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Review: Non-Invasive Continuous Blood Glucose Measurement Techniques

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Abstract

Diabetes is a metabolic disorder that results in human body due to insulin deficiency, insulin resistance or both. In the management of diabetes, glucose monitoring technology has been used for the last three decades. The aim of this review article is to describe concise and organized information about different techniques of non-invasive continuous blood glucose monitoring. Many research groups have been working to develop wearable sensors for continuous blood glucose monitoring, but at present, there are to our knowledge no commercially successful non-invasive glucose monitors on the market. To achieve an acceptable sensor system, a glucose sensor should have accuracy better than 15mg/dl (0.8 mmol/l). In future development, continuous glucose sensor systems may become predictable, selective, reliable and acceptable for patient use.

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Introduction

The main carrier of energy in human organism is glucose with recommended level between 88mg/dl (4.9mmol/l) – 125mg/dl (6.9mmol/l) [1,2]. There is a direct connection between glucose and insulin in the human body. Insulin is secreted by pancreas, and is responsible for keeping the blood glucose at a healthy level. After meal intake, food is converted into glucose and then released into the bloodstream. Insulin helps to transport glucose from bloodstream into cells, and used as an energy source [2]. Diabetes is a metabolic disorder that results in human body due to insulin deficiency, insulin resistance or both [3-5]. There are commonly two types of diabetes, type 1 and type 2. In type 1, the body does not produce enough or no insulin, called insulin dependent type. In type 2, the ability of body to produce insulin does not completely disappear, but the human body becomes resistant towards insulin, called insulin-independent type [6,7]. Any kind of diabetes can be harmful because in the long run excess of glucose (hyperglycemia) can cause multiple health problems such as heart strokes, birth defects, damaged nerve system, kidneys failure and blindness. Low level of glucose (hypoglycemia) can cause coma, confusion and even death.

The Diabetes Control and Complications Trial (DCCT) was a major clinical study conducted from 1983 to 1993 and funded by the National Institute of Diabetes and Digestive and Kidney Diseases. The study showed that keeping blood glucose levels as close to normal as possible slows the onset and progression of the eye, kidney, and nerve damage caused by diabetes. It demonstrated that any sustained lowering of blood glucose, also called blood sugar, helps, even if the person has a history of poor control [8]. In 1985, it was estimated that 30 million people had diabetes around the world, the figure rose up with 150 million in 2000 and at the end of 2012 International Diabetes Federation (IDF) estimated that 371 million people had diabetes, and this number will increase to 552 million in 2030 [9].

Figure 1 shows different classification of blood glucose measurements: invasive, minimally invasive and non-invasive [10]. Invasive method is known as Finger-pricking method. It has several disadvantages. Most of people do not like using sharp objects and seeing blood, there's a risk of infection, and, over the long run, this practice may result in damage to the finger tissue [11]. The minimally approaches are developed by using subcutaneous sensors for the measurement of glucose concentration in interstitial fluid (ISF). However, they suffer from limitations in terms of discomfort to patients, continuous calibration requirements, and high susceptibility to biofouling [12].

In vivo non-invasive (NI) blood glucose monitoring is a technique for the determination of glucose without taking blood sample. It can be inexpensive as compared to the invasive method that requires a fresh test-strip for each glucose measurement [13]. Most of the researchers have been concerned by the idea of the different methodologies of non-invasive devices for the determination of blood glucose; permit more frequent testing and tighter control of diabetes. A non-invasive measurement of the blood glucose is based on the ability of glucose molecule to interact with different physical or chemical processes happening in the body. Nevertheless, in spite of some encouraging results have been shown over the past 40 years, but at present, there are to our knowledge no commercially successful non-invasive glucose monitors on the market [14].

Non-invasive monitoring can be characterized into the following two major categories; (i) optical methods (ii) transdermal methods. In the transdermal methods, physical energy is used to access interstitial fluid (ISF) or blood and extract glucose values. However,

this method can change the skin properties and may cause blistering, irritation and erythema. On the other hand optical methods use light to access glucose molecule in ISF, blood or in anterior chamber of eye [15].

[18]. The major challenge for the measurement of blood glucose non-invasively is the physiological lag between ISF and blood glucose. This problem particularly relates with the spectroscopic technologies, which predominately probe ISF glucose, creating variations in

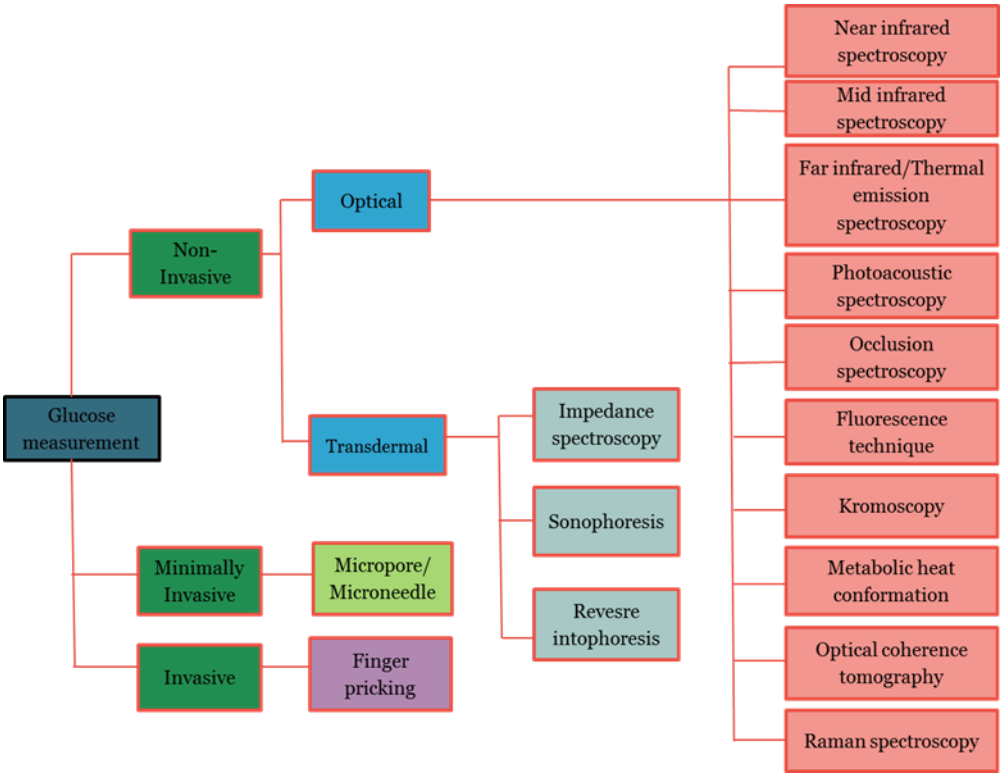

Figure 1: Different classification of blood glucose measurement [15].

Interstitial Fluid

Interstitial fluid (ISF) is known as intercellular or tissue fluid having microscopic compartments around the cell. Glucose is freely moved from capillary endothelium to the ISF by simple paracellular and/or transcellular diffusion. The concentration of the glucose in ISF depends on rate of change of glucose concentration in blood, metabolic rate and blood flow rate [16, 17]. There is a significant time difference (lag time) between 2 to 45 min in the peak glucose concentration of ISF and blood glucose, and the average lag time is 6.7min [15]. This lag time is the sum of the physiological and instrumental lag. The instrumental lag rises from biographer's measurement method and the physiological lag signifies the time requirements for the diffusion of blood glucose into the interstitial space from capillaries the calibration of techniques in which blood glucose is used as reference [19]. Lag means that the sensor must be recalibrated to a blood glucose value at fixed intervals. As hypoglycaemia and hyperglycaemia complications depend on the blood glucose so the disparity between ISF glucose and blood glucose may suggest that for closed-loop insulin delivery system ISF sensors are not ideally suitable. Further lag is encountered in the delivery and absorption of insulin for subcutaneous-subcutaneous closed loop system in which ISF is used to sense glucose and insulin is delivered subcutaneously [20, 21].

