Dual-wavelength polarimetry for monitoring glucose in the presence of varying birefringence

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Abstract. In a continuing effort to develop a noninvasive means of monitoring glucose levels using the aqueous humor of the eye, a dual-wavelength system is developed to show that varying birefringence, similar to what is seen with a moving cornea, can be compensated. In this work, a dual-wavelength, closed-loop system is designed and a model is developed to extract the glucose concentration information. The system and model are tested using various concentrations of glucose in a birefringent test cell subject to motion artifact. The results show that for a static, nonmoving sample, glucose can be predicted to within 10 mg/dl for the entire physiologic range (0 to 600 mg/dl) for either laser wavelength (523 or 635 nm). In the presence of moving birefringence, each individual wavelength produces standard errors on the order of a few thousand mg/dL. However, when the two wavelengths are combined into the developed model, this error is less than 20 mg/dL. The approach shows that multiple wavelengths can be used to drastically reduce the error in the presence of a moving birefringent sample and thus may have the potential to be used to noninvasively monitor glucose levels *in vivo* in the presence of moving corneal birefringence.
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1 Introduction

Diabetes mellitus afflicts about 180 million people worldwide and 18.2 million people in the United States.[1] In the United States, diabetes, along with its associated complications, is the sixth leading cause of death.[2] Diabetes mellitus is characterized by the inability of the body to produce or properly utilize insulin, a hormone that regulates the transport of glucose from the blood stream into the tissue.[2] When there is an insufficient level of insulin in the body, hyperglycemia occurs, an elevation of the blood glucose levels to much higher than normal. Alternatively, when blood glucose levels are below normal, a condition known as hypoglycemia occurs. Without treatment, consistently low glucose levels can lead to diabetic coma and possibly death, while consistently high glucose levels can lead to long-term complications such as coronary artery disease, hypertension, and retinopathy.[3–5] Research has shown that intensive control of blood sugar is an effective means to prevent or slow the progression of long-term diabetic complications such as kidney failure, heart disease, and blindness.[5] Since blood glucose levels frequently fluctuate due to daily activities such as eating and exercise, the intensive control of blood glucose requires frequent monitoring for those without the built-in insulin control system. It is recommended that measuring blood glucose at least five times a day can help diabetics in avoiding the secondary complications associated with abnormal glucose levels.[2]

Currently, the most common methods for measuring blood glucose levels are invasive. These methods require patients to break skin to obtain a blood sample using a lancet or needle, causing pain as well as possible infection. Because of this, very few patients adhere to strict monitoring of blood glucose. In the last few years, more than 100 companies and universities have been involved in research to develop noninvasive technologies to measure blood glucose using various approaches. Very few of these technologies, however, are currently available commercially. One such device available commercially is the GlucoWatch ©, which uses fluid extraction from the skin. However it is not marketed as an independent glucose sensor, since it is not intended to replace conventional blood glucose measurement methods, but rather supplement them and provide additional information on the patient's glucose fluctuations throughout the day.[6] This technology draws fluid through the skin and is thus not truly noninvasive. It also requires the analyzer pack in the watch to be replaced quite regularly, proving to be quite expensive over time. Other promising technologies currently being researched are near-infrared light spectroscopy, far-infrared radiation spectroscopy, Raman spectroscopy, fluorescence spec-

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troscopy, radio wave impedence, optical rotation of polarized light, and interstitial fluid harvesting.[7–9]

An optical polarimetric glucose sensor could be a very useful technique for noninvasive measurement of blood glucose. The primary advantage of such a device over current technologies is that it has the potential to obtain actual glucose concentration values noninvasively. It also could be more cost effective, as the device would not have disposables that need to be continuously replaced. This method also avoids the complications of the temperature sensitivity of IR absorption due to the large water peaks, and is less invasive than fluorescence techniques currently being researched, which require the implantation of fluorophore-doped polymers.[7,8]

Polarization applied to glucose detection is based on the ability of optically active molecules, such as glucose, to rotate the polarization plane of a light beam.[10,11] Fundamentally, the concentration of the optically active sample is proportional to the observed rotation value of the polarization plane for a given specific rotation and path length. Thus, the concentration of the sample can be calculated from the observed rotation for a given path length and specific rotation.

