Probing the dynamic structural changes of DNA using ultrafast laser pulse in graphene-based optofluidic device

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Abstract
The ultrafast monitoring of deoxyribonucleic acid (DNA) dynamic structural changes is an emerging and rapidly growing research topic in biotechnology. The existing optical spectroscopy used to identify different dynamical DNA structures lacks quick response while requiring large consumption of samples and bulky instrumental facilities. It is highly demanded to develop an ultrafast technique that monitors DNA structural changes with the external stimulus or cancer-related disease scenarios. Here, we demonstrate a novel photonic integrated graphene-optofluidic device to monitor DNA structural changes with the ultrafast response time. Our approach is featured with an effective and straightforward design of decoding the electronic structure change of graphene induced by its interactions with DNAs in different conformations using ultrafast nanosecond pulse laser and achieving refractive index sensitivity of $\sim 3 \times 10^{-5}$ RIU. This innovative technique for the first time allows us to perform ultrafast monitoring of the conformational changes of special DNA molecules structures, including G-quadruplex formation by K⁺ ions and i-motif formation by the low pH stimulus. The graphene-optofluidic device as presented here provides a new...
1 INTRODUCTION

Deoxyribonucleic acid (DNA) is fundamentally a genetic material maintaining the identity of different species of organisms.\(^1\) DNA is composed of a sequence of nucleotides containing four different types of bases including adenine, thymine, cytosine, and guanine (A, T, C, and G). Two strands of DNA can take place of hybridization by the specific pairing rule (A-T and C-G) to form a double helix bound together by the hydrogen bonds.\(^1,2\) The DNA molecular structures are critical in a variety of biological processes such as DNA strands separation in transcription or disordered telomerase level that leads the living cells to senescence and death.\(^3\) The monitoring of structural changes in DNA molecules is crucial in biomedical research because they are closely related to genetic stability, aging, and various diseases. Traditional techniques used for probing DNA and protein molecular structures include circular dichroism (CD),\(^4\) nuclear magnetic resonance,\(^5\) Fourier transform infrared spectroscopy,\(^6\) fluorescence spectroscopy,\(^7\) and X-ray crystallography\(^8\) but all lack quick response and require large consumption of samples, bulky instruments, and high expense. Recently, researchers are trying to probe the structural dynamics of biomolecules placed at large volume quartz cuvette by using free space ultrafast pump-probe spectroscopy.\(^9,10\) Levene et al have demonstrated zero-mode waveguides for studying single-molecule dynamics at micromolar (\(\mu\)mol) concentrations with microsecond (10^{-6} seconds) temporal resolution.\(^11\) However, it still remains a great challenge, in particular, the high demand to screen the DNA molecular structural dynamics in optofluidic devices with the combination of minimal sample volume and high throughput (in terms of high sensitivity and ultrafast response time).

Recently, there have been cutting-edge advances on single-molecule DNA sequencing, which involves a single DNA molecule passing through a graphene nanopore for ultrasensitive and identification of the nucleotides sequentially.\(^12-24\) They promise next-generation graphene-based DNA sequencing and structural monitoring technologies.

Graphene is an ideal material to probe DNA sequencing and structural dynamics monitoring compared to other traditional materials due to high surface-area-to-volume ratio, enriched interactions with biomolecules, extremely high charge carrier mobility, ultrabroadband light absorption, and excellent biocompatibility.\(^25-32\) Graphene has been used for varieties of ultrasensitive biochemical sensing applications including DNA sequencing, structural monitoring, hybridization, and other biomarkers.\(^12,25,33,34\) However, the dominant mechanism of those approaches mainly relies on the electrical signal measurements upon the biomolecule doping on the graphene surface, which suffers from severe background noise issues and slow detection speed. In the last few years, there are few reports on graphene and 2D materials based biochemical sensors using optical devices such as surface plasmon resonance and optical fibers.\(^25,26,35,36\)

To develop new optical detection technology, optofluidic devices\(^37-40\) with high sensitivity\(^41,42\) and ultrafast response time\(^43,44\) are promising for understanding the interactions between DNA molecules and graphene. The double-strand DNA (dsDNA) and single-strand DNA (ssDNA) have different interactions with graphene in terms of charge doping, which are attributed to the different adsorption geometry of dsDNA and ssDNA on graphene surface as indicated by theoretical calculations.\(^45,46\) The conformation of DNA structures and the interaction distances may be quite different when either ssDNA or dsDNA approaches graphene. However, there is no experimental demonstration on the ultrafast time scale monitoring of DNA interaction on the graphene surface due to the technical limitation of electrical detectors in terms of slow response time and large noise. The difference in the charge transfer from ssDNA or dsDNA to graphene surface has been reported by using electrical field-effect transistor (FET),\(^21\) but to probe the structural dynamics of ssDNA, dsDNA, and other cancer-related DNA molecules on the graphene surface using an ultrafast fiber optical approach has been elusive.

