REVIEW

Recent Advances in Electrochemical Impedance Spectroscopy-based Pathogenic Bacteria Sensing

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Abstract

Pathogenic bacteria have been throwing great threat on human health for thousands of years. Their real-time monitoring is in urgent need as it could effectively halt the spread of pathogenic bacteria and thus reducing the risk to human health. Up till now, diverse technologies such as electrochemistry, optics, piezoelectricity and calorimetry have been developed for bacteria sensing. Therein, electrochemical impedance spectroscopy (EIS)-based sensors show great potential in point-of-care bacterial analysis because of their low-cost, short read-out time, good reproducibility, and portable equipment construction. In this review, we will primarily summarize the typical applications of electrochemical impedance technology in bacteria sensing based on different electrodes in the last three years. As we know, the electrode materials play an extremely important role in the construction of EIS-based sensors because not only the immobilization of bio-recognition elements for bacteria, but also the sensitivity, economical efficiency and portability of the as-prepared sensors are mainly determined by the electrode materials. Therefore, in order to provide new researchers a clear preparation process for EIS-based sensors fabricated with different electrodes, we try to classify the EIS-based sensors according to the different electrode platforms. Moreover, present difficulties, future directions and perspectives for their applications are also discussed. It can provide guidance in future study of novel EIS-based sensors for rapid, sensitive and accurate sensing of diverse pathogenic bacteria.

Keywords: Electrochemical impedance spectroscopy; Pathogenic bacteria detection; Bio-recognition elements; Electrode material

1. Introduction

Pathogenic bacteria, ubiquitously spreading in nearly every corner of human living environment, could lead to serious infectious diseases such as foodborne disease, urinary system infections as well as sexually transmitted disease [1−5]. Therefore, their accurate, sensitive and rapid detection has been a major public health concern. Nowadays, the developed technologies in laboratory for pathogenic bacteria detection are mainly based on technologies including colony morphology recognition [6], fluorescence resonance energy transfer [7], electrochemistry [8,9], colorimetry [10], nucleic acid-based diagnosis [11], fluorescent and optelectric technology [12], nanopore technology [13] and calorimetry [14]. Therein, only three methods based on colony, polymerase chain reaction and enzyme linked immunosorbent assay are admitted by Food and Drug Administration, and the developed sensors have been come to commercial applications from laboratory prototypes [15]. Generally, these approaches usually rely on multistep processes including bacterial culturing, isolation and selective enrichment of target organisms to a detectable level. Obviously, these sensitive but time-consuming (more than 24 h) methods are unsuitable for applications in real-

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time monitoring and rapid detection of pathogenic bacteria. Therefore, although these methods have come to real-world implementation, centralized instruments and skilled personnel are also essential, limiting their further commercial applications in large-scale.

To the contrary, electrochemical sensors have already found great commercial success in the fields of personalized diabetes management [16], because electrochemistry provides the fabricated sensors with advantages including high specificity, sensitivity, portability and economical efficiency [8]. Moreover, their fast signal readout and easier miniaturization make them great potential in point-of-care bacterial analysis [17]. Consequently, electrochemical impedance spectroscopy (EIS)-based sensors have been applied for the identification and determination of bacteria for more than 50 years [9,18]. The initial utilization of EIS is in the field of microbiology monitoring such as biofilm formation and growth of overall bacterial [19]. The system is generally made of two planar electrodes immersed in culture medium, which could achieve the real-time detection of bacterial growth density by monitoring the electrochemical parameters of the growth medium [20]. Accordingly, dozens of real-time commercial products have been developed and the determination of metabolic activity of bacteria is also realized [21]. Based on this mechanism, EIS-based sensors have also been proved as an effective and informative technique for bacteria detection, which could reflect the information of bacterial species and concentrations by monitoring the occurring reaction on the employed electrode surface as well as direct tracing the interactions between the bio-receptor and target bacteria [22].

In bacteria sensing process, the binding of bacteria or metabolites produced by bacteria to the surface of employed electrode could change the electrical properties (diffusive electrochemical impedance, double layer capacitance, and charge transfer resistance, etc.) of the working electrode, either because of the inherent properties of bacterial cell membranes or by intercepting diffusing redox-active molecules from interacting with the surface [23]. In detail, if the electrochemical impedance is obtained in the sensing system without redox probes, the measured electrochemical impedance signal is a direct reflection of intact bacteria and could be easily influenced by the number, morphology and growth stage of the bacteria [9]. In the system that contains redox probes, the change in faradaic impedance is instead tested and obtained. Moreover, like general biosensors, in order to achieve the specific detection of certain pathogenic bacterium, bio-recognition elements such as antibodies [24−29], aptamers [30−32] and bacteriophages [33−36] are fixed on the surface of different working electrodes as shown in Fig. 1 via electrostatic adsorption or covalent coupling to capture/detect pathogens selectively and specifically. Therefore, the employed bio-recognition elements endow the obtained sensors with inherent sensitivity and discrimination.

In the last three years, a series of works on the study of EIS-based sensors have been reported and a great process has been made for bacteria sensing. Although several interesting review articles on the use of EIS in bacterial sensing have been published [9,37−39], the rapidly expanding literature review in the past three years has not yet been found. In this review, we will primarily summarize the typical applications of EIS in bacteria sensing in the last three years. Present difficulties, future directions and perspectives for the EIS-based sensors are also discussed.

2. The selection of electrodes

The electrode materials are equally important for the construction of EIS-based sensors. For such utilizations, portable electrodes such as glassy carbon electrode, gold electrode, carbon-based electrode, screen-printed electrode, indium tin oxide electrode and carbon paste electrode are most frequently used, which greatly promote the development of EIS-based sensors. The selection of electrode material for the construction of EIS-based sensor is usually decided on the cost, commercial availability and potential need for surface modifications [8]. Thus, frequently used materials contain glassy carbon [30,36,40−42], noble metals [43−47] such as gold, silver and platinum, carbon-based materials [24,48−50] such as graphene oxide (GO), carbon nanotubes, carbon nano-walls, and metal oxides [51,52] such as nickel oxide and indium tin oxide, etc. Improvements to electrode platforms via modification of materials with large surface area and conductivity have enabled the as-prepared sensor with enhanced test sensitivity and fast signal readout time.

With the miniaturization of electrodes, sophisticated interdigitated electrode arrays, which is usually called the second generation of electrode, are receiving great concern in recent years [26,29,32,53]. The interdigitated electrode arrays are commonly made of two individual electrode strips containing multiple microelectrodes [8]. Therein, each set of microelectrodes could thus work as a pole for bipolar electrochemical impedance test. The sensing platforms based on

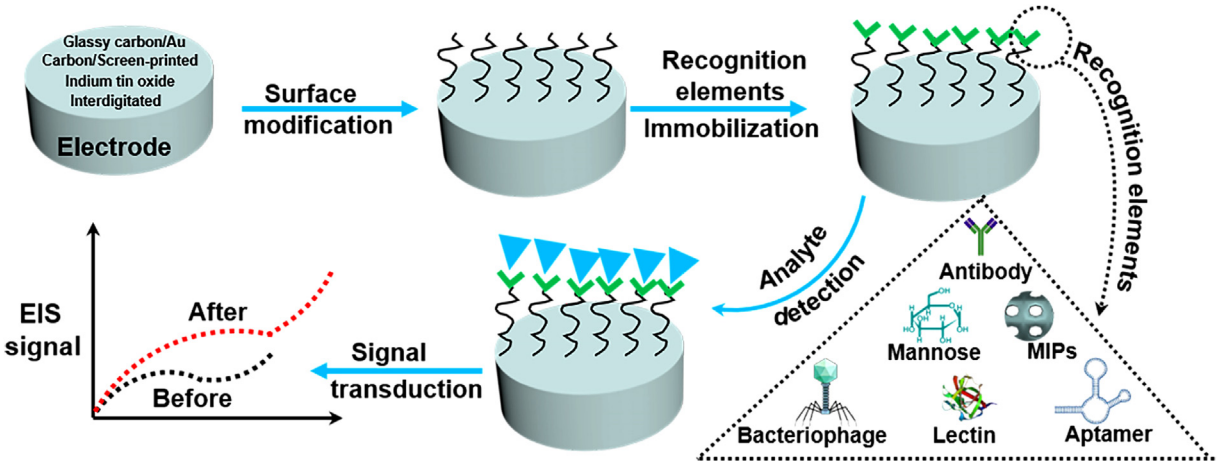

Fig. 1. The general fabrication process of EIS-based bacterial sensors via the modification of different electrodes (glassy carbon, Au, carbon, screen-printed, indium tin oxide, and interdigitated electrode) using different recognition elements (antibody, mannose, MIPs, bacteriophage, lectin, aptamer).

interdigitated electrodes provide outstanding space efficiency because both spacing and size of these electrodes are well-optimized [9]. Moreover, the interdigitated electrode arrays have obvious merits over conventional ones, such as low resistances, mall required sensing volumes, quick equilibrations as well as high signal-to-noise ratios [54]. Herein, we try to classify the EIS-based sensors for bacteria sensing according to the electrode platforms. As shown in Table 1, the related parameters of the constructed EIS-based sensors including electrode materials, analyte, linear range and limit of detection (LOD) are also summarized.

