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Emergence of integrated biosensing-enabled digital healthcare devices

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Digital biosensors facilitate real-time, remote, precise disease detection and biochemical analysis. Recent trends in biosensing methods have focused on miniaturization, automation, and multiplexing. The miniaturization of biosensors has led to the development of portable, flexible, and wearable devices that can be used for point-of-care diagnostics and continuous health monitoring. Furthermore, digital automation has enabled the high-throughput screening of samples, reducing the time and cost of analysis, while integrated multiplexing allows for the simultaneous detection of multiple analytes, increasing the efficiency and accuracy of analysis. This article examines recent scientific advances in developing miniaturized biosensing procedures for digital healthcare. Advancements in digital devices have also contributed to the development of integrated biosensing. The use of smartphones, smartwatches, and other digital devices as readout platforms for biosensors has made biosensing more accessible and user-friendly. The development of artificial intelligence and machine learning algorithms has allowed for the interpretation and analysis of complex biosensor data. This review compares biosensing with current state-of-the-art diagnostic technology. After incorporating biosensors with artificial intelligence in an internet of things platform, they will have enormous potential and market value in the future for personalized healthcare. Based on various device performances and impacts, sensing methods, designs, compatibilities, functionalities, technology integrations, and developments are systematically discussed in this article. The primary objective of this review was to present a comprehensive discussion from the point of view of both technological advancements and translational wisdom. It is essential to have intelligent point-of-care devices with digital technologies for real-time healthcare management. The vision of the future healthcare industry encompasses a range of biosensing methods that offer a glimpse into new possibilities for the market.

1. Introduction

Intelligent point-of-care (PoC) devices are crucial for managing healthcare and making decisions in real-time.[1,2] The internet of things (IoT) and associated health applications are increasing the commercial value of sensors. Biosensor nanotechnology is used to design wearable electronic devices with advanced materials.[3–5] The vision of the future that encompasses a range of sensing devices offers a glimpse into new possibilities whose impact is expected to have a positive effect on the healthcare industry.[6,7] Intelligent sensor devices promote the transformation of healthcare from a conventional hospital-based to a patient-based approach by means of monitoring an individual's biochemical signs, such as perspiration, blood, interstitial fluids, tears, and wound fluids, for diagnosis and treatment in a smart home care setting.[6,8–10] An innovative, worthwhile, and cost-effective solution could be provided for every healthcare application by a biosensor and an electronic system with computing support. This review emphasizes the efficacy of point-of-care (PoC) devices in field diagnostics with low resource settings; for example, where cost-effectiveness is essential or there is a low power supply or input, making such systems suitable for low-income countries for the quantification of certain bioanalyses, such as nucleic acids or proteins, to aid clinical decisions.[11–14] Devices configured for prognosis integrate sensor products that include processors, memory devices, and computing support to offer a comprehensive product that is simple to operate.

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The internet of medical things (IoMT) has inspired scientists to create new 'smart' healthcare systems that focus on early diagnosis, controlling disease spread, improving knowledge, and effective treatment and that support the use of technologies with cybersecurity-attentive strategies, thoughtful planning, and clear policies within healthcare establishments.[15,16] Several studies have reviewed the various services and applications of IoT in wearable devices and smartphones for diagnostic to control-based healthcare.[15–17] Additionally, display devices may be coupled to a visual display system to facilitate real-time monitoring. Therefore, there is a significant demand in the market for miniaturized biosensors that can overcome the difficulties presented by conventional techniques. Furthermore, analytical devices for climate neutral biosensing would be an important step toward sustainable society.[18] Healthy healthcare management models require the achievement of net zero carbon emissions in health systems.[18,19] According to existing requirements, the path to zero emissions is inextricably linked with the development of more resilient health systems and the achievement of global health goals. The objective of this article is to emphasize the climate neutral directions for utilizing digital and sustainable healthcare systems. In this paper, we present a review of the sensing methods, designs, compatibilities, functionalities, technology integrations, and developments based on various device performances and their impact. This article defines various sensor technologies and their usability in healthcare devices. Furthermore, new scenarios, their importance, challenges, innovative methods, and prospects are discussed in terms of next-generation technologies for sustainable healthcare management.

2. Sensing methods, designs, and technology for disease prognosis

It is considered that a more effective public health model could be achieved through the early management of control measures. When developing the most efficient logistic support for training, administering, and developing research items for control activities, it is necessary to evaluate all possible solutions and research avenues considering the risk. Fig. 1 shows some forward-thinking approaches to the design of sensors, technological advancements, and methodical research and development in the field of healthcare diagnosis and treatment.

Table 1 lists some innovative designs and methods reported for the development of sensor technologies.[20–37] Understanding various mechanisms through methodological investigation is important. Here, 3D printed CNT electrodes, distinct interaction, Janus 2D materials, biomimetic receptor, pH-sensitive drug sensing, hematopoietic stem cell differentiations are some of the unique processes involved in developing methods for sensing purposes.[32–37]

Healthcare has advanced with biological digital sensor systems, which enable more sustainable medical monitoring. These systems use cutting-edge technology to non-invasively track vital signs, biochemical markers, and physiological states in real time, providing important data for early disease detection, management, and individualized treatment regimens. They contribute to sustainable medical monitoring through numerous environmental and operational efficiency factors. Biological digital sensor systems have a lower

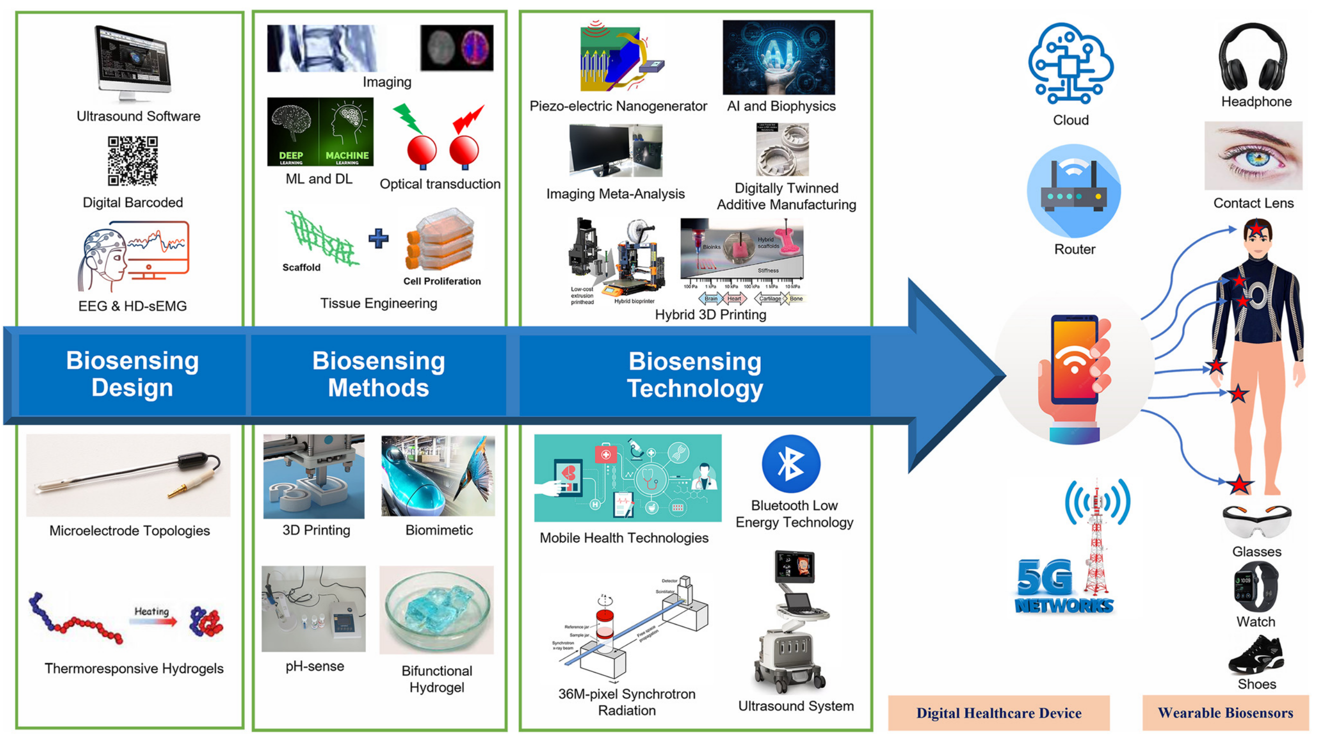

Fig. 1 Diagnostic and therapeutic innovations enabled by novel sensor design, technology, and development methods.

Table 1 Recently reported designs, methods, and sensing technologies developed using innovative design and procedures for sensing in relation to analysis, comparison, evaluation, integration, and implementation

Category	Detail	Ref.
Design	Medical software based on sensor design	20
	Digital barcoded particles and impedance spectroscopy	21
	Integrated EEG and HD-sEMG acquisitions	22
	Elliptical-shaped planar Hall sensor	23
	Microelectrode topologies for electrochemical oxygen sensing	24
	Thermoresponsive polyamine cross-linked perfluoropolyether hydrogels	25
Methods	Photolithography and light-cured inkjet printing methods	26
	Imaging methods in mechanosensing	27
	Multi-dimensional cardio-mechanical signals	28
	Human posture detection based on wearable devices	29
	Self-powered tetherless sensing and opto-spintronic RF-to-optical transduction	30
	Silicate-based electroconductive inks for electronics and tissue engineering	31
	3D printed CNT electrodes to the virulence factor pyocyanin	32
	Distinct interaction of carbohydrates with lectins	33
	Janus 2D materials	34
	Selective glucose sensing using a biomimetic receptor	35
	Nano-carriers based on pH-sensitive drug release	36
	Nanostructured bifunctional hydrogels for hematopoietic stem cell differentiation	37
Biosensing technology	Tunable seesaw-like 3D capacitive sensor	38
	All-fiber pyro- and piezoelectric nanogenerator for healthcare monitoring	39
	Medical biophysics using artificial intelligence and mathematical modeling	40
	The role of computer remote monitoring technology	41
	Digitally twinned additive manufacturing	42
	Molecular imaging meta-analysis	43
	Integrating digital light processing	44
	3D-printable carbon nanotubes-based composite	45
	Mobile health technologies for health record	46
	Development of a real-time technology to facilitate clinical applications	47
	Biomedical REAl-Time Health Evaluation (BREATHE)	48
	Motion and muscle artifact removal validation	49
	36M-pixel synchrotron radiation micro-CT	50
	An ultrasound-based biomedical system	51
	Vitamin D-conjugated gold nanoparticles	52

environmental impact than traditional medical monitoring equipment, demonstrating their better sustainability. These sensors reduce healthcare's carbon footprint by using less material and energy. Their non-invasive nature and remote patient monitoring reduce hospital visits and throwaway medical supplies, further supporting sustainability goals.[2–4]

These technologies have been applied to innovate and develop low-power sensor modes that can enable devices to function for long periods without compromising their performance. These modes typically use innovative algorithms and energy-efficient components to substantially minimize sensor power consumption, while increasing the battery life and therefore decreasing the battery replacement requirements. This extends the device's lifespan, reduces electronic waste, and thus maintain the flow of health data. Low-power sensor modes further boost patient compliance and thus the effectiveness of remote health monitoring. Patients are more likely to follow monitoring regimens if devices require less maintenance and last longer. For chronic disease management, continuous data gathering is essential for treatment adjustments. Low-power modes allow biological digital sensors to be used in distant or underserved locations with limited healthcare access. By making sensors work for long periods without sophisticated infrastructure or frequent maintenance, these technologies can improve healthcare accessibility for hard-to-reach people by enabling high-quality and remote monitoring.[6–9]

2.1. Biosensing materials, designs, and procedures

Biosensor designs are based on integrating diverse elements, including electronics, structural, and computational aspects, as well as spectroscopic methods, electrodes, and thermoresponsive sensing analytes, often each with a unique mechanism.[20–25] Diverse methods of detection, such as photolithography, imaging, cardio-mechanical signal detection, posture detection based on wearable devices, self-powered tetherless detection, and silicate-based electroconductive mechanisms, are used in different studies.[26–31] They offer a solution to issues related to the life-threatening potential by the delayed treatment of diseases and complications due to the fact that not all segments of human society have the financial means to pay for such specialized diagnoses. Physiological, aural, gustatory, olfactory, and haptic stimuli, as well as touch, taste, and smell experiences, and other sensory experiences in the environment or on the human body, can be useful in today's world and can be exploited in sensing applications.