Sensor's Accuracy

There are different sensors such as GlucoWatch, Diasensors, Apsire, Gluco-band, Gluco Track, Orsense,

SugarTrac, Hitachi Ltd, etc., have been proposed for non -invasive continuous glucose monitoring. However, the accuracy of these sensors still suffers from environmental and physiological interferences [22]. To achieve an acceptable sensor system, a glucose sensor should have accuracy better than 15mg/dl (0.8 mmol/l) and the concepts should be more robust towards environment-experimental setup conditions [23]. There are many ways to find out the accuracy (correctness) and precision (degree of reproducibility) of a glucose sensor against standard reference methods. Different multivariate statistical calibration models are constructed such as: multiple linear regressions, artificial neural network (ANN), principle component regression (PCR), ride regression, partial least square regression (PLS), support vector mechanics (SVMs) to map the measured quantity to the glucose value. Clarke grid analysis and correlation co-efficient 'r' are typical measures for the assessment of the glucose sensor accuracy [24-27].

Data Presentation

The prediction performance of a non-invasive sensor is measured by the use of statistical analysis. However most of researcher and clinicians tend to use Clarke error grid analysis (EGA) which is a frequently method used for the assessment of the clinical accuracy of glucose monitor's and for data presentation [13, 28]. It shows the monitor estimated glucose level on the y-axis with respect to reference glucose value on the x-axis, difference between these values and clinical significance of this difference. This Clark error grid consist of five zones labelled as A, B, C, D and E as shown in figure (2a). Zone A is clinically accurate, zone B is clinically acceptable, zone C shows unnecessary treatment, Zones D fail to detect glucose level and zone E shows the erroneous results [15, 29]. Two parameters are used for the quantification of the occurrence of data points in zones A & B: (i) r value which is the correlation between reference (true) glucose value and the non-invasive glucometer measurement. (ii) Percentage value of experimental data points which fall in zones A & B. A major drawback in Clarke's error analysis is that the boundaries of the zones are not connected sequentially, which means that small change in glucose values stated by a sensor can easily be transferred from a correct value zone A to a critical zone D and vice versa. Despite of this drawback, it has widely been used in the assessment of the glucose sensor accuracy.

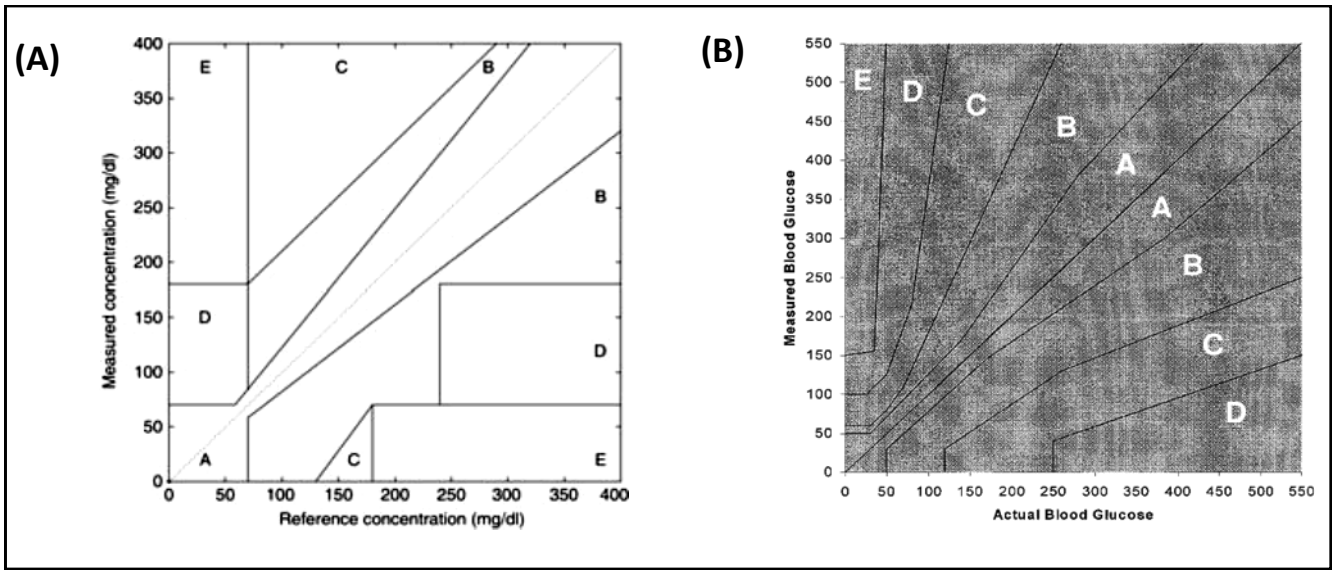

Figure 2. Glucose sensor error grids: (A) Clarke error grid [15] and (B) Parkes error grid (Published with permission) [31].

In 2000, Parke's et al. suggested a new error grid (figure 2b). It is based on the response of hundred diabetic patients. Unlike Clarke's error grid, Parke's error is separate for both Type-1 and Type-2 diabetes and zones boundaries are connected sequentially, preventing the glucose values falling from a corrected zone to a critical zone and vice versa. There are 95% data points which are clinically acceptable in Clarke's error grid but in Parke's error grid the rated is 98%. The major drawback is that this error grid is patient specific and is not universal for all continuous glucose sensors. [30, 31].

Evaluating a glucose sensor's accuracy is not straight forward, because regression, correlation and error grid all provide static accuracy data, despite of time-based structure of the data. In 2004, Kovatchev et al. introduced a continuous glucose error grid analysis (CG-EGA). Unlike original EGA, the CG-EGA examines time-based characteristics of the continuous glucose sensor (CGS) information, evaluating sensor readings and pairs of reference as a process in time signified by a bidimensional time series and taking into account inherent physiological time lags. It consist of two components: (a) point error grid analysis (P-EGA) accesses the sensor's accuracy based on the correct presence of blood glucose values and (b) rate error grid analysis (R-EGA) evaluates the sensor's ability to measure the rate of blood glucose fluctuation and direction. The estimated values of rate and point precisions are then merged in a single accuracy assessment presented for each one of three preset blood glucose ranges: hypoglycaemia, euglycaemia and hyperglycaemia. R-EGA and P-EGA consist of five zones labelled as AR, BR, CR, DR and ER as shown in figure 3 (a,b), having similar clinical meaning to the original EGA [32].

The purpose of this review is to discuss different techniques for non-invasive glucose monitoring based on optical methods in the visible and infrared ranges. This article covers history, principle, instrumentation, accuracy, merits and limitations of each technique.

Optical Methods for Non-Invasive Blood Glucose Measurement Techniques

Optical methods for non-invasive blood glucose measurement involve a selected band of electromagnetic radiations. After propagation through the tissue, these radiations interact with the components of tissues including glucose. The concentration of the glucose within the sampled tissue volume is analyzed by the

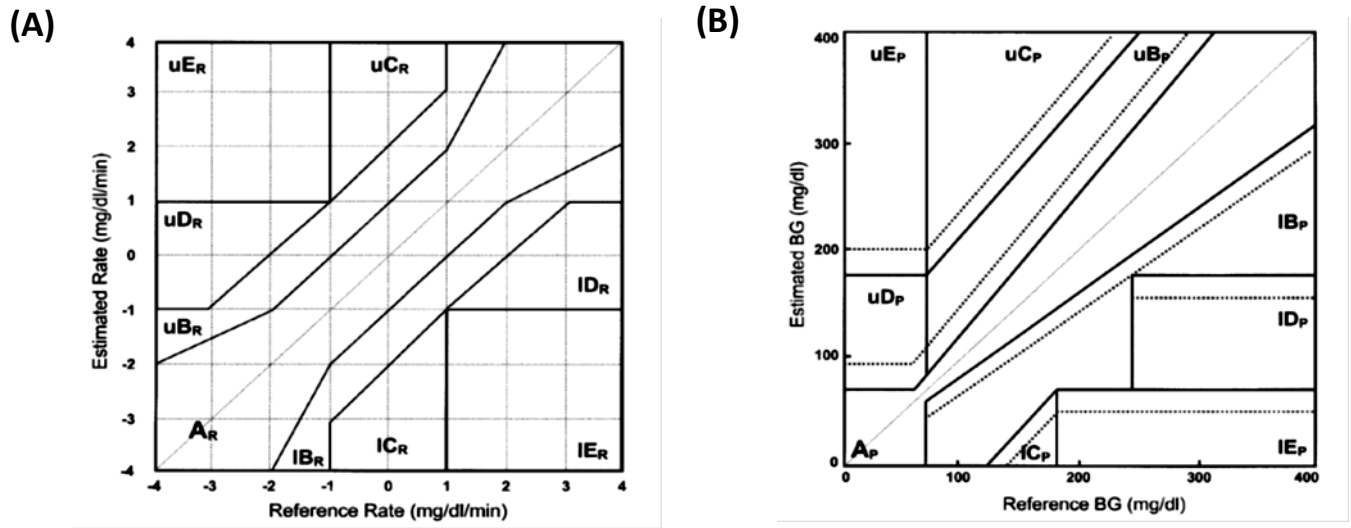

Figure 3. Continuous glucose error grid analysis (CG- EGA): (A) rate error grid analysis R-ECA and (B) point error grid analysis P-EGA (Published with permission) [32].