2.1. EIS-based sensors for bacterial sensing

2.1.1. Glassy carbon electrode (GCE) for EIS-based sensor development

In the fabrication of EIS-based sensors, GCEs have been receiving great concern due to their small thermal expansion coefficient, high chemical stability, and outstanding air tightness [56,57]. To further enhance the conductivity of the working electrode and immobilize more bio-recognition elements on GCE, gold materials such as Au nanoparticles (Au NPs) [30,36,40] and gold nanorods [58] have been applied for GCE modification.

Via electrochemical deposition of Au NPs on the surface of GCE as shown in Fig. 2A, Mulchandani's group successfully obtained the Au NPs modified GCE (GCE-Au) [36]. Then, M13 bacteriophage were immobilized on the surface of GCE-Au via cross-linking reaction of 3-mercaptopropionic acid and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride/N-hydroxy succinimide, obtaining a selective non-lytic M13 bacteriophage-based cytosensor for *Escherichia coli* (*E. coli*) sensing. The biosensor achieved a LOD of 14 CFU/mL. Interestingly, the as-prepared biosensor exhibited the similar sensitivity in phosphate buffer as in river water samples, indicating its good applicability to real samples. With the similar methods, anti-protein antibody (IgY) and aptamer were respectively fixed on the surface of AuNP-modified GCE, by Roushani et al. [40] and Dai et al. [30]. Accordingly, the immunosensors were obtained and the successful detection of *S. aureus* was achieved.

Molecularly imprinted polymers (MIPs) are man-made antibodies with customized binding sites complementary to that of the employed templates in both physical and chemical structures [59,60]. MIPs are found with obvious merits, such as easy synthesis, economic efficiency, and long-time chemical and physical stabilities in comparation with the natural antibodies. Thus, MIPs have been applied for the construction of various sensing platforms in diverse molecules sensing [61−63]. As shown in Fig. 2B, the molecularly imprinted sensors have achieved the specific detection of bacteria with the help of MIPs. Recently, combining with MIPs and EIS, Bian's group reported the preparation of a reusable sensor for rapid determination of pathogenic bacteria based on bacteria-imprinted polythiophene film (BIF) employing *Staphylococcus aureus* (*S. aureus*) as an imprinting template [41]. The BIF, as a polymer layer for specific recognition of *S. aureus*, is deposited on the surface of a GCE via electrocopolymerization of TE monomer in the presence of *S. aureus* (template) and followed by template removal. When the *S. aureus* rebinds on the BIF, the electrochemical impedance of the working electrode is increased. Accordingly, the BIF-based

Table 1. Parameters of the constructed sensors including electrode material, analyte, linear range and LOD in the last three years.

Electrode	Analyte	Linear range	LOD	Ref.
GCE	*E. coli*	10^3–10^7 CFU/mL	500 CFU/mL	[56]
Gold modified GCE	*E. coli*	10–10^5 CFU/mL	14 CFU/mL	[36]
AuNP modified GCE	*S. aureus*	10–10^7 CFU/mL	3.3 CFU/mL	[40]
Dual-aptamer-based sandwich GCE	*S. aureus*	1×10^1 to 1×10^5 CFU/mL	2 CFU/mL	[30]
Gold nanorods modified GCE	*S. aureus*	1.8×10^3 to 1.8×10^7 CFU/mL	2.4×10^2 CFU mL	[58]
3-Thiopheneethanol modified GCE	*S. aureus*	10–10^7 CFU/mL	4 CFU/mL	[41]
Synthetic receptor-transducing platform coupling	*E. coli*	1000 CFU/mL	120 CFU/mL	[55]
GCE	*Acinetobacter baumannii*	10^{-1} to 10^4 CFU/mL	0.030 CFU/mL	[42]
Gold electrodes	*E. coli; L. innocua; S. aureus; S. Typhimurium*	1.5 to 1.5×10^3; 1.5 to 1.5×10^4; 1.5 to 1.5×10^5; 15 to 1.5×10^4 CFU/mL	1.5; 1.5; 1.5; 15 CFU/mL	[45]
Gold electrode	*S. typhimurium* and *E. coli*	N/A	6.859×10^{23} L·mol^{-1} and 2.054×10^{17} L·mol^{-1}	[43]
Screen-printed gold electrode	*Salmonella* spp.	15 to 2.57×10^7 CFU/mL	5 CFU/mL	[46]
3D gold nano-/microislands and graphene electrodes	*E. coli, P. putida,* and *S. epidermidis*	2×10 to 2×10^5, 2×10 to 2×10^4, and 1×10^2 to 1×10^5 CFU/mL	20 CFU/mL	[44]
Gold disk electrode	*Salmonella*	2×10 to 2×10^6/2×10^2 to 2×10^5	17 CFU/mL; 1.3×10^2 CFU/mL; 1 CFU/mL	[33]
Lipid membrane modified gold electrode	*E. coli* DNA	10^{-9} to 10^{-19} mol·L^{-1}	10^{-19} mol·L^{-1}	[65]
Ag electrodes	*E. coli* and *Pseudomonas aeruginosa*	Up to 500 CFU/mL	500–1000 CFU/mL	[47]
Graphenic carbon electrodes	*E. coli* and *S. aureus*	2–20 CFU/mL	2 CFU/mL	[50]
Reduced graphene oxide-carbon electrode	*S. mutans, A. viscosus,* and *L. fermentum*	N/A	N/A	[48]
Boron-doped carbon nanowalls electrodes	*Pseudomonas syringae pv. lachrymans*	3.25×10^0 to 3.25×10^8 CFU/mL	119 CFU/mL	[24]
Carbon nanotube-based electrode	*S. aureus*	10^2–10^7 CFU/mL	1.23×10^2 CFU/mL; 1.29×10^2 CFU/mL	[34]
SPE	*E. coli*	10^2–10^8 CFU/mL	10 CFU/mL	[66]
SPE	*E. coli* DNA	1×10^{-10} μmol·L^{-1} to 1×10^{-5} μmol·L^{-1}	1.95×10^{-15} μmol·L^{-1}	[70]
Screen-printed carbon electrodes	*S. aureus*	10–10^8 CFU/mL	3 CFU/mL	[31]
Screen printed gold electrodes	*S. aureus*	10×10^1 to 10×10^7 CFU/mL	$10^{1.58}$ CFU/mL	[68]
GlycoMXene screen printed electrodes	*E. coli*	10^1–10^8 CFU/mL	10 CFU/mL	[67]
ITO coated polyethylene terephthalate (ITO:PET)	*Pseudomonas aeruginosa*	N/A	N/A	[51]
Fluorine doped tin oxide electrode	*Salmonella gallinarum,* and *Salmonella pullorum*	(1–1×10^5 cells) with 37 and 25 viable cells	51 and 37 cells, respectively in faecal samples and 218 and 173 cells, respectively in meat samples.	[52]
Anti-*E. coli*O157:H7 antibody-modified CPE	*E. coli*	1×10^{-1} to 1×10^6 CFU/mL	0.1 CFU/mL	[81]
Polyaniline nanofibers modified filter paper substrate	*S. aureus, E. coli, P. aeruginosa*	N/A	N/A	[35]

(*continued on next page*)

Table 1. (continued)

