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A precise non-invasive blood glucose measurement system using NIR spectroscopy and Huber's regression model

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Abstract

Diabetes is one of the prominent diseases around the world. Presently, invasive techniques need a finger prick blood sample . A repetitively painful procedure that produces the chance of infection. To resolve this issue, non-invasive measurement approach is proposed. In this paper, an efficient NIR wave based optical detection system is proposed with optimized post-processing regression model. After real-time data analysis, it has been found that the coefficient of determination (R^2) is improved with the value of 0.9084 using proposed regression model. Mean absolute derivative is also increased with 3.87 mg/dl corresponding to predicted blood glucose concentration. Mean absolute relative difference has exceeded to 3.25%, and average error is improved with 3.77% using proposed regression model. Average accuaracy has been analyzed 94–95% for predicted blood glucose concentration.

Keywords NIR spectroscopy · Non-invasive system · Blood glucose measurement · Regression model · Statistical analysis

1 Introduction

Diabetes is a condition where blood glucose level is high and the number of diabetic patients is increasing rapidly. The prevalence rate of type 2 diabetic patients has become double from 2015 in the world. The estimated diabetes prevalence for 2010 is 285 million and is expected to affect 438 million people by 2030. So, it is essential to monitor the blood glucose level regularly for treatment. The type 2 diabetes has been found in majority amongst the diabetic patients. Blood glucose measurement is necessary multiple times in a day for type 2 diabetic patient. Frequent measurement of blood glucose using invasive technique irritates patients. Pricking of the blood from fingertip may be responsible for trauma. This will increase the risk factor of blood infection diseases. To overcome such problems, non-invasive blood glucose measurement system has been designed. In this way, Photo-acoustic spectroscopy technique has been discussed for non-invasive blood glucose detection using kernels based calibration. The cost of implemented LASER power source and the photoacoustic sensor is comparatively

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high and the system occupies larger space. So, the setup is not portable and easily transferable. In-vitro testing has been done to validate the system for precise measurement. Still, the non-invasive device is not commercialized using this technique for frequent use. Pirnstill et al. (2012) explored blood glucose measurement through in-vivo testing using polarimetry. They measured glucose concentration from the anterior chamber of the eye which limits it's usage for continuous monitoring (Lekha and Kumar 2015). Shih et al. explained the glucose measurement through Raman spectroscopy technique (Shih et al. 2015). The experimental setup of Raman spectroscopy occupied a large area. Raman spectroscopy method is suitable for laboratory measurement. Pretto et al. explained the glucose measurement using temporal and spatial approaches through optical coherence tomography (OCT) (De Pretto et al. 2016). For validation of system, they have done in-vitro and in-vivo testing. Samples are collected from ratina using this approach. This technique is also not suitable for frequent masurement. Hence, represented non-invasive techniques are not advisable for continuous monitoring. Other techniques have also been discussed and implemented for glucose measurement such as electrochemical process, RF sensing (Turgul and Kale 2017). Sharma et al. also presented glucose measurement using long wave NIR spectroscopy. However, the system has not been designed for continuous glucose monitoring. Beside of this, they utilized long NIR wave for glucose molecule detection (Goodarzi and Saeys 2016). Results are precise and accurate by in-vitro testing. The long NIR wave will not give precise blood glucose concentration values of human blood because long wave has shallow penetration. They have done analysis using multivariate regression techniques only (Sharma et al. 2013). But these works have limitations in terms of real time measurement, implementation and frequent monitoring. So, there is a requirement of a compact system of non-invasive blood glucose measurement which would have better precision and accuracy (Futami et al. 2016). On basis of literature till present, it is concluded that non-invasive blood glucose measurement system is required to design for better results and frequent measurement. To overcome these limits , a non-invasive blood glucose monitoring system is proposed using short wave NIR absorbance and reflectance spectroscopy technique at 940 nm and 1300 nm. In proposed work, the system is implemented to estimate the blood glucose from human blood direcly. The contribution and innovation of this work is that two short NIR wave with specific wavelengths (940 nm and 1300 nm) is proposed to implement the absorption and reflectance spectroscopy. The analysis has been done using Huber's method based regression model for precise measurement. The flow of proposed work is represented in Fig. 1. From Fig. 1, channnel 1, 2 and 3 represent the absorption and reflectance spectroscopy. The measured data (in mV range) is collected and processed through 16 bit ADC with sampling rate 128 samples/sec. Collected data is calibrated with huber's model for blood glucose estimation. In proposed work, specific wavelengths (940 nm and 1300 nm) with absorption and reflectance spectroscopy are unique combinations for blood glucose measurement. The optimized huber's method based regression model makes the system with higher average accuracy and precision . This system implementation with optimized regression model is an innovative work for non-invasive blood glucose measurement.

