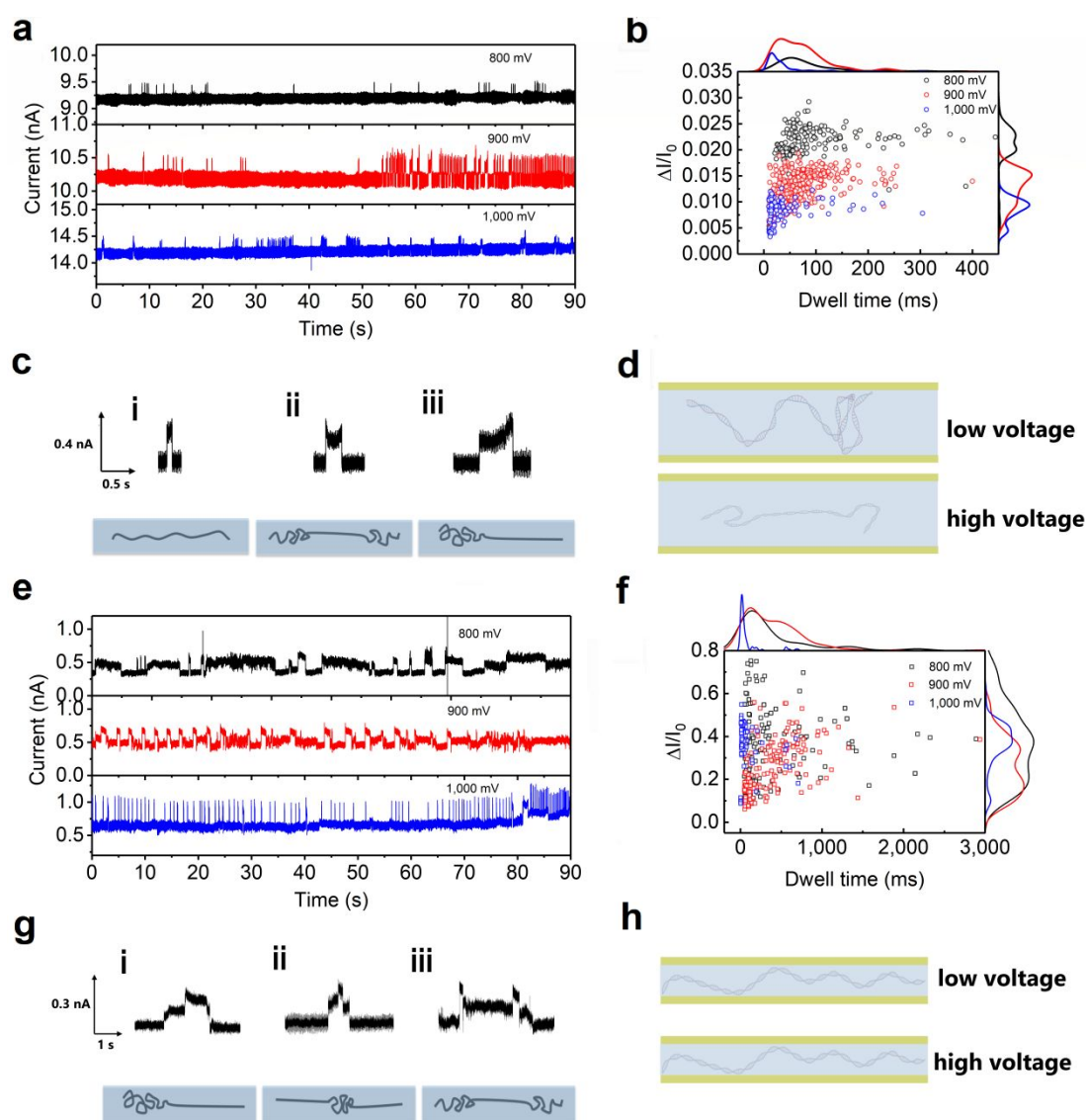


Figure 2. DNA translocation signals acquired from two different nanochannels. (a)-(d)

Nanochannel dimensions: $h = 30$ nm, $w = 500$ nm, $L = 10$ μ m. (e)-(f) Nanochannel dimensions: $h = 5$ nm, $w = 400$ nm, $L = 13$ μ m. (a) and (e) Current traces for λ -DNA translocation through a graphene nanochannel at various applied voltages. (b) and (f) Scatter plots of the pulse amplitudes versus translocation dwell time for λ -DNA at various applied voltages. (c) and (g) Representative pulses and their predicted DNA structures at 900 mV in 1M KCl solution. (d) and (h) Schematic diagram illustrating the regulation of DNA elongation at low and high voltages.