Electrode	Analyte	Linear range	LOD	Ref.
Unknow	Gram-negative and gram-positive bacteria		3.0 CFU/mL and 3.1 CFU/mL	[82]
Interdigitated microelectrode	*Salmonella Typhimurium*	10^2–10^6 CFU/mL	80 CFU/mL	[53]
Single-crystalline gold interdigitated microelectrode	*Listeria monocytogenes*	1.0 to 1.0 × 10^4 CFU/mL	7.1 and 9.2 CFU/mL in water and milk	[26]
Interdigitated electrode	*E. coli*	25–1000 CFU/mL	9 CFU/mL	[32]
Gold integrated electrode	*Aeromonas salmonicida*	1–10^7 CFU/mL	1 CFU/mL	[27]
Interdigitated microelectrode	*Salmonella typhimurium*	1.6 × 10^2 to 1.6 × 10^6 CFU/mL	73 CFU/mL	[28]
Interdigitated microelectrode	*Salmonella*	3.0 × 10^1 to 3.0 × 10^6 CFU/mL	19 CFU/mL	[84]
Interdigitated microelectrode	*Salmonella*	10^1–10^6 CFU/mL	10 CFU/mL	[29]
Interdigitated electrodes	*Pseudomonas aeruginosa* and *S. aureus*	N/A	1.5 × 10^8 CFU/mL and 1.5· × 10^5 CFU/mL	[85]
Interdigitated gold electrodes	*E. coli*	10^2–10^6 CFU/mL	100 CFU/mL	[86]
Au-decorated NiO nanowall electrodes	*Mycoplasma agalactia* DNA	N/A	53 ± 2 copy number/μL	[87]
Gold interdigitated electrodes	*Salmonella, Legionella,* and *E. coli*	N/A	3 bacterial cells/mL	[88]
Parallel-plate electrode	*Bacillus thuringiensis*	N/A	N/A	[89]
Gold nanoparticle-modified screen-printed carbon electrode	*E. coli*	N/A	N/A	[90]
Nanogap electrode	*E. coli O157:H7*	N/A	1 cell of *E. coli*	[91]
Screen-printed carbon electrode	*Salmonella typhimurium*	10–10^7 CFU/mL	10 CFU/mL	[92]
Alumina and Ag/Pd paste	*P. aeruginosa* and *S. aureus*	N/A	N/A	[93]
Interdigitated microelectrodes	*E. coli*	N/A	N/A	[94]
Gold electrode	*S. enteritidis* and *BL21*	N/A	1.0 × 10^3 cells/mL; 1.0 × 10^6 cells/mL	[95]
Gold-plated wire electrode	*L. monocytogenes*	10^3–10^8 CFU/ml	1.4 × 10^3 CFU/mL	[96]
Thermoplastic electrodes	*E.coli*	8.6 to 8.6 × 10^7 CFU/mL	27 CFU/mL	[97]
GCE	*Streptococcus Pneumoniae*	N/A	622 cells/mL	[98]
Gold electrode	*Enterococcus faecalis, Klebsiella pneumoniae, Pseudomonas aeruginosa,* and *Candida tropicalis*	10^1–10^5 CFU/mL	10 CFU/mL	[99]
Au NPs modified carbon SPE	*E. coli*	10–10^6 CFU/mL	15 CFU/mL	[100]
MXene/polypyrrol based GCE	*Salmonella*	10^3–10^7 CFU/mL	23 CFU/mL	[101]
SPE	*E. coli*	10^2–10^6 CFU/mL	36 CFU/mL	[102]
Interdigitated electrodes	*E. coli, Klebsiella pneumoniae* and *S. aureus*	N/A	N/A	[54]
Cationic covalent organic polymer based interdigitated electrode arrays	*E. coli*	30–10^{10} CFU/mL	2 CFU/mL	[103]
Interdigitated electrodes	*E.coli*	N/A	N/A	[104]

sensor could determinate *S. aureus* in the range of 10–10^7 CFU/mL with a LOD of 4 CFU/mL. Impressively, the as-prepared sensing platform exhibited good selectivity in recognizing *S. aureus* from the mixtures of multi-bacterial strain. Most significantly, in comparation with the previously reported methods, this sensing platform shows much short assay time (about 30 min), including the BIF synthesis, bacterial conjugation, and electrochemical impedance test. Obviously, the MIPs endow the EIS-based sensor the excellent selectivity for bacterial identification. With the help of MIPs, Grinsven's [55] and Rostamzad's [42] groups also prepared the EIS-based sensors, achieving the specific detections of *E. coli* and *A. baumannii*, respectively (Fig. 2C).

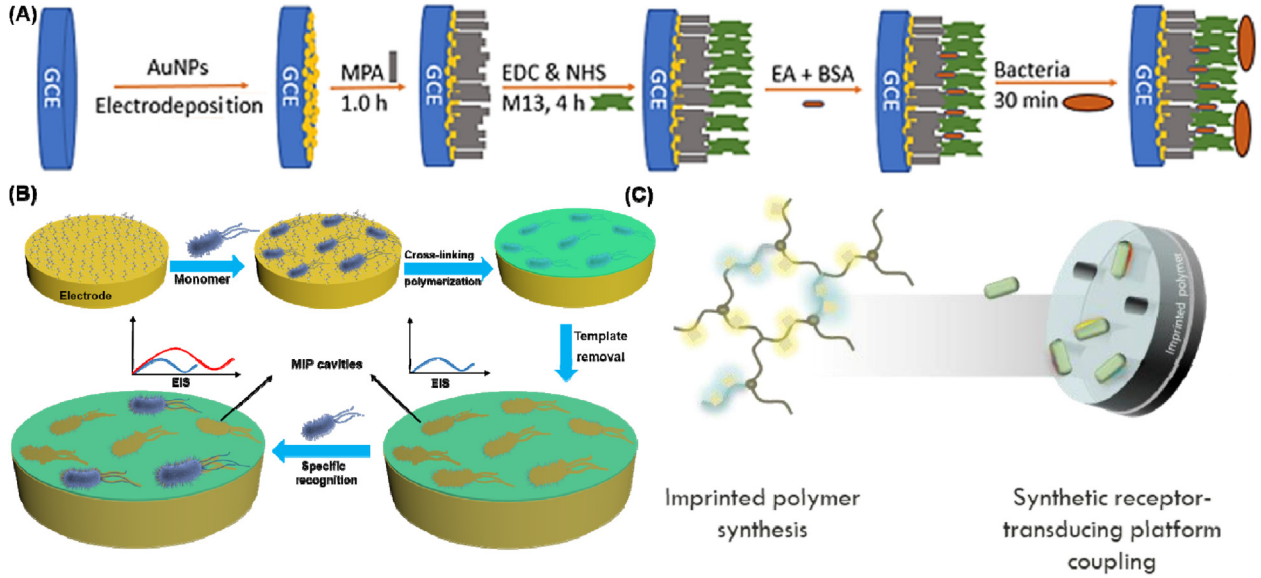

Fig. 2. Schematic diagrams for the fabrication of EIS-based sensors using GCE as a working electrode. (A) Cytosensor, GCE modified by Au NPs. Reproduced with permission [36]. Copyright 2020, Elsevier. (B) The general preparation of molecularly imprinted sensors and the specific recognition mechanism of MIPs. (C) GCE modified by bacteria-imprinted polymers. Reproduced with permission. Reproduced with permission [55]. Copyright 2021, Elsevier.

2.1.2. Gold electrode for EIS-based sensor development

Compared with the GCE, gold electrodes, due to their excellent conductivity and good plasticity, have also been frequently used in bacterial sensing as shown in Table 1, and the as-prepared sensors hence show obvious enhanced sensitivity [64]. Moreover, gold electrodes are ease of modification for thiolated compounds, which could easily form a monolayer on the surface of gold electrodes.

Albanese's group fixed nisin molecules on the surface of gold electrodes and obtained EIS-based biosensor [45]. Then, they investigated the electrochemical responses of the as-prepared biosensor after exposing to different bacteria. They found that the as-prepared biosensor could selectively detect *Salmonela* cells with a LOD of 1.5 × 10 CFU/mL. Afterwards, the developed biosensor also achieved the successful test of *Salmonella* in a milk sample. Except using antibodies, aptamers and MIPs as bacterial recognition elements, mannose was also tried for specific recognition of bacteria by Zhou's group as shown in Fig. 3A [43]. As we know, glycan is a kind of biomolecule widespread both on the surface and interior of bacterial cells. The interaction between glycan and bacteria are receiving great concern because they play an important role in the process of bacteria adhesion. The adhesion process of *E. coli* is primarily mediated by the specific recognition between glycans and fimbriae. Based on this phenomenon, Zhou et al. constructed a biosensor integrated with mannose functionalized nano-surface. Interestingly, the as-prepared biosensor could identify and evaluate the adhesive strength of bacteria. Diverse bacteria including *E. coli* and *S. typhimurium* were investigated on the designed surface by both surface enhanced Raman spectroscopy and EIS. The final results indicated that the mannose had a stronger adhesive strength to *S. typhimurium*. The developed biosensors provide both quantitative and qualitative information of specific recognition between bacteria and mannose.