spectrum, collected during propagation of light. In the non-invasive glucose sensing, selectivity is one of the most important parameter [33]. Selectivity means to determine a particular amount of analyte in a complex matrix without any interference of other compounds. In order to over-come the effect of interfering interactions, a number of selectivity generating steps (detection and multistage separation principles) are used frequently, and the response is based on the interactions which are mostly accessed by multivariate data analysis (chemometrics) [34]. In optical methods of glucose detection, sensor selectivity is a critical issue because a large numbers of metabolites are present in the human body which have similar optical signature as glucose [30]. When accessing the selectivity, a suitable mathematical modelling should be incorporated [35]. In different multivariate calibration models, selectivity issues have been explored and due to this, advances in non-invasive glucose sensing with different techniques are limited [36, 37]. However, selectivity can be improved by the use of higher number of measurement, (e.g., use of whole spectrum over wave length range and the spectral data is processed by different chemometrics methods) [34].

Infrared (IR) Spectroscopy

Infrared (IR) spectroscopy technique induces rotational and vibrational transitions, associated with chemical bonds within or between molecules. Each molecular bond of molecules vibrates, so dipole moments fluctuate, and, this fluctuation interacts with the electric field of the incident radiation. If the molecular rotational or vibrational frequency matches with the striking radiation's frequency then results in absorption, which is an energy transfer from light to heat. The magnitude and number of the vibrational modes are dependent on the configuration and number of atoms within a molecule. Each functional group of a molecule has a distinctive vibrational frequency that makes IR spectroscopy extensively used for identification of the molecular structure of samples. Spectral region based on IR range extends from 750nm-14,000nm and classified into three regions: Near Infrared (NIR), Mid Infrared (MIR) and Far Infrared (FIR). NIR and MIR are known as absorption spectroscopies and FIR known as thermal emission spectroscopy [15, 38, 39].

Near Infrared (NIR) Spectroscopy

Description

NIR spectroscopy was accepted as a technique in early 1960s with the work of Karl Norris of United States (Agriculture research service, Department of Agriculture) [40]. After that, NIR spectroscopy expanded in many fields like food processing, pharmaceuticals, process control, remote imaging and many others applications [41]. Recently many universities and industries use this approach in vivo glucose sensing for diabetes [42].

In the NIR spectroscopy, spectral region lying in the range of 750-2500nm, corresponds to overtone and combinations of fundamental vibrational transitions of (CH-OH-NH) groups [43]. This spectral region (700-1100nm) known as therapeutic window, where intensities of melanin, water absorption band and hemoglobin are enough low so that the light can transmit into deep tissues with up-to 90-95% efficiency [15, 44, 45]. Glucose has absorption peaks at 939nm, 970nm, 1197nm in the higher overtone region, 1408nm, 1536nm and 1688, 1925nm in the first overtone region and 2100nm, 2261nm, 2326nm in the combination region [46]. It is based on colleting absorption or reflectance spectra of the tissue with a spectrophotometer. Due to the chemical interaction within the tissue, the focused light in the body is partially scattered and absorbed. Tissue properties and characteristics can be measured by light attenuation resulting from absorbance and scattering properties, [47, 48] described according to the light transport

theory by equation I = I0, where I = transmitted light intensity, I0 = incident light intensity, d is the optical path length in tissue, and = (a, s), where s is the scattering coefficient and a is the absorption coefficient [22, 49]. Changes in the glucose concentration can affect the measured absorption coefficient (a) of the tissue through changes in the absorption corresponding to water displacement or changes in its intrinsic absorption. The intensity of light which is scattered by the tissue is also affected by changes in glucose concentration. Changes in hydration status and temperature of the body might have an effect on water absorption bands and act as noise sources for glucose sensing [50].

A novel technique, named pulse glucometry, aims to get rid of, or minimizes the influences of contradictory factors by getting optical reading from a blood-only compartment within the tissue using by instantaneous differential NIR spectroscopy. This technique relies on two instant measurements over a tissue sample that is typically a finger's tip. Changes in optical absorption between each measurement rely on a blood volume modification made by cardiac pulses. By a subtraction method, the interference of basal components is then separated. Pulse glucometry has been tested in humans showing promising results [51].

The proposed system consists of appropriate light source, optical fibers, photodiodes and different data processing techniques. Light returned from human tissue is collected by photo-diode through an optical fiber. NIR spectrometry measurement relates to several overlapping bands and so it needs multivariate calibration modeling. Classical statistical procedure method, partial least squares regression, support vector mechanics regression and artificial neural networks are used as multivariate analysis. Hence, aforesaid data processing techniques combined with the analysis of changes in the light intensity permits to extract the chemical components within tissue, including glucose and then finally display on the screen as shown in figure 3c [52, 53]. To check the clinical accuracy, the resultant regression was assessed by Clarke error grid analysis [27].

Best site in the human body for glucose detection with NIR spectroscopy is forearm skin, earlobe, oral and lip mucosa, cheeks, tongue and nasal septum [52]. Clinical results show that 75% of the measurement points fall in the A zones of Clarke error grid and rest are in the B zones as shown in figure 6. No data point are in other zones and the correlation coefficient between reference and non-invasive glucometer is equal to 0.85, which is very good [54].

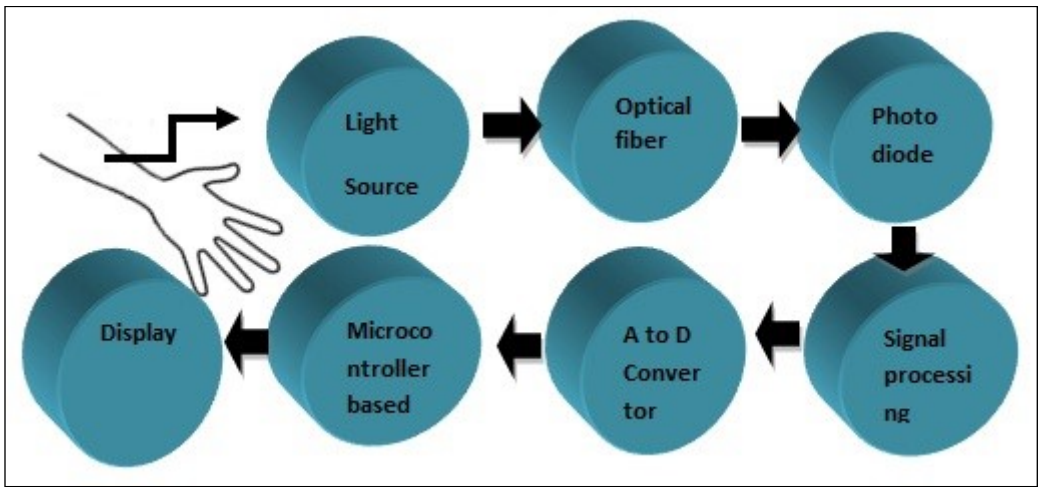

Figure 3c: Block diagram for proposed system [53].

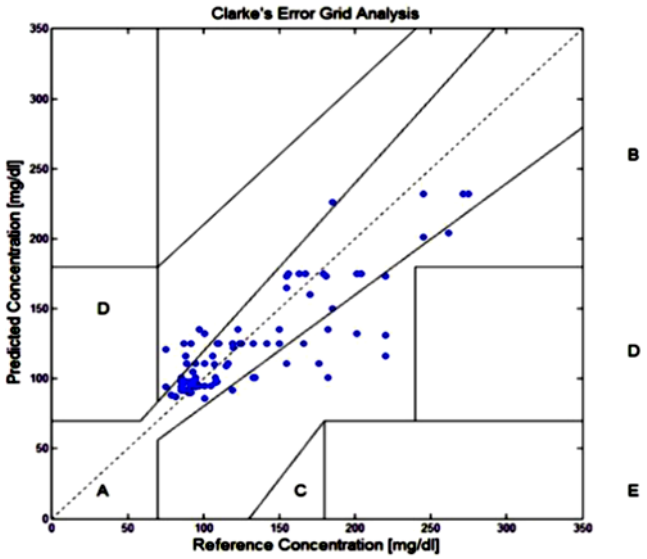

Figure 4: Clarke error grid analysis based on NIR spectroscopy (Published with permission) [54].

