Alexandria Engineering Journal 89 (2024) 224–243

Contents lists available at ScienceDirect

Alexandria Engineering Journal

journal homepage: www.elsevier.com/locate/aej

REVIEW

Wearable devices for glucose monitoring: A review of state-of-the-art technologies and emerging trends

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ARTICLE INFO

Keywords:
Continuous glucose monitoring
Commercial CGM
Artificial intelligence
Glucose wearable sensors
Non-invasive glucose monitoring
Diabetes management

ABSTRACT

Diabetes is a chronic condition that is characterized by high blood glucose levels and can cause damage to multiple organs over time. Continuous monitoring of glucose levels is essential for both diabetic and non-diabetic individuals. There have been major developments in glucose monitoring technology over the past decade, which have been driven by research and industry efforts. Despite these significant advancements, the area of glucose biosensors still faces significant challenges. This paper presents a comprehensive summary of the latest glucose monitoring technologies, including invasive, minimally invasive, and non-invasive methods. Subsequently, we bring together the electronic components, wireless communication technologies, and energy harvesting opportunities, along with the limitations and challenges associated with current glucose monitoring solutions. This is followed by highlighting the potential integration of health records generated by continuous glucose monitors and artificial intelligence (AI) techniques to define precise diabetes management protocols. This integration achieves accurate results with constrained prediction horizons employing a time series of continuous glucose readings. The paper emphasizes the need for further advancements in glucose monitoring technology to improve diabetes management and address the critical need in clinical practice for improved glucose monitoring technologies with translational implications.

1. Introduction

The International Diabetes Federation (IDF) estimates that 537 million people worldwide suffer from diabetes [1]. It was reported that by 2045, 700 million people are anticipated to be dietetics worldwide [2]. Diabetes poses significant health risks due to its high prevalence, diverse complications, and absence of a straightforward cure [3]. Over the past two decades, diabetes has surged into the top ten leading causes of mortality, marking a staggering 70% increase since 2000. It is directly responsible for 1.5 million deaths annually and is linked to the highest increase in male fatalities among the top 10 [4]. Conventional medical opinion classifies the consequences of diabetes into micro-vascular and macro-vascular, including retino/nephro/neuro-pathy, coronary heart disease, cerebro-vascular disease, and peripheral vascular disease as major causes of death and disability [5]. Additionally, consistent evidence from large-scale population research shows that diabetes is associated with an increased risk of developing cancer and a higher likelihood of dying from the disease [6]. As a result, there have been numerous efforts put into studying diabetes from a variety of perspectives [7]. Moreover, diabetes in pregnancy poses significant risks to both mother and baby, leading to complications such as preeclampsia, preterm delivery, and neonatal issues [8]. Achieving euglycemia during pregnancy is crucial to mitigate these risks, as poor glycemic control increases the likelihood of adverse outcomes.

There are two major forms of diabetes: type 1 and type 2. Type 1 diabetes (T1D) is caused by the pancreatic insufficient insulin production [9]. Contrarily, type 2 diabetes (T2D) is mostly brought on by sufferers' increasing insulin resistance and decreased insulin responsiveness, which results in inefficient utilization of insulin [3].

Self-monitoring of blood glucose (SMBG), involving the periodic measurement of blood sugar levels, has been a conventional method employed by for managing diabetes. Diabetics have continued to depend on SMBG, which relies on a variety of enzyme-electrode strips. However, self-testing glucose strips require a disturbing and invasive blood sample from fingertips, which lowers patient satisfaction and prevents them from providing frequent measurements. Moreover, the frequent occurrence of blood draws makes it more challenging for patients' injuries to recover in a reasonable timeframe. In the SMBG scheme, the

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https://doi.org/10.1016/j.aej.2024.01.021
Received 21 June 2023; Received in revised form 24 December 2023; Accepted 4 January 2024
Available online 25 January 2024

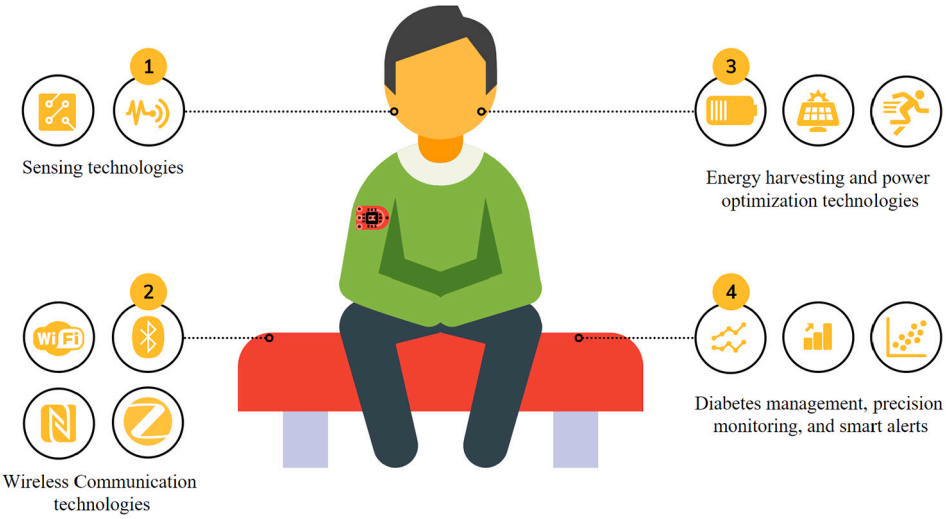

Fig. 1. Conceptual diagram which shows different research areas for wearable devices which are mainly sensing technology, energy management, communications and data analysis.

logbooks were used to manually document glucose readings, insulin dosages, nutrition, and activity [10].

After the SMBG era, lasted from 1980s to 2000s, the medication for diabetes has seen a radical transformation thanks to continuous glucose monitoring (CGM). In the past twenty years, CGM has proved its ability to introduce a revolutionary solution for diabetes management. It has paved the way to precision monitoring for diabetics [11]. In CGM, relevant metabolic indicators can be continually monitored to enable prompt symptoms identification and preventative interventions. Over the years, scientists have shown that the glucose content of several biofluids correlates with blood glucose levels. They have been shown that sweat, urine, interstitial fluid (ISF), tears, breath, and saliva of these methods exhibit linear correlations, which is highly beneficial. This correlation makes it easier to develop simpler, safer, more convenient, and less infectious CGM devices. These biofluids have potential application as viable analytes for non-invasive glucose monitoring [12]. The integration of non-invasive monitoring devices and patient-oriented protocols will enhance the viability of such systems, making them more resilient to adoption in both medical and commercial domains. [13].

Development of an accurate, safe, miniaturized, long-lasting, and patient-friendly CGM is not an easy process. It requires the integration of several aspects of science to address many challenges (Fig. 1). The miniaturization and slim design requirements that are needed in wearable technology impose strict limitations on the power supply, which in turn affects the precision and longevity of the device. The integration of energy harvesting techniques with low-power utilization and high energy efficiency has the potential to considerably enhance the operational lifespan of wearable devices. [14]. Some substrates that have been shown to be effective in implementing these form factors include removable tattoos, soft polymers, and hybrid structures integrating flexible printed circuit boards (PCBs) with conventional ICs.

A reliable source of energy is crucial to the functionality of many CGM devices. They need to be small and lightweight to be practical for extended periods of use. The majority of CGM devices, however, need cumbersome batteries to function. This conventional approach inevitably increases the size and weight of gadgets, reducing their portability and autonomy. Energy harvesters are a novel and promising idea for powering independent CGM devices. Therefore, there is an increasing need for cutting-edge energy supply systems that can provide reliable electricity without requiring regular recharging, as is the case with conventional batteries or devices.

With the advent of CGM devices, many methods have been developed for predicting blood glucose concentrations and their consequences [15]. Such methods allow the patient to take extra precautions, such as eating carbohydrates or pausing insulin, before the onset of hypoglycemia. Moreover, they enable the installation of smart alarms that would facilitate the creation of analyses to predict the impacts of the patient's lifestyle or therapeutic decisions. Physiological models were the norm until recently when data-based methods and hybrid models (which included features of both) entered the scene [16]. AI-based medical advancements are quickly turning into clinically effective solutions. Deep neural networks (DNN) can handle massive amounts of information from wearable, cellphones, and other monitoring devices in several medicine-related fields [17].

The several facets and applications of CGM have been reviewed and addressed in several publications. The outcomes of these studies are relatively insufficient and scattered. Table 1 illustrates a comparison between previous studies about the CGM system including this study. The comparison takes into account several aspects such as sensing principles, energy harvesting, wireless communication, wireless communication, diabetes management schemes, and commercial systems.

Herein, we explore the emerging trends achieved in developing wearable and continuous monitoring glucose sensors including:

1. The various glucose sensing mechanisms and the key elements of these sensors.
2. Sensor energy storage options describing the possibility of self-powered sensors utilizing state-of-the-art energy harvesting and power optimization schemes.
3. The essential electronic components for the signal path from the glucose sensor to the smartphone passing by conditioning circuits, microcontroller, power source, and its possible energy harvesting schemes.
4. The low-power wireless communication protocols enable the transmission of collected measurements in a secure and efficient way.
5. How CGM could be integrated with AI to enhance a wide range of diabetes care systems, from diabetes diagnosis, complications prevention, and glycemic control and treatment process including applications, equipment, and platforms that assist patients, doctors, and healthcare organizations.
6. A survey for the commercially announced CGM systems for both corporates and start-ups comparing their performance and different features.

2. Wearable biosensors role in bio-molecules sensing

Biosensors are analytical devices that integrate biological components with physicochemical sensors to detect specific biological ana-

Table 1
Comparing this review with relevant CGM work, based on various CGM aspects.

Paper	Title	Sensing principles	Electronic components	Wireless communication	Energy harvesting	Diabetes management	Commercial systems	Challenges and future perspective
[18]	Electrochemical glucose sensors in diabetes management: an updated review (2010–2020)	★ (electro-chemical)	⊗	⊗	★	⊗	☑	☑
[19]	Wearable non-invasive epidermal glucose sensors: A review	★	⊗	⊗	⊗	⊗	⯪	☑
[20]	Artificial Intelligence for Diabetes Management and Decision Support: Literature Review	⊗	⊗	⊗	⊗	☑	⊗	★
[21]	Comprehensive Review on Wearable Sweat-Glucose Sensors for Continuous Glucose Monitoring	☑ (Sweat focused)	⊗	☑	⊗	⊗	⯪	☑
[22]	Continuous glucose monitoring systems - Current status and future perspectives of the flagship technologies in biosensor research	☑	⊗	⊗	⯪	⊗	★	☑
[23]	An Overview of Wearable and Implantable Electrochemical Glucose Sensors	☑	⊗	⊗	⊗	⊗	⊗	★
[24]	Glucose biosensors in clinical practice: principles, limits and perspectives of currently used devices	☑	⊗	⊗	⊗	⊗	☑	☑
[25]	Non-Invasive Blood Glucose Monitoring Technology: A Review	☑	⊗	⯪	⊗	⊗	⊗	★
[26]	Review—Glucose Monitoring Sensors: History, Principle, and Challenges	☑	⊗	⊗	⊗	⊗	☑	☑
[27]	Smartphone-Based Electrochemical Systems for Glucose Monitoring in Biofluids: A Review	⯪	⊗	☑	★	⊗	⯪	☑
[28]	Subcutaneous amperometric biosensor for continuous glucose monitoring in diabetes	☑ (ISF focused)	⊗	⊗	⯪	⊗	☑	☑
[29]	Transforming Diabetes Care Through Artificial Intelligence: The Future Is Here	⊗	⊗	⊗	⊗	☑	⊗	★
This study	Wearable Devices for Glucose Monitoring: A Review of State-of-the-Art Technologies and Emerging Trends	★	☑	☑	☑	☑	☑	☑

☑ : Aspect is covered to the core of the paper.
★ : Aspect is sufficiently covered in the paper.
⯪ : Aspect is shallow-covered in the paper.
⊗ : Aspect does not exist in the paper.

lytes. Wearable biomolecules sensing has made it possible to measure and diagnose diseases and monitor patients continuously by providing data on biomarkers in biofluids, such as electrolytes (Na^+, K^+, Ca^{+2}, and Cl), metabolites (glucose, uric acid, and lactate), pH, vitamins, hormones (cortisol, for example), and immuno-detections (cytokines) [30]. Inspired by Organs-on-Chip technology, wearable biosensors leverage microenvironment regulation and tissue-specific functionalities to monitor bio-molecules in real-time [31]. Wearable bioanalytical innovations have the potential to be a viable substitute for cumbersome and costly bio-samples analysis, since they enable the non-invasive or minimally invasive assessment of molecular biomarkers in various biofluids. Although blood is the most well-understood sample for diagnostic measures, non-invasive or minimally-invasive wearable sensor systems find it appealing to target other biological fluids such urine, breath, tears, sweat, saliva, and interstitial fluids (ISF) since they are easier to access. The advantages of wearable biomarker sensing platforms are found in their cost-effectiveness, compact nature, adaptability, flexibility, dedication to provide continuous tracking, instant response, reduced sample size requirements, and greater sensitivity to low levels of biomarkers as compared to traditional laboratory methods. Biosensors play a crucial role in early-stage detection of biomolecules associated with diseases, such as interleukin-10 for heart diseases and human papilloma virus [32].