In Figure 2c, we highlighted three representative pulses at 900 mV and their corresponding predicted structures. When a long-chain DNA enters a nanochannel, the spatial limitation of the channel structure can stretch DNA from its folded state to the unfolded state^{13, 15-17}. The partial folding and curling of λ -DNA at low voltage increases the amplitude of the pulses¹⁸⁻²⁰. Among the three pulses shown in Figure 2c, pulse i has the shortest dwell time and lowest amplitude, indicating a low degree of DNA folding and a reduced surface contact between DNA and channel surface. Pulse ii exhibits a noticeable increase in the amplitude at the beginning and the end, but remains low amplitude in the middle, and a longer transmission time compared to pulse i. The increased amplitude and dwell time suggests that the DNA undergoes partial folding at both ends, leading to a reduced length and a prolonged ectopic duration. Similarly, pulse iii, with its asymmetric pulse waveform and the longest transmission time, suggests the folded state of DNA at one end¹³.

In the case of the channel with a height of 5 nm (Figure 2e-2f), DNA transports through the channel much slower than 30-nm channel (Figure 2a-2d). At 800 mV, the peak distribution of the dwell time is approximately 151 ms for the 5-nm channel, significantly longer than the 55 ms observed in the 30-nm channel. We note that the 5-nm channel is 1.3 times longer than the 30-nm channel, while the translocation speed is approximately 3 times slower. Moreover, the maximum dwell time in the 5-nm channel reaches 3,000 ms, which is considerably longer than the 300 ms observed in the 30-nm channel. As the voltage increased to 1,000 mV, the peak residence time of

DNA in the 5-nm channel decreased to 18 ms (Figure 2f). Two primary factors contributed to slowing down the DNA transmission within the narrower channel. Firstly, due to the height restrictions, DNA with folded segments needs to be stretched linearly before entering the narrow channel directly^{21, 22}. Secondly, due to the large contact area, the increased adhesion or friction between the graphene surface and DNA prolongs the residence time of DNA passing through the narrower channel.

The relative current change ($\Delta I/I_0$) is one order of magnitude larger for DNA in the 5-nm channel (Figure 2b) than in the 30-nm channel (Figure 2f). In addition, the 5-nm channel shows little to no change in the pulse amplitudes with increasing voltages, different from what we observed in the 30-nm channel. This is because DNA is already in an extended conformation upon entering the 5-nm channel, and its extended state remains relatively unchanged at different voltages. We note that both the 30-nm and the 5-nm channel satisfy the Odijk state, where the expansion variance σ^2 of the chain is satisfied⁸:

$$\sigma^2 = 0.00956 \frac{h^2}{l_p} L_b \quad (1)$$

where L_b represents the total length of the DNA backbone. A larger σ^2 indicates a stronger folding and curling effect of the DNA chain. Consequently, under the restriction of the Odijk scale, the lower the channel height, the closer the DNA is to the rod-like structure. Therefore, the DNA within the 5-nm channel is significantly more elongated than that within the 30-nm channel. The DNA is already in an extended conformation upon entering the 5-nm channel, and its extended state remains relatively stable even when the voltage is changed. On the other hand, the increased contact between DNA and the channel wall restricts the DNA elongation regulated by voltage, as illustrated in Figure 2h. Despite these restrictions, we were able to capture several signals of DNA folding in the 5-nm channel, with a significantly better accuracy than those captured in the 30-nm channel (Figure 2g). Unlike DNA, transporting Au nanoparticles through this nanochannel exhibits no decrease in pulse amplitude at a high voltage (Figure S6). This observation further confirms that the decreased $\Delta I/I_0$ at

high voltage (Figure 2b) is caused by the DNA linearization within the channel. Although the channel with a lower height is more prone to be blocked, the conductivity can be restored upon applying voltage for a certain period of time. This self-cleaning ability is closely related to the cleanliness and smoothness of graphene channel surfaces (Figure S7-S9).