Merits/Limitations

It is very simple and inexpensive technique as compared to other optical methods, [55] having higher signal-to-noise ratio minimizes the interference from fluorescent light [56]. It also allows to measure glucose concentration in deep tissues up to 1-100mm in depth [57]. However, there are many disadvantages such as glucose absorption coefficient in NIR spectra is very low and it shows broad, weak and overlapped band with not only stronger bands of water but also with protein, fats and hemoglobin. Glucose concentration is also affected by different body parameters like variation in blood pressure, skin hydration, triglyceride, albumin concentration and body temperature [58]. Environmental changes like humidity, atmospheric pressure and temperature could also affect the measured glucose values [42].

Mid Infrared (MIR) Spectroscopy

Description

MIR spectrum lies in the range of 2500-10,000nm. It has the same principle and proposed system as the NIR spectroscopy. Due to longer wavelength as compared to NIR, there is decrease in scattering and increase in absorption [38, 42]. As a result, the MIR light only penetrates up to 100μm in human skin [38]. Hence glucose has to be sensed in ISF of epidermis where blood capillaries are not reached [59]. To overcome the limited light penetration problem due to the large absorption coefficients, a method called attenuated total reflection (ATR) is applied that uses a flexible hollow infrared optical fiber with a diamond (ATR) prism. Due to the nontoxicity of the hollow optical fiber, mechanical and chemical stabilities, flexibility and the diamond (ATR) prism, glucose level is expected to be measured in oral mucosa with high reproducibility [60 -62]. Glucose concentration is measured by detectors with data processing technique such as partial least square regression [11]. Best site in the human body for glucose detection with MIR spectroscopy is finger skin and oral mucosa [42].

Merits/Limitations

It has sharp glucose peaks as compared to NIR region [59]. One of the drawback is poor penetration of light within tissue [63].

Far Infrared (FIR) or Thermal Emission Spectroscopy

Description

It is based on thermal radiations in the range 8,000-14,000nm, naturally emitted from the human body having spectral information about tissue analytes [64]. Glucose strongly absorbs energy in the wavelength range around 9,400nm [58]. The proposed system detects the naturally emitted human body radiations especially from tympanic membrane [65]. The information of this membrane is important because it shares the blood supply with hypothalamus, the center of core body temperature regulation [66, 67]. The signals collected from this organ have smaller path length as compared to oral mucosa or skin site [15]. It

has identical selectivity principle as absorption spectroscopy has for analyte measurements [64].

The proposed system consists of speculum, used for insertion into ear with a plastic cover for hygienic purpose. For transmission of IR radiation, an optical system consists of IR wave-guide with an optional valve at the end of wave-guide that acts as shutter. Detecting system consists of optical filters and a thermopile detector, sensitive to an infrared (IR) region. One of the sensing components is shielded by an IR filter sensitive to the IR glucose signature. An appropriate filter that doesn't have spectral bands characteristic to the measured analyte, shields the other sensing space. Spectrally changed IR radiation from the membrane illuminates each window. The distinction between the intensities of the two radiation path ways provides a measure proportional to the analyte concentration. The information from the body temperature sensor, ambient humidity sensor, ambient temperature sensor and the analyte concentration is sent to the electronics system. Then all the signals are further sent to microcontroller for processing, and finally results of the estimated analyte concentration is displayed on the screen as shown in figure 5 [52, 68, 69].

An orthogonal regression calibration model is used for data analysis. To check the clinical accuracy, resultant regression was evaluated by Clarke error grid analysis which shows that 81% of the measurement points fall in the A zones of the Clarke error grid and rest are in the B zones as shown in figure 4. A very good correlation coefficient was found which is r = 0.89 [64].

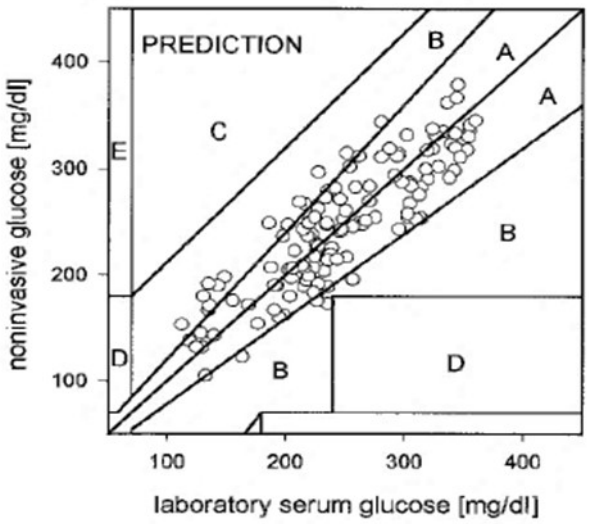

Figure 6: Clarke error grid analysis based on Thermal emission spectroscopy (Published with permission) [64].

Merits/Limitations

One of the advantages of this technique is there is no requirement for individually daily calibration. The drawback is that the intensity of radiations emitted from the tympanic membrane is affected not only by its temperature but also by its thickness [52].

Photoacoustic (PA) Spectroscopy

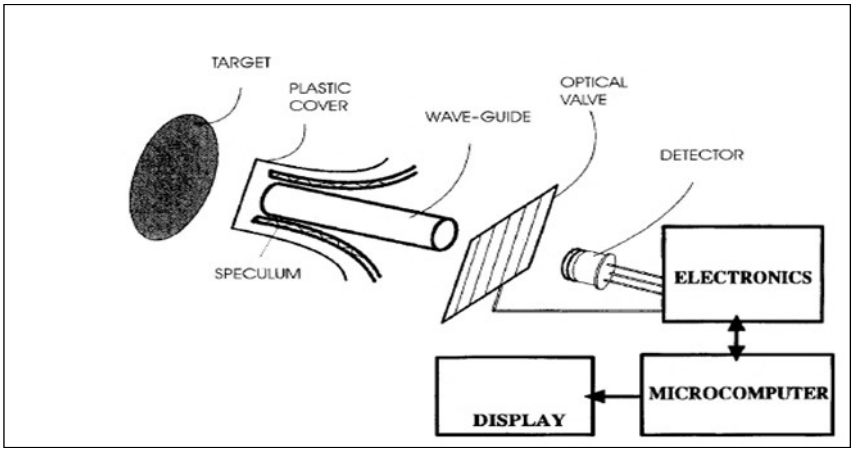

Figure 5: Proposed system for Thermal Emission Spectroscopy (Published with permission) [64].

Description

Photoacoustic technique was first discovered in the19th century by Alexander Graham Bell. With the development of laser in 1970s, this technique became more prominent for the analysis of gases [70, 71].

The proposed system is shown in figure 7. It consists of laser diode, projection system, transducer, optical fibers, microcontroller and display [72]. In this method blood glucose is excited with laser pulses for very short period ~ nano-seconds [73]. After the absorption of optical energy into cells, there is localized heating of PA cells which leads to volumetric expansion that means there is generation of acoustic wave, detected by confocal piezoelectric transducer [74-76]. The measured acoustic wave provides information not just only about the amount of glucose but also the total incident energy [77]. Glucose detection with this method is based on measuring the changes of peak-to-peak signal value which differs according to the glucose content [78]. These PA cells are cavities closed by an optical window at one end and by skin surface at the other end. There are problems associated with these closed cavities, like pressure variation inside the cavity leading to the distortion of the PA signal and temperature rises inside the cavity due to lack of air circulation flow. To partly overcome these problems, a newly designed windowless resonator is used in the ultrasound frequency range (50-60 KHz), leading to higher signal-to-noise ratio. In addition, by using of windowless PA cell instead of the closed resonator, influences of temperature and pressure can be reduced and therefore increasing the stability [79]. Best site in human body for PA spectroscopy of glucose is eye. Other sites are forearm and finger [42]. There is no diabetic human trials with glucometer based on photoacoustic spectroscopy [30].

Merits/Limitations

It has higher detection sensitivity [11]. The wide range in laser wavelength from Ultraviolet (UV) to Near Infrared (NIR) is suitable for PA spectroscopy [12]. However, this technique is an expensive technique. It is affected by chemical interferences and is also sensitive to environmental changes like pressure, temperature and humidity [42].

