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Kishor Kumar Sadasivuni
John-John Cabibihan
Abdulaziz Khalid A M Al-Ali
Rayaz A. Malik *Editors*

Advanced Bioscience and Biosystems for Detection and Management of Diabetes

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Editors

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Editors
Kishor Kumar Sadasivuni
Center for Advanced Materials
Qatar University
Doha, Qatar

Abdulaziz Khalid A M Al-Ali
KINDI Center for Computation Research
Doha, Qatar

John-John Cabibihan
Department of Mechanical and Industrial Engineering
Qatar University
Doha, Qatar

Rayaz A. Malik
Weill Cornell Medical College in Qatar
Doha, Qatar

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Preface

Diabetes is a serious public health issue that affects people all over the world. As the world population ages, the prevalence of this chronic complicated metabolic illness increases at an alarming rate. It will have the greatest influence in underdeveloped countries. Because diabetes is a chronic, complicated metabolic condition, a multidisciplinary team of health professionals with experience in diabetes management should offer diabetes care in conjunction with the patient and family. Despite the fact that diabetes mellitus was recently given priority status by the WHO, many public health planners are still uninformed of its scope and its consequences. The rising incidence of the condition and the long-term expense of therapy for both patients and the health sector, as well as the economic cost to nations, are all factors to consider. Adult prevalence rates ranging from 7% to 25% have been observed in studies done in diverse communities throughout the region. Furthermore, a growing number of nations are reporting the emergence of type 2 diabetes mellitus at a young age. The goal of incorporating diabetes mellitus into primary health care is to develop routine screening methods to identify, monitor, and manage diabetes's frequent complications. Treatment should just focus not only on decreasing blood glucose levels, but also on addressing other noncommunicable disease risk factors including smoking, dyslipidemia, obesity, inactivity, and hypertension. Not only is diabetes care in shambles, but so is our knowledge of the processes that underpin clinical problems associated with the illness. The major goals in caring for diabetic patients are to prevent or at least slow the development of clinical complications such as micro-vascular (eye and kidney disease) achieved through blood sugar and blood pressure control, and macro-vascular (coronary, cerebrovascular, and peripheral vascular) achieved through lipids, hypertension, and smoking control. However, we do not understand how increased blood glucose, circulating insulin, and changed blood pressure affect the pathophysiology of blood arteries and cause serious organ failure.

As a result, in the lack of such a knowledge foundation, current treatment techniques focus on risk management. If we want to control this condition properly, we need to start monitoring diabetes early and keep it up to date. The early detection of variations in blood glucose levels is the foundation of diabetic care. Effective treatment, especially for undetected hypoglycemia, requires careful and timely

monitoring. Blood glucose levels are usually checked before a meal, two hours after, and before bedtime. Although the development of blood glucose self-monitoring in recent decades has encouraged diabetes treatment in the quest for euglycemia, its cumbersome use may result in insufficient data collection of blood glucose. The pattern, frequency, level, and timing of blood glucose changes have been tracked using continuous glucose monitoring. Diabetes diagnosis and management need precise, sensitive, consistent, quick, and attentive glucose monitoring frequently. Diabetes can create various vascular and neurological issues that impact multiple organ systems in the short and long term if not treated properly. Regular community-based screening and prompt diagnosis in undiagnosed patients, sufficient patient education and support, continuous medical treatment, psychological counseling, and societal support are all required to avoid acute consequences. Accurate blood glucose monitoring while enhancing glycaemic control and patient quality of life is one of the most difficult elements of diabetes mellitus treatment. Regular monitoring by the doctor or the patient is necessary to keep the diabetes patient's health from worsening. These recommendations are intended to aid in the standardization of diabetes treatment at the elementary, secondary, and tertiary levels and advise policymakers as part of efforts to enhance health care. Above all, we must all endeavor to improve diabetes mellitus prevention to reduce this increasing burden.

This book intends to offer recent work carried on the leading technologies for noninvasive (NI) and minimally invasive (MI) glucose monitoring sensors, devices presently found in the field of medicine sciences. The type of framework used for accuracy determination and new approaches undertaken by scientists have been discussed. This book also mentions the upcoming trends to be seen in diabetic diagnosis and management by using the machine learning and artificial intelligence. We hope you enjoy reading the book and find it useful whether this is helping patients or health professionals to manage diabetics and its complications using the current innovative technologies. The book will summarize that the invention and replacement of use of new technologies with the existing ones for glucose detection are the future for diabetic patients.

Doha, Qatar

Kishor Kumar Sadasivuni
John-John Cabibihan
Abdulaziz Khalid A M Al-Ali
Rayaz A. Malik

Contents

Introduction

Kishor Kumar Sadasivuni and Mithra Geetha

Abstract Effective diabetes management begins with blood glucose monitoring. Diabetic care goes beyond monitoring blood glucose levels. This includes overall health, including blood pressure, weight, cholesterol levels, sleep, mood, medications, and eye, kidney, and foot health. Monitoring blood sugar is fundamental to managing diabetes. Micro and macrovascular complications are reduced with regular glucose testing. Despite the recent development of minimally invasive glucose monitoring techniques, most glucose monitoring methods are invasive, painful, time-consuming, and expensive in the long run. In order to improve the quality of life for patients with diabetes, non-invasive, needle-free, and CGM approaches are needed. The purpose of this chapter is to provide an overview of different chapters covering various devices and sensors for invasive, minimally-invasive, and non-invasive glucose monitoring currently available on the market or in development, as well as their accurate real-time response and sensitivity.

Keywords Diabetes mellitus · Glucose · Monitoring · Medications · Blood pressure

Diabetes mellitus, often known as diabetes, is a set of metabolic diseases characterized by elevated blood sugar levels in the human body over an extended time. Several different pathogenic mechanisms cause diabetes. These can range from autoimmune destruction of β-cells of the pancreas, resulting in insulin insufficiency, to anomalies that result in insulin resistance. Type 1 diabetes (β-cell destruction, usually leading to absolute insulin deficiency), type 2 diabetes (ranging from predominantly insulin resistance with relative insulin deficiency to predominantly an insulin secretory defect with insulin resistance), and gestational diabetes mellitus (GDM-any degree of glucose intolerance with onset during pregnancy) are the most common types. The global prevalence of diabetes was projected to be 463 million people in 2019 [1]. Data indicates that diabetes patients have surged worldwide, with India being

K. K. Sadasivuni (✉) · M. Geetha
Center for Advanced Materials, Qatar University, Doha, Qatar
e-mail: kishor_kumars@yahoo.com

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second only to China regarding the number of people with diabetes. According to the International Diabetes Foundation, the number of individuals diagnosed with diabetes would rise to 628.6 million in 2045, accounting for 6–7% of the global population [2]. Diabetes rates grow as the population, obesity, physical inactivity, and unhealthy diet all rise. The World Health Organization and the International Diabetes Federation have identified diabetes as a serious global problem [3].

The conventional view of diabetes mellitus pathophysiology remains that hereditary predisposition underpins disease progression, with genetic mutations affecting the stages of beta-cell activity, insulin secretion, contact with tissue cells, insulin receptor synthesis, and insulin action inside cells. The immune system targets and kills the insulin-producing beta cells in the pancreas in patients with diabetes type 1. As a result, the body's insulin synthesis halts. Type-2 diabetes mellitus can cause antibodies against islet beta-cell antigens to be elicited directly in certain people. In all diabetes mellitus, diabetes type 2 accounts for 80% of all cases. Because of beta-cell malfunction, this form of diabetes is caused by a relative insulin deficit. These individuals have a very gradual progression of insulin insufficiency, and they are classified as having latent autoimmune diabetes (LADA) with a delayed onset. Gestational diabetes (Type 3) has become a major public health concern during a woman's pregnancy. Placenta produces placental growth hormone (PGH) and proinflammatory cytokines such as tumor necrosis factor-alpha (TNF-) during a healthy pregnancy. Insulin sensitivity is reduced in adipose tissue, liver, and skeletal muscle due to these variables. This disease does not affect all pregnant women, but it does raise the dangers associated with pregnancy. It can occasionally cause difficulties for babies and can also obstruct the normal birthing process. However, after the delivery of a child, this syndrome largely subsides.

Chronic hyperglycemia can cause serious issues in a person's body, including damage to and even failure of organs like the kidneys and heart [4]. Diabetic complications might include blindness, renal illness, neurological and circulatory disease, limb amputations, stroke, and cardiovascular disease [5]. Patients may have polydipsia, polyuria, and polyphagia due to persistent hyperglycemia. Diabetic complications might also include cardiovascular disease and mortality [6]. Other comorbidities associated with diabetes include diabetic foot, diabetes retinopathy, ketoacidosis, and neuropathy. Recent research has discovered a strong link between glucose levels and heart rate variability (HRV). This strategy focuses on diabetes patients and alleviates their financial and health-related problems [7]. For patients, a technology that might give an early identification of such problems could be life-changing.

In 2017, the total cost of diabetes-related health care in the United States was predicted to be over $327 billion. According to the Mayo Clinic, quitting smoking and keeping the blood pressure and cholesterol under control are two of the top ten strategies to avoid diabetic problems. Regular exercise and drinking water as the primary beverage are not on this list, but they are equally vital. Diabetes can be managed with a balanced diet and, eventually, insulin injections [8]. Sleep disruption appears to have a role in diabetes, just as diabetes can create issues with sleep. Sleep deprivation raises hunger hormone ghrelin and lowers satiety hormone leptin levels [9]. People who suffer from sleep problems are more likely to seek consolation in high-sugar

meals Chapter "Review of Emerging Approaches Utilizing Alternative Physiological Human Body Fluids in Non- or Minimally Invasive Glucose Monitoring". Optimizing glycemic control by reducing blood glucose levels has been shown to reduce the risk of microvascular complications and long-term macrovascular disease [10]. Because Type 1 DM patients' insulin production by beta cells is reduced, pharmacological stimulation of insulin secretion or insulin absorption is no longer enough to keep them in a euglycemic state, and external insulin supplementation is the only way to keep them there.

The basis of diabetes management is timely recognition of the variation of blood glucose levels. Effective therapy, especially for undiagnosed hypoglycemia, is only feasible with good and early monitoring. Normally, blood glucose levels are tested before a meal, two hours after a meal, and before going to bed [11]. Although the introduction of self-monitoring of blood glucose (SMBG) has inspired diabetes care in recent decades in the pursuit of euglycemia, its inconvenient usage may result in inadequate blood glucose data collecting. Continuous glucose monitoring (CGM) has monitored the pattern, frequency, level, and time of blood glucose level fluctuations. Diagnosis and management of diabetes need regular glucose monitoring that is accurate, sensitive, dependable, fast, and attentive. Without adequate care, diabetes can cause a range of vascular and neurological problems affecting various organ systems in the short and long term. To avoid acute effects, regular community-based screening and timely diagnosis in undiagnosed individuals, adequate patient education and support, ongoing medical treatment, as well as psychological therapy, and societal support are all necessary. One of the most difficult aspects of diabetes mellitus therapy is correctly monitoring blood glucose while increasing glycaemic control and patient quality of life. To prevent the diabetic patient's health from deteriorating, regular monitoring should be performed by either the doctor or the patient Chapter "Current Status of Non-invasive Diabetes Monitoring".

Self-monitoring blood glucose levels give a consistent, trustworthy, and reliable method of detecting blood glucose levels. It's critical to monitor glucose levels in diabetic patients frequently [12]. The current standard of care for DM diagnosis is venous plasma glucose testing. Currently, all home blood glucose monitoring techniques need piercing the skin to get a blood sample. Because the treatments are invasive, this technique inhibits patient's cooperation and has severe disadvantages [13]. This invasive procedure aids patients in identifying and avoiding hypoglycemia and hyperglycemia. Various methods have been developed to assess glucose levels, including capacitive, coulometric, optical, enzymatic-electrochemical, and non-enzymatic electrochemical methods [14]. The major goal of these investigations is to create a less painful method and reduce infection risk [15].

The non-invasive method, which is a relatively new technology, relies on the body's glucose signals. It eliminates the need for "finger pricking" and allows for continuous blood glucose monitoring. A novel method for measuring glucose levels using an ECG monitor has been devised. The ECG is transmitted to a smartphone where it is temporarily stored and calculated heart rate variability characteristics. The algorithm then estimates a human's capacity to regulate glucose levels using advanced machine learning approaches. This strategy focuses on diabetes patients

and alleviates their financial and health-related problems Chapter "A New Solution for Non-invasive Glucose Measurement Based on Heart Rate Variability".

Procedures involving the application of fluorescent light to the body in a specific place and techniques involving the implantation of a sensor in the subcutaneous tissue cause interference with the process from surrounding signals such as ultraviolet and visible light. The primary recognition elements utilized in the construction of sensors include receptors, antibodies, enzymes, nucleic acids, lectins, and microbes [16] Chapter "Commercial Non-invasive Glucose Sensor Devices for Monitoring Diabetes". A biosensor is a transducer that converts a bimolecular binding event captured on the surface of a bio-receptor into a readable physical quantity [17]. The interaction of the optical field with an analyte as a detecting element completes the optical-based biosensor [18]. A label and an optical signal enhancer, such as gold nanoparticles, fluorescent or luminous labels, are used in a label-based sensing technique. The newest manufacturing processes and the major problems associated with the use of SPR, LSPR, SPR imaging, and PC biosensors to detect diabetes biomarkers are reviewed in Chapter "Optic Based Techniques for Monitoring Diabetics".

In 2017, over 51 million individuals globally used glucometers, with roughly 12% having type 1 diabetes, implying they are forced to take insulin therapy and use glucometers to monitor that medication by default. Diabetic patients must pay for constant or frequent self-monitoring and blood glucose testing strips (as much as $1 per strip) or continuous glucose monitoring sensors ($350 per month), glucagon, and other medications. Cardiovascular disease accounts for more than a quarter of the expenditures associated with diabetes patients. Regular finger pricking or continuous glucose meters and frequent trips to cardiologists are the most common treatments for these problems. A recently proposed approach addresses these issues with a single system. Simultaneously, the solution provides a gadget for continuous cardiac arrhythmia and assesses a person's capacity to regulate blood glucose levels.

The first indicators seen in children with diabetes are pro-insulin autoantibodies or insulin (PAA/IAA). High affinited IAA against pro-insulin was also linked to high IAA levels with HLA DPB1 * 04. HbA1c isn't the primary method for diagnosing diabetes, but it does offer enough information to do so. These diseases may be easily diagnosed using a boron-based probe produced using a targeted approach and aids in recognizing sugar on the cell surface. Because of their great stability and strong selection rate towards glucose, most glucose sensors use glucose oxidase (GOx). Mulyanti et al. developed software that was semi-numerical and used the transfer matrix approach. They also discovered that the concentration of glucose has a significant impact on the resonant wavelength shift. Jamil et al. [19] showed that the K-SPR technique with nano-laminated Au–Cr is extremely effective in detecting creatinine and urea Chapter "SPR Assisted Diabetes Detection". Acoustic spectroscopy is another method for detecting glucose signals using optical beams; however, it suffers from scattering effects, resulting in insensitivity. Multi-modal spectrography IC, which combines impedance and near-infrared methods, may also be used to assess glucose levels. In order to remove diverse systemic noises, new practices exploit indirect dielectric characteristics of the tissue surrounding the blood. The application of the Gabor filter for the analysis of facial contour data is a new approach for detecting

diabetes [20]. The concentration of acetone in human bodies is extremely low (0.1–0.8 ppm), however in diabetes mellitus, this amount rises to 1.8–5.0 ppm [21]. Due to ketonic species, notably acetone and aceto-acetic acid, which are generated when fatty acids are broken down, people with diabetes mellitus have insulin problem hormones in their bodies [22]. Many researchers have achieved a biosensor approach for diabetic diagnosis since exhale breath acetone is a simple diabetes biomarker.

The irradiation of a sample with monochromatic light causes molecules in the sample to scatter incident light, resulting in vibrational spectroscopy. The resulting spectrum describes the absorption of light by the molecules in the sample as a function of frequency, measured in wavenumbers. These spectra can be used to distinguish between distinct functional groups in a material Chapter "Infrared and Raman Spectroscopy Assisted Diagnosis of Diabetics". Surprisingly, the photo-acoustic approach is a technology that allows for a high level of sensitivity throughout the analysis procedure. It goes through the basic principles of photoacoustic spectroscopy and how they may monitor glucose levels Chapter "Photoacoustic Spectroscopy Mediated Non-invasive Detection of Diabetics".

Electrical bioimpedance can be used in both DC and AC applications. Georg Simon Ohm defined the impedance Z in Ohm's law in 1827, where Z is a complex number. Arthur Kennelly [23] was the first to express it in terms of a real (R) and imaginary (jX) portion, where $Z = R + jX$ and "j" is the imaginary operator. A lipid layer covers each cell, primarily for ion transport and protection. A cell membrane may be represented as a capacitor connected to a resistor in parallel. Rm (cellular membrane resistance) can be regarded as significantly greater than Rext (resistance of extracellular medium) at lower frequencies due to the cell membrane's unique isolating characteristic. This action prevents the ionic current from penetrating the cell, forcing it to pass through the extracellular media. Depending on the frequency of the excitation alternate signal, biomatological materials, particularly tissue, exhibit variable dispersion to the applied electrical field. This is due to the different types of free ions found in extracellular and intracellular fluid. The ionic potential generated by the external excitation signal will promote the flow of free ions at lower frequencies, although the cell membrane obstructs this flow, resulting in a high impedance. On the other hand, higher frequencies allow the ionic current to pass through the cell membranes and intracellular contents, lowering the resistance in most situations Chapter "Electrical Bioimpedance Based Estimation of Diabetics".

Millimeter and microwave sensing techniques have the potential to develop a medical device that non-invasively measures blood glucose without the need for finger pricking, a drop of blood, and the use of a test stripe; this allows for the least amount of hassle and the best way to deal with samples to examine and diagnose blood glucose levels Chapter "Millimeter and Microwave Sensing Techniques for Diagnosis of Diabetes". To enhance health outcomes, artificial intelligence (AI) is increasingly being used in medicine to discover patterns in complicated collections of clinically gathered data and self-monitored data. Machine learning (ML) gives computers the capacity to learn without being explicitly programmed ahead of time. Clinical knowledge is enhanced by machine learning algorithms, which have been demonstrated superior to utilizing only one in disease treatment Chapter

"Different Machine Learning Algorithms Involved in Glucose Monitoring to Prevent Diabetes Complications and Enhanced Diabetes Mellitus". Diabetic patients, clinicians, and smart healthcare systems are all areas where artificial intelligence may aid and improve diabetes treatment. AI technologies on diabetes allow for more effective data processing and tools and gadgets to help patients control their condition. Patients with diabetes now have new uses for AI, such as patient surveillance, fast decision-making, and risk prediction [24]. Several sophisticated Artificial Intelligence systems have been widely utilized to enable advanced analyses and give tailored medical help to diabetic patients Chapter "The Role of Artificial Intelligence in Diabetes Management".

With the rise in available data and processing capacity, data-driven techniques are proving to be more efficient. DSS has become more efficient because of improvements in AI/ML and glucose sensor technologies [25]. A diabetic DSS may be divided into two categories: patient DSS and clinical DSS (CDSS) Chapter "Artificial Intelligence and Machine Learning for Diabetes Decision Support". Researchers have mostly concentrated on the manufacturing of electrode surfaces in order to build nonenzymatic glucose sensors [26]. Long-term blood glucose control in diabetic individuals has been demonstrated to extend life expectancy [27]. Chapter Future Developments in Invasive and Non-invasive Diabetes Monitoring outlines the non-invasive glucose monitors that are used to manage diabetes. The benefits and drawbacks of the most recent commercial remote glucose monitoring systems have been evaluated Chapter "Future Developments in Invasive and Non-invasive Diabetes Monitoring".

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Review of Emerging Approaches Utilizing Alternative Physiological Human Body Fluids in Non- or Minimally Invasive Glucose Monitoring

Sunghoon Jang, Yu Wang, and Andre Jang

Abstract Diabetes can cause various acute as well as long-term complications in patients with blood sugar levels of over 600 mg/dL, such as blindness, kidney disease, nervous and circulatory system disease, limb amputations, stroke, and cardiovascular disease (CVD). Frequent and regular blood glucose monitoring by diabetics and physicians is an essential step in the management of diabetes. Over the last five decades, there have been numerous attempts to develop viable painless, non- or minimally invasive blood glucose monitoring techniques to replace all existing invasive methods, such as home blood glucose monitoring, which usually require drawing a blood sample by piercing the skin (typically, on the finger). This method strongly discourages the patients' compliance and has serious drawbacks as the procedure is invasive, causing discomfort, pain, and potential risks of infection or tissue damage. It is highly desired to have alternative non-invasive blood glucose monitoring techniques. This review investigates the principles of three major emerging general technologies, namely optical, Radio Frequency (RF)/microwave, and electrochemical glucose monitoring technologies. These glucose monitoring technologies can be classified as 15 specific techniques that use multivariate regression analyses to correlate feeble optical, Radio Frequency (RF)/microwave, or electrochemical signals from various body fluids to physiological glucose concentration. This review also offers how-to utilize glucose-sensing techniques to target variable areas by sampling physiological human body fluids as an alternative diagnostic medium to blood; for example, interstitial fluid, urine, sweat, ocular fluids, and saliva all

S. Jang (✉) · Y. Wang
Department of Computer Engineering Technology, New York City College of Technology of CUNY, 300 Jay Street, Brooklyn, NY 11201, USA
e-mail: sJang@citytech.cuny.edu

Y. Wang
e-mail: yWang@citytech.cuny.edu

A. Jang
Department of Physiology and Neurobiology, University of Connecticut, Storrs, CT, USA
e-mail: Andre.Jang@uconn.edu

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contain traces of blood glucose. The feasibility of adopting these emerging technologies in the commercial market is discussed regarding safety, cost-effectiveness, data management, and accuracy.

Keywords Blood glucose monitoring · Diabetics · Non- or minimally invasive · Optical · RF/Microwave · Electrochemical · Targeting areas · Physiological human body fluids

1 Introduction

Diabetes mellitus, commonly referred to as diabetes, is a disease in which the body does not produce or properly use insulin, causing high blood sugar levels over a prolonged period. This chronic disease is among the top leading causes of death globally that require long-term medical attention [1]. Often, diabetes can lead to many serious medical problems. These include blindness, kidney disease, nervous and circulatory system disease, limb amputations, stroke, and cardiovascular disease (CVD) [2, 3]. According to data from the 2020 National Diabetes Statistics Report, diabetes was the seventh leading cause of death in the United States, and an estimated 34.2 million children and adults or 10.5% of the United States population, including 7.3 million undiagnosed people—2.8% of all U.S. adults have diabetes. The estimated direct and indirect costs of diabetes-related health care in the United States have risen to approximately $327 billion annually in 2017 from $188 billion in 2007, a $90 billion in direct medical costs. Diabetes is a disproportionately expensive disease; in the United States, the individual medical cost per person associated with diabetes increased from $8417 to $9601 between 2012 and 2017. In 2017, the individual cost of health care was $16,750 for diabetes, while about $9600 of this amount was attributed to diabetes [4, 5].

The recent multi-center NIH studies have indicated that the health risks associated with diabetes are significantly reduced when the blood glucose levels are well and frequently controlled, indicating that it is prudent to measure the blood glucose as often as five or six times a day. Thus, it is very important that proper monitoring be done by diabetics at home or work [6]. At present, all existing home blood glucose monitoring methods require drawing a blood sample by piercing the skin (typically, on the finger). This method strongly discourages a patients' compliance and has serious drawbacks because the procedures are invasive [7].

Additionally, a recent Mayo Clinic report listed 10 ways to avoid diabetes complications. Their recommendations included: (1) Commit to managing your diabetes. (2) Do not smoke. (3) Keep your blood pressure and cholesterol under control. (4) Schedule regular physicals and eye exams. (5) Keep your vaccines up to date. (6) Take care of your teeth. (7) Pay attention to your feet. (8) Consider a daily aspirin. (9) If you drink alcohol, do so responsibly. (10) Manage your stress [8]. However, not included in this list are just as important as regular exercise and choosing water as your primary beverage.

2 Alternative Physiological Body Fluids to Blood

Since a non-invasive method of monitoring blood glucose would present major advantages over existing invasive techniques, many research groups have attempted to propose numerous attractive alternatives in terms of non- or minimally invasive glucose-sensing techniques within the physiological glucose concentrations (18–450 mg/dl) in human blood. These approaches have demonstrated promising results through in/ex vivo and in vitro experimental/clinical glucose evaluations. Through our previous study, we attempted to review the number of emerging non- or minimally invasive techniques and methods and provided a comprehensive list in terms of applying alternative physiological body fluids as opposed to blood [9].

Physiological body fluids are highly complex mixtures of a variable concentration of cells, proteins, macromolecules, metabolites, small molecules, including glucose [9, 10]. Although blood is the most commonly studied body fluid and is considered as the gold standard medium for detecting glucose concentration, other emerging biological body fluids such as interstitial fluid (IF), urine, sweat, saliva, or ocular fluids, are more accessible due to the significant advance of nanotechnology. The amount of glucose contained in the biological body is proportional to its concentration in the blood. These fluids have been utilized as attractive alternative sample media for non-invasive continuous monitoring. The glucose level in these body fluids is identical to the glucose concentration in the blood plasma. Table 1 summarizes the comparison and contrast of the key aspects, including glucose concentration for diabetics and non-diabetics, pH level, and time lag of the various physiological body fluids under the current review.

Blood has been the gold-standard medium for glucose monitoring since measurements carried out in this fluid were first introduced in 1953 [25, 26]. Blood is

Table 1 A summary of relevant glucose concentrations, time lag, and pH values measured in physiological body fluids of diabetics and non-diabetics

Body fluid	Glucose concentration for non-diabetics (mg/dl)	Glucose concentration for diabetics (mg/dl)	pH level	Time lag (min)
Blood	70–130 [2, 11]	36–720 [2, 11, 12]	7.35–7.45 [10, 12]	–
Interstitial fluid	65–118 [13, 14]	35.8–400 [12–14]	7.20–7.40 [10, 12]	~10 [14, 15]
Urine	10.8–27.1 [16, 17]	50.1–100 [16, 18]	4.50–8.00 [10, 12]	~20 [16, 19]
Sweat	1.1–1.98 [10, 12, 20]	0.18–18.0 [10, 12, 20]	4.60–6.80 [10, 12]	~20 [18]
Saliva	4.14–10.3 [12, 21, 22]	9.91–31.9 [21–23]	6.20–7.40 [10, 12]	~15 [23]
Ocular fluids	1.8–9.0 [18, 24]	9.01–90.1 [18, 20, 24]	6.50–7.50 [10, 12, 24]	~10 [10, 24]

Time lag is the time required to diffuse blood from the capillaries to the tissues [9]

complex plasma containing metabolites and electrolytes (sodium, potassium, chloride, calcium, bicarbonate, glucose, urea, and creatinine) [10]. The sensor using electrochemical/amperometric enzyme electrodes and transducers, employed the non- or enzyme glucose oxidase (GOx) and glucose dehydrogenase (GDH) utilizing the biochemical reaction, has become the most popular and commercially available blood glucose monitoring method in the market because of its suitable sensitivity, wide selectivity, good reproducibility, and easy manufacturability at relatively low cost, although it is an invasive method [26]. Several non-invasive methods are used to detect and monitor the glucose level in the blood, including Absorbance spectroscopy such as Near and Mid Infrared spectroscopy, Raman spectroscopy, Photoacoustic spectroscopy, Fluorescence spectrophotometry, Bio-impedance spectroscopy, Optical coherence tomography, and Thermal emission spectroscopy [27–37].

Interstitial fluid is the extracellular fluid that fills the spaces between most of the body's tissue cells and makes up a substantial portion of the liquid environment of the body. It has significant potential for medical diagnostics as it closely resembles blood plasma in composition but contains less protein [10, 38]. Since tiny molecular biomarkers are exchanged as biochemical information between blood and subcutaneous ISF through diffusion, the correlation between ISF and blood can be used to indirectly obtain the diagnostic information of patients. Methods for monitoring glucose via the skin have become very popular in recent years, where these approaches have been developed to counteract the challenges associated with patient compliance and invasive monitoring. Some of these approaches include Reverse iontophoresis, Electrochemical methods, Electromagnetic techniques, Metabolic heat conformation, Microwave resonator-based technique, Sonophoresis, and Bio-impedance spectroscopy [39–47].

Urine is a commonly collected sample for clinical and nonclinical testing, especially due to the ease of collection, usually without invasive procedures. Urine is composed of inorganic salts and organic compounds, including proteins, hormones, and a wide range of metabolites, including glucose [10, 48]. It is related to applying an enzyme and nanomaterials-based biosensor as important methods for monitoring glucose concentration within the physiologic range, including Colorimetric biosensing utilizing Enzymatic nanomaterials, Laser-generated photonic nanosensor, and Photonic crystal-based biosensor [48–51].

Sweating is a primary biological role of thermoregulation. Sweat is considered one of the most accessible body fluids for glucose detection. Sweat is easily accessible for sampling with sufficient quantities and rapid reproduction compared to all other body fluids. Sweat is an acidic electrolyte-rich fluid, and its production is induced by exercise, resulting in the secretion of metabolites, such as lactate, glucose, alcohol, and uric acid [10, 12]. More recent studies suggest a direct correlation between sweat and blood glucose concentration, although glucose levels in sweat are of a much smaller concentration than those in blood. Wearable sweat-based continuous glucose monitoring biosensors include non- or Enzyme-based electrochemical techniques, Optical fiber long-period grating (LPG), and Electrochemically enhanced

iontophoresis integrated with feedback transdermal drug delivery module are under development [43–45, 52–55].

Saliva is increasingly recognized as an attractive diagnostic fluid because it can be collected non-invasively without employing specific devices or trained personnel. More recent studies investigated and confirmed a significant correlation between salivary and blood glucose levels in diabetics and non-diabetics. Saliva is a complex mixture of 99.5% water and 0.5% electrolytes (amylase, lipase, mucin, glycoproteins, glucose, and antimicrobial enzymes) [10, 56]. Saliva can be utilized as an alternative to blood and can be monitored by a non-invasive measuring salivary glucose. Some non-invasive techniques for saliva glucose monitoring have been studied include Enzyme-based electrochemical/Amperometric/Colorimetric nano-biosensor and Functionalized carbon nano-tube FET/organic electrochemical transistor [23, 43–45, 56–61].

Ocular fluids include tears, aqueous humor, and vitreous humor, which are promising fluids because the glucose concentration of ocular fluids is highly correlated to blood glucose. Monitoring the glucose concentration in the fluids is considered a relatively new technique that is a worthwhile alternative to invasive methods for repetitive or continuous monitoring. Ocular fluids excreted from the body as an extracellular fluid contain glucose water, mucin, lipids, lysozyme, lactoferrin, lipocalin, lacritin, immunoglobulins, glucose, urea, sodium, and potassium [10, 12, 23]. Research working towards non-invasive monitoring methods of glucose in the ocular fluids consists of Chronoamperometric technique, Electrode/electrochemically embedded contact lens, CMOS/Amperometric needle-type electrochemical method, Optical coherence tomography (OCT), Fluorescence spectrophotometry, Ocular spectroscopy, and Optical polarimetry [62–68].

3 Emerging Non- or Minimally Invasive Glucose Monitoring Techniques

Through the literature search for the current review, we learned that techniques for non- or minimally invasive monitoring glucose via the skin had become the most popular approach in recent years, where these methods have been developed to counteract the challenges associated with patient compliance and invasive monitoring [18, 27]. The description and target areas of the leading approaches are presented in Table 2, mainly classified as Optical technology, including Absorbance spectroscopy, Raman spectroscopy, Photoacoustic spectroscopy, Optical coherence tomography (OCT), Fluorescence spectrophotometry, Ocular spectroscopy, and Metabolic heat conformation. The availability of the non- or minimally invasive glucose monitoring devices in the market is also shown in Tables 2, 3 and 4, respectively. Some devices have been withdrawn from the market due to inaccuracy, unreliability, inconsistency,

Table 2 Summarizes the principle and target areas/body fluids of the latest specialized approaches in terms of emerging non- or minimally invasive glucose monitoring techniques after mainly classifying categories as optical technology

Optical technology		
Specific technique	Description	Target areas (body fluids)
Absorbance spectroscopy[a,b,c]	Measures transmittance, reflectance (including diffuse reflectance), and interaction of the light when directed over the sample tissues for analytical purposes. Near-infrared absorption spectroscopy (**NIR**) uses a beam of light with 750–2500 nm. Mid-infrared absorption spectroscopy (**MIR**) uses 2500–10,000 nm, which are focused on the body to determine glucose concentration within tissues. The light and sample tissue interactions produce molecular-specific vibrational information of the absorption and scattering phenomenon in the infrared spectral domain [12, 27, 28]	Fingertip, palm, forearm, inner lip, and earlobe (blood and interstitial fluid) [12, 27, 28]
Raman spectroscopy[b,c]	Applies a spectroscopic technique using the scattering phenomenon of monochromatic light to observe vibrational and rotational states within molecules. When single-wavelength light hits a target, it produces scattered light traveling in all directions. The degrees of scattering due to glucose molecules are purely dependent on their concentration levels [27, 29]	Finger, arm, eye, wrist, hand (ocular fluids and blood) [27, 29]
Photoacoustic spectroscopy[b,c]	Employs laser pulses with a wavelength that is absorbed by a specific molecule in the body fluid to produce localized heating, dependent on the specific heat capacity of the targeted tissue, and measures the effect of light absorption to detect a glucose concentration in blood based on the velocity of ultrasonic waves generated in glucose solution by the photoacoustic principal [30, 69]	Finger, arm, and earlobe (blood and interstitial fluid) [12, 30, 69]

(continued)

Table 2 (continued)

Optical technology		
Optical coherence tomography (OCT)[c]	Includes optical methods with ultrasound, impedance, and heat capacitance. This technique applies the principles of low coherence interferometry with coherent radiation and determines the glucose concentration present by detecting the changes of optical characteristics of bio-tissues at micrometer resolutions, including intensity/delay of the reflected/scattered and transmitted light upon interaction with the subcutaneous tissue by employing an interferometer with coherent light, with a wavelength between 800 and 1300 nm [31, 32]	Forearm and eye (ocular/interstitial fluids and blood) [31, 32]
Fluorescence spectrophotometry[a,c]	Applies the principle of fluorescent light emission of an ultraviolet laser beam (340–400 nm) after absorbing radiation of a different energy level which causes a wavelength difference. The measurement of the concentration of glucose molecules in the blood is conducted utilizing a sensitive protein and intensity of fluorescence which are proportional [33, 34]	Finger, abdomen, upper arm, and eye (blood, ocular/interstitial fluids) [33, 34]
Ocular spectroscopy[c]	Utilizes the specially designed hydrogel-based disposable tear glucose-sensing contact lenses, which change color depending on the glucose concentrations. The fluorescence response from the lenses can be monitored using simple excitation and emission detection devices and serves as the tool for blood glucose detections from the tears [35, 36]	Eye (tears) [35, 36]

(continued)

Table 2 (continued)

Optical technology		
Metabolic heat conformation[a,b,c]	Measures physiological parameters associated with the generated quantity of metabolic heat dissipation, blood flow rate of local tissue, and degree of blood oxygen saturation between the skin and contacted conductor corresponding to the glucose concentration by employing the system consisting of thermal, humidity, infrared, and optical sensors [41, 42]	Fingertip, earlobe, and forearm (blood and interstitial fluid) [12, 41, 42]
Optical polarimetry[c]	Applies the phenomenon of the optical activity, which is a certain rotation of the polarized plane of the incident light (400–780 nm) passing through the aqueous humor of the eye and glucose, known as an optically active molecule. When the light is passed through the cornea and across the anterior chamber of the eye, the polarimetric signal that is converted into a time-varying voltage by the photodetector varies linearly with changes in glucose concentration [67, 68]	Eye (ocular fluids) [67, 68]

[a]Commercially available
[b]Withdrawn from the commercial market
[c]Under development

Table 3 Summarizes the principle and target areas/body fluids of the latest specialized approaches in terms of emerging non- or minimally invasive glucose monitoring techniques after mainly classifying categories as electrochemical technology

Electrochemical technology		
Specific technique	Description	Target areas (body fluids)
Reverse iontophoresis[a,c]	Applies a passage of low electrical current to enhance the transport of both charged and polar, neutral compounds across the skin to drive ions between two electrodes from the interstitial fluid and onto the skin's surface, where they can be analyzed in terms of glucose concentration. Transdermal reverse iontophoresis (RI) is a non-invasive technique that can sample body fluids across intact skin to achieve the purpose of blood glucose detection [39, 40]	Wrist, arm, and leg (sweat and interstitial fluid) [12, 39, 40]
Enzymatic electrochemical electrode[a,c]	Analyzes the glucose oxidation that took place in the presence of GOx, oxygen, and water to form gluconic acid and hydrogen peroxide. The hydrogen peroxide is then electrochemically oxidized at the electrode, which converts glucose oxidase activity into an analytical electrical signal in proportion to glucose concentration based on the rate of glucose oxidation by dioxygen, measured by the formation of hydrogen peroxide. Highly selective enzymatic reactions can be used to diminish the influence of electroactive interfering species [43, 44]	Finger, arm, and skin (blood, saliva, urine, tears, interstitial fluid, and sweat) [10, 12, 43, 44]

(continued)

Table 3 (continued)

Electrochemical technology		
Non-enzymatic amperometric electrode[a,c]	Uses metal–organic framework (MOF)-based nanocomposites and provides an alternative to an enzymatic method, which is impossible to implant into the human body for the long term and in situ monitoring since the immobilized enzyme would degrade quickly. Cost-effective non-enzymatic amperometric glucose biosensors with high sensitivity, selectivity, and stability could be commercially more feasible [43, 45, 46]	Finger, arm, eye, and skin (blood, saliva, urine, tears, interstitial fluid, and sweat) [12, 43, 45]
Colorimetric detection[a,c]	Determines the glucose concentration with the aid of a color reagent. When glucose is oxidized by glucose oxidase into D-gluconic acid plus hydrogen peroxide, the hydrogen peroxide is then detected with a highly specific colorimetric probe. In an enzymatic analysis, the color reaction is preceded by a reaction catalyzed by an enzyme [48, 49]	Finger, arm, eye, urine, and skin (sweat, tears, and urine) [12, 19, 48, 49]

[a]Commercially available
[b]Withdrawn from the commercial market
[c]Under development

Table 4 Summarizes the principle and target areas/body fluids of the latest specialized approaches in terms of emerging non- or minimally invasive glucose monitoring techniques after mainly classifying categories as RF/microwave technology

RF/microwave technology		
Specific technique	Description	Target areas (body fluids)
Microwave resonator-based[a,c]	Utilizes the interaction between electromagnetic waves and biological tissues since microwaves' reflection, transmission, and absorption are closely related to the dielectric properties of tissues, where the dielectric constant varies with glucose fluctuations. Microwaves can easily penetrate biological tissues of millimeter thickness, so glucose concentration variation in ISF has much higher sensitivity on phase and magnitude response of the sensor than its variations in blood [70–74]	Finger, hand, wrist, arm, and earlobe (interstitial fluid and blood) [12, 70–74]
Bio-impedance spectroscopy[a,c]	Measures the glucose-dependent electrical impedance changes as a function of frequency and provides proof of a change in blood impedance with glucose level fluctuations. Impedance is recorded as a frequency bypassing RF current between 100 Hz and 100 MHz across human biological tissues and skin. The glucose molecule is measured by its concentration-dependent interaction with red blood cells [75–78]	Thumb, upper arm, wrist, and abdomen (interstitial fluid and blood) [12, 69, 75, 77, 78]
Sonophoresis[a,c]	Uses low-frequency (20 kHz) 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, where it is measured transdermally with the combination of the low-profile cymbal array and an electrochemical glucose sensor consisting of amperometric electrodes and a novel glucose oxidase hydrogel. This technique creates micropores in the skin to enable the interstitial fluid containing glucose to come outside [69, 79]	Arm, wrist, and abdomen (interstitial fluid and blood) [12, 69]

[a]Commercially available
[b]Withdrawn from the commercial market
[c]Under development

and other issues. Meanwhile, others have never been introduced due to their unclear circumstance issues.

Electrochemical technology includes Reverse iontophoresis, Enzymatic electrochemical electrodes, Non-Enzymatic amperometric electrodes, and Colorimetric detection method, all presented in Table 3.

RF/Microwave detection technology includes Microwave resonator-based method, Bio-impedance spectroscopy, and Sonophoresis, presented in Table 4.

4 Conclusions

This study aimed to present and review the latest specialized approaches in emerging non- or minimally invasive glucose monitoring techniques after mainly classifying categories as optical, electrochemical, and RF/Microwave methods. These glucose monitoring methods convert the weak optical, electrochemical, or electromagnetic signal to glucose concentration. We also investigated the non- or minimally invasive glucose monitoring techniques which utilize various physiological body fluids as an alternative diagnostic medium. These techniques have a great potential for monitoring blood glucose levels as they increase accuracy, selectivity, sensitivity, and reliability of the measurement that would satisfy medical use criteria and meet the expectation as a less expensive alternative.

Our current study learned that optical and microwave methods have advantages over electrochemical methods because they offer purely non-invasive and continuous monitoring without stimulating discomfort to the human body. However, invasive or minimally invasive electrochemical glucose meters with more advanced enzyme and electrode materials have significantly improved because they are considered more reliable and affordable. Electrochemical diagnostic devices are equipped with software-based analytical performance and data management, capable of updating device features without recalibration, and less expensive. Therefore, the current dominating electrochemical glucose sensors in the commercial market will not be easily replaced even if they are invasive until promising non-invasive glucose meters with the more sensitive, efficient, intelligent, robust, and reliable measurements that can satisfy medical use criteria is introduced to the market.

5 Future Trends

This review covers the research progress of the latest technologies and their methods of non- or minimally invasive glucose monitoring with alternative physiological body fluids such as interstitial fluid, urine, sweat, ocular fluids, and saliva instead of blood glucose concentration. Considerable progress has been made in developing viable non- or minimally invasive glucose sensors in recent years due to devoted research efforts and the revolution of biomaterials, medicine, nanotechnology, and computer

science. Although there have been many dedicated research efforts with numerous progressions to develop a non- or minimally invasive glucose monitoring sensor, there are still several obstacles to achieving acceptable glucose monitoring because of the complicated nature of the operation and measurement process.

Through our more recent searches, we also learned that several non- or minimally invasive glucose monitoring devices using optical, electrochemical, and RF/microwave technologies had been introduced commercially in the market, and others are close to commercializing. However, we concluded that these methods are still far from being clinically reliable to meet market expectations. They require further systemic development and clinical evaluations due to a lack of consistency, stability, accuracy, and reliability. The remarkable advances in an emerging trend to integrate a series of functional modules, data mining algorithms, wireless communications, machine learning algorithms, and computational signal processing led to significant achievements allowing the creation of new hypotheses that enable deeper understanding and further investigations of non- or minimally invasive glucose monitoring devices. AI-driven wearable monitoring devices may be introduced to the current market, making it possible to collect a diverse range of continuous physiological signals to accurately monitor the following: glucose levels in diabetics, sweat, anxiety, heart rate, blood pressure, nutrition, calorie intake, and COVID-19 related symptoms in advance. Further continued development of sophisticated decision support hardware and software systems will yield great opportunities to introduce more reliable and affordable non-invasive glucose monitoring systems in the broad commercial market for medical use within the very near future.

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Conflict of Interest None.

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Sunghoon Jang is an Associate Professor and the chair of the CET department at NY City College of Technology of CUNY. Dr. Jang received a master's degree from the New Jersey Institute of Technology (NJIT) in Electrical and Computer Engineering and a doctoral degree in Biomedical Engineering from University of Connecticut. His research areas of interest are biomedical sensors and instrumentations, signal processing, control systems, optoelectronics, and laser optics. Professor Jang joined the ETET department at City Tech in 2003 as an Assistant Professor and became a chair and faculty member of the CET department in 2014. His current interests lie in non-invasive and minimally invasive optical and electro-chemical glucose sensors for diabetics. He has published numerous research papers and received research/academic grants within his areas of interest.

Yu Wang is an Associate Professor and the program coordinator of the Computer Engineering Technology (CET) department at New York City College of Technology of the City University of New York, where she teaches Electrical Circuits, Digital Systems, Data Communications, Software Interface, Microcomputer Systems Technology. Dr. Wang received a doctoral degree in Electrical Engineering from the CUNY Graduate Center and joined the CET department at City Tech in 2009. Her research areas of interest are engineering education, biomedical sensors, optoelectronics, real-time modeling systems, embedded system design, deep neural network, and machine learning.

Andre Jang is currently a graduate Ph.D. student at the University of Connecticut pursuing a doctoral degree in Physiology and Neurobiology. He received a master's degree in Physiology and Biophysics from Georgetown University in 2019. He received his B.S. in Biological Science from the University of Connecticut in 2018. His current research interests include studying drosophila olfaction and electrophysiology.

Current Status of Non-invasive Diabetes Monitoring

Sreedevi Paramparambath, Ishwar Maruti Islampure, T. Sabitakala, Muni Raj Maurya, Hajar Morsy, Swathi Yempally, Suresh Muthusamy, Senthil Kumar Ramu, Santhiya Pandiyan, Raghad Abuznad, Alaa Elsafiahmed, Aeshah Alruwaili, Muna Ibrahim, Peter Kasak, Ravikumar Ramlu Vidule, Ankanagari Srinivas, and Kishor Kumar Sadasivuni

Abstract In routine life, diabetes is usually measured by an invasive process. Although this technique is accurate, there are many drawbacks, especially if you need to take multiple readings regularly. Hence**,** it is necessary to develop a highly reliable non-invasive diabetes screening technology that is better than the pre-existing invasive technique**.** In recent investigations, human serums such as tears, saliva, urine,

S. Paramparambath · H. Morsy · S. Yempally · R. Abuznad · A. Elsafiahmed · A. Alruwaili · M. Ibrahim · P. Kasak · K. K. Sadasivuni (✉)
Center for Advanced Materials (CAM), Qatar University, 2713 Doha, Qatar
e-mail: kishorkumars@qu.edu.qa

H. Morsy
e-mail: hm1604839@qu.edu.qa

R. Abuznad
e-mail: Ra1704974@qu.edu.qa

A. Elsafiahmed
e-mail: sabithakalatatituri@jntuh.ac.in

A. Alruwaili
e-mail: aa1604608@qu.edu.qa

M. Ibrahim
e-mail: mi1701758@qu.edu.qa

P. Kasak
e-mail: peter.kasak@qu.edu.qa

I. M. Islampure
Robokidz Eduventures Pvt Ltd, Pune, Maharashtra, India

T. Sabitakala
Department of Chemistry, Jawaharlal Nehru Technological University, Hyderabad, India
e-mail: sabithakalatatituri@jntuh.ac.in

M. R. Maurya
Department of Mechanical and Industrial Engineering, Qatar University, Doha, Qatar

S. Muthusamy
Department of Electronics and Communication Engineering, Kongu Engineering College, Erode, India

K. K. Sadasivuni et al. (eds.), *Advanced Bioscience and Biosystems for Detection and Management of Diabetes*, Springer Series on Bio- and Neurosystems 13,
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and respiratory secretions have been found to reflect the presence of glucose in it. These factors increase the possibility of non-invasive blood glucose level estimation. Diabetes was a rare condition in past years compared to recent times, but this has become more widespread in recent decades due to changes in the eating habits and lifestyles mismanagement of human beings. In some cases, there are chances of diabetes in newly born infants. When the body cannot produce enough insulin or cannot use its insulin, blood glucose levels rise in the body. As a result, invasive methods for measuring blood glucose levels are used, which may cause major or minor problems for patients in the long run of life. To address this issue, a low-cost, non-invasive approach for detecting diabetes is urgently required by our society. Many new technologies have been researched and implemented; each has its advantages and disadvantages. The present chapter gives a qualitative overview of various non-invasive glucose monitoring systems beneficial for diabetic patients.

Keywords Invasive · Non-invasive · Diabetes · Spectroscopy · NIR

1 Introduction

In contrast to typical invasive laboratory testing of the blood sample, self-monitoring of glucose level provides a current scenario of diabetes with a continuous, dependable, and reliable approach for determining blood glucose concentration. Checking glucose levels frequently using invasive methods is a critical process for the treatment of diabetes. This invasive technique assists patients in preventing and detecting hypoglycaemic and hyperglycaemic conditions. Many commercial blood glucose monitors present in the market require a small drop of blood to be taken by pricking the skin with a lancet, which is generally a fingertip (often called a fingertip test). These are the intrusive blood glucose monitors that cause the patients a huge amount of discomfort because they are likely to be punctured several times a day for checking their blood glucose level.

Depending upon the amount and condition of the sample, human inaccuracy during sample collections, calibration errors, humidity, and poor cleanliness in the testing region, might increase the proportion of mistakes while using invasive monitoring techniques [1].

S. K. Ramu
Sri Krishna College of Technology, Coimbatore, India

S. Pandiyan
Computer Science and Engineering, Anna University, Chennai, India

R. R. Vidule (✉)
Department of Chemistry, SSGM College, Loha, Dist. Nanded, Maharashtra, India

A. Srinivas
Department of Genetics & Biotechnology, Osmania University, Hyderabad, India

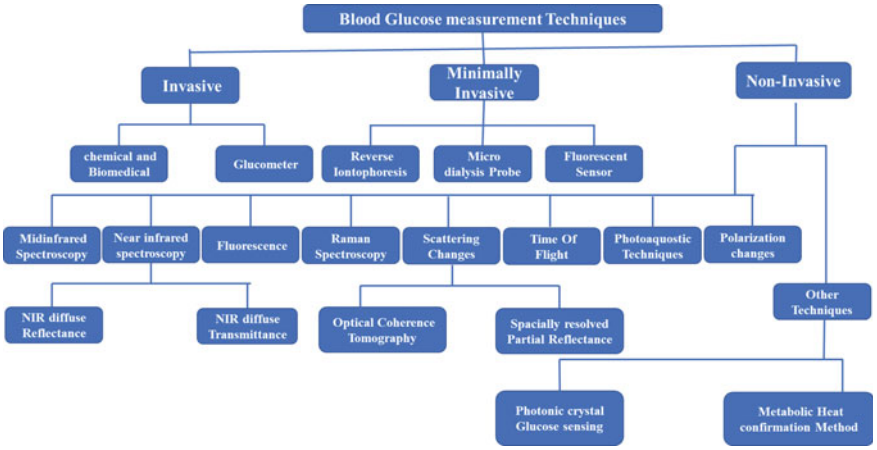

Fig. 1 Flowchart of blood glucose monitoring techniques

The non-invasive approach, a recent technology, requires glucose signals from the body. Non-invasive methods avoid "finger pricking" and help continuously monitor blood glucose levels. Techniques such as applying fluorescent light to the body in a specific location, in addition to the techniques involving the implantation of a sensor in the subcutaneous tissue, lead to a major disadvantage: the interference of nearby signals such as ultraviolet and visible light with the process.

Another approach that uses optical beams to detect glucose signals is acoustic spectroscopy. However, this process suffers from scattering effects, resulting in insensitivity. Near-Infrared (NIR) spectroscopy is also one technique that can also be used to measure the level of glucose in blood [2]. The level of glucose can also be evaluated with the help of multi-modal spectroscopy IC which combines impedance spectroscopy (IMPS) and multi-wavelength near-infrared spectroscopy (fNIRS) [1]. In Fig. 1 the flowchart of different blood glucose measurement techniques is shown.

This technology employs indirect dielectric properties of the tissue surrounding the blood and the precision of the glucose levels obtained by the suggested microchip to eliminate various systemic sounds.

A recent method for identifying diabetes is to use the Gabor filter to analyze face contour features [3]. Human respiration can potentially be used to diagnose diabetes. This indicates a good link with blood sugar since human breath includes acetone, which can be analyzed simply by exhaling it directly into the monitoring device [4]. In Fig. 2, the non-invasive glucose monitoring techniques are shown.

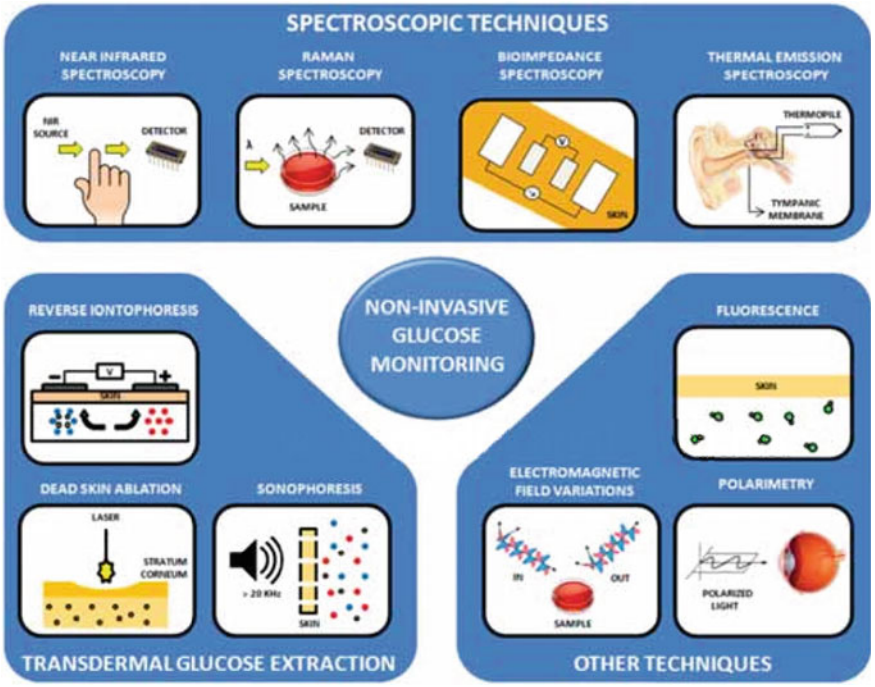

Fig. 2 Different non-invasive glucose monitoring. Reproduced with permission from [5] CC By © 2019 by Gonzales et al., Licensee MDPI, Basel, Switzerland

2 NIR Spectroscopy

The spectroscopical region of 12,500–4000 cm^{-1} belongs to Near-infrared (NIR) region, and its wavelength is 800–2500 nm. Both wavenumber and wavelength are being considered in the present chapter. The region in-between IR and the visible region is NIR spectroscopical region. Generally, NIR spectroscopy deals with reflection, emission, diffusion, and light absorption. NIR spectroscopy has advanced characteristics that have played a significant role in basic and applied science applications over the last two decades [6]. In the spectral range of near-infrared, the ability of light to penetrate soft tissues and biofluids is relatively high (>0.5 mm) as, compared to visible light and ultraviolet light, it scatters less. Apart from this, this technique can achieve both reflection and transmission for the sensing measurement of light [7]. The mathematical formulation for calculating sample absorption is done by Beer-Lambert law (Eq. 1) from the already known thickness and concentration.

$$I = I_o 10^{(-l.\varepsilon.c)} = I_o e^{-l.\mu_a} \tag{1}$$

where I is the intensity of light at depth within the absorption medium W/cm^2, initial light intensity is represented by I_0 (W/cm^2), absorption depth is represented by l, ε is the molar attenuation coefficient or molar extinction coefficient (L/mmol cm), it depends on the structure of absorbing molecules and the wavelength of incident light. Absorbing molecules concentration is represented by c (mmol/L). The absorption coefficient μ_a is proportional to the product of c and ε.

This model showcases the transmitted/reflected intensity of light as a function of concentration, the thickness of the sample, and absorption coefficient. In contrast, the scattered light effect is ignored in this phenomenon. Log(I_0/I) is used to define absorbance [8]. NIR absorption spectroscopy can quantify the glucose absorbance and its dependence on wavelength in the aqueous medium. Incident light absorption by water must be considered as it is the most abundant species in biofluids. Two absorption peaks, one between 1350 and 1520 nm and the other in-between 1790 and 2000 nm, are revealed in the NIR spectrum range for water. To measure glucose in the NIR range, wavelength windows in the range of 700–1100 nm, 1500–1850 nm, and 2000–2400 nm can be used [9–11].

On the contrary, light absorption in a shorter wavelength range is lower for water. So to obtain selective NIR spectroscopic results with the minimization of interfering effects of water, one should essentially use shorter wavelengths [7, 12]. Figure 3 shows the spectra recording equipment. The equipment consists of a NIR spectrometer, a light source, and a fiber optical measuring head. In NIR spectrometer, a 128 pixels InGaAs photodiode array detector is attached to a glass block, and it uses a polychromator with a holographic imaging diffraction grating. According to the modified Beer's equation, near-infrared diffused reflection difference spectra are obtained at the skin tissue to constantly forecast the blood glucose content, which is proposed and investigated without multivariate analyses. The difference spectra are presumed to be generated from four primary elements in the human skin (glucose, protein, fat, and water) and a scattering equivalent component called the baseline. As a result, the morphological similarity of the absorption spectrum between glucose and baseline is one of the roots of inaccuracies in predicting blood glucose levels in the near-infrared region. An artificial component integrated with baseline and fat is revealed when extracting the glucose components from the distinction spectra at baseline using fat's specific wavelength. It is predicated on the notion that a change in skin scattering induces both the variation in fat contribution and leads to baseline development.

We can reduce the blood glucose prediction mistakes by using the imaginary component. In contrast to multivariate analysis methods, the estimation procedure of blood glucose substances from observed reflection spectra is transparent, making it easier to evaluate the causes for fluctuations and contributions of the components in the observed reflection spectra. In Fig. 3, the typical blood glucose level profile is shown. Using radial-basis neutral networks (RBF) and partial least-squares regression (PLS), the calibration coefficient of matrices is calculated.

Glucose measurements are interfered with by chemical and physical parameters such as albumin, triglyceride, temperature, and pressure variation. Environmental changes such as variations in humidity, carbon dioxide, atmospheric pressure, skin

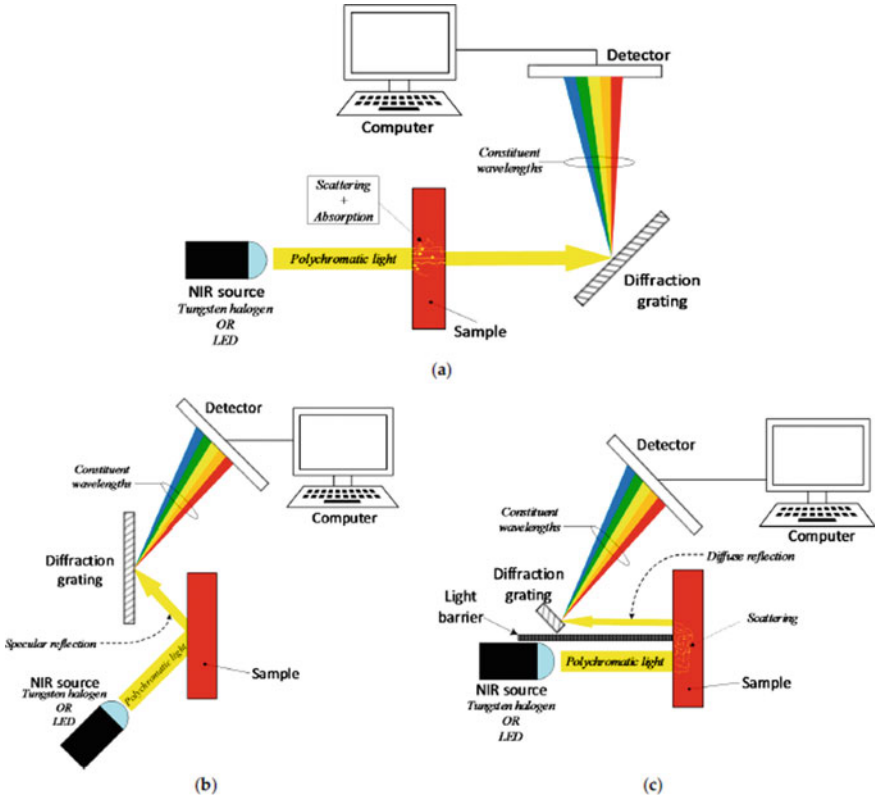

Fig. 3 Schematic representation of the three modes of NIR spectroscopy. **a** Transmittance mode. **b** Reflectance mode. **c** Interactance mode. Reproduced with permission from [5] CC By © 2019 by Gonzales et al., Licensee MDPI, Basel, Switzerland

hydration, and temperature also cause errors. The proposed technique may become a convenient tool for interpreting non-invasive blood glucose monitoring using near-infrared spectroscopy [13].

Rolamjaya Hotmartua et al. used NIR spectroscopy for Glucose detection from the earlobe. They first carried out the test by varying glucose concentration from 50 mg/dl to 2 g/dl, and 2nd test was carried out directly in the earlobe [14]. Samman et al. researched glucose monitoring for about 169 days and analyzed the accuracy as well as stability of the calibration method [15]. In brief, it can be said that the application of NIR spectroscopy in combination with regression analysis helps quickly to detect the glucose levels in a non-invasive manner, thereby providing an additional tool for the early detection of diabetic problems [9].

3 Raman Spectroscopy

The degree of scattering of monochromatic light is determined by Raman spectroscopy which is based on the Raman effect. Scattered light that travels in all directions is produced when a single wavelength light hits the target. Using the imaginary component can reduce the error in predicting the blood sugar level. Unlike multivariate analysis, this method makes it clearer to calculate blood sugar levels from the observed reflectance spectrum, making it easier to estimate the reason for the change and the component contribution in the reflectance spectrum. Rayleigh scattering occurs in visible radiation when the scattering is elastic. The phenomenon is known as Raman scattering if the scattering is not elastic [16]. The schematic representation of Raman scattering is shown in Fig. 4.

Raman shift is termed for such wavelength differences. The Raman shift represents the difference between the initial and final vibrational states of molecules under study [17]. The vibrational and rotational states of molecules are dependent on Raman spectroscopy. The functional group's vibrational modes are shown in the peaks of Raman spectra. It consists of a lens that seizes the scattered radiation. It also filters the radiation and allows the Raman scattered radiation to the detector for getting sensed. The signals are processed by computer and provide Raman shift correspondingly.

Raman spectroscopy is a favorable non-invasive biomedical method and analyses the problems associated with metabolism. For example, clinical tests and self-monitoring of glucose levels based on a finger prick technique blood sample are no longer painful. Raman spectroscopy is based on the elastic scattering of photons by certain molecules in the sample. The energy shift of the scattered photons is determined by the bonds of the interacting molecule, thereby resulting in molecular fingerprints. The advantages and limitations of Raman scattering for glucose monitoring are shown in Table 1.

It also has important benefits in biomedical diagnostics, including non-invasiveness, a short procurement time, and the capability to offer quick results. It has been shown that Raman spectroscopy and principal component analysis (PCA)

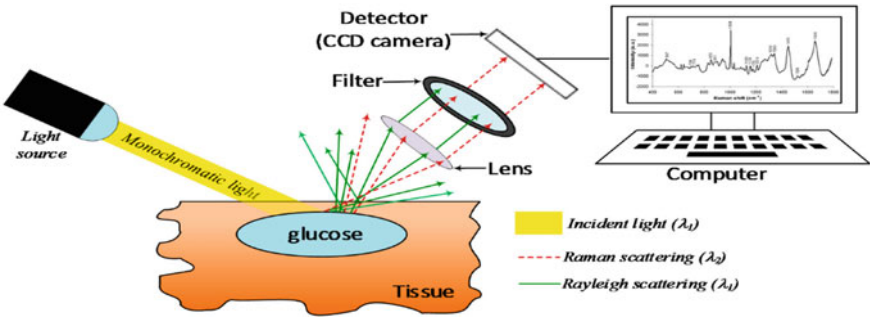

Fig. 4 Schematic representation of Raman spectroscopy. Reproduced with permission from [5] CC By © 2019 by Gonzales et al., Licensee MDPI, Basel, Switzerland

Table 1 The pros and cons of glucose detection using Raman spectroscopy

Pros	Cons
• Less susceptible to variations in temperature • Moderate sensitivity to water • It can be used on any surface, including opaque substrates, to measure scattered light • The elevated degree of specificity	• Susceptible to interference by other molecules such as hemoglobin • Intensity and laser wavelength are unstable • The collection time is long • Prone to noise interference (low signal to noise ratio), fluorescence, and turbidity

paired with support vector machine (SVM) has proven to be effective in classifying glycated hemoglobin levels using in vivo techniques [18].

4 Bio-impedance Spectroscopy

The bio-impedance analysis is a non-invasive, low-cost, and widely utilized method for determining body composition and assessing clinical status. There are numerous ways of interpreting the measured bio-impedance data. Apart from that, there are numerous applications of bio-impedance in the assessment of body composition and the evaluation of clinical status. In addition, bio-impedance spectroscopy is being used in various ways in healthcare institutions, including disease prognosis and monitoring of vital signs. Thus, we feel that this warrants a review of the most underlying facets and forecasts healthcare applications of bio-impedance spectroscopy [19].

The bio-impedance analysis is a low-cost, non-invasive method for evaluating body composition and helps in monitoring of clinical state. There are varieties of techniques to interpret measured bio-impedance data and a variety of bio-impedance applications in body composition assessment and clinical status assessment.

A wrist glucose monitor based on impedance spectroscopy has been invented. It is shown in Figs. 5 and 6. This monitor uses the skin as a dielectric to sample an LC resonance circuit data. There are numerous approaches for interpreting measured bio-impedance data and bio-impedance applications in body composition and clinical state assessment. The drawbacks and advantages are shown in Table 2. Bio-impedance is also used in healthcare facilities for various applications, such as disease prognosis and vital sign monitoring [20].

5 Thermal Emission Spectroscopy

Thermal Emission Spectroscopy (TES)—the based device is a novel, non-invasive hand-held BG monitor having the same dimensions and ease of use as an ear thermometer. Still, this technique is with more technological breakthroughs. The gadget

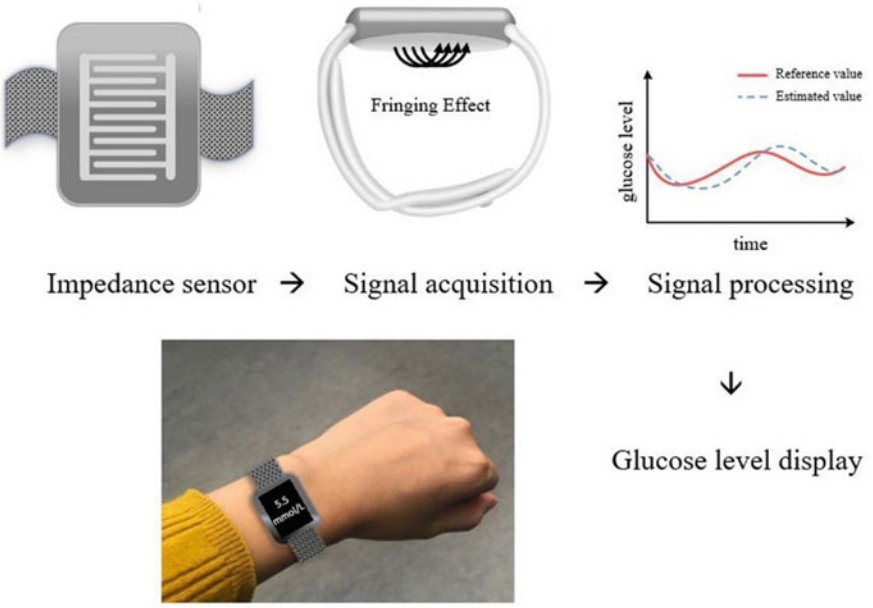

Fig. 5 Graphical abstract of glucose detection using bioimpedance spectroscopy. Reproduced with permission from [5] CC By © 2019 Gonzales et al., Licensee MDPI, Basel, Switzerland

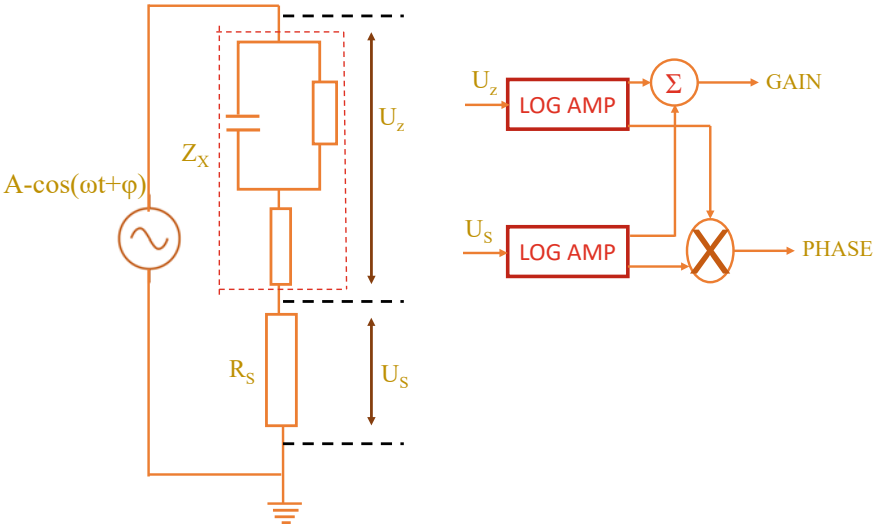

Fig. 6 Bioimpedance model measurement and architecture of gain-phase detector

Table 2 Advantages and disadvantages of glucose detection using bioimpedance spectroscopy

Advantages	Disadvantages
• Relatively low cost • Effort less investigation on skin	• Sensitive to changes in motion and temperature • Vulnerable to water content and sweat • Affects the cell membrane due to physiological conditions

is passive, and, in this technique, chronic external radiation does not injure the human tissues.

This gadget will help individuals with diabetes to live better lives since it will boost patient BG testing, which will lead to improved glycaemic management and lesser complications related to diabetes. Thermal emission spectroscopy (TES) detects infrared signals produced by changes in glucose content in the human body. According to this technique, the natural mid-infrared emission of the human body, particularly the eardrum, is regulated by the state of the emitting tissue. Its selectivity is based on the same premise as the absorption spectroscopy technique used for measurement analysis [21]. Figure 7 represents the pictorial representation of the principle of thermal emission spectroscopy for glucose detection.

The detection of glucose level using a non-invasive prototype based on thermal emission in the mid-IR spectral area was measured satisfactorily. Individual daily

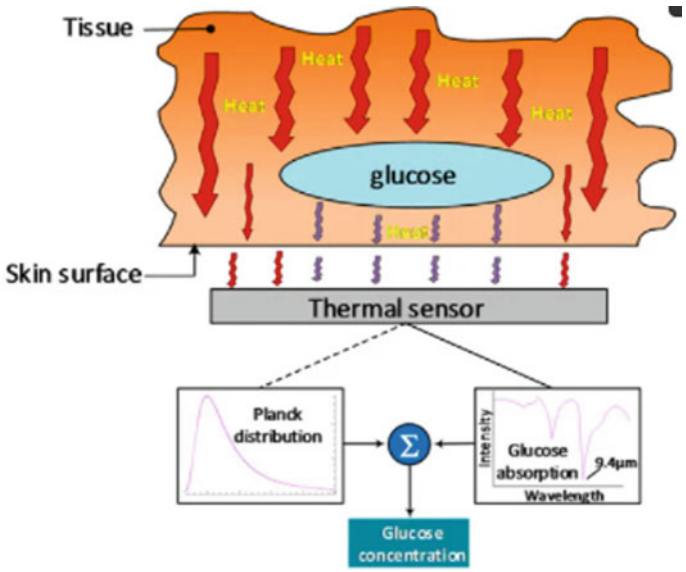

Fig. 7 Principle of thermal emission spectroscopy. Reproduced with permission from [5] CC By © 2019 by Gonzales et al., Licensee MDPI, Basel, Switzerland

Table 3 Pros and cons of glucose detection using thermal emission spectroscopy

Pros	Cons
• It is a passive method • There is no threat of tissue damage • Excellent selectivity due to the well-defined glucose spectra at 9.4 μm • There is no need for calibrating	• Sensitive to changes in motion and temperature • Radiation intensity is vulnerable to tissue thickness • It may not be efficient for sensing sudden variations of glucose

calibrations are unnecessary with this technology, which is one of its benefits [21]. One disadvantage of this technique is that the strength of infrared radiation emitted by an eardrum is influenced by its thickness and temperature. The other drawbacks and advantages of this method for glucose detection are shown in Table 3. Although the clinical outcomes acquired with TES are encouraging, they do not yet meet clinical accuracy criteria [22].

6 Optical Polarimetry

Optical polarimetry works on the principle of chiral molecules, i.e., the plane of polarization is rotated by the molecules. The chiral molecule glucose can rotate the plane of polarisation of a beam of light by an angle α in the clockwise direction. This glucose detection method is one of the basic techniques of non-invasive technology. When the beam of polarized light is incident on the glucose solution, the plane of polarization of the incident light is rotated by the presence of glucose.

At present, the sum of glucose level is comparative to the directional angle concerning the original incident direction formed by the polarisation direction [23–27]. The rotation amount is proportional to the optical path length, the laser beam wavelength, the temperature, and the analyte concentration.