In this work, we probed the different DNA molecular structural interactions with monolayer graphene at the ultrafast time scale of nanosecond using an optofluidic
We further demonstrated the monitoring of the conformational changes of recently discovered cancer-related DNA molecules including i-motif in the incidence of low pH stimulus and G-quadruplex in the incidence of K⁺ ions.

**2 | RESULTS AND DISCUSSIONS**

### 2.1 | Fabrication of graphene-optofluidic device

Figure 1A illustrates the schematic diagram of the pumping mode-locked ultrafast fiber infrared laser (see Figure S1) into the graphene-optofluidic channel for detecting different DNA molecules structures and structural changes. One atomic thick layer of graphene, as confirmed by the Raman spectrum (Figure S2), is coated on left fiber end-facet, which is used as a sensing material. DNA molecules with a concentration of 1 μM are loaded into the optofluidic device. The inset of Figure 1A shows the schematic diagram of the adsorption of DNA molecules on the graphene surface and the modulation of ultrafast laser signal. The transmitted light is detected by using an oscilloscope connected to the other end of the optical fiber output. Before introducing different DNA molecules into the graphene-optofluidic channel, we have tested our device for ultrafast refractometer by

**FIGURE 1** Ultrafast graphene-optofluidic device measurements and characterizations. A, Schematic diagram of ultrafast graphene-optofluidic device for probing interaction of DNA structures on two-dimensional graphene. B, Ultrafast refractive index sensing. C, Electric transport measurement as a function of ssDNA and dsDNA interaction with graphene. Inset: schematic diagram of ssDNA and dsDNA interaction with graphene in a transistor device. D, Raman spectra of graphene as a function of ssDNA and dsDNA interaction. Inset: shift in the Fermi level of graphene. DNA, deoxyribonucleic acid; ssDNA, single-strand DNA; dsDNA, double-strand DNA.
introducing different refractive index medium in the channel as shown in Figure 1B. Initially, the amplitude of the ultrafast laser pulse train is drastically reduced in the transmission spectrum from the graphene-optofluidic device, because of the attenuation by air (n = 1.00) guiding medium. The increase in the refractive index of fluid (water, n = 1.33, and ethanol, n = 1.36) in the graphene-optofluidic channel, enhances the intensity of the ultrafast laser, due to better guiding medium as compared to air. The ultrafast laser pulse intensity increases as a role of the upsurge in the refractive index of changed medium (Figure S3). This novel graphene-optofluidic device can be used as an ultrafast refractometer (10^{-9} seconds) with the sensitivity of $\sim 3 \times 10^{-5}$ RIU.

Then ssDNA (H22) and dsDNA (cH22) molecules are tested in the ultrafast graphene-optofluidic channel. From the chemical composition point of view, the DNA strand is a polynucleotide made up of many individual nucleotide units (phosphate, pentose sugar, and nitrogenous base). Previous studies have suggested that charge-charge interactions and $\pi-\pi$ assembling are predominant powerful forces for DNA molecules adsorption on the surface of graphene.\textsuperscript{12,21,25} Whenever DNA molecules (ssDNA and dsDNA) interact with the graphene surface, the Fermi level of graphene alters either to p-type or n-type depending on the charge transfer behaviors from DNA molecules to graphene. The interactions of ssDNA or dsDNA with graphene surface have been confirmed by two independent experiments, via the electrical transport measurement and optical Raman spectroscopy. Figure 1C shows the electrical measurements based on the graphene FET to probe the interactions between ssDNA or dsDNA and graphene. After the setting-up of a constant voltage between the source and drain contacts, the source-drain current can be monitored while sweeping the gate voltage from $-20$ to $100$ V. The I-V curves of graphene shift positively after ssDNA or dsDNA interaction, demonstrating effective p-type doping of graphene. The shift in the conductivity spectrum of graphene is much higher in the case of ssDNA as compared to dsDNA, indicating a more significant doping effect in terms of charge transfer from ssDNA to graphene surface which leads to further changes in the optical refractive index of graphene.