Raman Spectroscopy

Description

Raman Effect was first discovered in 1928 by Chandrasekhara Ramanan. In 1970 with the

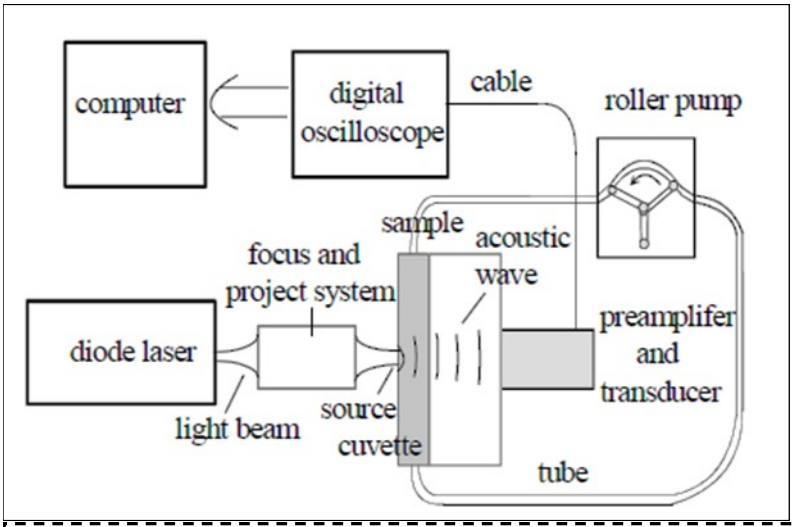

Figure 7: Experimental Photoacoustic set-up (published with permission) [72].

development of laser this technique became prominent with spectroscopic applications [80].

It is based on the inelastic scattering of monochromatic light. Inelastic scattering means frequency of the photons is changed when it interacts with the sample/ human body. The frequency of re-emitted photons is shifted-up or down with respect to original laser light, called Raman Effect. This frequency shift gives information about rotational, vibrational or low frequency transitions [81, 82] in human fluids containing glucose. The scattered light is influenced by molecular vibration so glucose concentration in human fluids can be estimated [83].

The proposed system consists of four major components; Laser source, sample, spectrometer and detector. Figure 8 shows schematic illustration of Raman spectroscopy for forearm site. Laser beam passes through filter, lenses and mirrors and is then focused to the sample. Back scattered light from the body passes through notch filter for rejection of the specular component of the light. After that, filtered light goes to spectrometer and the spectra is collected by a CCD detector [84]. Aqueous humor of the eye is also a good site for the detection of glucose because it contains a few Raman active molecules, which provide a measureable Raman signal. However, laser light wavelength should be low (700-900nm) to avoid toxicity [85-87]. An improvement in this technique is achieved with the variations such as surface-enhanced Raman spectroscopy, stimulated Raman spectroscopy, coherent anti-stokes Raman scattering and resonance Raman spectroscopy [88]. With this improvement higher intensity signals can be obtained [89]. Partial least square regression (PLS) is used as a calibration model to estimate the concentration of glucose [83]. Human trial shows a good correlation coefficient of r = 0.83 [90].

Merits/Limitaions

It has sharper signal peaks, less affected by water and less overlapped spectra [92]. However, this technique also suffers from some limitations such as instability of laser intensity, wavelength and interference with other biological compounds [42].

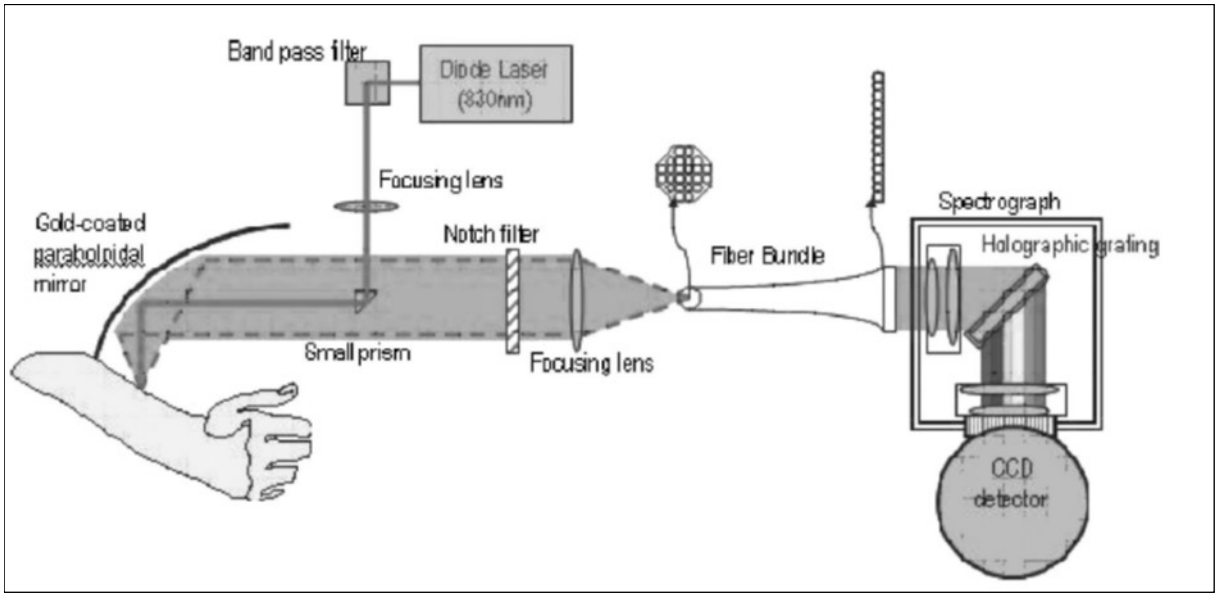

Figure 8: Schematic illustration of Raman spectroscopy (Published with permission) [91].

Optical Coherence Tomography (OCT)

Description

OCT was first demonstrated in 1991 by Fujimoto and co-workers. It is an emerging technique for performing cross-sectional imaging with high resolution in biological system [93, 94]. It is based on Michelson

interferometer with low coherence light source, fiber optics splitter, reference and scanning mirrors, lenses, photodetector and a display as shown in figure 9. Back scattered light from tissue is combined with light returned from the reference arm, detected by photodetector and then displayed on the screen [95-99]. The delay correlation between the reflected light in the reference arm and backscattered light in the sample arm is measured [11]. The idea of the mismatching refractive index between reference and sample indices has a potential application to measure the glucose level in blood both in vivo and vitro, using optical coherence tomography [100]. The (OCT) technology allows to measure the glucose induced changes in skin directly from the dermis layer [101]. Best site in human body for measurement of glucose concentration is forearm skin [22]. To estimate the concentration of glucose, optical coherence tomography signal slop (OCTSS) was evaluated by linear least squares. Human trial shows good correlation coefficient of r = 0.8-0.95 [30].

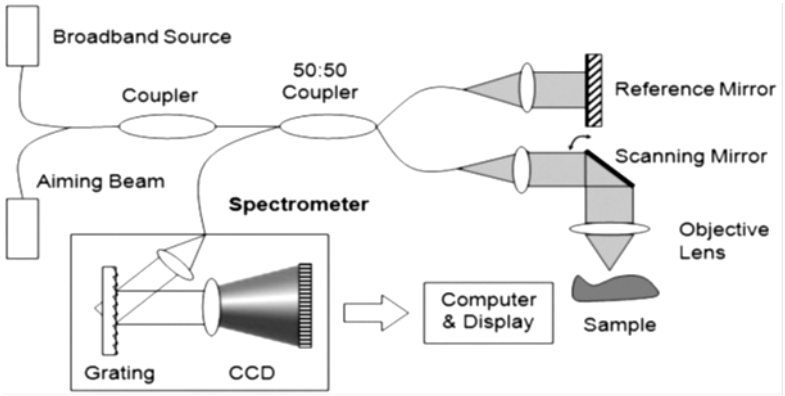

Figure 9 : Optical coherence tomography system [95].

Merits/Limitations

It has high resolution with 1mm depth in the tissue [102] and high dynamic range (> 100dB) [103]. The drawback is that the change in skin temperature of several degrees having significant effects on signals. Moreover, there is no clear indication that this technique has advantage over scattering techniques [22].

