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Development of a Discrete Spectrometric NIR Reflectance Glucometer ⋆

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Abstract:
Currently, there are no continuous, non-invasive blood glucose monitors. With over 366 million people worldwide expected to be diagnosed as diabetic by 2030, an alternative to the current invasive methods is critical. This paper investigates the use of a discrete spectometric, NIR reflectance glucometer to detect a change in glucose concentration in solution. At each wavelength, an LED is used to emit light, and a reverse-biased LED detects light using wavelengths 660 nm, 850 nm, 940 nm, 1450 nm, 1550 nm, 1650 nm. The discharge time of a reverse-biased LED is proportional to the temporal integral of the detected light intensity. The sensor's response to changing glucose concentration was tested in both water and porcine blood. Glucose concentration was increased by $0.5\,\mathrm{mmol\,l^{-1}}$ and compared with a finger stick glucometer. Each wavelength exhibited an expected change in adsorption given only an increase in glucose concentration. The inverted exponential increase in absorption is explained by Beer Lambert's law. Wavelengths 660 nm, 850 nm and 1450 nm showed minimal change to absorption, while 940 nm, 1550 nm and 1650 nm showed considerable change in absorption. The 1550 nm LED gave the greatest increase in absorption with a 7% rise over $4.3\,\mathrm{mmol\,l^{-1}}$ to $20.6\,\mathrm{mmol\,l^{-1}}$. Ratios of absorption responses ($R_{1550/1650}, R_{1550/1450}$ and $R_{940/850}$) each gave proportional increases in absorption with increasing glucose concentrations.

Keywords: Discrete NIR spectrometry, non-invasive, glucose sensor, LED-LED detection, Beer Lambert's Law

1. INTRODUCTION

Diabetes is a metabolic disorder resulting from the inability of the body to regulate the level of glucose in the blood. The prevalence of diabetes worldwide is ever increasing, with over 366 million people expected to be diagnosed by 2030 (Wild et al., 2004). Currently, individuals with diabetes need to use invasive methods, such as finger pricks, to monitor blood glucose concentration. The discomfort and possible complications caused by these methods lead to reduced frequency of monitoring by patients, reducing the effectiveness of diabetes prevention (Chowdhury et al., 2013). The majority of continuous glucose monitors (CGMs) require subcutaneous insertion of a filament for electro-chemical measurement of local interstitial glucose concentrations and require multiple calibrations each day. They are complex and have significant drift and dynamics (Zhou et al., 2018)

Futures in healthcare rely as much on enabling patient self-management as on new innovative technologies. A non-invasive glucose sensing method would facilitate more patient monitoring, reducing complications and improving quality of life.

Continuous non-invasive glucose sensing has been a topic of research for over 20 years (Liu et al., 2005). Techniques such as near-infrared (NIR) spectroscopy have been studied, but as yet, there have been no commercialized products providing a solution (Poddar et al., 2008). Products using NIR measurements have reported good correlation with blood glucose, but too many of the estimations were not clinically acceptable (Poddar et al., 2008; Smith, 2017; Nybacka, 2016). Different proteins and molecules within blood absorb different wavelengths of light to differing extents, allowing estimation of concentration of each compound (Delbeck et al., 2019).

The main difficulty in NIR detection is due to the weak absorption characteristics of glucose in a spectral region dominated by absorption from water, haemoglobin and lipids (Amerov et al., 2004). Conventional spectroscopy has been investigated through the wavelength range of 500 nm to 2000 nm with three main bands of interest: 2000 nm-2500 nm (combination overtone), 1400 nm-2000 nm(first overtone) and 750 nm-1400 nm (second overtone) (Yadav et al., 2015). Yamakoshi and Yamakoshi (2006) developed a pulse glucometer using spectrometry values from 900 nm to 1700 nm. Through PLS methods, they gained accurate results from glucose measurent, but required further work on their instrumentation to take the sensor out of the laboratory (Yamakoshi et al., 2009).

