Smartphone-based cancer detection platform based on plasmonic interferometer array biochips

Xie Zeng[1,*], Yunchen Yang[2,*], Nan Zhang[1,*], Dengxin Ji[1], Yun Wu[2], Qiaoqiang Gan[1,†]
1. Department of Electrical Engineering, The State University of New York at Buffalo, Buffalo, NY 14260, USA
2. Department of Biomedical Engineering, University at Buffalo, The State University of New York, Buffalo, NY 14260, USA

* *These authors contribute equally to this work*
† *Email:qqgan@buffalo.edu*

Abstract: We develop a nanoplasmonic interferometer imaging system based on intensity modulation to detect circulating exosomal proteins in real-time with high sensitivity and low cost to enable the early detection of cancer.

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Cancer is a serious socioeconomic problem. Effective screening and early detection are the only way to improve the chance of successful treatment and reduce cancer mortality. Sensitive biomedical devices integrated with smart-phones would yield promising mobile medical devices for cancer screening and early detection and introduce great impact on point-of-care diagnostics in developing countries and resource-limited areas. Surface plasmons (SPs) are coherent oscillations of conduction electrons on a metal surface excited by electromagnetic radiation at the metal-dielectric interface [1]. The extremely high sensitivity of the surface plasmon resonance (SPR) to the refractive index (RI) change on the metal surface has led to the development of SPR sensing systems, which typically use prisms to couple obliquely incident light into SP waves propagating on a flat, continuous metal film (typically gold) [2]. However, the conventional SPR systems are limited by expensive equipment and bulky footprint. Therefore, they are not suitable for cost-effective, point-of-care diagnostic tests. To overcome these challenges, nanoplasmonic biosensors have received significant attentions as attractive miniaturized platforms for sensitive, label-free and high throughput detection of bio-chemical analytes. However, most previously reported plasmonic sensing devices are based on wavelength modulation. Therefore, high spatial density multiplexed measurements are difficult to achieve in that broadband wavelength analysis because a spectrometer is required, which inevitably adds to the size and cost of the entire system.

In a previous report, we developed a plasmonic interferometer array (PIA) biosensor based on wavelength modulation generated by ring-hole nanostructures [3]. Using this type PIA biosensor, the sensitive detection of BSA surface coverage as low as 0.4 pg mm^{-2} was realized. In this study, we further developed the PIA biosensor using intensity modulation at a single wavelength by optimizing the geometry of the ring-hole nanostructure. **Fig. 1(a)** illustrates the ring-hole plasmonic interferometer structure with a nanohole in a metal film surrounded by concentric circular nanogrooves. When the incident light illuminates the structure at the normal direction, SP waves are launched at the grooves. They will propagate along the radial direction of the rings towards the central nanohole and interfere with the directly-transmitted light through the central nanohole (see **Fig. 1(b)** for the cross-sectional diagram). In this case, the transmitted light intensity at a given wavelength can be modulated by the radius of the circular ring and the effective RI for SPs at the metal/dielectric interface. To demonstrate the intensity-modulated biosensor, we used Focused Ion Beam (FIB) milling to fabricate a 5×5 array of ring-hole

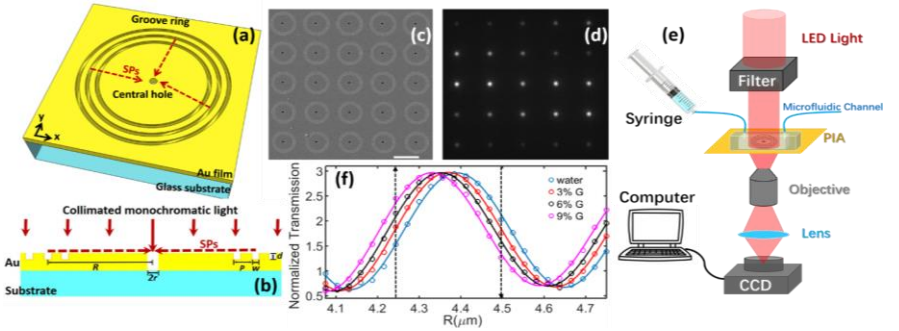

Fig. 1 (a) Schematic of a ring-hole plasmonic interferometer. (b) Cross-section view. (c) SEM image of a 5X5 array of plasmonic interferometer with increasing R from left to right, bottom to top. (d) Transmitted light of the interferometer array was imaged on the CCD camera. (e) Schematic diagram of the experimental setup. (f) Transmission of each interferometer was modulated sinusoidally by R, showing different sensitivity when glycerol-water solutions of increased concentrations were flowed on the sensor surface. Black arrows indicate the interferometers with highest sensitivities.

plasmonic interferometers on a 250-nm gold film. As we can see from its SEM image shown in **Fig. 1(c)**, the diameter of the ring, R, increases from 4.07 μm to 4.75 μm. To further enhance the coupled-SP intensity, three grooves were selected in this experiment with the groove period P = 480 nm, the width w = 240 nm, and the depth d = 70 nm. The diameter of the central hole was tuned to 620 nm to control the directly transmitted light intensity to match the SP-intensity and maximize the interference contrast. In our optical characterization, a collimated LED source was passed through a laser line filter to get a narrow-band red light with a centered wavelength λ = 665 nm. As a result, one can see from **Fig. 1(d)** that the transmitted intensity of each interferometer unit was modulated by R when n is fixed at ~1.33 (i.e., water environment under room temperature).