2.2. Nanobiosensing technology

Nanobiosensors, which use nanoparticles, are revolutionizing medical diagnosis. These sensors detect biomarkers at low concentrations with high sensitivity and specificity, making them essential for early illness detection. Graphene-based nanobiosensors can detect cancer biomarkers with unprecedented sensitivity, allowing earlier diagnosis and better patient outcomes.[5]

Nanobiosensors' fast response time contrasts with the typical lengthy processes for laboratory testing. In emergencies, like suspected myocardial infarction, rapid cardiac biomarker testing can greatly impact treatment decisions and outcomes. Nanobiosensors also enable non-invasive and minimally invasive health monitoring. For diabetic patients, wearable nanobiosensors can continually measure glucose levels without the need for blood sampling, thereby improving compliance and the patients' quality of life.[6]

Nanobiosensors combined with digital health technology enable remote patient monitoring and continuous health assessment outside of the typical healthcare settings. In chronic disease management, this capability makes healthcare delivery more convenient and efficient. Magnetic nanobiosensors use nanoparticles' magnetic characteristics and can often detect tumor-related proteins earlier than standard imaging methods. Early disease identification by such sensors could improve patient prognosis and survival by optimizing therapies.[10]

For the sake of being more specific, the focus is on the development of intelligent wearable nanobiosensing devices. These devices should be capable of being handled by laypeople and should assist in the continuous monitoring of vital parameters. As a result, the patient would be able to receive timely treatment and avoid major catastrophes. Real-time monitoring and reporting systems are essential for efficient healthcare management. Recent public health concerns, such as emerging, zoonotic, and lifestyle diseases, and antimicrobial resistance, require device-supported systems to understand and control diseases. Guidance and surveillance systems based on evidence have the potential to strengthen control by preventing transmission, eliminating risks, and controlling the progression of a disease. Biosensing technologies based on tunable seesaw-like 3D fiber pyro- and piezo-electric nanogenerators, AI-biophysics, and computational and digitally twinned additive manufacturing have been used extensively for monitoring and data collection.[38–42] Furthermore, meta-analysis, integrated digital light processing, 3D printing, mobile health, real-time processing, motion understanding, synchrotron radiation utilization, and ultrasound and nanomaterial-based technologies facilitate quality and quantitative data results.[43–52] Table 2 lists some biosensing materials, including conductive polymers, nanoparticles, and biocompatible materials.

Transducers and electrodes use conductive polymers like polypyrrole and PEDOT due to their excellent conductivity and biocompatibility. Based on conductivity and environmental stability, these materials have been combined in sensors through chemical vapor deposition and electrochemical polymerization techniques. Gold nanoparticles and quantum dots have high surface areas and catalytic capabilities. They can improve biosensor signal amplification and sensitivity through their size, surface area, and reactivity effects. Nanoparticle integration requires their synthesis, functionalization, and immobilization. Finally, silicones and hydrogels are biocompatible, flexible, and bio-analyte-permeable, making them ideal for wearable and implanted devices. For sensor integration, biocompatible and mechanically sound materials are molded, cured, or 3D printed. Table 2 shows the importance of material selection, their quality, and the painstaking processes required to develop and build dependable biosensing devices.

3. Prognostic complications and technological requirements

The diagnosis of many diseases has gotten more difficult in the modern world due to the arrival of emerging pathogens and new environments. Nonetheless, quick developments in the field of biomedical instruments are balancing the additional difficulties.

3.1. Disease markers and sensing process

Conventional blood sample analysis (blood testing) is quite common in hospitals and clinics for the evaluation of specific metabolites, which are potential carriers of disease. For example, diagnosis of the SARS-CoV-2 virus is mostly performed

Table 2 Overview of biosensing materials, design considerations, and integration procedures

Material category	Specific materials	Properties	Selection criteria	Application in sensor design	Integration procedures
Conductive polymers	Polypyrrole, PEDOT	High conductivity, biocompatibility	Conductivity, environmental stability	Transducers, electrodes	Chemical vapor deposition, electrochemical polymerization
Nanoparticles	Gold nanoparticles, quantum dots	High surface area, enhanced catalytic properties	Size, surface area, reactivity	Signal amplification, sensitivity enhancement	Nanoparticle synthesis, functionalization, and immobilization
Bio-compatible materials	Silicones, hydrogels	Non-toxicity, flexibility, permeability to bio-analytes	Biocompatibility, mechanical properties	Wearable sensors, implantable devices	Molding, curing, 3D printing

by reverse transcript polymerase chain reaction (RT-PCR).[53] This technique uses DNA or RNA receptors for the identification of SARS-CoV-2 RNA strands. Furthermore, because of the rapid advancements that have been made in the field of biomedical instrumentation, doctors are now more likely to accurately diagnose a variety of diseases and the complications associated with them. Conventional blood sampling, also known as blood testing, is performed quite frequently in hospitals and clinics for the purpose of determining the presence of metabolites that may be potential carriers of disease through a variety of techniques and instrumentation. For example, the reverse transcript polymerase chain reaction (RT-PCR) is commonly utilized for making a diagnosis of the SARS-CoV-2 virus.[53]

Meanwhile, infections and diseases caused by bacteria are spreading rapidly throughout the world. The consumption of raw, undercooked, or contaminated food has been reported to be the root cause of a variety of foodborne diseases caused by bacteria. These diseases include cholera, diarrhea, meningitis, and gastritis, to name just a few. Further, it is well established that the latter contributes to the development of stomach ulcers and colon cancer. Typical causative bacterial species are *Salmonella*, *E. coli*, *H. pylori*, and *L. monocytogenes*.[54,55] The recognition of SARS-CoV-2 RNA strands can be achieved using DNA or RNA receptors with this method. Furthermore, RT-PCR and the enzyme-linked immunosorbent assay (ELISA) are frequently used in serological tests for the detection of chikungunya virus, dengue virus, and bacterial species, such as *salmonella* and *H. pylori*.[5,8–10] ELISA is also used for the detection of cholesterol, glycated hemoglobin (HbA1C) and cardiac troponin-I, among other things. In addition to these methods, specialized equipment, such as electrocardiogram (ECG), electroencephalogram (EEG), and electromyogram (EMG) machines, are utilized to monitor the rate of the heartbeat, cognitive conditions, and muscular activities, respectively. Most of the time, imaging methods, such as computed tomography (CT) scanning and magnetic resonance imaging (MRI), are utilized to visualize the precise location(s) of cancerous and tumor cells. The use of thermal imaging techniques is also common to analyze the temperatures of the plantar feet of diabetic patients when they have foot ulcers (DFU).[56]

Moreover, diabetes can cause severe comorbid situations and is therefore referred to as a "silent killer". Diabetes can cause a number of serious health complications, including kidney disease, foot ulceration (which, in chronic cases, may require amputation), retinopathy, high blood pressure, and cerebral stroke. This is because diabetes and its complications and comorbidities often reinforce the formation of cancer or tumor cells, which can ultimately lead to death.[57] Despite significant technological advances in healthcare diagnostics, conventional methodologies still suffer from serious drawbacks.

3.2. Emerging risks and technological limitations

Global public health risks should be fought with innovative solutions that should strengthen identification, diagnosis, treatment, and control. The development of such connected health platforms can be made possible through the combination of artificial intelligence (AI) capabilities and miniaturized sensors. Understanding and refining measurement technology, its development, cost-effectiveness, adaptability, and the supply chain for products are real challenges today that research and development businesses need to focus on. Today, a multitude of experts are required to solve the most demanding sensing measurement issues and their integration with appropriate technology. Serious and continuous efforts are required for overcoming the regular challenges. In addition to pathogenic species, complications caused by the excessive consumption of unhealthy foods or junk food are also common throughout the entire world. This kind of food is a source of high cholesterol and fat content, which in turn leads to a high risk of arteries becoming blocked, preventing blood from flowing through them. The latter is extremely fatal, as it can result in complications, such as hypertension and acute myocardial infarction (heart attack). Consuming junk food can also lead to diabetes, a condition characterized by a pancreas that is unable to function properly.

4. Methodologies for wearable biosensor devices and associated digital technology

Digital representation by a device based on a biosensor can provide prompt information, allowing patients to get the care they need as quickly as possible. Technological advancements in the field of nanoscience and nanotechnology have allowed the development of novel nanobiosensors for PoC diagnostics. Incorporating appropriate sensor solutions developed by researchers based on data from experiments into technological products is of critical importance. The goal of the current field of sensor science and technology is to develop methods by which any measurable value or state can be converted into a digital representation by a device based on reliable performance. In addition to their usefulness as PoC devices, biosensors can also reduce the amount of time patients have to wait for the results of conventional tests. Recent advances in wearable biomedical sensors for products have proven this to be a challenging task. As a result, most of the research and development efforts have been directed toward developing novel approaches and methods to solve the sensing depth, as well as their incorporation into appropriate technologies. Fig. 2 shows some sensing methodologies and technological avenues for the development of healthcare devices and methods.

4.1. Wearable biosensor functionality

The functionality of diverse and unique materials offers unique sensing methodologies and technological avenues that may be useful for the development of healthcare devices. The principle of FRET-based red-emitting ion sensors and Cas12a activation offers opportunities for unique sensing methods and further functionality for development in the