We have also performed Raman spectroscopy to confirm the magnitude of charge transfer from ssDNA or dsDNA to graphene. Figure 1D presents the Raman spectra of graphene after interacting with ssDNA and dsDNA. The interaction of dsDNA with the graphene surface shows a quite small redshift in the 2D peak, suggesting a slightly p-doping effect. By contrast, a larger redshift from 2690 to 2729 cm$^{-1}$ was observed in the case of ssDNA due to the much stronger electron-withdrawing effect from graphene (highly p-doped). Here we propose that the electrical conductivity of graphene can be modulated by its interactions with different DNA structures, resulting in variations in the optical refractive index of graphene as shown in Equation (1).

\[
n_g = \left( \frac{-\sigma_{g,i}}{\omega \Delta} + \frac{i \sigma_{g,r}}{\omega \Delta} \right)^{1/2}
\]

where $n_g$ is the refractive index of the graphene, $\sigma_{g,i}$ and $\sigma_{g,r}$ are the imaginary and real parts of the electrical conductivity of graphene, $\omega$ is the frequency of light, and $\Delta$ is the thickness of graphene. The ultrafast fiber laser pulse output is altered by the refractive index of graphene ($n_g$) due to the interactions with the ssDNA and dsDNA nucleobases. The response time of the graphene-optofluidic device is more related to the repetition rate (2.5 MHz) of the ultrafast fiber pulse laser.

### 2.2 Probing graphene-DNA molecule interactions

Figure 2 illustrates the ultrafast optical measurement results of ssDNA (H22) and dsDNA (cH22) interactions with graphene surface and modulating an ultrafast laser output. Control experiments were performed using the standard CD spectroscopy. As shown in schematic Figure 2A, the unshared nucleobases of ssDNA tend to undergo maximum $\pi-\pi$ interaction with graphene, resulting in a p-doped shift of the Fermi level, which further leads to the refractive index change of graphene. Therefore, when the ultrafast laser pulse passes through ssDNA bound graphene, we can clearly observe the change of amplitude and pulse shape of the ultrafast laser. In contrast, the effect induced by the interactions between dsDNA and graphene is less significant due to the original pairing of the nucleobases. The aromatic rings of the dsDNA nucleobases stack next to each other and share electron probabilities with its complementary bases. Therefore, no much charge doping effect by dsDNA on graphene which in turn results in a modest change in the amplitude and shape of the ultrafast laser pulse, as schematically illustrated in Figure 2B.

Figure 2C displays the experimental results of the change in the amplitude and shape of the ultrafast laser pulse when it passes through the sensor chamber. The amplitude and shape of ultrafast laser pulse were distinctly different for ssDNA or dsDNA as compared to reference distilled (DI) water. The change in the amplitude and shape of the ultrafast laser pulse for ssDNA is more dramatic than dsDNA due to a more significant effect of charge induced p-doping in graphene (Figure 1C,D). The main mechanism of DNA interacting with graphene is...
FIGURE 2  Probing graphene-DNA molecules interactions. A, Schematic diagram of ultrafast laser pulse passing through ssDNA structural interaction with graphene. B, Schematic diagram of ultrafast laser pulse passing through dsDNA structural interaction with graphene. C, Ultrafast laser pulse shift for ssDNA and dsDNA bound graphene. Inset, an optical image showing the difference in the ultrafast laser pulses output when it passes through ssDNA and dsDNA bound graphene. D, CD spectroscopy of ssDNA and dsDNA structural interaction with graphene. E, Schematic diagram of CD spectroscopy with graphene-coated inside the cell to study the interaction of ssDNA and dsDNA with graphene. F, The shift in the ultrafast laser pulse depending on the distance and conformation of ssDNA on the graphene. Black, purple, blue, red traces correspond to the dynamic structural changes of ssDNA. G, The shift in the ultrafast laser pulse when dsDNA interacts with graphene. Black, purple, blue, red traces correspond to the dynamic structural changes of dsDNA. CD, circular dichroism; DNA, deoxyribonucleic acid; dsDNA, double-strand DNA; ssDNA, single-strand DNA
through π-π stacking, which is the root cause of ssDNA binding more strongly to the graphene surface than dsDNA.

