Modifying the Existing Non-invasive Optical Glucose Sensing Device and Demonstrating the Optical Rotatory Effect of glucose in the presence of Glucose Medium

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I. Identification and Significance of the Problem

Diabetes mellitus is the most common disorder of the endocrine system and affects nearly 16 million people in the United States and over 100 million people worldwide alone. Often, diabetes leads to such problems as renal failure, foot problems, heart disease, and vision impairment. 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, 2]. However, all current existing conventional methods of home blood glucose monitoring require obtaining a blood sample by pricking a fingertip with a needle or lancet and then use a sensor to a drop of the blood sample to indicate glucose levels [3, 4]. The recent multi-center NIH studies have indicated that the health risks associated with diabetes are significantly reduced when the blood glucose levels are well and frequently controlled, indicating that it is prudent to measure the blood glucose as often as five or six times a day. Thus it is very important that proper monitoring be done by diabetics at home or at work[3, 4]. However, all current existing conventional methods of home blood glucose monitoring require obtaining a blood sample by pricking a fingertip with a needle or lancet and then use a sensor to a drop of the blood sample to indicate glucose levels.

At present, all existing methods of home blood glucose monitoring require obtaining a blood sample by pricking a fingertip with a needle or lancet (referred to as a "stick"), allowing the puncture to bleed until a testing strip is adequately covered with blood, and then placing the coated strip into a glucose monitor for testing. This method strongly discourages patients' compliance and has the following serious drawbacks; i) the procedure is invasive. ii) it is painful and also increases the risk for infection iii) the procedure for testing is laborious and it requires thorough hygiene. iv) there is still a very small margin for errors. v) the procedure is expensive.

Clearly, non-invasive or less invasive methods of monitoring blood glucose levels would present major advantages over existing methods. There has been an increasing demand for continuous, non-invasive glucose monitoring techniques 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 and control. In this part of the proposal, we will review several of the newest minimally invasive and non-invasive glucose monitoring technologies under development or introduced to current market, for example, near infrared (NIR) spectroscopy, Mid infrared (MIR) spectroscopy, radio wave

impedance, optical polarimetry glucose sensor, fluid extraction from the skin, glucose sensing contact lens with fluorescence detection, etc. [5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18]

The promising technologies listed above are currently investigated as non-invasive tools to detect blood glucose levels. Although recent advances in basic research and clinical applications in the noninvasive glucose monitoring are very encouraging for the future of this field, the results of currently introduced techniques in this field are still far from satisfying requirements in terms of a noninvasive glucose sensor. Therefore, it is necessary to develop a new technique or to modify currently existing technique satisfying the criteria such as accuracy, low cost, simplicity in sampling and testing, portability, and safety in use.

Diabetic patients are generally advised to check their blood glucose level 5 to 7 times per day. Since this blood glucose tests are painful, intimidating, laborious, and expensive, they strongly discourage patient compliance. Thus it is necessary to develop a non-invasive blood glucose method which could provide fast, painless, and convenient glucose monitoring to diabetic patients.

II. INTRODUCTION

The first precision optical polarimeter using the Faraday Effect was introduced by Gillham [19, 20] in 1957. Rabinovitch and March [21] proposed a new concept for detection of the blood glucose concentration by measuring polarization rotation using the aqueous humor glucose of the eye. Subsequently Cote, Northrop, and Fox [22, 23] proposed a true phase optical glucose sensor to monitor glucose concentration. Jang and Fox [24, 25] demonstrated that a closed loop polarimeter using a single Faraday rotator in 1997 and also introduced a concept using double lock-in technique to optical glucose sensing [26]. Fox and Censor [27] described reflectors in different media and their effect on the conventional optical rotation. However, none of these prior efforts were successful in producing a practical result doing *ex vivo* experiment.

