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A Modern Review of the Non-Invasive Continuous Blood Glucose Measuring Devices and Techniques for Remote Patient Monitoring System

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***Abstract*—**Diabetes disease that arises from the higher glucose level due to insulin shortage or insulin opposition in the human body has become a common disease in the world. No medicine can cure it completely. However, by taking medicine, maintaining diets, and having exercises regularly, a diabetes patient can keep his glucose level within the specified limits and in this way, he/she can lead a normal life like a healthy person. But to control glucose levels, a patient needs to monitor them regularly. Various techniques are being used over the last four decades. This modern review article aims to provide a comparative study report on various blood glucose monitoring techniques in a very concise and organized manner. The review mainly emphasizes working principles, cost, technology, sensors, measurement types, measurement accuracy, advantages, and disadvantages, etc. of various techniques and then compares among each other. Besides, the use of algorithms and simulators for the growth of this technology is also presented. Finally, current research trends of this measurement technology have also been discussed.

***Keywords*—**Blood glucose measurement, sensors, measurement devices, invasive and non-invasive techniques.

I. Introduction

THE foremost energy transporter inside the human body is blood and it comes from its glucose. A healthy person has a glucose level in blood within a normal range of 88-125 mg/dl (4.9-6.9 mmol/l) [1], [2]. Mainly, the insulin inside the human body helps to regulate the glucose level. Insulin is a kind of hormone that discharges from the pancreas to regulate the blood glucose level at a normal range. When we take a meal with carbohydrates then it is transformed into glucose and released into the bloodstream. After that, insulin in the blood aids to carry glucose from the bloodstream into cells where glucose is converted to energy [2]. Thus, if enough insulin doesn't secrete from the pancreas or if enough insulin is secreted but the body cannot make good use of it then the glucose level in the bloodstream rises and creates metabolic chaos inside the human body [3]-[5]. Such type of disorder is called diabetes, which is now worldwide a chronic disease [6].

Based on insulin production, there are two kinds of diabetes disease, such as type 1 and type 2. If the body cannot harvest enough or any insulin at all then it is called type 1 diabetes disease and in this case, the patient depends on insulin to keep the controlled sugar level. On the other hand, if the body can still produce insulin but the body becomes resistant to the insulin then it is called type 2 diabetes disease and in such case, the patient can keep his body's glucose level controlled by taking any medicine but not the external insulin [7], [8]. If the glucose level falls below the normal lower limit of 88 mg/dl or 4.9 mmol/l then it is called scarcity of glucose in the body or commonly known as hypoglycemia. Alternatively, if the glucose level goes above the normal higher limit of 125 mg/dl or 6.9 mmol/l then it is called surplus of glucose in the body or commonly known as hyperglycemia. Any type of diabetes disease is detrimental in the long run because it invites other diseases like cardiovascular diseases, heart strokes, kidney failures, eye-sightedness or even complete blindness, birth defects, damaged nerve system, sudden coma, memory loss, confusion, and even death.

The number of diabetic patients was projected by the International Diabetes Federation (IDF) as 463 million in 2019 and they are expecting that it may rise to 578 million by 2030 and 700 million by 2045 [9]. Moreover, 4 million people died due to diabetes diseases and their complications, and this costs the world expenditures of US$727 billion in 2017 [10] and US$760 billion in 2019 [9].

To have a controlled level of glucose in the bloodstream and to manage diabetes very well, we have to determine blood glucose levels precisely and regularly [11]. At present, there are various types of machines or devices that we may purchase from the retail market to determine the glucose level continuously. In this article, various such machines or devices and their working principles or technologies are discussed in the brief and compared. However, researchers are trying to improve these technologies and hence current research trends are also discussed in this article.

II. Biological Issues

Interstitial or intercellular or tissue fluid resides inside the microscopic sections nearby the cell. Glucose molecules can freely move from capillary endothelium to this fluid by a simple process called para-cellular or trans-cellular diffusion process. The amount of the glucose molecules per unit volume in this fluid is dependent on the rate of change of glucose molecules per unit volume of the blood, the metabolic rate of the human body, and the blood flow rate inside the capillaries [12], [13]. There is a substantial time delay or time difference (from 2 min

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to 45 min) between the highest glucose concentration inside this fluid and that inside the blood. This is given by the sum of the physiological and instrument time delay. The average time delay is 6.7 min [14]. The instrument time delay arises from the researcher's measurement method, and time delay due to physiological parameter fluctuations indicates the time needed to diffuse glucose molecules from the blood into the interstitial spaces of the capillaries [15]. The major challenge of determining the blood glucose level using the non-invasive technique is the determination of this physiological time delay. This problem is principally related to the spectroscopic technologies, which mainly probes intercellular glucose level, produces dissimilarities in the calibration procedures where blood glucose level is used as a reference point [16]. If there is a time delay then the concerned sensors are to be calibrated again to a new blood glucose level at static time gaps. We know that hypo-glycemia and hyper-glycemia problems rely on the glucose molecule concentration. As such, the discrepancy between the glucose levels of the intercellular fluid and blood tells us that the inter-cellular sensors are not suitable for a closed-loop insulin supply scheme. Furthermore, a time delay is faced in the supply and captivation of insulin for the subcutaneous-subcutaneous closed-loop scheme in which inter-cellular fluid is utilized to detect that the glucose molecules and insulin are transported using the sub-cutaneous method [17], [18].

III. Types of Blood Glucose Measurement Methods

Blood glucose concentration detection techniques are divided into three broad groups, namely invasive, minimally invasive, and non-invasive techniques [19]. There are various sub-classifications of these techniques. This is depicted in a flow diagram of Fig. 1.

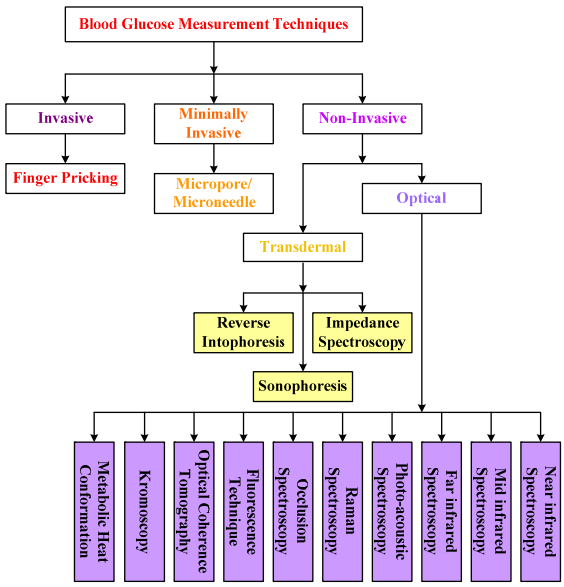


Fig. 1 Classification of blood glucose measurement techniques [14]

The invasive method needs to pierce the fingers of a patient to take a drop of blood sample onto a test strip to measure the blood glucose data. Therefore, it is also known as the finger-pricking method. However, this method is not so popular due to its numerous drawbacks. For example, many patients dislike to see blood coming out from their body, piercing fingers require a fresh needle and a test strip whenever a patient wants to measure his/her glucose level, and it gives some sort of pain to the fingers of the patients, there is a threat of being infected, and in the long run, finger pricking may yield permanent injury to the finger tissue [20].

Conversely, the minimally invasive technique uses subcutaneous sensors to measure the glucose level from the interstitial fluid. However, this method creates some sort of awkwardness to the patients, requires constant calibration, and is seriously susceptible to biofouling [21].

The third category is the in vivo non-invasive blood glucose measurement method by which glucose level is determined from the blood by using a kind of biological sensor having no physical connection with any parts of the human body, and there is no need to take blood samples on a test strip by using any needle to perforate the skin. As such, it is also inexpensive as compared to the invasive method [22]. Researchers are doing investigations on various types of non-invasive methods and algorithms to find the blood glucose level non-invasively. This would allow the diabetic patients to check their glucose levels more regularly and thus they would be able to keep the glucose level in their control.

The non-invasive determination methods are categorized into two major groups, such as (i) the transdermal method and (ii) the optical method.

The transdermal method uses the physical energy of the human body to have interstitial fluid or blood. Using some appropriate technology or algorithm, the glucose levels are then extracted. However, this method suffers from the problems of changes in skin properties and may originate blistering, burning, irritation, pains, and erythema.

Alternatively, the optical method uses photonic signals to get information from the glucose molecule inside the ISF, blood, or inner chambers of the eyes. Then glucose levels are detected based on microcontroller-based algorithms [14].

The transdermal and optical methods are sub-categorized further and are shown in Fig. 1.

IV. Working Principles of Non-Invasive Blood Glucose Measurement Devices

There are various forms of non-invasive blood glucose measurement methods available in the literature. This is shown in Fig. 1. In this section, a summary of the devices that are made using those techniques is given. Here only optical methods are discussed as these are now very popular methods.

