A NEW METHOD FOR A NON-INVASIVE GLUCOSE-SENSING POLARIMETRY SYSTEM

Sunghoon Jang, New York City College of Technology of CUNY; Hong Li, New York City College of Technology of CUNY

Abstract

Current methods of monitoring blood glucose use invasive technologies such as collecting blood samples. Development of an accurate non-invasive method will present a great advantage over current methods. Our research group developed a non-invasive glucose-sensing polarimetry system within physiologic glucose levels by applying advanced opto-electronics technology. The authors of this study demonstrated accurate results with the system presented here. In a previous study, the authors were successful in detecting the optical rotation of in-vivo and ex-vivo glucose concentrations within the physiologic range of 0-500 mg/dl due to a highly sensitive and stable closed-loop polarimetry system. Although preliminary results from this system were successfully demonstrated by the authors in a previous study, the complication of a closed-loop system creates issues for future applications because it will require more components and it is more difficult to design and analyze the system. The authors introduce here a new, simplified open-loop non-invasive glucose-sensing polarimetry system. Theories of the proposed method are introduced and preliminary results are demonstrated. This study investigated the development of an open-loop optical glucose-sensing system that used a simpler method to distinguish blood glucose levels within this physiologic range by using the aqueous humor of the eye. This is because it has extremely fast response and recovery profiles without significant delay, when compared with glucose concentrations in blood plasma. The results demonstrate that not only is this non-invasive glucose-sensing detector capable of monitoring glucose accurately enough to satisfy medical-use criteria, but is also capable of employing a more simplified method than existing conventional closed-loop optical glucose-sensing technologies.

Introduction

Diabetes mellitus is a serious disease when the human body does not produce or properly use insulin. It has been one of the major health problems in society. Often, diabetes can lead to many serious medical problems including blindness, kidney disease, nerve disease, limb amputations, and cardiovascular disease (CVD). According to the American Diabetes Association, the estimated cost of diabetes-related health care in the United States is approximately $91.8 billion, annually, including $23.2 billion in direct medical costs [1]. The recent studies [2] of multi-center National Institute of Health (NIH) [2] indicated that the health risks associated with diabetes are significantly reduced when blood glucose levels are properly and frequently controlled [3]. It is clearly indicated that it is prudent to measure blood glucose as often as five or six times a day. Thus, it is very important that proper monitoring should be done by diabetics at home or at work [4] [5]. At present, all existing methods of home blood-glucose monitoring require obtaining a blood sample by pricking a fingertip with a needle. This method strongly discourages patients' compliance, and has serious drawbacks because of its associated pain, inconvenience, and invasive nature [6].

A non-invasive method of monitoring blood glucose would present major advantages over current methods using invasive technologies. The authors attempted to develop and demonstrate accurate results with a non-invasive closed-loop optical-glucose system, within the physiologic glucose range of 0-500 mg/dl. The proposed open-loop glucose-sensing opto-electronic system used in this study also needed to be capable of monitoring very low glucose levels with the accuracy and precision that would satisfy medical-use criteria; this method is also expected to be fast and simple. The cost of the proposed testing device would be significantly lower than for existing methods because only a monitor with an optical sensor would be required, and the high monthly expense of testing strips would be avoided. In addition, patient acceptance for this methodology was expected to be high, due to its non-invasive nature, and the fact that it would be a simple and safe testing procedure.