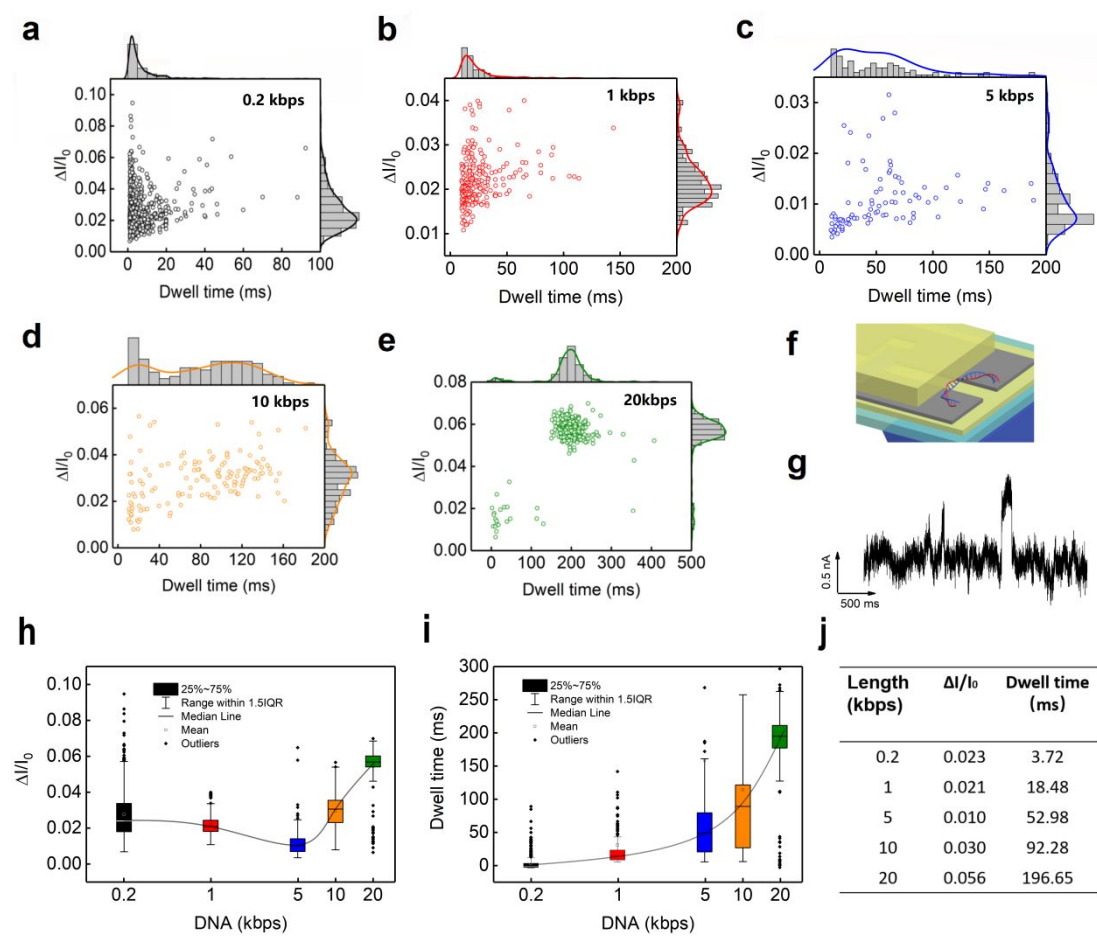


Figure 3. Transmission of DNA with different lengths through a nanochannel with dimension of $h = 4.3$ nm, $w = 400$ nm, $L = 10$ μ m. (a)-(e) Scatter plots of the pulse amplitudes versus translocation dwell time for DNA with different lengths (from 0.2 to 20 kbps) at 800 mV in 1M KCl solution. (f) The schematic illustration of DNA retention at the entrance to the channel. (g) Representative pulse showing DNA stuck at the entrance and followed with a normal transmission. (h) Pulse amplitudes varies with DNA length. (i) Dwell time varies with DNA length. (j) Median value of pulse

amplitudes and dwell time for different DNA lengths.