2 Detection of glucose molecule

The reflectance and absorption of light using specific wavelength causes respective glucose molecular vibration which can be observed in glucose spectra (Yasuhiro and Ikehata 2016). The molecular vibrations exist in overall NIR region are called harmonics or overtones. Molecular vibration depends upon bond vibration like wagging, bending, rocking,

Fig. 1 Block representation of proposed non-invasive glucose measurement system
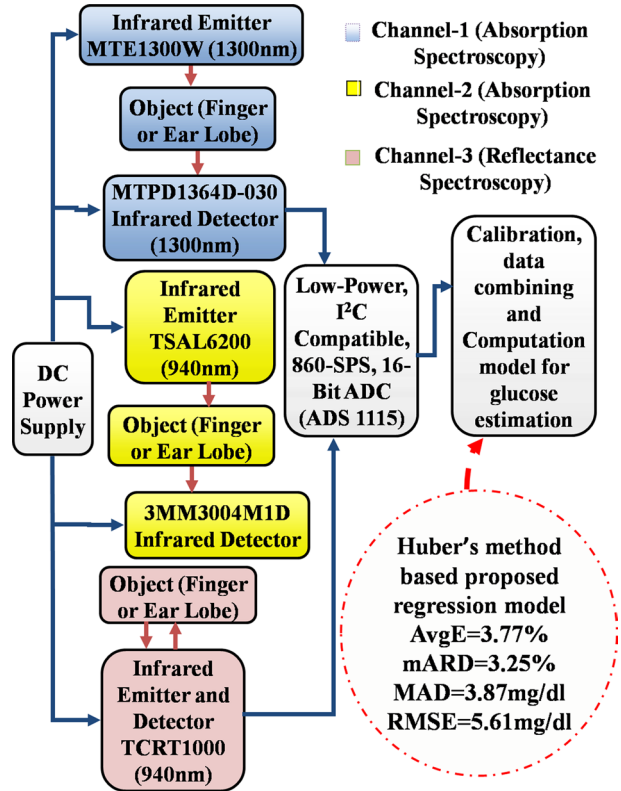
stretching and twisting. It has been analyzed that multiple bonds stretch and wag at different resonant frequencies. It is also examined that absorption of light will depend on molecular concentration of the medium (Ali et al. 2017). To determine informative bands for detection of glucose molecule, it is necessary to justify the resonant wavelengths of atomic bonds of blood glucose molecule. The structure of glucose molecule is shown in Fig. 2. In long wave NIR region, the vibrations between OH and CH are represented which can be known as first overtone. Due to observations of molecular vibrations in short wavelength NIR region, it is analyzed that absorbance and reflectance are sharper and stronger in first overtone compared to second and third (higher overtones) overtones. But the main drawback is that there is shallow penetration of the light in long wave NIR region (first overtone) in comparison with short wave NIR region (Yasuhiro and Ikehata 2016). As per the given Fig. 3, a sharper and effective absorption has been elaborated in second overtone of the O–H bond inter-atomic vibration at 970 nm. This represents the presence of water molecule. At 840 nm, O–H bond of water is conflicted with C–H bond of fat. During absorption of light in presence of glucose molecule, vibration of C–H bond is examined near 910 nm. The vibration of CH_2 is found near 930 nm. Glucose molecule detection is more precise using NIR long wave for in-vitro testing. NIR long wave will not give better results for in-vivo testing as long wave has shallow penetration. Opposite of this, short NIR wave has weak absorbance of glucose molecule but it has advantage of sharp penetration for in-vivo testing. Yang et al. (2018) also determined NIR informative wavebands for non-invasive blood glucose measurement. The glucose spectra in NIR region is represented in
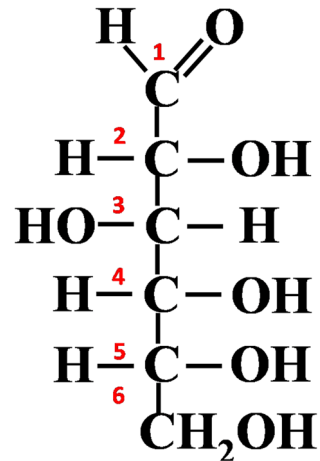
Fig. 3. Yadav et al. declared the NIR informative absorption peaks for glucose, water and lipid which is shown in Figs. 4, 5 and 6 (Yadav et al. 2015). Uwadaira et al. explored the accuracy of non-invasive blood glucose measurement by short wavelength near infrared spectroscopy. They found CH vibration near 920 nm without overlapping of OH vibration of water molecule (Uwadaira et al. 2010). Golic et al. elaborated near infrared spectra of sucrose, glucose and fructose. They analyzed CH_2, CH and OH stretching in glucose molecule at 930 nm , 960 nm and 984 nm respectively (Golic et al. 2003). Beckers also examined glucose apsorptions in short wave NIR region which is shown in Fig. 7. Haxha et al. proposed optical based non-invasive blood glucose monitoring. They selected 940 nm wavelength for detection of glucose molecule (Haxha and Jhoja 2016). They have mentioned that there is not any significant effect of finger width. Zhang et al. discussed on validation of NIR spectra for non-invasive blood glucose monitoring. They analyzed the absorption peak of glucose spectra at 1314 nm (Haxha and Jhoja 2016) which is shown in Fig. 8. Robinson et al. (1992) also selected the 940 nm for non-invasive blood glucose monitoring. Song et al. explored the non-invasive blood glucose measurement by using mNIR spectroscopy technique, in which three distinct wavelength (850 nm, 950 nm and 1300 nm) have been chosen for detection of blood glucose molecule (Song et al. 2015). According to literature of spectrum analysis of blood components, it is concluded that informative glucose absorption peaks exists in wave bands 920–960 nm and 1300–1320 nm. So, 940 nm and 1300 nm wavelength specific LEDs are suggested to use for blood glucose detection in proposed work. Therefore, it is proposed to involve the absorption and reflection spectroscopy concurrently for the precise blood glucose measurement.

