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Optofluidic glucose detection by capillary-based ring resonators

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ABSTRACT

Based on an opto-fluidic ring resonator (OFRR), a bloodless, sensitive, and cost-effective approach to detect glucose concentration is proposed. Fabrication and calibration of the OFRR sensor, as well as characterization of the sensor's performances are presented. Experimental results demonstrate that the OFRR sensor has a few unique features in glucose sensing, including a wide detection range of the glucose concentration up to 25 mM, an extremely small sample volume down to 100 nL, and a resolution of 0.035 mM one order of magnitude better than clinical requirements. Once being integrated with the fluid extracting system, the proposed approach can lead to a bloodless, sensitive and cost-effective device for frequently and accurately monitoring of the glucose concentration.

1. Introduction

According to the data published by the World Health Organization in 2010, over 346 million people worldwide suffer from diabetes [1]. Close control of blood glucose is essential to avoid the long-term adverse consequences of elevated blood glucose, including neuropathies, blindness and other sequelaes. Despite much effort has been made in investigating noninvasive methods for glucose detection [2–5], the only reliable method available presently is by a finger prick and subsequent glucose measurement. This finger pricking procedure may lead to an invasive, painful, and potentially infectious result [3]. As an alternative to blood, human interstitial fluid (ISF) has been investigated by a number of groups [6], because the glucose level in ISF has shown to have a good correlation with that in blood, while ISF is simpler in constitutes than those in blood and even serum as well. During the ISF measurement, ISF can first be extracted out from the human skin where negative pressure from a vacuum pump is imposed, and subsequently transferred to a biosensor such as surface plasma resonance. These procedures can be implemented with no blood and no sticking pain. However, major drawbacks in using ISF include very limited amount of sample that can be extracted, and inaccuracy induced by sample transferring.

To overcome the drawbacks in the current ISF measurement, we propose a new approach based on opto-fluidic ring resonator (OFRR) for glucose detection. The OFRR combines the optical ring resonator architecture with microfluidics. As a result the OFRR can offer advantages of high sensitivity and low sample consumption without any extra sample delivery system [7,8]. In what follows, we will first describe the sensing mechanism and calibration of the OFRR sensor, and then perform experiments for detection of aqueous glucose solutions at varies of concentrations.

2. Sensing principle

As shown in Fig. 1(a), the OFRR system consists of a tunable laser, a thin-walled capillary, a light guiding fiber taper and a photon detector. The capillary has a wall thickness of 2 μm and a diameter of 80 μm, and the length of capillary is usually a couple of millimeters, so that the sample volume can go down to 100 nL. The resonant light coupled into the OFRR via the tapered fiber circulates along the capillary cross section in the form of the whispering gallery mode (WGM). The WGM resonant wavelength (or spectral position), λ, is determined by [6],

$$2\pi R n_{eff} = m\lambda \quad (1)$$

where n_{eff} is the effective refractive index (RI), R is the OFRR radius, and m, an integer number, λ is the angular momentum of the WGM. When the analyst concentration inside the capillary varies, a change in n_{eff} and subsequently a spectral shift of the WGM will result [7–9].

A tunable diode laser with central wavelength at 980 nm from Philips was tuned at a rate of 2 Hz and scanned across approximately 100 pm with a current controller (LDX-3027, ILX Lightwave). Analyst was flowed through the OFRR by a syringe pump (KD 100, Scientific Inc) at a flow rate of 100 nL/min. When the analyst interacts with the WGM, the WMG spectral position shifts, which can be recorded by a

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photodetector (Infrared Photoreceiver 2034, New focus) at the distal end of the fiber taper.

3. Calibration of the OFRR sensor

For further quantitative detection, it is essential to establish bulk refractive index sensitivity (BRIS) by correlating the spectral shifts induced by different samples to their correspondingly known refractive index. We flowed five aqueous ethanol solutions with concentrations varying from 0% to 2% through the OFRR. As shown in Fig. 2(a), the spectra for different concentrations of ethanol solutions were recorded. The quality factor of WGM mode is 4×10^5. The solid line shown in Fig. 2(b) was linearly fitted with the data extracted from each solution, yielding a BRIS (the slope of the fitted line) of 80.14 nm/RIU. Note that both the quality factor and the BRIS are not as high as those published previously [9], as such a sensitivity is optimized to ensure both the resolution and the clinical dynamic range in the glucose concentration, which will be discussed in Section 4.