Besides glycan binding protein, repeated units of D-galactose, L-rhamnose and D-mannose, are also found in the O-specific chain of bacteria's surface. Based on this research, Rodriguez et al. [46] immobilized *Hechtia argente*a lectin on the surface of a gold electrode. Accordingly, the fixed lectin displayed apparent selectivity towards D-mannose, which is distributed on the lipopolysaccharide cell wall of *Salmonella* spp. In the sensing system, the binding of the *Salmonella* spp to the surface of working electrode had increased the electrochemical impedance of the biosensors with incremental concentrations of *Salmonella* spp in $15-2.57 \times 10^7$ CFU/mL, with a LOD of 5 CFU/mL.

Electrodes with larger surface area could load with more probes and thus enhancing the sensitivity of the as-prepared biosensor. Mahshid et al. in 2020, fabricated hierarchical 3D gold nano-/microislands (NMIs) with large surface area and unique plasmonic properties as exhibited in Fig. 3B [44]. Simultaneously, the graphene was also added to improve the charge transfer of the sensors. Because the morphologies, sizes, as well as compositions of the different cells could cause different

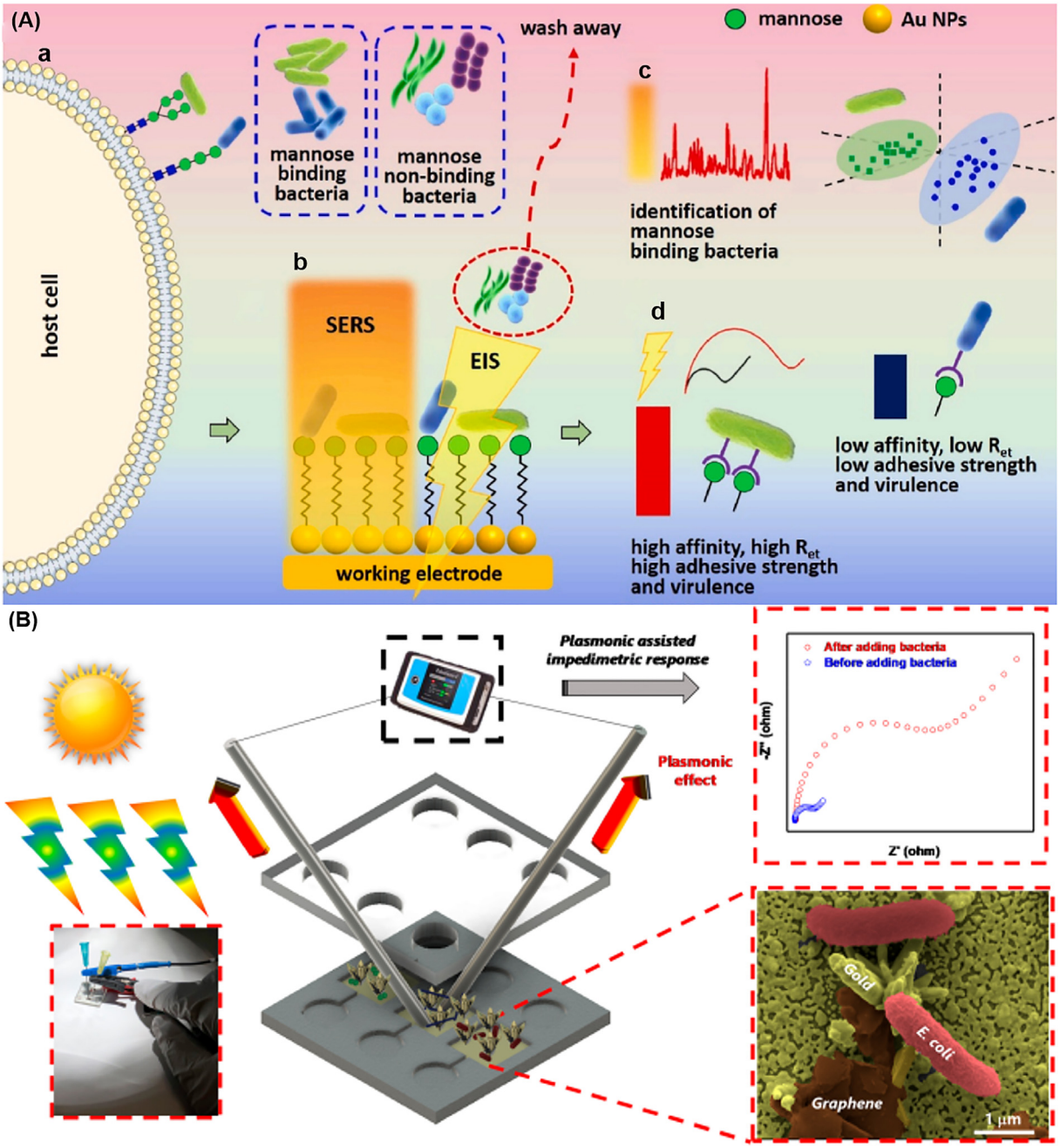

Fig. 3. Schematic illustrations of (A) the EIS-SERS dual-mode sensor based on mannose modification. Reproduced with permission [43]. Copyright 2022, Elsevier, and (B) the plasmonic-assisted impedimetric microfluidic sensor for bacteria sensing using electrodes with 3 d gold NMIS/Gr nanostructures [44]. Reproduced with permission. Copyright 2020, The American Chemical Society.

electron charge transfers, the obtained detection platform showed distinguishable EIS signal among different types of bacteria containing *E. coli* K12, *Pseudomonas putida* (*P. putida*), and *Staphylococcus epidermidis* (*S. epidermidis*). Moreover, the platform achieved the sensitive detections of *E. coli*, *P. putida*, and *S. epidermidis*, respectively, in the concentration ranges of 2×10^1–10^5, 2×10^1–10^4, and 1×10^2–1×10^5 CFU/mL with a LOD − 20 CFU/mL. Their research, in combination of 3D gold NMIs with large surface area and graphene with excellent conductivity, as novel plasmonic technology and electrochemical impedance technique, opens interesting doors in sensitive label-free bacterial detection. Recently, gold disk electrode, with high surface area, was directly applied for the immobilization of *Myoviridae* bacteriophage SEP37 by Wang's group [33]. Accordingly, a *Myoviridae* bacteriophage-based sensing platform was successfully constructed and used for *Salmonella* sensing in food matrixes. In their work, *Myoviridae* bacteriophage SEP37 was covalently fixed on the

surface of Au NPs modified gold disk electrode. The as-prepared biosensor achieved the successful detection of *Salmonella* in real food samples including spiked lake water, lettuce samples, and chicken breast meat samples under the optimal experimental conditions.

Lipid membrane is a kind of biocompatible material for anchor of both molecules and nanoparticles. Herein, Lincy et al. successfully immobilized lipid membrane containing cholesterol Au NPs and cationic, neutral and anionic lipid on the surface of gold electrode [65]. Because the insulation property of the as-prepared monolayer towards $K_3[Fe(CN)_6]/K_4[Fe(CN)_6]$ is obviously affected by the presence of lipid-Au NPs, the DNA hybridization results have demonstrated higher recognition efficiency between the hybridized dsDNA and unhybridized ssDNA for the as-prepared cationic/cationic lipid-gold composite in comparison with other composite membranes. Moreover, the obtained sensing platform exhibited a wide linear range from 10^{-9} to 10^{-19} mol·L^{-1} with a LOD of 10^{-19} mol·L^{-1}.

Besides the gold electrode mentioned above, silver (Ag) electrodes also showed good EIS sensitivity in bacterial sensing due to their smooth metal surface [47].

2.1.3. Carbon-based electrode for EIS-based sensor development

Similarly, carbon electrodes are in great demand due to their low cost and good compatibility with a large number of nanomaterials. Moreover, to further improve the sensing properties of carbon-based sensors, the architectures of the carbon electrode are also updated by construction of carbon-based electrodes with enhanced 3D structure or incorporation of 3D components.

Graphitic carbon electrodes mainly consist of 3D carbonaceous solids containing graphene layers and hydrophobic sp^2 carbon containing 2D graphene materials. Therefore, graphitic carbon electrodes could be modified via robust pi-pi stacking interactions between functional groups and graphitic carbon [49]. However, the surface of graphitic carbon materials is generally hydrophobic, and therefore, inefficient for bacterial cell attachment. Chen et al. reported an interfacial engineering method for improving the hydrophilia of graphitic carbon electrodes via modification using a common antibacterial material PHMG [50]. Firstly, they conjugated PHMG with perylene bisimide (PBI) to form PBI-PHMG composites as shown in Fig. 4A. PBI-PHMG with the optimized PBI content could retain PHMG's intrinsic antibacterial activity while PBI immobilized PBI-PHMG on the surface of graphitic carbon electrode via pi-pi stacking interactions. The obtained PBI-PHMG modified graphitic carbon electrodes are with positively charged surfaces, which could effectively attract, inactivate and damage the cells of bacteria. The released cytoplasm from damaged cells could obviously change the EIS signal of graphitic carbon electrodes, thus resulting in increased bacterial sensing sensitivity down to 2 CFU/mL for both *S. aureus* and *E. coli*.