There has been an increased demand for continuous, non-invasive glucose-monitoring techniques [7], due to the increasing number of people diagnosed with diabetes and the recognition of the fact that the long-term outcome of these patients can be dramatically improved by a careful, frequent and accurate glucose-monitoring method with control. In a previous study [8] [9] [22], the authors reviewed several of the newest, minimally invasive and non-invasive glucose-monitoring technologies under development or recently introduced. These include near infrared spectroscopy (NIR) [10], mid infrared spectroscopy (MIR) [11], radio wave impedance, optical rotation of polarized light [11], fluid extraction from the skin [12], and glucose-sensing contact lenses with fluorescence detection [11]. Although recent advances in basic research and clinical applications in non-invasive optical glucose monitoring are very encouraging for the future of this field, none of the attempts with non-invasive optical glucose-sensing techniques have resulted

thus far in the development of a sensor, which allows monitoring of glucose with sufficient accuracy and precision [7], [23]. Therefore, it is necessary to develop a new technique to satisfy criteria such as accuracy, low cost, simplicity in sampling and testing, portability, and safety.

Theory and Plan of Study

The first precision optical polarimeter using the Faraday effect was introduced by Gilham [13], [14] in 1957. Rabinovitch and March [15] introduced the concept of using the aqueous humor glucose as a detector of the blood glucose concentration by measuring the polarization rotation. Subsequently, Cote, Northrop, and Fox [16], [17] developed a true phase optical-glucose sensor to monitor glucose concentration. In 1997, Jang and Fox [18], [19] demonstrated that a closed-loop polarimeter could be realized with a single Faraday rotator.

In previous studies [18], [19], the authors introduced new, simplified non-invasive glucose-sensing polarimetry technology by introducing theories and demonstrating preliminary results. Conventional optical glucose sensors [7], [11], [20], [21] are very complicated in systemic design and performance because they adopted outdated closed-loop systems, which are inefficiently designed and implemented using additional optical components and electronic devices including a beam splitter, photo detectors, polarizers, Faraday modulators, and lock-in amplifier with additional analyzing devices. In this study, the authors attempted to investigate and develop the open loop-optical glucose-sensing system due to its simplicity for achieving higher accuracy and stability, while ensuring system sensitivity. The optical rotation due to the glucose cell will be proportional to the concentration of the glucose and the path length of the cell. The entire system sensitivity can be controlled by changing the gain constant of the lock-in amplifier.

Figure 1 shows a basic open-loop polarimetry system. The linearly polarized wave is emerging from the first polarizer, where θ represents the axis of the first polarizer. $\hat{x}$ is the horizontal component of θ and $\hat{y}$ is the vertical component of θ. The linear polarization of the interrogating beam is modulated by the optical chopper, which replaced the Faraday modulator used in previous research, and is then transmitted through a glucose cell, second polarizer, photo detector, and lock-in amplifier, respectively. As illustrated in Figure 1, the linearly polarized wave emerging from the first polarizer, can be represented as the following vector equation,

$$\boldsymbol{E}_1 = E\sin\theta\hat{x} + E\cos\theta\hat{y} \qquad (1)$$

The linear polarization of the interrogating beam is modulated by the action of the modulating optical chopper such that $\phi = \phi_c \cos\omega_c t$

Then, equation (1) becomes,

$$\boldsymbol{E}_2 = E\sin(\theta + \phi_c\cos\omega_c t)\hat{x} + E\cos(\theta + \phi_c\cos\omega_c t)\hat{y} \qquad (2)$$

When $\theta = 0$ and ϕ_c is small,

$$\boldsymbol{E}_2 \cong \mathrm{E}\sin(\phi_c\cos\omega_c t)\hat{\mathrm{x}} + \mathrm{E}\hat{\mathrm{y}} \qquad (3)$$

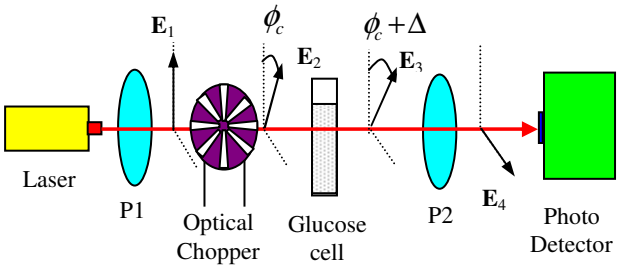


Figure 1. Block diagram of an open-loop glucose polarimetry system including glucose cell with first polarizer (P1) and second polarizer (P2)