These methods use a particular range (optical frequency) of the electromagnetic spectrum. The electromagnetic signal is propagated through the body tissue to interact with the glucose and other parts inside the tissues. Then the transmitted and reflected signal from the tissue is gathered and investigated to find the number of glucose molecules per unit volume of the tested tissues. Then a better selection algorithm is applied to determine the exact amount of right components without any

intervention of other parts in the sample. Then data is calibrated to compute the exact amount of glucose in the patient's body. Several algorithms and calibration methods are being established by several researchers around the world to increase the accuracy and precision levels of the data.

A. Near Infra-Red Spectroscopic Method

The systems that use the near-infra-red (NIR) spectroscopic method comprise a light-emitting source, optical fiber cable, photo-detector, etc. The optical signal, in the NIR region (700-1700 nm) for the Glucose spectra, is sent from the light source to the human body's tissue with a scanning rate of a spectral rate of 1800 spectra/s [23]. When it returns from there, it is captured by a photo-detector via the optical fiber. The collected signal is then converted into an equivalent voltage signal, which is very low in amplitude. So, it is then amplified via an amplifier. The amplified signal is then transformed into a digital signal and finally fed to the digital processor's input, such as the microcontroller [24]. After that, various signal processing techniques and multivariate analytic calibration models are applied to extract glucose levels in the blood according to the variation of the light intensity [23]. Finally, the extracted value is displayed on the screen, such as on an LCD unit with an appropriate unit of glucose level. Usually, the Clarke Error Grid (CEG) technique is utilized to check the clinical accuracy of the measured data [25]. A simple block diagram is depicted in Fig. 2.

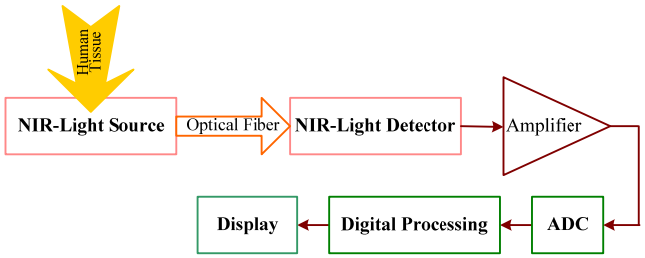


Fig. 2 Block diagram of the NIR-spectroscopic based blood glucose measurement (BGM) system

B. Mid and Far Infra-Red Spectroscopic Method

These two methods are very much similar to the near-infra-red spectroscopic method, but the main difference is that the parts of the body from where the measurement, i.e. the light emission and detection would be made and the emission spectra of the optical signal. The mid-infrared (mid-IR) mobile sensor-based Quantum Cascade LASER (QCL) with a sphere was used to find glucose contents transmitting and receiving LASER light to and from the human skin. The block diagram of such a system is presented in Fig. 3. The transmitted light is absorbed by the glucose molecules and then the back-scattered highly divergent light signal from the dermis layer is received by a miniaturized integrating sphere from where the signal is sensed by using a thermoelectrically cooled mercury cadmium telluride (HgCdTe) detector [26]. The spectra were smoothed using a Savitzky-Golay filter [27] and then the Principal Component Analysis (PCA) technique [28] is utilized to analyze and count the glucose content from the absorption co-efficient of the spectrum using a Fourier Transform Infra-Red (FTIR) transmission spectroscopy [29].

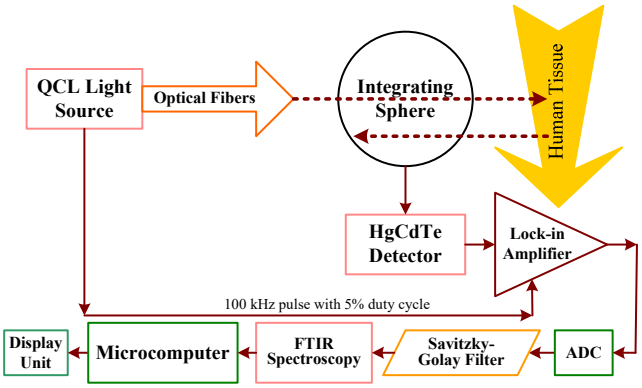


Fig. 3 Block diagram of the mid-infrared mobile sensor and QCL spectroscopy-based blood glucose measurement system

C. Photoacoustic Spectroscopy Method

The photoacoustic spectroscopy-based system comprises a LASER diode, a projection system, a transducer, optical fiber, a microcomputer, and a display unit [30]. In this method, very short period laser pulses (of the order of a few nano-seconds) are sent to the human body to stimulate blood glucose [31]. This generates heat energy into the local cells, expands those to yield the acoustic wave, which is then sensed by the piezoelectric transducer [32]-[34]. The peak-to-peak value of the reflected acoustic wave gives the amount of blood glucose data and also the total incident energy [35]. Finding the glucose level data by using such a method depends mainly on measuring the alterations of acoustic wave parameters that differ according to the glucose contents [36]. However, there are some detection errors in this method due to several limitations. To alleviate such errors partially, the ultrasound frequency band (50-60 kHz) is used to obtain a greater Signal-to-Noise Ratio (SNR). A simple block diagram of this kind of system is given in Fig. 4.

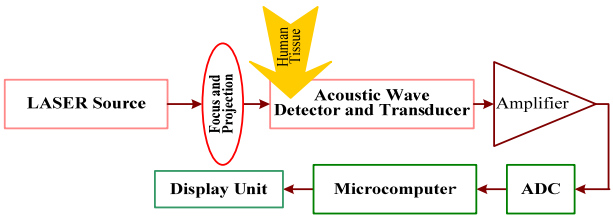


Fig. 4 Block diagram of the photoacoustic spectroscopy-based blood glucose measurement system

D. Raman Spectroscopy Method

This system consists of primarily a LASER source, lenses, prism, spectrometer, and detector. Fig. 5 depicts a schematic diagram of a Raman spectroscopy-based system. LASER beam, placed with a Raman imaging microscope, is transmitted through filter, lenses, and prisms to focus onto the human tissue. Back scattered light from the tissue is passed into a notch filter to eliminate unwanted components from the optical signal which is then sent to the spectrometer to be collected by a

detector [37]. The glucose contents are detected using the Charged Coupled Device (CCD) array detector from the Raman active molecules, which deliver a quantifiable Raman signal. In such a system, the LASER spectrum should be within a range between 700-900 nm [38]-[40]. However, this method also has some limitations that are evaded in its advanced versions like surface-enhanced Raman spectroscopy, stimulated Raman spectroscopy, coherent anti-stokes Raman scattering, and resonance Raman spectroscopy techniques [41]. The Partial Least Square Regression (PLSR) method is employed to calibrate the model to compute the glucose concentration in the blood [42]. A simple block diagram of such a system is depicted in Fig. 4.

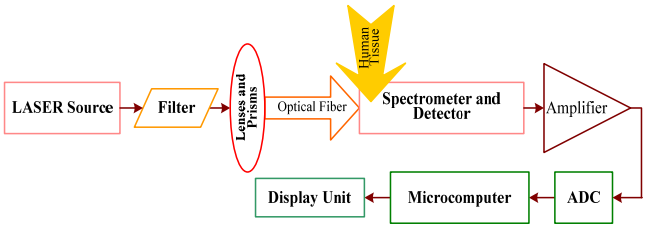


Fig. 5 Block diagram of the Raman spectroscopy-based BGM system

E. Optical Coherence Tomography Method

The Optical Coherence Tomography (OCT) process is employed for cross-sectional imaging in biological organs [43], [44]. It works based on the principles of Michelson's interferometer. This method uses a low coherence light source, optical fiber, optical coupler, optical splitter, mirrors, lenses, photodetector, and a display unit as depicted in Fig. 6. Two sections of the human body are used to measure the glucose level, viz. a tissue, and a reference arm. Back scattered light comes from the tissue and the reflected light comes from the reference arm as detected by the photodetector. Then they are mixed in a spectrometer and refractive indices between sample tissue and reference arm are analyzed by measuring the time delay between the reflected light and backscattered light [45]-[49]. The degree of mismatch between the refractive indices based on the OCT procedure indicates the amount of glucose level in the blood as evaluated by the Linear Least-Squares Regression (LLSR) method in the microcomputer [50]. Finally, the results are displayed on the screen.

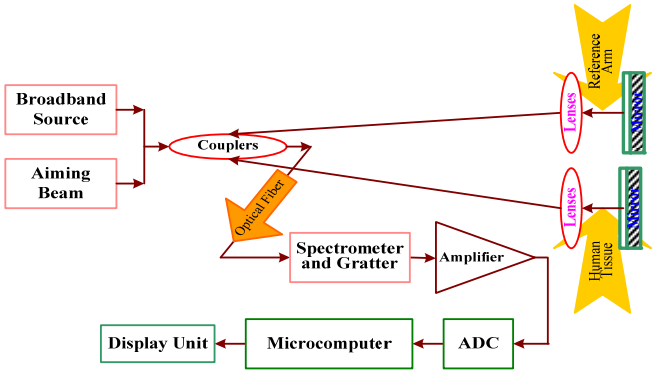


Fig. 6 Block diagram of the optical coherence tomography technique based BGM system

F. Metabolic Heat Conformation Method

Metabolic Heat Conformation (MHC) means there is a direct connection between body temperature and glucose quantity. The glucose level in the human body is directly dependent upon the hemoglobin level, oxygen supplied to the hemoglobin, blood flow rate, and metabolic heat. Therefore, the glucose level can be determined by measuring these parameters of the body. Such a schematic illustration is shown in Fig. 7.