We have confirmed the difference in the structural interactions between ssDNA or dsDNA and graphene by using standard optical CD spectroscopy, as shown in Figure 2D. CD optical spectroscopy reveals the structural information of different biomolecules such as DNA and protein. Figure 2E shows the schematic diagram of CD spectroscopy where graphene is coated on the inside walls of the cuvette for the studies on the interactions between ssDNA or dsDNA and graphene surface. Using CD spectroscopy, different DNA molecular structures can be recognized based on the variation in the absorption of right and left-handed circularly polarized UV light \( \Delta A = A_{LCP} - A_{RCP} \). ssDNA was characterized by a positive long-wavelength band at about 260-280 nm (peak III in Figure 2D), a negative band around 245 nm (at 241 nm, peak II in Figure 2D), and a negative band at 210 nm (at 211 nm, peak I in Figure 2D), which are consistent with the previous report. ssDNA has also been resolved in the changes in the CD peak of the positive band at 295 nm and a negative band around 260 nm (red curve in Figure 2D). As revealed by the CD measurements, the shift in the amplitude and wavelength of the polarized light through ssDNA/graphene are much higher than dsDNA/graphene, which is consistent with our experimental results by using the ultrafast graphene-optofluidic device. It confirms that different DNA molecular structures based on π-π interaction with graphene surface can be identified with our new approach.

We have performed the CD spectral measurements for ssDNA and dsDNA molecules structures with and without graphene as a control experiment. We could observe the difference in the spectrum shift for ssDNA (Figure S4a) and dsDNA (Figure S4b) due to the interactions of nuclear acids with graphene. The peak intensity (CD, mdeg) change for ssDNA is much higher since unshared nucleobase charges undergo maximum π-π interaction with the graphene (Figure S4a). This results in a stronger p-doping effect and affects the left and right circularly polarized light absorption as compared to dsDNA (Figure S4b). We repeated the CD spectral measurements for ssDNA and dsDNA without graphene placed on the cuvette and observed there is no CD spectral shift. It suggests graphene plays a key role in identifying different DNA molecules structures.

Figure 2F,G presents in-situ monitoring the interactions of ssDNA and dsDNA with graphene using ultrafast fiber laser pulse. As soon as ssDNA was injected into the graphene-optofluidic channel, the laser intensity and pulse shape changed immediately (Figure 2F), depending on the distance and conformation of ssDNA on the graphene. It can be seen that there were variations in the amplitude and shape of ultrafast laser pulses because of the interactions between graphene and ssDNA. The significant peak shift and amplitude enhancement of ultrafast laser pulse are associated with the highly nucleobase-dependent charge transfer between ssDNA and graphene. In comparison, it can be seen that there is no much change in the ultrafast laser pulse (amplitude and shape) when dsDNA interacts with graphene due to less transferring of electrons to nucleobases, as shown in Figure 2G.

### 2.3 G-quadruplex and i-motif DNA interaction with ions and pH stimulus

Figure 3 shows the experimental results of G-quadruplex (H22) and i-motif (cH22) ssDNA interaction with K+ ions and pH stimuli, respectively. The monitoring of structural changes of G-quadruplex and i-motif ssDNAs with the external stimulus (ions and pH) are vital in health care applications since they represent attractive drug targets for anti-cancer therapeutics. Figure 3A shows the schematic diagram of G-quadruplex DNA interaction with K+ ions and probing the structural changes information by using an ultrafast laser pulse. Figure 3B represents the structural change in quadruplex DNA when it is treated with K+ ions. Before K+ ions are added into the ultrafast graphene-optofluidic channel, quadruplex nucleobase can share electrons with the graphene surface. Once K+ ions are injected into the graphene-optofluidic channel, the quadruplex nucleobase tends to share charge carriers with surrounding K+ ions, leading to the reduction of the electron sharing with graphene. Therefore, the peak intensity of the ultrafast laser decreases due to reduced charge density in graphene (Figure 3B). We have also confirmed quadruplex structural changes with K+ ions using CD spectroscopy as shown in Figure 3C. The parallel quadruplexes are characterized by a dominant positive band at 260 nm (261 nm, a peak I in Figure 3C), whereas the spectra of antiparallel forms display a negative band at this wavelength and a positive band at 295 nm (293 nm, peak II in Figure 3C). In addition, all quadruplexes display another positive band around 215 nm (215 nm, peak III in Figure 3C). These results confirm that the quadruplexes will undergo structural changes with surrounding K+ ions which can be captured by our new optical device.

