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Artificial intelligence biosensors: Challenges and prospects

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Abstract: Artificial intelligence (AI) and wearable sensors are two essential fields to realize the goal of tailoring the best precision medicine treatment for individual patients. Integration of these two fields enables better acquisition of patient data and improved design of wearable sensors for monitoring the wearers' health, fitness and their surroundings. Currently, as the Internet of Things (IoT), big data and big health move from concept to implementation, AI-biosensors with appropriate technical characteristics are facing new opportunities and challenges. In this paper, the most advanced progress made in the key phases for future wearable and implantable technology from biosensing, wearable biosensing to AI-biosensing is summarized. Without a doubt, material innovation, biorecognition element, signal acquisition and transportation, data processing and intelligence decision system are the most important parts, which are the main focus of the discussion. The challenges and opportunities of AI-biosensors moving forward toward future medicine devices are also discussed.

Keywords: Wearable biosensor, Artificial intelligence, Biomarker, Wireless communication, Machine learning, Healthcare

1. Introduction

Owing to the unique location at the interface between the analog world we live in and the underlying communication infrastructures, sensors serve as ideal data information acquisition device for the realization of smart cities. Based on application scenarios, sensors can be classified into physical sensors (Bai et al., 2015; Bai et al., 2014; Chen et al., 2020; Chen and Wang, 2017; Chen et al., 2013; Lin et al., 2017; Lin et al., 2018; Meng et al., 2018; Meng et al., 2020; Wu et al., 2015; Yan et al., 2018; Yang et al., 2014a; Yang et al., 2015; Yang et al., 2014b; Yi et al., 2015; Zhang et al., 2020; Zhang et al., 2017; Zhou et al., 2020), chemical sensors (Chen and Wang, 2017; He et al., 2020; Li et al., 2016a; Li et al., 2015; Li et al., 2016b; Lin et al., 2013; Su et al., 2020a; Su et al., 2016; Su et al., 2020b; Wang et al., 2015; Wen et al., 2015; Zhang et al., 2013; Zhang et al., 2017; Zhu et al., 2015) and biosensors (Heikenfeld et al., 2018; Kim et al., 2019; Windmiller and Wang, 2013; Xu et al., 2019c; Yang et al., 2017). As one of the most important categories among them, biosensors have experienced a long development from classic electrochemical biosensors to wearable and implantable biosensors, and have been widely applied in food security, healthcare, disease diagnosis, environmental monitoring and biosafety (Zhang, 2017).

Recently, biosensing has entered a new stage due to the promotion and implementation of concepts such as big health, Internet of Things (IoT) and big data. The developing wearable biosensors aim to break through the limitations of centralized, reactive healthcare by giving individuals insight into their own physical dynamic. However, complex causality results in extreme difficulty in the output

analysis. Integration of artificial intelligence (AI) approaches including pattern analysis and classification algorithms with biosensors can bridge the gap between the data acquisition and analysis and achieve improved diagnostic and therapeutic accuracy. This review intended to introduce the most recent progress of AI-biosensors, and discussed the materials, wireless communication, machine learning and decision applied in AI-biosensors in the past several years. We also highlighted the possible future AI-biosensors (AI wearable sweat biosensors, AI-eatable biosensors, AI-glass biosensors, AI-implantable biosensors etc.) and related advanced programming function including AI-diagnosis, big data processing and self-learning/adaption. Such AI-biosensors involve with hybrid techniques of wireless biosensing technology and advanced machine learning algorithms, holding great promise for realizing continuous monitoring of healthcare and cloud-connected point-of-care (POC) diagnostics.

2. The evolution of biosensors

2.1. Basic concept of biosensors

The biosensor is an instrument that is sensitive to biological substances and converts the concentration into signals for detection. According to the International Union of Pure and Applied Chemistry (IUPAC), a biosensor (Fig. 1) is an integrated receptor-transducer device to provide selective quantitative or semi-quantitative analytical information about a specific analyte, which is schematically comprised of bio-sensitive materials as a biorecognition element, a physical or chemical transducer element, a signal transmission and amplifier element (Thévenot et al., 1999). From

traditional perspective, based on the type of transducer units, biosensors can be classified into bioelectrode sensors, semiconductor biosensors, thermal biosensors, photo biosensors and piezoelectric crystal biosensors. Based on the type of identification elements, biosensors can be divided into enzyme sensors, nucleic acid sensors, microbial sensors, cell sensors, tissue sensors and immunosensors. Based on the type of recognition elements, biosensors can be classified into bioaffinity biosensors, metabotropic biosensors and catalytic biosensors (Drummond et al., 2003; Garzon et al., 2019; Grieshaber et al., 2008; Sawant, 2017).

The idea of enzyme electrodes was first proposed by Clark and Lyons based on the enzyme GOx over an amperometric oxygen electrode (Clark and Lyons, 1962), which embarked on the first golden age of biosensors. Various biomarkers and biomaterials were selected as recognition elements of biosensors, including enzymes, antibodies, nucleic acids, cells, tissue sheets and microorganisms (Bohunicky and Mousa, 2010; Grieshaber et al., 2008; Wang, 2006). New biosensor transducers were also introduced during this decade, including electrochemical biosensors, thermal biosensors, semiconductor biosensors, optical fiber biosensors, piezoelectric, mass and acoustic biosensors. The second development of biosensors was large-scale commercialized applications. The YSI (Yellow Spring Instruments, Ohio) glucose analyzers addressed two major innovations for the popularity of early enzyme electrodes. The first innovation was to use polycarbonate membrane structure to reduce the concentration of glucose, the other was complete immobilization of GOx by cross-linking (Heller and Feldman, 2008). The recognition of nucleic acid led to

the development of DNA biosensors and DNA microarrays in the late 1990s (Kim et al., 2019). Affymetrix was a representative company in the field of DNA microarrays which was acquired by Thermo Fisher Scientific in 2016. The main players in the global biosensor market include Abbott, Siemens Medical, Nova Biomedical, Bayer, Johnson & Johnson, Medtronic and Roche. The third development opportunity was the emergence of nanotechnology in the late 1990s. Reflecting the growing emphasis on nanotechnology, nanomaterial-based biosensors have been widely reported and have become an important research direction in the field of nanobiology. Nanomaterials have attractive properties, at the nanometer size, the sensitivity of the sensor improves as the percentage of atoms on the surface of the sensor interface significantly increases. The small size effect can lead to changes in optical, thermal, magnetic and mechanical properties, especially suitable for the study of biological processes in living cells and the development of major diseases (Zhang, 2017).

