

Review Article

Noninvasive Glucose Measurement Using Machine Learning and Neural Network Methods and Correlation with Heart Rate Variability

Marjan Gusev ¹, Lidija Poposka,¹ Gjoko Spasevski,¹ Magdalena Kostoska,¹
Bojana Koteska,¹ Monika Simjanoska ¹, Nevena Ackovska,¹ Aleksandar Stojmenski,¹
Jurij Tasic,² and Janez Trontelj³

¹*Ss. Cyril and Methodius University, Skopje, Macedonia*

²*Innovation Technologies, Sevnica, Slovenia*

³*University of Ljubljana, Ljubljana, Slovenia*

Correspondence should be addressed to Marjan Gusev; marjan.gushev@finki.ukim.mk

Received 19 September 2019; Revised 1 December 2019; Accepted 10 December 2019; Published 6 January 2020

Academic Editor: Eduard Llobet

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Diabetes is one of today's greatest global problems, and it is only becoming bigger. Constant measuring of blood glucose level is a prerequisite for monitoring glucose blood level and establishing diabetes treatment procedures. The usual way of glucose level measuring is by an invasive procedure that requires finger pricking with the lancet and might become painful and obeying, especially if this becomes a daily routine. In this study, we analyze noninvasive glucose measurement approaches and present several classification dimensions according to different criteria: size, invasiveness, analyzed media, sensing properties, applied method, activation type, response delay, measurement duration, and access to results. We set the focus on using machine learning and neural network methods and correlation with heart rate variability and electrocardiogram, as a new research and development trend.

1. Introduction

A lot of problems arise when a human cannot control the insulin level and thus process the glucose concentration in the blood. This inability initiates diabetes [1], which is a disease where the blood glucose level is high. In this case, only a precise therapy and careful management can prevent a buildup of sugars in the blood and intolerance to glucose [2], increasing the risk of dangerous vascular complications [3], such as coronary artery disease (leading to heart attack) [4], peripheral vascular disease, kidney failure or stroke, and neural complications (diabetic neuropathy) [5], including peripheral neuropathy and autonomic nervous system failure.

Recent studies show that there are 424.9 million diagnosed diabetic patients in the world and that the number is expected to go up to 628.6 million by 2045 [6]. Glucose mea-

surement and diabetes treatment are very expensive; for example, in the USA, the costs rose from \$245M in 2012 [7] to \$327M in 2017 [8]. To indicate the size of this problem, diabetic patients present 6-7% of the total worldwide population according to the International Diabetes Federation [9].

Furthermore, cardiovascular disease is closely linked to diabetes. In fact, a study in the USA [10] concluded that 25% of diabetes patient costs are a consequence of cardiovascular disease and 15% of costs of physician office visits are related to cardiovascular disease. At the same time, diabetes is responsible for more than a quarter of all cardiovascular disease expenditure.

In addition, there is a high proportion of undiagnosed diabetes mellitus globally, especially in developing countries, and Beagley et al. [11] conclude that 45.8% of diabetes cases are undiagnosed and very often associated with cardiovascular risk.

Several studies analyze the history of development of glucose measurement devices [12–14] and a summary of the four generations of glucose monitoring [13] classified by the used technology.

The produced medical devices have been evaluated from the 1970s with the start of the first-generation glucose meters that used reflectance technology and were made as heavy devices requiring a relatively big amount of blood. Second-generation devices used a drop of blood, and due to the available technology, they were made as smaller devices with affordable prices that allowed personalized use.

Finger pricking as the main routine in these invasive techniques is troublesome for diabetic patients because it can lead to scarring, motivating the development of devices that enable glucose measurement to be done cheaply and in a noninvasive way. The third-generation devices started as minimally invasive devices that include an array of small needles on the skin and enabled continuous glucose monitoring (CGM) [15–17].

Recently, a new generation is rising on the horizon, although it is still the king of an alternative, rather than an actual application of these kinds of medical devices, due to its current early stage of development. Nevertheless, we will refer to it as the *fourth-generation* medical devices which include noninvasive methods, providing an environment for remote and real-time continuous monitoring. The noninvasive methods do not invade the human body and are based on various methods, including spectrometry or analysis of other parameters correlated with the glucose level [18].

In this paper, we aim to present the available methods and ongoing projects for noninvasive glucose measurement, focusing on the use of machine learning (ML) and neural network (NN) methods used in a lot of ongoing research to deal with estimation methods of the glucose level.

The focus is also set to the possibility of using an ECG or other methods that determine the HRV parameters for detection of the ability of a human to regulate the blood glucose level with noninvasive methods. This is especially important since the recent wearable ECG sensors successfully emerged on the market, and ECG and HRV can be measured efficiently by a noninvasive method that allows a possibility for remote continuous real-time monitoring.

