Sensitivity enhanced glucose sensing by return-path Mueller matrix ellipsometry

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Abstract Diabetes is a worldwide public health problem. According to the survey of the Robert Koch Institute, in Germany, at least 7.2 percent population (aged between 18 to 79 years) have diabetes. Therefore, the demand for glucose monitoring is increasing, especially for non-invasive glucose monitoring technology. In this work, we proposed a novel method to enhance the sensitivity of glucose monitoring by return-path ellipsometry with a quarter-wave plate and mirror. The coaxial design improves the sensitivity and reduces the complexity of optical system alignment by means of a fixed quarter-wave plate. The proposed system showed higher sensitivity compared to the transmission configuration.

Keywords Glucose measurement, Mueller matrix, return-path ellipsometry, optical polarimetry

1 Introduction

Diabetes is a worldwide public health problem. According to the survey of the Robert Koch Institute, in Germany, at least 7.2 percent population (aged between 18 to 79 years) have diabetes [1]. Diabetes patients cannot regulate their blood glucose levels when their blood sugar goes up. High blood sugar levels staying too long in the bloodstream cause serious health problems, such as nerve damage, vision loss, and kidney disease. Therefore, regular self-monitoring of blood glucose (SMBG) is essential in managing diabetes.

SMBG can be categorized into two types: invasive and non-invasive methods. The former methods include blood glucose monitoring and skin-attachable glucose sensors. However, these methods might cause discomfort and skin irritation which increase the risk of skin or tissue damage. Hence, the development of non-invasive glucose monitoring has been increasing in recent years. In the literature, the non-invasive methods of SMBG found are optical polarimetry [2], optical coherence tomography [3], Raman spectroscopy [4] and surface plasmon resonance [5]. Compared to these methods, the advantages of optical polarimetry are wide detection range, simple setup and capability of high scattering effects and weak signals. Nevertheless, the limitation of optical polarimetry is the resolution of glucose concentration. According to the guideline from Food and Drug Administration (FDA) in the United States, a minimum accuracy of 12 mg/dl is required for blood glucose monitoring test systems [6]. Phan and Lo used the Stokes-Mueller matrix polarimetry system to measure glucose concentration and claimed the limitation was 20 mg/dl [7]. Mukherjee et al. achieved a sensitivity of 20 mg/dl by a Mueller matrix polarimeter with dual photoelastic modulators [8]. Al-Hafidh et al. developed multireflection polarimetry which used micromirrors to enlarge the optical path length. They can achieve a 30-fold enhancement with 11 reflections [9]. However, their system required 11 mirrors which increase the complexity of assmebly, alignment and calibration. In this work, we proposed a simple method to enhance the sensitivity of glucose monitoring by means of a quarter-wave plate and mirror. The design is based on a coaxial design which can be easily applied to current optical polarimetry.

2 Measurement principle

The principle of optical polarimetry is based on the property of optical activity of glucose solution, i.e., the change of optical rotation is related to the concentration of the glucose concentration. The phenomenon can be described as [9]

$$\alpha = CL[\alpha]_{\lambda}^{T}, \tag{1}$$

where α is the measured optical rotation, C is the concentration of the solution, L is the optical path length and $[\alpha]_\lambda^T$ is the rotation power of the chiral material (e.g., sugar and glucose) which is related to temperature T and wavelength λ of the light source. Therefore, for low concentrations of glucose, high accuracy and sensitivity measurements for optical rotation are required.

Inspired by the concept of Chen et al. [10], we improve the measurement sensitivity of the optical rotation for glucose solution by return-path ellipsometry (RPE) [11]. In the configuration of RPE, the light beam transmits through the sample and returns by reflecting optical elements. Compared to conventional ellipsometry, the main feature is that RPE has a higher sensitivity to the optical properties of samples because of the double reflection from the sample.

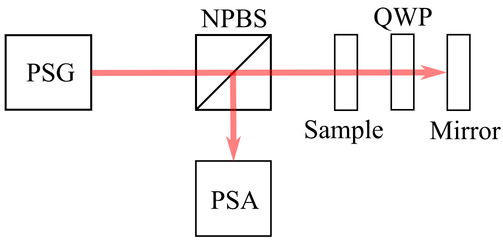

Figure 1: The schematic of the proposed return-path ellipsometry.