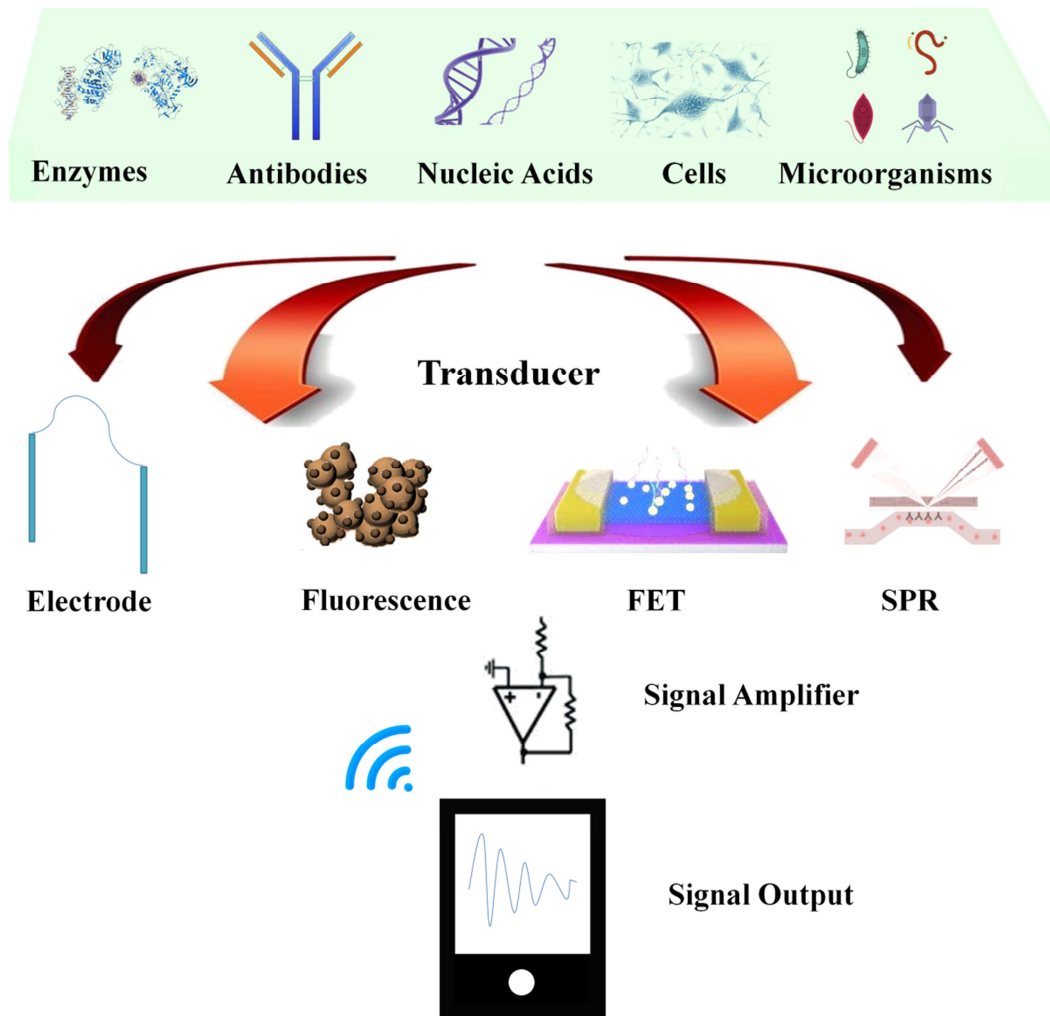


Fig. 1. Typical biosensor is generally defined as an analytical system which schematically consists of a biorecognition element, a transducer element, a signal transmission and amplifier element.

2.2. Wearable technology in biosensors

Owing to a growing consumer desire for health and fitness awareness and several other factors, such as the rapid development of material technology, the widespread use of smartphones and popularity of the internet technology, wearable biosensors have received considerable attention since they are minimally/non-invasive, enable continuous monitoring, and easy to carry and operate (Gao et al., 2016; Heikenfeld et al., 2018; Jia et al., 2013; Rogers, 2017).

Recently, the popularity of wearable technology has risen enormously, and the US market is projected to be in the tens of billions of dollars by 2022 (Akinwande and Kireev, 2019). Wearable biosensors have been available to consumers as indicators of heartbeats and biophysical activity, however, they fail to realize the detection of the individual's biophysical markers and biochemical markers. Inspired from this technological gap, efforts have been devoted to the development of wearable biosensors for minimally/non-invasively detection of biomarkers in accessible biofluids, such as sweat, saliva, tears, interstitial fluid (ISF) and wound fluids. The list of biomarkers in biofluids is too long to be discussed here in detail and we shall not dwell upon them, since such have been described in review papers (Bandodkar et al., 2019; Bariya et al., 2018; Chung et al., 2019). Nowadays, as the IoT, big data move from concept to implementation, wearable biosensors are facing new development opportunities with their appropriate technical characteristics.

2.2.1. Wearable sweat sensors

Human sweat carries complex available physiological information related to healthcare and disease diagnoses, and the main constituents include water (99%), ions (Na^+ , Cl^- , K^+ , NH_4^+ , etc.), small molecules (ethanol, cortisol, urea, lactate, etc.), peptides and small proteins (such as neuropeptides and cytokines) (Bariya et al., 2018; Hooton et al., 2016; Robinson and Robinson, 1954; Sonner et al., 2015). Sweat biosensors have been devoted to capturing chloride, glucose, lactate, urea, creatinine, alcohol, pH and even heavy metals (Dalirirad and Steckl, 2019; He et al., 2019; Kim et al., 2019; Lee et al., 2017; Yang et al., 2020). Compared to other non-invasive

biofluids (saliva, tears and ISF), sweat has many advantages in wearable biosensors. First, sweat contains a wealth of water-soluble biomarkers that are related to human health. Second, sweat can be continuously monitored at convenient locations as it is secreted on the body. Third, it can be continually secreted on-demand through exercising, iontophoresis or chemical stimulation for non-invasive wearable biosensing (Bariya et al., 2018; Robinson and Robinson, 1954; Sonner et al., 2015).

Before larger community for health monitoring, there are many key challenges must be addressed through technological solutions, such as low sweat rates, sample evaporation, contamination from skin, fresh sweat obtainment, sweat rate effects, sweat-blood correlation, low-concentration molecular detection, sensor stability and calibration, and so on (Bariya et al., 2018; Yang and Gao, 2019). Especially, the sampling method has a significant impact on the accuracy and reliability of sweat analysis results (Liu et al., 2020).

2.2.2. Wearable saliva sensors

Human saliva is a clear, slightly acidic mucoserous exocrine secretion into the oral cavity (Humphrey and Williamson, 2001). The concentrations of biomarkers in saliva such as glucose (Gupta et al., 2015), lactate, phosphate and uric acid (UA) are correlated to that in blood (Nunes et al., 2015; Seshadri et al., 2019), providing an attractive and valuable candidate for point-of-care (POC) (Yang and Gao, 2019). In addition, levels of HIF-1 α , VEGF, IL-1 β , TNF- α , IL-6, cytokines and matrix metalloproteinases (MMPs) in saliva have been reported to associate with gingivitis, periodontal disease and tumors as well as a reliable and stress-free tool with

diagnostic value responded to psychosocial stress (Afacan et al., 2019; Humphrey and Williamson, 2001; Jaedicke et al., 2016; La-Fratta et al., 2018; Rathnayake et al., 2013; Slavish and Szabo, 2019). Normal average production of saliva range from 500 mL to 1.5 L per day, dependent on the type of gland, time of day, age, gender and stimulus (Heikenfeld et al., 2019).