Direct microbial growth on the surface of working electrode produces a weak signal due to the small size of microbial cells. Therefore, modification on electrode surface to enlarge the surface area of the working electrode is an effective way to strengthen the electrochemical impedance signal. By immobilizing rugose graphene layer on the surface of the carbon electrode via electrochemical activation, a reduced graphene oxide-carbon electrode (rGO-CE) was formed by Zhang's group [48]. In their research, three oral bacteria, *Lactobacillus fermentum* (*L. fermentum*), *Streptococcus mutans* (*S. mutans*) and *Actinomyces viscosus* (*A. viscosus*), were incubated on the surfaces of rGO-CE. Consequently, the EIS signals for the growths of *S. mutans* and *A. viscosus* were found to be 3.3 times and 6.0 times, respectively, stronger than that of the previous work (Fig. 4B).

Increasing the surface-to-weight ratio of the fabricated electrode is an effective way to enhance the sensitivity of as-prepared sensor. Carbon nanowalls [24] and carbon nanotube-based electrode [34] are the emerging electrodes with prominent surface-to-weight ratio, and have been applied for bacteria sensing. Kowalski et al. fabricated the boron doped carbon nanowalls electrodes with strong mechanical property, good electrical conductivity, and high activity towards ferro/ferricyanide redox couple [24]. Then, anit(-*Pseudomonas syringae pv. Lachrymans*) antibodies, employed as the bi-recognition element, were successfully anchored on the surface of electrode by covalent linkage, obtaining the biosensors with high sensitivity towards seven strains of *Pseudomonas syringae pv. Lachrymans.* Patel et al. immobilized the bacteriophage on the surface of carbon nanotube-based electrode and applied it as a recognition element for identifying *S. aureus* in both aqueous medium and blood plasma samples [34]. The as-prepared biosensor displayed both high sensitivity and good selectivity towards *S. aureus* with a LOD of 1.23×10^2 CFU/mL in aqueous solution and 1.29×10^2 CFU/ml in blood plasma, respectively. The biosensor shows great potential in the construction of lab-on-a-chip platform for real-time monitoring other bacteria

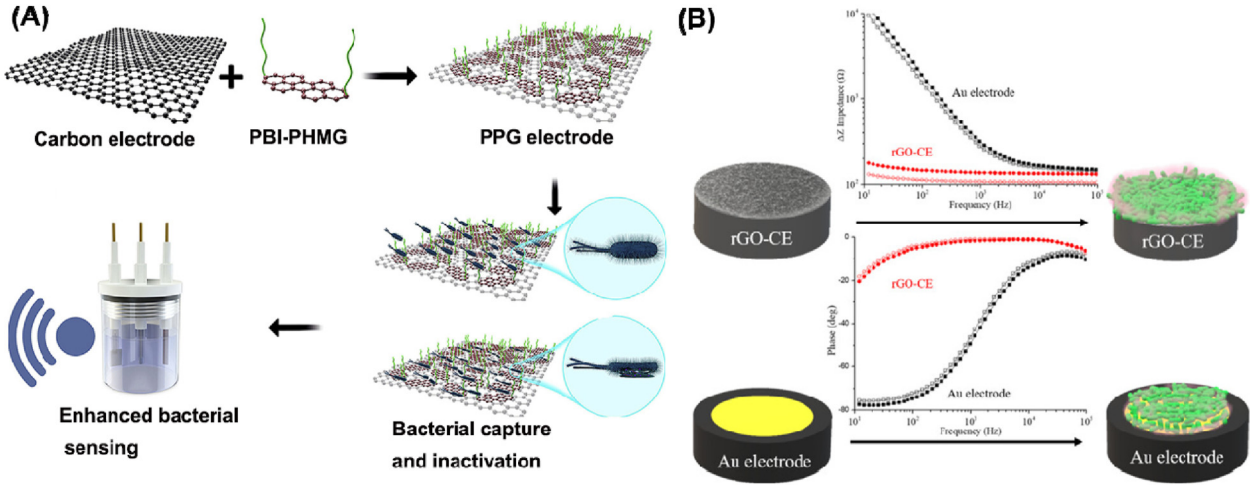

Fig. 4. (A) An interfacial engineering method for improving the hydrophilia of graphitic carbon electrodes modified using polyhexamethylene guanidine hydrochloride (PHMG) [50]. Reproduced with permission. Copyright 2020, Elsevier. (B) Increasing EIS signal of microbial biofilms via electrochemically generated graphene interface on carbon-based electrodes. Reproduced with permission [48]. Copyright 2020, The American Chemical Society.

such as *Listeria monocytogenes, Pseudomonas aeruginosa* and *Klebsiella*.

2.1.4. Screen-printed electrode (SPE) for EIS-based sensor development

SPEs have the advantages of simple structure, easy for scale production, low cost, and flexible design, and are substitutes for traditional microelectrodes, which show broad application prospects not only in electrochemical sensing [25,31,66−68], but also in fields of photovoltaic power generation [69]. With the introduction of SPEs, the sensitive detection of bacteria has been achieved.

In 2020, Kozitsina et al. had proposed a method for covalent fixation of anti-*E. coli* antibodies on the surface of a SPE [25]. The immobilization is achieved via a copper-triggered "click" reaction between acetylene fragments of propargyl-N-hydroxysuccinimide ester and a polyvinylbenzylazide film deposited on the surface of the electrode. By time-saving "click" reaction, the immobilization of anti-*E. coli* was achieved in only 30 min, much shorter than the conventional methods (a few hours). Accordingly, the denaturation of the immunoreceptor was obviously reduced, increasing the sensitivity of the as-prepared biosensors. The LOD of the immunosensor was 6.3 CFU/mL, with a linear range of 10^3−10^6 CFU/mL in *S. aureus* detection. The following stability tests in 30 days indicated that the as-prepared immunosensors were stable in PBS (pH = 7). Similar to the previous works, GO, as a kind of fast electron-transfer material, was deposited on the screen-printed graphene (G) on a hydrophobic paper as shown in Fig. 5A by Chou et al. [66], followed by the fixation of lectin Concanavalin A (ConA) as a bio-recognition element for the construction of GGO_ConA-based biosensor (Fig. 5B). The electrochemical characterization of the sensing system demonstrated fast electron transfer with an electroactive surface area of 0.16 cm^2. The electrochemical impedance of the biosensor was enhanced with the *S. aureus* concentration in the linear range of 10−10^8 CFU/mL with a LOD of 10 CFU/mL.

Besides the roles for enhancing electrical conductivity, gold materials were also used as supporting materials for easy modification of thiol-terminated aptamers [70]. Ahmadi et al. [31] doped carbon nano-onions and Au NPs on the surface of screen-printed carbon electrodes. Then, the aptamer was self-assembled on the surface of the electrode through the covalent modification of thiol groups with AuNPs. The developed aptasensor could test *S. aureus* with a LOD of 3 CFU/mL in the range of 10−10^8 CFU/mL. Later in 2021, by modification of antibiotic functionalized with thiol groups on screen printed gold electrodes, Guzel et al. fabricated an antibiosensor for the specific determination of gram-positive bacteria [68]. In detail, first of all, vancomycin were functionalized with thiol groups and then fixed on the surface of screen printed gold electrodes. After that, EIS was employed to characterize the electrochemical impedance change. As expected, the electrochemical impedance value displayed an apparent change upon the binding of thiolated vancomycin onto the surface of electrode. Then, the susceptibility test was carried out using *E. coli*, *S. aureus* and *Mycobacterium smegmatis* to verify the selectivity of the as-prepared biosensor towards *S.*