This wavelength will usually appear in the NIR upper region and the optical band is in the lower region (approximately 780–400 nm). The polarimeter measures the plane of polarised light when it passes through the sample. The pictorial representation of optical polarimetry is shown in Fig. 8. The maximum intensity of light is identified by a photodetector when the electric field rotation is comparable with the polarization axis of the analyzer. The photodetector cannot detect light when the polarization angle is perpendicular to the electric field rotation angle [28, 29].

The application of optical polarimetry in the skin is not feasible as the scattering of light in tissue and skin is high, decreasing the glucose's optical rotation [30]. The optical polarimetry can be used in the eyes anterior chamber as it has a good optical property [30, 31]. Eye glucose monitoring is shown in Fig. 8. For this method, a satisfied error accuracy is not obtained even though this method can be detected by visible light, easy operation, and obtaining results [32–34]. Currently,

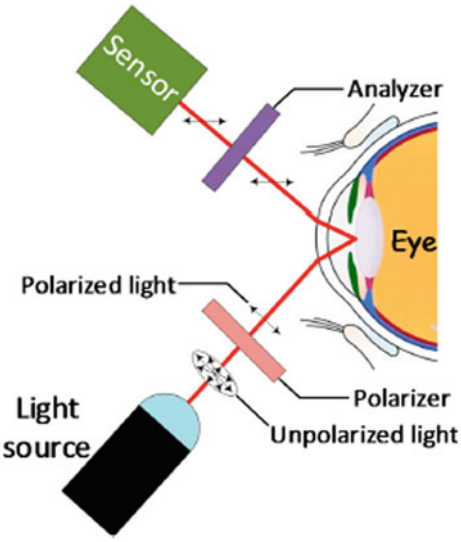

Fig. 8 Schematic representation of optical polarimetry in the eye for glucose detection. Reproduced with permission from [5] CC By © 2019 by Gonzales et al., Licensee MDPI, Basel, Switzerland

there are two new mechanisms for resolving the interference issues of the birefringence of the polarization of glucose overlooked in blood. Dual-wavelength polarizer and birefringence compensator are the two mechanisms used to resolve this issue. Dual-wavelength polarimetric glucose detection is shown in Fig. 9.

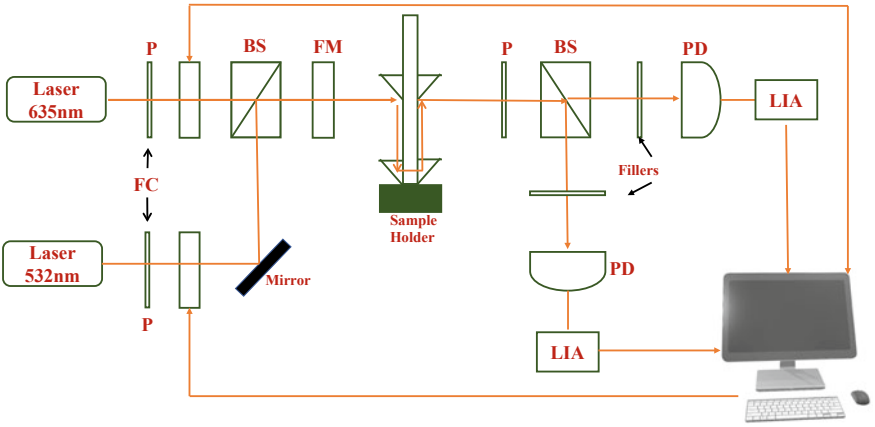

Fig. 9 Dual-wavelength polarimetric glucose detection

7 Fluorescence

Fluorescence technology is associated with the principle of fluorescent light emission. This fluorescent light emission results in stock shift, wavelength difference due to the effect of the light emission.

Unlike optical approaches, this approach of utilizing fluorescence requires contact between sample and sensor. Recently, new techniques have been developed for analyzing glucose and vitamin A using field instruments. Pickup et al. [47] studied glucose monitoring using the intrinsic tissue fluorescence. This technique utilizes the product of glucose metabolism, nicotinamide adenine dinucleotide phosphate (reduced) (NAD(P)H), a fluorescent cofactor. The test was carried out in in-vivo analysis, and later they were studied in vitro. The fluorescence sensitivity is highly required as the glucose concentration in the fluid is in the micromolar range.

The fluorescence techniques can be categorized into affinity-binding and glucose oxidase (GOx) based sensors. GOx based sensors have a certain limitation as the results depend not only on the concentration of glucose but also on the oxygen tension under in-vivo conditions.

Fluorophores, a specialized molecule that release fluorescent light with certain characteristics, are proportional to the analyte concentration under study. Some fluorophore molecules can bind with glucose molecules directly, but they are associated with interference, irreversibility, analyte depletion, and low selectivity. Therefore, the use of intermediatory molecules like receptors binds with glucose molecules more effectively, leading to changes in their local properties reversibly. This results in fluorescence alteration [67]. Different types of receptors are used for this such as boronic acid derivatives, enzymes, and glucose binding proteins, which are nature-derived and fabricated synthetic materials such as quantum dots and carbon nanotubes.

Fluorescence resonant energy transfer (FRET) has gained much attention based on binding assays. The energy transfer in this technique occurs between the donor and acceptor molecules, the light-sensitive molecules. When the acceptor molecules bind with glucose, the bond between acceptor and donor gets disrupted, increasing fluorescence due to less electron sharing. This is shown in Fig. 10.

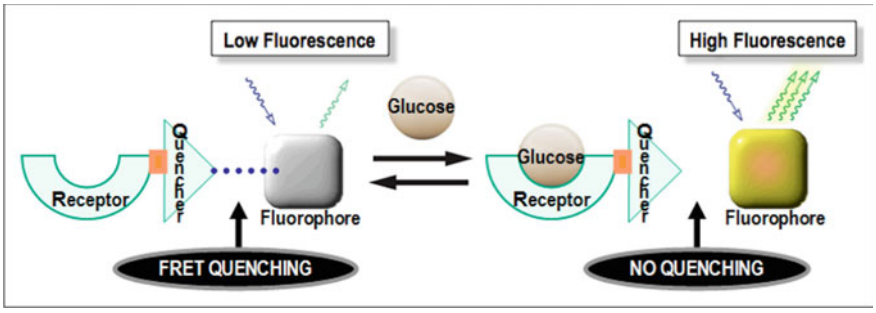

Fig. 10 Fluorescence glucose monitoring

The FRET and fluorescence lifetime techniques were used to measure glucose concentration by Lakowicz and co-workers [50]. They used reagents such as maltose-insulin-malachite green and ruthenium-Con A to fabricate a similar sensor. The fluorescence lifetime and fluorescence intensity of ruthenium dye is increased with an increase in glucose concentration. The advantage of this type of fluorescence sensor is that they are highly specific and highly sensitive to the analyte under study. Apart from that, it also eliminates the potential interferences. The drawback of this technique is the short lifespan of the fluorophore, foreign materials in biological media which can cause potential toxicity, etc.

There are so many other techniques that can non-invasively detect glucose concentration, such as Metabolic Heat Conformation (MHC), Photoacoustic Spectroscopy (PAS), Optical Coherence Tomography (OCT), Millimeter and Microwave Sensing, etc. Table 4 shows the list of recent research developments on MI and NI techniques in Glucose detection. Table 5 compares non-invasive and minimally invasive glucose monitoring devices that are currently accessible or about to be released in the market soon. Figure 11 depicts the position of non-invasive and minimally invasive methods and devices for monitoring glucose in the spectrum.

8 Conclusion

The scientific advancement of non-invasive glucose monitoring technologies in recent years is discussed in this chapter. Optical, microwave, and electrochemical methods are the three types of non-invasive blood glucose monitoring technologies available. The advantages of optical and microwave technologies, in general, are their non-invasive nature and ability to monitor continuously without causing discomfort to the human body. In terms of detection, there are still certain issues, such as sophisticated detection means, harsh detecting components, a time-consuming detection procedure, high detection equipment needs, and significant background signal interference. Future research will see if other physical characteristics and other indicators linked to blood glucose may be integrated to increase the accuracy of non-invasive skin glucose test results.

Table 4 List of recent research on MI and NI techniques for monitoring glucose levels

Institution	Technology	Comments	Target
Polytechnic University of Catalunya	NIR spectroscopy Photoplethysmography	• Principle: the relationship between PPG waveform and glucose levels • No calibration needed • Linear response even in hypoglycemia and hyperglycemia	Finger
Karunya University	NIR spectroscopy Photoplethysmography	• Blood viscosity, breathing, emotional state, and autonomous nervous system are linked to glucose levels • Analysis was done with machine learning	Forearm and finger
Tohoku University	MIR spectroscopy Trapezoidal multireflection	• Suitable for areas without a thick skin layer • Tuned at 8658 nm • Sensitive to contact pressure	Oral mucosa Inner lips
ETH Zurich	MIR spectroscopy Photoacoustic detection	• It uses Quantum Cascade lasers (QCLs) • Wavelengths: 8.47–10 nm	Forearm
RSP Systems	Raman spectroscopy	• Glucose sensing at a critical depth in the skin • Accuracy affected by time-lag • λ: 830 nm	Hand Palm
Electronics and Telecomm Research Inst. of Korea (ETRI)	Photoacoustic spectroscopy	• Insensitive to skin secretions • Acoustic signal: 47 kHz • λ: 8–10.4 nm	Fingertip
National Cheng Kung University (NCKU)	Optical coherence tomography	• It senses optical rotation angle (γ) and depolarization index (Δ) using the Mueller model • Increase in glucose increases γ and decreases Δ	Fingertip

(continued)

Table 4 (continued)

Institution	Technology	Comments	Target
Caltech	Millimeter-wave transmission	• Based on waveguides and patch antennas • f: 15–25 GHz, 16–36 GHz	Ear lobe
Cardiff University	Microwave split-ring resonance	• Glucose level change shifts resonant frequency • Up to 17.5 mm depth penetration	Abdomen
University of Bath	Reverse iontophoresis	• Based on the electro-osmotic flow principle • ISF extracted through hair follicles • Independent from skin characteristics variance • Some skin irritation is associated	Skin
Ulsan National Inst. of Science and Technology (UNIST)	Contact lenses—enzymatic detection	• Measures the level of glucose in tears • Electrodes embedded in the contact lens • The lag time is between 10 and 30 min • Interference from other electroactive species	Tears
University of Maryland	Contact lenses fluorescence	• Based on a glucose-silicone hydrogel • Decrease of fluorescence with the increase of glucose • It works with fluorophore Quin-C18 • Long storage seems not to affect the lens' response	Tears
KTH Royal Institute of Technology	Microneedle-enzymatic detection	• The measurement taken within the dermis • Based on passive fluid extraction • Microneedle length: 700 μm	Forearm

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Table 5 Comparison table of non-invasive and minimally invasive glucose monitoring devices

Device	Technology	Target	Type	Accuracy	Status
Combo glucometer (Cnoga Medical)	NIR spectroscopy (combination of four LEDs and four sensors to analyze absorption and scattering pattern) λ: 625, 740, 850, 940 nm	Finger	NI NCGM	PEG Zone A:96.6% Zone B: 3.4% MARD: 14.4%	Available
NBM-200G* (OrSense)	NIR spectroscopy (occlusion spectroscopy) λ: 610, 810 nm	Finger	NI Point-of-care	CEG Zone A: 69.7% Zone B: 25.7%	Dropped
HELO Extense (world global network)	NIR spectroscopy	Finger	NI NCGM	N/A	Available
GlucoTrack (integrity applications)	Combination of: • Ultrasound • Thermal • Electromagnetic sensing	Earlobe	NI NCGM	PEG Zone A: 62.4% Zone B: 37.6% MARD: 19.7%	Available
GlucoWise (MediWise)	mm-wave transmission spectroscopy f: 60 GHz	Hand	NI NCGM	N/A	Under development
SugarBEAT (NemauraMedical)	Reverse iontophoresis	Upper arm	MI NCGM	MARD:13.76%	Waiting for CE approval
Symphony (echo therapeutics)	Sonophoresis	Skin	MI CGM	CEG Zone A: 81.7% Zone B: 18.3% MARD: 12.3%	Unknown
WizmiTM (Wear2b Ltd)	NIR spectroscopy	Arm wrist	NI NCGM	CEG Zone A: 93% Zone B: 7% MARD: 7.23%	Proof of concept
LTT (light touch technology)	MIR spectroscopy/optical parametric oscillation λ: 6–9_m	Finger	NI NCGM	N/A	Under development
K'Watch (PK vitality)	Enzymatic detection/microneedles	Arm wrist	MI CGM	N/A	Pre-clinical tests
Eversense® (Senseonics)	Fluorescence	Upper arm	MI CGM	MARD: 14.8%	Available

(continued)

Table 5 (continued)

Device	Technology	Target	Type	Accuracy	Status
GlucoGenius	Metabolic heat conformation λ: 660, 760, 850, 940 nm	Finger	NI NCGM	N/A	Unknown

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Fig. 11 The chart with location of non-invasive and minimally invasive methods and devices for glucose in the frequency spectrum. Reproduced with permission from [5] CC By © 2019 Gonzales et al., Licensee MDPI, Basel, Switzerland

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Ms. Sreedevi Paramparambath is working as Research Assistant at the Center for Advanced Materials (CAM), Qatar University. She joined CAM in September 2020. She completed her master's in chemistry from Amrita University in 2019 and her bachelor's degree in chemistry from Calicut University in 2017 from India. During her masters, she has published 2 journal papers in the Materials today journal and has participated in two international conferences. After joining CAM, she is currently working on 3D printed Biosensors, Corrosion etc. she is a meticulous, focused, hardworking, keen learner who assists students and executes it well. She has a keen interest in the field of scientific research. She completes tasks diligently and focuses on quality and not only achieving but exceeding in the research works. She possesses good skills, making the researchers' job easier and more efficient.

Ishwar Maruti Islampure is working as System Engineer at Infosys Ltd., Pune Maharashtra. Having core interest in writing different topics related to use of information technology for the betterment of human beings and to keep environment eco-friendly.

Dr. T. Sabithakala is working as Assistant Professor in Dept. of Chemistry, Jawaharlal Nehru Technological University, Hyderabad, India. Dr. T. Sabithakala works in the areas of Inorganic and Organic Synthesis, synthesis of ligands and its binary and ternary metal complexes and characterization methods, the use of a wide array of spectroscopic and electrochemical tools to understand the biological, electrochemical and magnetic properties, synthesis of coordination polymeric complex and study of its Crystal structure, magnetic properties, DNA binding and electrochemical studies, separation of Regio isomers by using preparative HPLC.

Dr. Muni Raj Maurya received his Ph.D. in Engineering Science (2020) from CSIR-National Physical Laboratory, New Delhi, India. He is currently a staff researcher at the Centre for Advanced Materials, Qatar University. His research interests include investigation of the optical properties of nanocomposites semiconductor materials and the development of optically active nanostructures. His current research is mainly focused on nanomanufacturing, and device designs for sensor and nanophotonic applications.

Ms. Hajar yosry Morsy is a student at Qatar University, College of Science, Department of Chemistry. She has published two research articles on both journals on molecules and healthcare. She worked for two years in the Research & Graduate Studies Office-Center for Advanced Materials, also worked on two UREP projects at Qatar University. She got many certificates for academic excellence at Qatar University, as well as voluntary certificates.

Swathi Yempally M.Sc. (Physics) India. She received a bachelor's degree from Osmania University College for Women specializing in electronics. She has graduated with master's in physics from Osmania University with a specialization in Solid State Physics. She has two years of teaching experience after her graduation in INDIA. She is interested in designing and developing Volatile Organic Compounds (VOC) Sensors and advanced materials for various applications. She has assisted undergraduate students in UREP (Undergraduate Research Experience Program) and contributed to the development of VOC sensors to detect diabetes at Centre for Advanced Materials (CAM) QATAR UNIVERSITY.

Suresh Muthusamy received the bachelor's degree in Electrical and Electronics Engineering and the master's degree in Power Electronics and Drives from 2009 and 2011 from Anna University, Chennai and Anna University, Coimbatore, respectively. Currently, he is working towards his Ph.D. degree in Electrical Engineering at Anna University, Chennai, in Hybrid Renewable Energy Systems. Since 2011, he has been working as Assistant Professor Senior Grade in the Department of Electronics and Communication Engineering at Kongu Engineering College, Perundurai, Erode. He published more than 65 research articles in reputed international journal publications like Elsevier, Springer, Taylor and Francis, Wiley, ASME, etc. and indexed in SCI, SCIE, Scopus and Web of Science. His interests include hybrid renewable energy systems, power electronic converters, hybrid electric vehicles and battery management systems.

Senthil Kumar Ramu received the bachelor's degree in Electrical and Electronics Engineering from Anna University, India, in 2011. He got the master's degree in Power Electronics and Drives in 2013 from Anna University, Chennai, India. Also, he obtained his Ph.D. degree in 2021 from Anna University, Chennai, India. He is presently working as Assistant Professor at Sri Krishna College of Technology, Coimbatore, India. He published 37 research articles in various reputed international journal publications, including Elsevier, Wiley, Taylor, Francis, etc. His current research interests include power electronics and drives, soft computing techniques, Renewable energy systems, Electric vehicles, and signal processing Techniques.

Santhiya Pandiyan received the bachelor's degree in Computer Science and Engineering and the master's degree in Computer Science and Engineering during 2013 and 2015 from Anna University, Coimbatore and Anna University, Chennai, respectively. Currently, she is working towards the Ph.D. degree in Computer Science and Engineering at Anna University, Chennai, in Machine Learning. She worked as Assistant Professor in the Department of Computer Science and Engineering at Paavai Engineering College (Autonomous), Namakkal, for about 5 years 7 months. Since August 2021, she has been working as Assistant Professor in the Department of Computer Science and Engineering at Kongu Engineering College (Autonomous), Perundurai, Erode. She published 7 research articles in various international journals like Taylor & Francis and presented 5 papers in international conferences. Her areas of interest include Machine Learning, deep Learning, Internet of Things, Data structures, etc.

Ms. Raghad Abuznad is under bachelor's degree in Qatar University doing major Chemistry and Earth sciences. Her area of interest working in Material science and electrochemistry, she is doing her graduation project on the effects of temperature on smart material. She attended an interview with the Nobel prize winner in chemistry 2016, Prof. Fraser Stoddart was held at Texas university. She entered two UREP with different topics. She is a hard worker.

Ms. Alaa Elsafiahmed is a senior undergraduate student in Qatar University doing major in Chemistry and Earth Sciences. Her area of interest is working in Electrochemical sensors, and she is doing her graduation project on Catalytic Oxidation of Carbon Monoxide. She participated with two posters in Qatar University Annual Research Forum & Exhibition, and she is a member of the American chemical society. She met the winner of the Noble prize in chemistry 2016, prof. Frasr Stoddart in an interview held on Texas A&M University. She aims to present her research in international conferences and work in Center for Advanced Materials.

Ms. Aeshah Alruwaili is a senior student at Qatar University. Alruwaili, is a Chemistry major student. She is currently applying her internship as a chemistry teacher in Qatar schools. Alruwaili was known by her contributions in the chemistry group events and workshops in the science collage. As well as her interest in research specifically in physical chemistry and organic chemistry departments over her studying years, in addition to her knowledge related to computer science programming languages as a part of her interest and contribution in the university studying years, as well as her peer tutoring experience in chemistry courses.

Ms. Muna Ibrahim is under bachelor's degree in Qatar University doing major Chemistry and Earth sciences. Her area of interest working in Nanotechnology and electrocatalysts, she is doing her graduation project on electrocatalysts for oxygen evolution reaction. She participated on competition for the best Research poster, she also attended an interview with the winner of Nobel prize in chemistry 2016 Prof. Fraser Stoddart was held on Texas university. She aims to present her Research in international conferences by American chemical society as she is a member of this society.

Dr. Peter Kasak is a technical manager and research associate professor in the Center for Advanced materials at Qatar University. Dr. Peter Kasak obtained his Ph.D. in 2003 at the Department of Organic Chemistry at Comenius University in Bratislava. In 2001 he joined the group of Prof. R. J. M. Nolte at Radboud University Nijmegen. He was a Lisa Meitner postdoctoral fellow at the University of Vienna before starting research at Polymer Institute at Slovak Academy of Sciences, where he was a Senior researcher. From 2012, he has worked in the Centre for Advanced Materials at Qatar University. His main research interest is in developing stimuli-responsive systems, membranes, particles, nanostructures, (nano)composite and hydrogels; modification and characterization of nanopatterned surface for electrochemical impedance spectrometry to be applied for early detection of several diseases and prevention of biofouling. Furthermore, he has long-term experiences with heterogeneous and homogenous catalysis and electrocatalysis. His experiences include the formation of catalysts and polymers for the aqueous environment and electrochemical processes. A broad range of interest is also in modification material to improve super wettability, anticorrosive, biocompatible and anti-biofouling properties of materials and study of the mechanism of free radical polymerization.

Dr. Ravikumar Ramlu Vidule Asst. Professor, Dept. of Chemistry, & working as IQAC Coordinator, Shri Sant Gadge Maharaj Mahavidyalaya, Loha, Dist. Nanded. (MS)-431708, India. Mail id: ravidule@gmail.com, 80007840827. Published Fifteen Research papers in Reputed Journals. Participant in Academics and co-curricular activities. Actively engage and participating on environmental awareness programs by writing articles and delivering talks on All India Radio. Delivered talk in National and International conference, workshops, Refresher and Orientation courses. Currently started the campaign in India and abroad for the awareness of use of, MICROBEADS in PCCP (personal care cosmetic products). Writing articles to stop the use of single used plastic in newspapers. Wrote the chapters in the book: Blended Classroom: A Method for Encouraging Effective Global Education Learning Environment", Impact of Covid-19: In Teaching Learning Process in India. Challenges to The Academic Domain In The Aftermath Of Covid-19. Impact Of Covid-19 On Higher Education, Impact of COVID-19 on Textile Industry. Also, a core interest in Microbeads and other aspects been invited for the lecture. Invited as a speaker in Sacred Heart College, Kochi "Microbeads: A Threat for life on Earth" In Flasgship programme Prof. K.V. Thomas Endowment "National Seminar on New Frontiers in Materials and Environmental Sciences." 28th Jan. 2020, Invited as a Resource person in Pratibha College of Commerce and Computer Studies Pune College as "State Level Seminar on Emerging Environmental Challenges and its sustainable Approaches." 7–8th Feb. 2020, Given Short Presentation as a young researcher at Dr. T R Ingle memorial National Symposium, "Trends, Research

and Innovation in Chemical Sciences (TRI-2020), Feb 14–15, 2020, Organized by Dept., of Chemistry, SP College, Pune., An invited lecture (Webinar) “Nehur Yuva Kendra Ministry of Youth affair and Sports, Dist. Thiruvanthpuram, Kerala” conducting an internship for MSW students “Blended Learning as a new approach to social work.” Given talk dated on 30 Mar 2021: Talk title: Microbeads: A Threat for Life on Earth in the International conference on Materials of the Future: Smart Applications in Science and Engineering, Qatar University, Qatar, Emergent Materials Journal and Chemistry Africa Journal, Springer.

Dr. Ankanagari Srinivas Dept. of Genetics & Biotechnology, Osmania University, Hyderabad, Telangana 500007. India. He obtained his Master’s in Genetics from Osmania University and did his Doctorate in Life Sciences from University of Hyderabad. He had carried out several regulatory and non-regulatory pharmaceutical bioavailability and bioequivalence of drugs in Phase I and Phase II clinical trial projects of pharmaceutical industry. He was involved in analysis of biological samples for drugs/metabolites concentration and development, validation, and implementation of bio-analytical methods. He is currently engaged in academic and research activities at Department of Genetics & Biotechnology, Osmania University.

Dr. Kishor Kumar Sadasivuni is currently working as a group leader of Smart Nano Solutions at Center for Advanced Materials, Qatar University. Dr. Kishor’s research has its roots from the analytical chemistry he mastered during his Master’s degree in Andhra University, India. He received his Ph.D. in Materials Science and Engineering from the University of South Brittany at Lorient, France, in 2012 under Professor Yves Grohens and Professor Sabu Thomas. He has enormous knowledge and valuable experience in his field owing to over 12 years of active research experience of 12 years. Dr. Kishor has more than 250 research articles published in international peer-reviewed journals with a total citation of 5500 and h-index 41. He is also the author of 20 book chapters and the editor of 8 books. Dr. Kishor is an expert in nanomaterials engineering, especially sensing and flexible electronics. He has a keen interest in developing different devices based on smart materials by engineering IoT. Some of Dr. Kishor’s inventions are protected by 2 US patents and 2 Indian patents, and presently 5 patent disclosures have been submitted by him. His strong academic background and passion for research are remarkable and reflected in his fast-paced career growth. Dr. Kishor’s enthusiastic and sincere approach towards research works is reflected in the forms of various grants and awards offered to him. He is a group leader and is presently the lead principal investigator for 11 research projects, covering the NPRP, UREP, IRCC grants of Qatar National Research Fund and the

Qatar University. He is also involved in three other research grants as the principal investigator, summarizing a total grant amount of 3M$. Dr. Kishor is a team player and has collaborated actively with researchers (more than 450 co-authors as evident from the Scopus data) in several disciplines of computer science, biomedical sciences, industrial engineering, and electrical engineering from all over the world (USA, France, South Korea, Oman, Spain, Italy, Australia, Malaysia). Dr. Kishor's achievements have been recognized by several awards such as Tyre & Rubber Industry Leadership Acknowledgement Awards (TRILA); Young Research Scholar of the Year 2017. He has been included in the world's top 2% scientists according to a list compiled by Stanford University in the year 2019, and for this, he was recently honored by the QU.

A New Solution for Non-invasive Glucose Measurement Based on Heart Rate Variability

Marjan Gusev

Abstract Diabetes is one of the biggest global health problems, and its prevalence is increasing. According to the World Health Organization, 422 million people were diagnosed with diabetes in 2014. This number is expected to have grown in the last years. Correspondingly, the expenses for glucose monitoring and treatment are a growing problem. In order to address this, we introduce a new system for glucose level monitoring with an ECG monitor. The electrocardiogram is sent to a smartphone for temporary storage and calculation of heart rate variability parameters. Further on, using sophisticated machine learning methods, the system calculates the ability of a human to control the glucose level. The three most prominent advantages to using an ECG sensor, as opposed to a traditional (invasive) glucometer, are that (1) it is a cheaper long-term solution; (2) it is a non-invasive measurement method, and (3) it offers a more holistic picture of the patient's health because it tracks the function of the heart and glucose at the same time—for the same price. The market potential is estimated to be the size of the market for glucometers, which was 613$ million in 2016 and is expected to reach 915$ million by 2021. This paper presents a new solution for non-invasive glucose measurement based on Heart Rate Variability, elaborating functional details and the technological concept of how our product is realized.

Keywords ECG · Heart monitoring · Continuous glucose monitoring · Diabetes monitoring · Edge computing

1 Introduction

The autonomous nerve system (ANS) controls the inner body organs, including the functions of the heart and pancreas. Indirectly ANS regulates the heart rate and the glucose level simultaneously. Recent studies show a big correlation of glucose levels

M. Gusev (✉)
Faculty of Computer Science and Engineering, Ss Cyril and Methodius University in Skopje, Skopje, North Macedonia
e-mail: marjan.gushev@finki.ukim.mk

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with heart rate variability (HRV) [5]. This is the motivation behind our research and product development.

We propose a system comprised of a wearable ECG monitor to obtain an electrocardiogram (ECG) [16] and a smartphone, which processes short and long-term HRV parameters that serve for the analysis of glucose levels, in such a way that will provide relevant information on how a human body controls the blood glucose level. This approach targets diabetic patients and solves their pains from a financial and health-related standpoint.

The International Diabetes Foundation [17] stated that the number of people diagnosed with diabetes is estimated to go up to 628.6 million in 2045, which amounts to 6–7% of the worldwide population [3]. Of those diagnosed in developed countries, approximately 12% have type 1 diabetes, which means that they are by default required to take insulin therapy and use glucometers as a means of managing that therapy. This is the share of the target market we expect to make long-term. That amounts to about 51 million people worldwide in 2017. However, the number of customers is likely to be significantly more as type 2 diabetic patients are often prescribed insulin.

Diabetic patients have to deal with costs from continuous or frequent self-monitoring, as well as costs for blood glucose testing strips (as high as $1 per strip) or continuous glucose monitoring sensors ($350 a month), glucagon ($280), etc. [18]. In addition, diabetic patients present 6–7% of the total worldwide population, according to the International Diabetes Foundation [3].More than 25% of diabetes patient costs are a consequence of cardiovascular disease [4]. Costs are increased for expenses of physician office visits. Table 1 summarizes the problem, how it is solved today and how it can be solved with this solution:The analysis of related health problems of diabetic patients and correlated solutions is presented in Table 1.

The problems tackled within this paper are (1) the need for frequent or continuous glucose measurement and (2) related cardiovascular diseases. The usual way to treat these issues is through frequent finger pricking or continuous glucose meters, along with frequent visits to cardiologists. The newly proposed solution treats both problems with one system. At the same time, the solution offers a device for continuous monitoring of heart arrhythmia and monitors the ability of a human to control the blood glucose level.

The rest of the paper is organized as follows. State-of-the-Art solutions available on the market are presented in Sect. 2. Section 3 specifies the newly proposed solution with a description of the main functionalities and constituting units. Section 4 compares the existing technologies with the newly proposed solution and presents the major impact and benefits of the newly proposed solution. Finally, Sect. 5 gives relevant conclusions and future work.

Table 1 Analysis of related problems and correlated solutions

Problems related to diabetics	How it is solved	This solution
Need to track their glucose level	Invasive glucometer with Non-invasive ECG monitor	Test strips
Spend a lot of money because they need to track glucose levels frequently	Costly specialized devices for continuous measurement	Wearable ECG monitor with a 7-day battery and lifetime expectancy
Four times more likely to have cardiovascular disease	Expensive doctor's appointments	Measure cardiac activity and glucose levels in one device for one price

2 State-of-the-Art Solutions

Almost all of the glucometers sold today use invasive methods. Some methods use an array of small needles that collect blood samples from capillaries, and these are referred to as semi-invasive methods.

Several ideas for non-invasive glucose measurement have recently submitted applications for a patent, and only a few have been realized without recognized commercial success. The real problem with these solutions is that the measurement is activated on-demand. In our approach, this is enhanced by a software agent analyzing the big data concepts of incoming ECG streams, which is our technological value proposition.

There have been several initiatives to the use of non-invasive technology for monitoring glucose levels, including methods that collect interstitial fluids (sweat, saliva, tears, etc.) or are based on analysis of ultrasound, or using nanomaterials, or related-radio signals reflected from the human skin, eye, or similar organs. A nice overview of non-invasive glucose methods is summarized in the following articles [6, 15, 19, 24, 29, 32]. State-of-the-Art of non-invasive methods (existing solutions) includes: Non-invasive ultrasound or spectroscopy (light) technology (GlucoTrack) [20], Thin, flexible filament inserted under the skin to measure glucose every minute (FreeLibre) [11] (invasive), Measuring blood pressure, pulse wave, and vascular tone on two hands (Omelon) [8] (semi-invasive), Measures the blood capillary level by transmitting low-power radio waves sections of the body such as the earlobe or between the forefinger and thumb (GlucoWise) [12] (semi-invasive), Measures through a patch that inserts a sensor needle under the skin and wirelessly transmits results. (Dexcom) [7] (semi-invasive).Illuminates a small area on the patient's arm with near-infrared light, which is then scattered back out through the skin (Diasensor 1000) – not successful [21]. A wristwatch that samples the blood glucose level in an interstitial fluid which is painlessly drawn through the sweat glands via a small electric charge (GlucoW- atch) – not successful [9], and includes a pill-sized sensor implanted in the upper arm for 90 days by an on-body transmitter [10] (implanted–invasive). Note that several huge market players offer products for continuous glucose measurement based on reading the values from conventional glucose devices that work on the analysis of a drop of blood and transmit the solution wirelessly to a monitoring center, including Medtronic [22] or Agamatrix [1]. All these medical devices use invasive or semi-invasive methods instead of our non-invasive solution; besides, we have an unfair advantage since the innovation measures both the heart and glucose. Another benefit about them is that we are a small agile SME team that is ideally suited to developing a new product compared to a large corporation with well-established principles of operation. However, we lack direct sales channels and industry know-how, which external financing sources can achieve.

3 System Description

Our solution introduces a new way for diabetic patients to do continuous real-time self-monitoring at their homes. It is expected to significantly lower the costs of diabetic patients and improve their satisfaction.

3.1 Functional Description

The technological idea is to monitor glucose levels using ECG monitors. They are more affordable, easier to use, last longer, and offer better healthcare for the patient. This method will disrupt the traditional way of glucose measurement, which uses on-demand activation and invasive techniques.

Figure 1 presents the system design of such a solution. A patient will continuously wear a light ECG monitor to measure their glucose level, as illustrated in Fig. 2. For example, it can be worn for up to 7 days without re-charging and even in the unlikeliest places, like the shower. The monitor wirelessly connects to the patient's smartphone via a low-energy Bluetooth connection to send the collected data and limit energy consumption to enable more extended performance.

The smartphone processes the collected information and transfers data to a cloud server as a part of the remote telemedicine solution. The interface for the patient is presented in Fig. 2, displaying a continuous ECG signal, an indication of the heartbeat rate on the top right side, and the glucose level on the top left side.

Given that the patient's smartphone is connected to the Internet, the smartphone application will upload the data to the cloud, where it is accessible by the patient, their doctor, and a caregiver, anytime and from any computer device. Heart state monitoring and the calculations regarding glucose levels are enabled by the monitoring

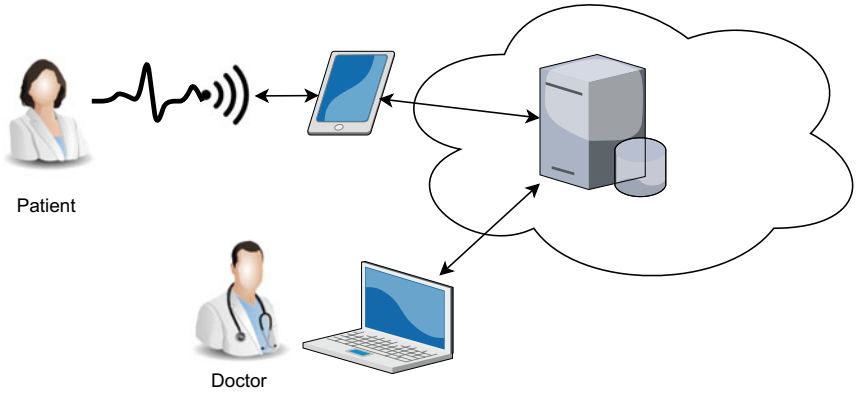

Fig. 1 System architecture of the proposed solution

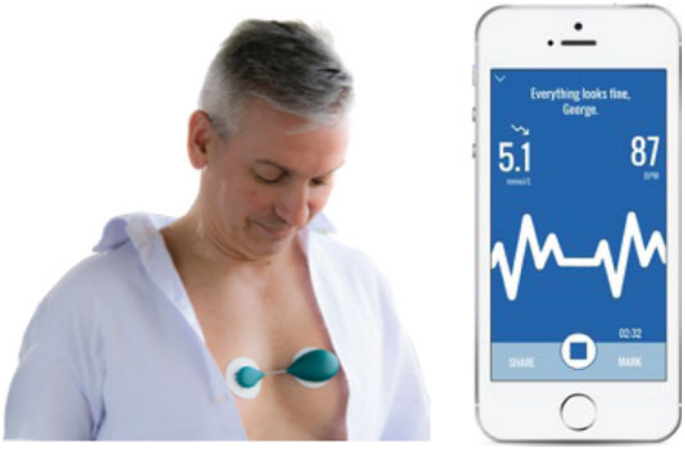

Fig. 2 Wearable sensor and user interface of the proposed solution

technology based on a Software as a service provision, which has been developed within the ECGalert project [16].

The complete solution is part of a *dew computing* solution since processing is located at the edge of the Internet network. At the same time, it allows independent, autonomous performance. In the case of Internet connectivity, it collaborates with the cloud server to exchange information. Cloud server collaboration enables other users to monitor their health status, including caregivers or doctors. This approach is complementary to edge computing, which aims at bringing the computing closer to the user. The dew computing approach brings the computing even closer to the user. The developed algorithms work on a smartphone, and the whole application can be used as an AI-based doctor at the user's pocket.

3.2 Technological Concept

Our early research results prove the dependence of the glucose levels on HRV parameters as a basis of developing algorithms from artificial intelligence, machine learning, and parallel processing to enable the simultaneous processing of multiple data streams with high volumes and speed. In addition, the ECG alert monitoring technology [23] is consistent with the modern trend of cloud computing. Access to measurement results is instant and available from anywhere, and approved by the consumers [2, 14].

Our earlier paper addressed the design issues [13], reflecting the methods to measure ECG targeting the computing architecture behind the new solution. Here we provide details on the technological concepts to develop such a solution.

HRV represents a statistical measure calculated based on heart rate that changes over time as controlled by the ANS. Although most methods to calculate the HRV use information by heart rate monitors, we found that to calculate a more precise HRV parameter which correlates to the ability to control the glucose level needs e more detailed approach and enhanced information about heartbeat types to eliminate the impact of the problems imposed by heart anomalies.

An electrocardiogram (ECG) represents a signal that measures the electrical properties of the working heart. ECG technology is widely used to detect anomalies in the heart by analyzing heart arrhythmia. For example, a ventricular heartbeat may occur earlier than expected since the ventricle initiates it instead of the sinoatrial node. A compensation interval usually follows this, and the heart then continues to beat as controlled by the ANS.

These changes influence the calculation of the HRV parameters. For example, SDNN is one of the HRV parameters that correlate to the glucose control ability is calculated as a standard deviation of time intervals between consecutive pairs of heartbeats. A slight variation from the heart rate will cause a significant indication in the SDNN. The example with the ventricular beat type will be manifested as a difference of both the smaller interval preceding the ventricular beat and the succeeding one.

Classical heart rate monitors realized as wrist devices, or smartwatches can not detect the beat type. Therefore, the wearable single-channel ECG monitors outperform these since they precisely identify the beat type and associated arrhythmia. Consequently, arrhythmia caused by heart malfunction and not reflecting the ANS controlling mechanism must be eliminated in the calculation. This is only possible by methods that analyze the ECGs similar to humans, and therefore, AI-based algorithms take over the detection role in our approach.

We have conducted a lot of research detecting the correlation between various HRV parameters and glucose levels for short-term HRV and instantaneous blood glucose measurements [31], then between 30-min ECG Measurements and average glucose levels [28], or long-term HRV correlation to the average glucose levels [27]. The overall conclusion was that specific long-term HRV strongly correlates to the average glucose levels. In contrast, specific HRV short-term HRV parameters relate to the instantaneous blood glucose levels.

These results were then used to analyze the distribution of HRV parameters [30], remove outliers, and develop machine learning and deep learning methods to detect the ability to control the glucose levels or to estimate the instantaneous plasma glucose level [25]. Measurements of 15 min ECG intervals showed the best R^2 score and R^2 loss function to estimate the blood glucose level with the smallest MSE and RSME errors. The developed solution was based on Adam optimizer and Relu activation function for 3 dense layers with 512 neurons each [26].

The best results to detect the ability to control glucose level range the accuracy validation of 91.96% and F1 score 81.34%, and 74.86% on the testing dataset. The corresponding DL model was developed applying the Z-score outlier removal, optimized by Adam with a learning rate of 0.001 using three hidden layers of 32, 256, and 64 neurons. Manual experiments performed similarly to the automated Auto Keras.

Table 2 Comparison of technology and economic features

Method	Measurement	Monitoring	Access	Price
Invasive methods	On-demand	Once	Local	$$$
Implanted sensors	Continuous	<2 weeks	Local	$$$
Infrared, ultrasound or radio waves	Continuous	<2 weeks	Local	$$
Measuring other physiological parameters	On-demand	>2 years	Local	$
This non-invasive ECG-based solution	Continuous	>2 years	Online	$

The developed prototype achieved our final goal to create a service based on an automated monitoring software agent, which will send estimated related results about the ability of the patient to control the blood glucose levels to a cloud server. This will enable continuous real-time monitoring with alerting features with notification about extreme glucose levels or the inability of a human to control the glucose level.

4 Discussion

Wearable ECG sensors do not cause any harm to the user; they are worn similarly to the clothes. Some users experience allergic reactions on the skin, and they are advised to use electrodes produced by specific antiallergic material.

Table 2 compares the technologies used for glucose measurements. Several features are analyzed for each analyzed method, including the type of measurement activation (on-demand or continuous), monitoring period (once, less than two weeks, or more than 2 years), access to results (local or remotely via the Internet), and price cost estimation per day of usage (small $, medium $$ or large $$$).The benefits of this solution go beyond just improving the customer's life. They also touch the lives of other stakeholders, as described in Table 3.

5 Conclusion

The possibility of measuring glucose with a non-invasive method and getting real-time results instead of having to prick their finger in regular time intervals is of immense value for customers. This is how this solution is better than the existing methods. The technological concept behind this solution is based on using the ECG generated by wearable monitors as input to calculate the HRV parameters instead of heart rate monitors. The ECG parameter provides information that eliminates those heartbeats caused by some heart anomaly and was not directly controlled by the ANS, which is also responsible for controlling the glucose level in the human body. In this paper, we have described a non-invasive glucose measurement system based on a wearable ECG sensor. This system is superior to existing state-of-the-art

Table 3 Impact of the new solution

Stakeholders	Impact
Patients	Non-invasive glucose self-monitoring Ability to monitor the function of two vital organs at the same time Real-time continuous monitoring Relief from constantly having to prick fingers deeper and harder Pay affordable prices for premium service
Caregivers	Taking care of patients remotely and in real-time Easier to efficiently monitor the conditions of more patients simultaneously
Doctors	Detect abnormalities in the early stages Prompt reaction and intervention increase healthcare quality Medication monitoring will drastically reduce errors
Society	Better and more effective healthcare for citizens Reduced costs for treatment of glucose issues Increased ability of diabetic patients to work Prolonged life expectancy and improved quality of life Increased number of employees and economic growth
Company	Increased R&D capability and intellectual property Company growth Increased target market
Environment	No disposal of medical waste (glucose strips)

because it measures glucose non-invasively and gets real-time results. To summarize the findings of our analysis, the main benefits are:

- No more finger pricking Safety from unwanted complications
- No hassle A continuous glucose monitoring solution that notifies you when glucose levels drop
- No need to renew for at least 2 years. A lifetime expectancy of the device for more than 2 years
- No fear of undiagnosed heart complications Measure the heart function along with glucose levels.

The affordability of this approach as a continuous monitoring tool for both heart arrhythmia and the ability to control glucose levels makes this solution a unique medical device affordable to masses, much like the conventional personalized wrist devices for measuring blood pressure. Future work includes monitoring other vital health parameters calculated from an ECG, including blood pressure.

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Prof. Dr. Marjan Gusev (Ph.D. in Computer Science) is a professor at Ss Cyril and Methodius University in Skopje, Faculty of Computer Science and Engineering. He is IEEE senior member for 20 years and holds a Ph.D. degree in Electrical Engineering from University of Ljubljana (Slovenia, 1992). His background comprises theoretical and technical skills in parallel processing, computer architecture and networks, e-Government and e-Medicine. Dr Gusev is an experienced IT Expert and Consultant, Professor and Innovator, Manager and Entrepreneur with a broad knowledge and deep understanding of core business aspects and application of IT in a variety of projects, including Cloud Computing solutions, Telemedicine, e-Services, University Management, workflow and document management systems, IT Service Delivery, and IT infrastructure. As an expert and consultant, he was involved in various IT initiatives and projects in Macedonia and broader, and participated in, coordinated, and evaluated many national IT projects and participated and coordinated more than 30 international projects, including TEMPUS, FP6, FP7 and H2020. He has published over 500 papers in eHealth, Parallel Processing, Cloud Computing, and High-Performance Computing. He received the award and certificate for the best scientist and researcher at the Ss Cyril and Methodius University in Skopje in 2012, the best professor award in 2015 and the best researcher for the last decade at the Ss Cyril and Methodius University in Skopje in 2021. His current research includes eHealth, post-cloud architectures including serverless computing, dew and edge computing, telemedicine with IoT.

Optic Based Techniques for Monitoring Diabetics

Hannaneh Monirinasab and Farzaneh Fathi

Abstract The development of a well-organized, label-free, and non-invasive diagnosis approach for diabetes is one of the major health concerns. Recently, glucose monitoring as a biomarker for diabetics using optical phenomena in blood or human fluids has attracted more attention. These optic-based sensing approaches include surface plasmon resonance (SPR) and localized SPR (LSPR) based methods and also recently developed photonic crystals (PCs) based structures for biomarker detection. These optic-based detection methods have brought a considerable revolution in the diagnosis of biological molecules due to their ability to detect the very trivial refractive index change near the gold surface. SPR which is an important optic-based sensing method happens when a polarized light hits a prism covered by a gold layer of the sensor surface. In SPR analysis, any minor mass variations and refractive index shifting close the gold layer can be sensed by angle changes of SPR peaks. In the detection of biomolecules, PC-based inverse opal (IO) structures are one of the templates for a label-free sensing system. PCs-based biosensors with their nano and 3 dimensional ordered microporous organizations are reliable, cheap, and robust materials that reveal a reversible change in the structural color and reflection optical spectra by changing glucose concentrations. In this chapter, current manufacturing techniques related to the application of SPR, LSPR, and PC biosensors for the detection of diabetic biomarkers like glucose, insulin, etc. were discussed.

Keywords Diabetic biomarker · Optic · Biosensor · Surface plasmon resonance · Photonic crystal

H. Monirinasab
Core Research Laboratory, Tabriz University of Medical Sciences, Tabriz, Iran

F. Fathi (✉)
Pharmaceutical Sciences Research Center, Ardabil University of Medical Sciences, Ardabil, Iran
e-mail: f.fathi@arums.ac.ir

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1 Introduction

A biosensor is defined as a transducer that transforms a bimolecular binding event using by capturing on the bio-receptor surface to a readable physical quantity which led to the discovery of biomolecules related targets like small molecules, proteins, DNA, cancer biomarkers, cells, viruses, bacteria, microorganisms, organelles, etc. [1, 2]. The Bioreceptor element covering the surface is a bio-recognition molecule such as antigens, DNA, antibodies, cell, or aptamer that can selectively attach to target molecules in the samples during test. Depending on the transduction mechanism and system for response transduction, biosensors can be involved in the optical, electrochemical, thermal, and piezoelectric or magnetic [3]. In general, biomarkers in biological samples, including blood, serum, urine, saliva, and tears, indicate the initial sign of disease can be detected using developed sensitive and selective biosensors. [4, 5]. Biosensors with a specific platform for non-invasive biomarker capturing and potency of sensor surface modification by nanomaterials result in more selective responses and high sensitivity that make them valuable and label-free diagnostic instruments for clinical analysis [6–8].

Optical based biosensor is completed by using the interaction of the optical field with an analyte as a detection element which can be classified into two general types: label-free and label-based form [9]. When the detected response is produced directly by the interaction of the analyte biomaterial with the transducer, it is a label-free form [10]. But, the label-based sensing method includes using a label and optical signal enhancer like gold nanoparticles fluorescent or luminescent labels [11]. Glucose, the main biomarker in diabetes, was detected using enzymatic and non-enzymatic electrochemical and optical methods [12–16]. For example, using the CeO2@CuO nanostructure, a modified screen-printed electrode was developed for the non-enzymatic detection of glucose [12]. Surface plasmon resonance (SPR) and localized surface plasmon resonance (LSPR) as an optically based detection method, with the ability to detect the very trivial refractive index (RI) change in gold sensor surface, have brought a considerable alteration in the diagnosis of biological molecules [17–19]. In LSPR based biosensors, the various shape of LSPR arrays like the triangle or rhombic structures on the substrate of LSPR biosensors led to show larger peak wavelength shift and enhancement of the sensitivity through stimulation of electromagnetic radiation [20, 21]. Moreover, the gold nanostructures used in the LSPR-based technique can exhibit a distinctive ultraviolet–visible (UV) absorption band [22]. Peak wavelength changes are caused by mass absorption and refractive index change on the silver and gold nanoarrays with various shapes or sizes [23]. Also, photonic crystal (PC) based IOs structures are templates for sensitive and non-invasive detection systems [24]. IO-based materials with their 3-dimensional nano-porous organizations have found useful optical sensing uses in detecting biomolecules like glucose [25]. In this chapter, the latest manufacturing methods and the main challenges of applying SPR, LSPR, SPR imaging, and PC biosensors to detect diabetic biomarkers like glucose, insulin, etc. are discussed.

2 SPR Method for Detection of Diabetic Biomarkers

2.1 Glucose

In SPR analysis, any minor mass variations and refractive index shifting close to the gold sensor surface can be sensed by an SPR curves shift of the modified gold surface (Fig. 1a) [26, 27]. Using SPR based assay, low mass, and contrition of analyte (such as glucose) which is the most challenging factor in clinical sample detection, gold chip surface modification led to developing a sensitive method to improve SPR based sensing system. Measurement of glucose concentration in blood and urine is an important index for diabetes diagnosis, monitoring, and treatment. Surface Plasmon Resonance (SPR) is a new technique for glucose sensing, and it can be different in method or optical fiber type and shape. Tilted fiber Bragg grating

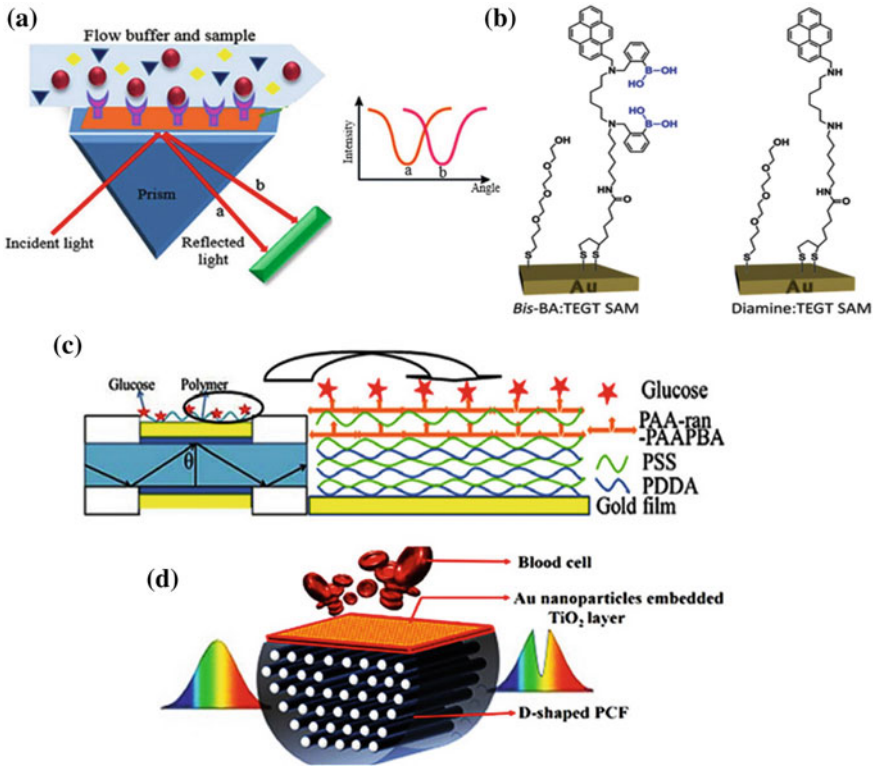

Fig. 1 **a** Representative image of SPR system. Reprinted with permission from [19]. **b** Tri (ethylene glycol)-terminated thiol (TEGT) self-assembly on the gold chip surface. Reprinted with permission from [33]. **c** schematic diagram of borate polymer immobilization. Reprinted with permission from [32]. **d** Detection of glucose range by developed D-shaped PC fiber. Reprinted with permission from [34]

(TFBG) is a new generation of optical fiber cladding by thin metal such as Ag and is utilized as glucose and H_2O_2 sensors [28]. Besides blood and urine, Transdermal extraction of interstitial fluid (ISF) can be minimally invasive blood glucose monitoring, further glucose/galactose-binding (GGB) protein modified SPR chip can sense glucose.[29] Glucose SPR sensors are based on two categories: enzymatic and non-enzymatic. P-mercaptophenylboronic acid (PMBA) modified Au chips is the non-enzymatic model for glucose detection. PMBA-Au chip and Au nanoparticle and 2-aminoethanethiol (AET) can amplify SPR signal and detect low constriction of glucose [30]. Molecularly Imprinted Hydrogels (MIHs) and Molecularly Imprinted Polymerization (MIPs) are other non-enzymatic chip modifications with recognition sites and biomimetic templates for the target analyte, as a result, they can bind analytes selectively in complex physiological fluids like urine. The sensitivity of MIHs and MIPs is lower than protein-based; however, it is enough for urine glucose detection at the physiologically level (1–20 mg/ml). Poly (allylamine hydrochloride) (PAA.HCl) into D-glucose 6-phosphate monobarium salt (GPS-Ba) is MIH chip modifications example used for polar glucose detection, and it can connect glucose non-covalently - hydrogen binding [31]. Boronic acid (BA) is low cytotoxicity and immunogenicity compound which forms cyclic boronate esters with diols (ex: glucose) in basic aqueous media. The sensing surface is fabricated by a self-assembled monolayer (SAM) of bis-BA derivative and tri (ethylene glycol)-terminated thiol (TEGT). TEGT can decrease non-specific protein adsorptions (Fig. 1b). Another form of boronic acid is poly (acrylamide-ran-3-acrylamidophenylboronic acid) (PAA-PAAPBA) polymer used to modify the surface of the Au sensor and carry it out as a glucose sensor (Fig. 1c). These sensors have a superior affinity, sensitivity, and stability [32, 33].

As mentioned previously, there are two categories for designing SPR-base glucose sensors: enzymatic and non-enzymatic. Various methods have investigated glucose detection by enzymatic sensors. The glucose oxidase (GOx) enzyme converts glucose to H_2O_2 and gluconic acid. GOx-based assays are well established. The covalent binding of GOx on Au or Ag surface makes it stable and reliable [35]. Zinc oxide (ZnO) is appropriate for attachment of GOx on Au surface in SPR measurements. GOx/ZnO/Au/prism system can detect 0-300 mg/dl glucose. Enzyme-based sensors are expensive and have low stability compared to non- enzyme ones [36]. In SPR biosensor-based photonic crystal fiber (PCF), we can monitor air holes' size and shapes, such as sensing layer thickness and the length of air holes to the pitch of D-shaped PCF. PCF sensors require to load and deliver the analyte samples frequently. To solve this challenge DPCF sensor was designed. DPCF sensor can detect glucose in range of 0–100 g/l with 0.83 nm/ (g/L) sensitivity in presence of hemoglobin (Fig. 1d) [34]. In this method, detection of blood glucose level was conducted by Au nanoparticle-TiO_2 surface in hemoglobin presence.

For the direct discovery of glucose molecules, triple mutant bacterial glucose/galactose-binding protein was reported. This modification was accomplished by changing lysine to arginine and adding serine at the glucose-specific coupling site. Then modified GGBP was immobilized on Au surface as glucose-specific binding properties in SPR measurement with a dissociation constant of 0.5 mM [37]. To measure glucose high-resolution circular birefringence (CB) properties, we can use

the Surface plasmon resonance prism coupler sensor. This device enables the sense of CB properties with a resolution of up to $8.9 \times 10 - 7$RIU for refractive indices in the 1.3–1.4. This SPR prism coupler contains a half-ball glass lens, a gold/chromium (Au-Cr) isotropic soft platform, and a Ta_2O_5 anisotropic layer and CB sample. When the concentration of glucose and refractive index change SPR sensor can sense [38]. Kretschmann-based SPR sensor with nano-laminated Au-Cr soft layer for measuring glucose refractive indices is a sensitive and user-friendly method. Refractive index changing of various glucose concentrations is analyzed at 670 and 785 nm optical wavelength. Minimum limit of detection (LOD) of Au-Cr K-SPRis 4 mmol/L. The developed biosensor can be implemented as a sample detector in lab-on-chip and point-of-care devices [39].

2.2 Insulin

Insulin is an important hormone that normalizes carbohydrate metabolism, and detecting it in human serum can be useful for medical diagnostics and checking patients with different forms of diabetes. Using SPR biosensor for insulin sensing is possible [40]. For example, Au NPs captured in hydroxyl/thiol-functionalized fourth-generation polyamidoamine (G4-PAMAM) dendrimers can enhance the surface density and insulin immobilization [41]. Type 1 diabetic patients are described by autoimmune aggression against pancreatic beta cells such as Proinsulin Autoantibodies (PAA). PAA is the preclinical marker, and SPR based sensor for serum detection can be designed by two types of PAA antigen: the genuine unmodified proinsulin (PI) and the recombinant chimeric thioredoxinproinsulin (TrxPI) [42]. Also, retinol-binding protein 4 (RBP4) is another diabetes marker that has a key role in obesity-induced insulin resistance and type 2 diabetes. Au surface with a single-stranded DNA (ssDNA) aptamers modification has a high affinity to RBP4 in SPR measurement [43].

2.3 Glycated Hemoglobin (HbA1c)

Over a long period in diabetic patients, hemoglobin protein has been glycosylated by glucose. HbA1C is accepted as a good biochemical marker of diabetes diagnostic. As mentioned, Glucose part, 4-vinylphenyl boronic acid (VPBA), and phenylboronate are boronic acid derivatives and are used for HbA1C detection [44, 45]. Aptamers are small, single-stranded DNA or RNA (ssDNA or ssRNA) emerging molecules and can bind to a specific target such as antibodies; thus, they have therapeutic and diagnostic applications as HbA1c, insulin, and Retinol binding protein 4 sensing. The application of aptamers is one of the most common modifications on the SPR Au chip for biomarker detection. In this work, the authors show that the amount of salt and the pH value can significantly affect the affinity between the aptamer and

HbA1c protein [46]. They exhibited that the pH value of 6 is the best condition for detecting HbA1c, with high sensitivity and a low LOD (2.55 nM). In this pH range, the aptamer and glycated hemoglobin have negative and positive charges, respectively, making the promoted interaction by electrostatic attraction and showing the enhanced SPR response compared with the other pH values. Utilized of fused deposition modeling (FDM) 3D printing and the HbA1c aptamers monolayer for developing high-sensitivity and rapid angle-scanning SPR can be interesting and attractive point-of-care device for HbA1c detection in diabetic patients [47]. In diabetic patients, non-enzymatic glycation reactions accelerate between glucose and proteins and form advanced glycation end products (AGEs), which have a key role in diabetic complications. An AGE generated from HbA1c is N-(carboxymethyl)valine (CMV). Thus CMV-Hb assay in nephropathy can be useful for diagnosing diabetes [48].

2.4 Glutamic Acid Decarboxylase (GAD)

SPR sensors play a key role in pre-diabetic markers detection. Glutamic acid decarboxylase (GAD) is an enzyme that converses glutamate to GABA. GAD synthesis is increased in the pancreas Beta-cell in high glucose concentration. As a result, GAD autoantibodies (Anti-GAD) presence is the main pre-diabetic marker used in type I diabetes mellitus prediction and diagnosis. SPR sensor for Anti-GAD antibody detection was designed by self-assembled monolayers (SAMs). The type of SAMs indicates different behaviors. 3-mercaptopropionic acid (3-MPA) and 11-mercaptoundecanoic acid (11-MUA) are the most common thiol compound used as SAMs. 3-MPA acts as a spacer between MUA and gold chip also reduces steric hindrance. The evidence ratio of MUA to MPA and the type of terminal group (hydroxyl or carboxyl) in mixed SMAs affect the sensitivity of sensors. Non-specific adsorption in the hydroxyl group is less than carboxyl. Biotin-GDA was immobilized on MUA-Streptavidin modified chip. Biotin–streptavidin can reduce non-specific binding. Heterogeneous lengths are activated better than homogeneous lengths by NHS/EDC also Streptavidin and Biotin-GDA immobilization is more. Based on evidence 10:1 ratio of 3-MPOH to 11-MUA SAM has high sensitivity as an anti-GAD sensor [49, 50].

2.5 Acetone Vapor

In diabetic patients, exhaled breath acetone positively correlates with blood glucose and is non-invasive monitoring. However, the concentration of acetone vapor is low and conventional devices for its detection are chromatography-mass spectrometry (GC–MS) and selective ion flow tube mass spectrometry. SPR based sensors can be the superior device for acetone vapor sensing due to its sensitivity and real-time measurement. Chitosan-PEG polymer, p-Toluene sulfonic acid doped polyaniline

(PANI), chitosan, and reduced graphene oxide (RGO) based SPR sensors are soupier materials for acetone vapor sensors [51, 52]. In Chitosan-PEG polymer SPR based biosensor, acetone vapor was detected in the range of 0.5–5 ppm with high sensitivity, selectivity, and linearity.

3 SPR Imaging (SPRi)

Surface Plasmon Resonance imaging (SPRi) is another type of label-free optical detection and monitoring of biomolecular events which follows the same principles of SPR. However, it uses images from the CCD camera and different detection methods. Magnetic nanoparticles (MNP) can covalently conjugate to insulin antibody (Abinsulin). Quantum dots to achieve enhanced SPR responses can be a good idea. Activated carboxyl CdSe/ZnS quantum dots (QD800) and insulin aptamers are immobilized on the modified cysteamine-PAMAM dendrimer SPR Au chip. After diluted and mixed Abinsulin-MNP, serum insulin is monitored level of insulin by aptamer-insulin-antibody sandwich microarray (Fig. 2a) [53]. SPRi technique and multiplex chips can measure the combination of hormones. A mixed SAM of thiolated polyethylene glycol (CH3O-PEG-SH) and 16-mercaptohexadecanoic acid (MHDA) are utilized as a biosensor to detect the diabetic biomarker.[54]. Furthermore, by Advanced glycation end products (AGEs) antibody–Protein G-modified gold surface is detected AGEs [55].

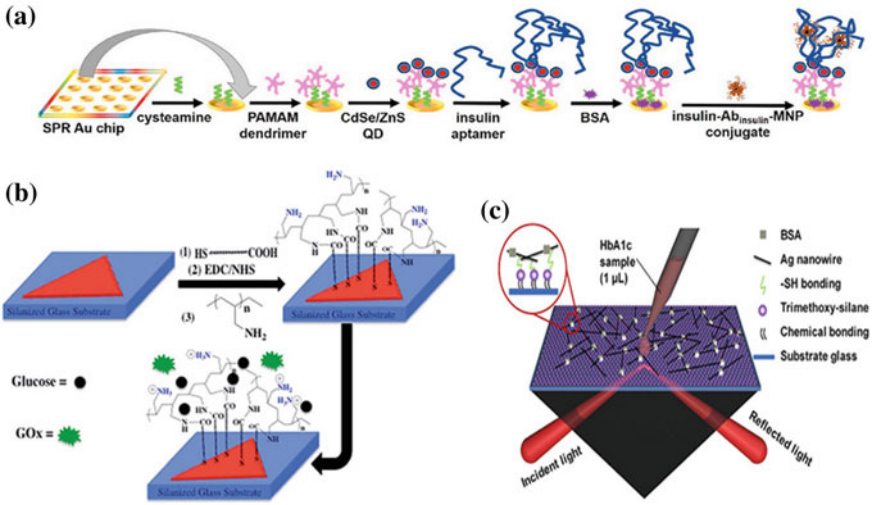

Fig. 2 Scheme of **a** SPR microarray aptamer-based biosensor for insulin detection. Reprinted with permission from [53], **b** glucose biosensor by polymer-modified gold nano-prisms. Reprinted with permission from [56], **c** plasmonic Ag nanowires for the on-chip detection of HbA1c protein. Reprinted with permission from [60]

4 Localized SPR (LSPR)

In LSPR, locally coherent oscillation of electrons at the surface of metallic structures due to creating surface plasmon resonance (SPR) by nanoparticles (NPs) or nanorods (NRs). LSPR sensitivity is higher than bulk SPR and can multi detection array with low sample volume. LSPR doesn't have bulk SPR obstacles such as steric hindrance and nonspecific proteins adsorption. The LSPR behavior is a sensitive function of nanoparticle shape, size, material, and surrounding medium refractive index. LSPR shift occurs by pH reduction; as a result, poly(allylamine) or gold NRs size changing in the presence of glucose oxidase (GOx) and glucose reaction, finally can sensing glucose and H_2O_2 (Fig. 2b) [56, 57]. Three-dimensional (3D) glucose-bismuth selenide (Bi_2Se_3) nanostructures and Gold nanoparticles (Au NPs)—thermo-active redox reaction of chloroauric acid (HAuCl4) are another method in Glucose sensing by LSPR [58, 59]. As mentioned previously, HbA_1c is the most important factor in diabetes monitoring; silver nanowire-based LSPR chip indicates good potential for detecting HbA_1c level in the blood (Fig. 2c) [60, 61]. For developing a non-enzymatic glucose sensor based on LSPR, Au nanorods on Ni foam surface can be chosen, Au NRs as plasmon catalysts, and Ni foam due to its high conductivity [62].

5 Photonic Crystals (PCs)

Photonic crystals (PCs) materials with having a spatially periodic dielectric arrangement make the circulation of photons similar to the periodic potential in semiconductors, which leads to the flow of electrons [63, 64]. The similarity of the potential periodicity of the semiconductor materials is like that of dielectric constant periodicity in PCs structures [65]. Recently the use of advanced PCs materials with distinctive optical and physical properties has been found more attention in biomedical applications like biosensors and imaging [66].

5.1 Brief Overview of PCs Physics

PCs were first completed in the late 80 s and then recognized in a directed mode arrangement in the 90s [67]. In nature, PCs exist in the wings of butterflies, peacock feathers, and opal gemstones, and a common characteristic between them is their rainbow color [68, 69]. This observed color of them dose not related to any absorption or pigment. Still, it is due to the interaction of light with the periodic or random construction of these natural material designs [69]. PCs are arrangements with a periodic variation of the RI in 1, 2, or 3 dimensions, and their working system is equivalent to that of electrons in crystalline structures (Fig. 3). A photonic bandgap (PBG) in PCs arrays occurs when the light cannot spread within the polarization

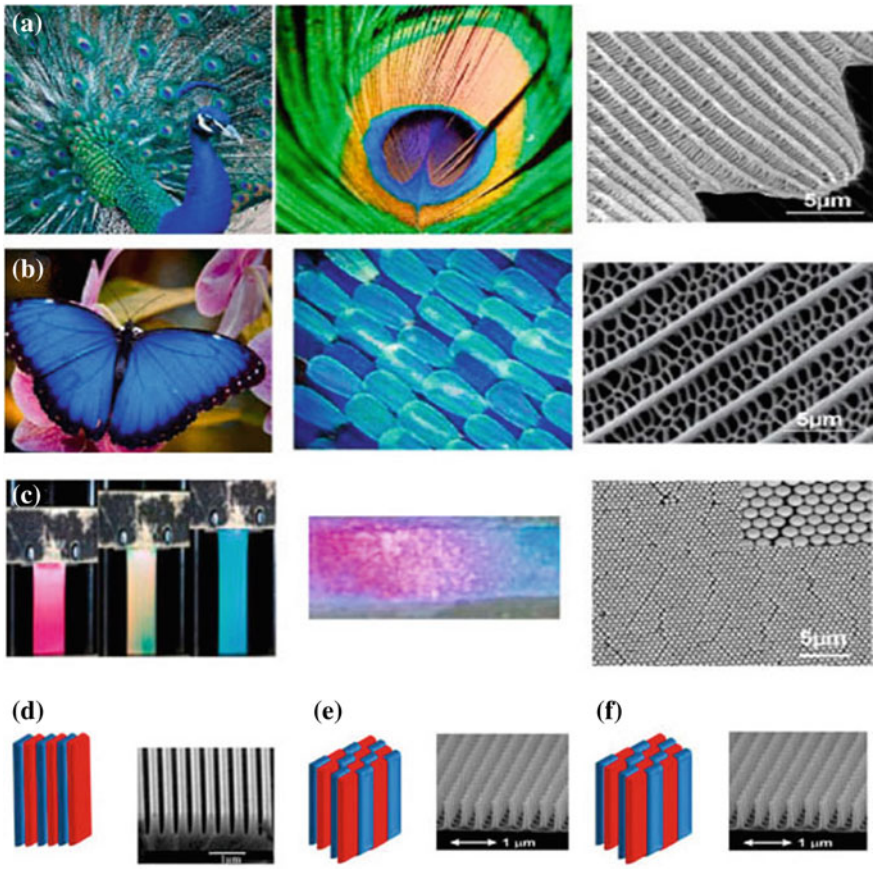

Fig. 3 Natural PCs (photonic crystals): **a** peacock feathers, **b** butterfly wing, **c** PCs opal films. Schematic picture of PCs arrays, **d** 1dimensional, **e** 2dimensional, **f** 3dimensional, with correlated scanning electron microscopy images. Reprinted with permission from [73]

directions of PC martials [70]. Like an electrical band-gap, the PBG is produced by a matrix or a crystal arrangement. A complete PBG is an individual character only observed in PCs where light propagation is banned in all directions [70]. For a more and deeper understanding of the PC structures and their optic behavior, several complete review papers and textbooks are accessible [71, 72].

5.2 PCs Biosensors

Stimulus-responsive hydrogel polymers introduced as filling materials in the 3-dimensional PC arrays could act as an optical detection system for various biological

markers [74]. Changing the hydrogel material volume of PCs structures in reaction to stimuli would be transformed to the reflected wavelength spectra. Phenylboronic acid (PBA) modified hydrogels are well identified as glucose-responsive hydrogels because of having a good affinity to diol-molecules like sugars [75]. The absorption of glucose molecules by attached PBA in the hydrogel matrix structures makes volumetric changes, leading to the hydrogel being the desired agent for glucose monitoring [76]. Using PC hydrogel arrays, the visual detection of glucose was done [76]. In designated biosensors, polystyrene colloidal structures are fixed in a PBA modified hydrogel surface to diffract light for sensitive detection on the hydrogel surface region (Fig. 4a). The volumetric variation of the hydrogel structures during glucose detection led to the Debye diffraction disk length change. This biosensor has the positive points of the fast fabrication of the PCs arrangements and the easy way of Debye ring diffraction display with more selectivity for glucose than other sugar molecules like fructose and galactose [76]. In developing of glucose biosensor based on PC hydrogels, this material displayed major sensitivity for glucose in lab devices, the element arrangement of the PCs altered from 917 to 824 nm (93 nm) within 3 min as the glucose amount improved from 0 to 10 mM, and the physical color of the PC s arrays transformed from red–orange, to green, and lastly, to cyan [77]. With a homebuilt portable optical instrument, this inexpensive smart bio-sensing system can offer a more suitable and well-organized approach for urine glucose discovery in medical analysis and point-of-care sensing. In another work developed by Chen et al., polystyrene microspheres were first self-assembled and this two-dimensional (2D) platform was then covered by a 4-boronobenzaldehyde-modified poly(vinyl alcohol) hydrogel (Fig. 4b) [78]. The developed biosensor was able to label-free and real-time detection of glucose in tears which covers both tears' and blood' physiological ranges. The physical color could move from red through yellow to green in this biosensor with increasing glucose range from 0 to 20 mM [78].

Photonic crystal fibers (PCF) show a very significant character in biosensors due to having flexible, sensitive, and bulky refractive index contrast [82]. The PCF-mediated biosensors recently are acceptably designed and found to propose very high sensitivity in the detection of biomarkers [83, 84]. A triangular lattice structure of PCF-based biosensor for monitoring glucose concentration was developed by Thenmozhi et al. in 2017[80]. By finite element technique, PCF structures are detected glucose with an average sensitivity of 19,135.70 nm/RIU, showing a blue-shift and increasing the RI of filling analyte. In this biosensor, glucose sensitivity material has flowed on PCF structures' central air cavity, which connects to six liquid core sections. With satisfying phase-matching conditions, the liquid-core mode pairs to defect mode wholly and shows loss peak used to sense glucose amounts (Fig. 4c) [80].