Despite the ease of collection (Kim et al., 2019; Yang and Gao, 2019), research on saliva tends to be more diagnostic capabilities than wearable biosensors. In particular, recent published wearable saliva sensors are usually based on the format of mouthguard or denture system which are potential biofouling by rich protein content, food, drink, and so on (Garcia-Carmona et al., 2019; Kim et al., 2019; Kim et al., 2015; Mannoor et al., 2012).

2.2.3. *Wearable tear sensors*

Unlike sweat, tears contain a wide variety of protein biomarkers (antibodies, neuropeptides, and protective proteins) suitable for the detection of ocular diseases such as dry eye syndrome (DES), diabetes, systemic sclerosis, cystic fibrosis, cancer and Parkinson's disease (Tseng et al., 2018; Yu et al., 2019). Contact lenses, an ideal platform as wearable biosensors for detection the levels of biomarkers in tears, are widely used for the lens wearer. Up to now, wearable biosensors have been successfully integrated into contact lenses for continuous monitoring of glucose and lactate etc. (Donora et al., 2019; Kim et al., 2017; Zou et al., 2020)

To remedy the issue of power supplying to the wearable electrochemical contact

lens, Falk et al. (2012) developed a biofuel cells, based on direct electron transfer, used as electrical power for self-powered contact lens biosensors. The gold wires covered with gold nanoparticles were used to fashion 3D nanostructured microelectrodes, and then biomodified with dehydrogenase as anodic and oxidase as cathodic, respectively. Except for power supplying, several other challenges still remain, such as repeatability and access to tears etc. The last but not the least challenge to use contact lens biosensors for continuous glucose monitoring is denaturation of enzyme due to the sterilization process (Tseng et al., 2018).

2.2.4. Wearable ISF sensors

Interstitial fluid (ISF) is a thin layer of fluid that surrounds cells and tissues. This fluid is formed by extravasation of plasma from blood capillaries and metabolic products of the tissue (Samant and Prausnitz, 2018). Blood is the most understood biofluids for clinical diagnosis, however, ISF which accounts for roughly three-quarters of extracellular fluid is more attractive for minimally/non-invasive and continuous monitoring (Heikenfeld et al., 2019). Proteomic analysis has confirmed the composition of ISF is highly similar to both plasma and serum, less than one percent of proteins are uniquely (Tran et al., 2018). To realize minimally/non-invasive and continuous monitoring, microneedles with wireless modules integrated on a patch for sampling the transdermal ISF were selected by several research groups (Bollella et al., 2019a; Bollella et al., 2019b; Mishra et al., 2017; Sharma et al., 2017). However, almost all of wearable ISF biosensors are based on electrochemical sensing. Therefore, there are still several limitations including loss of electrode materials, degradation of

enzymes, biocompatibility, etc.(Matzeu et al., 2015)

2.2.5. Wearable wound sensors

Wound is a worldwide significant problem which is affected by wound fluids pH, moisture, temperature, oxygen, microbial infection, C-reactive protein (CRP) and wound MMPs enzyme activity (Milne et al., 2014; RoyChoudhury et al., 2018; Salvo et al., 2017). The real-time monitoring of these biomarkers is important to wound management (Farooqui and Shamim, 2016; Jankowska et al., 2017; RahimRahimi, 2016). For example, UA can be used as an indicator for wound infection associated with bacterial infection and oxidative stress in wound area (Liu and Lillehoj, 2017).

Despite the advancements in wearable chronic wound sensing for continuous real-time monitoring, current wound management needs to be available for closed-loop therapeutic system, and the sensor materials must be biocompatible, flexible and stretchable.

2.2.6. Wearable or implantable blood biosensors

Heart failure (HF) is a public concern which affects more than five million Americans. Implantable cardiac monitoring sensors such as implantable cardioverter defibrillator (ICD) and implantable haemodynamic monitoring devices have potential to broaden the HF monitoring (Merchant et al., 2010). Furthermore, implantable sensors have been used as neural recording technologies to improve neurostimulation-based treatments, which opens a new door for human-machine-natural interaction. For example, "Neural dust" is a mm-scale

implantable sensor which contains a piezoelectric crystal providing ultrasound wireless power and communication. The backscatter wirelessly can achieve recording electrophysiological signal in vivo (Seo et al., 2016).

Blood is a reddish fluid that transports nourishment and oxygen and takes away waste products from cells. Although wearable biosensors have been used as an alternative to invasive blood biosensors, implantable blood biosensors are still of interest for intensive-care monitoring (Yang and Gao, 2019). The miniaturized biosensors, which can be implanted within human blood vessels for real-time monitoring of blood press (Fiala et al., 2013; Murphy et al., 2013; Starr et al., 2016; Theodor et al., 2013), blood flow (Ericson et al., 2004; Vennemann et al., 2020), blood-gas measurements (pH, PO₂, and PCO₂), electrolytes (Na⁺, K⁺ and Ca²⁺), glucose (Edagawa and Yasuzawa, 2012) and lactate, still an especially difficult challenge (Frost and Meyerhoff, 2002). Foreign body response is one of the major obstacles in the development of implantable blood biosensors. Moreover, functional loss of implantable biosensors remains a critical issue in limiting device reliability (Onuki et al., 2008).

2.2.7. *Wearable eatable biosensors*

Eatable biosensor, also known as ingestible biosensor, is a kind of digital medicine consisting of smart pills which contain eatable microchips, a wearable patch, a patient mobile app, and other accessories. Once the eatable sensor activated, it transmits a signal to the patch on the skin. Then, a record is sent to the patient mobile

app to achieve measuring medication-taking (Proteus, <https://www.proteus.com/> (accessed May 20, 2020)). Eatable biosensors have been employed for monitoring adherence to tuberculosis therapy (Belknap et al., 2013), gastrointestinal health (Mimee et al., 2018), and medication compliance (Chai et al., 2015).

Although these kinds of biosensors have potential to measure treatment effectiveness and more informed healthcare decisions, some key challenges remain before the commercial maturity of eatable biosensors, such as security and privacy, clinically compatible testing, and so on (Chai et al., 2015).

2.3. Fully integrated commercial wearable sensors

The commercial market for fully integrated wearable sensors is ever expanding. A wide range of successful wearable systems with integrated biosensors and wireless communication have been large-scale produced by flexible electronics technologies on the websites of commercial wearable device companies. Zensor is a wireless 3-lead electrocardiography (ECG) monitor which can be worn up to 14 days for collecting data on respiration rate, ECG, heart rate and motion. The electrodes are fully integrated into an adhesive patch which contains a magnetic connector, a flexible adhesive foam layer, a flexible substrate layer, a printed conductive layer, a conductive hydrogel patch and a flexible adhesive foam layer. Zensor, acquired by LifeSignals Group in 2020, has received FDA 510 (k) clearance (No. K151027) for arrhythmia detector and alarm (LifeSignals, <https://www.zensordevice.com/> (accessed Mar 26, 2020)).