3 Proposed system experimental setup

In this paper, dual wave NIR spectroscopy based non-invasive blood glucose system is proposed using Huber method based regression model (Huber et al. 2002). For precise measurement of blood glucose concentration, absorption and reflectance spectroscopy techniques are implemented at 940 nm and 1300 nm wavelengths using three channels. Light is received after absorption and reflection of incident light by glucose molecules. Hence, a combination of both spectroscopy techniques is appropriate for
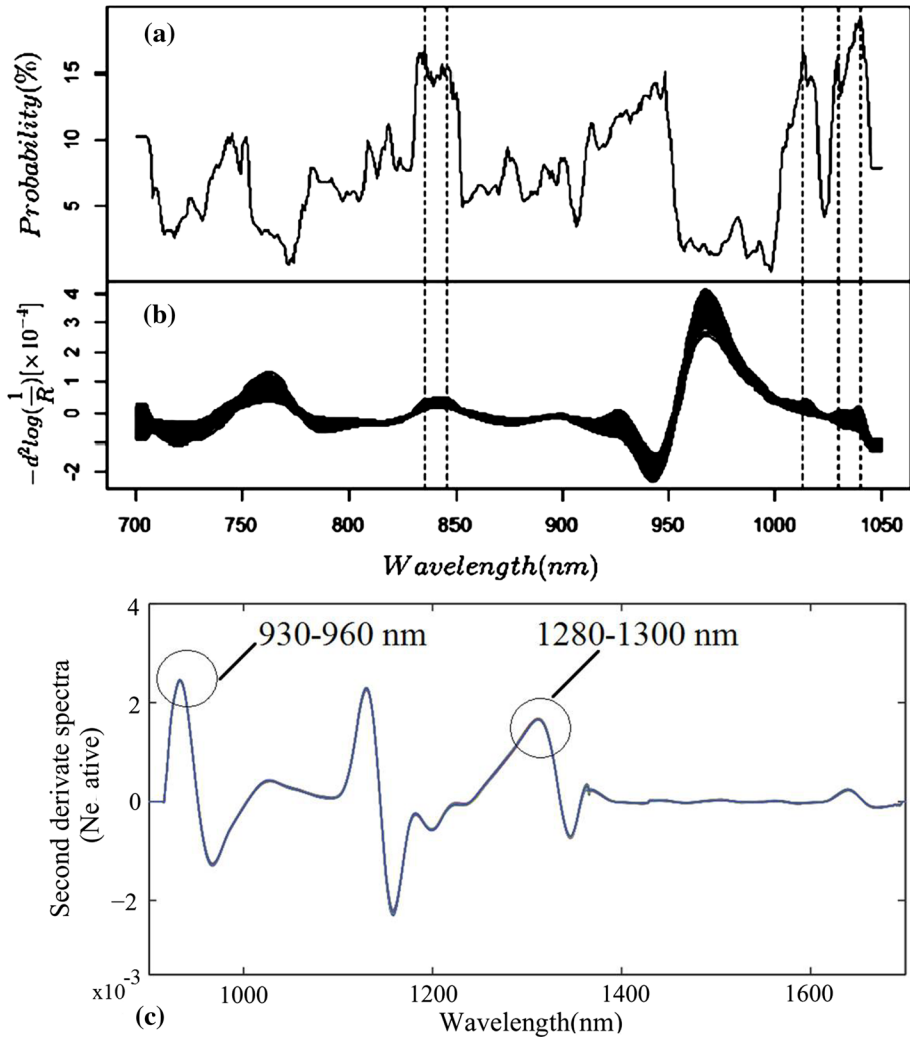
Fig. 3 a, **b** Glucose spectra in NIR region (700–1050 nm) (Yasuhiro and Ikehata 2016). **c** Glucose spectra in NIR region (900–1700 nm) (Yang et al. 2018)