Our approach has also been successfully applied to reveal the structural changes when the cytosine quadruplex is treated with surrounding H+, hydrogen ions or low pH (Figure 3D). When i-motif ssDNA in buffer with pH 4.5 is added into the graphene-optofluidic channel, it will interact with graphene by sharing electrons. After the output response was stable, we changed solution pH to 8.5 in the ultrafast graphene-optofluidic
channel, immediately i-motif will start responding to the surrounding solution (pH: 8.5), resulting in transformation in the structure. This structural change of i-motif DNA with surrounding pH can be easily captured by ultrafast fiber laser pulse passing through i-motif DNA-graphene as shown in Figure 3E. We have confirmed i-motif DNA structural changes with the CD spectrum, in buffers with different pH values as shown in Figure 3F.
The characteristic CD spectrum of the i-motif contains a large maximum positive band around 290 nm (290 nm, peak I in Figure 3F), a negative one around 265 nm (253 nm, peak II in Figure 3F), another small positive band close to 220 nm (222 nm, peak III in Figure 3F) at pH 4.5. After introducing pH 8.5 into the cuvette, the CD spectrum of structural change of i-motif contains a large maximum positive band around 280 nm (280 nm, peak IV in Figure 3F), a negative one around 250 nm (248 nm, peak V in Figure 3F), and another small positive band close to 220 nm (220 nm, peak VI in Figure 3F). The above results confirm the structural changes of i-motif DNA with the surrounding pH, which can be captured by using our ultrafast graphene-optofluidic device.

To further reveal the working principle of our ultrafast graphene-optofluidic device, we injected surfactants into the sensor chamber and observed the change in the amplitude and shape of the ultrafast fiber laser pulse. It is found that the change in the amplitude and shape of the ultrafast fiber laser pulse are enormous while passing through graphene-surfactants (Figure S5). This is because the adsorbing of more surfactant molecules leads to stronger charge interactions upon graphene.

2.4 | Density functional theory calculations of adsorption of DNA nucleobases on graphene

We carried out first-principle calculations to understand the interactions of different DNA molecules with graphene. Figure 4 shows the relaxed configurations of DNA nucleobases upon adsorption on graphene, which resembles the contact between nucleobase and graphene in

![Figure 4](https://example.com/figure4.png)

**Figure 4** DFT calculations of adsorption of DNA nucleobases on graphene. A,B, Side view of DFT models of adsorption of nucleobases (cytosine shown as an example) on graphene with (A) planar and (B) tilted configuration. C, Charge transfer from nucleobases to graphene in planar and tilted adsorption with a molecular concentration of $2.64 \times 10^{-10}$ mol cm$^{-2}$. DFT, density functional theory; DNA, deoxyribonucleic acid.
ssDNA (Figure 4A) and dsDNA (Figure 4B). The molecular concentration for nucleobases adsorbed on graphene here is set as $2.64 \times 10^{-10}$ mol cm$^{-2}$, similar to that observed in experiments in which monolayer coverage of nucleobases are adsorbed on graphene.$^{21}$ It is evident that the stable configuration of DNA nucleobases on ssDNA (planar) is significantly different from that of dsDNA (highly tilted). The charge transfer is then calculated from graphene to nucleobase for different nucleobases at each scenario (Figure 4C). The amount of charge transfer in all cases is within the range of 0.01–0.05e per nucleobase molecule, indicating that the interactions between nucleobases and graphene are very weak. This is consistent with earlier experimental and theoretical reports.$^{21,47}$ It is shown that the charge transfer for planar nucleobases (ssDNA) is considerably higher compared to tilted (dsDNA) adsorption, which is perfectly matching with our optical ultrafast graphene-optofluidic device (Figure 2C), CD spectroscopy (Figure 2D), and Raman spectroscopy (Figure 1D) results, respectively. The amount of charge transfer from graphene to nucleobases in tilted adsorption (dsDNA) cases is only $\sim$10% of that in planar adsorption (ssDNA). This implies that ssDNA has a much stronger interaction with the graphene as compared to dsDNA. We also notice that each type of nucleobase responds differently when the contact mode changes from planar to tilted. For example, guanine shows the second least amount of charges transferred in planar (ssDNA) adsorption but surpasses all other nucleobases when tilted (dsDNA). These highly nucleobase-dependent electronic signals justify the different interactions between graphene and ssDNA or dsDNA.