The Refresh Sweat Analysis system expands standardized electrochemical biosensor design of wearable continuous sweat monitoring platforms by utilizing application specific integrated circuit (ASIC) technology. The fully integrated system is composed of wearable sweat biosensors and MS02 ASIC chip. The programmable chip includes an Analog Front End (AFE) and process unit, specified to electrochemical biosensing. MS02 ASIC chip, which is made up of analog circuit, temperature sensing circuit, memory unit and I2C digital interface, can be used for measuring current and potential. The analog circuit exhibits a linear range from 0.1 nA to 100 μ A with a resolution of 10 pA (RIT, <http://www.refresh.cc/> (accessed Mar 26, 2020)). In the wearable fitness sensing technology market, numerous fully integrated commercial systems are emerging in various forms such as smart socks, garments, stretch belts, biostamps etc. Sensoria, an American company of wearable devices, has developed a full range of smart garment platforms for multiple activities, including textile sensors, mobile application and cloud. The Sensoria Core electronics module integrated embedded sensors and a 9-axis MEMS sensor into ultra-low power system on a chip (Sensoria, <https://www.sensoriafitness.com/> (accessed Mar 26, 2020)).

Driven by the huge glucose biosensing market, no assay is performed more frequently than that of glucose. Non-invasive, continuous glucose monitoring (CGM) platforms are trending in glucose self-monitoring. Commercial new types of wearable glucose biosensors have long been the key to a variety of blood glucose assays. Dexcom G6 CGM System is composed of a sensor, a transmitter and a smart device

application. The G6 System wireless communication using Bluetooth Low Energy is assured within the effective range of 6 meters and paired display device at regular 5-minute intervals. The sensor achieves glucose linear range of 2.2–22.2 mmol/L, life up to 10 days. The G6 System also aids in the detection of episodes of hyperglycemia and hypoglycemia (Dexcom, <https://www.dexcom.com/en-IE> (accessed May 20, 2020)). BioMKR one is a non-invasive CGM system displaying dynamic curves of glucose values based on near infrared spectroscopy (NIRS) sensor fusion technology. Dynamic calibration with a proprietary multivariate method is established to realize dynamic correction and remove the noise (Prediktor, <https://www.prediktormedical.com/> (accessed May 20, 2020)).

Epicore Biosystems smart patches expand on ‘skin-like’ designs of these wearable platforms with built-in batteries for non-invasively continuous monitoring of sweat biomarkers such as lactate, glucose and cortisol by utilizing microfluidic technologies. The information could then be analyzed by a paired mobile app for suggesting changes in diet, stress, or hydration (epicore, <http://www.epicorebiosystems.com/> (accessed May 20, 2020)).

These representative examples of fully integrated commercial wearable sensors highlight the far reaching of wearable sensors for individual healthcare. However, the current commercial wearable sensing technology for realizing large-scale production relies on many state-of-the-art manufacture strategies, such as inkjet printing (Wang et al., 2016b; Yin et al., 2010), transfer printing (Carlson et al., 2012; Kim et al., 2012), roll-to-roll (Bae et al., 2010; Krebs, 2009), flexible printed circuit (FPC) (Meng et al.,

2013), and aerosol Jet (Krzeminski et al., 2018). Despite the significant progresses have achieved in manufacturers, there are several remaining challenges for realizing the goal of low-cost large-scale production. For example, flexible printed circuits (FPC) technology as an industrial manufacturing process can realize large-scale production, but it also faces the disadvantages of complex manufacturing process and environmentally unfriendly. In contrast, transfer printing and roll-to-roll technologies are more commercially attractive, cost-effective and environmental values (Nathan et al., 2012). In the future, more efforts are still required to seamless system integration of flexible electronics manufacture processes, biocompatible skin adhesive interfaces, wireless communication, and AI data processing to ensure reliable and durable commercial deployment.

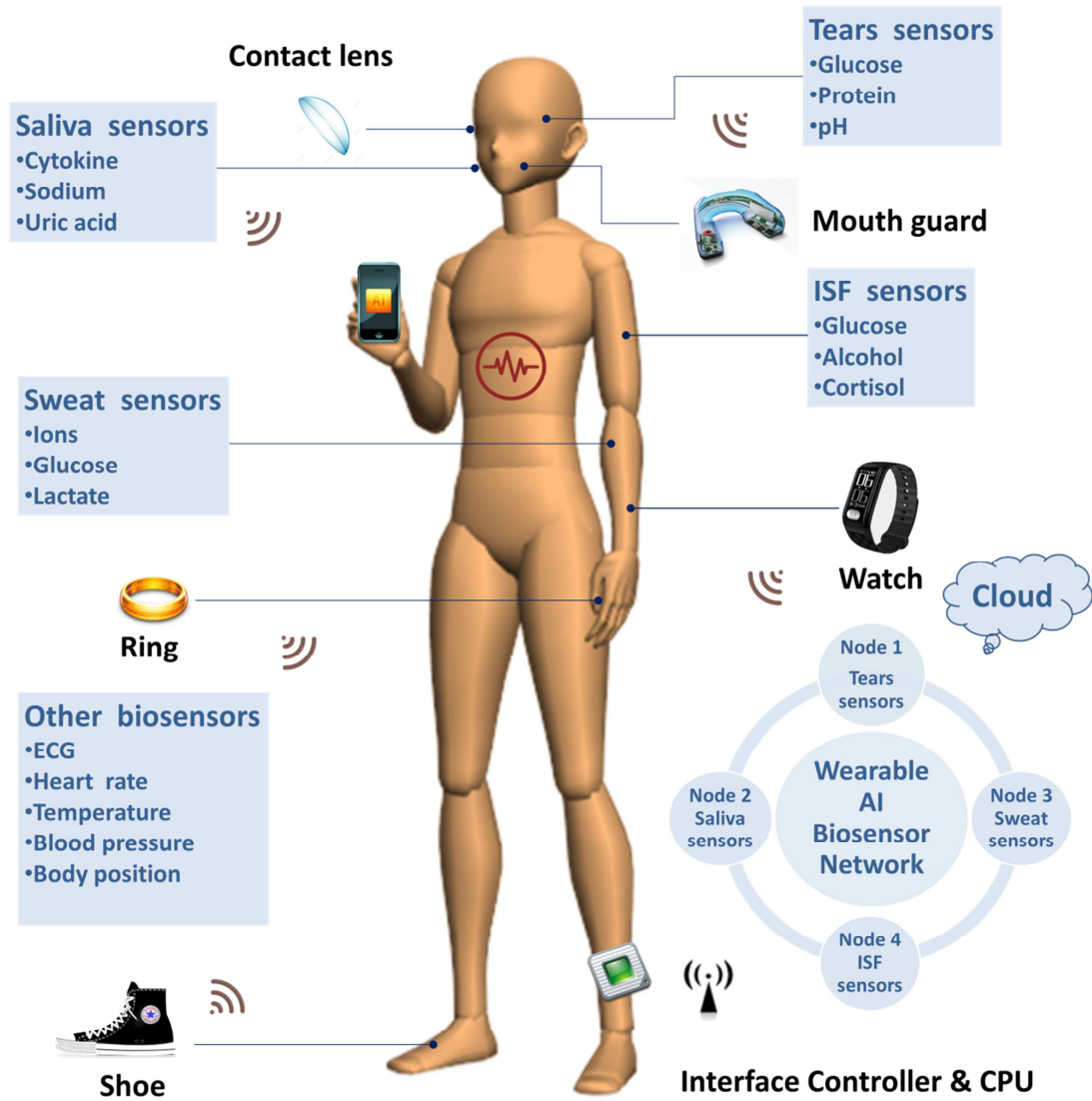


Fig. 2. Representative applications of wearable AI-biosensor networks (WAIBN).