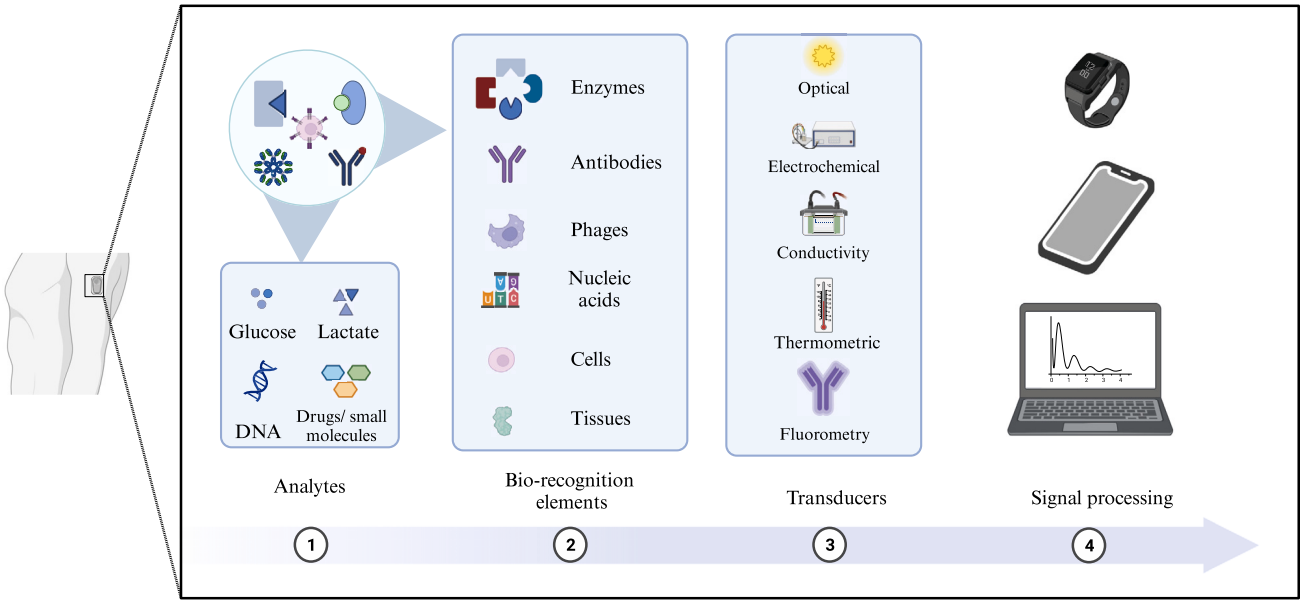

Fig. 2. Core Components of Biosensors. This schematic diagram depicts the fundamental components common to biosensors utilized across various applications: Recognition Element: Typically, a biomolecule, enzyme, antibody, or nucleic acid sequence that interacts specifically with the target analyte, initiating the sensing process. Transducer: Converts the biological response generated by the recognition element into measurable signals (electrical, optical, or other), enabling quantitative analysis. Interface Layer: Facilitates and enhances the interaction between the recognition element and the target analyte, crucial for achieving specificity and sensitivity in detection. Signal Processing Electronics: Components responsible for interpreting and processing the transduced signal, transforming it into quantifiable analytical data. Created with Biorender.com.

In the realm of flexible electronic devices, significant progress has been made in both fabrication techniques and in the use of micro/nanostructured assets [33]. These advancements have demonstrated considerable promise in various feasible domains, such as biological monitoring, smart automation, smart displays, and energy scavenging.

Biosensors can be classified into 5 main categories. Enzyme-based biosensors, also known as enzymatic biosensors, are designed to utilize enzymes to detect specific biomolecules, such as glucose, ethanol, and cholesterol. On the other hand, tissue-based biosensors use living tissues to detect the presence of certain biomolecules or toxins. Enzymatic glucose biosensors commonly employ enzymes like glucose oxidase (GOx) or glucose dehydrogenase (GDH) to catalyze glucose oxidation reactions. This catalysis generates detectable signals proportional to the glucose concentration, providing high specificity and sensitivity in glucose detection. On contrast, non-enzymatic biosensors operate without specific enzymes and instead use nanomaterials such as metal nanoparticles, carbon-based materials, or conducting polymers to facilitate glucose oxidation [34]. These sensors offer advantages like improved stability, reduced interference, and prolonged sensor lifespan compared to enzymatic counterparts.

Another type of biosensors is immunosensors which can detect the interaction between antibodies and antigens, making them useful for detecting specific biomolecules related to diseases or pathogens. Ionic liquids (ILs) are increasingly used in immunosensors due to their low volatility, thermal and chemical stability. Increasing the sensitivity of immunosensors is a key use for ILs. In terms of the benefits of employing adapted ILs include its consistency, reuse capability, and stability [35].

DNA biosensors are designed to detect specific DNA sequences, making them valuable for genetic testing and disease diagnosis.

Biosensors employ various technologies, including enzymatic, non-enzymatic, and nanotechnology-based approaches to measure glucose levels in bio-fluids. Beyond glucose monitoring, biosensors exhibit versatility in detecting various biomolecules. By modifying the sensor's biological recognition element, such as enzymes or antibodies, biosensors can detect diverse analytes like lactate, cholesterol, ketones, and various metabolites. This multifunctionality opens avenues for wearable devices to expand their scope beyond glucose monitoring, potentially enabling comprehensive health monitoring in real-time.

As shown in Fig. 2, the biosensing process begins with the selection of a specific recognition element tailored to the target biomolecule. This element can be enzymes, antibodies, aptamers, or other biological molecules that interact selectively with the analyte of interest. In glucose monitoring, enzymes like glucose oxidase or glucose dehydrogenase are commonly used as the recognition element.

Immobilization is a critical step where the selected recognition element is firmly anchored or attached to the surface of the transducer. This fixation is essential to retain the biological activity and specificity of the recognition element while allowing for efficient interaction with the target biomolecule [36]. Immobilization involves employing a sensing material possessing high electrical characteristics that ensures durability, biocompatibility, accessibility to the analytic agent, and a substantial contact area [37]. To stabilize enzymes, various approaches are employed, including physical adsorption based on van der Waals forces, covalent bonding, entrapment in a matrix, deposition on nanostructures, or ionic interactions. A variety of enzymes, including polyphenol oxidase, peroxidase, amine oxidase, and tyrosinase, may be used in the development of this kind of biosensors. The potential to combine sensitivity, selectivity, and rapidity in affordable biological detection methods has led to a variety of research on electrochemical devices and biosensors during the last several decades. Among the immobilization techniques, a novel approach was devised to immobilize hemoglobin efficiently using a nanocomposite of poly(styrene-alternative-maleic anhydride) bonded to 3-aminobenzoic acid (PSMA-g-3ABA) and multi-walled carbon nanotubes (MWCNTs). This technique included the creation of PSMA-g-3ABA/MWCNTs nanocomposite [38]. The nanocomposite film created a conducive milieu for the preservation of the biological activity and natural structure of hemoglobin. Using biocompatible materials such as PFu@(Fe_3O_4), poly(styrene-alternative-maleic acid) (PSMAC), or poly(p-phenylenediamine) PpPDA@(Fe_3O_4), immobilization of biomolecules such as hemoglobin can be achieved to construct nanocomposite/glassy carbon electrode [39,40]. In this case, the immobilized hemoglobin can exhibit preserved bioactivity and retain its natural conformation [41,42].

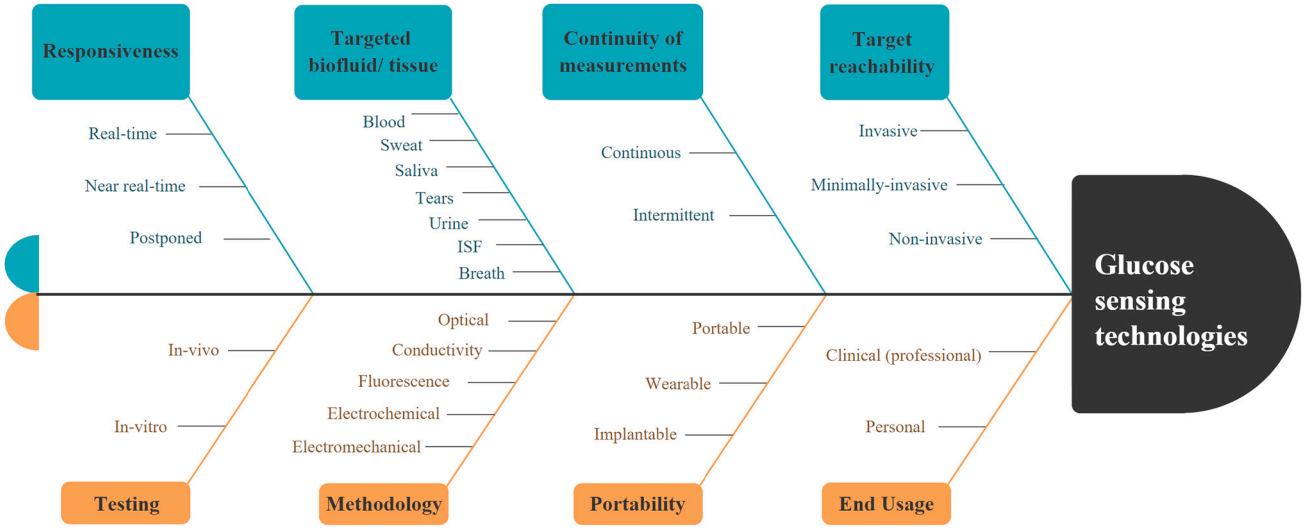

Fig. 3. Taxonomy of glucose sensing technologies.

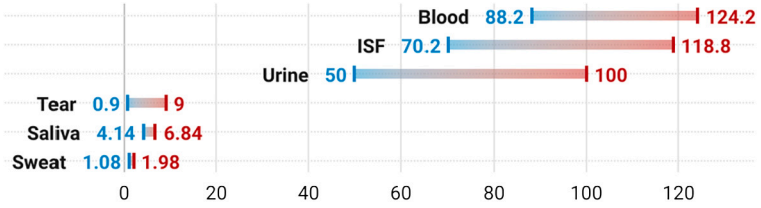

Fig. 4. Glucose concentration ranges in Bio-fluids for healthy individuals (mg/dL). Blood Plasma: Typically maintains glucose concentrations within a range of approximately 88.2 mg/dL to 124.2 mg/dL in fasting conditions. Postprandial levels can transiently rise up to 180 mg/dL. Interstitial Fluid (ISF): Shows glucose levels that closely mirror blood glucose concentrations, with minor delays and variations. Normally ranges from 70.2 mg/dL to 118.8 mg/dL, similar to blood glucose under fasting conditions. Urine: Displays glucose concentrations ranging between approximately 50 mg/dL to 100 mg/dL in healthy individuals. Saliva: Presents glucose levels typically reflecting a lower concentration compared to blood plasma, ranging between 4.14 mg/dL to 6.84 mg/dL in healthy individuals. Tears: Demonstrates glucose concentrations lower than blood plasma, spanning approximately 0.9 mg/dL to 9 mg/dL in healthy subjects. Sweat: Shows glucose levels in a range between 1.08 mg/dL to 1.98 mg/dL in healthy individuals, though concentrations can vary depending on factors such as physical activity and hydration status. These reference ranges are indicative of the normal glucose levels found in different bodily fluids among individuals without underlying health conditions. Variations outside these ranges might indicate potential health concerns or metabolic abnormalities, warranting further clinical evaluation and monitoring.