Metabolic heat Conformation (MHC)

Description

In 1982 Heilsen et al showed that after the glucose injection into the human body, there is a change in temperature within two minutes. This study is the foundation of research related to metabolic oxidation of glucose named as MHC [104]. In 2010, Zang et al proved that there is direct influence of glucose concentration with body temperature [105]. The homeostatic circadian rhythm of human body is related to metabolic heat, oxygen supply and concentration of glucose. Hence, glucose concentration can be measured by following the conceptual equation.

GLU = F (heat generated, blood flow, Hb, HbO2)

Where GLU= glucose concentration, Hb= hemoglobin and HbO2= oxygenated hemoglobin [106, 107].

The glucose measurement device is based on sensor having three functions as shown in figure 10.

First function is to measure radiation temperature of the finger. A thermopile detector (D3) inside the sensor is used for this purpose. Second is to estimate blood flow rate which can be measured by temperature difference between thermistor D1 and D2 during contact of finger with the sensor. Third is the measurement of Hb and HbO2 with the help of diffuse reflectance spectroscopy. Multi-wavelength spectroscopy is done with six wavelengths (470, 535, 660, 810, 880,

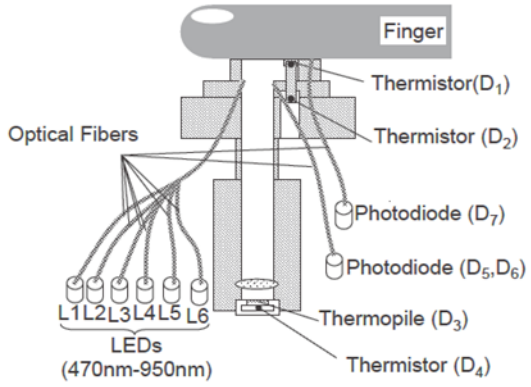

Figure 10: Sensor set-up (Published with permission) [106].

and 950 nm), that provides a reflectance spectrum for each of those measured substances and could then be converted to absorbance values via conversion formulas. Optical fibers lead light from the LEDs (L1-L6) to the individual's fingertip and to the photodiodes (D5-D7). Photodiodes are organized to measure the reflective and also the diffuse reflection on the topmost, inside and through the skin surface [106, 108-110]. If the perfusion (the process in which blood is delivered to the capillary bed in its biological tissue) is calculated with this technique then accuracy of glucose concentration could be increased [111]. To estimate the glucose concentration, regressions are applied stepwise and a calibration function is performed. To evaluate clinical accuracy of these regression analysis, Clarke error grid analysis is used that shows 90% of the measuring points fall in the A zones and 10% in the B zones. No measuring points fall in other zones. This shows a very good correlation coefficient of r = 0.91, as shown in figure 11.

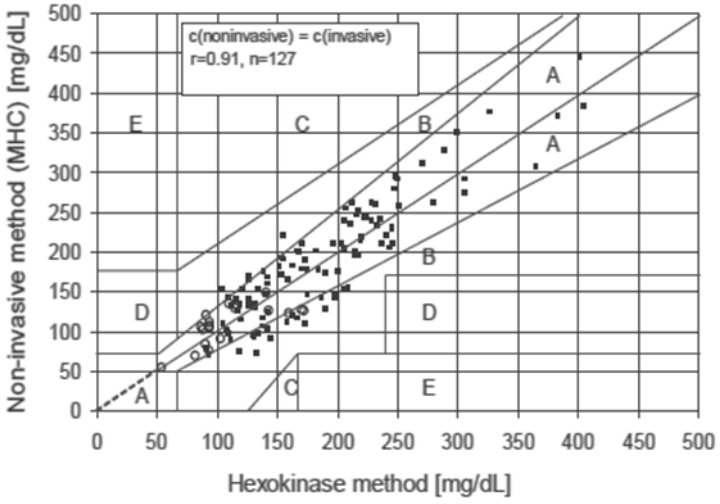

Figure 11 : Clarke grid analysis based on MHC (Published with permission) [106].

Merits/Limitations

It is feasible and low-cost technique. However, this technique suffers from interference due to environmental parameters [104, 106].

Fluorescence technique

Description

This technique was first introduced for the detection of glucose in 1984 [112], and it was further enhanced with the development of fluorescence resonance energy transfer (FRET) system, which means energy is transferred between two flourophore molecules if they are closer than the Forstre radius (the maximum distance over which energy transfer exist) [113, 114]. Figure 12 shows schematic illustration of the fluorescence technique. When ultraviolet laser light of wavelength 380nm falls on human tissue, then fluorescence is generatesd by the human tissue. The reflected light comprises of induced emission of light produced due to the interactions between the glucose molecules with water present in sample and the excitation light. A sensor detects this reflected light and generates signals indicative of the intensity of reflected light associated with glucose concentration distinctive characteristics of the emission light. To evaluate glucose concentration in the sample, partial least square regression (PLS) is used. [22, 115, 116]. Fluorescence based contact lenses based on polymer film have been developed for the detection of

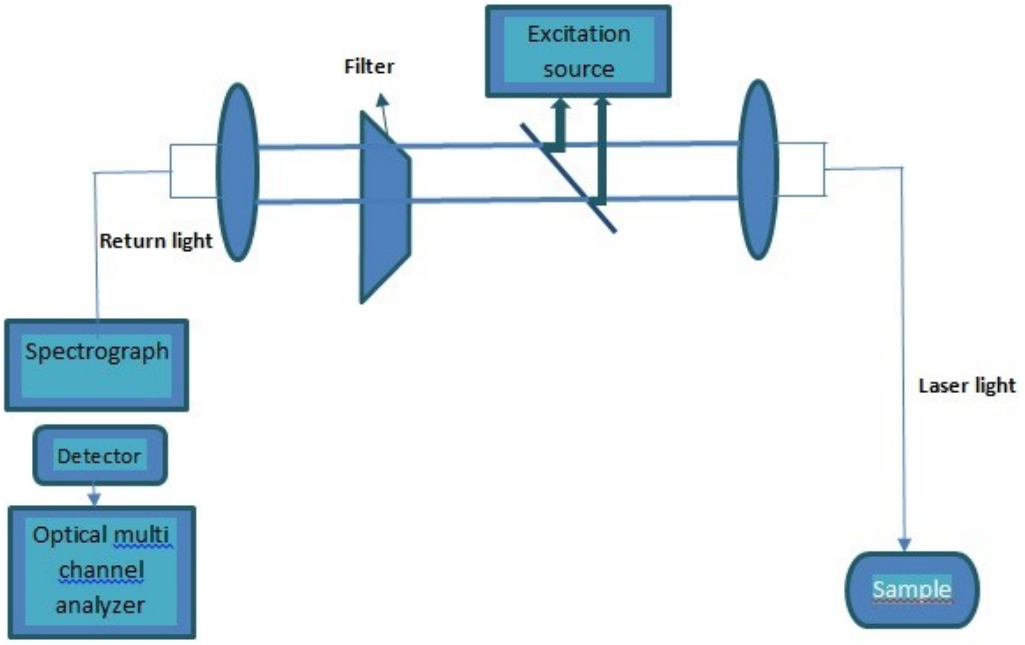

Figure 12: Schematic diagram of non-invasive glucose monitoring probe. Copyright © 2007, © SAGE Publications [121].

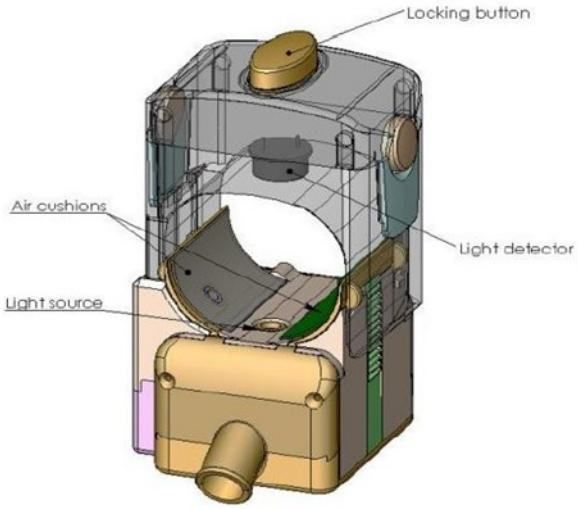

Figure 13: Schematic diagram of non-invasive glucose monitoring probe. Copyright © 2007, © SAGE Publications [121].

glucose concentration in tears. These contact- lens based sensor has been receiving a great attention because the device is disposable and portable. These contact lenses can change color according to the concentration of the glucose. Moreover, hydro-gel based soft lenses are safe for daily wear in diabetic patients [117, 118].