The 'x' component of the electric field can be expanded to yield,

$$\mathrm{E}_x \approx \mathrm{E}\phi_c\cos\omega_c t \qquad (4)$$

The frequency-doubling effect for crossed polarizers, where the axis of the second polarizer is at a right angle with respect to the axis of first polarizer, can be demonstrated by the following development, since optical detectors are sensitive to the intensity of light

$$\boldsymbol{I}_x = |E_x|^2 \cong |E\phi_c\cos\omega_c t|^2 = E^2\phi_c^2\cos^2\omega_c t = E^2\phi_c^2\frac{1}{2}(1+\cos 2\omega_c t) \qquad (5)$$

The change 'Δ' in linear polarization due to the optical rotation effect is

$$\boldsymbol{E}_3 = E\sin(\Delta + \phi_c\cos\omega_c t)\hat{x} + E\cos(\Delta + \phi_c\cos\omega_c t)\hat{y} \qquad (6)$$

It was found that the detected intensity will be

$$\begin{aligned}\boldsymbol{I}_x &= |\mathrm{E}_x|^2 \approx |\mathrm{E}(\Delta + \phi_c\cos\omega_c t|^2 \\ &= \mathrm{E}^2(\phi_c{}^2\cos^2\omega_c t + 2\Delta\phi_c\cos\omega_c t + \Delta^2) \\ &\approx \mathrm{E}^2\left[\frac{1}{2}\phi_c{}^2(1+\cos 2\omega_c t) + 2\Delta\phi_c\cos\omega_c t + \Delta^2\right] \\ &\approx \mathrm{E}^2 2\Delta\phi_c\cos\omega_c t \qquad \text{for small } \Delta, \phi_c\end{aligned} \qquad (7)$$

where: ϕ_c = optical rotation due to the optical chopper
Δ = additional optical rotation due to the glucose cell

If a lock-in amplifier is connected to the output of the

photo diode detector with a reference frequency ω_c, its DC output is

$$V_L = LE^2 \Delta\phi_c \quad (8)$$

where L is the gain constant of the lock-in amplifier and Δ directly contains information about the optical rotation due to the glucose molecule in the cell. From the above equation, we can conclude that the DC level of the lock-in amplifier in our open-loop optical-glucose sensing system will be dependent on the gain constant of the lock-in amplifier, intensity of the optical signal, and the optical rotations due to the optical chopper and the glucose medium. If we set all parameters as constant, other than the glucose medium, the system can detect the variance of DC levels due to optical rotation, which is proportional to the concentration of the glucose molecule in the medium.

The theoretical response from the lock-in amplifier as a function of the angle between the two polarizers is represented graphically in Figure 2. It was found that this open-loop polarimetry system worked efficiently when close to a 45° angle between the two polarizers. A key point is that the rotation change Δ, which is indicative of glucose concentration, is now modulated at the Faraday frequency for coherent detection.

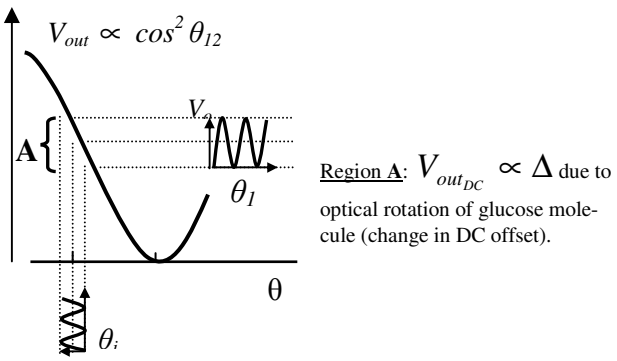


Figure 2. Graphical representation showing how the output from the lock-in amplifier depends on the angle (θ_{12}) between the two polarizers in Figure 1.