The optical effect results from conventional optical rotation with creating a signal at the Faraday modulator frequency that is indicative of the glucose concentration in the solution. Investigation of optical rotation in glucose solutions over a wide range of glucose concentrations including physiologic levels will be studied by presenting the real optical signal penetrated through anterior chamber of artificial eye. Obtaining the optical signal from living biological tissue is extremely important in this application because this issue has been a major huddle in order to bring this optical glucose sensor to commercial market. Result of the improved signal to noise ratio using various frequencies of conventional optical effect and further simplification of system by replacing HeNe laser and Faraday rotator to laser diode with modulator will be also demonstrated in this study. The study presented here introduces and provides basic scientific and engineering data on a new approach to optical glucometry. We will demonstrate optical rotatory effect of glucose in the presence of enucleated artificial eyes in order to show that the method is feasible in an *ex vivo* biological model.

The proposed glucose sensing optical device with implanting the opto-electronics system should be capable of monitoring very low glucose levels with the accuracy and precision that would satisfy medical use criteria; and this method is 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 contact lens would be required, and the high monthly expense of testing strips would be avoided. In addition, the patient acceptance for this new methodology is expected to be high due to its non-invasive nature, and its simple and safe sampling and testing procedure.

III. THEORY

Fig. 1 illustrates basic open loop polarimetry system. The linearly polarized wave emerging from the first polarizer, where θ represents the axis of the first polarizer, can be represented as the following,

$$\boldsymbol{E_1} = E\sin\theta\hat{x} + E\cos\theta\hat{y}$$

(1)

The linear polarization of the interrogating beam is modulated by the action of the modulating Faraday rotator such that

$$\phi = \phi_f \cos\omega_f t$$

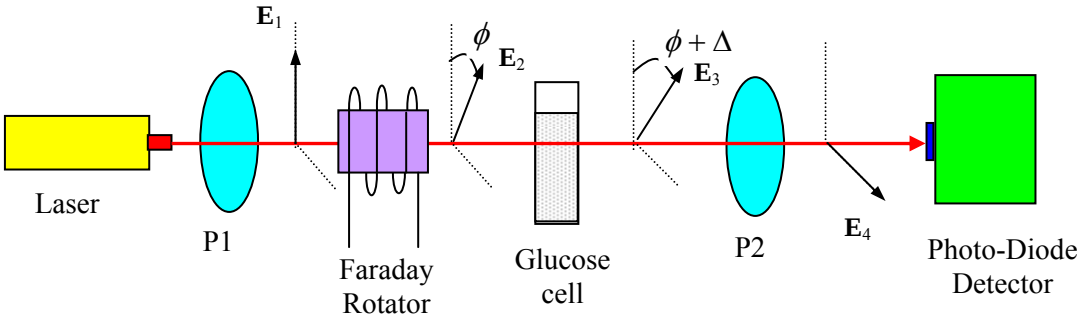


Figure 1: Block diagram of an open loop glucose polarimetry system with MORE cell. : P1 & P2 are polarizers.

Then equation (1) becomes,

$$\boldsymbol{E_2} = E\sin(\theta + \phi_f \cos\omega_f t)\hat{x} + E\cos(\theta + \phi_f \cos\omega_f t)\hat{y}$$

(2)

For $\theta = 0$ and ϕ_f *is small*,

$$\boldsymbol{E_2} \cong E\sin(\phi_f \cos\omega_f t)\hat{x} + E\cos\hat{y}$$

(3)

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

$$E_x \approx E\phi_f \cos\omega_f t$$

(4)

The frequency doubling effect for crossed polarizers (the axis of P_2 is at right angle to the axis of P_1) can be demonstrated by the following development, since optical detectors are sensitive to the intensity of light

$$\boldsymbol{I_x} = |E_x|^2 \approx \left|E\phi_f \cos\omega_f t\right|^2 = E^2{\phi_f}^2 \cos^2\omega_f t = E^2\phi_f^2\frac{1}{2}(1+\cos 2\omega_f t)$$

(5)

The change Δ in linear polarization due to the conventional optical rotation effect combines with the magneto optical rotatory effect follows as

$$\boldsymbol{E}_3 = E\sin(\Delta + \phi_f \cos\omega_f t)\hat{x} + E\cos(\Delta + \phi_f \cos\omega_f t)\hat{y}$$

(6)