2. Classification of Noninvasive Glucose Measurement

Glucose measurement is mostly classified by the level of *invasiveness* of the sensing devices, which are usually classified as invasive (devices that are implanted in the patient's body or that invade the body to access a blood sample), minimally invasive (devices that painlessly invade a very small part of the patient's body, such as skin to collect a minimal sample, like a skin part, sweat, tear, and saliva), and noninvasive devices (devices that do not invade the patient's body) [12–14].

Noninvasive blood glucose monitoring methods are based on measuring glucose concentration from its chemical, thermal, electrical, or optical *sensing properties* [14, 19–22]. Some other sensing properties can also be exploited for measurement since the human body shows different physiologi-

cal responses to changes in glucose, such as electric and acoustic impedance, thermal conductivity, and electromagnetic response.

Usual classification of noninvasive methods is based on the used technology, although there are several authors that classify methods based on the subject they analyze, such as differentiation of *media* they target, including tissues (skin, aqueous eye humor, oral mucosa, tongue, and tympanic membrane) and fluids (sweat, urine, saliva, and tears) [21].

Each measurement system is specified by its *size* that determines if it can be used in a specialized laboratory at the healthcare institution or as a part of a smart home system [23]. In addition, it can be a pocket-size measurement device, such as those personal finger pricking devices or a wearable device, which is worn on the patient's body.

A specific *method* is used to process the sensed information and produce intermediate results, including transdermal and optical methods [20] or including nanotechnology [14]. The way the information obtained intermediate results which are further processed may include a specific processing, such as multivariate analysis, multiregression, or various artificial methods, such as deep machine learning or neural networks, which are described in more detail in this paper.

Glucose measurement can be applicable for continuous and real-time monitoring or can provide only on-demand activation of a single measurement, treated to be just a substitute of the existing invasive methods. A measurement is defined to be a single measurement if it is activated on demand to access a sample and then to process a result, while the continuous measurement systems continuously take samples and calculate results.

In addition, if the results are displayed on to a single user, the corresponding medical device is specified to be used in self-monitoring only, and if the results can be shared over the Internet to authorized users, the corresponding systems are systems that allow shared authorized access to results.

Finally, the end results may be obtained immediately or with a certain delay. If the delay is less than 2 minutes, they become near real time, or if the delay is less than 30 sec, they are treated as real time. For example, a blood analysis in the lab may take more time, and these measurement systems are specified to deliver postponed results. Not to be confused, this delay is dependent on the measurement device and processing capabilities, while the time delay needed for glucose concentration to propagate to the analyzed media is usually called lag.

To present a more comprehensive way and specify the domain of noninvasive glucose measurement techniques, we have introduced a methodology based on criteria, which determine several dimensions of glucose measurement devices, as illustrated in Figure 1. Each classification criterion is displayed by a rounded rectangle, and each category within a given criterion is presented by a sharpened rectangle.

Glucose measurement systems can be classified according to the following criteria:

- (i) Size: describing the measurement device to be a point-of-care system, home system, portable pocket device, or wearable device

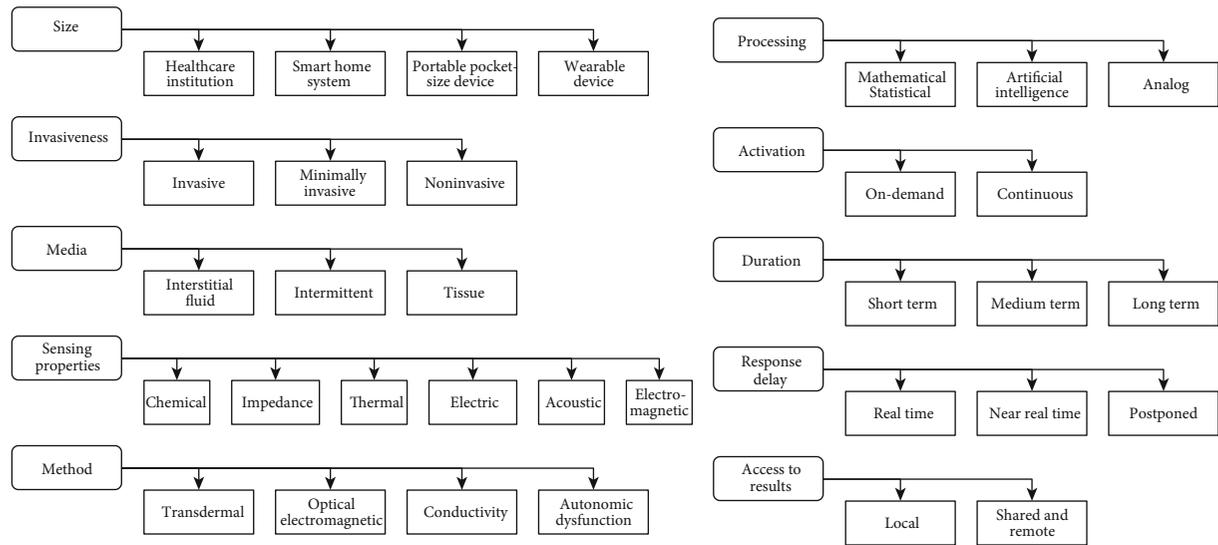


FIGURE 1: Classification of glucose measurements according to different criteria.