Now, we are facing another opportunity with the coming of age of AI-biosensors. The main driving forces are the development of fully integrated commercial wearable sensors and the seamless combination of AI, big data and IoT. In the future, more and more interest in rapid access to wearable biosensors that can be afforded by incorporating sensors into wearable AI-biosensor networks (WAIBN) (Fig. 2) to capture a holistic model of human subject will be given. The following section, we will emphasize basic architecture of AI-biosensors and highlight challenges and

obstacles that confront in each main related field, including materials innovation, biorecognition elements, signal acquisition and transportation, data processing and intelligence decision.

3. AI-biosensors

Over the past decade, there has been a growing emphasis on embedding wisdom in the world. The intelligent processing of biosensing information has changed biosensors. The combination of AI and biosensors has built a cross-disciplinary concept of AI-biosensors. The basic architecture of AI-biosensors is composed of three main elements: information collection, signal conversion and AI-data processing (Fig. 3). Information collection refers to a group of biosensors for continuous monitoring of physical, chemical, biological, environment or identity information. The signal conversion system translates information from information collection domain into electrical output signal with a defined sensitivity. AI-data processing can be grouped into interface, data classification, data model and analysis, and decision layer.

AI is a branch of computer science that studies the properties of intelligence by synthesizing intelligence. The deployment of AI systems has created a trillion-dollar industry that is projected to quadruple in three years. Improving healthcare and quality of life is listed as the first of the six future developments of AI in "America's Artificial Intelligence for the Next 20 Years Research Roadmap" (Gil and Selman, 2019). "Healthy China 2030" plan proposes to promote the development of wearable devices,

smart health electronic products and mobile application services for healthcare in China. The AI technology system is gradually improved, and the combination of AI technology and IoT will promote the rapid development of intelligent biosensors.

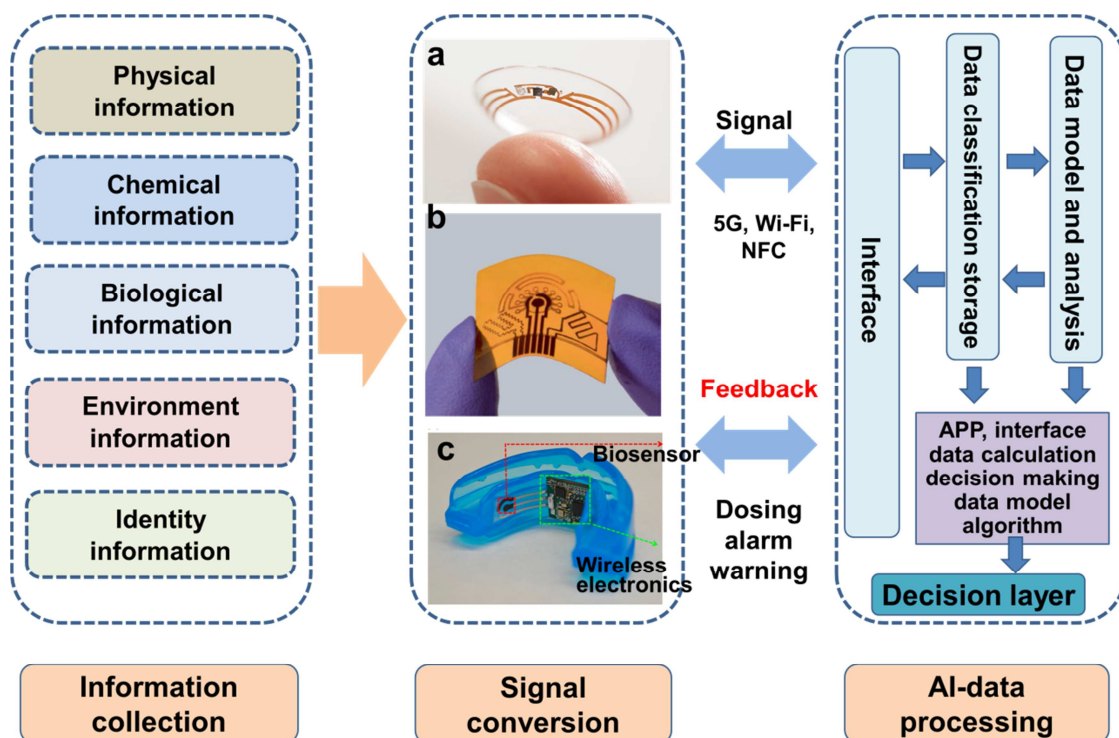


Fig. 3. Basic architecture of AI-biosensor networks (AIBN). (a) The contact lens sensor by Google and Novartis. Copyright 2014 Google X. (b) A flexible lab-on-skin patch. Reproduced from Yang et al., 2020 with permission from Copyright 2020 Springer Nature Limited. (c) Mouthguard biosensor integrated with wireless electronics. Reproduced from Kim et al., 2015 with permission from Copyright 2015 Elsevier B.V. All rights reserved.

3.1. Flexible bioelectronic materials and integration

Flexible bioelectronic materials such as flexible films, textiles, bandages, patches and tattoos serve as mechanical support for integrating electronic circuits which play an important role in AI-biosensors (Bandodkar et al., 2015; Jeong et al., 2017; Jia et al., 2013). Polyimide (PI) and polyethylene terephthalate (PET) are most widely used as flexible bioelectronics materials in biosensor integration technology owing to their

good performance, user comfort, high oxygen permeability and compatibility with roll-to-roll fabrication processes (Tseng et al., 2018; Yang et al., 2017). In addition, polydimethylsiloxane (PDMS) is selected as the best choice of flexibility stretchable substrates. The smart polymer has sensory properties that can change solubility, color, fluorescence, or shape when affected by temperature, electromagnetic pulses, biological molecules or pH, broadening the scope of flexible bioelectronics materials (Reglero Ruiz et al., 2018). Expansion to nanomaterials is an area of active interest and to a great extent depends on developing nanomaterials with favorable electrical and mechanical properties, which will facilitate the fabrication of AI-biosensors (Yang et al., 2017). Carbon materials are promising candidate materials for flexible bioelectronics materials with advantages both of good electrical conductivity and light weight flexibility (Wang et al., 2019). Intelligent hydrogels can respond to environment such as pH, ions, temperature and molecules (e.g., nucleic acids, peptides, enzymes, etc.), and can be varied to achieve responsive behavior even gel assembly or disassembly upon interaction with the target analyte (Culver et al., 2017).