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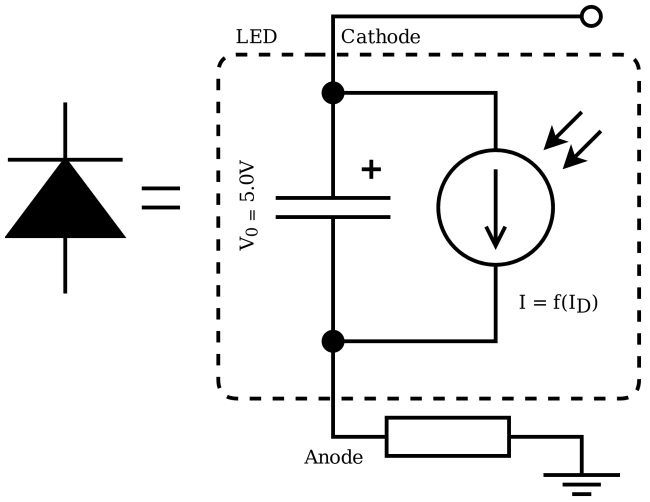

Fig. 1. Equivalent circuit diagram for the sensing diode within LED-LED detection.

1.1 LED-LED Light Detection

Conventional methods of light detection use LEDs to emit light and photodiodes to detect returning light. The current is then amplified and converted to a voltage, and sampled by a microprocessor through an analog to digital converter (ADC) (Kennedy, 2015). The sensing methodology used here has a forward-biased LED to emit, and a reverse-biased LED detect light. Rather than taking instantaneous measurements with an ADC, the reverse-biased LED uses its inherant capacitance to integrate the incoming light intensity over the sensing period (Stojanovic and Karadaglic, 2013; Lau et al., 2006). Thus, the output from the sensor represents the inverse of the detected light intensity.

Lau et al. (2006) demonstrates that the lower photocurrent producing efficiency of LEDs is an advantage as LED detection provides approximately an order of magnitude greater response to light intensity changes compared to photodiodes. The spectral detection region of the LEDs is also of slightly lower wavelength of the emission spectrum, creating a narrower detection range(O'Toole and Diamond, 2008).

Recently, the LED-LED sensing method has been employed with success in absorbance measurements for determining the concentration of solutions due to their spectrally sensitive absorption spectrum and their ease of implementation (Shin et al., 2016). Figure 1 shows the basic circuit diagram used in this study. Each wavelength to be detected had a pair of LEDs, one emitting and the other detecting the reflected light.

1.2 Beer-Lambert's Law

Beer Lambert's law describes the exponential attenuation of light travelling through a substance. The attenuation of light across a path length (d) is from the concentration of the solute (c) and how much light it absorbs (ϵ) (Mendelson, 1992), yielding:

$$I_D = I_E e^{\epsilon c d} \tag{1}$$

Where:

I_D: Detected light intensity
I_E: Emitted light intensity
ϵ: Absorption coefficients
c: Concentration of molecules
d: Optical path length

Blood consists of many constituents at varying concentrations and absorption characteristics, meaning absorption in Beer Lambert's law is the sum of all components:

$$A(\lambda) = \sum \epsilon_i(\lambda) c_i \tag{2}$$

$A(\lambda)$ represents the total absorbance through blood at a particular wavelength (λ). By using different absorption characteristics at varying wavelengths, the concentrations of each constituent can be calculated (Zhang et al., 2016).

1.3 Detection Wavelength

To take advantage of the light absorption bands of glucose at 750 nm-1400 nm, LEDs of wavelength 660 nm, 850 nm and 940 nm were used. Haxha et al used a 940 nm LED to monitor changes in glucose level (Haxha and Jhoja, 2016). In this region, haemoglobin is the dominant absorber, so any changes in blood oxygen level will skew the results (Bashkatov et al., 2005). Thus, an 850 nm LED was chosen because the isosbestic point of oxyhaemoglobin and deoxyhaemoglobin is at 800 nm, within the lower detection spectrum (Chan et al., 2013). At the isosbestic point, the absorption by haemoglobin is consistent, regardless of the oxygen saturation. This wavelength was used to account for the change in absorption by haemoglobin when assessing the change in glucose at the same wavelength.