3. Glucose sensing principles

Historically, Clark and Lyons opened the door for the first glucose sensor by developing an amperometric electrode for the enzymatic detection of blood glucose utilizing glucose oxidase (GOx or GOD) in 1962 [43,44]. A series of improvements for Clark's electrochemical sensor followed the invention, including employing non-physiological electron receptors as redox media rather than oxygen to engage in glucose catalysis passing by applying direct electron transfer (DET) through the enzyme itself instead of the mediator, and finally, the usage of nanoenzymes which offered superior catalytic properties, flexibility, and long-term stability [45].

Non-invasive monitoring technologies have emerged as a promising area for study in the field of blood glucose monitoring. In the following sub-sections, a discussion, and classification for non-invasive glucose monitoring are illustrated (see Fig. 3).

3.1. Classifications of glucose biosensors

There are several classifications for glucose sensors based on different criteria. The primary way to categorize glucose sensors is according to the degree of invasiveness of the sensing devices, dividing them into three categories: invasive, minimally invasive, and non-invasive. Another common practice is to classify blood glucose sensing as either "in vivo" or "in vitro" measurements. Extraction of tissue fluid from humans is performed in an in vitro setting to evaluate glucose levels, with the aim of providing an approximation of glucose levels in whole blood. On the other hand, the in-vivo measuring approach involves applying the device to a living subject and taking readings.

Collecting blood samples for direct access to the electrochemical sensor is traditionally achieved using Finger-prick, which is painful and infectious [46]. This method can be avoided partially or totally thanks to the correlation between the concentration of glucose in blood and the other reachable bio-fluids like ISF [47], urine [48], tear [49], saliva [50] and sweat [51] (Fig. 4). Moreover, many studies showed that the blood itself has several properties correlated to the glucose concentration, such as the blood refractive index, light scattering coefficient, bioimpedance, dielectric constant, loss tangent, permittivity, and conductivity allowing non-invasive glucose measurements [52–56]. Furthermore, the sensing could be based on glucose intrinsic properties like Raman shift, absorption coefficient, specific optical rotation, and complex permittivity changes across the signal path. The permittivity of a sample can change significantly as the concentration of one of its substances varies [57].

3.2. Interstitial fluid (ISF)

Glucose sensing based on the ISF is the most mature CGM technology. The glucose concentration in the ISF is highly correlated with the concentration in blood because of its ability to exchange nutrients with blood through capillaries by diffusion [58]. In ISF-based systems, subcutaneous ISF extraction is a crucial process [59]. The ability to extract epidermal ISF in a less invasive manner has been made possible by a

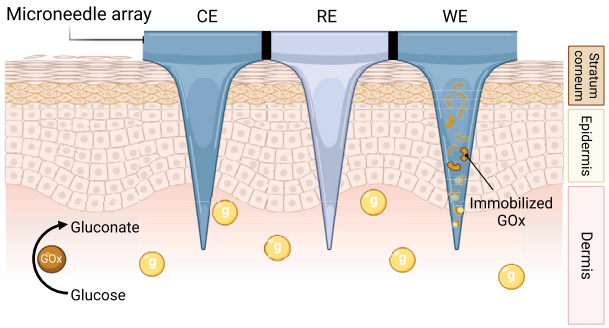

Fig. 5. Common configuration of amperometric microneedle sensors. The sensor's architecture includes an array of microelectrodes that facilitate sensitive and selective measurements of glucose levels. These microelectrodes are coated with specific enzyme coatings or materials that facilitate the oxidation or reduction of glucose molecules, generating electrical signals proportional to the glucose concentration. The system typically involves a working electrode (WE), a reference electrode (RE), and sometimes an auxiliary (counter) electrode (CE). The working electrode plays a pivotal role in catalyzing the electrochemical reactions involving glucose. The reference electrode helps maintain a stable electrochemical potential, enabling accurate measurements. The auxiliary electrode, if present, aids in stabilizing the current during measurements. Created with Biorender.com.

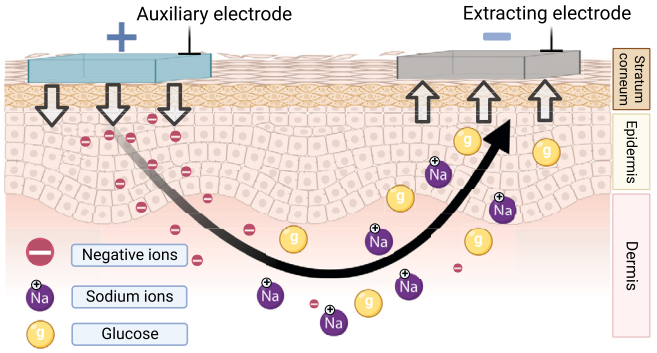

Fig. 6. Extracting Interstitial Fluid (ISF) using the Reverse Iontophoresis (RI) Approach. The diagram illustrates electrodes placed on the skin's surface. The electrodes are utilized to apply a controlled electrical current, facilitating the movement of charged molecules, such as glucose, across the skin barrier. The RI approach exploits the principles of electrochemistry and ion transport to induce the flow of ISF towards the skin's surface. This extracted ISF contains analytes like glucose, enabling non-invasive or minimally invasive glucose monitoring without the need for traditional blood sampling. Created with Biorender.com.

number of approaches such as microneedles (MNs) [60] and reverse iontophoresis (RI) [61].

Originally, MN has been used for painless drugs and vaccine insertion. Instead of insertion, it was used for extraction of the ISF as it is considered a rich resource of biomarkers [62]. Its diameter ranges between 200 and 350 μm, about 2 to 3 times the human hair diameter [63], and less than 1 mm in height. Microneedles can penetrate the outermost layer of the skin, known as the stratum corneum, without causing annoyance. This forms tiny pores, that can be utilized for carrying medications and vaccinations throughout the body. Microneedles have also been used in the fabrication of biosensors for diagnostic of glucose and other bio-analytes, in addition to their use in medication administration [64]. They can be employed to collect ISF and blood, based on the extent of skin penetration. In addition, they can serve as electrodes when placed on the surface of the skin. In the MN array, needles are grouped and employed to serve as working electrode (WE), counter electrode (CE), or reference electrode (RE). Then it is implanted in the skin to reach the ISF as shown in Fig. 5. MN devices can be injected by applying a patch with fingertip force or using an external applicator. MN-based biosensors can be integrated into a wristband-style device (Fig. 8 f, g).

RI has been used in a way that is now significantly better thanks to significant progress in flexible semiconductors and materials engineering. By applying a light current to the surface of skin tissue, RI can collect ISF, then glucose can be detected by an enzyme electrochemical sensor as shown in Fig. 6. The two primary elements in the ISF during typical physiological situations are Na^+ and Cl^-. The epidermis itself will increase Na^+ transportation making Na^+ the predominant carrier due to the negative charges contained on the surface of the skin. When a suitable voltage is supplied to the electrode to generate a mild current Cl^- and Na^+ move towards the skin's outermost layer [65]. The majority of the electroosmotic flow throughout RI travels down preferred, minimal resistance channels that are predominantly connected to hair follicles. Nevertheless, the skin thickness physiology, quantity, and location of follicles change significantly between people or between various areas of the skin, which has a significant impact on the consistency of ISF reached using the RI approach. Furthermore, the limited size as well as the low number of follicles channels may restrict the flow of glucose collection. Besides the skin irritation that could happen in case of long-term exposure to RI, difficulties with RI-based CGM devices result from interference from unwanted glucose streams such as sweat throughout activity and glucose accumulation on the skin, and uneven ISF extraction effectiveness. RI was used for the first time in wearable devices in 2012 by [66]. Bandodkar et al. [67] suggested a patched blood glucose sensor in the form of a tattoo that extracted ISF via RI. Li et al. [68] employed both RI and iontophoresis for CGM and insulin injection respectively creating a closed-loop system. As shown in (Fig. 8e), a transdermal device for glucose monitoring based on ISF extraction with a differential structure to remove the passive sweat effect was proposed by Pu et al. [59]. Chang et al. [69] published a fully integrated CGM watch that used RI to extract ISF.

3.3. Sweat

Sweat is a highly appealing bio-fluid for non-invasive, continuous monitoring systems due to its unique benefits. Besides the presence of the majority of sampling points on the outer surface of the body, continuous availability, simplicity of allocation, and ease of collection devices, it also combines physiologically significant electrolytes and bio-active components. Stick-on sensors applied on the skin need to be very resilient since the epidermis is constantly stretched and bent during the daily workout [70]. There has been a dramatic increase in research and development efforts focused on sweat-based sensors and systems for monitoring health to aid in the treatment of diabetic patients [71]. In the study of, [72] a flexible on-skin sweat-sensing solution that incorporates an elastic battery and an electrochromic panel is presented. It can function without connecting with any other components, the main components of these devices are effective stretchy Ag_2O-Zn batteries, 10 electrochromic displays, and a tiny MCU. The CGM device was based on an enzymatic or potentiostatic electrochemical biosensor. The results of the analysis can be seen instantaneously, directly on the interconnected electrochromic panel. Except for the microprocessor, everything is made using screen printing using elastomeric or silver inks to create the individual components. The sensors are able to detect a number of metabolites and electrolytes in perspiration, including Na^+, pH, glucose, and lactate.

3.4. Optical coherent tomography

Optical Coherence Tomography (OCT) is an imaging technology that uses light waves to capture changes in the refractive index generating high-resolution, cross-sectional images of tissues and structures in the body. As it offers a high signal-to-noise ratio (SNR) and resolution, recently, researchers have been exploring the potential of achieving an

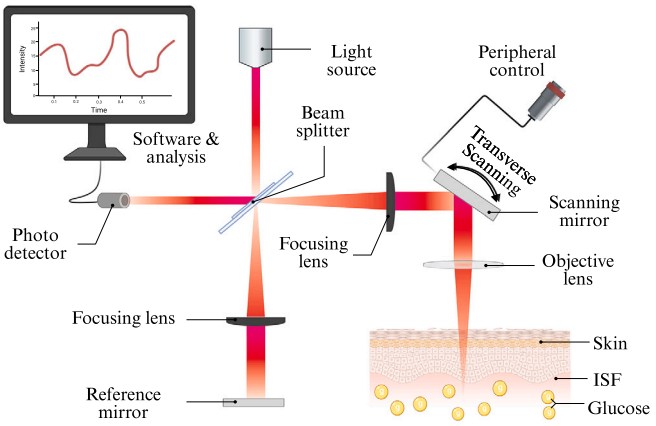

Fig. 7. The basic concept of OCT scanning for CGM. The figure depicts a simplified representation of an OCT system emitting a beam of near-infrared light into the skin. The emitted light interacts with tissue components, and the reflected light signals are captured and processed to generate depth-resolved images of the tissue microstructure.

OCT-based CGM to obtain varying glucose concentrations in a reliable way [73,74].

The basic principle behind OCT for CGM is that glucose absorbs light in a characteristic way, which changes the refractive index of the surrounding tissue. By measuring the changes in the refractive index, it is possible to estimate glucose concentration in the surrounding tissue. As shown in Fig. 7, this is done by comparing the reflected light waves from the tissue to a reference beam, which produces an interference pattern that can be analyzed to extract the glucose concentration [75]. Despite its promising features, OCT for CGM necessitates refined precision due to challenges like motion artifacts and temperature influences, which might affect its accuracy and reliability.

Compared to other CGM technologies, OCT offers several advantages as it is completely non-invasive and does not require any needles or skin pricks, which makes it more comfortable for patients. On the other hand, it still has many constraints like the need for high-precision imaging and signal processing, which can be affected by various factors such as motion artifacts, temperature, and changes in tissue properties [76]. OCT for CGM is still in the early stages of development, and more research is needed to optimize the technology and validate its accuracy and reliability.

3.5. Bioimpedance

The impedance of biomolecules to a current flow is measured using a technique called bioimpedance [77]. Bioimpedance is affected by the insulating, dielectric, or conducting properties of the biological medium. The relationship between glucose fluctuations and bioimpedance has been subjected to research. Bioimpedance variation in blood volume was found to be negatively correlated with glucose content [78]. Bioimpedance has been shown to be a stable and accurate method for estimating blood glucose with an optimal frequency range below 40 kHz [79]. A skin bioimpedance-based CGM device typically consists of sensors, measurement circuitry, and analytical algorithms (see Fig. 8 c). In comparison to existing noninvasive monitoring methods, the approach is more straightforward and cost-effective for prolonged continuous monitoring [80]. However, for applied purposes, the skin's surface is easily influenced by everyday physiological processes or the surroundings. The thickness and moisture level of the tissue must be considered in the electrode's design and the analytical algorithm as well. It should be emphasized that variations in skin's dielectric characteristics can result from a variety of variables, maybe not changes in BG levels.