The detected intensity will be

$$\begin{aligned}\boldsymbol{I}_x &= |E_x|^2 \approx \left|E(\Delta + \phi_f \cos\omega_f t\right|^2 \\ &= E^2(\phi_f{}^2 \cos^2 \omega_f t + 2\Delta\phi_f \cos\omega_f t + \Delta^2) \\ &\approx E^2\left[\frac{1}{2}\phi_f{}^2(1+\cos 2\omega_f t) + 2\Delta\phi_f \cos\omega_f t + \Delta^2\right] \\ &\approx E^2 2\Delta\phi_f \cos\omega_f t \qquad \textit{for small } \Delta, \phi_f\end{aligned}$$

(7)

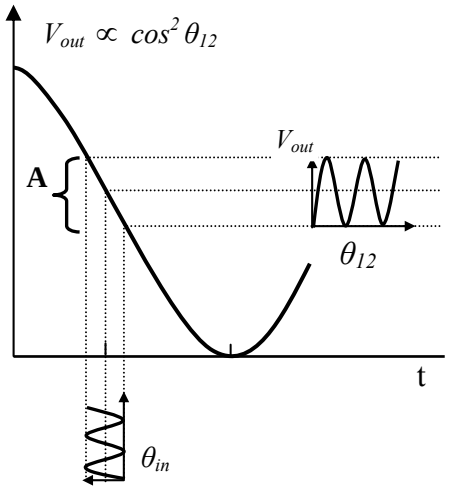
If a lock in amplifier is connected to the output of the photo diode detector with a reference at frequency ω_f, its output V_L is

$$V_L = LE^2\Delta\phi_f$$

(8)

where L is the gain constant of lock in amplifier. Δ directly contains information about the optical rotation due to glucose molecule in the cell.

The theoretical response from the lock in amplifier as a function of the angle between the two polarizers is presented graphically in Fig. 2. We found our open loop polarimetry system worked efficiently close to a 90 degree angle between the two polarizers. A key point is that the rotation Δ which is indicative of glucose concentration is now modulated at the Faraday frequency for coherent detection.



Region **A**: $V_{out_{DC}} \propto \Delta$ due to optical rotation of glucose sample (change in DC offset)

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

IV. METHOD and PRELIMINARY RESULTS

We performed a number of experiments to verify the basic theory and to demonstrate applicability on biologic tissue such as *ex vivo* goat eyes. The main components of the open loop optical glucose sensor using the optical rotation of glucose molecule are illustrated in Figure 3. A HeNe laser (approx. 2 mW effective output after first polarizer, 633 nm) and polarizer are used to provide linearly polarized light. The light was then passed through a Faraday rotator driven by a function generator at about 1.2 kHz.

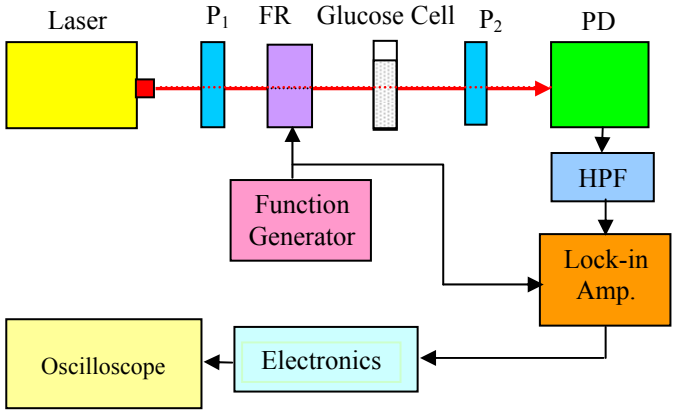


Figure 3: Block diagrams of an open loop optical glucose sensor using a single Faraday rotator concept. : P_1 and P_2 are polarizers; FR is a Faraday rotator; Glucose cell contains various glucose solutions in physiologic range; PD is the photo diode detector.

The optical rotation due to the glucose cell was 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 photo-diode amplifier. The lock-in amplifier provided an output signal that was a DC voltage proportional to the amplitude of the 1.2 kHz present in the detected signal from the photo-diode detector. This DC output voltage of the glucose signal was then monitored through the oscilloscope. 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 approximately 90° to each other. When additional glucose was applied to the glucose cell, the lock-in amplifier provided additional DC output.