The use of polarimetry to measure blood glucose concentration in the aqueous humor has existed for more than 20 years. In 1982, Rabinovitch, March, and Adams[12,13] were first to report the use of the eye as a potential sensing site for optical polarimetry to detect glucose levels in the body. Using a rabbit model, they proposed that glucose concentration in the aqueous humor is related to that in the blood with a slight time delay (on the order of minutes). Further, March, Rabinovitch, and Adams[13] reported that the acids (lactic, ascorbic, and amino) contribute to rotation in the aqueous humor composition of the rhesus monkey; however, these acids are on the order of ten times less than the rotation due to glucose. Previously, with direct extraction of aqueous humor, Pohjola's research showed that glucose concentration in the aqueous humor of the eye is correlated to that of blood.[14] Many groups have set out to improve the stability, repeatability, and accuracy of this approach. Coté, Fox, and Northrop[15] reported the potential for millidegree sensitivity through the development of a true phase technique *in vitro* and proposed a potential *in vivo* system. Following their work, Goetz reported a closed-loop feedback system with less than a millidegree standard deviation using a Faraday rotator for signal modulation and feedback.[16] To be able to measure other optically active compounds, King et al. developed another multispectral polarimeter using a single pockels cell *in vitro*.[17] In their study, they demonstrated *in vitro* a multispectral approach to compensate for the presence of multiple optically active compounds in a sample, such as ascorbic acid and albumin. To further improve repeatability and stability while preserving accuracy, Cameron et al. developed a Faraday-based system that demonstrated the potential to compensate for rotation due to the presence of other optically active components using a digital closed-loop feedback technique with submillidegree sensitivity *in vitro*.[18,19] This same group showed that the time lag between blood and aqueous humor glucose levels is on average less than 5 min in New Zealand rabbits, thus validating the ability of this sensing sight to correlate with blood glucose levels.[20] An eye coupling device was developed to couple the input laser beam through the anterior chamber of the eye for an *in vivo* system.[19] It was also determined that other optically active components in the aqueous humor, as well as the effects of the temperature and pH, are negligible in sensing glucose via polarimetry within physiological ranges.[21]

Other research groups have developed different polarimetric methods to measure glucose. Chou et al. reported on a polarimeter system utilizing an optical heterodyne approach and phase lock-in technology with sensitivity to detect glucose levels below 10 mg/dl *in vitro*.[22,23] More recently, Bockle, Rovati, and Ansari proposed a theoretical model utilizing Brewster's reflection angle off the lens of the eye for detecting glucose levels.[24,25] While these techniques, along with those previously mentioned, have shown results *in vitro*, no group has been able to use a polarimetric approach to accurately measure blood glucose *in vivo*, primarily due to the difficulties associated with the birefringence of the cornea coupled with motion artifact.[26] The motion of the eye masks the detected glucose signal due to the birefringence of the cornea. Anumula et al. presented a theoretical model and proposed a system to compensate for this, but his method still did not overcome the time-varying problem due to the motion of the cornea.[27] Baba and Coté designed and implemented a dual orthogonal polarization detection system to compensate for motion artifact, but the results showed low accuracy due to the open-loop nature of the system.[28]

This work describes a digital dual-wavelength dual closed-loop polarimeter used *in vitro* with the presence of motion-artifact-induced birefringence. This polarimeter system and algorithm minimize the effect of the time-varying birefringence signal due to motion artifact, and allow for repeatable, accurate glucose measurements in the presence of such motion.

2 Materials and Methods

2.1 *System Description and Theoretical Discussion of Birefringence*

To compensate for motion-induced birefringence using a dual-wavelength system, two different experiments were conducted to first characterize the birefringence of the sample cell and second to observe its effects on the output intensity for each wavelength. Initially, open-loop experiments were performed to determine the relationship between the output intensities of two light sources with respect to changes in the birefringence of the optical signal.

The block diagram of the system is shown in Fig. 1. The input light sources used were a red 635-nm laser diode (LaserMax, Incorporated, Rochester, New York), emitting 5 mW of power, and a green 532-nm laser (Oriel Instruments, Stratford, Connecticut), emitting 20 mW of power. Each light beam was passed through a Glan-Thompson 100000:1 polarizer (Newport Incorporated, Irvine, California), which converted the input light into linear, vertically polarized light. In the closed-loop system, each beam is then passed through a faraday rotator that rotated the light a fixed amount proportional to the rotation seen in the first harmonic, as described in Eqs. (1) and (2). A nonpolarized beamsplitter (Newport Incorporated) was then used to combine the two beams into a single ray and a Faraday rotator (Deltronic Crystal Incorporated, Dover, New Jersey) modulated the linear polarization vector of each laser by about 2 deg, driven by a sinusoidal