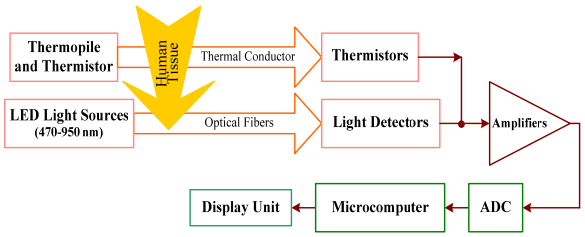


Fig. 7 Block diagram of the metabolic heat conformation technique based BGM system

In this method, the temperature is sensed from the finger by a thermopile detector inside the sensor. Then the blood flow rate is measured by the temperature difference between the two thermistors that are contacted with the finger. After that, hemoglobin and oxygenated hemoglobin levels are measured based on the diffuse reflectance spectroscopic method. Six LED light sources produce optical signals with six different wavelengths (470, 535, 660, 810, 880, and 950 nm) that are used to get a reflectance spectrum from the photodetectors connected at various surface areas of the finger, and then absorbance values are calculated using known formulas. [51]-[55]. Finally, the glucose concentration is computed based on stepwise regression analysis in the microcomputer and after performing the calibration, data are displayed.

G. Fluorescent Method

This method uses the method of Fluorescence Resonance Energy Transfer (FRET). In such an organization, energy is transported between two fluorophore molecules when their distance is less than the Forster radius (the maximum gap, of the order of 5-6 nm between the particles after which energy transfer doesn't take place) [56], [57]. Fig. 8 shows a block diagram representation of the fluorescent method.

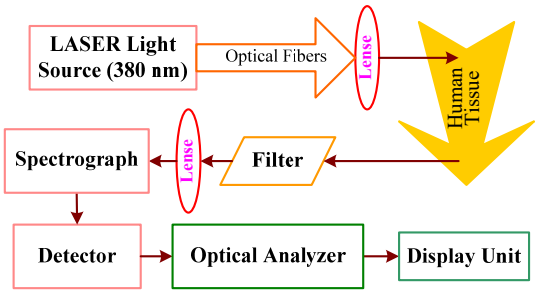


Fig. 8 Block diagram of the fluorescent technique based BGM system

An ultraviolet LASER light with a wavelength of 380 nm incidents on human tissue to create the fluorescence effect

there. When the light is reflected from there it contains two components, one is the reflected light coming from the induced emitted light because of the interactions that occurred between the glucose molecules in presence of water inside the sample and the second one is the exciting light. The photodetector senses these reflected optical signals and produces signals based on their intensity to provide necessary information to compute the number of glucose molecules per unit volume in the sample using the Partial Least Square Regression (PLSR) technique [58]-[60]. Special types of disposable and portable contact lenses have been made using polymer film to find glucose concentration in tears.

H. Occlusion Spectroscopy Method

The method is devised by using the fact that there is a direct relationship between glucose concentration level and the scattering characteristics of the human body. If the amount of glucose molecules per unit volume rises then the refractive index mismatch between the scattering body and their adjacent area reduces. Hence, the scattering coefficient and the optical path are abridged. So, if glucose concentration increases then a fewer number of photons are absorbed, and thus the reflected light intensity increases. To facilitate the measurement process, pressure is given by using a pneumatic cuff to stop blood flow for few seconds, and thus a pulse is induced into the blood to change its level. Simultaneously, a time-varying optical signal is passed and the transmitted signal through the sample is sensed by a photodetector from which the glucose level is estimated using the Deming regression analysis [61]-[63]. A system is shown in the block diagram of Fig. 9.

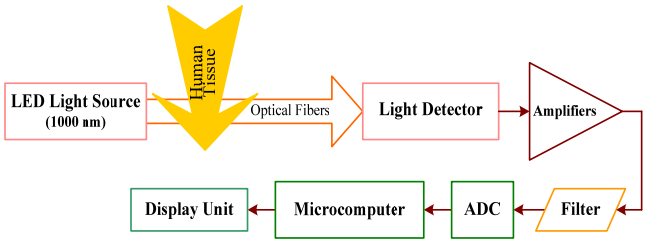


Fig. 9 Block diagram of the fluorescent technique based BGM system

İ. Kromoscopy Method

Kromoscopy method is a multi-channel, real-time correlated method having a series of overlapped band-pass filters in the wide band of frequencies to ascertain the amount of glucose concentration in the blood [64], usually within a range of wavelength in between 800-1300 nm near infra-red (NIR) spectra [65]. A simple block diagrammatic illustration is shown in Fig. 10.

In this method, an optical signal having infra-red (IR) spectra is passed through the human tissue. The transmitted optical signal is then decomposed into four parts using photo-detectors using band-pass filters. Each detector examines the tissue structure and then evaluates glucose concentration from interferents using a complex vector analysis method in the microcomputer [66]-[68].

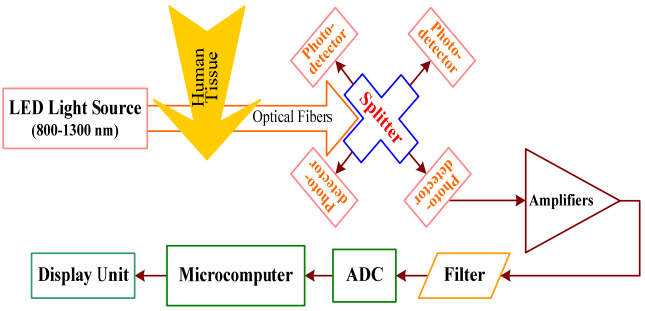


Fig. 10 Block diagram of a BGM system based on Kromoscopic method

J. Bio-Impedance Method

It has been observed that the bio-impedance shrinks linearly with the growing glucose level [69]. In this method, the input signal from the bio-impedance sensor is applied to the amplifier and signal conditioner circuit, which is interfaced with the microcontroller through its bus. The amplitude and phase angle of the current signal flowing through the load is influenced by its impedance. The current signal is converted to the voltage signal, which is then transformed into a digital signal by using an Analog to Digital Converter (ADC) through sampling and quantization techniques. The bio-impedance is measured in the frequency range of 10-100 kHz using silver electrodes as the electrical contact with the human body.

A special circuit generates the Discrete Fourier Transform (DFT) of the modified impedance signal and separates the real and imaginary quantities from the measured data. After processing the data in the microcontroller based on the bio-impedance variation using the multivariate Partial Least Squares (PLS) regression model, the glucose contents are computed and then finally, displayed on the display with the appropriate unit. This data can be transferred to a database using the Universal Asynchronous Receiver Transmitter (UART) interface of the micro-controller unit. The block diagram of such a system is illustrated in Fig. 11.

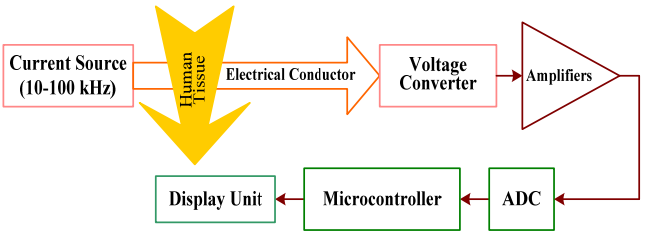


Fig. 11 Block diagram of a BGM system based on Bio-impedance method

K. Millimeter-Wave Antenna Method

The millimeter-wave antenna method uses a proximity micro-strip patch antenna with operating frequency in the range of millimeter-wave band of 50-60 GHz [70]. The patch antenna transmits electromagnetic wave energy to the human body and then S_{11} or the return loss parameter (in dB), which is the amount of power reflected from the antenna, is measured to ascertain the glucose contents. The complex part of the dielectric permittivity of blood-glucose solution changes with

glucose contents and frequency of the signal. The higher the glucose contents and frequency of the signal, the lower the relative dielectric permittivity (ε_r), and hence lesser the return loss is [71], [72]. The system block diagram of the millimeter-wave antenna-based method is shown in Fig. 12.