Methodology and Results

The main components of the closed-loop optical glucose sensor using the optical rotation of the glucose molecule are illustrated in Figure 3. A HeNe laser (approximately 1mW effective output after the first polarizer, 633 nm), and a first polarizer were used to provide linearly polarized light. The light was then passed through a Faraday modulator driven at about 1.2 kHz for the modulation of the polarization vector and detected by a photo diode detector after controlling its intensity by a second polarizer, which is called an analyzer. The lock-in amplifier provided an output signal, which is a DC voltage proportional to the amplitude of the 1.2 kHz present in the detected signal from the photo detector and then fed back to the Faraday modulator to close the loop. This dc output voltage is fully monitored and recorded by an oscilloscope, and a single Faraday modulator was used as a modulator and compensator to provide modulation and feedback compensation combined within the system. Therefore, the lock-in amplifier provided phase and frequency-locked detection of the 1.2 kHz component, which itself was proportional to the net rotation between the two polarizers positioned at 45° to each other. The optical rotation due to the glucose cell, with a path length of one centimeter, is proportional to the concentration of the glucose and the path length of the cell. Thus, sensitivity of the entire system can be controlled by changing the gain constant of the lock-in amplifier.

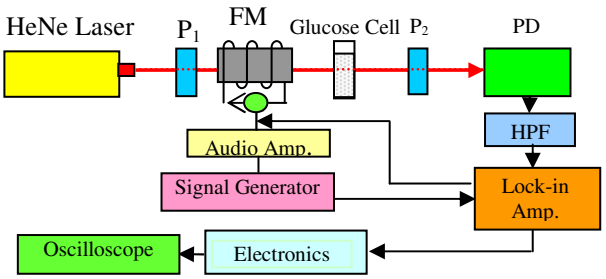


Figure 3. Block diagram of a designed and implemented closed-loop glucose-sensing polarimetry system: P_1 and P_2 are polarizers; FM is a Faraday Modulator; the glucose cell contains various glucose solutions within the physiologic range; PD is the photo diode detector; HPF is the high-pass filter

The closed-loop system was first calibrated by measuring the DC output signal from the lock-in amplifier, while applying various modulating frequencies in order to find the best fit for the current glucose-sensing system. The data shown in Figure 4 (a) was obtained from the DC output of the lock-in amplifier by changing the angle of the second polarizer. It was found that the system sensitivity was 37.01V/°, which means that every 10 millidegree of rotation gives about 370.1 mV DC offset. Since a practical glucose meter would need to detect a few millidegrees [22] of rotation, this system had a significant sensitivity. Figure 4 (b) shows a calibration run using the closed-loop system with a glucose cell containing dextrose-glucose in concentrations of 0, 100, 200, 300, and 500 mg/dl within the physiologic range. These data sets were obtained by using a single cell that was refilled with various glucose concentrations at each measurement. The averaged set of data from Figure 4 (b) was plotted after taking 10 measurements for each concentration to minimize errors due to the one-centimeter length of the glucose cell. The linear regression shown in Figure 4 (b) yielded –5.725 – 0.006 [glucose], which indicates that for every 18.5 millidegree/(100 mg/dl), the dextrose-glucose molecule contributes about 0.2 millidegree of optical rotation to the system.

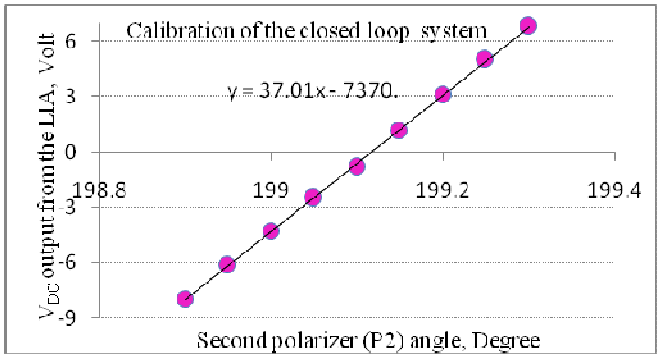


Figure 4-a. Plot of the DC output from the lock-in amplifier (LIA) as a function of the second polarizer rotation in the closed-loop optical-glucose system illustrated in Figure 3