Despite the extensive progress has been made in flexible bioelectronic materials, there are several remaining challenges for the effective integration of these components to obtain flexible AI-biosensors. Power is an important factor and it prefers to harvest from body motions or changes in heat or blood flow rather than from batteries (Xu et al., 2019b). Cost is another core factor to consider for commercial applications of devices. Flexible bioelectronic materials should be allowed to integrated functionalities into biosensors to reduce costs. Miniaturization

and integration are part of a trend of AI-biosensors, nevertheless, high-density sensors may lead to increased crosstalk. These problems can be addressed with the development of flexible electronic technologies which have been demonstrated as cost-effective approaches for realizing large-scale production of AI-biosensors integration. Flexible electronics, also known as organic electronics, have the potential to realize electronics on everything (Yin et al., 2010). There are also several companies working on flexible electronics. For example, the U.S. Department of Defense and FlexTech Alliance have established America's Flexible Hybrid Electronics Manufacturing Institute in San Jose. The institute is focusing on building manufacturing capacity with a goal of advancing U.S. manufacturing of flexible hybrid electronics.

3.2. Wireless communication

The AI-biosensors are ideally interfaced with wireless data communication to transmit the information between biosensors and smartphone-based platforms or other intelligent terminals. AI-biosensors based on wireless technology without cable can reduce the cost and constantly add new devices and flexibility. Wireless technologies focused on AI-biosensor networks (AIBN) with mass market adoption are Bluetooth, radio-frequency identification (RFID), near-field communication (NFC), Wi-Fi and ZigBee (Kassal et al., 2018). Bluetooth 4.0 is a good candidate for AIBN which has appropriate technical features and estimated high commercial prospects (Custodio et al., 2012; Kim et al., 2015). NFC is a kind of low-cost wireless communication technology developed on the basis of RFID and has been widely built in smartphones

nowadays. A complete NFC system often combines a reader like smartphone and a responder like passive NFC tag (Cao et al., 2019; Jeong et al., 2017). Commercial NFC tags are wireless, passive, flexible and low-cost (often less than \$0.5) with miniaturized format, and have also been fully integrated into flexible circuit board (Xu et al., 2019a). The RFID tags, based upon the International Standards Organisation high-frequency (HF) ISO 15693 RFID protocol, have been reported to be able to detect a variety of chemically biomarkers (Fiddes and Yan, 2013; Steinberg et al., 2014). RFID or NFC can be equipped to provide on-demand wireless data transfer between the smart bandage biosensors and computers or smartphones (Currano et al., 2018; Kassal et al., 2015). Wi-Fi (IEEE 802.11) is one of the most popular wireless technologies to offer connectivity. Power-efficient Wi-Fi with suitable system design and usage model components is a strong candidate in AIBN (Hao et al., 2019; Tozlu et al., 2012). ZigBee wireless communication system has been integrated in a low-cost chemical sensor array based on inkjet printing technology as wearable electronic nose (Lorwongtragool et al., 2014). Wireless body area network (WBAN) is a body centered wireless networking technology which is standardized by IEEE 802.15.6 (Darwish and Hassanien, 2011). Compared to Bluetooth and ZigBee, the WBAN standard has the advantages of ultra-low power consumption, high reliability and security protection (Wang et al., 2018).

3.3. Machine learning

AI-biosensors are valuable only when data can be used by us, and understanding what the data means is a prerequisite for using them. AI-data processing involves

learning from the data, including how to analyze data appropriately, draw the right conclusions from the data, and recognize if the data has been misinterpreted (Carlson et al., 2011). To achieve these goals, machine learning has two aspects of roles. First, machine learning can cut the quantity of data before wireless transmission so that ultralow powered AI-biosensors are achieved. The second aspect emphasizes on solving the data quality problem, including data consistency, monitoring accuracy and reliability. Machine learning consists of a wide spectrum of methods, techniques and evaluation of algorithms that aim at learning from data to find useful information or predictive models of a phenomenon. Many different types of machine learning methods exist, two main paradigms of machine learning methods known as supervised learning and unsupervised learning. In supervised learning, a series of training data with known labels is associated with the input data to find patterns or classification. In contrast, under unsupervised learning, no data is labeled. In this case, there is no notion of output to predict (Kourou et al., 2015; Tarca et al., 2007).

A variety of machine learning algorithms, including Support Vector Machines (SVMs), Principal Components Analysis (PCA), Hierarchical Cluster Analysis (HCA), Artificial Neural Networks (ANNs) and Decision Trees (DTs) have been applied in AI-biosensors for effective and accurate decision making (Table 1). Support Vector Machines (SVMs) are supervised machine learning algorithms based upon the idea to find the optimal separating hyperplane between two data classes for solving a two-class pattern recognition problem (Kotsiantis et al., 2007; Li et al., 2019). SVMs have set a trend recently, from which the data has been proved to increase the analysis

accuracy. For example, the parameters which obtained from biomolecular sensing using graphene nanoelectronics were further analyzed with an SVM to provide the highest accuracy of assignment (Puczkarski et al., 2017). Boubin and Shrestha (2019) used SVM to evaluate the accuracy of detection of blood glucose levels using breath volatile organic compounds. SVM has also been applied to resolve the fluorescence spectral overlap problem for simultaneous detection of lysozyme and adenosine triphosphate (Saber et al., 2020). For classification of albumin protein detected from lateral flow assay, a regression analysis was performed based on the feature parameters by using smartphone camera and linear SVM classifier was adopted (Foysal et al., 2019). Principal Component Analysis (PCA) is an unsupervised machine learning algorithm for achieving dimensionality reduction by replacing a set of variables with principal components (Li et al., 2019). PCA has been utilized for the extraction of vibrational data from glucose and fructose biosensors with the help of surface enhanced infrared absorption (SEIRA) (Kuhner et al., 2019). Similarly, Feng et al. (2010) used PCA to separate the measured SERS spectral features into two distinct sets with little overlaps for nasopharyngeal cancer detection. Stravers et al. (2019) adopted PCA for clustering the body fluid samples using surface plasmon resonance imaging. Furthermore, the measured fluorescence images were analyzed by PCA and PLSR algorithms for low levels of NT-proBNP determination (Squire et al., 2019). Hierarchical Cluster Analysis (HCA) is an unsupervised clustering method which forms a hierarchical structure to classify nearby objects into the same cluster within a data set (Lei et al., 2015; Li et al., 2019). For instance, Kim et al. (2020)