4. CGM electronic components

In this section, the signal path from the glucose sensor to the smartphone is described (Fig. 9). The description for each block is discussed in the following subsections.

4.1. Analog front end (AFE)

A wide range of glucose sensors is considered to be amperometric sensors, which generate a small current in the range of μA proportional to the variation in glucose concentration. This analog signal requires an interface that has a high transimpedance gain to convert its nature to a voltammetric signal. Then, the signal is amplified, filtered and converted to a digital signal.

AFE serves as a critical component responsible for conditioning and digitizing signals in Continuous Glucose Monitoring systems. An optimal AFE must fulfill multiple criteria: I) providing a wide passband and dynamic range capable of capturing fluctuations in glucose-related signals, II) integrating low power consumption without compromising performance, III) accommodating both high and low impedance electrodes, and IV) ensuring high precision in glucose measurements.

For instance, the AD5940, developed by Analog Devices, represents a robust off-the-shelf AFE solution. Its analog-to-digital converter (ADC) boasts impressive specifications, featuring a 16-bit resolution, 800 kSPS (thousands of samples per second), and a versatile multichannel SAR (Successive Approximation Register) architecture. This ADC incorporates essential elements such as input buffers, an integrated anti-aliasing filter, and a configurable boost amplifier (PGA). Additionally, its input multiplexer (mux) allows configuration for various measurement inputs, including internal channels, external current, and voltage inputs, providing adaptability for diverse sensor interfaces.

Another noteworthy AFE option is the AFE91000, particularly suitable for electrochemical glucose sensors. Engineered for micro-power applications, the AFE91000 operates at an overall current draw below 10 µA. Notably, power consumption optimization techniques, such as deactivating the TIA (Trans-Impedance Amplifier) amplifier and utilizing a built-in switch to bridge the reference electrode to the working electrode, contribute to substantial power reduction.

Single AFEs solutions may be used in replacement of the more conventional, bulky electronics. The vast majority of AFEs come as a standalone set for several sensor varieties. For instance, Analog Devices Inc.'s AD5940 is designed specifically to be utilized in electrochemical sensors. Multiplexing other kinds of sensors, such as optical and electrochemical sensors, onto a single AFE presents challenges that are not present with this design [88]. These days' CGM systems need AFEs that can do more than one thing and have various sensor inputs and outputs. The compact potentiostat, via adapting LMP91000, provide POC testing features, low-power monitoring, and high sensitivity [89].

4.2. Microcontroller

A microcontroller (MCU), classified as a tiny computer, is the brain behind most CGMs. The presence of connectivity is made possible with it. It minimizes several electrical components that are required for executing diverse operations on a compact chip [90]. It is widely used in CGM due to its ease of programming, low cost, compact size, and compatibility with biosensors. Some MCUs are designed to handle complicated wireless protocol stacks enabling the CGM device to schedule measurements to be transmitted every few minutes or even seconds. Engineers may customize the MCU to the specific requirements of their projects thanks to its adaptability.

The MCU is responsible for handling the bulk of the device's operations, including data collection and transmission. As a result, it uses a considerable amount of the device's overall battery power. Power-saving micro-controllers may significantly cut down on the amount of energy a device requires to operate. The ultra-low power MCU that can

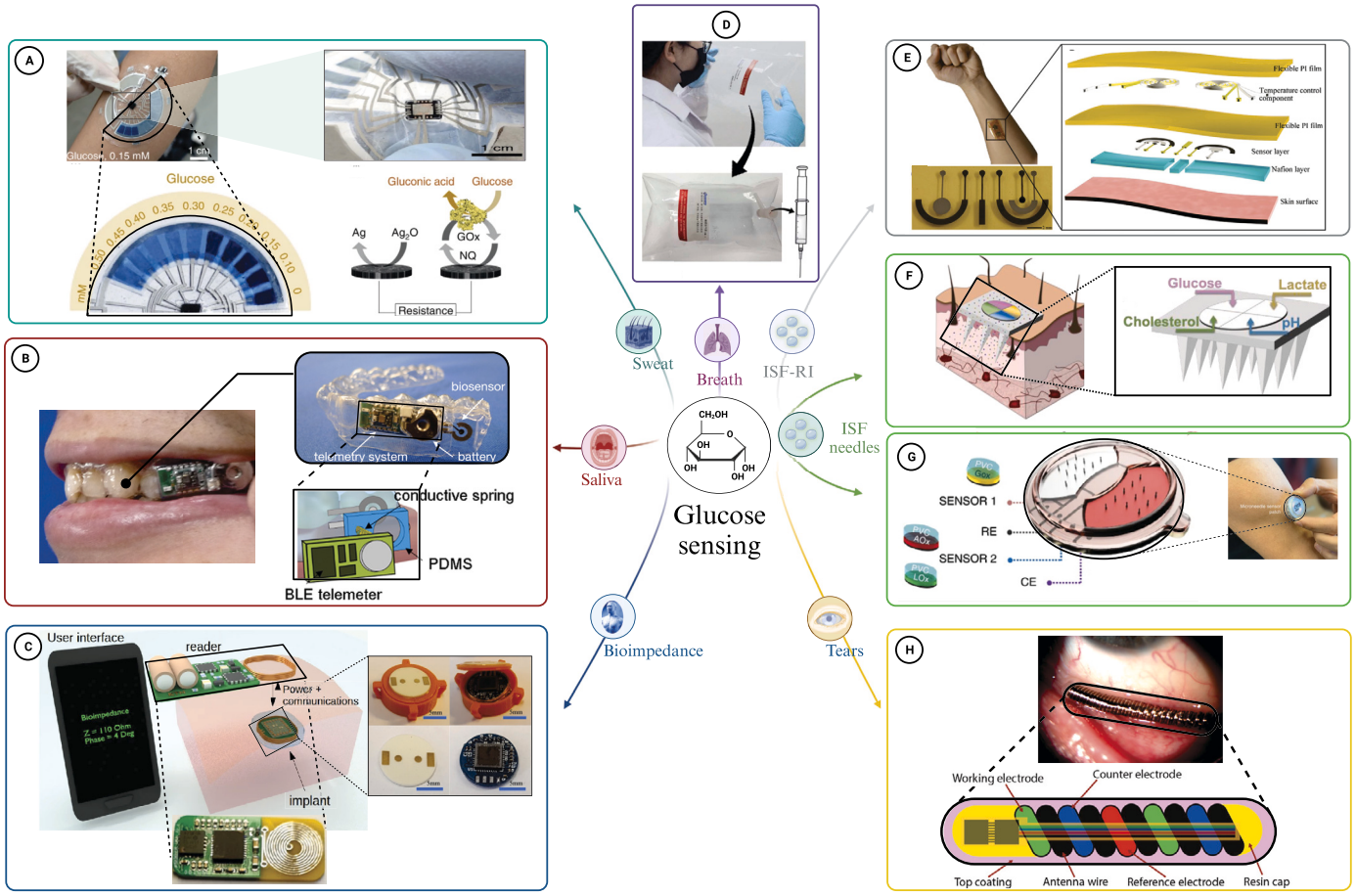

Fig. 8. Illustrative Schemes for continuous glucose monitoring from Literature. (A) A stretchable sweat-sweat system for glucose and lactate colorimetric monitoring. Reprinted under the open access license from [81], Copyright 2022 Springer Nature. (B) An in vivo salivary glucose monitor. Reprinted with permission from [82], Copyright 2020 American Chemical Society. (C) A bioimpedance spectroscopy based device that could be implanted in the body for glucose level monitoring. Reprinted under the open access license from [83], Copyright 2023 Springer Nature. (D) A temperature modulated semiconducting transition for glucose level detection in exhaled breath. Reprinted with license from [84], Copyrights 2020 Royal Society of Chemistry. (E) A transdermal device for glucose monitoring based on ISF extraction with a differential structure to remove the passive sweat effect. Reprinted with permission from [59], Copyright 2021 AAAS. (F) A colorimetric microneedle patch for sensing glucose, lactate, cholesterol and pH levels in ISF. Reprinted with permission from [85], Copyright 2022 Elsevier. (G) A wearable biosensor based on microneedles array for glucose/lactate level detection in ISF. Reprinted under the open access license from [86], Copyrights 2022 Springer Nature. (H) The NovioSense Glucose Sensor, worn behind the inferior conjunctival fornix, continually measures basal tear fluid glucose levels. Reprinted under the open access license from [87], Copyrights 2022 Springer Nature.

function in sleep modes is an excellent option. Data on glucose levels are sent from the AFE to the MCU by a serial communication link (often UART, SPI, or I2C) in the device. I2C is more desirable since the majority of AFEs support it for its simplicity and the necessity of only 2 wires for communication.

The CYW20736S is a system-in-package (SiP) module that is highly integrated and very small in size, making it ideal for use with BLE. As the CYW20736S SiP already has a BLE antenna, clock (at 24 MHz), and 512 Kb EEPROM built-in, just a few more components are required to make it into a fully functional independent BLE device.

4.3. Energy source

A dependable and consistent power source is crucial for ensuring the sustained operation of CGM devices. Presently, batteries stand as the most reliable energy source due to their encapsulation potential in biocompatible materials, enhancing device safety. However, batteries face challenges such as limited lifespan, reduced effectiveness, health hazards, and environmental unfriendliness. For addressing these concerns, energy harvesting from the patient's body and ambient surroundings emerges as a promising alternative, aimed at maximizing patient satisfaction while mitigating these drawbacks [91].

Active research into harnessing atmospheric energy for wearable and implantable devices has been ongoing for several years. Nevertheless, commercial self-powered CGM devices are not yet available. The harvested power, in most cases, fails to independently supply the device, necessitating integrated energy storage systems due to the inconsistency and instability of these energy sources. Eliminating periodic battery replacement procedures remains an aspirational goal for CGM devices powered solely through energy harvesting. These modifications seek to expand upon the challenges posed by traditional power sources and highlight ongoing efforts toward exploring alternative energy solutions in the context of Continuous Glucose Monitoring devices.

Energy harvesting often makes use of human-centric forms of energy like movement and thermal radiation. Fig. 10 provides a taxonomy of the many energy-harvesting methods that have the potential to be utilized in CGMs. An individual's internal temperature differs from that of their surroundings, which may be used by thermoelectric energy generators (TEGs) to harvest energy [92,93]. Furthermore, photovoltaic (PV) cells have shown promise in capturing the radiant heat that the human body emits. Energy may also be derived from the vibrations produced by the human body during activities like hiking, jogging, and even heartbeat. Electrostatic, triboelectric, electromagnetic (EM), and piezoelectric methods were used to successfully convert these vibrations to

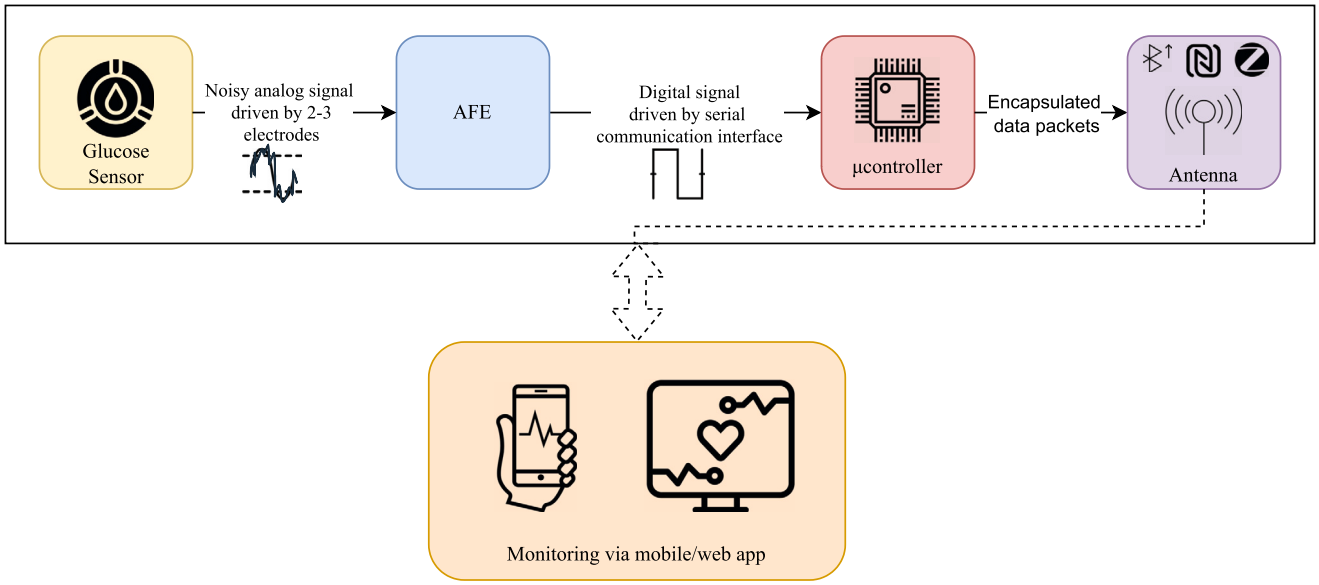

Fig. 9. Main components of CGM systems. The illustration showcases the key elements involved in the process of monitoring and analyzing glucose levels in real-time such as the glucose sensor, analog front end (AFE), microcontroller (MCU), wireless communication module/antenna, and data processing unit.

electric power [94]. Environmental forms of energy including sunlight and radio frequency (RF) waves, as well as infrared, have also shown great potential [95]. Ecocentric energy sources are typically dependent on their availability and need extra storage in order to ensure uninterrupted functioning. In order to achieve more reliable energy solutions, energy harvesting methods may integrate sources from the human body and the environment to constitute what are known as hybrid energy harvesters.

