



Intelligent biosensing strategies for rapid detection in food safety: A review

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ABSTRACT

With the development of the economy and progress in science and technology, people are paying increasing attention to food safety, and food safety testing technology has also developed rapidly. Biosensors, one type of detection technology, stand out due to their high sensitivity and specificity. In combination with emerging technologies, such as smartphones, 3D printing, artificial sensing and the Internet of Things (IOT), biosensor technology has been increasingly developed. The future development of food detection requires intelligence, portability and sensitivity. Based on these factors, we reviewed the research progress regarding the intelligence of biosensors in recent years, expound the research situation based on various biosensor intelligent technologies and equipment, and forecast the future applications of intelligent biosensors.

1. Introduction

Food is often contaminated with bacteria, viruses, fungi and parasites, causing diseases such as hemolytic uremic, irritable bowel and Guillain–Barre syndromes (Saravanan et al., 2020). In addition, in order to improve crop yield, frequent cases of pesticide abuse and improper use may lead to pesticide residues, further posing a serious threat to humans (Zhao et al., 2020). These possible residues of pesticides, veterinary drugs, illegal additives, etc., also affect people's health. Food safety has been a major global challenge to human health, particularly in developing countries (Lv et al., 2018). Therefore, the detection of toxic and harmful substances is very important for food safety. To solve the problems related to food safety, many strategies have been developed to detect biological and chemical contaminants in food. There are many different methods of detection, including culture and colony counting methods, immunology-based methods, and polymerase chain reactions (Lazcka et al., 2007). However, culturing methods are very time-consuming. Polymerase chain reaction (PCR) detection technology is relatively complex and requires the great technical expertise of detection personnel (Velusamy et al., 2010). Enzyme-linked immunosorbent assays (ELISAs) have a high false-positive rate (Li et al., 2017).

Sensors are detecting devices that can sense the measured

information and transform the perceived information into optical, electrical, and thermal signals or other information outputs in required forms according to certain rules to meet the requirements of information transmission, processing, storage, display, recording and control. Sensors can be miniaturized, digitized, intelligentized, multifunctionalized, and systematized and included in networks. Sensors can be divided into three types according to the effects of converting external input signals into electrical signals, namely, physical sensors, chemical sensors and biological sensors. Among them, biosensors are widely used in the food industry.

A biosensor is an analytical device used for the detection of analytes that combines a biological component with a physicochemical detector (Yao and Fu, 2014). It is made according to the principle that some bioactive substances have the ability of selective recognition. It is a sensor that uses immobilized enzymes, antigens, antibodies, aptamers, hormones or tissues, cells, and organelles as sensing elements (Mahmoudpour et al., 2021). Therefore, biosensors can be classified as enzymatic sensors, immunosensors, microbial sensors, tissue sensors and cellular sensors. Compared with traditional analysis methods, biosensing technology has irreplaceable advantages: first, biosensors can interact with biological macromolecules in real-time and analyze the changes occurring at any moment in the process; second, the whole

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process only takes 5–15 min, and many samples can be measured in a short time (Zhang et al., 2019). In food safety, biosensors can quickly detect food composition, food additives, pesticide and antibiotic residues, microbes and biotoxins. In general, biosensors have significant advantages of being affordable, easy to use, rapid response, high sensitivity, good specificity and multiplexing capability (Cheng et al., 2019).

Common traditional detection techniques include biological techniques, such as culture-dependent microbiological techniques to quantify viable bacteria (Davis, 2014), nucleic acid detection technology (e. g., multiplex PCR) (Moriconi et al., 2017), biochemical detection techniques (Zhang and Liu, 2016), immunological detection techniques (Hirakawa et al., 2015) and different biosensor-based methods. Different spectral methods include Fourier Transform infrared spectroscopy (FTIR) (Hansen and Holroyd, 2019), Raman spectroscopy (He et al., 2019), and hyperspectral imaging techniques (Pu et al., 2019). However, traditional analytical biosensors are bulky, expensive and difficult to operate, and their applications in resource-limited environments are greatly limited. In recent years, the development of biosensors has tended to yield miniaturized, integrated, intelligent and noninvasive biosensors. With the continuous maturity of detection instruments and methods, biosensors will have broader application prospects in fast on-site food detection. Therefore, the intelligent development of sensors has become necessary.

The traditional definition of intelligent technology is that due to the development of society, there are some new disciplines, such as information theory, cybernetics, etc., and the technology developed based on these new disciplines is called intelligent technology. Intelligent biosensor strategies mainly involve combining various intelligent technologies. The combination of biosensors and smartphones can realize portable field detection (Zhang et al., 2020). Using a smartphone as a colorimetric readout device, an Android app can analyze RGB values, making smartphones sensitive enough to detect H_2O_2 in milk (Peng et al., 2020). With the continuous development of Internet technology, smartphone biosensors can also use more complex algorithms to automate and process data in the cloud to significantly improve detection accuracy and shorten processing time. The 3D printing bioanalysis platform has great potential in electrochemical and optical devices and other fields (Muñoz and Pumera, 2020). It can be used as a detection platform as well as a smartphone adapter and is widely used in biosensors. Human sense biosensors are mainly included in electronic noses and tongues, computer vision technology, which are bionic simulators of the human senses of smell, taste, and vision. Sensor arrays can be used to accurately identify very similar analytes and a wide range of analytes in mixtures for fine fingerprint identification. The Internet of Things (IOT) applies biosensors in wireless transmission technology and wearable devices. Sensors and smartphones, through network wearable devices, are connected with the cloud, realizing the sharing of data communication and the ability to collect information and process data; thus, there are many opportunities for all walks of life (Thibaud et al., 2018). With the advent of 5G, the speed of data transmission will be further accelerated, which also provides more possibilities for applications in biosensors.

In this review, we focused on the research progress of biosensors and chemical sensors in intelligence development in recent years. In recent years, we have witnessed a boom in research in this area, with a large number of papers published, and several reviews of intelligent biosensors have been published, with a focus on smartphones (Kalinowska et al., 2021), Electronic nose (Dung et al., 2018), wearable biosensor (Jin et al., 2020), etc. However, as far as we know, there is no system introducing a variety of intelligent technology integration applications in food detection of biological sensors. We further combined with 3D printing, the Internet of things, artificial neural network, machine learning and big data, integration, system of intelligent technology, specifically introduced the application in the field of technology in rapid detection of food. Finally, we also give a specific outlook on the development of these intelligent biosensors in practical applications.

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2. Smartphone-based sensing strategies

With the development of the economy and the progress of science and technology, the application of smartphones is becoming increasingly widespread. Smartphones are indispensable devices for everyone, and smartphone-based sensors are also becoming more common. Due to their portability and availability, smartphones have been widely integrated with sensors, such as test bands, sensor chips and handheld detectors, for biochemical detection. Using the built-in functional modules of smartphones, smartphones are often used as controllers, analyzers and displays for fast, real-time monitoring, which can greatly simplify the design and reduce the cost of detection systems (Zhang and Liu, 2016). At the same time, smart phones have full processing power, can connect to the network, and simple operation interface, which is more conducive to non-destructive and portable food quality assessment, combined with the latest advances in the Internet of Things, deep learning algorithms and cloud computing, can also provide an opportunity to promote sustainable detection methods (Kalinowska et al., 2021). Smart chips and high-definition (HD) camera devices give smartphones high-speed computing and camera capabilities. Through an HD camera and color recognition app, detailed optical information of sample color can be easily obtained, such as the color attributes of Hue, brightness, saturation, or the color parameters red, green, and blue (Linfeng Chen et al., 2019). We can establish a linear relationship between the color parameters and the concentration of the target sample for visual detection.

2.1. Smartphone-based colorimetric biosensors

Based on quantitative colorimetric technology, smartphones have been used as real-time detectors in various fields, such as environmental monitoring and disease diagnosis (Guo et al., 2020; Zhang et al., 2020). Furthermore, smartphone-based colorimetric detection technology is also widely used in the food field. As shown in Fig. 1A, nanozyme is used as a signal amplifier for dual lateral flow immunoassays (LFIs) and integrated with a smartphone-based device for the simultaneous detection of *Salmonella enterica* and *Escherichia coli* O157:H7 (Cheng et al., 2017). In addition, Ouyang et al. (2020) established a color system based on an enzymatic method for detecting D-glucose concentrations. Smartphone photographs and Microsoft Photoshop software were used in this system for color determination. The enzymatic analysis system can detect D-glucose concentrations of 5 mM–40 mM, and other sugars do not interfere with the system. The system is also suitable for testing many samples (Ouyang et al., 2020).

