A comprehensive review on wearable Glucose Sensing Techniques: Challenges and opportunities

Jitendra B. Zalke¹, Sandeepkumar R. Pandey², Dr. N. P. Narkhede², Manthan D. Ingale², Arpita Nampalliwar², Karishma Nakhate²

¹Department of Electronics Design Technology, ²Department of Electronics Engineering, Shri Ramdeobaba College of Engineering and Management, Nagpur

Abstract

For the last several years, diabetes has been one of the major concerns worldwide. Diabetes occurs as a result of increased blood glucose levels. Long-term diabetes can lead to many diseases like heart diseases, stroke, nerve problems, etc. The diabetic patients need to measure their blood glucose levels regularly. In general, the glucose monitoring is typically performed by piercing the skin several times a day, known as an invasive technique, which is more disruptive and painful. The healthy alternative to this technique is minimally invasive technique which is less disruptive but requires special training to use. Non-invasive techniques do not require pricking of any body parts and hence, it is very easy to use. The various non-invasive techniques include electrochemical, optical, and photoacoustic methods which are used for glucose detection. With the advancement in material science and MEMS technology, wearable, non-invasive glucose sensing techniques are more popular in recent years. This review discusses various investigations of recent advancements in wearable, non-invasive glucose monitoring techniques, its research challenges, and opportunities.

Keywords: Wearable, Non-invasive, Blood Glucose monitoring, Diabetes, Optical, Photoacoustic.


1. Introduction

Diabetes mellitus (DM) is a chronic disease that occurs when the body does not produce enough insulin or when the body cannot effectively use the insulin that is produced. Insulin is hormone produced by the body that regulates blood glucose levels. Diabetes affects 537 million adults, with the total number of diabetics expected to rise to 643 million by 2030 and 783 million by 2045 [1]. Type-1 diabetes is caused by an autoimmune reaction in which the body stops producing insulin. This type of diabetes affects 5-10% of the population [2]. Type-2 diabetes is the most common type of diabetes. In this type of diabetes, our body doesn’t use insulin properly, and diabetes levels more than the normal level. Around 90-95% of people having Type-2 diabetes [3]. Gestational diabetes is a type of diabetes that develops during pregnancy and is time dependent on women who have never had diabetes. Because of this diabetes, a mother and her child may be at high risk for various health problems [2,4]. The common thing that can be done in all the types of diabetes is regular blood glucose monitoring. Since diabetes is a chronic disease, the only way to handle it is to take proper dosage of insulin injections which require monitoring of blood glucose levels frequently. The monitor blood glucose levels, researchers have investigated several techniques namely invasive, minimally invasive, and non-invasive [5]. Invasive glucose monitoring is a common and traditional method to measure the blood glucose level of the human body [6]. In this method, the patient needs to prick their finger with a small sharp needle called a lancet and put some drops of blood on the test strip. This method is very painful for children, old age, and intensive care unit (ICU) patients, where patients need to monitor their glucose levels several times a day [7,8]. Commercially, several pocket-friendly gluco-meters are also available which are invasive in nature. This takes a申报s a sample on a test strip and within a minute
it provides a reading of glucose level. These glucometers are expensive and also are not as accurate as fingertip sample test glucose method [9-11]. Some patients need to puncture their fingers several times a day as they have to monitor their glucose levels continuously. Because of this patients are inconvenient with this type of glucose monitoring technique. Also as we use disposable test strips for blood glucose monitoring it makes hazardous waste which is a threat to the environment [12, 13].

Minimal invasive (MI) technique is an improvement to the invasive method. In a minimally invasive technique, small sharp needleless sensors are fixed in a patient’s body. These sensors either take internally a small blood sample or a sample of substance from the body which can help to analyze glucose levels and do not harm other patients in the invasive method [14-16]. In this minimal invasive technique, biosensor is used to take glucose samples from the body which are made up of different biomaterials. These materials are harmless to the human body and do not react with an outside condition like humidity, corrosion, etc., [17-18]. Using this glucose monitoring technique, one can also monitor their glucose levels continuously. This method is highly effective and gives an accurate glucose level readings but there is some catch in minimal invasive monitoring such as it is uncomfortable for the human to wear for a long time, also it can generate harmful and hazardous waste which can harm humans and other living beings. Also, it needs special training to inject and use for glucose monitoring. Therefore it is necessary to develop a non-invasive and environmentally friendly method of blood glucose monitoring and control [19-20].