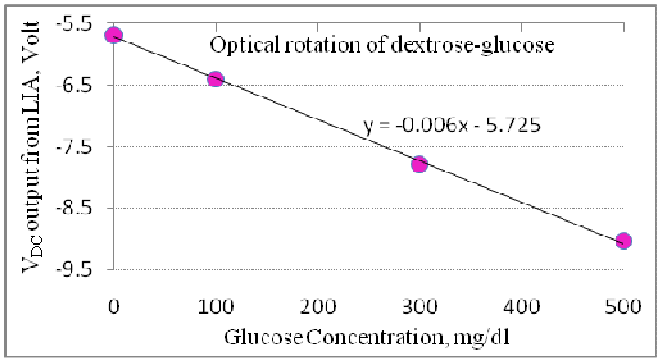
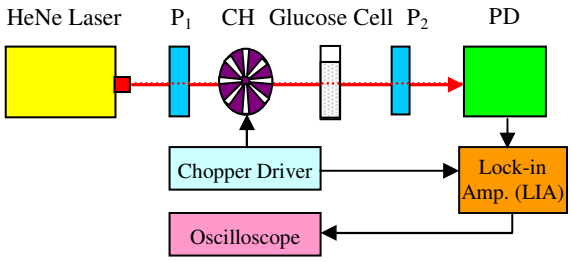


Figure 4-b. Plot of the waveforms includes DC output from the lock-in amplifier (LIA) against glucose concentration in the closed-loop glucose sensor



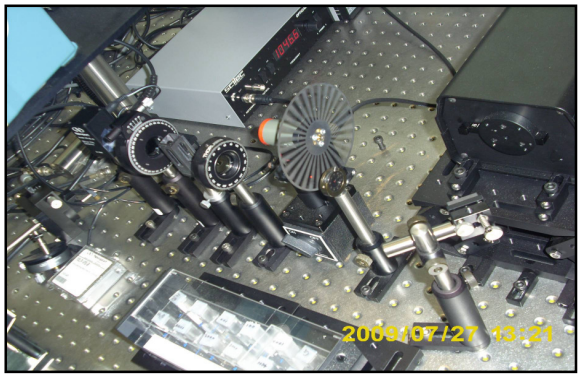


Figure 5. Block diagram and actual system of a designed and implemented open-loop polarimetry glucose sensor: CH is an optical signal chopper

The authors successfully demonstrated accurate results with the previously-designed non-invasive closed-loop polarimetry glucose-sensing system within physiologic glucose levels. This study also attempted to investigate and develop an optical glucose-sensing system, in order to achieve higher accuracy and ensure sensitivity with a simpler method using the open-loop glucose-sensing polarimetry system shown in Figure 5 by applying advanced optoelectronics technology.

The data shown in Figures 6-a to 6-i were obtained from the DC output of the lock-in amplifier with the angular orientation of the second polarizer. Various gains were also applied in order to calibrate system sensitivity and stability. Then, the system sensitivity was measured by monitoring the DC output of the lock-in amplifier using a fit of the data as shown in Figure 6-j. It was found that the system sensitivity was 6.442 V/°, which means that every 10 millidegree of rotation gives about 64.42 mV DC offset output. This sensitivity would be enough to detect a few millidegrees of rotation for a glucose molecule.

Although the system sensitivity was lower than the previously developed closed-loop glucose-sensing polarimetry system, the authors are confident and optimistic about this new open-loop system because the system sensitivity can be improved by a factor of 10 without encountering major problems. From previous experience, the optical rotation of the glucose molecule was observed within the physiologic range at the system sensitivity, 370.1 mV DC offset for every 10 millidegree analyzing the polarizer rotation. Due to the fact that an absolutely dark room was not available for testing this system, there were certain levels of interfering optical noise involved in the current study. To improve system sensitivity and stability, future measurements will be made in an absolute dark room.