With the demand for miniature and portable detection systems, microfluidic technology is increasingly applied in the detection field. Zhu et al. (2011) designed a hand-held microfluidic detection device based on a smartphone for various cell counts. The detection results are highly consistent with a hematology analyzer, and thus, the device can be used for rapid and sensitive detection. The device can also detect water quality (Zhu et al., 2011). This kind of structure that combines a

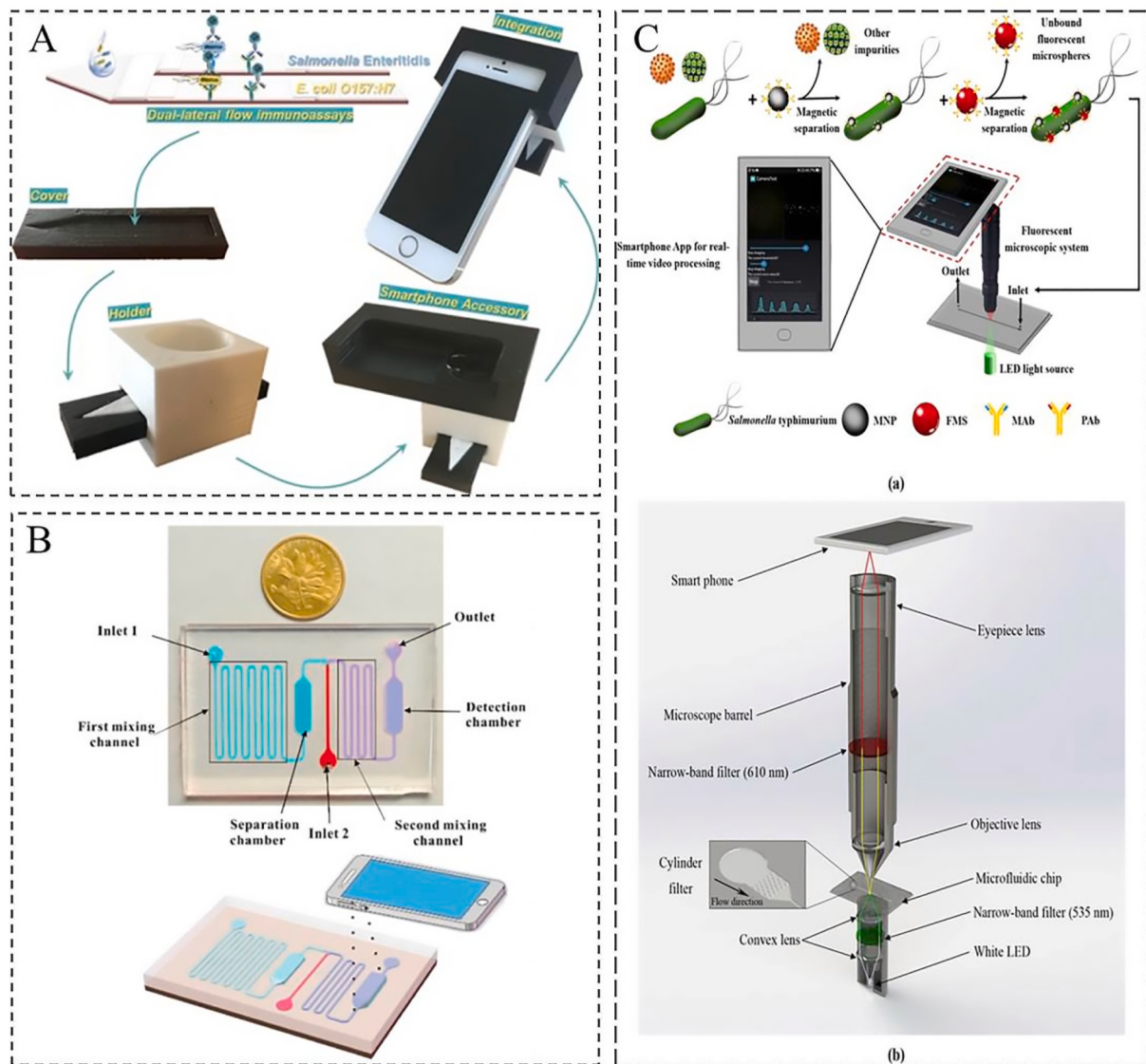


Fig. 1. A smartphone biometric imaging system for colorimetric detection. (A) Structure diagram of a dual lateral flow immunoassay combined with a smartphone. (B) A colorimetric biosensor used for rapid detection based on gold nanoparticle aggregation and smartphone imaging. (C) (a) The principle of the proposed microfluidic biosensor for the online, rapid and sensitive detection of *Salmonella typhimurium* and (b) the structure of the smartphone-based fluorescence microscopic system.

smartphone with a microfluidic colorimetric biosensor has also been used to detect *E. coli* O157:H7 (Zheng et al., 2019). As shown in Fig. 1B, this biosensor was based on the $\text{HRP} + \text{H}_2\text{O}_2 + \text{tyramine (TYR)}$ system. In the presence of *E. coli* O157:H7, the color of the detection chamber changed from blue to red, and the concentration of the target bacteria was determined by using the Hue-Saturation-Lightness (HSL) imaging app on a smartphone to detect the color change (Zheng et al., 2019). In addition, a paper-based microfluidic analysis device with a smartphone reader can also be used to screen for chlorpyrifos-oxon in human serum (Tsagkaris et al., 2021). With the development of gene editing technology, gene editing represented by CRISPR-Cas has been widely used. Parinaz Fozouni et al. (2021) designed a CRISPR/Cas13a-based system to detect COVID-19, and realized visual detection using smartphone (Fozouni et al., 2021).

Combining a microfluidics biosensor with a fluorescent label, Wang et al. (2019) developed a microfluidics biosensor for the online detection of *Salmonella typhimurium* based on immunomagnetic separation, fluorescent labeling and smartphone video processing technology (Fig. 1C). They used immunomagnetic nanoparticles to specifically isolate and

concentrate the target bacteria to form magnetic bacteria. Then, the magnetic bacteria were labeled with immunofluorescence microspheres to form fluorescent bacteria. Finally, the fluorescent bacteria were continuously injected into the microfluidic chip on the fluorescence microscope system based on smartphones, and the smartphone app based on the frame difference algorithm was used to count the fluorescent points online to obtain the number of target bacteria (Wang et al., 2019).

2.2. Smartphone-based fluorescence biosensors

Base on fluorescence imaging integration, Zhu et al. (2012) used a mobile phone-based fluorescence imaging and sensing platform to specifically detect *E. coli* O157:H7 and quantify its concentration in liquid samples, providing a compact, light and economical detection scheme (Zhu et al., 2012). To achieve trace detection and further improve the sensitivity of smartphone detection, methods such as preprocessing magnetic bead enrichment or microscopic amplification of imaging signals can be adopted. As shown in Fig. 2A, a microscopic device was

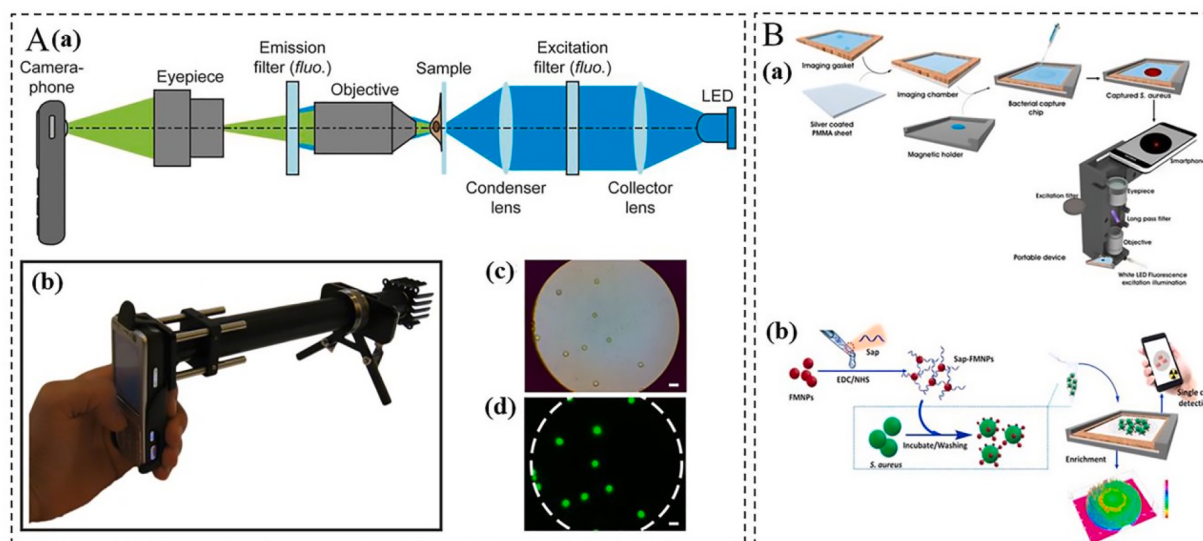


Fig. 2. (A) Mobile phone microscopy layout schematic, prototype, and sample images. (a) Mobile phone microscopy optical layout for fluorescence imaging. (b) A current prototype with filters and LEDs installed capable of fluorescence imaging. (c) Brightfield image of 6 mm fluorescent beads. (d) Fluorescent images of the beads shown in (c).

