



High-sensitivity DNA biosensor based on microfiber Sagnac interferometer

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Abstract: Nucleic acid detection with label-free biosensors circumvents the need for costly fluorophore functionalization steps associated with conventional assays by utilizing optical fiber transducers. In spite of their technological prowess, however, these biosensors' sensitivity is limited by the design/configuration of their transducers. Therefore, it is imperative to integrate novel optical fiber transducers with existing label-free approaches to overcome those limitations. Herein, we present a high sensitivity label-free fiber optic biosensor that employs polarimetric interference of a high-birefringence (Hi-Bi) microfiber to specifically detect DNA molecules. A slight target DNA concentration change is converted into an optical wavelength shift of polarimetric interference generated by the microfiber Sagnac interferometer. The sensor provides a log-linear response to target ssDNA concentrations range from 100 pM to 1 μ M and a minimum detectable concentration of 75 pM.

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References and links

1. A. Sassolas, B. D. Leca-Bouvier, and L. J. Blum, "DNA biosensors and microarrays," *Chem. Rev.* **108**(1), 109–139 (2008).
2. F. R. R. Teles and L. P. Fonseca, "Trends in DNA biosensors," *Talanta* **77**(2), 606–623 (2008).
3. J. Liu, Z. Cao, and Y. Lu, "Functional nucleic acid sensors," *Chem. Rev.* **109**(5), 1948–1998 (2009).
4. T. G. Drummond, M. G. Hill, and J. K. Barton, "Electrochemical DNA sensors," *Nat. Biotechnol.* **21**(10), 1192–1199 (2003).
5. L. He, M. D. Musick, S. R. Nicewarner, F. G. Salinas, S. J. Benkovic, M. J. Natan, and C. D. Keating, "Colloidal Au-enhanced surface plasmon resonance for ultrasensitive detection of DNA hybridization," *J. Am. Chem. Soc.* **122**(38), 9071–9077 (2000).
6. B. P. Nelson, T. E. Grimsrud, M. R. Liles, R. M. Goodman, and R. M. Corn, "Surface plasmon resonance imaging measurements of DNA and RNA hybridization adsorption onto DNA microarrays," *Anal. Chem.* **73**(1), 1–7 (2001).
7. J. I. Hahm and C. M. Lieber, "Direct ultrasensitive electrical detection of DNA and DNA sequence variations using nanowire nanosensors," *Nano Lett.* **4**(1), 51–54 (2004).
8. X. Tang, S. Bansarutip, N. Nakayama, E. Yenilmez, Y. L. Chang, and Q. Wang, "Carbon nanotube DNA sensor and sensing mechanism," *Nano Lett.* **6**(8), 1632–1636 (2006).
9. J. D. Suter, I. M. White, H. Zhu, H. Shi, C. W. Caldwell, and X. Fan, "Label-free quantitative DNA detection using the liquid core optical ring resonator," *Biosens. Bioelectron.* **23**(7), 1003–1009 (2008).
10. Y. Wu, D. Y. Zhang, P. Yin, and F. Vollmer, "Ultraspecific and highly sensitive nucleic acid detection by integrating a DNA catalytic network with a label-free microcavity," *Small* **10**(10), 2067–2076 (2014).
11. A. Candiani, A. Bertucci, S. Giannetti, M. Konstantaki, A. Manicardi, S. Pissadakis, A. Cucinotta, R. Corradini, and S. Selleri, "Label-free DNA biosensor based on a peptide nucleic acid-functionalized microstructured optical fiber-Bragg grating," *J. Biomed. Opt.* **18**(5), 57004 (2013).
12. H. M. R. Gonçalves, L. Moreira, L. Pereira, P. Jorge, C. Gouveia, P. Martins-Lopes, and J. R. A. Fernandes, "Biosensor for label-free DNA quantification based on functionalized LPGs," *Biosens. Bioelectron.* **84**, 30–36 (2016).
13. M. J. Yin, C. Wu, L. Y. Shao, W. K. Chan, A. P. Zhang, C. Lu, and H. Y. Tam, "Label-free, disposable fiber-optic biosensors for DNA hybridization detection," *Analyst (Lond.)* **138**(7), 1988–1994 (2013).
14. L. V. Nguyen, S. C. Warren-Smith, A. Cooper, and T. M. Monro, "Molecular beacons immobilized within suspended core optical fiber for specific DNA detection," *Opt. Express* **20**(28), 29378–29385 (2012).

