Beyond The Prick: The Hardware Revolution in Glucose Monitoring

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Abstract. Diabetes Mellitus (DM), a chronic metabolic disorder is globally in rise and demands effective and continuous management. Traditional methods of managing diagnosis is through pathology laboratories or from home monitoring kit. These methods are invasive and have a drawback of infection, expensive, and provide only intermittent measurements. To overcome these limitations, noninvasive techniques for measuring Blood Glucose (BG) are thoroughly studied. This paper presents a comprehensive review of the current state-of-art in the field of noninvasive glucose monitoring integrated with Artificial Intelligence (AI). Special emphasis is given to the studies related to Near Infrared Spectroscopy (NIR) which is the most sought out methodology for noninvasive glucose monitoring. This paper presents the system's circuit design, hardware implementation, and workflow along with the experimental results. The paper is concludes by highlighting the major challenges identified in the literature and proposing future research directions to overcome existing limitations.

Keywords: blood glucose monitoring · diabetes mellitus · hardware design · noninvasive measurement · NIR spectroscopy · optical method

1 Introduction

Glucose is a Greek word defining " sugar" and Blood Glucose (BG) is the sugar in blood. Glucose ($C_6H_{12}O_6$) is essential for functioning of human body. Blood carries it to all the body's cells which is used for energy [1]. Pancreatic endocrine hormones i.e., Insulin and Glucagon are responsible for regulating BG. An abnormal regulation of these hormones in turn effect BG levels. When BG is too high, it is known as Hyperglycemia and when BG is too low, It is known as

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Hypoglycemia. This condition is known as "Diabetes Mellitus"(DM). DM is collectively known for Type-I, Type-II, Gestational Diabetes and other genetically acquired diabetes [2].

From the statistics of W.H.O in 2022, the number of diabetic patients increased to 830 million from 200 million in 1990. If DM is neglected and left untreated, it may damage heart, blood vessels, eyes, kidneys and nerves such as diabetic peripheral neuropathy [3]. Common disorders caused due to DM are foot ulcers and in case of prolonged infection, it may also lead to limb amputation. A long-term accumulated damage on blood vessels of retina to the eye causes diabetic retinopathy which in turn leads to blindness. One of the major reasons for kidney failure is DM [3, 4].

Diabetes is diagnosed in clinical laboratory based on plasma glucose criteria. Different tests performed at the pathology are FPG (Fasting Blood Glucose), Post Prandial, OGTT (Oral Glucose Tolerance Test) and HbA1c(Glycated Hemoglobin). Each test has a category of diagnosis. FPG is performed after non caloric intake of at least 8 hrs. An individual is diabetic if FPG$>$126mg/dl. Post prandial is performed after 2hrs of taking food and an FPG test. If post prandial $>$140 mg/dl, an individual is considered as diabetic. OGTT test is performed after providing a glucose load equivalent of 75g anhydrous glucose dissolved in water. OGTT$>$200mg/dl is considered as diabetes. HbA1c is test performed to check the average glucose attached to hemoglobin for the past three months. If HbA1c $\geq$6.5%, an individual is considered as diabetic [5]. These parameters play an important role in understanding the hyperglycemia, hypoglycemia, and their patterns [6].

Apart from the pathology tests, blood glucose monitoring kit is the market solution for measuring blood glucose at home. It involves pricking of finger with lancet and dropping blood on strip and inserting it into the glucose meter. The test strip consists of glucoseoxidase enzyme. It reacts with glucose in blood and forms gluconic acid. This acid reacts with other chemical i.e., Ferricyanide present in the strip. Together they form Ferrocyanide which results in flow of electrons on the strip and displays the proportional measured glucose value on the screen of gluco meter [7]. It is known as an invasive method if a process involves blood work for measuring glucose levels. Invasive method of measuring blood glucose levels is fearful, painful and as a risk of infections. The complexity of lancet, amount of blood drop, testing site on finger may provide incorrect readings. Another disadvantage with invasive monitoring of glucose is the expenditure on pathology report and strips, lancets for home monitoring kits. Real time Continuous Glucose Monitoring (CGM) of glucose becomes burdensome with the above challenges citexue2022commercial,tang2020non,villena2019progress.

Many complications/surgical procedures require CGM specially during recovery. Real time CGM is not possible with the invasive method. A non-invasive monitoring of glucose is a pain and discomfort free approach [8–10]. The predominant sensing of blood glucose levels non-invasively is achieved through electrochemical method [10–13], thermal method [14–16], optical method [17–21].

Optical method which is currently most preferred approach for non-invasive BG monitoring is thoroughly elaborated.

Contribution of the work is as follows: This review is intended to present research gaps existing in the noninvasive monitoring of BG. While going through the current study, a researcher will have a complete insight on current advances of NIR from literature. Contribution of the work is as follows:

– Literature review on various hardware designed by implementing NIR method for obtaining BG levels is thoroughly explored.
– Sensor specifications, hardware design flow, working of the hardware, method of carrying out the procedure and result obtained in the field of noninvasive glucose monitoring is elaborately discussed.
– An insight on challenges in every approach and methods to transform for better prototype is suggested under each literature.

The remainder of this paper is structured as follows. Section 2 briefly presents methods to achieve non-invasive blood glucose monitoring is elaborated and the significance of NIR spectroscopy is justified. Existing literature in the area of NIR spectroscopy is extensively studied in section 3. Overview on commercial market solutions are also explored in the section. Section 4 discusses about the shortcomings and open problems in the field that can be considered as future scope. Section 5 summarizes the comprehensive study of the review work.

2 Methods of Blood Glucose Level Measurement

To mitigate the previous issues with invasive measurement of glucose, noninvasive approach is a smart healthcare solution. Non-invasive method is a convenient way for CGM measurement. Extensive research has been done in the field of various domains involving electrochemical method, electromagnetic method, thermal method and optical method. Figure 1 is an overview of methods implemented in noninvasive blood glucose measurement.

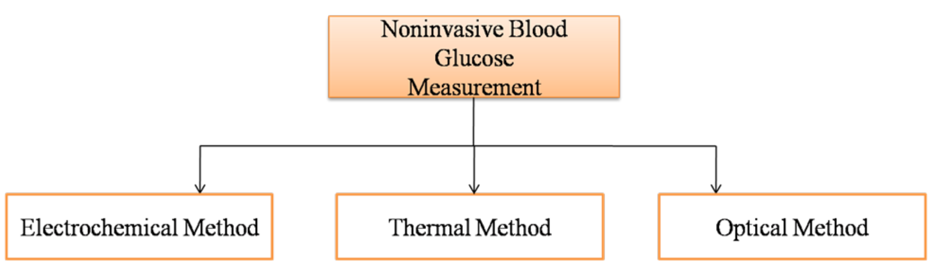

Fig. 1. Overview of Non Invasive Blood Glucose Measurement Methods.