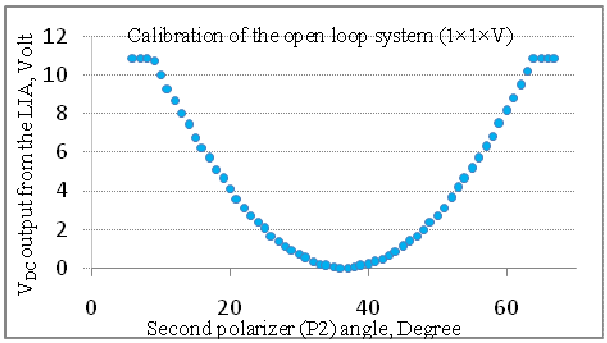


Figure 6-a

The general configuration of the system presented in Figure 7 is similar to the previous setup; however, the authors added an ex-vivo goat eye or an artificial eye to the system in order to detect penetrating light through the anterior chamber of the eye filled with aqueous humor. Also, the measured V_{DC} output depends on the glucose concentration,

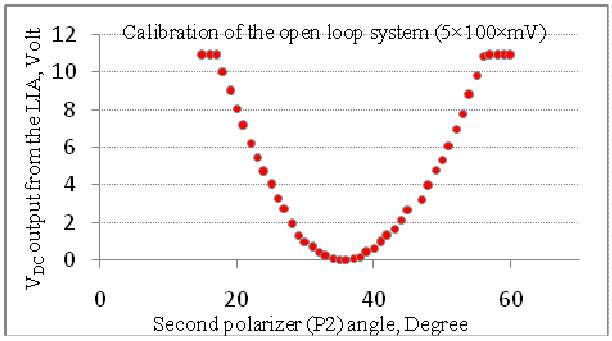


Figure 6-b

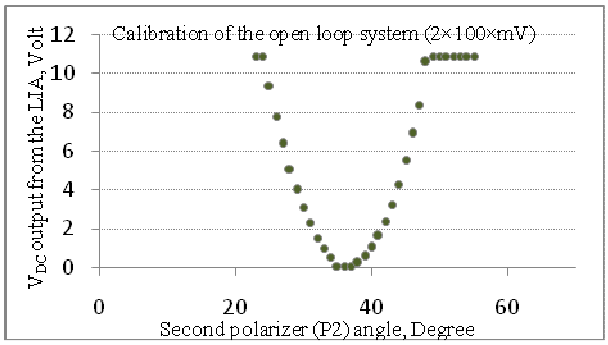


Figure 6-c

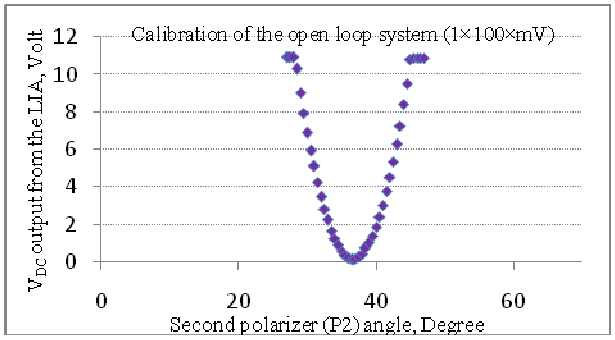


Figure 6-d

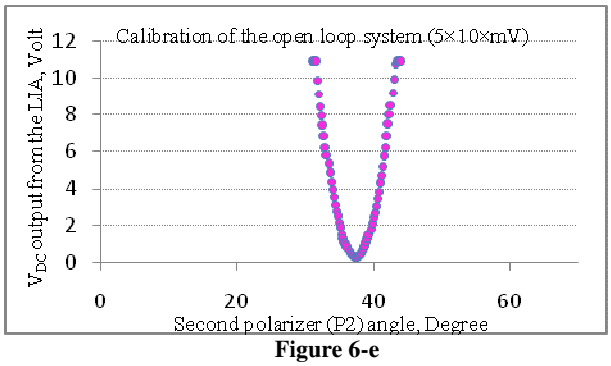


Figure 6-e

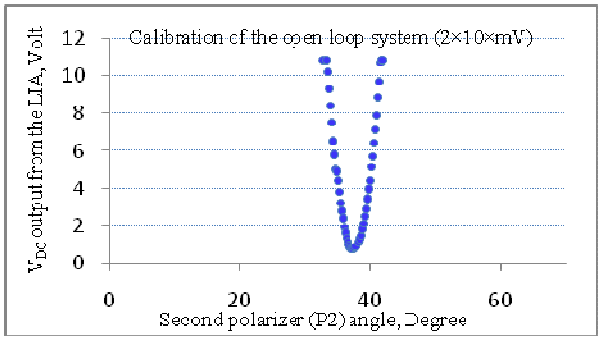


Figure 6-f

