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A Review of Non-invasive Electromagnetic Blood Glucose Monitoring Techniques

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Abstract

Diabetes is a big concern worldwide, and the International Diabetes Federation estimates there are over 450 million diabetics throughout the world. Researchers have been exploring a rapid and easy technique of calculating blood glucose. We already have reliable tests with improved precision for sensing blood glucose, but it comes with the expense of discomfort and agony because of employing a pricking needle. Technologies established during the previous few decades strive for a painless gadget that can be used as often as possible, dependable, efficient, and accurate. Most importantly, it must be straightforward to use with minimal hassles. This evaluation attempts to give the breakthroughs at present being researched for non-invasive electromagnetic (EM) glucose monitoring systems. This study acknowledges features and possibilities of accessible EM glucose monitoring techniques, just as basic qualities and execution elements for an ideal non-invasive instrument.

Keywords: Non-invasive, Blood glucose, Relative permittivity, Radiofrequency

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Introduction

Diabetes is regarded as the world's fastest-growing chronic illness.[1] According to estimates from the World Health Organization, the number of individuals with diabetes has increased from 108 million in 1980 to 422 million in 2014.[2] The International Diabetes Federation stated in 2017 that one of every eleven people had diabetes.[3] The rate has been growing more rapidly in the middle- and low-income nations and anticipates that by 2045, one in 10 people will have diabetes.[4] If diabetes develops in a person and is undiagnosed or untreated, in that case, multiple complications can occur, categorized into macrovascular complications (coronary artery disease, peripheral artery disease, and stroke) and microvascular complications (diabetic nephropathy, neuropathy, and retinopathy).[5] Regular blood glucose management is vital in the management of diabetes and enables patients to recognize the link between blood glucose levels, meals, activities, and key medication for diabetes. Traditional blood glucose monitoring techniques rely on the extraction of blood samples from the fingers that are intrusive, painful, and unpleasant. The preceding approaches employed a chemical reaction to determine the presence of glucose. The more of this process they could discover taking place, the more glucose was present in the sample, to begin with. Those detectors placed a drop of blood on a thin membrane that carried an enzyme called glucose oxidase with an electrode below. This enzyme allows blood glucose to react with oxygen to produce gluconic acid and hydrogen peroxide.[6] The electrode monitored oxygen and hydrogen peroxide changes, according to the quantity of glucose in the sample. Other methodologies assessed something like electrons created in the process or changes in how the test strip reflected light.

Nevertheless, studies have typically focused on glucose oxidase. There have been numerous adjustments during a long time, including reducing the electrodes to accommodate the small paper test strips. Implantable continuous glucose monitors are available as an alternative in contrast to specific people. However, they still have to be authenticated with finger sticks, and they have distinct drawbacks as well. To enhance treatment and simplify the lives of millions of people with diabetes, the necessity for a pain-free, rapid, easy-to-use, and accurate glucose monitoring device that does not invasively test glucose levels without finger pinching has become imperative. Non-invasive glucose monitoring systems, which indirectly detect glucose by detecting some physiological phenomena in the body, correlate with the glucose level and introduce noise in the process because of numerous blood and tissue factors. The noise might be external as well, such as the impact of temperature in the measurement. Therefore, it becomes vital to discern between the signal, the glucose content, and the noise. In these circumstances, the signal-to-noise ratio rises, which may be done by boosting the signal. Again, as it is an indirect measurement and relies on physiological phenomena, it becomes vital to match the signal and the real glucose level, known as calibration. It is crucial to understand the validity of the calibration, how frequently it is necessary to repeat the cycle, or how long it takes to become calibrated. Another concern because of the indirect measurement is the lag time, especially in scenarios that necessitate continuous monitoring, lag time plays a key part in accuracy.

Although various evaluations of current and emerging non-invasive blood glucose techniques[7-13] are available, a substantial

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quantity of new research leads to a need for continual updates in this field. This focused review's major purpose is to describe the fundamental issues faced by electromagnetic (EM) blood glucose monitors and evaluate the processes and accompanying instrumentation to be followed.

Different Non-Invasive Blood Glucose Sensing Techniques

This section outlines the early and current history of non-invasive blood glucose monitoring technologies. Several non-invasive blood glucose monitoring strategies have been studied and documented in the literature; however, Figure 1 provides a current state-of-the-art evaluation of these various different ways based on the transduction type. The innovations employed for non-invasive glucose detection comprise optical, electromechanical, electrochemical, and EM methods, and a considerable number of these glucose sensors are presently commercially feasible. From the graphic, it is obvious that the range of these approaches for non-invasive blood glucose testing has a common denominator, and this is the optical approach. It contains all the strategies to operate in broader optical wavelength bands of the spectrum. They take advantage of the light transmission, absorption, and dispersion qualities when traveling through the human body. Unfortunately, many optical advancements result in a very faint signal and low resolution and are also far from practical applications.