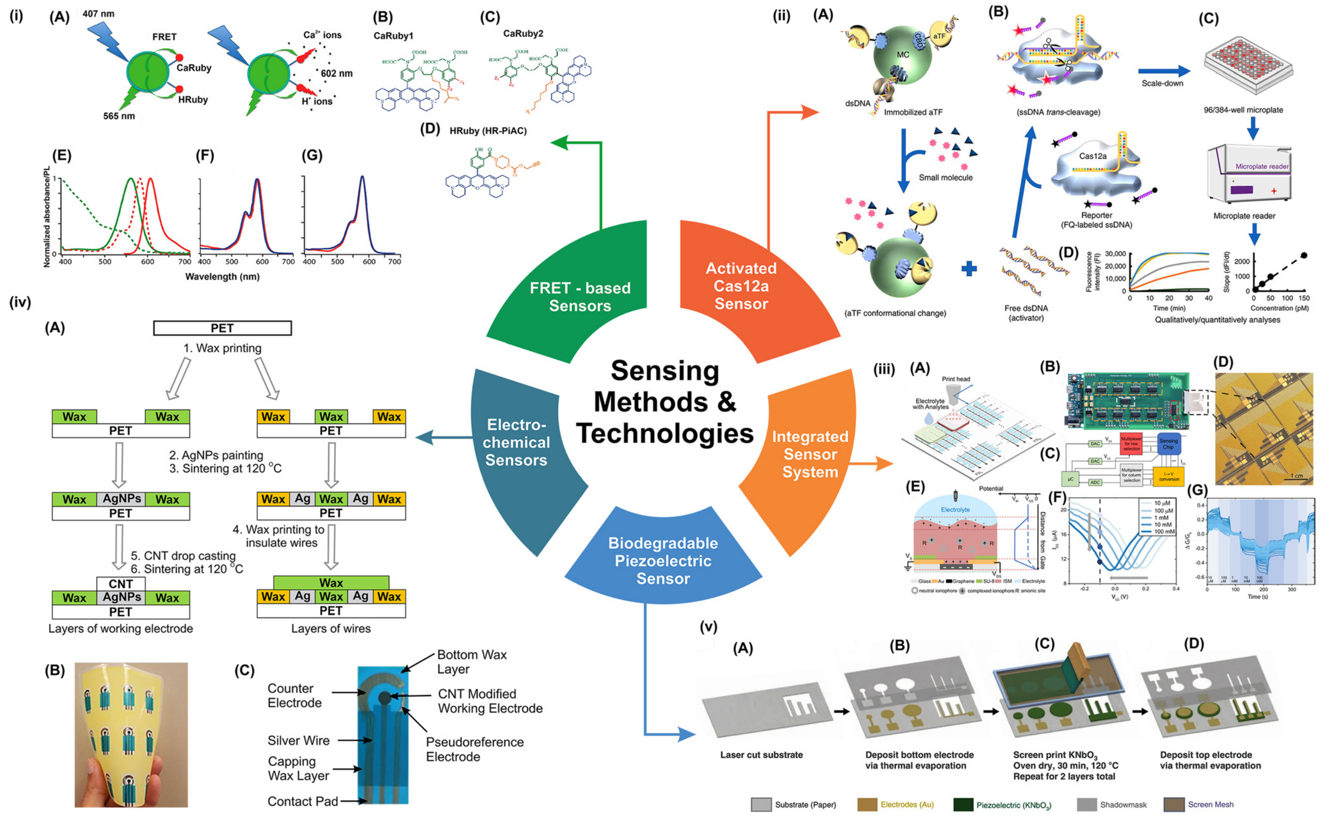

Fig. 2 Sensing methodologies and technological potential for the development of healthcare devices and methods. (i) (A) Principle of FRET-based red-emitting ion sensors. When a green-emitting quantum dot (QD: here CANdot®565) donor is coupled to a red-emitting rhodamine-based ion sensor, an analyte-dependent FRET signal is produced upon donor excitation at 405 nm. The custom red-emitting ion sensors used here are Ca^{2+} (or H^+) indicators, whose emission is suppressed by PET in the absence of their ligand. The binding of an analyte causes a strong fluorescence peak at 602 nm; (B–D). All sensors are based on a rhodamine moiety that has been extended (blue). For the lower and higher affinity families, CaRuby1 (M-mM range) and CaRuby2 (sub-M range), respectively, as the two Ca^{2+} sensor families incorporate a BAPTA moiety (green), without (B) and with (C) an oxygen introduced on one of the aromatic ring of the BAPTA. The pH sensor family (HRubies), (D) is distinguished by the addition of a phenol rather than a BAPTA. Through a piperazine carbamate link, HR-PiAC bears an alkyne moiety at the *ortho* position of the phenol. (E–G) Spectral properties of the retained donor/acceptor pairs' (E) normalized absorbance and emission spectra (dashed and plain lines, respectively) of QD565 (green) and CaRu-Me (red). CaRu-Me and QDCaRu-Me KDs were similar, as expected, because there was only a slight Ca^{2+} sensitivity in CaRu-Me absorbance when switching from an EGTA- to 2 mM Ca^{2+}-containing solution. $CaRu_2$-F and HR-PiAC should have similar properties because their absorbance is Ca^{2+} and pH insensitive, as shown in panels (F) and (G), where blue and red traces represent the absence and presence of the analyte, respectively.[58] (i) Illustrations adapted from ref. 58, CC BY 4.0 (**http://creativecommons.org/licenses/by/4.0/**), (ii) schematic diagram of the CaT-SMelor (sensing platform of CRISPR-Cas12a and allosteric transcription factors, aTF) functionality (A), on microcrystalline cellulose, aTF fused to a cellulose-binding domain (CBD-aTF), was immobilized. The functional dsDNA contained both the PAM sequence and the binding motif of the corresponding aTF, and it specifically binds the aTF's DNA-binding domain. aTF's conformation was changed in the presence of the target small molecule, resulting in the dissociation of dsDNA from the aTF-binding domain.[59] (B) Cleaving of a fluorophore quencher (FQ)-labeled ssDNA probe is initiated by activated Cas12a. (C and D) Target small molecules can be analyzed qualitatively or quantitatively by measuring the shift in the fluorescence signal.[59] (ii) Illustrations adapted from ref. 59, CC BY 4.0 (**http://creativecommons.org/licenses/by/4.0/**). (iii) (A) Schematic of a sensing chip with *NN* sensor units (N = 16 in this paper). Multiplexed measurements are possible by printing different surface functionalization membranes onto different regions of the sensor array. (B) Photograph of the measurement system and sensor array taken with an optical camera. (C) Color-coded block diagram of the measurement system with dashed boxes in B. (D) Graphene sensing arrays on a glass wafer as seen through a microscope. 1 cm is the scale bar. (E) Individual sensing unit schematic with the ion-sensitive surface functionalization membrane. On the right, the electrostatic potential as a function of distance from the graphene surface is depicted. ISM: ion-sensitive membrane; VM: membrane potential; VGS: gate to source voltage; VDS: drain to source voltage; VS: potential at source. (F) *I–V* curves were shifted to the left in a typical device from a Na^+ ISM functionalized sensing chip with an increased sodium ion concentration and VDS = 300 mV. The black dashed line represents the current level at VGS = 0.1 V, and the left-shift of the *I–V* curves causes a decrease in the current. (G) Normalized conductance transient responses of 215 working sensing units to changing concentrations of ionized sodium at VDS = 300 mV and VGS = 0.1 V.[60] (iii) Illustrations adapted from ref. 60, CC BY 4.0 (**http://creativecommons.org/licenses/by/4.0/**). (iv) A. Fabrication and layering of hand-painted CNT/AgNPs electrochemical sensors. The fabrication steps 1–6 were completed in order. In step 4, a wax layer was selectively printed to insulate wires, and in steps 5 and 6, CNTs were drop-cast on the working electrode before sintering. (B) Flexibility of 12 hand-painted CNT/AgNPs electrochemical sensors on a wax-on-plastic platform. (C) Hand-painted CNT/AgNPs electrochemical sensor image.[61] (iv) Illustrations adapted from ref. 61, CC BY 4.0 (**http://creativecommons.org/licenses/by/4.0/**). (v) (A) Laser cutting the substrate for cantilever devices, (B) thermal evaporation deposition of the Au bottom electrode, (C) screen printing of the $KNbO_3$ ink, which was repeated once, with a 30 min oven drying step at 120 °C between layers, and (D) thermal evaporation of the Au top electrode.[62] (v) Illustrations adapted from ref. 62, CC BY 4.0 (**http://creativecommons.org/licenses/by/4.0/**).

biomedical field.[58,59] Studies on these have shown that the chemical structure of such sensors can be based on a color indication against variable molecular compositions. Further, it was also shown that the free dsDNA then binds to the Cas12a-crRNA complex, triggering Cas12a's nonspecific ssDNA *trans* cleavage activity (activated Cas12a). Cas12a is thus activated and begins cleaving a fluorophore quencher (FQ)-labeled ssDNA probe. Highly integrated sensing systems can be developed through multiplexed measurements by using sensor arrays based on electronic and electrochemical methods.[60] It was shown that hand-fabricated CNT/AgNPs electrodes using a wax-on-plastic platforms could be developed for electro-immunosensing applications.[61] In another study, printing paper was designed for use with printed electronics because of its low surface roughness (2–3 m) and robust thermal properties (stable up to 200 °C)[62] in comparison to the surface roughness and thermal stability of other biodegradable substrates.

4.2. Wearable biosensor technology

The integration of appropriate sensor solutions into technology products based on experimental data is very important. Among the key aims in the current field of sensor science and technology is to take advantage of appropriate measurable values or states that can be converted into a digital representation by a device based on reliable performance. In this way, biosensors will be able to provide accurate and prompt information, allowing patients to get the care they need as quickly as possible. The incorporation of nanomaterials into suitable substrates has opened up a multitude of possibilities for anchoring bioreceptors, such as enzymes, DNA, and antibodies, along with provisions for further functionalization, resulting in rapid and highly sensitive biosensing platforms with very low detection limits. The miniaturization of biosensing devices has been greatly facilitated by the development of advances in capabilities for designing, fabricating, and analyzing in the micro/nano regime. A glucose oxidase (GOx)-modified electrode strip glucometer that can display blood glucose levels in a pocket-friendly module is a good illustration of a typical example of this. These glucometers are commercially available and are used by many people. The development of wearable nanobiosensing devices, which offer provisions for the constant and real-time monitoring of vital parameters, is essential to the focus on establishing affordable healthcare; however, this development is heavily dependent on the development of wearable nanobiosensing devices. Wearable biosensor technology is a rapidly developing area of research in the discipline of modern healthcare and biomedical instrumentation. It is estimated that the global market value of wearable sensors will increase annually by 24.1% from 2017 to 2023, eventually reaching the target of $99 billion.[64] The global market value of wearable sensors was reported to have reached the staggering mark of $22 billion in 2016. The need for wearable biosensing devices has emerged in response to rising dangers in the physical and mental health conditions of human beings, as well as the universal demand for real-time patient monitoring that requires as little intervention from outside sources as possible, and the increased likelihood that favorable outcomes will be achieved. It is possible to create highly sensitive, efficient, and cost-effective smart wound dressings for real-time health monitoring by combining the benefits offered by nanomodified electrodes with their integration with miniaturized electronics.[65,66]

4.3. AI-based biosensor technology

The benefit of artificial intelligence derives from the implementation of IoT-based technology, and, as a result, relies on the machine learning feature to make recommendations regarding suitable doctors or medications, or even to automatically call an ambulance in the event of an emergency. These recommendations are made based on the patient's previous medical records, which can be accessed from dedicated cloud servers. Furthermore, AI relies on this feature to make recommendations about suitable doctors or medications. To make smart decisions, the following factors are considered: (1) data, where devices contribute to a common data model; (2) parallel data processing, from acquisition to storage; (3) big data analytics and the use of AI for real-time decision; (4) privacy-oriented data processing with encryption and security.[67]

Due to recent developments in IoT, AI, and big data analytics, a continuous flow of data along with a patient's medical history can efficiently support personalized healthcare and can automate many tasks, such as archiving medical data and evaluating the effectiveness of medical interventions. Therefore, the implementation of highly reliable, accurate, miniaturized, sensitive, and efficient nanobiosensing devices possesses huge market potential to revolutionize and establish next-generation connected health platforms.[67,68] In the following section we highlight and evaluate the latest advancements in the field of wearable biosensing devices that are integrated with miniaturized electronics and AI, as well as devices that have the potential to be translated into IoT and AI platforms. In addition, this section focuses on devices that have the potential to be integrated into these fields. Smart sensor modules typically consist of a cost-effective flexible sensing strip, preferably modified with a suitable bio-nano hybrid, along with a portable electronic microcontroller integrated with a touch screen display (*i.e.*, smartphone or personal digital assistant (PDAs)) and Bluetooth. The latter is an important part of the overall module because it can enable real-time monitoring and wireless data transmission to nearby hospitals and clinics. This will allow for prompt interventions, which will ultimately lead to an effective connected health platform. In addition, the incorporation of Bluetooth feature would make it possible to manage local databases using cloud computing, with the electronic microcontroller serving as the central hub. For more effective patient monitoring and diagnostics, dedicated cloud servers may also be set up in nearby centralized clinics or hospitals at specific locations.