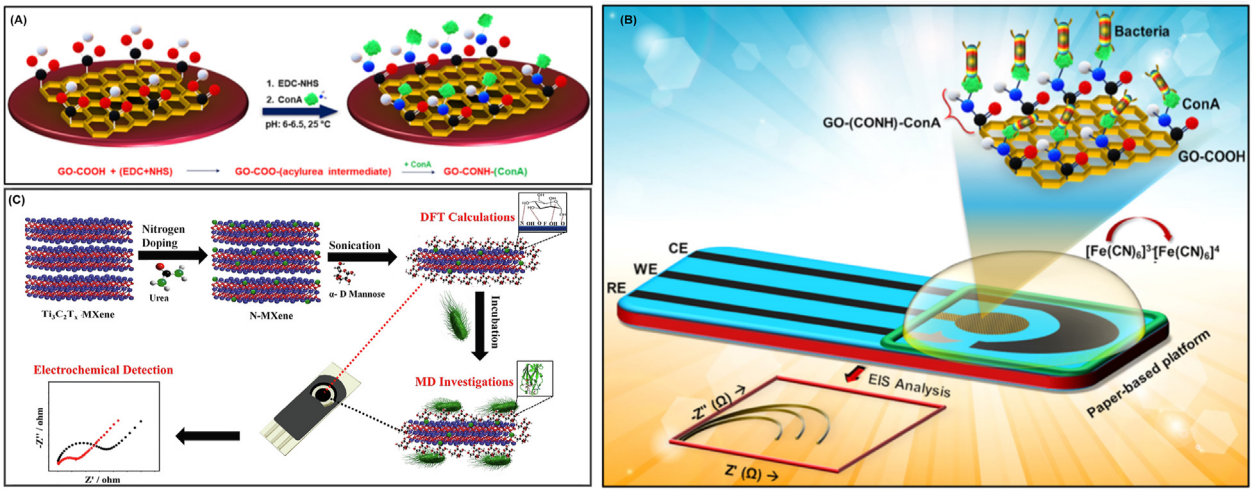

Fig. 5. (A) Schematic illustration of covalent immobilization process of ConA on the surface of GO. (B) The sensing mechanism of the sensing platform using ConA as recognition element. Reproduced with permission [66]. Copyright 2021, The American Chemical Society. (C) The construction of glycan-based sensing platform via hydrogen bonding for E. coli sensing. Reproduced with permission [67]. Copyright 2022, Elsevier.

aureus. What's more, *S. aureus* in various concentrations (10−10^8 CFU/mL) was tested to study sensitivity of the as-prepared sensor and the LOD was calculated to be $10^{1.58}$ CFU/mL.

MXenes with 2D structures are the emerging members of nanomaterial family, and widely applied in the fields of electrochemical nitrogen reduction reaction [71−74], sensing [75−78] and electromagnetic wave absorption [79,80]. Moreover, abundant binding sites and surface functional groups make MXenes the expected candidates for sensor fabrication. Ranjbar et al. reported the successful construction of a MXene-based nano-device for capturing, sensing, and filtering the *E. coli* [67]. Mannose carbohydrate, which could strongly bind to *E.coli*'s fimH protein via glucan multivalent interactions, is employed as the bio-receptor element as shown in Fig. 5C. MXene's layered structure was used to efficiently capture *E. coli* without mannose detachment. As expected, the constructed sensing platform achieved a sensitive detection for *E. coli* in a linear range of 10^1−10^8 CFU/mL with a LOD of 10 CFU/mL.

2.1.5. Indium tin oxide (ITO) and fluorine tin oxide (FTO) electrodes for EIS-based sensor development

ITO, with both excellent electrical conductivity and optical transparency, is a kind of ideal material for working electrodes in photoelectrochemical sensors. Moreover, ITO electrodes show good compatibility with some polymer films. As we know, polymer films in packaging industry would be easily contaminated by biofilm forming bacteria. However, few studies focus on the adhesion of bacteria on the polymer films. Bharatula et al. coated polyethylene terephthalate on the surface of ITO and obtained the bacteria growth substrates(ITO:PET) [51]. Then, the EIS results are compared with those of standard optical methods for the determination of *P. aeruginosa* biofilms formed on the surface of ITO:PET under static growth conditions. The electrochemical impedance displayed a quick drop after the attachment of bacterial and thus the EIS could rapidly monitor the static growth of *P. aeruginosa* biofilms over extended periods of time up to 4 days.

Compared with the ITO electrode, the fluorine doped tin oxide (FTO) electrode further increases electrical conductivity and heat resistance, which is very important for preparation of EIS-based sensing platform. Gandhi et al. fabricated a FTO-based sensor to study the interaction between *Salmonella* serovars (*Salmonella gallinarum* (*S. gal*), *Salmonella pullorum* (*S. pul*)) and specific antibodies [52]. Firstly, rGO was labelled with *S. gal* and *S. pul*-Ab via carbodiimide activation. Then, the modified rGO was fixed on the surface of FTO electrode. Under optimized sensing conditions, the obtained immunosensor showed a linear detection range (1−1 × 10^5 cells) with 37 and 25 viable cells of *S. gal* and *S. pul*, respectively. Moreover, the immunosensor achieved the successful detections of *S. gal* or *S. pul* up to 51 and 37 cells, respectively in faecal samples, and 218 and 173 cells, in meat samples, respectively.

2.1.6. Carbon paste electrode (CPE) and paper-based electrode for EIS-based sensor development

Besides the electrodes mentioned above, CPE and paper-based substrate are also involved in

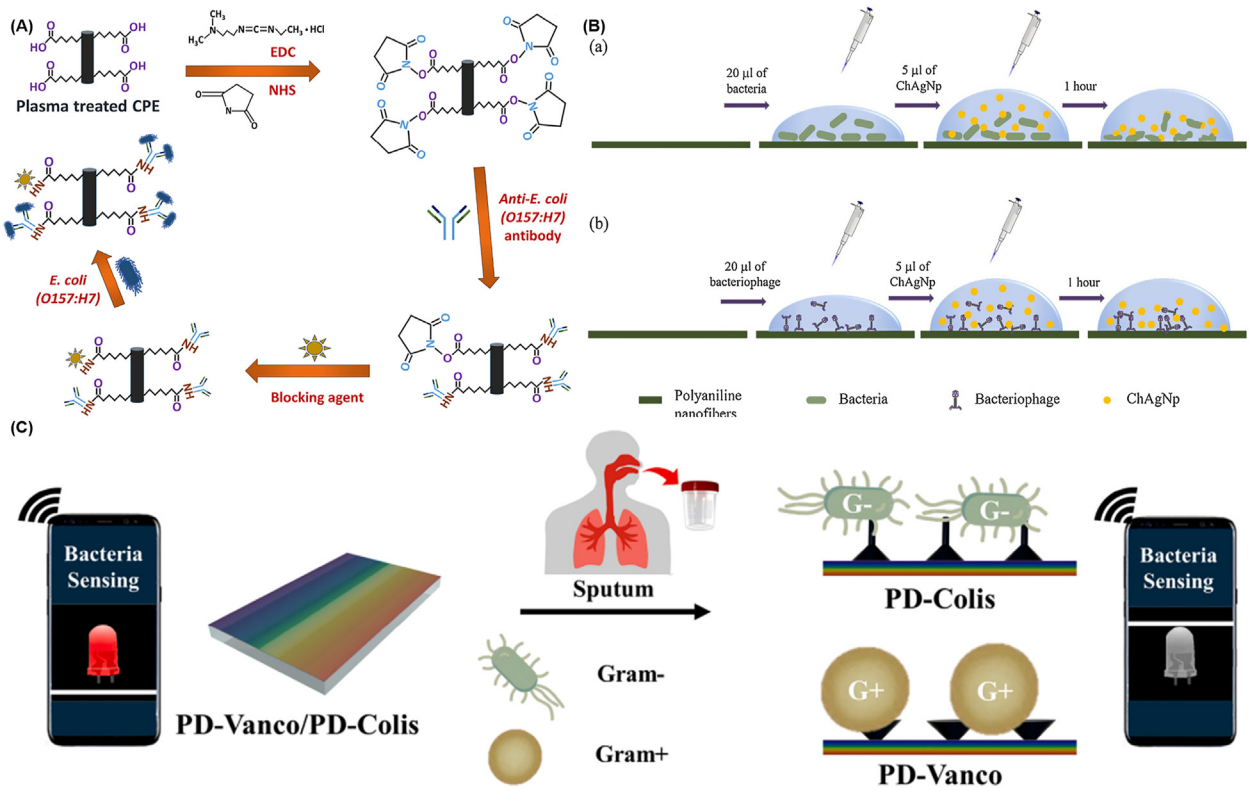

Fig. 6. (A) The fabrication process of a biosensor for E. coli detection. Reproduced with permission [81]. Copyright 2022, The American Chemical Society. (B) (a) Illustration of the interaction between the obtained chitosan capped silver nanoparticles (ChAgNP) and bacterial suspension (b) interaction between the ChAgNP and bacteriophage. Reproduced with permission [35]. Copyright 2020, Elsevier. (C) Schematic diagram of colistin-modified polymer dot (PD-Colis)- and vancomycin-modified polymer dot (PD-Vanco)-coated electrodes for specific sensing of both gram-positive and gram-negative bacteria in human sputum. Reproduced with permission [82]. Copyright 2022, Elsevier.

the preparation of EIS-based sensors. CPE is a new kind of electrode with small background current and low ohmic resistance, made from a mixture of conductive toner and adhesive. With the help of the nonthermal plasma technique, Vanjari et al. introduced the desired functional groups onto the surface of carbon powder as shown in Fig. 6A [81]. Then, the plasma treated carbon was applied to fabricate CPEs. Biotin-Streptavidin was selected as a model ligand-analyte combination to exhibit its applicability towards biosensor application. Later, the selective recognition of the target *E. coli* was realized using an anti-*E. coli* antibody-modified electrode. The as-prepared biosensing platform for *E. coli* sensing was achieved in $1 \times 10^{-1} - 1 \times 10^{6}$ CFU/mL with a LOD of 0.1 CFU/mL. Moreover, the as-prepared plasma functionalized CPEs showed high selectivity for the test of target *E. coli* spiked in pond water, making them an ideal participant for point-of-care of bacterial sensing.