Also, by applying the PCF structures and Raman spectroscopy, the development of glucose biosensors was done [85]. Due to the natural minor Raman scattering cross-section of glucose, Raman spectroscopy was not applicable for detecting this molecule. But quantitative glucose Raman detection in the range of 0–25 mM is possible using the very sensitive liquid-filled PCF platform [85]. Using PC structures naked-eye glucose detection and real-time monitoring of diabetes

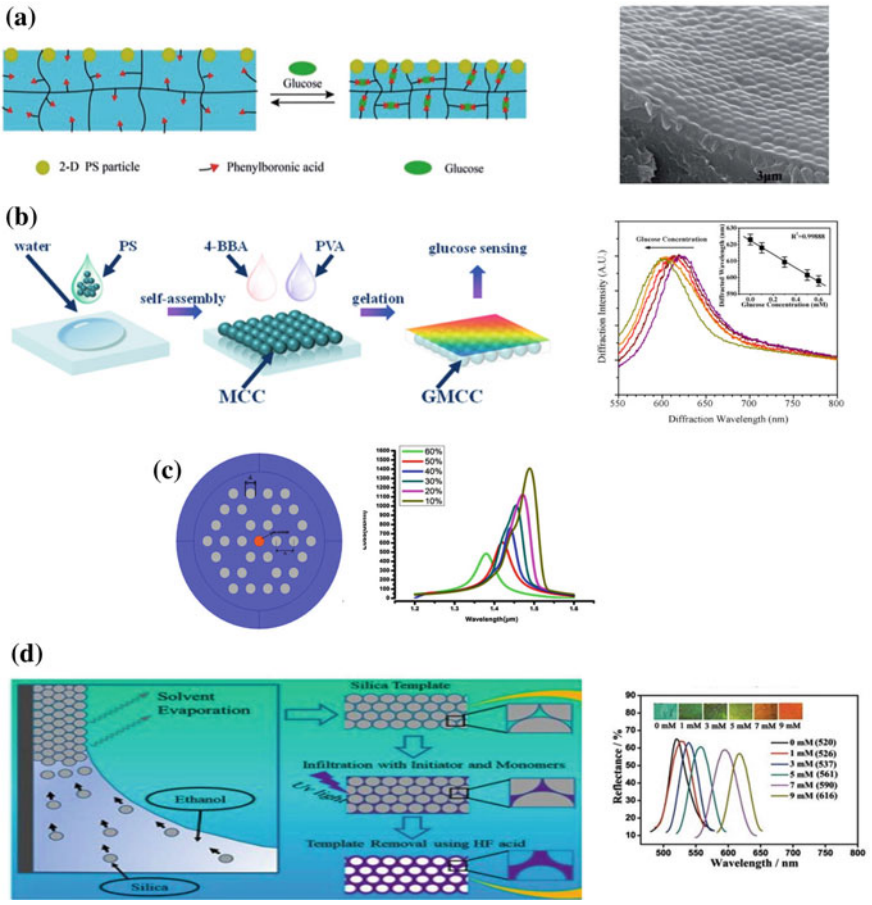

Fig. 4 Schematic image of the **a** 2-D PC hydrogel response to glucose and related SEM image of PC hydrogel film. Reprinted with permission from [79], **b** PC hydrogel sensor and biosensor response to glucose in the diffraction wavelength. Reprinted with permission from [78], **c** Cross-section of developed glucose PCF biosensor and related optical response of different glucose samples. Reprinted with permission from [80], **d** synthesis process of hydrogel IOs and optical signals of PCs in different glucose solutions. Reprinted with permission from [81]

is possible and displays hopeful use in the sense of diabetes mellitus. A vertical convective self-assembly technique prepared pCs arrays for this purpose with a novel kind of polymer microsphere including methyl methacrylate (MMA), N-isopropylacrylamide (NIPA), and 3-acrylamidophenylboronic acid (AAPBA) [86]. Developed opal closest-packing PCs structures with high solidity, periodically-ordered arrangements, and desired physical color exhibitions a redshift near 75 nm in wavelength and decreased reflection intensity during glucose molecules detection [86].

Also naked-eye glucose detection with a range of 3–20 m M is observable by changing the color PCs arrays from brilliant blue to bright green. For non-invasive detection of glucose, a PCs-based biosensor was developed by embedding colloidal microspheres within a polymer system of a polyacrylamide-poly(ethylene glycol) hydrogel with drooping phenylboronic acid molecules [24]. Phenylboronic acid was used as the molecular recognition factor to detect physiologic pH ranges. The improved PCs biosensor detected glucose in tear fluid with LOD of 1 μmol/L which was visible by shifting evident diffraction color in the visible spectral region from red to blue [24]. Inverse opal photonic crystal (IOPC) hydrogels commonly denote the polymer surface with the regular holes prepared using colloidal polymer microspheres as a template and to remove filling materials to prepare IOs nanostructures [25, 87]. IOs based biosensors can exhibit colorful signals with varying outer motivation, like pressure, humidity, pH, or thermal [88–91]. Recently, the IOPCs structures have been applied as a colorimetric biosensor for molecular recognition [92]. For example, IOs based films made from chitosan carbohydrate biopolymer could reversibly transfer their physical colors and absorbance peaks in reply to alcohols and phenols, which predicted the possible way to visually detect organic solvents [93, 94]. Glucose detection based on the IOs materials was done by Feng et al. (Fig. 4d) [89]. Using the natural structural color of IOs arrays, the developed hydrogel biosensor could be applied to detect carbohydrates with 1,2-cis-diol function and monitor diabetes without the need of complicated test tools [89]. An IO polymer membrane prepared from thermosensitive monomer and glucose-sensitive monomer was used for the colorimetric checking of glucose [95].

This system displays natural color based on Bragg diffraction rising from the 3-D organized arrays with periodicity in the visible light wavelength. The size of the hydrogel elements reversibly alters as the glucose amount differs in the divided holes of the IOs polymer layer surface [95].

PCs-based biosensors are reliable, cheap, and robust materials that expose a reversible alteration in the structural color and the intensity of the optical reflection peak with the variation in the glucose ranges. Using the colorimetric glucose-biosensing system, PC-based systems can detect the strong value of glucose amount around the threshold range for detecting diabetes mellitus. In Table 1, some examples of optical-based methods for detecting diabetic biomarkers were presented.

6 Conclusion

The development of optic-based sensing approaches includes SPR and LSPR based methods, and also photonic crystal-based structures have an important role in diabetics biomarker detection. These optic-based detection methods have brought a considerable revolution in diagnosing biological molecules due to their potency to detect the very trivial refractive index change on the gold surface. LSPR based biosensors for diabetic biomarker detection due to having different gold or silver nanoparticle structures produce sharp resonance absorbance bands in the visible

Table 1 Some examples of optical-based biosensors for the detection of diabetic biomarkers

Bio-sensing method	Detected biomarker	Immobilized molecules	Analytical performance parameters	Advantages	Ref
SPR	Glucose	p-mercaptophenylboronic acid and 2-aminoethanethiol	LOD = 80 nM	Ampilified SPR response	[30]
SPR	Glucose	D-glucose 6-phosphate monobarium salt into allylamine hydrochloride	LOD = 0.12 mg/ml	Amplified SPR response	[31]
SPR	Glucose	Tri(ethylene glycol)-terminated thiol and bronic acid	LOD = 0.02 mg/ml	Low cytotoxicity and low immunogenicity	[33]
SPR	Glucose	GOx/ZnO/Au	LOD = 20 mM	High specificity good linearity beyond the physiological range	[36]
SPR	Glucose	Bacterial glucose/galactose-binding protein	LOD = 10 mM	Continuous glucose monitoring devices and direct glucose detection	[37]
SPR	Glucose H_2O_2	Tilted fiber Bragg grating coated by silver /immobilized GOX	LOD H_2O_2 = 0.2 μm Linear range = 0–14 mM	High sensitivity miniaturized size remote operation	[28]
SPR	Glucose	Cr-Au and Ta_2O_5 layer	LOD = 3.72 mg/dl	Significant potential for non-invasive glucose sensing	[38]
SPR	Proinsulin autoantibodies	The genuine unmodified proinsulin recombinant chimeric thioredoxinproinsulin	childhood-onset diabetic patients = 67.12×10^{-9} M Adults = 167.4×10^{-9} M	Clinical use of SPR	[42]

(continued)

Table 1 (continued)

Bio-sensing method	Detected biomarker	Immobilized molecules	Analytical performance parameters	Advantages	Ref
SPR	HbA_1C	4-vinylphenyl boronic acid	LOD = 2.86 μg/ml	Sensitive boronic-based technique for targeting the sugars	[44]
SPR	Insulin	Bifunctional hydroxyl/thiol-functionalized polyamidoamine dendrimer encapsulated Au nanoparticle	LOD = 0.5 pM, linearity range = 5.25×10^{-6} μM	High stability enhanced sensitivity significantly	[41]
SPR	HbA_1C	Aptamer	LOD = 2.55 nM	Sensitive technique accuracy and correctness of HbA1c measurement	[46]
SPR	HbA_1C	Phenylboronate monolayer	Linear range = 0.43–3.49 μg/ml	Quantification of HbA1c	[45]
SPR	HbA_1C	Aptamer	LOD = 1 nM Linear rang = 18–147 nM	Cheap, rapid-prototyping, high-sensitivity	[47]
SPR	Carboxymethyl valine - hemoglobin	Related monoclonal antibody	Linear rang = 10-40 pmol	Good marker in patients with diabetic nephropathy	[48]
SPR	Monoclonal anti-glutamic acid decarboxylase	3-mercaptopropionic acid 11-mercaptoundecanoic acid	Linear range = 10–1000 nM	High sensitivity	[49]

(continued)

Table 1 (continued)

Bio-sensing method	Detected biomarker	Immobilized molecules	Analytical performance parameters	Advantages	Ref
SPR	Retinol binding protein 4	A single-stranded DNA aptamer	LOD = 75 nM(1.58 ug/ml)	The high efficiency sensitivity compared to conventional antibody-based methods	[43]
SPR	Aceton vapor	Chitosan–polyethylene glycol	LOD = 0.96 ppb	Non-invasively monitor and screen for diabetes	[52]
SPR	Aceton vapor	p-Toluene sulfonic acid doped polyaniline, chitosan, and reduced graphene oxide	LOD = 0.88 ppb	Non-invasive monitoring	[51]
LSPR	Glucose	Thermo-active redox reaction of chlorauric acid and glucose	Linear rang = 2–250 μmol/l	Sensitive, effective, reliable, simple, and convenient	[58]
LSPR	Glucose	Bismuth selenide nanostructures	LOD = 6.1uM Linear range = 10–100 μM	Highly stable ultrasensitive non-enzymatic glucose sensor	[59]
LSPR	HbA_1C	Silver nanowire-based chip	LOD = 3SB/m	Highly sensitive	[60]
LSPR	glucose	Au nanoparticles	Linear range = 5–20 mg/dl	Low-cost and real-time detection	[61]
Quantum dot-coupled-SPR	Insulin	Insulin Aptamer on PAMAM dendimer	LOD = 800 fm Linear dynamic range = 0.8–250 pM	High-throughput screening in clinical diagnostics- good sensitivity, specificity and reproducibility	[53]

(continued)

Table 1 (continued)

Bio-sensing method	Detected biomarker	Immobilized molecules	Analytical performance parameters	Advantages	Ref
SPRi	Insulin, glucagon, and somatostatin	(CH3O-PEG-SH)/MHDA	LOD = 1 nM for insulin, 4 nM for glucagon, and 246 nM for somatostatin	Multiplex measurement	[54]
LSPR	Glucose	pH-responsive nanoplasmonic polymer poly(allylamine)	LOD = 25 μM	The simplicity of operation and excellent reproducibility ultrasensitive cost-effective detection	[56]
SPR	Glucose	GOX entrapped in gel on Silver and silicon film	Linear range = 0–260 mg/dl	High sensitivity and selectivity, stability, and short response time of the sensor	[96]
LSPR	Glucose	U-shaped fiber optic/ Au NPs/GOX	Linear range = 0–250 mg/dl	Enhanced sensitivity and its use as a point Sensor with very small amounts of blood for sensing	[97]
LSPR	Glucose	Au nanorods- modifed Ni foam	LOD = 14 μM	Sensitivity Non-enzymatic	[62]

(continued)

Table 1 (continued)

Bio-sensing method	Detected biomarker	Immobilized molecules	Analytical performance parameters	Advantages	Ref
SPR based PCF	Glucose in presence of Hb	Au NP-TiO_2	Linear range = 0–100 g/l	first DPCF glucose sensor to detect blood glucose with hemoglobin	[34]
LSPR	Glucose	Gold nanorods	Linear range = 0.1–1 mM	Simple colorimetric assay	[57]
SPRi	Advanced glycation end products	Cysteine-tagged, protein-G	LOD = 10 ng/ml	High sensitivity, label free detection, rapid response	[55]
PC	Glucose	–	LOD = 3–20 mM,	Naked-eye glucose detection	[86]
Hydrogel PC	Glucose	–	LOD = 150 mM	Visual glucose sensing	[76]
PCF	Glucose	–	LOD = 0–25 mM	High sensitivity, flexibility, reproducibility, low cost, small sampling volume	[85]

SPR surface plasmon resonance; *LSPR* localized surface plasmon resonance; *PCF* photonic crystal fiber; *SPRi* surface plasmon resonance imaging; *PC* photonic crystal; *LOD* limit of detection; *GOx* Glucose oxidase; HbA_1C Glycated hemoglobin; *PAMAM* polyamidoamine; CH_3O-*PEG-SH* polyethylene glycol; *16-MHDA* mercaptohexadecanoic acid; *NPs* nanoparticles; *DPCF* D-shaped photonic crystal fiber.

light wavelength ranges, which is highly sensitive to the local refractive index near the surface of nanoarrays. In comparing SPR and LSPR based detection methods, SPR biosensors have a much higher refractive index sensitivity. Still, the sensitivity towards biomolecular binding interactions in LSPR sensor surfaces is more than that of SPR biosensors. This advantage of the LSPR biosensor makes it a valuable analytical approach for small biomarker discovery. Also, PC-based arrays, their nano and microporous 3D organizations, which are one of the templates for label-free sensing systems, have found attractive optical biosensor applications in detecting biomolecules like glucose. Introducing the biomarker detection based on PC arrays due to having large surface area and periodically ordered structures and specific reflective peaks makes them an effective platform for diabetic biomarker detection that can be applied to the clinical analysis. We believe that optical-based methods would have a hopeful future in biomedicine and clinical applications. However, main challenges are needed to develop large-scale and well-organized optical materials moving from laboratory toward industrial section.

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Hannaneh Monirinasab received the B.Sc. degree in Biology from Tabriz University in 2013, the M.Sc. degree in Clinical Biochemistry from Zanjan University of Medical Sciences in 2016. Her master thesis was about the novel hybrid nanoparticles developing for siRNA transfection. In addition, she started research and collaboration with biochemistry laboratory in 2010, when she was a B.SC student. She has commenced working at the Core Research Laboratory of Tabriz University of Medical Sciences as a Surface Plasmon Resonance (SPR) operator.

Farzaneh Fathi obtained her B.Sc. degree in Pure Chemistry (2008) & M.Sc. degree (2012) in Organic Chemistry from Tabriz University of Iran. She started her Ph.D. (2015) in Medical Chemistry in Tabriz University of Medical Science, under the supervision of Dr.Rashidi. She has been working on a Ph.D. thesis about developing Surface Plasmon Resonance-based biosensors to detect biomarkers. Until now, more than 25 research papers have been polished in this line. She is now an assistant professor at Ardabil University of medical science, Iran

SPR Assisted Diabetes Detection

Choudhary Arjun Sunilbhai, Md.Sabir Alam, Kishor Kumar Sadasivuni, and Jamilur R. Ansari

Abstract Autoimmune aggregation on pancreatic beta cells characterizes Type-I diabetes mellitus (DM) as resultant insulin secretion with absolute deficiency. Children have a high risk of Type-I DM because insulin antibodies are highly reactive towards proinsulin, and prone to diabetic risks. Radioligand binding assay (RBA) is the measurement of auto-antibodies which provides quasi-quantitative values of some specific auto-antibodies. To improve numerical immune response, an alternative method such as surface plasmon resonance (SPR) to pro-insulin autantibodies (PAA) measurements are done. HbA1c or glycosylated hemoglobin molecule is most common to diagnose Type-II diabetes mellitus. In high-risk cases, HbA1c can track diabetes easily. This study aims to determine HbA1c by vinyl phenyl-boronic acid-modified SPR. It was also observed that the concentration increases as the receiving signals increase. It shows that the variation of pH parameters plays a significant role in diagnosing diabetes. This study can provide the best alternative to avoid measuring difficulties of exhaling breath acetone by improving real-time analysis and obtaining accurate results without proper laboratory equipment setup by using optical SPR biosensors. In these biosensors, conducting novel poly-aniline doped (PANI) consists of metallic SPR layers, and chitosan behaves as sensing selective layers. This article provides direct detection of glucose in the blood by SPR biosensors. High levels of sugar in the blood cause diabetes mellitus. This study provides how Microring Resonator (MRR) and SPR based sensors monitor diabetes. Glucose in the blood can be detected using some specific sensor chip types. SPR setup utilized

C. A. Sunilbhai
P.D.M University, Sector 3A, Bahadurgarh, Haryana 124507, India

M. Alam
NIMS Institute of Pharmacy, NIMS University, Jaipur, Rajasthan, India

K. K. Sadasivuni
Center for Advanced Materials, Qatar University, Doha, Qatar
e-mail: Kishorkumars@qu.edu.qa

J. R. Ansari (✉)
P.D.M University, Bahadurgarh, India
e-mail: j.r.ansari@pdm.ac.in

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sensors onto the Kretschmann configuration based on prisms by spectral interrogation scheme utilization. The stability of sensor chips depends upon self-assembled monolayers mainly due to covalent bonding. Type-II diabetes, also known as adult-onset diabetes, is one of the biggest health issues adults face due to the lack of insulin in their bodies. An imbalance between energy utilization and caloric intake arises due to obesity. To avert obesity, gastric bypass surgeries (GBP) are performed. This research is developed for full-length insulin receptors (IR) by utilizing a high-five insect cell line. IR-insulin interaction by kinetics measuring improves the concept of the disease. To study interactions between IR ectodomains and insulin, the multiplex SPR assay was obtained. Reduced self-association properties with insulin analog known as lispro were used to introduce IR ectodomains (eIR). eIR-A isoform with human insulin recombination gives two binding pattern sites such as high-affinity site (K_{D1}) and low-affinity site (K_{D2}), with some range of dissociation constant (K_D). Glucose doesn't show any effect on insulin interactions with eIR isoforms. So, further development was anticipated for kinetics interpretation of eIR-visfatin interaction. In the knowledge of SPR sensors, those developed SPR assays are the first-ever SPR assay to use in studies of insulin-eIR interactions. It's also possible that these studies could be extended shortly to study full-length insulin receptors and insulin interactions.

Keywords Surface plasmon resonance (SPR) · Diabetes mellitus (DM) · Insulin receptors (IR) · HbA1c · Sensors

1 Introduction

Diabetes patients are rising all around the globe; by statistics, India stands in second position behind China. In the United States, Brazil, Russia, Mexico, and Indonesia, over 10 million diabetes patients are estimated. The number of diabetic patients increased to 7% in 2013 from 5.7% in 2007. At present, the scenario of diabetes patients has changed. Around 422 million people across the globe are affected by diabetes, and the majority of people reside in countries having low poverty rates. According to the International Diabetes Federation (IDF), stroke, kidney failure, and heart attack are major concerns caused by diabetes.

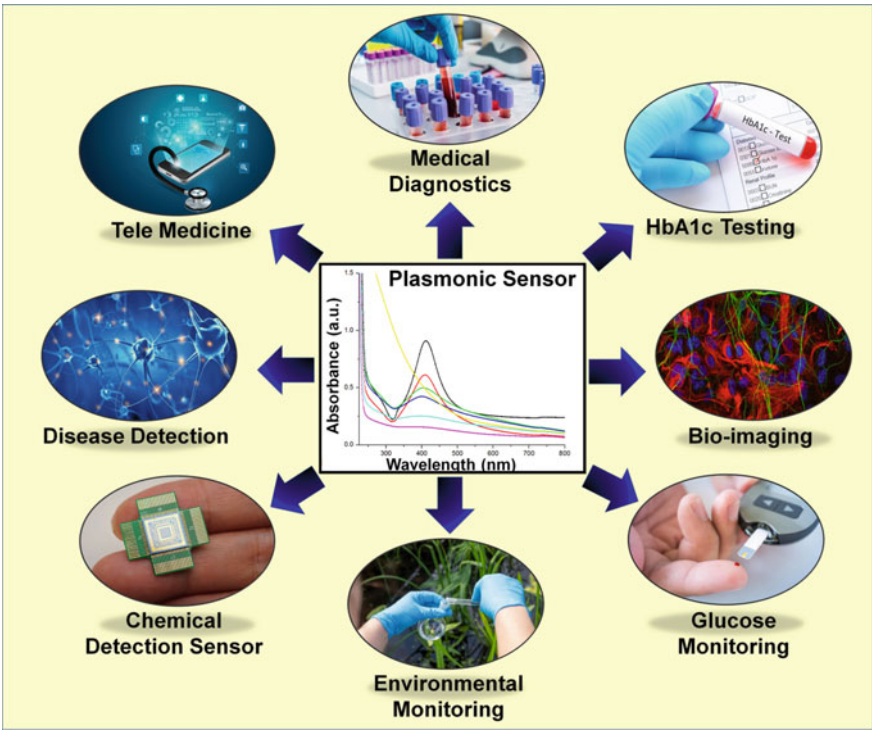
Due to the lack of insulin level in blood sugar, the sugar level rises, leading to diabetes. The human body requires glucose for energy and growth. The beta-cell failure to insulin hormone causes Type-I diabetes, while overweight patients have risk of Type-II diabetes [1]. The sugar level in an average person should be <8 mmoL/L after the meal, and it should be 4–6 mmoL/L during fasting. The person is diagnosed with pre-diabetes if he has a level 7.8–11.1 mmoL/L after the meal and 5.6–7 mmoL/L during fasting. But a person diagnosed with diabetes has the sugar level risen during fasting >7 mmoL/L and >11.8 mmoL/L after the meal. Type-I and Type-II diabetes can be controlled by regular workouts, maintaining a healthy diet, and insulin injections. To avoid Type-I and Type-II diabetes, one should maintain

a healthy diet. The diet should not include sugar-sweetened beverages, fats, rice, pasta, white bread, honey, maple syrups, cookies, pastries, and dried fruits. People who have Type-I diabetes should opt for whole grains, starchy foods, fruits and vegetables, milk, and yogurt, whereas those who have Type-II diabetes can opt for whole wheat, brown rice, oats, fruits, leafy vegetables, and beans.

Type I diabetics should prefer 35 cal per kg of their body weight daily, whereas Type II people can opt for 1500–1800 cal daily to achieve proper weight. To maintain glucose (sugar) level in diet, pancreas pressure is deduced to produce insulin hormone naturally. In diabetic treatment, it's also important to measure glucose levels regularly [2, 3]. The sugar level in blood is monitored by the common method of finger-pricking for a blood test [4, 5]. The route adopted via pricking, blood samples are observed by a glucometer and some test strips [6–8]. 5000 Q factor of polystyrene microring resonator was included in 1–5% glucose solutions produced 0.07 nm wavelength shift based can easily detect sugar concentration [9]. Due to reaction irreversibility, the glucometer sensor is not reusable [10]. Mulyanti et al. [11] developed a software-based on semi-numerical and transfer matrix method for examining the effect of glucose concentration with that of resonant wavelength shift based on MRRs with multiple values of free spectral range Q-factor, and it can easily detect sugar concentration. They have also reported that glucose concentration efficiently affects the resonant wavelength shift. Miyazaki et al. reported a 10-μm minimum glucose detection with a 0.02° resonance angle shift using Krestchmann-surface plasmon resonance (K-SPR) at 670 nm after 20-min duration using SPR sensors which are used widely [12]. SPR effectiveness was observed using different materials and thickness combinations [13–15]. Compared to other label-free methods, the K-SPR method has an advantage over others [16].

Jamil et al. [17] proved that the K-SPR approach with nano-laminated Au-Cr method is very efficient in detecting creatinine and urea. The dual SPR fluorescence assay can detect prostate-specific antigen at 10–50 nk concentration within 12 min [17]. Various K-SPR biosensors with fast analysis time and lowest detection limits were researched, utilizing micro-fluids for point-of-care application [18]. New sensor designs are improved by using some software by numerical simulation [19, 20]. This work used finite difference time domain (FDTD) numerical simulation for K-SPR sensing [21, 22]. By this work, K-SPR configuration with various glucose concentrations was observed by calculating refractive index changes of the sample at an optical wavelength of 670 nm and 785 nm. The refractive index plays a significant role in surface plasmon resonance. The resonance angle is directly related to refractive indices. When adsorption and desorption were done on the surface coated with metal nanoparticles in particular Au NPs, the refractive index of the second medium approaching the metal-dielectric interface and the resonance angle varied simultaneously [23]. In this experiment, the optimum wavelength of nano laminated Au/Cr film and incident were measured using FDTD software. Scheme 1 shows monitoring of various components by surface plasmon resonance-based sensors.

As the population, obesity, physical inactivity, and unhealthy diet rise, it affects diabetes [22, 24]. Diabetes is detected by measuring blood sugar levels, but it requires high-tech laboratory equipment, is time-consuming, and trained personnel [25]. For



Scheme 1 Schematic diagram showing monitoring of various components by surface plasmon resonance based sensors

diabetes, exhale breath acetone was considered the best biomarker for non-invasive diabetes detection [26, 27]. Human bodies have a very low (0.1–0.8 ppm) level of acetone concentration, but in conditions of diabetes mellitus (DM), this level increases to 1.8–5.0 ppm [28].

People suffering from diabetes mellitus (DM) experience insulin disorder hormones in their bodies due to ketonic species, particularly acetone and aceto-acetic acid, produced upon the breakdown of fatty acids under lipid metabolism [29]. Exhale breath acetone is an easy diabetes biomarker. Thus, many researchers have obtained this protocol for diabetic detection [30–32]. The meaning of conventional is to detect acetone, including gas chromatography- proton transfer reaction mass (PTR-MS), ion mobility spectrometry (IMS), mass spectrometry (GC–MS), etc. But those methods have some drawbacks, such as expensive and sophisticated equipment and complicated sample collection procedures [16]. The biosensors are generally devices that respond to the physical analyte via sending a signal to the other connected devices for interpretation of results like detection via computer [33, 34]. Based on the chemi-resistive transduction method, exhaled breath acetone biosensors were synthesized using semiconductor oxide materials [35, 36]. But the high operating temperature is the main issue for these biosensors [37]. The unreliable

selectivity also differs under the influence of contact resistance [38]. Optical biosensors ' advantages are wide dynamic range, electrical passiveness, greater sensitivity, high stability relatively, multiplexing capabilities, etc. are the advantages of optical biosensors [39, 40]. SPR based biosensors detect the shifts in the RIs due to the interaction of molecules at the surface of materials via surface plasmon resonance. When light is incident on the surface, the electron on the materials starts oscillating on the surface and reacts directly with the incident light. In the case of optical biosensors, the output results depend only on the materials' nature. Thus SPR based biosensors are considered promising biosensors. When the light beam is incident on the heavy metal-doped semiconductor, the light is reflected at a particular angle, and this angle is called the SPR angle. Any material or biomolecule presence at the interface occurs a shift in the SPR angle, and the shift thus produced is termed a dip. This research represents the fabrication process and mathematical simulation or modeling [33].

Some patients have Type-2DM, which can directly elicit antibodies against the islet beta-cell antigens. These patients have very slow insulin deficiency progress, and they are considered latent autoimmune diabetes (LADA) on slow-onset [41]. We have observed that pro-insulin auto-antibodies or/and insulin (PAA/IAA) are the first markers detected in childhood diabetes history [42, 43]. It was also observed that children with Type-I DM symptoms could develop IAA-positive autoantibodies due to beta-cell antigens [44, 45]. It was also reported that IAA- positive children rarely develop such diseases [43]. Achenbach et al. [46] have reported that Type-I DM is the highest risk for children. High IAA level with HLA DPB1*04 was also associated with high-affinity IAA against pro-insulin. Early exposure in context with HLA DR4 also shows that diabetic risk for children who identify as pro-insulin reactive IAA-positive are highest [46]. Radioligand binding assay (RBA) is the measurement of IAA/PAA, to achieve higher signals for the required reaction conditions and radiolabeled antigen for the binding equilibrium [46, 47]. In measurements of PAA, SPR is a very suitable method that can be used to measure PAA through antigen- antibodies. By SPR, some Type-I DM auto-antibodies can be measured. Thus based on the reports of Ayela et al. [48] who quantified auto-antibodies easily into IA-2 tyrosine phosphatase. Carlsson et al. [49] also reported an IAA-related quantification and detection method. This work was aimed to identify and characterize the PAA concentration in adult and children patients with two types of pro-insulin antigen alternative forms: pro-insulin (PI) and thyro-redox-in-pro-insulin (TrxPI) [50]. The rapid PAA response is from markers profile, clinical presentation, and genetic background [51, 52].

Diabetes is caused by a low level of insulin or a high level of glucose in the blood or body [53]. The pancreas in the beta cells cannot produce enough insulin in the blood due to Type-I diabetes. In contrast, Type-II diabetes is caused by unhealthy diets or low physical activity. Type-II diabetes is the most common type of diabetes worldwide. The pancreatic beta cells in the body are exhausted due to a high level of sugar in the blood or hyperglycemia [54]. For a long time, the sugar levels get very high in the blood Thus, HbA1c is hemoglobin derivative [55]. HbA1c isn't the main accepts to diagnose diabetes directly, but it provides sufficient information to diagnose the disease [56]. HbA1c diabetes is considered a biochemical marker and the best diagnostic tool for diabetes because the stability level of HbA1c in

the blood doesn't affect by any other parameters [57]. According to the American Diabetes Association (ADA), HbA1c levels should be less than 6.5% in the blood, considered normal [58]. Handheld devices can measure the glucose level in the blood, but this method isn't used to regulate diabetes [59]. But, mass spectrometry, electrophoresis, ion exchange, colorimetric method, etc., are much more appropriate for detecting HbA1c [60–62]. A boron-based probe prepared by the targeting method can easily detect these diseases. It helps to recognize the sugar on the surface of the cells [62], and such devices carrying out biological information or biological analysis like antibodies, organelles, microorganisms, cell receptors, tissue, etc., are known as biosensors [63, 64]. The electrochemical sensors which detect HbA1c have 1.25 μg/mL and 0.024% LOD value in general, but it still requires redox indicator for monitoring [65]. SPR based biosensor easily detects small sample analytes volumes; also these biosensors are capable to handle complex samples. When a layer is formed onto the surface for interaction with the analyte, SPR biosensors can measure highly specific measurements [66, 67]. This work shows that SPR biosensors coated with the gold surface, modified with XPBA (4-vinyl phenyl-boronic acid) efficiently detect HbA1c.

With biocompatibility, the SPR biosensors are highly precise and sensitive [68]. In detecting sugar and cholesterol in the blood, SPR sensors play a very significant role [69, 70]. SPR is the electrons oscillation collection on the surface under some electromagnetic field at the dielectric medium and metal. Most sensors utilize glucose oxidase (GOx) in glucose detection due to their high stability and high selection rate towards glucose [71–73]. In the form of polymer matrix or gel, the GOx entrapped are studied [74]. But these sensors-based technologies have some disadvantages, such as repeatability and long-term instability. In studies, no adhesive was used between the gel layer and metal film because the metal/gel formed is not stable. There are no changes observed in the refractive index due to the interaction between analytes and molecular elements, but an average change was observed in the embedded molecules [75]. Ansari et al. [76] had studied the variation of As(III) from 0.1 ppb to 1000 ppb with MoS_2 QDs and observed that when As(III) was varied from 0.1 to 50 ppb, the intensity of surface plasmon resonance increases and increasing the concentration of As(III) from 50–1000 ppb, there was suppression in the SPR as well as photoluminescence. Thus these QDs can also be employed to detect sugar and cholesterol in the blood. Jorgensen and Yee reported a response curve based on the matrix-gel/polymer shrink/expand in an aqueous medium for some sensors [77]. The vice-versa of this phenomenon is that such sensors sense some changes in the refractive index [74]. Polymers/matrix-gel utilization by sensors faces have high response time and low diffusion rate [78]. Ansari et al. [79] have reported ultra-small Ag NPs using resorcinol at a pH of 8. They have varied the pH from 3 to 11 and observed that the formation and morphology of dendrite nanoparticles were the least affected. They also reported that with variation in pH, one could easily control the surface plasmon resonance and photoluminescence of the desired material. These features can be efficiently utilized in the fields of diabetes for detecting levels of sugar and cholesterol in the blood. Dayakar et al. [80] have observed that modified electrodes show

excellent performance against anti-poisoned/interference activities in the glucose-based sample and exhibit enhanced results for non-enzymatic sensing. T. Dayakar et al. [81] have used an enzyme-free glucose-based sensor developed with Ag NPs and observed that bio-synthesized Ag NPs are efficient in fabricating cost-effective, eco-friendly, and non-enzymatic glucose monitoring devices. Thatikayala et al. [82] have developed a sensor for detecting glucose and hydrogen peroxide (H_2O_2) significantly. Yempally et al. [83] have observed that metabolic variation and pathological conditions are efficient tools for medical diagnosis, which occurs in human exhaled breath, in particular exhaled acetone which helps in diagnosis of diabetes.

2 Experimental Analysis

Miyazaki studied surface plasmon resonance at the metal interface surface where plasma wave was produced due to charge density oscillation at the metal-dielectric interface. This is called surface plasmon [12]. This surface plasma wave (SPW) will vanish because the energy is turned into heat and, at certain length non-radioactive decay. Surface plasmon and transverse magnetically (TM) polarized light beams matched each other, leading to the excitation of surface plasma wave; this phenomenon is known as surface plasmon resonance [84]. K-SPR conventional configuration is shown in Fig. 1. SPR depends on the refractive index of the metal [85]. The ligand and analytes binding onto the gold surface caused resonance angle shift [86].

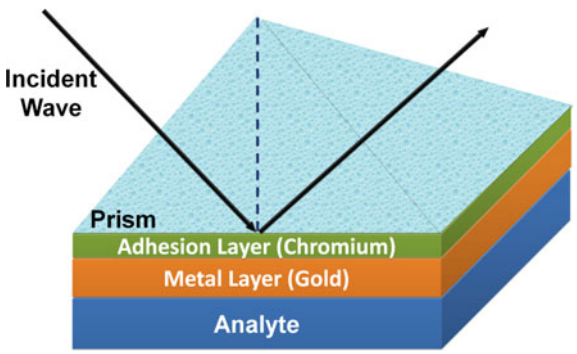


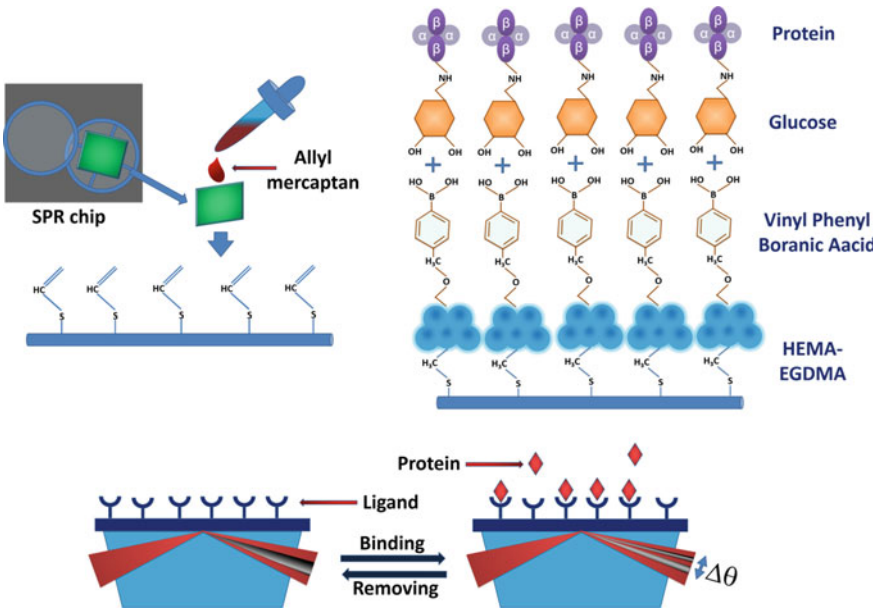
Fig. 1 The conventional configuration of Kretschmann-based SPR. Adapted with permission from [87]

2.1 Modification of SPR Chips

Gold surfaces did the modification of SPR chips. Before modification, the gold surface was washed for 10 min with a 10 mL solution of purified water, ethyl alcohol, acidic piranha with a 3:1 v/v solution of hydrogen peroxide/sulfuric acid. After this, at 30 °C temperature, this chip was dried and pressurized at 200 mmHg. Later on, it was incubated for 12 h with a 3 mM solution of allyl mercaptan at 25 °C temperature. Finally, this chip was dried in a vacuum oven at 220 mm Hg for further use.

2.2 Preparation of SPR Nanofilms

A solution was prepared with Ethylene glycol dimethyl-acrylate (EGDMA) as a cross-linker, while 4-vinyl phenyl-boronic acid (VPBA) and Hydroxy-ethyl-methacrylate (HEMA) was used as a monomer. The desolvation occurred when 0.1 mg of Azobisisobutyronitrile (AIBN) was added as the polymerization initiator in the solution. Scheme 2 shows that this solution was kept for 20–25 min under 365 nm UV and 100 W in the nitrogenous medium at the end. Acetate buffers solutions are cost-effective and are very simple to prepare and use. The final cleaning of the surface was carried out by purified water and sodium acetate buffers solution. These solutions purify and precipitate the nucleic acids on the surface, apart from



Scheme 2 Schematic preparation of SPR nanofilm. Adapted with permission from [89]

staining gels. In hematology, such cleaning procedures are often used to provide enhanced stability [88].

2.3 Analysis of SPR Chips

The coated and uncoated nanofilm was analyzed using the SPR chip surface using Fourier transform infrared (FTIR) - attenuated total reflection (ATR) based spectrophotometer, water contact angle measurements, and ellipsometer. FTIR-ATR characterized 2 cm^{-1} resolution in the range 400–4000 cm^{-1}. SPR chip thickness measures auto-nulling imaging ellipsometer. These measurements were taken at 50° incident angle and 532 nm wavelength incident light.

2.4 Kinetic Studies

The as-synthesized samples underwent kinetic studies based on HbA1c values, and the measurement was done. The observed value was pH 6. The given samples were prepared in the volume of 10 mL solutions and pH 6 phosphate buffer solution. 0.1 M NaCl and pH 7.4 phosphate buffer solution are used as desorption solution, at 10–200 μg/mL concentration range the scanning are performed. pH 6 buffer for 3 min and the same concentration sample for 10 min were allowed to pass to regain equilibrium while the desorption solution was passed for 3 min. After repeating this process 5 times, a re-usability sensorgram was reported.

2.5 Artificial Plasma Studies

The solution comparison and the actual sample used to provide the study of artificial plasma and the suitability of the system. HbA1c sample contained solution for sensor chip based on boronic acid compared with HbA1c contained in the artificial plasma.

2.6 Site-Directed Mutagenesis

On galactose/glucose-binding protein (GGBP) or, more specifically, pGGBP-6H constant, the PCR was performed using complementary oligonucleotide primers contained in GGBP gene mutations. This constructed GGBP was confirmed at the University of North Carolina by sequencing.

2.7 Protein Purification

GGBP mutant and Histidine-GGBP were prepared from Escherichia Coli sg1300921 strain. In the fabrication of tagged protein, the cell lysates with Ni^{2+}-NTA incubates. This resin was washed two times at 4 °C temperature, and this protein was dialyzed overnight under a normal atmosphere. Coomassie blue staining and 12% sodium dodecyl sulphate—polyacrylamide gel electrophoresis (SDS-PAGE) analyzed the purity level of the protein, which was more than 95% pure.

2.8 Thiol Coupling of Proteins on CM5 Surfaces

Carbonic anhydrase and GGBP mutants of research-grade CM5 chip were immobilized by coupling chemistry of standard thiol of 5 l/min flow rate in HBS-P running buffer (used throughout a typical experiment using surface plasmon resonance). Under specific conditions the protein were inducted in 10 mM pH 4.5 sodium acetate solution:- carbonic anhydrase-ll 500 μg/ml; L2385, E149 C, GGBP, A213S 80 μg/ml, 10 min; E149C, GGBP, 30–40 μg/ml, for 20 min. A pulse of solution used to remove non-specifically surface-bounded protein 3000, 4000, 4500, 10,000 resonance units of the surface was used for this experiment.

2.9 Amine Coupling of Proteins on CM5 Surfaces

With coupling chemistry on CM5 standard amines chip-surface, wild-type and E149C GGBP were immobilized, for 24 min, the protein was added in pH 4.5 and 10 mM sodium acetate. In this experiment, 2500 response units (RU) surface for wild type GGBP, while 4800 RU surface for E149C GGBP were used.

2.10 Ligand Injections

All the carbohydrate injections were prepared in an appropriate running buffer at 25 °C temperature. These injections with various concentrations were performed two or three times, and in between blank surface and protein surface, these injections were alternated.

2.11 Regeneration

SPR surface was regenerated by galactose/glucose-binding protein (GGBP) surface. Such regeneration occurs due to the flow of the channel meant for washing the given samples with running buffer injection. That's how the protein surface was regenerated.

2.12 Denaturation of E149C GGBP Surface

The active surface of 10,000 and 3000 RU E149C GGBP denatured by the automated protocol of the manufacturer, at 5 l/min continuous flow of running buffer solution which was applied to the instrument. In HBS-EP, glucose injections were performed after the unfolding of the protein. By changing the running buffer, the glucose signal was restored on the low-density surface by applying it to the desired sample and left in an inert atmosphere overnight.

3 Results and Discussions

Surface plasmon resonance (SPR) based sensors provide specific, accurate, sensitive, and highly efficient biosensors [68, 90]. SPR based biosensors are generally used for diabetes detection through blood and the detection of urea, cholesterol, glucose, etc. [69, 70]. At the surface of the metal, in the electromagnetic field, the electrons oscillate; this phenomenon is called surface plasmon resonance (SPR). Thus, a plasmon wave is generated at the surface, commonly known as the surface plasmon wave (SPW). But there is a condition for electron oscillation at the surface. The normal or high wavelength light can excite those electrons to oscillate at the surface, but the incident light must match well with the electron oscillation frequency; this condition is known as phase-matching conditions. The resonance wavelength depends on the metal and dielectric medium; thus, we observed that the interface/medium changed as the refractive index experienced some changes. A high sugar level in the blood causes diabetes, so sensing glucose through blood is the area of research and interest widely used in the medical fields as biosensors making industries [91] due to high stability and high glucose selection rate. An element of molecules recognizing glucose oxidase (GOx) is most often used in the sensors to detect glucose [71–73, 92]. GOx was entrapped in the polymer matrix or gel form in most studies [93]. Scientists across the globe widely use gels for molecular recognitions [94]. Still, no change detection is specified in the refractive index by analyte interaction with the molecular recognition element; but a minor change was reported in molecular embedded polymers [95]. Jorgensen and Yee reported a response curve based on the concept of matrix gel polymer, which can shrink/expand in an aqueous medium [77]. Still,

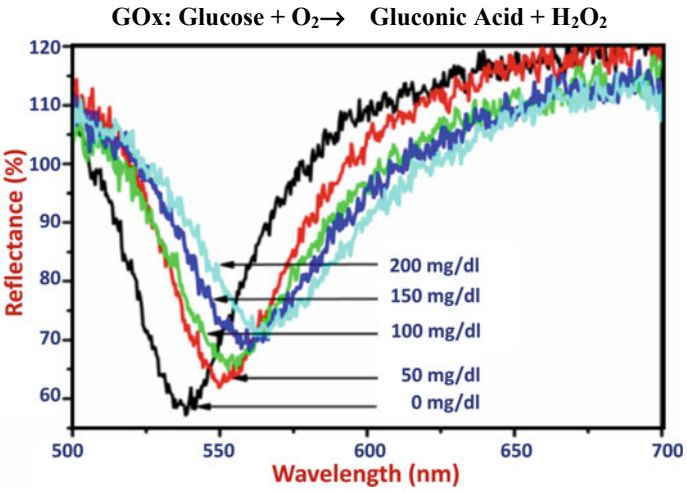


Fig. 2 SPR bands depict the varied glucose concentrations from 0 to 200 mg/dl over GOx immobilized sensor chip. Reproduced with permission from [91]

some sensors show opposite trends due to sensing changes in the refractive index [74, 93]. Matrix gel polymers utilized sensors have drawbacks such as these sensors have high response time and low diffusion rate [2, 78]. This article suggests how monolayer structure self-assembled layer by layer GOx attached to the glass slides of Ag-coated SF11 by covalent bonding techniques. This experiment was obtained on fetal bovine serum (FBS), and human serum (HS) and the results were measured by glucometer. Also, a graph of reflectance vs. wavelength was reported, which indicates that the SPR spectrum in water shows different glucose concentrations. The minimum percentage value of reflectance can be referred to as SPR wavelength [95, 96]. A red-shift in curve was also reported, while 0–200 mg/dl glucose concentration increases glucose interaction with oxygen and H_2O_2 occur redshift in refractive index changes as shown in Fig. 2.

There were minor changes in the refractive index due to glucose concentration in water solutions [95]. An experiment was performed without GOx immobilization for the sensor chip to obtain SPR spectra. Those results were in good agreement with the previous experiment. Figure 3 indicates the SPR curve graph plotted for varying glucose concentrations for the sensor chip without GOx.

Moreover, a glucose concentration vs. resonance wavelength graph was plotted by combining both experiment results with GOx and without GOx. We observed a total shift of 28 nm by varying glucose concentrations from 0 to 200 mg/dl for GOx immobilization with the sensors chip, as shown in Fig. 4 if there is no GOx immobilization on the sensors chip, in resonance wavelength minor shift experienced.

From Fig. 4, 0.14 nm/(mg/dl) of sensor sensitivity was calculated by the curve, and we observed that this sensitivity was more than double which was recently reported [74]. Figure 5 shows the second human serum blood serum and FBS experiment.

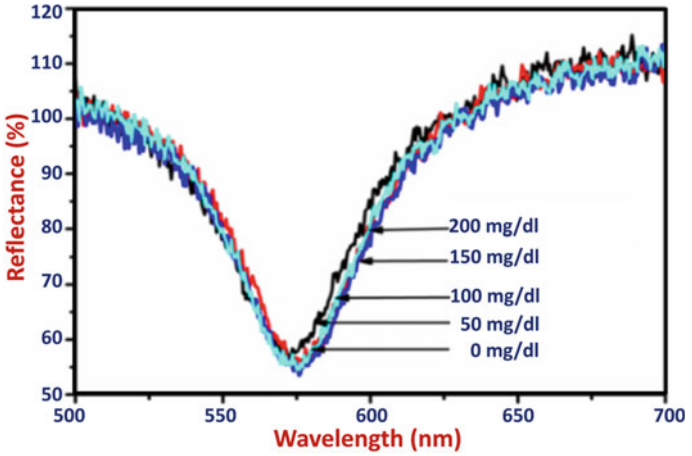


Fig. 3 Control experiment 1: SPR curve graph plotted for varying glucose concentrations from 0 to 200 mg/dl for the sensor chip without GOx. Reproduced with permission from [91]

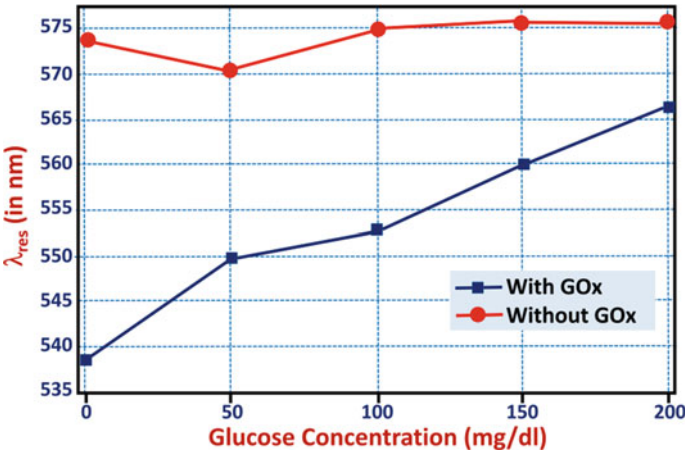


Fig. 4 SPR sensor-based chips depict response curves with and without GOx. Reproduced with permission from [91]

The human serum curve indicates a redshift for both curves 5.84 nm shift observed in resonance wavelength.

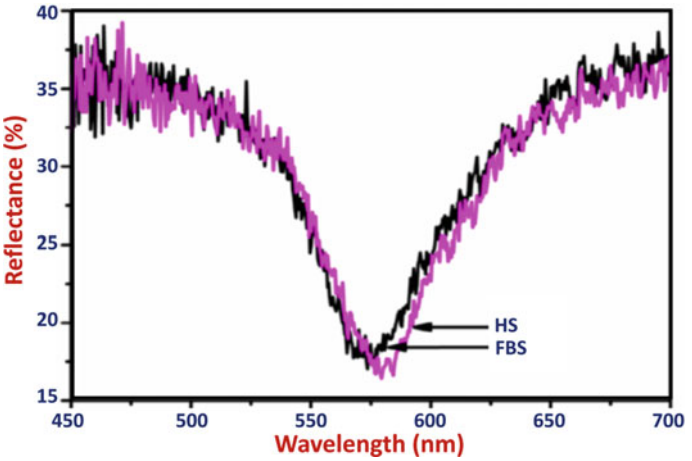


Fig. 5 SPR spectra depict the blood serums (HS and FBS). Reproduced with permission from [91]

3.1 Surface Plasmon Resonance (SPR)

Surface plasmon resonance optical biosensors related to this SPR-based concept; Rich and Myszka reported some outstanding SPR work reviews as shown in Fig. 6

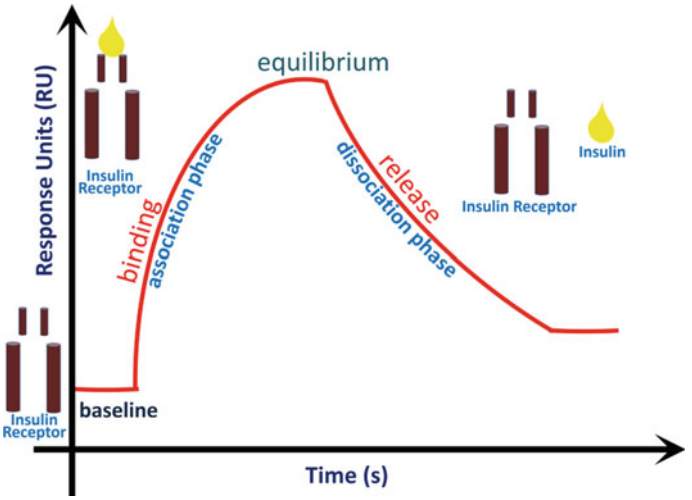


Fig. 6 An exemplary response curve (sensorgram) from SPR biosensors. The resulting modification was observed in response units (RU) versus time (s). The initial buffer injection provided a "baseline" effect, which was supported well with the association of insulin/insulin receptor (in association phase), later with the release of the bounded insulin (in dissociation phase). The equilibrium condition is reached when the association and dissociation phase meets. Adapted with permission from [101]

[97–100]. The two binding molecules interaction means one binding molecules bond with the chip surface while the second binding molecule allows the flow in the solution of the first binding molecules.

3.2 *Working Principle of SPR*

The oscillation of collective electrons between dielectric and metallic surfaces by incident light source via optical radiation is as shown in Fig. 7. Phase changes and light intensity can measure the binding process of the two molecules. The surface of the SPR chip is, in general, coated by silver or gold. As shown in the Figure, an incident monochromatic light source was converted when an electron fell on the metallic surface. These electrons get excited by the incident light source and generate electromagnetic waves. At the Au-coated surface, these surface plasmon waves are reflected at some particular angle. A molecule was bound on the aqueous side because the refractive index changed between the side and glass of the gold layer. These obtained results change the angle of light energy, which is coupled with the SPW. As far as the angle of incidence is concerned, it remains constant throughout in the wavelength modulation, albeit lights from varying wavelengths are used to excite the SPR, which depends upon the vibration of molecules. The molecule bound to the surface is proportional to the strongest coupling of SPR and the change in the refractive indices [102]. The lowest reflected light intensity angle change depends on the amount of the bound molecules of the surface, and the amount differs as the angle changes. Light wavelength was strongly bounded to SPW was observed, which depends on refractive index. This also equals the bounded molecules on the surface

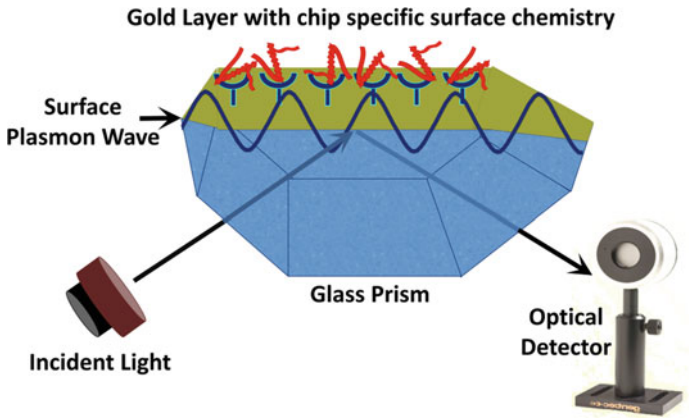


Fig. 7 A glass prism coated with a gold layer shows surface plasmon resonance. Adapted with permission from [101]

Fig. 8 Bio-Rad GLM SPR chip surface (with cartridge removed) shows vertical and horizontal strips corresponding to the 6 ligand and analyte channels. (Reproduced with permission from [101]

[103, 104] based on angular modulation; The ProteOn™ XPR36 protein interaction system studied in this article (Bio-Rad Laboratories, Hercules, CA, USA).

3.3 BIO-RAD™ ProteOn 360 SPR Biosensor

An early version of biosensors generally used analytes to analyze the study and interpretation as well as intercalation of the data. Still, the latest approaches show that the development was increased with the protein interactions studies. In this protein interaction, a total of 36 interactions occur simultaneously. But with the Bio-Rad ProteOn™ XPR, 36 protein interaction array system (Bio-Rad Laboratories, Hercules, CA, USA), which is placed "one-short" of novel high kinetics, and this approach utilizes six analytes and six ligands as shown in Fig. 8 [105].

3.4 Steps Involved in SPR

Ligand immobilization, analyte interaction, and surface recognition are the main steps involved in the surface plasmon resonance. These three steps are apart from equilibration and conditioning steps, whereas alkaline and acidic treatment include mild detergent in conditioning steps. After this step, thiols and anime coupling were

used. Biotin-binding onto the chip was used in the next step in studying the interactions and immobilized ligand response studies when an analyte is passed across it. Later, this analyte can be removed by the regeneration process to obtain regeneration in short time intervals, and a very strong acid was injected during this process [100, 102].

3.5 Analyzing Kinetics on a SPR Biosensor

Before the first inoculation, the response and time we're set to be default or zero for kinetics analysis preparation to obtain biosensors data. The non-specific bindings and refractive index changes in binding were corrected by subtraction [106]. R_{max} indicates the maximum response in which the ligand is not available anymore. In contrast, R_{eq} indicates that dissociation and association rates were equal following Eq. (1) and show analyte-A and ligand-B relation, which is as follows:

$$A + B \underset{k_d}{\overset{k_a}{\rightleftharpoons}} AB \tag{1}$$

Product [AB] have the association rate as

$$\frac{d[AB]}{dt} = k_a[A].[B] \tag{2}$$

Product [AB] have the dissociation rate as:

$$\frac{d[AB]}{dt} = -k_d.[AB] \tag{3}$$

Product [AB] have equal rate of association and dissociation:

$$k_a.[A].[B] = k_d.[AB] \tag{4}$$

here k_D is constant at dissociation equilibrium:

$$K_D \frac{k_d}{k_a} = \frac{[A].[B]}{[AB]} \tag{5}$$

The association constant $k_a(k_{on})$ have $(M^{-1}\ s^{-1})$ basic units. In contrast, dissociation constants $k_d(k_{off})$ have (s^{-1}) units, but the dissociation and association equilibrium have units M and this equilibrium is represented as k_d/k_a.

$$\frac{d[AB]}{dt} = k_a[A][B] - k_d[AB] \tag{6}$$

Association Phase

Biosensors ions kinetic data were analyzed by analyzing non-linear and linear regression. At some particular time the SPR signal representing as given by Eq. (7):

$$\frac{d[AB]}{dt} = k_a[A]_t[B]_t - k_d[AB]_t \tag{7}$$

The analyte concentration in the association phase is constant; thus, at some constant rate, it's injected.

$$[A]_t = constant \tag{8}$$

The unoccupied ligand [B] concentration at some time t ($[B]_t$) from the rest of maximum ligand B ($[B]_{max}$) are shown in Eq. 9. In Eq. 9, $[AB]_t$ is the difference between the rest of ligand and ligand concentration at some particular time.

$$[B]_t = [B]_{\max} - [AB]_t \tag{9}$$

$[AB]_t$ and $[B]_{max}$ are proportional to R_t and $R_{max,}$ respectively. Putting Eqs. (8) and (9) in Eq. (7), we have

$$\frac{dR_t}{dt} = k_a[A](R_{\max} - R_t) - k_d R_t \tag{10}$$

From Eq. (10), R_t can be obtained

$$R_t = \frac{R_{\max}[A]}{K_D + A} * \left(1 - e^{-(k_A[A]+k_d)t}\right) \tag{11}$$

Dissociation Phase

Dissociation rule follows first-order kinetics or simple exponential decay rule. In this phase, the analyte [A] concentration was reduced to zero. Now we will substitute [A] = 0 in Eq. (6):

$$\frac{d[AB]}{dt} = k_d[AB] \tag{12}$$

$$\frac{dR_t}{dt} = -k_d R_t \tag{13}$$

$$R_t = Re_0^{-k_d t} \tag{14}$$

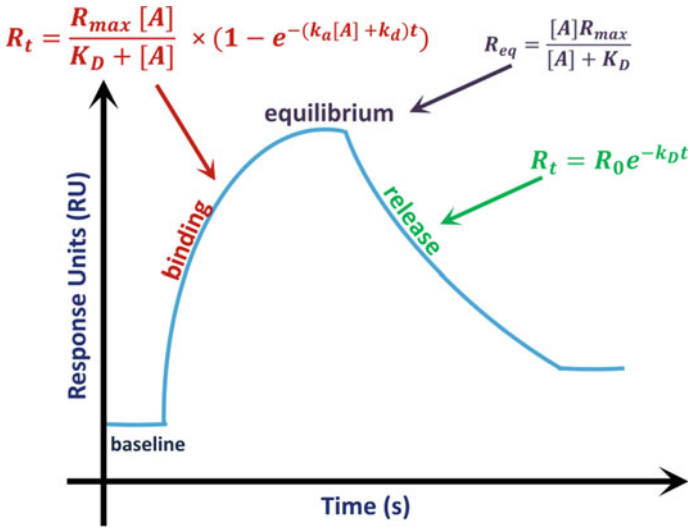


Fig. 9 The equations corresponding to binding, equilibrium and release determine the rate of association, equilibrium and dissociation constants. Adapted with permission from [101]

At the beginning of the dissociation phase, the signal was denoted by R_0 in Eq. (14). Figure 9 is the graphical representation of the interaction of association rates and dissociation rates that were shown in Eqs. (11) and (14).

The association data linearization gives on-rate also while the dissociation data linearization could be obtained by putting a log of the corresponding time and dissociation data. But the least square non-linear analysis is an alternative to this method [107]. Numerical integration and non-linear regression are the two commonly used analysis techniques. O'Shaughnessy proposed non-linear regression to compute the rate constant, which was an integral rate equation and numerical integration [108].

Using the non-linear regression method, bio-sensor ions clamp-program performs an excellent curve fit analysis. Using Levenburg-Marquardt non-linear algorithm minimization best curve fitting analysis was obtained for sensorgrams. Some models in general used for these are as follows:

$$(\mathrm{A} + \mathrm{B} \leftrightarrow \mathrm{AB}, \mathrm{A} + \mathrm{B}* \leftrightarrow \mathrm{AB}*)$$

(a) Mass transport limited model ($A_0 \leftrightarrow A$, $A + B \leftrightarrow AB$),
(b) Surface heterogeneity model ($A + B \leftrightarrow AB$, $A + B* \leftrightarrow AB*$)
(c) Simple bimolecular interaction model ($A + B \leftrightarrow AB$),
(d) Conformational change model ($A + B \leftrightarrow AB$, $AB \leftrightarrow (AB)*$)

where B/B* are ligands, A is the analyte and immobilized on the chip surface [109], whereas "global fit" and "local fit" are two fitting parameters. To determine k_a and k_d values, one particular involved concentration is known as "local fitting". The

concentration range of analyte generates k_a and k_d by fitting at the same time known as "global fit" also used in kinetics analysis performance.

3.6 Characterization of SPR Chips

The FTIR spectrometer performed the vinyl-phenyl-boronic-acid (VPBA) coated chip surface characterization was performed by FTIR spectrometer, and the results were observed in the range 400–4000 cm^{-1}. The peak observed at 1140 cm^{-1} was due to CeO vibrations manifested nano-film structure in ethylene glycol di-methyl-acrylate (EGDMA). Due to OeH stretching the peak was formed at 3467 cm^{-1}. The prominent and typical peaks at 1450 and 2950 cm^{-1} were obtained due to the presence of phenyl groups. Due to BeC stretching, the peak was observed at 1140 cm^{-1}, showing boronic-based polymer (BBP) [89]. Figure 10 shows the FTIR spectrum of the VPBA coated nano-film SPR chip.

Figure 11a–d and Table 1 show vinyl-phenyl-boronic-acid (VPBA) coated nanofilm SPR chips, allyl mercaptan modified SPR chip, and VPBA uncoated nanofilm SPR chip surface measured by an ellipsometer.

The thickness of 32 ± 1.2 nm revealed the surface morphology of the allyl mercaptan modified SPR chip. In the case of VPBA SPR chip surface, uncoated nanofilm the thickness was found to be 48 ± 2.1 nm, whereas for VPBA SPR chip surface coated nanofilm the thickness further increased to 50 ± 4.1 nm [89]. A liquid drop on the coated surface occurs at some specific angle for VPBA uncoated nanofilm chip surface, VPBA nanofilm chip surface, and allyl mercaptan modified chip surface angle values shown in Fig. 12.

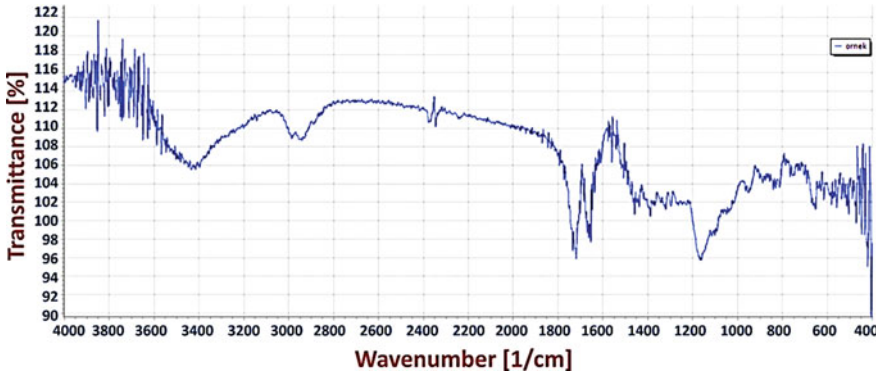


Fig. 10 FTIR spectrum show VPBA coated nanofilm based SPR chip. Reproduced with permission from [89]

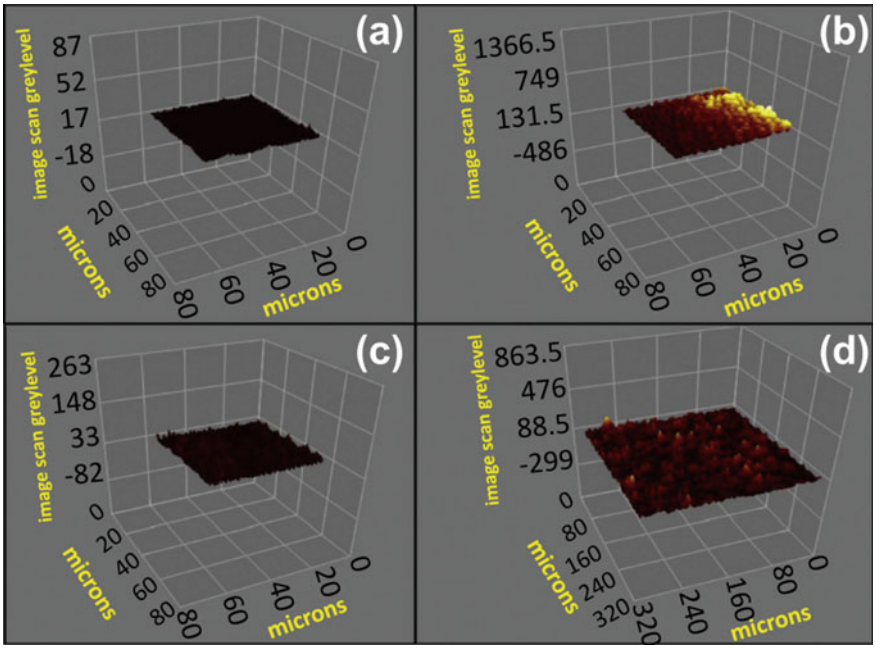


Fig. 11 The images as obtained from ellipsometry for **a** bare SPR chip surface, **b** allyl mercaptan modified SPR chip surface, **c** VPBA uncoated nanofilm SPR chip surface and **d** VPBA-coated nanofilm SPR chip surface. Reproduced with permission from [89]

Table 1 Ellipsometry values of SPR chip surfaces. Reproduced with permission from [89]

Surface	Thickness (nm)
Allyl mercaptan modified SPR chip surface	32 ± 1.2
VPBA uncoated nanofilm SPR chip surface	48 ± 2.1
VPBA coated nanofilm SPR chip surface	50 ± 4.1

3.7 Kinetic and Isotherm Analysis

The sensorgrams and the graph for glucose concentration versus ΔR shows the interaction between HbA1c solutions and SPR sensors at varying concentrations from 10 to 200 μg/ml in the presence of pH 6.0 buffer solution as shown in Fig. 13. This buffer solution is passed through the system for 5 min in the first step. After that, the HbA1c solution of a specific concentration was allowed to pass at room temperature for 8 min. As the concentration increases the ΔR increases which signify that 7 different HbA1c samples were varied at the room. The linear graph thus obtained shows that the equation has the value of $y = 0.0548x - 1.6212$, and the linearity shows $R^2 = 0.9471$ here, R^2 belongs to the binding.

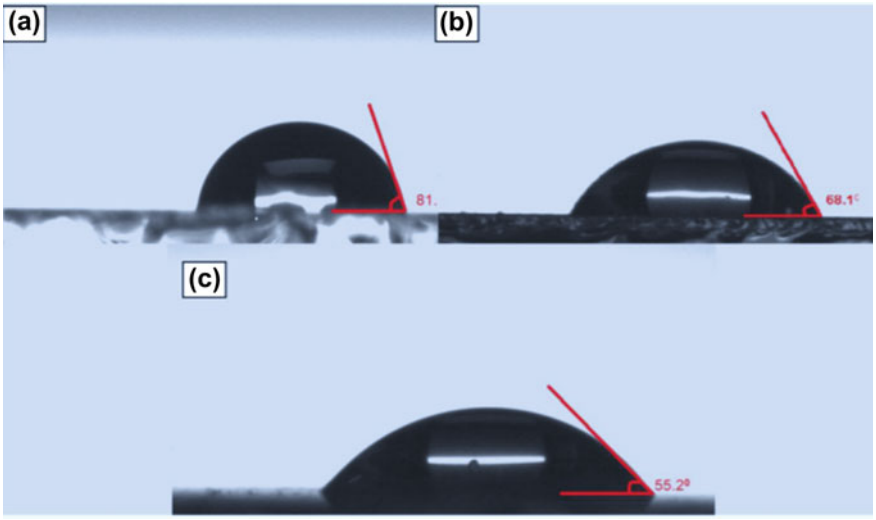


Fig. 12 **a** allyl mercaptan modified, **b** VPBA uncoated nanofilm and **c** VPBA coated nanofilm SPR chip surfaces contact angle images. Reproduced with permission from [89]

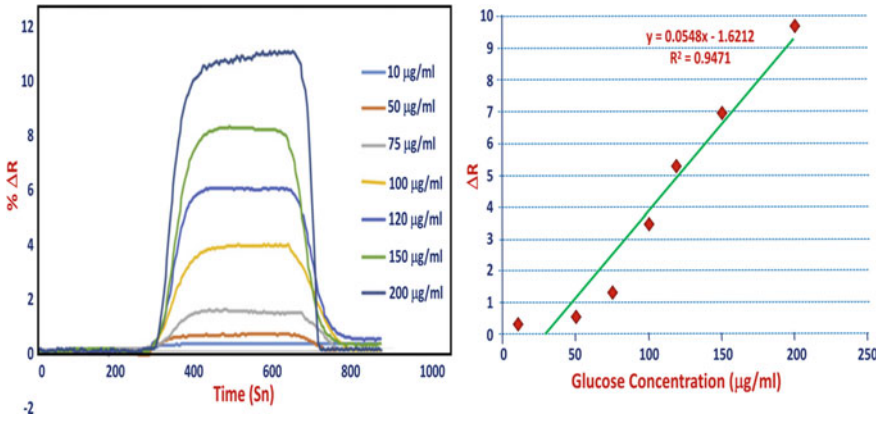


Fig. 13 The sensorgrams and the graph for glucose concentration versus ΔR show the interaction between HbA1c solutions and SPR sensors at varying concentrations from 10 to 200 gμ/ml. Reproduced with permission from [89]

The standard statistical method was used to report the results of the statistical experiments and repetitive experiments to determine relative standard deviation (RSD) and mean values.

3.8 Equilibrium Analysis and Association Kinetic Analysis

Equations (15) and (16) shows the values of the limit of detection (LOD) and limit of quantification (LOQ), respectively

$$LOD = 3\ \mathrm{S/m} \tag{15}$$

$$LOQ = 10\ \mathrm{S/m} \tag{16}$$

Here 'S' represents the standard deviation of intercept and 'm' represents the slope of the regression line. The LOD value was found to be 2.86 μg/ mL, while the LOQ value was found to be 9.52 μg/ mL. Scatchard isotherm examined the equilibrium analysis. Equation (17) is known as Scatchard equation.

$$\frac{d\Delta R}{dt} = k_a C(\Delta R_{\max} - \Delta R)k_d \Delta R \tag{17}$$

Equation (17) k_a and k_d are the association and dissociation constants, respectively. This constant (ka/kd) ratio gives reactions binding contract (K_A).

$$\frac{\Delta R_{eq}}{C} = K_A(\Delta R_{\max} - \Delta R_{eq}) \tag{18}$$

Equation (18) is the simplification of the Scatchard equation. In the Scatchard graph on the y-axis, interpret the dissociation constant. At the point where ΔR has the maximum value, binding takes place.

$$\frac{d\Delta R}{dt} = k_a C \Delta R_{\max} - (k_a C + k_d)\Delta R \tag{19}$$

Equation (19) shows that the resulting equation only applies association kinetics and calculates the amount. The plotted graph shows the relationship between analyte concentration and binding speed. Putting R_{max} value in Eq. (19) gives the value of k_a/k_d. But the amount is high, which helps to fill the surface of sensors.

$$S = k_a C + k_d \tag{20}$$

Equation (20) represents the line slope k_a and an interception gives k_d. Compared to the dissociation constants, the binding constant is much higher that's why it's much tough to calculate the k_D values. The ΔR_0 logarithmic value and ΔRt diffraction rate at 't_0' and 't' time result in the k_d values given by Eq. (21).

$$\ln\left(\frac{\Delta R t_0}{\Delta R t}\right) = k_d(t - t_0) \tag{21}$$

Due to the receptor's higher affinity values binding kinetics analysis, it can be said that lower k_d values and higher k_a values were obtained, which is 0.0233 mL/μg for k_d and 43 mL/μg for k_a.

3.9 GGBP-Glucose SPR Signal

Amino acid mutations improved protein stability for immobilization to cysteine [110]. There was the probability that the protein activity varied because of the immobilization technique. Due to the antigen-antibody, the biological system was reduced, and the affinity of antibodies was observed [111]. Using GGBP, we have observed that protein immobilizing was done with nitrilotriacetic acid (Ni^{+2}-NTA) on the chip surface, and the single polyhistidine-tag was found to be inadequate [112]. We have attached the reactive thiol groups on these chips' surfaces in an alternative method. These groups can react with the residue of cysteine; usually, one was introduced inside the protein by using site-directed mutagenesis. In the third approach, commercially existing Ni_2^+-NTA to attach the chips on polyhistidine-fusion proteins via the development of a nickel composite used between the imidazole rings of the histidines and the nitrilo-triacetic-acid (NTA) as reported by Gestwicki et al. [113]. As shown in the first two techniques in Table 2, E149C GGBP mutant and wild-type GGBP immobilized onto the surface plasmon resonance (SPR) surface. The first approach shows that by using non-specific EDC/NHS amine coupling onto the surface of carboxy-methyl dextran each protein was immobilized [114]. In contrast, in the second approach, the immobilization of E149C GGBP mutant was done through thiols coupling as a resultant in 100 micro-molar glucose presence, 17.7 RU were reproducible. Small SPR signal change was observed [115].