Various options, such as rechargeable batteries, supercapacitors, and capacitors, come with distinct advantages and limitations, impacting both longevity and form factor considerations. An exemplar application involving wireless power transfer for continuous blood glucose monitors emphasizes the need to optimize start-up energy requirements for efficient wireless power transfer cycles, thus reducing the wireless energy harvesting duration. Moreover, emerging trends toward hybrid/dual-source energy harvesting in specific applications showcase a strategic combination of solar cell, RF signal harvesting, and battery usage to extend battery life while minimizing environmental impact.

It was suggested by Zhao et al. [96] that a self-powered, fully integrated wristwatch can be used to monitor glucose levels in sweat in real-time. The smartwatch's components included electrochemical glucose sensors, bespoke circuitry, screen modules, elastic solar cells, and battery packs. Hence, the harvested energy is enough for powering all these components. Materials with piezoelectric properties may be mechanically deformed repeatedly to induce piezoelectricity. During physical activity, mechanical energy may be captured and used to power glucose monitors worn by the user. A self-powered glucose sensor was described by Yu et al. [97], which makes use of the piezoelectrical phenomenon utilizing a triboelectric nanogenerator (TENG) nanowire. Whenever a compressive strain of 0.79 percent is applied to the biosensor, the piezoelectrical impact improves the device's efficiency in all forms, leading to a greater than 200 percent raise in the yield signal's intensity as well as a doubling and a tripling of the sensing resolution and sensitivity.

Recent advancements in continuous glucose monitoring propose a groundbreaking method that taps into the body's own analytes for energy. Bandodkar et al. [98] introduced an approach where bodily substances generate electrical signals directly proportional to their concentration levels, eliminating the need for conventional power sources like batteries. By utilizing this energy-harvesting technique, the need for batteries is eliminated, enabling compact, cost-effective glucose and other biomarkers monitoring. This method allows for compact and cost-effective modules capable of real-time data transmission using near-field communication (NFC) technology (discussed in the next section). This holds a promising future for self-sustaining, non-invasive monitoring devices with implications beyond glucose monitoring, potentially revolutionizing health monitoring paradigms.

5. Low power wireless communication

Wireless communication is a crucial part of CGM. It enables the transmission of collected measurements to the data centers for further complicated real-time analysis with high-performance hardware. Wireless CGM systems have the merit of separating the devices from the electrodes, which enhances wearability in CGM systems where the sensor is meant to be put directly on or close to the skin. On the other hand, the excessive use of energy throughout transmitting data is a major contributor to the higher power usage that comes with the wireless connection. This limits the system's lifetime due to battery constraints.

It becomes evident that reducing power requirements is imperative. The average current drawn by wireless nodes plays a pivotal role in determining battery life. For instance, for a 10-year coin cell battery lifetime, the average current drawn must be under specific thresholds, such as 2.5 µA for CR2032 coin cells. Duty cycling, where the wireless node alternates between active and sleep states, emerges as an effective strategy to reduce average current consumption when data throughput requirements are low. This approach allows for intermittent wake-ups, significantly lowering power usage during sleep periods [99].

Bluetooth low energy (BLE) and near-field communication (NFC) are two wireless standards that have found widespread use in CGM platforms and make it possible to transfer and analyze data in real-time.

NFC has to be in close contact with the receiver circuitry, while low energy BLE is a major power consumer. Due to their own limitations, neither method is suited for high-density data exchange, which occurs when there are many clients with multiple sensors that interface with receivers at a fast rate. Wireless communication is impacted by any change in the environmental. Hence, it is essential to choose carefully the right communication technology in terms of reliability, power consumption and data rate. A brief description for both NFC and BLE 5 is shown in the following subsections. Data protection and user privacy become issues with the online storage and analysis of such information, leading to significant investigation of cryptography methods.

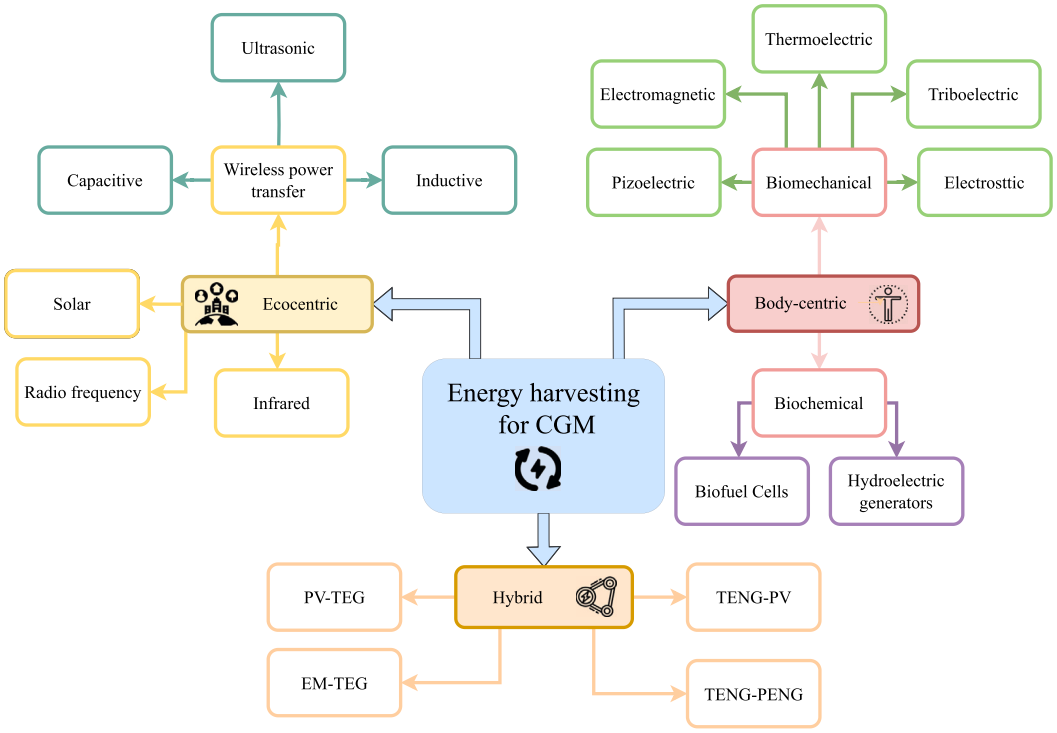

Fig. 10. Potential energy harvesting schemes for CGM Devices. This diagram categorizes potential energy harvesting methods into three classifications - Ecocentric, Body-centric, and hybrid, aimed at CGM devices sustainably.

5.1. Bluetooth low energy

Bluetooth Low Energy (BLE), introduced by Bluetooth Special Interest Group SIG in 2011, was designed for a low-power communication purposes that do not require high throughput or a large distance [100]. The intention of this protocol is to simplify how to deploy services that rely on ultra-low-power electronics [101]. Bluetooth is being used by an increasing number of CGM devices to wirelessly share data. By establishing a local area network, Bluetooth enables a number of devices to communicate with one another and synchronize their data in real-time. Bluetooth operates at ultrahigh frequencies (UHF) of the industrial, scientific, and medical (ISM) radio spectrum of 2.4 GHz. BLE utilizes 37 general-purpose physical channels as well as three advertising channels [102]. It can exchange data at speed of 1-2 Mbps within the range of a few tens of meters. Devices that use the BLE protocol fall into one of two categories: master or slave. A master device (like a smartphone or PC) serves as a central hub that may pair with several slaves. A slave device (like CGM) is responsible for the service advertisement and response to the master's requests [103]. BLE uses Advanced Encryption Standard (AES) to secure the data over the link between the sensor device and the mobile application. Data security concerns and interference with Wi-Fi are the two constraints of Bluetooth [104].

Over the past two decades, the power consumption for a typical Bluetooth or BLE device has decreased substantially, approximately 20-fold, due to standard expansions. However, despite these improvements, achieving the necessary low average current draw remains a challenge, particularly considering the average modern BLE Rx power consumption, which ranges from 2 to 6 mW, inhibiting continuous activation [105]. Several MCUs were designed to support the BLE stack layers like CC26XX/CC13XX series by Texas Instruments, STM32WB series by STMicroelectronics, nRF52810 System on Chip (SoC) from Nordic Semiconductor and CYW20736S System in Package (SiP) by Infineon. This make them more appealing to be employed for the BLE-based CGM devices

5.2. Near field communication

NFC protocol works at close distances (few cms) and utilizes the 13.56 MHz band for communication [106]. Unlike Bluetooth, data are transmitted in NFC without pairing at speeds of 106 kbps, 212 kbps, and 424 kbps [107]. Close proximity between two NFC-enabled devices allows for the instantaneous exchange of any and all forms of data. With NFC, data is stored in a tag that has storage of about 48 bytes to 1 megabyte of data. The radio frequency identification (RFID) system is the basis of this technology. Compared to RFID tags used for identification, this tag may either be scanned only or editable, allowing the system to make changes at a point later. NFC supports both active and passive scanning modes [108]. When in active mode, two NFC ports (the initiator and the target) may use a radio frequency field to detect and collect data from other NFC nodes in direct range. With passive mode, the sender is the only one that actively produces the radio-frequency field, while the receiver just reacts to it. NFC's improved level of security is a result of its faster set-up and reduced communication range compared to Bluetooth. Moreover, the power may be sent by NFC, allowing detecting devices to collect power from the cellphone and, therefore, reducing their dimensions. Almost all modern smartphones have built-in NFC functionality because of it supports bidirectional communication. On the other hand, the constrained power availability and restricted operability in the absence of a reader restrict the applicability of NFC to certain scenarios that demand low power and low data rates, with size being the primary consideration.

6. Diabetes management

The widespread use of wearable and technological systems has resulted in a significant volume of information becoming publicly available. The availability of various data sources from CGM, along with recent breakthroughs in Artificial intelligence (AI) techniques, has paved the way for a new mindset of algorithm design [109]. Hence, it can personalize blood glucose prediction with enhanced efficiency. The opportunity to use cutting-edge AI techniques in diabetes management is

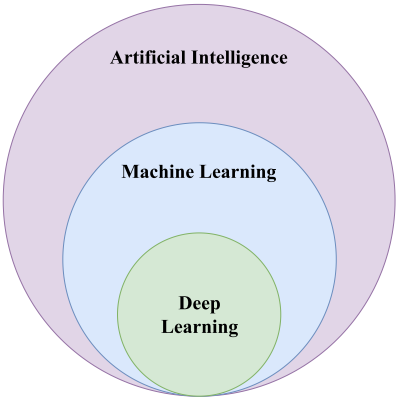

Fig. 11. The hierarchical interrelationship between AI, ML, and DL.

significant considering the present situation which will in turn help to enhance diabetic care. Since healthcare records from many resources are typically diverse, high-dimensional, and sparse, they are often underrepresented in care settings.

Using machines to make decisions and forecast the long-term impacts of illnesses and their repercussions is not a novel use of artificial intelligence. Most basic jobs in modern society are aided by computers and algorithms. Coordination between trustworthy machines and algorithms is used to take into consideration a number of aspects, including equality, accuracy, accountability, dependability, and acceptability [110].