Figure 2 demonstrates that a narrower channel induces the extension of DNA molecules, leading to a longer residence time, and a higher $\Delta I/I_0$ during DNA transportation. This fully stretched DNA within the nanochannels makes it possible to detect its structure and length with high accuracy. In Figure 3a-3e, we observed a linear dependence between DNA lengths and the residence time, with shorter DNA strands passing through the channel faster. Figure 3h and 3i depicted the measured $\Delta I/I_0$ and dwell time for DNA with different chain lengths, respectively, with their median values summarized in the table of Figure 3j. We observed no significant difference in $\Delta I/I_0$ for different lengths, except for 20 kbps DNA. The blocking efficiency of 20 kbps DNA is much greater. The relatively consistent $\Delta I/I_0$ can be attributed to the compressed two-dimensional structure of DNA within the channel, where the curvature of DNA has minimized correlation to its length. Therefore, the cross section of the channel occupied by DNA is constant regardless of the DNA length, resulting in the same blocking effect for different lengths of DNA. Moreover, different folding effect of DNA upon entering the channel can also lead to the differences in the blocking effect. Therefore, the $\Delta I/I_0$ exhibit a not localized distribution, with a certain distribution range^{13, 23, 24}. In contrast, the median value of the dwell time is linearly related to the DNA length (Figure S10). The result agrees with the diffusion of DNA in nanoslits obtained by fluorescence tracking microscopy. This relationship directly links to the friction and adsorption between DNA and graphene surfaces^{25, 26} (S11, Supporting Information).

In the confined channel where the DNA is fully stretched, the differences between DNA of various lengths become more pronounced. The contact probability between DNA and the graphene wall is directly proportionate to the length of the DNA segment. This probability is significantly increased when the DNA is compressed into a two-dimensional plane structure, making it possible for nanochannels to identify DNA of

different lengths. We also observed some outliers in the scatter plot, particularly noticeable in the case of long DNA strands (bottom-left in Figure 3e). These atypical short-term signals arise from the stagnation of DNA at the entrance of the channel, where the DNA struggles to overcome the entropy barrier. As shown in Figure 3g, these pulses are significantly different from normal transmission signals. The normal transmission has an obvious transmission current plateau, while the hole retention is only the tip pulse^{13, 27}. These outliers, however, are not so pronounced for short DNA strands because they overlap the translocation signals (Figure 3a and 3b). On the other hand, the relatively low entropy barrier for the short-chain DNA entering the channel results in a low probability of DNA staying at the orifice.