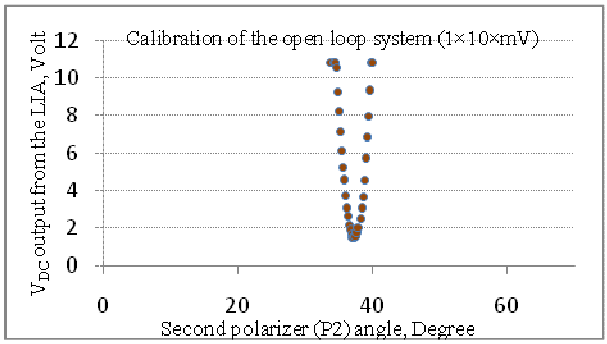


Figure 6-g

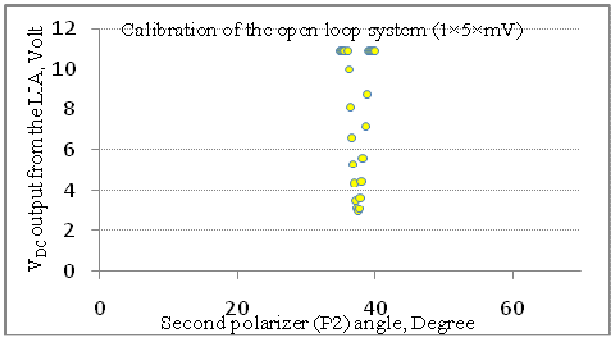


Figure 6-h

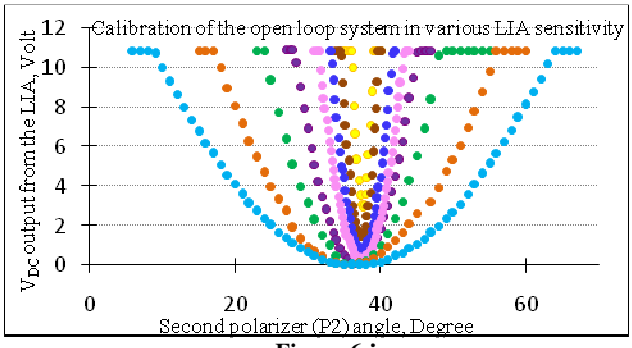


Figure 6-i

which can be detected by the lock-in amplifier. The system analysis with an ex-vivo goat eye or artificial eye will be completed in a future study. In this present study, the authors have presented a simplified, non-invasive glucose-sensing polarimetry system by presenting theories and demonstrating preliminary results. In a follow-up study, the authors hope to achieve the intrinsic optical rotatory effect using conventional optical rotation in the presence of ex vivo living tissue or an artificial eye.