3.9.1 GGBP SPR Control Experiments

The GGBP SPR control experiment verified the obtained E149C GGBP glucose-specific SPR signal. The first control experiment shows glucose and E149C GGBP interaction. Wild-type GGBP suggests that calcium presence was required in proper refolding [116]. In Fig. 14, 1.5 mM CaCl (calcium chloride) in the presence of protein was refolded, with a lower density surface, proving that glucose activity was restored. Some results suggest that the SPR signal of glucose-specific and is proportional to the uniformly folded protein. The baselines of these sensor grams have been normalized and kept at zero, and we have shifted the x-axis to analyze appropriate data.

Now in a negative control experiment, protein was bounded with the glucose. In 100 M glucose, carbonic anhydrase on-chip surface was coupled by thiol. These controlled experiments results show that SPR resonance depends on folded active E149C GGBP.

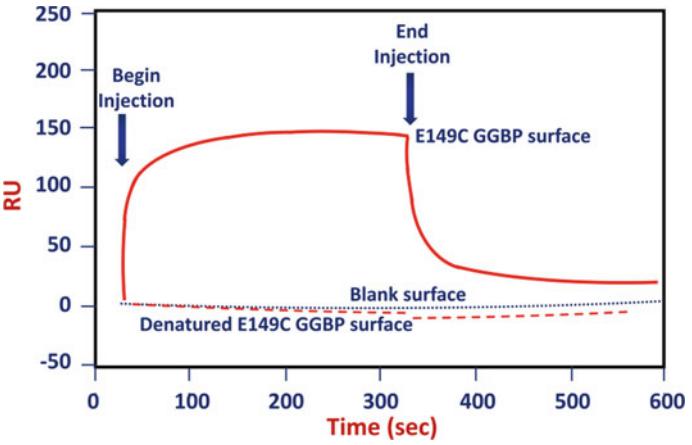


Fig. 14 100 mM glucose was injected over a surface bearing thiol coupled E149C GGBP (~10,000 RU; solid red line), the denatured E149C surface (dashed red line), and a blank surface (dotted blue line) as shown by the sensorgrams. Reproduced with permission from [5]

3.10 Comparison of GGBP Mutants

Based on the E149C position within GGBP, in E149C addition, other site-specific attachments were considered. It was assumed that K137C was attached with GGBP via the C-terminal domain at distal ends, as shown in Fig. 15.

The E149C was attached with the protein by protein central location near the binding cleft opening. G74C was attached with the GGBP on the N-terminal domain, while GGBP mutants were attached with thiol except for K137C; which produced SPR signals; Table 2 shows the values of water contact angles at 68.1 ± 0.30, 55.2 ± 0.12, 81.1 ± 0.23 respectively, while empty chip or bare chip or uncoated chip surface with liquid drop angle is 81.4 ± 0.18. The surface is hydrophobic because the drop contact angle was greater than 90°.

Calcium absence inhibits protein folding [115], and there is a possibility that calcium-binding and protein folding interfere with mutations.

3.11 GGBP-Glucose Equilibrium-Binding Constant

E149C GGBP-glucose binding affinity was reported at ~ 7 μM, and the relevant concentration of the glucose range was determined in the range 1–30 mM. E149C, L2385 GGBP and A2113S are those triple mutants characterized as single cysteine mutants. E149C GGBP mutant shows ~7 μM binding affinity with decreasing SPR-binding data, and triple mutant shows ~5 mM. But these values were considered weaker compared to glucose affinity in wild-type GGBP determination into the solution (K_d ~ 0.2 mM) [117].

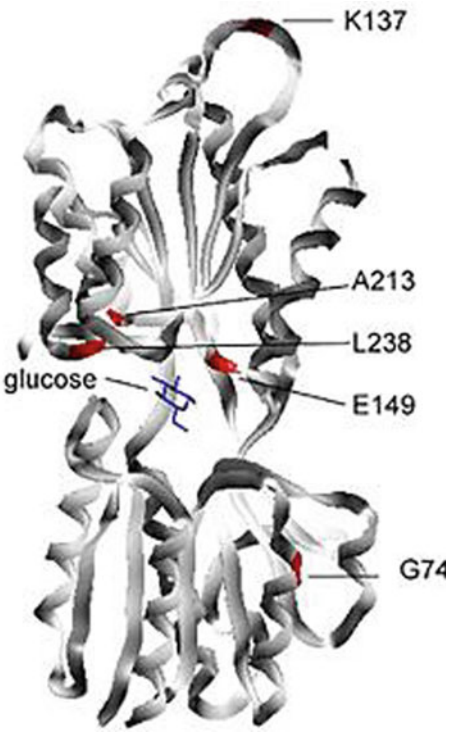


Fig. 15 The ribbon image of GGBP bound to glucose as generated from the Protein Data Bank file 2GBP using Sybyl 6.7 (Tripos). Locations of site mutations K137, A213, L238, E149 and G74 are observed. Reproduced with permission from [5]

Table 2 Bare and coated SPR chip surfaces show varying water contact angles. Reproduced with permission from [89]

Surface	Water contact angle^0
Empty Chip	81.4 ± 0.18
Allyl mercaptan modified chip surface	81.1 ± 0.23
VPBA uncoated nano-film chip surface	68.1 ± 0.30
VPBA nano-film chip surface	55.2 ± 0.12

These decreased binding affinities created a mutant, and it can be used in the glucose assays diagnosis for continuous monitoring. k_d values and signal intensity were reported of these sensors at 25 °C temperature after 3 weeks storage in HBS-P buffer contact on the instruments.

3.12 GGBP Mutant Specificities to Other Carbohydrates

Glucose sensors specificity is very important in clinical applications. Thus different kinds of carbohydrates immobilized on E149C, A213S, L238S GGBP surfaces were used to obtain immobilization and mutations, as shown in Table 3.

Glucose and galactose are the wild-type GGBP ligands, whereas lactose, rhamnose, and maltose don't show binding affinity. There is no particular SPR signal reported in the case of carbohydrates, but a very small SPR signal was observed for low-density E149C GGBP surface [118]. Compared to the low-density E149C GGBP surface and small SPR signal, a large SPR signal was observed on a higher

Table 3 The panels of carbohydrates were tested by varying analytes to find the specificity with the GGBP surfaces

Analyte[a]	E149C 3000 RU surface, SPR reaction with 100 mM carbohydrate (RU)	E149C, A213S, L238S 10,000 RU surface SPR reaction with 10 mM carbohydrate (RU)
Maltose	0.01 ± 2.16	−16.21 ± 1.65
Control[b]	1.71 ± 3.81	1.02 ± 7.33
Galacstose	10.32 ± 2.05	46.64 ± 2.81
Glucose	16.73 ± 3.63	61.54 ± 3.42
Lactose[c]	−2.16 ± 5.54	−17.83 ± 5.32
Rhamnose	3.92 ± 2.62	−13.53 ± 6.14

[a]Carbohydrates in HBS-P as shown in Table 3 with varying concentrations applied to GGBP mutant surfaces. Double-referenced sensorgrams observed the SPR signals
[b]Buffer only (no carbohydrates).
[c]High density (~10,000 RU)at the E149C surface based upon saturating concentrations of the glucose. The varying concentrations have opted as can be seen in Fig. 16.

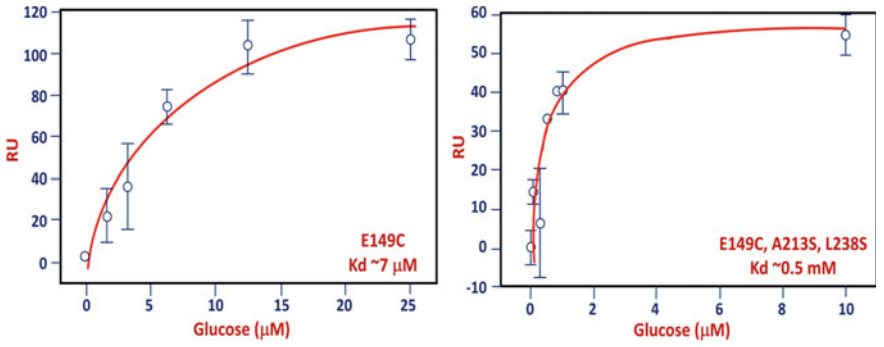


Fig. 16 SPR signal change dependence on varying glucose concentration. The K_d is ~7 μM for E149C GGBP and ~0.5 mM for E149C, A213S, and L238S GGBP for these data sets we have used (10,000 RU protein on every surface). The double referencing system investigated all these data. Reproduced with permission from [5]

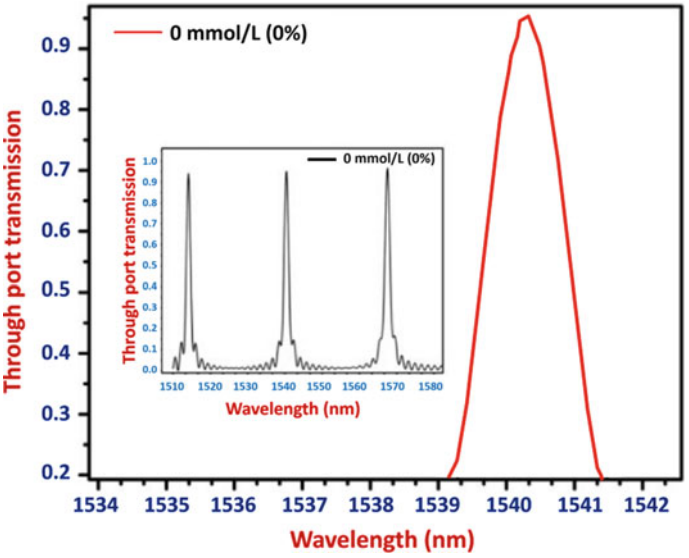


Fig. 17 The transmission of mid-range radar sensor as observed by port point for index background for 0 mmol/L (0%) glucose concentration. Reproduced with permission from [87]

density triple mutant surface. These signals exist because of the excluded volume effects, similar to the excluded volume effect reported [119]. Diabetes monitoring microring resonator responds while wavelength integer and round trip length are independent; hence constructive light interference was observed, which later arises due to large intensity and sharp resonance[120]. It was also observed that a 0 mmol/L (0%) level of glucose concentration was used for sensor-based on mid-range radar sensor (MRR) response. These curves in Fig. 17 indicate the diabetes monitoring ability of the sensors.

Inside mid-range radar sensor (MRR) wave-guide changes light propagation in cladding layer effects due to the presence of glucose analyte [121]. MRR wave-guide phases velocity decrement indicates an increment in effective refractive index values [122]. For glucose concentration, each variation with MRR based sensor uses the finite difference time domain (FDTD) method. From the data shown in Fig. 18a we observed the relationship between resonance shift and refractive index variation. The MRR based sensors can properly diagnose and monitor diabetes. The MRR based sensor was simulated for varying concentrations of glucose which was done using FDTD protocol. Figure 18b shows that a resonance shift of the microring resonator with increasing glucose concentration was induced. It was observed that with a very low glucose concentration, there was a resonance shift. Figure 18a can play a microing resonator-based-sensor for observing diabetes, which occurs due to SPR shift due to lower frequency. As the glucose concentration increases, MRR resonance shift-induced, as seen in Fig. 18b. The cladding layer refractive index variation and resonance shift show linearity between them.

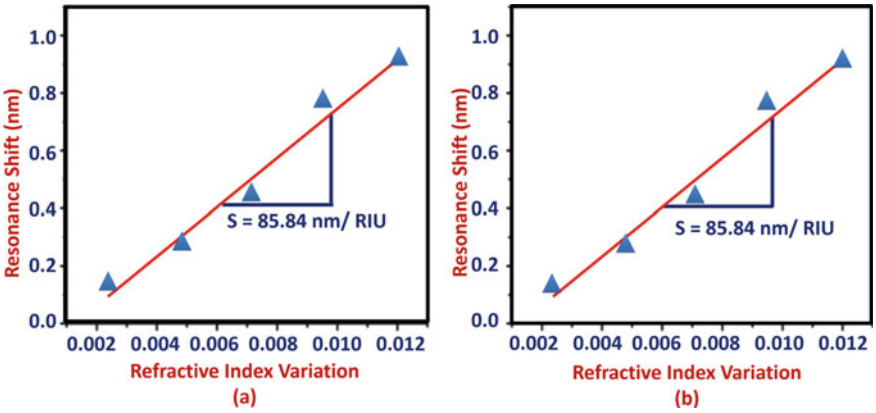


Fig. 18 FDTD approximation for **a** by the port transmission spectra of the MRR based-sensor with varying glucose concentrations and **b** resonance shift response to the refractive index variation. Reproduced with permission from [87]

Linear curve slope calculation gives MRR based-sensor sensitivity. These sensitivity values were estimated to be 85.84 nm/RIU, and it depends on the glucose levels in human blood and the ratio of refractive index and resonance shift. On gold layers, an evanescent field generates because of the interaction between chromium adhesive layer surface and incident wave. After that, this field interacts with the gold plasmon [123]. The gold plasmon and evanescent field interactions give surface plasmon waves [86]. For the occurrence of surface plasmon resonance, a certain incident angle is required. The incident wave observed by the gold layers then turns the wave energy into a surface plasmon wave [124]. The sensor's response curve based on SPR in the index background of 0 mmol/L (0%) glucose concentration is as shown in Fig. 19.

In Fig. 20a the observed response curve is for glucose concentration varying from 0–277.5 mmol/L. These curves are also very helpful for sensor ability to monitor diabetes. The relationship between SPR resonance angles and analyte refractive index suggests large-angle shifting [125]. If we consider 0 mmol/L(0%) glucose concentration as a baseline, a response angle shift occurs, as shown in Fig. 20a.

Also, SPR based sensors sensitivity depends upon the ratio of analyte refractive index changes and resonance angle shift response to refractive index variation at 670 nm wavelength as shown in Fig. 20b.

This sensitivity measured was observed to be 116.69°/RIU in immunoassay (IA) research and studies where SPR is used widely. In general, SPR based immunoassays (IAs) are precise, quick, easily performed and portable, highly sensitive, and it require minimal samples for pre-treatment and thus is inexpensive. We need highly trained experts to control and operate because radioactive atoms are included in the signal generating labels in IAs. There can be some health hazards related to that special attention needs to be taken to handle the reagents [126]. SPR based bio core system

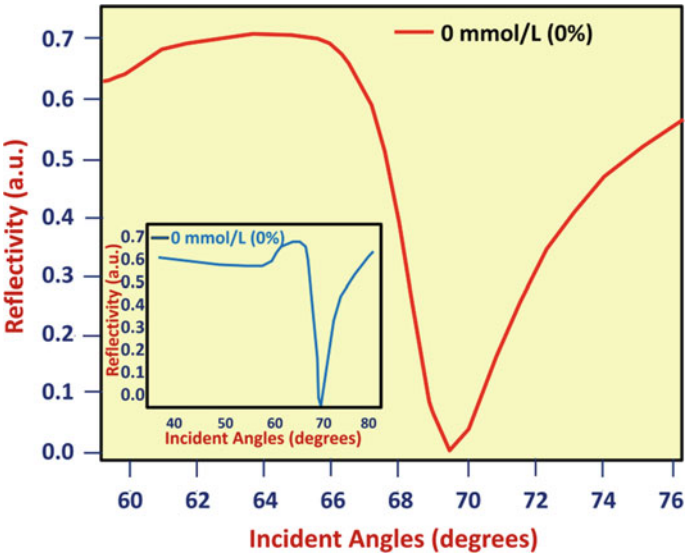


Fig. 19 The sensor's response curve based on SPR in index background of 0 mmol/L (0%) glucose concentration. Reproduced with permission from [87]

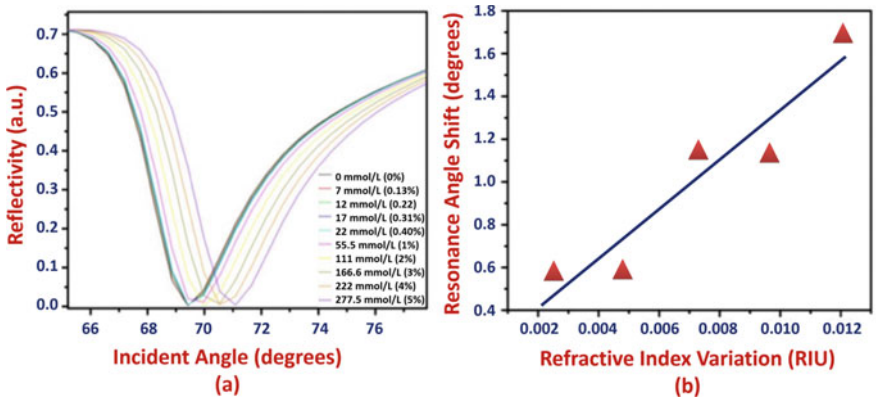


Fig. 20 SPR based-sensor response curve using FDTD approach for **a** varying concentration of glucose from 0 to 277.5 mmol/L and the corresponding **b** resonance shift response to refractive index variation at 670 nm wavelength. Reproduced with permission from [87]

was very important for the rapid development of analytes, probe bio-molecular interactions, and immunoassay immunological components screening [49, 126]. Furthermore, assay protocols, immobilization chemistries, and many surface-functionalized SPR chips are the main characteristics of SPR-based IAs development.

4 Conclusion and Future Outlook

With the help of surface plasmon resonance (SPR) sensors, we have studied and determined HbA1c or glycosylated hemoglobin, which is one of the most important aspects in diagnosing diabetes. Experimentally observed the synthesis action of nano-film-coated vinyl phenyl-boronic acid (VPBA). The interaction between boronic acid and glucose due to the cis-diol 2.86 μg/mL detection limit was calculated. This applied approach calculates accurate results beyond the validity of which aforementioned clinical values have been proved. SPR based biosensor combined with glucose/galactose-binding protein (GGBP) suggests that the glucose can be detected directly. SPR based sensors and GGBP produce an optimal signal bunch through cysteine residues. Site-specific immobilization reduces the GGBP specificity towards galactose and glucose, then after ~0.5 mM, kD GGBP mutant weakened glucose binding affinity is produced. Lower glucose response can greatly help hypoglycemia detection—the ability of continuous glucose monitoring devices improved by miniaturized SPR combination. We have also observed that fiber optic SPR platforms are much suitable for continuous sensors fabrication. Also, the long period grating platform (LPG) is a refractive index-based sensor that is most useful with optical fibers having 125 μm diameter. The glucose-selective and biocompatible membrane that GGBP surrounds immobilizes the surface sensor, which keeps out antibodies, proteases, and layers of biomolecules. The results of these studies suggest that immobilized GGBP optical biosensors have sensors potential applications for clinical diagnostics. SPR simulation and mathematical modeling show similar results to the PANI-doped layer. Here mathematical modeling shows a shift result of 80 nm, and SPR angle shows a shift of 6.41^0. Also, a 0.1 order dielectric constant was reported by biosensors. As compared to the gold and silver SPR curve, PANI/chitosan shows a much sharper SPR curve. MRR and SPR based sensors have a sensitivity of 85.84 nm/RIU, while SPR based sensors have a sensitivity of 116.69°/RIU. Thus we conclude that the as-synthesized and characterized SPR based sensors are quite helpful to detect diabetes by glucose with higher durability and stability. Under the spectral interrogation scheme, this sensor has a sensitivity of 0.14 nm/(mg/dl). Also, in conclusion, by the SPR technique, we have observed that we can develop an immunoassay for PAA concentration and fast affinity quantitation in sera. This method saves time and shows high analytical capacity. SPR technique has a major contribution to etiopathogenesis. In DM patients, the various concentrations of glucose were detected by the K-SPR approach studied in the range 670–785 nm glucose level. Nano-laminated Au/Cr-SPR sensor with 50 nm thickness detects glucose at high and low concentrations sensors, and SPR response curve was successfully observed in glucose detection. These sensors have some advantages, such as real-time analysis and sound sensitivity. By using enzyme immobilization, sensor sensitivity can be further increased. With the advancement in technologies, it is expected that prevailing SPR based sensors can be further modified with various nano-composites. It would prove to be cost-effective and efficient way for the diagnosis of diabetes and HbA1c as future remediation and applications.

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Choudhary Arjun Sunilbhai received M.Sc. in Physics from P.D.M University, Bahadurgarh, India. He has research experience in various nano-materials, metallic nanoparticles, synthesis routes and fluorescence sensing. His research interests include nano-electronics, perovskites materials, sensors & devices, quantum technology and biomedical applications.

Dr. Md Sabir Alam is currently working as an Associate Professor at the Department of Pharmacy, NIMS Institute of Pharmacy, NIMS University Jaipur, Rajasthan, India. He obtained M. Pharm in Pharmaceutics from RGUHS Bangalore and Ph.D. degree in Nano-pharmaceutics. His main area of research is Pharmaceutical Nanotechnology and its biomedical application with specialization in drug delivery for various targeted diseases, including psoriasis, neurological disorders, cancer targeting, antimicrobial, and antimalarial activity. He is having eight years of teaching and research experience. He has authored more than 15 research and reviews articles in international peer-review journals, 8 book chapters, and 2 patents. His area of interest includes synthesis, characterization application of various nanocarriers for drug delivery/delivery for treating neurological disease, cancer and malarial disease. Dr. Sabir Alam also focuses on revealing the role and impact of process variables in synthesizing various nanoparticles via process, optimization approaches using QbD, DoE.

Dr. Kishor Kumar Sadasivuni is currently working as a group leader of SmartNanoSolutions at Center for Advanced Materials, Qatar University. Dr. Kishor's research has its roots from the analytical chemistry he mastered during his Master's degree in Andhra University, India. He received his Ph.D. in Materials Science and Engineering from University of South Brittany at Lorient, France in 2012 under the supervision of the Professor Yves Grohens and Professor Sabu Thomas. He has enormous knowledge and valuable experience in his field owing to over 12 years of active research research experience of 12 years. Dr. Kishor has more than 250 research articles published in international peer reviewed journals with a total citation of 5500 and h-index 41. He is also the author of 20 book chapters and the editor of 8 books. Dr. Kishor is an expert in the nanomaterials engineering, especially the sensing and flexible electronics. He has a keen interest towards development of different devices based on the smart materials by engineering IoT. Some of Dr. Kishor's inventions are protected by 2 US patents and 2 Indian patents and presently 5 patent disclosures have been submitted by him. His strong academic background and passion for research is remarkable and reflected in his fast paced career growth. Dr. Kishor's enthusiastic and sincere approach towards research works are reflected in the forms of various grants and awards offered to him. He is a group leader and is presently the lead principal investigator for 11 research projects, covering the NPRP, UREP, IRCC grants of Qatar National Research Fund and the Qatar University. He is also involved in other three research grants as the principal investigator, summarizing a total grant amount of 3M$. Dr. Kishor is a team player and has collaborated actively with researchers (more than 450 co-authors as evident from the Scopus data) in several disciplines of computer science, biomedical sciences, industrial engineering, and electrical engineering from all over the world (USA, France, South Korea, Oman, Spain, Italy, Australia, Malaysia). Dr. Kishor's achievements have been recognized by several awards such as Tyre & Rubber Industry Leadership Acknowledgement Awards (TRILA); Young Research Scholar of the Year 2017. He has been included in the world's top 2 % scientists according to a list compiled by Stanford University in the year 2019 and for this he was recently honored by the QU.

Dr. Jamilur R. Ansari is currently working as an Assistant Professor of Physics at P.D.M University, Bahadurgarh, India. He obtained his M.Sc. from Jamia Millia Islamia, New Delhi and PhD degree in the field of Physics from G.G.S. Indraprastha University, Delhi, India. He is having 16 years of teaching and research experience with publications in SCI journals. Dr. J. R. Ansari has been acknowledged as the outstanding contributor for reviewing in 2020 by IOP Journal. He has guided 11 students in their M.Sc. Project and published a few papers with them. His research focuses on MXenes, perovskites, metal-semiconductor, 2D materials, QDs, self-assembly which involves photo-catalysis, solar cells, sensing and biomedical applications.

Infrared and Raman Spectroscopy Assisted Diagnosis of Diabetics

Nicole M. Ralbovsky and Igor K. Lednev

Abstract Type II diabetes mellitus (T2DM) is a metabolic disorder characterized by chronically elevated glucose caused by insulin resistance. Although T2DM is manageable through insulin therapy, the disorder is a risk factor for much more dangerous diseases, including cardiovascular disease, kidney disease, retinopathy, Alzheimer's disease, and more. T2DM affects 450 million people worldwide and is attributed to causing over 4 million deaths each year. Current methods for detecting diabetes typically involve randomly or after fasting testing a person's glycated hemoglobin and blood sugar levels. However, these methods can be problematic due to an individual's daily levels or being affected by diet or environment and the lack of sensitivity and reliability within the tests themselves. Vibrational spectroscopic methods have been pursued as a novel method for detecting diabetes accurately and early on in a non-invasive manner. This review summarizes recent research which has used infrared or Raman spectroscopy to develop a fast, simple, and accurate method for non-invasively diagnosing diabetes. It is proposed that vibrational spectroscopy can improve and revolutionize how diabetes is diagnosed, allowing for faster and more effective treatment.

Keywords Metabolic disorder · Insulin therapy · Insulin resistance · Methods

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N. M. Ralbovsky
Analytical Research and Development, Merck & Co., Inc., Kenilworth, NJ, USA
e-mail: nicole.ralbovsky@merck.com

I. K. Lednev (✉)
Department of Chemistry, University at Albany, State University of New York, Albany, NY, USA
e-mail: ilednev@albany.edu

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1 Introduction

Diabetes is commonly regarded as a group of metabolic diseases characterized by elevated glucose levels due to defects in insulin secretion and insulin action. Chronic levels of hyperglycemia in an individual can lead to severe complications, including the damage to, and even failure of, organs such as the kidneys and heart [1]. Due to many health complications associated with the disease, accurate and early detection is of incredible significance [2]. However, one-third of current type II diabetes cases are undiagnosed, and current diagnostic tests are heavily debated [3, 4]. Most commonly, various blood glucose tests, such as the oral glucose tolerance test and the fasting blood sugar test, are performed, which require the individual being tested to undergo some level of fasting and can be affected by short-term lifestyle influences and changes. Another test, called the glycated hemoglobin (HbA1c) test, provides an average blood sugar level for the past two to three months. Although the HbA1c test does not require fasting, it is expensive and does not accurately reflect glycemia. Further information regarding these tests is highlighted elsewhere [5, 6]. Because limits exist in the currently used methods, this review critically evaluates vibrational spectroscopy and its potential to contribute toward the identification of diabetes simply and accurately.

The two major methods associated with vibrational spectroscopy include Raman spectroscopy and infrared (IR) spectroscopy. Raman spectroscopy involves irradiating a sample with monochromatic (i.e., laser) light resulting in molecules scattering incident light. The majority of scattered light is at the same wavelength as the incident light and is called Rayleigh scattering. The small portion of the light scattered at a different wavelength is called Raman scattering. The difference in energy between the incident and Raman scattered light is a "Raman shift" and corresponds to a frequency for the vibration, measured in wavenumbers (cm^{-1}). The resultant Raman spectrum is considered a vibrational "fingerprint," specific to the analyzed sample. IR spectroscopy is complementary to Raman spectroscopy and uses infrared light to irradiate the sample, exciting molecular vibrations. The resultant spectrum describes the absorption of the light by the molecules in the sample as a function of its frequency, again measured in wavenumbers (cm^{-1}). Vibrational spectroscopy is useful for identifying different functional groups present in a sample. Both methods provide complementary information regarding the molecular structure and composition of the sample. Importantly, due to their specificity, each can be used to identify differences between biological samples obtained from different types of donors, such as those with or without a disease. Furthermore, research has already shown that known differences in the biochemical composition of biological fluids exist because of diabetes. It has been observed that higher levels of certain enzymes, total cholesterol, triglycerides, and low-density lipoprotein and lower levels of high-density lipoprotein, hemoglobin, and red blood cell content were found in the blood of individuals with type 2 diabetes mellitus compared to non-diabetic subjects [7, 8]. Due to these differences, which have been previously observed and documented [9, 10], it is hypothesized that vibrational spectroscopy may be successful in detecting

the alterations in composition, in addition to others that have been reported, within biological samples and capitalize on this detection for diagnostic success.

Due to the importance of detecting diabetes accurately and effectively, other reviews have been published on the topic. However, the scope of this alternative but informative review differs greatly from this review. Many reviews focus broadly on any methods useful for monitoring glucose [11–15], glycated hemoglobin [3, 16], or other biomarkers [17] levels to generate a diagnosis. Different reviews have focused on any method which could be useful for detecting diabetes [4, 18], and some work has been done to investigate non-enzymatic methods for glucose sensing [19–22]. While further reviews focus on the utility of either Raman spectroscopy [23, 24] or IR spectroscopy [25, 26], or both [27–31] for general medical diagnostics, there is a gap in the literature that focuses specifically on vibrational spectroscopy for diagnosing diabetes. In this regard, the current review will analyze and discuss research published between 2015 and the present. In particular, articles that focus on applying either Raman spectroscopy or IR spectroscopy to diagnose diabetes are considered. Modifications of either method will be considered, such as incorporating fiber-optic techniques or hand-held devices. Studies conducted using any form of biological material (including cells, tissue, and body fluids) will be reviewed, in addition to those studies which may or may not utilize chemometric methods. Although it is preferred to incorporate the use of multivariate analysis for objective and accurate diagnostic results, the use of such methods is not always necessary for identifying diabetes, as will be discussed. This work will review the many applications of Raman spectroscopy and infrared spectroscopy for the inexpensive, rapid, simple, and accurate identification of diabetes.

2 Raman Spectroscopy

In more than half of the manuscripts reviewed herein, Raman spectroscopy has been used to successfully identify various spectroscopic biomarkers to identify diabetes. The spectral fingerprint produced using Raman spectroscopy can be vital for identifying differences between healthy donors and those donors with a disease. One of the first reports on the application of Raman spectroscopy for investigating the disease mechanism of diabetes was made by Professor Ozaki et al. in 1982. Raman spectroscopy was employed to investigate the biochemical differences between a diabetic cataractous lens and a normal lens [32]. Amongst the many important projects Professor Ozaki carried out, this work, in particular, was crucial to opening the door for further investigations into using vibrational spectroscopy as a tool to detect and monitor this disease.

The articles reviewed in this section include those using regular Raman spectroscopy to identify diabetes and different variations of the method. For example, several research projects have incorporated the use of surface-enhanced Raman spectroscopy (SERS). The advantage of SERS resides in its capacity to detect biomolecules at ultralow concentrations due to the adsorption of molecules onto

rough metal surfaces, such as silver or gold nanoparticles. The SERS effect can enhance Raman scattering by factors up to 10^{10} or larger, allowing for a more sensitive analysis of the analyte in question [33, 34] Portable [35] and fiber-optic [36] Raman spectroscopic systems are other popular variations of Raman spectroscopy used in the following reviewed manuscripts for diagnostic applications. These methods represent the transition of the instrument toward use in clinical settings; the systems are typically much smaller, more portable, and easily able to be adapted into different settings as compared to a typical Raman spectrometer. The instruments can be less expensive than bench-top instruments, occupy significantly less space, and can often be used intraoperatively, making real-time analysis much more achievable.

In addition, many of the studies reviewed in this section incorporated chemometric methods for identifying and diagnosing diabetes. Generally, chemometrics refers to extracting chemically relevant information from complex datasets [37]. By applying chemometric methods to data that exists as a matrix (e.g., spectral data), machine learning algorithms can be built to separate, sort, and recognize patterns within chemical data. The built models can recognize differences and similarities between classes or groups of data and can use that information to generate predictions on new data presented. Incorporating multivariate analysis into a study can lead to more accurate and objective results than studies that do not rely on chemometrics. In this way, these algorithms can be used for many different types of medical screening and diagnostic applications [28, 38–40].

The following research studies focus on identifying diabetes through detection of glycated hemoglobin, blood glucose levels, other novel biomarkers, or strictly through chemometric models.

2.1 Monitoring Glycated Hemoglobin (HbA1c) Levels for Indicating Diabetes

Several research studies focused on detecting glycated hemoglobin (HbA1c) within the individuals they studied. Elevated levels of HbA1c have been indicated as a well-known biomarker for diabetes, and the HbA1c test provides an average blood sugar measurement of the past two to three months by measuring the percentage of blood sugar attached to hemoglobin [41, 42]. A recent review has focused on the future outlook of using Raman spectroscopy for sensing glycated hemoglobin [43]. One of the earlier papers to investigate Raman spectroscopy for detecting HbA1c was reported by Barman et al. in 2012 [44]. More recently, González-Viveros investigated various commercial lyophilized HbA1c in distilled water. Principal component analysis (PCA), an unsupervised chemometric method, showed good separation between the commercial HbA1c and two solutions with known concentrations (Fig. 1). A nonlinear regression model based on a feed-forward neural network (FFNN) was then built to predict the unknown concentration of HbA1c in different solutions, which resulted in a low root mean square error of 0.08% $\pm$ 0.04 after five-fold

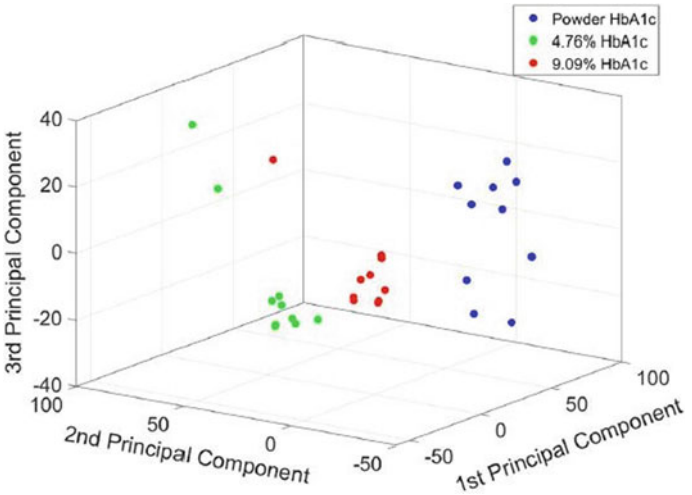

Fig. 1 HbA1c concentrations representation by three PC. Each point represents a sampled spectrum. Reproduced with permission from Elsevier B.V. [45]

cross-validation (CV) [45]. While this work does not directly investigate diagnosing diabetes, the successful results indicate that future work could extend toward monitoring the levels of HbA1c in blood samples for both detecting and monitoring the progression of the disease.

Using a Raman probe system (Fig. 2), Villa-Manríquez et al. collected Raman spectra from three different regions of the body, including the index fingertip of the right hand, ear lobe, and the forehead of 15 healthy volunteers and 71 patients with diabetes (of whom, 49 had high HbA1c levels and 22 had low HbA1c levels). Chemometrics analysis methods were used for discrimination, including PCA and support vector machine (SVM) analysis. Raman spectra of the forehead were the most successful for differentiating the low HbA1c level group and healthy volunteers, reaching 100% sensitivity and specificity each. The fingertip Raman spectra showed 100% sensitivity and 80% specificity for separating the healthy volunteers and the high HbA1c level group. A receiver operating characteristic (ROC) curve was used to confirm the results obtained after external validation conducted using an independent test dataset, indicating a successful in vivo method for identifying diabetic individuals [46].

Lin et al. utilized a near-IR laser tweezers Raman spectroscopy (LTRS) system, a method that allows for analysis of single biological particles or cells in suspension [47], to investigate variation in hemoglobin levels within red blood cells obtained from T2DM individuals (n = 45) and healthy volunteers (n = 45). Linear discriminant analysis (LDA) could accurately discriminate between the groups, reaching 100% sensitivity and 90% specificity after external validation. The major spectral differences were assigned to proteins and heme groups [48]. These two studies are clear examples of successful methods which employ Raman spectroscopy for detecting

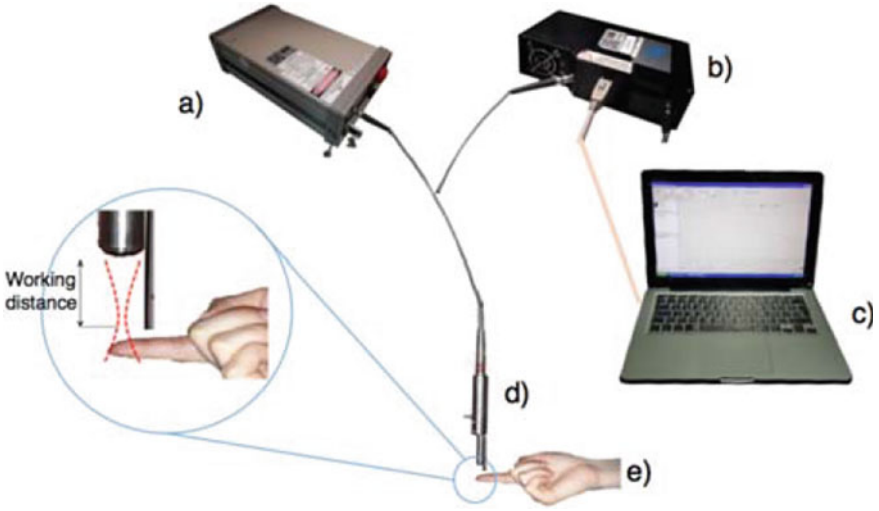

Fig. 2 Experimental setup scheme. **a** Laser of 785 nm, **b** spectrometer, **c** computer, **d** Raman probe, and **e** sample. Reproduced with permission from Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim [46]

elevated or variated levels of HbA1c, with the potential to improve accurate detection of T2DM.

2.2 Monitoring Blood Glucose Levels for Indicating Diabetes

The classic gold standard for diagnosing diabetes is testing an individual's blood sugar levels, such as through the oral glucose tolerance test (OGTT); however, this test, and others, require the patient to fast, are time-consuming, and may have poor reproducibility [49]. Through Raman spectroscopy, numerous researchers have pursued improved and alternative methods for identifying elevated blood glucose levels within individuals. In one work, a method for noninvasive monitoring of blood glucose levels was explored through Raman spectroscopic analysis of microvessels in the superficial layer of the human nail fold of 12 random volunteers. PCA in combination with a backpropagation artificial neural network (BP-ANN) was used to predict the blood glucose levels of the individuals. The levels were compared to those obtained using the OGTT, with the results showing a root mean square error of prediction of 0.45 mmol/L and R^2 of 0.95; the predicted glucose concentrations were further evaluated using the Clarke error grid, which compares how similar blood glucose values are to sensor readings at isolated points in time [50]. Here, results indicated the predicted concentrations fell within Clarke error zones A and B, which means they were within 20% similarity to that provided by the OGTT or

outside of 20% similarity but would not lead to inappropriate treatment, respectively. Additional validation of the chemometric model was not reported [51].

A fiber-optic Raman probe was also used to relate Raman spectra to blood glucose levels in similar work. Here, 20 individuals were given a standard glucose drink, typically used in OGTT. Raman spectra were recorded transcutaneously every 10 min for 160 min, while finger-prick measurements were drawn to record the blood glucose levels. Partial least squares regression (PLSR) modeling was used to predict glucose concentration in the blood using Raman spectral data. Results after external validation showed an accurate comparison could be made, and 97% of the predictions fell within zones A and B of the Clarke error grid [52]. Alternatively, Ju et al. used a SERS sensor to detect in situ glucose levels in a mouse model of Streptozotocin (STZ)-induced type I diabetes via a functional poly(methyl methacrylate) microneedle (F-PMMA MN) array (Fig. 3). It was shown that the microneedle array could directly measure glucose levels within interstitial fluid without causing lasting damage to the skin. A commercial glucometer was used to compare glucose level measurements; results show 93% of the glucose readings obtained using the F-PMMA MN array fell within zones A and B of the Clarke error grid, indicating a novel minimally invasive method determining blood glucose levels for diabetes detection [53].

Lastly, in different works, a wearable Raman probe system was employed. Ten human volunteers were administered 2 g/kg of sucrose. Both Raman spectra were obtained transcutaneously from the inside of the wrist, and glucose reference values, via a glucose meter were recorded every 20 min for two hours. A nonlinear PLS model was built to predict the glucose values based on the Raman spectra, with results indicating an average R^2 value of 0.844 after CV. This work indicates a very intriguing potential to investigate blood glucose levels for monitoring disease progression in a noninvasive manner [54].

These four studies show that Raman spectroscopy has great potential to measure blood glucose levels accurately and is minimally invasive. While this research requires repetition in large-scale human studies, the success shown here indicates this method could be considered in future work.

2.3 Monitoring Novel Biomarkers for Indicating Diabetes

In addition to monitoring HbA1c and blood glucose levels, other biomarkers were also explored as a potential route toward identifying diabetes with greater levels of accuracy and repeatability. Although not all novel biomarkers have a well-known biochemical connection to diabetes, the exploratory nature of Raman spectroscopy allows for the detection of biomolecules that have not been considered in the past.

The first set of research studies in this section focused on analyzing serum for identifying novel biomarkers. Recently, leucine and isoleucine amino acids were investigated as biomarkers for early T2DM screening using SERS. Here, blood from 40 rats was deposited on substrates prepared from conductive silver paste smeared onto glass and analyzed; Specific Raman bands were found to correlate with the

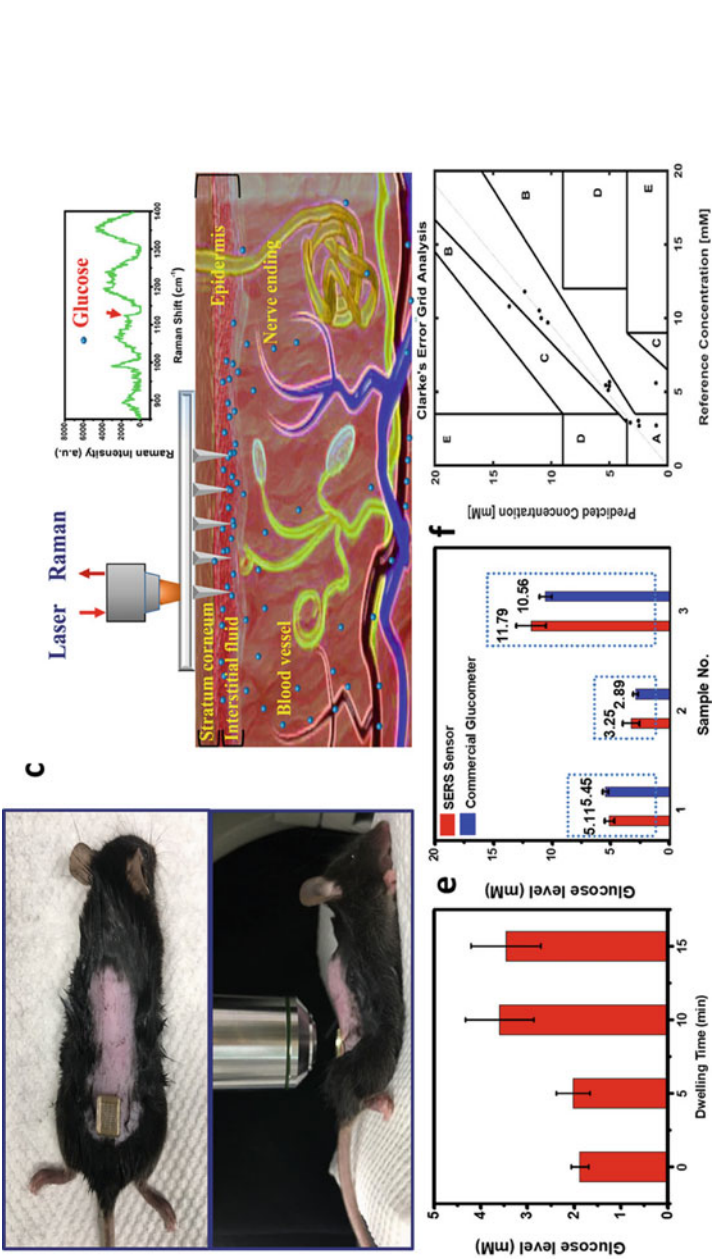

Fig. 3 **a** Photograph of the F-PMMA MN array pressed onto the skin on the back of a mouse. **b** Mouse under anesthesia on the stage of the Raman microspectroscopy system for measurements. **c** Schematic illustration of the glucose measurement using the F-PMMA MN array for in vivo transdermal detection based on surface-enhanced Raman spectroscopy. **d** Glucose level measured using SERS biosensor for a range of dwelling time from 0 to 15 min. **e** Glucose levels were measured using our SERS glucose biosensor (red) compared to those obtained from a commercial glucometer (blue). We selected three mice with different blood glucose concentrations for testing in which the excitation power was 16.5 mW out of the needle tip at 785 nm and the exposure time was 10 000 ms. Each mouse was tested sequentially five times. **f** Clarke error grid analysis of the in vivo glucose measurements using our SERS glucose biosensor in a mouse model of STZ-induced type I diabetes. Reproduced with permission from the American Chemical Society [53]

two amino acids, in addition to glucose, with the intensities corresponding to T2DM biomarkers. Further, when the rats were administered two different antidiabetic drugs (pioglitazone and herbal extract *Momordica spinosa (Glig.) Chiov)*, the intensity of these Raman bands in newly collected spectra were shown to decrease, thus indicating these amino acids as potential spectroscopic markers for monitoring the progression of the disease as well as the efficacy of treatment [55]. Similarly, the same research group used SERS substrates to analyze blood collected from 50 rats. Here, they identified valine, leucine, isoleucine, creatine, glucose, and fructose spectral bands as early indicators for predicting the presence of diabetes. These spectral bands were also sensitive to antidiabetic drug treatment in the rats. Here, the herbal extract *Rotheca myricoides Hochst* and the antidiabetic drug pioglitazone resulted in the decrease in intensity of the spectroscopic bands associated with the aforementioned biomolecules; PCA also indicated spectral differences existed between the various groups [56]. Both papers indicate an interesting potential for the early identification and treatment monitoring of T2DM based on the novel and alternative Raman spectroscopic biomarkers. Early detection of the disease can help mitigate potential issues that arise due to it and provide the afflicted individual with more effective treatment opportunities [57–59].

In human studies, Silveira Jr. et al. leveraged Raman spectroscopy for investigating the levels of glucose and lipid fractions in 44 serum samples. The concentration of glucose, triglycerides, cholesterol, and high- and low-density lipoproteins were determined using a colorimetric method. A PLSR model with leave-one-out cross-validation (LOOCV) was then built to predict the known concentrations of the biochemical components based on the Raman spectra and indicated triglycerides and cholesterol concentrations could be estimated with r values of 0.98 and 0.96, respectively. The r values were slightly lower (0.75–0.86) for the other biochemicals [60]. González-Solís et al. analyzed serum samples from 15 individuals diagnosed with T2DM and from 20 healthy controls, with spectral differences due to glutathione, polysaccharides, phenylalanine, tryptophan, and proteins being observed. PCA with LDA was then employed to discriminate between the two groups, reaching 96% sensitivity and 99% specificity after CV [61]. In one last report using blood, albumin was purified using membrane electrophoresis from plasma samples of 40 T2DM patients and 50 healthy volunteers (where five donors from each class were set aside for an independent external validation group). SERS spectra were collected, and PCA with LDA was shown to successfully differentiate between diabetic and healthy spectra with 100% specificity and 80% sensitivity after external validation [62]. These studies indicate that alternative blood-based biomarkers may increase the sensitivity and specificity for identifying and diagnosing diabetes using Raman spectroscopy.

In non-blood-based studies, urinary extracellular vesicles were shown in one paper to be useful as a potential diabetes biomarker, with cluster analysis (CA) of the obtained Raman spectra showing significant differences between controls ($n = 10$) and T2DM ($n = 45$, 19 with good glycemic control and 26 with unsatisfactory glycemic control) individuals. On the other hand, endothelium-derived extracellular vesicles successfully separated cells cultured in differing glycemic conditions. PLSR

analysis indicated spectral bands associated with saccharides, lipids, proteins and protein conformation, and nucleic acids could separate the three groups. Although no validation was reported, this research indicates a different and much less invasive method for detecting potential diabetes biomarkers [63]. Flores-Guerrero utilized a probe-based Raman spectrometer to investigate urinary albumin in individuals with T2DM. Diabetic kidney disease is a main complication of T2DM and is commonly identified through urinary albumin excretion. Urine samples from ten individuals with T2DM were analyzed, indicating several specific Raman peaks that could be assigned to albumin. Due to the ability of Raman spectroscopy to detect urinary albumin, the authors propose a promising method for detecting T2DM noninvasively in future work [64]. Each of these independent studies is important for their potential to be used for the early identification of diabetes via the minimally invasive monitoring of biomarkers that have previously not been focused.

In a different study, the nonenzymatic glycation of collagen scaffolds was analyzed in T2DM mice at various time points. While the Raman peak positions due to collagen did not change between the groups, the relative intensity of the peaks after normalization increased as diabetic time progressed. These bands were positively correlated to the expression of anti-advanced glycation end products obtained by immunofluorescence imaging of the scaffolds, suggesting Raman spectroscopy can be used to monitor how the structure of collagen scaffolds is affected by nonenzymatic glycation in T2DM mice [65].

In one of the largest studies carried out using Raman spectroscopy, skin glycated proteins were investigated using a portable Raman spectroscopy system and fluorescence spectroscopy (Fig. 4). Ninety-four individuals who were either nondiabetic had insulin resistance or were diabetic were evaluated. Increased skin autofluorescence was noted for those individuals with insulin resistance and those who had diabetes compared to healthy individuals. Raman spectral bands related to changes in skin hydration, type I collagen, and protein glycation were noted for diabetic patients. A positive but weak correlation was also noted between the level of skin autofluorescence and the ratio of Raman bands indicative of glycated proteins. Although further

Fig. 4 Clinical procedure with fluorescence and Raman techniques. Reproduced with permission from WILEY-VCH Verlag GmbH & Co. KGaA, Weinheim [66]

work is needed, this information could be used in the future for noninvasive screening of diabetes and help to contribute to understanding the biochemical progression of the disease [66].

These studies indicate several opportunities to explore new potential biomarkers for diagnosing diabetes using Raman spectroscopy. Although the biochemical basis for many of these biomolecules is not well established, there exists an exciting opportunity to increase the sensitivity and specificity of diagnosis with additionally verified biomarkers.

2.4 General Application of Chemometric Methods for Indicating Diabetes Within Various Biological Samples

Although detecting new and known biomarkers using Raman spectroscopy for diagnosing diabetes has been fruitful, several research groups have leveraged the power of chemometric methods to simply investigate diagnosing the disease without requiring or depending on the presence of specific biomarkers. One of the greatest advantages of Raman spectroscopy is its ability to probe a sample's entire biochemical signature. By leveraging the contribution of all biochemical components, instead of narrowing the focus to one or two specific biomarkers, chemometrics can capitalize on the multitude of information obtained in a spectrum to objectively achieve highly sensitive and specific levels of diagnostic accuracy.

Several studies focused on analyzing blood samples using Raman spectroscopy and chemometrics. In another study by González-Solís et al., superparamagnetic clustering, a type of clustering-based chemometric method, was investigated to analyze Raman spectra of serum samples from 15 individuals diagnosed with T2DM and from 20 healthy controls. Results showed 97.5% sensitivity and 91.2% specificity for correctly diagnosing the class of serum; however, no validation of the model was reported [67]. Blood plasma samples obtained from healthy ($n = 8$) and type I diabetic individuals ($n = 12$) were investigated using Raman spectroscopy and Raman optical activity, electronic circular dichroism, and IR spectroscopy. LDA was used to evaluate each method individually, as well as combined. Interestingly, the best results were obtained when the combined data reached 92% sensitivity and 100% specificity after LOOCV. Raman spectroscopy was used in combination with PCA to successfully differentiate serum from individuals with T2DM, diabetic retinopathy, or those who are healthy. Mahalanobis distance, which measures the similarity between two sets of data for discrimination, was also shown to separate the Raman spectral data successfully; no validation of either method was included in the manuscript. However, these results were found to be more successful than those obtained by relying on the comparison of prominent Raman peak positions and intensities [68].

Two different studies focused on analyzing blood from animal donors to diagnose the disease. Red blood cells from healthy humans, healthy rats, T2DM humans, and STZ-induced and Alloxan-induced diabetic rats were investigated using Raman spectroscopy. In a unique experimental decision, PCA combined with an SVM classifier could successfully separate all five red blood cells, although a validation mechanism was not reported. Additional spectral differences were noted between the classes. It was determined that the STZ-induced diabetic rats were more similar to the human T2DM group than the Alloxan-induced diabetic rats [69]. Most recently, a study was shown to successfully separate the blood serum of rats given a high-fat diet treatment and considered pre-diabetic from those fed a normal diet, using partial least squares discriminant analysis (PLS-DA) combined with a ROC curve. The external validation results showed the algorithm was 100% successful at making donor-level predictions [70]. While these studies' potential is exciting, it must be noted that the work should be repeated in human trials.

Other attempts to use Raman spectroscopy combined with chemometrics for diagnosing diabetes were made using other, non-blood-based, biological samples. A portable SERS system was used in one study to analyze urine samples collected from 20 diabetic patients and 21 healthy volunteers. PCA and LDA were used for analyzing the SERS data and indicated 85% sensitivity and 90.5% specificity of the method for discriminating between the two groups. The model was deemed accurate, yielding an area under the ROC curve of 0.836, although no further validation was reported [71]. Alternatively, a portable Raman spectrometer was used to collect in vivo Raman spectra from four different skin sites: left earlobe left inner arm, left thumbnail, and left median cubital vein, each from 11 individuals with T2DM and 9 healthy controls. ANNs separated the two groups with 88.9–90.9% accuracy for the varying sample sites. A second model built using PCA and SVM resulted in lower levels of diagnostic accuracy. Both methods were validated using a tenfold CV. The results of the ANN model were comparable to those obtained using the invasive capillary blood glucose test, showcasing the technique's success for generating objective and noninvasive diagnoses [72].

Vieira et al. used Raman spectroscopy to investigate spectroscopic changes in the dorsal root ganglia (DRG) due to diabetic neuropathy. STZ-induced diabetic neuropathic (hyperalgesia) rats were analyzed before and after photobiomodulation therapy (PBMT). PBMT is shown to treat neuropathy by relieving pain. Raman spectra showed characteristic DRG bands had increased intensities in the hyperalgesia rats, which were then reduced in the spectra collected after PBMT therapy. An LDA model was built to differentiate between the different groups with 86% success, although no validation was reported. Further research here may provide a new avenue for monitoring the treatment of diabetes and identifying potential routes for detecting the onset early on [73]. In one study by Pacia et al., a confocal Raman imaging system was used to analyze mice models' endothelium representing diabetes, hypertension, or cancer metastasis from controls. Hierarchical cluster analysis (HCA) of the Raman spectra indicated sensitivity and specificity levels between 88 and 96% for successfully distinguishing between groups. However, no model validation was reported (Fig. 5) [74]. Interestingly, these works reveal that various chemometric methods

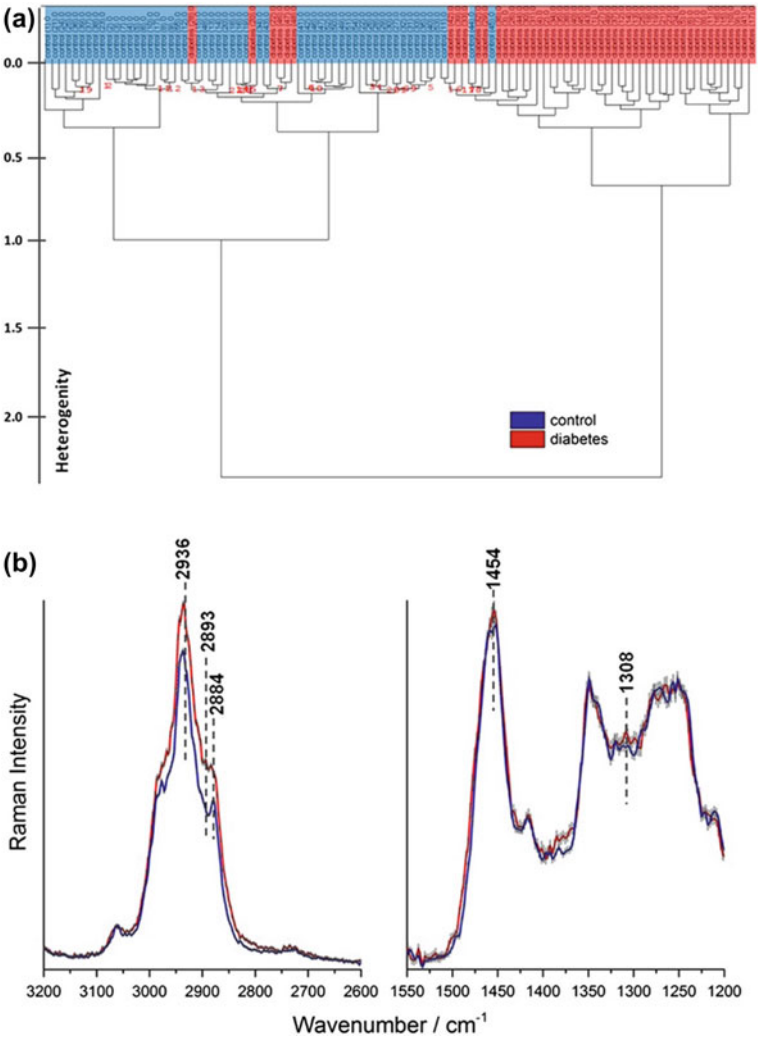

Fig. 5 The analysis of single and average spectra of the endothelium in the murine model of diabetes. The result of HCA analysis for the single endothelium spectra was obtained for db + (blue) and db/db (red) mice. **a** The average spectra of the endothelium of control (blue) and diabetes (red) mice with the standard error on each data point, **b** in the 1550–1200 cm^{-1} range, the Raman intensity is about threefold magnified relatively to the high wavenumber region. Reproduced with permission from John Wiley & Sons, Ltd. [74]

can be used to analyze Raman spectral data to achieve the same task. While some methods work better than others, and some studies do not report using a validation mechanism, all are shown to achieve similar levels of success. Further, utilizing Raman spectroscopy with chemometric methods to distinguish between healthy and diabetic biological samples shows as much success as those studies that focus on utilizing specific new or known biomarkers for diagnoses.

Raman spectroscopy has been heavily explored in recent years to identify diabetes biomarkers and directly diagnose the disease itself. Many different avenues have been explored, but the results of all recent studies described herein signify the great potential of the method. The obvious next step would be to pursue large-scale studies that can confirm the method's statistical significance and indicate its potential application for clinical use. This is further discussed in the Critical Evaluation section.

3 Infrared Spectroscopy

Similar to the research completed using Raman spectroscopy, infrared spectroscopy was also explored for detecting diabetes in various recent research. Several groups capitalized on the advantages of IR spectroscopy to identify novel biomarkers or biochemical components useful for identifying the disease. The articles reviewed in this section include those which have used either far-, mid-, or near-IR radiation. Near-IR radiation (~14,000–4000 cm^{-1}) is highest in energy and typically excites combination modes or overtones of molecular vibrations, mid-IR (~4000–400 cm^{-1}) typically excites fundamental vibrations, and far-IR (~400–10 cm^{-1}), which is the lowest in energy, is used for rotational spectroscopy and low-frequency vibrations. [75] The mid-IR region is most typically used in the research reviewed herein due to the absorption radiation of most organic compounds and inorganic ions being within that region. Notably, near-IR spectroscopy is not considered a form of vibrational spectroscopy, but due to its complementarity, the few studies which used it are still included in this review.

The most common infrared spectrometer used in the reviewed work herein is the Fourier transform infrared (FTIR) spectrometer due to its simultaneous collection of spectral data across a wide spectral range and transforming that data into a spectrum. Further, the attenuated total reflectance (ATR) accessory is also often used with FTIR spectroscopy. It enables the user to directly measure samples in the solid or liquid state without further sample preparation, typically required for transmittance FTIR [76]. In addition, many of the studies reviewed in this section incorporated chemometric methods for diagnosing diabetes due to the aforementioned benefits.

The following research studies focus on identifying diabetes through detection of glucose levels within bodily fluids, detection of novel biomarkers, or through the strict use of chemometric models.

3.1 Monitoring Blood and Saliva Glucose Levels for Indicating Diabetes

Similar to those studies conducted using Raman spectroscopy, numerous researchers have pursued using IR spectroscopy to improve the identification of elevated glucose levels to diagnose diabetes. Liu et al. evaluated the precision of four different non-invasive glucose sensing methods based on near-IR (NIR) spectroscopy, including pulse-based differential NIR spectroscopy, occlusion-based differential NIR spectroscopy, traditional NIR diffuse reflectance spectroscopy, and position diffuse NIR reflectance spectroscopy. By evaluating the measurement precision, it was determined that traditional NIR diffuse reflectance spectroscopy and position diffuse NIR spectroscopy have the greatest potential to be used in the future as glucose sensing methods [77]. Then, Jintao et al. employed a NIR fiber optic probe system to analyze plasma obtained from diabetic and normal rats to develop an in vivo blood glucose assay (Fig. 6). Spectral data were collected at 0, 15, 30, 45, 60, 90, 120, 180, and 360 min after glucose injection, with blood glucose levels, were recorded simultaneously. Two chemometric methods were employed for analyzing the data, including a PLSR model and an ANN non-regression model, each evaluated using external validation. After validation, the most optimal PLSR model reached a correlation coefficient of 96.22%. The ANN model was less successful, with the most optimum

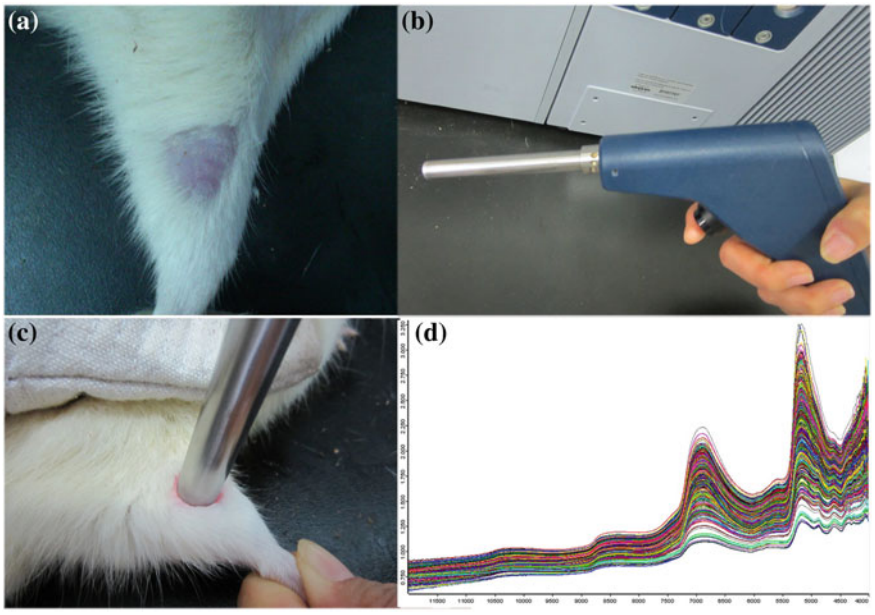

Fig. 6 The process of collecting NIR spectra **a** rat's hind leg shaved; **b** the NIR fiber-optical probe; **c** collection of the NIR spectra; **d** NIR spectra. Reproduced with permission from Elsevier B.V. [78]

model achieving a correlation coefficient of 92.79% after validation. Unsurprisingly, the regression model showed great success for this type of study, suggesting the influence of selecting a chemometric method on accomplishing the desired diagnostic goals. [78]

In different work, attenuated total reflectance Fourier transform infrared (ATR-FTIR) spectroscopy was used to evaluate the saliva of non-diabetic, diabetic, and insulin-treated diabetic rats to identify biomarkers related to glucose. Two different chemometric methods, including PCA-LDA and HCA, both with LOOCV, were used to differentiate between the three groups. Interestingly, both methods reached 95.2% accuracy. Further, two spectral bands correlate with glycemia strongly and were shown to classify diabetic rats with greater than 93% sensitivity and specificity. The potential for non-invasive diabetic detection is clearly illustrated through the analysis of saliva herein [79]. While more research is necessary to pursue IR spectroscopic detection of glucose levels for diagnosing diabetes, these studies present strong support for the potential of the method to achieve this goal.

3.2 Monitoring Novel Biomarkers for Indicating Diabetes

New and alternative biomarkers have also been explored using IR spectroscopy to identify diabetes easier and more accurate. Several research studies focused on the analysis of fingernails for meeting this need. In one in-depth study, the characterization of microstructures (including both surface morphology and roughness as well as density and calcium content), materials (modulus and hardness), and macromolecules (disulfide bond content, protein content and related secondary structure) of fingernail plates were investigated. Specifically, human fingernail plates of T2DM controlled ($n = 20$), T2DM uncontrolled ($n = 25$), and healthy people ($n = 30$) were analyzed using FTIR spectroscopy. The results indicated that the general quality of the nail plate degrades within the T2DM controlled group but degrades even further in the T2DM uncontrolled group. Specifically, the T2DM uncontrolled group has the most porous, the least amount of dense materials (minerals) present, highly altered surface morphology, increased surface roughness, decreased amount of modulus and hardness of the nail, and decreased calcium and protein content. These values were optimal in healthy individuals and fell in the middle for the controlled T2DM group. This research poses an interesting avenue for exploring secondary complications due to T2DM, with the potential to translate the changes observed within fingernail plates into an early and noninvasive diagnostic mechanism in the future [80]. Coopman et al. also investigated fingernails, this time using ATR-FTIR spectroscopy as a tool for assessing glycation in diabetics. Fingernail clippings were obtained and analyzed from 105 healthy individuals and 127 individuals with T2DM. Using fructosamine 3-kinase, glycation and deglycation experiments of the clippings were performed. Glycation was indicated by spectral features, including increased absorption at 1047 cm^{-1}; after deglycation, there was a general decrease in the area under the curve between 970 and 1140 cm^{-1}. It was found that the glycated nail protein

concentrations of diabetics were significantly higher than those of healthy controls, with ROC analysis yielding 82% specificity and 90% sensitivity with a cut-off value of 1.28 μmol/g nail, illustrating an alternative method for the non-invasive and effective detection of diabetes [81]. Lastly, an investigation of fingernails was executed by Monteyne et al. Here, 52 individuals with T2DM and 107 healthy controls were included in the study. Of the 107 healthy control fingernail samples, 21 were glycated in vitro at different concentrations with a glucose solution, and all individuals' fingernails were analyzed using NIR spectroscopy. The effect of glycation had a noticeable impact on the spectral signatures, indicating a potential avenue for monitoring the onset and progression of diabetes. PLS-DA was performed to differentiate between the T2DM group and the healthy individuals, where 100% diagnostic accuracy was achieved when tested using an independent validation set. Interestingly, the advantage of incorporating chemometrics for diagnosing diabetes completely non-invasive and objective is again supported herein [82]. This triplet of large studies increasingly indicates IR spectroscopy as a potential method for a completely noninvasive method for detecting diabetes, suggesting an emphasis may be placed on analyzing fingernails in future work.

Tissue samples were analyzed in two different studies for diabetes detection. In one study, Varma et al. analyzed tissue from histologically normal kidneys ($n = 4$), histologically normal kidneys obtained from diabetic subjects ($n = 4$), and kidneys with evidence of diabetic nephropathy ($n = 5$). Spectral data were obtained from the glomerular basement membrane, tubular basement membrane, and mesangium of the tissue samples. PCA with LDA was shown to distinguish between the two control groups and the diabetic group and between all three groups with a very high level of separation for each tissue section analyzed (Fig. 7). The authors also identified differences in intensities of two different spectral frequencies, which could be used for an alternative separation of the groups; notably, the results of chemometrics are more definitive. However, a validation mechanism was not reported [83]. Kidney tissue sections were then studied by a different group using probe-based NIR spectroscopy. The sections were obtained from 27 individuals with normal histological findings, 26 individuals with diabetic neuropathy, and 11 with T2DM. The spectral signatures indicated differences in carbamoylation and glycation between the groups; these differences were restored after treatment with the deglycating enzyme fructosamine 3-kinase. PCA and soft independent modeling of class analogy (SIMCA) with CV showed that the groups could easily be separated [84].

Other researchers studied bodily fluids, including blood and saliva, were studied by other researchers for developing a diagnostic test for diabetes using IR spectroscopic detection of alternative biomarkers. Mazmuder et al. used FTIR spectroscopy to study serum samples from 85 humans, including individuals with T2DM who did or did not have retinopathy ($n = 30$, each) and healthy controls ($n = 25$). SVM models could discriminate between all three groups with an overall accuracy of 90.5% after ten-fold CV. The differences between spectral signatures indicated a variety of biochemical components as potential spectroscopic biomarkers, including carbohydrate and polysaccharide content, total lipid content, protein phosphorylation, and the Amide II group [85]. Recently, a method was devised to detect methylglyoxal (MGO),

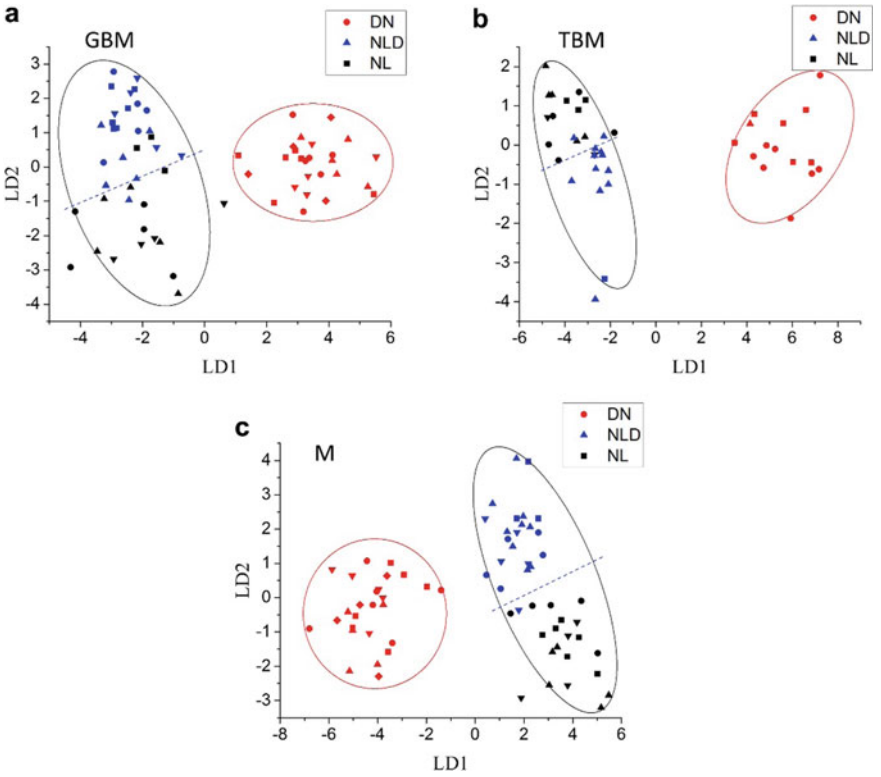

Fig. 7 Linear discriminant analysis (LDA) of spectral data extracted from the glomerular basement membrane (GBM), tubular basement membrane (TBM) and the mesangium (M) of patients categorized as normal diabetic (NLD), normal nondiabetic (NL), and diabetic nephropathy (DN). LDA was performed using the complete spectral data set for each of the features studied: **a** GBM, **b** TBM, and **c** M. Reproduced with permission from the International Society of Nephrology; published by Elsevier Inc. [83]

a disease-causing factor of diabetic cardiovascular complications. Here, the reaction between MGO and o-phenylenediamine produced a product with strong absorption in the far-IR range. Spectral analysis indicated that MGO could be detected at concentrations between 5 and 2500 nmol/mL, and the concentration of MGO within test blood samples was determined with 95% accuracy. The results indicated the method could be used in future clinical applications to determine the concentration of MGO and relate its presence to diabetes. [86] ATR-FTIR spectroscopy was then used in one study to differentiate between the saliva of individuals with diabetes ($n = 20$), individuals with different kinds of psoriasis ($n = 35$), and healthy controls ($n = 20$). The collected spectral data showed differences in the Amide I and Amide II bands, suggesting the secondary structure of proteins is altered between the groups. It was further found that the protein secondary structure between individuals with plaque

psoriasis is similar to that found within patients with diabetes. Based on this information, the authors were able to conclude ATR-FTIR spectroscopy could be used as a tool to explore any potential link between psoriasis and diabetes, and further aid in developing effective treatment plans [87].

Lastly, femurs of type I diabetic (n = 6) and control (n = 5) rats were investigated using FTIR spectroscopy. The results of the analysis indicated several important characteristic differences between the two groups; these include decreased levels of mineral content, microhardness, and collagen maturity in the diabetic femurs, as well as an increase in carbonate content and size and maturation of hydroxyapatite crystals. These factors suggest that diabetes harms bones, providing information for relating the structure and function of diabetes on bone health as well as for potential diagnostic applications [88].