- (ii) Invasiveness: determined as an invasive, minimally invasive, and noninvasive technique
- (iii) Media: where the measurement is conducted, including interstitial fluid, intermittent, and tissues
- (iv) Sensing properties: analyzed by the medical device, including chemical, impedance, thermal, electrical, acoustic, or electromagnetic properties
- (v) Method: defined by the used technology to analyze the sensed information, such as transdermal, optical, and thermal conductivity and electromagnetic response, autonomic dysfunction (HRV-based), and nanotechnology
- (vi) Processing: specified by the method used in processing the result, which may include analog (comparison result or indication from the sensed information), mathematical and statistical methods (multivariate analysis with calibration, multiregression, etc.), and artificial intelligence (machine learning, neural network methods, deep learning, etc.)
- (vii) Activation type: determined by the way the measurement is activated: either on-demand activation or continuous measurement
- (viii) Duration type: determined by the measurement time: short term (less than 1 minute), medium term (less than 1 hour), and long term (expressed in days)
- (ix) Response delay: defined by the time required to process the results, including real-time systems (immediately or up to 30 sec), near real-time systems (up to 2 minutes), and postponed systems (more than 1 hour)
- (x) Access to results: specified by the access locality of the results, including self-monitoring systems and systems that use shared authorized remote access

3. Transdermal Noninvasive Glucose Measurements

Transdermal methods use the following technologies:

- (i) The reverse iontophoresis technique [24] accesses the interstitial fluid by a low electric current across the skin between two electrodes [25]. Sodium ions cause convective flow carrying glucose molecules in the opposite direction to that of normal medications (from the skin outward) [26]. Sensing is realized by detecting the glucose oxidase. An FDA-approved medical device is the GlucoWatch [27] targeting a wrist skin, capable of measuring 78 readings per wear (up to six per hour), after 2-hour calibration. It operates by a small current passing between two skin surface electrodes that draw ions and glucose-containing interstitial fluid to the surface and into hydrogel pads incorporating a glucose oxidase biosensor [28, 29]. According to our classification, it is a wearable device, using a noninvasive method to analyze interstitial fluid by sensing the chemical and electrical properties by a transdermal method with analog reading of local near real-time results for medium-term continuous glucose measurement. There are also other commercially unsuccessful medical devices, including GluCal [22, 30]
- (ii) Impedance spectroscopy measures the dielectric properties of a tissue, by passing a small alternating current across a tissue and measuring the impedance frequency spectrum in the range of 100 Hz–100 MHz [31], which is dependent on the glucose interaction with red blood cells [32]. Several issues including water content, temperature variation, sweating, and motion [33] require frequent calibration and equilibration, which generates a lot of implementation problems. Pendra is an FDA- and

CE-approved medical device [34], realized as a wrist watch based on impedance spectroscopy, with sensing conducted by an open resonant circuit, capable of performing up to 4 measurements per minute. However, it lacks a successful commercialization due to calibration problems (the need to change the tape after 24 h and requiring at least 1 h equilibration). GlucoBand is another medical device without successful commercialization, being oriented more to the wellness market instead of the medical one [35]

- (iii) The skin suction blister technique is based on analysis of a blister obtained by a vacuum suction over a small area of the skin [36] as a well-tolerated painless procedure with a low infection risk. Glucose concentration in the analyzed blister is lower than that seen in plasma but correlates well with the concentration in the blood [37], especially to the HbA1c value, which corresponds to a three-month average glucose values. Symphony is a commercially unsuccessful product which is applied to a permeated skin to analyze the electrochemical properties [38] by using a sensitive biosensor which measures the transdermal glucose flux
- (iv) The sonophoresis technique uses low-frequency ultrasound to increase skin permeability and causes expansion and contraction of gaseous inclusions that open pathways for interstitial fluids to transport glucose to the epidermis [39], where it is measured by a conventional electrochemical sensor [40]. This technique is sometimes considered minimally invasive as it creates micropores in the skin to enable the interstitial fluid containing glucose to come outside [22]. SpectRx is a product that is not yet commercialized, which uses laser to create micropores in the outermost skin layer to collect interstitial fluid containing glucose

Bruen et al. [41] discuss several wearable and noninvasive methods based on monitoring the interstitial fluid and wearable devices based on detection of the sweat (eyeglass, flexible wristband, etc.), breath analysis, saliva analysis (tattoo printed on a tooth, etc.), and ocular fluid (smart contact lens). Wearable glucose monitoring using epidermal sensors was reviewed by Kim et al. [42]. Concentration of glucose in interstitial fluid depends on blood glucose levels [43], although there is a significant time difference for transmission of the corresponding blood glucose levels to the interstitial fluids [44].