precise measurement. According to Fig. 1, NIR spectroscopy technique is implemented at individual channel using specific wavelength. At channel 1, absorption technique is implemented using 1300 nm wavelength. Absorption and reflectance techniques are used using 940 nm wavelength at channel 2 and channel 3 respectively. Infra-red emitters (MTE1300W—for 1300 nm, TSAL6200—for 940 nm, TCRT1000—for 940 nm) and detectors (MTPD1364D—for 1300 nm, 3004MID—for 940 nm, TCRT1000—for 940 nm) are embedded on 2-layer PCB. TCRT1000 is a single SMD (surface mounted device) packaged IC. All detectors with daylight blocking filters are used. So, there is no need of dark room for measurement. The voltages (mV) are applied as the input of ADS 1115 A/D converter. Assembling of components is represented in Fig. 9. Received light on detectors is obtained after absorption and scattering through glucose molecules.
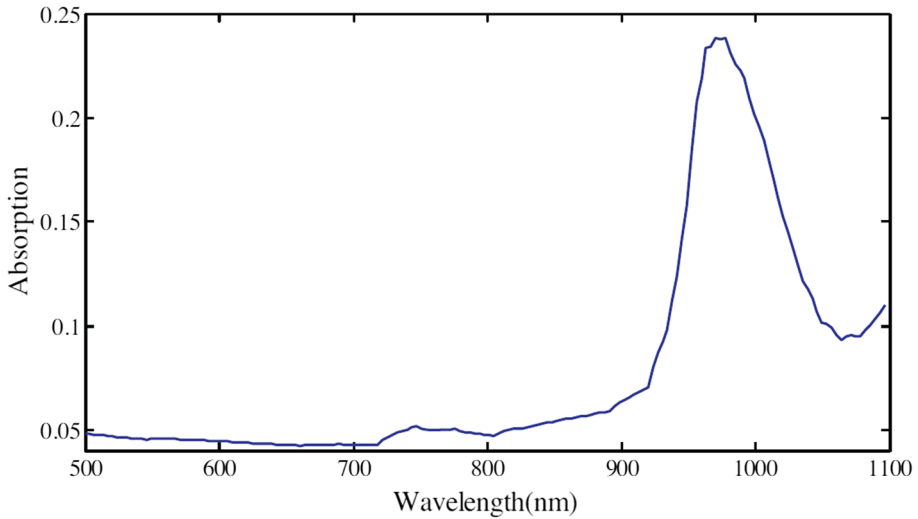
Fig. 4 Glucose spectra in NIR region (Yadav et al. 2015)
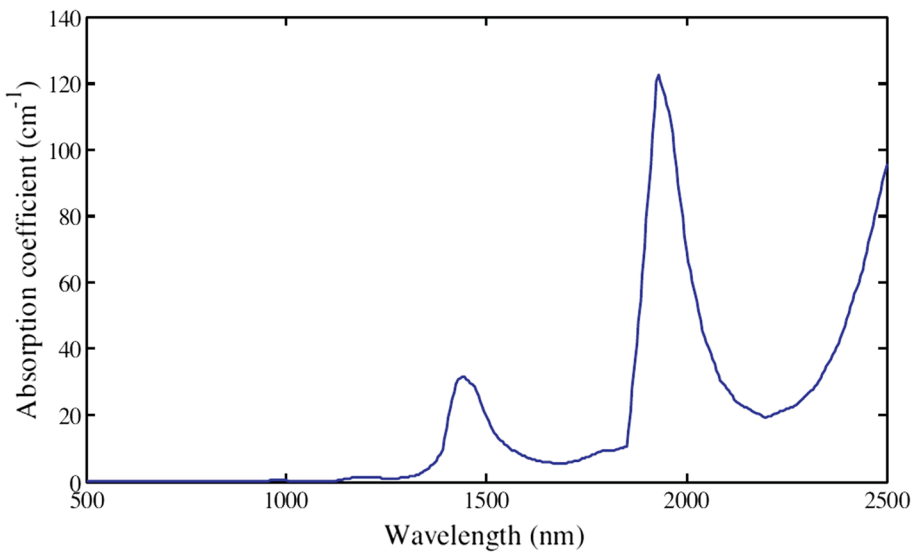

Fig. 5 Water spectra in NIR region (Yadav et al. 2015)