Electrochemical techniques have finally experienced more widespread application in non-invasive glucose sensing throughout the past few years. Multiple investigations have indicated that the glucose content in saliva mimics its level in blood. Researchers have pointed out this relationship's advantage by inventing an electrochemical sensor that can be worn like a mouthguard and transmit a wireless signal about the glucose level. Glucose sensing using smart contact lenses has become

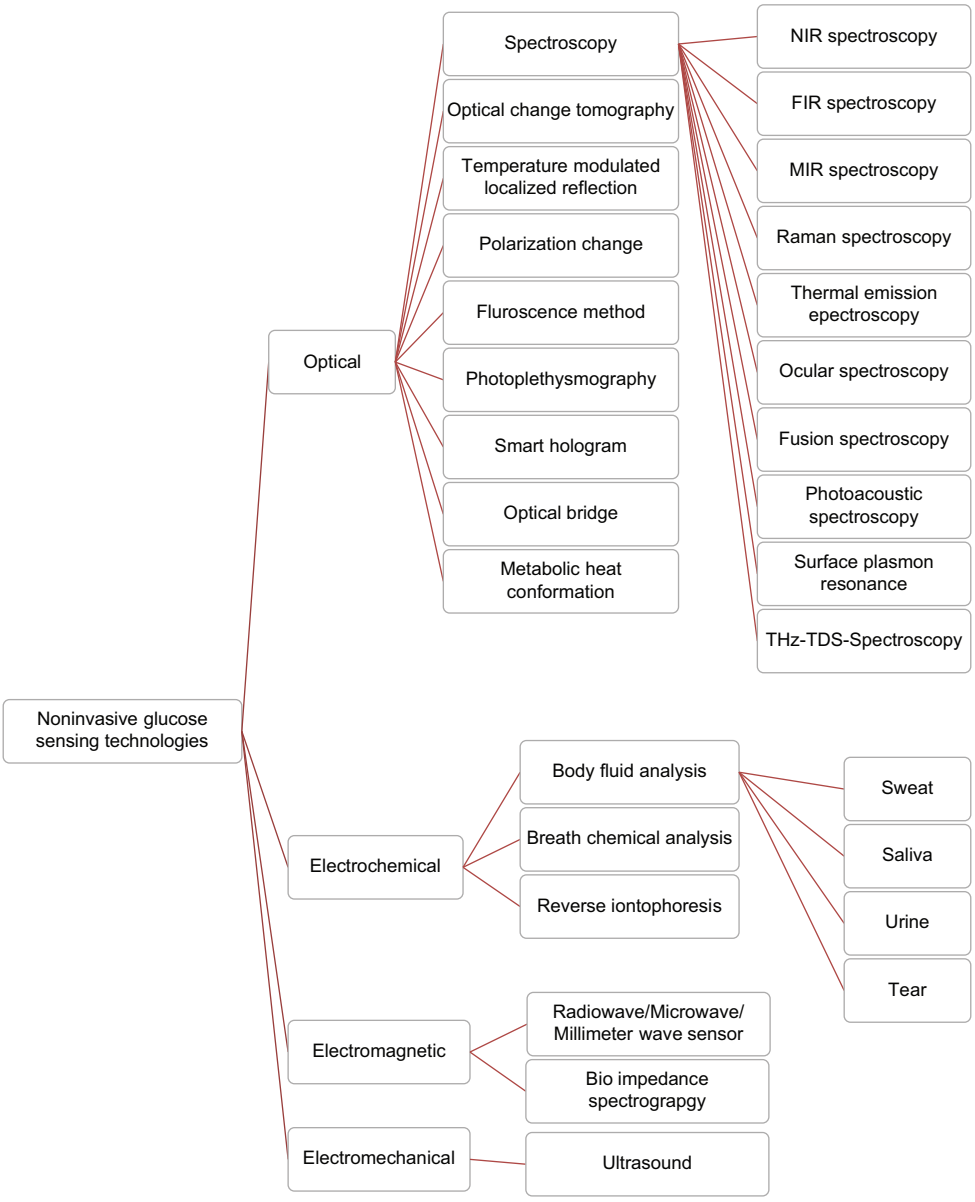

Figure 1: Non-invasive glucose estimation procedures

an important topic of study that captures glucose from tears and has exhibited promising effects; nevertheless, the obtained signal intensity is not as great as saliva. Furthermore, a few sweat-based glucose monitors have been explored that correlate the concentration of glucose in sweat with that in blood reliably. Scientists have devised a patch biosensor that monitors glucose in the fluid between the human skin cells or interstitial fluid pulled out using electricity or ultrasound. Even if there is some advancement in the development of electrochemical techniques, which detect the glucose in bodily fluids and exhaled breath, it delivers issues to the human body because measuring glucose from tears, perspiration, and saliva entails battling against the body's ever-changing physiology. Ultrasound innovation is useful because of its ability to penetrate deep into the skin and tissue, delivering somewhat precise scanning in such a manner. The ultrasonic method assesses the transmission time of the ultrasound through the biological tissue. The higher the glucose content, the faster the ultrasonic pulse passes through the medium, shortening the period of propagation. The acoustic velocity in liquids and soft-tissue relies on compressibility governed by the intermolecular bonding forces and the medium's density. Glucose levels in the extracellular fluid influence density and adiabatic compressibility and directly determine acoustic velocity through a direct link. In any case, ultrasonography alone misses the point since it is hampered by temperatures that interfere with its ability to produce precise results.

Despite significant breakthroughs in optical, electromechanical, and electrochemical technology, it has been shown impossible to achieve correct glucose readings without penetrating the skin. Research may reveal that a compact glucose sensor may provide correct glucose levels as continuous glucose tracking in the laboratory, although recreating such results in the current world might be challenging. Overall, none of these technologies has been commercialized effectively, and how can we be confident of the feasibility of these items when many are merely qualitative or operate only over a threshold? The authors will investigate whether EM processes can provide precise glucose readings and a superior alternative to current glucose monitoring systems in this review. This brings about our discussion topics, how to enhance the EM non-invasive testing equipment, the basic hurdles that are still present, and the most significant aspect of checking glucose levels.