introduced a HCA method to classify the types of medical chemicals by the bacteriophage-based colorimetric sensor array. In addition, four kinds of VOCs detected by a fluorescent cross-responsive sensor array were accurately clustered without mistaking by HCA (Lei et al., 2015). Artificial Neural Networks (ANNs) are a branch of artificial intelligence that can be deemed to be an extension to the simulation of human brain. ANNs are nonlinear models for classification of complex relationships (Kotsiantis et al., 2007; Li et al., 2019). As an example, ANN has been utilized as a non-linear model calibration of the flow injection manifold determination of catechol and hydroquinone (Boroumand et al., 2019). Zhang and Tao (2019) have devised an ANN algorithm to solve complex physical/chemical causes by individual differences for physiological monitoring. In recent years, deep learning is a new research direction in machine learning. An ultra-sensitive microbubbling assay was introduced to quantify femtomolar-level protein biomarkers, and CNN was utilized to identify and count the number of microbubbles in the images by digital-readout method which only required a smartphone camera (Ravi et al., 2017). Decision tree (DT) is a widely used classifier in machine learning which is an effective tool to handle with the big picture of complex behavior. For example, papain in a nanoscale cubic space on a Si surface was analyzed combined with decision tree identified attributes. A nanoscale cubic space which consisted of four Si surfaces was created to capture free papain. The tetrapeptides were evaluated with different numbers of atoms when bonded to papain. In addition, a decision tree which was created from eighteen tetrapeptides was utilized as an effective tool in order to analyze the behavior of

papain. The twelve tetrapeptides were proved to fit the active site (Katsuhiko, 2019).

Despite the best possible classification accuracy, the application of ensemble algorithms increases the storage and computation. The key question of choosing the best possible machine learning algorithm for AI-biosensors is which algorithm can be represented on a given application problem instead of the algorithm itself (Domingos, 2012). In diabetes management, some companies commercialize machine learning algorithms to realize automatic and continuous monitoring of blood glucose levels and recommend adjustments in healthcare. DreaMed Diabetes claimed that the Advisor Pro software decision-support platform approved by the U.S. Food and Drug Administration (FDA) utilized the combination of event-drive, machine learning and fuzzy logic technologies to process data from a range of connected devices, including insulin pumps and self-management glucometers (DreaMed, <https://dreamed-diabetes.com/> (accessed April 8, 2020)). Bigfoot Biomedical is a startup medical technology company focused on developing automated insulin delivery systems with Model-Based Design, providing a way to people suffered from type 1 diabetes (Bigfoot, <https://www.bigfootbiomedical.com/> (accessed April 8, 2020)). The Iceland-based startup Medilync claimed its glucose monitoring device utilized machine learning to continuously monitor blood sugar level of patients (Medilync, <https://medilync.com/> (accessed April 8, 2020)).

Table 1

Machine learning for intelligent biosensing.

Biomarker	Biosensing mechanism	Platform	AI algorithm	Ref.
Lysozyme and	Fluorometric	Nanosheets	SVM	Saberi et al. (2020)

ATP				
Blood glucose	Electronic-nose	Portable device	SVM	Boubin and Shrestha (2019)
Biomolecular	Tunnel junctions	Graphene nanoelectrodes	SVM	Puczkarski et al. (2017)
Albumin protein	LFA	Smartphone cameras	SVM	Foysal et al. (2019)
Benzene, toluene formaldehyde	Electronic-nose	Sensor array chamber	SVM	Wang et al. (2016a)
Blood glucose (type 1 diabetics)	CGM	Wearable biosensors	SVM, ARIMA, RF	Rodriguez-Rodriguez et al. (2019)
Glucose, fructose	SEIRA	Noninvasive sensors	PCA	Kuhner et al. (2019)
Nasopharyngeal cancer detection	SERS	Confocal Raman micro-spectrometer	PCA, LDA	Feng et al. (2010)
Body fluid identification	SPR	SPRi device	PCA	Stravers et al. (2019)
NT-proBNP	Immunoassay	Photonic crystal-enhanced fluorescence	PCA, PLSR, SVM	Squire et al. (2019)
Medical chemicals	Bacteriophage-based colorimetric sensing	Multi-array sensor system	HCA	Kim et al. (2020)
VOCs	Fluorescent sensing	Cross-responsive sensor array	HCA	Lei et al. (2015)
Catechol and hydroquinone	Spectrophotometric	Injection flow manifold	ANN	Boroumand et al. (2019)
Physiological monitoring	Physical and biochemical sensing	Skin-friendly electronics	ANN	Zhang and Tao (2019)
Blood glucose	Enzyme sensing	Contact lens	Neural network	Quan et al. (2019)
Protein biomarkers	Microbubbling assay	Smartphone cameras	CNN	Ravi et al. (2017)
Papain (protein)	Nanoscale cubic space	Si substrates	DTs	Katsuhiko (2019)

3.4. Smartphone-based platforms

Smartphone-based sensing systems have received special attention with the worldwide popularity of smartphones. Due to the integration of numerous sensors and functions such as processing and communication, smartphone-based platforms are playing an important role in AI-biosensors for data processing, sharing, storage and interaction with cloud. With a flood of smartphone app swarming into the field of AI-biosensors for processing data returned by add-on biosensing modules, the use of

smartphone-based platforms is no longer a novel topic. These smartphone-based sensing systems often consist of a smartphone and add-on biosensing modules devices such as electrochemistry, fluorescence, plasmon resonance, or carry around an extra hardware component such as cameras, Bluetooth, USB, and audio port to increase accessibility, control the detection process and receive the detection data (Xu et al., 2017). For example, Google's Project Ara modular smartphone and multi-technique biosensor platform were integrated with PCB prototype of the module for diagnosing and monitoring the health, of which the size and power of the design was minimized (Sun et al., 2016). Although the smartphone performs the same data acquisition, processing and decision tasks as a computer, it is essentially an entertainment device and has several limits. For one thing, the functionality of each smartphone app is independent of each other. For another thing, since smartphones have more personal information from AI-biosensors, data security will receive more and more attention.

4. AI-biosensor networks (AIBN)

The development of biosensors for real-time monitoring is a field of sustained academic and industrial research interests, and AI is a potent tool to enhance the performance of biosensors. Therefore, AIBN has the potential not only to provide an early indication of various application scenarios (such as diseases, assisted living, environmental monitoring, military, biosafety, and other commercial areas), but also to change our lifestyle with so-called "smart" applications. For example, real-time monitoring by WAIBN can raise standards of healthcare and fitness services. Implantable AI-biosensor networks can help people by providing continuous

monitoring of POC diagnostics at risk patients. A number of embedded AI-biosensors monitoring systems can be developed to monitor the health status of the elderly and communicate in emergency situations. Ambient AI-biosensor networks, regarded as one of the technological foundations of ambient intelligence, can collect a huge amount of important information from the surrounding environment. With the popularity of smartphones and the realization of smart cities, the applications of AIBN can be further enlarged (Fig. 4).