4. Detection of glucose concentrations

In order to test the real response of the OFRR sensor to the glucose concentration, we flowed six glucose aqueous solutions in various concentrations of glucose. The concentrations of theses samples were designed to cover the dynamic level of glucose for both healthy persons and diabetes patients. In what follows, testing

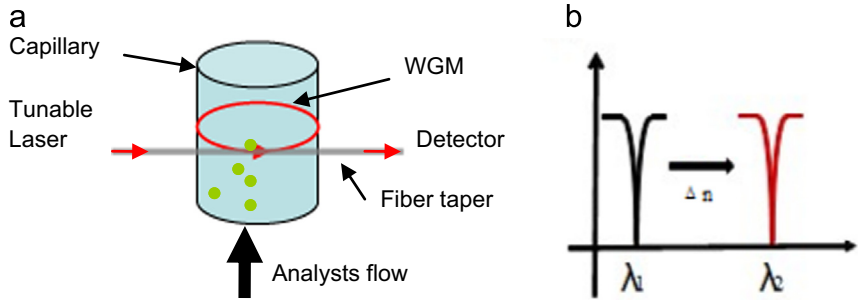

Fig. 1. (a) The optofluidic ring resonator (OFRR) is a piece of thin-walled capillary whose circular cross section supports a high-Q whispering gallery mode (WGM) that provides the multiple interaction opportunities for the evanescent field with analysts flowed in the capillary. (b) A spectral shift of WGM will be induced by the variations in refractive index of ISF with varied glucose concentration.

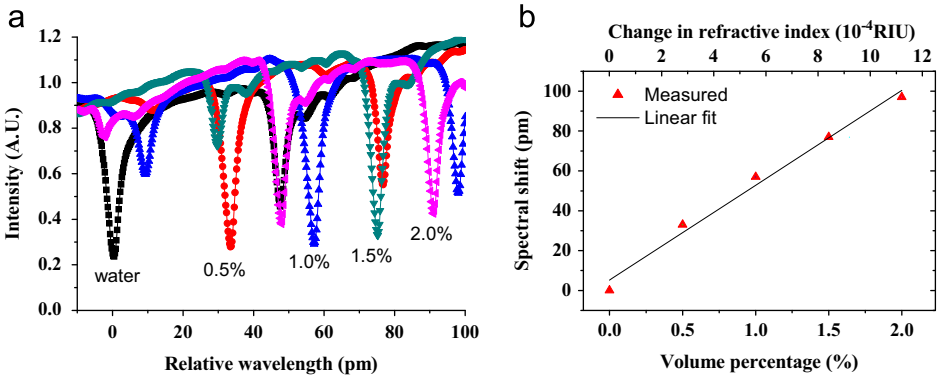

Fig. 2. Calibration of OFRR sensor with aqueous ethanol solutions. Line with square symbol corresponds to (a) Spectral shift of the WGMs wavelength as a function of time when varied concentrations of ethanol solutions are flowed through. (b) A linear relationship between the refractive index of ethanol solutions and the spectral shift.

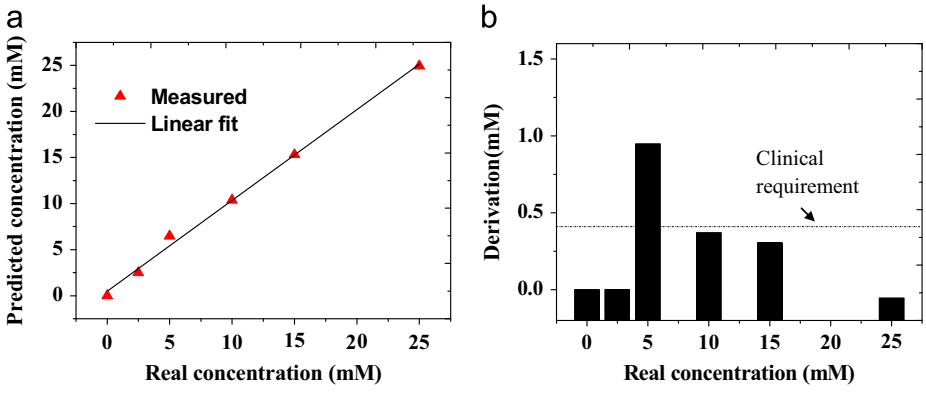

Fig. 3. Results of glucose concentrations predicted with the calibrated model. (a) Comparison of predicted concentrations to real values. The triangle symbols represent the predicted concentrations, and the solid line is the linear fit. (b) The derivation of the predicted glucose concentrations to the corresponding real values.