EM Non-Invasive Blood Glucose Sensing Techniques

Bioimpedance Spectrography

The resistance to the flow of an applied electric current through biological tissue is known as bioimpedance. As illustrated in Figure 2, a device provides an input current that is unnoticeable to humans for bioimpedance measurement. The current is a flow of electrical charge that is injected into the body through the first set of driving electrodes, which always take the route of least resistance. As the current flows, it losses energy, and the ensuing energy loss produced by the tissue is detected by the change in the voltage by the second set of electrodes. Ohm's law ties the voltage to current and impedance, and so a measurement of the voltage differential and current flow can identify the resultant bioimpedance.

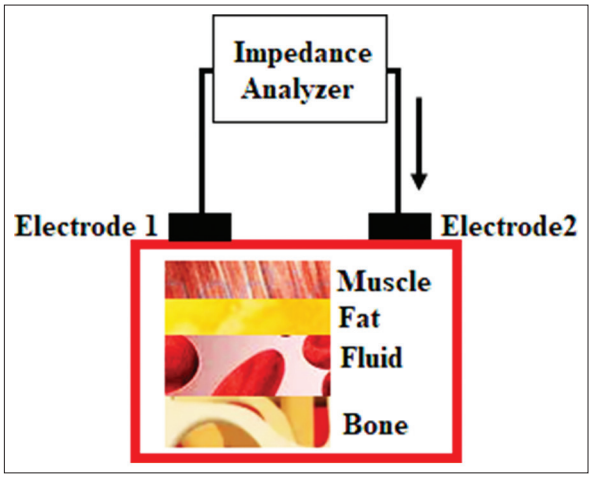

Figure 2: A schematic showing tissue impedance spectroscopy

The bioimpedance can measure an indication of the fluids in the body. This is because the human body comprises roughly 60–65% of water. Water is disseminated through cells and tissues, transmits electrical current as it comprises dissolved ions such as Na^+, K^+, and Cl^-, which may migrate. Fat, bone, muscle, fluid, proteins, and minerals are all human body components. Different tissues all have various electrical characteristics, which are dictated by the composition of the substance. Electrical current always takes the path with the least amount of resistance. In biological tissue, fat and bones function as an insulator and do not conduct considerable current. Fat-free mass and fluid transmit electricity through ionic conduction, and the applied current travels through the tissue muscle and electrolytic fluid, including the blood. As a result, the fluid component of the tissue will dominate the observed impedance.

In 2003, the first presentation of a non-invasive human continuous glucose monitoring framework employing impedance spectroscopy was presented by Caduff *et al.*[14] The glucose sensor utilizes an EM field in the frequency range from 1 to 200 MHz that collaborates with the skin surface to screen its electrical changes in the body, notably in the blood. Glucose alone does not impact the dielectric spectrum in this frequency range. However, variations in electrolyte balance, particularly the sodium and potassium gradients at varied glucose concentrations, lead to modest conductivity changes in the tissue layers that the device may evaluate as impedance variations. This is why the sensor can be treated as a serial resonate contour terminating in fringing operating capacitance. The sensor's impedance at a resonant frequency relies on impedance variations inside the skin and buried tissue. The impedance model of the glucose sensor implanted on the skin is provided in Figure 3, where L is the inductance of the external coil, C is the coupled capacitance of the sensor positioned on the skin, R is the average resistance of the skin, and buried tissue. This RLC resonant circuit's impedance is measured across the given frequency range, utilizing a Vector Network Analyzer or a resistive divider. A frequency sweep and temperature measurement are played every minute, and glucose levels are estimated using an algorithm based on frequency, impedance, and temperature variations. The Swiss business Pendragon Medical, Ltd., Zurich, Switzerland, produced an enhanced digital watch for glucose monitoring called the Pendra based on Andreas Caduff's research and was endorsed by Conformité Européenne. The item was accessible in the market for a

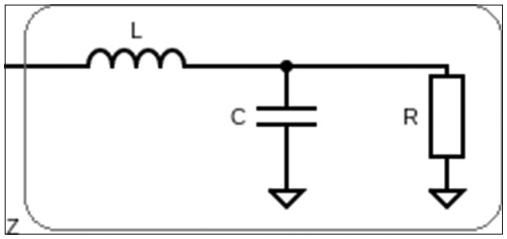

Figure 3: Simple impedance model of the sensor mounted on the skin

brief time and became outdated after 2005 despite being promising. Albeit the findings were encouraging, the concept included a few obstructions that quickly annoyed the glucose-related signal, not letting an acceptable tracking of glucose swings. Hence, the idea was revised and strengthened with more sensors to solve the annoyances observed, such as temperature, perspiration, or perfusion changes, to further progress toward real-time monitoring of glucose fluctuations *in vivo*. To handle these issues, Caduff's group[15] further conducted clinical trials using the multi-sensor idea whereby several sensors were combined to investigate the connection between changes in the blood perfusion and moisture qualities of the skin and the dielectric conduct of the skin and hidden tissue. He employed an impedance spectroscopy-based differential sensor to assess the skin and basic tissue's dielectric characteristics in the light of externally imposed physiological changes. The sensor incorporated the capability to accomplish varied EM fields' penetrations into the various tissue layers by employing two sets of isolated capacitive fringing field electrodes. Besides, galvanic response-based sweat and humidity sensors monitored the skin and essential tissue moisture levels. An embedded piezoelectric pressure sensor detected the skin's pressure through the sensor assembly, and a micro-spectrophotometer detected changes in the skin's optical characteristics. The observed skin impedance in a limited frequency range of 27–57 MHz and the remaining sensors' characteristics helped figure out between impedance variation produced by glucose variations and the changes induced by other perturbing influences. The blood glucose was determined using a multiple regression variable change technique. The multi-sensor notion looked to offer the likelihood to account for and correct for distinctive irritating impacts. To ensure accurate real-time glucose monitoring with a reduced number of explanatory variables, Caduff *et al*.[16] changed the earlier global regression modal using a combination of Akaike's Information Criterion and Cross-validated prediction error as a quality criterion to get a sensible statistical model. Besides, all the different sensors were merged into a single housing to measure the information stream's phase difference and logarithmic power levels. The study findings demonstrated that a global model could be constructed using the training data, and extrapolation is conceivable for the same patient retest data set. This clinical investigation needed an initial 75 min run-in period for stabilizing glucose levels in the patients and one baseline adjustment or patient-tailored calibration procedure at the beginning for future glucose level measurements. A scaled down housing integrating extra sensors, batteries, and communication capacity were built subsequently with a flexible wearable wristband[17] to emulate a more dependable and realistic hyperglycemia variation monitoring system. However, no data are available about the usefulness of the instrument for home or self-measurement applications.