Paper-based sensing systems have been maturely applied for creating disposable analytical devices because they are user friendly and affordable. Herein, paper-based substrate was used for the preparation of EIS-based sensors by Mukherji's group [35]. The EIS-based sensor was based on the interaction between bacteria and chitosan stabilized Ag NPs as shown in Fig. 6B. The EIS decreased obviously at low frequencies (10—100 Hz) with a droplet of bacterial suspension, dropped on the surface of polyaniline nanofibers' modified filter paper substrate, and encountered to chitosan stabilized Ag NPs. This is because that the cell membranes of bacterial were destroyed by the chitosan stabilized Ag NPs, and the intracellular fluid was then partially released onto polyaniline nanofibers. As a consequence, the constructed sensors achieved the bacterial detection with a LOD of 10^3 CFU/mL.

To avoid the use of wires in the three-electrode system and realize portable measurement of the sensors, Park's group fabricated a wireless electrochemical biosensor that could distinguish between gram-negative and gram-positive bacteria for the specific recognition of pneumonia pathogens in human sputum [82]. The specific binding with the bacterial cell wall of gram-positive and gram-negative bacteria is realized by using vancomycin-conjugated polymer dot-coated and

colistin-electrodes (PD-Vanco and PD-Colis) as shown in Fig. 6C. The PD-Vanco and PD-Colis coated electrodes were proved with high sensitivities determined by the LOD for both gram-positive (3.1 CFU/mL) and gram-negative (3.0 CFU/mL) bacteria. More importantly, the combination of a wireless sensing system with the as-prepared sensor realized the in-line bacterial sensing and achieved point-of-care bacterial monitoring via a smartphone.

2.1.7. Interdigitated microelectrodes for EIS-based sensor development

As shown in Table 1, sophisticated interdigitated electrodes (IDEs) are the most frequently used electrodes for bacterial sensing in the last three years. This is mainly because that IDEs with low ohmic drop, rapid reaction kinetics, high signal-to-noise ratio and small physical size are the ideal transducers of different EIS-based biosensors to sensitively measure the electrochemical impedance change caused by the biological reactions on the surface of the IDEs. In 2020, Lin et al. reported the preparation of a typical EIS-based sensor for bacterial sensing using IDEs as the working electrode [53]. Firstly, anti-*Salmonella typhimurium* antibodies were modified on the surface of nickel nanowires (NiNWs) to obtain the antibodies modified NiNWs (NiNWs-anti). After that, biotinylated aptamers against *Salmonella typhimurium* were fixed on the surface of microelectrode through electrostatic absorption. Then, the *Salmonella* cells were captured, concentrated and separated employing the NiNWs-anti and forming the bacteria-NiNW-anti composites (Fig. 7A). After incubation on the electrode, the increased electrochemical impedance change of the working electrode could be observed. Accordingly, an EIS-based aptasensor was successfully prepared and achieved the *Salmonella* detection in 10^2—10^6 CFU/mL with a LOD of 80 CFU/mL.

Jiang et al. reported the construction of gold interdigitated micro-immunosensor based on Mn-MOF-74 for the sensitive determination of *Listeria monocytogens* (*L. m*) [26]. First of all, the capture antibodies (Ab1) were modified on the surface of the magnetic beads and thus the immunomagnetic beads (MBs@Ab1) were obtained. The as-prepared MBs@Ab1 were applied to selectively separate *L. m* cells in the matrices. Then, the immunosensor (MnMOF-74@Ab2) was transferred to the matrices to generate a sandwich composite (MBs@Ab1-*L. m*-Mn-MOF-74@Ab2) as shown in Fig. 7B. Mn^{2+} was then released from the sandwich composite via the action caused by hydrogen peroxide. Accordingly, the released Mn^{2+} could obviously change the electrochemical impedance of electrodes, thus realizing the sensitive test of *L. m* with LODs of 9.2 and 7.1 CFU/mL in milk and water, respectively.

The small physical size of IDEs is their unique merit for construction of portable sensor. Chen et al. reported an inexpensive and portable EIS-based biosensor using IDE arrays to successfully test *E. coli* [32]. They realized the manipulation of the affinity between the *E. coli* (*E. coli* BL21 series) and IDE array by functionalizing the IDEs' surface with an *E. coli* outer membrane protein Ag1 aptamer as shown in Fig. 7C. To find out the major factors influencing the sensitivity of the obtained biosensor in *E. coli* sensing, the author investigated the roles of the substrate material applied in the construction of the IDE, the aptamer concentration, as well as the composition of the carboxy aliphatic thiol mixture. After detailed characterizations, they finally found that the constructed sensor could achieve the sensitive detection of *E. coli* with a LOD of 9 CFU/mL. Apparently, via direct changing the molecular recognition elements employed in the biosensor, this sensing platform could be applied in determination a series of other microorganisms.

Queirós also reported a portable label-free electrochemical immunosensor for *Aeromonas salmonicida* sensing in seawater [27]. In their work, anti-*A. salmonicida* (AbSalm) antibodies were covalently immobilized to the gold surface of the microfabricated electrodes and were applied as sensing probes for the specific detection of *A. salmonicida*. The constructed immunosensor was made up of a fluidic integrated electrochemical-cell-chip with separated chambers enclosing three electrochemical cells. The sensitivity, specificity and repeatability of the developed biosensor were also studied. A linear relationship of the electrochemical impedance signal and the bacterial concentration was observed in 1—10^7 CFU/mL, with a LOD as low as 1 CFU/mL. The following recovery studies indicated that the as-prepared biosensor was qualified in real sample detection.

Microfluidic technology is an effective method to realize the miniaturization of the sensors. Recently, a microfluidic biosensing platform based on immunomagnetic separation, enzymatic catalysis and EIS analysis was constructed for sensitive and rapid *S. typhimurium* sensing by Lin's group [28]. First of all, the magnetic nanoparticles (MNPs) functionalized with capture antibodies, the bacterial sample, the enzyme probes functionalized with detection antibodies, as well as glucose oxidase (GOx) were synchronously injected into the microfluidic chip. After incubation, the mixture formed MNP-bacteria-probe sandwich composites. After that, the glucose solution with high