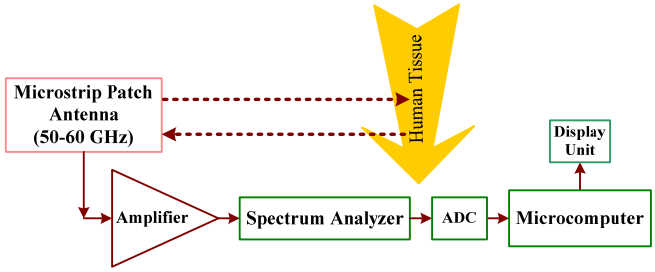


Fig. 12 Block diagram of a BGM system based on millimeter-wave patch antenna method

L. Microwave Sensor Based Method

A portable planar microwave sensor-based non-invasive glucose level detecting method is available for fast, accurate, and effective measurement of blood glucose [73]. Hexagonal-shaped Complementary Split Ring Resonators (CSRRs), fabricated on a dielectric material are used as the sensing [74] components, which are attached through a planar microstrip-line to a RADAR board functioning in the microwave frequency range of 2.4-2.5 GHz [75]. The human body resonates with the electromagnetic fields when it is exposed to the CSRR sensing components that can sense extremely subtle discrepancies in the electromagnetic properties of the glucose contents. Data is analyzed using a Vector Network Analyzer (VNA) that can record prominent smidgeons of frequency-shift output responses when the sensor is in contact with the human body [76]. The sensor responses are enumerated by relating the Principal Component Analysis (PCA) based on Machine Learning Algorithm (MLA). The working block diagram is shown in Fig. 13.

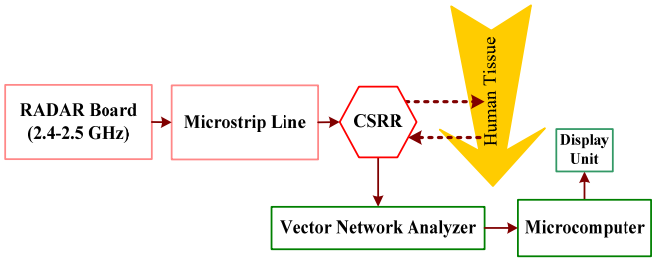


Fig. 13 Block diagram of a BGM system based on microwave sensor

M. Radio Frequency Antenna Method

A small-size transplantable Radio Frequency (RF) antenna is used as a biosensor to monitor the glucose level inside the human body. In this system, the antenna is prepared using a fully bio-compatible material, viz. cubic silicon carbide (SiC). SiC is a kind of semiconducting material that possesses the properties of both biocompatibility and sensing. Besides, it is chemically inert, tribologically superior, and hemocompatible. The SiC-based antenna can detect the changes in its nearby medium through the changes of its parameters, such as input impedance and resonance frequency. The S_{11} or return loss parameter (in dB) is used to determine the glucose contents. Then it is measured and analyzed using Vector Network Analyzer. This property of the RF antenna is utilized to ascertain the plasma glucose of a person with an operating frequency of the order of 10 GHz [77]. Sometimes, a Cu patch antenna is used with the SiC antenna as a reference antenna. Besides, a semi-insulating 4H-SiC substrate layer is given to keep the RF losses at a minimum level during the system operation. The simple block diagram of this scheme is exemplified in Fig. 14.

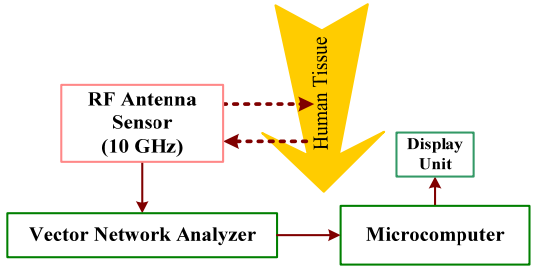


Fig. 14 Block diagram of a BGM system based on RF antenna sensor

N. Ultrasound Sensor Method

The ultrasound sensor-based method uses the transmission time of ultrasound waves in the low-frequency range of the order of 20 kHz or more through the human body fluid. It has been observed that the glucose concentration rises with the propagation time of the ultrasonic wave. The inter-molecular bonding forces and the body's fluid density determine the amount of compression of the fluid or tissue and hence the acoustic velocity at ultra-sound wave frequency there [64]. As a result, any variations of the glucose concentration in the cellular fluid change the density and adiabatic compressibility as well as the acoustic impedance. The ultrasound wave, produced by a transmitter, is transmitted through the human tissue's extracellular fluid to make changes of the glucose concentration based on the strength of intermolecular bonding forces and the density of the fluid [36]. This ultrasound wave voyages through the tissue with a characteristic velocity and is received from the opposite end of the tissue. The received signal is then adjusted for environmental effect, for example, the impact of ambient temperature on the propagation velocity, otherwise, the precision of the results would be compromised. The method of heat capacity and conductivity measurement non-invasively utilizing the ultrasound or spectroscopy technology respectively to measure the glucose contents based on such a two-parameter approach was applied in a product named Gluco-Track [78] though this was a not successful product commercially, good clinical trial results were found out in the literature [36]. However, another research group of Lee et al. conveyed their results on rat skin in a paper after laboratory trials [78]. The simple block diagram of this type of ultrasound sensor-based system is exposed in Fig. 15.

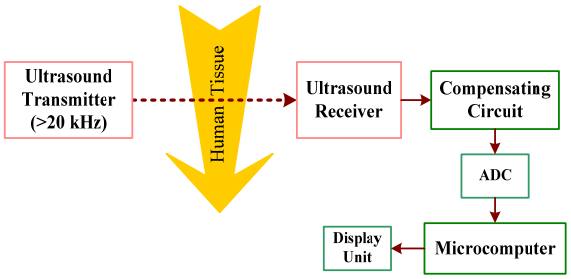


Fig. 15 Block diagram of a BGM system based on ultrasound sensor

O. Surface Plasmon Resonance Method

When a group of coherent charge-density waves, also known as Surface Plasmon Polaritons (SPPs), are agitated by an electromagnetic field emitted onto a highly conductive and chemically inert thin metallic layer, viz. gold (Au) then the Surface Plasmon Resonance (SPR) phenomenon is observed. This phenomenon was used to devise an SPR sensor for finding the low-valued sugar concentrations [79]-[82]. The SPR yields an exponentially decreasing (evanescent) highly sensitive electric field that causes to alter the refractive index of the neighboring medium and thus the SPR peak to occur. Due to the shift of the resonant frequency, also called the SPR shift, in the reflected curve, the fluctuations of the refractive index (η) in the boundary are measured and this indicates the glucose level variation of the medium under test [79].

As per the block diagram of Fig. 16, the basic structure uses the Kretschmann arrangement with a monochromatic LASER light source to radiate a Transverse Magnetic (TM) polarized or p-polarized light wave through a prism [83]. In non-resonant situations, the ray is totally reflected when it touches the prism-metal boundary, but it doesn't resonate with the free electrons available on the metallic surface, and thus only an evanescent electric field exists. This field is vertical to the metal layer. However, at the resonance angle of incidence, θ_R, the momentum of the incoming light becomes equal to that of the electromagnetic field created by the plasma vacillations of the free electrons. This creates a coupling between the free electrons oscillations and the evanescent field and as a result, the photons are absorbed through the metallic sheet, triggering a severe intensity loss in the received power. Therefore, the resonating angle can characterize the tissue if its refractive index (η) can change based on the absorbed optical power.

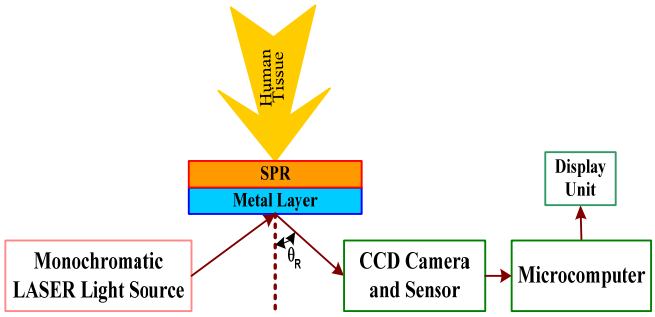


Fig. 16 Block diagram of a BGM system based on Surface Plasmon Resonance method

Furthermore, SPR can also be obtained by transmitting a polychromatic light signal to the prism-metal boundary at a constant angle of incidence. When the momentum at a certain arriving wavelength equals that of the SPPs then a minimum of the light ray at that specific wavelength may be present in the returned light ray as well. Thus spectral interrogation mode yields. This resonance wavelength can change heavily the refractive index of human tissue [84].

The block diagram of the Surface Plasmon Resonance (SPR) phenomenon-based system is demonstrated in Fig. 16.

P. Advantages of Non-invasive Measuring Devices

There are many advantages that we may get using non-invasive blood glucose measurement devices instead of their invasive or minimally invasive counterpart. The important advantages are listed as follows based on the literature survey:

- Less expensive, affordable cost
- Painless or pain-free
- No extra needle is required
- Minimum health risk
- Continuous monitoring is possible
- Compact in size
- Simple fabrication process
- High sensitivity
- More accurate and precise data
- Possibility of integrating with the Internet-of-Medical-Things (IoMT)
- Wearable and non-wearable versions
- Intelligent implantable medical devices
- Prospective biologically interfaced neural networks
- Possibility of remote monitoring.