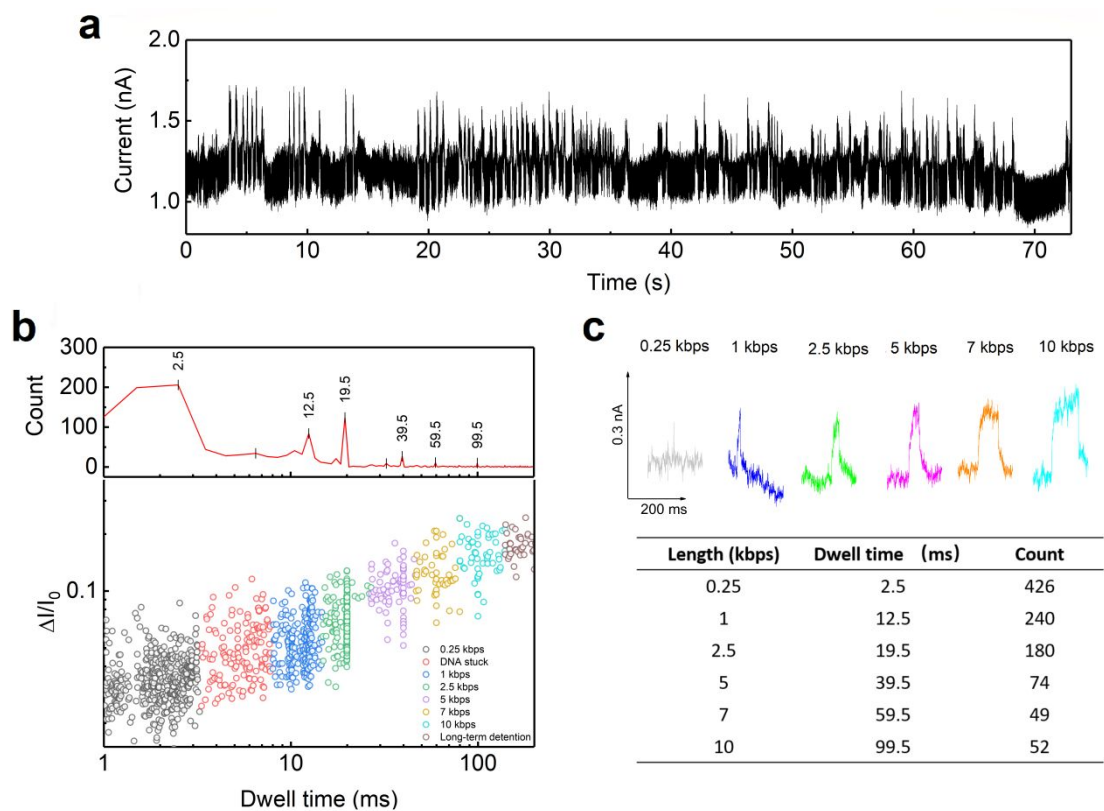


Figure 4. Distinguishing DNA strands of different lengths in a DNA marker mixture, using a channel with dimension of $h = 4.3$ nm, $w = 400$ nm, $L = 10$ μ m. (a) Current traces for DNA marker translocation through a graphene nanochannel at 1,000 mV. (b) Top: Distribution curve of dwell time, with extracted peak positions indicated. Bottom: Identification of clusters in the scatter plot representing the pulse amplitudes versus

translocation dwell time. (c) Representative translocation pulses of DNA with different lengths. Table below lists the corresponding peak locations and number of events identified by clustering obtained in panel b.

In Figure 4, we present the ability of the graphene nanochannel in distinguishing DNA with different lengths. We performed the experiment using DNA makers consisting of mixture of DNA fragments with six lengths, 0.25, 1, 2.5, 5, 7 and 10 kbps (see the electrophoresis gel diagram in Figure S12). We observed various amplitudes of pulses in the current trace in Figure 4a (as well as in Supplementary Video 3). This variation in pulse amplitudes is further revealed in the scatter plot in Figure 4b, along with a wide range distribution of the dwell time. The scattering data exhibit clear clusters corresponding to different kinds of pulses generated by the translocation of DNA with different lengths. We identified 6 peaks from the event counts of different dwell times on the top of Figure 4b. We used these peaks as median values to cluster the groups of the scattering points, and identified six groups with each corresponding to a fixed length of DNA (Figure 4b). The representative pulses of each group are shown in Figure 4c, along with a table listing the dwell time and event number of each group. We fit the dwell time and the number of base pairs to a linear function (Figure S10), the slope is closely match to that obtained from Figure 3. We noted that the dwell time offers higher resolution in distinguishing different DNA lengths compared to the pulse amplitudes (spatial resolution), consistent with previous observations shown in Figure 3e and 3h. We observed a large event number for DNA fragment of 0.25 kbps, indicating a relatively high capture rate of short-chain DNA due to its lower entropy barrier for entering the channel. In contrast, the larger entropy barrier for the long-chain DNA entering the channel results in a lower event number. This result validates the channel's ability to distinguish different lengths of DNA, across a wide range from 0.25 kbps to 10 kbps, which is challenging to achieve using existing nano-holes. We repeated these results with additional channels to validate the nanochannel's ability to differentiate DNA fragments (Figure S13). The higher channels showed a reduced lag

effect for DNA fragments of different lengths, indicating faster DNA transmission due to incomplete stretching (Supplementary Video 4 and 5). Reducing the channel height is beneficial to improving the accuracy in DNA identification. However, it should be noted that low channel height could hinder the entry of DNA, resulting in a low capture rate. Therefore, optimizing the channel height and length is crucial depending on the specific target sample.

