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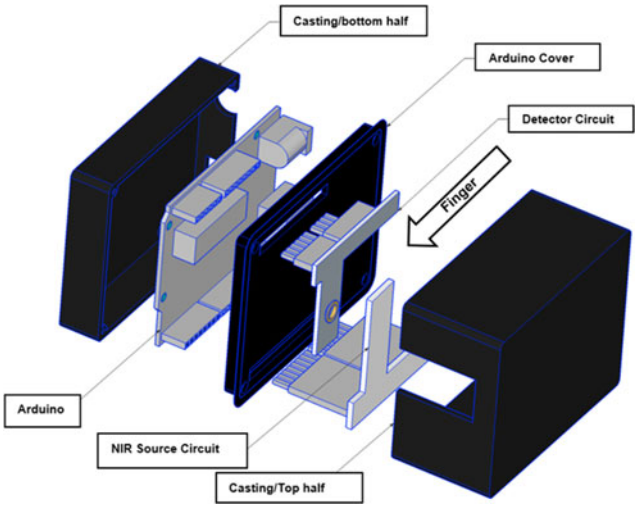

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Optical Based Noninvasive Glucose Monitoring Sensor Prototype

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Abstract: Diabetes mellitus claims millions of lives every year. It affects the body in various ways by leading to many serious illnesses and premature mortality. Heart and kidney diseases, which are caused by diabetes, are increasing at an alarming rate. In this paper, we report a study of a noninvasive measurement technique to determine the glucose levels in the human body. Current existing methods to quantify the glucose level in the blood are predominantly invasive that involve taking the blood samples using finger pricking. In this paper, we report a spectroscopy-based noninvasive glucose monitoring system to measure glucose concentration. Near-infrared transmission spectroscopy is used and *in vitro* experiments are conducted, as well as *in vivo*. Our experimental study confirms a correlation between the sensor output voltage and glucose concentration levels. We report a low-cost prototype of spectroscopy-based noninvasive glucose monitoring system that demonstrates promising results *in vitro* and establishes a relationship between the optical signals and the changing levels of blood–glucose concentration.

Index Terms: Remote sensing and sensor, optical sensing and sensors, optical spectroscopy.

1. Introduction

Diabetes is becoming a serious and alarming illness. There are 415 million adults that have diabetes, and this number is expected to rise to 642 million by year 2040 [1]. According to [2], Diabetes is the most probable cause of one in ten deaths among people 20-59 years old. In the U.K., three people get diagnosed with Diabetes every ten minutes, and the most disturbing fact is that about 500 000 people have diabetes and are still undiagnosed [2].

Diabetes is also known as Diabetes Mellitus (DM). It is a medical condition which occurs when the body is unable to regulate blood sugar levels. There are two types of Diabetes: type-1 and type-2. Diabetes type-1 is a condition when the body is unable to produce any insulin which is used to regulate the blood sugar levels. Insulin is an essential for human body to convert glucose into energy [2]. Diabetes type-2 occurs when the body is not making enough insulin or is making insulin which is repelled by the body [3]. This usually occurs in people 40+ years of age. Diabetes type-2 is spreading worldwide more rapidly than type-1 [1]–[3].

Diabetes affects the body in various ways. It leads to many serious illnesses such as cardiovascular diseases, eye problems, kidney problems, brain dysfunction, and premature mortality. It has also become one of the common causes of limb amputations which lead to disability [3]. Heart and

kidney diseases which are caused by Diabetes are increasing at an alarming rate and claiming thousands of lives every year [3]. According to [1]–[3], 50% of the Diabetes patients are anticipated to be suffering from nerve damage.