Optical detectors convert received light into voltages. These voltages are converted in decimal form through A/D converter. The output is obtained serially in frames from A/D converter. Each frame consists of detectors output values in a decimal form corresponding to one sample. These collected frames are used to design an optimized regression model for precise measurement. The prototype of proposed non-invasive blood glucose measurement system is represented in Fig. 10. The finger hose is the place where
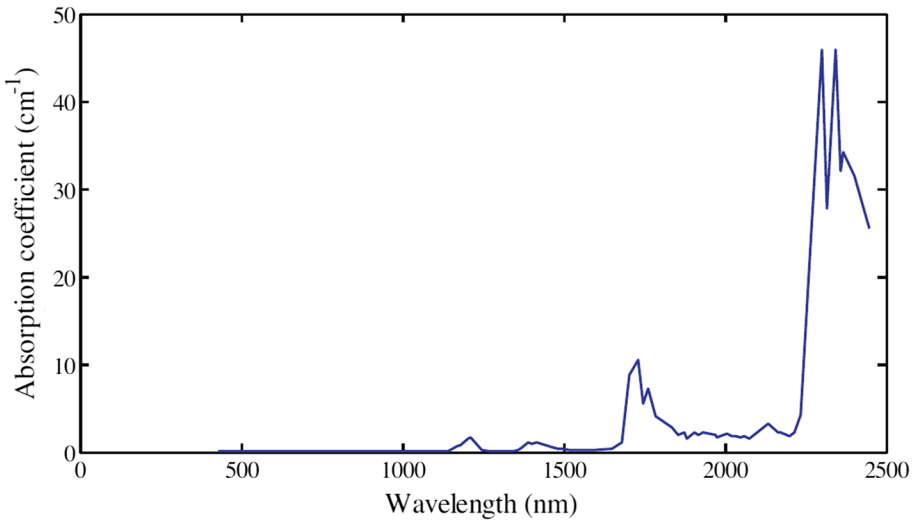
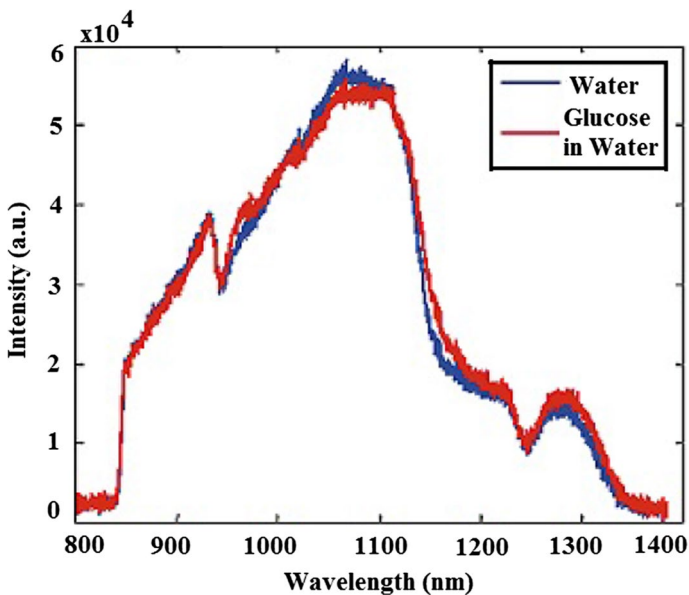**Fig. 6** Lipid spectra in NIR region (Yadav et al. 2015)

Fig. 7 Spectra of distilled water and a high concentrated glucose solution in NIR region (Beckers xxxx)

finger should be placed as an object for measurement. Here, in this work; the sensors (emitters and detectors) are tightly fixed at appropriate distance (with space for placing the finger and earlobe). This space is a hose for finger or earlobe for measurement. During measurement, the finger or earlobe was kept in that space with fixed position of object (finger or earlobe). So, there is no chance to alter the results significantly.

**Fig. 8** Glucose spectra in NIR region (Zhang and Liu 2013)
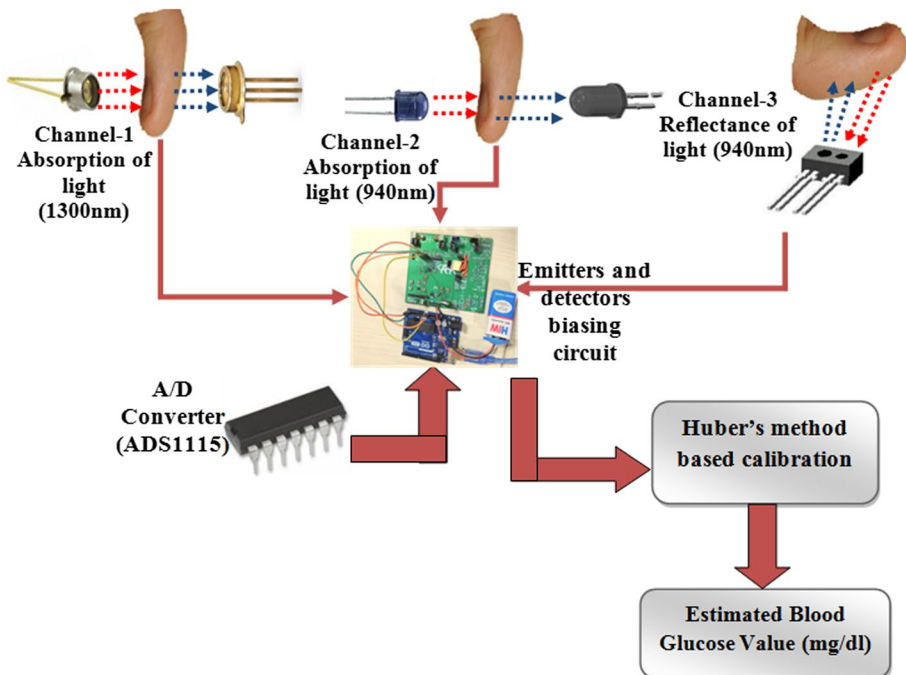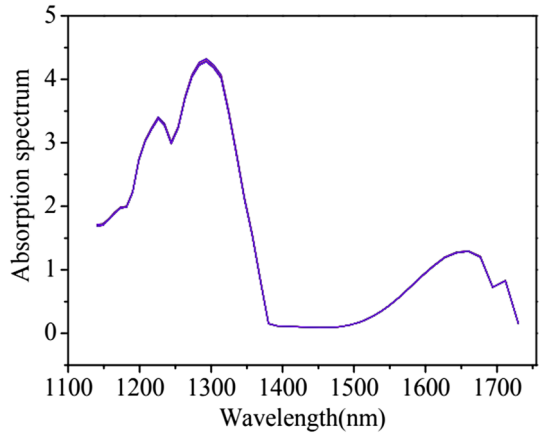
Fig. 9 Architecture level of proposed non-invasive glucose measurement system