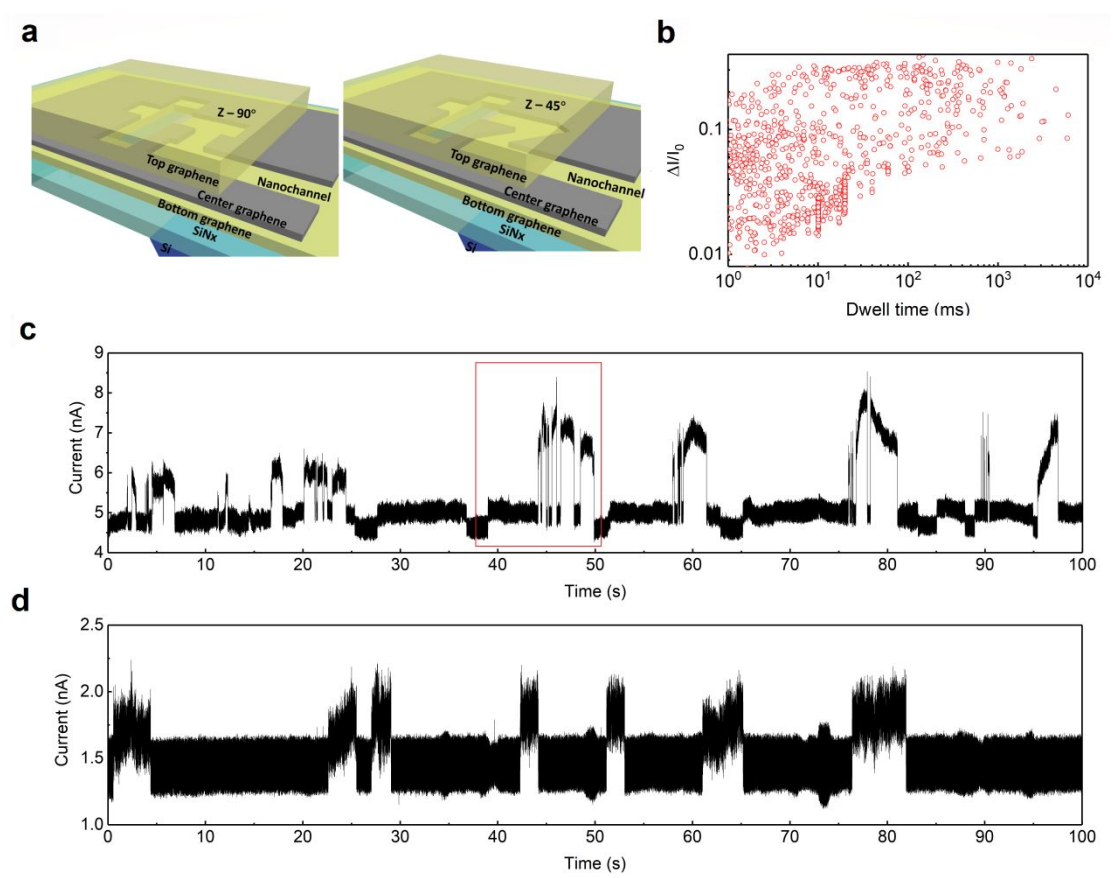


Figure 5. Delaying DNA transmission using Z-shaped graphene channels with angles 90° and 45°. (a) Diagram of Z-shaped nanochannel (photo in S14, Supporting Information). (b) Scatter plot showing the pulse amplitudes versus translocation dwell time for DNA marker at 1,000 mV, using the channel with an angle of 90°. Current traces for DNA marker translocation through a Z-graphene nanochannel with angles of 90°(c) and 45° (d) at 1,000 mV.

Retaining DNA and proteins within the nanochannel for an extended period is crucial