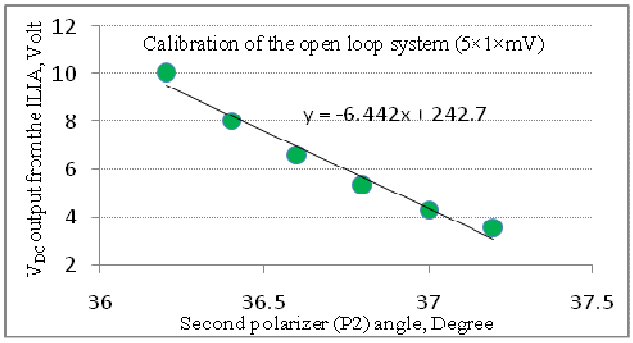


Figure 6-j

Figure 6. Demonstrated calibrations of the open-loop glucose-sensing polarimetry system. (a) to (h) are plots of V_{DC} output from the lock-in amplifier as a function of the second polarizer rotation in the open-loop system illustrated in Figure 5 at various lock-in amplifier sensitivities. (i) is a composite plot of all sensitivities in the lock-in amplifier. (j) is a plot of the V_{DC} output from the lock-in amplifier in the linear regression range at the sensitivity 5×1×mV

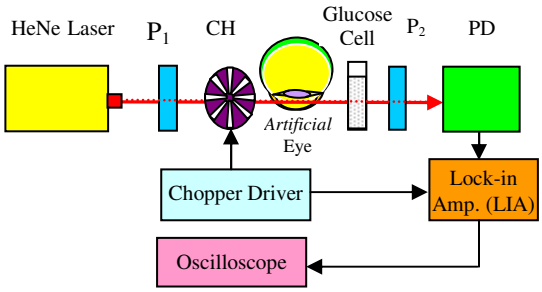


Figure 7. Schematic block diagram of the open-loop glucose-sensing polarimetry system including an artificial eye

Conclusion

Optical glucose-sensing techniques using the optical rotatory effect of glucose have many advantages over existing invasive and noninvasive methods, since the method is based on shining a brief pulse of light into the front of the eye. The authors previously showed that it is possible to isolate the lens/aqueous reflection and detect polarizational changes. However, measurements in the presence of a living eye will present many challenges because the tissues are more variable than nonliving optical components due to the nature of corneal birefringence. Further work will optimize this system in order to achieve the desired sensitivity, stability and accuracy. Once these hurdles are overcome, the optical glucose-sensing method studied and developed in this study can be miniaturized using current integrated optics, electronics, and advanced micro-fabrication technologies. This technique also has great potential for providing an inexpensive, fast, reliable, accurate, and compact non-invasive glucose sensor for diabetic patients in the near future.

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Biographies

SUNGHOON JANG is currently an Assistant Professor in Electrical and Telecommunications Engineering Technology at New York City College of Technology of CUNY. He received the B.S. degree in Electrical Engineering from the Kyung-nam University, Korea, and his M.S.E.E degree in Electrical and Computer Engineering from New Jersey Institute of Technology, and his Ph.D. degree in Biomedical Engineering from University of Connecticut. Dr. Jang is a member of IEEE and BME. His technical areas include digital signal processing, opto-electronics, and control systems in Biomedical Engineering. He has published a number of papers in these areas. Dr. Jang teaches in Electrical and Telecommunications Engineering Technology. Professor Jang may be reached at sjang@citytech.cuny.edu.

HONG LI is currently an Associate Professor in Department of Computer Systems Technology at New York City College of Technology of CUNY. She received her M.S. degree in Mathematics from P. R. China and Ph.D. degree in Mathematics from The University of Oklahoma. Her research has been focused on system modeling and parameter estimation in variety fields of applications. She has published a number of papers with group of researchers in the fields of civil engineering and biomedical engineering. Professor Li also has years of experience of software development in industries before she joined CUNY as faculty member. Professor Li may be reached at hli@citytech.cuny.edu.