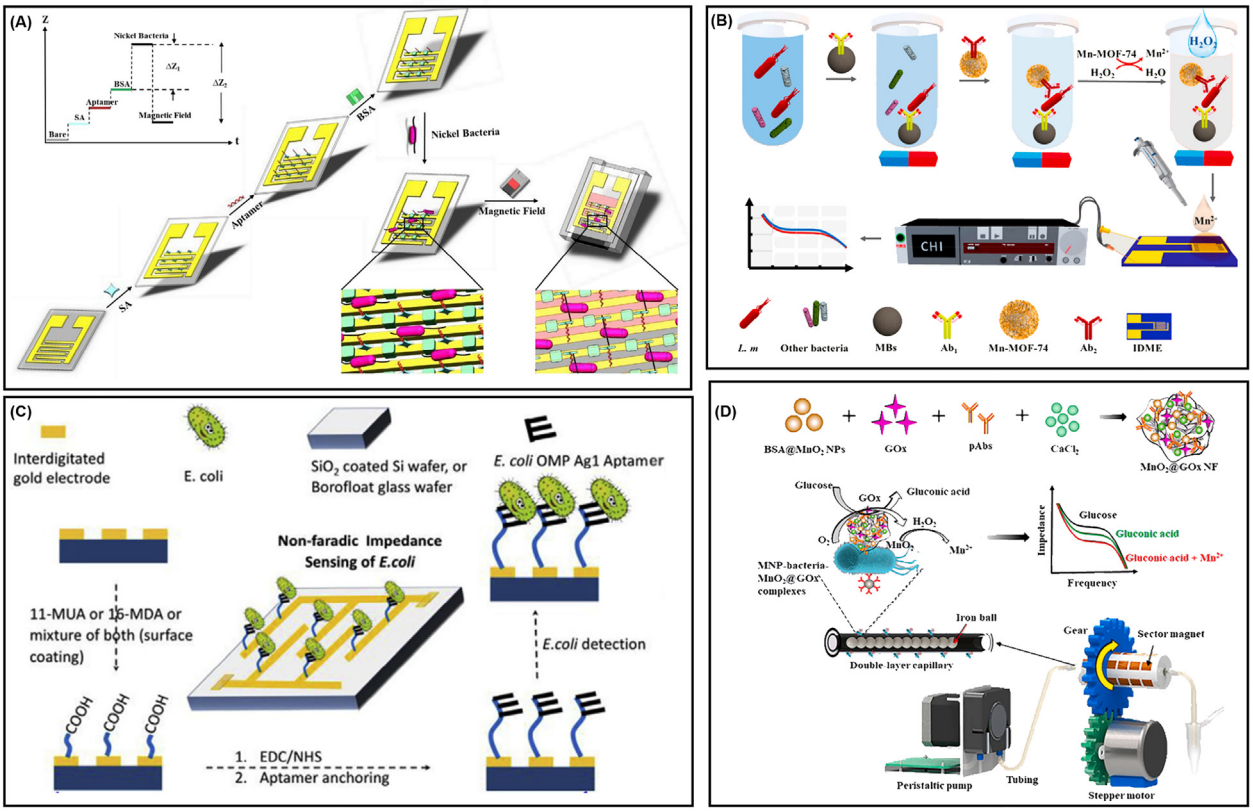

Fig. 7. (A) The fabrication process of a biosensor for Salmonella typhimurium detection based on gold interdigitated microelectrode. Reproduced with permission [53]. Copyright 2020, Elsevier. (B) The sensor for L. m detection based on a sandwich model containing immunomagnetic beads and Mn-MOF-74 impedance probe. Reproduced with permission [26]. Copyright 2021, Elsevier. (C) Schematic process of the E. coli sensor based on the E. coli OMP Ag1 aptamer modified IDEs. Reproduced with permission [32]. Copyright 2020, Elsevier. (D) Illustrations of the EIS-based biosensor for Salmonella sensing. Reproduced with permission [29]. Copyright 2021, Elsevier.

electrochemical impedance was injected into the chip and catalyzed by the GOx inside into gluconic acid with good conductivity and hydrogen peroxide with poor conductivity. Based on the change of electrochemical impedance, the as-prepared biosensor achieved the quantitative detection of *S. typhimurium* in the concentrations from 1.6×10^2 CFU/mL to 1.6×10^6 CFU/mL with a LOD of 73 CFU/mL. Besides, this biosensor also showed good feasibility for practical utilizations by testing the *S. typhimurium* in chicken meat samples.

It has been reported that the H_2O_2 could trigger reduction of MnO_2 into Mn^{2+} [83,84]. Enlighted by this reaction, Lin's group fabricated a MnO_2-based sensor for *Salmonella typhimurium* detection. Firstly, the magnetic nanobead (MNB) solutions functionalized with capture antibodies were injected from outer periphery of this ring channel to form multiple ring MNB nets at specific locations with high gradient magnetic fields. Then, the bacterial sample was also injected, leading to the selective capture of target bacteria onto the nets, and the MnO_2 NFs functionalized with detection antibodies were injected to form MNB-bacteria-MnO_2 NF composites. Then, H_2O_2 with high electrochemical impedance was injected to reduce MnO_2 NFs to generate Mn^{2+} with high conductivity, resulting in obvious electrochemical impedance decrease. Then, the electrochemical impedance change was tested and thus achieved the quantitative determination of *Salmonella*. More interestingly, this biosensor could separate 60% of *Salmonella* from bacterial sample (10 mL) and realized the linear detection of *Salmonella* in the concentration from 3.0×10 to 3.0×10^6 CFU/mL with a LOD of 19 CFU/mL. MnO_2 was also applied by Lin's group in the construction of cascade reaction signal amplification with GOx to further enhance the sensitivity of the bacterial senor [29]. Firstly, as shown in Fig. 6D, magnetic nanoparticles (MNPs) modified with anti-*Salmonella* monoclonal antibodies were injected into a capillary in the presence of a rotary high gradient magnetic field. Later, the bacterial sample was injected into the capillary and the target bacteria could be captured onto the MNPs. After the organic-inorganic hybrid nanoflowers were prepared using MnO_2, GOx and anti-*Salmonella* polyclonal antibodies (pAbs), they were injected to label the bacteria, leading to the generation of MNP-bacteria-nanoflower sandwich composites. Finally, glucose with low conductivity

was injected and oxidized by GOx inside to generate H_2O_2 with low conductivity and gluconic acid with high conductivity, leading to apparent electrochemical impedance decrease. Moreover, the generated H_2O_2 gave rise to a cascade reduction of MnO_2 into Mn^{2+}, resulting in further electrochemical impedance decrease. After the systematical characterization, the as-prepared biosensor was found with improved sensitivity (LOD = 10 CFU/mL) compared with the previous study.

3. Conclusions and perspectives

Apparently, great achievement has been made in the construction of EIS-based sensors for diverse pathogenic bacteria sensing in laboratory in the last three years. Moreover, the as-prepared sensors show obvious advantages such as low cost, short read-out time, easier automation, and portable equipment construction compared with other technologies including electrochemistry, optics, piezoelectricity and calorimetry. Though electrochemical impedance methods have enabled the accurate determination of pathogenic bacteria, literature review in this field remains limited and few sensors have been commercialized. It means that knotty problems are still exited in the commercialization of EIS-based sensors. In our opinion, the main limitations are shown as follows.

(1) Most of the EIS-based sensors show insufficient sensitivity compared with that for nucleic acid sensing. The LODs of these sensors (generally more than 1 CFU/mL) can not meet the demand of pathogenic bacteria sensing, especially in complicated bacteria samples such as sewage or food.

(2) The bio-recognition elements (antibodies, aptamers and bacteriophages) used in EIS-based sensors for specific sensing greatly increase the cost of biosensors. Moreover, their prices have been remaining high in the near future. Continuing advances in the economical bio-recognition elements are expected to combat these challenges.

(3) The participated bio-recognition elements would easily lose their biological activity in the processes of immobilization, detection and storage. Therefore, their low stability further limits the commercial applications of EIS-based sensors. The development of ideal alternatives of bio-recognition elements such as MIPs should be encouraged.

Despite the reasons above, up till now, prototypes of the EIS-based sensors in laboratory have been developed while their further applications in commercial are still limited. Although difficult issues are still exited, the EIS-based sensor is still the most promising device for routine applications by untrained users. The resolutions of these difficult issues will enable the translation of these sensing platforms from laboratory prototypes to real-world implementation. As this class of sensors continues to mature, approaches to combine low cost and stable bio-recognition elements, miniaturized instrument, and depth calculation to monitor and detect target bacteria from complex solutions will enable the systematic and specific sensing of particular pathogen in the complicated sensing environment such as sewage, air, food and beverages.

Acknowledgements

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基于电化学阻抗谱的致病菌检测传感器的研究进展

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摘要

几千年来，致病菌对人类健康构成了巨大威胁。实现致病菌的实时监测可有效阻止致病菌的传播，从而降低对人类健康的威胁。迄今为止，已有电化学、光学、压电和量热等多种技术用于细菌的检测。其中，基于电化学阻抗技术的传感器由于其成本低、读取时间短、重现性好、设备便携等优点，在实时细菌检测中展现出了巨大的应用潜力。本文主要综述了近三年来电化学阻抗技术在细菌传感中的典型应用。众所周知，电极材料在基于电化学阻抗的传感器的构建中发挥着极其重要的作用，因为细菌生物识别元件的固定化，以及所制备的传感器的灵敏度、经济性和便携性都主要取决于电极材料。因此，为了向新入行的研究人员提供基于不同电极材料制备电化学阻抗传感器清晰的制备过程，我们尝试根据不同的电极平台对基于电化学阻抗技术的传感器进行分类。此外，还讨论了目前的难点、未来的应用方向和前景。我们希望通过本文的综述，能够为刚进入该领域的研究人员开展基于电化学阻抗技术，制备快速、灵敏、准确地检测多种致病菌的传感器研究提供指导。

关键词：电化学阻抗谱；致病菌检测；生物识别元件；电极材料