for obtaining comprehensive information²⁸⁻³¹. This prolonged confinement is particularly of interest for certain studies aiming to monitor the reactions or behaviors of trapped analytes²⁸. For this purpose, we designed Z-shaped channels with angles of 90° and 45° respectively, as illustrated in Figure 5a. This introduced bend in the channel aims to further slowdown the DNA transmission. When the angle is set to 90°, the DNA fragments can translocate the channel without getting stuck, as demonstrated by the current trace in Figure 5c. Unlike the results in Figure 4b, the scattering plot of current blockages vs. dwell times obtained from this 90° Z-shape channel are widely dispersed without clear clusters (Figure 5b). We observed the significantly extended transmission time and large amplitude of the current pulses, even for the fast translocated events. Additionally, the current trace reveals noticeable partial blocking of the channel, for instance, the elevation of current baseline from 39 s to 50 s due to the retention of DNA. This retention of DNA, leading to partial blockage of the channel, does not block other DNAs to transport through, as evidenced by the current pulses during 39 to 50 s in the red rectangular of Figure 5c. In contrast, the channel with a 45° angle demonstrated a stronger blocking effect in the current trace (Figure 5d and Supplementary Video 6) compared to the channel with a 90° angle. Additionally, the channel with a 45° angle captured only long-term blocking pulses, with no pulses detected on the elevated baseline. This ability of Z-shape nanochannels in capturing and restricting DNA makes it promising in the board application of biosensing.

In summary, we have successfully fabricated 2D graphene nanochannels with ultra-flat and clean surface using femtosecond laser processing and wetting transfer assembly. We demonstrated the high sensitivity of the nanochannels in detecting dynamics of DNA transporting through by monitoring the ionic current. By preparing the channel with height close to the diameter of DNA double helix, and length longer than the fully stretched DNA train, we detected different DNA conformations within the confined space, and further altered their folding states by changing the voltage. Attributing to the viscosity and friction between DNA and graphene surface within the nanochannel, we observed a linear correlation between the residence time and the length of DNA

fragments. Based on this finding, we showcased the nanochannels' ability in identifying DNA fragment based on the number of base pairs it contains. This provides a new detection method for DNA structure recognition. We further extended this approach to fabricate Z-shape nanochannels and demonstrated their ability to retain DNA within the channel for a extend period without completely blocking the channel. As summarized in Table 1 in the supplementary, the 2D nanochannels presented here has narrowest height and the channel is long enough for DNA to be fully stretched, offering a unique platform to analyze DNA in confined space. We also believe that the arbitrary shaped nanochannel can be potentially adapted for broad applications such as protein characterization or monitoring enzyme reaction.

ASSOCIATED CONTENT

Supporting Information.

Supporting Information S1–S15, which covers: S1. Materials and methods. S2. Odijk model. S3. Nanochannel fabrication. S4. Schematic of fluid cell and setup for ionic current measurement. S5. Theoretical analysis of current pulse. S6. Au nanoparticles transporting through nanochannel. S7. Baseline stability for long time testing. S8. Ionic current blockage and recovery. S9. DNA transporting through a SiN_x channel. S10. Linear fitting of dwell time vs. DNA chain length. S11. The relationship between DNA transport speed and length. S12. Electrophoretic gel bands of DNA marker. S13. Differentiate DNA lengths by using different nanochannels. S14. Photograph of a Z-shaped graphene nanochannel on the SiN_x membrane. S15. Table summarizing different nanochannels and their methods in detecting.

Supplementary Video 1: Acquisition process of λ -DNA in a 30 nm heigh channel in 900 mV.

Supplementary Video 2: Acquisition process of 20 nm Au nanoparticles in a 30 nm heigh channel in 900 mV.

Supplementary Video 3: Acquisition process of DNA-marker transmission current in a 4.3 nm high channel in 1,000 mV.

Supplementary Video 4: Acquisition process of DNA-marker transmission current in an 8.4 nm high channel in 1,000 mV.

Supplementary Video 5: Acquisition process of DNA-marker transmission current in a 10.5 nm high channel in 1,000 mV.

Supplementary Video 6: Acquisition process of DNA-marker transmission current in Z shape channel (45°) in 1,000 mV.

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Author contributions

Z. L. and Y. C. planned and conducted the experiments, and they wrote the manuscript. Y. C. fabricated the samples, and characterized and tested them. Z. L. and J. T. supervised and directed the research. X. H., C. Y. and Q. Y. provided theoretical and technical support for the experiment, and put forward reasonable suggestions for the experiment. The manuscript was written based on contributions by all authors. All authors have given approval to the final version of the manuscript.

Notes

The authors declare no competing financial interest.

ACKNOWLEDGMENT

This work was supported by the Natural Science Foundation of China (Grant 12174207, 11974190).

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SYNOPSIS

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ToC figure