15. E. Heydari, J. Buller, E. Wischerhoff, A. Laschewsky, S. Döring, and J. Stumpe, "Label-Free Biosensor Based on an All-Polymer DFB Laser," *Adv. Opt. Mater.* **2**(2), 137–141 (2014).
16. S. Y. Niu, Q. Y. Li, R. Ren, and S. S. Zhang, "Enzyme-enhanced fluorescence detection of DNA on etched optical fibers," *Biosens. Bioelectron.* **24**(9), 2943–2946 (2009).
17. X. Liu and W. Tan, "A fiber-optic evanescent wave DNA biosensor based on novel molecular beacons," *Anal. Chem.* **71**(22), 5054–5059 (1999).
18. X. Fan, I. M. White, S. I. Shopova, H. Zhu, J. D. Suter, and Y. Sun, "Sensitive optical biosensors for unlabeled targets: a review," *Anal. Chim. Acta* **620**(1-2), 8–26 (2008).
19. J. Homola, S. S. Yee, and G. Gauglitz, "Surface plasmon resonance sensors: review," *Sens. Actuators B Chem.* **54**(1-2), 3–15 (1999).
20. N. M. Hanumegowda, C. J. Stica, B. C. Patel, I. White, and X. Fan, "Refractometric sensors based on microsphere resonators," *Appl. Phys. Lett.* **87**(20), 201107 (2005).
21. A. N. Chryssis, S. S. Saini, S. M. Lee, and H. Yi, "Detecting hybridization of DNA by highly sensitive evanescent field etched core fiber Bragg grating sensors," *IEEE J. Sel. Top. Quantum Electron.* **11**(4), 864–872 (2005).
22. X. Wang, K. L. Cooper, A. Wang, J. Xu, Z. Wang, Y. Zhang, and Z. Tu, "Label-free DNA sequence detection using oligonucleotide functionalized optical fiber," *Appl. Phys. Lett.* **89**(16), 163901 (2006).
23. W. Yu, T. Lang, J. Bian, and W. Kong, "Label-free fiber optic biosensor based on thin-core modal interferometer," *Sens. Actuators B Chem.* **228**, 322–329 (2016).
24. D. Sun, T. Guo, Y. Ran, Y. Huang, and B. O. Guan, "In-situ DNA hybridization detection with a reflective microfiber grating biosensor," *Biosens. Bioelectron.* **61**, 541–546 (2014).
25. B. Song, H. Zhang, B. Liu, W. Lin, and J. Wu, "Label-free in-situ real-time DNA hybridization kinetics detection employing microfiber-assisted Mach-Zehnder interferometer," *Biosens. Bioelectron.* **81**, 151–158 (2016).
26. W. B. Ji, H. H. Liu, S. C. Tjin, K. K. Chow, and A. Lim, "Ultrahigh Sensitivity Refractive Index Sensor Based on Optical Microfiber," *IEEE Photonics Technol. Lett.* **24**(20), 1872–1874 (2012).
27. Y. Huang, Z. Tian, L. P. Sun, D. Sun, J. Li, Y. Ran, and B. O. Guan, "High-sensitivity DNA biosensor based on optical fiber taper interferometer coated with conjugated polymer tentacle," *Opt. Express* **23**(21), 26962–26968 (2015).
28. Y. Huang, B. Yu, T. Guo, and B. O. Guan, "Ultrasensitive and in situ DNA detection in various pH environments based on a microfiber with a graphene oxide linking layer," *RSC Advances* **7**(22), 13177–13183 (2017).
29. G. Brambilla, F. Xu, P. Horak, Y. Jung, F. Koizumi, N. P. Sessions, E. Koukharenko, X. Feng, G. S. Murugan, J. S. Wilkinson, and D. J. Richardson, "Optical fiber nanowires and microwires: fabrication and applications," *Adv. Opt. Photonics* **1**(1), 107–161 (2009).
30. J. Lou, Y. Wang, and L. Tong, "Microfiber Optical Sensors: A Review," *Sensors (Basel)* **14**(4), 5823–5844 (2014).
31. L. Tong, R. R. Gattass, J. B. Ashcom, S. He, J. Lou, M. Shen, I. Maxwell, and E. Mazur, "Subwavelength-diameter silica wires for low-loss optical wave guiding," *Nature* **426**(6968), 816–819 (2003).
32. K. Li, G. Liu, Y. Wu, P. Hao, W. Zhou, and Z. Zhang, "Gold nanoparticle amplified optical microfiber evanescent wave absorption biosensor for cancer biomarker detection in serum," *Talanta* **120**, 419–424 (2014).
33. L. P. Sun, J. Li, S. Gao, L. Jin, Y. Ran, and B. O. Guan, "Fabrication of elliptic microfibers with CO₂ laser for high-sensitivity refractive index sensing," *Opt. Lett.* **39**(12), 3531–3534 (2014).
34. J. Li, L. P. Sun, S. Gao, Z. Quan, Y. L. Chang, Y. Ran, L. Jin, and B. O. Guan, "Ultrasensitive refractive-index sensors based on rectangular silica microfibers," *Opt. Lett.* **36**(18), 3593–3595 (2011).