V. Challenges of Non-Invasive Blood Glucose Measurement Devices

Despite numerous advantages, lots of challenges are being faced with non-invasive blood glucose measurement devices. These have discoursed in the following few paragraphs:

Several types of electromagnetic biomedical sensors are being used in the mm-wave band. But the main challenge in this band is to detect small changes in the signals from the human tissues. If such small changes can't be detected properly then accurate detection of blood sugar levels is also impossible. Besides, there may be complex interactions among the electromagnetic wave signals due to the diffraction and transmission from the tissue surfaces, and there is a great challenge of addressing this issue while designing sensors at the mm-wave band.

Cable stabilization is another issue to diminish amplitude and phase angle drifts during the blood glucose monitoring and measurement process.

Measured data may be unsatisfactory due to the influence of environmental and physiological dynamics during near-infrared measurements, such as the human body and atmospheric temperature or relative humidity, skin color and textures of the patients, etc.

There are so many measurement techniques and algorithms, data collection, analysis, and validation methods. These also

create huge challenges for the researchers to select the suitable one for their works.

If the non-invasive measurement techniques are indirect then the calibration is needed every time, before using the scheme, against the real-time blood glucose levels from which glucose concentration is ascertained from invasive and non-invasive measurements multiple times at various frequency levels. This is done to minimize the impact of individual quasi-stable factors, such as tissue thickness and structure. This makes the system complex, less user-friendly, and time-consuming as well as creates discomfort and dissatisfaction to the patients. As an example, it was found that the OrSense NBM-200G requires a calibration time of 3 hours per day with four measurement data per hour [85]. As such, the challenges are to minimize the calibration frequency and even to eliminate this procedure. However, though most of the non-invasive BGM devices need to calibrate several times, the OrSense NBM-200G device requires only one calibration every 3 hours per day [86].

To make the non-invasive BGM devices highly efficient and simple for a wide variety of users, the most challenging task is to select such a technology that can estimate glucose levels without fresh calibration and getting interfered with any human factors, such as skin properties [87]. We know that the transmission of light at a particular wavelength depends on the thickness, color, and structure of the human skin, bone, blood, and some other materials through which the optical signal travels [88]. Due to these factors, the impedance spectroscopy-based device named Pendra was found impractical for commercial use after several clinical trials on a good number of patients in European countries [89].

The additional critical challenge faced by the non-invasive BGM devices is their practical applicability at home/office. To use such devices there, these must be very simple and portable considering the human factors. Regrettably, most companies hide this information. For example, the Glucowatch device requires that the electrodes should be in place for a minimum duration of 60 minutes during the measurement, but this creates lots of discomfort to the patients [90]. As another example, the GlucoTrack device requires the patient to wait for several minutes before measuring the glucose levels if the patient takes a shower, or performs any physical activities, or enters the house after passing a long time outside [90].

VI. Current Research Trends of Measuring Methods

There are numerous capacities of blood glucose monitoring devices where researchers can carry out their research works. Some of these current research fields are explained in the following sub-sections:

A. Sensors

A non-invasive blood glucose measurement method uses various physical or chemical processes by which the glucose molecules interact inside the human body while flowing through the blood vessels. To get such information, we need some types of artificial biological sensors based on which the non-invasive blood glucose examination devices are being made commercially and these are now available in the market [91]. To realize non-invasive blood glucose measuring devices, various types of photonic sensors are uses. In the literature, the names of numerous photonic sensors are found. In this sub-section, ongoing research trends with such artificial biological sensors are described.

Glucose sensors [14], [92] are being used to quantify the blood glucose data non-invasively to avoid the patient's discomfort and to help them to control diabetes mellitus. The majority of blood glucose sensors used in glucometers are categorized as amperometric and optical sensors.

In the amperometric glucose sensors, the changes in glucose level are measured as a function of current. Sensors contain electrodes that can estimate the current level produced by an enzymatic reaction typically between glucose, an enzyme, and a mediator, and thus it requires an invasive method of measurement. Therefore, the researchers are trying to develop several types of sensors for the non-invasive way of blood glucose measurements and now, we are in the modern era of glucometers with biosensors having auto□calibration options to provide accurate blood glucose values [93]. Photonic sensors like photodiode, photo-transistor, LED, LASER, etc. are being used. Modeling of the sensor designs and simulation at different spectrums are the current areas of research on the non-invasive way of measurement of the blood glucose level of the biological tissues [94]. The researchers are also working on different types of sensor materials with varying pore sizes and surface textures. The application of responsive polymers in implantable biosensors is being investigated. The ultra-sound sensors are also being used to detect the acoustic signal and hence to determine glucose level [78], [95].

A recent research article reports a highly sensitive, non-invasive sensor to get the glucose data from the interstitial fluid in real-time. The system has a chip-less tag sensor that is placed on the patient's skin and a reader by embedding it in a smartwatch. It has investigated on flexible and wearable assembly of non-invasive type sensors on a flexible ultra-thin dielectric as the sensor substrate using microwave resonator as a sensing technique. This is ideal for wearable sensors and consumes no electrical power with high sensitivity and capacity for distant communication [96].

Another recent research paper presented spectroscopy-based non-invasive blood glucose observing scheme to measure the glucose level. Near-infrared transmission spectroscopy is employed and *in vitro* experimentations were conducted, and so had the *in vivo*. The findings of these experimentations were that there is an association between the sensor output voltage and glucose amount [97].

An improved Split Ring Resonator (SRR)-based microfluidic sensor operated at microwave frequency has been characterized at resonant frequency shift. Then the normalized peak attenuation level was found to design the SRR sensor by using the metamaterial-inspired material, such as polydimethylsiloxane, which is biocompatible as well as economical [84].

An epsilon negative (ENG; i.e., with negative dielectric permittivity, $-\varepsilon_r$) unit-cell based resonator was used to design a sensor device having a microwave notched filter at its

transmission frequency to get glucose level data from the human body [98].

The other types of sensors used in non-invasive techniques are pyroelectric detectors, thermistors, microwave antennas, etc. Short pulsed LASER rays are used to create thermal energy inside the body. So, the design of such sensors and enhancing their accuracies and precisions are getting important to the current researchers.

Infrared (IR), Micro-Electro-Mechanical System (MEMS), and ultrasonic MEMS technologies are being used to design sensors for continuous glucose monitoring [99]-[101]. In a paper, a MEMS capacitive pressure-based sensor was found to monitor the glucose level continuously [102].

Biosensors are being also designed using Carbon Nanotubes (CNTs), nano-materials, and gold nano-particles as well. They may be employed in the design of blood glucose sensors due to their reliability, accuracy, and faster response [103], [104].

B. Probe Design

The design of the probe is an important issue. From the literature, it was observed that the glucose values vary on the complex di-electric permittivity (ε_r) of an aqueous solution and thus the glucose level can be measured from the value of ε_r using an open-ended coaxial probe. The obtained results were validated against a commercial probe [105].

Another article investigated the designed probe at a near-field microwave frequency band to detect the glucose concentration level. The designed probe can radiate the signal from its plane in both of its directions. However, the design can be modified to emit the signal unidirectional to maximize the signal emission of the probe and thus to reduce the energy loss. The probe may have multiple layers for better signal transmission unidirectional capacity and higher sensitivity as compared to that of a bidirectional probe [106].

C. Algorithm for the Analysis

A glucose-sensing device is said to be accurate and precise if its sensitivity is more than 15 mg/dl (0.8 mmol/l). After getting the sensor output, several types of analysis are performed based on several types of algorithms. In the literature, numerous multivariate statistical calibration models are found. These algorithms are valuable to simulate and validate various types of non-invasive glucose sensors. The research works are currently going on these algorithms. Some of these important models are Multiple Linear Regression (MLR), Artificial Neural Network (ANN), Principle Component Regression (PCR), Ride Regression (RR), Partial Least Square Regression (PLSR), Support Vector Mechanics (SVM), Optimal Control Algorithm (OCA), etc. They are used to fit the measured data to the glucose values. Besides, Clarke Error Grid (CEG) analysis and correlation co-efficient, '*r*' are distinctive measurement methods to assess the accuracy level of the glucose sensor [25], [107]-[109].

The complex permittivity data were taken out from the measured complex reflection coefficient (S_{11}) employing the ANN algorithm. The data were tailored to the Debye relaxation model to estimate the glucose concentration (that is, per unit volume of glucose molecules) at an anticipated frequency. The proposed model is valid for glucose levels of 0 to 16 g/dl in the frequency range of 0.3-15 GHz [105].

The wearable bio-medical device provides model inputs by taking all the required measurements for a patient's blood glucose-insulin values. To establish the proposed control scheme, several patient-specific parameters should be defined concerning a particular day and sampling time. Then a predictive control technique is used to get glucose level data as the controlled variable from which the optimal control steps from the previous sampling instant of the blood-glucose level and the computed value at the prior day is obtained through the Optimal Control Algorithm (OCA). In addition, the patient's blood is monitored to figure out the safe limits of the blood glucose, which are named as preferred blood glucose set-points, or reference values for each time [94].