Wearable body sensors have recently received an increased extensive attention in healthcare applications for continuous and real-time monitoring of physiological parameters and personal health of patients and non-patient. [4]–[10]. These sensors are deployed to measure heart rate, blood SPO2 level, body temperature, and glucose detection from the sweat [4], [10]–[13]. In this regard, it is highly important to develop non-invasive wearable sensors and systems that determine and monitor the glucose levels in blood in the real-time. Traditional invasive methods of examination of the glucose levels on the human body require a patient to prick his/her finger (puncturing the skin) to collect a blood sample in order to determine his/her blood glucose levels. This method poses difficulty for the patients with Diabetes due to the fact that they need to prick their finger several times a day in order to control the glucose levels, and this method causes pain. Patients feel discomfort and distress and perhaps agony, depending on the severity of puncturing the skin. Sometimes this invasive method can damage the finger tissue. Moreover, the needle can induce fatal body infections into the blood stream [3]. In other words, the most common commercially available glucose monitoring devices are invasive that require a blood sample to determine the glucose concentration on the human blood [14], [15]. Continuous Glucose Monitoring (CGM) or implantable systems are well known in the healthcare industry but they are invasive and require replacement after a couple of days, and carry limitations such as limited battery life [16]–[20]. Therefore, there is an urgent need to develop non-invasive glucose monitoring devices that are easy to use, low cost, and mobile and do not pose any of the above hazards to the users.

A number of optical technologies, such as Electromagnetic Sensing [21], [22], Reverse Iontophoresis [21], [23], Near Infrared spectroscopy [21]–[25], Raman spectroscopy [21], [26], and Fourier transform Infrared (FTIR) spectroscopy [21], have been investigated to develop non-invasive glucose monitoring sensors/systems. Near Infrared (NIR) spectroscopy has gained attention because of its ability to analyse samples without any prior manipulation, penetrate human tissues and affordable equipment [21], [27].

There are several non-invasive methods used to detect and monitor the glucose level on human body. The GlucoWatch sensor reported in [28], in order to measure the glucose, brings interstitial fluid through the skin to the external analytical platform using iontophoresis. The downside of this sensor is that it has induced irritation problems in patients, therefore it has been withdrawn from the market. Pleitez *et al.* [29] has reported non-invasive sensor system based on resonance-enhanced pulsed photoacoustic spectroscopy with a windowless resonator cell positioned on the skin of the fingertip. This sensor system configuration is complex and it needs further improvements of the cell and its integration to a portable miniaturized device is still necessary. Dachao *et al.* [30] also have reported a non-invasive sensor device that uses ultrasonic energy at the skin level to determine the glucose levels, however the sensor has also not been miniaturized in order to be considered as wearable sensor, and it uses a commercial biosensor which are very expensive and complex to be fabricated. Google has reported a digital contact lens patent idea that can measure the glucose levels on the blood from the tears [31], [32]; however, this lens is still in the development stage and is very expensive and complex to wear when compared to our proposed ring sensor. Also, there are doubts that the amount of glucose in tears can correlate strongly with blood glucose of the user, and this would lead to inaccurate measurement of the glucose level in blood. Also the contact lens would not be conformable and almost impossible to be used by patients and non patients that already wear contact lenses to improve their vision. According to Google, the proposed contact lens will be based on graphene which is a very strong 2-D transparent material and expensive. In general the contact lens proposed by Google, which is still in developed phase, would be expensive, complex and difficult to wear, and still has accuracy doubts. Therefore, the above stated non-invasive glucose sensors [28]–[32] are very complex to use and would not be available for an affordable price. In this regard our proposed sensor prototype would very convenient to use for any patient and non patient at an affordable price. In this paper, a prototype of a non-invasive wearable glucose monitoring system is developed and demonstrated experimentally which is based on the optical spectroscopy

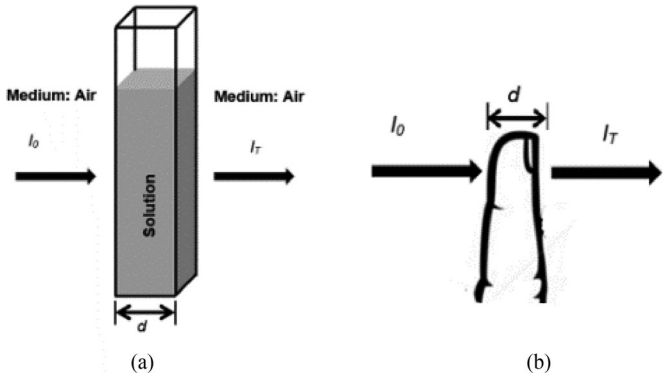

Fig. 1. Transmittance spectroscopy. (a) Light beam passing through solution. (b) Light beam passing through human fingertip.

that quantifies the glucose level on the human blood. The proposed device prototype has been tested on real human body for determining the glucose level in the blood.