4. Optical Noninvasive Glucose Measurements

When light meets biological tissues, it can suffer reflection, scattering, and transmission being proportional to the structure and chemical components of the sample [21], as a basis of plenty of optical-based noninvasive glucose measurement methods [45, 46]. These are differentiated according to the analyzed band of electromagnetic radiations and interpreta-

tion of glucose levels from the received spectrum [20] by selectivity and interference to other compounds using multivariate calibration vectors [47] and several detection and multistage separation principles [48].

The following optical noninvasive methods have been analyzed to more or less successfully detect the diabetes level:

- (i) Infrared spectroscopy is based on rotational and vibrational transitions of molecule chemical bonds, and the corresponding fluctuation is measured by the incident radiation [49]
- (ii) Near-infrared (NIR) spectroscopy is based on the investigation of a visible and near-infrared range, including wavelengths 0.59–0.95 μm [50], 1.21–1.85 μm [51], and 2.12–2.38 μm [52] chosen due to weak water absorption and relatively high energy of the measured signal [21]. Although measurements do not depend on skin pigmentation, they depend on molecular structure and absorption spectrum ability, so several wavelengths are used for multivariate analysis with calibration. Although several medical devices (SugarTrac, Dream Beam, Diasensor, MedOptix, etc. [22, 30]) have been developed using the NIR spectroscopy method, they still are commercially unsuccessful
- (iii) Midinfrared (MIR) spectroscopy gives more distinct glucose peaks [21] analyzing the wavelength spectrum 8.38–9.71 μm [53]. Measurements of a specific wavelength before and after interaction with matter are compared, and effects on stretching and bending of molecules are used to determine glucose concentrations. A sensor using depth-selective MIR spectroscopy of skin based on total infrared reflection photothermal deflection has been described in [54] and absorption spectroscopy based on a few wave numbers in [55]
- (iv) Raman spectroscopy [56] evaluates scattering of single wavelength light, which is dependent on rotational or vibrational energy states within a molecule and highly specific absorption bands with respect to original laser light [57]. A multivariate analysis is applied to detected molecule quantity and reduced interference from water compared with MIR or NIR spectroscopy. There are several research projects by LightTouch Medical, C8 Medisensors [58], and Massachusetts Institute of Technology applying the Raman spectroscopy method on skin [22]. Development of a Raman spectrometer suitable for home-use noninvasive glucose monitoring was also reported in [59]
- (v) Photoacoustic spectroscopy measures ultrasonic waves created by tissue absorption of pulsating light created by a laser diode [60], as their interaction generates heat and causes pressure variations in the sample in the form of acoustic signals monitored by a piezoelectric transducer [61]. A theoretical study of resonant photoacoustic