The open loop system was first calibrated by measuring the DC output signal from the lock-in amplifier with applying various modulating frequencies in order to find the best fit for the current glucose sensing system. Then the system sensitivity was measured DC output of the lock-in amplifier using a fit of the data. The data shown in Figure 4 was obtained from DC output of the lock-in amplifier by changing angle of the 2nd polarizer. We found the system sensitivity of 36.3633 V/Degree, which means every 10 millidegree of rotation gives about 363.63 mV DC offset. Since a practical glucose meter would need detect a few millidegrees of rotation, this system had significant sensitivity.

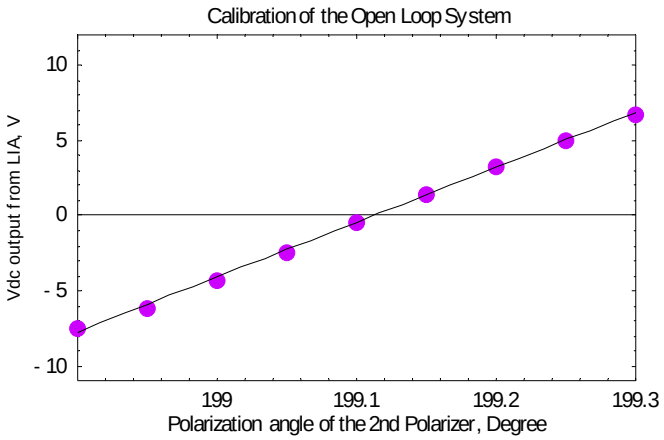


Figure 4: Plot of V_{DC} output from lock-in amplifier as a function of 2nd polarizer rotation in the open loop optical glucose system illustrated in Figure 3.

A sample set of the waveforms from five different glucose concentrations was transferred to a mathematical program after taking the voltage waveforms from the digital oscilloscope. From the oscilloscope the DC offset signal is significantly dependent on the glucose concentration. Fig. 5 shows a calibration run using the open loop system with glucose cell containing physiologic range d-glucose at concentration of 0, 100, 200, 300, and 500mg/dl. The conventional optical rotation is presented in Figure 5. These data sets shown in the figure were obtained by using a single cell that was refilled with various glucose concentrations at each measurement. The averaged set of the data from Fig. 5 was plotted after taking 10 measurements for each concentration to minimize errors due to the 1 cm in length of the glucose cell. Linear regression shown in Figure 5 yielded –5.71455 – 0.00673568[Glucose] means 18.5 millidegree/(100 mg/dl).

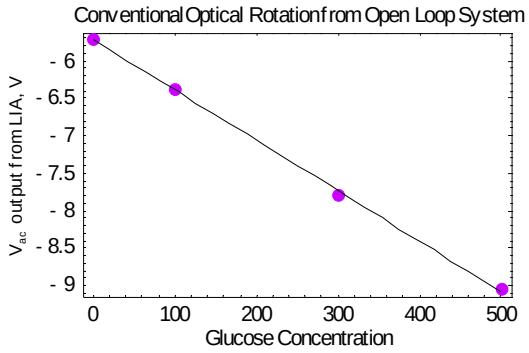


Figure 5: A plot of the waveforms includes V_{DC} signal output from lock-in amplifier against glucose concentration in the open loop optical glucose sensing system.

V. PLAN of STUDY in NEAR FUTURE

We have attempted simplify further in order to obtain an improved system sensitivity which will be very important factor for achieving our ultimate goal of the noninvasive glucose sensing technology depicted in Figure 6. We also calibrated this system preliminary by measuring optical rotation due to second polarizer and glucose solution in the cell. Very remarkable sensitivity has been observed in preliminary attempts from our modified system.