Radio wave/Microwave/Millimeter-wave Sensor

The radiofrequency (RF) component of the EM spectrum encompasses various frequencies ranging from 3 kHz to 300 GHz. It starts from middle frequency to extremely high frequency. Many studies have explored the relationship between fields from different frequency ranges in the EM spectrum and the human body. The fields are typically divided into the following ranges based on the absorption of energy by the human body:[18,19]

- Frequencies ranging from about 100 kHz to less than about 20 MHz, absorption in the trunk decreases rapidly with decreasing frequency, and significant absorption may occur in the neck and legs
- Frequencies ranging from around 20 MHz to 300 MHz, at which relatively high absorption can occur in the entire body
- Frequencies in the range from roughly 300 MHz to several GHz, at which considerable local, non-uniform absorption occurs; and
- Frequencies above around 10 GHz, at which energy absorption occurs mainly at the body surface.

The electrical properties of the medium considerably impact the propagation of the EM wave. It may be represented by three factors ε, μ, and σ termed permittivity, permeability, and conductivity of the medium, respectively. The conductivity of material directly corresponds with the propagation of EM waves; attenuation of the EM waves rises with the rise of conductivity.[21] The permeability of biological tissue is similar to that of open space; hence, bodily tissue is fundamentally nonmagnetic. At the same time, the permittivity of natural tissue is a crucial function of frequency. The inability of the charges in the tissue to respond to the higher frequencies of the applied fields causes permittivity to decrease with frequency, resulting in lower permittivity levels. The ability of a material to polarize when exposed to an electrical field is defined by relative permittivity. This polarization begins from numerous distinct dielectric mechanisms: Electronic, atomic, dipolar or orientation, and ionic polarization.[22] Many processes will be active for a given material at different frequencies, as shown in Figure 4a. The slower processes fade out with increasing frequency, and each mechanism has its own relaxation frequency.

The relative permittivity (or dielectric constant) of a medium should be a real value if it does not absorb any energy from incident radiation. The relative permittivity must be expressed by a complex number if the medium absorbs energy from the incoming radiation. A medium's complex permittivity is defined by: [23]

$$\varepsilon^* = \varepsilon' - j\varepsilon'' \quad (1)$$

where

ε′ and ε″ are the real and imaginary parts of the complex permittivity and $j = \sqrt{-1}$

A measure of lossiness of material is ε″, the larger the value of ε″ the lossier is the material.

Equation (1) can be expressed into dimensionless form as:

$$\varepsilon_r^* = \varepsilon_r' - j\varepsilon_r'' \quad (2)$$

Where, ε_r^* is the complex relative permittivity. ε_r' and εr″ are the real and imaginary components of the complex relative permittivity, respectively.

The component εr′ indicates the efficiency with which the field energy is converted to heat by the sample. In contrast, the other component εr′ measures the capacity of the material to be polarized by the external electric field. The imaginary fraction of permittivity (εr″) is always more than 0 and typically <εr′. Both dielectric loss and conductivity are accounted for

in the loss factor. In Figure 4b, the vector diagram of complex relative permittivity is shown, with the summation creating an angle (δ) with the real axis, ε_r'. The ratio of energy lost to energy conserved determines a material's relative lossiness. The parameters εr*, ε_r', and ε_r'' are all affected by the radiation frequency. At the specific relaxation frequency, reductions in relative permittivity are followed by a peak in the imaginary component of the permittivity. An incident EM wave on a material may be bounced (reflection or scattering), attenuated, or transmitted through it, according to the principle of energy conservation, and the material's response to the incoming wave is based on its fundamental properties.[24] The term skin depth or penetration depth describes the attenuation properties of a medium in which the EM wave amplitude is reduced to 1/e or 36.8% of its original value. Its value in a lossy medium (good conductor), where σ≫ωε is expressed as: [21]

$$\text{Skin depth, } \delta = \sqrt{\frac{2}{\grave{u}\,\mu\sigma}} \qquad (3)$$

Where, μ = permeability of the medium
σ = conductivity of the medium
ω = angular frequency.