- spectroscopy for noninvasive glucose detection was reported in [62]. Aprise is a medical device that was clinically tested [63]. It utilizes the photoacoustic properties of the blood to infer the prevailing glucose levels, when ultrasound waves illuminate the tissue with laser pulses and acoustic signals are analyzed for the depth profile of the light absorbance of the skin above a blood vessel
- (vi) Ocular spectroscopy is applied to tears by using a hydrogel-bound contact lens [64] and using a spectrometer to measure the change in the reflected light received when a light source illuminates the lens. A lot of weakness has been detected in the application of this method, such as delay of glucose concentration, biocompatibility, and difference between the eyes [65]
 - (vii) Scattering is the effect when the radiated signal is reflected by the tissue parts, such as cell membranes and collagen fibre in the blood and the interstitial fluid. Since the glucose changes the refractive index of the tissue, measuring the reflected signal provides information to calculate the glucose level [66]. Precision is affected by large interindividual differences and sensor drift, motion, temperature, water, and protein density [21]
 - (viii) Occlusion spectroscopy is similar to scattering and optical coherence tomography methods measuring the scattering effects on arterial flow, instead of systolic flow. It uses enhanced light transmission of erythrocyte aggregation to calculate the glucose concentration [67]. The precision is vulnerable to many intravascular variables such as drug treatment, intrinsic erythrocyte aggregation, free fatty acid concentration, and chylomicrons [68]. OrSense is a medical device using near-infrared occlusion spectroscopy, detecting the red optical signal from blood due to changes in the glucose concentrations in blood vessels or finger, which has not yet been commercially successful
 - (ix) Electromagnetic sensing uses electromagnetic sensors to measure the conductivity of dielectric parameters changed by the glucose concentration on a specific resonant frequency of 2.664 MHz [69]. Precision of the glucose measurements is strongly affected by environmental temperature and physiological blood dielectric parameter changes. TouchTrak is a high-cost medical device using electromagnetic sensing [22] and is not commercially successful. GluControl GC300 is a medical device, which has no significant proof of its accuracy and is poorly described [30].
 - (x) Thermal emission spectroscopy measures the naturally emitted infrared signals generated in the human body due to changes in glucose concentration, similar to clinical tympanic membrane thermometers, based on wavelengths of 9.8 μm and 10.9 μm [70]. This method can be applied on the skin of the forearm, fingertip, or ear to detect glucose concentrations [53]. Infratec develops a portable handheld glucose measurement device built on a thermal emission spectroscopy method, not being yet commercialized [22]
 - (xi) Temperature-regulated localized reflectance uses the scattering of a localized reflected light signal with wavelengths of 0.59 μm and 0.935 μm [71]. Measured temperature variations between 22°C and 38°C are related to glucose concentration [50]. Precision of measurements is affected by probe position, physiological parameters, and disease conditions
 - (xii) The metabolic heat conformation technique uses thermal and optical sensors to measure thermal generation, blood flow rate, and hemoglobin and oxyhemoglobin concentrations strongly related to glucose concentration [72]. Multivariate statistical, regression, and cluster analyses, including multiwavelength spectroscopy (wavelengths 0.47 μm , 0.53 μm , 0.66 μm , 0.81 μm , 0.88 μm , and 0.95 μm), are used to calculate the glucose value [73]
 - (xiii) The far-infrared (thermal infrared) technique uses the dependence of the cutaneous microcirculation on the local glucose concentration, which is observed by inducing controlled, periodic temperature variations in the skin and assessing MIR light scattering [53]. The far-infrared dielectric properties of sugars in the condensed state are dominated by vibrational modes of their intermolecular hydrogen-bonded network [74]. The basic principle of absorption is due to the existence of particular vibrational and rotational transitions of weak bonds and bonds of heavy atoms with wavelengths between 10 μm and 1000 μm
 - (xiv) Terahertz time-domain spectroscopy measures the radiation absorption obtained from single-frequency (wavelength 0.9 μm) very short laser pulses (in the order of picoseconds). The method is based on time-domain analysis to get the phase change from reflected and scattered signals which allows the detection of the optical properties dependent on glucose concentration [75]. An ultrafast laser pump with a specific pulse shape can allow a broad frequency sweep and by applying time-domain signal processing of the detected spectroscopic information can extract crucial frequency-dependent information and determine glucose levels [76]
 - (xv) Millimeter and microwave sensing allows going deeper into the tissue to reach regions with sufficient blood concentration using lower energy per photon and less scattering for accurate glucose

readings [77]. The sensing is realized by a near-field antenna using reflection methods

- (xvi) Ultrasound technology is based on measurement of the propagation time of ultrasound waves through the extracellular fluid, which is dependent on the glucose concentration due to the strength of intermolecular bonding forces and the density of the fluid [78]. Precision is affected by the ambient temperature. The noninvasive ultrasound or spectroscopy (light) technology measuring the heat capacity and conductivity as a two-parameter approach was used with GlucoTrack [79], which is still a not commercially successful product, although reporting good clinical results [78]
- (xvii) The polarimetry method estimates the optical rotary dispersal of polarized light by a millidegree precision polarization through tissue less than 4 mm thick across the anterior chamber of the eye [80]. Multiple linear regression or similar methods used for multispectral polarimetry minimize glucose prediction errors [81]. There is a time delay for glucose peak concentrations to propagate in the aqueous humour [82]
- (xviii) The fluorescence method relies on measuring the glucose levels in tears, since they reflect concentrations similar to those in blood, and the idea is to build a glucose-sensitive fluorescence system to monitor glucose metabolism by detection of either intrinsic cell fluorescence or fluorescent reporters of cell metabolism [83]. Fluorescence uses the principle of varying light emission from molecules in different states [84, 85]. GluMetrics uses the fluorescence method on an intravascular target, based on a glucose sensing polymer that glows in the case of high glucose concentration, but still not a commercially successful product [22]
- (xix) Optical coherence tomography is based on irradiation of a low-power laser source with coherent light to the skin and an in-depth scanning system to record the backscattered radiation (wavelength between $0.8 \mu\text{m}$ and $1.3 \mu\text{m}$) [86]. Since the dermal layer is dependent on the glucose concentration, measurements include induced changes [87]. Precision is sensitive to motion, tissue heterogeneity, and interfering analytes [88]. GlucoLight is a portable medical product that targets the skin and is still not being commercialized [22]
- (xx) Kromoscopy is based on a near-infrared analog of human color perception [89]. Four detector channels with complementary bandpass functions are used for the evaluation of collected electromagnetic radiation [90]. Complex vector analysis is applied for observed significant differences in channel responses for glucose and urea over different wavelengths of NIR light