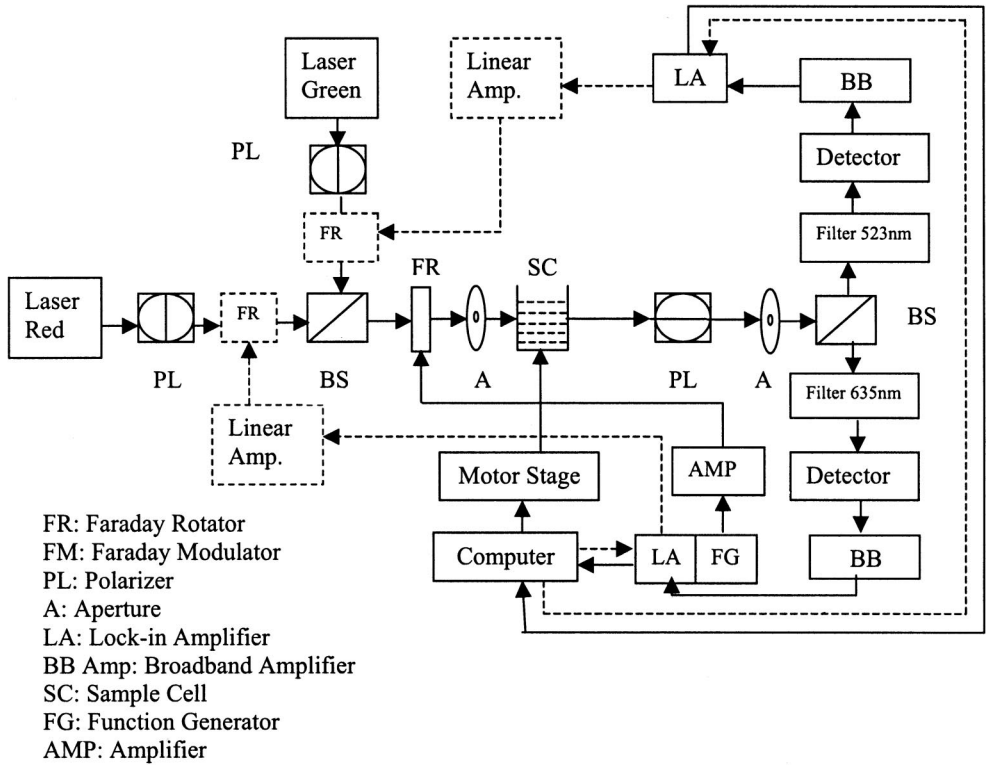

Fig. 1 Block diagram of the system with the closed-loop system distinguished from the open-loop system by the addition of the dashed line.

voltage source at a frequency of 1.09 kHz. An aperture was used to reduce the beam diameter below 1 mm. This modulated signal was then propagated through a rectangular sample cell (Starna Cells Incorporated, Atascadero California) constructed of birefringent material with a path length of 1 cm. The sample cell was filled with glucose-doped water of varying concentrations (0 to 600 mg/dl) and was mounted on a motorized stage (18143, Oriel Instruments, Stratford, Connecticut). This stage was controlled by a PC via RS232 to move the sample up and down. A visual basic program was used to control the speed and distance of the translation of the motor stage. The birefringence of the sample cell varies with the location on the test cell. By moving the sample cell up and down on the translation stage, a scenario similar to the birefringence changes of the cornea due to motion artifact was created. From the test cell, the light passed through another Glan-Thompson polarizer with a transmission axis oriented perpendicular to that of the initial polarizer. One last aperture was placed after the polarizer to prevent any scattered light from being directed toward the detectors. The combined beam was separated by a beamsplitter (Newport Incorporated) and transmitted to two detectors (Thorlabs Incorporated, Newton, New Jersey). Each detector had a filter window, 635 and 532 nm, respectively, placed before them to record only one of the two wavelengths. The output signals were amplified by a broadband amplifier (Melles Griot Electro-Optics, Boulder, Colorado). Two digital lock-in amplifiers, SR830 (DLIA, Stanford Research Systems Sunnyvale, California) and SR850 (Stanford Research Systems), were used to measure the relative amplitude of the signal present at the modulation frequency, allowing for precise measurement of the signal of interest at 1.09 kHz while rejecting other frequency components. The two output voltages from the lock-in amplifiers were sent via GPIB interface to a PC program written in Labview 5.1 (National Instruments, Austin, Texas).