As a consequence, high frequencies have a shallow penetration depth, but lower frequencies may penetrate deeper through a variety of media. A change in blood glucose concentration causes changes in the dielectric boundaries of the blood, such as conductivity and permittivity. In reality, when the frequency increases from a few hertz to gigahertz, the dielectric constant decreases from a few million to a few units, while the conductivity rises from a few millimhos per centimeter to almost a thousand. The dielectric features of absorption, reflection, and transmission of RF waves through biological tissue are dependent on glucose content. The Cole-Cole model represents blood permittivity on glucose dependence, with blood permittivity fluctuating in response to glucose concentration.[25]

$$\hat{\varepsilon}(\omega) = \varepsilon_c'(\omega) - j\varepsilon_c''(\omega) = \varepsilon_\infty + \sum_n \frac{\Delta\varepsilon_n}{1+(j\omega\tau_n)^{(1-\acute{a}_n)}} = \frac{\sigma_i}{j\varepsilon_0} \qquad (4)$$

Where, ω is the angular frequency, $\varepsilon_c'(\omega)$ is the frequency-dependent dielectric constant, $\varepsilon_c''(\omega)$ is the frequency-dependent dielectric loss, n is the order of the Cole-Cole model, ε_∞ is the high-frequency permittivity, $\Delta\varepsilon_n$ is the magnitude of the dispersion, $\boldsymbol{\tau}_n$ is the relaxation time constant, α_n is the parameter that allows for the broadening of the dispersion, and $\boldsymbol{\sigma}_i$ is the static ionic conductivity. Sensors based on the EM induction approach have detected differences in the dielectric properties of blood caused by changes in glucose level.[26] The sensor, as shown in Figure 5, consisted of two coils coupled around a fluid ring that was controlled by a peristaltic pump that mimicked the hydraulics of the human heart. The primary coil was activated with a 40 kHz AC source; the fluid under test links the secondary coil with the primary coil. The conductivity of the different glucose concentration test fluids was evaluated using the observed current in the secondary coil. The conductivity of the solution changes as the glucose content in the solution fluctuates. The output voltage was shown to fluctuate linearly with the examined range of test fluid glucose levels, and a falling tendency was maintained with the rising of glucose levels. They also changed the measurement temperatures in the body temperature fluctuation range to interpret the best potential temperature fluctuation effect on glucose concentration estimate. However, another study of this technology selected two identical sensor cells serving as test and reference cells in their EM interaction model.[27,28] The output voltage of the first test cell derives from glucose and temperature change in the tested animal blood sample. In contrast, the second reference cell voltage adjusts for the influence of temperature on the measurement. The differential voltage signal from the two cells corresponds to glucose amounts varying in the tested blood sample. This innovation evaluates the dielectric boundaries of the test fluids in the same way as

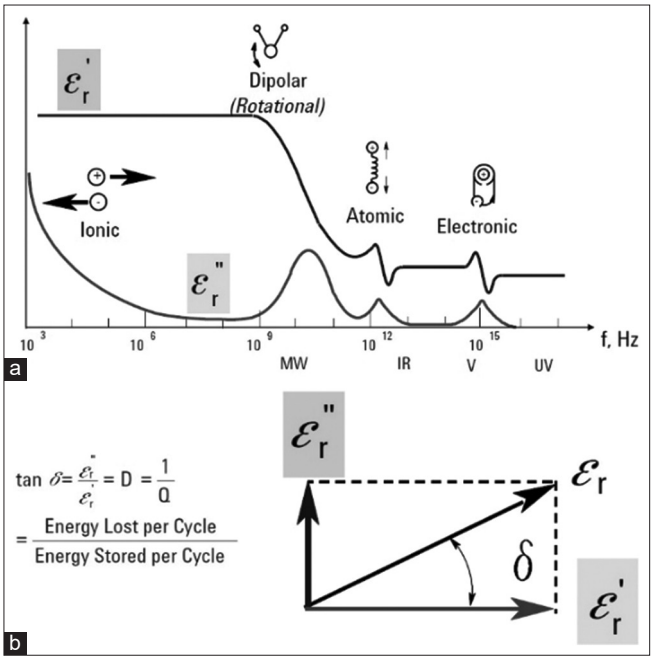

Figure 4: (a) Frequency response of dielectric mechanism, (b) loss tangent vector diagram [20]

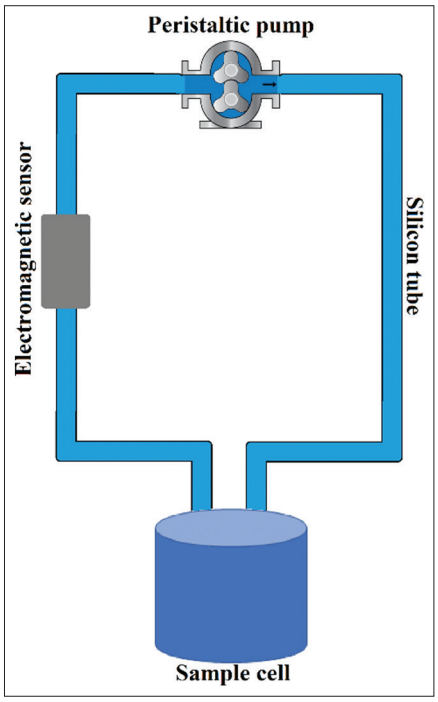

Figure 5: Diagram of the electromagnetic sensor set-up

bioimpedance spectroscopy does. Bioimpedance spectroscopy makes use of an electric flow, whereas EM detection makes use of EM coupling between two inductors. They noted that detection of glucose in the blood sample was achievable at a resonance frequency of 2.66 MHz applied to the primary coil of both the cells. However, the resonance frequency relies on temperature, dielectric property of blood, loops in the coils employed, and the size of the tubing assembly. They demonstrated that their set-up could detect a minimal resolution of ±2 g/l in the tested blood samples and revealed a linear relationship for a lower glucose level concentration.