Non-invasive blood glucose monitoring is a method of detecting human blood glucose levels without cutting, pricking and harming the human tissues. This is one of the most popular and easy to use diagnosis techniques. Non-invasive sensors may use saliva, sweat, tears, or skin interstitial fluids as a body fluids. There are many methods for non-invasive glucose monitoring: electrochemical method, Electro-Mechanical method, optical method, microwave spectroscopy, heat propagation method, and ultrasound method [21, 22]. With advancements in technology, wearable sensors for biomedical applications is playing an important role in monitoring the physiological parameters of the living being. These parameters are useful for analyzing and diagnosing the health conditions of living beings. The miniaturization of technology enables the development of micro-sized wearable sensors. Development of these micro-sized wearable sensors promised the need for the patient’s comfort, safety, simplicity of operation, flexibility and ease of handling. The large numbers of flexible, biocompatible, user-friendly and wearable sensors are emerging out of the state-of-the-art technology that can perform a variety of parameter measurements in biomedical applications [6-7]. The wearable sensor technology is useful in monitoring health parameters of living being. Also it is useful in various medical therapy, drug delivery, etc. The various wearable sensors that monitor the living being’s health parameters are classified:

**Physical Parameters:** The various physical parameters that can be monitored by the wearable sensors include vibration, motion, acceleration, heart rate, stress, temperature, etc. [23-25].

**Biochemical Parameters:** The presence of various chemicals such as sodium, ammonium, potassium, chloride, uric acid, di-nucleotide, pH, fluoride content, lactate, glucose, blood oxygen saturation, and so on can be monitored and measured by wearable sensors [23-26].

The wearable sensors detect and monitor various physiological parameters to determine a patient’s state of health regularly. This is particularly very useful for those patients who are hospitalized and need sudden intensive care regarding health. In case of sudden Intensive care, doctors are generally required to obtain information regarding critical biological parameters. In majority of cases, these parameters are unknown and is really critical for the doctor to take the decision. The wearable sensors are very useful in such cases. These sensors are mounted on
patientsbody can measure and do the analysis of the various parameters like calcium, lactate, uric acid, pulse rate, cholesterol, urea, oxalate, creatinine, oxygen saturation, blood pressure etc. [6]. The wearable sensors that monitor the various physical parameters of human/animals can be invasive, minimally invasive or non-invasive in nature [23-32].

2. Wearablesensingtechniques

2.1 General architecture of wearable system

Figure (1) shows a system-level overview of the wearable sensors and system. It consists of various sensing transducers, signal conditioning and processing elements, wireless transmission channels, to enable multiplexed on-body measurements. To sense a physical or biological parameter, a wearable sensor can be mounted on a subject. Analog circuits are used to implement the signal conditionings path for each parameter sensor in respect to the matching of the transducer signal. The microcontroller’s computation and serial communication capabilities are also employed to calibrate, make up for, and relay the conditioned signal to a on-board wireless transmitter. The transceiver enables wireless data transmission to a Bluetooth-enabled mobile device with a custom-developed application that has a user-friendly interface for sharing the data via email, SMS, and soon or uploading it to cloud services as needed.

![Figure 1: General Architecture of Wearable Sensor System][26]

Modern wearable sensing services are supported by communication technology improvements. Some wearable sensors can connect to others sensors or smart phones via body area networks (BANs) or personal area networks (PANs). The wearable sensing device may at same times end the data acquired to other remote service over a cellular network, depending on its design or characteristics. Specialized networks like actical communication networks and satellite communication networks may be used, depending on the objective. Intra-body networks, BANs, and PANs are examples of modern communication technology breakthroughs. In wearable sensing, these networking technologies are used to connect wearable sensor devices to other gadgets such as smartphones, communication hubs, or actuator devices over short distances communications [33-36].