The output intensity for each wavelength in the original, nonbirefringent open-loop system is governed by Eqs. (1) and (2), where θ_m is the depth of the Faraday modulation, ω_m is the modulation frequency, t is time, and ϕ_1 and ϕ_2 represent the total rotation from each wavelength. The rotations from each wavelength can be further broken down into ϕ_{g1} and ϕ_{g2}, which represent the rotation angle induced by the optical activity of glucose, as well as ϕ_{f1} and ϕ_{f2}, which are the rotations caused by the Faraday rotators. For the closed-loop system, the amplitude of the fundamental harmonic of the output (ω_m) for each wavelength is forced to zero using the two Faraday rotators after the initial polarizers and light sources. The voltage across the Faraday rotator necessary to do this is proportional to $2\phi_n\theta_m$, in which n is a subscript for either 1 or 2, depending on the wavelength.[18] Given that the modulation depth is kept constant, one can determine the rotation due to glucose from this feedback voltage.

$$I_1 \propto E_1^2 = \left(\phi_1^2 + \frac{\theta_m^2}{2}\right) + 2\phi_1\theta_m \sin(\omega_m t) - \frac{\theta_m^2}{2}\cos(2\omega_m t), \tag{1}$$

$$I_2 \propto E_2^2 = \left(\phi_2^2 + \frac{\theta_m^2}{2}\right) + 2\phi_2\theta_m \sin(\omega_m t) - \frac{\theta_m^2}{2}\cos(2\omega_m t), \tag{2}$$

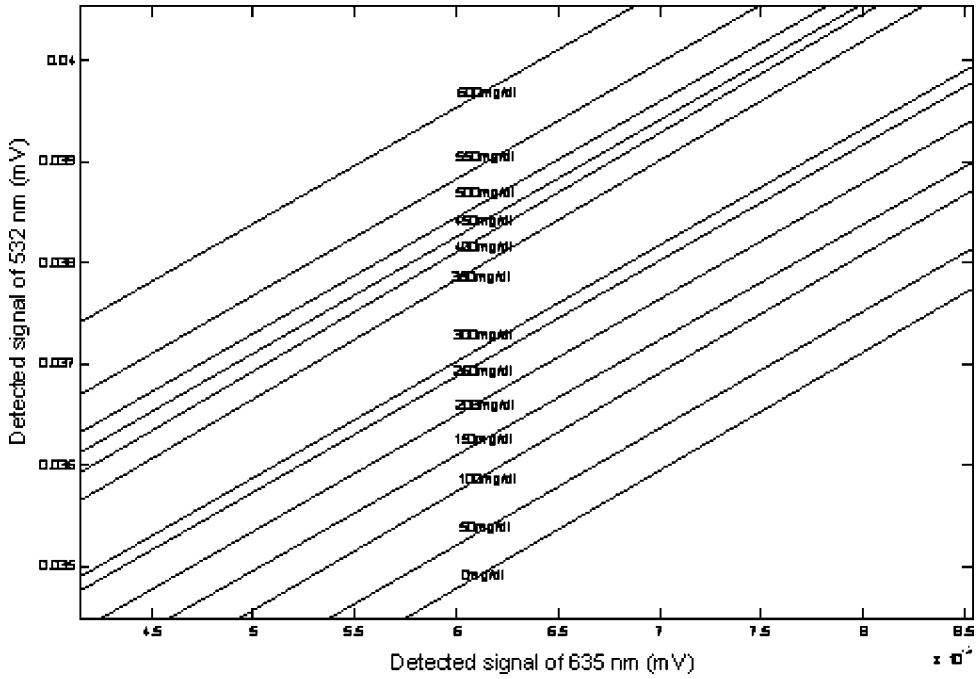

Fig. 2 Regression relationships between the two detected signals from 0 to 600 mg/dl in the presence of motion.

$$\phi_1 = \phi_{g1} - \phi_{f1}, \quad \phi_2 = \phi_{g2} - \phi_{f2}. \tag{3}$$

A series of experiments were performed to assess the relationship of the two detected wavelengths in the open-loop system as the birefringence of the sample cell was changed. To do this, the test cell was filled with water and the intensities from each detector were measured as the test cell was moved up and down. The cell was limited in its range of motion to insure that the birefringence did not exceed the rotation capabilities of the compensating Faraday rotators. The same procedure was performed for individual glucose samples instead of water between the concentration range of 0 to 600 mg/dl in 50-mg/dl increments. All sample solutions were introduced randomly into the system. For the glucose-doped water experiments, all samples were prepared from a 1000-mg/dl stock glucose solution. This solution was prepared by dissolving 1.0 g of D-glucose (EM Science) into 100-ml deionized water. Individual samples between the concentration range of 0 to 600 mg/dl in 50 mg/dl increments were prepared by diluting the stock solution. For each sample, the data collection was performed while randomly moving the sample cell to various locations. The voltages from the red and green wavelengths were plotted against each other as the sample cell was moved for each of the different glucose concentrations (Fig. 2).

A second set of experiments was conducted on the test cell itself to determine its fast axis and to relate the birefringence of the test cell to previous work conducted on the rabbit cornea.[21] The sample cell was placed on a rotating mount in the same location along the optical train with water solution in the cell. The sample cell was rotated from 0 to 180 deg in 10-deg increments at five different locations on the sample cell and the intensity was recorded (Fig. 3).