Another study group developed a two-port EM spiral sensor resonating at microwave frequencies for real-time monitoring of glucose levels in pig blood sample.[29] The sensor was developed on a double-sided printed circuit board, and a microwave vector network analyzer was used to assess the transmission-reflection characteristics of the blood samples under test. The authors observed a linear fluctuation trend of the microwave reflectance coefficient with glucose concentration fluctuations in the blood sample. In another effort,[30] an open EM waveguide resonating at 20 GHz was deployed to monitor the glucose levels of numerous test solutions.

Fingers seem to be an excellent choice among the many potential measurement locations in the human body because they have a sufficient quantity of fresh blood flow uniformity. In an experimental trial with the human subject, one study positioned the projected circular spiral sensor at the test subjects' wrist and thumb to analyze the relationship between the sensor's forward transfer function and rising blood glucose levels.[31] The forward transfer function of the measurement was recorded from 100 MHz to 5GHz to produce blood glucose prediction for human participants. The calibration data for the human volunteers were created using a mixture of principal component analysis and multiple regression. Another research group used an antenna-based sensor to measure blood glucose levels.[32] Fluctuations in blood glucose levels cause variation in dielectric characteristics of blood, resulting in changes in coupling between antennas when placed in the near field region. The difference in the input impedance of the antenna alters its resonant frequency. This shift could monitor the change in blood's permittivity and conductivity, which estimates glucose content in the blood. A small antenna operating at 4.8 GHz was proposed to detect blood glucose measurement from the fingertip.[33,34] The fingertip covered its major detecting surface, and it was fitted with a precise pressure sensing circuit to monitor the fingertip pressure dependency with the resonant frequency during measurement. The fundamental notion for pressure measurement was that the resonant frequency shift because of glucose change would be buried beneath the transition from pressure fluctuation, generating measurement inaccuracy.

Table 1 presents the different real-time direct EM blood glucose sensors adapting different frequencies for measurement of the blood glucose concentration in live human subjects and anesthetized animals.

Discussion

To appropriately calculate blood glucose, most of the preceding studies demonstrated that the EM sensing needed particularly sensitive systems and extremely challenging, which could take a considerable number of characteristics into consideration. While these characteristics are addressed, good reproducibility of the collected raw data from the produced sensor may be predicted. The following are the key participants in the process:

- Choice of sensing frequency – the influence of one component that is not deemed or described is the optimal operating frequency. Few studies have utilized lower frequencies for tissue penetration, while others have employed a higher range. They have not said why they chose

Table 1: Summary of research on real-time direct EM blood glucose sensors.

Reference	*Frequency of choice*	*Operating principle*	*Measurement site*	*Measurement resolution*
[35-37]	1.4 GHz	The dielectric properties of the tissues in the vicinity influence the resonant frequency and bandwidth of a microwave resonant circuit based on a split-ring resonator	Abdomen area (below the ribcage) of the test subject	---
[38-40]	2.4 GHz	The Whispering Gallery Mode sensor head determines the degree of the change in transmission coefficient caused by a change in blood glucose level	Skin tissue on the test subject's arm	10 mg/dL of real blood glucose level
[41]	2.45 GHz	Radar-driven hexagonal-shaped complementary split-ring resonators based sensors monitor glucose levels by transmitting EM waves with a short wavelength into blood vessels	Fingertip of the test subject	2.5 mmol/L
[42,43]	27–40 GHz	Transmission and reflection characteristics are measured using a waveguide to waveguide active transmission port positioned on the tested tissue	The ear of an anesthetized rat	The spikes in glucose level
[44]	58–62 GHz	The transmitted mm wave signals are correlated with fluctuations in glucose levels utilizing a pair of facing patch antenna sandwiching the animal tissue between them	Pig's ear	40 mmol/L
[45]	60 GHz	The transmission coefficient measured between two rectangular microstrip patch antennas is dependent on the permittivity fluctuation along the signal path, which may be related to variations in blood glucose level	Thin tissue of the test subject's hand	1.33 mmol/l

EM: Electromagnetic

the specific operating frequency for their equipment. In the very high-frequency (VHF) band of the EM spectrum, high absorption may occur throughout the body. This VHF range stands out as a prospective research option since there is no known frequency choice for non-invasive EM blood glucose monitoring

- Temperature – because early studies showed that temperature influences measurement significantly, a differential approach is adopted to offset temperature impact and measurements demonstrated reproducibility when the temperature impact was controlled for. The sensor is calibrated for temperature variations in the skin or sensing environment using the reference component
- Applied force – in the case of wearable sensors, applied pressure is one element that has appeared to influence sensor response in previous investigations. At that point, when the tissue is pushed, compressed, or stretched, the effective permittivity fluctuates, resulting in this effect. Accordingly, the sensor's response should be calibrated to assemble data on the permittivity change brought about by glucose levels. Nonetheless, to distinguish the required information, this procedure needs both a multi-sensor framework and a sophisticated algorithm
- Motion artifact – a tiny air gap between the sensor and the skin may be created by placement of the sensor at the measuring site. Small reactions of the test subject can introduce measurement inaccuracies, even in static test environments. Any sensor must be resistant to motion-induced artifacts caused by tiny changes in sensor position, as well as other difficulties, to achieve the goal of continuous blood glucose monitoring.
- Multipath signal propagation – in a transmission-based blood glucose detection device, the unwanted propagation path of EM waves might overwhelm the received signal. The experimental setup architecture can make use of EM absorbing material to reduce multipath signals by suppressing the effects of diffracted and surface waves, which may significantly improve the system's sensitivity
- Separation distance – the separation distance between the two coils has a key effect in determining the conductivity variations as a consequence of a change in glucose concentration in the case of an EM sensor consisting of two induction coils connected through the medium under consideration. Similarly, the position and antenna-tissue distance in an antenna array configuration has to be adjusted to have the optimal transmission results.