Given the plethora of different biomarkers which were identified in the research reviewed herein, it is obvious that there is great potential in alternative methods to identify diabetes which may reach even greater levels of accuracy than current tests can achieve. Of course, large-scale studies are required to pursue and investigate these hypotheses further to understand which the most promising, and further analysis are is required to understand the biochemical basis for the novel IR spectroscopy-determined biomarkers.

3.3 General Application of Chemometric Methods for Indicating Diabetes Within Various Biological Samples

The ability to pinpoint new and known biomarkers for diagnosing diabetes using IR spectroscopy has shown varying levels of success. A great advantage of chemometric methods resides in the ability to overlook specific biomarkers while monitoring minute changes in overall spectral data. Further, the advantages of incorporating chemometrics into diagnostic studies include the ability to make accurate and quantitative decisions without the need for subjective interpretation. The building and use of chemometric models allow for the method to be used in a variety of settings using the same standard, increasing the efficiency and efficacy of early and accurate diagnoses. In this section, research that has applied chemometric methods to identify diabetes using IR spectroscopy and without the use of biomarkers are reviewed.

Analysis of blood was used in most of the research covered in this section. ATR-FT mid-IR spectroscopy was used to analyze serum samples from 65 patients with T2DM and 55 healthy volunteers. A SVM model optimized using a genetic algorithm (GA) reached 100% sensitivity, 95.45% specificity, and 97.87% accuracy for discriminating between the two groups during external validation, indicating one of the most successful reports yet for detecting T2DM [89] Yang et al. employed ATR-FTIR spectroscopy for the detection of prediabetes via analysis of peripheral blood. Here, fasting blood glucose levels and glucose levels at hour 2 during the OGTT were

measured from 112 individuals to determine the control group and the prediabetic group. ATR-FTIR spectra were recorded from those blood samples simultaneously; classification and regression trees (CART) and extreme gradient Boosting (XGBoost) ensemble algorithms were both used to develop the prediabetes diagnostic tests. The CART model achieved 80% specificity and 95% sensitivity, while the XGBoost model reached 100% specificity and 85% sensitivity. The accuracy for the CART and XGBoost models were 86.67% and 93.33%, respectively. All results were reported after external validation. The superior XGBoost method indicates a real potential for the accurate detection of prediabetes within individuals [90]. Guang et al. also utilized ATR-FTIR spectroscopy in combination with XGBoost to analyze whole blood samples, here to diagnose T2DM. Whole blood was collected from 51 T2DM individuals and 55 healthy individuals. The most optimum XGBoost model achieved a sensitivity of 95.23%, specificity of 96%, and accuracy of 95.65% after external validation, further illustrating the success of IR spectroscopy with chemometrics for identifying diabetes [91]. Interestingly, this chemometric method of XGBoost was not explored in any other recent studies, despite its success in these two works.

A different study used IR spectroscopy to investigate non-alcoholic steatohepatitis (NASH), which is associated with the occurrence of T2DM as well as cardiovascular complications. In the largest study reviewed, 395 severely obese individuals who underwent a bariatric procedure were considered in the study; 66 of those individuals had NASH. Spectra of serum from the individuals were analyzed using a logistic regression model, with the performance evaluated using the area under the ROC curve (AUROC). After external validation, the AUROC was 0.77, with an associated sensitivity of 69% and specificity of 76%. When a composite model was built, incorporating aspartate aminotransferase levels, triglyceride levels, and waist circumference in addition to the IR spectral data, the AUROC increased to 0.84 after external validation. While intriguing, this study could potentially benefit from a different and less complicated method of analysis to reach higher classification results; however, based on the sample size, this study provides one of the most realistic evaluations of IR spectroscopy for identifying diabetes [92]. In a related manner, Bernardes-Oliveira utilized ATR-FTIR to investigate blood plasma obtained from 50 healthy pregnant women and 50 pregnant women with gestational diabetes mellitus. Several different chemometric methods were employed for separating the two groups, including LDA, quadratic discriminant analysis (QDA), and SVM. The best results were obtained with a GA-LDA model, which reached accuracy, sensitivity, and specificity levels all of 100% after validation using an independent test set. Lipids and proteins were found to be the most useful spectral features for separation. These results indicate a very successful route for low-cost and minimally invasive detection of gestational diabetes mellitus [93].

In a final study, pancreatic tissues were examined from healthy and the non-obese diabetic model for type 1 diabetes mice as well as from humans and analyzed using both Raman spectroscopy and FTIR spectroscopy. Analysis of the data collected through orthogonal PLS-DA with external validation resulted in the successful understanding of the biochemical profiles of the different pancreatic tissues. This work provides a stepping stone for generating in vivo diagnostic assessments through the

analysis of pancreatic biochemistry, but results of the chemometric modeling were not reported [94].

Interestingly, the methods which were used to analyze IR spectroscopic data to detect diabetes were just as successful as those summarized using Raman spectroscopy. IR spectroscopy can identify potential novel biomarkers for monitoring the progression of the disease, and the spectra can be further analyzed via chemometric methods for objective and accurate detection of diabetes. Clearly, due to the high number of publications and research generated in the last five years alone, the utility of the method is quite promising.

4 Critical Evaluation

There has been an evident success in advancing vibrational spectroscopy for detecting diabetes in the past five years. Both infrared and Raman spectroscopy have shown the obvious potential to not only monitor spectroscopic biomarkers throughout both the onset and various forms of treatment of the disease but to also be able to objectively detect the disease within biological samples with high levels of diagnostic accuracy. It would be difficult to argue against the capacity of vibrational spectroscopy for future use in clinical settings for detecting and diagnosing diabetes. While other analytical methods for diagnosing diabetes have also been shown to be useful, including chromatography-based tests, enzymatic-based assays, and antibody-based immunoassays, these are beyond the scope of this review and the reader is referred to other work for more information [95–98].

A summary of all studies in this review which were conducted using Raman spectroscopy and using IR spectroscopy is seen in Tables 1 and 2, respectively. These tables synthesize the category of study, which was accomplished, the type of sample which was used (with animal models noted as appropriate), the number of samples analyzed in the study, the type of chemometric methods used, if any, and the type of validation that was employed if any. It is important to summarize these factors, as they can have a noticeable impact on the results that are reached, especially including the sample size used and the method of validation employed.

Based on this summary, there are some interesting conclusions that can be drawn. Although more research was accomplished using Raman spectroscopy, those studies which used IR spectroscopy more frequently analyzed a greater number of samples. This is an important distinction to make, as large-scale clinical trials are necessary to validate findings that are made in smaller work [100]. While small-scale studies can show success, the true nature of that success will not be realized until a large study is conducted. Additionally, 12 of the 43 studies reviewed utilize animal models instead of human samples. While animal models are well established for studying diabetes [101, 102], repeating the work using human donors, which typically have more complex regulatory measures. A positive study conducted within animals does not guarantee its success within humans [103, 104]. Therefore, a statistically significant number of human donors is of utmost importance to ensure that a research plan

Table 1 Summary table of all research studies reviewed herein which used Raman spectroscopy

Reference	Study Category	Sample	# of Samples	Chemometric method	Type of validation
Birech [55]	Novel biomarkers, SERS	Whole blood	40, rats	None	N/A
Chege [56]	Novel biomarkers, SERS	Whole blood	50, rats	PCA	None reported
Flores-guerrero [64]	Novel biomarkers, probe	Urine	10	None	N/A
González-solís [61]	Novel biomarkers	Blood serum	35	PCA, LDA	CV
González-solís [67]	General chemometrics	Blood serum	35	SPC	None reported
González-Viveros [45]	HbA1c	Commercial HbA1c	3	PCA, FFNN	Fivefold CV
Guevara [72]	General chemometrics, portable	Various skin sites	20	ANN, PCA, SVM	Tenfold CV
Ju [53]	Blood glucose, SERS	Interstitial fluid	Not reported, mouse	None	N/A
Li [51]	Blood glucose	Nailfold	12	PCA, BP-ANN	None reported
Lin [62]	Novel biomarkers, SERS	Blood plasma	80	PCA, LDA	External validation
Lin [48]	HbA1c, LTRS	Red blood cells	90	PCA, LDA	External validation
Pacia [74]	Novel biomarkers	Tissue	26, mice	HCA	None reported
Paolillo [66]	Novel biomarkers, portable	Skin	94	None	N/A
Ralbovsky [70]	General chemometrics	Blood serum	47, rats	PLS-DA, ROC	External validation
Roman [63]	Novel biomarkers	Extracellular Vesicles	55	CA, PLSR	None reported
Shi [65]	Novel biomarkers	Collagen scaffolds	10, mice	None	N/A
Silveira Jr [60]	Novel biomarkers	Blood serum	44	PLSR	LOOCV

(continued)

Table 1 (continued)

Reference	Study Category	Sample	# of Samples	Chemometric method	Type of validation
Singh [68]	Novel biomarkers	Blood serum	Not reported	PCA	None reported
Singh [52]	Blood glucose, probe	Blood serum	20	PLSR	External validation
Šťovíčková [99]	General chemometrics	Blood plasma	20	LDA	LOOCV
Vieira [73]	Novel biomarkers	Dorsal root ganglia	48, rats	PCA, LDA, LDA-LDA	None reported
Villa-Manríquez [46]	HbA1c, probe	Various skin sites	86	PCA, SVM, ROC	External validation
Wang [69]	General chemometrics	Red blood cells	Not reported, rats and humans	PCA, SVM	None reported
Zheng [54]	Blood glucose, wearable probe	Skin	10	PLSR	LOOCV
Zou [71]	General chemometrics, portable SERS	Urine	41	PCA, LDA, ROC	None reported

can be applied to the general population and not a small subset of individuals, as is commonly targeted in work reviewed herein. Unfortunately, no recent research has accomplished this goal yet.

The category of study employed is notably diverse between the research reviewed herein. Many (in fact, 19 of the 25 studies using Raman spectroscopy and 12 of the 18 studies using IR spectroscopy) focus on identifying new or known biomarkers for diabetes; interestingly, 22 of these also utilize chemometrics in addition to monitoring spectral biomarkers. Many of the noted novel biomarkers highlighted in the previous papers are common biochemical components that are not necessarily specific to diabetes or have not been previously linked to the development and progression of diabetes. While some biomarkers, such as glycated hemoglobin and blood glucose levels, are well-established biomarkers for the disease, the papers which applied chemometrics methods without searching for the presence of biomarkers are shown to be just as successful as those which focus solely on detecting them. While understanding the biochemical differences between healthy and diseased individuals is important, a significant advantage of vibrational spectroscopy is the ability to pinpoint spectroscopic differences without fully understanding the biochemical cause, saving both time and effort for making a diagnosis. Additionally, multiple biochemical components contribute to the vibrational spectrum produced, including contributions from biochemical components that the scientific community may not yet consider for the disease in question. Through probing the entire biochemical composition of

Table 2 Summary table of all research studies reviewed herein which used infrared spectroscopy

	Study category	Sample	# of Samples	Chemometric method	Type of validation
Anty [92]	General chemometrics	Blood serum	395	ROC	External validation
Bernardes-Oliveira [93]	General chemometrics	Blood plasma	100	LDA, QDA, SVM, PCA, GA	External validation
Bottoni [87]	Novel biomarkers	Saliva	75	PCA	None reported
Bozkurt [88]	Novel biomarkers	Femurs	11, rats	None	N/A
Caixeta [79]	Glucose monitoring	Saliva	21, rats	PCA, LDA, HCA, ROC	LOOCV
Coopman [81]	Novel biomarkers	Fingernails	232	ROC	None reported
De Bruyne [84]	Novel biomarkers, probe	Tissue	64	PCA, SIMCA	CV
Fang [89]	General chemometrics	Blood serum	120	PCA, GA, SVM	External validation
Guang [91]	General chemometrics	Whole blood	106	PCA, XGBoost	External validation
Jintao [78]	Glucose monitoring, probe	Blood plasma	30, rats	PLSR, ANN	External validation
Liu [69]	Glucose monitoring	Various skin sites	Not reported	None	N/A
Mazmuder [85]	Novel biomarkers	Blood serum	85	PCA, LDA, SVM	Tenfold CV
Monteyne [82]	Novel biomarkers	Fingernails	159	PLS-DA	External validation
Nord [94]	General chemometrics	Tissue	Not reported, mice and humans	Orthogonal PLS-DA	External validation
Sihota [80]	Novel biomarkers	Fingernails	75	None	N/A
Varma [83]	Novel biomarkers	Tissue	13	PCA, LDA	None reported
Wu [86]	Novel biomarkers	Blood serum	3	None	N/A
Yang [90]	General chemometrics	Whole blood	112	PCA, XGBoost, CART	External validation

the sample and not limiting the focus to a specific biomarker or two, the specificity and accuracy for identifying a disease can potentially be increased [105]. For this reason, those papers that incorporate chemometric methods should be focused on in the future. The advantages of chemometrics allow it to be used as an objective and accurate approach for identifying diabetes without limiting the focus to one or two notable biomolecules.

It should be noted that the studies reviewed herein which incorporated the use of chemometrics faced their own set of limitations. While almost every study mentioned reached high levels of diagnostic accuracy, comparable with currently employed diabetes diagnostic methods, proper validation of the applied chemometric method is not always observed (Tables 1 and 2) [106]. There are two main types of validation typically used in diagnostic studies. The first is considered cross-validation and refers to the general method of testing the model's performance with the same set of data used to build it. Cross-validation may often overstate the success of a model due to overfitting and provide overly optimistic results; this is especially true when studies are conducted with small sample sizes [100, 107, 108]. Methods of cross-validation include leave-one-out (spectrum or sample) and n-fold cross-validation. Leave-one-out cross-validation involves the automatic process of leaving either a single spectrum or all spectra from one sample out of the model building process; the data left out is then used to test the model's performance. This process is repeated until all data has been left out. Similarly, n-fold cross-validation randomly divides the total dataset into n groups and builds the model with n-1 groups; the group which is left out is again repeatedly used for evaluating the model's performance. On the other hand, external validation is a much more reliable and trustworthy method for interpreting the capabilities of a chemometric model. External validation refers to testing a model with independent data (i.e. data that was not involved in the model building process). Successful external validation is a key indication that a model is not biased to the data used to build it. It is likely to be successful when expanded to a real-world application, such as use within clinical settings [100, 107]. While crucial, external validation requires a larger number of samples to be incorporated into a study, which is not always feasible due to various issues such as the availability of volunteers or funding.

Interestingly, among those studies which incorporated chemometrics, all reported results achieved sensitivity, specificity, and accuracy levels greater than 80% and up to 100%. While the definition of a successful varies for several reasons, all studies that used chemometrics can be considered as erring on the side of success based on these parameters alone. Interestingly, the types of samples used, the number of samples studied, and the chemometric method employed vary among these studies widely. Within this small subset of research, a pattern for a useful combination of vibrational spectroscopy cannot be established. While various biological samples were used among these studies, including urine, saliva, fingernails, and others, blood seemed to be the most frequently employed, suggesting this biological specimen as the one to focus on in the future. Unsurprisingly, among those studies that focused on identifying biomarkers and using chemometrics, glucose and glycated proteins were the most commonly targeted biomolecules. A variety of chemometric techniques are

used in relatively similar frequency levels, suggesting that the method chosen may not significantly impact the success of the research. Again, it should be noted that all studies reviewed here are considered small compared to large-scale clinical trials. While some results are reported after external validation, all results should be taken with a degree of caution.

Assuming the "perfect" (ideally a large-scale trial using human samples and with proper external validation of the chemometric method) trial can be implemented to verify the real success of vibrational spectroscopy for detecting diabetes, there remain further hurdles to overcome to introduce the method to clinical settings. While this topic is beyond the scope of this review, several prominent research groups have addressed this issue [21, 22, 109, 110]. Importantly, vibrational spectroscopists must prove to those in the medical community that spectroscopy can be used as a valid means for diagnosing T2DM for the method to enter clinical settings smoothly. A unified approach to analyzing samples and the chemometric model employed would also make implementation much more straightforward to understand.

Despite the many issues which still need to be addressed, it is clear that vibrational spectroscopy holds unique advantages for diagnosing diabetes. Both IR and Raman spectroscopy is easy-to-use, fast, and simple methods that provide objective and accurate diagnostic predictions. The specificity of the methods provides crucial details that can differentiate between stages of the disease and monitor disease progression and the effects of treatment. Vibrational spectroscopy is shown herein to have an incredible potential to revolutionize and simplify the way diabetes is diagnosed, creating great opportunities for early intervention and treatment, with the potential to prevent the onset of diabetes-related complications and even save lives.

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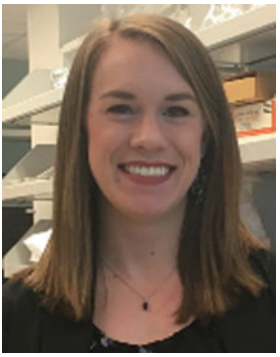

Nicole M. Ralbovsky earned her Ph.D. from the University at Albany in December 2020; there, she worked under the advisement of Professor Igor K. Lednev and conducted research using vibrational spectroscopy and machine learning to investigate and develop novel methods for improved medical diagnostics. Nicole joined the pharmaceutical company Merck in November of 2020 and is currently a Senior Scientist in the Data Rich Measurements subgroup of Analytical Research and Development. Nicole's efforts at Merck focus on using Raman hyperspectral imaging, multivariate data analysis, and process analytical technology to build deep process and scientific understanding of vaccine process research and development.

Igor K. Lednev is a Distinguished Professor in the Department of Chemistry at the University at Albany, State University of New York. His research focuses on developing novel laser spectroscopy for forensic purposes, medical diagnostics, and understanding the fundamental mechanism of protein folding and aggregation. He coauthored over 250 publications reaching h-index of 61. He is a cofounder and CTO of startup company SupeMEtric LLC. Lednev is on editorial boards of Journal Raman Spectroscopy, Forensic Chemistry and Spectroscopy magazine. He served as an advisory member on the White House Subcommittee for Forensic Science. He is a Fellow of the Society for Applied Spectroscopy and the Royal Society of Chemistry. He received several prestigious awards, including Gold Medal Award from the Society for Applied Spectroscopy, Guest Prof. Fellowship from the Friedrich-Schiller-University, Jena, Germany and Research Innovation Award from Research Corporation.

Photoacoustic Spectroscopy Mediated Non-invasive Detection of Diabetics

Deepak Devadiga and T. N. Ahipa

Abstract Day by day, the number of diabetic people is increasing worldwide. Since abnormal glucose levels in human blood cause diabetes, analysis of blood glucose concentrations is essential during diabetes therapy. Moreover, the existing glucose monitoring approaches commonly emphasize the invasive analysis method, which is generally time-consuming, painful, costly. Besides, these methods are prone to cause tissue damage. On the other hand, the non-invasive method of analysis overcomes this set of limitations. Different optical approaches have been used for the non-invasive detection of blood glucose levels. Interestingly, the photo-acoustic approach is one such technique that provides a high level of sensitivity during the method of analysis. Thus, this chapter introduces diabetics, followed by the importance of non-invasive technology compared to invasive technology. Further, it discusses the general principle of the photoacoustic spectroscopy and its application in monitoring glucose levels.

Keywords Photoacoustic spectroscopy · Glucose · Diabetes · Sensors · Non-invasive method · Blood

1 Introduction

Diabetes mellitus is a group of metabolic disorders identified by high blood sugar levels in the human body over a prolonged period and is well known as diabetes. However, diabetes occurs mainly in two instances, one where the pancreas secretes little insulin or no insulin at all and the other one where the insulin produced by the pancreas fails to work; this condition is known as the insulin resistance condition. The millions of cells in our body need food in an elementary form to make energy. When

D. Devadiga · T. N. Ahipa (✉)
Jain University, Jain Global Campus, Bangalore, India
e-mail: tn.ahipa@jainuniversity.ac.in

D. Devadiga
e-mail: d.deepak@jainuniversity.ac.in

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we consume food, our diet is broken down into basic sugar called glucose that supplies the body with the required energy for everyday activities. As the produced sugar cannot reach the cells, the insulin is released by the pancreas to act as a carrier and help the sugar reach into the cells and produce energy. Whenever the insulin fails to help this process, the sugar level in the blood increases dramatically. Eventually, it causes hyperglycemia, resulting in severe medical conditions such as kidney failure, tissue damage, blindness, heart disease, stroke, etc. Finally, it leads to death if left untreated [1]. The World Health Organization and International Diabetes Federation have addressed that diabetes is a primary concern affecting the world. Moreover, the current diabetes infection rate is around 382 million and is anticipated to reach approximately 592 million in 25 years [2–4]. Further, Cho et al. [4] mentioned that 451 million individuals were affected by diabetes in 2017. The patient numbers are likely to increase to more than 693 million by 2045 across the Globe [5].

There are two kinds of diabetes, *i.e.,* diabetes type 1 (sudden drop in glucose levels due to insufficient insulin production in the pancreas) and diabetes type 2 (high glucose levels due to ineffective use of insulin).

Diabetes type 1: The body's immune system is mainly responsible for fighting harmful foreign invaders like bacteria and viruses. Whereas, in people with diabetes type 1, the immune system attacks the insulin producing beta cells and destroys them in the pancreas. Thereby, the production of insulin stops in the body. Every 25 years, the prevalence of diabetes type 1 in children doubles [6, 7]. At present, the average loss of about 11–12 years of the life span was noted in the diabetes type 1 patients [8, 9]. Moreover, loss of life span is slightly higher in patients diagnosed before age 15 compared to those diagnosed after age 30 [9]. However, no therapeutic approach has been effective in preventing or curing diabetes type 1 [10, 11]. Since insulin is not produced in the body of patients who have diabetes type 1, insulin is regularly injected into their body, i.e., either by using injections insulin is injected into soft tissue, like the arm, buttocks, or stomach, numerous times per day or by using insulin pumps, which supply the insulin into the body via a small tube. In addition, blood sugar testing is essential to manage diabetes type 1, as glucose levels can go up and down quickly.

Diabetes type 2: This type of diabetes is caused by relative insulin deficiency because of beta-cell dysfunction [12–14]. Moreover, it frequently exists with insulin resistance. In all the cases of diabetes mellitus, 80% of the cases are of diabetes type 2. However, till today it remains an ill-defined type of disease. Also, there is no precise diagnostic criteria exist for diabetes type 2. Currently, 6 years were shortened in the life span due to diabetes type 2. However, it reaches 12 years in patients with diabetes type 2 at a younger age [15]. Several medications are available to treat diabetes type 2, but none of them has been proven to affect the progressive decline in beta-cell function over time significantly. RISE study on the patients with early diabetes type 2 revealed that function of beta cells was improved on treatment for 1 year with metformin, insulin plus metformin, or metformin plus GLP-1 analog. However, these positive effects vanished in 3 months when the treatment withdrawed [16]. Similar results were noted in the ACT NOW study, where the positive effects

of pioglitazone on beta-cell function is vanished after discontinuing the treatment [17, 18].

Both types of diabetes do not have an effective treatment, which means that regular monitoring of glucose in diabetic patients is essential for the rest of their lives. Numerous approaches have been developed to estimate glucose levels, including capacitive, coulometric, optical, enzymatic-electrochemical and non-enzymatic electrochemical [19–30].

Current measurement approaches are focused mainly on the invasive method, which uses the patient's blood. Most of the time, these technologies are expensive and may damage tissues. Moreover, these invasive approaches are always associated with a high risk of infection [31]. In contrast, various optical techniques have been available nowadays and used to monitor glucose levels in a non-invasive manner [32–34]. The main aim of these studies is to develop a technique with less pain and low infection risk. In these techniques, fingertips (where the interstitial fluid is present) are commonly used for measurement. Also, these measurements can be made by using a variety of natural areas, like saliva, earlobe, sweat. In this context, the photoacoustic approach emerged as one of the available non-invasive approaches, which is not affected by light scattering during the analysis and provides high sensitivity [31, 35].

2 History of Photoacoustic Spectroscopy

According to Rosencwaig, [36, 37] Tyndall, Rontgen, and Alexander Graham Bell, discovered the photoacoustic effect in 1881. Bell and Charles Summer Tainter were working together in the making of photophone. Further, Bell found that when modulated light irradiated on selenium (and other solid materials), it started to emit a sound and was attained by passing modulated light through a rotating disk with holes. Further, Bell used the spectrophotometer to study this phenomenon, and he noted that the intensity of emitted sound mainly depends on the wavelength of the incident light. Moreover, he attributed this observed sound effect to the optical absorption process [38].

However, the photoacoustic effect was applied in gas studies nearly after fifty years of its discovery. Since then, it has become a well-established method for analyzing gases, and the underlying concepts have been well understood [39]. On the other hand, Rosencwaig studied the photoacoustic effect in the field of solids after 90 years of its discovery. This delay was probably because of the unavailability of high-power light sources and sensitive sound detectors [40]. In particular, the 1st photoacoustic spectra acquired by Rosencwaig were on the materials like carbon-black, Cr_2O_3 crystal, and rhodamine-B powder [37]. Further, Rosencwaig has introduced photoacoustic spectroscopy technique as a new tool for solid research [40]. After this, he noted that photoacoustic spectroscopy allows similar spectra to be produced on any kind of semi-solid or solid system, whether it is amorphous, smear, gel, crystalline, etc.

In addition, since only the absorbed light converts into sound, the effect of light scattering on photoacoustic spectra is negligible [41].

Rosencwaig has also made a groundbreaking application of photoacoustic spectroscopy in the field of biology [40]. He recorded the photoacoustic spectra (200 to 800 nm) over many biological samples such as hemoglobin extracted from red blood cells, smears of whole blood, and plasma-free red blood cells. In addition, photoacoustic spectra (250 to 650 nm) of guinea pig epidermis were also obtained under different conditions. Also, he described the block diagram for the single-beam photoacoustic spectrometer comprising digital data acquisition. In 1980, Princeton Applied Research Corporation manufactured the 1st commercial spectrometer (Model 6001) [39, 42].

Moreover, dried solids comprising hemoproteins such as soluble proteins (cytochrome c) and insoluble or membrane-bound proteins (cytochrome P-450) were studied. Certain experiments have confirmed that this technique can determine the absorbing substances like some drugs in the dried urine samples (e.g., urine drops on filter paper) [42].

3 Conventional Methods of Glucose Monitoring

Diabetes mellitus has been named the "invisible killer" due to hypoglycemia and hyperglycemia [26]. Normal fasting blood glucose concentration level is around < 100 mg/dl (5.6 mmol/L), concentration level in between 100–125 mg/dL (5.6 to 6.9 mmol/L) is considered as prediabetes. Moreover, diabetes is higher than 126 mg/dL (7 mmol/L). However, glucose level concentration is less than 70 mg/dl (3.9 mmol/L) is termed hypoglycemia [19].

The glucose concentration level can be measured using serum, plasma, or whole blood. Although the serum or plasma samples were preferably chosen for analysis because the reading obtained using whole blood samples are typically has 15% lower values owing to the excess water content level in the blood cells. Intrinsically, traditional procedures for the analysis (invasive). At first, the glucose analysis was only possible in labs by using glucose's reducing property and condensation reactions. Still, it had some drawbacks, such as toxicity, cross-reaction, and non-specificity. Because of these drawbacks, this method was phased out from the clinical practices. Therefore, the latest approaches are based on enzymatic and hexokinase processes. Both processes have a specificity, high accuracy, and limited cross-reaction. Even though the laboratories use both processes, home testing and point-of-care use the enzymatic approach owing to its relative affordability and simplicity [1].

3.1 Invasive Methods of Glucose Monitoring

Most commercially available devices for continuous blood glucose measurement use electrochemical sensors due to their quick response for glucose detection in the blood and cost-effectiveness [43, 44]. Additionally, various commercially available devices use the lancets to prick the blood at the primary stage for monitoring blood glucose levels [45]. However, frequent monitoring (3–4 times in a day) via this process may cause panic and tissue damage attributable to the fingertip prickling to collect the blood sample [46]. Moreover, invasive methods are irritating and not recommended for continuous monitoring; they may also cause blood-related infections.

3.2 Minimally Invasive and Non-invasive Methods of Glucose Monitoring

Intensive research has been focused on non-invasive glucose detection systems because of the pain, risks, and discomfort associated with the conventional method of approach. Thus, it can be divided into two main groups: minimally invasive and non-invasive, detecting people with diabetes. Minimally invasive methods involve the extraction of somebody's fluid (e.g., interstitial fluid and tears) to quantify glucose concentrations via the enzyme reactions. Non-invasive methods entirely rely on some form of radiation, and it does not require any body fluids. Additionally, glucose monitoring systems can be divided into four sub-groups: electrical, thermal, optical, and nanotechnology [1].

Glucose monitoring in thermal methods includes identifying the physiological indices linked to the metabolic heat generation due to the glucose molecule, and it operates in the far-infrared region. In contrast, electronic methods generally involve analyzing the dielectric properties of the glucose molecules at lower frequencies by using electromagnetic radiation, ultrasound, and current. In a general context, the optical method includes all the techniques developed to operate in the ultraviolet and optical spectrum bands because they take advantage of the reflective, absorbing, and dispersing properties of light while transmitting through biological media. Additionally, there is a new area called nanotechnology for glucose monitoring. Presently, only two methods have started exploring this area extensively (surface plasmon resonance and fluorescence), along with optical methods. Nevertheless, various possible methods can be established, such as plasmonic and carbon nanotubes [47–50]. However, they are still at a very early stage of growth, and most of their present advancements are being made on the theoretical side. However, it is worth noting that most of these techniques are focused on minimizing noting that most of these techniques are focused on minimizing their impact physiological variability and the diverse environmental factors irrespective of the form of the technology used during the time analysis [1].

4 Theory of Photoacoustic Spectroscopy

Usually, when a substance absorbs light, there are several paths that energy can go. As shown by Eq. 1, light is always conserved,

$$1 = A + T + R \tag{1}$$

where

A—Absorbance

T—Transmittance

R—Reflectance.

The light that hits the sample must either be absorbed or transmitted through the material or reflected off the material. Photoacoustic spectroscopy relies on the absorbed path of light since it releases heat. As the light strikes the sample, the photons are absorbed, and the electrons are excited. This energy was further released as heat, and acoustic waves were formed as the heat expanded. The process is shown in Fig. 1.

Electrons are excited either vibrationally or electronically as light is absorbed. Electrons move to a higher energy level in the case of electrical excitation. As they fall back to their original state, i.e., ground state, the extra energy is released as heat. Another form of heat generation is via the collisional deactivation process, which involves atom's collision. The collision of atoms produces energy in the form of heat. Even so, in the case of electronic excitation, energy can also be dissipated by radiative emissions or chemical reactions, as described in Fig. 1. The energy emits photons in the radiative emission process, making it useless for photoacoustic spectroscopy (that needs heat). This process decreases the amount of heat formed because energy is spent elsewhere. Chemical reactions in heat can occur, but only part of the absorbed energy goes to heat.

But on the other hand, radiative emissions and chemical reactions have little impact on vibrational energy. The vibration's lifetime is long enough to avoid interferences because of the chemical reactions and radiative emissions. The atoms thus have as much time as required to execute the collision deactivation process, which efficiently uses the entire amount of energy for heat transfer.

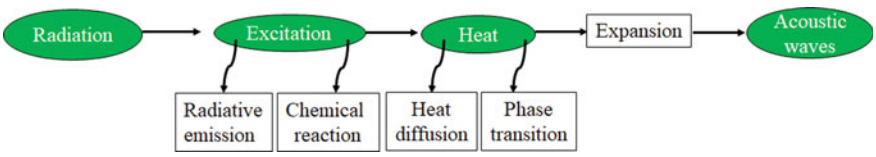

Fig. 1 Schematic illustration for the generation of acoustic waves

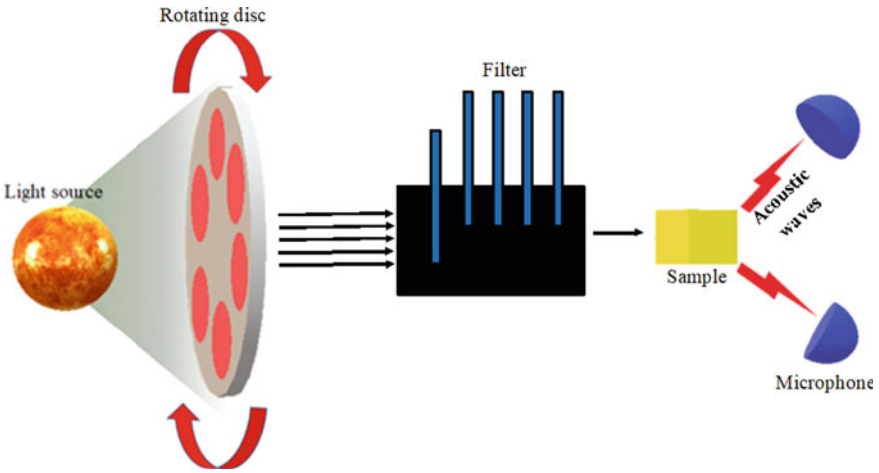

Fig. 2 Primary components of the photoacoustic spectrometer

The thermal expansion also occurs with the formation of heat. The expansion of heat produces localized pressure waves which can be analyzed as acoustic waves. Nevertheless, as in the case of energy formation, heat may also be lost through the environment. Heat diffusion decreases the temperature across the emitted energy source, which reduces the pressure fields. When acoustic waves are sent after each pulse of light, the sensor will analyze those waves. Similarly, each pulse of light will change the frequency of each pulse of light, and the produced acoustic wave will be analyzed and plotted as a spectrum pertained to a sample material.

Due to the tremendous technological advancement in recent years, technological development in amplifiers, light sources, and sensors has advanced dramatically. Figure 2 depicts a schematic configuration inside a photoacoustic spectrometer. Usually, light sources use infrared lasers or wire filaments such as tungsten that emit high light intensity. To give the pulses of light to the sample, the light source is either switched off or switched on to create the pulsing effect or the spinning disk with the openings to monitor the pulses of light passing through it. Further, the mirror channels the waves of light to a series of filters, which can be modified to adjust the wavelength of the light entering the sample. If the light goes through the filter, it reaches the contact window, where the sample is placed. Moreover, two microphones are mounted inside to collect the acoustic waves and sent to monitor the formed electrical signal. Similarly, various wavelengths are examined, and a sample spectrum is produced.

5 Recent Advancement in Photoacoustic Spectroscopy for the Detection of Glucose

A photoacoustic sensor based on an external cavity diode laser and a cheap piezoelectric film transducer for the glucose analysis has been shown by Bayrakli et al. [31] Further, the laser operation was shown to be amplitude-stabilized single mode. Additionally, a 9 GHz range of fine-tuning was reached using this setup. Moreover, they used a PVDF-based piezoelectric film transducer as a detector that produces the electrical signal concerning the acoustic signals obtained by the glucose molecules after absorbing the laser beam. They observed the detection limit of about 50 mM (900 mg/dl) for the analyzed samples. Finally, they concluded that these sensor's sensitivity could be improved to detect glucose concentration levels in the interstitial fluid below the skin. Additionally, they stated that reduced noise levels and the enhanced acoustic signal could be obtained by improving the laser quality and finding effective photoacoustic resonators with different geometries in the future.

A near-infrared (NIR) optoacoustic spectrometer is used by Ghazaryan et al. [51] to detect physiological glucose concentrations in the aqueous phase, it provided the glucose spectra between 850 and 1900 nm and measured at the multiple concentration ranges. Additionally, they implemented the dictionary learning and ratio metric techniques with a training data set. They validated their application for the measurement of glucose concentration with optoacoustic in the data set of the probe. Further, the authors noted the superior signal-to-noise ratio for the dictionary learning method compared to the ratio metric method over a wide range of glucose concentrations. Moreover, they observed the linear relationship between the concentration of physiological glucose and the intensity of the optoacoustic signal. The results are in line with the findings of optical spectroscopy. Therefore, they described physiological glucose concentration monitoring efficacy via NIR optoacoustic spectroscopy, which allowed the glucose-sensing with a precision of $\pm$ 10 mg/dl.

For the first time, Dasa et al. [52] designed a supercontinuum laser-based multispectral photoacoustic sensing system, and they used it to monitor cholesterol and glucose in the wavelength around 1540–1840 nm (first overtone region). Additionally, they demonstrated how this designed system could recognize the absorption properties of different analytes and then choose an acceptable wavelength range for further analysis. Moreover, they performed a simple ratiometric analysis and demonstrated the viability of this system for reliable glucose monitoring over a wide variety of concentrations. Furthermore, this study varied the concentrations from 0-8 g/dL, covering the commonly encountering glucose concentrations inside the human body (0-400 mg/dL). Previous studies [51, 53, 54] revealed that the photoacoustic signal linearly varies with the glucose concentration; hence, they also performed the linear regression examination to predict different glucose concentration levels with clinically acceptable accuracy concerning the standard Clarke error grid analysis. Results revealed that this system could be used as label-free and non-invasive continuous glucose monitoring.

Kottmann et al. [33] proposed a photoacoustic system composed of a mid-infrared quantum cascade laser used to monitor glucose present in the human tissue. That study used the fiber-based quantum cascade laser-photoacoustic framework and the new dual quantum cascade laser-photoacoustic set-up. Unlike traditional methods, this approach is entirely non-invasive. It does not record blood glucose concentration directly but the glucose concentration level in the interstitial fluid. However, it is related to the blood glucose level with a delay time of $\leq$ 15 min at the measurement sites. In addition, the authors analyzed the efficacy of an oral glucose tolerance test for healthy individuals. They conducted tests with the photoacoustic cell by closely contacting the forearm to obtain continuous monitoring results for about 90 min. At the same time, blood glucose concentrations were assessed by fingertips every 10 min, and blood glucose levels were measured from the glucometer. The findings suggested that the approach with a single quantum cascade laser produces positive results but does not always have a definite correlation with the blood glucose measurement data from the glucometer. The dual-wavelength protocol substantially increases the measurement stability, and the blood glucose level instability of $\pm$ 30 mg/dL is obtained at a confidence level of about 90%. The authors concluded that detection sensitivity could be increased by using higher laser power up to the permissible exposure level for short-term irradiation. It should be stressed that no specialized data treatment, such as the principal component evaluation comprising the entire wavelength tuning ranges, has been implemented to show viability under practical circumstances, i.e., for continuous individual measurements. In addition, more progress is required from the experiments involving more than two wavelengths characteristic of glucose absorption, involving many quantum cascade lasers or even a quantum cascade laser array of pre-selected fixed wavelengths. Finally, the authors stated that experiments on diabetic patients need to be carried out to assess the efficacy and to determine the potential of their designed diagnostic method.

To improve the detection sensitivity of the photoacoustic method, a measurable depth of the blood glucose concentration level was experimentally identified by Wadamori et al. [55] Here, the measurable depth of the photoacoustic spectroscopy mainly depends on the modulation frequency of the chopped light falling on the sample. Further, they established a relationship between the thickness of the sample and the used modulation frequency. During this set of experiments, the authors utilized the photoacoustic detector composed of an acoustic resonance pipe, and an optical microphone and a two-layer model consisting of sheets of silicone with different optical absorption properties. Furthermore, they noted the measurable depth around 2–3 mm in these experiments with a 1000–2000 Hz modulation frequency. In addition, they discussed theoretically the reason for the measurable depth to be more profound when compared to the sample's thermal diffusion length. In addition, these thermoelastic wave analyses clarified the relationship between the observable depth in a tissue and the propagation of the photoacoustic signal.

Photoacoustic technique comprising of tunable pulsed laser for glucose level detection was presented by Ren et al [56]. This set-up used the light source (532 nm pumped Nd: YAG optical parametric oscillator pulsed laser) for excitation and acoustic signal detector (confocal PZT transducer). Further, the authors prepared

the various concentrated solutions of glucose. It was further loaded into the quartz cuvette, then irradiated with a laser beam, and obtained the time-resolved photoacoustic signals with an average of 512 times. Furthermore, the authors received the photoacoustic peak to peak values from the wavelength range from 1300 to 2300 nm (near-infrared spectral range) for all glucose solutions. Moreover, the authors used the variance and one-order derivative spectral strategy in four photoacoustic peaks to peak signals to determine the typical glucose wavelengths. Eventually, the authors used the least square fitting algorithm to adjust the photoacoustic peak to peak values and the corresponding glucose concentration levels to obtain the optimal typical glucose wavelengths. The expected concentrations were determined by using the least square fitting algorithm. The estimated error in concentration was all less than 0.62 mmol/dl.

Pai et al. demonstrated the use of near-infrared photoacoustic spectroscopy for continuous non-invasive glucose analysis [57]. They designed a different photoacoustic measuring system, and photoacoustic observations were performed for glucose samples at various excitation wavelengths in the near-infrared region. A variety of frequency and time domain characteristics and amplitude and area-based characteristics were obtained using photoacoustic analysis. The authors noted that these properties were proportional to the glucose content of the sample, and they obtained similar results for the photoacoustic tests of whole blood samples at various glucose concentrations. Consequently, in vivo photoacoustic tests were calibrated using a quadratic fit on a cohort of 30 volunteers and further compared the obtained results with the reference glucose levels. The experiments were performed using a standard blood glucose meter. The authors performed a comparison of 196 measurement pairs of predicted and reference glucose level concentrations using the Clarke Error Grid. The result exhibited a point distribution of 87.24% and 12.76% over zones A and B, with no measurement pairs dropping in inappropriate zones C, D, and E of the error grid. Also, the authors observed the expected mean absolute difference of about 12.57 $\pm$ 13.90 mg/dl and the mean absolute relative difference of about 9.61 $\pm$ 10.55%.

Sim et al. [58] proposed a strategy to overcome the problems of non-invasive measures of glucose by increasing the reliability of micrometer-scale detection. Before spectroscopic measurement, authors collected the skin's microscopic spatial details from the same laser used for spectroscopic analysis. The authors noted the inhomogeneity in the microscopic image of the fingertip skin with a mid-infrared laser; this observation was attributed to the secretion from the eccrine sweat glands that greatly influenced the mid-infrared spectra. Further, they selected the intact positions where the secretion products were barely intrusive; hence, temporal and spatial heterogeneity were reduced. Numerous attempts have been made for many decades to design non-invasive methods of detecting glucose. However, due to the skin secretion materials, the repeatability and accuracy are still below compared to those of the invasive methods. Finally, the authors stated that their strategy has tremendous potential to build such a technology to overcome these long-standing problems.

6 Advantages of Photoacoustic Spectroscopy

Some of the advantages of photoacoustic spectroscopy are listed below, [1]

- This method is relatively simple.
- Not susceptible to the sensing of sodium chloride, albumin, and cholesterol.
- Scattering particles are not influencing the photoacoustic signal.

7 Disadvantages of Photoacoustic Spectroscopy

Some of the disadvantages of photoacoustic spectroscopy are listed below, [1]

- This approach is sensitive to variations caused by motion, pulsation, acoustic noise, and temperature.
- It requires a long integration time.
- It has a low signal-to-noise ratio.

8 Future Outlook

Photoacoustic spectroscopy has the potential for efficient glucose measurement in the blood shortly as the non-invasive method if extensive research works are carried to produce the devices with the following properties.

- The device should produce a wide range of glucose measurements of about 30–600 mg/dl,
- User friendly, portable, and durable device,
- A device with a borderline cross indication
- Low cost.

9 Conclusion

This book chapter started with the introduction to people with diabetes, followed by the history of photoacoustic spectroscopy. Further, the conventional methods for glucose monitoring and minimally invasive and non-invasive methods have been discussed. Furthermore, the theory behind photoacoustic spectroscopy instruments and the recent advancements of photoacoustic spectroscopy for detecting glucose and their advantages and disadvantages have been covered in detail. The commonly used sources of light, wavelength region, and the detectors in glucose detection setup based on photoacoustic spectra are described in Table 1. At present, low specificity, low sensitivity and interference are the main hindrances in the measurement of non-invasive blood glucose levels due to the various imperfections noted in the utilized

Table 1 Various types of sources, wavelength regions, and the detectors used for the glucose detection using photoacoustic spectra

Source	Wavelength (nm)	Detector	References
High energy supercontinuum laser	1500–1900	Ultrasonic transducer	[52]
External cavity quantum cascade laser	8000–11,111	Ultrasound transducer	[58]
Continuous-wave quantum cascade laser	9090–9950	Miniature electret microphone	[33]
Two pulsed laser diodes	905 and 1550	Piezoelectric transducer (Lead Zirconate Titanate)	[57]
Laser diode	1550	Microphone	[55]
532 nm pumped Nd: YAG optical parametric oscillator pulsed laser	600-2500 nm	PZT ultrasonic transducer	[56]
External cavity diode laser	1050–1700	Piezo transducer (polyvinylidene fluoride)	[31]
Optical parametric oscillator laser	850–1900	Ultrasound detector	[51]

software and hardware components. However, the rapid changes in technological advancement and the further advance in the quality of the previously reported analysis method can make a potential alternative for detecting glucose levels.

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Deepak Devadiga obtained his B.Sc. degree in 2016 in physics, chemistry, and mathematics from Poornaprajna College, Mangalore University, Udupi, Karnataka, India and received M.Sc. in Chemistry from Manipal Academy of Higher Education, Manipal, India. He is currently pursuing Ph.D. in chemistry at JAIN (Deemed-to-be University), Bangalore, India, under the guidance of Dr. Ahipa T.N. (Assistant Professor and group leader, Organo-electronics lab). His research interest includes designing and synthesizing luminescent liquid crystalline molecules for various electronic device applications.

Dr. Ahipa T.N. has obtained his Ph.D. degree in Chemistry from the National Institute of Technology Karnataka (NITK), India, in 2014. Later, he joined the Centre for Nano and Material Sciences (CNMS), JAIN (Deemed-to-be University), India, as Senior Research Associate (2014–2015). Since 2015, he has been working as an Assistant Professor. His research interests include Synthesis of Conjugated Molecules and Polymers for Solar Cells, Liquid Crystals, Synthesis of Non-fullerene Acceptors, and Development of Hole Transporting Materials. He has published 1 book chapter and 38 research articles in internationally reputed peer-reviewed journals. He is a life member of the Asian Polymer Association and the Indian Council of Chemists. In addition, he has the following Awards to his credit: Young Scientist award by SERB, Govt. of India (2015), and Junior Research Fellowship Award by Indian Plywood Industries Research and Training Institute, Govt. of India (2009). He serves as a reviewer for many of the internationally reputed journals. He has supervised/co-supervised one PhD and nine master theses. Presently, he is handling two sponsored projects funded by the government of India.

Electrical Bioimpedance Based Estimation of Diabetics

Pedro Bertemes-Filho

Abstract The improvement of life quality of diabetic patients requires periodic measurements of blood glucose, such as those affected by Diabetes Mellitus. They need to put a blood droplet on a dispensable reagent strip to measure the blood glucose level. Currently available devices for this purpose are invasive, in-involving painful, non-hygienic, and expensive measurement methods. Non-invasive devices, such as those using near-infrared (NIR), intend to be an alternative even though considered a low precision method compared to biochemical ones. Despite that, the creation of computational models to improve the precision of non-invasive blood glucose monitors combining multiple non-invasive technologies has recently been investigated, such as the use of electrical bioimpedance (BIA) data. BIA has been successfully used for cancer diagnosis and biomaterial characterizations due to its safety, low cost, effectiveness, portability, and applicability. The technique measures the impedance spectra of the material under study and then obtains its biological properties using a fitting model. This book brings the physical concepts of the BIA technique, including hardware and modeling for characterization. It also discusses the most reliable and promising applications for detecting blood glucose levels, both invasive and non-evasively. The usability, accuracy, precision, and performance of using the BIA approach are assessed and focused on diabetic diagnosis.

Keywords Blood glucose · Diabetes mellitus · Invasive · NIR · Electrical bioimpedance

1 Electrical Bioimpedance: Physical Concepts

The opposition flowing sensed by an electrical current across any biological material can be defined as bioimpedance (BIA, where "A" stands for analysis). It can be extended to DC (direct current) or AC (alternate current) applications. Generally, if the application involves the characterization of biomaterial, for example, tissue, then

P. Bertemes-Filho (✉)
Universidade do Estado de Santa Catarina, Joinville, Santa Catarina, Brazil
e-mail: pedro.bertemes@udesc.br

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an impedance spectrum is required (i.e., electrical bioimpedance spectroscopy—EBS).

To better describe the physical concepts on bioimpedance, the previous basic definition of electrical impedance comes to be essential to establish. The impedance Z was defined by Georg Simon Ohm in Ohm's law in 1827, where Z ($=V/I$) is a complex number. It was only in 1893 that Arthur Kennelly represented it in terms of a real (R) and imaginary part (jX) [1], where $Z = R + jX$ and "j" is the imaginary operator. The difficulty of the materials produces the real part to DC flow (resistance), and the imaginary part (reactance) is produced by the combination of the self-induction of voltages in conductors by the magnetic fields of currents (inductance) and the electrostatic storage of charge induced by voltages between conductors (capacitance) [2].

When it comes to biological materials, many other variables may modify the electrical bioimpedance, such as sample shape, internal structure or chemical composition, sample moisture, and temperature [3]. Tissue can be represented by cells suspended in an extracellular fluid composed of 20% plasma and 80% interstitial fluids [4]. A single cell contains a lipid layer for mainly ion transport and protection. A cell membrane can be modeled as a capacitor parallel with a resistor. If we consider intra-cellular and extracellular mediums as uniform and isotropic, they can be modeled as simple resistors, as shown in Fig. 1. At lower frequencies and due to the unique isolating property of the cell membrane, R_m can be considered much higher than R_{ext}. The reactance generated by the membrane capacitance C_m is high. This effect impedes the ionic current from penetrating the cell, forcing the current

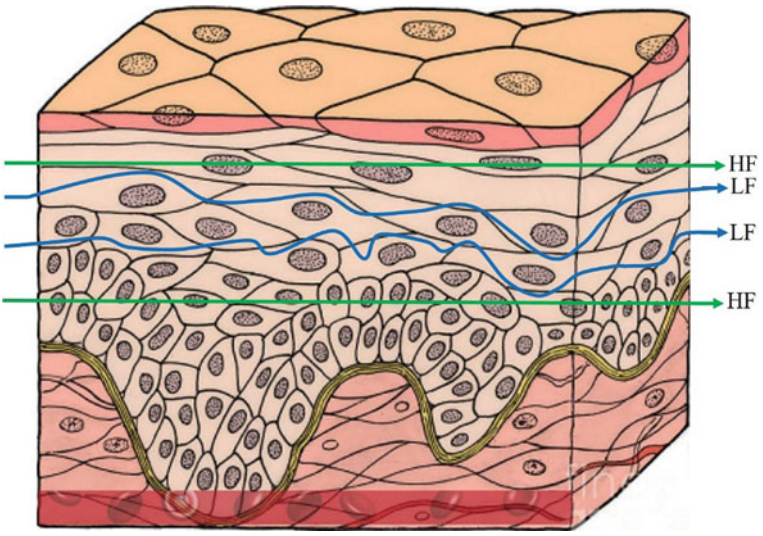

Fig. 1 Illustration of the ionic current flow across a type of skin tissue at lower (blue lines) and higher (green lines) frequencies

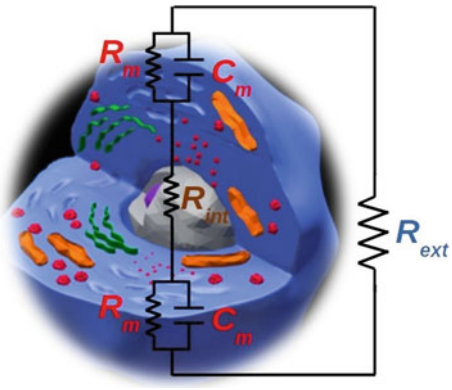

Fig. 2 Equivalent electrical circuit for a single cell, where R_{ext} represents the resistance of extracellular medium, R_m and C_m represents the cellular membrane resistance and capacitance, respectively, and R_{int} represents the resistance of the intracellular medium

flow through the extracellular medium. On the other hand, the membrane reactance decreases at higher frequencies, allowing ionic current flow inside the cell [5].

Figure 1 brings a typical illustration showing how the cells interact with the electrical field at both low (blue lines) and high frequency (green lines). This mechanics permits calculating the impedance changes in tissue which, in turn, is used for characterization and then differentiating a normal tissue from a cancerous one, for example [6]. Characterization of biological samples can only be possible by fitting the measure impedance data into a proper electrical equivalent model, where sample properties are extracted [7].

The electrical equivalent model presented in Fig. 2 is just a simple data representation. However, bioimpedance is a complex number that also includes anisotropy and inhomogeneities. Therefore, it cannot be modeled with simple electrical components such as resistors (R) and capacitors (C), even if many RC models are connected in series or parallel. The electrical extraction properties of the biomaterial under study require the use of non-linear equations expressed in terms of fractional polynomials, such as the one suggested by [7]. The Cole equation has been widely used for tissue characterization over the last 50 years, where "α" (*alpha*) is a number from 0 and 1, ω_C is the cutoff frequency of the material, R_0 ($=R_{ext} + R_{int}$, assuming $R_m >> R_{ext}$ and $R_{ext} >> R_{int}$) and R_∞ ($=R_{ext}//R_{int}$,) where "//" denotes a parallel operation) represents the impedance at the lowest and highest frequency, respectively. Each biological material has its alpha value, which best describes the dispersion behavior of the electrical field inside of it. Table 1 brings the alpha values for a few biologically important materials. A more detailed list of such alpha values can be found in [8]. Equation 1 represents just a single-dispersion, but two Cole models can also be connected in series for studying wide frequency range applications of multiphase materials, such as blood, bovine milk, cancerous tissue, etc.

$$Z_{biol} = R_0 - \frac{R_0 - R_\infty}{1 + (j\omega/\omega_C)^{1-\alpha}} \tag{1}$$

Examples of biomaterial characterizations are shown in Fig. 3, where constant

Table 1 Cole-Cole alpha parameters obtained from approximately 10 Hz to 20 GHz [8]

Tissue	f_C (kHz)	Alpha
Liver	1120.0	0.219
Bladder	846.0	0.077
Blood	947.0	0.092
Muscle (transverse)	175.0	0.093
Stomach	3060.0	0.122
Nerve	53.0	0.251

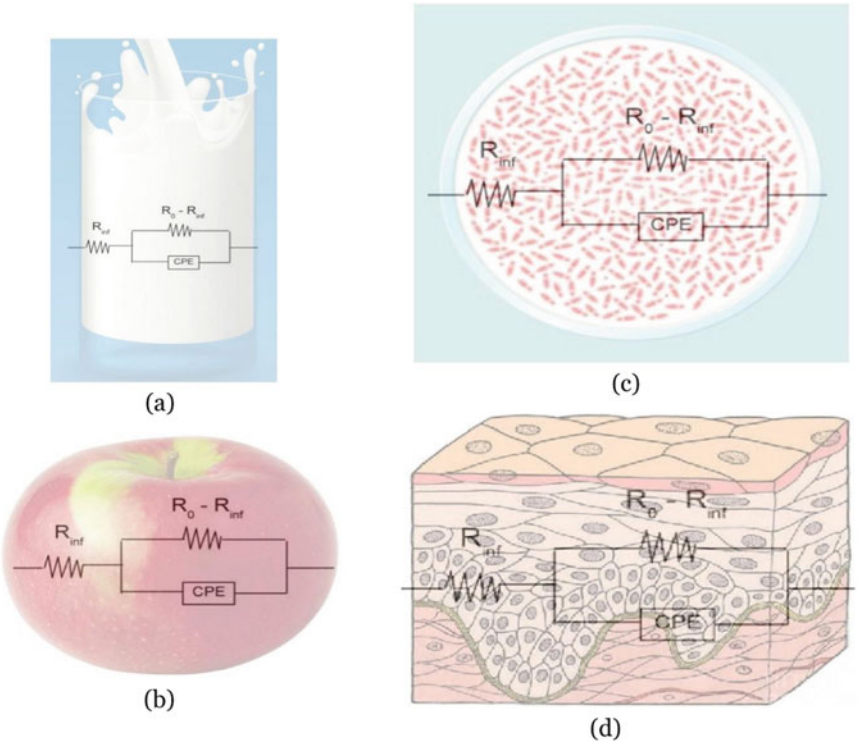

Fig. 3 Different types of biomaterial complexity using BIA technique for characterization, where R_0 represents the resistance at the lowest measured frequency whereas R_{inf} represents the highest frequency one. **a** Bovine milk. **b** Apple fruit. **c** Bacteria culture. **d** Slab of skin tissue

phase element (CPE) is a special case of the general fractional component whose impedance Z_{CPE} is equal to $1/(s\alpha C)$ in the s-domain, where C is the capacitance and α is its order. As a result, a phase angle ϕ_{CPE} $(= \alpha\pi/2)$ can be calculated for each material type as it is constant at all frequencies, depending only on the α value.

It is known from impedance spectroscopy studies undertaken over the last 80 years that biological samples, especially tissue, have different dispersion to the applied electrical field according to the frequency of the alternate excitation signal. This is because of the different free ions within both extra- and intracellular fluid. At lower frequencies, the ionic potential created by the external excitation signal will facilitate the free ions' flowing. The cell membrane impedes this flow, resulting in a high impedance when the amount of extracellular fluids is very small in cancer tissue. On the other hand, at higher frequencies, the ionic current also flows through the cell membrane and its intracellular contents, decreasing the impedance for most cases.

It can be concluded from the interactions of different ions types within a biological material that bioimpedance spectroscopy can easily differentiate tissue types and biomaterial structures in a rapid, effective, and low-cost manner.

2 Basic Hardware Structures

Most BIA systems inject a sinusoidal current with a constant amplitude over a wide frequency range by two electrodes to the sample, measure the resulting voltage by the other two electrodes, and then calculate the transfer impedance. This is a so-called tetrapolar technique whose contact impedance can be neglected from measured data. Figure 4 the ionic equipotential lines created by injecting (+I) and sank (−I) current inside a tissue sample. For example, the tetrapolar technique gives more accurate

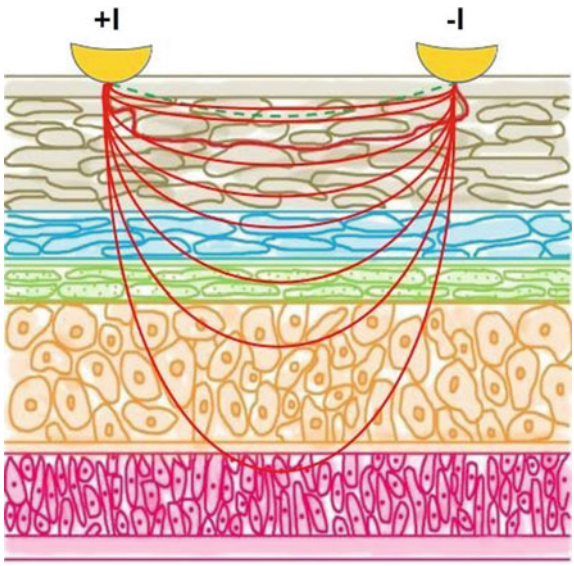

Fig. 4 Representation of the ion equipotential lines created by an alternate electrical excitation current

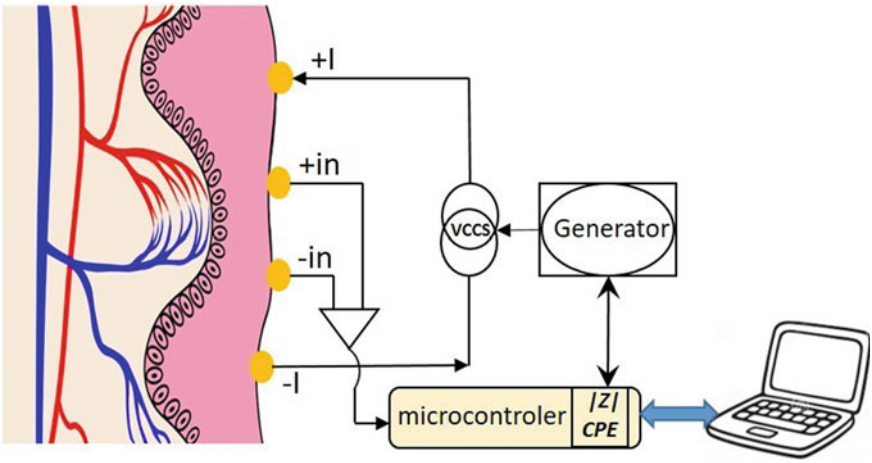

Fig. 5 Schematic diagram of a basic BIA hardware using the 4-electrode technique

information about the sample properties than the bipolar technique. However, electronic accuracy plays a great role in the measurements. All stray capacitance in the instrumentation, cables, and connectors degrades the BIA performance, especially at higher frequencies.

Blood analysis with BIA requires surface electrodes connected with minimal hardware, comprising mainly a current source and a front-end circuit. Figure 5 shows a hardware example for this application. The whole BIA setup can be built either as an all-in-one or a standalone system. A low-power microcontroller generates the signal and calculates both impedance modulus and phase. This type of system optimizes size and battery life by using low-cost integrated circuits (ICs), such as the AD5933 (Analog Devices, Inc., Norwood, MA), the AFE4300 (Texas Instruments Inc., Dallas, TX), the ADAS1000 (Analog Devices, Inc.) and the MAX30002 (Maxim Integrated, Inc., San Jose, CA). IC integrating bioimpedance meters contain the signal generator, excitation, and measuring circuits, including a small processor for calculating the impedance and doing the control interface.

A bioimpedance meter can easily be built from scratch either for in-vivo or in-vitro measurements by having some background in electronics. However, some commercial electrical impedance spectrometers (EIS) can also do in-vitro measurements. EIS is the standard device for measuring impedance in a frequency range. There is a wide range of manufacturers for these devices, such as Agilent, Zurich Instruments, HP, or Emerson. Commercial impedance analyzers may cost more than one thousand dollars, which can offer many tools to do impedance measurements such as high robustness to noise, high-quality layouts for high-speed signals, radiofrequency isolation, ultra-precise components for ultra-precise measurements, advanced measurements algorithms, and user-friendly software to make the measurements as much easy as possible.

In electronics, it is common sense that measuring impedance demands no more than applying Ohm's law, where a voltage is divided by a current. Therefore, low-cost devices have been increasing in this area over the last 10 years. A well-known low-cost device used for BIA measurements is the integrated circuit from analog devices AD5933 [9–12]. This device can do impedance measurements up to 300 kHz and cost no more than $60. On the other hand, it uses a bipolar technique, and it can perform measurements over 300 kHz if required. This is why most BIA designers prefer to build custom BIA hardware from scratch. In addition, a customized BIA gives the researcher more flexibility and efficiency in terms of hardware, signal processing, and applications.

It is important to mention that the flexibility and freedom while constructing custom instruments can be a drawback for standardization. The number of combinations when building a BIA hardware can be enormous and may be impossible to resume. An example of a simple BIA hardware is shown in Fig. 6, where current is injected through the connectors shown in Fig. 6d and voltage across the tissue is measured between the connectors shown in Fig. 6e.

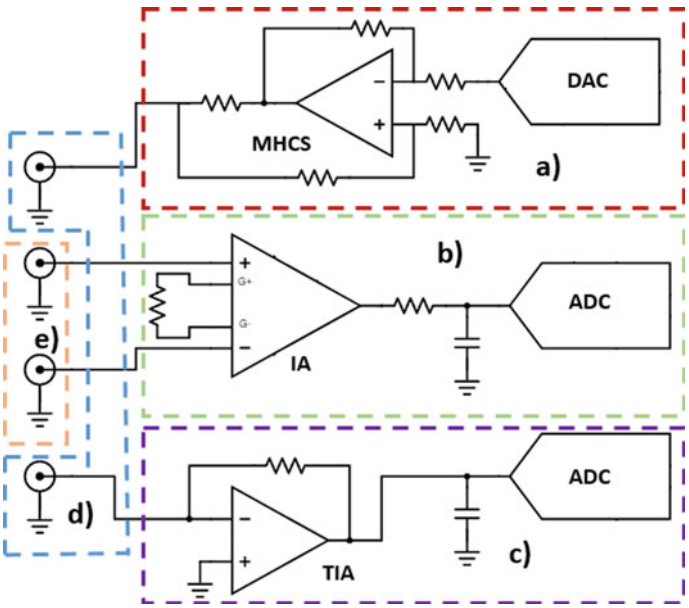

Fig. 6 Schematic diagram of a typical BIA hardware. **a** Current generator. **b** Voltage meter. **c** Current meter. **d** Current generator and current meter connections. **e** Voltage meter connections

2.1 Current Excitation Circuit

The current generation shown in Fig. 6a is divided into a digital to analog converter (DAC) and a voltage-controlled current source (VCCS). A DAC is a voltage source that may not be embedded into a Digital Signal Processor (DSP). DAC allows generating different shapes of a single frequency and multi-frequency waveforms, such as sine wave, sawtooth, triangle, or square. If multifrequency waveforms are used, some of the most common for BIA are multisine, Discrete Interval Binary Sequence (DIBS), or Maximum Length Binary Sequence (MLBS) [13]. VCCS is used to convert the voltage output from the DAC into the current injected into the tissue. The VCCS shown in figure x5 is well-known in the bioimpedance field, such as the modified Howland current source (HCS). Prof. Bradford Howland firstly proposed this source in 1962, published by [14] and modified by [15]. The modified HCS has been widely used in bioimpedance due to its simplicity, stability, high bandwidth [16, 17], and high output impedance [18].

Most BIA system uses a modified Howland current source (MHCS) with the grounded load. For the academic purpose and better understanding, we describe a proposed blood analysis design here, as shown in Fig. 7. The inverting input is fed by a binary signal supplied by the microcontroller ($V_{I/O}$). In contrast, the non-inverting input is biased with a trimmer voltage of 1.66 V to cancel the output current offset produced by the microcontroller signal. According to the transfer function of the MHCS shown in Eq. 2, $I_{out} = Z_4{*}(V_{1.66} - V_{I/O})/Z_5$ assuming $R_2 = R_3 = R_4 = R$ and $R_1 = R + R_5$ [18]. For example, if the input voltage $V_{I/O} = 3.3$ Vp and $R_5 = 3.3$ kΩ, the MHCS will produce an output current I_{out} of 1 mAp. The capacitor C_2 blocks DC currents coming from the MHCS, then avoiding DC currents flowing to the patient and preventing DC feedback to input, whereas C_1 prevents oscillations at higher frequencies.

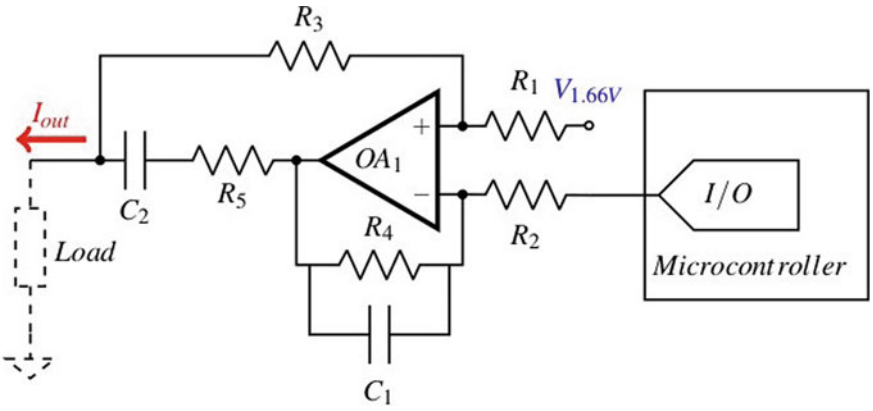

Fig. 7 Proposed current source for bioimpedance analysis of blood

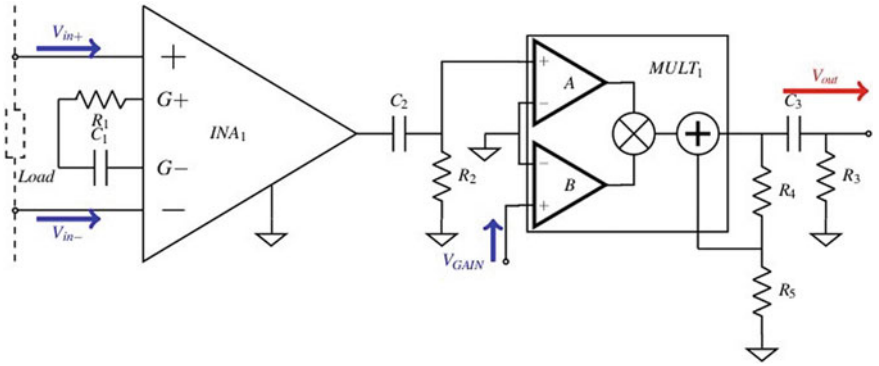

Fig. 8 Basic voltage acquisition system for a typical BIA hardware

$$I_{\text{out}} = \left[\frac{R_1 \cdot Z_4 - R_2 \cdot R_3 - R_2 \cdot Z_3}{R_2 \cdot Z_5 - (R_1 + \text{R}_3)}\right] * V_{1.66} - \frac{Z_4}{R_2 \cdot Z_5} * V_{I/O} \tag{2}$$

2.2 Voltage and Current Meters

Most of the acquisition systems used an Instrumentation Amplifier (IA), as shown in Fig. 8. This type of amplifier has a differential input and a single-ended output. It offers a high input impedance, high Common Mode Rejection Ratio (CMRR), and low DC offset. Usually, an IA feeds an Analog to Digital Converter (ADC) through a low-pass filter to digitize the analog signal.

Filtering is most often performed to remove unwanted signals and most types of noise from the data. The most common form of filtering is the low-pass one, which limits the bandwidth of the data by eliminating signals and noise above the filter's corner frequency. For example, the importance of low-pass filtering appears when the goal is to avoid the 50/60 Hz inference from the power supply. ECG, EMG and EEG biosignals usually apply this technique for rejecting the 50/60 Hz. In the case of Fig. 8, V_{out} is expected to be a DC value as a function of the impedance modulus, and then the AC component of the measured signal is removed by filtering it out.

Nonetheless, it is important to ensure that the ADC sample rate is at least double the maximum frequency generated by the DAC, guaranteeing the fulfillment of the Nyquist theorem.

A practical example of a voltage acquisition system is shown in Fig. 8. The instrumentation amplifier INA1 performs the differential voltage across the load at the first stage. The IA should be chosen according to the load properties and frequency range that best suits the characterization required. High input impedance, high voltage gain, and low output and input noise are highly recommended. As shown in Fig. 8, R1 and C1 form a high-pass filter for preventing the amplification of any DC signals

and then saturation of the *INA* output due to that signals. Before connecting the *INA* output to other signal processors, adding an extra high-pass filter (R2 and C2) to remove both the amplified DC offset signal of INA and the electrode polarization mismatch is recommended.

To obtain both modulus and phase of the measured impedance, at the second stage of the signal processing is used a complete four-quadrant, voltage output analog multiplier (MUX), shown as $MULT_1$ in Fig. 8. Using a MUX is the simplest method for having a precise and real-time impedance measurement converted into digital. The key point of a MUX is its transfer function ($=V_{INA}*V_{GAIN}*G_{LOOP}$), where R4 and R5 define the loop gain and V_{GAIN} allows a fine gain tuning by the microcontroller. Even this signal processing is precise and accurate, the output voltage V_{out} contains a DC level which, in turn, is removed by the high-pass filter formed by C_3 and R_3.

Instead of using MUX, one can digitize the INA output voltage directly by an AD converter, then process the signal for extracting both modulus and phase of the material impedance under study. However, if the impedance modulus is the only figure required, then a wide-bandwidth active rectifier and a second-order active filter will do the job. On the other hand, if the impedance phase is the only variable to be evaluated in the impedance spectra, a phase-retrieve circuit can be used, such as a simple multiplier and a second-order active low-pass filter.

Measuring modulus and phase accurately across a load in a wide bandwidth is quite difficult, as parasite capacitance degrades the signal. Therefore, most BIA designs measure the current flow in the load by using a shunt resistor connected in series with the load. The main advantage of measuring the load current is to compensate for the phase shift errors due to stray and cable capacitance, which, in the end, increases the accuracy of the measured biological impedance. Most current-measuring circuits use a trans-impedance amplifier (TIA), composed of a buffer and a differential amplifier. TIA has the advantage of not using an external resistor in series with the load, increasing the voltage swing of the MHCS. On the other hand, using a shunt resistor does not intercept the current return path avoiding errors produced by the TIA, then maintaining the ground reference [19].

A practical circuit for measuring the current flow through the *Load* is shown in Fig. 9. It uses a shunt resistor R_1, a high input impedance buffer (OA_1) for neglecting leakage current, a differential amplifier (OA_2), and a voltage reference of 1.66 V, for example, to centralize the V_S into the dynamic range of the ADC.

It is also recommended that both modulus and phase of load current I_{Load} be measured to calculate the load's impedance more accurately. That measurement can be performed by a MUX, as explained above. Then, both modulus and phase of I_{Load} ($=V_{1.66}/R_1 - V_S/R_1$), assuming $R_2 = R_3 = R_4 = R_5$, are used to calculate the biological load under study. It is important to emphasize that both V_S across the load and shunt resistor are frequency-dependent, then care should be taken when doing such a calculation. Generally, the impedance modulus is then calculated by the ration $|V_{out}|/|I_{Load}|$, whereas the phase by the difference between $\phi Vout$ and $\phi Load$.