Figure 1 shows the schematic of the proposed return-path ellipsometer, which consists of a polarization state generator (PSG), non-polarizing beamsplitter (NPBS), quarter-wave plate (QWP), mirror and polarization state analyzer (PSA). The polarization effect of optical elements or interaction at boundaries can be described by Stokes vectors and Mueller matrices [12]. Stoke vectors $\mathbf{S}$ describe the polarization state of light beams. s_0 represents the total intensity. s_1, s_2 and s_3 denote the relative difference (linear or circular). Mueller matrices $\mathbf{M}$ represent the characteristics of the altering of Stokes vectors when light interacts with matter.

$$\mathbf{S} = \begin{bmatrix} s_0 \\ s_1 \\ s_2 \\ s_3 \end{bmatrix}, \mathbf{M} = \begin{bmatrix} m_{11} & m_{12} & m_{13} & m_{14} \\ m_{21} & m_{22} & m_{23} & m_{24} \\ m_{31} & m_{32} & m_{33} & m_{34} \\ m_{41} & m_{42} & m_{43} & m_{44} \end{bmatrix}. \tag{2}$$

The PSG can generate light with different polarization states $\mathbf{S}_{\text{PSG}}$ and the PSA can measure the state of polarization of light $\mathbf{S}_{\text{PSA}}$. Then, the measured Mueller matrix can be obtained by

$$\mathbf{S}_{\text{PSA}} = \mathbf{M}_{\text{meas}} \cdot \mathbf{S}_{\text{PSG}}. \tag{3}$$

The measured Mueller matrix $\mathbf{M}_{\text{meas}}$ in the return-path ellipsometry can be described as

$$\mathbf{M}_{\text{meas}} = \mathbf{M}^{\text{r}}_{\text{BS}} \cdot \mathbf{M}_{\text{S}}(\alpha) \cdot \mathbf{M}_{\text{QWP}}(-\theta) \cdot \mathbf{M}_{\text{M}} \cdot \mathbf{M}_{\text{QWP}}(\theta) \cdot \mathbf{M}_{\text{S}}(\alpha) \cdot \mathbf{M}^{\text{t}}_{\text{BS}}, \tag{4}$$

where $\mathbf{M}_{\text{BS}}$, $\mathbf{M}_{\text{QWP}}(\theta)$ and $\mathbf{M}_{\text{M}}$ are the Muller matrices of the NPBS, QWP and mirror, and r, t and θ denote the reflection and transmission of the NPBS and fast-axis orientation angle of the QWP. It should be noted that the Mueller matrix of optically active medium is the same for propagation and propagation back to the medium [13]. If every optical element is ideal, $\mathbf{M}^{\text{r}}_{\text{BS}}$ and $\mathbf{M}_{\text{M}}$ are diagonal matrices, where the diagonal elements are 1, 1, -1, and -1. $\mathbf{M}^{\text{t}}_{\text{BS}}$ is a diagonal matrix with diagonal elements 1, 1, 1, and 1. For simplicity, the Mueller matrix of an optically active medium can be treated as a circular retarder [8]

$$\mathbf{M}_{\text{S}} = \begin{bmatrix} 1 & 0 & 0 & 0 \\ 0 & \cos\alpha & \sin\alpha & 0 \\ 0 & -\sin\alpha & \cos\alpha & 0 \\ 0 & 0 & 0 & 1 \end{bmatrix}. \tag{5}$$

The QWP whose retardance is 90° can be expressed as

$$\mathbf{M}_{\text{QWP}} = \begin{bmatrix} 1 & 0 & 0 & 0 \\ 0 & \cos^2 2\theta & \cos 2\theta \sin 2\theta & \sin 2\theta \\ 0 & \cos 2\theta \sin 2\theta & \sin^2 2\theta & -\cos 2\theta \\ 0 & -\sin 2\theta & \cos 2\theta & 0 \end{bmatrix}. \tag{6}$$

If the fast axis θ is 0, the measurement result can be simplified as

$$\mathbf{M}_{\text{meas}} = \begin{bmatrix} 1 & 0 & 0 & 0 \\ 0 & \cos 2\alpha & \sin 2\alpha & 0 \\ 0 & \sin 2\alpha & -\cos 2\alpha & 0 \\ 0 & 0 & 0 & -1 \end{bmatrix}. \tag{7}$$

From Eqs. 5 and 7, it is clear that the measured rotation angles by the return-path ellipsometry are twofold compared to the measured rotation angles by the transmission configuration because the optical path length increases twice. Therefore, with the return-path configuration, we can enhance the sensitivity two times. In Eq. 7, the rotation angle of the glucose concentration can be calculated by

$$\arctan \frac{m_{32}}{m_{22}} = \arctan \frac{-m_{23}}{m_{33}} \tag{8}$$

It is worth noting that if the QWP in the configuration is removed, the measured Mueller matrix becomes a 4×4 identity matrix, i.e., the sensor cannot measure the rotation angle induced by the optically active medium.

