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Review Article

A review of microfluidic impedance sensors for pathogen detection

Chen Li, Mu Yuan* and Zhian Li

Department of Quality and Safty, China Jiliang University, Hangzhou 310018, China

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***Corresponding authors:** Mu Yuan, Department of Quality and Safty, China Jiliang University, Hangzhou 310018, China, E-mail: yuanmu@zohomail.cn

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Abstract

The development of rapid, sensitive and specific methods for the detection of foodborne pathogens is important to ensure food safety. Currently, detection methods such as counting methods, immunoassays, and biosensors have been developed for detecting foodborne pathogenic bacteria, and impedance sensors combined with microfluidic technology have received extensive attention. This paper outlines the advances and applications of microfluidic impedance biosensors for the detection of foodborne pathogens. And reviews the current advances in microfluidic impedance sensors based on transducer materials and detection techniques, including detection technology based on interdigitated microarrays electrode, electrophoresis technology, nanotechnology, etc. Finally, the challenges and development trends of current microfluidic impedance sensors are discussed.

Introduction

Recently, diseases caused by foodborne pathogens pose a serious threat to public health and food safety and constitute a major obstacle to global socio-economic development [1,2]. Among them, bacteria are the most common foodborne pathogens [3]. Among these bacteria, Salmonella, Listeria, Escherichia coli O157:H7, Staphylococcus aureus, and Bacillus cereus are the main foodborne pathogen bacteria [4]. Therefore, the rapid detection of foodborne pathogenic bacteria and the development of detection technology are of great significance.

In the past few decades, great efforts have been made in the rapid detection of foodborne pathogens, and various detection techniques have been studied. In addition to conventional bacterial culture counts, there are a variety of other methods, such as nucleic acid-based, immunology-based, and biosensors (eg, optical, electrochemical, and mass spectrometry-based biosensors) for rapid detection of foodborne pathogens [5,6].

Many detection strategies, such as electrochemical, fluorescence, chemiluminescence, and colorimetric methods, have been developed for establishing point-of-care biosensors [7]. Impedance biosensors are one of the effective ways to detect foodborne pathogens based on biosensors because of their portability, speed, sensitivity, and suitability for on-site detection [8-10]. Recently, microfluidic technology has been deeply studied [11]. This technology can integrate enrichment, capture, detection, analysis, and other processes into the chip to improve detection performance [12]. It combines with biosensing to provide high-throughput analysis and integrated micro-distribution, realizing the advantage of intelligent instant diagnosis in the detection of bacteria [13-15]. The combination of microfluidic technology and impedance biosensors provides a broader perspective for the detection of pathogens, especially in the field of biosensors, where the development of new technologies (such as nanotechnology, etc.) provides strong technical support to promote the pathogen enrichment process and improve impedance signals and improves detection sensitivity. This paper briefly introduces the principle of microfluidic impedance detection and reviews the progress and application of impedance sensors based on microfluidic technology in the detection of foodborne

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pathogens, especially recent development. Finally, the problem and development trend of the current microfluidic impedance sensors are discussed.

Microfluidic impedance detection technology and principle

Microfluidic impedance biosensors are instruments based on microfluidic systems that convert biological concentrations into electrochemical impedance signals for identification and detection. They are widely considered to be promising analytical tools for on-site inspection due to their fast response time, high sensitivity, and simple operation, and facilitate the development of miniaturized and automated instrumentation. The specificity and effectiveness of biomarker ligands to capture target bacteria, the signal-transformation level of the bio-impedance of the transducer material, and the auxiliary enrichment ability are all important factors in determining the sensitivity of the microfluidic impedance sensor. Various contaminants in the actual sample may act as inhibitors, resulting in false negative results. There are many factors hindering the realization of truly "one-step" detection on a chip, sufficient reaction time is undoubtedly the important one, which significantly affects the collision opportunity between molecules, thereby affecting the binding between molecules, including the labels and targets, as well as the capture antibody and the labeled complex, and finally affecting the detection sensitivity. Therefore, how to control the reaction time has attracted much attention for on-chip detection [16]. A large number of research literature show that the use of IDAM-based detection technology, dielectrophoresis technology, and nanotechnology can improve the capture rate of bacteria and improve the impedance signal level to improve the detection sensitivity of microfluidic impedance sensors.

Principle of microfluidic impedance detection

The principle of impedance detection of microfluidic impedance biosensors is that based on a microfluidic system, a specific complex formed by the biometric molecule with an analyte at the surface of the conductive (or semiconductor) transducer, directly or indirectly alters the electron transfer capability of the recognition surface. Then establish a relationship between the change in electron transfer capability and the concentration of the analyte to achieve the purpose of detection.