2. NIR Spectroscopy

2.1. Basic Concepts of Near-Infrared Spectroscopy

The NIR spectrum operates at a wavelength ranging from 750–2500 nm. The molecular formula for glucose molecule is C6H12O6, which consists of C-H, O-H and C = O bonds. The presence of these bonds causes the absorption of NIR light in blood or other human bodily fluids. The process in Ref. [27] involves introducing IR light beam to the test samples and a sensitive IR detector detects the amount of IR light. The NIR transmittance spectroscopy can be used for finger tips and earlobes whereas for forearms and cheeks, reflective spectroscopy is used due to the fact that the NIR have very weak penetration power [33]. When the NIR light passed through a tissue, glucose showed one of the weakest absorption rates [34]. It should be stated that NIR spectroscopy is famous due to its straightforward concept and its applications. This technique can be used for blood monitoring as water content can be avoided by selecting a specific range. This can provide better readings while reducing interference. NIR instrumentation is not expensive as compared to Mid-infrared (MIR) spectroscopy. Materials and parts can be accessed easily [35].

2.2. Theoretical Model

The Beer-Lambert Law provides a mathematical formulation of the method that allows the calculation of absorbance of a sample from the concentration and the thickness of the sample [36]. The absorbance value is also related to the transmittance. The Beer-Lambert Law is a combination of two laws, illustrated in Fig. 1, that are combined to form a mathematical model of expressing how light is absorbed by matter; (a) the intensity of transmitted light decreases exponentially as concentration of the substance in the solution increases, and (b) the intensity of transmitted light decreases exponentially as the distance travelled through the substance increases.

The transmittance is related to the optical depth and the absorbance (A) as [37]–[39]

$$A = \varepsilon c l \tag{1}$$

$$T = (\varphi_e^t)/(\varphi_e^i) = e^{-\tau} = 10^{-A} \tag{2}$$

or

$$A = \log_{10}(T) = \log_{10}\left(\frac{I_0}{I_\tau}\right) = \varepsilon c l \tag{3}$$

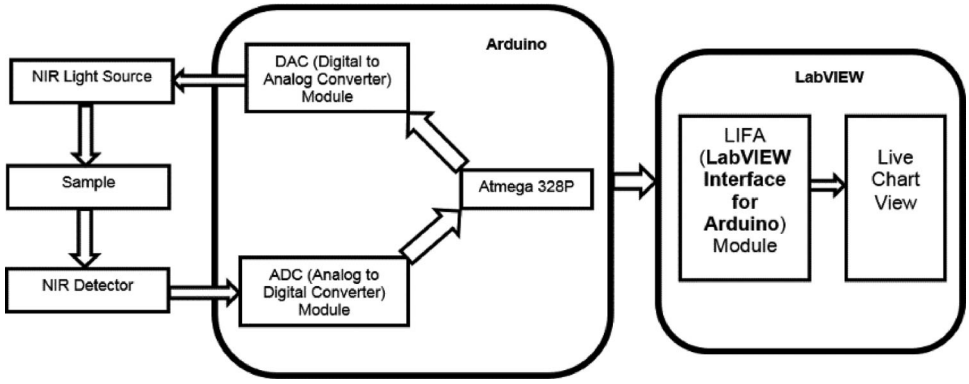

Fig. 2. System block diagram of non-invasive glucose monitoring sensor.

where A is Absorbance, T is Transmittance, τ is optical depth, ϕ_e^t represents the radiant flux transmitted by the sample surface, ϕ_e^i is the radiant flux received by the sample surface, I_0 is the intensity of light entering the sample, and I_T is the intensity of light leaving the sample.