AI is the field of computer science that strives to develop models or approaches that can investigate data and manage complexity in a variety of scenarios [111]. AI is involved in modern data-driven solutions that facilitate advanced analysis for information and offer personalized diabetes assistance [112]. AI encompasses a wide range of complex techniques referred to as machine learning (ML), deep learning (DL), and cognitive computing. Scientists traditionally train AI models using enormous volumes of data and procedures, allowing the machine to explore and benefit from causal links. Deep learning AI systems find useful insights for therapeutic help while doing some hard and time-consuming activities efficiently. Fig. 11 shows the relation between AI, ML, and DL. Cognitive AI systems take things a step further by comprehending, reasoning, interacting, and learning. These systems comprehend by efficiently and comprehensively analyzing and interpreting accessible data, whether structured or unstructured. They think by recognizing items and links, drawing connections, attempting to claim assumptions, and assessing evidence [113–115].

Deep multilayer perceptrons (DMLPs), convolutional neural networks (CNNs), and recurrent neural networks (RNNs) are the three types of supervised machine learning DNNs that have been identified in the diabetic research. The DMLP is the foundation for several DNN systems; it is a feed-forward neural network that relies on completely interconnected layers and other basic neuronal connections. Since multilayer perceptrons could indicate either ANNs or DNNs, the word “deep” is emphasized to show that methods have deep structures with a minimum of 3 layers [116]. Weight matrices, bias scalars, and nonlinear activation functions like sigmoid, tanh, and rectified linear units (ReLU) are all linked to a DMLP’s unique collection of parameters. By acting as preceptors, CNNs are able to analyze the data from high-dimensional arrays, allowing them to outperform traditional neural networks, especially, in imagery tasks. Most CNN designs include a sub-sampling layer, also known as a pooling layer, to combine maps of features. Convolutional processes improve the effectiveness of training via back-propagation by decreasing the number of links among neurons across layers [117].

In contrast to conventional feed-forward neural networks, an RNN’s input includes data from preceding time series. Since RNNs can process data sequentially, they are able to effectively capture periodic characteristics. Back-propagation training may be challenging for vanilla RNNs due to the prevalence of gradient diminishing and explosion difficulties. These issues have been resolved thanks to the introduction of gate functionalities and the persistence of long-term data in modern RNN cells such as long short-term memory (LSTM) and gated recurrent units (GRUs) [118,119]. Models constructed using RNNs have served as frameworks for a wide variety of predictive and regression problems. A recent development in RNN is the attention technique, which enables models to narrow down in specific sub-sequences inside inputs in order to map relationships independent of relative closeness [120].

Applying AI algorithms to CGM data offers various real-world applications that can significantly impact personalized treatment strategies and continuous monitoring capabilities. This integration can enable predictive analysis, identifying future glucose fluctuations, hypo- or hyperglycemic events, and trends. This predictive capability allows for proactive interventions, aiding in the prevention of extreme glucose fluctuations and enhancing patient safety. Moreover, AI insights derived from CGM data facilitate the creation of individualized treatment plans. By analyzing historical data, AI can recommend optimized insulin dosages, dietary modifications, or lifestyle adjustments tailored to each patient. This personalized approach leads to improved glycemic control and better treatment outcomes, enhancing overall patient care. The continuous monitoring capabilities of AI-integrated CGM systems offer real-time alerts and decision support. These systems can detect deviations from normal glucose levels, generating timely alerts for patients or healthcare providers. Such interventions can prevent severe hypo- or hyperglycemic episodes, ensuring timely care and reducing the risk of complications. Additionally, the integration of CGM data with AI facilitates remote monitoring and telemedicine. Patients can share their real-time glucose data with healthcare providers, allowing for remote consultations and adjustments to treatment plans without frequent in-person visits. This accessibility to specialized care enhances patient convenience and ensures timely interventions. AI’s ability to analyze CGM data alongside patient behavior patterns offers valuable insights and feedback. Patients gain a deeper understanding of how their actions impact glucose levels, encouraging better adherence to treatment plans and healthier lifestyle choices. Educational resources and personalized recommendations empower patients to self-manage their condition more effectively. Furthermore, aggregated and anonymized CGM data, analyzed using AI, contributes to data-driven research and clinical trials. This approach aids in identifying novel biomarkers, refining treatment strategies, and advancing diabetes care through large-scale observational studies and research initiatives.

ML could improve our understanding of diabetes by better diagnosis, discovering novel disease subtypes, modeling complicated interactions with other comorbidities for cardiovascular risk, tracking medication response, and offering individualized real-time counseling for lifestyle changes or other therapies [121]. Fig. 12 shows the potential applications of integrating AI with CGM devices.

According to recent studies, modern sensors, pumps, smartphone apps, and other advancements in AI are making it simpler and more efficient for diabetics to manage their health, reducing the number of hypoglycemia events, increasing patient satisfaction, and improving reported results [122–124]. Fig. 13 illustrates how can AI help in the diabetes management process.

A meta-review of reported human studies using the most recent automated, personal or real-time continuous glucose monitoring devices (RT-GCM) found that a variety of AI-powered RT-CMG devices are being introduced to the market, allowing diabetics and their physicians to evaluate and enhance diabetes management, decrease hypoglycemic occurrences, particularly at night, and to enhance A1C scores [29].

AI will bring in a radical transformation in diabetes treatment, migrating from traditional management approaches to the development of tailored data-driven personalized medicine [125]. It was confirmed that the amount of insulin injected and the nutrition obtained had an impact on blood glucose fluctuations. According to that, some research

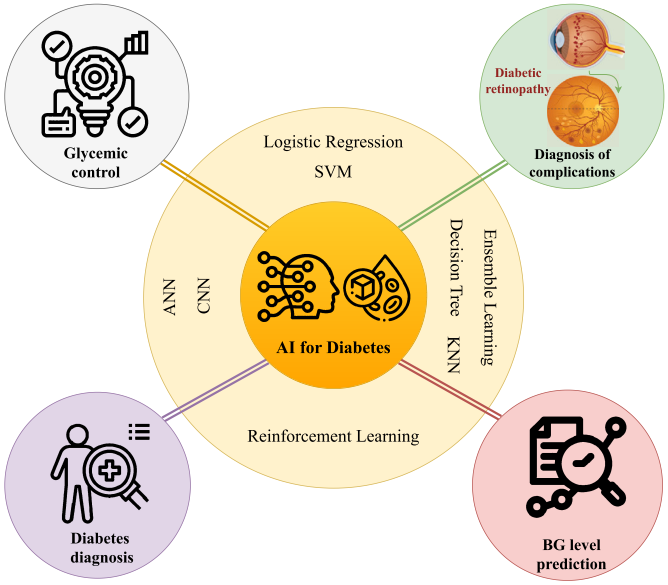

Fig. 12. AI different applications in diabetes. This figure showcases the multi-faceted role of Artificial Intelligence (AI) in diabetes management, encompassing key applications such as diabetes diagnosis, blood glucose level prediction, glycemic control, and identification of diabetic complications such as diabetic retinopathy. AI-driven algorithms and machine learning techniques are utilized to enhance diagnosis, forecast glucose levels, optimize glycemic control, and detect complications promptly.

made the model more accurate by including everyday occurrences like glucose, insulin, meals, and physical activity [126]. Although such models increase prediction accuracy and minimize dependency on a single variable, they are less stable. Additional variables that have been shown to be significant for diabetic results include sleeping, feelings, anxiousness, diabetic distress, and psychiatric co-morbidities such as depressive episodes and disordered eating [127–129]. Precision monitoring in diabetes is accomplished by integrating CGM readings with the recording of these internal and external factors.

Multiple machine learning models can be combined to improve accuracy, making the model less sensitive to different starting parameters and noise, thereby increasing robustness [139].

The previous two decades have seen a significant acceleration in the development of deep learning thanks to advances in computing both hardware and software technologies that have allowed DNN designs to grow in architecture and complexity. Table 2 compares several recent efforts that employ the ML models. Guardian Connect from Medtronic was the first AI-based CGM device approved by the FDA for diabetics [29]. Using self-learning, Guardian Connect can warn users with a PH of 60 minutes before any dangerous changes in blood glucose levels. About 98.5% of hypoglycemia incidents were detected by the Guardian Connect system, allowing patients to take extra precautions to restore normal blood glucose concentration. The following datasets are commonly used by researchers to train the proposed models:

- OhioT1DM: A total of 12 T1D patients provided 8 weeks of data, including BG measurements from Medtronic Enlite CGM sensors every five minutes; BG concentration from SMBG; bolus and basal insulin dosage; patient-reported nutrition with estimated carbohydrate intake; self-reported times of workout, sleep, work, stress, and illness; and physiological data from Basis Peak fitness bands [140].
- DirectNet: A total of 110 T1D patients with ages range of seven to seventeen had their past blood glucose readings rearranged by 5-minute intervals. The measurements were collected over the course of three months, and in separate episodes, with the consent of both patients and their parents, to guarantee their privacy and peacefulness [141].
- Diabetes UCI: The data on 70 T1D patients came from two different places: an SMBG medical recorder and paper files for recording nutrition, physical activities, and insulin doses at previously scheduled times [142].

6.1. Challenges of AI

Though AI/ML has shown promise in revolutionizing diabetes management and CGM devices, several technical hurdles stand in the way of its commercialization and adaption in clinic practice.

Due to the fact that AI models, most of the time, need high-quality data for developing and training the models, obtaining such data must be a top priority. AI has the potential to de-skill professionals by fostering dependency. Since AI requires professional refining on a regular basis, this might lead to a vicious circle of insufficient precision [143]. With a rising number of medical devices and applications on the market, interoperability has been identified as a possible challenge to their adoption in glycemic control [144]. Cost, access, and implementation are all obstacles to the use of AI in diabetes treatment. Data-driven forecasts frequently only utilize a certain approach to predict BG levels, which will result in biased findings. Most predictions based on physiological models only take into account a single element, making it harder to ensure their prediction accuracy and stability. In order to construct multi-model, multi-data-driven approaches that provide the best prediction accuracy, ensemble learning techniques are typically used.

7. Commercial CGM systems

Due to the aging population that is more susceptible to diabetes and rising government spending, the market for continuous glucose monitoring is expanding quickly. By 2028, it is anticipated that the total global market for continuous glucose monitoring devices would amount to 13.24 billion dollars, with a compound annual growth rate (CAGR) of 10.8% [145]. In a study of around 300 thousand T2D patients, 58% of patients discontinued the medication after one year of starting it [146]. According to [2], the majority of diabetics (50.1%) are unaware of their disease. Personal CGM devices tackle this problem by giving patients a very alluring alternative for controlling their blood glucose levels.

While earlier commercial CGM devices' functionality was significantly inferior to that of SMBG, CGM accuracy has increased significantly over the years. For SMBG and CGM systems [147], the 2013 edition of ISO 15197 is a reference with more stringent accuracy requirements. Enzymatic sensors and electrochemical processes are the foundation of the most effective commercial CGM systems to date. Historically, GlucoWatch was the first professional CGM that used reverse iontophoresis to extract glucose via the skin. Glucose was then detected by an amperometric biosensor. It was able to offer a glucose measurement every 20 minutes for 12 hours, with mean absolute relative difference (MARD) ranging from 19.0 to 21.3% [148]. In the past quarter century, CGM commercial platforms have made advances in pricing, size, lifetime, accuracy, price, and user experience. Fig. 14 shows the FDA-approved CGM devices timeline along with some promising startups.

The Guardian CGM device, which may alert patients to possible severe hyper/hypoglycemia, was initially developed by Medtronic in 2004. The same manufacturer also produced the first effective closed-loop system in 2006. Dexcom launched the STS, its first real-time CGM, during that same time. Abbott introduced the FreeStyle Navigator to the US market in 2008. The earliest CGM systems needed blood glucose validation before making any insulin injections. Before the rise of FreeStyle Libre 2, all commercial CGMs needed to be calibrated using SMBG, which presented a challenge if they were utilized in a closed-loop insulin delivery system.