Note that metabolic heat conformation and thermal emission can be differentiated from optical methods as a special class of thermal methods [91].

5. ML and NN Methods for Noninvasive Glucose Measurement

In order to extract knowledge from the gathered measured data, many studies use ML and NN methods. There are several studies that successfully include ML and NN techniques in methods of extraction and monitoring of glucose levels. Monte-Moreno [92] proposed a system for a simultaneous noninvasive estimate of the blood glucose level based on machine learning techniques and using a photoplethysmograph (PPG) sensor. The system idea is to find the relationship between the shape of the PPG waveform and the glucose levels. The system was tested on 410 individuals, and it used several machine learning techniques. The best results were obtained by the random forest technique. The distribution of the points on a Clarke error grid placed 87.7% of points in zone A, 10.3% in zone B, and 1.9% in zone D.

Yadav et al. [93] measured the blood glucose noninvasively by using the galvanic skin response and temperature measurements along with PPG. They used the multiple linear regression (MLR) and artificial neural network (ANN) techniques to estimate the blood glucose concentration from the multisensors. A significantly low mean absolute percentage error (MAPE) (9.21%) and high R^2 (0.94) demonstrated the accuracy of this multisensory approach.

Malik et al. [94] detected fasting blood glucose levels (FBGLs) in a mixed population of 175 healthy and diseased individuals in India. Their detecting algorithm uses machine learning techniques such as logistic regression (LR), support vector machine (SVM), and artificial neural network (ANN). The occurrence of elevated FBGL was estimated noninvasively using the status of an individual's salivary electrochemical parameters such as pH, redox potential, conductivity, and concentration of sodium, potassium, and calcium ions. The best performance for classifying high FBGLs was achieved by the SVM using RBF kernel showing approximately 85% accuracy, 84% precision, 85% sensitivity, and 85% F1 score.

A noninvasive nocturnal hypoglycemia monitoring system for type 1 diabetes patients is presented by Ling et al. [95]. The system uses an extreme learning machine-based neural network model. The results show that hypoglycemia in type 1 diabetes mellitus children can be detected noninvasively from the real-time heart rate and corrected QT interval. The testing performances of the proposed algorithm for the detection of hypoglycemia achieved sensitivity of 78.00% and specificity of 60.00%.

Reddy et al. [96] proposed a noninvasive blood glucose measurement method based on microwave transmission and the machine learning technique. The blood glucose concentration is detected by analyzing the reflected microwave signals.

The machine learning technique is used to facilitate real-time processing and to provide an alert for the patients with

hyperglycemia conditions. The system can also suggest a precise dose of insulin to intake.

Carter et al. [97] proposed a noninvasive diagnostic method using concentrations of twenty-two elements in toenails and personal information such as age, gender, and smoking history. The authors used seven different machine learning techniques to perform the robust classification of type 2 diabetes. They compared the performance of forty-six distinct machine learning models on resampled training data and testing data. The best results were achieved with the random forest model (seven out of nine test samples were predicted correctly).

Das et al. [98] measure the galvanic skin response of 11 diabetic patients and 8 normal controls. The novel noninvasive system is based on the principle of skin impedance spectrogram and heart rate variability. To compute the heart rate variability, they acquired ECG signals from 20 normal controls and 20 diabetic patients. In the study, they use features such as Welch's power spectral density estimation. Artificial neural networks were used to classify GSR signals, and the obtained accuracy is 100%. During the analysis of diabetes mellitus, they have proven that there is a change in some parameters related to heart rate variability.

A compact microwave sensor has been proposed [99] for glucose sensing based on the utilization of the artificial neural network and has been simulated with the proposed models and measured with a fingertip as well as glucose/water solutions. It has been concluded that the presence of biological tissues decreases the measurement sensitivity. However, the sensor can measure the glucose level when the solution is directly placed on the sensor.