Although the proposed system is cheaper compared to previous works. The NIR spectroscopy with short wavelengths is implemented on PCB using specified optical emitters and detectors. The data acquisition has been done through 16 bit ADC ADS1115. The optical emitters and detectors are biased using resistors and capacitors for efficient output. The overall cost of the emitters, detectors, ADC and used passive components is comparatively low which makes system cheaper than others. To calculate the optical density (OD) for the human finger medium, transmittance of the light (T) is required to

Fig. 10 Prototype view of proposed non-invasive glucose measurement system
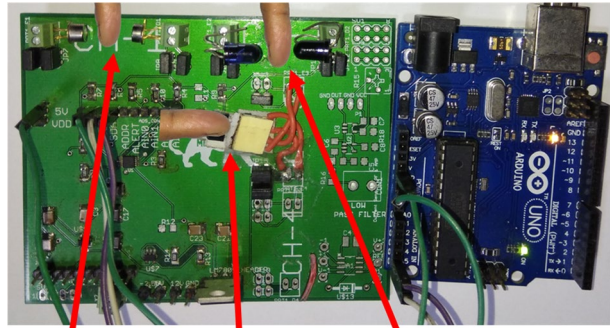
Channel 1 Channel 3 Channel 2

measure. It is the ratio of transmittance power (P_T) from medium to the incident power (P_i) from the LED source. It can be represented in Eq. (1).

$$T = \frac{P_T}{P_i} \tag{1}$$

The optical density (OD) of human finger medium can be represented in Eq. (2).

$$OD = -log_{10}T \tag{2}$$

During experimental analysis, the transmittance of the light is found to be 0.3403 and optical density is calculated 0.46 for the 1300 nm wavelength. For 940 nm, the transmittance of the light is found 0.2547 and optical density is calculated 0.59.

4 Mathematical modeling for prediction of blood glucose concentration

For precise measurement and system validation, an optimized Huber's method based regression model is proposed (Huber et al. 2002). During data collection, sample data consists of outliers. Outliers are generated from operational mistakes. Outliers in the data make severe effects of statistical inference. Single outlying observation from samples may increase the error in prediction of blood glucose concentration. Huber's method based regression model has been introduced to improve the post-processing regression model in the presence of the outliers of samples. Hence, this model is an efficient model for estimation of blood glucose concentration. This proposed model described the relationship between voltages obtained from three channels and referenced blood glucose concentration at the same time. To design the proposed computation model, the output voltages from the detectors have been taken after placing the fingertip, and at the same time, reference blood glucose is measured using SD-check GOLD one-touch conventional invasive glucometer (Larin et al. 2002). Each value of detectors is independent variable x which is associated with response variable y. The proposed regression model is developed using 25 subjects. These 25 subjects have been taken from the age group of 18–70. The data has been taken from people following the protocols of random blood glucose test mode. The overall accuracy is considered in terms of mean absolute relative difference (mARD), Mean absolute derivative

(MAD), RMSE and average error. In proposed work, overall error is reduced with compare to regression and non regression based measurements. To analyze the system performance, the average error is calculated from the predicted glucose concentration using proposed regression model. The average error (mean error) can be calculated as

$$AvgE = \frac{1}{n} \sum_{i=1}^{n} \left| \frac{V_{MD} - V_M}{V_{MD}} \right| \times 100 \tag{3}$$

In Eq. (3), $AvgE$ is an average (mean) error and n is the total subjects V_{MD} is the minimum deviated value, and V_M is the measured value. The average error is mean error or deviated error from the predicted value. After applying Huber's method based regression model, there is 3.4% average error found in the predicted value of glucose concentration. To analyze the accuracy of the estimated blood glucose value, mean absolute relative difference (mARD), mean absolute deviation (MAD) and RMSE are calculated in Eq. (4), (5) and (6).

$$mARD = \frac{1}{n} \sum_{i=1}^{n} \left| \frac{BG_{Predct} - BG_{Ref}}{BG_{Ref}} \right| \times 100 \tag{4}$$

$$MAD = \frac{1}{n} \sum_{i=1}^{n} \left| BG_{Predct} - BG_{Ref} \right| \tag{5}$$

$$RMSE = \sqrt{\frac{1}{n} \sum_{i=1}^{n} \left| (BG_{Ref} - BG_{Est}) \right|^2} \tag{6}$$