Conclusion

The non-invasive measurement of glucose levels using EM waves is a challenging task. Based on the precise monitoring of the change in the permittivity of blood according to variations in glucose levels, an appropriate sensor design is required to arrive at a worthy evaluation of measurement accuracy. Due to the small quantity of this variance, a number of aspects impacting accuracy must be carefully evaluated. The difficulties are greater, demanding more precision, sensitivity, adaptability, and low-cost options. The vector network analyzer has been used in the majority of the reported EM sensors, which is a pricey device. It will be a low-cost choice if it is substituted with the received signal strength indicator in the measuring setup. Although, a couple of studies have just handled this issue; however, they need data about the simplicity of use, client experience, and home usage pertinence.

References

1. Chorbev I, Sotirovska M, Mihajlov D. Virtual communities for diabetes chronic disease healthcare. Int J Telemed Appl 2011;2011:721654.
2. Salunkhe VA, Veluthakal R, Kahn SE, Thurmond DC. Novel approaches to restore beta cell function in prediabetes and type 2 diabetes. Diabetologia 2018;61:1895-901.
3. The International Diabetes Federation. Diabetes Facts and Figures in IDF Diabetes Atlas. 9th ed. International Diabetes Federation; 2019. Available from: https://www.idf.org [Last accessed on 2021 Apr 21].
4. Sarker A, Das R, Ether S, Saif-Ur-Rahman KM. Non-pharmacological interventions for the prevention of type 2 diabetes mellitus in low and middle-income countries: Protocol for a systematic review and meta-analysis of randomized controlled trials. Syst Rev 2020;9:1-7.
5. Maden B, Qiu G, Santos A, Merschen RJ. An overview of diabetes and its impact on cath lab care. Heart Dis 2013;21:360.
6. Amor-Gutiérrez O, Costa-Rama E, Teresa Fernández Abedul M. Determination of glucose with an enzymatic paper-based sensor. In: Laboratory Methods in Dynamic Electroanalysis. Netherlands: Elsevier; 2020. p. 257-65.
7. Lin T, Gal A, Mayzel Y, Horman K, Bahartan K. Non-invasive glucose monitoring: A review of challenges and recent advances. Curr Trends Biomed Eng Biosci 2017;6:1-8.
8. Gonzales VW, Mobashsher AT, Abbosh A. The progress of glucose monitoring-a review of invasive to minimally and non-invasive techniques, devices and sensors. Sensors 2019;19:800.
9. So CF, Choi KS, Wong TK, Chung JW. Recent advances in non-invasive glucose monitoring. Med Dev 2012;5:45.
10. Losoya-Leal A, Camacho-León S, Dieck-Assad G, Martínez-Chapa SO. State of the art and new perspectives in non-invasive glucose sensors. Rev Mexicana Ingen Bioméd 2012;33:41-52.
11. Bolla AS, Priefer R. Blood glucose monitoring-an overview of current and future non-invasive devices. Diabetes Metabolic Syndrome 2020;14:739-51.
12. Shokrekhodaei M, Quinones S. Review of non-invasive glucose sensing techniques: Optical, electrical and breath acetone. Sensors 2020;20:1251.
13. do Amaral CE, Wolf B. Current development in non-invasive glucose monitoring. Med Eng Phys 2008;30:541-9.
14. Caduff A, Hirt E, Feldman Y, Ali Z, Heinemann L. First human experiments with a novel non-invasive, non-optical continuous glucose monitoring system. Biosens Bioelectron 2003;19:209-17.
15. Caduff A. Multisensor concept for non-invasive physiological monitoring. 2007 IEEE Instrumentation and Measurement Technology Conference IMTC 2007. United States: IEEE; 2007.
16. Caduff A, Talary MS, Mueller M, Dewarrat F, Klisic J, Donath M, *et al*. Non-invasive glucose monitoring in patients with Type 1 diabetes: A Multisensor system combining sensors for dielectric and optical characterisation of skin. Biosens Bioelectron 2009;24:2778-84.
17. Caduff A, Mueller M, Megej A, Dewarrat F, Suri RE, Klisic J, *et al*. Characteristics of a multisensor system for non invasive glucose monitoring with external validation and prospective evaluation. Biosens Bioelectron 2011;26:3794-800.
18. Durney CH, Massoudi H, Iskander MF. Radiofrequency Radiation Dosimetry Handbook. Brooks Air Force Base, TX: US Air Force School of Aerospace, Medical Division; 1985. Available from: http://www.goaegis.com/RF_Dosimetry_Handbook.pdf [Last accessed on 2019 Oct 25].
19. ICNIRP guidelines. Guidelines for limiting exposure to time-varying electric, magnetic, and electromagnetic fields (up to 300 GHz). Health Phys 1998;74:494-522.
20. Application Note. Agilent Basics of Measuring the Dielectric Properties of Materials. Agilent Technology; 2006. Available from: http://www.