installed on a smartphone and light-emitting diodes (LEDs) were used as the excitation light source for the brightfield imaging of *P. falciparum*-infected sickle red blood cells and *M. tuberculosis* infections; the fluorescent images of the blood cells and microbes clearly show that this smartphone fluorescence imaging system laid the foundation for applications in other areas (Breslauer et al., 2009). As shown in Fig. 2B, the tagged *S. aureus* cells were magnetically captured in a detection cassette, and then, a LED was used as the excitation light source, which was amplified by a microscopic device. Finally, the amplified fluorescence signal was imaged by a smartphone camera. The results showed quantitative detection capability with a minimum detectable concentration as low as 10 cfu/ml by counting individual bacterial cells (Shrivastava et al., 2018).

Furthermore, smartphone fluorescence imaging technology can also be used to detect metal ions. Yanke Shan et al. (2019) designed a biosensor based on a smartphone micro fluorescence microscope for collecting fluorescence signals, and an image processing application program was constructed for the quantitative measurement of Hg^{2+} (Shan et al., 2019). Based on thymine- Hg^{2+} -thymine coordination chemistry, highly specific detection of Hg^{2+} with a linear region between 1 nM and 1 μ M and a limit of detection of 1 nM was obtained using the smart Hg^{2+} detection approach.

3. 3D printing-based sensing strategies

Additive manufacturing, also termed 3D printing, enables the economic, dynamic and rapid fabrication of customizable three-dimensional (3D) devices catering to specialized functions (Zafir Mohamad Nasir et al., 2020). Additive manufacturing allows for the rapid printing of 3D objects designed using 3D modeling software. The 3D object is digitally controlled to deposit a continuous layer of material until the final structure is created. Due to its unique printing method and design flexibility, it can significantly reduce material waste, reduce production costs and build biosensors that are more flexible than traditional devices (Emon et al., 2019; Jiang et al., 2018). In addition, some degradable materials such as polylactic acid (PLA), polycaprolactone (PCL) and polybutylene succinate (PBS), 3D printing devices based on these materials can also avoid environmental pollution and achieve environmental friendliness (Bardot and Schulz, 2020; Lyu et al., 2021). In food detection, new methods are usually developed and combined with new technologies to simplify detection procedures and

improve sensitivity. Therefore, it is very important to follow the development of new technology for detection research. 3D printing has long been applied in biomedicine, energy applications and other fields (Browne et al., 2020; Shen et al., 2019). In recent years, 3D printing has been increasingly applied to food detection. In biosensors, electrodes, detection boxes and micro devices can be made by 3D printing. Through the flexible and intelligent design of 3D printing, to achieve portable and flexible rapid detection, but also make the sensor more intelligent to meet the needs of people.

3.1. 3D printing based biosensors

The electrode produced by 3D printing has high precision and uniformity and can be used in electrochemical biosensors to ensure the consistency of the quality of the manufactured sensor, thus ensuring the reliability of the detection results. It has been confirmed that 3D-printed composite electrodes have successfully detected microorganisms, pesticide residues, DNA, H_2O_2 and so on (Bao et al., 2019; Boobphahom et al., 2019; Lopez Marzo et al., 2020). In addition, 3D technology allows flexible design and a wide selection of materials to produce electrodes of different materials and shapes. Fig. 3A shows the fabrication of 3D-printed graphene electrodes by fused deposition modeling (FDM), which were then used for the electrochemical detection of the mycotoxin zearalenone (ZEA). Chemical and electrochemical pretreatment procedures were applied to remove the inert polylactic acid external layer from the graphene electrodes, exposing and activating the inner graphene surface. These procedures enhanced the sensitivity of the electrodes towards the electrochemical detection of ZEA. The activated 3D-printed graphene electrodes displayed a good linear response ($r = 0.995$) over a wide concentration range (10–300 μ M). This proof-of-concept application opens up a wide range of possibilities for the fabrication of 3D-printed electrochemical devices for use in food analysis and food safety (Zafir Mohamad Nasir et al., 2020). Furthermore, 3D-printed electrodes made of metallic materials can be used for DNA detection (Loo et al., 2017). As shown in Fig. 3B, by 3D printing a helix electrode with gold plating, a DNA recognition element (SH-L probe) with covalent gold-thiol interactions was fixed on the surface-modified electrodes, and then, the modified electrode and DNA targets were incubated to achieve DNA hybridization, specificity recognition and methylene blue inherent reduction signals for signal analysis. The results showed reasonable linearity. Flexible biosensors