According to the Beer-Lambert law [37]–[39]

$$T = e^{-\sigma \int_0^l N(z)dz} = 10^{-\varepsilon \int_0^l c(z)dz} \tag{4}$$

Alternatively, the above equation can be rewritten as [32]

$$\tau = \sigma \int_0^l N(z)dz \tag{5}$$

$$A = \varepsilon \int_0^l c(z)dz \tag{6}$$

where σ is the attenuation cross section; N is the number density of the attenuating species in the sample, l is the sample thickness; ϵ is the molar absorptivity coefficient; and c is the molar concentration.

These relations under conditions of uniform attenuation can be written as follows [40]:

$$T = e^{-\sigma N l} = 10^{-\varepsilon c l} \tag{7}$$

$$\tau = \sigma N l \tag{8}$$

$$A = \varepsilon c l. \tag{9}$$

This proves that the Beer-Lambert law clearly establishes a correlation between the absorbance of light by a sample and the concentration of the sample.

3. Experimental Setup

3.1. Measurement System:

As reported by [41] the absorption spectra of major intracellular absorbers where the molecular exctinction coefficients of oxygenated haemoglobin and melanin and the absorption coefficient of water are represented in (see 41, ref. [2]). It should be stated that the tissue optical property governs the wavelength that depends primarily on the concentration of water and skin pigments. The absorption pattern of these active absorbers is less sensitive in the near infrared and red wavelength spectrum. Most of these biological cells and tissues are transparent in the wavelength region of 700–1100 nm. This spectral region is also called the optical window of cells and tissues

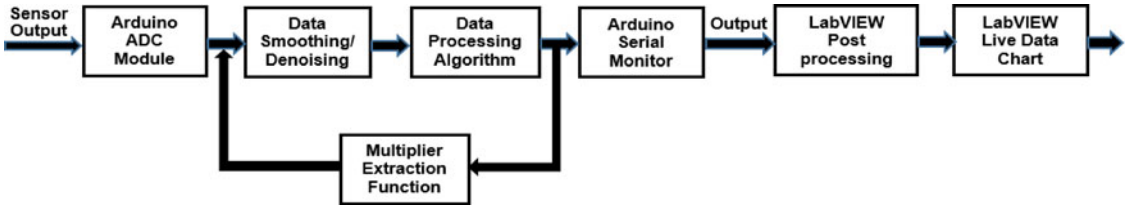

Fig. 3. Data processing block diagram.

[41], [42]. Thus, a light at operating wavelength of 940 nm is chosen in this study as it has been used in previous studies conducted by other researchers [9], [19], [33], [43]. A 3 mm T-1 Infrared emitting diode with peak wavelength of 940 nm was used as a light source. A Silicon PIN Photodiode, BPX-65 was obtained from Osram Opto Semiconductors with sensitivity in wavelength range of 350 nm to 1100 nm. The photodiode has its peak spectral sensitivity around ± 5 from 940 nm and radiant sensitive area of 1 mm^2 with half angle of $\pm 40^\circ$.

Fig. 2 represents the system block diagram, illustrating how different components are linked. The process starts with the measurement of the sample thickness, which then is placed in between the NIR light source and the detector. The sensor output is collected and converted using the Analog to Digital Converter (ADC) module. The data is then filtered (remove the noise from the data) and the values of absorbance and concentration are calculated using a data processing algorithm. The data processing algorithm is based on the equations mentioned in the Section 2.2. A multiplier extraction function is implemented to takes the previous calculated value as a reference to compare the future datasets. A multiplier is extracted and the data is parsed to LabVIEW using the LabView Interface for Arduino (LIFA) module [34], [44]–[46], which then is displayed on a live data chart widget. This process flow is illustrated in Fig. 3.

3.2. In-Vitro Sample Preparations

To estimate the pure element spectra, a high-concentration solution of glucose (111 mMol) was prepared and its NIR spectra were measured. Electric balance and high precision measuring tube of 50 ml were used to measure glucose powder and distilled water. A total of two glucose aqueous solutions were prepared for in vitro testing.

4. Testing and Analysis

The modelled system was tested in two stages. In-vitro testing was performed in the first stage and In-vivo testing was performed in the second stage.