academy.cba.mit.edu/classes/input_devices/meas.pdf [Last accessed on 2020 Nov 21].
21. Qureshi UM, Shaikh FK, Aziz Z, Shah SM, Sheikh AA, Felemban E, *et al*. RF path and absorption loss estimation for underwater wireless sensor networks in different water environments. Sensors 2016;16:890.
22. Dorey RA. Ceramic Thick Films for MEMS and Microdevices. United States: William Andrew; 2011.
23. Chaplin M. Water and Microwaves. Water Structure and Science. Available form: http://www1.lsbu.ac.uk/water/microwave_water.html [Last accessed on 2020 Nov 21].
24. de Castro Folgueras L, Alves MA, Rezende MC. Dielectric properties of microwave absorbing sheets produced with silicone and polyaniline. Mater Res 2010;13:197-201.
25. Karacolak T, Moreland EC, Topsakal E. Cole-cole model for glucose-dependent dielectric properties of blood plasma for continuous glucose monitoring. Microwave Optical Technol Lett 2013;55:1160-4.
26. Tura A, Sbrignadello S, Cianciavicchia D, Pacini G, Ravazzani P. A low frequency electromagnetic sensor for indirect measurement of glucose concentration: *In vitro* experiments in different conductive solutions. Sensors 2010;10:5346-58.
27. Gourzi M, Rouane A, Guelaz R, Alavi MS, McHugh MB, Nadi M, *et al*. Non-invasive glycaemia blood measurements by electromagnetic sensor: Study in static and dynamic blood circulation. J Med Eng Technol 2005;29:22-6.
28. Gourzi M. New Biosensor for Non-invasive Glucose Concentration Measurement. Sensors 2003;2:1279166.
29. Melikyan H, Danielyan E, Kim S, Kim J, Babajanyan A, Lee J, *et al*. Non-invasive *in vitro* sensing of D-glucose in pig blood. Med Eng Phys 2012;34:299-304.
30. Hofmann M, Bloss M, Weigel R, Fischer G, Kissinger D. Non-invasive Glucose Monitoring Using Open Electromagnetic Waveguides. 2012 42nd European Microwave Conference. United States: IEEE; 2012.
31. Buford RJ, Green EC, McClung MJ. A Microwave Frequency Sensor for Non-invasive Blood-glucose Measurement. 2008 IEEE Sensors Applications Symposium. United States: IEEE; 2008.
32. Sen K, Anand S. Design of Microstrip Sensor for Non Invasive Blood Glucose Monitoring. 2017 International Conference on Emerging Trends and Innovation in ICT. United States: IEEE; 2017.
33. Turgul V, Kale I. A Novel Pressure Sensing Circuit for Non-invasive RF/Microwave Blood Glucose Sensors. 2016 16th Mediterranean Microwave Symposium (MMS). United States: IEEE; 2016.
34. Turgul V, Kale I. Simulating the effects of skin thickness and fingerprints to highlight problems with non-invasive RF blood glucose sensing from fingertips. IEEE Sen J 2017;17:7553-60.
35. Choi H, Luzio S, Beutler J, Porch A. Microwave Non-invasive Blood Glucose Monitoring Sensor: Human Clinical Trial Results. 2017 IEEE MTT-S International Microwave Symposium. United States: IEEE; 2017.
36. Choi H, Luzio S, Beutler J, Porch A. Microwave Non-invasive Blood Glucose Monitoring Sensor: Penetration Depth and Sensitivity Analysis. IEEE International Microwave Biomedical Conference (IMBioC). United States: IEEE; 2018.
37. Choi H, Porch A. Design and *in vitro* interference test of microwave non-invasive blood glucose monitoring sensor. IEEE Trans Microwave Theory Tech 2015;63:3016-25.
38. Liu T, Chang SJ, Chen CJ, Liu JT. Portable and Non-invasive Blood Glucose Monitoring Over a Prolonged Period using Whispering Gallery Modes at 2.4 GHz. 2020 IEEE Ukrainian Microwave Week (UkrMW). United States: IEEE; 2020.
39. Liu L, Kandwal A, Cheng Q, Shi H, Tobore I, Nie Z, *et al*. Non-invasive blood glucose monitoring using a curved goubau line. Electronics 2019;8:662.
40. Liu LW, Kandwal A, Kogut A, Eremenko ZE, Kogut Z. E, Islam MT, *et al*. *In-vivo* and *ex-vivo* measurements of blood glucose using whispering gallery modes. Sensors 2020;20:830.
41. Omer AE, Shaker G, Safavi-Naeini S, Kokabi H, Alquié G, Deshours F, *et al*. Low-cost portable microwave sensor for non-invasive monitoring of blood glucose level: Novel design utilizing a four-cell CSRR hexagonal configuration. Sci Rep 2020;10:1-20.
42. Siegel PH, Lee Y, Pikov V. Millimeter-wave Non-invasive Monitoring of Glucose in Anesthetized Rats. 2014 39th International Conference on Infrared, Millimeter, and Terahertz Waves (IRMMW-THz). United States: IEEE; 2014.
43. Siegel PH, Tang A, Virbila G, Kim Y, Chang MC, Pikov V. Compact Non-invasive Millimeter-wave Glucose Sensor. 2015 40th International Conference on Infrared, Millimeter, and Terahertz waves (IRMMW-THz). United States: IEEE; 2015.
44. Cano-Garcia H, Kshirsagar R, Pricci R, Teyeb A, O'Brien F, Saha S, *et al*. Millimeter-wave sensing of diabetes-relevant glucose concentration changes in pigs. J Infrared Mill Terahertz Waves 2018;39:761-72.
45. Saha S, Cano-Garcia H, Sotiriou I, Lipscombe O, Gouzouasis I, Koutsoupidou M, *et al*. A glucose sensing system based on transmission measurements at millimetre waves using micro strip patch antennas. Sci Rep 2017;7:1-11.