BG_{Predct} is predicted blood glucose concentration value which is obtained after computation from the proposed regression model. BG_{Ref} is Reference blood glucose concentration value which is obtained from the invasive blood glucose measurement device. The differences between these values are shown in Fig. 11. According to the observation of these 25 subjects, 3.25% mARD found from predicted glucose values using the proposed computation model. According to the proposed post-processing model coefficient of determination (R^2) is obtained as 0.9084. These represented parameters show the precise, robust model for measurement from the proposed experimental setup. The RMSE is calculated with the value 5.61 mg/dl using the proposed system. MAD is found to be 3.87 mg/dl using optimized regression model. For validation of proposed system, 200 independent subjects are tested using non-invasive system. During statistical analysis, $mARD$ and $AvgE$ found to be 5.18% and 5.30% respectively. MAD and $RMSE$ are calculated 6.25 mg/dl and 9.24 mg/dl respectively. Predicted and referenced blood glucose concentration using proposed Huber's method based regression model is represented in Fig. 11. Hubers method based regression model is found more precise compared to other existing regression models like artificial neural network, partial least square model, multiple linear regression etc. for proposed work. This method based regression model is calibrated using MATLAB 2015a software for validation and testing.
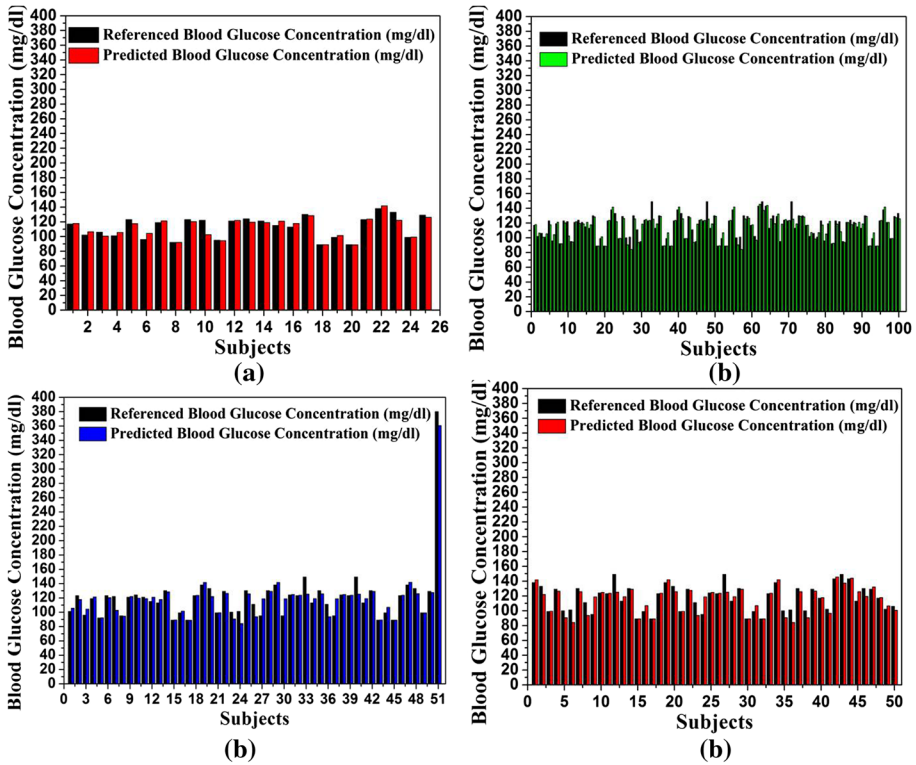
Fig. 11 a Predicted and referenced blood glucose concentration using proposed Huber's method based regression model. **b** Validation of proposed system after testing on 200 subjects

5 Clarke error grid analysis

Clinical accuracy of predicted glucose concentration is quantified using Clarke error data analysis. This is explored by Clarke (2005) and became standard for system validation. The values exist in zone A & B will be desirable as there is a minor difference between predicted and referenced blood glucose concentration. During Clarke error grid analysis, it is concluded that all subjects are found in zone A and B using the proposed non-invasive system. After analysis of statistical parameters, the proposed non-invasive system is tested with 200 independent new subjects. These data are taken from persons aged 18–70 years. All predicted blood glucose concentration values are found in zone A & B during Clarke error grid analysis after modeling of the system, which is shown in Fig. 12. Thus, System is trained and validated for medication. According to Table 1, it is concluded that 3.25% mARD is improved to the 7.01% mARD of previous work. This shows the effective difference. MAD, average error and RMSE are improved with the value 3.87 mg/dl, 3.77% and 5.61 mg/dl respectively. Real time analysis of device validation has been done from human blood. Blood glucose concentration of diabetic patient (380 mg/dl) has been taken to validate the system. Minimum glucose concentration (80 mg/dl) has been taken of non diabetic patient (random glucose test). The maximum measurement limit depends upon the maximum glucose molecule detection which is proportional to the maximum absorbed light
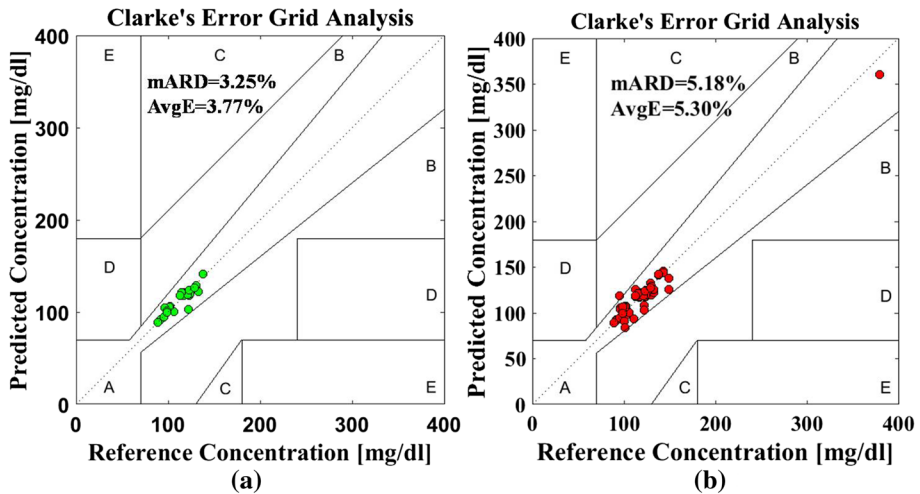
Fig. 12 Clarke error grid analysis of predicted blood glucose values using proposed Huber's method based regression model. **a** With 25 subjects. **b** With 200 subjects