2.2 Elements of Wearable Biosensors for Sensing Biochemical Parameter

Wearable biosensors have sparked new discoveries in a wide range of novel technologies, from environmental to biomedical. Wearable biosensors can give continuous, real-time physiological information by...
measuring biochemical markers in biological fluids such as sweat, tears, urine, and saliva in a dynamic, non-invasive manner. These sensors can detect vital parameters for monitoring altering bodily fluids in real-time. It comprises a transducer that can convert the interaction between the biological recognition layer element in the sensor and the target molecule into a quantifiable signal. Any biosensor depends on an abiological component (to be studied) being present and being easily accessible under typical circumstances. Wearable biosensors make use of numerous well-known elements, such as receptors, nucleic acids, cells, and various types of enzymes.

Typical elements of biosensors are as shown in figure (2). Wearable biosensors can be designed to measure and analyze a large variety of samples including cell cultures, body fluids, food samples, etc. These samples are applied to the transducers. The transducer is typically a combination of bio-receptors and electrical interface. The bio-receptors are made to interact with the chosen analyte/sample in order to produce an ultrasensitive transduced signal. The transducer (electrical interface) is the bio-receptors must have high selectivity for the analyte among a variety of different chemical or biological components. Typical recognition elements used to design biosensors are enzymes, nucleic acids, antibodies, cellular structures/cells, or biomimetic materials. In a majority of sensor designs, enzymes are among the most common.

When the bio-receptors interact with the analyte/sample, produce a measurable change by the transducer (electrical interface). It may be electro-active substances, pH change, heat, light, mass change, etc., depending on the bio-receptors and analyte used. Various technologies can be employed to detect and measure the effects such as an optical, piezoelectrical, or electrochemical. Several importaoptical technologies, including organic light-emitting diodes (OLEDs) and organic photodiodes (OPDs), optical fibres, textiles, colorimetric, plasmonic, and fluorometric sensors, can be used for optical sensing. Nowadays, an electrochemical sensor has been widely used in biomedical field. The physiochemical parameters, such as pH, sodium, etc., are converted by these sensors into a quantifiable electrical signal. Any change in current, voltage, or impedance can represent an electrical signal. The design of numerous sensors for measuring biological conductivity and impedance uses materials such as gold, aluminium, copper, silver, chromium, stainless steel, nichrome, and platinum, according to recent study. Because of characteristics like portability, high sensitivity, simplicity of construction, and low cost, electrochemical sensors are widely used for measurement of physiochemical parameters. Biosensors are used to determine thioglucose level from bio-fluids. The biosensor electro desreact with enzymes used for glucose detection such as glucose oxidase (GOx), hexokinase, orglucose-1-dehydrogenase (GDH) [32]. GOx is one of the most popular enzymes, and it does the reduction of oxygen to hydrogen peroxide and also glucose to glucono-1. Detection of glucose can be accomplished through the production of hydrogen peroxide [29, 37]. The variable level of oxygen will also cause significant interference to the biosensor, including variations in sensor response and linear detection range [38].

3. Research review in wearable glucose sensing with various body fluids.

Figure (2): Element of a Biosensor.
Human health diagnosis using wearable sensors is a nemerging field. Data regarding a user’s health, such as heart rate, calories burnt, steps taken, blood pressure, sweat rate, and other specific biochemicals, amounts of exercise time, etc., can be collected using wearable technology. Currently, various body fluids like sweat, saliva, and tears are being explored for glucose sensing with the help of wearable devices [23, 25, 27]. This section discusses the research in wearable devices for glucose sensing and the various challenges and research opportunities.

3.1 Sweat

Sweating is a biological function that allows the body to maintain its temperature through evaporation. This biological fluid contains metabolites, electrolytes, and biological macromolecules that are secreted by sweat glands in sufficient quantities and rapid reproduction [39]. Sweat reaction takes place quickly and the sweat gland is highly porous. Therefore, sweat samples can be used to determine glucose levels in the body [31]. Humans sweat glucose concentrations vary from 0.06-0.2 mM, which equates to 3.3-17.3 mmol/L [40-41]. However, significant challenges still exist in collecting accurate sweat glucose data, such as temperature variations in the environment, skin contamination, occasional sampling without iontophoretic stimulation, slow product ion rate, and the mixing of old and new samples. Despite the correlation, it is extremely challenging to measure sweat glucose levels since they are solow (100 times slower than blood glucose levels), which calls for the employment of extremely sensitive equipment. Eccrine glands, which number in the millions, are dispersed throughout the human body and release sweat at various locations. Before adopting the best spot to put these sweat glucose monitoring sensors, it is crucial to have a complete grasp of sweat gland characteristics and operation. Although sweat glands are found throughout the body, they are most prevalent on the forehead, armpits, palms, and soles of the feet [40-41].