Low-cost continuous glucose and noninvasive BG detection system is presented [100] based on a combination of the conservation-of-energy method with a sensor for collecting oxygen saturation (SPO_2), blood flow velocity, and heart rate. Also, methods for a basal metabolic rate (BMR) and BV detection are proposed based on human body heat balance and PPG signals. The system includes a module for multisensor information fusion. The intelligence is implemented by using a decision tree and backpropagation neural network. The reported achieved accuracy is 88.53%.

Artificial neural networks (ANNs) combined with particle swarm optimization (PSO) are proposed to model the nonlinear relationship between the blood glucose concentration and near-infrared signal [101]. The weight coefficients of the ANNs represent the difference between individual and daily physiological rule. The Bland-Altman method has been applied to show that the predictions and measurements are in good agreement. The PSO-2ANN model is concluded to be a nonlinear calibration strategy with accuracy and robustness using $1.55 \mu\text{m}$ spectroscopy, able to correct the individual difference and physiological glucose dynamics.

Another low-cost portable noninvasive blood glucose measurement system based on near-infrared light is presented in [102]. Regression analysis is applied to model the relationship between the detector output voltage and the glucose concentration. The accuracy of the device has been tested by comparing the noninvasively estimated and invasively measured blood glucose. The neural network method

is used to estimate the glucose concentration. The results of the prediction of glucose concentration show that the system errors are in the clinically acceptable region.

Todd et al. [103] review existing research in methods of extraction and monitoring of glucose levels, especially focusing on the performance of ML methods, such as fuzzy logic, neural networks, and decision trees. The most promising result with the accuracy of nearly 98% was produced by neural networks and recurrent neural networks.

The presented work in [104] focuses on the design of low-cost, painless, and noninvasive blood glucose measurement system by using near-infrared LED and four photodiodes. The attenuated light is transformed into a voltage signal. The voltage signal is calibrated using the Levenberg-Marquardt-based artificial neural network to obtain the glucose concentration. The accuracy of the proposed system has been tested by comparing it with invasively measured blood glucose. The errors obtained are in a clinical range.

6. HRV-Based Noninvasive Glucose Measurement

An ECG is the electrical signal representation of the heart action potential. The heart rate is being controlled by the autonomous nerve system, the same that regulates the blood pressure and the glucose level. Thus, the last group of methods is used to produce medical devices including wearable ECG sensors and different HRV trackers, mainly represented by smart watches, smartphones, or similar devices, including belts, special shirts, and patches.

The autonomic nervous system constituted the parasympathetic and sympathetic parts which operate independently of each other or interact cooperatively to control heart rate, cardiac output, myocardial contractility, cardiac electrophysiology, and the constriction and dilatation of blood vessels [105]. Thus, HRV is an essential tool to diagnose the cardiac autonomic neuropathy for both clinically asymptomatic and symptomatic patients as a serious complication of diabetes mellitus.

Heart rate variability is a physiological phenomenon consisting of oscillations in consecutive heartbeat intervals controlled by the autonomic nervous system and is caused by the ability of the heart to handle the ever stresses and relaxations placed on the body. Several studies show that there is a correlation between HRV and the glucose level of the subjects.

Recent studies [106–108] show a big correlation between the HRV from one side and glucose level from the other side, since they show that diabetes caused progressive autonomic dysfunction and decreased variability in the heart rate [109, 110].

The overall result is the differentiation of diabetic patients from normal whenever a reduction of HRV parameters is detected. Kudat et al. [107] investigated cardiovascular autonomic neuropathy in diabetics and healthy controls by analysis of heart rate variability and concluded that diabetes patients had lower values for time-domain and frequency-domain parameters than other normal subjects. They have analyzed that diabetes mellitus is a cause of autonomic

dysfunction in the gastrointestinal and urogenital systems besides the cardiovascular system but focused their research on autonomic dysfunction.

Five different tests have been introduced by Ewing et al. [111] of short-term R-R alterations to identify cardiac autonomic neuropathy in patients with diabetes, based on heart rate response to respiration and to standing, during and after a provoked increase in intrathoracic and intra-abdominal pressures (Valsalva maneuver), and blood pressure response to orthostasis and isometric exercise.

An increase in the ability to detect minor changes in cardiac autonomic function with long-term HRV monitoring is reported [112] when compared with standard tests of autonomic function. There was evidence of significant HRV reductions for those diagnosed with diabetes compared with nondiabetic subjects, indicating that the presence or absence of neuropathy may conceal important information. Some studies included data recorded by wearable heart rate sensors. They have also confirmed high accuracy at detecting diabetes (0.8451) by a semisupervised training method, semi-supervised sequence learning, and heuristic pretraining and show that they outperform hand-engineered biomarkers from the medical literature [106].