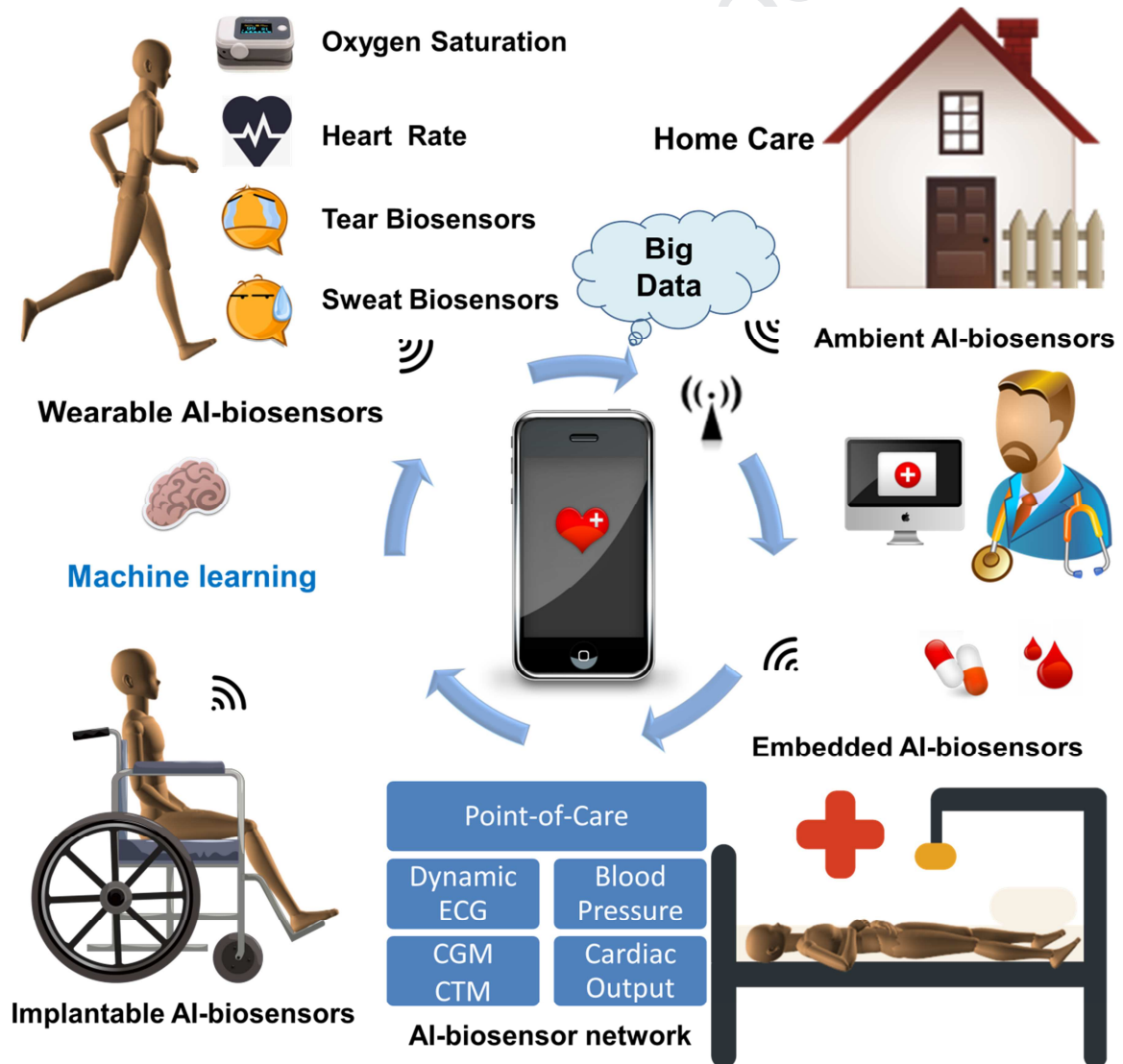


Fig. 4. Representative examples of AIBN including wearable AI-biosensor networks, implantable AI-biosensor networks, embedded AI-biosensor networks and ambient

AI-biosensor networks. The interface can inform a user with wireless data communication between AI-biosensors and smartphone-based platforms or other intelligent terminals. Big data processing on clouds can be aggregated as necessary.

5. Conclusion and outlook

In conclusion, this paper reviewed the evolution of biosensors, highlighted the cooperation between AI and biosensors performance. Emphasis is placed on the related fields of flexible bioelectronic materials and integration, wireless communication, machine learning and smartphone-based platforms for the development of AI-biosensors. Thinness, miniaturization, integration and less power-hungry are the future of AI-biosensors for healthcare. To this end, more technology research efforts should be focused on detection of low-level, specific biomarkers in biofluids and system integration. Biomarkers must bridge the gap between biophysical markers and biochemical markers to capture a holistic model of the individual. Much efforts should be devoted to developing flexible electronic materials for integrating chip technology, IoT, big data and AI to realize self-learning, self-assembly and self-adaptation of AI-biosensor systems. The collected data will be fed into machine learning algorithms to monitor vital signs, spot abnormalities and track treatments (Xu et al., 2019b). In addition, it is necessary to consider the relationship between human-machine-natural interaction. By developing AIBN, we can not only take closed-loop decisions depending on what they sensing or the received input, but also learn from the environment, previous interactions and adaption.

Despite growing progress made in the past few years in the field of AI-biosensors

toward healthcare, many key challenges remain before the commercial maturity of AI-biosensors. Firstly, flexible bioelectronic materials are critical factor for commercial applications. Human body and its inner organisms are intrinsically flexible and elastic. In this case, it is necessary for integration of electronics in flexible material platforms (Kim et al., 2012; Nathan et al., 2012). Owing to extremely flexible mechanical properties, flexible bioelectronics bring advantages to match human body and organs (such as skin, eye and muscles) with minimal mechanical damages to tissues and reduce side effects after long-term integration. Furthermore, the high quality interfaces between flexible bioelectronics and target organs have enabled body-to-signal transduction with high signal-to-noise ratio (Choi et al., 2019; Choi et al., 2016). Secondly, current healthcare has many constraints including high expense, limited accuracy and treatments. Therefore, there is a great demand to improve the current healthcare facilities. An analysis by Frost & Sullivan suggested such cross-cutting uses of AI "have the potential to improve patient outcomes by 30 to 40 percent, while cutting treatment costs by as much as 50 percent." The impacts of AI technologies over the longer term are likely to be even more profound (Gil and Selman, 2019). Driven by the smart medical device industry, the market demand for AI-biosensors will continue to expand. In the future, with the support of nanotechnology, medical AI-biosensors will be the role of innovative solutions to provide the foundation of key technologies, and continue to develop towards the direction of miniaturization, scalability, low power consumption, low cost, high sensitivity, multifunction, safety, non-toxicity and degradation.

AI-biosensors integrated into a system with limited space is paramount. We expect that this review can serve as a baseline to solve the challenges that currently exist for AI-biosensors. By seamless system integration among five aspects of AIBN technology we mentioned above, AI-biosensors will provide a new platform for future innovation, and have the potential to transform nearly every aspect of healthcare.

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Highlights

1. Progress for future wearable and implantable technology from biosensing, wearable biosensing to AI-biosensing is summarized.
2. We emphasized the important components including materials, biorecognition elements, signal acquisition and transportation, data processing and intelligence decision for future wearable AI-biosensor networks.
3. The challenges and opportunities of AI-biosensors moving forward toward future medicine devices are also discussed.

Declaration of interests

☒ 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.

☐ The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: