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Pain-free Blood Glucose Monitoring Using Wearable Sensors: Recent Advancements and Future Prospects

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***Abstract*—Keeping track of blood glucose levels non-invasively is now possible due to diverse breakthroughs in wearable sensors technology coupled with advanced biomedical signal processing. However, each user might have different requirements and priorities when it comes to selecting a self-monitoring solution. After extensive research and careful selection, we have presented a comprehensive survey on non-invasive/pain-free blood glucose monitoring methods from the recent five years (2012–2016). Techniques from bioinformatics, computer science, chemical engineering and microwave etc. are discussed here in order to cover a wide variety of solutions available for different scales and preferences. We categorize the non-invasive techniques into non-sample and sample based techniques which we further grouped into optical, non-optical, intermittent and continuous techniques. The devices manufactured or being manufactured for non-invasive monitoring are also compared in this paper. These techniques are then analyzed based on certain constraints which include time efficiency, comfort, cost, portability, power consumption etc. a user might experience when using such techniques. Re-calibration, time and power efficiency are the biggest challenges that require further research in order to satisfy a large number of users. In order to solve these challenges, Artificial intelligence (AI) is been employed by many researchers. AI based estimation and decision models hold the future of non-invasive glucose monitoring in terms of accuracy, cost effectiveness, portability and efficiency etc. The significance of this work is two-folds: 1. To bridge the gap between IT and medical field and 2. To bridge the gap between end users and the solutions (hardware and software).**

***Index Terms*—Non-invasive blood glucose monitoring devices, Non-invasive techniques to monitor blood glucose, minimally-invasive techniques to monitor blood glucose, Invasive techniques to monitor blood glucose.**

I. Introduction

THE basic human body vitals like heart rate, blood pressure, blood glucose, oxygen saturation etc. need to be monitored regularly to ensure a healthy life and to avoid complications that can occur due to the disturbance in the levels of these vitals [1]–[4].

Diabetes is one of the most common chronic diseases that occurs due to an imbalance in the glucose levels of the body [5]–[10]. It has two major categories; type 1 and type 2 [11]. In type 1 diabetes, the pancreas does not produce enough insulin whereas, in type 2, the body is unable to properly utilize the produced insulin [12]–[14]. Research is being done on the development of artificial pancreas to benefit type 1 diabetes patients to help control the glucose concentration [15]. More than 90% of the diabetes patients are suffering from type 2 diabetes [16]–[18]. According to a prediction by International Diabetes Federation, the rate of the people affected by diabetes will increase greatly and by 2035, 592 million people will be diabetic [19]. The rapid growth in the number of diabetics can be seen in Figure 1 created by using the information published in [20]–[22]. There is no cure for diabetes so far but monitoring the glucose levels regularly helps in keeping diabetes in control [23]–[25]. Self-management is one of the most feasible and helpful/useful solutions to control diabetes.

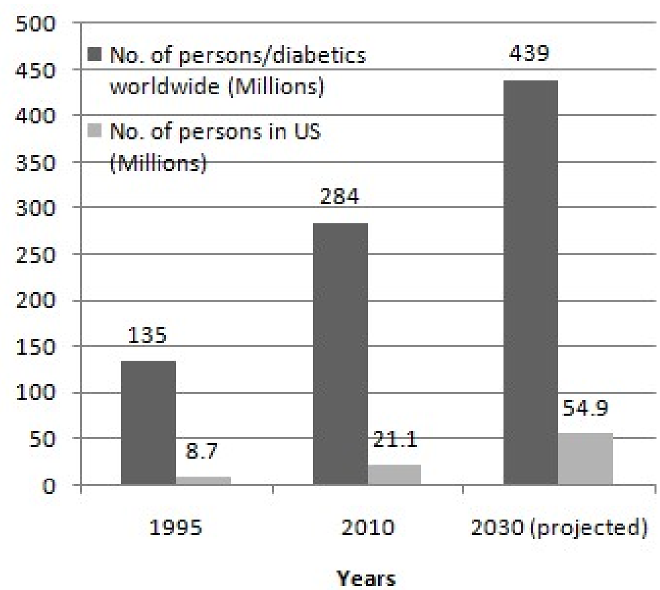

Figure 1: Growth in the number of diabetics over the years

Hyperglycemia and hypoglycemia are the conditions caused by very high and very low blood glucose levels respectively. Doctors advice frequent monitoring (4–5 times a day) of

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glucose levels to reduce such conditions/events [26]. The complications arising from imbalanced glucose levels in diabetes patients include strokes, cardiovascular diseases, blindness, chronic kidney failure, amputations etc. [27]–[29].

The blood glucose is measured in milligrams per unit deciliter (mg/dl) and different ranges of blood glucose levels are discussed in Table I. The nature of the blood glucose monitoring techniques can be categorized as non-invasive, minimally invasive and invasive.

Invasive devices are inconvenient as they cause pain while taking the blood sample and they are costly as they require test strips for blood samples [30]. In the recent years, non-invasive devices are being developed by using wearable sensors based on optics, biochemistry, microwave, saliva and tear etc. to help diabetics avoid pain and infections.

In the past few years, researchers have reviewed the advancements of glucose monitoring from time to time [24], [33]. In [33], different techniques used for non-invasive glucose monitoring along with the devices are discussed, but the review covers the research done until early 2012. The work done till 2014 is reviewed at [24], but it only discusses the glucose monitoring based on near-infrared (NIR) spectroscopy. Due to the advancement in biomedical signal processing and wearable sensors, many new methods are proposed every year, including methods other than NIR spectroscopy to estimate the glucose concentration that needs to be surveyed and analyzed.

After extensive research and careful selection, we present a comprehensive survey on non-invasive/pain-free blood glucose monitoring from the recent five years (2012–2016). The significance of this work is two-folds: 1. To bridge the gap between IT and medical field and 2. To bridge the gap between end users and the solutions (hardware and software).

We searched five (5) major databases: IEEE Xplore, ScienceDirect, PubMed, ACM Digital Library and Springer for non-invasive blood glucose monitoring from the recent 5 years i.e. 2012–2016. After searching the databases for keywords: non-invasive blood glucose self-monitoring, about 2500 research articles were found but only 300+ were selected after screening their abstracts. Thorough full text screening of the related papers narrowed it down to 116 papers and 84 papers were selected for discussion in the following sections.

In this paper, we categorize the non-invasive monitoring into non-sample and sample-based techniques. Non-sample based methods are grouped into optical and non-optical techniques whereas sample-based techniques are grouped as intermittent and continuous monitoring methods. The advancements in the non-invasive/pain-free blood glucose monitoring are analyzed in the recent 5 years (2012–2016) based on cost effectiveness, portability, energy and time efficiency of the methods along with a discussion on the devices available in the market for this task. With the advancement in technology, to develop robust systems for healthcare, the focus should be power/energy consumption, portability, response time, re-calibration and cost etc. Every research has different goals and to achieve those goals, trade-offs need to be made. The users can select the systems according to their personal priority and requirements. This work provides an overview of research done in the healthcare monitoring domain using techniques from the computer sciences, biomedical, electrochemical, antenna propagation and related fields.

Table I: Different ranges of Blood Glucose levels [31], [32]

State	Range mg/dl
Normal (fasting)	70–130
Hypoglycemia	below 70
Hyperglycemia	above 180

The rest of the paper is organized as follows, Section 2 discusses the non-invasive glucose monitoring devices. Section 3 and Section 4 analyzes different non-sample and sample based techniques to monitor the blood glucose non-invasively respectively. Section 5 sheds light on the major challenge and possible solutions. Section 6 describes future prospects of the non-invasive blood glucose monitoring and Section 7 concludes the paper.

II. Non-Invasive Glucose Monitoring Devices

As mentioned in Section 1, the blood glucose monitoring techniques can be categorized as invasive, minimally invasive and non-invasive as shown in Figure 2.

Invasive techniques can be painful at times and carry the risk of infections as they require sensors to be implanted subcutaneously or extraction of the interstitial fluids [34], [35]. The miniaturization and safety is very important to avoid severe injuries to the body [36]–[49].

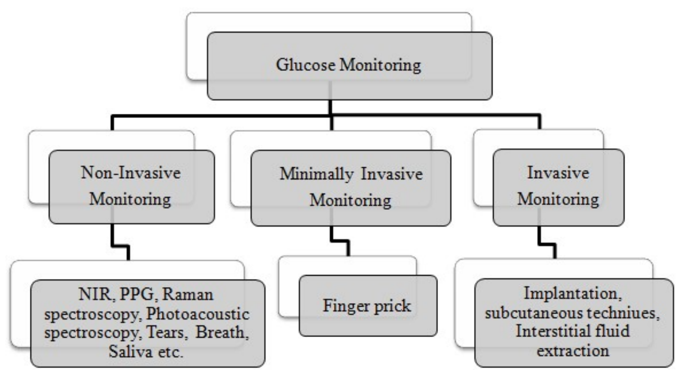

Figure 2: Categories of Glucose Monitoring

Minimally invasive techniques require small blood samples to estimate the glucose concentration. They are more accurate than the non-invasive methods but can cause a little pain as a needle prick is required to take the sample as shown in Figure 3 [30], [50], [51]. Frequent testing can make the user uncomfortable and can result in poor management of diabetes [52]–[56].

Non-invasive techniques do not need any incision or implantation so they are pain-free and very convenient but less accurate and there is a lag between the glucose levels in blood and other fluids e.g. saliva, tears etc. These methods often need to be calibrated for every individual.

Self management tools help to calculate the glucose concentration over time, before and after food intake etc. [9], [57]. These systems can also contain insulin pump and insulin

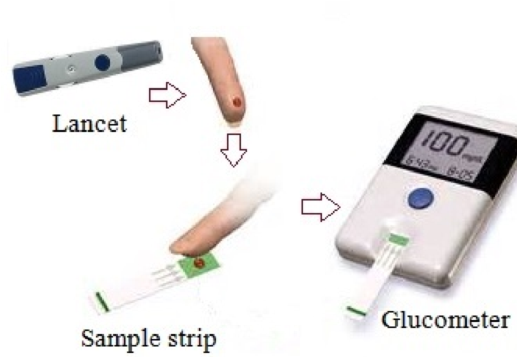

Figure 3: Conventional blood glucose monitoring device

management modules for insulin infusion and management [58]. Most of the solutions available in the market are of invasive nature and use electrochemical biosensors to detect the glucose concentration in the blood sample.

During the past decade, developing non-invasive blood monitoring devices has been of great interest for the researchers as well as the medical equipment manufacturing companies. The accuracy of these devices plays an important role in calculating the insulin dosage, if the glucose level measured by the device deviates largely from the original glucose levels, the patient can end up taking a high dosage of insulin which can be very harmful [59]–[62]. Some of the non-invasive blood glucose monitoring devices are discussed in this section and summarized later in Table II.

A. Non-Sample based: Optical Monitoring

Techniques that are not dependent on samples for estimating the glucose concentration, measure the concentration through the skin by utilizing light, electric current, ECG etc. and are grouped as optical and non-optical techniques based on the use of light.

Optical techniques use different wavelengths of light as the main component to measure the glucose concentration. It includes NIR spectroscopy, photoplethysmography, photoacoustic spectroscopy etc. The optical techniques are cost effective and comfortable for the users but they are susceptible to the environmental conditions e.g. temperature, pressure, skin hydration, humidity etc.

1) TensorTip$_{TM}$ Combo Glucometer: TensorTip$_{TM}$ COG is one of the non-invasive tissue photography based, CE certified glucose monitoring solutions. Users need to calibrate the device for a couple of weeks by using blood samples but after that, the device can be used to monitor the glucose levels painlessly and conveniently by putting the finger inside the device as shown in Figure 4(a). The device has a smartphone interface and is also able to manage the history of glucose monitoring [63]. Calibration based on an individual's blood sample allows for personalization that offers more accuracy. The device is portable and uses rechargeable battery making the device a cost effective solution. Rechargeable batteries can also come as a disadvantage as they have a self discharge issue and recharging is time consuming.

Figure 4: Non-Invasive blood glucose monitoring devices (a). TensorTip Combo Glucometer, (b). Glucosense, (c). GlucoWise, (d).GlucoTrack, (e). iQuickIt Saliva Analyzer, (f). Smart Contact Lens, (g). Noviosense

2) Grove's Device: Grove Instruments designed a non-invasive glucose meter based on NIR spectroscopy that can measure the glucose concentration from the fingertip or earlobe within 20 seconds. The device is battery operated, portable and accurate as it takes the readings from the blood on the capillary level instead of skin. Real-time estimation makes it a time efficient solution whereas the lack of individual based calibration can affect the accuracy for certain users [64].

B. Non-Sample based: Non-Optical Monitoring

The non-optical techniques use a small amount of current, electrocardiogram signals, microwave technology etc. and are painless but are less portable and can be a little uncomfortable for the user.

1) Glucosense: Glucosense, based on photonic technology is a non-invasive blood glucose monitoring device under development [65]. The device shown in Figure 4(b) is claimed to be pain-free, easy to use, affordable, portable and generate alerts for hypoglycemia. The user needs to touch the device to know about the glucose levels. The device consists of a silica glass that has ions sensitive to the infrared light and when the user touches the glass, the reflected spectrum changes according to the glucose concentration. The laser used to acquire the readings is low-powered that makes the device a power efficient solution. The device takes about 30 seconds to estimate glucose levels which makes it less time efficient as compared to other devices.