3 | CONCLUSION

In this work, we have demonstrated the ultrafast graphene-optofluidic device to probe the structural dynamics of DNA molecules by using ultrafast fiber nanosecond pulse laser. The standard CD spectroscopy was carried out to confirm the structural interactions between ssDNA or dsDNA and graphene. The density functional theory (DFT) calculations reveal that the charge transfer from graphene to ssDNA is considerably higher than that from graphene to dsDNA, which is perfectly matching with our experimental results by ultrafast graphene-optofluidic device and CD spectroscopy. Finally, we have also demonstrated ultrafast monitoring the structural interactions of recently discovered cancer-related telomeric G-quadruplex and i-motif DNAs with K$^+$ ions and low pH stimulus. The method demonstrated here may find significant practical applications in ultrafast photobiology, photochemistry, medical, and healthcare.

4 | EXPERIMENTAL SECTION

4.1 | DNA Molecules

DNA samples were purchased from Sangon Biotech, Shanghai. The sequences were summarized in Table S1. Stock solutions of oligonucleotides (100 μM) were prepared by Milli-Q water. The concentrations of oligonucleotides were qualified on a BioPhotometer (Eppendorf, Germany) by measuring the absorbance at 260 nm. For ultrafast graphene-optofluidic experiments, the DNA concentration was 1 μM. For the CD experiment, the DNA concentration was 5 μM. The DNA deposition, incubation, and rinsing steps were performed at room temperature in a class 100 hood in the cleanroom.

4.2 | Fabrication of the graphene-coated optical fiber sensor

The experimental method of transferring graphene film onto the optical fiber end-facet is similar to our previous work.$^{30}$

4.3 | Characterization

The Raman spectra were collected using a micro-Raman system (Horiba Jobin Yvon, LabRAM HR 800) with a 514 nm excitation laser. The characteristics of graphene-FET devices were measured through a probe station (Cascade M150) equipped with a semiconductor property analyzer (Keithley 4200).

4.4 | Fiber laser cavity

The graphene saturable absorber based fiber laser cavity was build similar to our previous work.$^{48}$

4.5 | Ultrafast graphene-optofluidic channel

The graphene-optofluidic channel has a constant length of the fluid channel at 100 μm with a diameter of 125 μm, which can be loaded with microliter (4.91 μL) of the DNA solution for detection.

4.6 | Computational Details

We used DFT module as implemented in the Vienna ab initio simulation package$^{49}$ to calculate the adsorption of nucleobases on graphene. The Perdew–Burke–Ernzerhof
form of the generalized gradient approximation was used to describe electron exchange and correlation. The plane-wave kinetic energy cut off was set as 600 eV. A semi-empirical functional device developed by Grimme (DFT-D2) was employed to describe dispersion forces. All structures were relaxed until the ionic forces are smaller than 0.01 eV Å⁻¹. For accurate calculations of the electronic structures, we used 20 × 10 × 1 Γ centered grids for sampling the Brillouin zone. We used Bader charge analysis to calculate the charge transfer between nucleobases and graphene.

ACKNOWLEDGMENTS
The authors acknowledge financial support from the National Natural Science Foundation of China (21874096, 21575095, 51602305, 61604102 and 61875139), the 111 Project, and the Priority Academic Program Development of Jiangsu Higher Education Institutions (PAPD), the China Postdoctoral Science Foundation (2018M633118), Shenzhen Nanshan District Pilotage Team Program (LHTD20170006) and Australian Research Council (ARC, FT150100450, IH150100006 and CE17010039). Q. Bao acknowledges support from the Australian Research Council (ARC) Centre of Excellence in Future Low-Energy Electronics Technologies (FLEET). This work was performed in part at the Melbourne Centre for Nanofabrication (MCN) in the Victorian Node of the Australian National Fabrication Facility (ANFF). The authors also gratefully acknowledge computational support from the Monash Campus Cluster, NCI computational facility and Pawsey Supercomputing Facility.

CONFLICT OF INTEREST
The authors declare no conflict of interest.

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**SUPPORTING INFORMATION**

Additional supporting information may be found online in the Supporting Information section at the end of this article.

**How to cite this article:** Shivananju BN, Zhou L, Yin Y, et al. Probing the dynamic structural changes of DNA using ultrafast laser pulse in graphene-based optofluidic device. *InfoMat.* 2021;3:316–326. [https://doi.org/10.1002/inf2.12114](https://doi.org/10.1002/inf2.12114)