HRV parameters can be classified as a time series domain, a frequency domain, and other domains [113] such as long-term (24 h), short-term (5 min), and ultra-short-term measurements (less than 5 min) [114–116]. Most of the studies [109, 113] conclude that long-term HRV variability is more sensitive for detecting diabetes autonomic neuropathy from the conventional short-term measures.

7. Discussion

A comprehensive overview of the progress of glucose measurement is elaborated by Villena Gonzales et al. [14]. They specify using various glucose detection techniques based on electric, thermal, and optical methods, and recently, the nanotechnology approaches are essential for minimally invasive and noninvasive glucose measurement technologies.

Several properties of glucose are manifested under different phenomena. García-Guzmán et al. [19] conclude that chemical, electrical, optical, thermal, acoustic, or any combination of these glucose properties can achieve greater accuracy in the determination of glucose concentration in blood and that both optical and electrical properties are the most suitable for noninvasive glucose measurement. In this paper, we also give advantage to the analysis of glucose properties by the analysis of autonomic dysfunction.

Methods using sweat-based glucose monitor wearable biosensors are reported as ongoing projects [117, 118].

A hybrid approach [19], which includes sensing of more than one physiological parameter, is becoming popular, such as electrochemical or combination of measuring the sound speed, conductivity, and heat capacity obtaining thereafter a weighted average or a combination of absorption spectroscopy and complex bioimpedance measurements [119]. In addition, a complex big data analysis of several parameters with corresponding artificial intelligence methods are hot topic research and can produce promising results.

Data analytics in processing various glucose properties for noninvasive and minimally invasive techniques is an emerging technology [120] contributing to the field of diabetes informatics and providing a more data-rich approach to understanding and managing diabetes.

Analyzing the accuracy, the American Diabetes Association [121] recommends the control of all glucometers both at the start of usage and at regular intervals and also the accuracy of blood glucose to be <5% of the measured value or accuracy better than 15 mg/dl (0.8 mmol/l) [20]. Solnica et al. [122] conclude that all glucometers examined have small deviations from laboratory reference values (<10%), although there are reports that, yet, some of the glucometers do not meet the recommendations and standard requirements.

Besides the accuracy, there are other socioeconomic parameters that can be treated as a barrier to the adoption of the noninvasive glucose monitoring [19], including commercialization uptake in the global economy. It is believed that next-generation glucometers or continuous glucose sensor systems may become excellent predictable and selective devices and probably in the future become a fully reliable source of information and acceptable for patient use [20].

Lin et al. [91] specify major challenges for development on noninvasive glucose measurements, extracting issues in obtained specificity and sensitivity, variable physiological time lag, need for the calibration process, and usability. Talking about usability, one needs to describe if the device is a wearable or pocket-size hand-held device. For example, GlucoWise is a U-shaped sensor that fits over the corner of the hand between the thumb and forefinger. Analyte is a hand-held device that is inserted into the ear, whereas GlucoTrack is clipped to the earlobe [123].

A roadmap of continuous glucose measurement initiates next generations of noninvasive techniques [124], and some of the future key challenges [22] include the following:

- (i) Improvement of the sensitivity and positive predictive rate in the detection of glucose levels and corresponding accuracy and precision of glucose measurement medical devices
- (ii) Development of a wearable continuous noninvasive glucose measurement system

Note that besides the lack of precision, robustness, and stability, the cost-effectiveness that is measured as a price per use is the key factor to accept a certain technology and make it commercially successful.

8. Conclusion

In this paper, we have presented an enhanced set of noninvasive techniques for glucose measuring based on HRV and using sophisticated artificial intelligence algorithms. Those methods are important since they enable the patients' comfortable continuous monitoring of the blood glucose levels.

Usually, the noninvasive measurements have been classified as transdermal and optical methods. We specified

autonomic dysfunction as another class, based on an important observation that wearable ECG sensors are capable of measuring HRV. This trend in modern real-time remote noninvasive monitoring by wearable mobile medical devices could be correlated with methodologies for glucose monitoring. Reduction in HRV variability is an indicator of autonomic diabetes dysfunction, and thus, the technology based on wearable ECG sensors may have promising results in the determination of the ability to control the blood glucose level. Although these methodologies may have promising results in terms of patients' comfort, they still lack the needed accuracy. In order to get a better understanding of the gathered measurement data, many of those measurement methods use ML and NN techniques to achieve better accuracy.

Expenses and proving benefit are probably those that need to be made more affordable and demonstrated in further research. However, it takes a lot of time to market the technology from one side and to change the behavior of both the patients and doctors.

Future trends include the use of new sophisticated techniques, such as the use of artificial intelligence algorithms or sensing other psychophysiological parameters, such as the autonomic dysfunction based on heart rate variability, as discussed in this article. Nanotechnologies are also a promising technique, although they are commonly treated as minimally invasive techniques.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

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