Table 3 presents a summary of commercial CGM devices for comparison. MARD, derived from the absolute relative difference (ARD), was used to compare the accuracy of the different systems (Eq. (1)

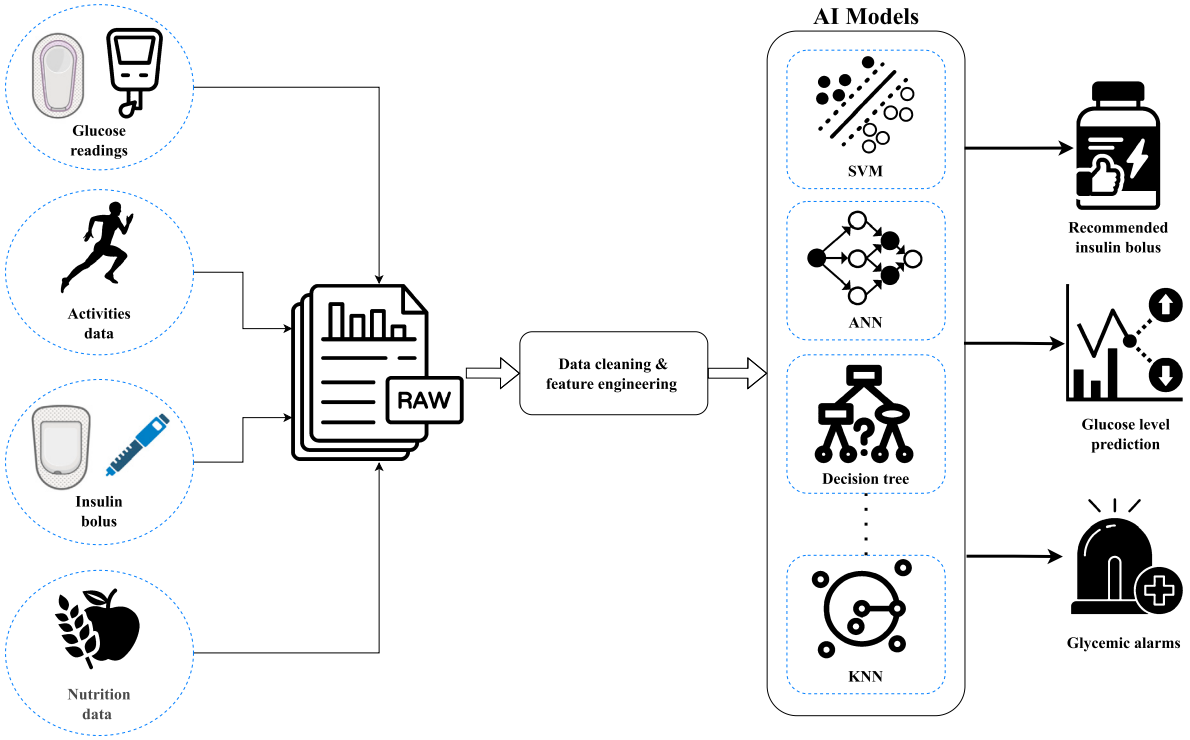

Fig. 13. Diabetes management Framework. This schematic diagram outlines a comprehensive diabetes management framework encompassing key elements such as CGM measurements, insulin administration, dietary control, physical activity, and healthcare intervention towards effective diabetes care and patient well-being.

and (2)). In terms of overall MARD, Freestyle Liber III has achieved the best commercial sensor score with 7.9% [149]. Eversense was the first fluorescence-based and fully implantable glucose to be approved by FDA. Since Eversense is implanted underneath the skin, it has the best lifespan. Its worst drawback is the implant operation, which requires the patient to perform surgery again each 180 days. The other CGMs use monitoring that is nearly painless. Dexcom is one of them, and their devices can be utilized in a closed loop with insulin pumps since they are more accurate. The devices from Abbott offer the least warm-up periods and the greatest usage duration [150]. Based on skin bioimpedance, the Pendra wristband CGM was created by Pendragon in 2003. Unfortunately, post-marketing evaluation research found that it was inaccurate and unreliable, with a MARD of 52% then the product was subsequently taken off the market [151]. Despite the fact that various research organizations have been working on sweat-based CGM for decades, there are currently no feasible ones on the market. For tears, it should be mentioned that Google and Novartis had an unsuccessful trial to develop a smart contact lens to monitor the glucose levels in tears [152].

$$\mathrm{ARD}_i = \frac{|y_i - x_i|}{x_i} 100\% \tag{1}$$

$$\mathrm{MARD} = \frac{1}{N_{\mathrm{ref}}} \sum_{i=1}^{N_{\mathrm{ref}}} \mathrm{ARD}_i \tag{2}$$

where x_i and y_i are the blood glucose levels collected from the reference technique and the sensor under test, respectively, and N_{ref} is the total number of times reference tests have been conducted.

8. Challenges

Current glucose monitoring solutions, while advanced, still face several challenges that impact their effectiveness, usability, and widespread adoption. In this section, the barriers that could delay or facilitate CGM devices implementation are discussed.

Accuracy and Variability: Accuracy issues persist in some glucose monitoring systems, especially when readings are compared against laboratory measurements. Disparities between the integrated measuring technique and the calibration method (both methods generally measure inside blood, preferably capillary blood) are the key factors influencing accuracy when evaluating CGM devices [153]. Variability in accuracy across different devices and users poses a challenge. Trials evaluating the precision of recently developed commercial CGM devices in noncritically sick patients indicate that the accuracy varied among the trials, but shown improvement with time. Various studies have assessed the precision of various CGMs by comparing them to Point-of-Care blood glucose tests. The MARD values observed in these publications ranged from 9-16% [154–157].

Calibration and Sensor Drift: Some CGM systems require frequent calibration, which can be cumbersome and affect accuracy. Sensor drift, where readings gradually diverge from actual glucose levels over time, is another concern [158].

Interference and Lag Time: External factors like medications, temperature changes, and certain substances can interfere with sensor accuracy, leading to inaccurate readings. It is crucial to acquaint doctors with circumstances in which the use of CGM may not be accurate or dependable. Multiple factors might influence the accuracy and reliability of the devices including interfering chemicals, or radiologic substances, which can affect the process of glucose detection, transmission, or data capture using the reader device [159]. Additionally, some CGM systems have a lag time between blood glucose changes and sensor readings. CGM systems are subject to the impact of the temporal delay that occurs between changes in glucose levels in the ISF and the compartment (i.e., blood) from which comparison measurements are taken.

Cost and Accessibility: High costs associated with acquiring and maintaining continuous glucose monitoring devices, along with limited insurance coverage, can restrict accessibility for some patients, limiting their use in routine care [160].

User-Friendliness and Integration: User interface complexities, including difficulties in interpreting data and navigating device interfaces,

Table 2
A collection of efforts for machine learning based BG monitoring.

Study	Model(s)	Features	Dataset	Target	Error Analysis (Evaluation)
[130]	Vanilla LSTM, Temporal Convolution Network (TCN) and classic Autoregression with Exogenous inputs (ARX)	BG, insulin, carbohydrate intake, physical activity	8 week's data collected from 6 anonymous T1D patients under insulin pump therapy (Medtronic Enlite CGM sensors)	predicting BG levels	Root Mean Square Error (RMSE), temporal gain (TG), normalized energy of the second-order differences (ESOD)
[131]	autoregressive moving average (ARMA) model and (LSTM)	BG, insulin, carbohydrate intake, physical activity	29 real patients	short-term personalized glucose prediction	(RMSE) and mean absolute error(MAE) RMSE 3.13, 6.41 and 8.81 mg/dL and MAE 1.98, 5.06 and 6.47 mg/dL for 5-, 15- and 30-min PH
[132]	multi-layer Convolutional Recurrent Neural Network (CRNN)	glucose readings, insulin bolus, and meal data	In silico form UVA/Padova dataset and clinical data collected from T1D in a 6 month clinical trial using G4 Dexcom platinum	short-term personalized glucose prediction	Simulated data: RMSE = 9.38 ± 0.71 mg/dL (30 min PH), 18.87 ± 2.25 mg/dL (60 min PH) Real data: RMSE = 21.07 ± 2.35 mg/dL (30 min PH), 33.27 ± 4.79% (60 min PH)
[23]	logistic regression analysis	CGM, daily entries of meal and bolus insulin	six-week study in 12 T1D adults using CGM and a clinically validated wearable sensor wristband	predict glucose levels and hypo/hyperglycemia	RMSE: 35.3 ± 5.8 mg/dL
[133]	Fast-adaptive and Confident Neural Network (FCNN)	CGM, meals, insulin, exercise	12 subjects with T1D	BG level	RMSE, MAE, gRMSE, and PTD root mean square error of 18.64 ± 2.60 mg/dL and 31.07 ± 3.62 mg/dL for 30 and 60-minute prediction horizons, respectively
[134]	Random forest, ANN, SVM, linear logistic regressions, and extended tree classifiers	CGM data, meal intake and insulin boluses	OhioT1DM	BG concentrations to appropriate preventive action (snack or change in basal insulin)	the area under the receiver operating characteristic curve (AUC-ROC) = 0.7 GMEAN = 0.65
[135]	SVM, multilayer perceptron networks (MLP)	interstitial glucose concentration, meals, insulin doses, and SMBG values, activity	10 subjects with 12 week data of FreeStyle Libre commercial CGM, Fitbit Alta HR wristband for activities and sleep patterns	hypo/hyperglycemia during sleep period	Sensitivity: 78.75% (SVM), 69.52 (MLP) Specificity: 82.15% (SVM), 78.98 (MLP) Accuracy: 80.77 (SVM), 77.38% (MLP) Gmean: 79.19% (SVM), 72.90% (MLP)
[136]	LSTM fed through a NN with 2 hidden dense layers	previous BG level measurements	OhioT1DM	BG level prediction with 1hr PH+ certainty	RMSE: 18.67 (30 min PH), 31.4 (60 min PH)
[137]	Non-Linear Autoregressive Neural Network (NAR) LSTM fed through a NN with 1 hidden dense layer	previous BG level, insulin intake	Real time data from 451 patients	BG level for different PHs	RMSE for 30, 45 and 60 min PH of 19.47, 26.47 and 32.38 mg/dL respectively
[138]	Enhanced RNN with reduced boltzman machines (RNN-RBM)	BG level history	10 subjects with T1D randomly selected from DirecNet dataset	prediction of near-future blood glucose levels	RMSE: 15.59 mg/dL for 30 min PH

can be a barrier to adoption. Integration of glucose monitoring data into electronic health records or other systems might not be seamless.

Wearability and Longevity: Wearability issues, such as adhesive-related skin reactions or discomfort caused by continuous wear of devices, can affect long-term adherence. Some sensors might have limited wear time, necessitating frequent replacements [161].

Interpreting results: Some users, particularly older adults, may face challenges in interpreting the results provided by CGM devices, which can impact their ability to effectively manage their glucose levels.

Device adhesion and detachment: CGM devices may become detached unintentionally, affecting the accuracy of glucose monitoring and causing inconvenience for users, as reported in a study involving adults aged 50 to 85 years with diabetes [162].

Regulatory Compliance and Standardization: Compliance with stringent regulatory standards, including ensuring device accuracy, safety, and reliability, adds complexity to device development and approval. The International Organization for Standardization (ISO) standard ISO 15197 offers exact standards for evaluating the reading accuracy of SMBG devices. However, there is currently no matching counterpart available for CGM devices. The current guidelines, FDA-iCGM special controls [163], IEC 60747-14-10, and CLSI POCT05, are not only inadequately standardized in terms of specifications and worldwide acceptance, but they also raise a number of significant problems that remain unresolved. Lack of standardization across devices can also hinder interoperability and data sharing.

Another type of challenges specifically faces the AI-integrated CGM devices which suffer from:

Erroneous readings and false alarms: Physical compression of tissue around the sensor can lead to erroneously low glucose readings and false alarms, impacting the reliability of the device.

Alarm fatigue: Users may experience alarm fatigue due to frequent alerts from the CGM device, which can lead to desensitization and reduced responsiveness to important alerts [160].

Addressing issues related to invasiveness, accuracy, usability, cost-effectiveness, and regulatory compliance is crucial for the development and adoption of more effective, user-friendly, and accessible glucose monitoring solutions. Advancements in technology that overcome these challenges will greatly enhance diabetes management, improve patient adherence, and positively impact overall health outcomes for individuals living with diabetes.

The adoption timeline for advanced glucose monitoring technologies, encompassing minimally invasive, non-invasive, and AI-integrated systems, hinges on a combination of facilitators and barriers. Technological advancements, robust clinical evidence, regulatory approvals, and seamless healthcare integration serve as key facilitators. However, challenges like stringent regulations, cost considerations, acceptance by healthcare providers, and data interoperability pose potential delays. Envisioning the timeline involves an initial phase of specialized use, followed by gradual integration into mainstream practice over several years, eventually leading to widespread adoption, contingent upon overcoming these barriers through collaboration among stakeholders.