4.4. Fabrication, electrochemical, and other sensing performances

A recent study by Lim *et al.* focused on the fabrication of an all-in-one flexible wireless sodium (Na^+) sensor (Na^+).[69] The latter was developed using a combination of microfabrication, screen printing, and electrodeposition techniques, whereby the working/sensing electrode area consisted of Au/CNT/Au nanocomposites. That recent study presented a schematic of the flexible wireless Na^+ sensor along with its various components used during its fabrication. Here, a wireless, modular sodium sensor system was outlined, where electrochemical deposition was used to create a multilayered integrated device and sodium sensor on Au pads.[69] The initial Au working area was defined as a 2 mm diameter region using conventional photolithography. Then, pristine SWCNTs were continuously dropped on the circular Au surface, followed by the electrodeposition of Au nanoparticles. To ensure the selectivity of the flexible sensor toward Na^+, a 3 μL droplet of a synthesized ion-selective membrane solution was further coated on the nanomodified electrodes.

The development of the sensor through fabrication based on electrochemical, and other sensing performances is shown in Fig. 3. One study reported paper made from CF/GO/cellulose, whereby to enable the assembly of GO sheets onto the surface of the cellulose fibers, cationic polyacrylamide (CPAM) was used to control the interfacial interactions.[70] In same study, high-performance, long-lasting paper-based sensors for portable electrochemical detection were demonstrated.[70] In another study, a lens-free optofluidic plasmonic sensor was used for the real-time and label-free monitoring of molecular binding events over a wide field-of-view.[71] Also, Roy *et al.* developed screen-printed microfluidic technology to monitor diabetic foot ulcers using a portable potentiostat (DFU).[72]

The fabrication of a nanomodified microfluidic smart wound dressing accepted in that analysis was demonstrated in several studies. The microcontroller was then sealed on top of the tape at the rear of a band-aid. In such circumstances, Kapton tape served as a heat sink that could draw the microcontroller heat and dissipate it through the edges of the tape.[73] Only the working electrode could be quantified electrochemically, which

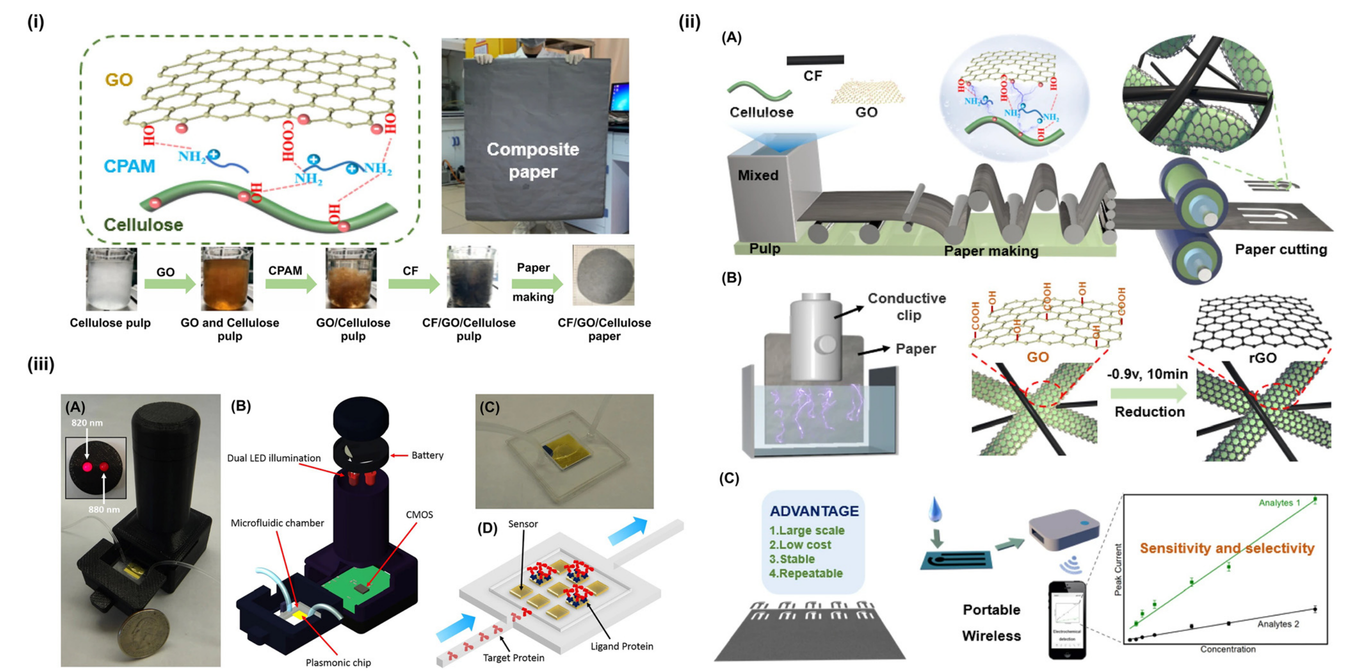

Fig. 3 Development of sensors through various fabrication processes based on electrochemical and other sensing performances. (i) Preparation and characterization of CF/GO/cellulose paper.[70] (i) Illustrations adapted from ref. 70, CC BY 4.0 (http://creativecommons.org/licenses/by/4.0/). (ii) Large-scale preparation of high-performance paper-based electrochemical sensors. (A) Papermaking on a large scale. By controlling interfacial interactions, the composite paper was prepared and composed of cellulose, carbon fibers (CFs, confers conductivity) and graphene oxide (GO, confers electrocatalytic activities). (B) GO reduction *via* electrochemistry. Electrochemistry is a simple and scalable method for GO reduction. (C) Paper-based electrochemical sensor concept. The goal was to develop high-performance, long-lasting paper-based sensors for portable electrochemical detection.[70] (ii) Illustrations adapted from ref. 70, CC BY 4.0 (http://creativecommons.org/licenses/by/4.0/). (iii) (A) Photo of an on-chip sensing device with a plasmonic substrate at the bottom of a microfluidic channel. Inset: the lensless device's head, which contains two spectrally distinct LEDs (with peak wavelengths of 820 nm and 880 nm) for simultaneous illumination of the microfluidic chip. (B) On-chip biosensing device composed of a battery, two LEDs, a plasmonic chip, a microfluidic chamber, and a CMOS imager chip comprise. (C) Illustration of the microfluidic system's inlet and outlet ports. (D) Schematic of the flow-over scheme for delivering target samples to the plasmonic substrate.[71] (iii) Illustrations adapted from ref. 71, CC BY 4.0 (http://creativecommons.org/licenses/by/4.0/).

reduces the proof-of-concept costs. As supported by voltammetric and chronoamperometric analysis, they observed a linear performance between the sensor current and different concentrations of tyrosine, within 5 nM–500 μM, with detection limit and sensitivity considered at 0.71 nM and 0.67 μA nM^{-1} mm^2, with reproducible results in both simulated and human serum samples noted in actual time.[72] In contrast to the earlier all-in-one wireless Na^+ sensor, Roy *et al.*'s bandage was extremely cost-effective, because it eliminates the need for tedious microfabrication of the bandage/electrode and due to the ease of integrating miniaturized electronics on screen-printed nano-enabled bandages for real-time data acquisition. Utilizing such intelligent wound dressings could enable the real-time monitoring of the ongoing condition of diabetic foot ulcers, resulting in more expedient treatment while mitigating the risks of comorbidities and, in the worst-case scenario, amputation.

Another study on the development of smart bandages was conducted by Kassal *et al.* for monitoring uric acid concentrations, as an indicator of wound status.[74] Bandages were manufactured by screen printing Prussian blue carbon ink onto the surface and then printing as Ag/AgCl pseudo-reference electrodes. The overall design of the bandage was based on a standard two-electrode configuration, which is advantageous for device miniaturization and microcontroller integration. For the selective detection of uric acid, the Prussian blue carbon working electrode was modified with uricase enzyme *via* glutaraldehyde cross-linking. The bandage was then incorporated with a portable potentiostat the size of a credit card equipped with an RFID/NFC interface for data transmission to a smartphone or PDA. Real-time chronoamperometric analysis at −0.3 V *versus* Ag/AgCl indicated a linear response to uric acid concentrations between 100 and 800 μM. The sensitivity coefficient of the developed smart bandage in uric acid detection was reported to be ∼2.4 nA μM^{-1}. Furthermore, repeated calibrations of the smart bandage-based sensor yielded a consistent sensitivity coefficient of ∼2.39 ± 0.04 nA μM^{-1}. The wearable sensor exhibited a selective response solely toward uric acid, thus significantly negating interference due to common electroactive wound metabolites, such as ascorbic acid, creatinine, lactate, and glucose. The UA biosensor exhibited excellent linearity over the full physiological concentration range independent of the instrument, with R^2 = 0.9987 for the CHI 440 electrochemical analyzer, R^2 = 0.9985 for the wearable potentiostat, and with excellent agreement between the two instruments of R^2 = 0.9967. The sensitivity coefficient (SC) of the biosensor was calculated from the slope of the calibration plots and found to equal −2.4 nA μM^{-1} UA with both instruments. Bending created natural mechanical stress on the wound dressings due to the human body's curvature, mobility, and flexing at the application site. The bandage was folded and released 80 times at 180° to test how mechanical deformation impacted the UA biosensor. Every 20 bends, the reaction to a 400 μM UA standard was monitored. It was found that after repeated bending stress, the smart bandage biosensor's electrochemical response did not change (RSD = 5.60%).[74]

The efficacy of paper microfluidics toward IoT/AI-based connected health platforms based on IoT/AI has recently been investigated with the development of a SARS-CoV-2 immunosensor, to monitor COVID-19 in possible patients. In 2020, COVID-19 transformed into a pandemic. Yakoh *et al.* created a paper-based lateral flow assay (LFA) immunosensor for detecting IgG, IgM, and spike protein.[75] The hydrophobic sample boundaries were developed using a wax barrier on paper substrates. In addition to voltammetry and amperometry techniques, electrochemical impedance spectroscopy (EIS) has been extensively studied as a sensing tool. The use of small-amplitude sinusoidal signals at the electrode–electrolyte interface, within a frequency spectrum, enables distinguishing between bulk and interfacial processes. The calculation of the overall impedance follows Ohm's law and is given as the following equation (where the bold font in eqn (1) indicates the phasor notation):

$$Z(\omega) = \frac{V(\omega)}{I(\omega)} \tag{1}$$

where

$Z(\omega)$ = complex impedance generated over a defined frequency range,

= $\mathrm{Re}\{Z(\omega)\} + j\mathrm{Im}\{Z(\omega)\}$

$V(\omega)$ = sinusoidal voltage applied across an electrode system,

$I(\omega)$ = time-varying current flowing across the electrode system,

ω = angular frequency of the applied sinusoidal voltage signal.

In any electrode–electrolyte-based sensor, the bulk and interface regions yield unique impedance signatures at various frequencies that can aid analyzing the charge-transfer kinetics in greater detail, and ultimately sensor calibration with ultrahigh sensitivity and a low LOD.[76]

A wireless electronic health patch and piezoelectric energy harvesting and flexible sensing devices were developed with an integrated mechanism and fabricated in ultrathin devices for better usability[77,78] (Fig. 4). In another work by Zhang *et al.*, the development of a smartphone-based electrochemical sensor for the detection of bull serum albumin (BSA) and thrombin was investigated.[79] The sensing strip for BSA detection was primarily a screen-printed carbon electrode based on a three-electrode setup.

The carbon working electrode was modified with anti-BSA (antibody) and a layer of nitrocellulose membrane, relying on the typical immunoresponsive sensing of BSA in the 5 mM $[Fe(CN)_6]^{3-/4-}$ redox probe. However, the sensing strip for the detection of thrombin was based on Au interdigitated electrodes. A characteristic of an electronic system indicates whether the sensor is properly associated, connected, or transmitted. The main constituent is any signal condition associated with the biosensor device that indicates the physical environment.