Arising number of people are interested in increasing sensors and systems that allow monitoring of glucose levels, including smartphones [42]. A sweat glucose sensor that measures electrochemical signals can determine glucose levels. The sweat-collating layer, glucose biosensor, and substrate with a sweat-stimulating requirement makes up a complete electrochemical sensor. With blood glucose and with every point in time, the sensor can detect glucose levels. The sensor sustained a high correlation (i.e., 0.95), which was obtained [43]. There are several wrist-wearable sensors developed recently that can measure glucose levels in sweat [44]. Academic institutions are becoming more and more interested in wearable Lab-On-Chip (LOC) platforms because they can accurately track wearers' health. They make it possible for users to gather data about someone's health status continuously, non-intrusively, and in real-time.

Fabric-flexible plastic-based dermal-based LOC platforms are two categories for sweat-based wearable LOCs. In platforms made of fabric, the skin and sensor are in constant contact, enabling the continuous and real-time measurement of specific biomarkers in the sweat. Flexible materials utilised in the platforms enable them to simulate and selectively detect skin temperature, sodium, potassium, lactate, and glucose [45]. The majority of dermal-based platforms are tattoo-based LOC platforms, in which electrodes are printed on the skin. These electrodes can be used to measure glucose levels. These tattoo s are non-disruptive to the user's daily activities, biocompatible, single-use, and highly resistant to mechanical deformation and appeal. In 2012, there was a report of the first LOC platform based on tattoos. An electrode is used in this instance in the
form of screen-printed Ag/AgCl ink on temporary tattoo[46].

Because sweat can be collected relatively easily and contains a wealth of biochemical information, it makes for an appealing biofluid form noninvasive physiological monitoring of the wearer [46–47]. These benefits have sparked a lot of work to create different types of sweat chemical detecting equipment for metabolite and electrolyte monitoring. Analyte detection may be carried out via electrochemical or colorimetric techniques as well as a variety of wearable platforms, such as wristbands, temporary tattoos, or patches [48–50].

Even while on-body sweat analysis is a many benefits and has been the subject of many recent studies, there are still a number of substantial obstacles that must be overcome before reliable, noninvasive, real-time sweat monitoring can be successfully implemented. These difficulties include:

1. Irregular or low rates of perspiration production while exercising;
2. Propensity for skin (bio) marker contamination;
3. Mixing and carrying over of recent and previous sweat;
4. Unreliable sample transportation across the detector surface; and
5. Inability to regulate sample volume and evaporation effective[53]. There is a strong association between the blood and salivary glucose concentrations in diabetes patients, and it is been found that diabetics tend to secrete and have a higher salivary glucose concentration than control participants [54].

In a study, a non-enzymatic electrochemical sensor was created to measure salivary glucose. Its detection limit was set at 1.9 g/ml, and its working range ranged from 0.5 to 50 g/ml. The study’s results revealed a highly significant correlation ($r = 0.96$) with blood glucose levels measured by the finger prick method [55]. Research that developed anoptical salivary glucose sensor revealed that, when measured at a wavelength of 630 nm, the glucose content increased the absorbance of light [56]. Another study found that the bio-conjugated nanoflowers could accurately predict salivary glucose levels between 0.2 and 300 mg/dl in less than 10 minutes [57].

Devices that regularly check blood sugar levels have tried to incorporate salivary glucose sensors. In one of the research, salivary glucose sensors were built into a smart toothbrush. This sensor, made of boron, provided a non-enzymatic electrochemical salivary glucose monitoring [58]. The major disadvantage of the salivary glucose detection is that, the patient is not allowed to take any sweet food intake like tea, coffee, or meal before the test, otherwise it will generate the false results for glucose detection.