3 Experiment setup

Figure 2 shows a prototype of a return-path ellipsometer. The principle is based on dual rotating-compensator [14] and return-path Mueller matrix ellipsometry. Therefore, the ellipsometer can measure full Mueller matrices [15] and the optical rotation can be solved by the measured matrices. The setup consists of a laser with a wavelength of 638 nm from Integrated Optics, a linear polarizer (LPVISE100-A, Thorlabs, Inc.), an NPBS, two QWPs (WPQ10ME-633, Thorlabs, Inc.), a silver mirror (PF10-03-P01, Thorlabs, Inc.) and a Stokes polarimeter (PAX1000VIS, Thorlabs, Inc.). QWP1 is mounted on a stepper motor rotation mount (K10CR1, Thorlabs, Inc.). The sample is a cuvette with an optical path length of 30 mm.

4 Experimental results

Before the measurements of glucose concentration, the NPBS and QWP2 need to be calibrated first. The NPBS has strong polarization distortions which induce polarization changes in the measurements and cause calculation errors. The calibration procedure of the NPBS can be found in Ref [16]. The measured Mueller matrix of the NPBS is

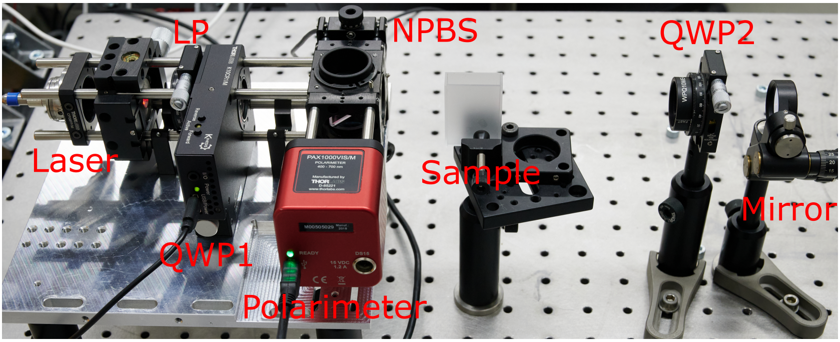

Figure 2: Photograph of the return-path ellipsometer, where LP, QWP and NPBS are linear polarizer, quarter-wave plate and non-polarized beamsplitter, respectively.

shown as

$$\mathbf{M}_{\text{NPBS}} = \begin{bmatrix} 1 & -0.167 & -0.004 & 0.002 \\ -0.175 & 1.010 & 0.006 & 0.002 \\ 0.002 & -0.005 & -0.981 & -0.251 \\ -0.003 & 0.005 & 0.261 & -0.945 \end{bmatrix}. \tag{9}$$

As can be seen, the NPBS is not a perfect element. Therefore, careful calibration of each optical element in the system is necessary and important. In Section 2, the fast axis of the QWP should be adjusted to 0°. Then the product of $\mathbf{M}_{\text{QWP}}$, $\mathbf{M}_{\text{M}}$ and $\mathbf{M}_{\text{QWP}}$ is a 4×4 identity matrix. After the fast axis adjustment of the QWP, We obtained the Mueller matrix as

$$\mathbf{M}_{\text{QWP}} \cdot \mathbf{M}_{\text{M}} \cdot \mathbf{M}_{\text{QWP}} = \begin{bmatrix} 1 & -0.003 & 0.014 & -0.009 \\ 0.010 & 0.992 & -0.003 & -0.004 \\ 0.009 & 0.004 & 0.996 & 0.034 \\ -0.009 & 0.004 & -0.041 & 0.993 \end{bmatrix}. \tag{10}$$

The result is very close to the ideal condition (4×4 identity matrix). The error sources might be the alignment and wavelength mismatch between the laser and the QWP.