The electrical impedance (Z) is defined as the ratio of the voltage increment change to the current change, $V(t)/I(t)$. According to this definition, the impedance Z is the quotient of the voltage-time function $V(t)$ and the resulting current-time function $I(t)$:

$$Z = \frac{V(t)}{I(t)} = \frac{V_0 sin(2\pi ft)}{I_0 sin(2\pi ft + \varnothing)} \quad (1)$$

Where V_o and I_o are the maximum voltage and current signals, f is the frequency, t is the time, φ is the phase shift between the voltage-time and the current time function, and Y is the complex conductance or admittance [17]. At the same time, the impedance is a complex value, which can be expressed as two parts: real part Z_{Re} and imaginary part Z_{Im}:

$$Z = Z_{Re} - jZ_{Im} \quad (2)$$

Where j is the plural sign, $j^2=-1$, Z_{Re} is the real impedance, and Z_{Im} is the imaginary impedance.

Therefore, the results of impedance measurement can be described by two different forms of electrochemical impedance spectroscopy EIS: a Nyquist diagram with the real part as the X axis and the imaginary part as the Y axis. Each point of the Nyquist diagram corresponds to a frequency in the impedance, with low frequencies on the right and high frequencies on the left. Another form of EIS is the Bode diagram with the logarithm of the frequency as the X axis, the absolute value of the impedance, and the phase angle as the Y axis. The Bode diagram can show the relationship between the frequency and the impedance value and the phase angle.

In order to express the characterization of surfaces, layers, or membranes after binding of immobilized biomolecules and bacteria, EIS is typically analyzed by using an equivalent circuit. And it contributes to analyzing the impedance changes of the electrolyte and the medium on the electrode, so as to determine the main factors of the system impedance change. From an electrical point of view, a simple equivalent circuit in series with a resistor and capacitor is sufficient to indicate the behavior of the impedance test system when the two electrodes are immersed in a conductive medium. The equivalent circuit model is composed of resistance, capacitance, and other components. Commonly used electrical components generally include electrolyte solution resistance, electric double layer capacitance, electron transfer resistance, Warburg impedance, etc. Each component represents one or more electrode processes and electrochemical properties.

The Randles equivalent circuit model is usually used to fit the Nyquist impedance spectrum. When performing Faraday impedance measurement in a solution containing a redox system. In Randles equivalent circuit, the electrolyte resistance R_s and Warburg impedance Z_w represent the properties of the bulk solution and the diffusion characteristics of the redox couple, which are not affected by the surface reaction of the electrode;

Double layer capacitance C_{dl} and electron transfer resistance R_{et} characterize the dielectric and insulation properties of the electrode/electrolyte interface (Figure 1A). The Faraday AC impedance spectrum Nyquist the diagram is composed of a semicircle that intersects the coordinate axis and a straight line after it (Figure 1B). When the voltage changes in a high-frequency band, the impedance spectrum is a semicircle, corresponding to the electron transfer process in an electrochemical system. The electron transfer resistance Ret is equal to the semicircle's diameter. And the intercept of the semicircle on the real axis corresponds to the electrolyte resistance R_s. When the voltage change is in a low-frequency band, the impedance spectrum is a straight line, corresponding to the ion diffusion process of the electrolyte solution. Yang, et

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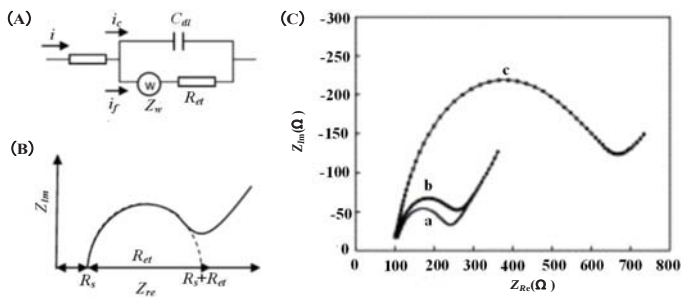

Figure 1: Equivalent circuit diagram and electrochemical Nyquist diagram [18].
(A) Diagram of Randles equivalent circuit; (B) Nyquist diagram; (C) Nyquist diagram in three detection situations: a. bare electrodes; b. the electrodes are immersed in phosphate buffer solution; c. the electrodes are immersed in the Salmonella typhimurium solution.

al. [18] used AC impedance spectroscopy to study the impedance change mechanism of Salmonella typhimurium when adsorbed on a gold electrode in the environment containing 0.01M $Fe(CN)_6^{3-/4-}$ redox probe, using Randles equivalent circuit to fit the Nyquist impedance spectrum. The obtained results are shown in Figure 1 (C). Compared with the two cases of bare electrodes and immersing the electrodes in phosphate buffer solution (curves a and b), When the electrodes are immersed in the Salmonella typhimurium solution (curve c), the diameter of the semicircle representing the electron transfer resistance R_{et} is increased from 0.3 kΩ to 0.9 kΩ, and the double-layer capacitance C_{dl} is reduced. This not only indicates that the adsorption of Salmonella typhimurium on the electrode leads to an increase in impedance but also shows that the mechanism of impedance change is mainly caused by changes in electron transfer resistance and electric double layer capacitance.