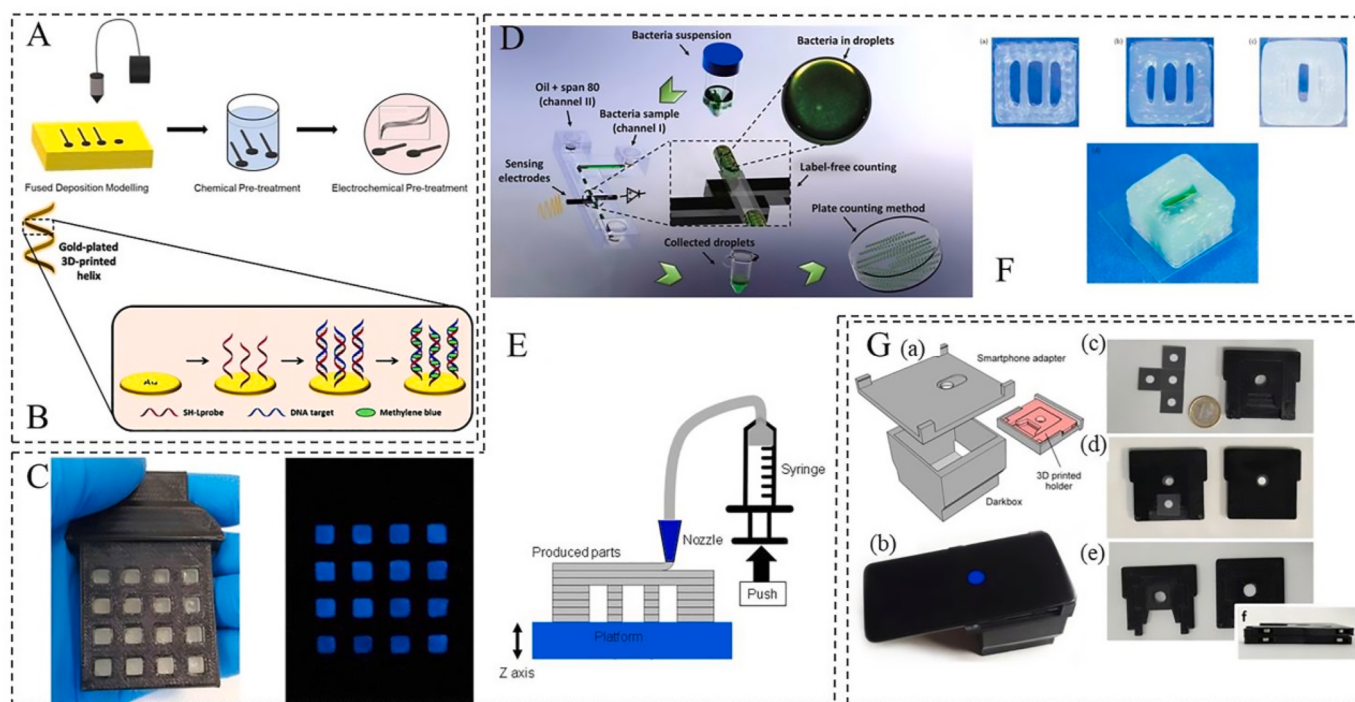


Fig. 3. (A) Schematic representation of the fabrication of graphene/poly(lactic acid) filaments of 3D-printed graphene electrodes and their pretreatment for the detection of ZEA. (B) Schematic representation of the biosensing protocol utilized. A DNA recognition element, SH-L probe, was first covalently immobilized onto the gold-plated 3D-printed helix electrode. Subsequently, a blocking step with MCH (not shown) was performed to cover up the remaining electrode surface. The modified electrode was then incubated with a DNA target for the hybridization reaction. Finally, the electrode was exposed to methylene blue solution, and the methylene blue molecules intercalated into the double helix structure of the hybridized double-stranded DNA. (C) Picture of a 3D-printed cartridge containing 16 alginate slices of yeast-estrogen bioreporters. (D) Schematic representation showing the procedures used to detect *E. coli* K12 bacteria by performing C^4D measurements and plate counting. The bacteria retained in droplets generated in the microchannel are detected by using sensing electrodes integrated into the microfluidic device. Then, the droplets containing bacteria are collected and determined by the conventional method of plate counting to serve as a reference and compared with the proposed C^4D approach. (E) Schematic of extrusion-based 3D printing. Using a tapered nozzle (0.64 mm inner diameter), the material was printed onto a glass substrate fixed on a build platform. A stepper motor was used to pressurize the syringe. (F) Photographs of the 3D printing process of the microfluidic device: (a and b) top views of the unfinished 3D-printed micromixer showing the internal structure, (c) top view of the completed 3D-printed micromixer, and (d) perspective view of the completed 3D-printed micromixer. Green deionized water was added to the mixing chamber for better visualization of the internal structure. (G) (a) Schematic drawing of the device. (b) Device connected to a One Plus 6 smartphone. (c) Unfolded paper-based biosensor and 3D printed holder. (d) The two components of the 3D printed holder; each part contains a 5-mm hole to enable the addition of a luminol solution and acquisition of the CL signal with a smartphone. (e) 3D printed holder (top and bottom view) housing the paper-based biosensor. (f) Detailed view of the assembled holder showing the N52 grade neodymium magnets designed to keep the paper biosensor folded.

can be made by printing electrodes from specially flexible materials, such as graphene or ionic conductors that are highly malleable, transparent and biocompatible (Yin et al., 2019). In addition to applying biosensors to skin and body fluids, these sensors can also be used for rapid detection of food. For example, the 3D porous graphene flexible nano-enzyme electrode prepared on polyimide not only maintains the advantages of 3D printing technology in low cost and mass production, but also has excellent mechanical flexibility and conductivity. Through simultaneous detection of xanthine (XT) and hypoxanthine (HX) and intelligent analysis and digital output of machine learning model based on artificial neural network (ANN) algorithm, it can be used as a novel electrochemical nanosensing platform for intelligent evaluation of fish freshness (Zhu et al., 2021). This research opens the door to future improvements in 3D-printed electrodes, maximizing their performance through better electrode design, better material selection and further functionalization processes. In addition, this proof-of-concept work opens the possibility of customizing food safety and inspection testing equipment in the field.

In addition to printing electrodes, 3D printing can also be used to prepare molecularly imprinted polymers (MIPs). For example, 3D-printed MIPs selectively identify N-acylated hyperserine lactones (AHLs) and enhance the fluorescence of samples through 3D-printed molecularly imprinted technologies. MIPs were formed by embedding

yellow carbon quantum dots (CQDs) with furanone as the template molecule by the sol-gel method. Under the optimal test conditions, there was a good linear relationship between analyte concentration and fluorescence intensity, and the reaction occurred within 2 min 3D printing CQD@MIPs is personalized and portable, and retains MIPs' characteristics of economy, direct preparation, and efficient and specific target identification in complex environmental substrates, which has great application potential in food safety (Ding et al. 2020, 2021; Yang et al., 2020).

3.2. 3D printing-based sensor reaction devices

In addition to printing electrodes, 3D printing technology can also be used to make reaction devices in biosensors. 3D printing technology can be used to manufacture reaction detection boxes or build microfluidic devices. Cevenini et al. (2018) used 3D-printed cartridges to fix cells and exploited a newly developed bioluminescent yeast-estrogen screen (nanoYES) and a small, low-cost compact camera as photodetectors to detect chemicals that have estrogen activity (Cevenini et al., 2018). A yeast cell culture was diluted, mixed with trehalose and sodium alginate, and then poured into a cellulose membrane to form a gel. The gel slices of the mixture were put into the hole of the 3D-printed cartridge. As shown in Fig. 3C, the bottom of the cartridge hole is printed with black

thermoplastic acrylonitrile butadiene styrene (ABS), while the rest is printed with white ABS. This configuration increases the strength of the bioluminescence (BL) signal acquired through reflection while avoiding cross-talk between adjacent wells. Through intelligent design, 3D printed microfluidic devices can be more portable and miniaturized for detection, and 3D printing creates real 3D structures in one step, thus greatly improving the current manufacturing technology of microfluidic devices. Duarte et al. (2019) designed a microfluidic device based on capacitively coupled contactless conductivity detection (C^4D) through 3D printing (Duarte et al., 2019). The microfluidic device can count *E. coli* cells incorporated inside droplets without labeling. As shown in Fig. 3D, the microfluidic device is completely fabricated into a T-junction shape by 3D printing and contains two channels for disperse and continuous phases and two sensing electrodes for C^4D measurements. The disperse phase containing *E. coli* K12 cells and the continuous phase containing oil and 1% Span®80 were pumped. The droplets with incorporated cells were monitored in the C^4D system by applying a 500-kHz sinusoidal wave with a 1 Vpp amplitude. The proposed approach demonstrated the ability to detect *E. coli* cells in the concentration range between 86.5 and 8650 CFU droplet⁻¹. The number of cells per droplet was quantified by plate counting and revealed good agreement with the Poisson distribution (Yao et al., 2019). Yao et al. (2019) designed a microfluidic device to detect *Listeria monocytogenes*. Fig. 3E is a model diagram of extrusion-based 3D printing. Using a tapered nozzle (0.64 mm inner diameter), the material was printed onto a glass substrate fixed on the build platform. A stepper motor was used to pressurize the syringe. Layer by layer, the microfluidic device shown in Fig. 3F is finally formed.

3.3. 3D printing-based sensor accessory equipment

In detection by biosensors, some accessory devices are often needed to place readout devices, batteries, diodes, etc. Some accessories can provide a cassette for colorimetric/fluorescence detection, and some can be used as micro devices (Qingshan Wei 2020; Shan et al., 2019; Shrivastava et al., 2018; Wang et al., 2019). A multienzyme chemiluminescence foldable biosensor was designed for the field detection of acetylcholinesterase inhibitors (Montali et al., 2020). The sensor comes with a 3D-printed mini dark box that can be used for detection by smartphones. The scaffolds that hold the paper-based biosensors are also 3D printed. All components of the dark box were printed with a black acrylonitrile-butadiene-styrene (ABS) copolymer. The mini black box includes a slot for inserting the bracket and an adapter for connecting the smartphone (used as a portable light detector) (Fig. 3G) so that measurements can be taken outside the laboratory without interference from ambient light. Through the integration of 3D printing devices to make the biosensor more intelligent. The distance between the stand and the smartphone (approximately 5 cm) is enough for the smartphone camera to correctly focus the biosensor. Future developments in 3D printed biosensors will include research into new biofunctionalization, immobilization, and doping procedures, as well as bioactive printing materials based on nanocomposites.

4. Artificial sense-based sensing strategies

4.1. Electronic nose-based sensing strategies

An electronic nose is a kind of analysis equipment used for the rapid detection and identification of mixed odors. It mimics the human sense of smell by the working principle of a special chemical sensor. When interacting with a mixture of gases, it produces a unique odor profile, which is compared with the standard odor profile, identifying the mixed components (Sliwinska et al., 2014). The core of the artificial nose is the sensor matrix. In a certain type of odor detection and recognition system, the excitation of its sensing elements leads to the production of a certain signal. This makes it possible to generate unique responses (smell

fingerprints) to specific odor samples (Wasilewski et al., 2017). Bio-electronic noses are sensors made from biological materials that are directly connected to sensors used for odor recognition and convert biological signals into electrical or optical signals that are useful for analysis. At present, electronic noses have been applied to medical analysis, medical diagnosis, food detection, security screening and other fields (Han et al., 2018; Saidi et al., 2020; Santana Oliveira et al., 2019; Srinivasan et al., 2020). An electronic nose is basically composed of three elements (Fig. 4A.a), namely, (1) a sample processing system, (2) a detection system, and (3) a data processing system (Peris and Escuder-Gilabert, 2016). E-nose devices are able to contribute greatly to numerous applications involving the quality assessment of agricultural and food products. Semeano et al. (2018) developed an air-sensitive mixed gel material that uses an optical electronic nose to monitor tilapia decay (Semeano et al., 2018). Tan and Kerr detected the degree of roasting of cocoa beans by an electronic nose system and gas chromatography/mass spectrometry (GC/MS) (Tan and Kerr, 2018).