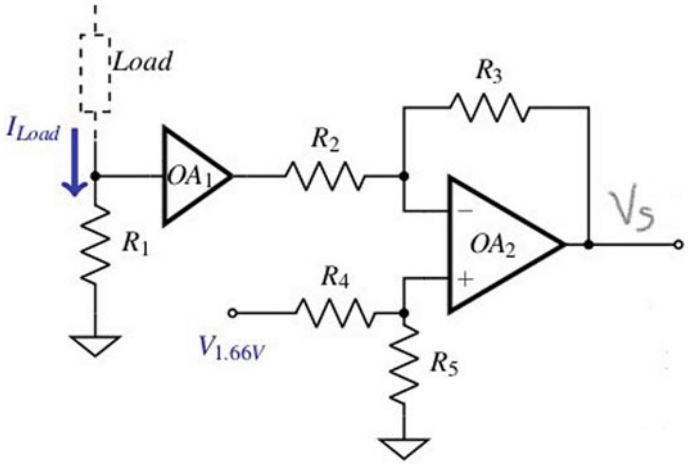

Fig. 9 Schematic diagram of a practical current measuring circuit across the load understudy

3 Extracting Glucose from BIA

BIA technique is a non-invasive method, as already discussed in the above sections, which can be employed to detect blood glucose. BIA is a type of technology considered "transdermal," however other technologies have also been used. They can be divided into different sub-technologies, as shown in Fig. 10. Depending on the environment and the accessed body place for measurements, every technology has its

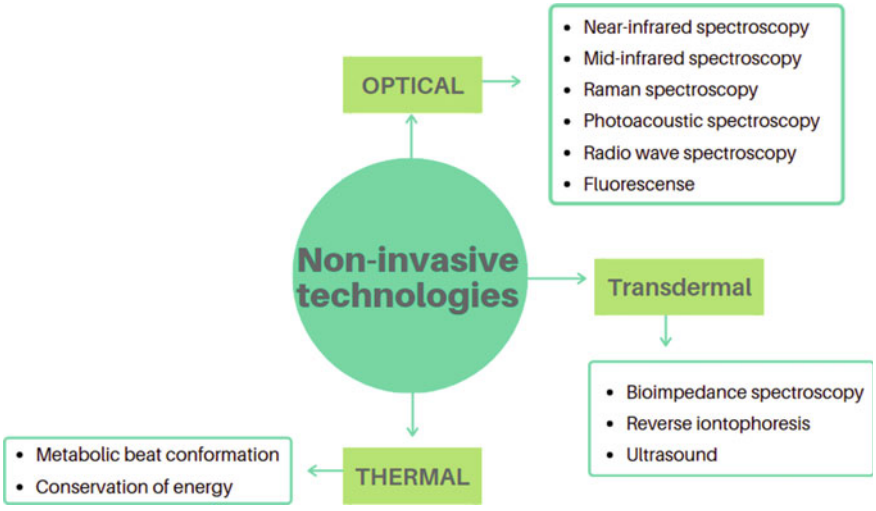

Fig. 10 Diagram showing the most of non-invasive blood measuring technologies

working features, advantages, and disadvantages. For example, transdermal is very sensitive to environmental variables such as temperature or sweating [20]. Optical methods depend on the properties of the tissue, such as color tone in the case of skin [21]. Over the last 10 years, relevant technologies have been launched in the market, such as GlucoWatch® G2 Biographer, Pendra®, OrSense NBM-200G, and Glucose. However, some are not precise enough to predict blood glucose levels, and others were removed from the FDA (USA) market. This chapter presents the solution using only the electrical bioimpedance (also called electrical bioimpedance spectroscopy—EBIS).

Monitoring glucose has been a classic area of research in BIA. Over time, accuracy has been increased but not enough to have clinically acceptable results [22, 23]. Recent studies have presented BIA as a promising non-invasive technique for detecting glucose in the blood [24, 25]. However, it is difficult to choose a proper body site to connect the electrodes because it depends on electrode geometry, circuitry topology, measuring technique, etc.

Glucose can be found in interstitial fluids, and most researchers use it to set up the system [26, 27]. Interstitial fluids are present in every tissue as a component of the extracellular fluids. Interstitial glucose concentration is well correlated with blood glucose concentration, but glucose's appearance in interstitial fluids is delayed compared to it in the blood [28, 29]. Nevertheless, many researchers consider this delay a positive point to glucose monitors because they are more accurate than plasma laboratory analysis. Interstitial glucose is the real glucose that tissue cells use for their metabolism. Blood glucose can eventually exhibit some peaks while interstitial glucose keeps stable. Making insulin corrections during the fake glucose peaks can negatively impact glucose levels because glucose levels do not need to be reduced [30, 31].

Predicting blood glucose by using the spectra of both impedance modulus and phase requires a good analytical or numerical model to be computed. This type of processing deals with measuring exogenous variables (modulus and phase) correlated with variable to be predicted, and modeling how these variables produce effects in variable to be predicted. In addition, if a tissue characterization is required, bioimpedance spectra are necessary to properly extract tissue properties, such as intra- and extracellular components and membrane capacitance. We have seen here that these properties are calculated using a fractal model, shown in [7], containing at least four variables to be fitted over the measured frequency range. The Multiple Linear Regression (MLR) method has been used quite successfully for simple cases with single dispersion materials. When it comes either with complex materials or large data to be processed, other different models have been used for that purpose, such as Support Vector Regression (SVR) and Artificial Neural Network (ANN).

MLR is a linear modeling method that uses the linear relation between a dependent variable and many independent variables. The MLR algorithm has been used to predict blood glucose non-invasively, such as the one that uses the metabolic energy conservation technique [32]. In contrast, the presented by [33] used multiple measured data (capacitive fringing field sensors, optical sensors, and skin hydration

levels). MLR can be used by modeling the blood impedance modulus or phase concerning glucose level measured in milligrams per deciliter (mg/dL).

While linear regression minimizes the error between the actual and predicted values through the line of best fit, SVR manages to fit the best line within a threshold of values, otherwise called the epsilon-insensitive tube. It uses the same basic idea as Support Vector Machine (SVM), but applies it to predict real values rather than a class. It also acknowledges the presence of non-linearity in the data and provides a proficient prediction model. Some SVR applications for blood glucose non-invasively prediction are pulse glucometer [34] and electrochemical measurement of saliva [35]. It can also be used in other re- related areas such as blood glucose level prediction using daily diet information, exercise, and past blood glucose measurements [36]. Most BIA systems measure over 30 discrete frequency points either for modulus or phase, then end up with a large amount of data, especially if other biosignals are also acquired to predict the blood glucose level better.

Handling a large amount of data means dealing with many input data, where an ANN is highly recommended. The more data fed into the network, the more generalized and accurate the predictions are. ANN systems can learn system behaviors using examples to model them without any specific programming or knowledge about the system. It can be used for linear and non-linear problems. ANN has been widely used to predict blood glucose levels non-invasively together with other types of technologies, such as NIRS [37], palm sweat [38], or multisensor systems including photoplethysmogram, heart rate, galvanic skin response and temperature measurements [39]. Another application where ANNs have been used related to glucose is predicting future glucose levels in different time intervals [40].

4 New Trends for Diabetic's Meter

Many studies are trying to deal with the problem of separating the sources producing similar physiological effects as the glucose builds. The use of different sensor technologies helps in this task. Two physiological impacts can have the same behavior: producing thermal effects but different producing coloring effects. The combination ultrasonic, electromagnetic, and thermal has shown an increment of accuracy [41]. Mid-infrared spectroscopy and photoacoustic detection are examples where combining different technologies improves the results compared with using a single technology [42].

When the information comes from multiple sensors, computational algorithms may be used to analyze this information as a set. A neural network has shown a good performance combining near-infrared spectroscopy (NIRS) and bioimpedance analysis (BIA) measurements [24]. Photoplethysmogram, galvanic skin response, and temperature measurements can be combined using multiple linear regression and an artificial neural network to estimate blood glucose levels [39].

Novel approaches have been using nanoparticles as non-enzymatic biosensing of glucose [43] and graphene nanocomposite acting as a non-invasive sensor for measuring blood glucose in diabetic patients [44].

5 Conclusion

It can be resumed that even the Self-Monitoring Blood Glucose (SMBG) market is stabilized using invasive methods, there is a big research gap and enormous interest in the development of non-invasive SMBG devices. It was shown in this chapter that:

i. Current technologies suffer from a lot of problems such as the lack of accuracy and disturbances;
ii. Bioimpedance (BIA) technique has been showing a robust, low cost, and promising technique for tissue characterization and then also to blood glucose estimation;
iii. The use of BIA together with NIR has already proven to be a more accurate joint technique for blood glucose estimation;
iv. Combining multi-sensor measurements with algorithms seems to be a way forward to more accurate glucose estimations in diabetic patients.

Some future outlooks for the non-invasive SMBBG may include the use of biosensors highly sensitive to specific ions or other substances when a patient undergoes a glycemia peak; the use of a multi-agent sensor network for real-time monitoring; the use of AI together with wireless sensors for long term and home care applications.

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Pedro Bertemes-Filho Graduated in Electrical Engineering in 1995 at the State University of Santa Catarina and Ph.D. in Medical Physics at the University of Sheffield. Awarded by Fulbright at Dartmouth College and visiting researcher in the University of Ljubljana. Titular Professor at UDESC since 2004, lecturing electronic instrumentation, sensors and transducers, introduction on biomedical engineering and coordinating research groups in biomedical engineering and electrical bioimpedance. Senior IEEE member since 2020. Reviewer of more than 12 international journals. Secretary of the ISEBI from 2019 to 2022. International lectures in renowned Universities, such as Uruguay, Ljubljana, Sheffield, Copenhagen and Mexico. Areas of research interest are focused on electrical bioimpedance and bioinstrumentation, Biosensor and e-Health. Edited international books, such as “Bioimpedance in Biomedical Applications and Research” and “Medicine-Based Informatics and Engineering” by Springer.

Millimeter and Microwave Sensing Techniques for Diagnosis of Diabetes

Nithusha Kallingal, M. S. Sajna, Mizaj Shabil Sha, Mithra Geetha, Ishwar Maruti Islampure, Nagendra Prasad Devarapalli, Muni Raj Maurya, Asan Abdul Muthalif, Sumaya Al-Madeed, Ravikumar RamluVidule, Ankanagari Srinivas, and Kishor Kumar Sadasivuni

Abstract Diabetes mellitus is a metabolic syndrome described by hyperglycemia derived from insulin secretion, insulin action, or combined form deficiencies. Diabetes is considered one of the emerging epidemics of this century; this necessitates the research on the early diagnosis and essential control of diabetics. Along with the diagnosis and treatment of this disease, it is crucial to give due importance to the studies on the prognosis and prevention measures for diabetes. In the present chapter, the non-invasive millimeter and microwave sensing techniques are summarized that can be helpful for the prognosis and diagnosis of diabetes. These

N. Kallingal · M. S. Sajna · M. S. Sha · M. Geetha · N. P. Devarapalli · M. R. Maurya · K. K. Sadasivuni
Center for Advanced Materials (CAM), Qatar University, 2713 Doha, Qatar
e-mail: mizaj.s@qu.edu.qa

M. Geetha
e-mail: mithra.geetha@qu.edu.qa

N. P. Devarapalli
e-mail: nagendraprasad@cutmap.ac.in

K. K. Sadasivuni
e-mail: kishorkumars@qu.edu.qa

I. M. Islampure
Robokidz Eduventures Pvt. Ltd., Pune, Maharashtra, India

A. A. Muthalif
Department of Mechanical Engineering, Qatar University, Doha, Qatar
e-mail: drasan@qu.edu.qa

S. Al-Madeed
Department of Computer Science and Engineering, Qatar University, Doha, Qatar
e-mail: s_alali@qu.edu.qa

R. RamluVidule (✉)
Department of Chemistry, SSGM College, Loha, Dist. Nanded, Maharashtra, India
e-mail: ravidule@gmail.com

A. Srinivas
Department of Genetics and Biotechnology, Osmania University, Hyderabad, India

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techniques are commonly used in measuring the dielectric properties of solutions such as glucose parameters and used in non-contact or subsurface skin sensing. Invasive methods cause discomfort and pain during diagnosis, as it takes blood drops to monitor glucose levels in the body. Millimeter and microwave sensing techniques have the potential for developing a medicinal gadget that non-invasively measures the blood glucose without following the usual procedure of finger pricking, taking a drop of blood, and using the test stripe; this facilitates minimum hassle and the best possible way to deal with the samples to examine and diagnose blood glucose levels. Painless glucose testing methods can aid in the proper management of diabetes for people of all ages, as current approaches like continuous glucose monitors or finger-prick tests cannot guarantee appreciable efficiency or convenience.

Keywords Prognosis · Diabetics · Millimeter · Microwave · Non-invasive

1 Introduction

1.1 Overview

Diabetes is a physiological chronic illness/disease where a person develops the potential to undertake blood glucose processing known as blood sugar in the impaired form [1]. The total number of human beings affected globally due to diabetes has quadrupled in three decades. In this current century, every 1/11th person is affected due to diabetes. Asian countries, including China and India, are becoming new epicenters of diabetes patients in the coming decades throughout the world. From a clinical perspective, whenever a situation under medical diagnosis of a person is referred towards abnormal grades of sugar level in the blood, they are said to be diabetic or are suffering from a form of Diabetic Mellitus (DM) [2]. Diabetes is a mystery illness; physician Aretacus made this prognosis of Cappadocia (81-138 AD), which still holds today [3]. For almost two millenniums or even after a brief time of two millennia, the root cause of diabetes aliment remains obscure. Variable or abnormal sugar levels in some cases indicate binary levels of a pre-existing condition in the sample of the affected person, and this condition is referred to as hyperglycemia or hypoglycemia. The first condition, i.e., is the production of excessive amounts of glucose. The latter says hypoglycemia lowers the production of excessive amounts of glucose. The latter says hypoglycemia lowers the glucose level in the normal range.

1.2 Types of Diabetes

Diabetes is classified into the following three types:

I. Type 1 diabetic
II. Type 2 diabetic
III. Type 3 diabetic, i.e., Gestational diabetes (Fig. 1).

1.2.1 Type 1 Diabetics (Auto-Immune Condition)

Type 1 diabetics are also known as Juvenile diabetes [5]. The juvenile form of diabetes is due to the incapability of a person's body to produce insulin. Insulin is a hormone responsible for allowing glucose to enter cells as energy while also keeping glucose levels in the bloodstream at normal ranges. It is necessary as it helps supply energy to the body to carry out routine activities and promote day-to-day functions. In general, for type 1 diabetic patients, the physical management/metabolism becomes dependent on insulin. Therefore, artificial insulin is to be injected in one form or other daily for the person to stay alive.

1.2.2 Type 2 Diabetics (Permanent Chronic Condition)

In type 1 diabetes, the immune system mistakenly attacks the insulin-producing beta cells in the pancreas. It causes permanent damage and prevents the pancreas from

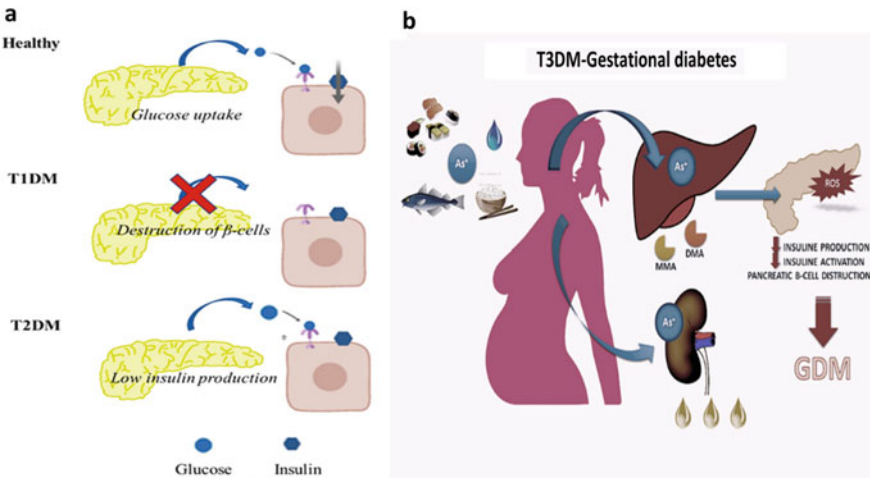


Fig. 1 Schematic representation of the three different types of diabetics: **a** Type I, Type II (Reproduced with permission from [3] CC By © 2019 by Vieira et al., Licensee MDPI, Basel, Switzerland) and **b** Type III: Gestational diabetes (Reproduced with permission from [4] CC By © 2019 by Salmeri et al., Licensee MDPI, Basel, Switzerland)

producing insulin. The body generally produces insulin in such chronic conditions, but it is not effectively used up as it would have [6].

1.2.3 Type 3 Diabetics (Gestational Diabetes)

Hyperglycemia and gestational diabetes are globally becoming significant public health issues during the stage of pregnancy in women. Although not all pregnant women are affected by this condition, the onset increases risks during pregnancy. Sometimes it causes problems for newborns and sometimes does not favor the proper birth process. However, this condition mostly subsidizes after the birth of a child [7]. The consequence of gestational diabetes cannot be ignored once and for all the time (Fig. 2).

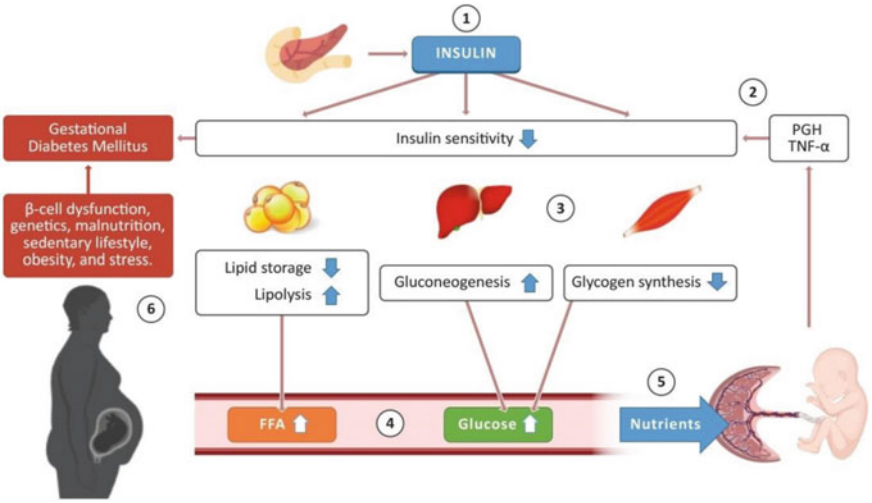


Fig. 2 The process of gestational diabetes. The pancreas distributes insulin, which stimulates specific activities in certain tissues to control blood sugar levels in the blood (1). Through a healthful gestation, the placenta generates the placental growth hormone (PGH) and proinflammatory cytokines such as tumor necrosis factor-alpha (TNF-α), stimulating a reduction in insulin sensitivity in adipose tissue, liver, and skeletal muscle (2). As a result, fat tissue limits lipid storage and promotes lipolysis; the liver promotes indigenous glucose (gluconeogenesis); skeletal muscle glycogen fusion is reduced. (3). Free fatty acids (FFA) and glucose levels in the blood rise because of such activities. (4), They are essential as nourishment for the placenta and fetus' growth (5). Nonetheless, certain pregnant women have susceptible factors that cause gestational diabetes mellitus (Reproduced with permission from [8] CC By © 2019 by Lizárraga et al., Licensee MDPI, Basel, Switzerland

Less common types:

I. Monogenic diabetes
II. Cystic fibrosis diabetes.

2 Diagnosis of Diabetes

"Endocrinology 2.0," as suggested by existing textbooks monographs and scientific journals, suggests that hormones play an essential role in diagnoses which are thus ignored by current medical practitioners [10].

Obesity is still considered one of the regular signs for identifying diabetes mellitus (Fig. 3). Currently, 354 million diagnosed and undiagnosed diabetic patients are present in the world [11].

The current diagnostic methods for diabetes include extraction of medical analysis samples through urine, blood which are generally invasive methods where the affected body of a patient is invaded for sampling.

Invasive and Non-invasive

In the last ten years, point-of-care devices (POCD) have played a significant role in detecting diabetes as they are made to check the glucose levels in the blood, such as glucometers. The POCD is categorized into invasive or minimally invasive

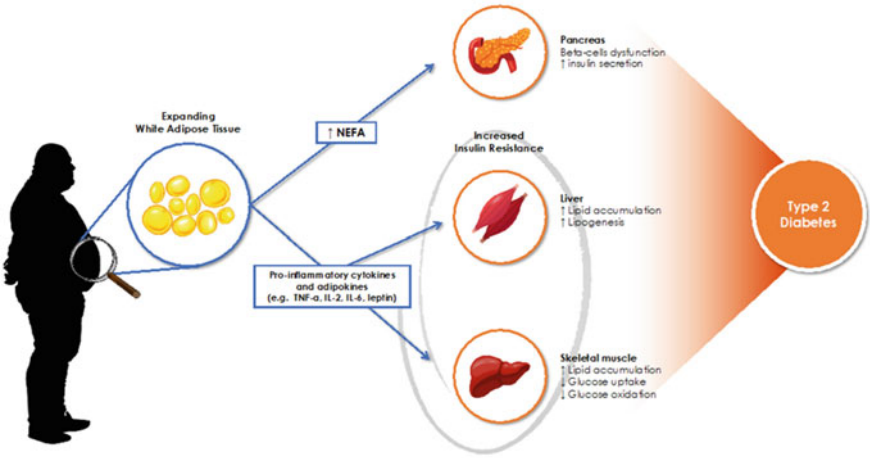


Fig. 3 Schematic illustration of connection amongst obesity on type 2 diabetes (NEFA-Non-esterified fatty acids) (Reproduced with permission from [12] CC By © 2019 by Hwalla et al., Licensee MDPI, Basel, Switzerland)

nature; after collecting blood from the tip of the finger, an approximate calculation of glucose is made. The chemical reactions involved are enzymatic glucose-oxidase, glucose-fragments binding, glucose spectral features, color reflectivity, etc. An electrical signal is then applied to the glucose concentration to induce it. Blood is collected from the fingertip is a painful process prone to infection and has high costs. Hence, a non-painful and invasive free biosensor technique for monitoring glucose levels has been developed. Research has been undertaken in the last ten years and is still ongoing to create a suitable substitute as a non-invasive glucose testing device (NGD). This strategy is adopted by companies that produce clinical equipment and is used for non-intrusive glucose assessment. Various devices are mentioned in Table 1 and summarized, along with their manufacturers, advantages, and disadvantages. Some techniques such as Raman spectroscopy, optical coherence tomography (OCT), fluorescence technique, light scattering, photoplethysmography (PPG), photoacoustic and near-infrared (NIR) are all-optical techniques that depend on rays of light at various wavelengths for the identification of glucose concentration by using optical parameters. This concept is used for developing NGD devices [13].

Red/near IR or mid-IR absorbance spectrometry techniques employ the splitting of luminosity at living tissue aiming towards observation or notice of any visual marks of sugar content occurring in blood. These procedures involve several drawbacks such as high pricing vulnerable to fluctuations in physiological parameters like body temperature, blood pressure, the pressure of the atmosphere, temperature, or humidity. Another procedure for detecting glucose levels indirectly is by electrochemical techniques, which monitor external fluids of the body like saliva, breath condensate, sweat, or tears. Later, a comparison between measured glucose concentration to the amount of glucose in the blood is carried out. Although the non-invasive techniques have better sensitivity, they are criticized for being vulnerable to metabolic changes. Apart from that, they are weakly associated with glucose levels in the blood because of the disparity between changes in sugar concentration in interstitial fluid (ISF), sweat, or blood. The suggested ideas seem to be in their infancy, making it hard to assess their usability [13, 14].

Figure 4 illustrates various classifications and arrangements to monitor blood sugar levels: invasive, minimally, and non-invasive. Bedside medical equipment or personal assessment care meters are examples of fully intrusive systems. Moreover, monitors are designed for intensive care units and employ sensitive sensors within 1%. Continuous monitoring is achievable with these devices, which increases the quantity of available clinical data. Typical approaches like drawing blood from the skin are still used in homes (precision of six to seven percent). Sugar content is found via electrochemical, colorimetrical, or optical replicable stripes for finger-stick blood samples. Attempts have been made to achieve a lower risk of invasiveness; by reducing the amount of blood taken to only a few microliters and measuring body regions that are less sensitive to pain, e.g., forearm, upper arm, or thigh. Some disadvantages like lack of accountability when sleeping or while performing manual tasks, unnoticed periods of hyper-or hypoglycemia, infection risks, nerve damage, and the uneasiness of puncturing the finger multiple times a day, etc., often lead to non-compliance of the technique [15–17].

Table 1 Gadgets for non-invasive blood glucose monitoring available in the market (Reproduced with permission from [13] CC By © 2019 by Omer et al., Licensee MDPI, Basel, Switzerland)

Device/company	Technique	Placement	Needs	Attributes
NovioSense (Noviosense BV)	Electrochemical enzymatic-based tear analysis	Lower eye lid (inferior conjunctival fornix)	Continuous monitoring provided a sample	Compact, painless, flexible, wireless power, smartphone connected for data analysis
Smart Contact Lens (Novartis & Google)	Electrochemical enzymatic-based tear analysis	Eye	Continuous monitoring provided a sample	Painless, power efficient, portable, low relief, hazardous when overheated, withdrawn from market!
iQuicklt Saliva Analyzer (Quick LLC)	Saliva analysis	Saliva of the mouth	Intermittent monitoring provided a sample	Portable, convenient to use, accurate, time efficient (real-time readings), under development and clinical trials
TensorTip Combo Glucometer (Cnoga Medical)	Photometric and photography-based techniques	Fingertip	Intermittent monitoring without a sample	Convenient to use, accurate when calibrated on individual-basis, smartphone compatible, battery operated (rechargeable), cost-effective, certified!
Glucosense (Glucosense Diagnostic Ltd.)	Low-powered laser sensors that use photonic technology (infrared light)	Fingertip	Intermittent monitoring without a sample	Convenient to use, portable, affordable, power-efficient, time-efficient (30 s), under development!
Groves's Device (Groves Instrument Inc)	NIR spectroscopy	Fingertip or earlobe	Intermittent monitoring without a sample	Fast processed readings, time-efficient (20 s), compact, portable, uses capillary-level blood, less accurate due to lacking subjective calibration

(continued)

Table 1 (continued)

Device/company	Technique	Placement	Needs	Attributes
GlucoTrack (Integrity Applications)	Thermal, ultrasonic, and microwave EM technology	Earlobe	Intermittent monitoring without a sample	Affordable, convenient use, high accuracy due to earlobe placement, unit-connected results processing/display, complex processing, FDA approved!
GlucoWise (MediWise)	RF/Microwave	Amid fingers (thumb and forefinger)	Intermittent monitoring without a sample	Convenient to use, affordable, accurate, Bluetooth-based data transmission, compact, integrable with insulin pumps, uses capillary-level blood, time-efficient, fast readings (10 s), hurtful due localized energy usage, under development!

The minimally invasive method also causes irritability to the patient as it uses the interstitial fluid sample within intravenous sensors. Even with this approach, the patient's treatment is delayed because of their discomfort. Due to this, research groups have been working to evolve glucose monitoring devices that are non-invasive. Yet, neither patents nor papers show a high level of accuracy for the non-invasive technique compared to the invasive one [18, 19].

Non-invasive Method

An alternative method of painless, intermittent glucose monitoring is blood with other fluids in the body that might contain glucose, like tears, sweat, urine, or saliva. On the other hand, constant tracking can be achieved by directly measuring body tissues such as skin, eye, oral mucosa, tongue, or tympanic membrane.

It is possible through non-invasive glucose monitors, which differentiate glucose information from other overlapping components (proteins, urea, uric acid, hemoglobin, water, etc.). Similar sensors can detect blood sugar levels either directly, depending on the chemical composition of the glucose molecule, or by monitoring the impact of blood sugar on other procedures, for example, temperature or pH shifts.

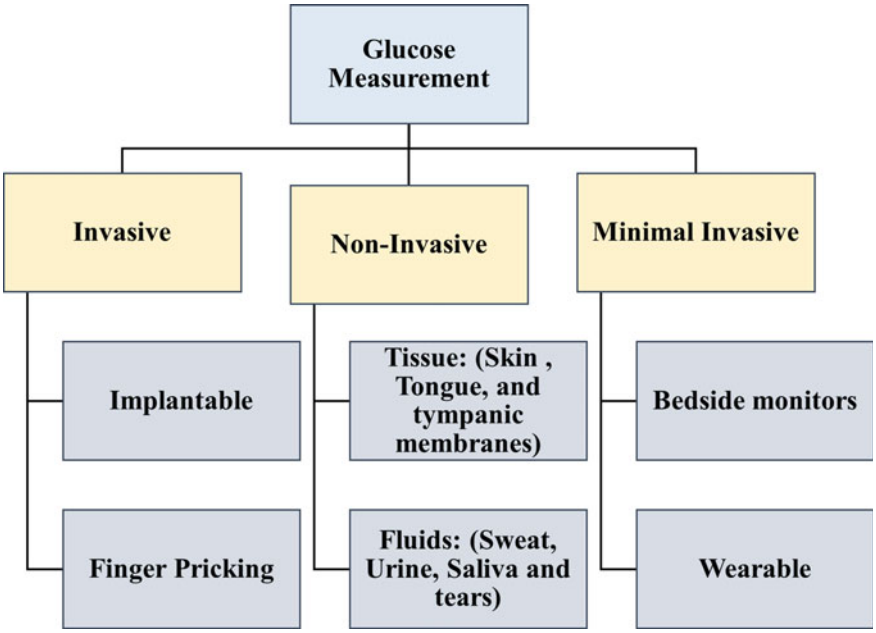


Fig. 4 An overview of non-invasive blood glucose management systems

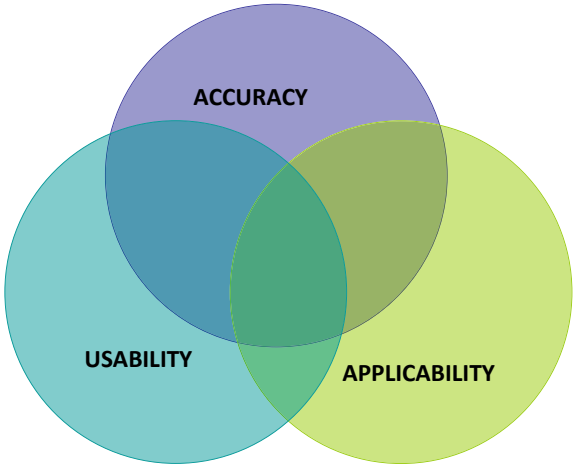
Reverse iontophoresis, polarimetry, metabolic heat conformation, ultrasound, thermal emission, electromagnetic, photoacoustic, Raman, light absorption, and bioimpedance spectrometry have been used throughout various non-invasive studies. In addition to the methodology and sample region, the measurement surroundings should also be considered. Sweltering, skin shade, surface bumpiness, skin thickness, exhaling artifacts, the flow of blood, bodily motions, ambient temperature, pressure, and slow response all impact the results in transdermal monitoring [14](Fig. 5).

The most difficult aspects of developing fully non-invasive blood sugar examining technology are precision, serviceability, and appropriateness for easy handling at home by many persons. The best way to overcome these challenges is to develop a device that will create a significant breakthrough in this field (Fig. 6). A gadget like this can replace the existing benchmark of intrusive glucose biosensors and enhance the lives of millions of diabetic patients around the world. However, many systems still have several significant drawbacks, including low glucose sensitivity and specificity and the need for a lengthy and frequent calibration. This shows how difficult it is to balance generalizability and application. It is vital to make the device usable and acceptance level assessment better, which may reveal main user problems and provide a significant action in the commercialization of these gadgets.

The inability of existing non-invasive gadgets to replace a standard glucose measuring meter is one of its primary drawbacks. As a result, these devices must be constantly improved to improve the algorithm, software, and device features to increase their performance further. Furthermore, more clinical research is needed

Fig. 5 Skills in advancement for minimally and non-invasive glucose detection (Reproduced with permission from [20] CC By © 2019 by Villena Gonzales et al., Licensee MDPI, Basel, Switzerland)

Fig. 6 Confronts of non-invasive blood sugar examination. An effective non-invasive glucose monitoring device should surmount the sequence of precision usableness and should face the challenges



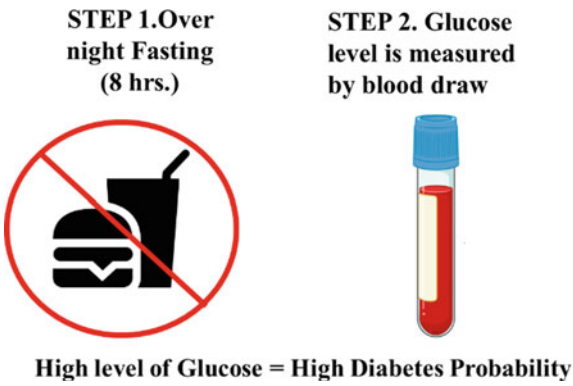


Fig. 7 Schematic illustration of fasting plasma glucose test

to assess whether non-invasive devices will improve glycemic management in individuals. It is similarly worth noting that the existing analysis ignores the issue of inexpensiveness. Consumers may choose non-invasive blood sugar detecting tools because they do not need lancets or strips, though several methodologies that have been reviewed are expensive [21].

2.1 Testing Methodologies

The testing methodologies/methods of diabetes include [22].

I. Fasting plasma glucose (FPG).
II. A1 C test.
III. Random plasma glucose.

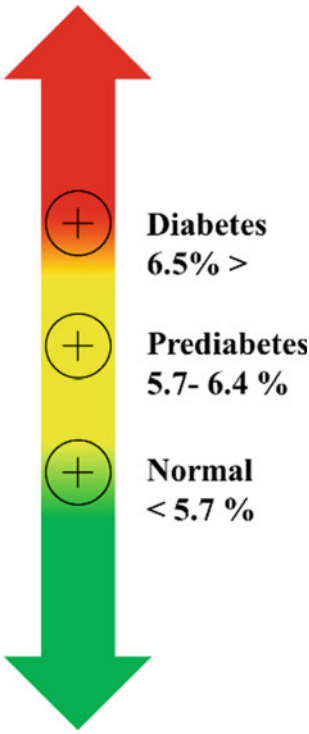
2.1.1 Fasting Plasma Glucose (FPG) Test

The FPG methodologies are an instantaneous measurement parameter that requires pre-condition of receptor's body to fast for at least 8 h, except sips of water intake. The fasting condition is generally done at night, and tests are conducted in the morning for reliable results [23] (Fig. 7).

2.1.2 The A1C Test (HbA1C, Glycated Hemoglobin Test)

As opposed to the FPG test, the A1C/HbA1C test is used to diagnose not affected/inconsistent overeating and drinking before the test. The chart of the A1C test is shown in Fig. 8. Averaging down sugar levels over 3 months is considered to provide accurate sugar levels in the blood.

Fig. 8 The A1C test results



Other symptoms such as age, anemia, or other stipulated problems are also considered during the tests undertaken. This is done because the A1C test is inconsistent when the person does not have anemia or any other blood-related disorder.

2.1.3 Random Plasma Glucose (RPG) Test

Sometimes health care professionals use the RPG test for diagnosing the symptoms in a patient. This blood test does not follow any pre-conditions that need to be followed. This can be done at a given time of day. The glucose challenge test is used through the oral testing methodology for pregnant women. Oral glucose tolerance test requires fasting for about 8 h and then taking glucose. This is done by drawing blood every hour 2–3 times (Fig. 9).

Pre-diabetes

A combined study in 1997 and 2003 by the authority board on the diagnosis and categorization of diabetes mellitus could recognize a group of individuals whole glucose were neither in the range of classified diabetes patient. Still, it was high enough to be not classified with the normal levels. Such a condition on the borderline is referred to as pre-diabetes by medical professionals. A1C (5.7–6.4%) (39–47 mmol/mol).

Fig. 9 RPG test

It can be considered as an increased risk for diabetes. Generally, it is measured in cases of diabetes which is supposed to have obesity dyslipidemia with extreme triglycerides and/or to have a low-level HDL cholesterol and hypertension.

3 Millimeter and Microwave Techniques for Sensing

3.1 Background: Mechanism of Millimeter and Microwave Techniques

The well-known microwave frequency band stretches around 300 MHz to 30 GHz, while the millimeter wave spectrum spans in the range of 30–300 GHz; the subsequent wavelength ranges are 1000–10 mm and 10–1 mm, correspondingly. The frequency and wavelengths correlated with microwave and millimeter waves are shown in Fig. 10. These frequencies allow interrogating signals to permeate dielectric objects and react with their interior composition. The millimeter microwave sensors provide useful spectroscopic approaches that do not necessitate exact alignment [24]. This technique focuses on microwave spectroscopy, also known as dielectric spectroscopy. Because there is less dispersion by the tissue, millimeter and microwave radiation can penetrate deeper into the tissue [25]. In this approach, mm-wavelengths are commonly employed in parts that use soft tissue's reflection and absorption features. The link between mm-wavelength radioactivity and blood sugar decreases permittivity as the sugar level rises. On the other hand, the conductivity increases in response to a rise in blood sugar levels [26]. Radar, reflection, resonant perturbation, and transmission are the four techniques used in mm-wavelength sensing [27].

The radar technique involves transmitting an electromagnetic signal to an object close to the transmitter [28]. The statistics, which comprises the dielectric characteristics of blood glucose, will subsequently be sent to the receiver by the transmitter. This is distinct at various glucose concentrations [28]. The primary data is evaluated

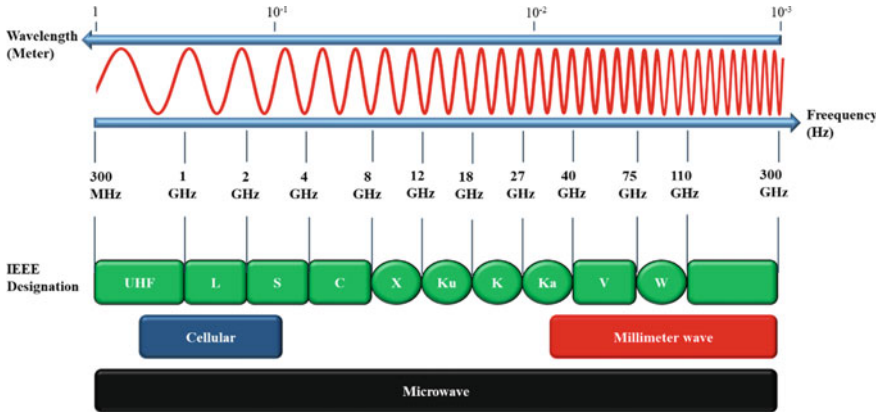


Fig. 10 Millimeter wave in the spectrum band

using traditional signal processing methods, which aid in identifying blood glucose levels [29].

The fundamental goal of the mm-wavelength sensing reflection method is to quantify the reflection boundary for detecting the changes in permittivity due to blood glucose variations. Using a coaxial probe, the reflection factor estimates the permittivity, which leads to blood glucose monitoring by reflection in the mm-wave sensor [30]. A vector network analyzer, such as the Anritsu 37397C, measures the reflection coefficient across the open coaxial probe. Similarly, an antenna can be used in the open coaxial probe sensor attached to the vector network analyzer [31]. The resonant frequency is relevant in determining shifting blood sugar substances related to the reflection coefficient. The link between resonant frequency and variable sugar levels in the blood is assumed to occur with the drop in the intensities of resonant frequency, which occurs by the rise in glucose concentrations.

The resonant perturbation approach offers some of the greatest sensor execution for mm-wavelength light to date [27]. This method aims to determine resonant frequency fluctuations and link such changes to dielectric characteristics. The microfluidic subsystem design and the substrate integrated waveguide (SIW) re-entrant cavity resonator model are the two aspects of this particular method. A microfluidic-integrated SIW re-entrant cavity with a quality element allows evaluating dielectric characteristics of fluids such as the blood samples [32]. When these two systems function together, they provide a sensitive and accurate sensor. Transmission approaches are comparable to reflection techniques in which the reflection parameters are also evaluated. mm-wavelengths can be used in transmission methods to assess fluctuations in glucose levels based on dense permittivity variations throughout a single channel. A sensor can operate in the K band (27–40 GHz) to carry out the benefits of transmitted data. The transmission method requires two measurement ports, whereas the reflection method requires one. Transmission methods are simply reflection systems, but they operate two times because of dual

ports. According to recent research, the transmission coefficient and blood sugar used for examining purposes have a good association [24] (Fig. 11).

Microwave sensing deals with frequency in the range of GHz, having corresponding wavelength frequencies between 10 cm and 1 mm. Signal with wavelength order in millimeter range is often referred to as millimeter waves. The electrical impulses being localized in human bodies can be detected by microwave components acting as distributed elements like phase voltage, current, etc., which changes significantly over physiological extendedness of device dimensions/body on the order of wavelength. Here, quasi-optical techniques can also be deployed for application in millimeter-wave systems [33, 34].

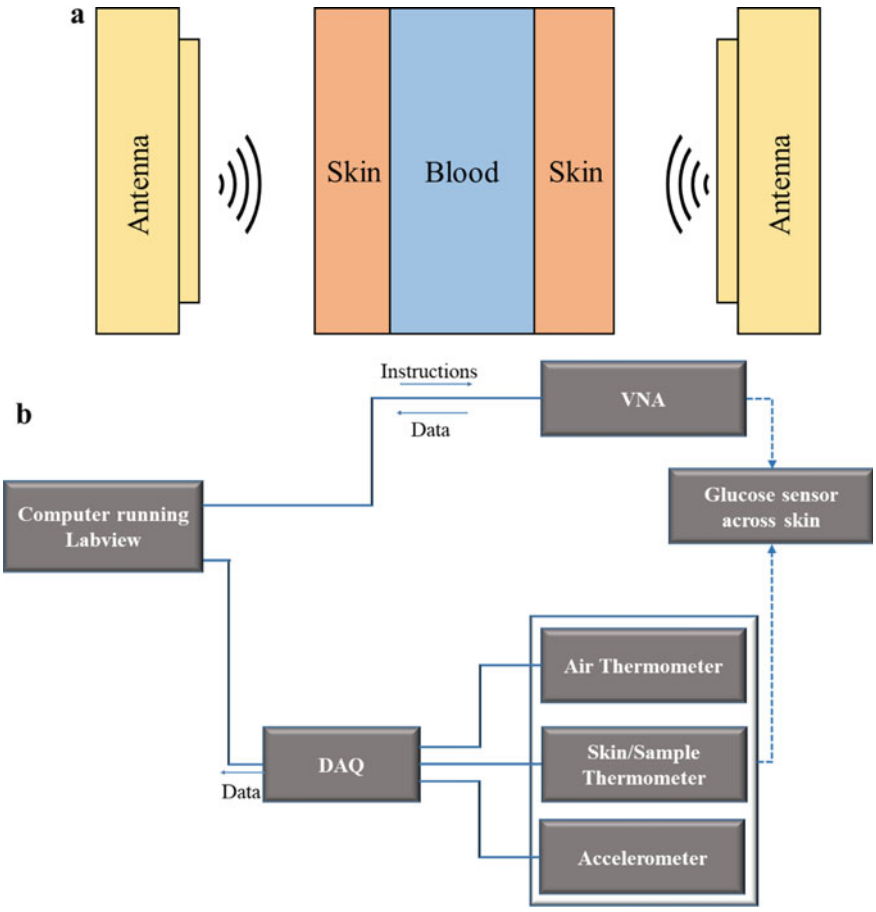


Fig. 11 Millimeter microwave sensor layout for blood sugar recognition. **a** The mm-wave glucose sensor concept is set up with two patch antennas. The skin/blood patient area or a reservoir is located among the two antennas. **b** A diagram of the sensor scheme with data and instruction flow used by Labview

Millimeter and microwave sensing techniques can directly measure the quantities correlated to dielectric properties and, hence, inspect biological material. This technique uses methods such as protein thermal unfolding and refolding lipid bilayer membranes, large aqueous-based molecules, single-cell characteristics, etc. are used in this technique [35]. Here, they introduce a combined millimeter-wave radar system for detecting various glucose levels in laboratory-prepared fake blood models (Fig. 12). The study's goal is to see if mm-wave radars can be used for the non-invasive monitoring of glucose levels in diabetic patients. The proposed concept utilizes signal processing techniques to detect various glucose dilutions and compare them with reflected mm-wave readings. According to the measurement statistics and processed findings, the examined mm-wave radar discriminates glucose dilutions in blood samples across test tubes with extreme sensitivity. This expanded analysis verifies preliminary discoveries and demonstrates a high-resolution recognition capacity. This research also displayed how signal-processing algorithms may process raw records to identify glucose levels accurately. The findings are significant and should open up the way for further research into the possibility of recognizing blood within the physical body [29].

There is another method developed by researchers using the microwave sensing technique for predicting the glucose concentration from the solution of blood plasma. They were designed with three sensors using microwave technology. Figure 13 is the setup of glucose detection using sensors from the blood of a human being. The plasma solution is prepared using various concentrations of glucose, which is added to the blood sample with the addition of ascorbic and lactic acid. The results show an excellent performance of the sensors with good outcomes, and the sensitivity is varied by the amount of glucose [36].

There is a strong relationship between blood glucose concentrations and MMW transmission across the rat ear. It also shows the signal fluctuations above the noise floor when transmitter power is within safe exposure quantities. However, rigid

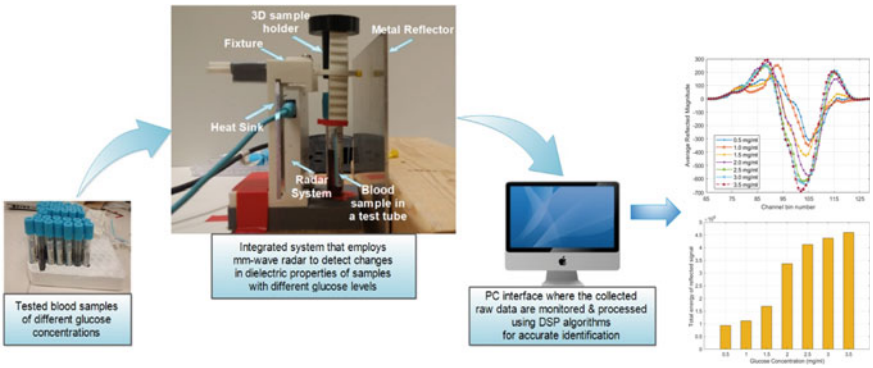


Fig. 12 Test setup: fake blood samples, radar antenna directed to sample tube on a 3-D printed fixture, and PC for supervising/processing (Reproduced with permission from [13] CC By © 2019 by Omer et al., Licensee MDPI, Basel, Switzerland)

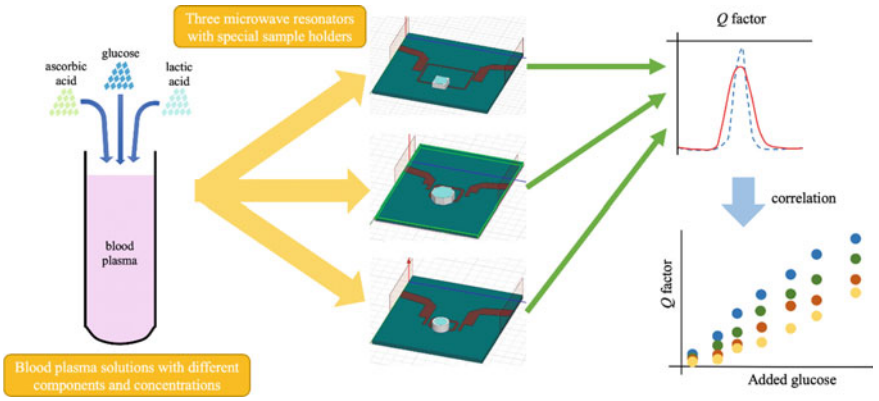


Fig. 13 Measuring glucose from real human blood plasma solutions (Reproduced with permission from [36] CC By © 2019 by the Juan et al., Licensee MDPI, Basel, Switzerland)

waveguide hardware can only be used on immobilized animals. A tiny lightweight fitting containing an MMW CMOS transceiver chipset and an input/output antenna has been designed and built up for active human and animal studies. In addition, experiments were conducted to determine whether the transmission of MMWs via solutions of saline and saline plus sugar could be replicated both in vivo in rat ears and in vitro in the blood (Fig. 14). Measurements in in-vitro and in-vivo, CMOS transceiver design, and packaging of non-invasive glucose monitoring tools are presented in this chapter. Furthermore, millimeter-wave absorption by the solutions having glucose content was evaluated in customized liquid transmission cells, and the results were demonstrated concerning the rat [37].

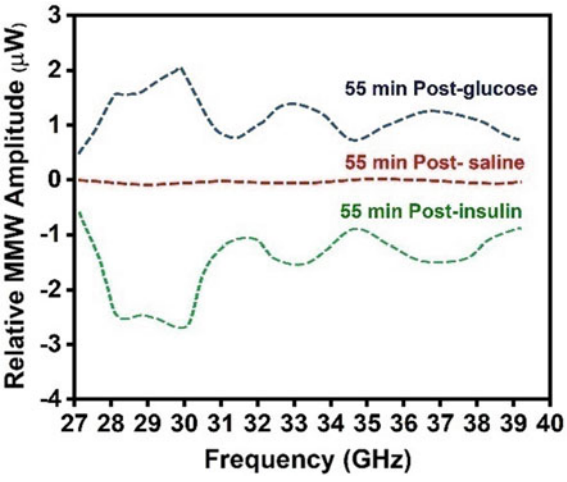


Fig. 14 Schematic diagram of variations in MMW transmission via the rat ear were evaluated when 1gm/kg glucose, 5 ml saline (control), and 2U/kg insulin is injected

Table 2 The advantages and disadvantages of the millimeter/microwave technique

Method	Advantages	Disadvantages
Millimeter and microwave	• Robust and intense signal saturation • Sharp sensitivity for blood sugar concentration changes • No possibilities of ionization	• Low selectivity • Vulnerable to additional substances in the blood • Susceptible to changes of biological factors, inhaling, perspiring level, and cardiac movement

4 Advantages and Disadvantages

The advantages and disadvantages of the millimeter/Microwave non-invasive technique are given in Table 2.

5 Future Scope

Microwave and millimeter-wave NDT&E have been used in various applications Microwave and millimeter-wave imaging for flaw discovery and assessment in diverse composite constructions using near field focus. Synthetic aperture techniques are a few examples. Biological applications, microwave microscopy, composites, and new uses are constantly being developed. There are several advantages to using microwave and mm-wave NDT&E technologies in near-field applications. These approaches are non-contact, one-sided, and require coupling to transfer the signal into the material under test (unlike ultrasonic approaches). They are also monostatic, low-power, and small. Easily adaptable to existing industrial scanners, real-time in-field operator-friendly does not need operator expertise in the field of microwave engineering allows images with high resolutions to be obtained because the spatial resolution in the near-field is a function of probe dimensions (which in these frequency arrays are quite small) rather than operating wavelength robust, tough and repeatable, as well as sensibly priced [38]. Generally, the non-invasive methods are classified into three: optical, microwave, and electrochemical.

The millimeter microwave method lies in the microwave category, so the other methods do not ensure efficiency or ease of operation. But the main advantage of the millimeter microwave method is the strong selectivity according to the variation of glucose levels. This method has excessive non-invasive behavior, which delivers a continuous examination of blood sugar without inducing difficulties in patients. The proposed benefits of millimeter and microwave properties can be used to perform microanalysis up to the basic functional unit of the body. Synthesis of observational cells and the associated immense ways of diagnostics is to be leveraged for different inventions in the bio-medical field using this technology. Unfortunately, in line with the research studies, the assessed rates may not be closely linked with real sugar

levels, and thus the linear range is restricted, necessitating more algorithm modification. Personal characteristics such as old skin tones, skin form, and so on in the sample part will produce huge inaccuracies in the measurement results, resulting in uniformity and steadiness. In terms of analysis, there are certain issues, such as sophisticated detection ways, harsher detecting components, a time-consuming monitoring procedure, detection accuracy support requirements, and significant background signal interference. These constraints can restrict its potential as a household commercial glucose monitor. Suppose more physical parameters such as pH, temperature, humidity, frequency, and other biomarkers involved in blood glucose can be blended to fix the results obtained, improve the performance of painless skin glucose testing and significance to their blood sugar, and achieve continuous monitoring of patients with high blood sugar and low blood sugar. In that case, this could be a promising direction for future research.

6 Conclusion

This chapter evaluated the advancement of research works involved in non-invasive glucose monitoring using millimeter microwave sensing. Non-invasive methods are quite good and less time-consuming than conventional invasive methods. It also offers uninterrupted real-time monitoring of blood sugar levels. This chapter summarizes the different optical and microwave, millimeter-wave biosensor modalities. The millimeter and microwave technologies-based point-of-care devices for glucose level monitoring have been presented. The chapter also discussed the electromagnetic spectrum in which most of the research occurs. We also compared the different glucose monitoring devices existing in the market. Combining all these sections, we have tried to show how all the current aspects, connected to glucose detection, model the technical evolution and development of millimeter and microwave technology that can monitor glucose concentrations non-invasively.

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Nithusha Kallingal obtained her B.Sc. degree in 2014 in Polymer Chemistry from S.N.D.P.Y.S.S. College, Perinthalmanna, Calicut University, Kerala, India, received her M.Sc. in Biopolymer Science (2016) from Cochin University of Science and Technology, Kochi, Kerala, India and obtained her M.Phil. in Biomedical Technology (2018) from Sree Chitra Thirunal Institute for Medical Science and Technology, Kerala, India. She is currently a staff researcher at the Center for Advanced Materials, Qatar University.

Dr. Sajna M.S received her Ph.D. degree in Physics (2018) from Mahatma Gandhi University, Kottayam, India. She has carried out her Post-Doctoral Research under the UGC-DSK National Fellowship Scheme at the University of Kerala, Trivandrum, India. Her research interests are Glassy materials, Rare-earth doped systems, Laser Science, Thin films, Fluorescence, Nonlinear optics, Plasmonics & Sensors. Presently, she works as a staff researcher at the Centre for Advanced Materials, Qatar University.

Ms. Mizaj Shabil Sha obtained her B.Tech. degree in 2017 in chemical engineering from Government engineering College, Calicut, Calicut University, Kerala, India and received her M. Tech in Process control in 2019 from Kerala technical university, Kerala, India. She is currently a staff researcher at the Center for Advanced Materials, Qatar University.

Dr. Mithra Geetha has experience as a Research Scholar and successfully got awarded Doctorate in Biotechnology at Indian Council of Agricultural Research—Central Tuber Crops Research Institute India. She has many research publications in leading scientific research journals with good impact factors. In her current position, she's a staff researcher at Qatar University's Center for Advanced Materials. Her credentials include molecular and microbiological testing. She is acquainted with cell culture techniques, fermentation techniques, and biofuels. Possess comprehensive knowledge of bioinformatics, statistical analysis, and analytical chemistry.

Mr. Ishwar Maruti Islampure is working as System Engineer at Infosys Ltd., India. Having core interest in writing different topics related to use of information technology for the betterment of human beings and to keep environment eco-friendly.

Dr. D Nagendra Prasad is a researcher at Centre for Advanced Materials, Qatar University. He obtained his post-graduation from Bharathidasan University, India and received Ph.D. from BITS Pilani India in 2019. He carried out his research work in the area of DNA- nanoelectronics. He has acquired 8 years of teaching and 6 years of research experience. He published 4 journals and presented at 4 international conferences. His research interests are Micro/Nano device fabrication & Characterization, Molecular electronics, MEMS & NEMS for LOAC, and Computational microfluidics using COMSOL package.

Dr. Muni Raj Maurya received his Ph.D. in Engineering Science (2020) from CSIR-National Physical Laboratory, New Delhi, India. He is currently a staff researcher at the Center for Advanced Materials, Qatar University. His research interests include investigation of the optical properties of nanocomposites semiconductor materials and the development of optically active nanostructures. His current research is mainly focused on nanomanufacturing, and device designs for sensor and nanophotonic applications.

Dr. Asan G. A. Muthalif (PI) is an Associate Professor at the Mechanical and Industrial Engineering Department, College of Engineering, Qatar University. He obtained his Bachelor and Master's degrees in Mechatronics Engineering, IIUM. He earned a Ph.D. from the University of Cambridge (Dynamics and Vibration Research Group), the UK in 2008. He has authored and co-authored more than 90 publications in refereed journals and conferences. He has 3 edited books and 16 book chapters. He has completed more than 30 research projects/grants as a principal- and co-investigator. He has supervised / Co-supervised 9 PhDs and 28 Masters students. Dr. Asan is a certified Professional Engineer (PEng) and Professional Technologist (PTech). His research interest is in Mechatronics, Smart Materials and Structures (piezoelectric, magnetorheological fluids, SMA), and bio-mechatronics, will contribute to the successful completion of this project.

Prof. Sumaya Al-Maadeed (PI) (expert in signal processing) received her BSc in computer science from Qatar University in 1994. She received her MSc in mathematics and computer science from Alexandria University, Egypt, in 1999 and went on to get her Ph.D. in computer science from Nottingham University in 2004. Dr Al-Ma'adeed has published around 90 papers in these areas and is currently an associate professor and head of the Computer Science and Engineering Department at Qatar University. Dr. Al-Maadeed will establish that the sensor data can be acquisition and kept into the necessary software for further scrutinization. To formulate the data for classifier induction, Preliminary data will be collected from the sensors and the necessary pre-processing techniques will be performed.

Dr. Ravikumar Ramlu Vidule Asst. Professor, Dept. Of Chemistry, and working as IQAC Coordinator, Shri Sant Gadge Maharaj Mahavidyalaya, Loha, Dist. Nanded. (MS)-431708, India. Mail id: ravidule@gmail.com, 80007840827. Published Fifteen Research papers in Reputed Journals. Participant in Academics and co-curricular activities. Actively engage and participating on environmental awareness programs by writing articles and delivering talks on All India Radio. Delivered talk in National and International conference, workshops, Refresher and Orientation courses. Currently started the campaign in India and abroad for the awareness of use of, MICROBEADS in PCCP (personal care cosmetic products). Writing articles to stop the use of single used plastic in newspapers. Wrote the chapters in the book:-Blended Classroom: A Method for Encouraging Effective Global Education Learning Environment", Impact of Covid-19:- In Teaching Learning Process in India. Challenges to The Academic Domain In The Aftermath Of Covid-19., Impact Of Covid-19 On Higher Education., Impact of COVID-19 on Textile Industry. Also a core interest in Microbeads and other aspects been invited for the lecture. Invited as a speaker in Sacred Heart College, Kochi "Microbeads: A Threat for life on Earth" In Flasgship programme Prof. K.V.Thomas Endowment "National Seminar on New Frontiers in Materials and Environmental Sciences." 28th Jan. 2020., Invited as a Resource person in Pratibha College of Commerce and Computer Studies Pune College as "State Level Seminar on Emerging Environmental Challenges and its sustainable Approaches." 7-8th Feb. 2020., Given Short Presentation as a young reasercher at Dr. T R Ingle memorial National Symposium, "Trends, Research and Innovation in Chemical Sciences (TRI-2020), Feb 14-15, 2020, Organized by Dept., of Chemistry, SP College, Pune., An invited lecture (Webinar) "Nehur Yuva Kendra Ministry of Youth affair and Sports, Dist. Thiruvanthpuram, Kerla" conducting an internship for MSW students "Blended Learning as a new approach to social work." Given talk dated on 30 Mar 2021: Talk title: Microbeads: A Threat for Life on Earth in the International conference on Materials of the Future: Smart Applications in Science and Engineering, Qatar University, Qatar, Emergent Materials Journal and Chemistry Africa Journal, Springer.

Dr. Srinivas Ankanagari Dept of Genetics and Biotechnology, Osmania University, Hyderabad, Telangana 500007. India. He obtained his Master's in Genetics from Osmania University and did his Doctorate in Life Sciences from University of Hyderabad. He had carried out several regulatory and non-regulatory pharmaceutical bioavailability and bioequivalence of drugs in Phase I and Phase II clinical trial projects of pharmaceutical industry. He was involved in analysis of biological samples for drugs/metabolites concentration and development, validation and implementation of bio-analytical methods. He is currently engaged in academic and research activities at Department of Genetics & Biotechnology, Osmania University.

Dr. Kishor Kumar Sadasivuni is currently working as a group leader of SmartNanoSolutions at Center for Advanced Materials, Qatar University. Dr. Kishor's research has its roots from the analytical chemistry he mastered during his Master's degree in Andhra University, India. He received his Ph.D. in Materials Science and Engineering from University of South Brittany at Lorient, France in 2012 under the supervision of the Professor Yves Grohens and Professor Sabu Thomas. He has enormous knowledge and valuable experience in his field owing to over 12 years of active research research experience of 12 years. Dr. Kishor has more than 250 research articles published in international peer reviewed journals with a total citation of 5500 and h-index 41. He is also the author of 20 book chapters and the editor of 8 books. Dr. Kishor is an expert in the nanomaterials engineering, especially the sensing and flexible electronics. He has a keen interest towards development of different devices based on the smart materials by engineering IoT. Some of Dr. Kishor's inventions are protected by 2 US patents and 2 Indian patents and presently 5 patent disclosures have been submitted by him. His strong academic background and passion for research is remarkable and reflected in his fast paced career growth. Dr. Kishor's enthusiastic and sincere approach towards research works are reflected in the forms of various grants and awards offered to him. He is a group leader and is presently the lead principal investigator for 11 research projects, covering the NPRP, UREP, IRCC grants of Qatar National Research Fund and the Qatar University. He is also involved in other three research grants as the principal investigator, summarizing a total grant amount of 3M$. Dr. Kishor is a team player and has collaborated actively with researchers (more than 450 co-authors as evident from the Scopus data) in several disciplines of computer science, biomedical sciences, industrial engineering, and electrical engineering from all over the world (USA, France, South Korea, Oman, Spain, Italy, Australia, Malaysia). Dr. Kishor's achievements have been recognized by several awards such as Tyre & Rubber Industry Leadership Acknowledgement Awards (TRILA); Young Research Scholar of the Year 2017. He has been included in the world's top 2 % scientists according to

a list compiled by Stanford University in the year 2019 and for this he was recently honored by the QU.

Different Machine Learning Algorithms Involved in Glucose Monitoring to Prevent Diabetes Complications and Enhanced Diabetes Mellitus Management

Wai-kit Ming and Zonglin He

Abstract Diabetes mellitus (DM) is a group of metabolic disorders resulting from dysregulation of blood glucose (BG). Hence, it may lead to various vascular and neural complications involving multiple organ systems, either short- or long-term. During the past two decades, various computer-assisted systems based on machine learning algorithms haves based on machine learning algorithms have become available and have achieved satisfactory performance in glucose monitoring and predicting the prognosis of diabetic patients. The increased availability of multidimensional health data has shed light on machine learning for a novel BG prediction and diabetes management method. So far, various machine learning algorithms have been productive in predicting BG and diabetes progression and prognosis. Hence, machine learning algorithms have been regarded as accurate, with less operation cost and higher efficacy in predicting potential diabetes in the undiagnosed population, profiling personalized BG dynamics, establishing personalized decision support systems, and building BG alarm events in DM patients. However, real-world data concerning the efficacy of various machine learning algorithms in diabetes prediction and management is still limited, and internationally acceptable guidelines have not been established to estimate and quantify the potential lifestyle-relevant variables related to the BG level. This chapter has been written to address the current progress in the application of machine learning in glucose monitoring and DM management. Different machine learning algorithms have also been discussed on the validity and feasibility of the algorithms fit for purpose.

Keywords Machine learning · Surveillance · Prediction · Diabetes mellitus · Management

W. Ming (✉) · Z. He
Department of Preventive Medicine and Public Health, School of Medicine, Jinan University, Guangzhou, China
e-mail: kming@connect.hku.hk

Z. He
e-mail: hezonglin0leon@stu2015.jnu.edu.cn

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1 Introduction

Diabetes mellitus (DM), which entails a global health crisis, is a group of metabolic disorders that results from dysregulation of blood glucose (BG), either due to the failure of the body to secrete insulin (type I diabetes mellitus, T1DM) or the inability of the body to respond to insulin action (type II diabetes mellitus, T2DM), as well as first recognition during pregnancy (Gestational Diabetes Mellitus, GDM) or other specific types [69]. The patients may present with chronic hyperglycemia, manifesting polydipsia, polyuria, and polyphagia.

Clinically, the current mainstream diagnostic investigation method of DM is venous plasma glucose measurement [28], and 2-h oral glucose tolerance test (OGTT) remains the internationally accepted gold standard for DM diagnosis, where the venous plasma glucose levels are obtained for fasting, as well as 1-h- and 2-h-post a certain amount of glucose intake (normally 50 g or 75 g).

The mainstream view of the pathophysiology of DM remained that genetic predisposition underlies DM development, where what control the biological steps of beta-cell action, insulin secretion, insulin interaction with tissue cells, insulin receptor production and insulin action inside the cells that were altered or mutated [22]. T2DM patients are getting increasingly insensitive to the physiological effects of insulin. Therefore, more insulin is needed to maintain the original effects of insulin to induce cells to uptake glucose [29]. Nevertheless, for T1DM patients, as their insulin production by beta cells is impaired, therefore, eventually, for both T1DM and T2DM patients, the pharmacological induction of insulin secretion or insulin absorption is no longer sufficient for maintaining the euglycemic state. External insulin supplementation is the sine qua non for diabetes management [39].

DM without proper management may lead to a variety of vascular and neural complications involving multiple organ systems either in a short- or long-term manner, and it is the multiple complications secondary to DM that lead to the heavy burdens of the patients, causing increased medical cost and decreased quality of life [22]. In this sense, regular community-based screening and prompt diagnosis in undiagnosed patients, sufficient patient education and support, continuous medical care, and user-friendly continuous BG monitoring, as well as psychological dredge and social support, are required to prevent acute complications (e.g., ketoacidosis) and minimize the risk of long-term complications (e.g., nephropathy, retinopathy, diabetic foot, cardiovascular disease, or stroke) [14, 29].

Therefore, on the one hand, in the community, timely screening of diabetes in undiagnosed patients could help prevent further development of diabetic complications, hence reducing disease burden and improving quality of life. On the other hand, for DM patients, BG monitoring is of vital significance. It is acknowledged that optimizing glycemic control through lowering BG levels and minimizing glucose variability could prevent the development of microvascular complications and long-term macrovascular disease [47, 54]. BG serves as the most important risk factor and prognostic factor in DM patients owing to its predictive values in disease progression; it is difficult to manage because of its multifactorial nature, as well as inter-and

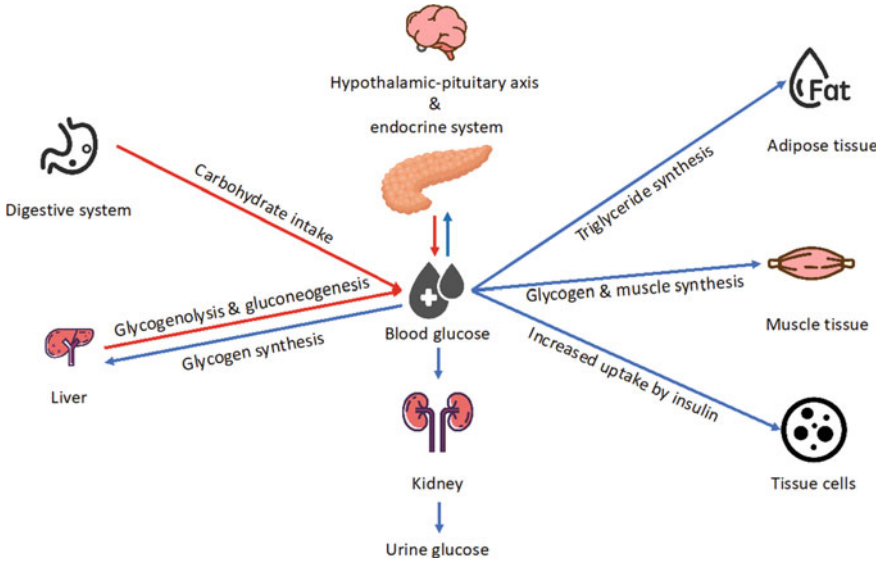

Fig. 1 Systems and organs related to blood glucose level

intra-personal variability associated with nutritional, behavioral, and pharmaceutical management, as shown in Fig. 1 [54].

Specifically, timely acknowledgment of the fluctuation of blood glucose levels underlies the foundation of diabetes management. With proper and timely blood glucose monitoring, efficacious treatment, dysglycemia (especially undetected hypoglycemia) identification, and treatment plan modification (including medical nutrition therapy, exercise therapy, and pharmaceutical interventions) become possible. Normally, the blood glucose level is checked before the meal, 2 h post-meal, and before sleep [1].

The emergence of self-monitoring of blood glucose (SMBG) has inspired diabetes management in the previous decades, aspiring for euglycemia. Yet, its inconvenience in use may lead to incomplete BG data collection [1]. Moreover, portable blood glucose meters have allowed patients and healthcare workers to obtain dynamic blood glucose level data. With the development of technology, the advent of continuous glucose monitoring (CGM) has made surveillance of fluctuation pattern, frequency, level, and timing of BG level variation possible, and it is proven useful in alarming hypoglycemia. Nevertheless, the CGM devices could be expensive and require continued capillary glucose testing for calibration. Despite the gradual transition from SMBG to more advanced glucose monitoring devices, some reluctance to monitor the blood glucose has been noted given the costs, complexity in use, and low awareness of the necessity. Though SMBG has been available for many DM patients, the need for frequent testing and continuous replenishment of consumables has undermined the patients' compliance. Besides traditional serum glucose monitoring, novel materials have also inspired glucose monitoring. For instance, non-invasive and non-enzymatic

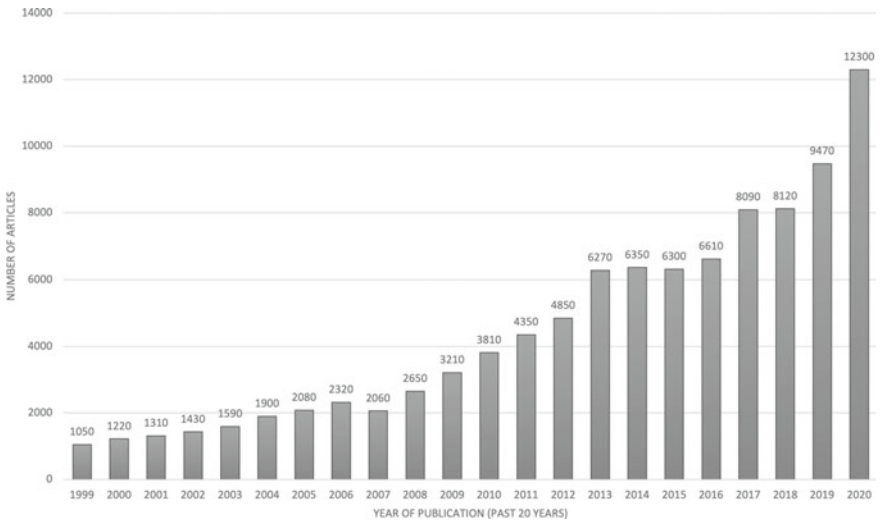

Fig. 2 The number of published articles in Google Scholar includes "Blood glucose" and "Machine learning"

sensing using advanced nanomaterials gained popularity, despite lacking sufficient clinical evidence in the accuracy and stability of long-term glucose monitoring [15, 56, 59]. Hence, accurately monitoring the blood glucose while improving glycaemic control and the quality of life of these patients is now one of the biggest challenges in DM management. The recent boom in BG levels prediction arises with the explosion of interest in Artificial Pancreas Project, a closed-loop control system for BG control [60], and a gross estimate of the number of academic papers concerning "blood glucose" and "machine learning" in the Google Scholar database is shown in Fig. 2.

Artificial intelligence (AI) is progressively utilized in medicine to find patterns in complex sets of clinically collected data and self-monitored data to improve health outcomes [38]. Among many AI-based algorithms, machine learning (ML) can equip computers with the ability to learn without the need to be explicitly programmed in advance [49]. The ML algorithms provide the added value of the expertise of clinicians. It is better than using only one in disease treatment [11, 68], especially in better DM management and complications prevention (Gadekallu et al. 2020; [51].

In the present chapter, the following contents will be addressed: (1) the role of ML algorithms in DM management; (2) difference between various ML algorithms; (3) insights into future ML application.

2 The Role of ML Algorithms in DM Management

Specifically, the ML takes part in the DM managements mainly in three main aspects: (1) assisting precise BG level prediction; (2) detecting DM-associated complications and BG alarm event (BG anomalies); (3) establishing personalized decision support/education systems.