The Machine Learning (ML) and Neural Network (NN) based methods as well as association with heart rate variability and electrocardiogram are being explored as part of finding a new way of research, innovation, and development to measure the blood glucose level continuously [110].

Numerous Machine Learning (ML) based regression models are being analyzed to develop an optimized regression method. Thus, Classical Least Squares (CLS), Partial Least Squares (PLS), multiway PLS (mPLS), Multiple Linear Regression (MLR), Support Vector Regression (SVR), Logistic Regression (LR), Principal Component Regression (PCR), Multiple Polynomial Regression (MPR), Multivariable Fractional Polynomial (MFP), Neural Network Fitting (NNF), and many more models are being employed to obtain an optimized model to ascertain the blood glucose concentration level precisely [111]. Feed Forward Back-Propagation Deep Combination of Artificial Neural Network (FFBPDANN) was also employed to get better results that are obtained using the Artificial Neural Network (ANN) model [112]. Due to the multiple layers and functions, the model is very simple, realistic, and accurate. The hidden layers and their neuron numbers were verified from 20 to 4 to get an optimum value. This is also verified by employing the Artificial Intelligence (AI) model [which are Radial Basis Function (RBF) network, Support Vector Machines (SVM), Feed Forward Artificial Neural Network (FFANN), Random Forest (RF), k-Nearest Neighbor (kNN), Multilayer Perceptron (MLP), and Naive Bayes (NB)] to determine its effectiveness, and thus to validate the Deep Artificial Neural Network (DANN) model [113]-[115].

The test results are called efficient if the convergence time and errors are low but the accuracy is very high. However, it is possible to adjust the number of layers for different test cases to get better results. For this purpose, several training algorithms are applied to train the networks, such as Levenberg Marquart (trainlm), Scaled Conjugate Gradient (trainscg), Resilience Back-Propagation (trainrp), Deep Combination (trainlm, trainscg and trainrp), etc. For example, trainbr training algorithm is used for better detection though its convergence rate is very slow, while trainlm training algorithm is used as an alternative for better classification. The Mean Square Error (MSE) Levenberg Marquart (trainlm) may be employed to

improve the whole training process [116].

Monte Carlo Simulation (MCS) method was also utilized to simulate the propagation of the light signal in skin tissues for the wavelengths ranges from 1200 nm to 1900 nm because skin tissues are the strong scatterers [117], [118]. The MCS can model and simulate the photon transport mechanism in skin tissue layers. Then the light flux is separated into many photons, and each photon is detected using optical property history of the tissue layers, such as the absorption coefficient (μ_a), scattering coefficient (μ_s), refractive index (η), etc. These optical properties of the tissues depend on the wavelength. The skin tissue has three layers, epidermis, dermis, and deeper subcutaneous layers. The depths of these layers are of the order of a few sub-mm to several mm. The optical sources and light detectors were also simulated [119].

D. Design Software

Various design software is used for sensor, device, and probe design and optimization works. Microwave sensors were designed and optimized using a 3-D electromagnetic simulator (Computer Simulation Technology, CST Microwave Studio software) to obtain the highest sensitivity and concentration resolution to get glucose level data [120]. Besides, an electromagnetic solver tool in CST Microwave Studio was employed to determine the resonance performance of the bare Split-Ring Resonators (SRR), masked SRR, and masked SRR through simulation data. The software is used to plot the electric and magnetic field distribution, to get the resonance frequency, to measure transmission and reflection coefficients, etc. [121].

On the other hand, the thumb and the index finger's tissue models were designed in CST Microwave Studio software in a research article. The model could imitate the tissue curvature and its different layers, such as skin, fat, blood, muscle layers, fluid, etc. of the order of 2-3 mm in thickness. Besides, the dielectric properties (such as relative dielectric constant, loss tangent, etc.) of these different layers could be set at different values at a particular operating frequency of the order of GHz range [122].

Design and simulation of MEMS-based capacitive pressure sensor for the detection of blood glucose level were performed by using the electromagnetics interface of the COMSOL Multiphysics software tool. Model definition, materials, and its parameter selection, operational parameter's value set-up, sensitivity analysis, etc. were carried out using the same software tool [102].

Besides, using the COMSOL Multiphysics software tool, a 3-D sensor design and 3-D body modeling were also carried out in another paper. The cross-section of a 3-D abdominal model was generated using the COMSOL Multiphysics comprising skin, fat, muscle, internal organs, and vertebrae (specifically, lumbar vertebrae) bone. The thicknesses of the different layers varied from 3-35 mm [123].

However, the physics-based sensors may be drawn in 3D at SolidWorks and then imported to COMSOL Multiphysics for further simulation and analysis by setting up values of various variables and operational parameters [124].

In another article, the sensor was modeled and fine-tuned to keep the reflection coefficient at the resonant frequency very low by using the COMSOL Multiphysics [125]. In this and two more articles, it was found that the mathematical models of the dielectric properties of physiological saline-glucose and blood-glucose solutions were implemented in MATLAB numerically and finally, imported to the COMSOL software for numerical design and evaluation of the microwave glucose sensor [125]-[127].

A very recent article presents a microwave biosensor that was designed and simulated using Keysight's Advanced System Design (ADS) electromagnetic simulator on a Gallium Arsenide (GaAs) substrate. Later, it was implemented using micro-fabrication technology to obtain a highly sensitive and resonator-based glucose sensing device. The design parameters are optimized in ADS to attain a low center frequency to enhance the penetration depth and interaction area. High-Frequency Structure Simulator (HFSS) was used to get the simulated electric field intensity patterns at the resonance frequency [128].

E. Future Blood Glucose Measuring Methods

Non□invasive glucose monitoring forms the future of glucose monitoring systems. In this sub-section, some current possible future blood glucose monitoring methods are mentioned. The new technologies that may are creating great interest among researchers are Raman spectroscopy, RF sensors, SPR sensors, optical coherence tomography, photo□acoustic spectroscopy, microwave sensors, and fluorescence [129]-[133]. At present, none of these techniques are employed commercially to manufacture bio-medical devices, like in blood glucose measurement devices. To apply these techniques, they must meet the criteria for being the ideal sensors that may produce accurate blood glucose data.

For non-invasive measurement of glucose measurement, the temperature of the human body could also be employed instead of using external light sources to estimate the glucose level. One such temperature-based blood glucose measurement method is called the Metabolic Heat Conformation (MHC) scheme. This method employs the metabolic oxidation process of glucose inside the human body [134], [135].

VII. Comparative Analysis of Measuring Methods

To get a comparative picture about various types of blood glucose monitoring technologies and devices, it is required to know the error analysis methodologies, approving body's criteria for approval. In the next sub-sections, these issues are addressed gradually.

A. Error Analysis

To examine the accurateness and effectiveness of any type of Blood Glucose Measurement (BGM) device, there are several techniques, guidelines, practices, and standards. The Mean Average Relative Measurement (MARD) and the Error Grids are such metrics to evaluate the accuracy of any device. The standard ISO-15197 describes the guidelines, requirements, and specifications to certify the effectiveness and suitability of any devices before applying them to the human body. Therefore,

most of the countries in the world use ISO prescriptions through their national regulatory bodies before permitting any BGM device for commercial purposes in the country. However, many countries have their guidelines too, for example, the United States. So, a manufacturer must know the regulatory requirements of a particular country and comply with those to commercialize their BGM devices there. The researchers also should know it before adopting any technologies for a BGM device.

1. Mean Absolute Relative Difference

To test the accuracy and precision of the projected glucose level, different parameters, such as Mean Absolute Deviation (MAD), Mean Absolute Relative Difference (MARD), Root Mean Square Error (RMSE), etc. may be computed.

MARD is the most extensively used parameter to evaluate the accuracy and precision of any BGM device because of its easiness [136]. MARD gives the average of the absolute error between all BGM values and corresponding matched reference values. The computation is performed by taking the average of all the absolute errors. Then it is expressed as a single number in percentage. It provides the closeness of the measured data to the real data. The smaller MARD value tells that the BGM device is more accurate than that with the larger MARD value.

The procedure to compute the MARD value is to use two sets of data to be taken at the same instant during clinical trials of a particular BGM device- one set of data is taken by the said device and the other set of data is taken by a standard laboratory method (e.g., YSI-2700). After that, both data are compared and analyzed [137].

Since the MARD value is computed between paired data sets, it can be obtained from the mean value of the Absolute Relative Differences (ARD), therefore, we may use (1) and (2) to compute the MARD value.

$$ARD_k = \frac{|y_{BGM}(t_k) - y_{ref}(t_k)|}{y_{ref}(t_k)} \times 100\% \quad (1)$$

$$MARD = \frac{1}{N_{ref}} \sum_{k=1}^{N_{ref}} ARD_k \quad (2)$$

where y_{BGM} is the data measured by the BGM device, y_{ref} is the data measured by the standard reference device at k^{th} time, t_k, $k = 1, 2, \ldots N_{ref,}$ and t_k is the time when data are measured.