In the second absorption band, glucose has a dominant absorption peak at 1550 nm as well as at 1650 nm. Figure 2 shows the approximate absorption by glucose, water, lipids and albumin from 500 nm to 2000 nm. At 1450 nm absorption is dominated by water, meaning variations in concentrations of glucose and other blood constituents cause a minimal change in absorption. At 1550 nm and 1650 nm, glucose is the dominant absorber, so a rise in glucose level is expected to increase absorption at these wavelengths. LEDs at 1550 nm and 1650 nm were chosen as the absorption of lipids vary greatly, potentially allowing extraction of the lipid concentration, which is also clinically useful.

When calculating the change in absorption, the displacement of water by glucose must be included (Amerov et al., 2004). The relatively strong absorption properties of water in the NIR spectrum causes significant changes in total absorbance when glucose is added. Upon dissolution of glucose, water molecules are displaced from the optical path length. At wavelengths where water dominates absorption (1450 nm), the total absorbance is expected to drop with increasing glucose. At 1550 nm and 1650 nm, glucose is the dominant absorber of light, so even with displacement of water, the absorbance is expected to increase with glucose concentration.

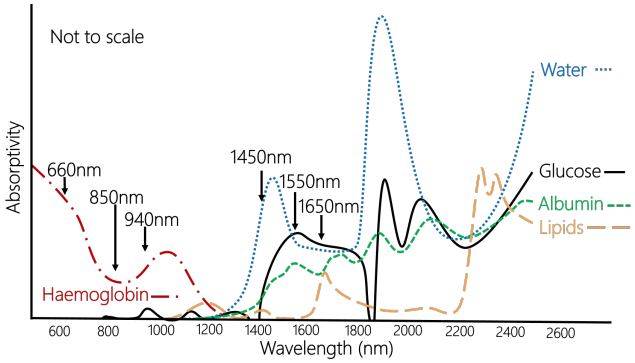

Fig. 2. Absorption spectrum of the major light absorbers in the NIR range, not to scale. Derived from (Yadav et al., 2015; Amerov et al., 2004)

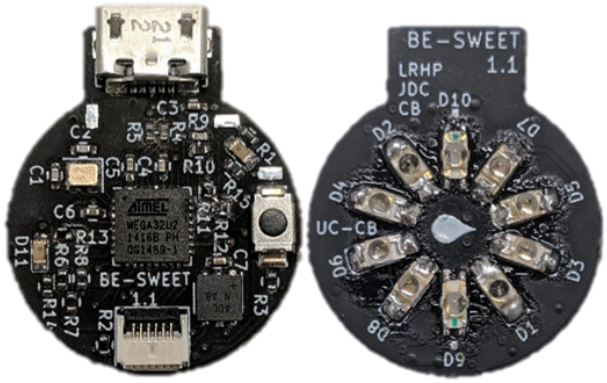

Fig. 3. Diagram of the developed glucose sensor.

2. METHODS

2.1 Sensor Design

To measure absorption of light at the required wavelengths, a sensor with 12 LEDs was built. Each of the six wavelengths have an emitter and detector LED. The sensor was designed in a rosette shape to ensure the path of each wavelength travelled through the same space. Figure 3 shows the sensor. The 660 nm and 940 nm LEDs are contained in the same package to minimise the footprint. An ATMEGA32U2 running at 16 MHz was used to power the emitting LED and to time the discharge of the reverse-biased LED. The LEDs used were XZM2MRTNI55W-8 (660,940 nm), 15412085A3060 (850 nm), MTSM5014-843-IR (1450 nm), MTSM5015-843-IR (1550 nm) and MTSM5016-843-IR (1650 nm).