In glucose concentration measurements, the glucose solution of 5% from B. Braun SE was first placed in a quartz cuvette with an optical path length of 30 mm and a wall thickness of 10 mm. Deionized water was used to dissolve the glucose concentration to 50 mg/ dl, 117 mg/dl and 150 mg/dl. An additional sample with deionized water was prepared for reference. An ultrasonic bath was used to speed up the dissolving process. Figure 3 shows the measurement of the glucose concentration. For the transmission measurements, the laser beam only passes the cuvette once. For the return-path measurements, the laser beam passes the cuvette forward and backward.

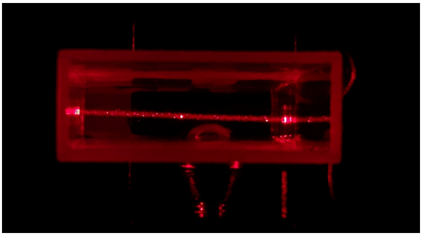

Figure 3: Photograph of the glucose measurements.

Figure 4 shows the measurement results for optical rotation angles with different glucose concentrations by the transmission and return-path ellipsometers. Table 1 demonstrates the fitting result (linear fitting) of the measurements. It can be seen that the slope of the return-path configuration (0.0047) is higher than the slope of the transmission configuration (0.0014), which proves the concept of sensitivity enhancement for glucose sensing. The coefficients of determination (R^2) in both methods are close to 1, i.e., the polarization model derived in Section 2 can well explain the optical rotation for different glucose concentrations.

Table 1: Fitting results for optical rotation angles with different glucose concentrations by the transmission and return-path ellipsometers.

Configuration	Linear fitting	R^2
Transmission	$y = 0.0014x + 0.0116$	0.98
Return-path	$y = 0.0047x - 0.0501$	0.93

However, the accuracy of the return-path configuration is lower than the accuracy of the transmission configuration. The reasons might be the alignment of the cuvette and the temperature of the glucose concentration. Because of the return-path configuration, the laser beam will pass the cuvette twice with four boundaries. If there is a small alignment error, the cuvette might induce polarization errors. As shown in the literature [13], the glucose concentration is sensitive to the temperature which was not controlled in the experiments. In addition, a pipette is used to transport a measured volume of the deionized water and glucose solution to the cuvette. The maximum permissible systematic error and random error of the pipette are ±0.5% and ±0.15% which might lead deviations of the concentration.

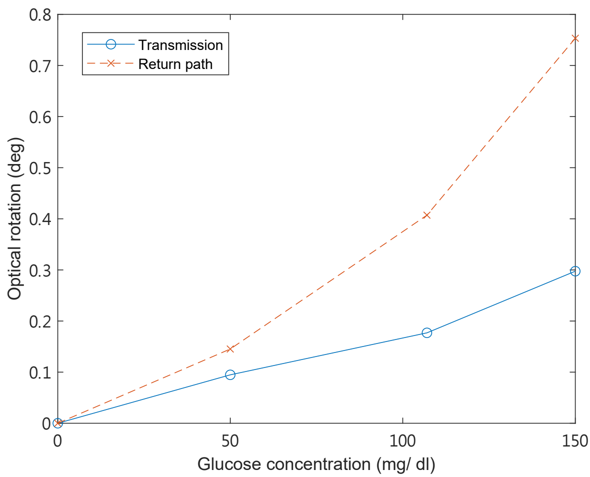

Figure 4: Measurement results of optical rotation for different glucose concentrations.

5 Conclusion

In this work, we proposed a novel glucose sensor by return-path Mueller matrix ellipsometry. Compared to the work from Phan and Lo and Mukherjee et al. (transmission Mueller matrix ellipsometry), the sensitivity of the measured rotations angle increases two times because the light passes the sample forward and backward. In principle, if the return-path configuration is applied to their systems, the sensitivity of their systems can be enhanced to 10 mg/dl which fulfills the FDA regulation. The proposed sensor uses a coaxial design, decreasing the optical system alignment's complexity. The measurement sensitivity is enhanced by using a fixed QWP (fast axis 0) and a mirror, i.e., the optical path length is twofold. For high-speed measurements, a liquid crystal or a division-of-amplitude photopolarimeter can be used to achieve several μs per Stokes vector. Currently, we only use the glucose concentration which has no scattering and depolarization effect. For real applications, both effects should be taken into account. Therefore, we will add intralipid with different glucose concentrations for the next step. In the future, we plan to evaluate the sensitivity, accuracy and uncertainty of the glucose sensor and study the calibration and stability of the system.

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