through the object. The minimum received light intensity refers to the maximum blood glucose detection. In this experimental work, 80–380 mg/dl is considered to be precise range for blood glucose measurement. Non invasive blood glucose measurement by optical detection is an efficient but challenging approach for general purpose. The blood pressure depends upon the flow of blood in blood vessels. The variation in blood pressure will affect the blood glucose concentration in proposed work as received light intensity is directly proportional to the concentration gradient of glucose molecule. The concentration gradient will be changed with respect to the changes in blood pressure. Cholesterol level depends upon the low density lipoprotein, high density lipoprotein and triglycerides which can be estimated through albumin or fat. The resonance wavelength of fatty acid is different from glucose molecule. The size of the finger or finger width doesnt affect the blood glucose concentration as received light intensity doesnt depend on optical path (finger width). To prove this, an experimental analysis has been done which shows that S/N ratio is unaffected with change of path. A subject aged 30 has been taken for analyis. The blood glucose has been measured with time intervals of 2 h for a day. At that time, the data has been collected from earlobes and multiple combinations of finger. During experimental work, it has concluded that there is not significant effect of change in object and finger width. It has also been found that the received light intensity is same for both fingers and ear lobes which doesn't affect the SNR ratio also. Hence, system behavior is same for both finger and ear lobe. Finger colour doesnt affect the blood glucose concentration also. The referenced and predicted blood glucose concentration through different objects are represented in Fig. 13.

6 Conclusion

A dual wave NIR spectroscopy technique based non-invasive glucose measurement system is proposed the measurement system comparatively is accurate using NIR shortwave along with visible light blocking filter. During statistical analysis, the performance parameters

Table 1 Comparison with previous work

|	Larin et al. (2002)	Song et al. (2015)	Pai et al. (2018a)	Pai et al. (2018b)	Ali et al. (2017)	Proposed work
R^2 value	0.95	–	–	–	–	0.908
mARD (%)	–	8.3%	8.84%	7.01%	–	3.25%
Avg error (%)	–	19%	–	–	8–10%	3.77%
MAD (mg/dl)	–	–	32.88	5.23	–	3.87
RMSE (mg/dl)	–	–	43.64	7.64	–	5.61
CEG (A&B)	–	100%	92.86%	100%	98%	100%
Used model	Human	Human	Vitro	Vitro	Human	Human
System cost	Costly	Cheaper	Costly	Costly	Cheaper	Cheaper
Limitation	Physiological activity	Position change of IMPS circuit	Imbalance blood pressure	Imbalance blood pressure	Blood pressure and cholesterol	Imbalance blood pressure
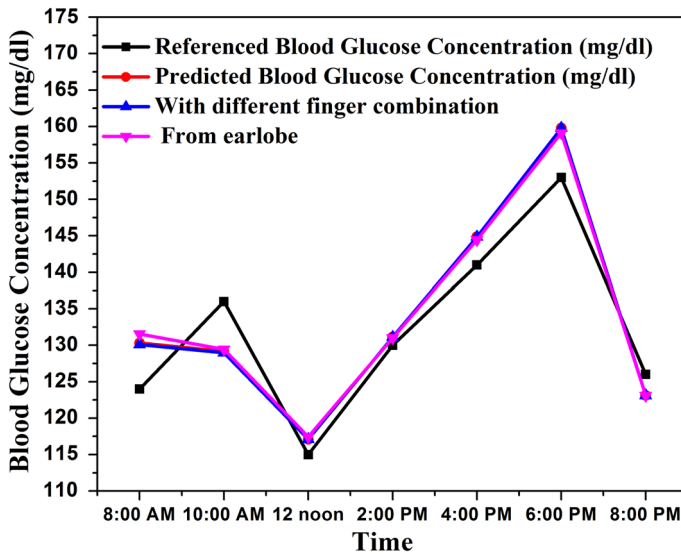
Fig. 13 Referenced and predicted blood glucose concentration through different objects

such as mARD, average error and RMSE are improved in comparison with to previous proposed works. The proposed post processing computation model became more efficient and optimize with correlation coefficient of 0.908. Real time validation of device has been done through SD-check invasive glucometer.

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