4.2. Electronic tongue-based sensing strategies

An electronic tongue, also known as an artificial tongue or taste sensor, is an analytical device used primarily to classify the smell of various chemicals in liquid samples (Fig. 4B). The electronic tongue consists essentially of three elements: (i) an automatic sampler (although not a necessary component), (ii) a set of chemical sensors with different selectivities, and (iii) software with appropriate algorithms for processing signals and obtaining the corresponding results (Fig. 4A.b). With adequate calibration and training, the electronic tongue can determine the qualitative and quantitative characteristics of more chemical species in complex samples with high sensitivity, accuracy and specificity (Ghasemi-Varnamkhasti et al., 2018). The electronic tongue can be divided into an electrode sensor-based electronic tongue and a photocolometric sensor-based electronic tongue according to the different signal expressions of the sensor. MIPs can be used to make electronic tongue sensors, but an important limitation is the difficulty in integrating MIPs into the electrode surface. Herrera-Chacon et al. developed an electronic tongue biosensor for the detection of volatile phenol and retained the molecularly imprinted polymer on the gel, which was then deposited on the electrode surface (Herrera-Chacon et al., 2018). Furthermore, the electronic tongue can also be applied to trace detection. For example, Facure et al. (2017) developed an electronic tongue based on the analysis of organophosphorus pesticide enzyme impedance (Fig. 4C). It is based on a graphene hybrid nanocomposite sensing unit. Polymers conduct during reduction in the presence of graphene oxide and gold nanoparticles for the preparation of nanometer composite materials, gold nanoparticles are deposited on the electrode, impedance spectra are collected for the samples, and data is processed through principal component analysis to deal with resistance; as a result, the sensor is able to identify organophosphorus at nanomolar concentrations (Facure et al., 2017). In addition, electronic noses and electronic tongues combined with gas chromatography-mass spectrometry (SPME/GC-MS) can be used to establish a more comprehensive quality evaluation method. Zhu et al. analyzed the flavor and quality indexes of apples by SPME measurement, were able to carry out a detailed evaluation of five varieties of apples, and provided a genealogy map by combining sensory evaluations (Zhu et al., 2020). At present, the combination of an electronic tongue and machine learning may become a new research direction. Machine learning refers to a class of algorithms that automatically analyze patterns from data and use the patterns to predict unknown data. Machine learning can effectively handle large data of complex matrices or samples. Therefore, the introduction of machine learning methods into biosensors can obtain reasonable analysis results from noise and low resolution sensor data, and extract features or predict the type and concentration of analytes (Cui et al., 2020). A voltammetric electronic tongue (VE-tongue) imaging system was developed (Shi, 2018). As shown in Fig. 5A, the VE-tongue is composed

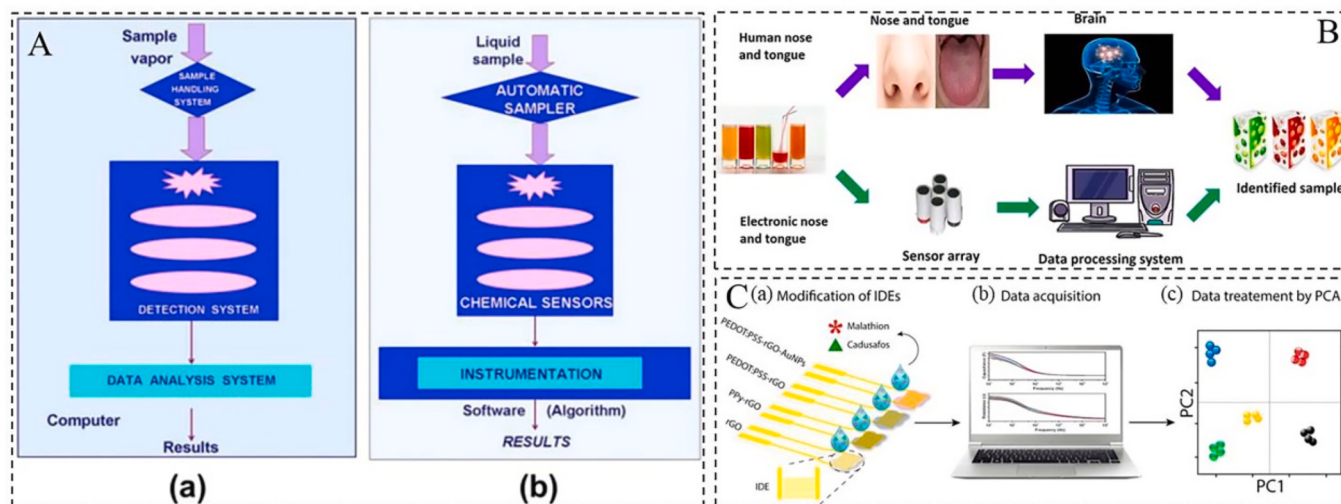


Fig. 4. (A) Schematic representation of (a) an electronic nose and (b) an electronic tongue. (B) Comparison of the operation principles of the senses of taste and smell of an electronic tongue and electronic nose. (C) Schematic illustration (a–b) of the impedimetric e-tongue system based on graphene hybrid nanocomposites for the detection of trace levels of OP pesticides. (c) PCA was the statistical technique used to treat the electrical resistance data collected by the e-tongue.

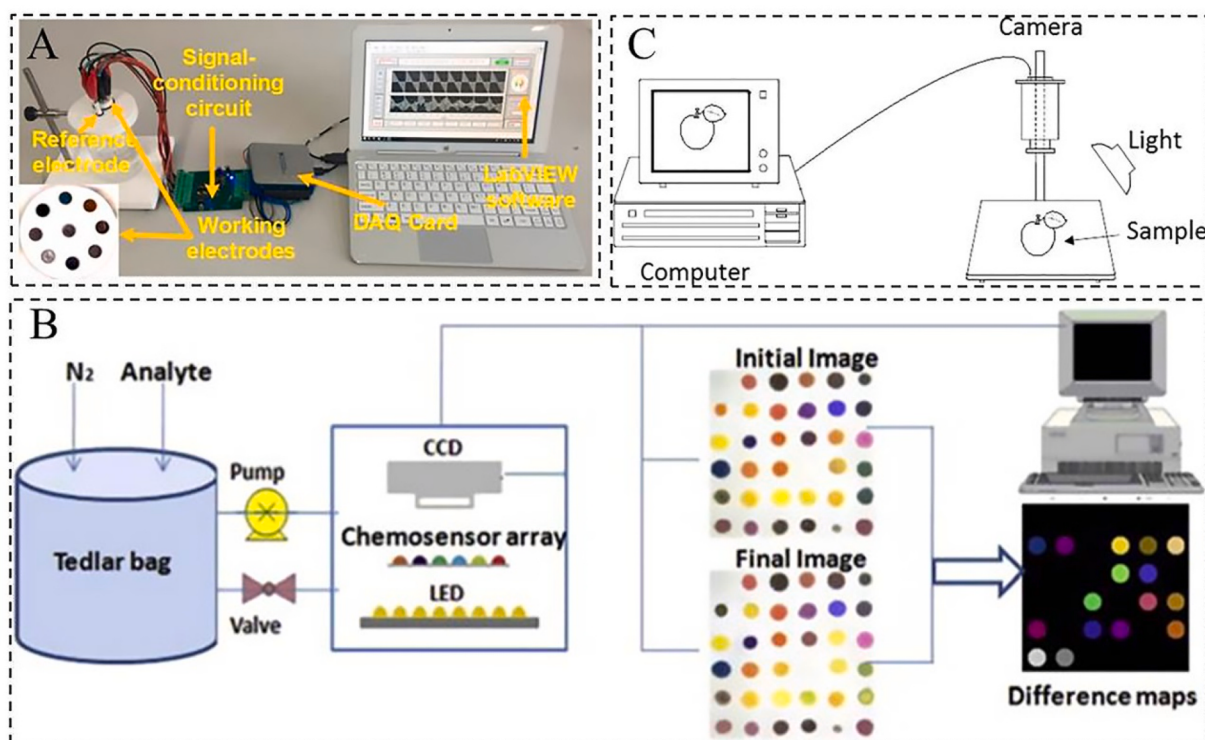


Fig. 5. (A) The self-developed VE-Tongue system. (B) 6 × 6 colorimetric sensor array and schematic diagram of the detection system. (C) Schematic structure of an image analysis system.

of four parts: a sensor array consisting of an integrated three-electrode system with one of eight different working electrodes (platinum, gold, titanium, palladium, silver, wolfram, nickel and glassy carbon), a platinum auxiliary electrode and an Ag/AgCl reference electrode. A voltammetry electronic tongue combined with deep learning and transfer learning techniques was used to identify the age of Pu erh tea. To make the deep learning model suitable for processing virtual tongue signals, a one-dimensional convolutional neural network is developed for automatic feature extraction and classification. Transfer learning is introduced to train the model to reduce the training complexity and improve the generalization ability of the neural network. The results show that

the model is superior to other traditional machine learning methods in the classification of Pu erh tea (Yang et al., 2021b).