Merits/Limitations

It is an extremely sensitive technique. Single molecule detection can be achieved by the fluorescence method and there is little or no damage to the human body [119]. It has also some limitations such as Ultraviolet light suffers strong scattering phenomena and fluorescence depend on several parameters of the skin such as redness, pigmentation and thickness [120].

Occlusion Spectroscopy

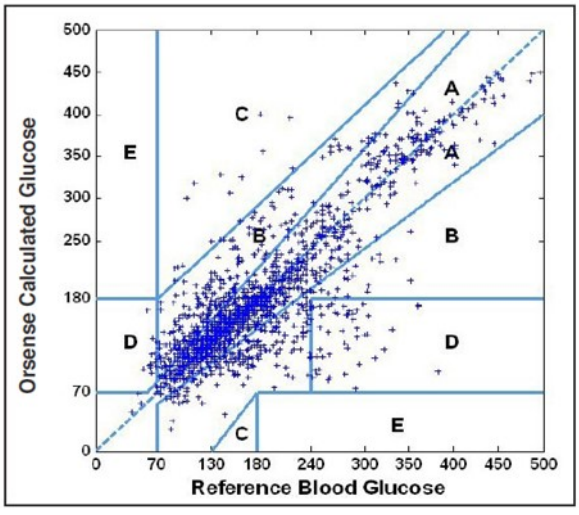

Figure 14: Clarke grid analysis based on Occlusion spectroscopy. Copyright © 2007, © SAGE Publications [121].

Description

Occlusion spectroscopy is based on light scattering phenomena. There is an inverse relationship between glucose concentration and scattering which leads to shorter optical path and less absorption. Figure 13 shows schematic diagram of non-invasive glucose monitoring probe [121, 122].

In this technique, pressure is applied by using pneumatic cuff to cease blood flow for few seconds. This pressure induces a pulse inside blood or changes the blood volume. At the same time, light is passed to the sample and the transmitted light is detected by a detector which estimates the glucose concentration. This temporary cessation of blood flow in human body (finger's root) enhances the generated signal; thereby improving the signal-to-noise ratio. This dynamic signal enhances the sensitivity to glucose and the robustness to interferences, which results in a more accurate glucose measurement. Best site for glucose detection in human body for occlusion spectroscopy is finger's root [123-125]. Deming regression analysis was used to evaluate the glucose concentration. Furthermore, to check the accuracy of the regression analysis, a Clarke error grid analysis was used. It showed that 69.7% of the measuring points fall in the A zones and 25.7% in the B zones as shown in figure 14 [121].

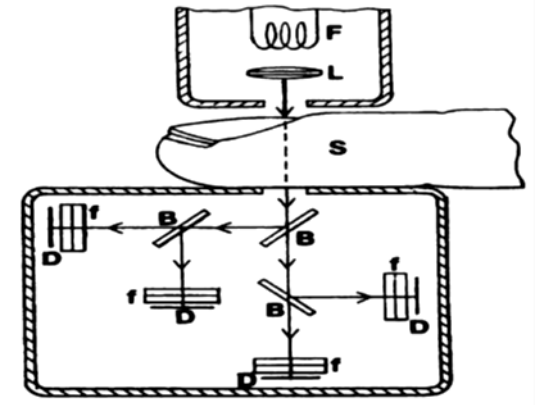

Figure 15 : Schematic illustration of Kromoscopy (Published with permission) [129].

Merits/Limitations

It has high signal-to-noise ratio which is necessary for accurate glucose measurement [121]. One of the drawback is that for the compensation of signal drift there is a need of appropriate methods [126].

Kromoscopy

Description

Kromoscopy was first developed by Optix Corp [13]. It is a multi-channel, real time correlated method with a series of overlapped broad band-pass filters for the determination of selective quantification of analyte, such as glucose[127]. Selectivity of a four-channel kromoscopic signal is demonstrated by the resolution of glucose information collected over 800-1300nm NIR spectra [128]. In this technique, IR radiations are passed through the sample and transmitted light evenly divided into four detectors having band pass filters as shown in figure 15. These four detectors are arranged in such a way that the light reaching each detector has examined the same structures in the tissue. To evaluate target analyte such as glucose from interferents, a complex vector analysis is used. In vitro glucose and urea is successfully differentiated in a binary mixture [129-131].

Merits/Limitations

It has higher signal-to-noise ratio [130]. The drawback is related to limited theoretical basis for improvement in the sensitivity over photometric method [13].

Multisensor technology

Description

Multisensor data fusion technology consists of the combination of different sensors within the same device for the detection and compensation of those perturbations which are responsible for non-accuracy of

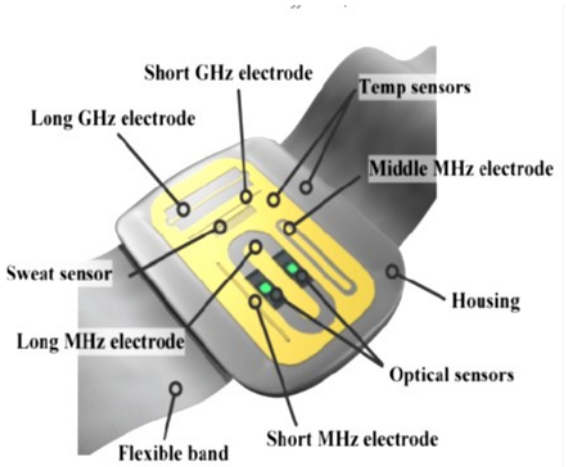

Figure 16 : Schematic illustration of the multisensor system, having electrodes of dielectric sensor and optical diffuse reflectance sensor (Published with permission) [134].

the non-invasive sensor [132]. To get multisensor technology, one approach is by combining two techniques such as bioimpedance/dielectric spectroscopy and absorption spectroscopy. Bioimpedance measurements include electrodes of different geometries and shapes, different frequency ranges such as from KHz to GHz, as well as optical modules (MIR

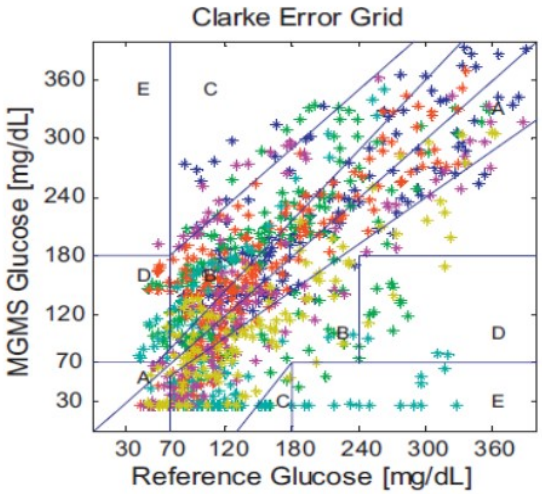

Figure 17: Clarke error grid analysis based on multisensor technology (Published with permission) [134].

spectroscopy), humidity, temperature sensor and an accelerometer [133]. These sensors allow the measurement of exogenous (humidity, temperature, etc.) as well as endogenous (sweating, movement, skin perfusion, etc.) [132].

Fig 16 shows the schematic illustration of multisensor system, having electrodes of dielectric sensor and optical diffuse reflectance sensor. The two identical diffuse reflectance sensors are used for the measurement of optical properties of the skin. Dielectric properties of the skin are studied in three frequency regions: low frequency (kHz) sensor, high frequency (MHz) sensors and even higher frequency microwave (GHz) sensors. The dielectric capacitive fringing field sensors are used to measure the dielectric changes of skin and the underlying tissue within the frequency range [134].

To estimate the glucose value from the multisensor technique, a suitable calibration model is needed. Usually partial least square regression is used for the estimation of model parameters from a suitable set of information. To check the clinical accuracy of the resultant regression, a Clarke error grid analysis is used. Figure 17 shows that Clarke A+B values are 89%. The correlation coefficient between reference and non-invasive glucometer is equal to 0.87, which is very good [23, 132, 134].

Another approach for multisensor technology is by combining three techniques such as ultrasonic, thermal and electromagnetic. Figure 18 shows Gluco-Track glucose monitor, developed on the basis of such combined technology. It consists of a main unit (MU), which drives three different sensor pairs located at the tip of personal ear clip (PEC) [135]. The thermal channel consists of a sensor and a heater located on the ear clip in close juxtaposition to the ear lobe. The electromagnetic channel consists of the capacitor plates located on the opposing portion of the ear clip and the ear lobe works as a dielectric. The ultrasonic channel consists of piezo elements located on the opposing portion of the ear clip and thus opposite sides of the ear lobe [136].