2.1 Electrochemical Method

Electrochemical method is a technique to measure potential, charge, current and to determine analyte's concentration and to characterize analyte's chemical reactivity [10]. Ultra-thin skin like nano structured biosensor ($3\mu m$) is designed with paper battery that absorbs glucose from intravascular BG. Reverse iontophoresis is employed in this approach. Correlation of (>0.9) is clinically achieved on in vivo human trials [11]. The proposed method cannot be reused, thus increases the cost and hence it cannot be implemented for CGM. Similar approach is implemented in designing a watch band employing a Nafion-coated flexible electrochemical sensor patch. Accuracy of 83.4% in Clarke error grid is obtained by testing it on 23 volunteers [12]. Accuracy of the proposed model can be improved. The designed watch can be tested on a large dataset by considering parameters such as other medical complications, age, physical activity, sleep pattern etc. Saliva based noninvasive measurement of blood glucose is explored in. Parameters such as pH, oxidation redox potential, conductivity, individual concentration of sodium, potassium and calcium are mapped to te fasting blood glucose values obtained from venous blood. F-71 Laqua lab (Japan) pH/ORP meter and Horiba Laqua twin series ion selective were used to measure the parameters. Machine models SVM using RBF kernel showed accuracy of 85% and precision of 84%,85% sensitivity and 85% of F1 score [13]. Saliva based implementation for detecting BG is not feasible for CGM and as a wearable. In the proposed study, only 175 diabetic and normal people were considered. The accuracy can be improved by considering other parameters. This research is conceptualized on reverse iontophoresis. A major drawback of reverse iontophoresis is the effect on readings/measurements when there is a change in pH of skin and its temperature.

2.2 Thermal Method

Thermal method of detecting BG is to analyze time and temperature at which the physical changes occur when analytes is heated or cooled. Individual's tissue composition and analyte concentration determines the thermal emission characteristics [14]. Photo acoustic spectroscopy was proposed in a study where in vitro with glucose solution and in vivo with Oral Glucose Tolerance Test (OGTT) was performed. Correlation coefficient of 0.58 and 0.80 was achieved. Drawback of the study is the duration of test i.e., of 3 hrs [14]. The study was also tested only on 3 volunteers whereas in a study of Metabolic Heat Conformation (MHC), the experiment was conducted on 12 healthy volunteers [15]. Though the correlation between predicted and actual BG was 0.936,the proposed method can be further enhanced by reducing the size of the prototype. A study proposed thermal emission spectroscopy where periodic thermal cycling and detection of amplitude and phase shift signal is correlated. The drawback of the study is the detection of glucose levels from aqueous solutions which is not possible as a wearable solution for continuous glucose monitoring [16].

2.3 Optical Method

Terahertz (THz) time domain spectroscopy is implemented to study the optical properties of human skin [17]. In a study of implementing THz spectroscopy, BG was measured from the thumb-index web-space. The accuracy obtained through back propagation neural network is ±5% [18]. The designed equipment has a disadvantage of being a massive and huge in size, thus making it non suitable for CGM. Time taken for obtaining BG measurement and its low spatial and depth resolution is a drawback with THz spectroscopy. Raman spectroscopy is widely used in determining BG in various studies. In a study, BG from interstitial fluid was measured below a depth of ($250\mu m$)thumb which is comparable to the BG obtained from the home-based glucose monitor [19]. Drawback of Raman spectroscopy is the inability of reducing the size of designed equipment due to which continuous glucose monitoring is a challenge to achieve. It is prone to hemoglobin interference, unstable laser wavelength and intensity with long collection time. Optical Coherence Tomography (OCT) is implemented in a study where the BG levels are extracted from optical rotation angle and depolarization index. The study was conducted by consuming glucose solution and determining the BG levels. The prototype used for the study is complex and huge due to which it cannot be used as a wearable for CGM [20]. OCT is very susceptible to temperature changes, motion and other physiological parameters which is a disadvantage for CGM. In a study of Optical Polarimetry (OP) glucose concentrations are determined by dual-wavelength polarimetry in the presence of motion. The study was conducted on nine animals but not tested on human. Mean average relative difference of 4.49% is obtained [21]. The proposed method was not tested on human. The apparatus was huge making it not possible for implementing it as a wearable CGM. Drawback with OP is its sensitivity to temperature, motion and its interference from optically active compounds.

Significance of NIR
Electromagnetic spectrum is the optical radiation with wavelengths between 10nm and 1mm which describes the ultraviolet, visible, infrared regions, X-ray, gamma-rays and radio ranges [22]. Infrared region handles the Near Infrared (NIR) spectroscopy, Mid Infrared (MIR) spectroscopy, Far Infrared (FIR) spectroscopy from 2500cm-1 to 20 cm-1 i.e., from 800 nm to 500 μm. NIR ranges from 800nm to 2500 nm which allows the study of overtones, harmonic or combination vibrations. MIR from 2500nm to $25\mu m$ which allows the study of fundamental vibrations and rotation-vibration structure of small molecule ,FIR from 25 μm to 500 μm which allows the study of low heavy atom vibrations i.e., metal-ligand or the lattice vibrations [23, 24]. MIR and NIR are used in detecting molecules, quantitative information in a tissue. MIR cannot penetrate more than few micrometers as it is operated only in reflectance mode whereas NIR can penetrate for more than 0.5 mm. NIR sensing and measurement can be achieved in both as it operated only in reflectance mode reflection and transmission [10].

NIR works on the principle of absorption and scattering due to molecular vibrations. Transmittance, Reflectance and Interactance are the three modes of measurement. In transmittance, light source irradiated polychromatic light onto the sample and a diffraction grating on the other side splits the transmitted radiation into wavelengths before being sensed and analyzed by a detector. In reflectance mode, the emitter and detector are on the same side of the source to detect reflection. Light barrier is used in between the incident and reflected beams to separate the field of view of the detector from illuminated area. Depending on the purpose of the study, a particular mode can be implemented. Transmittance is preferred for analyzing fluids or thin transparent media whereas for thick and dense solids, reflectance or interactance is preferred [10].

NIR is the most implemented region for measuring BG levels non-invasively [8, 9, 25]. Glucose is found at peak in wavelengths at 940nm, 970nm, 1197nm ,1408nm, 1536nm,1688nm and 1925nm, 2100nm, 2261nm, 2326nm [26]. 940nm is mostly implemented for the purpose as other components such as water, platelets, red blood cells are intervention is low and concentration of glucose is high. The attenuation of optical signal by other blood constituents is minimum [27]. A recent study proposed multiple photonic band near infrared(mbNIR) in Shallow Dense Neural Networks (SDNN) for detecting BG levels non-invasively. The model achieved an accuracy of 97.8% with 96% precision and 98.7% specificity [28]. Another study a custom-built sensor (VIS-NIR) for prediction of BG non-invasively. Classification algorithm i.e., SVM outperforms regression where 99% F1 score ,99.75% of Clarke error grid fall under clinically accepted zones [29]. iGLU-2.0 a wearable gluco meter is proposed in a study. A short NIR is implemented to measure serum blood glucose. Regression model is used to measure accurate serum blood glucose. Deep neural network is executed whose average error and mean absolute relative difference is 6.09% ,6.07% for capillary blood and 4.88% ,4.86% for serum BG is achieved [30]. Similar wearable model for detecting BG non-invasively was proposed with Vis-NIR. Correlation coefficient of 0.86 and standard error of 6.16 mg/dl is achieved between estimated and reference BG concentration [31].