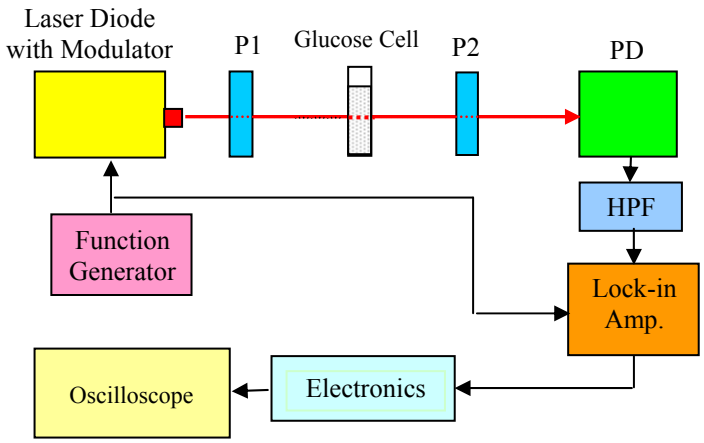


Figure 6: Schematic block diagram of the modified open loop polarimetry system replacing Faraday rotator by laser diode with modulator.

The general configuration of the system presented in Figure 7 is similar to the previous setup but we added an *ex vivo* goat eye to the system in order to detect penetrated light through anterior chamber of goat eye filled with aqueous humor and to measure V_{DC} output depends on the glucose concentration from the lock in amplifier.

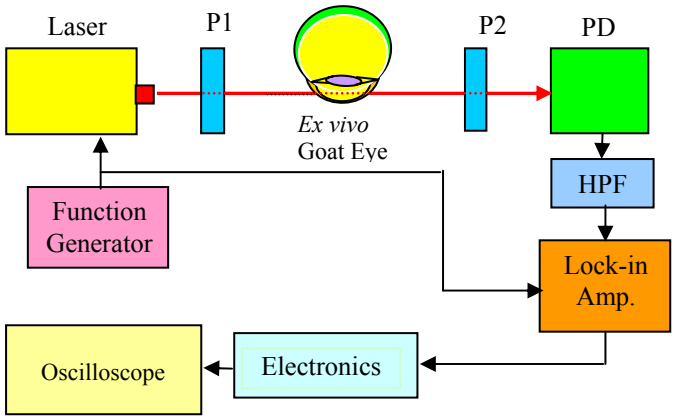


Figure. 7: Schematic block diagram of the open loop polarimetry system including an *ex vivo* goat eye. The lock-in amplifier gives V_{DC} output depends on reference signal input from signal generator used to modulate Faraday modulator and output signal from photo diode detector.

The method to demonstrate optical rotatory signals in the presence of artificial and enucleated goat eyes has been discussed and promising preliminary results have been successfully demonstrated in this study. As far as we are aware, this is the first time that this type of optical rotatory effect of glucose solutions has been proposed or investigated for minimally invasive glucometry, and also will demonstrate in *ex vivo* living tissue using additional optical lenses and media to help better light propagation through anterior chamber of eye for further study within near future to complete current study. We are looking forward to doing more measurements with glucose cells including the glucose solution within much lower concentrations than physiologic range in the presence of the goat eye. When the wave travels through the medium in the anterior chamber filled aqueous humor, it undergoes the rotation, called optical rotatory effect. We are

also looking forward to achieve the intrinsic optical rotatory effect using the conventional optical rotation in the presence of *ex vivo* living tissue. On reflection from an ideal optical system with a mirrorlike reflector, conventional optical rotation due to glucose solution should be cancelled[11]. However shining light travel through cornea/aqueous interface will create optical rotation mainly due to glucose molecule.

Optical glucose sensing techniques using the optical rotatory effect of glucose have many advantages over currently existing invasive and noninvasive methods, since the method is based on shining a brief pulse of light into the front of the eye. Measurements in a living eye present many challenges because the tissues are more variable than nonliving optical components. Our previous research has shown that we can isolate the lens/aqueous reflection and detect polarizational changes[12]. Further work will be needed to determine the ultimate sensitivity and accuracy. Once these huddles are overcome, the optical glucose sensing method introduced in this study can be miniaturized using current integrated optics, opto-electronics, and semiconductor technology and has the potential to provide a low cost, fast, and compact noninvasive glucose sensor for the diabetic patients within near future.

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