A calibration model such as partial least square regression is used to predict the glucose values. To estimate the clinical accuracy of the resultant regression, a Clarke error grid analysis is used. Figure 19 shows that 94% measurement data points fall in Clarke A+B zones.

Merits/Limitations

The combination of different techniques decreases the errors resulting from each technique separately, thereby increasing the final result's accuracy. However, from a practical approach, increasing the number of sensors or methods may cause the device to be more complex.

Table 1

The following table shows the over-view of the status and websites of companies, working on different non-invasive continuous blood glucose monitoring techniques by using different target sites of the human body [1, 11, 22, 27, 30, 42, 54, 64, 135, 137].

Summary and conclusion

In this review, we have described the most important non-invasive blood glucose monitoring techniques. Most of them have been suffering from the same difficulties such as environmental factors (pressure, temperature and humidity) and physiological processes e.g., temperature variation, sweating and blood perfusion that acts as disturbing factors. None of the devices in the production meet the standards for an ideal sensor. Therefore, tremendous research efforts are required for the development of a reliable continuous glucose monitoring device that is wearable, portable, and unobtrusive. A major challenge is to differentiate weak glucose signals from the underlying spectral noise; thereby high signal-to-noise ratio is still required for all non-invasive techniques. It is very important that the spectral information due to the glucose is not disturbed by other components present in the blood or skin. The glucometer must be specific to the glucose concentration. Different multivariate statistical calibration models such as ANN, PLS, PCR, SVMs, are used to map the measured quantity to the glucose value. Signal-to-noise ratio can be improved by the use of digital filters with the above mentioned modeling techniques. Hence, it is necessary to give high attention towards calibration modeling. Calibrations is done by converting the raw data points (e.g., light intensity, response current) into useful glucose reading as well as compare these glucose values with the reference (true blood glucose) values.

Under laboratory conditions, it is relatively easy to measure data points and find correlation with blood glucose level as compared to normal environment. The challenge is to develop a stable and clinically reliable sensor which can continuously measure the glucose concentration with accuracy better than 15mg/dl (0.8mmol/l) in the normal environment of patient's daily life. We are still far away from achieving this goal due to many technical issues. In order to handle all the aforementioned issues, the concepts should be more robust towards environment / experimental setup conditions together with multiple approaches from multidisciplinary research involving material scientists, chemists, pharmacists, engineers, and physicists.

We recommended that metabolic heat conformation (MHC) is feasible and low-cost method as compared to rest of the techniques, because of equipment which are used in this method is inexpensive and clinical results show a very good correlation coefficient of r = 0.91 as well. However, there is a need to concentrate on environmental effects as well as physiological processes in the human body. By combining MHC with some other techniques such as NIR spectroscopy (using sensor fusion technology), and providing additional information such as heart rate and body physical activity, one may be able to further improve the performance of non-invasive blood glucose sensor to a satisfactory level.

Acknowledgments

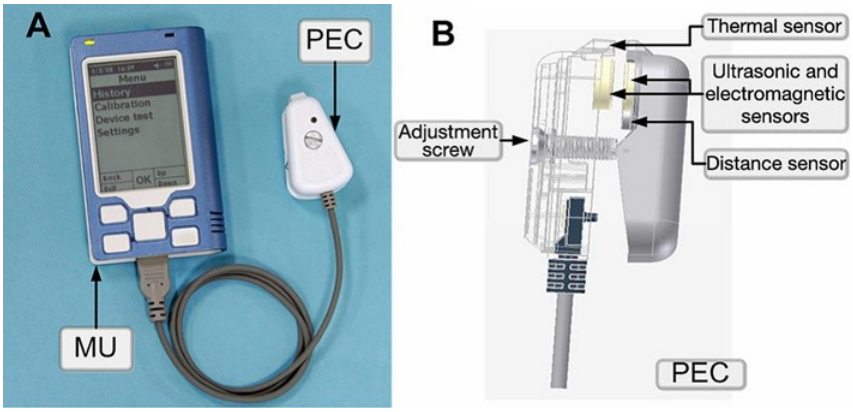

Figure 18: (A) MU with PEC and (B) Side view of PEC. Copyright © 2010, © SAGE Publications [135].

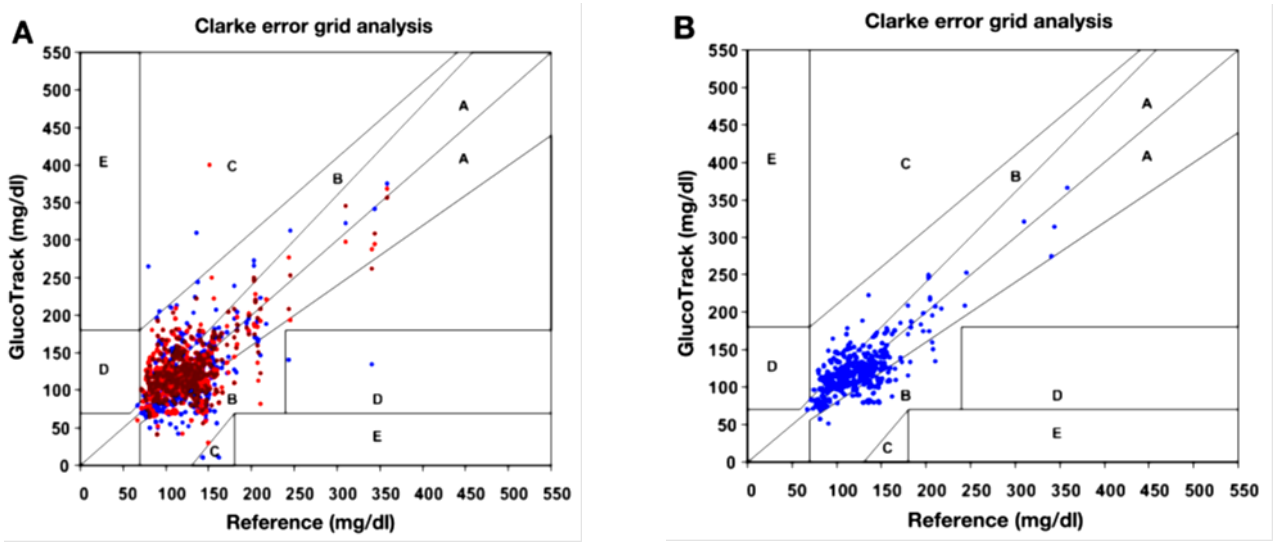

Figure 19 : (A) raw glucose readings per each technology [(•), electromagnetic; (•), thermal; (•), ultrasonic] and (B) final combined glucose result. Copyright © 2010, © SAGE Publications [135].

Table 1

Technology	Company/ Device	Target Site	Technique regarding accuracy	Environment Factors	URL
Ultrasonic, electromagnetic and thermal technology	Gluco-Track	Ear-lobe skin	94%	Temperature and humidity sensitive	www.integrity-app.com
Fluorescence	Eye sense	Contact lens -tears	n/a	No effect	www.integrity-app.com
Occlusion spectroscopy	Orsense Ltd	Finger-tip skin	69.7%	No effect	www.Orsense.com/Glucose
Raman spectroscopy	Medisensor	Skin	83%	No effect	www.C8medisensor.com/ us/home.html
Thermal emission spectroscopy	Infratec Inc	Tympanic membrane	89%	Temperature sensitive	www.diabetesmonitor.com/ meters.htm
Optical coherence tomography	Glucolight Corporation	Skin	80-95%	Temperature sensitive	www.glucolight.com
Metabolic heat conformation	Hitachi Ltd	Finger-tip skin	91%	Interference with environmental parameters	www.hitachi.com/news/ cnews/040223.html
Bio-Impedance	Biosensors Inc	Wrist skin	49%	Temperature sensitive	www.biosensors-tech.com
Photoacoustic spectroscopy	Glucon/ Aprise	Forearm skin	71%	Humidity, Pressure and temperature sensitive	www.glucon.com
Near infrared spectroscopy	LifeTrac system Inc/ sugarTrac	Skin	80-90%	Humidity, Pressure and temperature sensitive	www.sugartrac.com

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