2.2 *Theoretical Description for Motion Artifact Compensation*

If the birefringence of the sensing site did not change, then the glucose concentration could be easily extracted from ϕ by simply measuring the feedback voltage that it takes to null the first harmonic (i.e., setting ϕ_f equal to ϕ_g). However, when motion artifact is introduced into the system, ϕ becomes a function of birefringence, glucose, and the feedback of the Faraday for a given wavelength: $\phi = \phi_g + \phi_b - \phi_f$, where ϕ_b is the rotation caused by the birefringence, making it impossible to distinguish rotation due to glucose from the rotation due to birefringence of the sample with just one wavelength, as Eq. (1) now has two unknowns (glucose and birefringence). To correct for this effect, a second wavelength has been introduced to provide an additional Eq. (2). Note from Fig. 2 that the individual birefringence at each wavelength does not need to be constant, but rather only that the relationship (i.e., slope) between the birefringence at the two wavelengths is proportional regardless of the glucose concentration. Secondly, it should be noted that the only assumption that was made in the original derivation was the small angle assumption, namely that as long as $\theta_m \sin(\omega_m t) + \phi$ is small, then the $\sin[\theta_m \sin(\omega_m t) + \phi] = \theta_m \sin(\omega_m t) + \phi$.[26] This is true since the birefringence and glucose rotation in the test cell and in the eye are less than the modulation depth, and the modulation depth is less than 2 deg. Further, for the closed loop system, the voltage applied to the feedback Faraday rotators is such that we ensure that $\phi = 0$.

Once it was determined that a relationship could be developed between the effects of the motion artifact on the intensity difference of the measurement at the two detectors using two equations, a series of closed-loop experiments were per-

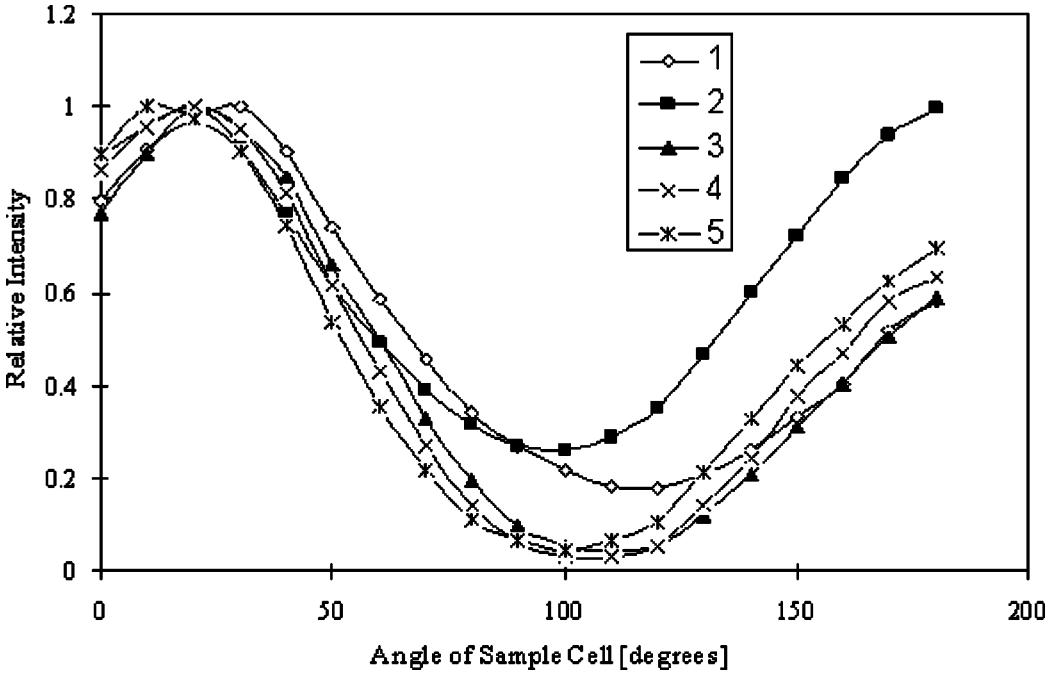

Fig. 3 Intensity change of the detected signal as a function of the angle of rotation of the test cell recorded at five different locations on the test cell. Note that the maximum and hence fast axis appears between 10 and 30 deg depending on the location of the beam on the test cell.

formed to compensate for the effects of motion artifact on measuring the glucose concentration. The dual digital closed-loop controlled polarimeter is identical to the open-loop system with the exception of the addition of the feedback loops and two Faraday rotators (Deltronic Crystal Incorporated, Dover, New Jersey), as shown with dashed lines in Fig. 1. The two output voltages from the detectors were sent via a GPIB interface to a PC as inputs into the digital control algorithm, which was written in Labview 5.1 (National Instruments, Austin, Texas). Using this control algorithm program, the outputs from the D/A board of the two lock-in amplifiers were sent to two line drivers, which provided the necessary current to drive each Faraday compensator. The two linear drivers were employed because the maximum current output of each lock-in amplifier is only 10 mA, which was insufficient to drive the Faraday compensation components. As mentioned, the function of the rotators was to compensate for rotation of the polarization vector due to both the glucose sample and the induced birefringence signal changes from motion artifact by forcing the amplitude of the first harmonic to zero.

A series of experiments was performed to determine the relationship of the two detected wavelengths in the closed-loop system, as glucose concentrations were varied during the presence of motion artifact. From the open-loop experiments, it was shown that the change in glucose concentration did not appreciably affect the slope of the linear fit of the red versus green light sources with birefringence; however, it did change the *y* intercept of the fit. This is discussed in greater detail in Sec. 3.

For the closed-loop experiments, an output from each of the detectors at the two wavelengths was taken. Using the slope measured in the open-loop system with these two values, we calculated the *y* intercept. This was done for glucose concentrations from 0 to 600 mg/dl in increments of 50. From this data, a linear fit was applied to describe the glucose concentration measured as a function of the *y* intercept of the red and green light relationship. Multiple measurements were then taken while varying both the glucose concentration and the motion of the sample cell to verify the validity of the model.

3 Results and Discussion

3.1 *Characterization of the Test Cell Birefringence*

The open-loop system was used with varying concentrations to show the effects of both the birefringence and the glucose concentration changes on the detected voltage. The system was calibrated such that the output and input polarizers were cross-polarized when there was no glucose in the test cell while the beam was directed at some arbitrary location on the test cell. The presence of glucose in the test cell caused a rotation in the plane of polarized light, and this rotation shows up in the first harmonic component of the output signal, as shown in Eqs. (1) and (2). Any deviation from this location or any addition of glucose would produce a different intensity and hence a different voltage in both detectors. For a given concentration of glucose, a line was fit describing the linear relationship that exists between the red and green feedback voltages as the birefringence of the sample cell was changed through moving the translation stage up and down (Fig. 2). The direction of the applied motion of the test cell is not particularly important as long as changes in birefringence occur in translation. From the figure, it can be observed that the slope of this fitted line remained relatively constant, while the intercept varied with the glucose concentration present in the test cell. In fact, the mean of the slope across the 13 concentrations was 1.158 and the standard deviation of the slope was 0.013, justifying the assumption that changes in the slope are

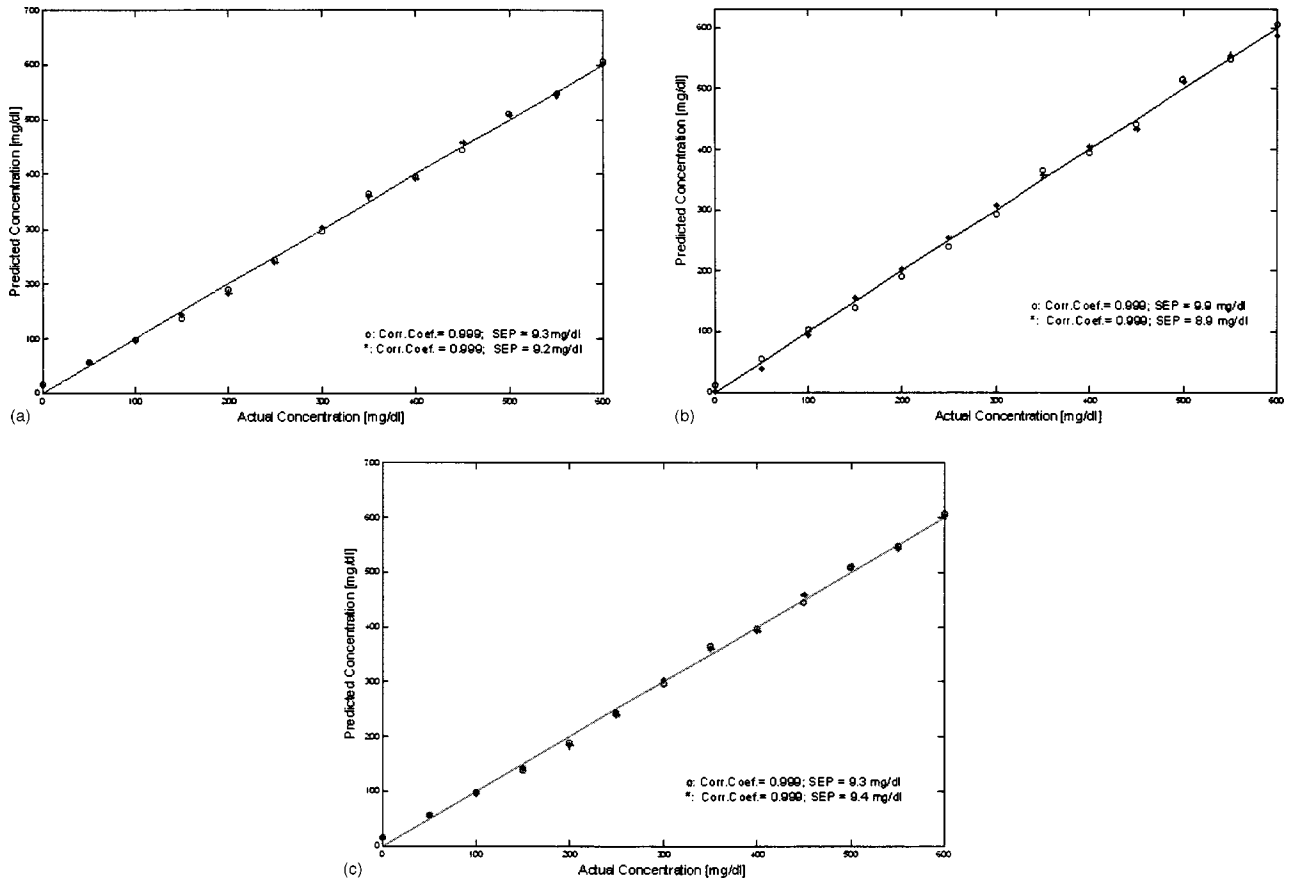

Fig. 4 Actual versus predicted glucose concentration for glucose-doped water for sample experiments without motion, where (a) includes two separate experiments run at 635 nm using a single closed-loop system (○: experiment 1, ∗: experiment 2); (b) two separate experiments run at 523 nm using a single closed-loop system (○: experiment 1, ∗: experiment 2); and (c) two experiments run using the dual-wavelength (635 and 523 nm) closed-loop system (○: experiment 1, ∗: experiment 2).

negligible. This assumption is necessary for the development of the calibration and prediction method used for the closed-loop system. Determining the effects of both birefringence and glucose concentration changes for the open-loop system was performed to develop this algorithm, as well as provided a range of voltages that would need to be fed back into the Faraday compensators to force the fundamental frequency component of the output signal back to zero. However, our group has shown that the open-loop system is not as stable as the closed-loop system and hence, due to noise and drift, the lines are not equidistant. The voltage changes in the closed-loop system are, however, linear and equidistant with concentration, as shown for the case of non-moving birefringence in Fig. 4.

From the curves in Fig. 3, one can see that as the test cell was rotated from 0 to 180 deg at a given vertical location, the fast axis of the test cell varied from 10 to 30 deg from horizontal, as determined by the peak value on the plot (i.e., value at which the fast axis is aligned with the polarizer). Thus, given that the direction of the applied motion of the test cell was vertical and not along the fast or slow axis, there was a significant change in birefringence produced. In fact, the changes in birefringence were actually larger than those reported to occur in the rabbit cornea.[21] Therefore, since the system can compensate for the larger birefringence changes of the moving test cell, it is believed that it should be able to compensate for the lesser birefringence changes of the cornea.

3.2 *System Performance with and without Motion Artifact*

To assess the performance of the motion compensation algorithm, the data were compared with a previously developed single-wavelength close-looped system[17,27] for two different cases: motionless and with motion. The motionless system was calibrated and then the glucose concentrations were extracted through linear regression. The experiments were repeated twice and the results from both experiments are shown in Fig. 4. In each experiment, two datasets were recorded for the two wavelengths, 635 and 523 nm, for varying glucose samples (0 to 600 mg/dl), respectively. The signal from the test cell filled with water (0 mg/dl) was used as a background signal and was subtracted from all other signal values. Least-squares linear regression (LSLR) was then used to calibrate the model. The predicted versus actual glucose concentrations were plotted for the single wavelength system for both the red and green light source, as shown in Figs. 4(a) and 4(b), respectively. The dual-wavelength closed-loop system for a motionless sample was also plotted for comparison with the two single wavelength methods in Fig. 4(c). One can see that a

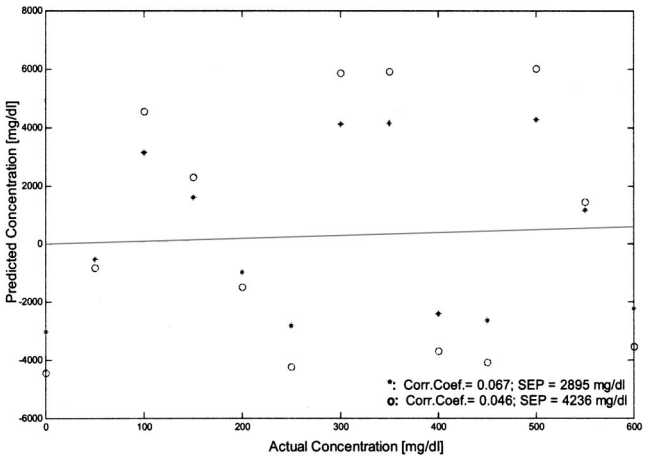

Fig. 5 Actual versus predicted glucose concentration for glucose-doped water coupled with varying birefringence signal using the single wavelength closed-loop system for each wavelength (*: 635-nm wavelength, ○: 523-nm wavelength). Note that using either single-wavelength system does not allow for any reasonable predictive capability with motion artifact.

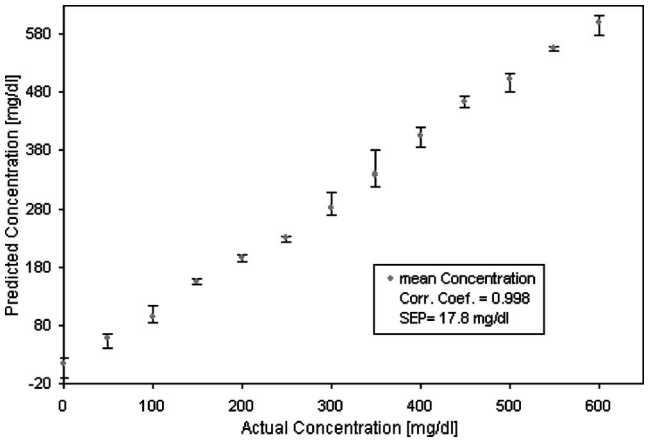

Fig. 6 Mean predicted concentrations with error bars for three repetitions using the dual-wavelength (635 and 523 nm) closed-loop system in the presence of motion artifact. Note that by using two wavelengths, the system is now capable of predicting glucose in the presence of motion.

high degree of linearity exists for all three cases, since each correlation coefficient exceeds 0.999 and the standard error of prediction (SEP) is less than 10 mg/dl. This corresponds to a system accuracy of less than 0.4 millideg, which is comparable to results shown previously by Cameron and Coté.[18,26]

The same procedure was conducted again while introducing motion into the system. As shown in Fig. 5, the predicted glucose concentrations cannot be obtained using a single closed-loop system at all, since the signal could not distinguish the changes due to glucose from the changes due to varying birefringence in the sample. Thus, the single wavelength model breaks down completely in the presence of birefringence changes due to motion. The dual-wavelength system was used and three datasets were taken varying the glucose concentration from 0 to 600 mg/dl to verify the repeatability of our results. The data showed a high degree of linearity with a correlation coefficient of 0.998 and a standard error of prediction of less than 17.8 mg/dl, as depicted in Fig. 6. No outliers were present in any of the datasets. The SEP is greater than the motionless system and this could be attributed, in part, to the algorithm and method of calibration. The motionless system was calibrated while fixing the birefringent test cell at a specific location. Therefore, the calibration corresponded specifically to measurements made at that exact location. The linear fit from that calibration describes only the effects of glucose changes on the voltage fed back to the compensator. However, when motion is induced in the system, we essentially move from the realm of one regression approximation describing the system to two: an approximation fitting the red versus green light in the presence of motion, and an approximation fitting the intercept calculated versus the glucose concentration. As in any linear regression fit, there is an associated error with that fit.

4 Conclusion

With diabetes on the rise, a reliable noninvasive glucose sensor has yet to be developed to meet the need for glucose regulation. While polarimetric approaches have achieved very promising results *in vitro*, no one has yet to develop a device using such an approach that could be used *in vivo*, in part, because of the noise (i.e., birefringence) induced through motion artifact of the cornea. This work presents the next step toward the development of a noninvasive glucose sensor, which may eventually be capable of detecting glucose levels through the aqueous humor of the eye by compensating for birefringence changes due to motion artifact. It has been successfully shown that the glucose concentration could be measured *in vitro* when motion artifact is present through the use of a dual-wavelength closed-loop system, something that was not possible with the previous single-wavelength methods developed. Since the birefringence changes of the test cell were compensated for, it is believed that the smaller changes that occur in the eye could also be compensated. Future research will focus on improving the accuracy of the system and the introduction of rabbit eyes into the system, which are likely to provide a more complex birefringent medium.

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