2) GlucoWise: GlucoWise is one of the devices based on radio wave technology that can be used for self monitoring of the blood glucose levels non-invasively i.e. without taking any blood samples for type 1 diabetics. The device provides intermittent monitoring by taking glucose readings from the

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Table II: Summary of Non-Invasive Blood Glucose Devices

Device	Company	Technique	Sample	Intermittent/ Continuous	Usage	Advantages/ Characteristics
TensorTip Combo Glucometer	Cnoga Medical	Tissue photography/ Photometric techniques	No sample	Intermittent	Fingertip	Painless, ease of use, Individual based calibration for high accuracy, PC and a Smartphone interface, rechargeable batteries, can manage history.
Groves's Device	Grove Instruments Inc.	NIR spectroscopy	No sample	Intermittent	Finger/earlobe	Portable, fast results, compact, battery operated
Glucosense	Glucosense diagnostics Ltd.	Photonics technology/ Fluorescence spectroscopy	No sample	Intermittent	Finger	Pain-free, compact, portable, ease of use, cost effective.
GlucoWise	MediWise	Radio wave	No sample	Intermittent	Between forefinger and the thumb	Pain-free, compact, comfortable, cost effective, time efficient, increased penetration, Bluetooth to transmit data or alerts, compatibility with insulin pumps.
GlucoTrack	Integrity Applications	Electromagnetic, ultrasound and thermal technology	No sample	Intermittent	Earlobe	Pain-free, No frequent calibration, cost effective, comfortable, earlobe has very little fat and a lot of capillary vessels.
iQuickIt Saliva Analyzer	Quick LLC	Salivary analysis	Sample	Intermittent	Mouth saliva	Pain-free, ease of use, portability.
Smart contact lens	Novartis and Google	Tear analysis	Sample	Continuous	Eye	Low power, comfortable, pain-free
NovioSense	Noviosense	Tear analysis	Sample	Continuous	Lower eye lid	Painless, wireless power, smartphone compatibility, compact, flexible/bendable.

area between the thumb and the forefinger as shown in Figure 4(c). The device measures glucose concentration on the capillary level, which makes it more accurate than the devices measuring glucose from the skin. It is claimed that the device is pain-free, cost efficient, convenient and is compatible with smartphones and insulin pumps. The shape and the size of the device are also very efficient and the device also has bluetooth to transmit data and alerts [62], [66], [67].

The device is time efficient as it takes about 10 seconds to estimate the glucose concentration. The device is portable and easy to use so it can be used while driving, sleeping, exercising etc. From the user's perspective, comfort, ease of use, cost, portability and an above average accuracy are priorities. There might be harmful effects due to the use of localized energy but this can only be evaluated once the device is ready for the market after the clinical trial.

3) GlucoTrack: GlucoTrack merges the Electromagnetic, ultrasound and thermal technology to estimate blood glucose levels measuring at the earlobe. The device is claimed to be painless, cost effective, comfortable and does not need frequent calibrations. Using the earlobe as the measuring site helps with the accuracy of the device as there are no bones and less fat in the earlobe. The device has two main components, an ear clip that measures the blood glucose from the earlobe and the main unit is where the results are displayed as shown in Figure 4(d) [68]–[70]. GlucoTrack received FDA approval and a final CE mark in 2015 and 2014 respectively. Using three different techniques to measure glucose levels can improve the accuracy but make the device processing complex, resulting less power and a less time efficient solution.

C. Sample based: Intermittent Monitoring

Sample based devices are dependent on fluid samples e.g. saliva, tears, breath etc. for glucose concentration estimation. These methods are accurate, convenient, portable etc. but there is a lag between the change in glucose concentration in blood and other fluids. Sample based devices are grouped into intermittent and continuous monitoring devices based on the frequency of the vitals information acquisition and monitoring.

Intermittent monitoring is when the samples are acquired periodically to estimate the glucose concentration. It is a cost effective method for patients having rather stable glucose levels but the abnormal changes in the vitals in between the monitoring can not be predicted/detected. Every single measurement requires a new sample.

1) iQuickIt Saliva Analyzer: iQuickIt Saliva analysis is under development and uses saliva samples instead of blood samples to measure glucose levels [71]. It uses disposable draw wick sticks for the samples and can transmit the readings to other smart devices. It is claimed that the device measures glucose levels painlessly and accurately and that it is easy to use. The device is shown in Figure 4(e). Since the device is still under clinical trials, nothing can be said for sure but it has been designed to provide the results in real-time making the device time efficient. The information regarding the processing or power consumption aspect has not been discussed yet. More can be known after the clinical trials and FDA approval, when the device is available in the market.

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D. Sample based: Continuous Monitoring

In continuous monitoring, the vitals are monitored regularly, which is a better fit for patients having a history of severe hypo or hyperglycemia i.e. unstable glucose levels. This kind of monitoring can help in predicting and avoiding severe hypo or hyperglycemia episodes but it can be a little expensive and a little uncomfortable in some cases.

1) Contact Lens: Smart contact lens shown in Figure 4(f) uses tears to monitor the glucose concentration. It consists of a wireless transmitter to send glucose readings and uses a static electrical charge for power [72], [73]. It provides continuous monitoring of glucose levels, is portable, low power, easy to use etc. but can make the user uncomfortable and overheat causing possible damage to the eye. The device/product is under development, proper analysis will be possible after the clinical trials, FDA approval and availability in the market.

2) Noviosense: Noviosence, a device under development, uses tears to measure the glucose levels using electrochemical means [74]. The device is a 2cm long and flexible spring as shown in Figure 4(g). The device is claimed to have a wireless module to transmit data and to power the device. The sensor is low power, painless, portable, sensitive etc. but can cause a little discomfort for the users since eyes are a sensitive part of the body.

III. Non-Invasive Non-Sample based Glucose Monitoring

Non-Invasive techniques are pain-free, convenient and no incision or injury needed but they are not as accurate as the conventional invasive techniques. The ubiquitous use of computer sciences in healthcare gives birth to designing non-invasive methods for basic vital monitoring like heart rate, blood pressure, blood glucose etc. [75]–[78]. Computer science and data processing have played a vital role in medicine and healthcare inventions by helping in diagnosis improvement, disease prediction etc. [79], [80].

Several techniques have been used over the years to measure/monitor the blood glucose non-invasively. We have categorized these techniques into sample and non-sample based glucose monitoring. The non-sample based methods are further grouped into optical and non-optical monitoring. Figure 5 describes the general flow of non-sample based optical monitoring systems whereas Figure 6 describes a state-of-the-art system model for non-sample based optical monitoring .

Non-sample based monitoring techniques utilize light, current etc. instead of fluid samples to measure the glucose concentration.

A. Optical Monitoring

The methods based on light as the main component to estimate are known as optical methods. Table III summarizes the optical techniques for glucose monitoring.

1) Near Infrared Spectroscopy: Near infrared spectroscopy is one of the most widely used non-invasive technique in which the spectrum from the part of the body is acquired when light from the near infrared range falls on it. This technique is simple and harmless but factors like thickness of the skin, fatty tissues, blood altering illness, medication and thermal properties of the skin etc. affect the accuracy/performance by affecting the light absorbance.

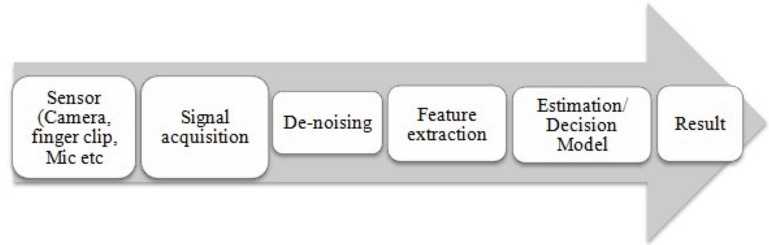

Figure 5: Non-sample based optical monitoring system general flow

In [81], the authors propose a near infrared spectroscopy based blood glucose monitoring system using a smartphone. The data was acquired by capturing the laser light transmitted by the fingertip with a smartphone camera. The transmitted light intensity was found to be inversely proportional to the glucose concentration as more light is absorbed with higher glucose concentration. An application was developed to extract the intensity of RGB pixels from every frame. The concentration of glucose is determined by using the blue and green component intensities in the modified Beer-Lambert law and it was found that the glucose concentration measured by the smartphone is linearly proportional to the actual glucose concentration. The experiments were performed with both the glucose solution and then blood. The glucose levels were examined 15 and 45 minutes after drinking cola. The application utilizes android platform, is sensitive but needs a powerful processor in order to avoid slowing down other applications. The experiment results were calculated using MATLAB. The overall solution proposed is cost effective but highly dependent on light conditions and different skin area exposure for every user. The performance can also be affected if the user is suffering from other chronic illnesses.

In [28], NIR spectra was acquired using the fiber probe on the tongue and after the denoising and reconstruction of the spectra, least square support vector machine (LSSVM) was used to build the calibration and the prediction model for the diabetes classification with a reasonable accuracy. Non-linear calibration models are designed for better accuracy and LSSVM is utilized because of its capability in non-linear models. The diabetes classification model was found to yield better results than the glucose concentration estimation. For the experimental setup, the probe was used on user's tongue and the reflected signals were collected from the tip of the tongue. Acquiring data from the tongue rules out the difference in user's skin thickness, the fats and offers a high signal-to-noise ratio (SNR). The environmental conditions e.g. pressure, temperature, humidity etc. can affect the system performance.

Light beam with a wavelength of 1310nm has been used in [82] to detect the glucose concentration in aqueous solution. The light beam was split into two beams, one beam was passed through the solution while the other was captured directly. Absorbance and optical distance changes the transmitted light intensity. The measurement is done by deriving a relationship between the power outputs of the light beams against different glucose concentrations in the solution. The power output was found to be inversely proportional to the glucose concentration. Thickness of the skin and fatty tissues can also affect the transmittance of light. The experiment was conducted on aqueous solutions with different concentrations of glucose. The proposed method is energy consuming, not portable or accurate enough and testing on real blood is necessary to prove the effectiveness of the system.

Photoplethysmography (PPG) is used to measure the flow of blood volume in a certain part of the body. Light falls on the surface of the body part and a portion of that light is absorbed by the blood and the other portion is reflected back or traversed through the body part and represents the volume of blood i.e. it can be used to acquire PPG signal. The PPG is cost effective, painless and convenient [83]. This data can be termed as BigData if the data is gathered from a large number of subjects for a long period of time.

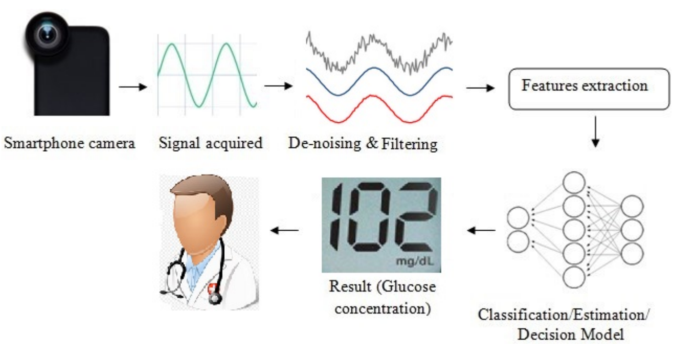

Figure 6: A generic state-of-the-art non-invasive blood glucose monitoring system model

In [84], transmission PPG acquired by an LED and a photodiode embedded finger clip was used to estimate the blood glucose levels based on difference in optical intensity. The PPG waveform reflects the cardiac cycles and according to the authors, the transmittance of light is inversely proportional to the glucose concentration in the blood. The acquired signals were converted to electrical signals, filtered for noise removal using a series of filter e.g. a high pass filter, amplifier and a 4th order low pass filter to finally get the PPG signal. The PPG signal was then filtered using an adaptive adaline neural network filter to remove motion artifacts. An invasive glucometer was used to collect the actual glucose levels of the subjects which were used along with the filtered PPG signals to predict the glucose levels using artificial neural networks for Field Programmable Gate Arrays (FPGA). The data was collected from 50 individuals for 3 different wavelengths. The model was trained and tested using MATLAB toolbox for neural networks and the accuracy in the estimation was found to be 95.38%. Fatty tissues and motion artifacts can affect the system performance. The signal acquisition is simple, portable and convenient but the processing is complex and time consuming besides adding processing load.

B. Paul et al. [85] discuss transmission PPG based blood glucose monitoring system that uses a modified pulse oximeter to acquire the PPG signals. According to the authors, with an increase in the glucose concentration, the absorbnce of the light in the blood decreases. The acquired signals were in the form of photo current which was converted to measurable voltage values before being filtered. The filtered signals then use labVIEW for processing and the AC component of the PPG has been used to estimate the glucose levels. The experiments were performed on 5 individuals before and 2 hours after the food intake. The results were validated by comparing with the glucose measurements of an invasive glucometer. The proposed method requires proper equipment to acquire the PPG signals which makes the simple and convenient acquisition method costly and less portable. The signals need to be transferred to a computer for further processing that makes it time consuming.

When light falls on the skin, a part of it is absorbed and the remaining portion is reflected and can be used to measure the oxygen saturation level by taking the difference of oxy-hemoglobin and deoxy-hemoglobin. Glucose concentration and the oxygen saturation are linearly dependent and inversely proportional to each other i.e. the more the calculated oxygen saturation, the less the glucose concentration. Near infrared light is used to measure the skin oxygen saturation in [34] as the wavelength of the light affects the penetration depth, the lower the wavelength the further it goes and the better results are yielded. The data is acquired in the form of skin tissue images and the temperature distribution on the skin and transferred to a computer for further processing. The environmental conditions e.g. temperature, humidity etc. can affect the data acquisition process and hence the system performance. The relation between the oxygen saturation level of the skin and the glucose concentration in the blood is derived and applied on the acquired data to estimate the glucose levels of subjects from different age groups and genders. The experiments were performed to examine the fluctuations in the glucose concentrations before and after meal. The equipment required for data collection makes it less portable and costly. The processing is simple but the procedure is a little time consuming since the data needs to be transferred to a computer and then processed.

2) Photo acoustic Spectroscopy: The change in the media/medium pressure caused by the ultrasonic/sound waves can be used to measure the blood glucose concentration with high sensitivity and is known as the Photo acoustic spectroscopy [86], [87]. It can be combined with other techniques like near infrared spectroscopy to yield better results. In [88], The photoacoustic signals were obtained after optical to thermal conversion of the incident light. Glucose concentration in aqueous solution was estimated based on the change in optical absorption coefficient and the change in pressure. The photoacoustic signal samples were acquired using a 1550nm laser light and a microphone in a photoacoustic cell. Photoacoustic signals for different glucose concentration were collected and a linear relationship was found between these signals and the glucose concentration. The signal acquisition process is independent of light scattering in tissues but sensitive to pressure and temperature variations. The overall procedure is costly in terms of energy and time.

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Table III: Summary of Optical Non-Invasive Techniques for Blood Glucose Monitoring

Ref.	Year	Technique	Equipment/site	Advantages	Disadvantages	Purpose
[84]	2015	PPG, NIR, ANN	Finger clip with an LED and a photodiode	Cost effective, FPGA helps in making hardware implementation fast.	Adaptive filters need to be applied which adds to the processing, FPGA ANN are challenging, PPG is susceptible to noise.	Blood glucose sensing
[81]	2014	NIR spectroscopy	Laser, HTC X Smartphone	Cost effective, portable, easy to use, can be used frequently because it is convenient, sensitive to changes, easy calibration	A lot of factors e.g. medication etc. can affect the absorption of light and in turn the results.	Blood glucose monitoring
[85]	2012	PPG, NIR spectroscopy	Modified pulse oximeter	Pain-free, frequent monitoring, no chance of infections, no contact with pointed objects	It is dependent on the environment, also the angle of the incident light.	Glucose measurement
[28]	2014	NIR, LSSVM	Optical fiber probe, Human tongue, NIR Quest512 Spectrometer, tungsten halogen lamp	High vascularity, fatty tissues are less, the tongue has no skin so no thickness issues Environmental conditions affect the acquisition.	Susceptible to noise	Blood glucose concentration and diabetes identification
[87]	2016	NIR and MEMS technology, photoacoustic spectroscopy, Regression model	NIR sensor, MEMS sensor, Ear lobe	Pain-free, comfortable, less interference in the data, Calibration approach, using the two technologies together make it more accurate and sensitive, compact size, power efficient, earlobe skin is not very thick so deep penetration also no bones.	Environment e.g. temperature, humidity, pressure etc. dependent, performance is surface and surface area dependent.	Blood glucose monitoring system
[34]	2016	Skin oxygen saturation and partial oxygen pressure	CCD camera, thermal camera	Pain-free, oxygen distribution image	Light conditions affect	Glucose evaluation
[88]	2015	Photoacoustic, optical and thermal spectroscopy	Laser diode, Mic	Reliable, pain-free, improved sensitivity, compact size	Temperature and pressure dependent	Glucose monitoring
[89]	2015	Photoacoustic spectroscopy, NIR	Pulsed laser diodes, piezoelectric transducer	Painless, Sensitive, harmless, less optical scattering	Absorption behavior can be non-uniform	Glucose measurement
[82]	2015	NIR spectroscopy	Laser, spectroscope, thermal sensors	Pain-free, user friendly, cost effective	Not very accurate due to the limited data	Glucose concentration measurement
[90]	2015	Optical coherence tomography	Not clearly mentioned/Light source, coupler, interferometer	High resolution images, deep penetration and better SNR.	Trade-off between the depth and the transverse resolution, temperature and pressure dependent	Blood glucose monitoring

In [89], the sensor uses the measured change in the pressure of the body part i.e. finger, earlobe etc. caused by the sound waves generated by them. Two pulsed laser diodes and piezoelectric transducer were used to gather the photoacoustic signals. It was found that the higher the glucose concentration, the stronger the response photoacoustic signals are. The signals were amplified, averaged to improve SNR and reduce noise before transferring to a computer for further processing. Features were extracted from the signals and the glucose concentration was estimated by the photoacoustic amplitude. Regression analyses were used for calibration and the system was validated by an invasive glucose meter. The solution lacks time and energy efficiency and also the temperature and pressure can affect the performance along with non-uniform absorbance.

3) Optical Coherence Tomography: In Optical Coherence Tomography (OCT), high resolution optical imaging using the reflected or the scattered light is utilized. It is quite similar to the ultrasound technique where sound is used instead of light. Microscopic characteristics can be examined and analyzed non-invasively using OCT. In [90], the glucose concentration is estimated by acquiring 2D OCT images using an interferometer. The correlation coefficient between the OCT and the skin depth is optimized on the basis of the tissue scattering coefficient. The relation between the OCT slope and the blood glucose concentration is utilized to estimate the glucose concentration. The calibration of the OCT non-invasive system is done by using the invasive techniques to measure blood glucose level. The technique is temperature and pressure dependent i.e. the environmental conditions can affect the performance. The calculation for estimating the glucose concentration is time consuming and the process assumes there are no other affecting parameters.

B. Non-Optical Monitoring

The techniques that are not dependent on light are called the non-optical techniques. Table IV summarizes the non-optical techniques for glucose monitoring.

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Table IV: Summary of Non-Invasive Non-Optical Techniques for Blood Glucose Monitoring

Ref.	Year	Technique	Equipment/site	Advantages	Disadvantages	Purpose
[23]	2014	ECG, ANN	Compumedics ECG device	Pain-free, no need for frequent calibration	No portability, accuracy is not good, too many input parameters makes it complex and put a load on the processor	Hyperglycemia detection
[91]	2016	ECG, ELM (extreme machine learning)	ECG	Fast convergence and scalable computations	The ECG parameters used for estimation can be affected by any other heart conditions.	Hypoglycemia monitoring
[92]	2012	Reverse Iontophoresis	Forearm, skin-gel electrodes	High sensitivity, use of potassium improved the correlation	Use of electric current can be uncomfortable for certain individuals, analyte correlation dependant, frequent calibration is required, not accurate enough for clinical use	Glucose measurement
[93]	2016	Microwave technology	Microwave sensor (microstrip ring patch antenna)	Compact, cost effective, painless, more accurate because it uses resonant method	They can be affected by the environmental conditions.	Measurement of the dielectric properties of the aqueous glucose
[94]	2016	Microwave technology	Microwave sensor (microstrip spiral patch antenna)	Compact, cost effective, pain-free, high quality	Atmospheric conditions can introduce noise	Blood glucose monitoring
[95]	2016	Microwave technology	microstrip two faced patch antenna	high penetration, high sensitivity, ease of use	VNA effects the miniaturization of the system also the convenience, Atmospheric conditions affects the working.	Glucose sensing
[62]	2016	Millimeter wave/Antenna	Glucowise (2 sensor patch antennas)	Painless, convenient, portability, less interference.	Localized energy can cause harmful effects	Glucose sensing
[96]	2016	Wireless technology	Wearable wireless sensor	User friendly, portable, pain-free, high accuracy, low power consumption, cost effective	Wireless technology is prone to the interference	Blood glucose measurement
[97]	2015	Microwave	Microstrip triangular patch antenna	Affordable, small size, linearity	Low power handling	Glucose measurement
[98]	2014	Dielectric spectroscopy/ Microwave technology	Patch resonator	Small size, high sensitivity	High error rate on higher frequencies	Monitoring of blood glucose levels
[99]	2012	Optical, Dielectric spectroscopy	Optical, temperature, humidity, movement, dielectric sensor, upper right arm	No physiological and environmental perturbation problems due to unfavorable conditions	Results are not yet comparable to the enzymatic needle sensors	Continuous glucose monitoring
[100]	2014	Antenna, Cole-Cole model	Antenna, network analyzer, wrist	accurate calibration model	Environmental conditions can affect the results, individual based calibration is needed	Blood glucose level estimation

1) Electrocardiograph (ECG) signals: ECG signals are used to monitor the working of one's heart and any abnormalities in the functioning of the heart are reflected on the ECG signals. ECG signal happens to paint a good picture about high and low glucose levels so it can be used to check one´s blood glucose levels [23].

H. T. Nquyen et al. in [23] uses 16 parameters from the ECG signal and ANN to detect hyperglycemia/normoglycemia events i.e. if the glucose level is greater than 150 mg/dl, it is hyperglycemia and if it falls between 60-150 mg/dl, it is a normoglycemia event. Among the 16 parameters, 5 ECG intervals e.g. heart rate, QT interval etc. are utilized as main variables. The ECG data is acquired using the Compumedics device, the extracted parameters are fed into an ANN and the output of the model indicates normo or hyper state, The experiments were performed on 10 individuals (T1) and a geometric mean accuracy of 67.94% was obtained. In [91], Extreme Machine Learning (EML) is used with ECG signals to detect hypoglycemia and hyperglycemia. EML has a fast learning property that makes the system time efficient and its ability to deal with the problem of overfitting makes it a better fit solution. Heart rate and QT interval are the main variables used in the proposed model as hyperglycemia causes the heart rate and QT internval to increase. The experiments were performed for 10hrs overnight on 16 children (T1) with a 70 % sensitivity in results. Using ECG is pain-free but any kind of heart condition e.g. arrhythmia etc. and the medications will affect ECG signals and that might end up affecting the accuracy of the measured glucose concentration.

2) Reverse Iontophoresis: Reverse iontophoresis is when a small current is applied to the skin, the glucose molecules move closer towards the skin and makes it easier to measure the glucose concentration [101].

In [92], two skin-gel electrodes are used with a small current by constantly reversing the polarity and the glucose concentration in the gel is measured using standard glucose monitoring devices like Gluco Pap etc. The accuracy of the

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technique is greatly dependent on the calibration and the correlation between the glucose level of the blood and the extracted analyte. The technique is quite close as to taking a blood sample without actually drawing any blood which makes it pain-free and convenient. The limitation being the longer the process takes, the chances of getting skin burns due to the current gets higher. Also the current level is kept too small to be bearable for the skin which limits the accuracy.

3) Microwave/Antenna: Resonance frequency can be used to estimate the blood permittivity which can be used to measure the blood glucose levels. A microstrip patch antenna can be used to measure the blood glucose levels based on the frequency shift. When microwaves falls on a part of the body, a part of them is absorbed/transmitted and the other part is reflected. Any of the part can be used to study the details about the part of the body e.g. the glucose concentration etc. In [97], a microwave antenna is designed to estimate glucose concentration. A finger is placed on the patch of the antenna and the change in the resonance frequency is measured. Ansoft HFSS is used to simulate the antennas [98]. The operating frequency and the shape of the antenna patch can be different e.g. a ring [93], a spiral [94], rectangular [95] and triangular [97]. In [100], an antenna was used for real time estimation of blood glucose levels non-invasively. A shunt capacitor circuit was utilized to track the change in glucose concentration using the Cole-Cole model. An antenna and a network analyzer were utilized collect readings from the wrist of an individual every 15 seconds. The difference in resonant frequency for both the diabetic and non-diabetic individuals was measured over time after food intake. It was found that individual based calibrations are required for blood glucose estimation. A calibration technique based on the shift in resonant frequency was proposed. The results were validated by comparing to the results of a standard glucometer and Clarke grid analysis. The results yielded proved to be in good correlation with the results of a glucometer. The environmental conditions e.g. temperature, sweat and blood pressure can introduce noise and affect the performance of the antennas.

4) Miscellaneous: Different sensors can be used to measure the glucose concentration in the blood non-invasively by processing the light reflected by the skin. The wavelength of the source light varies i.e. infrared, fluorescence or ultrasound and so the penetration depth of the light. The relation between the measured reflected light and the actual glucose levels is different for different individuals because of different body structures and conditions. Accurate mathematical relations can be derived between the two using differential equations to have an accurate estimation of the blood glucose concentration [96]. The skin and tissue dielectric properties change due to physiological factors such as variations in blood glucose, temperature etc. A combination of optical, humidity, temperature and dielectric sensors were used to estimate blood glucose levels. Identification models using variety of techniques like least absolute shrinkage and selection operator (LASSO) were utilized for linear regression. The data was acquired in 150 channels from the upper right arm of 6 T1DM subjects. The data was preprocessed, the first 75 minute recording was removed and the signals were filtered to remove spikes. It was found that though the accuracy is not yet comparable to the currently used enzymatic technique, the LASSO method improves the glucose concentration estimation accuracy of the multisensor [99].

IV. Non-Invasive Sample based Glucose Monitoring

There are techniques that require a sample e.g. saliva, tears, urine, breath etc. to estimate the glucose concentration in the blood and are termed as sample based techniques. Sample based glucose monitoring is further categorized as intermittent and continuous monitoring. Table V summarizes the sample based techniques for glucose monitoring whereas Figure 7 describes the general flow of sample based monitoring systems.

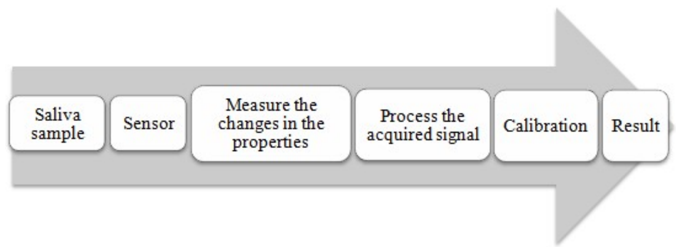

Figure 7: Sample based monitoring system general flow

A. Intermittent Monitoring

If the samples are taken to measure the glucose concentration periodically over the time, it is called as intermittent monitoring. Intermittent monitoring is cost effective and is a better fit for the patients in a stable condition.

1) Salivary Analysis: The biochemical markers found in saliva are believed to represent the human body as well as a mirror. Using saliva for diagnostic or monitoring purposes has a lot of advantages like convenience, cost effectiveness, accuracy, sensitivity, portability etc. but the correlation varies for every individual, the saliva viscosity is affected by the environment, also there is lag in the glucose concentration changes between the blood and the saliva [19], [102]–[104]. In [19], a disposable biosensor for measuring the saliva glucose levels is proposed that can act as a standalone electrochemical device for glucose monitoring. The saliva sample is taken and amperometric measurements are carried out to measure the glucose level. Though the clinical trials were carried out accurately, the sample acquisition procedure is a bit complex and time consuming. The overall procedure is costly, energy consuming and will take about 90 seconds to measure the glucose concentration. [102] uses a scanner to record the color changes in a filter paper when the saliva is placed on it. The glucose concentration is calculated by analyzing the RGB components of the scanned paper strip. The whole procedure takes atleast 50 seconds, 3-5 seconds for sample acquisition and then color scanning after 45 seconds i.e. the sensor's response time. Among the three colors, the blue color was found to be the most sensitive. The process is convenient for the user and simpler as compared to the centrifugation process but it is time consuming and requires proper equipment to

Table V: Summary of Sample based Non-Invasive Techniques for Blood Glucose Monitoring

Ref.	Year	Technique	Equipment/site	Advantages	Disadvantages	Purpose
[19]	2015	Salivary analysis	On-chip Saliva biosensor	Sensitivity, pain-free, convenient, fast.	Saliva viscosity is affected by environment, the correlation can vary for different persons.	continuous salivary glucose monitoring
[106]	2012	Breath analysis, regression analysis (SVOR-support vector ordinal regression)	12 metal-oxide semiconducting sensors, e-nose	Independent of environmental conditions (temperature, humidity etc.), low cost sensors	The setup is complex and can be performed in a laboratory with specific equipment	Blood glucose monitoring
[102]	2015	Salivary analysis	Optical biosensor, paper strip	Cost effective, affordable	Not sensitive to low glucose levels, prone to interference	Glucose sensing
[103]	2015	Salivary and tear analysis	Biosensor	Painless, high sensitivity	More sample volume is needed for better signals, complicated process to remove proteins from the samples	Glucose detection
[104]	2015	Saliva Analysis	Disposable biosensor	Painless, simple, high accuracy, sensitive, ease of use, cost effective	Prone to motion artifacts, possibility of data noise	Glucose sensing
[105]	2015	Salivary analysis	Cavitous sensors	Pain-free, continuous, wireless module for telemetry, customized mouth piece	Can be a little uncomfortable to use	Glucose monitoring
[109]	2012	Tear analysis	Contact lens, Glucose sensor, wireless transmitter	High sensitivity, reduced chances of infection, time efficient	Increase in eye temperature, visionary issues, harmful effects of the equipment on the eye	Tear glucose monitoring
[107]	2014	Breath analysis	E-nose	Improved accuracy, convenient, pain-free	Not fit for clinical use	Blood glucose prediction
[108]	2014	Breath analysis	E-nose	Individual based prediction model, takes into account the humidity and alveolar air, cost effective, portable	The prediction model is not accurate enough for practical use.	Diabetes screening and blood glucose level prediction

estimate the glucose concentration which affects the energy consumption and portability of the process.

The authors in [105] utilizes sensitive cavitous sensors with a customized mouthpiece to measure the salivary glucose concentration. The glucose concentration is estimated by amperometric measurements with an interval of 180 seconds. The mouthpiece also includes an embedded wireless module to a setup for telemedicine. The use of MEMS technology in the proposed system offers portability, telemetry and reduced power consumption but it is time consuming and the mouthpiece can be a little inconvenient for the users. In [104], the authors propose a glucose monitoring system that uses a disposable glucose sensor and amperometric measurements at an interval of 18, 20 and 21 seconds. Different sizes of the sensor were compared with respect to the sensitivity. The correlation found in the fasting state seems quite promising. It is claimed that the proposed glucose sensor is cost effective, easy to use, has a high accuracy and sensitivity but is prone to motion artifacts and the complex process is time consuming as well as affects the portability.

2) Breath Analysis: The amount of acetone in one's breath is directly proportional to the blood glucose concentration which means breath analysis can be used to estimate blood glucose levels [106]. The change in the conductivity of a set of sensors sensitive to different components/elements in the breath respectively can be used for signal acquisition. The data is labeled with four levels according to the glucose concentration. The same data signals were processed using SVM (support vector machine) and SCR (sparse representation based classification) to compare the performance and accuracy of SVOR. SVOR was found to be the most accurate among the three. The sample acquisition method used is fast, simple and relatively low in cost as compared to the alternate/conventional method but transmitting data first to a computer for further processing is very time consuming. The processing algorithm is better suited for such classification but it does not work very well with the dataset outliers and is a bit complicated as compared to alternate machine learning algorithms thus consume more resources [106]. In [107], 10 sensors are used to acquire the breath samples which are then digitized and processed. Local and global regression models have been fused together to improve the accuracy of the prediction and to reduce the variant interference caused by individuals but the system is still not fit for clinical use. The data acquisition is convenient but the process is time consuming since the signals are extracted from the samples and are then transferred to a computer to further process for estimating glucose concentration. In [108], the authors utilized e-nose to acquire the breath samples and designs the individual based prediction models for blood glucose monitoring since the correlation between the blood glucose and the breath components can be different for different individuals. The authors claim that using the individual based design makes the prediction more accurate but the procedure is a bit complex and time consuming since it requires the samples to be collected and then converted to signals to be able to be used for prediction models. The prediction models still need improvements to be able to use for practical use.

3) Tear Analysis: Tears can be used to measure the blood glucose concentration as they have prominent biomarkers same as in the blood. In [103], both saliva and onion induced tears are used to estimate the blood glucose levels by centrifugation process. The results from the tear samples were found to be more accurate as compared to the saliva samples. The proposed method uses a complicated procedure to remove proteins from the collected samples also the volume of the samples were found to be directly proportional to the accuracy of the proposed method. The procedure to get to the final results is time consuming and complex.

B. Continuous Monitoring

If the samples are collected to estimate the vitals round the clock, it is termed as continuous monitoring. For the patients having unstable vitals, continuous monitoring is more suitable to predict hyper or hypoglycemia episodes.

1) Tear Analysis: In [109], the authors propose a tear analysis based continuous glucose monitoring system. The glucose sensor mounted contact lens has been used to get the tear samples and a wireless transmitter on the lens is then used to transfer the information to a reader wirelessly connected to the lens. The glucose levels are estimated in real-time making the proposed system time-efficient. The lens are designed in a way that the mounted modules do not get in the way of vision and utilize RF power. The time to get the results was found to be about 35 seconds while testing the proposed contact lens. The solution presented is portable, time efficient and can provide a better control on glucose levels but the temperature increase because of the equipment can have harmful effects on the eye.

V. Major Challenge & Possible Solutions

To provide convenient and pain-free blood glucose monitoring, non-invasive blood glucose monitoring systems are being designed, most of which are based on optically acquired signals. The accuracy of existing non-invasive glucose monitoring systems has been a great challenge for developers and researchers but is still far less than that of the invasive systems which makes them not fit for clinical and patient use [110].

Individual based calibration helps in improving the accuracy of such systems limiting the number of users to one as the user is required to calibrate the device once and later provides accurate results for that specific user.

In order to develop accurate systems without the need for individual based calibration, a larger dataset and a larger feature set is required so that the data from a large number of individuals can be studied to train a vast variety of parameters.

The mathematical models used for signal analysis sometimes fail to develop precise relation between the acquired input signal and the variations in blood glucose levels [111]. Choosing better data acquisition (procedure and equipment), noise canceling, signal processing and analysis systems will also help develop an accurate non-invasive blood glucose monitoring system.

VI. Future Prospects

The rapid increase in the number of diabetics gave birth to the need to develop reliable non-invasive self-monitoring solutions. The ultimate target of all the research being done in the field of glucose monitoring is to develop tools beneficial for diabetes patients. The monitoring systems need to utilize the concepts of artificial intelligence and expert systems to develop state-of-the-art monitoring systems as shown in Figure 8.

Since the main focus of this manuscript is to discuss the glucose level estimation so we will mainly talk about the glucometers being designed for self-monitoring the blood glucose concentration. Accuracy of a glucometer is very important as the dosage of the insulin is dependent on the results acquired from the glucometer. An overdose of insulin can be very harmful for the patients and can cause an increase in the heart rate, seizures and unconsciousness etc. A good glucometer is the one that meets the maximum allowed error standards set by IOS (International Organization for Standardization) and possess all or most of the following features/qualities:

a) ***Affordability:*** The self-monitoring tools should be cost effective in order for everyone to be able to benefit from them. The invasive solutions available in the market these days can be a bit costly since they need a one-time use test strip every time they use the glucose meter to measure glucose concentration. The strips are expensive and make it an expensive solution. Non-invasive solutions that have a low cost of operation and low total cost of ownership need to be designed for all kinds of target customers. More research needs to be done to be able to use devices like smartphones as a glucometer which will save the cost of buying a dedicated device for monitoring blood glucose.

b) ***Time efficient:*** The doctors advise the patients to check their vitals (glucose levels) about 4-5 times a day. If the glucose meter has more delay to display the results, it discourages the patients to measure the glucose concentration frequently as it wastes time and is inconvenient. So one of the most important qualities a glucose meter should have is that it should take the least possible time for processing and displaying the results. The least delay offered by non-invasive devices discussed in earlier sections is about 10 seconds. Future research should focus on reducing this delay up to maximum 3–5 seconds.

c) ***Portability:*** Portability is another important feature; the users should be able to use the devices anywhere anytime. The devices should be small sized and convenient to carry around. If the functionality of a glucometer is embedded into smartphones, the solutions will become portable besides being cost effective.

d) ***Power efficient:*** With portability comes the need for power efficiency. If the system consumes less power and has convenient recharge options, it adds to the portability. Usually for making the systems more time efficient, more resources are utilized that end up consuming more power making the solution, less power efficient. Sometimes a trade-off is needed between time and power. Systems that are adaptive to the user requirements are needed to be investigated in future research

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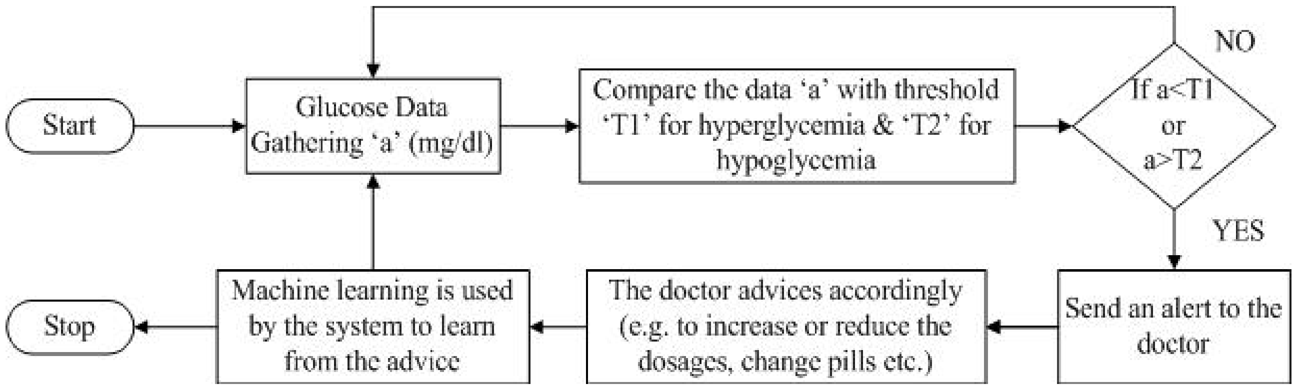

Figure 8: State-of-the-art artificial intelligence based blood glucose monitoring system

in order to trade-off between time and power according to user preference or the circumstances.

*e) **Re-calibration:*** The devices need to be re-calibrated in order to perform accurately over time for different individuals. Frequent re-calibrations are painful as they require invasive methods. The purpose of choosing non-invasive methods is to avoid pain and risk of infection, so the re-calibrations should be kept to longest possible period of time. The devices having individual calibrations seem to perform better and they do not require frequent re-calibrations. Future research should focus on developing non-invasive solutions that do not require recalibration or the least possible recalibration.

Secondary features to enhance the functionality, efficiency and user experience, that need to be focused on are usability, safety, record storage and history management, record/data transfer to computer and verbal instructions etc. Multi-functional solutions are required and components interoperability is a must in order to provide users with these features. The proposed solutions need to be evaluated on the basis of user satisfaction. Large scale clinical evaluations need to be carried out and more feasible error models are needed to be designed.

For serious/unstable cases, there should be solutions available e.g. to detect the level of waste materials/products built up so they can know when an emergency dialysis is needed etc. Methods for early detection of organ failure due to diabetes are also need to be investigated in depth in future research.

VII. CONCLUSION

Portable, time efficient, compact, cost effective, accurate, easy to use and power efficient methods to monitor blood glucose levels are needed in order to keep diabetes in control. Besides having the aforementioned qualities, if the technique is also comfortable and pain-free, it will be very convenient for the users to manage their glucose levels. Moreover, factors like blood altering illnesses, medication, dehydration etc. should be kept in consideration while designing non-invasive models. Much research is being done in the field of medicine in collaboration with several other fields such as computer sciences, biology, chemistry, physics and electrical engineering etc. during the recent years to develop more reliable and stable implantable sensors for invasive monitoring. Minimally invasive techniques with reduced processing time and sample volume are introduced whereas pain-free, sensitive and portable non-invasive monitoring methods are being developed to have a better control on the glucose levels.

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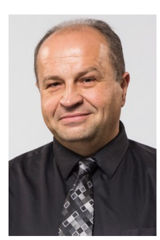

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