1. Introduction

Specific and quantitative detection of DNA sequences is of great importance for public health research, environmental science, biological engineering, disease diagnosis, and pharmaceutical research. Research in all of these fields requires an accurate and cost-effective DNA detection platform. In addition, development of novel detection platforms could help the exploration of unknown biological functions of DNA [1–3]. Various approaches for fast, sensitive DNA detection have been developed, including electrochemical conductance [4], surface plasmon resonance [5,6], and use of nanowires/nanotubes [7,8], optical ring resonators [9,10], and fiber/waveguide optic sensors [11–14]. A large number of DNA detection approaches depend on fluorescence as the transition signal. Fluorescent labeling permits low detection limits, however, when used to detect small molecules, it can be troublesome, time-consuming, and difficult, due to interference with the analysis process [15–17]. Although techniques based on electrochemical transducers have achieved very high DNA sensitivity, optical fiber biosensors, which are, free from costly fluorophore functionalization

steps, simple to fabricate, easily functionalized as well as multiplexed, and made from inexpensive optical fibers [10].

Refractive index (RI)-based optical label-free detection mechanisms measure the RI change induced by molecular interactions, which is related to the sample concentration or surface density, instead of total sample mass [18]. Traditional optical fiber DNA sensor has very limited sensitivity, because light is strictly confined within the optical fiber core region, which restricts the interaction enhancement between light and biomolecular quantity, and further limits sensitivity (See Table 1 for a comparison of label-free DNA sensors). It is therefore highly desirable to develop optical transducers that exhibit ultimate detection limits. Optical microfiber sensors are an exemplary candidate technology that could demonstrate such a capability in the optical domain and in a label-free fashion. An optical microfiber, with a diameter close to wavelength of the guided light, possesses strong evanescent fields and high waveguide dispersion for high-sensitivity biochemical measurement [24–32]. Herein, we introduce a novel, high-sensitivity label-free fiber optic biosensor that employs polarimetric interference of an elliptical silica microfiber to specifically detect single-stranded DNA (ssDNA) hybridization. Combining use of the strong capabilities of ssDNA technology with the high sensitivity of optical microfiber sensors endows our sensor with great advantage over previous performance limitations in nucleic acid detection. This integrated biosensor exhibits a 1000-fold improvement in molecular sensitivity compared with conventional hybridization-based optical fiber acid sensors, and has detection limits down to ~75 pM of a 26-mer ssDNA.

Table 1. Detection limits of various label-free DNA sensors.

Technology platform	Structure	Bulk solution RI sensitivity	Detection limit
Electrochemical conductance	Electrochemical conductance		<pM [4]
	Nanowires		~fM [7]
Surface plasmon resonance	Wavelength modulated surface plasmon resonance	13800 nm/RIU [19]	10 pM [5]
	Surface plasmon resonance imaging		10 nM [6]
Ring resonator/Microcavity	Microcavity	30 nm/RIU [20]	80 pM [10]
Optical fiber	Capillary opto-fluidic ring	37.1 nm/RIU [9]	10 pM [9]
	Fiber bragg grating	29 nm/RIU [21]	0.7 µg/mL [21]
			100 nM [11]
	Long period grating	62 nm/RIU [12]	209 nM [12]
	Fiber fabry-perot interferometer		76 µM, 1.7 ng [22]
Optical microfiber	Fiber Mach-Zehnder interferometer	61 nm/RIU [23]	1 µM [13]
	Micorfiber bragg grating	304.5 nm/RIU [24]	0.5 µM [24]
	Microfiber Mach-Zehnder interferometer	11571 nm/RIU [25]	0.1 nM [25]
	Microfiber Mach-Zehnder interferometer (Coated with conjugated polymer)	~5000 nm/RIU [26]	0.1 nM [27]
	Microfiber Mach-Zehnder interferometer (Coated with graphene oxide)	1448 nm/RIU [28]	4 pM [28]
This work	High-birefringence microfiber Sagnac interferometer	13488 nm/RIU	75 pM

2. Experimental details

2.1 High-birefringence (Hi-Bi) microfiber Sagnac interferometer

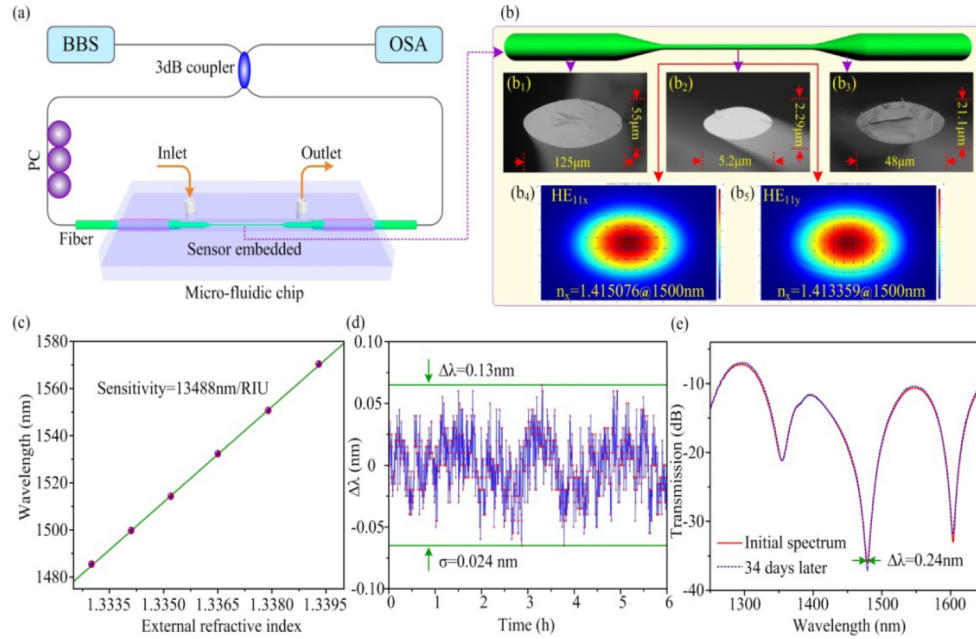


Fig. 1. (a) The schematic of the optical setup of Hi-Bi microfiber Sagnac interferometer. (b) Elliptical microfiber profiles and the transverse electric field amplitude distributions of the x- and y-polarized modes. (c) Relationship between the dip wavelength and the external refractive index. Error bars represent the standard deviations of ten independent measurements. The data in (d) show the wavelength stability within a shorter period of time. (e) The transmission spectrum of the interferometer after 34 days is similar to the initial profile.

Figure 1 shows the schematic diagram of the Sagnac interferometer based on the Hi-Bi elliptical microfiber. A section of the Hi-Bi elliptical microfiber that contains two transition regions and a central uniform waist region was fusion-spliced into a fiber loop mirror. The microfiber waist has a micron-scale size (5.2 μm) so that light can be extended through the whole silica region and considerable birefringence ($\sim 10^{-3}$) can be achieved [33]. Light from the broad-band light source (BBS) splits into clockwise and counterclockwise beams via 3dB coupler as it enters the loop. After light passes through the polarization controller, the x or y polarization of the counter-propagating beams are transformed into the opposite (y or x polarization), and therefore experience a smaller or larger effective index, respectively. The phase difference between beams that propagate with different polarization states is governed by the birefringence and the length of the microfiber. The polarimetric interference is given by recombination of both rotated lights at the coupler. The spectral characteristic is measured by using an optical spectrum analyzer (OSA, Yokogawa AQ3670C) with a resolution of 0.02 nm. The extinction ratio can be higher than 25dB by adjusting the polarization controller, as shown in Fig. 1(e).

In the interferometer loop, the birefringence at the waist is much higher than the birefringence at the transition region of the microfiber. We can show that the phase difference between the polarizations is approximately expressed as $\Phi = (2\pi/\lambda)BL$, where L is the uniform microfiber length (10 mm), $B = n_{\text{eff}}^x - n_{\text{eff}}^y$ is the modal birefringence with n_{eff}^x and n_{eff}^y is the x- and y-polarized mode indices, respectively. Any change of the external RI may

modify the magnitude of the birefringence (B) via the evanescent field and hence shift the interferometric wavelength determined by Φ . Considering a small refractive index variation of Φ , we can obtain the wavelength sensitivity with $S = d\lambda/dn = (\lambda/G) \cdot \partial B/\partial n$ [34], where n is the external RI, $G = B - \lambda \partial B/\partial \lambda$ is the group birefringence. The magnitude of G is determined by not only the birefringence but also the dispersion property. The equation above suggests that the sensitivity depends on three parameters: wavelength (λ), RI-induced birefringence variation ($\partial B/\partial n$), and relative group birefringence (G). An extremely high sensitivity can be achieved as $G \rightarrow 0$.

We measured the spectral response of the sensor to RI by immersing the microfiber into water-alcohol solutions of varying concentrations. The RI was measured using a handheld refractometer with a sensitivity of 0.0001 (Reichert, AR200) to obtain the peak shifts with respect to the RI of the solutions. All experiments were performed at a fixed temperature of 25°C. When the RI levels vary from 1.333 to 1.3393, the interference fringes shift to the longer wavelength. Figure 1(c) illustrates the relationship between the wavelength shift and RI variation. We obtained a sensitivity of 13488 nm/RIU for the dip with wavelength around 1500 nm. Our results show a 220-fold improvement in RI sensitivity over the conventional optical fiber sensor [12,21,23]. The measured temperature sensitivity is only 8.24 pm/°C at 1553 nm in air due to the low thermal-expansion coefficient of the silica fiber. Short-term wavelength stabilities were recorded continuously at a rate of one spectrum every 20 s. Figure 1(d) shows the wavelength stability within a 6 h time period, with a standard deviation of 0.024 nm. Figure 1(e) shows the transmission spectrum of the interferometer after 34 days, compared to the initial profile, and demonstrates robust long-term stability of the microfiber sensor.

2.2 Surface activation and hybridization

DNA oligonucleotides and phosphate buffer saline (PBS, pH 7.4) solution were synthesized and purified by Sangon Inc. (Shanghai, China). The oligonucleotides sequences are as follows:

Probe ssDNA: 5'-TCCAGACATGATAAGATACATTGATG-3'.

Complementary ssDNA: 5'-CATCAATGTATCTTATCATGTCTGGA-3'.

Non-Complementary ssDNA_A: 5'-CTCACGTTAATGCATTTTGGTC-3'.

Non-Complementary ssDNA_B: 5'-GGTTGGTGTGGTTGG-3'.

Target ssDNA was diluted in PBS to concentrations of 1 pM, 10 pM, 100 pM, 1 nM, 10 nM, 100 nM, and 1 μM, respectively. A probe ssDNA concentration of 10 μM was used. After each cycle, the microfiber interferometer was cleaned using a piranha solution consisting of 1 vol of 30% H₂O₂ and 3 vol of concentrated H₂SO₄. Poly-L-lysine (PLL) (0.1% w/v in water, the molecular weight 150,000–300,000 g/mol) was used for fiber surface functionalization. Ultrapure water was used to clean fluids and buffers out of the biosensor.

The surface activation of the optical microfiber was performed as follows. First, before performing any tests, the optical fiber was cleaned for 30 min in a bath with a piranha solution consisting of 1 vol of 30% H₂O₂ and 3 vol of concentrated H₂SO₄. Next, the microfiber was cleaned with ultrapure water for 10 min. After that and each subsequent step, cleaning process with ultrapure water was used to remove non-specifically bound molecules. Second, poly-L-lysine (PLL) was allowed to react with the positive charges of amino-groups for 1 h. PLL contains amino-groups with positive charges that can bind to the negatively charged microfiber surface through ionic absorption [24]. Thus, the microfiber could be functionalized with a monolayer PLL. Third, probe ssDNA (at a concentration of 10 μM) reacted with PLL via NH-NH linkage for 1 h. Finally, the target ssDNA was hybridized to the probe ssDNA (at varying concentrations) for 1 h, followed by cleaning with ultrapure water. After target ssDNA detection, piranha solution was used to etch off the deposited DNA and PLL molecules to prepare the probe for the initiation of another cycle.

In each cycle, reagents were added in the following sequence: piranha solution, ultrapure water, PLL, probe and ssDNA targets. Light from the BBS (with wavelengths in the 1250-1650 nm range) was sent into the interferometer and the transmission spectrum was monitored during the course of surface activation and hybridization using an OSA. All measurements were recorded continuously at a rate of one spectrum every 20 s with the exception of piranha solution or water cleaning steps in between the addition of an analyte. During hybridization experiments, the sensor probes can be fixed in PDMS (polydimethylsiloxane) based micro-fluidic channels designed specifically for microanalysis biosensing tests. Biosample solutions can be injected into the micro-fluidic chip via a pump, as described in our previous work [24].

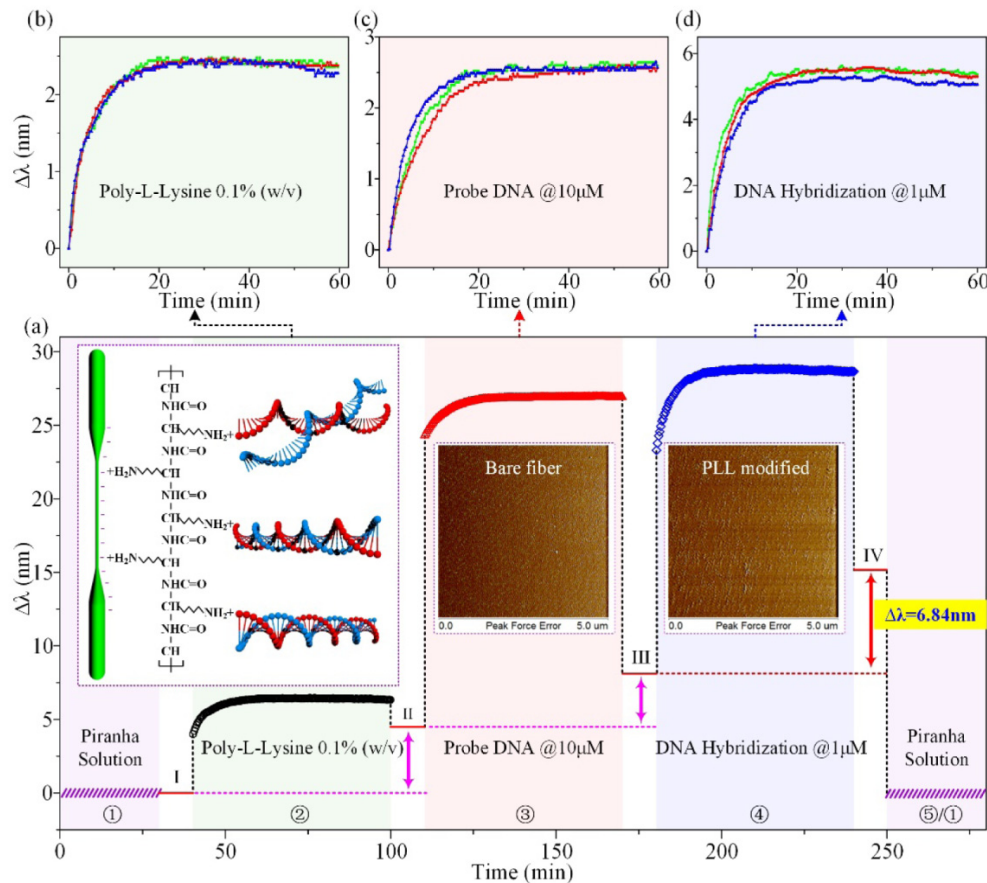


Fig. 2. (a) Sensorgram for Hi-Bi microfiber Sagnac interferometer surface activation and 1 μ M complementary target DNA detection. (b) PLL modification. (c) Probe ssDNA incubation. (d) Target ssDNA hybridization. I-IV: Surface activation and hybridization performed in ultrapure water buffer. Insets show the AFM images of PLL coating on the microfiber surface, and the scheme of surface functionalization of microfiber biosensor.

3. Results and discussion

Since the Hi-Bi microfiber Sagnac interferometer can access information in real-time, data could be collected at each stage of the experiment. Figure 2(a) shows the spectra of the real-time dip wavelength shift, in the response from the PLL functionalization throughout target ssDNA hybridization. The total wavelength shift at the beginning of each activation phase is caused by small, additive changes in the RI of the dissolved materials. As the data shown in Fig. 2(a), the net wavelength shifts for PLL modification, probe ssDNA incubation, and 1 μ M

target ssDNA hybridization are 4.5 nm, 3.62 nm, and 6.84 nm, respectively. The transmission spectrums of the high-birefringence microfiber Sagnac interferometer at each stage of surface activation are shown in Fig. 3. After target ssDNA detection, the Hi-Bi microfiber Sagnac interferometer was regenerated by washing with piranha solution to etch off the deposited DNA and PLL molecules. Three replicates of PLL modification, probe DNA incubation, and 1 μ M target DNA sample hybridization were conducted in real-time, within a 60 min test period, as shown in Figs. 2(b)-2(d). These results indicate that our proposed sensor shows no change in accuracy with repeated use. The recovery method described above was used for more than 40 successive cycles in a single interferometer, across a period of months. Figure 1(e) shows the transmission spectrum of the interferometer in water after 40 measurement cycles. Our recovery method proved to be highly effective, which ensures its utility for practical applications.

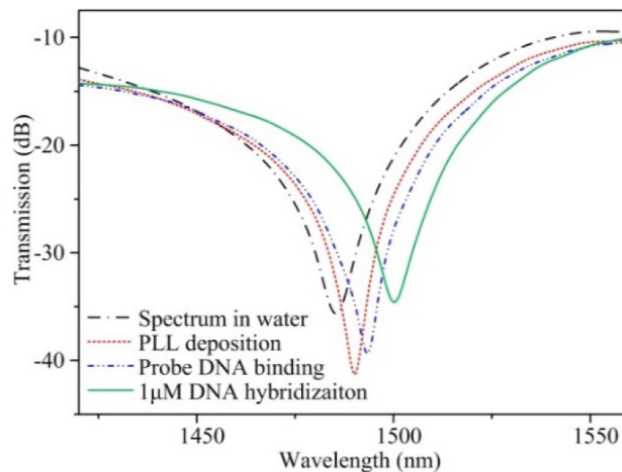


Fig. 3. Transmission spectrum of the high-birefringence microfiber Sagnac interferometer at each stage of surface activation.

The working range and dose-response of the Hi-Bi microfiber Sagnac interferometer-based DNA sensor was investigated using a series of complementary ssDNA solutions ranging from 10^{-12} M to 10^{-6} M, with each experiment performed at least three times. As shown in Fig. 4, the first reliable signal is obtained at 100 pM. The net wavelength shift has a good linear relationship to the logarithm of concentration of target ssDNA sequence in the range of 100 pM to 1 μ M, with a correlation coefficient of 0.9962. The linear regression equation was calculated as $\Delta\lambda = 0.6731\ln(x) + 2.1939$ (nm L^{-1}) with a detection limit (LOD) of 75 pM at a signal-to-noise ratio of 3σ (where σ is the standard deviation of the blank trial). Table 1 compares this result to previous studies [5,6,9,10,25,27], and shows that the LOD is competitive with other similar sensors. In addition, our integrated biosensor exhibits a 1000-fold improvement in molecular sensitivity over the conventional hybridization-based optical fiber DNA sensor [12,13,21,22]. The detection capability can be further improved with following approaches: First, enhance the sensitivity by tailoring the transverse geometry of the microfiber to approach zero group birefringence [33,34], meanwhile, taking into consideration of a balance between spectral resolution and sensitivity. Second, improve the wavelength resolution by use of approaches that have been utilized for long period grating sensors [12].

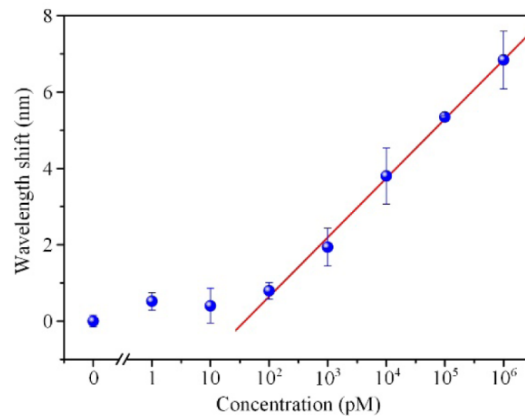


Fig. 4. Optical responses to different levels of complementary DNA concentrations (The result at zero concentration represents the result of blank trial). Error bars represent the standard deviations of three independent measurements with a single interferometer.

Two hybridization experiments were carried out to assess whether our DNA sensor responds selectively to the target ssDNA. As shown in Fig. 5, two non-complementary ssDNA (ssDNA_A and ssDNA_B, each at 1 μ M concentration) were used for hybridization. As expected, we observed that only the complementary target causes a significant change in the wavelength shift. In contrast, the signals produced by the non-complementary ssDNAs were less than 6.2% (ssDNA_A) and 6% (ssDNA_B) of the complementary ssDNA. This result suggests that our sensor has good selectivity for target DNA.

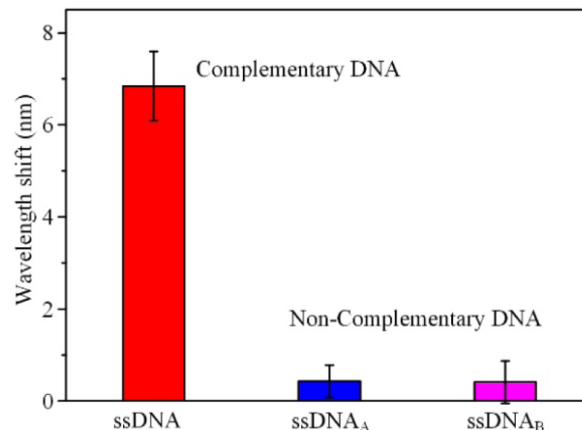


Fig. 5. Measured responses to matched and mismatched (ssDNA_A and ssDNA_B) DNA with the same bulk concentration of 1 μ M.

4. Conclusion

In conclusion, we introduce a high-sensitivity label-free fiber optic biosensor that utilizes polarimetric interference of an elliptical silica microfiber to specifically detect single-stranded DNA hybridization. Combining use of the strong capabilities of ssDNA technology with the high sensitivity of optical microfiber sensors endows our sensor with great advantage over previous performance limitations in nucleic acid detection. This integrated biosensor exhibits a 1000-fold improvement in molecular sensitivity compared with conventional hybridization-based optical fiber acid sensors, and can detect as little as ~ 75 pM of a 26-mer ssDNA oligo with a log-linear range from 100 pM to 1 μ M. This improvement results from the high

refractive index sensitivity characteristic of the high-birefringence microfiber Sagnac interferometer. Further improvement in the LOD could be accomplished by modifying the sensor with conjugated polymer [27] or graphene oxide [28].

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