4.1 In-Vitro testing

Two glucose aqueous solutions were prepared for the In-Vitro testing and the concentrations of both of the solutions were kept similar at all times. A reference reading was taken from the solvent. An initial solution of $\sim$ 111 mMol was prepared and with each increment, the concentration of glucose solutions was increased by 111 mMol. A number of readings were taken for each concentration to form a reading set. In the end, an average of the each of the reading sets was taken and these results are illustrated in Fig. 4 below.

The graph in Fig. 4 represents a trend that establishes a relationship between the output voltage and the concentration value of the solution. If the concentration (mMol) increases the (readout) output voltage increases as well. It should be stated that a linear behaviour for the relation between the output voltage and the concentration is expected theoretically by the equations mentioned in the Section 2.2. The regression analysis of the in-vitro results was performed in Matlab software. The table (see Table 1) shown below demonstrates the regression analysis results of the dataset illustrated in Fig. 4.

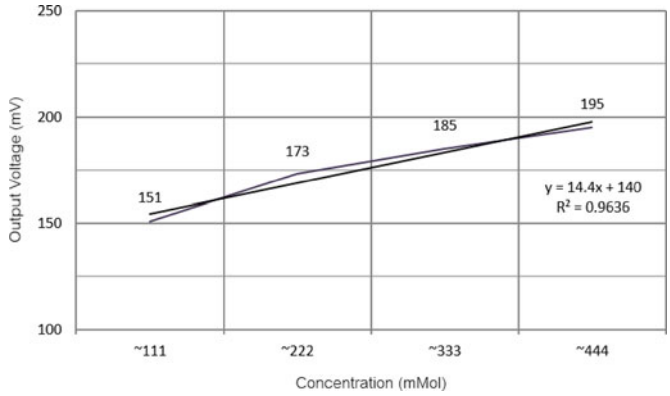

Fig. 4. Test results for glucose aqueous solution concentration.

TABLE 1
Regression analysis results of the glucose aqueous test

Regression Statistics	
Multiple R	0.981615
R Square	0.963569
Adjusted R Square	0.945353
Standard Error	33.49885
Significance F	0.018385

Significance F value is less than 0.05 and the R square term is equal to 0.96, indicating that 96% of the variability in the response is explained by the explanatory variable.

4.2. In-Vivo testing

In this section, we illustrate the testing on human body tissues to check the efficiency and error rate of the developed non-invasive glucose sensor measurements. As NIR light has the tendency to penetrate an earlobe and the first webbing of a human index finger, the index finger is chosen for the test due to easy convenience. The average circumference of a female's finger is between 4.9 cm to 5.7 cm, giving a cross sectional area of 1.96 cm^2 to 2.60 cm^2. A male's average cross sectional area is between 2.60 cm^2 to 3.602 [47]. An increased circumference leads to less penetration because it increases the distance travelled by the IR light which in turn influences the sensor reading value. Fig. 5 shows the 3D model of the experimental set up of the proposed non-invasive glucose monitoring system.

Fig. 6 shows the proposed and developed experimental setup of the non-invasive glucose sensor system. In this figure we show the system implementation of the non-invasive glucose measurement finger tissue test prototype. Once the finger tissue is placed in between the source (NIR) circuit and the detector circuit (Photodiode), shown in Figs. 5 and 6, and also illustrated in Fig. 6, the system initiates the spectroscopy process. In this case, readings are taken for several different individuals. In particular it should be stated that, when the finger tissue is placed in between the source and the detector, the space between the source and the detector is kept dark, isolated from the external (visible) light, in order to avoid the interference from any external light.