To calibrate the sensing performance, a PDMS-based microfluidic channel was bonded on the sensor chip to introduce glycerol-water solutions with different concentrations to control the bulk RI (**Fig. 1(e)**). When the water is injected into the microfluidic channel, each element shows different brightness, demonstrating the intensity interference at a single wavelength transmitted through the array as the function of R. As shown in **Fig. 1(f)**, the extracted intensity is normalized by the transmitted light intensity through a reference hole without grooves, showing an interference period of ~490 nm, therefore verifying the interference mechanism.

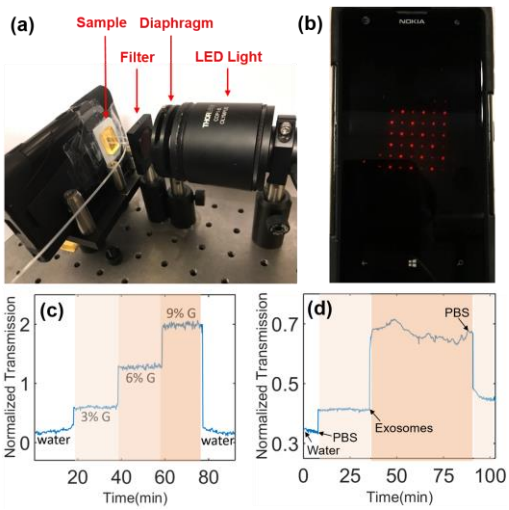

Fig. 2 (a) Proof-of-concept experiment setup of the mobile PIA biochip integrated with the smart-phone imaging system. (b) The screen of the smart-phone (Nokia Lumia 1020) with the PIA biochip transmission image. (c-d) Real-time response of (c) bulk refractive index and (d) surface binding changes measured by the PIA biochip coupled with the smart-phone-based microscope.

Next we continued to investigate the possibility of detecting exosomal EGFR using a smart-phone-based microscope. As shown in **Fig. 2(a)**, a miniaturized plano-concave lens with a diameter of 1 mm was embedded in a homemade phone-case and aligned with the smart-phone camera, comprising a portable microscopy system with the magnitude of approximately 10X. By adjusting the simple optical system shown in **Fig. 2(a)**, the transmitted light through a 6×6 plasmonic interferometer array was detected by the built-in CMOS camera of the cell phone (**Fig. 2(b)**). A series of glycerol-water solutions (i.e., 3%, 6%, and 9% glycerol solutions) were first tested on the PIA biochip to quantify its sensitivity and resolution. As shown in **Fig. 2(c)**, after the glycerol solutions were flowed into the PIA biochip, the transmission intensity through the plasmonic interferometer increased with increasing concentration of glycerol solutions. After washing off the biochip with deionized water, the transmission intensity signal returned back to the baseline. We estimated that the sensitivity and resolution of the PIA biochip coupled with the smart-phone imaging system are 1.35×10^{4}%/RIU and 1.27×10^{-4} RIU, respectively. Finally, we investigated the feasibility of exosomal EGFR detection using the mobile PIA sensing setup. As shown in **Fig. 2(d)**, the transmission signal intensity increased after PBS solution injection due to the RI change (i.e., from Water 1.3328 to PBS 1.3343). The exosomes derived from A549 cells were suspended in PBS buffer. A quick increase of the signal intensity was observed right after the exosomes entered the PIA biochip. Then the signal intensity leveled off and reached plateau at time of 3×10^{3} seconds. The dynamic change of the transmission signal intensity demonstrated the successful capture of exosomes via anti-EGFR antibodies on the biochip. Finally, PBS was flowed through the PIA biochip to wash off all non-specifically bound exosomes. These experimental results successfully demonstrated the feasibility of the mobile PIA biochip in detecting exosomal protein biomarkers for cancer diagnosis.

In conclusion, we reported a highly integrated, portable ring-hole PIA biochip, which is a highly sensitive, cost-effective, fast/real-time and label-free optical sensor for specific sensing of biomolecules, such as exosomal proteins. The proposed high performance and compact sensor system is critical for overcoming size, cost and detection time barriers of conventional technologies. This smartphone-based, highly sensitive, and low cost PIA biochip is promising for label-free sensing with great impact on point-of-care diagnostics [4].

References

[1] H. Raether, Springer, (1988).
[2] J. Homola, Chem. Rev. **108**, 462-493 (2008).
[3] Y. Gao, Z. Xin, B. Zeng, Q. Gan, X. Cheng, F. J. Bartoli, Lab on a Chip **13**, 4755-4764 (2013).
[4] X. Zeng, Y. Yang, N. Zhang, D. Ji, X. Gu, J. Jornet, Y. Wu, Q. Gan, IEEE Journal of Selected Topics in Quantum Electronics **25**, 1-7 (2019).