In colorimetric sensors, a low-cost photoelectric tongue system based on a colorimetric sensor array is used to predict heavy metal residues in fish (Han et al., 2018). Huo et al. (2014), using a sensor array, built a fully functional prototype device to detect the level of green tea (Fig. 5B). First, the initial image of the green tea solution was obtained, and then, the final image was subtracted from the initial image to obtain the color curve of each green tea liquid. Using the artificial tongue color, Chinese green tea of nine different producing areas and grades were identified; all the green tea samples, either by liquid or gas analysis,

were classified according to geographical origin and grade level using the different models, so they were easy to identify. It has been proven that the colorimetric artificial tongue has good reproducibility (Huo et al., 2014). The future application of electronic tongues still faces many challenges: how to reduce interference is the main research direction of the future to further improve the accuracy; at the same time, different samples need to be tested to build a large database, which is one of the problems faced by electronic tongue systems (Chen et al., 2020); there are reports combining sensor array and machine learning methods as much as possible to reduce external environmental influence; In future studies, further studies at the molecular level can be done by combining electronic tongue with other technology. For example, a low-cost photoelectric tongue system based on colorimetric sensor array is used to predict heavy metal residues in fish (Han et al., 2018). In addition, an artificial neural network can be applied to an electronic nose, which can act like a brain when interpreting the response signals from sensors. During training, the neural network adapts synaptic weights to learn patterns of different smells. After training, when faced with an unknown odor, the neural network inputs its patterns through different layers of neurons and assigns the category labels that respond most, making immediate and accurate detection results (Kalinowska et al., 2021).

4.3. Computer vision-based sensing strategies

In addition to the electronic nose and electronic tongue, computer vision is also a kind of artificial sensory sensor. Computer vision refers to a computer image analysis system (Fig. 5C) that can acquire, process and analyze images. The main reason for creating this system is to mimic the operating mode of human vision. Generally, a computer system consists of five elements, namely, lighting, cameras, computer software, and high-resolution displays (Sliwinska et al., 2014). Image analysis systems are very extensive used, especially in the food industry. An image analysis system is a fast, accurate, and noninvasive method of evaluating the quality of products that are already in production. In addition, the system can detect structural defects in meat and the beginning of spoilage, which are invisible to the human eye. Computer vision can be used to detect cells in the medical field (Uslu et al., 2019). Computer vision can be used for the detection of heavy metals, microorganisms and other substances in food. In the detection and application of arsenic in water, it has been reported that a flow module coupled with a drip system is used to form second-order data by computer vision technology. Without chemical pretreatment, arsenic is extracted from water samples in the form of arsine and reacts with a drop of silver diethyl dithiocarbamate to form a colored complex. The whole reaction is recorded with a digital microscope, and video is obtained over time to form a satisfactory linear response (Belén et al., 2020). At present, with the growing demand for real-time monitoring, computer vision is applied to real-time monitoring to realize process monitoring. Aghbashlo et al. (2014) used computer vision technology to monitor the drying process in real-time; this technology does not need to use samples and can be used for online testing tools to process shape, size, color and texture. By extracting various insights from the captured image and absorbing that information in an appropriate way, a clear relationship between image data and product quality can be established (Aghbashlo et al., 2014). Since the computer vision system cannot obtain the aroma, taste or other quality indicators of food, in the future, computer vision can be combined with a biological electronic nose/tongue to obtain more complete and accurate information through data fusion.

5. Internet of Things (IOT)-based sensing strategies

The IOT refers to the “global network of uniquely addressable interconnected objects based on standard communication protocols” (Atzori et al., 2010). The IOT is a new model that is rapidly spreading in modern wireless telecommunications. The basic idea is that there are all

kinds of things or objects around us, RFID tags, sensors, actuators, mobile phones, etc., and their convergence point is the Internet. The basic idea behind the IOT is the ubiquity of things around people and the ability to measure, infer, understand and even modify the environment (Botta et al., 2016). In 2008, the IOT was reported by the US National Intelligence Council as one of the technologies with a potential impact on the interests of the US in 2025. The development of IOT technology can also be more widely used in assisted living, mobile office, e-health, intelligent transportation, logistics and transportation, industrial automation, security, environmental monitoring, food safety and other fields (Capella et al., 2020).

5.1. IOT-based real-time detection

With the maturity of the Internet, wireless networks are connected to desktops and mobile devices, and they can now be widely used in sharing of public information in health care because many physical sensors can be used to measure temperature, pulse and biological signals, such as heartbeats; thus, health-related data can be obtained through the Internet (including Wi-Fi) in real-time using these sensors and collected on a central server. Using mobile devices as part of an analytics system allows us to monitor food, environmental pollution and healthcare with minimal time and place constraints. In principle, monitoring can be performed at home, in a supermarket or wherever samples are provided. Although basic network technologies are available, further development of terminal analysis units, namely, biosensors, is needed to achieve this goal. However, due to the different types of mobile phones, on-site detection may be difficult. Therefore, a detection mode that separates the detection method from mobile phones has become a requirement, and IOT technology can be used to realize food pollution monitoring (Seo et al., 2016). An immunosensor system with a Complementary Metal Oxide Semiconductor (CMOS) image sensor used as the detection means can be made into a pocket-sized device that can be used for the detection of food-borne pathogens. Smartphones are used for monitoring, and data are uploaded to the Internet to realize data sharing and remote detection (Fig. 6A). The detection process can be divided into three steps: 1) antigen and antibody binding, 2) cross-flow signal generation, 3) quantization signal processing, and 4) data upload to the server. Biological sensors can be combined with the IOT technology to determine if there is something wrong with food before it is bought or to immediately issue a warning after food pollution analysis finishes, thereby blocking supply routes as soon as possible. This concept can also be used to monitor infectious diseases and control their spread and can be further applied to wearable biosensor data through the IOT management. Such a structure can also be further implemented in a cloud-based framework for remote monitoring; that is, the data flowing from the end device go straight through the modem/router via the WiFi Protected Access (WPA) standard protocol for storage and processing in the cloud. The wide coverage of a Wi-Fi router makes it easier to ensure stable sensor connections over a large area. Once delivered to the cloud, sensor data are stored and subsequently processed to extract meaningful information (Fig. 6B). Using this structure, Giannetto et al. developed screen printed electrode-based immunosensors based on a remote-controlled IOT-WiFi acquisition board, which can perform sensitive detection of highly specific biomarkers related to celiac disease (Giannetto et al., 2018).

At present, the focus of applying the IOT to food safety is still the food supply chain, and the logistics tracking of food data is still in the initial stage of food safety and quality testing (Bouzembrak et al., 2019); however, as the possibilities for storing and sharing large data sets grow, the growing IOT will be a key part of improving food security and achieving more sustainable agriculture. With an interconnected network of devices, collecting and sharing information about product violations in the food supply chain is more likely to be detected early (Griesche and Baeumner, 2020).