2.2 Beer-Lambert's Law

While the intention of the sensor is to detect glucose in pulsatile human blood, testing was first done in vitro to verify a response to changing glucose. The 1450 nm and 1550 nm wavelengths would be the focus as glucose has no absorption at 1450 nm and dominant absorption at 1550 nm. Compared to 1450 nm, the reflected light intensity at 1550 nm should increase with the addition of glucose. Thus, the ratio of 1450 nm and 1550 nm should represent a Beer-Lambert response curve with increasing glucose concentration. 1650 nm is also expected to increase with glucose, but not as much as 1550 nm.

2.3 Water Testing

The first test conducted was with glucose added to deionised water. To minimize the effect of outside variables during testing, 40 litres of water was kept at body temperature inside an insulated container. Glucose was added in increments of 3.60 g to increase the concentration by 0.5 mmol l^{-1} at each step. The concentration was increased from 0 mmol l^{-1} up to 20 mmol l^{-1}. The target physiological range of blood glucose in a person is between 4 mmol l^{-1} and 8 mmol l^{-1}. While blood glucose levels may climb above 20 mmol l^{-1} in hyperglycemic patients. Thus, measuring a range from 0-20 mmol l^{-1} provides a physiologically relevant range to show a response to glucose.

A sensor was placed in a resealable bag 200 mm below the surface of the water, minimising the effect of light reflecting off the surface of the water. Upon each addition of glucose, the water was stirred for 20 seconds and allowed to come to a rest. Data were recorded over 30 seconds and the average over this time was used for calculations. The test was conducted in a dark room with no light source other than the sensor.

Table 1. Experimental procedure

Test	Volume l	G_{start} mmol l^{-1}	G_{step} mmol l^{-1}	G_{end} mmol l^{-1}
Water	40.20	0	0.50	20.0
Blood 1	1.10	4.9	0.50	16.8
Blood 2	0.94	4.3	0.50	20.6

2.4 Pig Blood Testing

The next step in testing the sensor's response to glucose was to add glucose to blood under the same conditions as the test in water. Two litres of pigs blood were used for testing. To reduce the effects of clotting, 1.8 g of EDTA for 1 l of pig blood was added as an anticoagulant. The fresh pig blood was kept in an insulated container between 0-4 °C during transport and was raised to room temperature for testing. An ACCU-CHEK Performa Glucometer was used to measure the blood glucose content throughout the test for sensor calibration. Table 1 gives the test conditions. The sensor was mounted underneath the flask, in contact with the glass.

The first test was done within 3 hours of obtaining the fresh blood. Figure 4 shows the setup for both tests. The first test had 1.1 l of blood and an initial blood glucose level of 4.9 mmol l^{-1}. For each measurement, 0.09 g of glucose powder was stirred into the blood for 30 seconds and allowed to settle. One minute of data were recorded and the average reading taken. The second test was conducted two days after the first to further reduce the blood glucose content. The blood stayed between 2-8 °C during waiting period and was brought to room temperature for testing.

3. RESULTS

As the sensor integrates reflected light intensity during a measurement, an increase in absorption is directly proportional to an increase in discharge time of the receiving

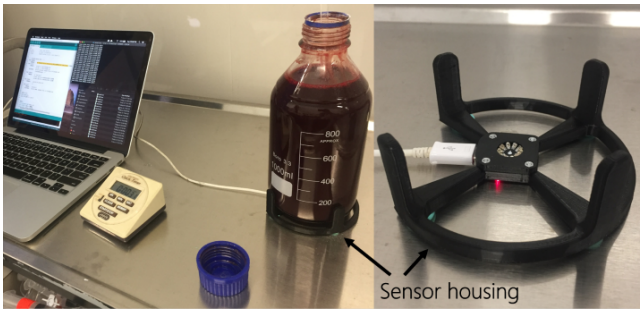

Fig. 4. Experimental setup for pig blood testing.

LED. This inverse relation is in contrast to conventional photodiode measurement, where an increase in absorption reduces the detected voltage. Figures 5 and 6 show the time taken for each LED to discharge. A higher discharge time results from higher absorption by light travelling through the solution, and therefore higher concentration. The value α is used to represent the proportionality between discharge time and light intensity.

4. DISCUSSION

4.1 Water Testing

Testing showed the predicted relationship between glucose levels and light absorption. An increase in absorption at 940 nm, 1550 nm and 1650 nm was recorded, while at 660 nm and 850 nm, there was a decrease in absorption. Figure 5 plots the discharge time of each wavelength at increasing glucose levels. At 1450 nm and 850 nm, the data were very noisy with slight upwards and downwards trends respectively over the range of glucose. At 660 nm there was a slight decrease and at 940 nm, an increase. This increase is due to the slight absorption peak at 940 nm.

4.2 Pig Blood Testing

Testing in blood gave different results to just water. Figure 6 shows that at 1450 nm and 1650 nm there was decreased absorption with increasing glucose. This difference is represented in the change in absorption at 850 nm, as this wavelength represents the total haemoglobin count. Absorption at 1450 nm, 660 nm, 940 nm and 1650 nm were consistent between tests.

Table 2. Relative Reflection Intensity (α/I_D) readings for an empty flask

$\lambda(nm)$	660	860	940	1450	1550	1650
α/I_D	0.72e5	0.40e5	0.21e5	2.63e5	2.17e5	0.54e5

As the sensor was placed in a resealable plastic bag, there was a slight difference in absorption compared to glass. Testing was done with an empty flask and the baseline recording is shown in Table 2. All wavelengths except for 1450 nm and 660 nm had lower responses without blood. As the testing was done under ambient lighting, the increase in 660 nm and 1450 nm is due to room lighting and sunlight.

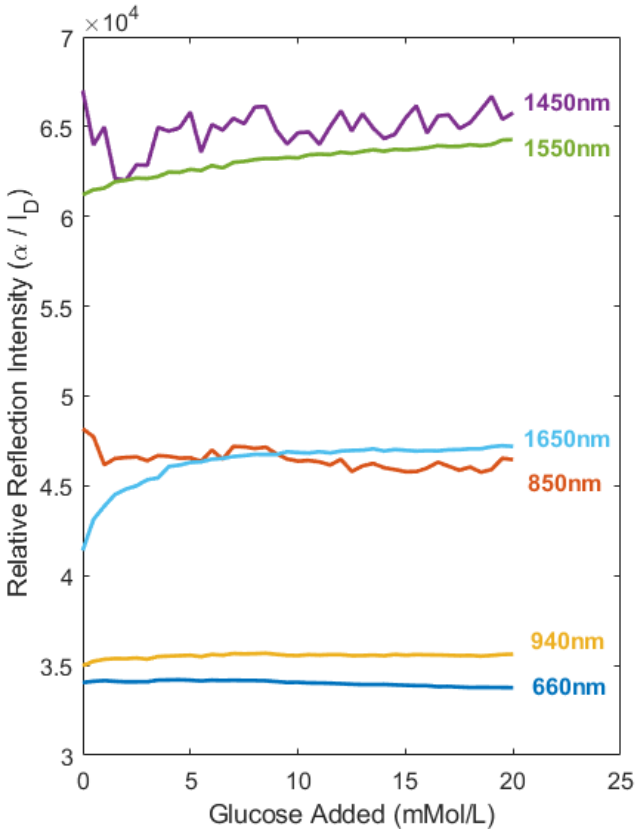

Fig. 5. Change in reflected light intensity in water with an increase in glucose concentration.

4.3 Wavelength Ratios

The three main wavelength relationships of interest were between 1450 nm and 1550 nm, 1550 nm and 1560 nm and 940 nm and 850 nm. At 1450 nm and 1550 nm is the greatest difference between glucose absorbance coefficients and at 940 nm and 850 nm is the isobestic point of haemoglobin and a slight absorbance by glucose. At 1650 nm and 1550 nm, there is a difference in absorption by albumin and lipids as well as glucose. In Figure 6, the noise variation in readings are present in all wavelengths. Taking the ratio of each wavelength pair removes the constant noise component during each measurement such as ambient lighting.

Figure 7 shows the relationship to glucose. For better comparison, each response is normalised and centred at zero. The absorbance at 1650 nm has the largest decrease, so the ratio of 1550 nm to 1650 nm was also calculated ($R_{1550/1650}$). This ratio gives the greatest response to the normalised data, with $R_{1550/1450}$ second greatest. $R_{940/850}$ gives the lowest response to increasing glucose.

4.4 Beer Lambert's Law

The response of each ratio in Figure 7 follows the inverted Beer Lambert's law. At low glucose concentrations of glucose, reflected light intensity exponentially decreases. As the only factor in Equation 1 that changes is the concentration, the observed changes in light absorption can be attributed solely to the addition of glucose. At wavelengths with no glucose absorption peaks (660 nm,

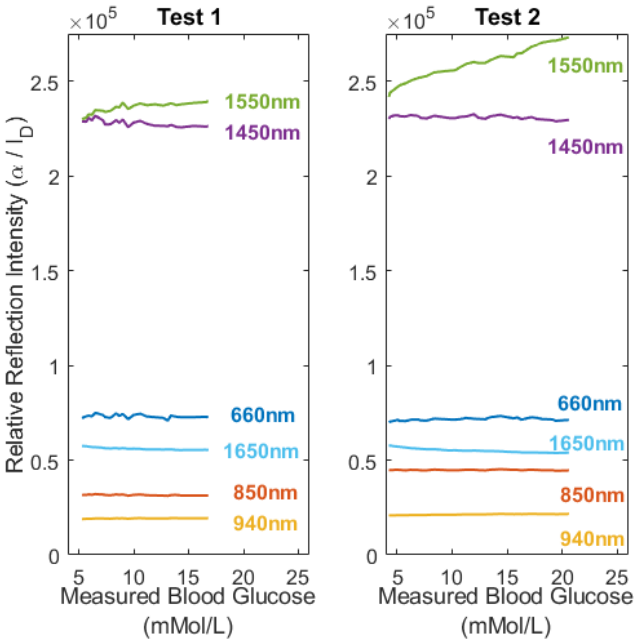

Fig. 6. Change in reflected light intensity in pigs blood with an increase in glucose concentration.

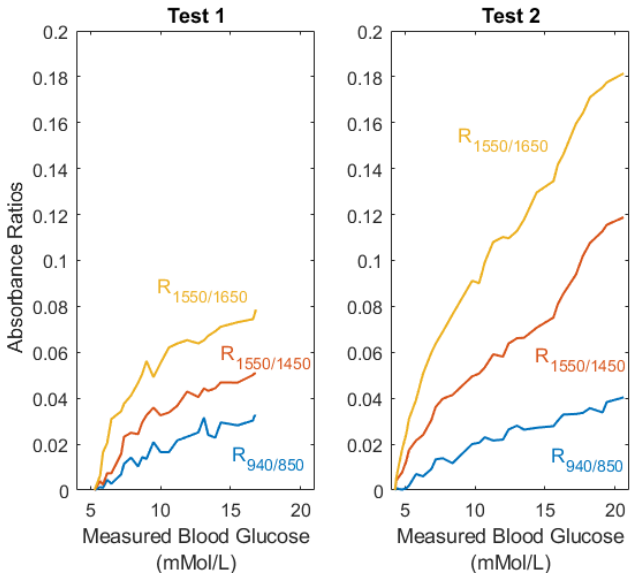

Fig. 7. Normalised and centred absorbance ratios of $R_{1550/1650}$, $R_{1550/1450}$ and $R_{940/850}$ in pigs blood over an increasing glucose level.

850 nm, 1450 nm), the reflected light intensity has minimal change, providing further validation.

The development of a non-invasive blood glucose monitor has been the focus of intense interest for several decades. Among possible approaches, NIR spectroscopy has shown much promise. However, definitive results have remained elusive. This paper investigated the LEDs as light detectors at selected spectral wavelengths, creating a discrete spectrometer. The designed glucose sensor was tested in water and pigs blood.