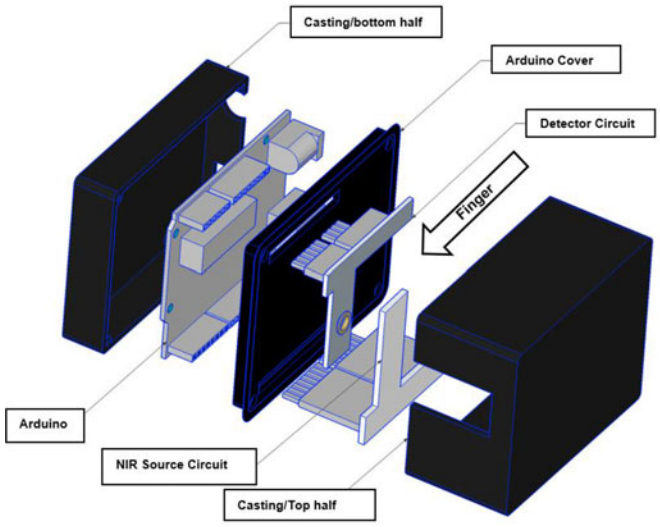

Fig. 5. Three-dimensional exploded view of the testing non-invasive glucose monitoring system.

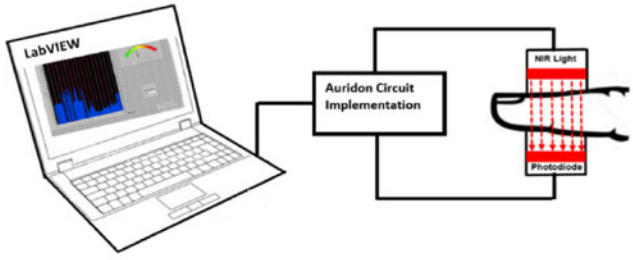

Fig. 6. Finger placement in Biological tissue testing apparatus.

The testing stage was focused on testing the proposed system's capabilities on a group of six individuals. The test was carried out jointly with competent health professionals in the Faculty of Health & Social Sciences at the University of Bedfordshire. A commercial invasive sensor, "TRUEresult twist" [48] was used to benchmark the performance of our developed system. Our preliminary results are benchmarked also using the Clarke grid analysis [49] where the Clarke grid analyses show promising results and most of the markings (obtained test results) appear in the acceptable region. Invasive and non-invasive readings were taken with the time difference of one minute. The Clarke grid analysis of the datasets is given in Fig. 7. The non-invasive values range from $\sim$ 70–110 whereas invasive values range from 70–105. As can be seen from Fig. 7, the obtained data points from the test measurements are within the acceptable region, confirming the accuracy of our proposed and developed non-invasive glucose sensor.

The measurements presented below in Table 2, are taken when the system was fully calibrated. The calibration process was performed 24 hours before the actual testing of the system. The calibration process involved taking invasive and non-invasive values, and compared the readings to get the value of the molar absorptivity coefficient. We took a range of measurements for each patient and a specific result dataset for each patient is included in Table 2.

The results have been compared on determining and benchmarking the glucose levels on five volunteers. The glucose meter allows accurate convenient testing and requires a tiny sample size of 0.5 microliter. The test results are displayed as fast as 4 seconds. Table 2 represents some of the benchmarking test results between commercial invasive sensor [48] and our proposed non-invasive sensor. In this table, we show the accuracy of the proposed non-invasive glucose sensor prototype on determining the glucose level in the blood. If we calculate the average values of the glucose

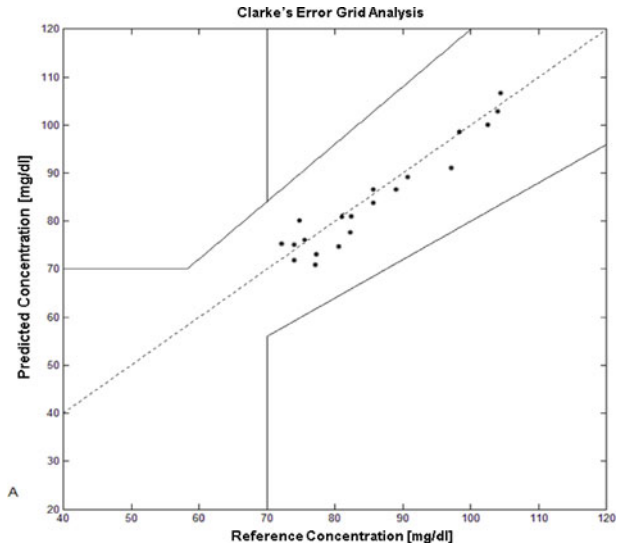

Fig. 7. Clarke Grid analysis of the in-vivo results.