2.1 BG Levels Prediction

BG levels are variable and multifactorial, directly affected by insulin, physical activity, and dietary intakes, and influenced by numerous factors. Owing to the dynamic nature of BG levels, some scholars also conceptualized a physiological model that could consider the daily events that influence BG levels, including insulin uptakes, food intakes, exercise, sleep, and even seasonal variation [41].

A comprehensive understanding of the pathophysiology and biological mechanisms underlying DM development and progression is the foundation of incorporating physiological parameters in the ML algorithms. Generally, a physiology-based approach to ML strategies would fractionize the parameters related to BG regulation into three distinct categories, viz., BG dynamics, insulin dynamics, and meal absorption dynamics [40]. Two methods are generally used to incorporate the physiology-based data, namely the lumped (semi-empirical) model and the comprehensive model, where the former would only consist of a few equations and parameters, taking all the organs and tissues as a whole. At the same time, the latter manages data separately according to various organs and tissues [6].

Moreover, the increasing popularity of mobile health applications, biosensors, wearables, and many devices for self-monitoring and healthcare management has also made possible the generation and collection of automated and continuous health-related personal data to feed the ML algorithms [62], such as body mass index, stress level, amount of sleeping time, underlying diseases, medications use, smoking habit, menstruation, alcoholism, allergies, and geological factors [62].

Nevertheless, compared to the physiology-based approach, another approach coined the data-driven strategy also internalize self-collected data and other easily available parameters to predict BG. Regarded as the black box, although sometimes this approach can achieve a high accuracy rate, it is sometimes difficult to interpret the results since it lacks biological and physiological theoretical support underlying the mechanisms of the algorithms [62]. In sum, it could be divided into three different models, namely a time series model, machine learning model, and hybrid model.

Specifically, for DM patients, necessary alarms could be noted through BG prediction to avoid disease progression and over-or under-regulation of BG levels, causing hypoglycemia or hyperglycemia. Sudharsan et al. have shown that robust ML models for hypoglycemia prediction in T2DM patients could effectively identify vulnerable patients needing to manage hypoglycemia [55, 64]. Oviedo et al. conducted

a methodological review regarding the prediction models of BG levels, risks, and events. They found that the algorithms setup and performance metrics of the ML algorithms currently reported were mainly focused on a closed-loop system (an artificial pancreas) [40]. As reported by Woldaregay et al., in terms of BG level prediction, feedforward neural networks remain the most used algorithms (20%), followed by hybridization of the physiology-based model and machine learning techniques (19%), recurrent neural networks (18%), and support vector machines (SVMs) (11%) [62].

2.2 Detection of DM-Associated Complications

Continuously increased ML models attempting to manage DM-associated complications have been built and assessed. Studies have proven the efficacy of ML-assisted T2DM care programs in the community by identifying population-level effects and mostly benefited patient sub-groups [14, 66]. Makino et al. has demonstrated the use of machine learning (scikit-learn), building a prediction model from 24 factors of interest in predicting the progression of diabetic kidney disease, and an accuracy of 71% was achieved [34].

A systematic review by Kavakiotis et al. has summarized the efficacious role of ML and data mining techniques in diabetes screening and diagnosis and detection and management of complications [26]. Nevertheless, complications secondary to T1DM were scarcely investigated using ML prediction models [26]. T2DM prediction in the community is beneficial for the early detection of T2DM in populations with high-risk factors. It might robustly capture cases with early dysglycaemia but present with no obvious clinical symptoms [13].

On the other hand, pre-hospital screening is also an important application of ML algorithms. Haq et al. proposed a filter method based on a decision tree for incredibly important feature selection and incorporated two ensemble learning algorithms, Ada Boost and Random Forest, for feature selection; the proposed algorithm could reach a test accuracy of 99%, 99.8% with k-floods and 99.9% with LOSO validation, in identifying populations at risk of DM [23].

DM risk classification is vital and challenging, as the medical data is non-linear, non-normal, and complex [7, 35]. A variety of ML algorithms have been developed for the prediction and diagnosis of diabetes disease, viz., (1) supervised algorithms including decision tree (DT), random forest (RF), linear regression, logistic regression (LR), Gaussian process classification (GPC), aïve Bayes (NB), as well as neural networks like artificial neural network (ANN) and feedforward neural network (FFNN); and (2) unsupervised algorithms such as k-nearest neighborhood (KNN), linear discriminant analysis (LDA), quadratic discriminant analysis (QDA), and support vector machine (SVM) [8, 35]. And the efficacy of such algorithms has been evaluated and reported by various researchers, with an accuracy of DM prediction ranging from 70 to 99% [4, 5, 9, 21, 25, 27, 33, 42, 43, 48, 58, 61, 65].

3 Different Machine Learning Algorithms

ML algorithms were established to reproduce human neural networks in silico in the 1980s. ML is generally composed of three key components: learning algorithms, computational power, and data [18]. As a subset of AI, ML models can be regarded as algorithms that can either self-learn or learn from preset parameters. The main objective is to identify effective variables and the underlying correlation [36, 38]. ML models are normally developed through the following steps, namely, problem identification, goal setting, data collection and sorting, ML model building, validation, assessment of impact, deployment, and monitoring, as well as future modifying [12], as shown in Fig. 3.

The ultimate aim of establishing machine-learning algorithms is to provide optimal personalized decision support of DM management, specifically by developing better closed-loop insulin delivery systems taking into account glycemic variability in DM patients [62].

The value of health-related data to expedite precision medicine development has been well underlined [37, 46, 50]. Therefore, biomarkers and pharmacogenetics parameters may also be incorporated into the ML algorithms to predict management efficacy and responses in patients [19, 31], the onset the progression of the disease course, as well as BG levels [67].

Several factors may influence the eventual clinical implementation during the model design, such as data type and size, model interpretability, and the use of a balancing model. Nevertheless, every type of ML algorithm has its limitations, which

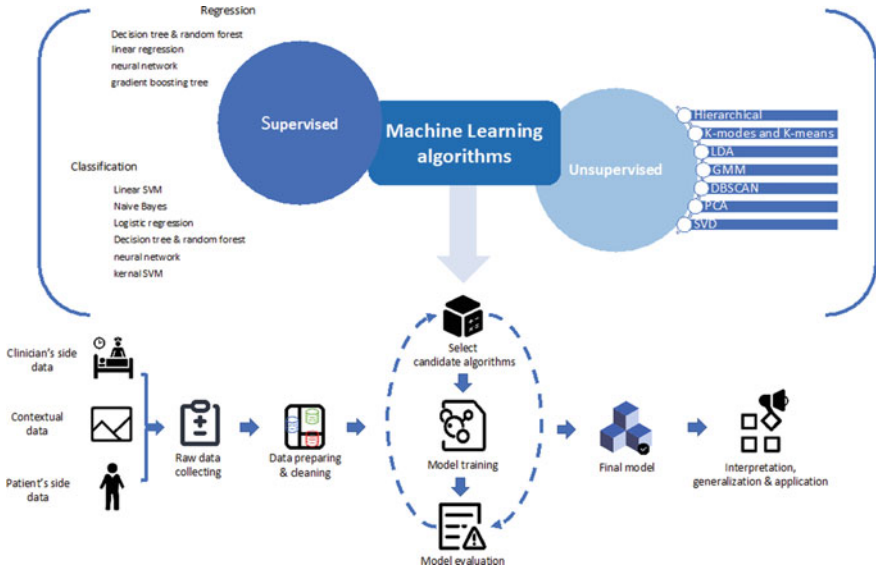

Fig. 3 A graphical summary of the machine learning algorithm process

may only work at full efficacy in specific circumstances. In a systematic review on ML models for community-based T2DM, ANN outperformed all the counterparts, closely followed by logistic regression, decision trees, and random forests [32]. There exists nothing like universally acceptable and ever-winning ML algorithms that fit in every situation. Therefore, to generate relevant and robust results, the currently available ML frameworks should be adjusted in a tailor-made manner to improve further productivity and efficiency [18].

3.1 Artificial Neural Network (ANN)

An artificial neural network (ANN) is a computational model inspired by biological nervous systems. It comprises various processing elements similar to neurons and axons-like connections called weights [44].

The topology of the ANN could be classified into two main types, namely the feedforward networks and recurrent/feedback networks. The feedforward network is the most used one, where feedback information could be sent back to the former level. In contrast, information could only be sent in one direction (forward) from the earlier stage to the next level in the forward network. Therefore, ANN has excellent efficacy and significant advantages and could adjust to the data flexibly to model and solve a real-world problem.

3.2 Support Vector Machines (SVM) and Gaussian Process Regression

Support vector machines (SVM), a supervised learning algorithm, have been largely utilized for various purposes, such as identification and recognition of patterns, categorization or classification, regression, and prediction [10]. The use of SVM could minimize the errors incurred by empirical classification.

Support vector regression (SVR) is the most widely used in BG level prediction and modeling among the many SVM algorithms. For instance, Reymann et al. has developed an SVT-based Mobile platform with a radial basis function as a kernel to predict BG levels [45].

Although Gaussian process regression is non-parametric, it could estimate uncertainty and capture noise and smoothness parameters from data input [62]. For instance, Tomczak et al. has reported the feasibility of Gaussian process regression in BG level prediction using categorical inputs such as the type of measurement (e.g., insulin dose, meal intake, physical exercise, pre-prandial BG measurement, and others) [53].

3.3 Decision Tree and Random Forest

A decision tree (DT) uses a structure built using input features to predict or classify the target outcomes using various input variables. The decision rules could be easily extracted, and hence it is generalized and extended for multiple kinds of application.

Random forests also called random decision forests, serve as an ensemble learning approach for classification and regression applications. It learns through a multitude of decision trees having been constructed, and it can thus directly start feature selection, generating the model of the class or the mean of prediction [24]. Two methods are generally utilized when measuring variable importance, namely the Gini importance index and permutation importance index [2].

For instance, Xiao et al. developed a kind of BG predictor using random forest and support vector regression to evaluate the improved performance gained using a mixed strategy to select an optimal feature pattern [63]. Moreover, Georga et al. predicted the BG levels using random forest regression in a multivariate and multidimensional dataset [17].

3.4 Logistic Regression

Logistic regression (LR) is generally utilized for classification purposes, and the dependent variable ought to be categorical, owing to its significant role in classification compared to regression. With advantages in robustness and easy handling of non-linear data, the logistic regression could predict the probability of a binary variable (the dummy output variables) based on one or more predictor variables [57].

4 An Example of the Application of ML Algorithms Predicting BG Levels in Pregnant Women with GDM in Resource-Limited Regions

Gestational diabetes mellitus (GDM) is glucose intolerance (hyperglycemia) with the first onset or discovered upon pregnancy. Unmanaged GDM could lead to severe adverse outcomes compromising both mothers and offspring. Nevertheless, pregnant women living in low- and middle-income areas or countries may fail to undergo routine antenatal examinations, leading to a missed diagnosis of GDM. The reluctance to experience the full course of oral glucose tolerance test (OGTT) or the unavailability of a sufficient testing kit may be blamed. To tackle the problems, an AI model that included 9 algorithms was trained using data collected from 12,304 pregnant women from November 2010 to October 2017 who underwent routine prenatal tests in the Obstetrics and Gynecology Department of the First Affiliated Hospital of Jinan University, Guangzhou, China.

The pregnant women's age and fasting blood glucose level were chosen as the critical parameters input for model building. For validation, fivefold cross-validation was conducted for the internal dataset. An external validation dataset constituted with 1655 cases collected from the electronic database of the Prince of Wales Hospital, Hong Kong SAR.

With 9 ML algorithms (SVM, RF, AdaBoost, kNN, NB, decision tree, LR, eXtreme gradient boosting, and gradient boosting decision tree) built, SVM reached the best performance, obtaining an accuracy of 88.7% in the external validation set.

Later, a mobile application was developed, and a prospective and multicenter study was conducted to test the clinical efficacy of the mobile application incorporated with the ML algorithms we developed in GDM screening for pregnant women in resource-limited areas, using only fasting blood glucose value and their age [52]. Although further experiments are needed, this study has provided direct evidence that ML algorithms could, on the one hand, provide a highly accurate diagnosis of undiagnosed patients with high efficacy, and on the other hand, render the cost at an extremely low level. Hence can become an appropriate tool used in the real world instead of merely an algorithm-chasing high performance in silico.

5 Outlook

Considering the ML algorithms involved in DM managements, several questions emerge (1) who is using the algorithms; (2) what kinds of data are input in the algorithms, and (3) how is the efficacy and interpretability of the models?

Owing to the "black box"-like low interpretability of ML algorithm, the promotion and further generalized application of ML is doubted, despite that the predictive performance is considerably convincing and promising [20, 30]. Nevertheless, machine learning is only effective when large samples are used due to the input data's multi-dimensionality [3], hence, the studies' small sample size models may be under-estimated. Moreover, ML models devoid of appropriate external validation suffer from limited applicability and extendibility and lacks clinical impact. Even if the ML model is suitable for clinical application, challenges exist in practice due to real-world scenarios' complexity and variability.

Moreover, the user of the ML algorithms matters. Although some ML models could achieve a prominent accuracy and clinical significance level, the data needed to feed the model may not be easily collected and utilized. Therefore, ML algorithm builders should consider the real-world situation and consider the future users of the algorithms instead of an utter inaccuracy chasing. Concerning the future users of the ML algorithms, the source of the parameters for the model building could be both from the patients' side (BG levels, insulin intake, calories intake each diet, exercise, and others) and from clinician's database (bio-physiological parameters, laboratory investigations, ancillary examinations, and others). Moreover, it is also necessary to consider any relevant contextual information, such as intra- and inter variability

among the patient's lifestyle changes, environmental factors, the time series (diurnal vs. nocturnal), and other relevant factors parameters [62].

Therefore, achieving a universal model that accurately predicts and easily collects data from the target population isn't easy. The high accuracy remains controversial if the algorithms were extrapolated to a larger population or a different population. Lacking specific clinical evidence so far, the ML algorithms could still not replace routine diabetes screening and diagnosis and provide clinical suggestions for management for potential DM-related complications predicted. In this sense, future studies should also value the interpretability and applicability of the ML algorithms developed. The assessment of the clinical efficacy and cost-effectiveness of the ML algorithms in the clinics remains urgently needed.

6 Conclusion

Machine learning algorithms have been regarded as accurate, with less operation cost and higher efficacy in predicting potential diabetes in undiagnosed populations, profiling personalized BG dynamics, establishing personalized decision support systems, and building BG alarm events in DM patients. However, real-world data concerning the efficacy and cost-effectiveness of various machine learning algorithms clinically is still limited, and internationally acceptable guidelines have not been established to estimate and quantify the potential lifestyle-relevant variables related to BG level.

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Dr. Wai-kit Ming is an Assistant Professor in Epidemiology and Public Health at the City University of Hong Kong. Before joining the City University of Hong Kong, he was the Head of Community Medicine at the School of Medicine and the Assistant Dean of the International School at Jinan University, Guangzhou, China. He was a visiting research fellow at the University of Oxford and the National Perinatal Epidemiology Unit in the United Kingdom. He served as the CEO of a medical device company and has thirteen national patents for medical devices. His research team has extensive interdisciplinary collaboration experience, including artificial intelligence medicine. He has had a long history of cooperation with the United States, the United Kingdom, Australia, and local universities on national-based clinical research projects. Dr. Ming's work revolves around AI medicine research that has major population health impacts locally and internationally. He has had two scholarly papers published as covers of a journal and over fifty other scholarly papers published, mainly in JCR Q1 and Q2 journals.

Dr. Zonglin He having received MBBS from the International School of Jinan University in 2021, Dr. He is now pursuing a research postgraduate degree in the Hong Kong University of Science and Technology, focusing on the research of stem cell biology. He is an experienced researcher with demonstrated history of conducting research in the field of public health, health economics, as well as clinical research and clinical translation of basic medical research. So far, he has published 15 SCI/SSCI articles, with 235 citation (H-index 6).

The Role of Artificial Intelligence in Diabetes Management

Amine Rghioui, Jaime Lloret, and Abdelmajid Oumnad

Abstract Diabetes is one of the major health complications in the world. It increases the need to focus on prevention and early detection to improve management and diabetes treatment. For effective treatment of diabetes, rapid diagnosis and ongoing medical care are necessary to prevent acute complications and minimize the risk of long-term complications. Several technologies like Artificial Intelligence (AI), Internet of Things (IoT), communication technologies, embedded systems, and smart devices are used to improve the quality of life of diabetic patients and reduce the costs of hospitalization. Artificial Intelligence (AI) is a booming field, and its applications to diabetes are growing even faster. In this work, many intelligent algorithms are presented to support advanced analytics and provide individualized medical assistance to diabetic patients. The algorithms are detailed and compared deeply as many healthcare companies are applying these technologies. The short-term outlook indicates that they are likely to have considerable success in clinical practice. Moreover, we present some Artificial Intelligence initiatives to resolve the diabetic problem. Therefore, we evaluate the accuracy of an Artificial Intelligence (AI) model using a Machine learning algorithm and diabetic data. Finally, we discuss the current issues and future challenges.

Keywords Healthcare · Artificial intelligence · Machine learning · Diabetic patient

A. Rghioui (✉) · A. Oumnad
Research Team in Smart Communication-ERSC-Research Centre E3S, EMI. Mohamed V University, 10000 Rabat, Morocco
e-mail: rghioui.amine@gmail.com

J. Lloret
Integrated Management Coastal Research Institute, Universitat Politecnica de Valencia, 46370 Valencia, Spain
e-mail: jlloret@dcom.upv.es

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1 Introduction

When the pancreas does not work the way it should be producing the amount of insulin needed or when the body does not use the insulin produced correctly, humans are affected by a chronic disease known as Diabetes. Important organs of the human body like the blood vessels, the nerves, and the eyes can be damaged by high or low blood sugar levels. To avoid these worsening of the state of health of the diabetic patient, daily monitoring should be carried out either by the doctor or by the patient himself. Diabetes is a chronic disease that affects more than 463 million people worldwide.

Diabetes can cause short-term complications (hypoglycemia, malaise, etc.) and long-term complications in the event of poor blood glucose control (blindness, cataracts, thrombosis, nephropathy, etc.). To avoid such consequences, advice and treatment allow patients to live normally. Therefore, for effective treatment of diabetes, prompt diagnosis, patient education in self-management, and ongoing medical care are necessary to prevent acute complications and minimize the risk of long-term complications [1, 2].

Artificial Intelligence (AI) and the Internet of things (IoT) are two new technologies that can help patients and doctors to solve several problems of diabetes. Artificial Intelligence can be defined as "a branch of computing that aims to create methods that analyze information and help manage complexity in a wide range of applications". Artificial intelligence involves implementing several techniques that enable machines to imitate a form of real intelligence. Artificial Intelligence is implemented in a large and growing number of fields of application. The application of AI technologies on diabetics is possible for efficient data processing and tools and devices to manage this disease [3, 4].

Artificial Intelligence can help and facilitate 3 main areas of diabetes care: diabetic patients, doctors, and smart healthcare systems. AI has added new uses for patients with diabetes, introducing patient supervision, rapid decision making, and risk prediction.

This chapter discusses the current advances and challenges in introducing Artificial Intelligence for diabetes disease treatment. We will also cite a wide variety of intelligent Artificial Intelligence algorithms widely used to support advanced analyses and provide personalized medical assistance to diabetic patients. In another part, we will talk about the applications and initiatives that exist in the literature and where Artificial Intelligence techniques are used to solve the problems of diabetic patients.

To this end, this chapter is organized in such structure: Section 2 is a review of related works. Section 3 proposes the Intelligence Artificial and its application for monitoring diabetic patients. Section 4 details some applications and initiatives that use Intelligence Artificial technologies to manage diabetic disease. Section 5 describes our application for data classification for diabetic patients using machine learning algorithms and the obtained results that help in the practical evaluation. In the end, Section 7 is the conclusion of this chapter.

2 Related Work

Different articles that use Artificial Intelligence techniques for personalized and automated diabetes management exist in the literature. This section presents a summary of the recent works that deal with diabetes disease management and the systems that have been designed to help diabetic patients. Some of these works are given below:

In recent years, many advances have been made in health care and, more specifically, in solving the problems of diabetic patients. Several new Artificial Intelligence techniques have been developed to help patients and doctors either develop new applications for the management of diabetes, or applications that continuously monitor blood glucose levels for diabetic patients. We also find the classification and prediction of diabetes in diabetic patients.

For the applications, we find: Xiao et al. [5] proposed a new wireless electrochemical sensor used for diabetic patients to monitor the blood glucose level in real-time. This sensor is characterized by low power consumption and low cost. We also find the work of Wang and Lee [6], where they developed a new blood glucose sensor that controls and monitors the level of glucose in diabetic patients. This sensor takes real-time measurements and contains an alarm that indicates the glucose level.

Ahmed et al. [7] developed a new system that predicts glucose concentration in patients with diabetes using GlucoSim, a software that helps analyze patient information. This system aims to avoid hyperglycemia and severe diabetes complications.

Rghioui and Jaime [8] presented a work to predict diabetes by classifying the glucose level measurements in several diabetic patients, using J48, Naives bayes, RandomTree, SMO, OneR, and ZeroR. They also compared the performance of these machine learning algorithms based on accuracy and execution time. The results showed that the performance of the J48 algorithm is better than that of the other algorithms.

Kumar and Umatejaswi [9] presented analyses of several data mining approaches such as classification and grouping to diagnose the type of diabetes and its severity level for each patient. In [10], the authors aim to consolidate the prediction of the functioning of depression in diabetic patients by applying machine learning techniques. The authors used four algorithms for the prediction, SVM, Kmeans, Fcmean, and PNN; the results obtained show that the SVM classifier is more stable than the others. In [11], the authors compared the performance of several machine learning algorithms for predicting the length of stay of short- and long-term hospitalized diabetic patients. The results showed that the SVM method is the most reliable method for predicting the length of stay of short-term hospitalized diabetic patients. In [12], the authors studied and predicted diabetic patients using real data sets and proposed an approach based on three major steps: cleaning, modeling, and storytelling. Next, they applied the k-nearest neighbor algorithm to classify the patients, and finally, they evaluated the performance of this approach using the receptor operating characteristic (ROC) and the F1 score.

In our article, we will talk about Artificial Intelligence and its application for the monitoring and surveillance of diabetic patients. We will also mention the patient monitoring applications based on Artificial Intelligence technology. Finally, we will describe our application which aims to classify data for diabetic patients using machine learning algorithms and then we will discuss the results of our practical evaluations.

3 Artificial Intelligence and Diabetes

Artificial Intelligence was born in the 1950s with the mathematician Alan Turing to implement different techniques that allow machines to imitate a form of real intelligence. So, it is a process of imitating human intelligence that relies on creating and applying algorithms executed in a computer environment to enable these environments to think and act like human beings.

Therefore, Artificial Intelligence can be defined as "all the theories and techniques implemented to create machines capable of simulating intelligence", according to Larousse. Computers or programs capable of performance are usually associated with human intelligence and amplified by technology. According to this definition, many people consider that Artificial Intelligence is a technology dedicated only to computing. Still, on the contrary, AI is a field with broad roots ranging from mathematics to statistics through computer science, philosophy, and psychology. AI is found implemented in a large number of application areas.

According to mainstream search engines, the term "Artificial Intelligence" has become a buzzword in recent years; its frequency of use has increased in recent years. Figure 1 illustrates the rapid increase in the number of publications referring to "Artificial Intelligence" on IEEE Xplore, regardless of disciplines and fields.

Diabetes is a disease that results from various disorders that include how the body converts food into energy [13]. When diabetic patients do not respect their medication, their ies cannot produce insulin the way they should. A large amount of glucose persists in the body, a disorder commonly known as hyperglycemia. This can cause serious or life-threatening health problems [14].

In eating, the sugar level in the blood increases, the carbohydrates are then transformed mainly into glucose. The pancreas senses the rise in blood sugar. Insulin acts like a key; it permits glucose to enter the body's cells: in muscles, in fatty tissue, and in the liver, where it can be processed and stored. Glucose then decreases in the blood.

Type 1 diabetes (which affects around 6% of diabetics) is generally found in young people with symptoms of intense thirst, abundant urine, and rapid weight loss. Type 1 diabetes is treated by injecting insulin into the body with a syringe or pen or insulin pump.

Diabetes type 2, known as non-insulin-dependent (which affects 92% of people with diabetes), usually develops in people over 40. Overweight, obesity and lack of physical activity reveal the causes of type 2 diabetes in genetically predisposed

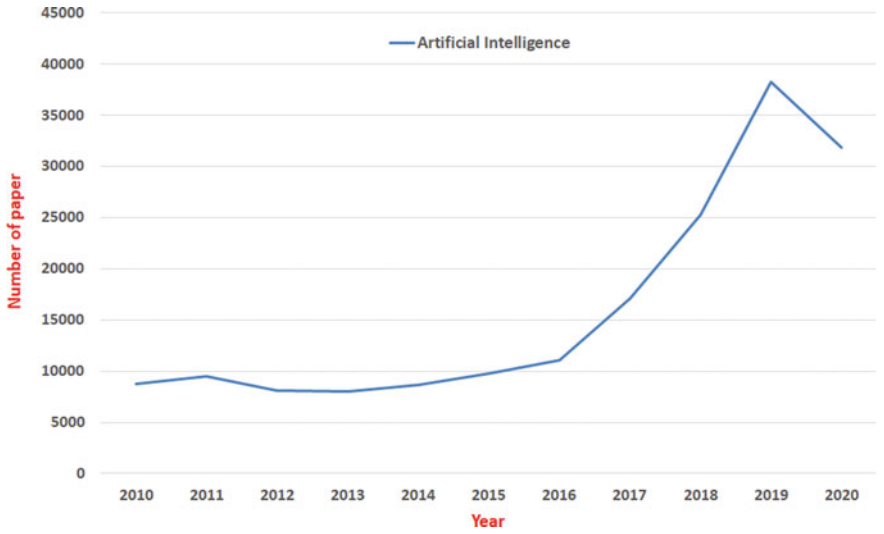

Fig. 1 Number of publications referring to the "Artificial Intelligence" in IEEE Xplore

people. This type of diabetes can be treated initially by lifestyle and dietetic measures, then quickly by oral and/or injectable anti-diabetic treatments. The other types of diabetes concern the remaining 2% (diabetes secondary to certain diseases or the taking of drugs).

4 Initiatives that Solve Diabetes Using Artificial Intelligence Techniques

Artificial Intelligence is gradually being deployed in many formats in health and brings many benefits to managing chronic diseases like diabetes; this technology is being progressively deployed in diagnosis, prediction, monitoring and management of the disease information. Several initiatives are utilizing Artificial Intelligence techniques to manage the diabetic disease. Some of the examples are listed below:

Diabetic Patient Monitoring Using Machine Learning Algorithms: the authors develop a wireless blood glucose monitoring system using 5G technology. The data collected by the sensors connected to the patient's body measures several health parameters such as blood sugar, body temperature, and physical activities. The monitoring system collects and analyzes patient data using multiple classification algorithms, allowing patients with diabetes to get future predictions of their blood sugar. In this paper, the classification algorithms used are Naïve Bayes, ZeroR, Random Forest, J48, SMO, and Simple Logistic; they are applied to the dataset to test which is the most powerful to determine the level of risk of the patient [15].

FreeStyle is a sensor attached to the skin for 14 days that measures the level of glucose in the blood without calibration. A soft and sterile 5 mm microfilament is inserted under the skin when this sensor is applied. The measurements are collected on the device and are available in real-time. The data can be downloaded using the software. The benefits for patients are numerous; they no longer need to prick their fingers and expose their disease; the sensor only needs to be changed every two weeks. Thus, the controls are easier and allow a better patient adaptation. However, the sensor remains visible, which can cause discomfort for users.

The K'Watch measures blood sugar just in contact with the skin. Unlike many existing devices, it uses an everyday object to measure blood sugar. It is equipped with micro-needles (<0.5 mm) that collect and analyze the chemical composition of the interstitial fluid located just under the skin's surface. The use of the watch is discreet and promotes better blood sugar control.

Diabetes Prediction: To predict the risk of developing diabetes in patients, several studies have been performed with an assessment of existing models of diabetes risk assessment using machine learning algorithms for prediction and classification. The researchers also selected some of these algorithms and applied them to diabetes data. Experimental results have proven the stability of risk assessment approaches for diabetes. A study by Rghioui et al. [16] used various machine learning algorithms for classifying diabetic patients using the WEKA tool; these algorithms are compared based on their precision and accuracy. Their new system has been monitored by machine learning algorithms (Naïve Bayes, OneR, J48, SMO, Simple Logistic, Random Forest, and ZeroR). The simulation results have shown that the SMO algorithm has an excellent classification, with the highest accuracy of 99.67%, a sensitivity of 99.86% and an accuracy of 99.56%. In this sense, we believe that different assessment models should be developed for different races and that AI models focused on diabetic patients promise to improve the efficiency of diabetes prediction.

Lifestyle Guidance for Diabetes Patients: Good diabetes treatment requires a better understanding of patients' food systems and how carbohydrates affect blood sugar. To properly fix an insulin level, the total amount of carbohydrate ingested by the patient should be measured. A food meter should be used to ensure better blood sugar management. Several applications using graphical analysis technologies to analyze food content are under development in recent years. Zeevi et al. [17] applied a machine learning algorithm using artificial intelligence techniques to integrate blood parameters, eating habits, and physical activities of diabetic patients. This algorithm accurately predicts blood sugar responses during meals. The results of this experiment indicated that personalized diets could successfully reduce the rise in blood sugar. With the technical advancements in machine learning and machine learning, it can be concluded that AI would play a crucial role in improving the lifestyle of the diabetic patient and thus help in the management of diabetes.

5 Use Case: Prediction of Glycemic Using Artificial Intelligence Techniques

In this part, we classify the glucose level data by applying different mathematical classification algorithms. The algorithms used for this classification are Naive Bayes (NB), J48, ZeroR, SMO (Sequential Minimal Optimization), Random tree, and OneR. The main idea of the classification of diabetes in this study is to allow early prediction and avoid complications of diabetes. This prediction of the disease enables the treating of patients before the disease worsens and fails and their health condition becomes critical.

All the experiments were carried out using functions included in the Weka (Waikato Environment for Knowledge Analysis) software; it is an open-source tool that does preprocess, classification, regression, clustering, and data association rules. The mentioned tool provides many classifiers; it consists of two principles methods, the machine-learning standard and data mining algorithms. These methods are based on the JAVA environment. WEKA can also be used to cluster and associate the data. In addition, this tool can process the ". arff" files in its explorer to perform the classification [18].

We used the database that included 40 diabetic patient glucose levels, 30 men and 10 women aged from 25 to 60 years for a total of 30 days, during 30 days. The format of this database contains five columns designated by Date, Day, Glucose Level, and Request. Table 1 describes the attributes of the database.

Evaluating classification algorithms is one of the key points in any data mining process. In this part, we will study the analysis results and the classification of the data. After applying the preprocessing and preparation methods, we analyze the data visually and determine the distribution of values about effectiveness and efficiency. This study uses a confusion matrix and then calculates different performance measures, focusing on the most important criteria [19, 20]. The prediction process consists of four different outcomes: true positive (TP), true negative (TN), false positive (FP), and false-negative (FN). These four results constitute the confusion matrix. Column A shows results tested positive, and Column B shows results tested negative. The first row shows the predictive results for the positive class, and the second row shows the predictive results for the negative class. The confusion matrix is shown in Fig. 2.

We can construct several equations using the confusion matrix to determine the accuracy, precision, sensitivity, and F-measure values. Table 2 gives the TP, FP, TN,

Table 1 Attributes and data type

N°	Attributes	Data type
1	Sex	Boolean
2	Age	Numeric
3	Day	Numeric
4	Glucose level	Numeric
5	BGL	Boolean

Fig. 2 Confusion matrix

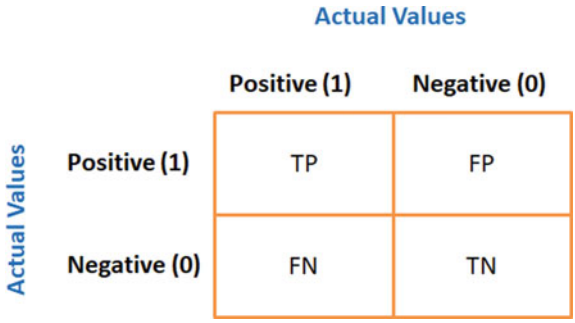

Table 2 TP, FP, FN, and TN Values obtained for each algorithm

Algorithm	TP	FP	FN	TN
Random forest	1757	12	7	774
Random tree	1755	18	9	768
Simple linear regression	1753	345	11	441
ZeroR	1756	16	8	770

and FN values obtained for the above algorithms.

$$Accuracy = \frac{TP + TN}{TP + TN + FP + FN} \tag{1}$$

$$Precision = \frac{TP}{TP + FP} \tag{2}$$

$$Specificity = \frac{TN}{TN + FP} \tag{3}$$

$$Sensitivity = \frac{TP}{TP + FN} \tag{4}$$

$$F_{Measure} = \frac{2 * Precision * Sensitivity}{Precision + Sensitivity} \tag{5}$$

According to Eq. (1), we can define the accuracy of the classification that is the percentage of correctly classified instances for all instances. Equation (2) presents the Precision: the ratio of the true value of a positive rate to the total of the true value of a positive rate and the false value of a positive rate. Specificity is defined by Eq. (3). The sensitivity given by Eq. (4) is defined by the ratio of the true value of a positive rate to the total of the true value of a positive rate and the false value of a negative rate. F-Measure is given by Eq. (5). Accuracy, Precision, Sensitivity, Specificity, and F_Measure are the five metrics used to evaluate a method based on the parameters

of the confusion matrix. The results of various measurements are given in Table 3 (Figs. 3, 4 and 5).

Mean Absolute Error (MAE): is the amount used to measure how close the forecast or prediction is to the eventual outcome. The mean absolute error is an average of the absolute errors, where the prediction and the true value are. Root Mean Square Error (RMSE) measures the differences between values predicted by a model and the values observed. The Relative Absolute Error (RAE) is the Mean absolute error divided by the classifier's error. The Root Relative Squared Error (RRSE) takes the total squared error and normalizes it by dividing by the total squared error of the simple predictor.

Table 3 Classified instances

Algorithms	Correctly classified instances (%)	Incorrectly classified instances (%)	Time to build a model (s)
Random forest	99.05	0.95	1,1
Random tree	98.94	1.05	0,01
Simple linear regression	86.03	13.97	1,37
ZeroR	99.25	0.75	0,05

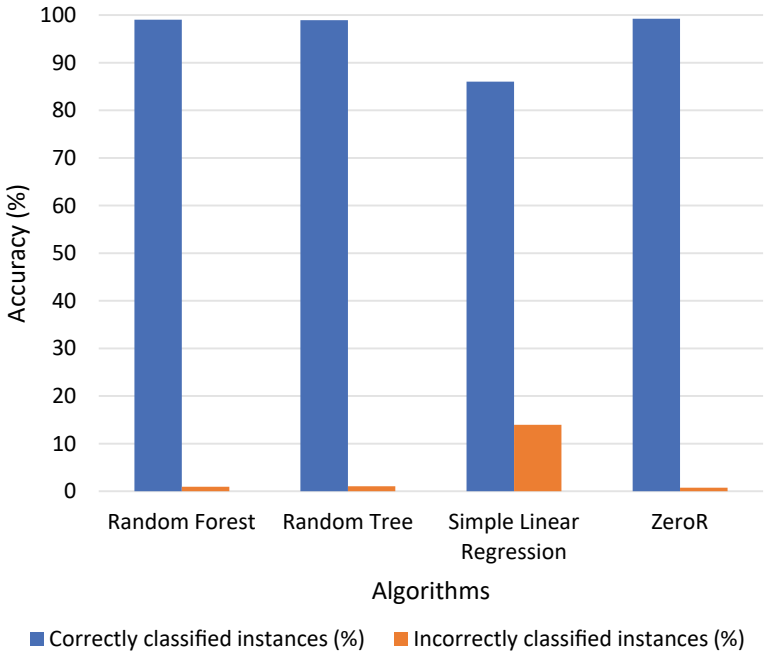

Fig. 3 Correctly and incorrectly classified instances graph

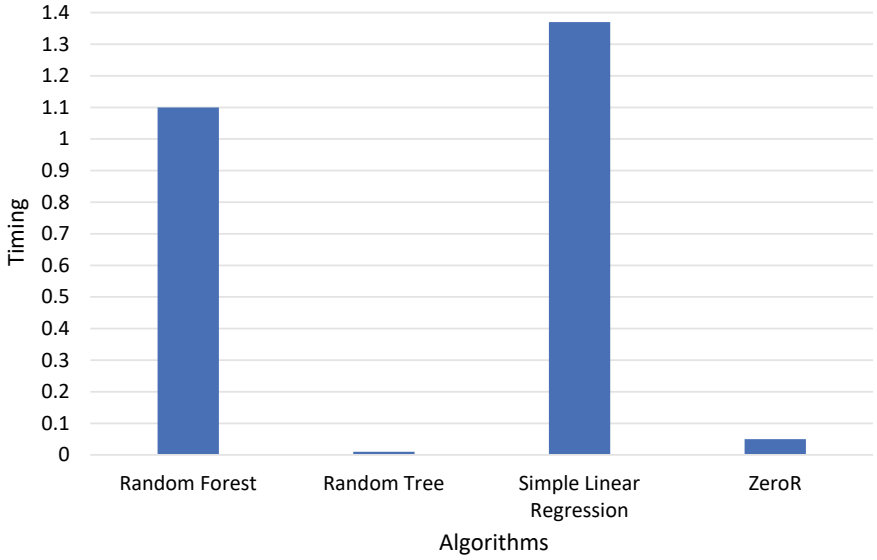

Fig. 4 Training time for different algorithms graph

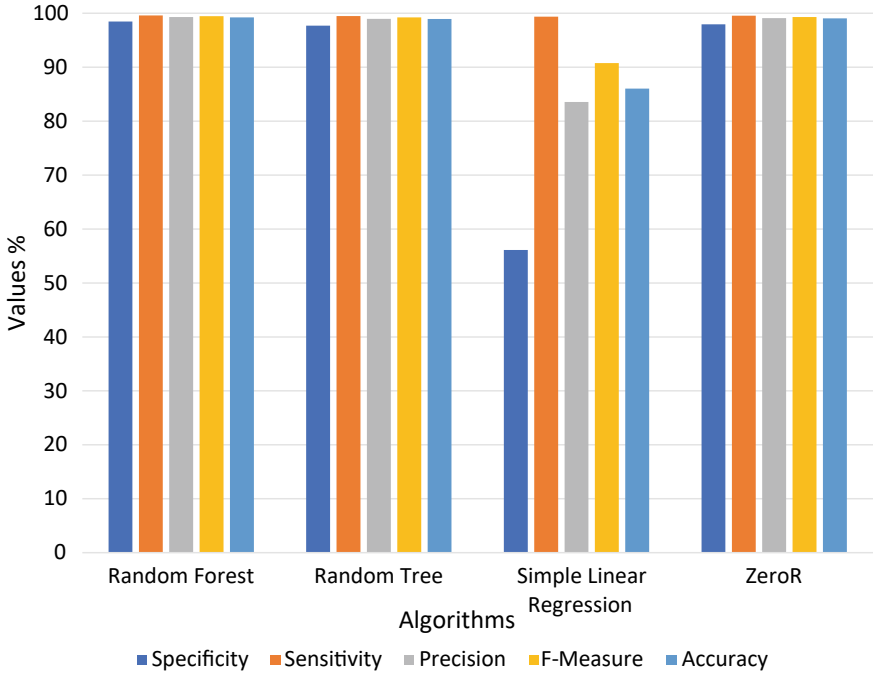

Fig. 5 TP, FP, Precision, F-measure graph for different algorithms

Figure 6 shows the error rate results. Here four different parameters are used to represent the error rate of the four classification algorithms (Mean Absolute Error (MAE), Root Mean Squared Error (RMSE), Relative Absolute Error (RAE), and Root Relative Squared Error (RRSE). The figure shows that Random Forest and ZeroR algorithms have the lowest error rate.

Table 4 shows that the precision of the random forest (99.32%) is higher than the precision of the random tree, simple linear regression, and ZeroR. It also shows that the random forest has the highest value of correctly classified instances and the lowest of misclassified instances compared to other classifiers (see Fig. 3).

As presented in Table 5, the lowest warning error rate (0.075). It can also be noted that the Random Forest has the best compatibility in terms of the reliability of collected data and their validity, as shown in Fig. 6.

After creating the predicted model, the evaluation of the efficiency of the algorithms studied can now be analyzed. Table 4 shows that the Random Forest gives the highest value of TP. The FP rate is lower when using Random Forest classifiers.

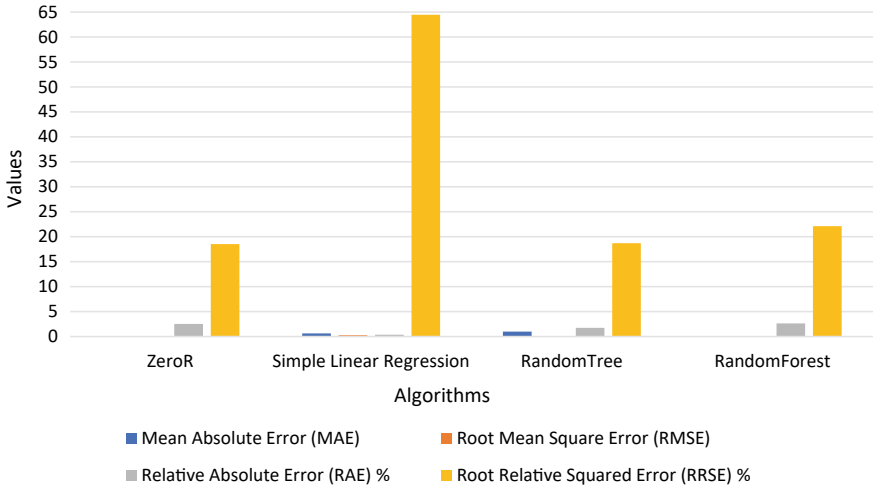

Fig. 6 MAE, RAE, RMSE, RRSE of different algorithms

Table 4 Values of specificity, sensitivity, precision, F-Measure, and accuracy for each algorithms

Algorithms	Specificity (%)	Sensitivity (%)	Precision (%)	F-Measure (%)	Accuracy (%)
Random forest	98.47	99.60	99.32	99.46	99.25
Random tree	97.71	99.49	98.98	99.24	98.94
Simple linear Regression	56.11	99.38	83.56	90.78	86.04
ZeroR	97.96	99.55	99.10	99.32	99.06

Table 5 Comparison of MAE, RMSE, RAE, and RRSE errors

Algorithms	Mean absolute error (MAE)	Root Mean square error (RMSE)	Relative absolute error (RAE) %	Root relative squared error (RRSE) %
Random forest	0.0075	0.0863	1.7469	18.6933
Random tree	0.0112	0.0121	2.6341	22.1198
Simple linear regression	0.2749	0.3563	64.4506	77.1839
ZeroR	0.0108	0.0856	2.5389	18.5296

These results explain why Random Forest outperforms other classifiers. Our experimental results provide the highest accuracy for classifying the diabetes dataset given by Random Forest (99.25%). Random Forest presents a good classifier in terms of effectiveness and efficiency, including Sensitivity, Precision, and Specificity. The Random Forest model gives good results as compared with other methods. Other models have generally shown low accuracy and low capacity and allow an intense precision and capacity. Therefore, for a more detailed evaluation of machine learning models, the Random Forest model is used for the comparative analysis.

6 Conclusion

The application of Artificial Intelligence to help patients manage their diabetes is at the beginning of its evolution. While significant advancements are being made in AI, these advancements focus on narrow applications of the technology to specific health issues. The need for an examination for the diagnosis of diabetes is widely accepted. The implementation of machine learning can help improve the quality of life of diabetic patients and provide good precision for clinical decisions. Much research has recently resulted in developing the first diabetes prediction algorithms. The most significant advances in applying AI techniques in health and especially in diabetic patients have led to a change in diabetes management systems. Many studies have already been published on the application of AI to diabetes in a wide range of management areas. Research in this area should continue and seek to uncover the opportunities and benefits of applying AI methodologies in diabetes management that differentiate these strategies from other conventional approaches.

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Amine Rghioui was born in Morocco in 1989. He received the B.S. degree from the Faculty of Sciences, Fez, Morocco, in 2012 and M.S from the Faculty of Sciences, Kenitra, Morocco, in 2014. He received his Ph.D. in electronics and telecommunications at Mohammadia School of Engineering. He is currently a member of the Electronic and Communication laboratory at Mohammadia School of Engineering in Rabat. His research interests include wireless sensor networks, Internet of Things and connected objects, Big Data.

Dr. Jaime Lloret (jlloret@dcom.upv.es) received his B.Sc. + M.Sc. in Physics in 1997, his B.Sc.+M.Sc. in electronic Engineering in 2003 and his Ph.D. in telecommunication engineering (Dr. Ing.) in 2006. He is a Cisco Certified Network Professional Instructor. He worked as a network designer and administrator in several enterprises. He is currently Associate Professor in the Polytechnic University of Valencia. He is the Chair of the Integrated Management Coastal Research Institute (IGIC) and he is the head of the "Active and collaborative techniques and use of technologic resources in the education (EITACURTE)" Innovation Group. He is the director of the University Diploma "Redes y Comunicaciones de Ordenadores" and he has been the director of the University Master "Digital Post Production" for the term 2012–2016. He was Vice-chair for the Europe/Africa Region of Cognitive Networks Technical Committee (IEEE Communications Society) for the term 2010-2012 and Vice-chair of the Internet Technical Committee (IEEE Communications Society and Internet society) for 2011–2013. He has been Internet Technical Committee chair (IEEE Communications Society and Internet society) for 2013–2015. He has authored 22 book chapters and has more than 450 research papers published in national and international conferences international journals (more than 200 with ISI Thomson JCR). He has been the co-editor of 40 conference proceedings and guest editor of several international books and journals. He is editor-in-chief of the "Ad Hoc and Sensor Wireless Networks" (with ISI Thomson Impact Factor), the international journal "Networks Protocols and Algorithms", and the International Journal of Multimedia Communications. Moreover, he is Associate Editor-in-Chief of "Sensors" in the Section sensor Networks, he is an advisory board member of the "International Journal of Distributed Sensor Networks" (both with ISI Thomson Impact factor), and he is IARIA Journals Board Chair (8 Journals). Moreover, he is (or has been) associate editor of 46 international journals (16 of them with ISI Thomson Impact Factor). He has been involved in more than 450 Program committees of international conferences, and more than 150 organization and steering committees. He has led many local, regional, national and European projects. He is

currently the Working Group of the Standard IEEE 1907.1. He has been general chair (or co-chair) of 40 International workshops and conferences. He is IEEE Senior, ACM Senior and IARIA Fellow.

Dr. Abdelmajid Oumnad Professor in the Department of Electrical Engineering at Mohammadia School of engineering (EMI) and member of the Laboratory of Electronics and Communication (EMI). He received his Ph.D. in electronics of the Claude Bernard University in Lyon; He is a professor in Electronics and Communication Technology at the Department of Electrical Engineering in Mohammadia School of engineering in Rabat.

Artificial Intelligence and Machine Learning for Diabetes Decision Support

Josep Vehi, Omer Mujahid, and Ivan Contreras

Abstract Artificially intelligent decision support systems are proving instrumental in the quest of enabling diabetes patients to lead a normal life. These systems provide suggestions to the patients to enhance their judgments regarding their glycemic profile. A variant of such systems, the clinical decision support systems, helps clinicians and healthcare professionals make clinical decisions. For a diabetes patient, it is imperative to keep their blood glucose level inside a lower bound of 70 mg/dL and an upper bound of 140 mg/dL. This range is known as the normoglycemic range. Such systems aim to utilize artificial intelligence and machine learning techniques to estimate relationships between patient-related data and the glycemic outcomes and then propose preventive/protective measures to keep the glycemic profile of the patient in the specified range. Apart from tracking and correcting the glycemic profile of a diabetes patient, the decision support systems are also responsible for detecting/predicting adverse glycemic events like hypoglycemia and suggest proactive measures to be taken by the patient so that adversity is avoided. The recommendations given by such systems to patients with diabetes may consist of information about meal intake in the form of carbohydrates, insulin delivery, medicine/drug consumption and other lifestyle-related advice such as physical activity and sleep routine, etc. On the other hand, the clinical decision support systems aid healthcare professionals in diagnosing diabetes and its comorbidities. Such systems may also assist the doctors by issuing prognosis of the illness as well as help them in drug prescriptions. This chapter discusses the latest trends in artificial intelligence and machine learning-based decision support in diabetes healthcare. Moreover, it also weighs up the challenges designers face in this domain. This chapter could be a thorough guide to the researchers planning to work in diabetes decision support.

J. Vehi (✉) · O. Mujahid · I. Contreras
Modelling, Identification and Control Laboratory, Institut d'Informatica i Applicacions, Universitat de Girona, 17003 Girona, Spain
e-mail: josep.vehi@udg.edu

O. Mujahid
e-mail: omer.mujahid@udg.edu

I. Contreras
e-mail: ivancontreras@udg.edu

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Keywords Disease prediction · Algorithm · Healthcare · Clinical decision · Hypoglycemia

1 Introduction

Patients with type 1 diabetes have to make about 180 diabetes-related decisions per day [1]. For a person that aspires to a normal life, diabetes could prove to be a constant struggle. From decisions regarding physical activities to choices concerning meals, a person with diabetes has to consider it all to avoid adversity. Accurate insulin dose measurements, carbohydrate intake calculations, and physical activity monitoring based on real-time blood glucose values are all parts of the decision-making process that a diabetes patient goes through every day. A large number of decisions and the greater complexity of some of these decisions make the lives of people with diabetes very difficult. For this reason, a tool that could assist this decision-making process is imperative.

Moreover, diabetes patients are at a higher risk of other comorbidities [2]. Diabetic foot, diabetes retinopathy, ketoacidosis, and neuropathy are complications arising from diabetes. A tool that could provide an early diagnosis of such complications may prove life-changing for the patients. In technical terms, one such tool that performs all the tasks mentioned above and assists diabetes patients in improving their decision-making capability is known as a decision support system (DSS). A DSS aids patients of a specific disease in decision making and provides other services such as early detection of complications and predictions of adverse events. A diabetes DSS has to assist patients in managing their medications such as insulin adjustments recommendations, warning about adverse glycemic events such as hypoglycemia and hyperglycemia, carbohydrates counting, behavioral and lifestyle adjustments, and data visualization/interpretation [3]. Moreover, a good diabetes DSS must educate the patients about their disease and provide personalized solutions.

Artificial intelligence (AI) and machine learning (ML) are set to restructure diabetes healthcare in several ways [4]. Data-driven approaches are proving to be more efficient with increased available data and computational power. ML and Neural Networks (NNs) based prediction and classification techniques are now accurate enough to integrate into a DSS [5]. Improvement in AI/ML techniques and advances in glucose sensor technology have made the realization of efficient DSS possible [6, 7]. Glucose sensor technology has made collecting a large amount of blood glucose data possible [8, 9]. A DSS based on data-driven approaches improves the knowledge-based DSS of the past that only worked on rule-based reasoning or case-based reasoning techniques in terms of output accuracy and design flexibility [10]. A diabetes DSS could be classified into a patient DSS and a clinical DSS (CDSS). As the name suggests, a patient DSS assists diabetes patients while a clinical DSS assists healthcare professionals. A patient DSS could be embedded inside a smart device that a diabetic patient can carry at all times. The most suitable device to host

a patient DSS is a smartphone. Since most of the patients carry a smartphone device virtually, the DSS can monitor the patient's health efficiently.

On the other hand, a CDSS is usually deployed in the doctor's workplace PC. Figure 1 shows a general overview of the chapter. The left section represents the needs/requirements of a patient DSS, while the right section portrays what a good CDSS be constituted of. The center section represents the ML/AI techniques used to design both sets of DSS. This chapter discusses the cutting-edge technologies and trends in the field of AI/ML-based DSS for diabetes. The chapter unfolds by first discussing the needs/requirements of diabetes patients and what they expect from a

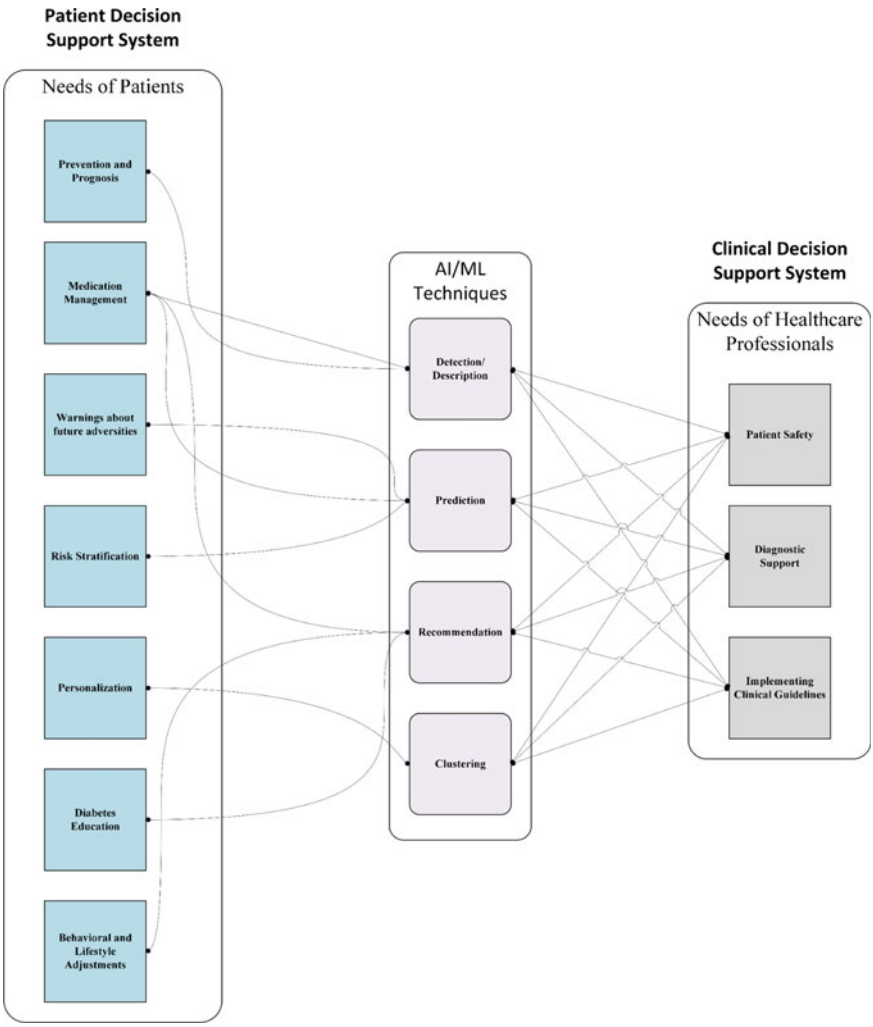

Fig. 1 A high-level graphical representation of AI/ML-based DSS

DSS of this type. Next, a brief description of a diabetes clinical DSS is given and how it can make the lives of diabetes healthcare workers easy. After that, AI and ML-based approaches for a diabetes DSS are discussed. The chapter then provides an account of the challenges faced by the designers of such DSS' before concluding in the follow-up section.

2 Needs of the Patients

A diabetes DSS has to fulfill the patients' needs to be classified as a capable aiding system. Along with the ease of use, a diabetes DSS has to be responsive, interactive, and trustworthy. Other than that, a DSS should fulfill the following needs of a diabetes patient.

2.1 Prevention and Prognosis

A diabetes DSS must be able to perform a prognosis. Prognosis is predicting the course of an illness after it has happened. It is understood that diabetes can result in many other complications in the body. Diabetes patients must keep track of their disease and the overall health of their bodies. A DSS aims to keep the glycemic profile of a diabetes patient in the normal range. This is done by regulating the BG levels with the help of insulin delivery, carbohydrates intake, and physical activity. The more a diabetic patient stays outside of the normoglycemic range, the greater are their chances of developing diabetic comorbidities. A diabetes DSS can help patients keep track of their glycemic profile and provide insight into the severity of diabetes they suffer from, the chances of creating other complications, and the actions required to avoid such complications [11].

2.2 Medication Management

Medication management is one of the most important traits for a DSS. In a disease like diabetes, where the course of medication is not fixed but varies according to the patient's glycemic profile and physiological characteristics, having a DSS that can help the patient manage their medications is essential. Diabetes patients are often dependent on medicines like insulin. The delivery of insulin to the bloodstream is timely and in the correct measured quantity. Moreover, several types of insulin are injected based on time of the day, the quantity of carbohydrates intake and the intensity of physical activity, etc. For a diabetes patient, it is a cumbersome task to calculate the right amount of the right type of insulin throughout the day [12]. However, it is important to mention that not all diabetes patients are insulin-dependent. Most

type2 diabetes or prediabetes patients use drugs other than insulin, such as Alpha-glucosidase inhibitors and Biguanides, to manage their BG. A DSS may prove vital in such a scenario where the medication management is done by the automated system and suggested to the patient.

2.3 Warning About Future Adversities

Diabetes patients live in constant fear of adverse glycemic events. Hypoglycemia and hyperglycemia are decrease and increase of BG above critical levels, respectively. Both of these conditions come with their complications and harms. Being the more threatening of the two, Hypoglycemia is also the more feared among diabetes patients [13]. A DSS must predict and inform the patient beforehand about the occurrence of any such event. Such predictions result in peace of mind for diabetes patients and prevent the patients from going into the jaws of calamity. For instance, hypoglycemia can cause loss of cognitive ability, hearing, and in extreme cases, death. Normally when a patient recognizes a hypoglycemic episode, it is too late. A patient needs to anticipate the occurrence of hypoglycemia in advance to avoid its event [14, 15]. A DSS with the mechanism of hypoglycemia prediction may prove crucial for the patients.

2.4 Risk Stratification

Risk stratification means measuring or quantifying the risk of occurrence of an adverse event. Furthermore, it might also mean assessing the prospect of how fatal an adverse event is after it has happened [16]. A DSS with the functionality for risk stratification may prove useful for patients by informing them about the danger of an event with the predicted percentage values. A patient's DSS may be used to predict comorbidities or any sort of organ failure that can occur due to diabetes. An AI/ML-based DSS takes its cues from the data it is trained on, and learning from patterns in the data can output the risk associated with a comorbidity or organ failure. Risk stratification makes the accurate delivery of medication doses possible and contributes to the mental peace of diabetes patients [17]. When patients can observe the quantified risk related to comorbidities caused by diabetes on the user interface of their DSS, they may manage their disease better and escape the stress of uncertainty.

2.5 Personalization

Personalization in medicine means customizing treatments for patients according to their individual needs [18]. Like every individual patient has unique physiological

dynamics, there is a need for special treatments to cure any illness. In diabetes, each patient may be treated individually by assessing specific information such as the insulin tolerance, glycemic variability, age of patient and body-mass index, etc. Personalization helps minimize the risk of diabetic comorbidities and increases the efficiency of the treatment [19]. It also saves a lot of money wasted otherwise in treating a patient with the conventional hit and trial method. A personalized DSS may help patients overcome diabetes more effectively and increase patient trust in such systems.

2.6 Diabetes Education

The most important thing for a diabetes patient is to understand their disease and, even more so, to grasp the idea of their personalized variant of the disease [20]. People with diabetes must first understand the basics of diabetes and how it may be managed. Secondly, they must learn how to use diabetes devices like glucometers, CGMs, insulin pumps etc. They must also develop problem-solving strategies while facing adversity. A DSS can educate diabetes patients and help them manage their disease.

The lack of diabetes literacy and numeracy is linked with various studies' below par diabetes outcomes [21, 22]. Lower diabetes literacy and numeracy results in poor glycemic control, less time in range and weaker knowledge of the disease itself. The lack of a diabetes patient's literacy or numeracy is not always evidently obvious. For this particular reason, a DSS that could educate diabetes patients becomes vital.

2.7 Behavioral and Life Style Adjustments

A diabetes DSS can induce behavioral changes and lifestyle adjustments in diabetes patients. Diabetes is one of those diseases where lifestyle adjustments make a huge difference to a patient's health [23]. A weight loss of 5–6% of the total body weight and 150 min of moderate-intensity physical activity per week is recommended for most diabetes patients [24]. A DSS may guide the patients about their eating habits, physical activities, sleep patterns, and other things like alcohol consumption and stress management, etc.

3 Clinical DSS: Demands of Healthcare Professionals

A diabetes CDSS is a type of DSS meant to assist healthcare workers, doctors, and clinicians in the quest to treat diabetes patients. Such a DSS improves the making ability of professionals while treating a diabetes patient by providing important

suggestions and showing a broader picture to the clinicians by depicting multiple outcomes to a scenario. Like the diabetes DSS meant for the patients, the CDSS can also be a knowledge-based system or based on data-driven approaches. A CDSS can cover various areas of the healthcare system and assist healthcare workers in multiple forms [25]. Some of the tasks that a diabetes CDSS can perform are presented below.

3.1 Patient Safety

Improved patient safety is one of the prime goals of any CDSS. In diabetes, medication errors are common and can be reduced with the help of a CDSS. According to a study, approximately 65% of inpatients are exposed to one or more types of harmful drug combinations [26]. Along with assistance in medication management, CDSS also helps the healthcare workers in other areas. A CDSS installed in a hospital ICU ward significantly reduced the hypoglycemia cases by alerting the nurses about the occurrence of a hypoglycemia episode [27].

3.2 Diagnostic Support

Diabetes CDSS can provide diagnostic support to clinicians while treating diabetes patients. In diabetes healthcare, such CDSS may assist the healthcare professional in identifying the development and diagnosis of diabetes and the diagnosis of other diabetic comorbidities. Diagnostic errors are real in primary care and are termed a high-priority problem by the world health organization (WHO) [28]. AI/ML-based diagnostic tools may pave the way towards accurate diagnosis and ease the burden of the existing healthcare system.

3.3 Implementing Clinical Guidelines

Studies show that clinical guidelines have adhered to more with the help of CDSS [29]. It has been seen that because of low clinician adherence, new clinical guidelines have been very hard to implement. The experts do not automatically adopt new clinical policies, opposing the general belief. CDSS can also notify clinicians about the patients that haven't complied with a specific management plan and could also aid the professionals to reach out to such patients.

4 What Can AI and ML Offer?

AI is a vague term and can be defined as a collection of algorithms that enable a certain computer processor to make decisions that imitate the human decision-making process [30]. Though AI is incapable of replicating the intuitive ability of the human mind, the aim of comparison with the human mind is only to specify the goal of achieving optimal solutions just like a normal human mind would strive for. In the following section, we will talk about how ML/AI-based techniques help design a DSS that could fulfill all the needs of diabetes patients and healthcare workers.

4.1 Detection/Description

Detection in ML terms refers to identifying an event in a time series data. It may also be referred to as a description. ML detection could identify unusual glycemic events in BG time-series data [31]. Identifying these events could prove to be helpful in a DSS when the aim is prevention or prognosis of an adverse event. The description of an adverse event using ML could be performed by using labeled time series data. This data could contain a BG time series, an insulin time series, and a time series that specifies meal intakes in the form of carbohydrates. By learning from this past labeled data, the ML algorithm could then identify patterns in the data that correspond to the occurrence of unique events and, on the occurrence of any such marks in the future, notify the patient about their circumstance. Detection could be performed by using several ML/AI techniques. It could be taken as both regression or a classification problem. As a regression problem, the ML algorithm tries to map the input–output relations with the help of a mathematical function. After obtaining the function, it computes unknown outputs for known inputs. So, for instance, if the known result is the past BG value, insulin value, and carbohydrate value, the unknown output will be the current BG value. The calculated BG value could then be used to inform the patient about any abnormality. The ML algorithm tries to draw a line between two or more labeled classes in a classification scenario. A new sample falling in any of these classes is a part of that class group. Adverse events, hence, could be mapped with the data as classes of data.

4.2 Prediction

Prediction means estimating future values in a time series data. For prediction, it is necessary that the estimated value is somewhere in the future and not in the present. This is the prime difference that distinguishes prediction from detection. Though prediction could be performed on any data, it is most commonly associated with time-series data. This is because timestamps related to time-series data act as an

extra feature in determining the output and result in more accurate predictions. ML-based prediction can prove vital in a DSS that warns the patient about an adverse glycemic event in the future. In case of hypoglycemia, a warning before the future occurrence of a hypoglycemic event may prove to be lifesaving [32]. Prediction too may both be treated as a regression or classification problem.

4.3 Recommendation

AI-based recommender systems have found their application in many areas of life. In diabetes healthcare, AI-based diabetes recommender systems may recommend medication doses, lifestyle choices, and meal portions to the patients. Recommender systems use various AI-based techniques, including ML and deep learning (DL), to perform recommendations. It is important to understand that the recommender system could be standalone or aid the other systems mentioned above in a DSS. In the case of a standalone recommender system, the DSS will only give away recommendations to the patients. It will not appraise the patient about the possibility of an adverse event in the future or the level of threat they face from a particular adverse event. A scenario where the recommender system collaborates with other systems gives recommendations after a prediction or detection is performed. Such DSS' are not mere recommendation DSS but can also act as a warning or educatory systems.

4.4 Clustering

The division of data points into groups of similar characteristics is called clustering. Clustering, though a famous machine learning technique, can prove vital in personalizing a DSS for a particular patient [33]. Personalization means tailoring a system to fulfill the demands of personalized treatment for individual patients in the best possible way [34]. A customized system might not work with the same efficiency for a person it is not designed for. This logic might become almost impossible to have a customized DSS for each patient separately. We, however, can use clustering to group patients with the same characteristics together and then design a DSS that could fulfill the needs of that particular group of people.

5 Challenges for the Designers

AI-based methodologies come with their own set of limitations. Most AI-based techniques are data-driven and can enhance performance only when a sufficient amount

of good quality data is available. Good quality data in a data-driven setup essentially means data that is consistent, free of noise, and available in large quantities. The problem arises when there is a lack of such data. This directly affects the performance of a data-driven algorithm, whether an ML model or a neural network. There is always a scarcity of good-quality clinical data in healthcare applications—the reason for this is the natural and technical constraints involved in clinical data collection.

ML designers also face many non-technical obstacles while deploying models for clinical DSS. Coming up with safety protocols that can ensure patients' safety is complicated. Legal issues involving data privacy and moral dilemmas are always challenging for AI/ML designers. In a scenario where good quality data is already scarce for AI/ML designers to work with, privacy-related laws make it even harder for them to experiment freely. Another issue that poses a challenge for the designers is gaining user's trust. Since there is a lack of transparency about AI/ML models; the users often find it hard to trust the results of an AI/ML-based DSS. It is known that AI-based models are virtual black boxes with certain inputs and outputs. What happens inside these black boxes is often hidden from a user's eyes. In a DSS that uses neural networks, the trust issue is even greater since it is almost impossible to comprehend the computational structure of a neural network. This leads to a lack of trust among the patients and causes significant problems for the designers. Furthermore, the inability of users to understand extremely specific terminologies of AI/ML also creates problems for the designers. The designers then look for languages that are more common to a layman to be used in the DSS.

6 Conclusion

Decision support in diabetes holds great importance because of the huge number of decisions a diabetes patient has to make every day. AI/ML-based diabetes DSS can transform the entire structure of the diabetes healthcare system. Such DSS' are user-friendly, flexible, and can be customized according to patients' needs. Healthcare professionals can also benefit from these technologies by using CDSS. CDSS are variants of DSS designed to assist clinicians and healthcare workers. Different AI techniques such as description, prediction, clustering, and recommendation integrate various methodologies inside such DSS. These DSS could be deployed using smartphone devices and integrated with CGM sensors for continuous decision support. In the case of CDSS, patient's electronic health records and secure messages could be used to analyze patterns in the patient's data and assist healthcare workers by providing them decision support. Though there are challenges for the designers in the shape of unavailability of high-quality data, privacy laws and user trust issues, the future of AI/ML-based DSS is bright. Designers should strive for faster and more accurate models, better and friendlier user interfaces, and more flexible DSS to gain patients' trust and help ease the burden of the current healthcare system.

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Dr. Josep Vehí is full Professor at the University of Girona and research associate at the Girona Biomedical Research Institute. He is member of the "IFAC Technical Committee on Modelling and Control of Biomedical Systems". His research interests include machine learning and its applications to biomedicine, modelling and control in biomedicine, modelling and simulation of biological processes and fault diagnosis in complex systems. He is co-author of more than 150 peer-reviewed International journal papers and 12 books and chapters of books.In 2000 Prof. Vehí founded the "Modelling, Identification and Control Laboratory" (MiceLab). Since 2005, MiceLab is recognized and funded as a "Consolidated Research Group" by the Generalitat de Catalunya. The group has extensive experience in diabetes and is one of the leading groups in the development of the artificial pancreas worldwide. Since January 1st, 2018 Prof. Vehi belongs to the prestigious centre of excellence in diabetes CIBERDEM: "Centro de Investigación Biomédica en Red de Diabetes y Enfermedades Metabólicas Asociadas". Professor Vehi has been researching technologies for diabetes since 2004, obtaining more than three million euros of funding in competitive research projects that have led to several patents and tools, modules, and a prototype of a control device for use in clinical trials. Prof. Vehí has led and participated in several national and European research projects on diabetes technologies. Professor Vehi has promoted and carried out several clinical studies collaborating with the main researchers at the University Hospital, Dr. Josep Trueta of Girona, the Hospital of the University of Valencia and the Hospital Clínico de Barcelona.

Omer Mujahid received B.Sc. degree in electrical engineering and M.Sc. degree in electrical communication engineering from CECOS University of IT & Emerging Sciences, Pakistan, in 2013 and 2017. He is currently pursuing his Ph.D. from the University of Girona, Spain. He is associated with the Modelling Identification & Control Engineering (MICE) Lab at the Institute of Informatics and Applications (IIiA). His research interests include machine learning for diabetes health care and reconfigurable computing.

Dr. Ivan Contreras is a Ph.D. researcher at the University of Girona. He focuses on system optimization, data analytics, and predictive modeling in economics and healthcare. He has worked five years as a research assistant in the IE Business School, and in the Complutense University of Madrid to optimize investment decisions in the stock market and forex. Since 2014, Ivan has been a member of the MiceLAB group, where he is applying his expertise in the development of machine-learning techniques and its application for complex engineering problems, mainly in diabetes management.

Commercial Non-invasive Glucose Sensor Devices for Monitoring Diabetes

Manickam Tamilselvi, Pandia Raj, Ravikumar Ramlu Vidule, and Srinivas Ankanagari

Abstract Diabetes disease is one of the metabolic disorders having a great consequence on natural life quality. Over 500 million people are affected worldwide. To better manage diabetes in patients, more glucose measurements within a short period are needed. At present, the existing glucose monitoring devices available in the market are invasive and cannot be used for monitoring glucose levels continuously. Noninvasive Glucose Monitoring (NGM) can be used continuously to check glucose levels in the body without blood draws, skin puncturing, or causing any trauma or pain. The devices available are wristwatch-like and can be easily worn. It is important to develop noninvasive and easy usage as it is economical, compact, painless, and easy for frequent glucose monitoring. The glucose biosensors are either electrochemical or optical-based. The various bands available in the electromagnetic spectrum are used in glucose analysis and detection. Raman spectroscopy technologies are gaining attraction to measure glucose in interstitial fluid (ISF), allowing accuracy between 5.6 and 20.8%. In addition, optical-based techniques using infrared light beams allow sensing the presence of glucose in the skin. The glucose detection in human sweat is also becoming relevant to check its levels. The noninvasive glucose sensor devices have enormous demand in the global market. Several clinical trials of noninvasive glucose monitors are enlarged in the twenty-first century. To develop NGM sensors, an exhaustive, detailed understanding of NGM systems components is required, which includes medical applied technologies, device surface, material chemistry, electrochemistry sensing, and the systems

M. Tamilselvi
Pharmanova Medical Research, George Avenue, Chennai, Tamil Nadu 600073, India

P. Raj
Department of Physics, Kongu Nadu Science College, Bharathiar University, Coimbatore, Tamil Nadu, India

R. R. Vidule
Department of Chemistry, Shri Sant Gadge Maharaj College, Loha Dist. Nanded, Maharashtra, India

S. Ankanagari (✉)
Department of Genetics and Biotechnology, Osmania University, Hyderabad, Telangana, India
e-mail: asrinivas@osmania.ac.in

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interface. This chapter focuses on leading technologies and devices available to check noninvasive glucose monitoring in diabetic patients and assess accuracy in the market regulatory framework.