μm

It can be inferred that NIR is the sought and most used technology for detecting BG non invasively.NIR is not sensitive to water and therefore it can reach through stratum corneum and epidermis with high blood concentration without being effected by skin pigmentation.The prototype to build an NIR is affordable to buy as it constitutes of low cost materials. It works well for non -invasive method of detecting BG levels. The amount of signal intensity is proportional to the concentration of the analyte. It works in the presence of interfering medium such as glass, plastic or containers [10]. Challenges associated with NIR is its heterogeneous distribution of glucose molecules due to which concentration of glucose becomes low. This may give false readings. Proper glucose sensitivity site is required for determination of BG. Many researchers have worked on the challenges and provided enhanced versions for better detection of glucose molecule. In the further section, enhancement in the prototype by overcoming the setbacks of NIR and a model for accurate detection of BG will be thoroughly discussed.

3 Hardware Approaches in The Study Of Non Invasive Blood Glucose Monitoring

This section presents various research approaches through NIR spectroscopy for obtaining BG non-invasively. Noninvasive BG monitoring is achieved by principle of absorbance and transmittance photometry. A portion of light is lost when it interacts with human body tissues due to scattering and absorption by the tissues. Scattering is due to the mismatch between the refraction index of extracellular fluid and cell membrane in tissues. Cellular membrane is assumed to be constant whereas refraction index of extracellular fluid varies with glucose concentration.

3.1 Principle of Noninvasive Blood Glucose Measurement

According to Beer-Lambert Law, absorbance of light in any solution is in proportion with the concentration of the solution and the length path travelled by light ray. When a tissue is low in glucose, less light is absorbed by the BG and the light reflected has more intensity with more path length. Similarly, high BG leads to more absorbance of light and less light reflectance with lesser intensity and small path length.

Light transport theory is given as,

$$I_{ref} = I_{inc} e^{-\mu_{att} L_o} \tag{1}$$

where, I_{ref} is the reflected light intensity, I_{inc} is the incident light intensity, L_o is the length of optical path inside the tissue, and

$$\mu_{att} = \sqrt{3\mu_{ab}}(\mu_a b + \mu'_{sc}), \tag{2}$$

where μ_{ab} is the absorption coefficient with

$$\mu_{ab} = 2.303\epsilon C_h \tag{3}$$

where ϵ is the molar extinction coefficient, C_h is the tissue chromophore concentration, and μ_{sc} is the reduced scattering coefficient, with

$$mu'_{sc} = \mu_{sc}(1 - ang), \tag{4}$$

where ang is the average of cosine of scattering angles defining scattering coefficient. Path length decreases with the increase in glucose concentration. As assumed before that refractive index is constant, an increase in glucose concentration decreases scattering. It can also be concluded that $\mu_a b$ depends on BG concentration. Increase in the glucose concentration increases the absorption coefficient $\mu_a b$. As effective attenuation coefficient μ_{att} increases, it also increases the attenuation level. It can be concluded that an increase in the attenuation decreases the intensity of reflected light [32].

3.2 Design and Development of a Non-Invasive Glucometer System

Excellent research has been carried out in the field of NIR for noninvasive glucose monitoring. This section is aimed to explore the design and development of hardware implemented for the studies and challenges addressed by each model.

Rajeswari S.V.K.R. et.al present a noninvasive BG monitoring device using Machine Learning (ML) algorithms [28]. The design is divided into 4 layers where the input was the developed sensor system with 940 nm emitter, and 1700 nm detector for finger and wrist as presented in Fig 2. The analog data was processed using a DAQ in the data acquisition layer. In the data processing layer, a data analytic framework was employed on the digital dataset obtained from the communication layer. EDA (Exploratory data analysis), Data integration with smart watch and other parameters were noted. Machine Learning algorithms were applied on the framework applied dataset. Data analytic framework applied dataset was found to obtain a maximum 99.02%, mean absolute error (MAE) of 0.15, mean square error (MSE) of 0.22 for finger, and accuracy of 99.96%, MAE of 0.06, MSE of 0.006 for wrist prototype with ridge regression (RR) were achieved. 98% of the data points were within ± 1.96 standard deviation (SD), 100% were under zone A of the Clarke Error Grid (CEG), and statistical analysis showed $p<0.05$ on evaluated accuracy.

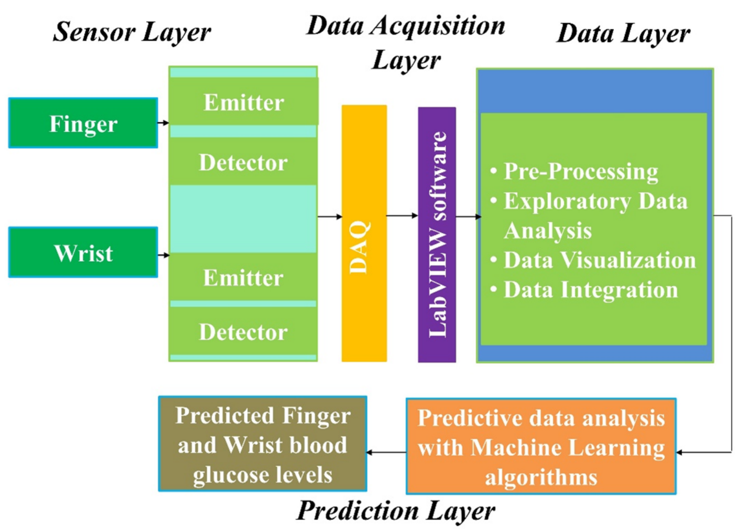

Fig. 2. Block diagram of NIR spectroscopy based noninvasive blood glucose monitoring [28].

Srichan C et.al aim to design a noninvasive accuracy enhanced blood glucose sensor through deep sensor neural network [29]. The design consists of following parts- Multiple photonic band near infrared (mbNIR) sensor, NIR LED light sources of wavelengths of 850nm,950nm and 1150 nm which are enclosed in a box with microcontroller and NIR photoreceivers as shown in Fig. 3. Multi-band phototransistor array as NIR was designed for absorbance and reflectance spectroscopy. To make the measurement unaffected, stray light blocking filters are introduced.

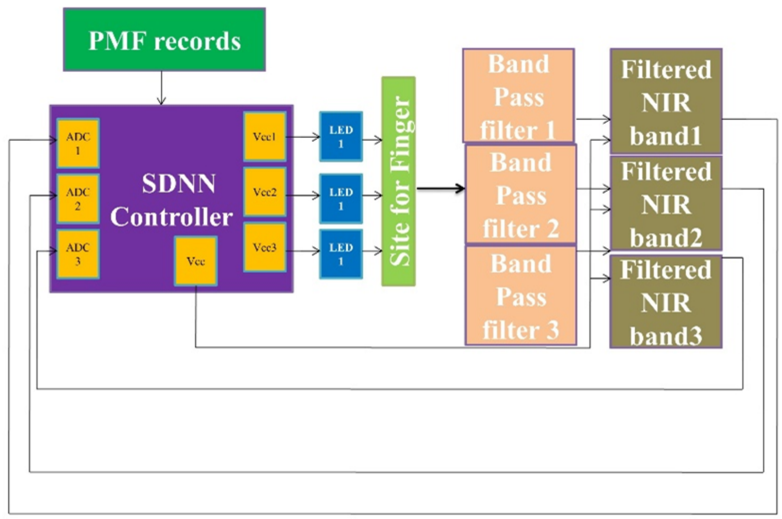

Fig. 3. Block diagram of PMF and mbNIR based noninvasive blood glucose monitoring [29].