TABLE 2
Comparison of results between commercial invasive sensor [34] and our proposed non-invasive sensor on five volunteers

Person 1 value mg/dl		Person 2 value mg/dl		Person 3 value mg/dl		Person 4 value mg/dl		Person 5 value mg/dl	
Invasive device	Non-invasive prototype	Invasive device	Non-invasive prototype	Invasive device	Non-invasive prototype	Invasive device	Non-invasive prototype	Invasive device	Non-invasive prototype
82	78	74	80	77.5	72	97	90.1	105	103
82	76.5	74	80.2	77.5	70	97	90	104.8	100
82	76	74	79	77.3	69.4	97.0	89	105	99.46

levels of the five persons (see Table 2) for the invasive and our proposed non-invasive sensors; these values are 86.9 mg/dl for invasive and 84.6 mg/dl for the non-invasive. For most of the test subjects, the invasive values were higher than the non-invasive values but in case of second test subject, the non-invasive values were higher than the invasive values. But the data variability is similar to that of the other datasets of other test subjects. According to the Clarke grid analysis, the non-invasive values are within the acceptable range. We have measured the finger thickness using a Vernier caliper. After aggregating and filtering the data, average values were determined for men and women. There was not much variation in their finger thicknesses, as the ranges of most common finger sizes for women and men are not that different. Moreover, our proposed sensor system does allow the users to input their finger sizes during the calibration stage. The total cost of the sensor was around £40 including the cost of the 3-D printed casing. As the commercially available systems are invasive and expensive, the total production and maintenance cost of the system is relatively low than the currently available invasive systems [11].

In our future work, we will also utilize multivariate calibration by using Multiple Linear Regression, where the dependent variable is modelled as a summation of the independent variables and least

squares method is utilized to estimate the regression coefficients. A Multiple Linear Regression model can be as follows:

$$Y = a_0 + a_1 x_1 + a_2 x_2 + \cdots + a_n x_n \tag{10}$$

where Y is the estimate property, x represents the wavelength variables, and a is the regression coefficients of the model.

It should be stated that a uniform attenuation is assumed for glucose in fingers. The light mainly interacts with the glucose and has less interaction with other materials present in the sample. There could be other factors such as skin roughness which can cause light scattering, different body fluids concentration, etc., that may affect the glucose measurement. However, if we closely observe the data given in Table 2, we can realise that for the same person and the same invasive reading, there are different non-invasive readings but the differences are within the acceptable range. In our future work, we will investigate the impact of other parameters in the accuracy of the proposed sensor.

5. Conclusion

This research successfully demonstrated the relationship between the sensor output voltage and the glucose concentration, where the sensor output voltage increases as the glucose concentration increases, which have been verified and demonstrated by in-vitro experiments. The proposed non-invasive glucose monitoring system has low manufacturing and maintenance cost and showed good accuracy in vitro. The demonstrated results of the proposed non-invasive glucose sensor prototype show a very promising future for the implementation of NIR technology in biomedical field especially in optical spectroscopy for real-time and continuous non-invasive glucose monitoring. Our proposed NIR spectroscopy experiment demonstrates a great potential for non-invasive continuous monitoring of the glucose levels in the human body.

There are some other possible variables which were not included in this proposed model such as skin roughness which can cause light scattering, different body fluids concentration, etc., which could have impact on the system performance, and in order to improve further the calibration and system sensitivity, in our future study, we will investigate the impact of those variables in the sensor system performance. This will further optimise and refine the existing model, and generate a much stronger relationship between system inputs and outputs. Consequently, this will lead to further improvement of the proposed non-invasive system performance. Our future work will be also focused to further improving the accuracy and robustness of our device in order to perform real-time measure and continuous monitoring of the glucose levels and transmit the data into portable devices. Multivariate regression will be deployed to make the system more robust for in-vivo testing. This would have a great impact on personal health monitoring and recording the history of patients with diabetics and non-patients.

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