Inappropriately, the MARD value is severely reliant on the characteristics and details of the measurement method being employed. As such, comparing the MARD of different devices may be misleading [138]. Hence, the MARD value can't be acceptable completely to define the accuracy level of a BGM device. However, the MARD value may be accepted with some degree of uncertainty [137].

The value of Root Mean Square Error (RMSE) is another parameter that can be computed using (3) [139]. This formula was found appropriate to measure the accuracy level of blood glucose measurement and evaluation system in [140].

$$RMSE_k = \sqrt{\frac{1}{N_{ref}} \sum_{k=1}^{N_{ref}} \left| y_{CGM}(t_k) - y_{ref}(t_k) \right|^2} \quad (3)$$

2. Error Grids

To evaluate the clinical accuracy of the blood glucose measurement (BGM) devices, error grids are being used to evaluate qualitatively the tested device [141]. The 2-D grid is a kind of scatter plot of data obtained from the BGM test device and its reference device. It is divided into several zones from where suitability decision on the device is taken based on the percentage of points situated in different zones.

At present, four error grids techniques are employed to evaluate the BGM device accuracy as per different literature reviews, such as Clarke Error Grid (CEG), Parkes Consensus Error Grids (PCEG) for type 1 and type 2 diabetes, and Surveillance Error Grid (SEG). In each method, the plots are divided into five different zones. In CEG and PCEG methods, these zones are designated by five characters from A to E. In the SEG method, these are identified by five color-coded patterns. Due to some pitfalls of the CEG method, the PEG method for two types of diabetes disease was developed. Due to the new regulatory guidelines enacted by ISO and FDA, the device manufacturers are to face severe penalties if there is any inaccuracy in reading is traced [142], and as such CEG and PEG methods are being phased out as tight glycemic control is essential [143]. So, the SEG method was developed and adopted. As per this method, different colors from green to red indicate no risk zone to extreme risk zone for hypo- or hyperglycemia states of the diabetes patients respectively.

However, the Clarke Error Grid (CEG) method was developed to enumerate the medical accuracy of blood glucose data under test as compared to a referenced data using a standard meter [144]. The use of such a technique was found in Diabetes Care published in 1987 [145]. Finally, the EGA was adopted as one of the "gold standards" to decide on the BGM device's accuracy. The Clarke Error Grid (CEG) is a scatter plot of data obtained from a reference BGM meter and a new BGM meter to be tested. The scatter plot is divided into 5 decision-making zones as follows (Fig. 17):

1. If data points are in Region A then these values are within 20% of the reference sensor's values,
2. If data points are in Region B then these values are outside of 20% of the reference sensor's values but won't lead to inappropriate treatment,
3. If data points are in Region C then these values are going to provide unnecessary treatment,
4. If data points are in Region D then these values indicate a potentially dangerous situation and would fail to detect any types of diabetes disease,
5. If data points are in Region E then these values may confuse hypoglycemia for hyperglycemia and vice versa.

Table I provides a summary of each zone. In general, A, B, and Green zones signify the accuracy of the trialed device. The other zones denote the potentially dangerous conditions and need to take applicable remedial actions.

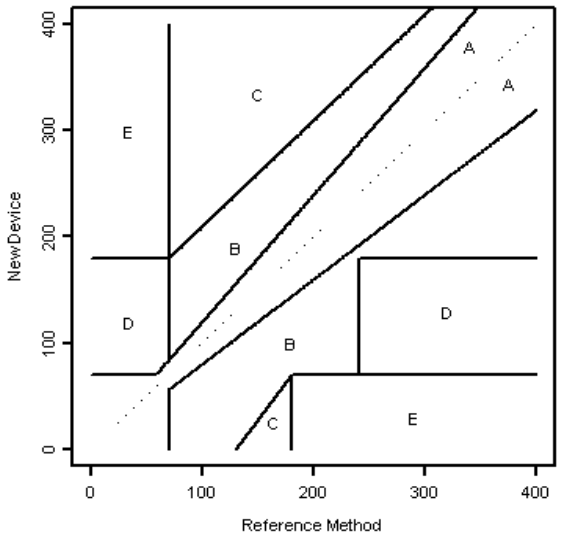


Fig. 17 The Clarke Error Grid (CEG) [144]

TABLE I
CLARK, PARKES, AND SURVEILLANCE ERROR GRIDS TO DECIDE ON THE CLINICAL ACCURACY ASSESSMENT AND EVALUATION OF BGM DEVICES

Risk Zone (Color)	Clarke Error Grid [144]	Parkes Error Grid Type 1 Diabetes [146]	Parkes Error Grid Type 2 Diabetes [146]	Surveillance Error Grid [142]
	A to E	A to E		Green to Dark-red
A (Green)	Clinically correct decisions	No effect on clinical action		No risk
B (G/Y)	Clinically uncritical decisions	Altered clinical action or little or no effect on clinical outcome		Mild risk
C (Y/R)	Over corrections that could lead to poor outcome	Altered clinical action or little or no effect on clinical outcome		Moderate risk
D (Red)	Dangerous failure to detect and treat	Altered clinical action: potential significant medical risk		High risk
E (Dark red)	Erroneous treatment	Altered clinical action: potential dangerous consequences		Extreme risk

3. ISO 15197 Standard

The International Standards Organization (ISO) defines and develops specifications for procedures, services, and products of high quality, reliable and safe products in a wide range of industries, including next-generation medical devices, and others [147], [148].

ISO 15197:2013 and ISO 15197:2015 are the newest standards, released in 2013 and 2015 respectively, for blood glucose measurement devices [149]-[151]. The new standard has tighter accuracy requirements. However, following the new guidelines provides better confidence to patients, clinic owners, and physicians that the measured glucose data are reliable and adequately accurate every time [152].

According to the new standard, 95% of the blood glucose data should fall within ±15 mg/dL for glucose concentrations less than 100 mg/dL or ±15% at glucose concentrations of 100 mg/dL concerning the reference method. Moreover, 99% of the readings must be inside zones A and B of the Parkes (Consensus) Error Grid for diabetes type 1 [153].

ISO released a harmonized version, EN ISO 15197:2015 for the European Union countries in 2015 though it did not bring any modification to necessitates for the performance appraisal of the BGM devices [154], [155].

B. Approving Agencies

There are various bodies to approve bio-medical devices in different countries. Some countries have their bodies approve the BGM devices as per their set guidelines and specifications in their lands or territories. Some regions follow the ISO requirements in their territories, for example, the European Medicines Agency. If any BGM device fulfills the ISO guidelines then that device receives the CE mark [156]. However, there is no specific standard for non-invasive blood glucose monitoring devices. Therefore, the BGM device manufacturers comply with the respective national body's rules, regulations, and practices.

Table II provides the regulatory standards to approve the BGM devices in some countries in different parts of the world. Since ISO standards are being changed from 2003 to 2013 and then again in 2015, therefore, the countries that are following the ISO standards, any version of it is acceptable for the new products but the manufacturers should also check the respective national regulatory body's requirements before releasing their products in a particular territory. It may be mentioned that in the regions that follow the ISO guidelines if any manufacturer can comply with the requirements of version 2003 then most of the regions also accept it [152].

C. Device Comparison

Finally, an overview of the status of various devices, with the device and company names, non-invasive continuous blood glucose measurement technologies being applied, placement sites of the human body, device images, accuracy rates, device statuses, etc. are shown in Table III. Various devices are found in the literature and the market, such as GlucoWatch, Diasensors, Apsire, GlucoWise, Gluco-band, GlucoTrack, Orsense, Eversense, Hello Extense, SugarTrac, etc. though their accuracy (that is, how closely a measured value by the BGM device under clinical trial agrees with the reference value of a given standard device, or in other words, how much the measured values are correct) and precision (that is, how closely individual measured value agrees with each other of the same device under trial, or in other words, how many time the measurement can be made very closely indicating the degree of reproducibility of the measured data) are questionable due to the interventions of environmental and physiological parameters as well as experimental set-up.