Keywords Commercial · Noninvasive · Glucose sensor · Diabetes · Easy use

1 Introduction

Diabetes is a well-known metabolic disorder, and a global challenge disease with over 500 million people affected, as per WHO estimation [1]. Diabetes affects the quality of life of the patient in case if no proper management of the disease is taken, leading to dangerous problems related to health [2]. There are three different diabetes known, Type I, Type II, and Type III. Type I comes from childhood, hence also known as juvenile diabetes [3]. In children or young people, their immune system destroys insulin-producing beta cells in the pancreas. It affects about 5% of people, including both males and females. Type II is the most common lifelong disease where the insulin is secreted but cannot be used properly, known as insulin resistance. It affects middle-aged or older people and is also called adult-onset diabetes. This diabetes is associated with shorter life expectancy, and 90% of cases are Type II diabetes. Type III is gestational diabetes. In this condition blood, glucose levels become high during pregnancy. It affects women who are pregnant and have no history of diagnosed diabetes. In the U.S, every year, 2–10% of women are affected with Type III diabetes [4].

Diabetes has become one of the twenty-first century health challenges [5]. The adults with diabetes over two decades have tripled, with a rise every year of approximately 8 million new cases of diabetes diagnosed. It is becoming an important demand for monitoring blood glucose, diabetes if untreated, can lead to kidney disease, amputation of the lower limb, blindness and heart stroke, increasing the chances of death. Since these complication conditions can arise in diabetic patients over time, there is a growing demand for effective management in people with diabetes to monitor blood glucose and avoid complications. This necessitated designing reliable and robust periodical glucose monitoring devices/sensors to manage diabetes efficiently [6, 7]. In recent years the market for these devices has grown rapidly [8, 9].

A variety of glucose sensors are developed for monitoring blood glucose to manage diabetes. A glucose sensor is a "compact analytical device or unit incorporating a biological or biologically derived sensitive recognition element integrated or associated with a physio-chemical transducer" [10]. The biological recognition element identifies the target molecule and transduce, converting the recognition event into a signal that can be measured, followed by processing the signal into a form that can be read [11–13]. The receptors, antibodies, enzymes, nucleic acids, lectins, and microorganisms are the major recognition elements used in the design

of sensors [14, 15]. The transducing signal is optical, electrochemical, piezoelectric, thermometric, or magnetic [16]. The common electrochemical sensors include amperometric, conductometric or potentiometric types [17–19]. Clark and Lyons, in 1962, first proposed a biosensor concept to measure glucose [11]. The first commercially developed biosensor for glucose measurement was successfully introduced by Yellow Springs Instrument Company (Model 23A YSI analyzer). The first-generation glucose sensors used oxygen substrate and detected hydrogen peroxide production. The disadvantage of this generation glucose sensor is the requirement of high potential to operate and get the high selectivity to measure hydrogen peroxide. This limitation made the development of second-generation glucose sensors to replace oxygen with redox mediators [20]. The self-monitoring home-based glucose monitor is a pen-sized device launched in 1987 by Medisense Inc as ExacTech. The third-generation glucose biosensors were developed without mediators. There are no reagents used and capable for direct transfer from enzyme to the electrode. This led to a needle-type device that can be implanted to monitor blood glucose continuously.

Currently, most of the available devices in the market are mostly invasive. There is a need to develop noninvasive and easy usage, which should be economical, compact, and painless for frequent blood testing, helping to regulate blood glucose levels. To maintain normal blood glucose levels, sensors and devices have been developed during the last half-century in which continuous monitoring of glucose and noninvasive systems have significantly improved. The in vivo continuous glucose monitoring (CGM) blood glucose was demonstrated in 1982 [21]. CGM gives data in real-time to have control of blood glucose levels. Currently, two CGM systems include subcutaneous glucose monitoring and blood glucose monitoring. Due to protein contamination of electrodes and thromboembolism, CGM cannot directly measure blood glucose. Instead, needle type implanted electrode in interstitial fluid measures glucose reflecting blood glucose level [22, 23]. The needle-type glucose biosensor was approved by US Food and Drug Administration (US FDA) and marketed by Minimed, Sylamr, CA USA in 1982 [24]. However, device accuracy is lower than the traditional glucose biosensors, and its clinical usefulness was not established [25]. Noninvasive glucose monitoring (NGM) is achieved with optical approaches. The optical approach uses light physical properties, which includes Raman spectroscopy [26], polarimetry [27], photoacoustics [28], infrared absorption spectroscopy [29] and optical coherence tomography [30] in interstitial fluid (ISF) or eye. Here, we present the platforms used in the developments made in noninvasive glucose monitoring and discuss in the context of regulatory compliance.

2 Noninvasive Glucose Monitoring Care and Device Standards

2.1 Continuous Glucose Monitoring

Diabetes having high blood glucose levels leads to a life-threatening condition. Constant monitoring of blood glucose levels throughout the day helps monitor long variation levels of glucose in the body. This will lead to deciding on balanced food, medication, and physical activity [31]. More frequent blood glucose measurements can better manage diabetes and illnesses related to this disease. Two methods of measuring glucose in blood levels are available. One approach is pricking a finger with the help of a lancet. This can be painful and uncomfortable for many, making testing less frequent, and consequently, blood sugar levels control is poorer. The other is noninvasive glucose monitoring which is user-friendly and more useful. In general, all patients intend to have a noninvasive measurement that can help them monitor glucose levels continuously with ease. In the European countries, patients are keen in pain-free blood glucose level monitoring methods so that it helps them to manage with ease [32].

At present, people can easily avail noninvasive commercial glucose meters due to highly developed technologies. The NGM sensors help check blood glucose levels with ease and get measurements throughout the day. For instance, the metallic trace sensing element is taped on the patient skin, and the tag uses no power to monitor glucose levels [33]. Many improvements in the NGM techniques have been developed [34]. On the other hand, the current noninvasive patented techniques work with a beam of invisible infrared light passing onto the skin to count the glucose molecules. The process is painless, much faster, and cost-effective.

Moreover, one can check several times a day measurements variations in the glucose levels in the blood during the day and at night. The noninvasive device is wristwatch-like, measuring glucose continuously and helps to take treatment and manage the disease [35]. The device can communicate with the mobile phone; therefore, it checks information and takes instantaneous action to regulate blood glucose levels. For several diabetic patients who are critical, such as Type 1 diabetes, sudden changes in glucose levels, constant and accurate monitoring is essential to save patients' lives. In the case of other people, there will not be significant glucose level changes and need not be monitored [6].

2.2 Noninvasive Definition

The term noninvasive refers to devices and procedures with no skin disruption, involves no contact with skin, makes any break in mucosa or internal body cavity. Noninvasive procedure draws blood without skin puncturing and instigating any trauma or pain to check the body levels of glucose. Noninvasive monitoring of glucose

helps to prevent acute and chronic complications**.** The procedures for noninvasive do not pierce the skin; they only touch the surface of the body. The noninvasive method improves diabetic patients' life quality by managing hyper and hypoglycemia, and physiological complications can be avoided [36].

2.3 Medical Device Definition

According to US-FDA, "Medical device is an instrument, apparatus, implement, machine, contrivance, implant, in vitro reagent, or other similar or related article, including a part or accessory which is: recognized in the official National Formulary, or the United States Pharmacopoeia or any supplement to them intended for use in the diagnosis of disease or other conditions, or in the cure, mitigation, treatment, or prevention of disease, in man or other animals, or intended to affect the structure or any function of the body of man or other animals, and which does not achieve its primary intended purposes through chemical action within or on the body of man or other animals and which is not dependent upon being metabolized for the achievement of any of its primary intended purposes" [37].

2.4 Accuracy Standards

Invasive techniques cause discomfort, and the diagnosis is slow to help the diabetic patient. On the other side, the high level of accuracy and sensitivity makes the invasive methods continue. Moreover, it is also used as the reference method for calibration. On the contrary, the noninvasive techniques are less accurate but provide continuous and quick results for managing glucose levels by the patient. The major considerations involved in noninvasive glucose monitoring are accurateness, usefulness and applicability.

Moreover, the device's sensitivity, specificity and less calibration time are needed. The accuracy and usefulness of devices are assessed by mean-absolute-relative-difference (MARD) [38], and the requirements and specifications are given by ISO15197 [39]. The standards and the metrics are important in researching and developing a noninvasive sensor to achieve and get the accuracy levels.

3 Types of Noninvasive Glucose Biosensors

Modern biosensors are miniaturized to the micro and nano levels (microsensors and nanosensors) to measure glucose in liquid samples to get real-time continuous monitoring. These glucose biosensors are either electrochemical or optical-based. The glucose biosensor based on electrochemical sensing uses the electrical signal

produced by the glucose oxidase (GOx) oxidation to measure concentration. The enzyme GOx converts glucose to gluconic acid and hydrogen peroxide (H_2O_2). The H_2O_2 produces protons on deprotonation in dissolved oxygen and gives away two electrons in the potential oxidative conditions. This method is widely used for glucose monitoring [40–42]. Electrochemical sensing is limited in use since in sensing endogenous electroactive species interfere, causing false-positive noise.

The optical-based glucose biosensors use fluorescence sensing, which can be conducted with sensing elements such as enzymes, bacteria or plant lectins. The fluorescent probes of dye or quantum dots can diffuse into cells with biofunctional properties to monitor using UV excitation external source. The photoillumenscence (PL) response in the dye or quantum dot UV excitation can be instigated through Forster resonance energy transfer (FRET) to get programmable and distinct PL. The PL spatial measurements can then help resolve the target analyte and capture at distinct time points. This type of glucose biosensors based on fluorescence is important for noninvasive and continuous glucose monitoring [43, 44].

The limitations involved in the use of Enzymatic glucose and H_2O_2 sensors (EGHS) like denaturation of the enzyme, protease digestion, difficulties with immobilization paved the way to use nanomaterial assisted electrochemical processes to develop Non-enzymatic glucose and H_2O_2 (NEGH) sensors [45]. In developing NEGH, nanomaterials have the advantages of ideal electrode materials because of increased surfaces areas, lower charge transfer resistance and window potentials. The carbon, metal/metal oxide and nanocomposite nanomaterials are the new platforms with nano morphologies like rods, wires, fibers, twisters, quantum dots, crystals, and core shells. Dayakar et al. used a bio-based route to produce AgNPs from Ocimum and coated on glassy carbon electrode with high sensitivity, response time, linear range, and lower detection limit to develop a glucose monitoring device [46]. Dayakar et al., with the Ocimum leaf extract, fabricated nanostructure with core–shell Ag@CuO has anti-poised activity and anti-interference in samples containing glucose [47]. To investigate in breath samples, Swathi et al. fabricated a nanocomposite based on cellulose acetate and graphene acetone sensor for people with diabetes [48]. The application of non-enzymatic electrodes promises for fourth-generation glucose sensor glucose oxidation analysis.

4 Principles of Noninvasive Glucose Monitoring

Raman spectroscopy uses the degree of the monochromatic light scattering causing the Raman effect to determine Raman scattering [49]. It gives high specificity and is less sensitive to temperature changes and water. It is highly suitable for surfaces including the opaque substratum and can measure scattered light. However, interference from blood protein, long collection time, and low signal-to-noise ratio are drawbacks [50]. The fluorescence emission with a specific wavelength when another energy level radiation is absorbed causes Stoke's shift, and it is used in the fluorescence technique [51]. This technology is very sensitive and allows for detecting

single molecules of glucose. It has high specificity because of the unique properties of molecules that measure glucose levels based on fluorescence intensity and decay times. It is also protected from light scattering effects. However, the technology is susceptible to oxygen and pH level changes. It is limited by photostability and recognition loss capabilities [43, 44, 52].

The photoacoustic spectroscopy is based on laser pulse that the molecule can absorb with localized heat in the tissue [41, 53]. The heat absorbed generates ultrasound waves detected by the sensor to track peak-to-peak changes to sense the levels of glucose variations in blood [54]. It is a simple method that is not affected by water and other molecules like cholesterol, albumin, or NaCl. The scattering particles present in the medium do not influence the photoacoustic signal. The main problem associated with this technology is that it is susceptible to temperature changes, motion and noise due to acoustics. It also has a lower signal-to-noise ratio and integration time is long. The near-infrared spectroscopy works on molecular vibrations and bond rotation caused by absorption of wavelengths 780–2500 nm and scattering [55]. It measures transmittance, interacting and reflectance [56]. It is not affected by water; the intensity of the signal correlates well with the concentration of glucose. It is also not affected by glass or plastic interfering substances. However, it is affected by heterogenous glucose distribution, and too low a glucose concentration can affect accuracy.

Electromagnetic waves measure blood glucose levels noninvasively by relating the antenna's resonant frequency to analyze conductivity and permittivity of the skin [57, 58]. It is then related to levels of glucose. The antenna acts as an electromagnetic sensor that can radiate or receive power. It is made out of conducting material with shape and size designed. The structure can be excited with time-varying currents and with the help of a waveguide or transmission line. The water content in different tissues has permittivity in the human body, and water molecules can be polarized with an electromagnetic field. As the frequency increases, the lining of water molecules takes slowly and stores energy in the tissue. When permittivity drops, frequency increases, causing dispersion with different frequency ranges, affecting the body's EM waves. The glucose present in blood and other dielectric material around the antenna changes the characteristics of the antenna. The antenna's performance in terms of resonance frequency can be correlated to the glucose concentration in the blood. Various antenna types, including narrow and wideband, have been designed and tested recently. Among the antenna used, planar antenna structure microstrip antenna are used. Its advantages include compatibility with integrated circuits and configurations with low cost and lightweight.

5 Platforms for Noninvasive Glucose Monitoring

The noninvasive monitoring methods of glucose in the blood keep its level under control and are classified into optical and transdermal forms. The visual methods

use NIR spectroscopy, Raman Spectroscopy, Photoacoustic and Fluorescence spectroscopy, wherein the light properties interact with different concentrations of glucose to detect its quantity. The optical methods also use techniques for thermal emission, reverse iontophoresis, bioimpedance, photoacoustics, absorbance spectroscopy, ocular spectroscopy, polarimetry, electromagnetic sensing, temperature modulated localized reflectance, ultrasound, metabolic heat conformation and optical coherence tomography [59]. The transdermal methods use impedance and reverse iontophoresis based on transdermal properties where measurement of glucose due to electricity or ultrasound through the skin uses the temperature change in metabolic heat conformation and conservation of energy [60]. The technologies involved in the skin physiology of noninvasive monitoring systems include device surface, material chemistry, electrochemistry sensing and system interfaces. With these methods, the effective realization of developing platforms of noninvasive glucose monitoring requires the scientific problems consideration, legal, economic and commercial concerns, and education of the patient and physician [34].

With the introduction by Clark and Lyons enzyme glucose biosensors, the field continues to be the research activity focus and improving the life of diabetes patients [61]. Many research groups are developing noninvasive functional glucose monitoring devices [62]. A watch-type biosensor uses a very low volume for clinical analysis in the relevant ranges, consumes less power, and is cost-effective [63]. FDA-approved glucose sensor (Glucose electrode) checks glucose variation in the skin on passing light through it; the sensor measures the reflected light because of glucose interaction [64]. Noninvasive glucose monitoring devices are GlucoTrack™, G2 biographerdevice, GlucoWatch® and OrSenseNBM-200G. In Glucowatch, the sensor contains glucose oxidase enzyme; using the technique iontophoresis, glucose is determined through cathode disk. Glucowatch® device alerts patients by raising beep alarm sound if glucose level goes beyond 35%. It includes accompanying software, which interprets changes in glucose data. Activity markers are used for data analysis, exercise, meals, and insulin injection, and up to 8500 readings are stored in internal memory. In GlucoTrack™ device and OrSense NBM-200G- a sensor probe with a light source can detect red and near-infrared, and RNIR spectral range and the presence of pneumatic cuff makes to occlude the blood flow and systolic pressure. To monitor glucose levels, in turn, produces an optical signal. The sensor-based fabricated CeO_2 identifies glucose with higher 0.495 $\mu A\ cm^{-2}\ nM^{-1}$ sensitivity, lesser detection of 6.46 nM limit and broader linear ranges from 0 to 600 nM. In the protein sensors also CeO_2 based bioelectrode is considered a suitable candidate [65].

Most of the existing noninvasive devices use electromagnetism (EM) techniques to detect glucose levels in the blood [66]. The EM sensor devices are metallic constructed for EM waves receiving or radiating. To detect glucose levels, a reflection of transmitted waves is used. To monitor the glucose variation using the EM sensors is based on two key aspects: (i) the medium under test (MUT) dielectric properties direct the EM waves compartment and (ii) the dielectric properties changes with the glucose levels. Consequently, the EM waves released from the sensor when it is exposed to the body, the transmitted and reflected waves carry useful information from the underlying tissues influencing their properties. More specifically, the S

parameters change to connect in MUT with glucose fluctuations due to the phase and magnitude shifts. Monitoring these variations, determining blood glucose levels (BGLs), and technologies based on EM present some advantages [67].

Other research data results provided by patch antennas have indicated high-level glucose sensitivity towards its variations. The study experiments for serum-based demonstrated $\|\Delta S21\|$ of 0.25 dB change equivalent to a 55.6 mM (~1001.8 mg/dl) amount. Noninvasive ease of using the device is required for glucose level monitoring, especially for patients to regulate blood glucose levels. It is very sensitive, wearable and helps monitor glucose levels continuously by using a multisensory system. This wireless device senses both hypo and hyperglycemic variations [67]. A chip-less tag sensor over the skin of a patient measures variation in glucose levels in the interstitial fluid. It can be detected with ~1 mM/l accuracy of 38 kHz resonance frequency shift [33].

Based on integrating Reverse Iontophoresis on a flexible substrate with amperometric glucose detection, a tattoo-based, wearable noninvasive glucose monitoring platform was developed [68]. Using the screen-printing, a single transitory tattoo platform was fabricated with electrodes for iontophoretic and glucose sensing, making body-compliant and flexible wearing, for glucose measurements of single-use. This platform removed the Glucowatch® discomfort reducing the iontophoretic current applied for extraction of ISF. The tattoo-based electrodes were evaluated for performance before or after the meals by recording and comparing glucose signals in human subjects. The results were validated using a commercial glucometer for the simultaneous blood glucose measurement with disposable use; wireless electronics integrated into the sensor [34].

One of the approaches that involve minimal invasive is sweat testing. It is released in normal conditions from the body and contains glucose, reflecting its levels in the blood. However, since sweat availability and the rate of sweating can vary from individual to individual, glucose levels can be lower compared to blood. To overcome the problems associated with sweat, Juliane et al. developed a device that can be used for personalized measurement [69]. In this device, sweat is collected from the patient by placing a finger on the sensor for 1 min. To absorb sweat polyvinyl alcohol hydrogel in the sensor in contact with an electrochemical sensor detects and allows to measure glucose. Based on calibration with a finger prick, the reading is corrected to collect data, and an algorithm is used to interpret. The device can predict glucose levels with above 96% accuracy in volunteers tested.

Sweat is considered physiologically important electrolytes and metabolites, and the technology involves a sensor array platform in a wearable patch type to help continuous monitoring applications [70]. This device has integrated signal transduction, processing and wireless transmission. An additional NGM based on impedance spectroscopy device is a wristwatch used to detect a pattern of levels variation in glucose. It performs measuring impedance with an open resonant circuit (1–200 MHz) with four measurements/minute and has 20–60 mg dL^{-1} glucose/ohm sensitivity range. Currently, three devices are available in the market of US and Europe after clearing their regulatory approval [34]. Further improvement on iontophoretic stimulation in sweat is needed for consistent, controllable, and

reproducible sweat generation without exercise. Concerning epidermal microfluidic devices, focus on improving sweat collection for flow and replenishment is needed. To overcome advancements in continuous epidermal glucose monitoring will be critical for realizing its prospective impact. The glucose detection with Accu-Chek® in human sweat is relevant to test its levels. The glucose level is detected with glucose binding to sensor interface by electrochemical impedance spectroscopy, and quantified level ranges 0.01–200 mg/dl in human sweat. This is also helpful in monitoring the level of glucose and alcohol in pre-diabetics, people with diabetes, and during alcohol consumption.

Raman Spectroscopy is considered one of the promising technologies for glucose measurement in interstitial fluid. Lundsgaard-Nielsen et al. showed confocal Raman Spectroscopy in a clinical trial involving type 1 Diabetes independent validation data with 25.8% MARD [71]. Researchers at Samsung Advanced Institute of Technology (SAIT), Samsung Electronics used Raman spectroscopy to check the glucose level. In an hour, the results are read after the initial calibration, which is tested in the pigs.

Noninvasive glucose evaluation techniques are also done using Heart Rate Variability (HRV) and artificial intelligence-based algorithms. The various criteria of measurements and dimensions involved in these noninvasive glucose measurement approaches are invasiveness, size, sensing properties, media analyzed, the method applied, type of activation, delay in response, duration of measurement, and the results access. There is another type of glucose sensor in that the wearable EGC sensor measures the HRV, in case of a decrease in the HRV indicates diabetes is autonomic dysfunction. The method can also be used to monitor glucose levels in the blood but needs improvement in accuracy though it provides a comfort level to the patients. Many of those measurement methods used in current have MI and NI techniques to achieve better accuracy [32].

Currently keeping in demand for glucose monitoring systems, considerable improvement has been made so far. Due to improved technology, several devices are already on the market; many of these devices are using spectroscopic technique NIR. Furthermore, the significant thing is that NI devices manufacturers aim for non-continuous glucose monitoring (NCGM) and use techniques based on MI for continuous glucose monitoring are more appropriate. Noninvasive devices based on optical or vibrational should measure a controlled atmosphere thus, it is noncontinuous, whereas a minimal invasive glucometer is not sensitive to mechanical vibrations, temperature, light, etc. and it is continuous. Optical coherence tomography is used in the detection of concentrations of glucose. The light beam on metal is focused through the prism that forms resonating surface plasma polaritons sensitive to glucose levels changes at certain angles. In the NIR-based blood glucose detection method, the absorption of light by blood glucose shows that the transmittance of laser light is 30 times higher than near infrared-light with a wavelength of 650 nm in human fingers and water [72].

The glucose monitoring system is portable, and it is a self-monitoring device within built web and android applications that are safe and easy to use for patients [73]. Photoplethysmography (PPG) assesses BGL through a noninvasive method.

Earlier work with an optical sensor has shown improved blood glucose level estimation. In this system, data acquisition is built with a sensor to record subjects' PPG signal with Single Pulse Analysis for the efficient assessment of values of BGL [74].

In recent times, for the management of diabetes, the development of biosensors for noninvasive glucose monitoring is getting more attention. Combining NGM plus real-time glucose with accurate, stable long-term measurements needs to have a critical assessment for the accuracy of large-scale studies. Additionally, sensing with other physiological parameters like pH, temperature, or humidity efforts should combine to get measurements accurately for epidermal glucose and for calibration and accuracy to correlate the blood glucose levels [35]. There are advantages and disadvantages to these platforms. NIR spectroscopy is a well-established analytical technique that removes all interferences but requires multivariate analysis and is available only on a macro scale. Raman spectroscopy measures directly from biofluids, but it is used transcutaneous and requires long-standing time. Bioimpedance spectroscopy is low cost, simple, safe and fast, but has lengthy calibration time and is susceptible to interferences. In thermal emission spectroscopy though the accuracy is acceptable, has a radiation effect, and the results of measurements are not satisfactory [75]. The benefits of advanced noninvasive glucose sensors help patients feel pain-free and not disposable. The other benefits include reading history data in tabular and graphic formats, reduction in the cost of life cycle and on the long term it can be less expensive than compared to the finger-prick device, user-friendly, data easiness to read, large color touch screen, self-diabetes management and long term calibration validity becomes easier [76].

For many companies, technology based on noninvasive glucose monitoring signifies exciting research and an exceedingly desired market. Thirty years ago, the first noninvasive glucose device was released on the market. At present, the global market of digital diabetes management is projected to reach $17.09 billion by 2025. The Blood Glucose Monitoring (BGM) devices' accuracy ranges between 5.6 and 20.8% in the US. The clinical trials of noninvasive glucose monitors are increased in the twenty-first century; 16 trials were conducted from 2016–2020, whereas in 2000–2015, only five trials were conducted as per NIH [77]. The detection of glucose by using these noninvasive technologies of glucose sensors is available in the market, whereas some are withdrawn from the market due to accuracy issues [37]. For example, Glucowatch and Pendra are withdrawn from the market.

The sensors based on NIGM in tears, saliva, urine, and sweat are becoming more and more significant. The study conducted by Masakazu et al. considered tears for NIGM clinical applications [78]. There was a significant association for glucose concentrations in tears and plasma using random intercept model analysis in diabetic patients ($P < 0/001$) by NanoZyme copper calorimetric sensing, Naveen Prasad et al. could detect urine glucose at low concentrations. To find the change in blood glucose levels throughout day and night, many devices have been developed to manage diabetes easier and more measurements to take [79]. Dongwoon Anatech has developed saliva-based glucose monitoring and completed a clinical trial in December 2020. The device is called D-SaLife, which is based on microcurrent control technology to estimate glucose in saliva. The result of the reading is color-coded by meter

and recorded in the mobile app. In 2019, the iQ Global Group, an Australian biotech company, developed Saliva Glucose Biosensor. This small strip can be disposed of and transmitted measured glucose level to the smartphone when exposed to saliva. In a recent clinical trial study conducted by Stefan et al. on the prototype for Raman-based NIGM device developed by GlucoBeam, RSP Systems A/S, Denmark, when tested on type I diabetic patients, the study established calibration models. It showed the proof of concept for the real-time application [80].

Tensor Tip Combo Glucometer by Cnoga Medical Ltd. (Israel) requires calibration and uses light passing through the finger to quantify; the signal is detected due to the molecule's presence by VIS–NIR spectroscopy. The MARD accuracy is 14.4%. GucoTrack by Integrity Applications uses thermal-based electromagnetic sensing combined with ultrasound. It is used on earlobe and is having MARD 19.7%. Health Care Computer developed metabolic heat confirmation-based technology. It is used on finger and gives 87% accuracy. Wizmidevice is developed by Wear2b Ltd. (Israel), which uses NIR spectroscopy. A wrist LTT device is developed by the Quantum Science and Technology, Light Touch Technology Ltd. (Japan) research group, which uses MIR spectroscopy. It uses a finger to measure the glucose. The Biovotion device is developed by Biovotion Ltd. (Switzerland). It is based on Bioimpedance Spectroscopy and uses the arm to measure glucose.

DiaMonTech helps manage people with diabetes at comfort with more frequent measurements done. This technology uses a shoebox-sized device as a prototype. In the human clinical trials, DiaMonTech attained identical accuracy as the test strips in preclinical tests. For diabetes Type 2, in case of any abnormal case, it checks glucose levels within the acceptable range. The HELO Extense uses a technology based on color indicator detecting glucose concentration. Low sensitivity, specificity, and interference are some of hardware and software limitations [6]. Abbott Diabetes Care developed FreeStyleLibre. It is a sensor patch kept on the arm and can be used for glucose levels measurement of interstitial fluid present between cells underneath the skin. It is available in the US, Canada and Europe. GlucoWise sensor is placed on the earlobe or space between the forefinger and index finger of the skin.

The measured reading is sent directly to the app on a smartphone. Meds measure glucose levels using radio waves and accuracy more than another wireless glucose monitor type. SugarBEAT measures glucose levels with a skin patch transmitter and low-level electricity passing over through interstitial fluid in the skin. The developed transmitter by UK biotech Nemaura Medical is rechargeable. Data can be sent to Bluetooth every 5 min to the user's phone. Using an associated app, readings are monitored [81]. Bypassing non-perceptible electricity over the skin of the arm, leg and abdomen, the device with the patch is placed on the skin to measure the glucose through the interstitial fluid. Google's smart contact lenses developed by Google's eye care division and Novartis. It uses a chip in lens to measure glucose with and reading details can be transferred to smartphones via antenna.

6 Medical Device Regulation Updates

Glucose monitor display falls into medical device classification II. The special control for the labelling of the device must take into user and follow information for use on the glucose continuous system monitoring. The device is not to replace practices advised by the physician. As per FDA, a device monitoring glucose in adults (age 18 and older) with diabetes is indicated to identify trends and pattern tracking. The gadget is suggested for use as an adjunctive device to supplement, not to substitute info acquired from basic home-based devices monitoring glucose. The system should enable finding the incidents of hyperglycemia and hypoglycemia to enable long-term and severe treatments (access data FDA). The FDA will take decisions centred on various evaluations and the reliability effectiveness of the device results. There is no primary endpoint for clinical accuracy study based on Continuous Glucose Monitoring devices. Before premarket submission, the manufacturer can obtain feedback from the FDA to clarify study design and analysis [82]. As EU MDR manufacturers want to market their CGM devices, they must certify by the Notified bodies stats that the new device complies with all the specifications as per the EU MDR. Conducting clinical trials or PMS is not required [83]. Europe's CGM Market is growing exponentially. CGM is a new idea of glucose regulation that allows user to monitor frequently their glucose levels. CGM develops awareness of the patients regarding food intake and variation of blood glucose levels before and after food. CGM helps patients manage effectively due to complications arising from diabetes [84].

7 Future Outlook

Noninvasive procedure helps diabetes patients manage their quality of life by checking their BGL safely and easily. Thus, managing blood glucose levels is a basic concept of managing diabetes. Glucose sensors need to advance in getting more accuracy, cost-effectiveness, convenience to use as well as the sensor/device should allow software-based data analysis and management. The companies must develop and improve hardware technologies that provide enhanced accuracy, wearability, and biocompatibility that keep patients quality life. Current revised medical device regulations are helping to improve and regulate devices to apply diabetes management. Educating self on CGM is critical and guarantees quality life [85]. Shortly due to the available technologies which are improving day by day, will bring multiple choices of glucose monitoring devices that will be available in the market.

Without a thorough understanding of physical and physiological factors that affect the BGL, glucose monitoring accuracy cannot be accomplished. Since physiological variation will affect the technology, patient-to-patient body regulation varies, including metabolism, blood components, and other circulating body fluids. As most noninvasive technologies are based on optical sensing measurements, variations in

time may occur between various body parts, introducing calibration errors. Moreover, temperature, light, and measurement area may also affect the glucose detection levels in the blood [86].

8 Conclusion

- Continuous glucose monitoring with NI device is valuable in controlling hyperglycaemic events and helps improve patent life quality.
- Getting the accuracy level in the NI device used for monitoring blood glucose is a challenge. The device should have accurate reading before it is considered genuine.
- The hardware and software limitations result in interference and are the major hindrances to high sensitivity and specificity. The new developments in material and computer sciences in the future preclude and bring in more sensitive and noninvasive monitoring devices.
- The difference in the individuals or difficult and tedious detection parts of the device or the correlation of measured glucose level by the device and the individual blood glucose level leads to errors in results measured. This can impact commercial glucose detecting devices' stability, reliability, and consistency.
- The electrodes and devices integrated with smartphone and wireless transmission are emerging to get real-time monitoring and improve the diabetic patient's life quality.

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Manickam Tamilselvi received her Doctoral degree from the University of Hyderabad. She continued her post-doctoral research in signal transduction in Academia Sinica, Taiwan, Kobe Women's University in Japan, INRA in France and Indian Institute of Science, Bangalore. She worked in CROs as a Bio-Analytical Scientist and Regulatory Affairs Manager in clinical research and healthcare. She completed several projects in clinical research organizations. She is currently working as a Quality Manager in compliance and clinical trial monitoring in life sciences, pharma and healthcare industry.

Pandia Raj is presently working as Research Scholar, at Department of Physics, Kongunadu Arts and Science College (Bharathiar University), Coimbatore, for his doctoral programme focusing on photocatalytic water splitting through dye-sensitised solar cell (DSSC) studies for natural water via bismuth vanadate BiVo4 prepared through hydrothermal method and XRD, UV, PL, FTIR, Raman spectroscopy photocatalytic characterisation and bismuth oxide based photocatalytic materials like $BiFeO_2$, $BiWo_2$ and $CuBiO_2$ nano materials to study photo current density and other properties.

Dr. Ravikumar Ramlu Vidule Asst. Professor, Dept. of Chemistry, & working as IQAC Coordinator, Shri Sant Gadge Maharaj Mahavidyalaya, Loha, Dist. Nanded. (MS)-431708, India. Mail id: ravidule@gmail.com, 80007840827. Published Fifteen Research papers in Reputed Journals. Participant in Academics and co-curricular activities. Actively engaged and participating on environmental awareness programs by writing articles and delivering talks on All India Radio. Delivered talk in National and International conference, workshops, Refresher and Orientation courses. Currently started the campaign in India and abroad for the awareness of use of, MICROBEADS in PCCP (personal care cosmetic products). Writing articles to stop the use of single used plastic in newspapers. Wrote the chapters in the book: Blended Classroom: A Method for Encouraging Effective Global Education Learning Environment", Impact of Covid-19: In Teaching Learning Process in India. Challenges to The Academic Domain In The Aftermath Of Covid-19, Impact Of Covid-19 On Higher Education, Impact of COVID-19 on Textile Industry. Also a core interest in Microbeads and other aspects been invited for the lecture. Invited as a speaker in Sacred Heart College, Kochi "Microbeads: A Threat for life on Earth" In Flasgship programme Prof. K. V. Thomas Endowment

"National Seminar on New Frontiers in Materials and Environmental Sciences." 28th Jan. 2020, Invited as a Resource person in Pratibha College of Commerce and Computer Studies Pune College as "State Level Seminar on Emerging Environmental Challenges and its sustainable Approaches." 7–8th Feb. 2020, Given Short Presentation as a young researcher at Dr. T R Ingle memorial National Symposium, "Trends, Research and Innovation in Chemical Sciences (TRI-2020), Feb 14–15, 2020, Organized by Dept. of Chemistry, SP College, Pune, An invited lecture (Webinar) "Nehur Yuva Kendra Ministry of Youth affair and Sports, Dist. Thiruvanthpuram, Kerla" conducting an internship for MSW students "Blended Learning as a new approach to social work." Given talk dated on 30 Mar 2021: Talk title: Microbeads: A Threat for Life on Earth in the International conference on Materials of the Future: Smart Applications in Science and Engineering, Qatar University, Qatar, Emergent Materials Journal and Chemistry Africa Journal, Springer.

Srinivas Ankanagari obtained his Master's in Genetics from Osmania University and did his Doctorate in Life Sciences from the University of Hyderabad. He had carried out several regulatory and non-regulatory pharmaceutical bioavailability and bioequivalence of drugs in the pharmaceutical industry's Phase I and Phase II clinical trial projects. He was involved in analyzing biological samples for drugs/metabolites concentration and development, validation and implementation of bioanalytical methods. He is currently working as Asst. Prof. in Genetics, engaged in academic and research activities at the Department of Genetics & Biotechnology, Osmania University.

Future Developments in Invasive and Non-invasive Diabetes Monitoring

Frédéric Harb, William S. Azar, Hilda E. Ghadieh, Rachel Njeim, Youssef Tawk, Joseph Costantine, Rouwaida Kanj, and Assaad A. Eid

Abstract Blood glucose monitoring is the cornerstone of effective diabetes management. Regular glucose testing reduced the risk of developing long-term micro-and macro-vascular complications. Despite the recently growing development of minimally invasive glucose monitoring techniques, most glucose monitoring methods are invasive, painful, time-consuming, and pricey in the long run. Painless, needle-free, and CGM approaches are needed to enhance the life quality of patients with diabetes. This chapter offers an up-to-date compte-rendu on the leading technologies for invasive, minimally-invasive and non-invasive glucose monitoring devices and sensors currently being used in the market or developments alongside their accurate real-time responses and sensitivity. Besides, the new non-invasive approaches currently under development by different research groups and developers and their fidelity to assess hypo- to hyperglycemic variations described. The chapter concludes by featuring the

F. Harb
Department of Life and Earth Sciences, Faculty of Sciences, Lebanese University, Fanar, Lebanon
e-mail: frederic.harb@ul.edu.lb

W. S. Azar
Department of Physiology and Biophysics, Georgetown University School of Medicine, Washington, DC, USA

W. S. Azar · H. E. Ghadieh · R. Njeim · A. A. Eid (✉)
Department of Anatomy, Cell Biology and Physiological Sciences, Faculty of Medicine and Medical Center, American University of Beirut, Beirut, Lebanon
e-mail: ae49@aub.edu.lb

AUB Diabetes, American University of Beirut, Beirut, Lebanon

Y. Tawk · J. Costantine · R. Kanj
Department of Electrical and Computer Engineering, Maroun Semaan Faculty of Engineering and Architecture, American University of Beirut, Beirut, Lebanon
e-mail: yt03@aub.edu.lb

J. Costantine
e-mail: jc14@aub.edu.lb

R. Kanj
e-mail: rk05@aub.edu.lb

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future trend of glucose measurement tailored to the needs of patients with diabetes based on the body target used for detection.

Keywords Diabetes mellitus · Glucose · Non-invasive glucose monitoring · Minimally invasive glucose monitoring · Continuous glucose monitoring

1 Introduction

Diabetes mellitus has become a major international health issue [1]. The burden of diabetes is amplified because the disease is associated with a range of complications, including nephropathy, neuropathy, and retinopathy. The global prevalence of diabetes in 2019 was estimated at 463 million individuals and has been prognosticated to rise by about 11% by 2045. A fasting blood glucose (BG) concentration less than 5.6 mmol/L is considered normal. A concentration between 5.6 and 6.9 mmol/L is considered prediabetes, while a concentration greater than 7 mmol/L, using two separate tests, is consistent with diabetes. Hypoglycemia is defined as having a BG concentration <3.9 mmol/L. A concentration of <2.8 mmol/L can cause defective glucose counter-regulation and impaired awareness of hypoglycemia. In contrast, hyperglycemia can result in multiple metabolic abnormalities associated with long-term microvascular and macrovascular complications [2–6]. Alternative consequences of diabetes include cardiovascular disease and death [7]. Furthermore, one in two individuals living with diabetes does not know that they have diabetes. The growing load of diabetes in low- and middle-income countries may cause considerable financial pressure on individuals and health systems.

Diabetes mellitus is divided into Type 1 (T1DM) and Type 2 (T2DM). Prediabetes, as defined earlier, presents with various symptoms, including weight loss, increased urinary frequency and urgency, polydipsia, and impaired vision. Prediabetes is a serious condition that puts the patient at a higher risk of progressing to T2DM. In T1DM, the immune system attacks the pancreas and destroys the pancreatic β-cells that make insulin. In T2DM, however, the pancreas can still produce insulin, but the body does not adequately respond to it. Furthermore, overweight individuals have a higher chance of developing T2DM, which makes a healthy diet helpful in attenuating diabetes and its complications in these individuals. Siegel et al. found an increase in BG in subjects with hypertension treated with thiazides consistent with a proportional increase in body mass index. This increase in BG occurred in all groups studied, scaled according to obesity. Among individuals with hypertension, there is an increased prevalence of T2DM and impaired glucose tolerance [8, 9], which explains why hypertension, obesity, and diabetes or prediabetes are commonly referred to as "metabolic syndrome" [10, 11].

Interestingly, sleep disorders have also been associated with diabetes in a bidirectional relationship. Just as diabetes can cause sleep problems, sleep disturbance also plays a role in diabetes. Acquiring insufficient sleep or less healthful slow-wave sleep has been linked to hyperglycemia in individuals with diabetes and prediabetes

[12, 13]. However, it is not clear whether the relationship is causal or whether more variables are at work. It is thought that sleep deprivation increases levels of ghrelin, the hunger hormone, and decreases levels of leptin, the satiety hormone. To neutralize lower energy levels, people who have sleep disturbances are prone to seek comfort in foods that raise blood sugar, putting them at a higher risk for obesity, a major risk factor for diabetes.

Diagnosis and management of diabetes require accurate, sensitive, reliable, rapid, and attentive glucose monitoring daily. Since both types of diabetes cannot be cured, the only possibility for patients is to monitor BG levels and treat them accordingly. Unfortunately, BG levels of patients with diabetes must be controlled for life, and the patients will remain vulnerable to events of hypoglycemia and hyperglycemia. To monitor and estimate BG levels, many techniques have been developed, including the optical [14], coulometric [15], capacitive [16], and electrochemical [17, 18] detection methods. Many devices use glucose oxidase and glucose dehydrogenase to measure BG [19]. These sensors are based on enzymatic reactions and show remarkable sensitivity and specificity. Yet, they present some disadvantages, including poor stability and reproducibility [20]. Consequently, researchers have focused on developing nonenzymatic glucose sensors mostly based on the fabrication of electrode surfaces that oxidize glucose without enzymes. This type of detector is advantageous in its simplicity, manufacturability, portability, selectivity, stability, sensitivity and low cost [21–23].

Long-term BG management in patients with diabetes has been shown to extend life expectancy [24]. To optimize treatment plans, BG management should be combined with monitoring lifestyle changes such as diet and physical exercise [25]. This chapter provides an outline of non-invasive glucose sensors used to control diabetes. The different biological fluids used for continuous glucose management will also be addressed.

The most up-to-date commercial remote glucose monitoring technologies have been reviewed, and their benefits and limitations have been weighed. We will discuss various sensing methods for glucose monitoring as well as the most recent commercially available products. Finally, findings and predictions for the future will be discussed.

2 Diabetes Monitoring with Glucose Sensors

2.1 Description

In patients with diabetes, long-term management of BG through daily self-testing and patient adherence to treatment is vital in preventing diabetes and its complications. Patients with diabetes can monitor their BG levels at home using electronic devices. One of them is the glucometer, a hand-held electronic system that tests the sugar content of a small droplet of blood. Continuous BG management is highly beneficial,

for it provides insight into the effectiveness of a recommended medication. In other words, regular testing of BG levels can reflect how well patients are adapting to their care plan. BG concentrations differ significantly between healthy adults, adults at high risk, and adults with diabetes. They also vary during the day and usually rise after each meal. Consequently, hyperglycemia can cause glucose toxicity, leading to cell dysfunction and diabetic complications [26].

2.2 Suitable Body Fluids Used for Glucose Monitoring Levels

Blood has long been recognized as the most common bodily substance that humans use for measurements and medical tests. BG levels are usually measured in a droplet of capillary blood at the fingertips. Capillary glucose levels closely match systemic arterial BG levels. Other available body fluids appropriate for testing include urine, interstitial fluid (ISF), sweat, ocular fluid, and saliva for non-invasive screening. Urine is a non-invasive and readily available fluid used in diagnosing diabetes. Urine is made up of various metabolites, including glucose, proteins, salts, and nitrates, which explains why the pH of urine fluctuates between acidic (pH 4.8) and basic (pH 8). During hyperglycemic events, glucose can be excreted and measured in the urine. Since urine is transient, it cannot be used for continuous glucose monitoring.

ISF is a thin film of fluid that encloses the body's cells. It is composed of water, carbohydrates, salts, fatty acids, amino acids, hormones, leukocytes, neurotransmitters, coenzymes, and cell byproducts. ISF glucose levels vary from BG levels, and correlation measurements are needed. The bloodstream is the body's transport system for transporting substances like glucose on a systemic level. At the same time, the ISF is the compartment where substances like glucose diffuse into tissues and cells locally. Accordingly, blood collects glucose absorbed from the gastrointestinal tract or released from glucose stores, flowing through capillary walls into the ISF. In other words, BG concentration is a measure of the overall amount of glucose present in the blood. In contrast, the concentration of glucose in the ISF depends on local factors, such as local diffusion from the blood and metabolism by surrounding tissues. ISF is readily accessed from subcutaneous tissue. Minimally invasive microneedles have been conceived to gather ISF. They are applied to the skin with an adhesive film for up to two weeks, allowing continuous glucose monitoring (CGM).

Sweat is a thermoregulatory substance that serves to control body temperature. It is secreted by sweat glands all over the body, making it the most available bodily fluid. Sweat is mildly acidic (pH 5.5–6.5) and primarily consists of water, electrolytes, and urea. Sweat also contains low glucose, antibodies, and cytokines [27]. Glucose levels in sweat were associated with BG levels, but they lag by around 8 min from BG levels [28]. Saliva is a versatile fluid that includes multiple analytes excreted from the blood that can influence an individual's hormonal, mental, dietary, and metabolic condition. Saliva may be used as a non-invasive glucose sensing sample. Salivary glucose levels range between 0.23 and 0.38 mM in healthy individuals, while in patients with diabetes, salivary glucose levels fall between 0.55 and 1.77 mM. Further studies are

needed to establish a stronger association between BG and salivary glucose levels before using saliva in clinical settings. Significant research has been conducted in this area, and several new technologies for non-invasive and CGM in saliva have been documented [29].

2.3 *Sensing Techniques for Glucose Detection*

The many benefits of daily surveillance have led to the appearance of many glucose monitoring devices on the market, which, for the most, are built on biosensors. A biosensor is an analytical instrument that uses a physicochemical transducer to convert biological elements into electronic signals. Figure 1 is a schematic diagram of a biosensor. The biorecognition element in this system can detect an analyte such as glucose [30]. The biological signals are then converted into electrical signals by the transducer/detector.

The electronic circuit interprets the signals and translates the results into an easy-to-understand format by converting the biorecognition event into a measurable electrical or optical signal that correlates with analyte–bioreceptor interactions. The most common method for BG monitoring employs a portable electronic instrument known as the glucometer. The glucometer measures the amount of glucose in a droplet of blood drawn most often from the fingertips and mounted on a disposable test strip pre-treated with specific chemicals. Electrical signals result from the different chemical interactions on the test strip and are then interpreted by a reader. Even though this procedure is inexpensive and straightforward, it instantly provides a BG calculation and creates only minimal pain. This procedure is not suitable for CGM, because repeated pricks increase the risks of infection and tissue injury over time.

A non-invasive technique refers to any surgical procedure that does not require the insertion of an instrument into the body. In this approach, the patient does not feel the discomfort that accompanies a blood draw [31]. This segment discusses some of the many non-invasive glucose monitoring strategies that have been developed, including electrochemical techniques, microwave sensing, Raman spectroscopy, near-infrared spectroscopy, iontophoresis, and stepped-impedance resonators, among others.

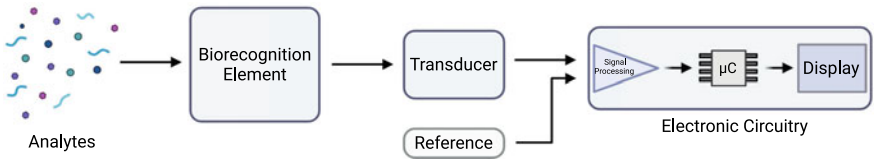

Fig. 1 Schematic diagram of a biosensor (created with BioRender.com)

2.3.1 Non-enzymatic Biosensors

Today's research largely focuses on non-enzymatic biosensors, most of which are engineered to identify single analytes. Non-enzymatic sensing is cheaper and longer-lasting than enzymatic electrochemical sensing. Nevertheless, it carries several disadvantages, including high working potential, slow electro-kinetics, and weak sensing parameters. Accordingly, scientists are focusing their efforts on exploring new nanomaterials to construct non-enzymatic sensors characterized by a higher conductivity, a more efficient catalytic activity, and more advanced physical and chemical strengths. In this respect, the development of sensing components for the specific identification of glucose has greatly advanced [32–36].

2.3.2 Electrochemical Methods

The electrochemical technique was created to detect glucose levels in tears, saliva, sweat, and blood [37, 38]. In this procedure, glucose concentrations are indirectly quantified by adding a thin layer of the enzyme glucose oxidase to a platinum electrode through a semipermeable dialysis membrane. The amount of glucose is estimated by measuring the proportional decrease in oxygen and increase in hydrogen peroxide [29]. This glucose monitoring technique evolved into the current finger pricking process, which utilizes tiny blood samples measured in vitro using test strips and a glucometer. This invasive, uncomfortable, and painful enzymatic approach is non-continuous, for it measures snapshots in time of BG levels. It can therefore miss cycles of hyperglycemia or hypoglycemia that happen outside of the measurement window. Tools that depend on other biological fluids have been developed to alleviate consumers from the discomfort and inconvenience associated with finger pricking during BG tests. Hendrikus and his colleagues have created an electrochemical glucose sensing apparatus that employs an electrode-like hollow coil biosensor with a versatile wireless sensor system to detect glucose in tears [38]. Claussen et al. used a photolithographic technique that included graph nanosheets, platinum nanoparticles, and glucose oxidase to create an electrochemical biosensor that measures glucose concentrations in saliva and tears [37]. Zhang et al. created another system focused on electrochemical sensing with carbon nanotubes that uses saliva [39]. Given the high accessibility of non-invasive biological fluids, it is anticipated that further research on devices that employ such fluids for glucose detection will be conducted in abundance.

2.3.3 Microwave Sensing

Radiofrequency or microwave instruments may characterize the permittivity of various materials using electromagnetic waves. Researchers have thoroughly analyzed the dielectric properties of biological tissues [40]. The single-pole Cole–Cole Model was recently used to study biological tissues with varying glucose content

and model their wideband dielectric properties [41]. The Cole–Cole-Model offers an accurate and detailed biological tissue representation over a broad frequency spectrum, facilitating experiments on various human tissues, including skin, fat, bone, brain, and breast. Inductive and capacitive sensors detect glucose similarly to how dielectric permittivity is seen [40]. The sensor configuration is a fluid inductor consisting of a center and a coil. The inductor's stray capacitance changes in response to glucose when it comes in contact with the inductor. Improvement in BG levels in the body can be compared with impedance measurements. Stepped impedance resonator (SIR) is another instrument capable of calculating dielectric permittivities. SIRs are microwave resonator-based biosensors that can identify the concentration and physical properties by interacting with the resonator's electromagnetic waves (EM). Similar to inductive, capacitive sensors, the association of electromagnetic waves with the tested material is expressed in the SIR's S-parameters and the change in central frequency [42]. The physical properties of the substance are correlated with the resonant frequency transition. However, in contrast to inductive, capacitive sensors, SIRs are planar. They can be manufactured with printed circuit boards, which puts them at an advantage in decreasing circuit size and in the potential inclusion of wearables. Variations in glucose concentration affect the biosensor resonator's equivalent sequence inductance and shunt capacitance.

2.3.4 Near-Infrared Spectroscopy

Near-infrared spectroscopy (NIRS) assesses the various chemical constituents of biological samples using light absorbance. This approach probes tissue with light waves. The reflected spectra from wavelengths between 400 and 2400 nm allow for specimen study. NIR radiation can reach deeper into the skin than visible or mid-infrared radiation (MIR) [43]. Various windows mediate spectral measurements of NIR within the NIR spectral area that show low-intensity absorption bands for water, hemoglobin and lipid, which allows for light transmission into tissues. The receiver, transmitter, light source, and detector are mounted on opposite sides of a thin and muscular soft tissue such as the earlobe to carry out NIR measurements. NIR wavelengths are administered at the level of the transmitter, and the signal is attenuated by blood glucose, which is then evaluated at the receiver end. The disadvantage of using this method is that tissues can scatter lights, causing interference from different elements with comparable absorption characteristics. As a result, the system needs calibration for the measured glucose levels to match the actual BG levels [44].

2.3.5 Optical Methods

Surface plasmon resonance (SPR) happens when polarized light strikes a chemically inert and conductive electrode, interacting with media having different refractive indices. The light beam reaches the metal via a prism in the basic Kretschmann configuration, creating resonating surface plasmon polaritons (SPP) responsive to

alterations in glucose levels at a resonance angle, θR. Photon absorption leads to dark lines in reflected lights caused by changes in the glucose level detected by the sensor [45, 46]. Recent developments are focused on improving sensitivity by surface alteration [47, 48].

Another type of optical method is the fluorescence technique, in which the Stokes shift theory underpins the fluorescence technique. A wavelength alteration is produced upon the absorption at a certain energy level radiation, resulting in the emission of a particular fluorescent light. Fluorophores are specific molecules that bind to the glucose, leading to fluorescent light emission relative to glucose concentration in the analyzed sample [49]. However, since the interaction between glucose and fluorophores molecules is needed, applications will need physical samples such as blood [50], tears and saliva [51], and transdermal glucose from buffer solution [52].

2.3.6 Metabolic Heat Conformation (MHC)

MHC technique measures glucose levels by assessing the physiological parameters of metabolic heat and local oxygen availability [53]. MHC considers glucose metabolic oxidation, which generates heat as a byproduct that correlates with oxygen and glucose levels in the organism. Heat can be transferred in the form of convection, radiation or evaporation. Radiation and convection heat are related to skin and atmospheric temperatures, while evaporated heat is the sum of skin evaporations [54]. The sensor would register the following parameters: hemoglobin (Hb), blood flow rate, thermal output, and oxyhemoglobin concentration (O_2Hb). They are determined by multi-wavelength spectroscopy, fingertip temperature, ambient and background radiation. They are measured in a fingertip. The data are then evaluated by various statistical tools such as discriminant, regression, and multivariate analyses. However, this technique is often susceptible to temperature fluctuations and sweat intrusion.

2.3.7 Reverse Iontophoresis (RI)

RI is a minimally invasive technique circulating a minor electrical current at the skin surface to reach the ISF. The current is mainly formed by the movement of sodium ions which causes the ISF to flow convectively or electro-osmotically, allowing for the movement of glucose molecules from the anode to the cathode [44]. A glucose sensor measures glucose levels at the cathode via the enzymatic approach.

RI is one of the most well-researched glucose tracking systems. However, the technology has some drawbacks such as skin irritation, susceptibility to sweating, and low accuracy in measuring rapid changes in glucose content [55].

3 Commercial Non-invasive Glucose Meters

3.1 Glucowatch®

GlucoWatch® is a non-invasive automatic glucose monitoring device worn on the wrist, similar to a Watch Fig. 2. The software can monitor glucose concentration trends in patients with diabetes and has been accepted as a supplement to traditional BG meters in monitoring diabetic patterns. GlucoWatch® uses iontophoresis.

This procedure removes ISF from the skin's surface to quantify glucose levels in the pH range of 7.2–7.4. The process starts with a 300 μA electric current that passes at the back of the unit between two electrodes in contact with the skin. The electric current extracts the ISF and transports it to two storage disks that act as the cathode and the anode. GlucoWatch® can measure a maximum of six readings every hour and notifies the user if glucose levels deviate by more than 35% from the acceptable range. One of GlucoWatch®'s main drawbacks is its need for frequent recalibration using the pricking process, making it costlier for the user. Since the device uses conductivity sensors and thermo-transducers, the accuracy of its measurements can be influenced by changes in both skin temperature and perspiration. GlucoWatch® detects glucose 15 min later than normal enzymatic measurement approaches. Other drawbacks of GlucoWatch® include prolonged warm-up time, skin rashes, and sweating, which led to the product's removal from the market in 2008 [56].

Fig. 2 The Biographer®: non-invasive glucose monitoring device [56]

3.2 *GlucoTrack*™

Integrity Applications Ltd created GlucoTrack™, a real-time non-invasive glucose monitoring system Fig. 3. The device can detect BG concentrations by employing three non-invasive glucose monitoring techniques: electromagnetic, ultrasonic, and heat capacity.

Because of the convergence of various methods, GlucoTrack™ has very high accuracy and precision. It is also capable of reducing noise by minimizing the influence of interferences. The device consists of a monitor with a personal ear clip (PEC) attached to the earlobe. The PEC is outfitted with sensors and a calibration system, allowing for accurate measurement of BG concentration. The ample blood flow that the earlobe receives makes it a highly accessible location and a preferred candidate for BG measurement. The device is also easy to use in that it does not interfere with the user's daily tasks. The unit must be calibrated against intrusive post-prandial and basal BG references before its use. However, the calibration is only accurate for a single month. It has a good level of efficacy in clinical trials, and the findings are compared to most glucose analyzers and glucometers on the market. The product has the advantage of being lightweight, portable, and comfortable for patients. However, it will only be commercialized once the manufacturer is able to increase the efficiency of its calibration technique and refine its algorithm for better handling of data [57].

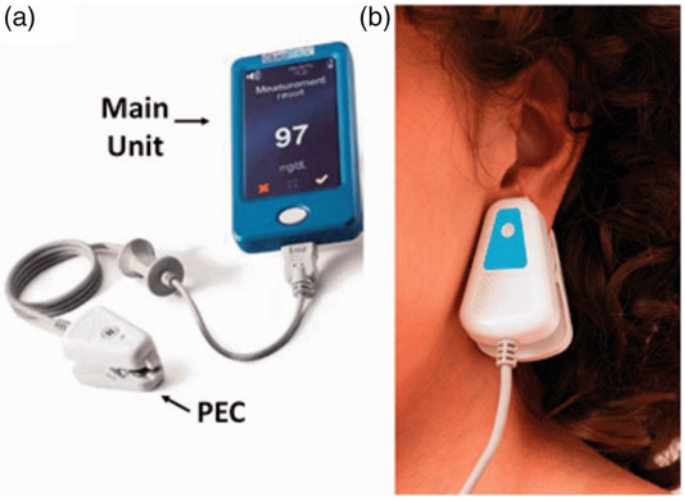

Fig. 3 GlucoTrack™: non-invasive monitoring device [57]

3.3 Abbot FreeStyle® Libre

Abbott FreeStyle® Libre was granted CE Mark on September 3rd, 2014, and it is currently being used in several countries around the world Fig. 4. The FreeStyle system does not require any finger prick for calibration. It only simply requires the user to wear it for 14 days at the back of the upper arm.

Glucose levels are measured by the minute in ISF via a 5 mm × 0.4 mm needle implanted subcutaneously by an applicator held in place with an adhesive material. However, when BG levels rapidly fluctuate, the levels of ISF glucose are not reliable in that they do not correctly match the level of BG. A finger prick measurement by standard glucometer is needed in this situation and hypoglycemic events or when the symptoms are inconsistent with the device's measurements. Abbott FreeStyle® Libre can require about an hour to equilibrate before obtaining the glucose measurement, which takes a fraction of a second. The device will store a maximum of 90 days of data and can accurately predict where BG levels are heading [58].

Fig. 4 Abbot FreeStyle® libre: glucose monitoring system [58]

3.4 Medtronic Guardian™

The Medtronic Guardian™ Sensor is a CGM sensor worn on the back of the user's arm or the abdomen. The FDA approved the technology as the first hybrid closed loop (HCL) insulin delivery system ever created. Individuals wear the Guardian™ Sensor for up to 7 days. Guardian™ Sensor covers 30 days of sensor wear to ensure that patients with diabetes receive safe and valid measurements. The unit is connected to software that obtains data from the Medtronic diabetes management system and generates a dataset that physicians can use to track the success of their patients.

4 Sensors in Development

Numerous scientific centers and universities are encouraged to develop novel methods for non-invasive glucose monitoring. The Ulsan National Institute of Science and Technology (UNIST) focuses on designing soft contact lenses for glucose monitoring. In addition, Infratec and MIT reflect novel paths that other organizations might further explore. Moreover, while some groups continue to investigate NIR/MIR spectroscopy technologies, others have begun to consider other options. In this regard, it is worthwhile to note the work of Siegel et al. at Caltech [59–61]. Over the years, they have made steady progress using millimeter waveguides and achieving interesting outcomes with a solid association with the conventional invasive approach in rodents and humans [59, 60]. Furthermore, the research conducted at the University of Western Ontario [62] is unique, though solely theoretical at this stage. They also began investigating the use of nanoparticles in conjunction with the fluorescence-resonance energy-transfer principle, aiming for a higher accuracy level in detecting glucose levels in tears. Moreover, a recent study by Hanna et al. shows promising results in the field of non-invasive glucose monitoring based on an electromagnetic diabetes monitoring device (eDiamond©). A team of researchers at the American University of Beirut proposes a highly accurate, non-invasive continuous glucose monitoring wearable multisensory system [63]. The unique electromagnetic topology of the system is inspired by the human vasculature's anatomy, which allows the generation of highly sensitive responses Fig. 5. The proposed sensors have been tested on blood, tissues, and diabetic rodents, as well as in clinics. During clinical experiments, non-invasive measuring findings revealed a high association (>0.9) between blood glucose levels and the physical parameters with no time lag.

Furthermore, their proposed wearable device detects hypo- and hyperglycemic differences wirelessly and with high accuracy. To sum up, their modules are engineered to reach several body positions simultaneously, paving the way for the construction of an artificial pancreas in a closed-loop system.

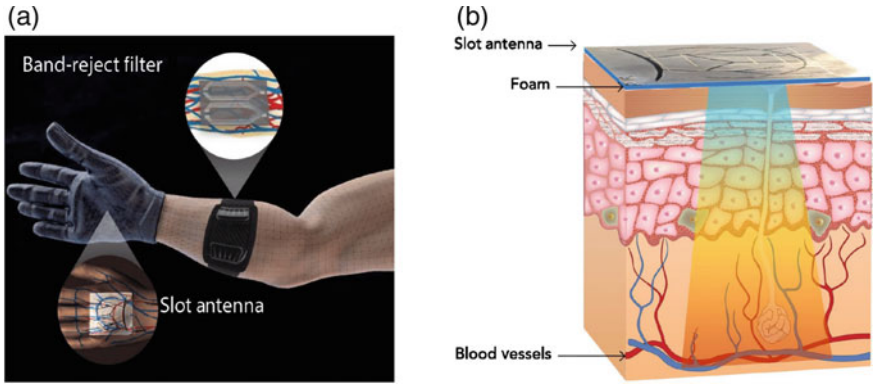

Fig. 5 eDiamond©: a noninvasive continuous glucose monitoring wearable multisensory system inspired by the human vasculature anatomy [63]

5 Glucose Monitoring Informatics (GMI)

Extensive research is underway to advance algorithms that improve sensor sensitivity, accuracy and performance, facilitate data readability, and make up for possible disturbances and confounders such as temperature, sweat, blood perfusion, and tissue scattering. Such algorithms are also applied in the engineering of closed-loop systems in automated insulin pumps for patients with diabetes. These algorithms are either corrective or predictive. On the one hand, corrective algorithms suppress noise distortion and minimize other confounding variations to improve the signal's quality. On the other hand, predictive algorithms forecast potential glucose levels or improve current assessments based on many datasets [46].

6 Tools and Standards for Assessing Accuracy

Testing the accuracy and efficacy of glucose detection systems can be done through various methods, protocols, and criteria. Metric measurements for evaluating accuracy include the mean-average-relative-measurement (MARD) and the error grids. The standard ISO 15197 (refer to the official website for more details: https://www.iso.org/obp/ui/#iso:std:iso:15197:ed-2:v1:en) is widely employed around the globe to specify the quality standards, criteria, and parameters that glucose measurement devices must meet to be suitable for use in humans. The ISO guidelines allow national authorities to determine whether a specific device is appropriate for commercialization. The United States follow their own unique set of rules and criteria. The presence of such guidelines encourages researchers to focus on specific areas of interest, which explains why some technologies lag behind while other more accurate and advanced technologies blossom.

7 Conclusion

With about 7.8 million new cases diagnosed each year, diabetes mellitus is becoming more and more common worldwide. The most critical aspect of diabetes treatment is monitoring and controlling BG. Patients with well-controlled BG levels are at a lower risk of developing debilitating or fatal diabetic complications, thus allowing them to lead healthier lives. Many scientific attempts have been advanced to create a simple and accurate measuring sensor to detect BG. Patients with diabetes can regularly track their BG levels thanks to the new painless, non-invasive glucose screening. Despite continuous technological advances in non-invasive glucose monitoring, extensive research is warranted for accurate glucose monitoring. Sensitivity to variables (body temperature, environmental temperature, sweating, etc.) that fluctuate in everyday life can limit wearable devices. Current non-invasive glucose tracking devices, such as the ones discussed in this chapter, which are now available in the consumer technology industry, may provide screening and diagnosis of disease and substantially affect health. Yet, will this be enough to monitor the glucose level and fight the disease closely? The response would most likely be affirmative for many. However, a modern legislative system with technical development is still in progress for those who need constant surveillance and precise data. Owing to many shortcomings in the hardware and applications currently in use, poor sensitivity, low precision, and interference continue to be the biggest obstacles. However, with the unfolding of innovations and the continued development of existing ones, researchers are certain that the emergence of a truly non-invasive glucose meter is only a matter of time.

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Frédéric Harb is an associate professor in Biophysics at the Lebanese University—Faculty of Sciences since 2014. He obtained his Ph.D. on Brownian diffusion and electrophoretic mobility of a model membrane protein inserted in a supported lipid bilayer (Aix-Marseille University, 2012). He is responsible for several courses at the faculty. He acts as the vice-coordinator for the Neuroscience Master and the deputy director of the faculty of Sciences at Byblos campus (Lebanon). He focuses his work on the biophysical parameters of biological membranes and, more recently, the myelin sheath. Moreover, his current interdisciplinary research is focused on diabetes and its complication. He authored, till now, more than 10 publications in peer-reviewed journals.

William S. Azar graduated from the American University of Beirut (AUB) with a BS in Biology and holds a Master's degree in Physiology and Biophysics from Georgetown University. William is currently in his second year of Medical School at Georgetown University. William has developed a strong interest in diabetes and metabolism and has participated in several research projects in the AUB diabetes program. He is currently exploring the role of NETosis in the pathogenesis of diabetic kidney disease in a basic science laboratory at Georgetown University.

Dr. Hilda E. Ghadieh graduated from the University of Balamand with a Bachelor of Science in Biology (B.S.) and Master of Science in Biology (M.S.), concentration Immunology. Dr. Ghadieh earned her Doctor of Philosophy (Ph.D.) degree in Biomedical Sciences-Molecular Medicine from the University of Toledo, College of Medicine and Life Sciences, USA. During her 5 years of pre-doctoral studies, Dr. Ghadieh garnered several impactful observations related to diabetes and its cardiometabolic manifestations. She has delineated the key role of insulin clearance in insulin resistance by using a broad range of in vivo and ex-vivo phenotyping methods. To further assess the unifying underlying mechanisms linking non-alcoholic fatty liver disease to atherosclerosis, Dr. Ghadieh pursued a post-doctoral research fellowship-in cardio-metabolic disease at Ohio University, Department of Biomedical Science, Heritage College of Osteopathic Medicine, Ohio, USA. Currently, she is a research associate at American University of Beirut, Faculty of Medicine, studying the pathogenesis of diabetic kidney disease while linking it to other metabolic derangements. In these processes, Dr. Ghadieh has developed multiple collaborations with national and international laboratories that enabled her to publish several manuscripts in reputable refereed journals, as attested by serving as the sole first author on 6 papers, and as a first co-author on 5 others in addition to co-authoring 10 other manuscripts, and many are still in progress. This intellectually stimulating environment allowed her to receive numerous awards and honors. Dr. Ghadieh attended major scientific meetings where she had the privilege to give oral talks and present posters. Moreover, Dr. Ghadieh has been providing mentor-based training for numerous undergraduate, graduate, and medical students, ensuring the best training for her mentees. Furthermore, Dr. Ghadieh has developed an expertise in writing manuscripts and grant proposals. Thus, she reviews papers for peer-review journals and serves as an editorial board member on several of them.

Rachel Njeim graduated from the Lebanese American University with a PharmD degree and holds a Master's degree in Pharmacology and Toxicology from the American University of Beirut (AUB). Rachel is currently pursuing a Ph.D. in Biomedical Sciences at AUB, majoring in Physiology and Pharmacology in the hopes of establishing a research-academic career. Medical research allows Rachel to contribute to the advancement of science in identifying novel approaches to treat several chronic diseases with a special emphasis on diabetes and diabetes-associated complications. She is currently exploring the reno-protective role of mesenchymal stem cells in diabetic kidney disease, focusing on NETosis. Her degree has yielded 8 peer-reviewed articles in international journals and a book chapter in the most prestigious cancer book, Cancer Medicine.

Youssef Tawk is an Associate Professor in the ECE Department at the American University of Beirut, Lebanon. Dr. Tawk received the Ph.D. degree from the University of New Mexico, Albuquerque, NM, USA, in 2011, the master's in engineering degree from the American University of Beirut in 2007 and the Bachelor of Engineering degree with highest distinction from Notre Dame University Louaize in Fall 2006 where he served as the valedictorian of his graduating class. Throughout his education and career, Dr. Tawk has received many awards and honors such as the 2018 and 2014 Science and Technology Innovation award for his patents on reconfigurable microwave filters and optically controlled antenna systems in addition to the 2011 IEEE Albuquerque Chapter Outstanding Graduate award. He has more than 150 IEEE journals and conference papers many of which received finalist positions and honorable mentions in several paper contests. He is the co-author of two books, one book chapter, and co-inventor on 7 US patents. His research interests include reconfigurable RF systems for microwave and mm-wave applications, cognitive radio, optically controlled RF components, phased arrays, and phase shifters based on smart RF materials.

Joseph Costantine is an Associate Professor at the Electrical and Computer Engineering Department at American University of Beirut and a World Economic Forum young scientist. He received his doctorate from the University of New Mexico in 2009, his masters (M.E.) degree from American University of Beirut and his bachelor's degree from the second branch of engineering faculty at the Lebanese University. He has 11 Provisional and Full U.S. patents. He has published 2 books, 1 book chapter and more than 150 Journal and conference papers. His research interests reside in reconfigurable antennas, cognitive radio, RF energy harvesting systems, antennas and rectennas for IoT devices, RF systems for biomedical devices, wireless characterization of dielectric material and deployable antennas for small satellites. He is a senior member of the IEEE since June 2019 and an associate editor for the IEEE Antennas and

Wireless Propagation Letters since July 2018. He received many awards and honors throughout his career, including the Air Force summer faculty fellowship with Kirtland's space vehicles directorate in NM, USA, the 2017 first prize at the Idea-thon of international healthcare industry forum, the 2019 excellence in teaching award from American University of Beirut, and the 2020 distinguished young alumni award from the School of Engineering at the University of New Mexico.

Rouwaida Kanj received the M.S. and Ph.D. degrees in electrical engineering from the University of Illinois Urbana-Champaign in 2000 and 2004, respectively. She is currently a tenured Associate Professor at the American University of Beirut. From 2004–2012 she worked as a research staff member at IBM Austin Research Labs. Her research focuses on advanced algorithmic research and development and smart analytics methodologies for Design for Manufacturability Reliability and Yield, emphasizing statistical analysis, optimization, and rare fail event estimation for microprocessor memory designs and machine learning applications Very Large Scale Integration. More recently she is also involved in memristor-based memory design and reliability and the design of reliable circuits and systems for healthcare and in-memory compute. This is in addition to her earlier work on noise modeling and characterization of CMOS designs. Dr. Kanj was a recipient of three IBM Ph.D. Fellowships, is the author of more than 81 technical papers, 36 issued US patents and several pending patents. She received an outstanding technical achievement award and 6 Invention Plateau awards from IBM. She received the prestigious IEEE/ACM WILLIAM J. MCCALLA ICCAD best paper award in 2009, and two IEEE ISQED best paper awards in 2006 and 2014, and the IEEE ICM best paper award in 2020. In 2018 her work on statistical yield analysis methodology was nominated for the ACM/IEEE Richard Newton Award. She is currently a senior member of IEEE and serves on the technical program committees of several IEEE of several IEEE conferences. Dr. Kanj received the M.S. and Ph.D. degrees in electrical engineering from the University of Illinois Urbana-Champaign in 2000 and 2004, respectively. She is currently a tenured Associate Professor at the American University of Beirut. From 2004–2012 she worked as a research staff member at IBM Austin Research Labs.

Assaad A. Eid is a professor in the Department of Anatomy, Cell Biology and Physiological Sciences at the Faculty of Medicine, American University of Beirut. As a research scientist, Dr. Eid is involved in internationally funded, cutting-edge basic, translational, and clinical science research in diabetes and diabetes-induced complications. Dr. Eid research activities are part of advancing efforts to find novel treatments that identify a potential cure for the most recognized debilitating complications of diabetes. Dr. Eid research work ranges from the basic, translational to the clinical aspects of the disease and combines a series of cellular, molecular, genetic behavioral, and bioengineering work approaches in cells, animal models of type 1 and type 2 diabetes and human tissues. Dr. Eid is also an entrepreneur scientist, who in collaboration with multidisciplinary colleagues co-founded 2 startups based in the United States of America "Teucer Biotech" and "eDiamond" focusing on developing medical diagnostic tools for kidney diseases and biomedical devices for glucose monitoring, respectively. Besides leading one of the highly funded research activities in Lebanon and the Middle East, Dr. Eid co-founded in 2017 the "AUB Diabetes" to integrate scientific and clinical knowledge to enhance our understanding of the underlying pathologies of diabetes from both translational (bench to bedside) and clinical perspectives. In addition to several national and international scientific awards, Dr. Eid achievements in research and entrepreneurship are recognized in more than 75 peer-reviewed publications and book chapters, in addition to 4 patents. Besides, Dr. Eid was appointed in 2016 as Visiting Professor at Paris Descartes University, Paris, France and was appointed as international collaborator in the Neuronetwork for Emerging Therapies at the University of Michigan at Ann Arbor in 2019. Dr. Eid's numerous honors include his selection to join the Interacademy Medical Panel—Young Physician Leaders and a young affiliate member of The World Academy of Sciences for the developing world. In addition, he received the first prize in the startup competitions of the Beirut International Healthcare Industry Forum. Among Dr. Eid's greatest accomplishments is his training of young scientists. Eight scientists have received their Ph.D. degrees under him. He has also trained 8 postdoctoral fellows in his laboratory. More than 40 Master students have trained under him to major in physiology, human morphology, neurosciences, or biomedical engineering.