Personalized Medical Features (PMF)are determined for every individual. The light scattered from the finger is filtered by band pass filter and the filtered band is fed to ADC as depicted in Fig. 1. Features importance was extracted using exclusion method. To find if a feature is important or not, a particular feature is dropped and accuracy is calculated. Accuracy drop was noted and important features were included. Feature importance of 0.48 was obtained when BMI, height, weight, age, blood pressure was included whereas feature importance of 0.52 was obtained when only mbNIR was considered. PMF and mbNIR are combined used to train shallow dense neural network (SDNN). Shallow denser neural network (SDNN) controller is implemented to predict the noninvasive values with PMF thus increasing accuracy and precision.

The model is tested on 401 collected dataset from hospital. Accuracy of 98.5% along with 98.0% precision,96.2% sensitivity, 99.3% specificity is achieved. A cohort study by considering 234 individuals who were not included in the training set was considered and the model was tested on them. Testing accuracy of 96.6%,91.7% precison, 91.7% sensitivity and 97.8% specificity was achieved. This model was executed on fasting BG values of 126mg/dL. DM prediction is achieved through ten-fold cross validation of input data, error of ±15, 95% confidence level at 60-400mg/dL. For predicting real time blood glucose level, the samples(n=234) fall under curve A under Clarke Grid Analysis.The proposed study was not conducted on real time normal and diabetic individual dataset. The designed hardware is huge making it challenging to carry. Continuous glucose monitoring is a drawback with the size of the prototype. Researchers can take this as future work and convert it to a wearable for continuous glucose monitoring and test it on real time.

A. M. Joshi et.al aimed to build a wearable for noninvasive serum glucose monitoring (iGLU 2.0) and compared the performance using regression model and deep neural network (DNN)[30]. The design consists of following parts - 940nm for absorption and reflectance spectroscopy and 1300nm for absorption spectroscopy is utilized as depicted in Fig. 4. Arduino Uno microcontroller is used for data acquisition. All detectors are inbuilt with daylight blocking.

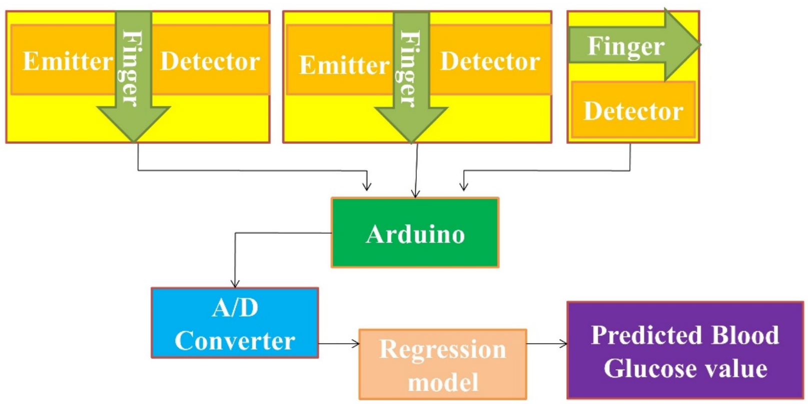

Fig. 4. Block diagram of noninvasive serum glucose monitoring [30].

Finger is placed in between 1300nm emitter detector pair, 940nm emitter detector pair and a 940nm detector. Arduino receives signal. A/D converter is externally used to convert analog values into digital. Regression model is applied on the obtained dataset to predict BG values. Sample from Total 1024 samples are taken for an individual and averaging for each is done in a time span of 8 seconds. Capillary glucose is measured from gluco meter and serum glucose from laboratory. Millivolts at three detectors are also taken into consideration which are converted into respective glucose values. The samples considered are fasting, post prandial and random. Sigmoid activation function is applied to DNN and the model is trained by Levenberg-Marquardt back propagation algorithm. Accuracy was best achieved by 10 hidden layers. Polynomial regression with degree 3 is implemented to predict capillary and serum blood glucose.50 samples of capillary glucose and 37 samples of serum samples are considered from normal, pre diabetic and diabetic people. The device is tested on 2 volunteers for its stability. Average error and Mean absolute relative difference of 6.09% and 6.07% for capillary blood glucose and 4.88% and 4.86% is achieved.

The model can be tested on at least 100 diabetic individuals while considering other health parameters such as BMI, age, weight, height, stress and sleep pattern. The proposed study is huge for a wearable. The size can be reduced and modified as a smart watch. The limitations stated can be considered as future work for enhancing the designed module.

Rachim, V. P. et.al developed a wearable-band type NIR biosensor for non-invasive glucose monitoring [31]. The design consists of following parts - Four LED's of wavelengths 950 nm (SFH7060),850 nm (VSMY2853G),660 nm (SFH7060) and 530 nm(SFH7060), are used as transmitters. A photodiode of 400-1100nm is used. Four channels with two output components PPGdc and PPGac is used. A low pass filter (LPF) with cut off frequency of 0.3 Hz, 2nd order LPF and High pass filter (HPF) with 0.3 Hz-10 Hz is used. Arduino Duo, 32-bit ARM core microcontroller is used.

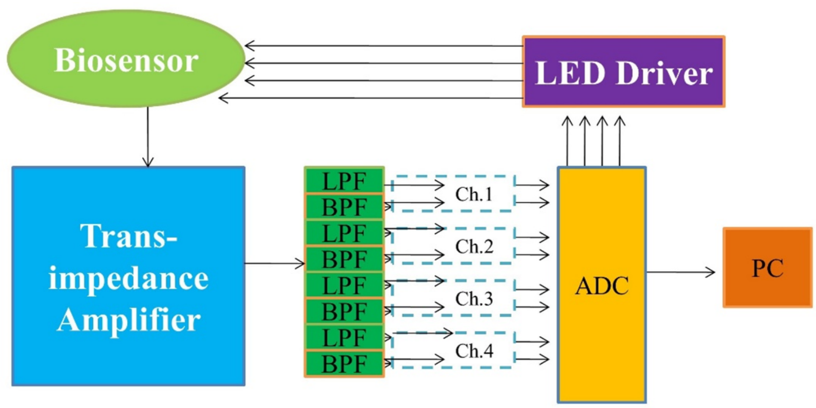

Fig. 5. Block diagram of NIR biosensor for noninvasive blood glucose monitoring [31].

Analog signal from biosensor is collected for data acquisition as shown in fig.5.Trans-impedance amplifier (TIA) is implemented for converting current to voltage. LED driver controls the four LED'S inside the design using bipolar NPN transistors. Low pass filter (LPF) and High pass filter (HPF) are used to form a band -pass filter. All analog signals are fed to A/D conversion. Data analysis is performed in PC by implementing MATLAB R2017b. Combined VIS-LED and NIR-LED are used in the study.PPG signals are collected which is noise prone. Pre-processing of PPG signal is done to remove baseline wander using digital wavelet transform (DWT) and wavelet decomposition (WD). Simple moving average algorithm is used for data smoothing. To find the relationship between extracted features and reference glucose, partial least squares (PLS) algorithm is applied. The model is validated by 10-fold cross-validation procedure.The designed system is tested on 12 healthy volunteers whose blood glucose ranged from 70mg/dL to 152mg/dL.BG is measured noninvasively through wrist and invasively through glucometer.8 pairs of data is collected in the gap of 10 min. Carbohydrate rich meals are given to the volunteer and BG is tested after 20 min of consumption in 120 min experiment time. 24 features are extracted from multiple Vis-NIR PPG signals. Average correlation coefficient (Rp) between estimated and reference BG concentration of 0.86 with standard prediction error of 6.16 mg/dL is achieved.Measurement was taken when not in motion. PPG is measured only during steady state in the study whereas an accelerometer can be used in the design to monitor body movements and eliminate noisy signals. Experiment was conducted only on 12 volunteers whereas for a device to be commercialized, it has to be tested on more than 100 diabetic and non diabetic individuals. Real time parameters such as weight, height, BMI,sex, sleep pattern, stress, age of a person must be considered. The limitations in the study can be considered as future work for enhancing the designed module.

Al-dhaheri et. al proposed noninvasive glucose monitoring by implementing PPG signal [32].Circuit arrangement and components: The design consists of following parts- One NIR based 940nm wavelength for detecting PPG signal. Arduino Uno, digital butterworth filter, HPF of 0.8 Hz cut off frequency is used to remove baseline drift/low frequency signals. To detect 50 Hz power line interference, twin-T notch filter with a potentiometer is implemented. LM324 amplifier is used for amplifying the signal. To remove high frequency components after amplification, a low pass filter with cut off frequency of 8 Hz is used.

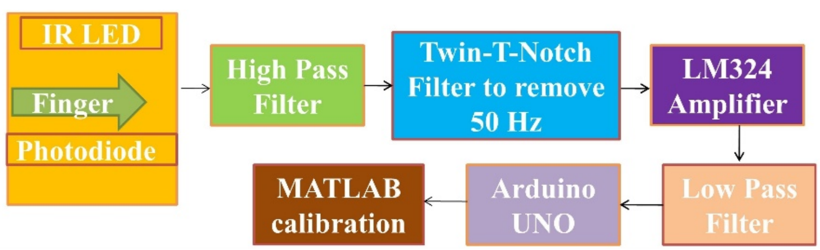

Fig. 6. Block diagram of PPG signal based non invasive blood glucose monitoring [32].

Finger site is constructed in between IR LED and Photodiode as depicted in fig.6. HPF is implemented to block the low frequency signals. The analog signal is filtered with twin-T-Notch filter and the signal is amplified by LM324 amplifier. LPF is implemented to remove high frequency components. The analog signal is fed to Arduino UNO microcontroller to convert A/D and data analysis is carried out in MATLAB. HPF with Ten volunteers were selected for testing the model.BG was measured several times a day before and after meals invasively with a glucometer and non-invasively with the designed hardware. Data pre-processing is done to acquire a clean signal.15 readings of an individual is considered before and after meals. Customized calibration model is designed for individual. From the peaks of the PPG data, mean voltage value is calculated. It is observed that intensity of voltage changes with changes in BG concentration. Regression analysis is done for calibrating the model. Root Mean Square Error (RMSE) of 8.264mg/dL -13.166 mg/dL, average RMSE of 10.44mg/dL with correlation coefficient R2 of 0.839 is obtained. The predicted BG falls under clarke error grid.940 nm is a short-wave IR rays whereas for PPG, 520 nm to 560 nm green light is used. With 940nm, BG can be determined though NIR.I Wavelength and type of light is misinterpreted by the author in the study. As stated for the previous study, PPG with accelerometer can eliminate noisy signals by monitoring movements of a body for CGM. In this study, hypertension is ignored. This model can be enhanced by considering hypertension and other parameters such as weight, height, BMI ,sex, sleep pattern, stress, age of a person etc for CGM.

Sridevi, P. et.al proposed a BG detection using NIR-940nm in vitro with glucose solutions and in vivo prediction of BG in diabetic individuals [33]. The design consists of following parts - DC source of 9V, LM7805 voltage regulator, NIR LED of 940nm source and photo detector, Arduino board.

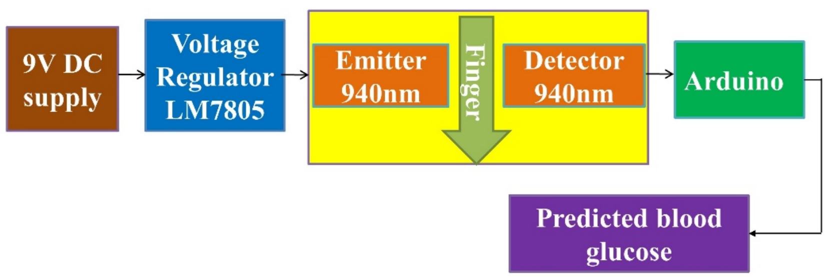

Fig. 7. Block diagram of PPG signal based noninvasive blood glucose monitoring [33].

The circuit is powered with 9v DC supply as shown in fig.7.Voltage regulator LM7805 is implemented to maintain constant output voltage of 5V. Emitter detector pair of 940nm is constructed with site for inserting finger for BG measurement . Arduino is used to convert the analog values into digital which is displayed at the output. First an in vitro experiment is carried out using ten solutions of glucose concentrations ranging from 20 to 350 mg/dL. For the in vivo test,20 diabetic individuals are considered. Reference glucose values were obtained from the gluco meter kit.It was observed that in an in-vitro experiment, as the test tube has high reflectance when compared with human finger, the amount of absorbance is less and reflectance is more i.e., voltage obtained at the detector is high. This is due to lighter medium of test tube whereas, human finger constitutes layers of skin, blood components and orgenelles and therefore absorbance is more. In an in-vivo experiment, as BG is found more in a diabetic individual, absorbance of light is more and reflected light is less. In normal individual, amount of light absorbed is less due to low BG concentration and hence the voltage at the end is higher than a diabetic individual. Linear relationship is obtained between glucose solution and diabetic individual with correlation coefficient of 0.93. Error rate of 2.43% is obtained by comparing invasive and noninvasive BG measurements. The designed prototype is tested only on 20 diabetic individuals which can be increased to 100 for calibration of the device. Normal, pre-diabetic and diabetic individuals at different ages must be considered in the study for designing a precise equipment. Non linearities such as motion, meal intake, BMI, stress etc can be considered as future work. Future work can also include miniaturizing the device for wearable real time CGM.

M. R. Haque et.al proposed a noninvasive Hemoglobin, Glucose and Creatinine measurement based on NIR-PPG signal from fingertip video [34]. The design consists of following parts- 6 of 850nm and a white LED,Nexus-6p camera(30fps).

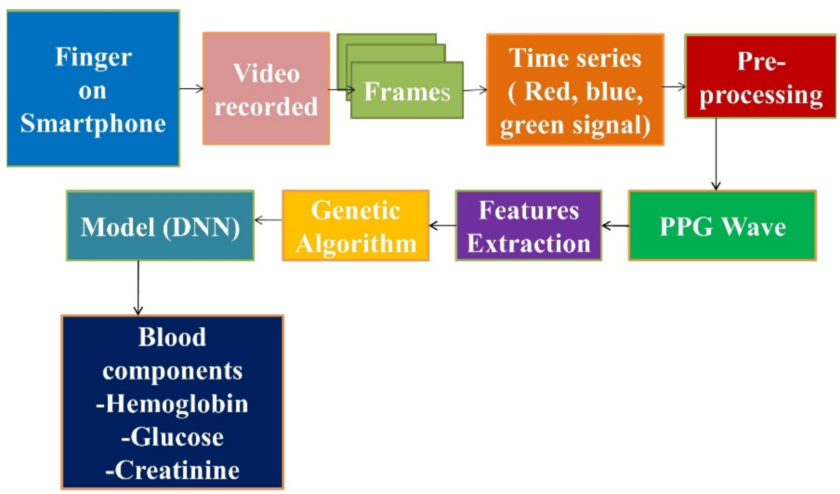

Fig. 8. Block diagram of fingertip video based noninvasive Hemoglobin, Glucose and Creatinine monitoring [34].

The sensor is designed by using six LED's of 850nm in circle and white LED in centre . White LED is used to increase the intensity of the six LED's. It is mounted as a wearable. Fingertip video is recorded using smart phone for 15 sec illuminating the finger through as depicted in fig.8.The frames are extracted from the video recorded. Time series method is applied on all signals.PPG wave is drawn from the signal. 46 features from the PPG signal are extracted. The designed model is tested on 93 subjects.PPG signals are obtained whose derivatives of 1st and 2nd order and Fourier analysis is done. To avoid overfitting and redundancy, correlation-based feature selection (CFS) and genetic algorithm is applied.21 features from PPG signal,19 from 2st and 2nd dervative,6 features from Fourier analysis is extracted.DNN model with 10 -fold cross validation is implemented to validate the model. Hemoglobin, Glucose and Creatinine are predicted from the model.Hb, GI and Cr levels are estimated with an accuracy of R2=0.922 for Hb, R2=0.902 for GI, R2=0.969 for Cr.The proposed method of detecting Hb, GI, Cr non-invasively is an innovative approach. The application can be experimented on various smart phones with different camera qualities for calibration and validation. Life of a smart phone depends on its battery charge, which becomes challenging to use in case of emergency and low charge in the smart phone. CGM is challenging in the proposed approach. This method can be taken as a future work and transform it into a wearable smart band or watch.

Kalaivani V et.al developed a 940nm source and 870-1100nm photo detector based non invasive BG monitoring device [26]. Circuit arrangement and components: The design consists of following parts- TSAL6100 940nm source and 870nm-1100nm photo detector, Optical sensor OPT101, Arduino Uno, ATmega328,Op-Amp LM358.

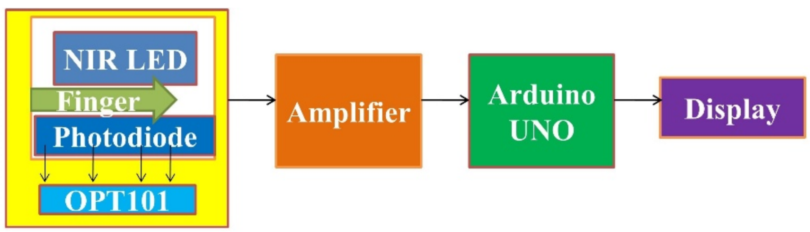

Fig. 9. Block diagram of noninvasive blood glucose monitoring with OPT101 reflective sensor [26].

The sensor is constructed by using 940nm NIR LED and 870nm-1100nm photodiode as shown in fig.9.OPT101 transimpedance amplifier is used to convert optical into electrical signal without noise. The signal is amplified with noninverting amplifier. The analog signal is converted into digital by Arduino UNO and the value is displayed at the output. The designed system is tested on 5 normal volunteers. Finger is placed in between the source and the detector. Reflected light from the finger is calculated for BG estimation. Embedded C programming is implemented for converting the voltage values into estimated BG measurements. The proposed method is tested on 5 normal volunteers. For a device to be calibrated and validated, it has to be tested on many volunteers. Reference BG levels (invasive method) are not considered in the study. Correlation analysis is ignored in the study. The study can be further enhanced by considering reference measurements and their correlation with predicted BG levels.

Haxha, S et.al proposed a low-cost equipment for in vitro and in vivo method of non invasive glucose monitoring [27]. Circuit arrangement and components: The design consists of the following parts-Power supply of 12V,940 nm LED ,750-2500nm LED ,350-1100nm Silicon pin photodiode (BPX 65) from OSRAM

Opto Semiconductors, ADC module, Arduino, voltage regulator, voltage divider, microcontroller.

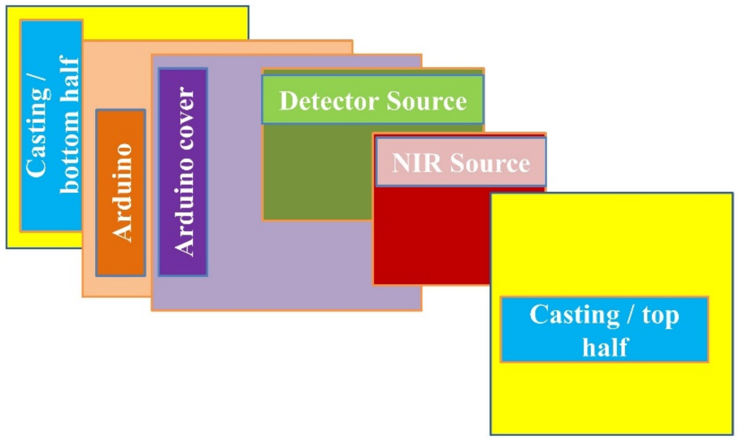

Fig. 10. Block diagram of non invasive blood glucose monitoring device for in vitro and in vivo trials [27].

The NIR source and detector is covered with Casting top and bottom half as depicted in fig.10.Detector source is connected to the arduino cover which guards the arduino for collecting analog signals. The bottom of the arduino is covered with bottom casting. The study is carried out in 1 aqueous solution for in vitro and a group of 6 individuals for in vivo study. During an in vitro testing, aqueous solution of 111mMol is prepared and tested. The concentration is increased by 111mMlol and tested for glucose concentration. It was observed that as glucose concentration increases, there is an increase in the output voltage. During an in vivo testing, index finger tissue is placed in between the source and detector. The space between source and detector is kept dark isolated from external light. Data processing algorithm is implemented to calculate absorbance and concentration. For Regression analysis of in vivo, R2=0.96, standard error of 34.49, significance F of 0.018 is obtained. Clarke grid analysis is obtained for in vivo where the noninvasive values were under acceptable region.There is a misinterpretation in an in vitro trial. According to Beer Lambert's law, light from source is absorbed by the molecule present in a medium. Amount of light absorbed is dependent on the concentration of the molecule and remaining is reflected away. The reflected light at the photodiode is measured in voltage. As concentration of glucose increases, absorbance is more and reflected light is less and therefore amount of voltage at the output is lesser than glucose absorbed. This is given in contrast in for in vitro study. The in-vivo study is tested only on 6 individual's index finger tissue. For a real time CGM, this method is challenging, correlation between reference glucose levels and predicted glucose levels is not explored. These limitations can be considered as future work.

Tronstad C et.al proposed an multisensor system through NIR, bioimpedance, skin temperature-based BG prediction for detecting Hypoglycemia from plasma glucose non invasively [35]. Circuit arrangement and components: The design consists of following parts- Spektron 880nm-2200nm LED, Tungsten halogen light source(LS-1 model, Ocean Optics),custom probe, Siemens Drager 520469 temperature probe.

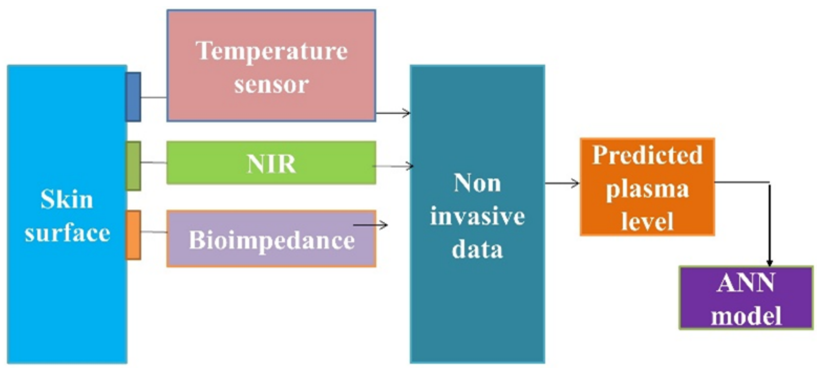

Fig. 11. Block diagram of multisensor system for non invasive blood glucose monitoring device [35].

Multisensor system i.e., temperature sensor, NIR, bioimpedance are used to predict Hypoglycemia from the skin as depicted in fig.11. Non-invasive data from multisensor is collected.ANN model is implemented on the data to predict the plasma level. The study is conducted on 20 Type-1 volunteers with impaired hypoglycemia. The volunteers were instructed to avoid hypoglycemic period of 48 hrs and they fasted from 10 pm at night.BG was controlled with insulin infusion based on weight and variable glucose infusion to clamp BG.YSI 2300 STAT Plus glucose analyzer is used for venous BG values as reference values. Simultaneously BG were recorder from the attached electrodes through probes and NIR sensor. It was observed that for hypoglycemic range under D zone of Clarke-error grid, performance is poor. Threshold based hypoglycemia detection is inaccurate. It was overall observed that NIR was the main predictor of BG trends whereas bioimpedance can be included for correcting confounding properties such as skin hydration and tissue perfusion. Prototype developed for the study is huge for a wearable. Possible reason for poor accuracy and unreliability is due to huge wavelength of LED chosen i.e., 880nm-2200nm.Glucose is peak at 930-970nm,1040-1100nm and 1280-1300nm where other blood constituents are low for interference. Accuracy can be improved while also considering the model for normal, diabetic (hypoglycemic and hyperglycemic) individuals.

Jintao, X et.al proposed an in vivo noninvasive BG measurement on normal and diabetic induced rats using NIR spectroscopy [36]. The design consists of following parts- 12000cm^{-1} (833.33 nm)-400(2500nm)NIR spectra, Bruker Optik FT-NIR spectrometer, PbS detector and fiber optic probe.

Fig. 12. Block diagram of Bruker-optik FT NIR-spectrometer for non invasive blood glucose monitoring device [36].

Bruker optik FT-NIR spectrometer is used with 2500nm NIR spectra as shown in fig.12. Fiber optic probe is placed on the rat's shaved leg and measurements are noted. The study is carried out on 12 normal and 18 diabetic induced rats. 180-200g weighing rats were divided into two groups after feeding a standard diet for 1 week. The first group are considered as normal whereas second group were fed HFD with 12% W/W glucose and coconut oil for 4 weeks. After fasting of 9hrs, plasma and spectra samples were obtained at intervals of 0min,15min,30 min,45 min,60 min,90 min,120 min,180 min and 360min. Oral Glucose tolerance test (OGTT readings are considered as reference BG values.It was observed that in normal rats, pancreatic tissue has oval and round cells whereas pancreatic cells are reduced or destroyed in diabetes rats. Partial linear regression is applied on the nonlinear dataset. Lower root mean square error of validation (RMSEP) of 0.419 and higher correlation coefficient of 96.22% is achieved.

Challenges and future scope-The proposed method can be tested on human volunteers by considering diabetic individuals of different age groups thus eliminating the method of inducing glucose. The device developed is huge for CGM and therefore it can be reduced for a wearable for CGM as future work.

4 Discussion and Future work

NIR spectroscopy has been widely used by many studies. Many researchers have developed NIR models for noninvasive blood glucose monitoring device. However, most of the models developed are not suitable for measuring continuous monitoring of glucose in real time. For continuous monitoring of blood glucose, device has to be small in the form of a wrist watch or smart band to be tied around wrist which is not possible from [28, 30, 31, 33–36]. Smart watch model was developed by [31], but haven't tested on larger dataset. The design considered can take reading at steady state position which is a contrary to real time CGM.

A real time CGM must be a wearable and noninvasive. The circuit structure can be minimized and developed as a wearable. For calibration of the designed hardware, Ethical clearance must be obtained from hospital where the device will be used for measuring from patient's BG levels. Random sampling method must be carried out among a group of volunteers after fabrication of the device. Invasive readings must be taken at the time of measuring BG values non-invasively which serve as reference BG levels. Relationship between hardware BG values and reference BG values must be carried out. An algorithm must be developed to convert the obtained values from the hardware to their respective BG levels. The predicted BG levels must be tested for clinical accuracy. Almost all studies on noninvasive glucose monitoring in the literature cover a hardware that is huge, non-portable, non-wearable device that may be miniaturized and transformed as a wearable as future work.

5 Conclusion

In today's lifestyle changes and era, it has become essential to monitor BG levels. Pathology lab reports and home monitoring kits are very expensive for CGM. Amount of blood drawn for pathology test may reduce blood levels. Home monitoring kits may provide instant solution with a drop of blood but continuous pricking of finger is prone to infections and pain. Recording wrong readings are also possible due to pricking the finger at wrong site and insufficient amount of blood drop for testing BG levels. This review covers all studies explored in the field of non invasive BG monitoring i.e., electrochemical method, electromagnetic method, thermal and optical method. Implementing optical NIR method for the advancement of the study is also justified. Principle and working of NIR is elaborated along with hardware proposed and trials conducted. Device developed in the literature is discussed with sensor specifications, hardware design flow, working of the hardware, method of carrying out the procedure and result obtained. Each literature is concluded with challenges in the proposed method and possible future work.