### 3.2 Saliva

Saliva is transparent, slightly acidic, fluid produced by the sublingual, submaxillary, parotid, and minor mucous glands that lubricates and cleans the mouth tissues as well as aids in taste and digestion [51, 52]. Saliva can be used as an alternative to blood form noninvasive glucose monitoring because the collection of samples is easy, noninvasive, and very convenient than collecting a sample of blood. Saliva-based glucose monitoring has the advantage of fusing the samples collected easily and thus is cost-effective.

### 3.3 Tears

Human eyes generate tears in response to irritations, as a result of strong emotions, and in order to maintain lubricated and moist surfaces in the eyes [59]. Tears are composed of water, protein, lipids, and electrolytes, but they also include a minimal amount of glucose, which is correlated with blood glucose levels [60]. Tear glucose sensing is a good solution over invasive self-monitoring blood glucose (SMBG) for diabetes management. Tear glucose monitoring has advantages like cost-effective, convenient for sample collection, etc. [61].
In healthy people, glucose levels in tears sample typically range from 3.6 mg/dL to 16.6 mg/dL [62]. In diabetics, however, glucose levels are typically higher. Tears are a better target for wearable technology since markers in them diffuse straight from the bloodstream and hence their glucose concentrations are more tightly connected. This is one of the reasons why there have been so many distinct types of tear-based glucose sensors developed over the last few decades, each of which uses a number of cutting-edge approaches to enhance device performance [63].

A ratio-metric fluorescent membrane has recently been developed that can measure tear glucose in the range of 0.1 to 10 mM [64]. A three-layer contact lens with a detection limit of 211 nM and the ability to sense tear glucose in the 500 nM to 1 M nage has been created [65]. Numerous wearable contact lenses that can track various physiological indicators have emerged in recent years, and some of the lenses’ outputs are available through smartphones [66, 67]. An integrated device that can function with extremely small samples and doesn’t strain the eyes has been demonstrated by a study on tear glucose sensing, which has a wide dynamic range, low detection limit, and speed analysis. The sensor measured tear glucose levels between 0.72 mg/dL and 11.6 mg/dL, which are equivalent to blood glucose ranges between 20 mg/dL and 660 mg/dL [68]. However, only animal samples were used to test the suggested device.

In order to provide a simple and continuous sensing of the significant body fluids discussed above, wearable glucose sensing devices employ appropriately adapted absorbent materials, superhydrophobic/superhydrophilic surfaces, repidermal microfluidic channels that are used as an efficient sampling technique. Recently investigated mechanically flexible and multiplex measurement now have been expanded to include numerous sensors with on-site embedded circuits for wireless data communication and signal pre-processing for glucose detection. Combining different materials has demonstrated that the enhancement of surface area and porosity offered, for instance, by nanofibers on electrodes modified with nanoparticles, can support sensor performance with high sensitivity, low limit of detection (LOD), and wide line range. Due to the improved selectivity of conducting nanoparticles, non-enzymatic electrical sensors have been created that have better LODs, sensitivity, and stability than enzymesensors [69].

4. Discussion and Conclusion

This review highlights the techniques of wearable glucose sensing and emphasizes the significant advances made in the field of non-invasive blood glucose monitoring utilizing wearable devices and sensors during the last several years. The devices use a variety of wearable methods and technologies, as well as unique approaches that use on-invasive techniques to provide valuable insights into several physiological data. Wearable glucose sensing systems have several limitations, including the fact that they don’t provide precise glucose sensing data since all bio-fluids contain less glucose than actual blood, resulting in low accuracy. To ensure precise results, future studies and research will have to overcome these challenges and improve accuracy and sensitivity. Furthermore, bio-fluid purity and technological advancement of devices will be essential in the growth of wearable non-invasive devices.

5. References


14) BaoLi Zhang, Xiao Peng Zhang, Bo Zhi Chen, Wen Min Fei, Yong Cui, Xin Dong Guo. Microneedle-assisted technology for minimally invasive medical sensing Elsevier, Volume 162, March 2021, 10583010.1016/j.microc.2020.105830.


SmartToothbrush.Sensors