results including the sensitivity, resolution of detection, as well as the dynamic range will be discussed.

Using the spectral shifts with the various glucose concentrations, a linear relationship is fitted with a slope of 1.84 pm/mM, representing that the OFRR has a spectral shift of 1.84 pm to a change in glucose concentration of per milli-molar. Since the scanning range of the tunable laser is approximately 100 pm, the dynamic range for this OFRR sensor is estimated to exceed 25 mM, which covers the clinical level of glucose concentration even for severe diabetes.

The resolution (RSL) can be estimated according to the relationship, RSL $= \langle \text{Noise} \rangle / S$, where $\langle \text{Noise} \rangle$ representing the noise level, and S is the sensitivity of the OFRR. Taking the sensitivity value of 1.84 pm/mM and the noise level of 0.065 pm as measured in the experiments, an RSL as low as 0.035 mM can be deduced, one order of magnitude lower than 0.42 mM required in clinics [10].

Fig. 3(a) further compares the concentrations predicted by the calibrated model and the real values, showing good agreement. The corresponding differences are further analyzed in Fig. 3(b). The maximal difference is 0.9 mM and all the others are lower than 0.42 mM required by the clinical requirement [10].

5. Conclusion

In conclusion, we have demonstrated a glucose sensing technology based on that the OFRR can offer a high sensitivity, low sample consumption, a large dynamic range and a low resolution. All these features presented by this approach ensure the feasibility and practicality in utilizing the OFRR for glucose sensing. Additionally, the ease and low cost to integrate the OFRR with the microfluid extraction system open a door to developing an autonomous device for frequent self-monitoring of glucose in a bloodless, painless, cost-effective manner.

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References

[1] Shaw J, Sicree R, Zimmet P. Global estimates of the prevalence of diabetes for 2010 and 2030. Diabetes Research and Clinical Practice 2010;87(4).
[2] Heise HM, Marbach R, Janatsch G, Kruse-Jarres JD. Multivariate determination of glucose in whole blood by attenuated total reflection infrared spectroscopy. Analytical Chemistry 1989;61(2009).
[3] Wang SY, Hasty CE, Watson PA, Wicksted JP, Stith RD, March WF. Analysis of metabolites in aqueous solutions by using laser Raman spectroscopy. Applied Optics 1993;32:925.
[4] Larin KV, et al. Specificity of noninvasive blood glucose sensing using optical coherence tomography technique: a pilot study. Physics in Medicine and Biology 2003;48:1371.
[5] Luo YH, Huang FR, Li SP, Chen Z. Detection limit of glucose concentration with near-infrared absorption and scattering spectroscopy. Chinese Physics Letters 2008;25:1117.
[6] Thennadil SN, Rennert JL, Wenzel BJ, Hazen KH, Ruchti TL, Block MB. Comparison of glucose concentration in interstitial fluid, and capillary and venous blood during rapid changes in blood glucose levels. Diabetes Technology and Therapeutics 2001;3:357.
[7] White IM, Oveys H, Fan XD. Liquid-core optical ring-resonator sensors. Optics Letters 2006;31:1319.
[8] Zhu H, White IM, Suter JD, Zourob M, Fan XD. Opto-fluidic micro-ring resonator for sensitive label-free viral detection. Analyst 2008;133:356.
[9] Li H, Fan XD. Characterization of sensing capability of optofluidic ring resonator biosensors. Applied Physics Letters 2010;97:11105.
[10] ISO 15197:2003(E) [EB/OL] (2003)[2010-10-25]. ⟨http://www.iso.org/iso/catalogue_detail.htm?⟩ csnumber=54976.