References

1. MedlinePlus: Blood sugar (2019), https://medlineplus.gov/bloodsugar.html
2. Norman, J.: Normal regulation of blood glucose. insulin regulation of blood sugar and diabetes (2016), www.endocrineweb.com/conditions/diabetes/normal-regulation-blood-glucose
3. World Health Organization: A global brief on diabetes mellitus (2025), https://www.who.int/news-room/fact-sheets/detail/diabetes
4. Rajeswari, S., Ponnusamy, V., Zdravkovic, N., Kisic, E., Padmajothi, V., Vijayalakshmi, S., Anuradha, C., Malathi, D., Ramasamy, N., Janardhan, K., et al.:

Development of a near infrared region based non-invasive therapy device for diabetic peripheral neuropathy. Scientific Reports **14**(1), 27993 (2024)
5. American Diabetes Association: Diagnosis | ADA (2025), Www.diabetes.org. https://www.diabetes.org/diabetes/a1c/diagnosis
6. Satuluri, V.R., Ponnusamy, V.: Enhancement of ambulatory glucose profile for decision assistance and treatment adjustments. Diagnostics **14**(4), 436 (2024)
7. Lee, H., Hong, Y.J., Baik, S., Hyeon, T., Kim, D.H.: Enzyme-based glucose sensor: from invasive to wearable device. Advanced healthcare materials **7**(8), 1701150 (2018)
8. Xue, Y., Thalmayer, A.S., Zeising, S., Fischer, G., Lübke, M.: Commercial and scientific solutions for blood glucose monitoring—a review. Sensors **22**(2), 425 (2022)
9. Tang, L., Chang, S.J., Chen, C.J., Liu, J.T.: Non-invasive blood glucose monitoring technology: a review. Sensors **20**(23), 6925 (2020)
10. Villena Gonzales, W., Mobashsher, A.T., Abbosh, A.: The progress of glucose monitoring—a review of invasive to minimally and non-invasive techniques, devices and sensors. Sensors **19**(4), 800 (2019)
11. Chen, Y., Lu, S., Zhang, S., Li, Y., Qu, Z., Chen, Y., Lu, B., Wang, X., Feng, X.: Skin-like biosensor system via electrochemical channels for noninvasive blood glucose monitoring. Science advances **3**(12), e1701629 (2017)
12. Chang, T., Li, H., Zhang, N., Jiang, X., Yu, X., Yang, Q., Jin, Z., Meng, H., Chang, L.: Highly integrated watch for noninvasive continual glucose monitoring. Microsystems & Nanoengineering **8**(1), 25 (2022)
13. Malik, S., Khadgawat, R., Anand, S., Gupta, S.: Non-invasive detection of fasting blood glucose level via electrochemical measurement of saliva. Springerplus **5**(1), 701 (2016)
14. Tanaka, Y., Tajima, T., Seyama, M., Waki, K.: Differential continuous wave photoacoustic spectroscopy for non-invasive glucose monitoring. IEEE Sensors Journal **20**(8), 4453–4458 (2019)
15. Malchoff, C.D., Shoukri, K., Landau, J.I., Buchert, J.M.: A novel noninvasive blood glucose monitor. diabetes care **25**(12), 2268–2275 (2002)
16. Zheng, P., Kramer, C.E., Barnes, C.W., Braig, J.R., Sterling, B.B.: Noninvasive glucose determination by oscillating thermal gradient spectrometry. Diabetes Technology & Therapeutics **2**(1), 17–26 (2000)
17. Cherkasova, O., Nazarov, M., Shkurinov, A.: Noninvasive blood glucose monitoring in the terahertz frequency range. Optical and Quantum Electronics **48**(3), 217 (2016)
18. Kaurav, P., Koul, S.K., Basu, A.: Non-invasive glucose measurement using subterahertz sensor, time domain processing, and neural network. IEEE Sensors Journal **21**(18), 20002–20009 (2021)
19. Lundsgaard-Nielsen, S.M., Pors, A., Banke, S.O., Henriksen, J.E., Hepp, D.K., Weber, A.: Critical-depth raman spectroscopy enables home-use non-invasive glucose monitoring. PloS one **13**(5), e0197134 (2018)
20. Chen, T.L., Lo, Y.L., Liao, C.C., Phan, Q.H.: Noninvasive measurement of glucose concentration on human fingertip by optical coherence tomography. Journal of biomedical optics **23**(4), 047001–047001 (2018)
21. Pirnstill, C.W., Malik, B.H., Gresham, V.C., Coté, G.L.: In vivo glucose monitoring using dual-wavelength polarimetry to overcome corneal birefringence in the presence of motion. Diabetes technology & therapeutics **14**(9), 819–827 (2012)
22. Zwinkels, J.: Light, electromagnetic spectrum. In: Encyclopedia of color science and technology, pp. 1062–1069. Springer (2023)

23. Fox, G.: The brewing industry and the opportunities for real-time quality analysis using infrared spectroscopy. Applied Sciences **10**(2), 616 (2020)
24. Theophanides, T.: Introduction to infrared spectroscopy. Infrared Spectroscopy-Materials Science, Engineering and Technology **2012**, 1–10 (2012)
25. Jain, P., Joshi, A.M., Mohanty, S.: Everything you wanted to know about noninvasive glucose measurement and control. arXiv preprint arXiv:2101.08996 (2021)
26. Kalaivani, V., Devika, E., Arulladakanthan, R., Santhoshini, A.: Designing and implementation of non invasive blood glucose and hemoglobin detection using nir. International Journal of Innovative Technology and Exploring Engineering (IJITEE) **9**(11), 229–232 (2020)
27. Haxha, S., Jhoja, J.: Optical based noninvasive glucose monitoring sensor prototype. IEEE Photonics Journal **8**(6), 1–11 (2016)
28. Rajeswari, S., Vijayakumar, P.: Development of sensor system and data analytic framework for non-invasive blood glucose prediction. Scientific Reports **14**(1), 9206 (2024)
29. Srichan, C., Srichan, W., Danvirutai, P., Ritsongmuang, C., Sharma, A., Anutrakulchai, S.: Non-invasively accuracy enhanced blood glucose sensor using shallow dense neural networks with nir monitoring and medical features. Scientific Reports **12**(1), 1769 (2022)
30. Joshi, A.M., Jain, P., Mohanty, S.P., Agrawal, N.: iglu 2.0: A new wearable for accurate non-invasive continuous serum glucose measurement in iomt framework. IEEE Transactions on Consumer Electronics **66**(4), 327–335 (2020)
31. Rachim, V.P., Chung, W.Y.: Wearable-band type visible-near infrared optical biosensor for non-invasive blood glucose monitoring. Sensors and Actuators B: Chemical **286**, 173–180 (2019)
32. Al-Dhaheri, M.A., Mekkakia-Maaza, N.E., Mouhadjer, H., Lakhdari, A.: Noninvasive blood glucose monitoring system based on near-infrared method. Int. J. Electr. Comput. Eng **10**(2), 1736–1746 (2020)
33. Sridevi, P., Arefin, A.S., Ibrahim, A.S.M.: A feasibility study of non-invasive blood glucose level detection using near-infrared optical spectroscopy. Bangladesh Journal of Medical Physics **14**(1) (2021)
34. Haque, M.R., Raju, S.T.U., Golap, M.A.U., Hashem, M.: A novel technique for non-invasive measurement of human blood component levels from fingertip video using dnn based models. IEEE Access **9**, 19025–19042 (2021)
35. Tronstad, C., Elvebakk, O., Staal, O.M., Kalvøy, H., Høgetveit, J.O., Jenssen, T.G., Birkeland, K.I., Martinsen, Ø.G.: Non-invasive prediction of blood glucose trends during hypoglycemia. Analytica chimica acta **1052**, 37–48 (2019)
36. Jintao, X., Liming, Y., Yufei, L., Chunyan, L., Han, C.: Noninvasive and fast measurement of blood glucose in vivo by near infrared (nir) spectroscopy. Spectrochimica Acta Part A: Molecular and Biomolecular Spectroscopy **179**, 250–254 (2017)