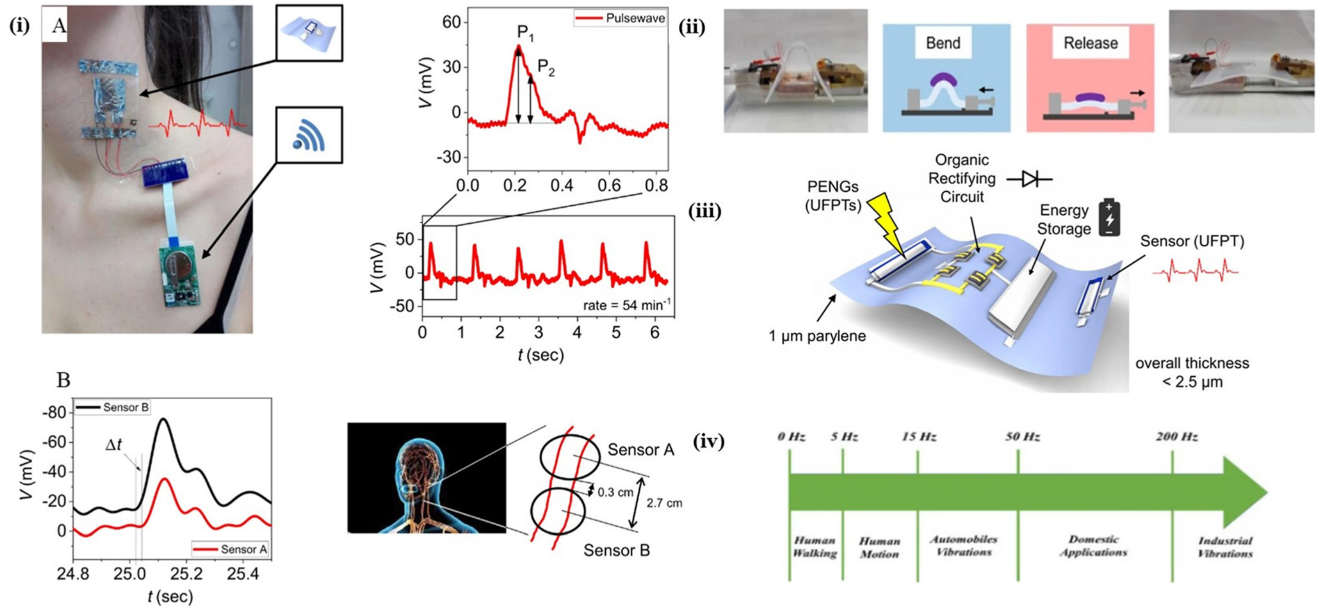

Fig. 4 Wireless electronic health patch and self-powered wearable sensors. The wireless e-health patch's attachment points, where the ultraflexible transducer serves as an imperceptible sensor that adheres to the skin without adhesive. The patch has the ability to monitor (A) human pulse waves (with P1 and P2 peaks), from which the rate (here: 54 min^{-1} for a 32 year-old woman) and artery augmentation index AI (here: AI 56%) can be calculated. (B) Pulse wave velocity (PWV) is used to calculate the blood pressure of human arteries in the neck. The PWV is calculated by measuring the signal delay *t* for a given sensor distance *x*. PWV in this case was 9 m S^{-1} for a 34 year-old man.[77] (i) Illustrations adapted from ref. 77, CC BY 4.0 (**http://creativecommons.org/licenses/by/4.0/**). (ii) Energy collection. Photographs and diagrams of the bending process.[77] (ii) Illustrations adapted from ref. 77, CC BY 4.0 (**http://creativecommons.org/licenses/by/4.0/**). (iii) Piezoelectric energy harvesting and sensing device with extreme flexibility. A scheme depicting a variety of ultraflexible devices integrated on a 1 m thin parylene substrate, as well as photographs of the fabricated devices.[77] (iii) Illustrations adapted from ref. 77, CC BY 4.0 (**http://creativecommons.org/licenses/by/4.0/**). (iv) Frequency levels of common mechanical energy sources for self-powered wearable sensors based on piezoelectric and triboelectric nanogenerators.[78] (iv) Illustrations adapted from ref. 78, CC BY 4.0 (**http://creativecommons.org/licenses/by/4.0/**).

5. Wearable electrochemical biosensing performance

The electrosensing of thrombin was based on its ability to cleave the Arg–Gly bond of a defined octapeptide sequence linked to BSA, immobilized onto the Au interdigitated electrode surface. Higher concentrations of thrombin would then lead to a greater degree of Arg–Gly bonds and remove the linked BSA, which could be calibrated as a measure of enhanced charge-transfer kinetics at the electrode–electrolyte interface. The core of the smart biosensor was based on an Arduino microcontroller capable of communicating with an AD 5933 impedance analyzer chip. The latter sent clock signals through the ADF 4001 clock chip to generate a sinusoidal signal of 200 mV amplitude, within the frequency range 10 Hz to 10 kHz. The corresponding impedance spectra during BSA and thrombin detection, with the respective R_{ct} values, were displayed on a smartphone by means of wireless data transmission. The LODs for BSA and thrombin, obtained by using the portable smartphone-based biosensor, were calculated to be 1.78 μg mL^{-1} and 2.97 ng ml^{-1}, respectively, with a high degree of selectivity in a mixture of human serum albumin and an 11-peptide sequence.

Table 3 provides an overview of wearable sensors for biomedical applications. This table summarizes various wearable sensors designed for biomedical applications, highlighting their target analytes, sensing strategies, linear ranges, and sensitivities.

5.1. Wearable smart biomedical products

In the research and development section, the expert domain should contribute to the design and development of a conceptual sensor to measure physical entities. Improvement in performance requires innovation, technology, designs, prototypes, and testing for the development of sensor products, and support throughout the development cycle, from prototype to production. The reported wearable smart biomedical sensors mostly utilize separate battery-based power sources. When designing electronic circuits, this frequently necessitates a large number of empty slots, which can compromise the need for miniaturization. To produce effective miniaturized electronics, we need to follow Moore's law, which stipulates that the number of transistors per chip will double every 18 months. A large empty battery slot on the circuit board could be annoying. In addition, the disposability of batteries is one of the difficult issues, as the simple burning of electronic waste (e-waste) could produce biohazards. In recent years, extensive research has been

Table 3 List of recently developed wearable electrochemical biosensing platforms for healthcare monitoring applications

Sl. no.	Wearable sensing surface	Target analyte	Sensing strategy	Linear range	Sensitivity	Ref.
1	PANI on bandage	Wound pH	Potentiometry	2.69–8.00	56 mV pH^{-1}	66
2	ZIF-67/C_3N_4 on cellulose paper	*S. aureus*	Impedimetry	1 fM–10 μM	0.25 kΩ fM^{-1} mm^2	80
3	Prussian blue carbon/uricase on PET sheets	Uric acid	Amperometry	0–600 μM	2.45 μA mM^{-1}	81
4	Graphite on a cellulose-polyester cloth	pH	Amperometry	6–9	4 mV pH^{-1}	82
5	Graphene-AgNW on contact lens	Intraocular pressure	Frequency response analysis	5–50 mm Hg	2.64 MHz mm Hg^{-1}	83
6	GOx/chit/CNTs on Prussian blue/Au electrodes	Glucose	Amperometry	0–200 μM	2.35 nA μM^{-1}	84
	LOx/chit/CNTs on Prussian blue/Au electrodes	Lactate		0–30 mM	220 nA mM^{-1}	
7	Flavin/carbon-polyethylene film	Wound pH	Voltammetry	2.55–8.12	60 mV pH^{-1}	85
8	Laser-treated polyimide	Wound pH	Voltammetry	2.8–8	56 mV pH^{-1}	86
9	Uricase on carbon film	Uric acid	Amperometry,	0.2–1 mM	Not specified	87
	Ag/PANI on bandage	Wound pH	impedimetric	5.5–8.5		
10	LOx/chit/carbon electrodes-based eyeglasses	Lactate	Amperometry, potentiometry	0.1–14 mM	0.8 μA mM^{-1}	88
	Valinomycin/PVC/carbon electrodes-based eyeglasses	Potassium		0.1–100 mM	60.6 mV mM^{-1}	

conducted on the development of self-powered wearable or mobile biosensors to address these issues.

5.2. Self-powered sensors based on nanogenerators

This section highlight some fundamental self-powered nanogenerators and their applications in wearable biosensors based on artificial intelligence. In response to the drawbacks of implementing battery-powered smart wearable biosensors, the current strategy is to fabricate nanogenerators that can serve as a highly reliable source of renewable energy to generate electricity in order to power wearable sensors. As discovered by Wang and co-workers,[89,90] nanogenerators employ suitable nanomaterials to transform mechanical energy (input) into electrical energy (output). The latter can be harnessed in two ways, either by piezoelectric effect or triboelectric effect, and the resulting devices are known, respectively, as piezoelectric nanogenerators (PENGs) or triboelectric nanogenerators (TENGs). These are essentially capacitive devices and therefore depend on the displacement current density J_D for output power generation.[91] The displacement current density is given as eqn (2):

$$J_D = \frac{\partial D}{\partial t} = \varepsilon_0 \frac{\partial E}{\partial t} + \frac{\partial P}{\partial t} \quad (2)$$

where $\boldsymbol{D}$ = electric displacement vector,
ε_0 = permittivity of free space,
E = electric field intensity,
P = polarization density.

Since there are no external electric fields while the latter is generated solely by induced polarization charges, the second term in eqn (2) becomes an essential factor in determining the output power density.[91]

The viability of self-powered nanogenerators lies in their ability to be integrated with miniaturized electronics for the development of personalized mobile healthcare devices. For example, Zhang and co-workers reported a PVDF-based flexible and implantable PVENG based on PVDF, which was capable of capturing energy from pulses generated in the ascending aorta.[92] Their study also performed *in vivo* and *in vitro* studies of energy harvesting through vibrational artery pressure by employing a flexible and implantable PENG device, as shown in Fig. 6. The PVDF-based PENG device outputted 681 nW, 10.3 V, and 400 nA *in vitro*. One arterial pulse produced 7–9 nC. The PENG generated 1.5 V and 300 nA when implanted in a porcine's ascending aorta (*in vivo*). The PENG device's instantaneous output power peaked at 30 nW for 700 ms. The PVDF-based PENG could charge 1 F to 1.0 V in 40 s.

Another innovative research was carried out by Xue and co-workers on the development of a self-powered electronic skin to monitor glucose concentrations in body fluids.[93] They employed a novel piezoenzymatic coupling reaction strategy employing GOx–ZnO nanowires, whereby mechanical pressure (due to bodily movements) could convert electric energy, which was in turn affected by the glucose concentration because of the electrocatalytic influence of GOx. The GOx enzyme was immobilized on an array of ZnO nanowires, while the latter were grown on titanium foil. The PENG device was manufactured by sandwiching an array of GOx–ZnO nanowires between two layers of 50 m thick aluminum foils covered with PDMS, the latter of which was used to prevent electrical leakage. The device's overall dimensions were 0.6 cm × 0.6 cm, allowing it to be easily integrated or implanted beneath the skin to monitor glucose levels. The developed PENG device yielded consistent variations in output voltage from 133–6 mV, as the glucose concentration increased from 0–0.125 ng L^{-1}. The electrocatalytic oxidation of glucose molecules by GOx effectively increased the surface carrier density in the ZnO nanowire array, which eventually lowered the piezoelectric output voltage because of the piezoscreening effect. The PENG device also generated voltage responses to interferants, such as fructose and urea, that were significantly different from those of glucose, indicating that the PENG-based electronic skin was highly selective to the presence of glucose in bodily fluids.

In addition to PENGs, TENGs have also been incorporated into self-powered wearable biosensing units. Recent advancements in implantable TENG are beneficial for self-powered biomedical devices that operate at personalized level. They are also very useful for tracking and evaluating various physiological movements, particularly for chronic conditions like arrhythmia, atherosclerosis, hypertension, and coronary heart disease.[94] Implantable TENGs had biocompatible electrodes, triboelectric layers, and spacers, with 50 μm thick of nanostructured polytetrafluoroethylene (n-PTFE) as one triboelectric layer and Al foil (100 μm thick) acting as both another triboelectric layer and the electrode.[94] To improve leak-proof performance, structural stability, and biocompatibility, PTFE and PDMS (patterned pyramid arrays) layers were applied to the entire device. The implantable TENG was inserted between the epicardium and the pericardium in the pericardial sac, which was then attached to the pericardium at each corner. The operation of the TENG-based sensor was carried out based on the contraction and separation of triboelectric layers in tandem with the relaxation and contraction of the heart, generating a continuous electric output by coupling electrostatic induction and contact electrification. *In vivo* investigation of the self-power generation showed open-circuit voltage and short-circuit current of 10 V and 4 μA respectively.[94] The heart rate recorded by the developed self-powered sensor was compared with a conventional electrocardiogram (ECG) output and was found to be ~99% accurate for point-of-care applications. Fig. 5 shows a personalized healthcare model based on advanced sensing and information technology devices.

5.3. Implantable sensor and digital health system

The digital health system has attracted special attention due to the explosive growth of biomedical applications and the rapid evolution of implantable devices and electronics. This technique involves the monitoring, tracking, and recording of a person's vital signs to collect information about the individual. Smartwatches, armbands, and glasses are examples of implantable or wearable sensors that have become an integral part of our daily lives. An implanted cardiac pacemaker was the first implantable health device manufactured for patients. Kaefer *et al.*[95] created an implanted gold nanoparticle sensor for long-term body concentration monitoring. Fig. 6 shows the output performance of their implantable wearable sensor.

Noninvasively, they evaluated tissue kanamycin levels in anesthetized rats implanted with a gold nanoparticle-based sensor. The implantable sensors showed comparable kanamycin tissue concentrations in the rats after two, three, and four weeks of implantation.[95] The use of biosensors and digital health systems has improved diabetes control, which is a serious disease known as "the silent killer". Such non-invasive glucose monitoring systems can track blood glucose continuously without uncomfortable finger-prick testing needed. This technique improves patient comfort and increases glucose level accuracy, decreasing diabetic complications. Biosensors and digital health systems can enable real-time data analysis and individualized healthcare. This integration empowers patients with personalized food, exercise, and medication advice for proactive diabetes treatment. By using biosensor data, machine learning algorithms can predict blood

Fig. 5 Outlining the features and operating principles of a wearable biosensing system, which can play a pivotal role in personalized healthcare models. This advanced device incorporates an array of sensors, utilizes artificial intelligence for data analysis, leverages cloud computing for storage and processing, and employs IoT technology for seamless connectivity. The system is designed to monitor vital health parameters in real-time, facilitating immediate detection and follow-up. It maintains a continuous, real-time connection with healthcare infrastructure, including hospitals, medical professionals, and ambulance services. This integrated approach can ensure timely medical intervention and enhances patient care by providing healthcare professionals with immediate access to critical health data.

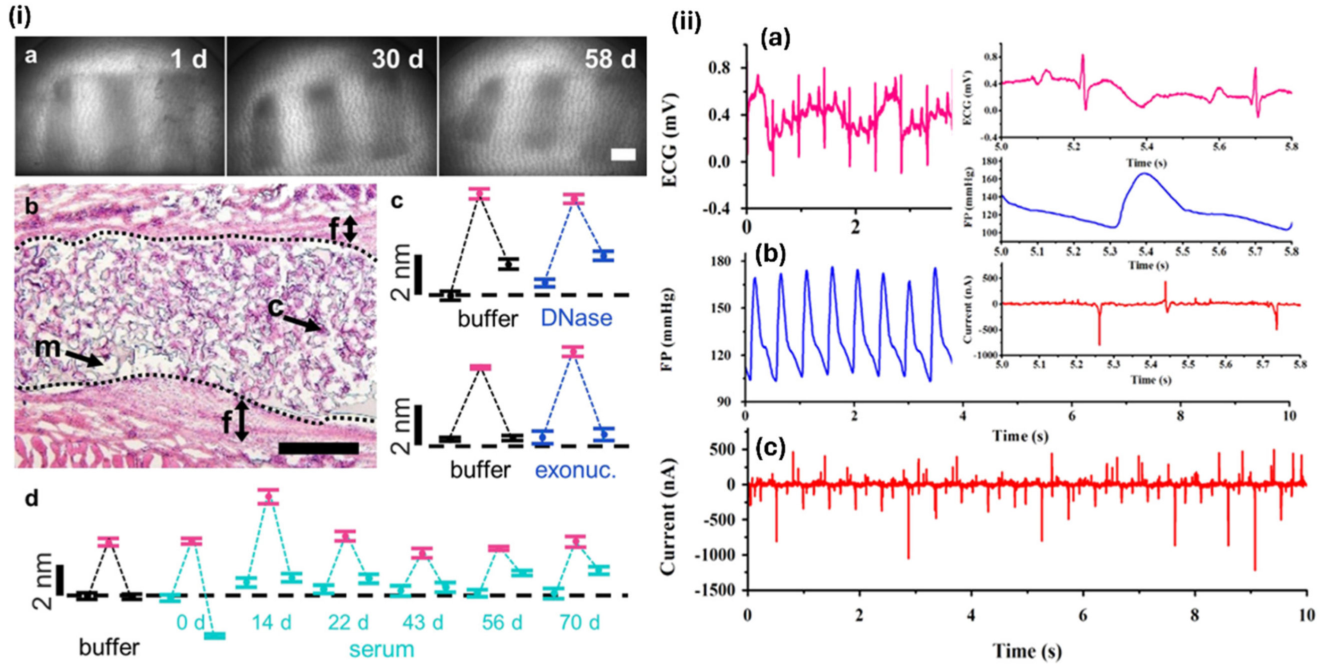

Fig. 6 Long-term stability of an implanted sensor under physiological conditions: (i) (a) transcutaneous images over time (1, 30, and 58 days) post-implantation in rat skin, revealing the maintenance of integrity. (b) Histological section post 65 days, showing the well-integrated sensor architecture with minimal fibrous tissue formation, highlighting cellular integration into the sensor's macropores. Figures (c) and (d) demonstrate the sensor's consistent response to varying concentrations of kanamycin, even after exposure to DNA-degrading enzymes or long-term storage in rat serum, showcasing its reliable and reversible functionality. Reproduced with permission from ref. 95, Copyright © 2021 American Chemical Society. (ii) (a–c) Waveform of the output current, along with the fetal phonocardiography (FP) and electrocardiogram (ECG) signals, with the enlarged waveform presented in the inserted figure for a flexible polyvinylidene fluoride (PVDF) film coated by an aluminum layer piezoelectric implantable sensor. Reproduced with permission from ref. 92, Copyright © 2015 Elsevier Ltd.

glucose changes and warn of hyperglycemic or hypoglycemic situations. These biosensor and digital system advancements improve diabetes control and promise a healthier future. They make diabetes care more effective, individualized, and less invasive by giving extensive insights and prediction tools.[45,95]

6. Recent advancements in sensor-based detection and diagnosis

Diverse disease categories caused by pathogenic microorganisms, genetic predispositions, or unhealthy behaviors are prevalent in society and many regions globally. They include infectious, non-infectious, lifestyle, and chronic diseases. Pandemic diseases, such as the SARS coronavirus, emerging diseases, such as monkeypox, and endemic diseases, such as visceral leishmaniasis, pose a threat to life and an economic burden on society and individuals. Several infectious or zoonotic diseases that can cause illness in humans have emerged in recent decades. The early detection or diagnosis promotes disease prevention directly. Early knowledge of the status of a disease or infection facilitates treatment and promotes a higher quality of life.

Integrated sensor device systems make the detection of diseases and the identification of microorganisms more accessible and accurate. Developed public health models can ensure adaptable, timely and quality support for eliminating and controlling healthcare-related infections. Table 4 presents some recent advancements in detection and diagnosis for biosensing applications.[96–128] Sensors based on diverse functionalities and constituents, such as capacitive pressure sensing, healing wearable sensors, pressure, wireless, FRET-based genetically encoded sensors for silver ions, oxygen sensors on an optofluidic platform, location tracking, metamaterials based on soft tactile, electrospinning-based PVDF-TrFE nanofiber sensors, glycine–chitosan-based biodegradable piezoelectric sensors, and DNA-regulated CRISPR-Cas12a sensors, represent important advances in the biosensor field.[96–106] Detection is based on diverse approaches, including paper-based devices, 3D-printing electrochemical, MoS_2 quantum dots, 2D nanomaterial-enhanced plasmonic functionality, smartphone-integrated colorimetric, PVDF-TrFE nanofiber, electronic, machine learning, fluorescent DNA, non-enzymatic glucose, and silicon nanowire biosensing platforms for the (bio)detection of various analytes ranging from metal, pollutants, cells, genetic materials, and even post-translational modification.[107–117] Biomedical real-time health evaluation is done to diagnose cancer, obesity, bipolar disorder, cardiac issues, SARS-CoV-2/COVID-19, cerebral palsy, diseased skin, *etc.*, as well as for the detection of non-invasive signs, such as for sleep apnea.

6.1. Biomaterials compatibility, functionality, and diverse applications

Biocompatibility and functionality are studied through the testing and demonstration of human body adaptation, clinical

Table 4 Recent advances in detection and diagnosis for biosensing platforms related to several applications

Category	Detail	Ref.
Sensor	Graphene porous foams for capacitive pressure sensing	96
	Transparent, healing, and adhesive hydrogel for wearable sensors	97
	High-performance pressure sensor for wearable electronics	98
	Battery-free wireless sensor for bacteria	99
	FRET-based genetically encoded sensor for silver ions	100
	Oxygen sensor on an optofluidic platform	101
	Enhanced location tracking in sensors	102
	Metamaterials enabling soft tactile sensors	103
	Electrospinning-based PVDF-TrFE nanofiber sensor	104
	Glycine–chitosan-based biodegradable piezoelectric sensor	105
	Functional DNA-regulated CRISPR-Cas12a sensor	106
Detection	Paper-based devices for environmental pollutants	107
	3D-printing electrochemical (bio)sensors	108
	MoS_2 quantum dots for Fe^{3+} detection and cell imaging	109
	Electrochemical biosensor for miRNA detection	110
	2D nanomaterial-enhanced plasmonic biosensor	111
	Smartphone-integrated colorimetric sensor	112
	PVDF-TrFE nanofiber sensor	113
	Electronic nose sensor array signals and machine learning	114
	Fluorescent sensor for DNA detection	115
	Non-enzymatic glucose detection	116
	Silicon nanowire biosensing platforms for post-translational modification	117
Diagnosis	Biomedical REAI-Time Health Evaluation (BREATHE) kit	118
	Quantum sensors in diamond	119
	Mechanophore activation in hydrogels for cancer therapy	120
	Bioactive-functionalized gold nanoparticles for obesity control	121
	DNAzyme-based lithium-selective imaging for bipolar disorder patient understanding	122
	Cardiac signals for gastric fundus	123
	Electromyography sensors	124
	SARS-CoV-2/COVID-19 sensors	125
	Machine learning in cerebral palsy	126
	Non-invasive signs for sleep apnea	127
	Multisensor measurements in healthy and diseased skin	128

characteristics, analytical chemistry, physicochemical behavior, *in vitro* experiments, animal models, and *in vivo* capabilities. Important compatibility testing for materials technology and biomedical devices is required to ensure their safe use with human physiological systems. Before launching a device, several regulatory issues, compliance, safety regulations, standards, and precautions must be addressed and passed to prevent any potential risk to the human body. In addition to other standards, biosensor products should offer a technological advantage based on sensitivity and specificity. The functionality of medical devices varies as a result of their distinctive characteristics. Due to a greater understanding of intricate biological mechanisms, various functionalities have emerged. The advancement of next-generation materials and materials is beneficial for biocompatibility testing and can accelerate the regulatory approval process for medical devices. Table 5 details the biocompatibilities of some sensor technologies, as well as their functionality and applications.[129–158] Biocompatible materials for living cells, bone, biological fluid, yak hair, cellular loading, membrane systems for biomedical and electronics purposes have already studied.[129–136] Functionalities related to cytotoxic, DNA binding, photocatalytic, H_2O_2 detection, antioxidant, transcutaneous measurement, eye-movement tracking, physiological conditions, mitochondria sensors for metabolic state, nanocomposites, gas permeability, DNA methylation, and cancer sensing are important research areas for healthcare devices.[137–145] Applications include carboxymethylcellulose (CMC) optical fibers, silicon carbide sensors, smartphone-based colorimetric biosensors, molecularly imprinted sensors, flexible sensors, piezoelectric ceramics sensors, gas sensing, AI-based sensing, pattern recognition sensor arrays, BioMEMS sensor, electro-immunosensing, strain monitoring, and thermal biosensing application for biomedical healthcare.[146–158]

Recently developed biosensing platforms offering both the biocompatibility of sensor materials and technologies as well as a variety of functions are discussed. Various sensor technologies' biocompatibility, functionality, and applications[96–106,129–158] are outlined in Fig. 7.

Products that are based on analytes and are particularly well designed and novel can measure biological reactions in disease-specific mechanisms. By understanding the pathogenic mechanism, biomarkers, sensing technology, and the utilization of materials, it is possible to produce medical devices that can enable standard biocompatibility testing.

6.2. Future prospects in device industrialization

Industrialization of integrated biosensing-enabled digital healthcare devices appears promising due to various drivers. Sensor technology is enabling the development of more sensitive, accurate, and real-time systems that can detect a wide range of physiological and biochemical markers. This progress, along with the IoT and wearable technology, is facilitating seamless health data transmission and analysis, improving remote monitoring and patient care. The desire for personalized medicine highlights the need for healthcare solutions tailored to individual patients based on their unique health data, obtained by these modern biosensing technologies. There is a shift in focus toward preventive healthcare, which aims to maintain wellness and prevent diseases from requiring significant medical intervention, emphasizing the importance of early detection and continuous monitoring by these devices.[64–68]

AI and machine learning combined with biosensing data is changing the approaches to diagnosis and individualized

Table 5 Recently developed biosensing platforms, indicating both the biocompatibilities of sensor materials and technologies as well as the variety of the functions that these offer and the many different applications of the sensor technologies

Category	Detail	Ref.
Biocompatibility	Biocompatible carbon dots-decorated α-FeOOH nanohybrid sensor for wastewater and living cells	129
	Biocompatibility for bone replacement materials	130
	Biocompatible polymers for electronic applications	131
	Thin-film transistor for biological fluid sensing	132
	Bioplastic film derived from discarded yak hair	133
	Biomechanical cellular loading and compliance experiments	134
	Biological impact of bioconjugated gold nanoparticles	135
	A composite membrane system for biomedical purposes	136
Functionality	Cytotoxic, antimitotic, DNA binding, photocatalytic, H_2O_2 sensing, and antioxidant properties	137
	Transcutaneous measurement of essential vitamins	138
	Eye-movement tracking	139
	Monitoring regional body temperature	140
	Mitochondria sensors for the metabolic state in glioblastoma	141
	Chitosan–ZnO nanocomposites	142
	Gas-permeable sensors for heart monitoring	143
	Biosensor for detection of DNA methylation	144
	Graphene oxide for cancer sensing	145
Application	Carboxymethyl cellulose (CMC) optical fibers for environment	146
	Silicon carbide for healthcare applications	147
	Smartphone-based colorimetric biosensors	148
	Molecularly imprinted nanoparticles for biomedical applications	149
	Flexible sensors for biomedical applications	150
	Piezoelectric ceramics for biomedical applications	151
	Graphene nanoplatelets for gas sensing aerogels	152
	AI-based applications in medical technologies	153
	Pattern-recognition-based sensor arrays	154
	BioMEMS applications	155
	Hand-fabricated CNT/AgNPs electrodes for electro-immunosensing	61
	Strain monitoring and fracture recovery of human femur bone	156
	Thermal nanoimprint lithography for biosensing application	157

treatment. These technologies are improving health data analysis, enabling more accurate diagnosis and individualized healthcare. Technology makes these devices more affordable and accessible, creating new opportunities for improving global health outcomes and expanding their use into emerging countries. Technology businesses, healthcare providers, and research institutes are collaborating to drive innovation and address population healthcare requirements.[40,53]

In order for the sector to be sustainable and scalable, the environmental effects and accessibility of healthcare equipment must be considered. More intelligent, integrated, and patient-centric healthcare solutions are projected to improve patient care and health outcomes as the sector matures. A new era of accessible, personalized, and preventive healthcare is emerging as digital healthcare devices support effective disease management and empower individuals with the tools and information needed for proactive health maintenance.[42–44]

6.2.1 Emerging device technologies. Emerging technologies provide us with the opportunity for progress and to improve activities related to medical diagnosis and treatment. Table 5 outlines some health management advances in the biosensing field based on device development.[163–174] Developments include devices and systems for drug delivery, an ultrahigh pressure sensor, implantable pressure sensor, non-invasive wearable sensor, seizure, stretchable piezoelectric, implanted pH sensor, stretchable hybrid electronics for a skin sensor, bioimaging and wearable light-touch contact, and systems for strokes, *etc.*[163–174]

6.2.2 Commercialization and management. Electrochemical platforms, low-cost electromyography, non-invasive wearables for HbA1c and glucose *etc.*, are used for biomarker sensing and commercialization.[175–178] Health management schedules for oral wearable sensors, stretchable strain sensors for joint motion and respiration monitoring, finger-based pulse oximeters, glucose monitoring systems among adults with type 2 diabetes, bipolar disorder treatment systems *etc.*, have become standard elements of intensive care and follow-up plans.[179–183] Table 6 outlines some health management advances in the biosensing field based on device development.[175–183]

Research progress has led to the conclusion that today's and future materials advances, optimizing the industrial structure, and building a modern environmental governance system integrating modern technologies (AI, IoT, cloud *etc.*) can help progress toward achieving global sustainability (Fig. 8).

6.2.3 Effective biomaterials for indispensable health coverage. Research developments have led to the conclusion that using cutting-edge materials with environmentally friendly functionality, optimizing industrial structure, establishing a contemporary environmental governance framework, and all of these things help to attain global sustainable healthcare. Biomaterials-induced sterile inflammation, mechanotransduction, and principles of biocompatibility

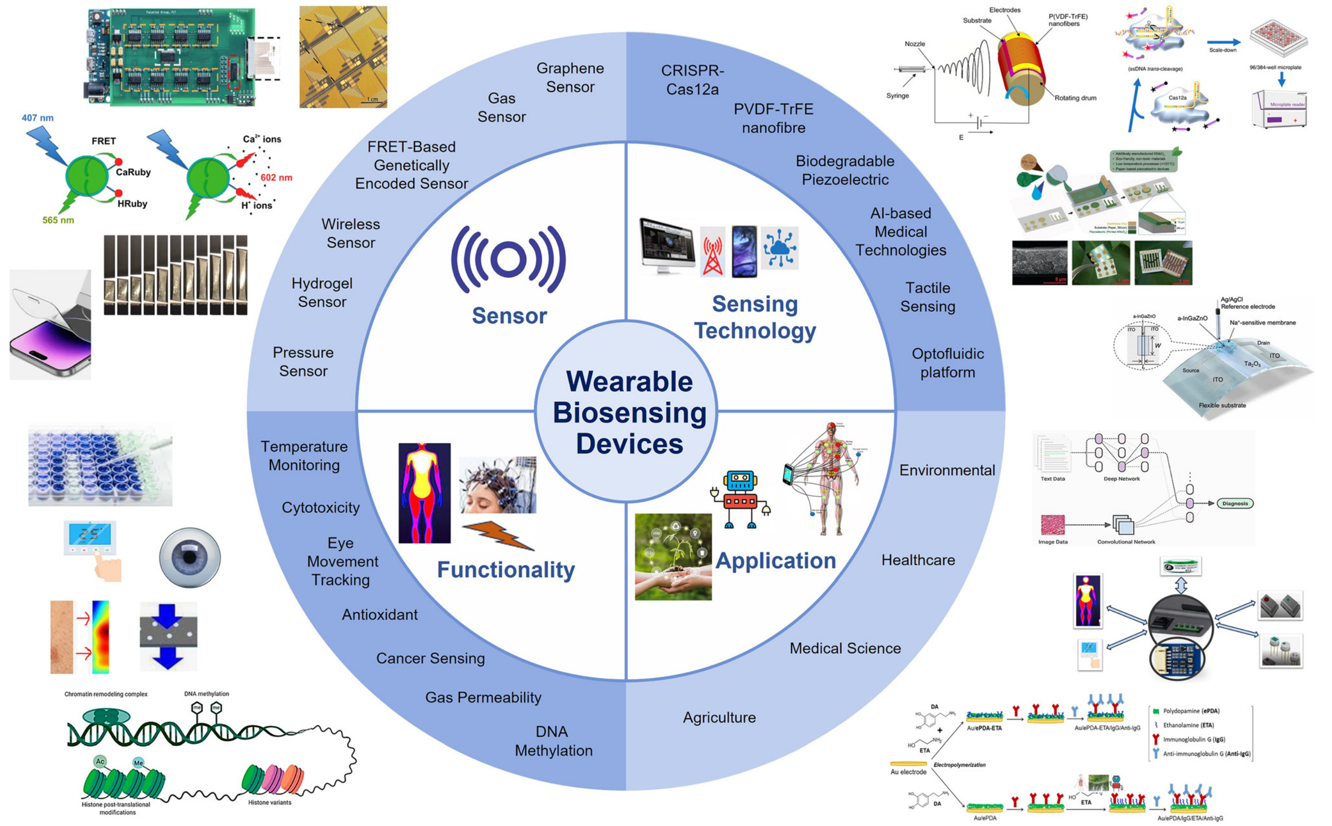

Fig. 7 Biocompatibility of some reported sensor technologies, as well as their functionality and applications, are illustrated here, which can be found in ref. 96–106 and 129–158. Figures adapted from ref. 58–60, 71 and 158–162, CC BY 4.0 (**http://creativecommons.org/licenses/by/4.0/**).

control must be considered in biocompatibility pathways.[184] Effective biomaterials should offer strength, biodegradation, biocompatibility, and an immunological benefit.[185,186] Biofunctionalized composite scaffolds that can enhance osteonecrosis therapy and smart delivery platforms employing core–shell nanofibers for sequential drug release in wound healing are important applications.[187,188]

6.3. Next-generation technologies and future outlook

Future technologies that work together to improve productivity might benefit from more focus and an industrial point of view. Digital twins and quantum computing will ultimately change many processes in the healthcare industry's use of large-scale public health data. With a more intelligent approach, artificial intelligence is a fantastic field that will help improve public health and safety. The internet of things (IoT) can offer real-time display setups, data processes, and valuable information. Without human intervention, IoT devices can gather and transfer data over a wireless network. Furthermore, cloud computing offers internet-based services for data storage, servers, databases, networking, and software. A cost-effective solution for IT infrastructure is cloud-based systems. Through careful design and production, 3D printing technologies create prototypes to produce devices. The use of 3D printing for additive manufacturing requires the coordination of hardware, software, and materials. Through broadband cellular networks, the fifth generation of technology, or 5G, will expand the mobile ecosystem, opening new opportunities for infinitely usable data transfer and device functionality for real-time usage. By using the right applications, robotic process automation can mimic many human tasks and reduce risk due to the sterility, accuracy, and multiplicity of work functions. Using appropriate algorithms and platforms, data analytics uses machine learning and AI to help with data processing, preparation, analysis, prediction, and understanding. In a society free of disease, where the healthcare sector can produce and offer technical support for control management, well-characterized sensor devices are key. Innovative concepts were used to develop a variety of sensor applications to build platforms for effective healthcare management.[13,67,68]

This paper asserts that carbon neutrality has made some progress.[189,190] In addition, it is necessary to establish a comprehensive standard for risk and climate neutrality assessment in healthcare management.[18,62,190] There are approximately 2 million unique types of medical devices on the market today, which are categorized into over 7000 generic device groups.[191] Access to high-quality, cost-effective, and appropriate health products is crucial for advancing universal health coverage, addressing health emergencies, and promoting healthier populations, even during

Table 6 Health management platforms based on biosensing research for the commercialization of devices

Category	Detail	Ref.
Device	Soft implantable drug delivery device	163
	An ultrahigh sensitive paper-based pressure sensor	164
	Ultrathin composite coating for implantable pressure sensor	165
	A non-invasive wearable device for sweat pressure	166
	An edge-device for accurate seizure detection	167
	Stretchable piezoelectric sensing systems	168
	An implanted pH sensor read using radiography	169
	Stretchable hybrid electronics for skin	170
	Label-free serum albumin nanoparticles for bioimaging and drug delivery	171
	Excitation–emission matrix for UV-treated cell culture	172
	A wearable light-touch contact device	173
	Portable, open-source solutions for estimating stroke	174
Commercial	Electrochemical biosensing platform	175
	Low-cost electromyography	176
	Non-invasive wearables for HbA1c and glucose	177
	Silicon nanodisk huygens metasurfaces for biomarker sensing	178
Health management	Oral wearable sensors	179
	Stretchable strain sensor for joint motion and respiration monitoring	180
	Finger-based pulse oximeters	181
	Glucose monitoring systems among adults with type 2 diabetes	182
	Bipolar disorder treatment management	183

pandemics.[191,192] In recent decades, the sensor market in the healthcare sector has expanded significantly. Nanosensors developed by biomaterials can work efficiently in diagnostic devices for assessing anti-bacterial and anti-cancer activities based on electrochemistry communications.[193–196] Advances in organ-on-a-chip materials and technologies through research in biosensors and bioelectronics with designed interfaces brings further possibilities for device development and their industrialization.[197–199] The study provides a concise analysis of research tendencies in synthesis techniques as well as the difficulties associated with their implementation in industrial settings for layered materials, *i.e.*, 2D materials, such as films, which can be used in the context of electronics, spintronics, optoelectronics, twistronics, or solar cells, while powders exhibit large surface areas and are employed in the construction of batteries, sensors, and catalysts. The three state-of-the-art mass production techniques refer to films. Films can be used in the context of electronics, spintronics, optoelectronics, twistronics, or solar cells.[200] The pandemic and related global human health threats can be controlled by well-defined public health management; therefore, it is important to understand technological adaptation and carry out development on a regular basis.[201,202] Integrated sensors now feature more cutting-edge technologies without sacrificing functionality. Herein, we have highlighted the key issues raised by new and pervasive diseases and provided recommendations for how the advanced materials community can address them. Therefore, future research should be conducted to improve health care management.

6.4. Healthcare transformation through wearables and AI

The personalized health ecosystem is transforming our lives through the use of wearable sensors that monitor our vital signs and habits. The advent of big data, AI, and micro-manufacturing has given rise to a broad spectrum of products, software, and services. These innovations offer healthcare solutions that address diverse issues, such as alarm fatigue, clinical variation, and the management of patient care transitions. To enhance personalized health, advancements in diverse sensors, 5G technology, and AI have led to the development of upgraded wearable sensors. These sensors can noninvasively monitor biochemical indicators in body fluids for disease prediction, diagnosis, and management.[203]

Non-invasive electrochemical sensors can detect biomarkers in tears, saliva, perspiration, and skin interstitial fluid (ISF), offering a comprehensive view of an individual's health status. Integrating AI into healthcare presents significant opportunities to improve disease diagnosis, treatment selection, and clinical laboratory testing.[204] AI tools, by analyzing large datasets and identifying patterns, can outperform human capabilities in various healthcare domains. The benefits of AI include enhanced accuracy, cost reduction, time savings, and the minimization of human errors. AI has the potential to revolutionize personalized medicine, optimize medication dosages, boost population health management, establish care guidelines, provide virtual health assistants, support mental health care, enhance patient education, and foster trust between patients and physicians.

The benefits of AI have already been recognized in various healthcare sectors, including cardiac arrhythmia monitoring, diabetes management, and assisted surgeries.[205] AI and machine learning (ML) techniques also enhance the analysis of analytical data from low-resolution or noisy datasets, improving signal strength, sensitivity, specificity, and measurement time.

Understanding technology is crucial for optimal performance. Wi-Fi and Bluetooth serve as primary connectivity methods for interfacing IoMT devices with a central hub. Bluetooth connectivity, suitable for short-range communications up to 10 meters with a maximum speed of 3 Mbps, can link sensors to portable devices, like tablets, smartphones, and PCs. This method is particularly useful in operating rooms, intensive care units (ICUs), and other settings with numerous devices. Wi-Fi modules must incorporate optimized scanning algorithms to ensure persistent network connections for mobile devices in environments with high radio frequency (RF) noise.[47]

7. Potential challenges

The advent of integrated biosensing-enabled digital healthcare devices represents a substantial advancement in medical technology, with the potential to provide more individualized, efficient, and easily accessible healthcare solutions.[9]

Fig. 8 Design framework and methods used for applying sensing devices in an industrial setting, demonstrating the innovative concepts in sensor development that can lead to an effective healthcare management platform. The visuals present a futuristic laboratory equipped with advanced sensor technology, incorporating various innovative ideas in digital healthcare.

Nevertheless, harnessing the complete capabilities of these advancements is not devoid of obstacles, with the key challenges shown in Fig. 9.

The intricate nature of creating devices capable of precisely and consistently monitoring real-time health indicators presents a substantial challenge. Another crucial concern is the need to guarantee the privacy and security of sensitive health data obtained and communicated by these devices. This necessitates the implementation of strong encryption and secure data handling methods to protect against unwanted access and cyberattacks.[12]

Ensuring interoperability and standardization among different healthcare systems and technologies is crucial for the efficiency of these devices, but remain difficult tasks. Intricate legal frameworks add more complexity to the process of bringing these technologies to the market, as strict approval procedures and compliance obligations can impede the pace of innovation and adoption. In order to ensure responsible use, it is imperative to address ethical considerations, specifically those related to permission, autonomy, and the possibility of surveillance.[27]

Moreover, there is a potential danger that this sophisticated healthcare technology could worsen current disparities in health, highlighting the importance of ensuring fair and equal access to their advantages. In order to achieve widespread adoption, it is also essential to overcome skepticism and opposition from healthcare providers and patients. Additionally, incorporating these new technologies into conventional healthcare practices requires substantial training and assistance. Ultimately, the development and deployment of these devices require significant investment.[63] Therefore, it is important to carefully weigh the cost against the potential improvements in healthcare. This makes the process of integrating biosensing-enabled healthcare devices complex, but ultimately worthwhile.

8. Conclusions and future perspective

Recent years have witnessed significant advancements in disease management techniques, largely influenced by experiences gained during pandemics. These improvements in diagnostic and treatment methods have notably enhanced the success rates of both diagnosing and treating diseases compared to earlier practices. In envisioning the future of integrated biosensing and digital healthcare devices, this article anticipates significant advancements and transformations will further be made building on the progress already made. The field is poised to move beyond the current state-of-the-art,

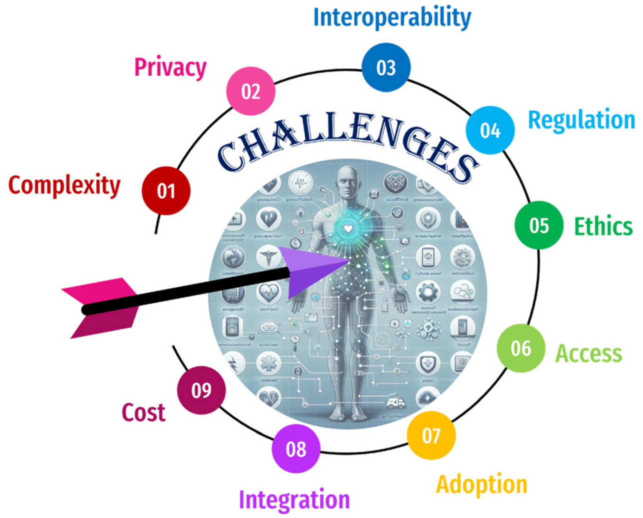

Fig. 9 Challenges in the development of integrated biosensing digital healthcare devices. Nine primary challenges encountered in the evolution of integrated biosensing-enabled digital healthcare devices, with the figure depicting the complexity and interrelated nature of issues, ranging from technical and privacy concerns to regulatory compliance and cost considerations.

leveraging the lessons learned from pandemic experiences to enhance disease management. Future perspectives will likely focus on the development of ideal point-of-care devices, which, despite two decades of research, are yet to be fully materialized in the market. These devices, crucial for rapid and accurate diagnosis during pandemics, for instance, are expected to shift the paradigm toward patient-centered, non-laboratory testing. The article also highlights the increasing relevance of wearable sensors and systems in clinical applications. The past decade has seen these technologies evolve from research tools to integral components of public healthcare, improving monitoring, intervention, and outcomes. The future holds promise for more remote monitoring, particularly for older adults and chronic disease patients, though challenges in cost and reimbursement remain to be addressed. Another key area of advancement is in the realm of advanced materials and the internet of things integration. Biosensors are becoming increasingly vital in these technological landscapes, contributing to a more sustainable world.

The present review sheds light on how digital biosensors have revolutionized disease detection and biochemical analysis through their real-time, remote, and precise capabilities. The trends toward miniaturization, automation, and multiplexing in biosensing methods are particularly noteworthy. These trends have led to the creation of portable, flexible, and wearable devices that enable continuous health monitoring and point-of-care diagnostics. Digital automation and integrated multiplexing have enhanced the efficiency and accuracy of these devices, while the incorporation of smartphones and other digital devices as readout platforms has made biosensing more user-friendly. Artificial intelligence and machine learning are set to play a more pivotal role in the interpretation and analysis of complex biosensor data. The integration of these technologies into IoT platforms is expected to unlock tremendous potential and market value for personalized healthcare. The future of digital healthcare and biosensing is rich with possibilities. It encompasses a range of innovative biosensing methods and devices that are set to revolutionize the market. This article systematically discusses these advancements, emphasizing the need for intelligent point-of-care devices that synergize technological innovations with real-time healthcare management. This comprehensive discussion bridges technological progress with translational wisdom, outlining a vision for the future healthcare industry that is both ambitious and attainable.

Data availability statement

The data used in this review article was extracted from published literature and research. The article does not describe any new experimental or primary data. All data sources are cited in the reference section of this article.

Disclosure

The authors have utilized ChatGPT to enhance readability, graphics and language. Following this application, the authors meticulously reviewed and edited the content as necessary, assuming full responsibility for the publication of contents and adopted figures.

Author contributions

Anshuman Mishra, Pravin Kumar Singh, Nidhi Chauhan, Utkarsh Jain: writing, review, data collection, visualization; Souradeep Roy, Ayushi Tiwari, Shaivya Gupta, Santanu Patra, Trupti R. Das, Ahmad Soltani Nejad: data analysis, writing, reviewing & editing; Yogesh Kumar Shukla, Prashant Mishra, Ashutosh Tiwari: conceptualization of the work, assisting in writing, reviewing & editing.

Conflicts of interest

The authors declare no conflict of interest.

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