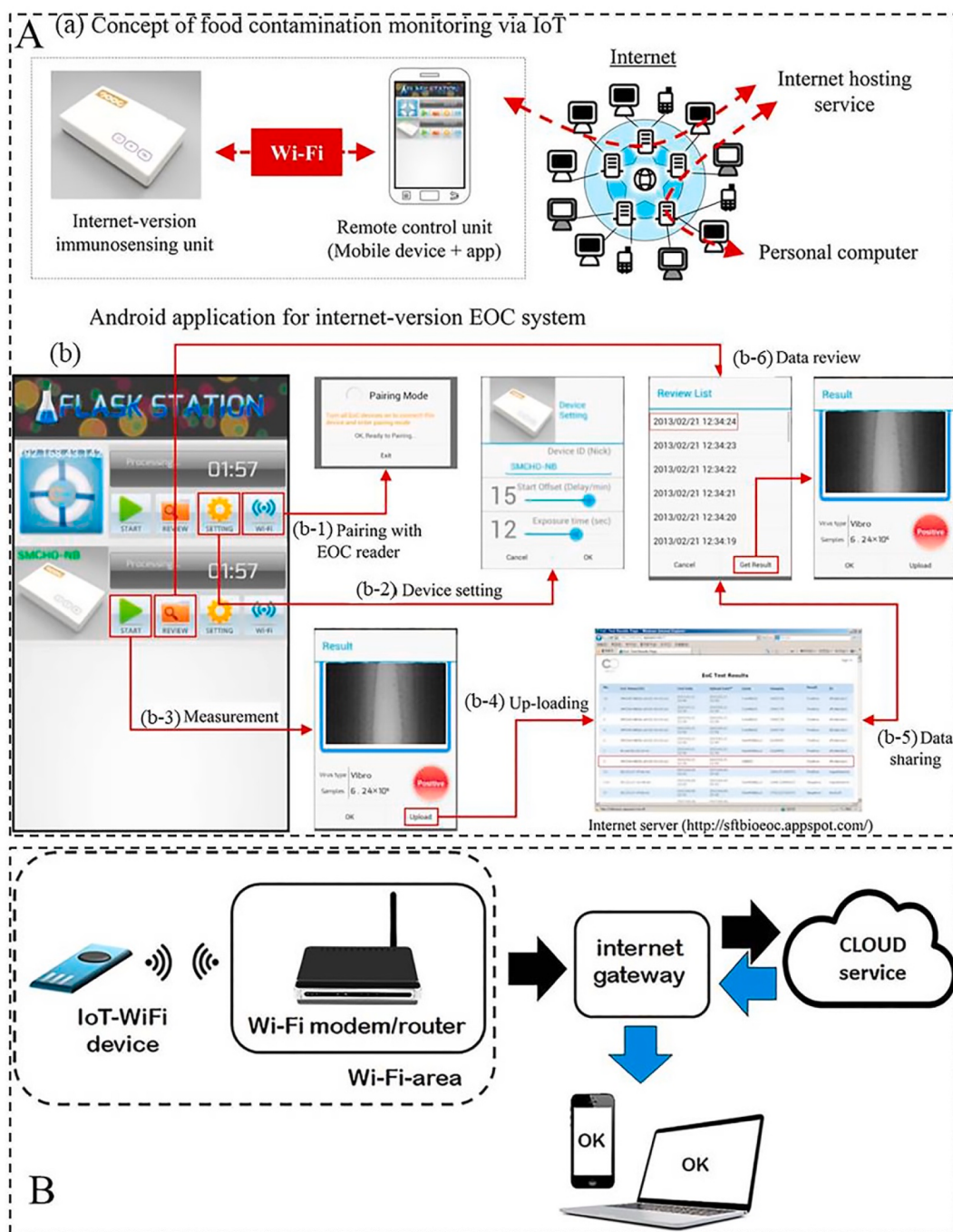


Fig. 6. (A) Concept of food contamination monitoring via the IoT using an Android application for the Ethernet Over Cable (EOC) system. To demonstrate the concept, we employed the internet-version immunosensing unit (EOC reader Rev 3.0) and remote control unit, comprising a mobile device and apps installed on the device (a). The analytical results related to food contamination are directly transmitted to a public server for data storage and shared through the Internet. The Android application program named 'Flask Station' was used to control the EOC reader and upload the analytical data regarding food contamination to a server (b). The program menu comprises various functions for pairing with the EOC reader (b-1): device setting (b-2), analysis start (b-3), uploading of data to the server (b-4), and preview of the information (b-6). The program can connect simultaneously with a maximum of 128 Internet-based EOC readers via a Wi-Fi network. Refer to the text for details. (B) Generic architecture of a cloud-based system.

5.2. IOT-based wearable sensors

The past few years have seen rapid innovation in wearable sensors that affect every area of our daily lives. With the emerging IOT, wearable sensors hold great promise not only in healthcare and fitness applications but also in a variety of other applications, from environmental monitoring to safety/forensics (Wen et al., 2020). At present, the main research on wearable sensors focuses on biomedical and personalized

health care, from tracking physical parameters of the body to monitoring biological organs, excrement and other data, including chemical information in the environment related to the user's health. Wearable sensors also enable the rapid diagnosis of diseases (Lee et al., 2018). Wearable sensors have the advantages of being minimally invasive/noninvasive and portable and achieving sustainable monitoring and simple operation (Jin et al., 2020). Wearable sensors can be applied more widely due to their diverse conduction mechanisms. The materials

used range from traditional metals and semiconductors to flexible 2D materials, polymers and biological materials, which are combined with different signal transmission technologies such as Bluetooth, wireless networks and radiography, making them promising for environmental monitoring and food detection. In the medical field, wearable sensors are often used to monitor data in sweat and tears, and people with diabetes and prediabetes can use wearable sensors to track their blood sugar to regulate alcohol intake (Fig. 7A). Biological sensors are realized through gold-zinc oxide thin film electrode stacks, stacked electrodes with flexible substrates, electrochemical impedance spectroscopy (EIS) and Faraday chronoamperometry (CA); the specificity of the sensing area of alcohol and glucose enzyme complex tests depend on the interface between electrodes and sweat, and their biomolecular interactions are probed by impedance and current changes. The sensor can maintain a steady response for more than 120 min under conditions of continuous

sweating (Bhide et al., 2018). A wearable biosensor could monitor alcohol and glucose concentrations in real-time (Jung, 2019; Zhao et al., 2019). Later, wearable biosensors gradually attracted attention in food detection due to their portability and miniaturization. Mishra et al. (2017) proposed a disposable glove-based sensor capable of detecting toxic substances, including organophosphates, using custom ink and snake-shaped microstructures to achieve two-dimensional stretching (Fig. 7B). The different fingers of the sensor have different functions. The enzyme is fixed on the index finger, and the thumb is used to collect organic phosphorus and toxin residues. The articles are placed in the collector of the thumb, and the thumb and the sensor on the index finger are connected to complete the electrochemical reaction. The detection results of organophosphorus on the surface of different fruits and vegetables are shown in Fig. 7C; the rapid response speed and cost advantages provide considerable prospects for the in-field detection of



Fig. 7. (A) Picture of a combined biosensor. (B) Flexible glove biosensor. (C) Sampling and detecting OP pesticides on the surfaces of different fruits and vegetables. (D) Photos of actual measuring conditions of wearable glove-embedded sensors on food samples. (E) Robotic sense fingers: schematics, fabrication, and analytical performance. (a) Schematics of robotic finger immersed in lemon juice, coffee, and chili powder placed on a table for the subsequent detection of sourness, caffeine, and spiciness, respectively. (b) Image illustrating the robotic hand used to develop the glove-based sense fingers. (c) Prototype of the screen-printed robotic sense fingers with long connections to the wrist where the electronic interface is located. Robotic fingers are identified with colored rings: green for carbon-printed sour fingers; blue for GOx Prussian blue-printed sweet fingers; and red for carbon-printed spicy fingers. Scale bar, 5 cm. (d) Images and (e) corresponding electrochemical data of (i) robotic sour finger dipped in orange juice and the square wave voltammetry (SWV) signature of ascorbic acid, (ii) robotic sweet finger in cherry juice and amperometry data of glucose, and (iii) spicy finger on green pepper and SWV feedback response to the presence of capsaicin. Dotted lines correspond to the blank PBS response. (F) Schematic diagram of the fabrication process of the plant-wearable biosensor based on 3D porous laser-induced graphene (LIG) and the application of in situ pesticide analysis for agricultural products.

organophosphorus and chemical pesticides in food safety (Mishra et al., 2017). Raymundo-Pereira et al. (2020) reported a similar sensor used for pesticide detection. In real samples of apples, cabbage and orange juice, simple touch gloves can be used to detect the concentration with high performance and high resolution, and the designed sensor has strong resistance to bending, good stability, good reproducibility, anti-jamming capability, etc. (Fig. 7D). This kind of glove-type sensor can also be used for the analysis of other chemicals, which provides a new model for the rapid detection of food (Raymundo-Pereira et al., 2020).

With the development of artificial intelligence and computer technology, robots can perform some simple tests instead of humans. Ciui et al. (2018) reported a robot with a fingertip sensor that can quickly screen food flavors and detect additives. Fig. 7E shows the concept of a “robotic taste sensing finger” and its applicability to “sensing” and distinguishing the main tastes of food samples. The stretchable taste sensors on the robot’s gloves, printed using wireless electronic board integration, can be used for real-time data transmission and can directly detect glucose, ascorbic acid, and capsaicin, which means that the index and ring fingers can accurately identify sweet, sour and spicy. In addition, the device can also be used to detect the presence of sugar and caffeine in drinks (Ciui et al., 2018). According to the principle of wearable sensors, to meet the requirements of rapid nondestructive detection, intelligent plant wearable biosensors have been further developed for in situ analysis of organophosphorus pesticides on crop surfaces (Zhao et al., 2020). Laser-induced graphene technology is used to prepare snake-shaped electrodes, which are soft and stretchable and can adapt to the irregular surface of crops. The sensor surface contains organophosphorus hydrolase, which can selectively capture and identify methyl parathion and wirelessly transmit the data to a smartphone, thus realizing the real-time analysis of the surface of agricultural products (Fig. 6F). This structure provides a revolutionary method for pesticide residue analysis and a new idea for future biosensor design.