In water, the change in absorbance was solely due to the increase in glucose concentration and the displacement of water molecules. At 1650 nm and 1550 nm, the signal gave the greatest rise in absorption. The response at 1450 nm was expected to reduce due to the displacement of water. However, it remained noisy, slightly increasing with glucose level. This high variation is likely due to the minimal effect of water displacement due to glucose. The high absorption of light by water at 1450 nm means minimal light entering the solution returned to the sensor, so the majority of the light returned will be reflected off the surface of the water.

The intensity of reflected light was much higher for 660 nm and 940 nm as water and glucose absorb minimally at these wavelengths. Absorption of 660 nm and 940 nm light in the pig blood were much higher due to the presence of haemoglobin. It is also expected the glass of the flask reduced the amount of reflected light reaching the sensor as the LED discharge times for an empty flask were very similar to those with blood present. The exact absorption by the glass is not further explored as the purpose of this paper is to measure a change in absorption with increasing glucose concentrations, so a constant effect from glass does not affect the conclusions.

Testing in pig blood yielded different absorption responses to testing in water. The presence of haemoglobin reduced the intensity of reflected light in the first absorption band and the presence of other lipids and albumin in the blood gave an opposite response than that of water at 1650 nm. At 1650 nm, glucose, water, albumin and lipids have similar absorption coefficients. As glucose displaces the other molecules from the optical path, the corresponding increase in absorption by glucose does not account for the reduced absorption by displacement. Thus, the absorption in blood at 1650 nm decreases with increasing glucose levels. In contrast, the increased absorption from glucose at 1550 nm is more than the reduction in absorption from displacement, so the overall absorption at 1550 nm increases with increasing glucose concentration.

Ratios of absorbance at various wavelengths were calculated to test the response to glucose. Figure 7 shows that the three ratios investigated all follow Beer Lambert's law for light absorption. The wavelength 1450 nm was chosen for testing as water is the primary absorber. By comparing the increasing absorbance at 1550 nm to the decreasing absorption at 1450 nm, the effect of glucose concentration can be seen. Water has minimal absorption in the first absorption band, so the ratio between 940 nm and 850 nm shows the relationship between glucose and haemoglobin. At the isobestic point of haemoglobin (850 nm) the decrease in absorption is due to the displacement of haemoglobin and at 940 nm, the increase in absorption is from the increased absorption of glucose. This behaviour can also be seen at 660 nm as absorbance decreases with increasing glucose.

The ratio of 1650 nm to 1550 nm gave the largest change with increasing glucose in blood. Other than 1650 nm, all other wavelength absorptions were as expected. Moving forward, testing will be done in vivo to determine the absorption response. The sensor will be designed for use as a pulse glucometer, using the same principles as pulse oximetry. In vivo testing will isolate the response in the blood from the pulsatile signal, similar to work by Yamakoshi et al. (2009).

5. CONCLUSION

A sensor was developed to measure the light absorption by glucose in the NIR spectrum. Using discrete spectroscopy at 660 nm, 850 nm, 940 nm, 1450 nm, 1550 nm and 1650 nm, varied responses were found through testing in both water and pig blood. The results obtained can be explained by Beer Lambert's law as the only factor affecting absorbance is the change in glucose concentration. The glucose concentrations tested were within the expected physiological range of blood glucose concentrations.

Using LED-LED detection methods, the sensor integrates the reflected light intensity of the six wavelengths. The ratio of $R_{940/850}$ increases with glucose due to the absorption peak at 940 nm and minimal change at the isobestic point of haemoglobin (850 nm). In the first overtone, $R_{1550/1450}$ gives an increase in absorption because glucose is the dominant absorber at 1550 nm, while water is the only absorber at 1450 nm. The final ratio calculated was $R_{1550/1650}$ which gave the greatest rise due to the displacement of other absorbing molecules (lipids, albumin).

Future work on the sensor will involve an increase in output light intensity to increase the amount of light reaching the sensor. Non-invasive testing on pulsatile human blood will be completed and compared to the absorption in water and pig blood.

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