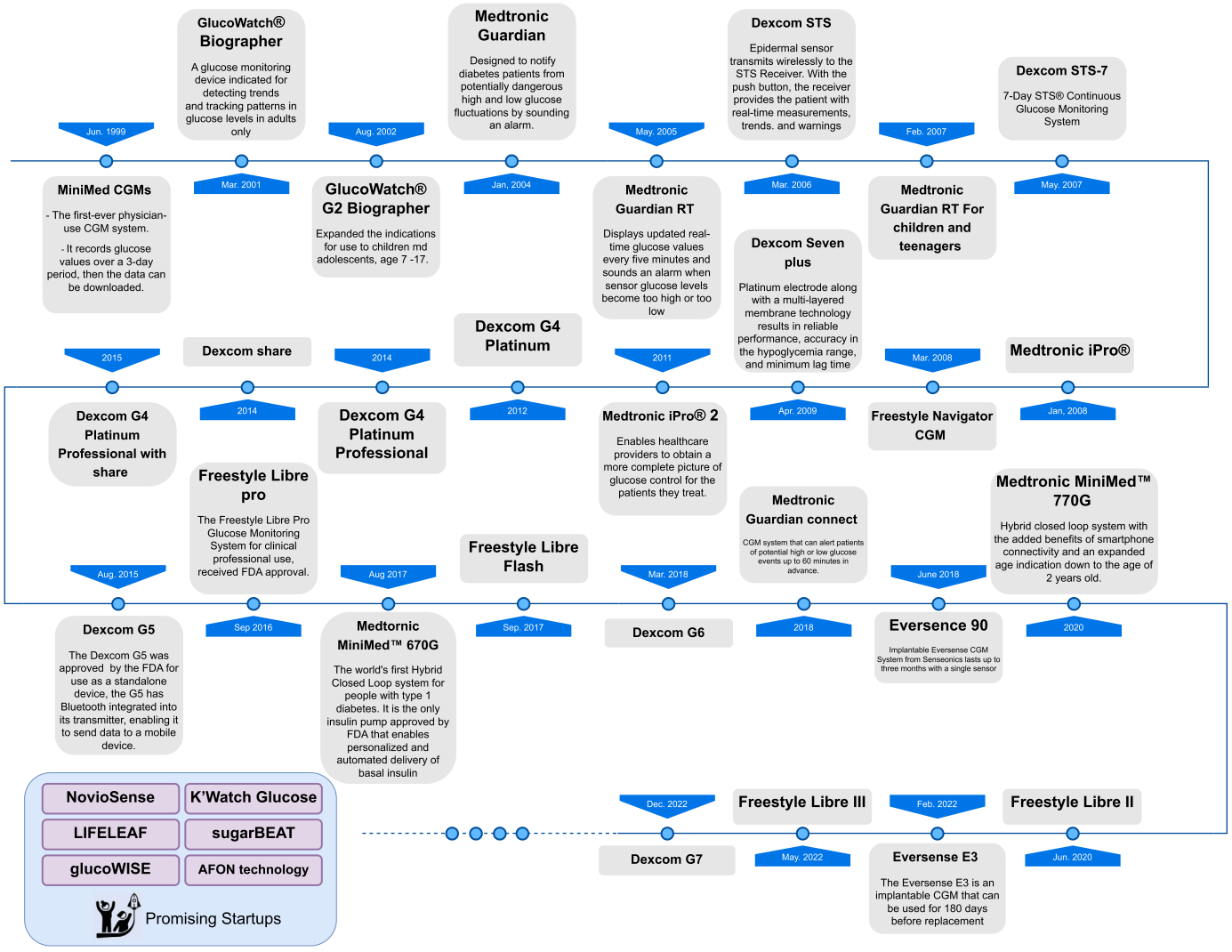

Fig. 14. Timeline of FDA-Approved CGM devices which shows that the first FDA approved device was in 1999 and there is 29 FDA approved version since 1999 till 2022.

Overcoming these challenges is pivotal for realizing the substantial benefits these innovations offer in enhancing diabetes management and patient outcomes.

9. Discussion and future prospective

An interdisciplinary look at CGM different technologies is presented in this review study. Developing reliable, non-invasive CGM systems for widespread usage involves participation from experts in several fields. Despite the fact that commercial CGM devices have been developed, there is still room for improvement in their accuracy to collect more trustworthy data for diabetes diagnosis. The little glucose content in various biofluids necessitates a high sensitivity to make it useful in clinical practice. Another critical issue that should have been addressed more thoroughly is electrochemical sensors' biofouling, particularly ISF-based ones. Biofouling is the accumulation of proteins, cells, or other molecules on the surfaces of a biosensor as a result of contact with the biofluid [164]. Biosorption of the desired analyte rapidly prevents it from reaching the sensor surface, leading to a delayed response, a lower biosensor sensitivity, and a limited sensor lifetime. Excellent antifouling coating materials made from a layer of biopolymers (such as polyethylene glycol) or zwitterion molecules are two desirable approaches to resolving this issue, together with sensitive automated calibration processes. Sensor surface materials should be chosen to keep enzymes on the sensor and prevent the leakage of any potentially harmful sensor components while minimizing biofouling effects and excluding concurrent electroactive interference. Integrating diabetics with CGM devices requires seamless technological interoperability. It is possible for there to be one-way or two-way communication. Since the MCUs can only work with digital data, the glucose sensor signal must be handled first. By using an AFE, signal conditioning electronics may be kept to a minimum. Communication protocols including I2C, SPI, and UART are often used to set up the connection between AFE and the MCU. The protocols used by AFE and the microcontroller must be interoperable with one another. The primary communication options for integrating CGM devices with the central hub are BLE and NFC. Bluetooth allows sensors to communicate with mobile devices like smartphones and PCs and has a limited data transfer rate with a high throughput of 2.1 Mbps at distances of up to 100 meters. BLE is best suited for data transmission in high-density environments like hospitals and operation rooms. The gateway devices are linked to the data-center through private Wi-Fi, which offers improved reliability and security. Loss of Internet or BLE connection, while the measuring equipment is in motion, poses a risk of losing vital data and delaying healthcare delivery to diabetics. Therefore, both the Wi-Fi or BLE modules have to provide optimal scanning methods to ensure mobile devices may continue to access the network even in highly congested radio frequency (RF) conditions. Besides wireless data transfer, NFC-based sensor solutions provide wireless power

Table 3
Comparing different CGM vendors and start-ups.

Device name	Sensing mechanism	Bio-fluid	Needs calibration?	Sensor lifetime (days)	Over-all MARD (%)	Insulin pump compatibility	hypo/hyper glycemia prediction
Dexcom G7	Electrochemical Microneedle	ISF	✗	10 + 12-hour grace period	8.2	☑	☑
MiniMed 770G	Electrochemical Microneedle	ISF	☑	6-7	8.68-10.96	☑	☑
GlucoMenDay	Electrochemical Microneedle	ISF	☑ 1 per day	14	9.6	GlucoMen Day	☑
FreeStyle Libre 3	Electrochemical Microneedle	ISF	✗	14	7.9	✗	☑
Eversense E3	Fluorescence	ISF	1-2 per day	180	8.5	☑	☑
NovioSense*	Electrochemical micro spiral coil	Tears	N/A	14	12.5	☑	-
K'Watch Glucose*	Electrochemical Microneedle	ISF	-	7	18	-	-
LIFELEAF*	optical	Blood	-	-	-	-	-
sugarBEAT*	Electrochemical Microneedle	ISF	☑ 1 per day	14 hours	12.3	☑	✗
glucoWISE*	Radio waves around the 40 GHz range (millimeter waves)	Blood	-	-	-	-	-

* Start-up, not approved by FDA.

transfer. An NFC microchip and a coupling antenna have the potential to be used instead of batteries or wiring to create a totally flexible construction for the CGM device.

On the other hand, self-powered solutions offer a potential future for glucose monitoring due to their compact design, lightweight, ease of wear, and lack of environmental impact. Consistent with this trend, self-powered glucose monitoring has taken important steps in the recent years. While many advances have been made in developing self-powered sensors capable of continuous glucose monitoring, most of these systems remain in the proof-of-concept stage. There is more work to be done before self-powered glucose monitoring devices, both implanted and wearable, can become a reality.

While there is currently no recognized treatment for Type 2 diabetes [165], early detection and management are essential to preventing the condition and may delay or perhaps stop the significant consequences that are linked to diabetes. Advanced computing techniques, such as artificial intelligence (AI), are on the rise because of their promising uses in data analysis. Subsets of AI like ML and DL will remain the most popular approaches for some time to come because of their useful applications in areas like smart alarms developing an accurate AP. The latest breakthroughs in AI algorithms increased the effectiveness of diabetes management in a variety of contexts, including complications prevention and therapy. As a result, cutting-edge smartphone algorithms may soon be utilized to predict glucose variations, speed up the decision-making cycle, and aid the medication delivery mechanism in precisely managing glucose-related symptoms. We have shown that many in-vitro tests have been performed, but in-vivo trials are still necessary to verify the system's safety. In order for the monitoring system to be clinically approved, it must overcome obstacles related to minimally invasive procedures and prolonged utilization.

The development of alternative energy sources is another area of potential. On the one hand, there is an ongoing development in the field of self-powered devices, and many are working to create useful miniaturized self-powered CGM. However, alternative battery technologies are being adopted, and batteries are becoming bendable, printable, and lightweight; these developments aligned with the desire for next-generation wearable and implanted glucose monitoring devices.

The accessibility of genetic information, like that supplied by metabonomics analyses, may enhance the use of AI technologies for the customization of diabetes treatment. Increasing access to digitalized glucose data from diabetics, new AI applications, and rising academic areas like AP and precision medicine all point to the possibility of a shift toward a novel diabetes care framework. This novel perspective supports individualized diabetes care by adapting clinical procedures, diagnostics, and therapies to each patient's specific needs. However, doctors and researchers need to consider the ethical consequences of incorporating AI technologies into medical decision-making. Furthermore, they need an investigation into the moral threats posed by the disclosure of sensitive information.

10. Conclusion

In conclusion, this survey has provided an in-depth analysis of various aspects of glucose sensing and CGM technology for diabetes management. We have explored the key elements of glucose sensors, the sensing principles of sensors, energy storage options, AI integration, and commercially available CGM systems from both established companies and startups. The advancement of minimally/noninvasive monitoring biosensors that target glucose in tears, sweat, saliva, and urine has recently attracted a lot of attention. This led to the concept of non-invasive and continuous glucose monitoring. While non-invasive optical-based methods for glucose monitoring exhibit significant potential and are actively being researched and developed, challenges regarding accuracy, calibration, and regulatory approval need to be addressed for these technologies to reach their full potential. On the other hand, minimally invasive sensors based on ISF extraction hold tremendous promise in bridging the gap between invasive and non-invasive glucose monitoring methods. Their potential for continuous monitoring, reduced invasiveness, relatively high accuracy, and wearability positions them as a viable option for individuals seeking a more comfortable and less intrusive method for glucose monitoring. The study showed that a huge effort has been done over the past few decades to develop wearable devices for glucose monitoring. Hence, a discussion of the different components of the wearable device was illustrated in this study. One major part of wearable devices is wireless communications. The wireless communications module enables the collection of the sensor readings from the wearable device and sending them to a data center. However, we found that wireless communication is the main constraint on the battery lifetime. We discussed two commonly used communication protocols in wearable devices and these are NFC and BLE. It has become clear that advancements in developing precise CGM technology have the potential to revolutionize diabetes management. The development of self-powered glucose sensors, the integration of AI in CGM systems, and the emergence of a wide range of commercial CGM solutions are some of the key advancements that are improving the accuracy, convenience, and effectiveness of diabetes care. Challenges such as accuracy, reliability, and cost-effectiveness still exist, and ongoing research and development in this field are necessary to overcome these

challenges and bring more effective solutions to the market. Overall, it is important to continue research and development to incorporate a number of functional modules in the future, which calls for multidisciplinary and bridge collaboration across the domains of nanomaterials, medical science, AI, electrochemistry, flexible electronics, and other disciplines. This will enable the development of more durable and trustworthy, accurate and effective, lightweight and convenient, smart and innovative non-invasive CGM devices, and secured closed-loop systems to fulfill diabetics and market expectations.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgement

The authors would like to thank the Information Technology Academia Collaboration (ITAC) for funding this project with grant number CFP225. Also, we would like to thank Nile University for funding the master's degree for Mohammad Mansour.

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