The development of wearable biosensors is still in the development stage; special attention needs to be paid to the enzyme-electronic interface, and several factors related to wearable applications, such as mechanical properties (flexibility and tensile properties), operational stability (such as pH and temperature), biological fouling, selectivity, and low target concentration, must be considered (Kim et al., 2018). Despite this, wearable biosensors integrate the research of sensors, electronics, wearable devices, the IOT and other disciplines. With scientific efforts in various aspects, wearable sensors will have broad prospects.

6. Other sensing strategies

There are other intelligent detection strategies based on biosensors, among which artificial neural networks (ANNs) are one of the most widely used. ANNs have been a research hotspot in the artificial intelligence since the 1980s. In essence, ANNs are computational algorithms that abstract the neural network of the human brain from the perspective of information processing, establish a simple model, and form different networks according to different connections. They contain a series of mathematical equations that simulate biological processes, such as learning and memory. Thus, their development first involves a learning process that adaptively responds to input variables according to learning rules. ANNs can learn through the Internet and adapt to it like a living thing. They can be trained with enough data to “learn” processes. After the development of back propagation training algorithms, their popularity in many applications has increased dramatically (Ferentinos et al., 2012). ANNs have been used in biometrics for accurate pollutant detection and classification (Basu et al., 2018). Currently, there is increasing interest in the use of ANNs in food science because they have shown promising results in sensory analysis, pattern recognition, classification, microbial prediction and food process optimization (Argyri et al., 2010). Mishra et al. (2015) proposed an ANN-based automated

flow-based biosensor designed for the quantification of binary organophosphate mixtures in milk. They used the ANN method to establish the binary combination analysis of low concentration organic phosphorus in milk. The results show that the biosensor is stable and able to recognize binary mixtures well at different absorption levels (Mishra et al., 2015). Maleki et al. (2017) integrated a biosensor with an ANN, detected catechol with a modified electrode, and applied the test results to neural network training with a back propagation algorithm. The input and output parameters are the current and catechin concentration, respectively. The modeling results of ANNs are in good agreement with the experimental results, which indicates that ANNs can be well applied in biosensors (Maleki et al., 2017). Yang et al. (2021) reported a pathogen identification system using a paper chromogenic array (PCA) enabled by machine learning. PCA consists of a paper substrate impregnated with chromogenic dyes. When pathogens release volatile organic compounds, they undergo color changes. These changes can be digitized and used to train multi-layer neural networks to achieve high-accuracy (91–95%) identification and quantification of specific pathogens (Yang et al., 2021a). Based on this kind of biosensor combined with ANN technology can be used as a nondestructive approach, which holds great potential to significantly advance culture-free pathogen detection and identification on food, and is readily extendable to other food commodities with complex microflora (Jia et al., 2021). In addition, the application of ANNs in immunosensors can also quantitatively identify various viruses in blood (Chakraborty et al., 2017). As an artificial intelligence algorithm, ANNs have been preliminarily applied in food detection. In the future, ANNs will focus on the expansion of the training scale and further combination with deep learning to achieve high sensitivity detection.

In addition to ANN, there are some other intelligent technologies that can be organically combined with biosensors, such as big data and cloud storage. Through the collection and determination of a large number of microbial data, the construction of big data is conducive to the detection of pathogenic bacteria and the diagnosis of related diseases in the future. Combined with machine learning technology, automatically learn and improve the collected data (Sosnowski et al., 2020). Through cloud storage, the data obtained by biosensors are analyzed, transmitted to external platforms (such as various wireless receivers or mobile terminals), and uploaded to the Internet cloud, which can further assist the establishment and analysis of big data. The self-powered sweat lactic acid analyzer makes use of this technology. The biosensor is made of hydrophilic porous carbon film to absorb skin sweat naturally, and the electrochemical sensor will link the voltage signal with the lactic acid concentration to achieve real-time and continuous detection of lactic acid. After uploading it to the cloud storage, a big data platform will be established. To facilitate data integration and analysis (Guan et al. 2019).

7. Application of intelligent biosensor in practical detection

At present, intelligent biosensors are developing vigorously in the field of detection, among which biosensors based on smartphones and 3D printing technology are the most widely developed, and some sensors have been applied in actual samples. Using smartphones and 3D printing devices, allergens in complex samples can be detected (Kalinowska et al., 2021). HSL analysis of the data read by smartphones can also realize the rapid detection of *Salmonella* in chicken with sensitivity of 1.6×10^1 CFU/mL (Guo et al., 2019). A smartphone can also be used as a fluorescent reading device to detect ochratoxin A in beer, which is then transmitted wirelessly to the computer for more detailed data analysis, with results comparable to commercial equipment (Bueno et al., 2016). IOT and wearable biosensors started late, which are not as widely used as biosensors based on smart phones and 3D printing in practice. Today, wearable biosensors are more widely used in the medical field. Wearable biosensors have been applied to real-time monitoring of glucose, uric acid and other substances in human sweat, and through the network to upload data, health status analysis (Salim and Lim, 2019). The

application of wearable sensors in agriculture and food industry can also achieve rapid detection of fruit and vegetable pesticides (Zhao et al., 2020).

Due to the constraints of complex environment, system stability, intelligent technology development and other factors, intelligent biosensors can not completely replace traditional biosensors at present. In addition, the lack of central supervision and professional participation in the development of smart biosensors is another factor restricting the promotion of smart biosensors in practical applications (Tapiero et al., 2020). Therefore, the intelligent development of biosensors needs the supplement of other intelligent technologies and related regulations. However, it is certain that with the development of science and technology, intelligent biosensors can achieve better interaction and real-time, coupled with the integration of big data mining, cloud computing and deep learning, can provide more general solutions for analyzing large quantities of sample. Obviously, intelligent biosensors will play an increasingly important role in popularizing detection techniques for field analysis.

8. Conclusions and future perspectives

In the past few decades, sensors have been developed rapidly in many fields (health, environment, and food) (Martin Varguez et al., 2020). In food detection, biosensors stand out due to their advantages of high sensitivity, high selectivity and low cost. With the rise and development of computers, the Internet, 3D printing, artificial intelligence and other technologies, bio/sensors are gradually integrated with them, showing better performance. The integration of multiple technologies enables biosensors to be further miniaturized and portable to meet the needs of field testing in different environments. Biosensors combined with smartphones, 3D printing, artificial senses, and the IOT are reviewed in this paper, and other combination detection strategies are also presented; this paper also analyzes respective principle and performance of these various detection strategies. First, smartphones used as reading devices are portable and can be used for rapid on-site inspection. At the same time, 3D printing technology can be applied to smartphones to provide attachment support sensing platforms, further perfecting smartphone applications in detection. However, because of diverse smartphone models with different cameras, test results may vary. Based on this, an IOT wireless sensor system was developed to separate sensing devices and smartphones. Second, artificial bionics technology can be applied in the detection field to carry out the sensitive detection of volatile substances and can also simulate human vision and taste to carry out the qualitative and quantitative analysis of measured objects. The application of wearable devices in medical treatment has inspired food detection. Designed wearable detection devices can easily and quickly obtain detection results. The data can be uploaded to the network by IOT technology to realize data sharing and remote monitoring. In addition, some network-based intelligent technologies are also combined with biosensors. The use of the IOT, ANNs and machine learning can further optimize the detection data and improve the qualitative and quantitative accuracy of samples.

Future biosensors may further combine artificial intelligence, the IOT, large data sets, cloud computing and other technologies to optimize the structure of reading devices with new technologies and simplify the attachment of sensors through constant coupling. The future development of biosensors will be the combination of multidisciplinary and multifield research, through which biosensors will be made more intelligent, miniaturized, portable and sensitive.

CRedit authorship contribution statement

Junjie Zhang: Writing – original draft. **Huixian Huang:** Visualization, Software. **Guangchun Song:** Visualization, Software. **Kunlun Huang:** Writing – review & editing. **Yunbo Luo:** Writing – review & editing. **Qingliang Liu:** Conceptualization, Investigation. **Xiaoyun He:**

Supervision. **Nan Cheng:** Conceptualization, Supervision.

Declaration of competing interest

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

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