D. Recommendations

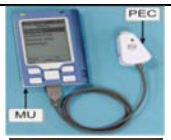
Since the non-invasive method is yet to get approval for clinical purpose, the key technological obstacles must be removed completely before so that its application and commercialization is possible in several countries. At first, the non-invasive blood glucose measuring technologies must be made reliable, safe, user-friendly, and cost-effective to substitute the existing portable devices, like implantable biosensors, or minimally invasive devices. So, in this paper, some important recommendations are given as follows:

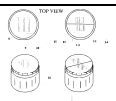
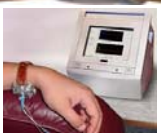
- The performance of continuous BGM devices should be pragmatic and comply with the regulatory requirements,
- More monetary investment should be ensured to perform comprehensive clinical trials of the BGM devices to have concrete evidence on the reliability of these devices for all patient groups of various ages and disease types,
- There should be a standard procedure to measure, store and report the BGM device data of clinical trials,
- The reported data should be consistent and accessible to the regulatory bodies and experts,
- There should be clear guidelines on how to approve the BGM device for commercial purposes and how to place the same in the market,
- Before marketing the BGM device, there should be an awareness build-up program to seek cooperation from a diverse group of people and also the information must be communicated to the stakeholders,
- Several investigations are also essential to find the use of non-invasive BGM devices in particular areas, such as, to determine their suitability and duration of use in ICUs,
- The frequency of measurements should also be stated in the clinical trial report,
- The measurement accuracy and precision rates are also need to be mentioned in the trial data
- Any comments or observations during the measurements should also be included in the clinical trial report,
- Finally, any types of side-effects either short-term or long-term must be identified and mentioned explicitly in the clinical trial report.

TABLE II
GUIDELINES TO APPROVE THE BLOOD GLUCOSE MEASUREMENT (BGM) DEVICES IN FEW COUNTRIES

Agency	Country	Guidelines/Standard	Release Year	Device Type	Glucose Level	Criteria	Reference
Food & Drug Administration (FDA)	USA	UCM 380325	2016	BGMS	≥75 mg/dL <75 md/dL	95% within ±12% 98% within ±15%	[157]
Food & Drug Administration (FDA)	USA	UCM 380327	2016	SMBG	Entire range	98% within ±15 mg/dL 95% within ±15% 99% within ±20%	[158]
European Medicines Agency (EMA)	EU	EN ISO 15197	2015		≥100 mg/dL	95% within ±15%	[159]
Health Canada (HC)	Canada	Medical Devices Regulations	2019				[160]
Agência Nacional de Vigilância Sanitária (ANVISA)	Brazil	RDC 40/2015	2015				[161]
China Food & Drug Administration (CFDA)	China	CDS CCG	2009	CGM	<100 mg/dL	95% within ±15%	[162]
Pharmaceuticals and Medical Devices Agency (PMDA)	Japan	ISO 15197	2013	BGMS SMBG			[163], [164]
Therapeutic Goods Administration (TGA)	Australia	Class 1 IVD	2010		Entire range (Type 1 Diabetes)	99% within Zones A & B of Parkes EG	[165]-[167]

TABLE III
COMPARATIVE STUDY OF VARIOUS NON-INVASIVE CONTINUOUS BLOOD GLUCOSE MEASUREMENT (BGM) DEVICES

Measurement Technology	Device and Company Name	Placement Site	Accuracy Rate	Device Image	Status of the Device	Reference
Ultrasonic, Electromagnetic, and Thermal	Gluco-Track (Integrity Applications)	Ear-lobe	96%		Approved and commercialized in Europe	[168]
Fiber Optic Sensor Technology	FiberSense (EyeSense)	Contact lens, tears	95%		The product is available in the market since 2019	[169]
Electric Signal	NovioSense	Basal tear fluid	95%		Phase II clinical trial	[170], [171]
Micro-current Technology	D-SaLife (Dongwoon Anatech)	Saliva	-		Clinical trials completed and trying to get the approval of FDA and KFDA	[172]
Raman Spectroscopy	C8 MediSensors	Abdomen Skin	83%		Approved for sale in Europe	[173]

Measurement Technology	Device and Company Name	Placement Site	Accuracy Rate	Device Image	Status of the Device	Reference
Thermal Emission Spectroscopy (TES)	Infratec Inc.	Tympanic membrane inside the ear canal	89%		The first clinical study with the TES technology showed promising results	[174], [175]
Optical/LASER Technology	GlucoSense (Glucosense Diagnostics under University of Leeds, UK)	Finger	95%		Performed one clinical trial. Aiming for more after further development	[176]
Optical Coherence Tomography	GlucoLight (GlucoLight Corporation)	Skin	80-95%		Approved by the American Diabetes Association	[177]
Metabolic Heat Conformation	No formal name was given (Hitachi Ltd.)	Finger-tip	91%		Not yet approved for sale	[178]
Bio-Impedance (Electromagnetic Impedance Spectroscopy (EIS) and Electromagnetic Impedance Tomography (EIT))	Biosensors Inc.	Wrist skin	49%		Available in the market	[179]
Photoacoustic Spectroscopy	Aprise Sensor (Glucon Inc.)	Forearm skin	71%		Under development stage, about to commercialize	[180], [181]
MIR Spectroscopy/Optical Parametric Oscillation	No formal name given (Light Touch Technology under National Institutes for Quantum and Radiological Science and Technology)	Finger	99%		Under development stage, about to commercialize	[182]
Metabolic Heat Conformation	G2 Mobile (Eser Digital)	Finger-tip	87%		Available in the market	[183]
mm-Wave Transmission Spectroscopy (f = 60 GHz)	GlucoWise (MediWise)	Hand	-		Under development stage	[184], [185]
Fluorescence	Eversense® (Senseonics)	Upper arm	95%-99%	 Sensor Transmitter	Available in the market	[186]-[188]
Near Infrared Spectroscopy	Combo Glucometer (Cnoga Medical)	Finger	98-100%		Available in the market	[189]
Occlusion Spectroscopy	OrSense Ltd. (NBM-100G)	Finger	95.5%		Approved by the American Diabetes Association	[86], [190]

Measurement Technology	Device and Company Name	Placement Site	Accuracy Rate	Device Image	Status of the Device	Reference
Impedance Spectroscopy	Pendragon Medical (Pendra®)	Wrist Skin	52%		Approved by CE, but now out of the market due to poor accuracy, trying to develop a multisensory concept	[89]
Near-Infrared Spectroscopy	Tech4Life Enterprises	Nail	-		Currently undergoing trials in several countries.	[191]
Near-Infrared Spectroscopy	HELO Extense (World Global Network)	Finger	>95%		Available in the market	[192]
Reverse Iontophoresis (Electric Current)	SugarBEAT (Nemaura Medical)	Upper Arm	78%		Waiting for CE approval	[193]
NIR Spectroscopy	Wizmi (Wear2b Ltd)	Arm Wrist	94%		Proof of concept	[194]
Near-Infrared Spectroscopy	SugarTrac (LifeTrac System Inc.)	Earlobe	88%	-	Currently in clinical trials, not yet approved or available to the consumers	[195]

VIII. Conclusion

In the present review article, the most important non-invasive blood glucose measurement technologies are explained to manufacture various kinds of BGM devices. Most of these BGM devices have some limitations and problems due to environmental factors (e.g., pressure, temperature, air flow, and humidity) as well as physiological parameters e.g., body temperature, sweating, body fluid, and blood perfusion. This causes the measurement values to be incorrect and as a result, these sensors can't fulfill the criteria of an ideal sensor. However, if multiple sensors are used in a BGM device then these effects may be minimized, but in practice, aggregating more sensors in a particular device makes it more complex and increases the manufacturing cost. As a result, strong research plans are undertaken to improve and invent a reliable continuous blood glucose measuring device. Remarkable signs of progress were observed with wearable and portable sensors. However, there are still some major challenges to the researchers. One such challenge is to distinguish the weak glucose signals from the spectral noise, because there may be some other parts with the blood inside the body, like water molecules, ions, etc. The non-invasive techniques must ensure that the glucose spectrum is not influenced by such parts. So, to achieve the high Signal-to-Noise Ratio (SNR) for the non-invasive methods is of paramount importance.

Different multivariate statistical calibration models, such as ANN, DNN, MLS, MLR, LR, NNF, PCR, PLS, mPLS, SVM, SVR, etc. are utilized to chart the measured signal with the glucose level data. If the SNR can be enhanced using any digital filter then these algorithms are supposed to work better. Calibrations are performed by transfiguring the raw data (e.g., light intensity, response current, etc.) into the glucose level data and then finally, comparing the glucose data with the reference or true data obtained from any standard device.

Another challenge is to design and implement a sensor that can provide stable and reliable data during clinical trials as well as real-time measurement at different situations with an acceptable accuracy range. As such, the sensors should be robust in design, and for this purpose, multidisciplinary research works involving biologists, pharmacists, chemists, material scientists, electrical and electronic engineers, mechanical engineers, computer engineers, mathematicians, statisticians, and physicists must be carried out rigorously.

The other important issue is to make the non-invasive BGM devices user-friendly. Since this device can offer a convenient way of measuring the glucose data painlessly by the patient himself or herself, such device is supposed to popularity among the users for the self-monitoring of the blood glucose levels continuously. In this regard, some of the BGM devices discussed here have already made substantial advancements in the recent past. However, continuous efforts must constantly be made to develop it further by improving the performances in terms of accuracy, precision, cost minimization, reliability, safety, user-friendliness, side-effect-free, etc. There is also a need to emphasize the environmental impacts and to consider several physiological processes of the human body.

If all such issues can be addressed then the researchers of non-invasive BGM devices would certainly be able to curtail the measurement errors that would yield some of the attractive devices shortly.

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