Varshney, et al. [19] used the microfluidic impedance method to detect E. coli O157: H7, and used an equivalent circuit to fit the electrochemical impedance Bode diagram to analyze the impedance change mechanism. In the equivalent circuit model, two double-layer capacitors C_{dl} and electrolyte resistor R_s are connected in series and connected in parallel with the dielectric capacitor C_{di} (Figure 2A). The double layer capacitance C_{dl} represents the influence of the ion type on the electrode surface capacitance; the electrolyte resistance R_s represents the change in the conductivity of the electrolyte solution; C_{di} represents the dielectric capacitance of the electrolyte solution. The test results are shown in Figure 2 (B). In the low-frequency band (10 Hz ~ 1 kHz), the change of impedance signal is dominated by the double layer capacitor C_{dl}. In the middle frequency band (1 kHz ~ 50 kHz), the impedance signal is dominated by the electrolyte resistance R_s. In the high-frequency range (50 kHz ~ 1 MHz), the impedance signal is dominated by the dielectric capacitor C_{di}. It can also be concluded that in the detection range, the impedance increases with the increase of the concentration of E. coli (Figure 2C). When the E. coli is adsorbed on the electrode, the electrolyte resistance R_s increases, and the increase of R_s becomes the main reason for the change in impedance.

Analysis of influencing factors of cavitation bubble collapse by micro-jet

The Interdigitated Array Microelectrode (IDAM) comprises a pair of microstrip electrode arrays, each array being composed of a plurality of finger electrodes having a width and a pitch of micrometers in parallel, and the electrodes are in mesh with each other to form an interdigitated electrode array [20-22]. IDAM has high sensitivity, can shorten the detection time, improves the signal-to-noise ratio, and directly detects the impedance change of the dielectric between the electrodes. According to the experiment of Ruan, et al. [23], the anti-E. coli antibody on the surface of the ITO-coated ordinary glass electrode showed only 16% capture efficiency for E.coli O157:H7, compared to IDAM per unit volume in the detection area. The increased number of target cells increases capture efficiency to 35% [24,25] and significantly increases 3-fold impedance response and 10-fold sensitivity [26,27].

Gomez, et al. [28] created the first integrated silicon-based microfluidic IDAM chip for microbial metabolic impedance detection. They developed a flow cell embedded in platinum IDAM to detect the metabolic activity of a few live bacterial cells. Varshney [29] integrated the microfluidic flow cell with the embedded gold IDAM into an impedance biosensor to quickly detect pathogens in the ground beef sample. They combined the IDAM chip on the microchannel made by PDMS. The entire flow cell consisted of a detection microcavity and an inlet and outlet microchannel (Figure 3). Bacterial cells in the active layer above the microelectrodes were collected using a detection microchamber having a size of 6 mm×0.5 mm×0.02 mm, a volume of 60 nL namely. The target bacteria were isolated and concentrated by immunomagnetic separation technique. The device was used to detect E.coli O157:H7 in pure culture and beef samples. The detection limits were as low as 1.6×102 and 1.2×103 CFU/mL, respectively, and the detection time was less than 30 min. Among the microfluidic impedance sensors, the detection technology using IDAM as the transducer material is the most common. IDAM is also made of many materials, such as gold, ITO, Pt, Ti, Rh, etc. For example, Dasditer [26] used a gold-finger array microelectrode immobilized antibody to detect Salmonella typhimurium. in a microfluidic chip. Chen, et al. [30] detected Listeria based on the microfluidic impedance of ITO interdigitated array microelectrodes. Examples of pathogens detected by microfluidic impedance sensors of different IDAM materials are shown in Table 1.

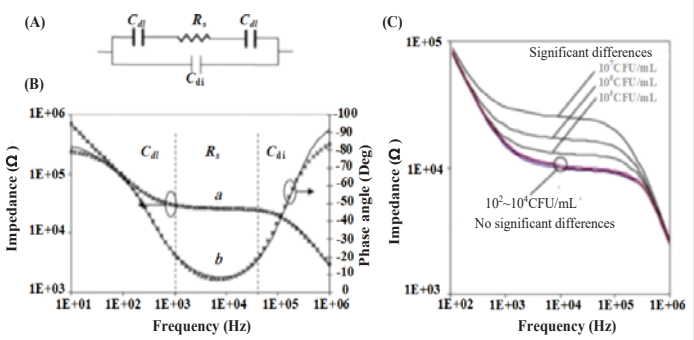

Figure 2: Equivalent circuit diagram and electrochemical impedance Bode diagram [19].
(A) Equivalent circuit; (B) Electrochemical impedance Bode diagram; (C) Bode diagram of impedance at various concentrations of E. coli O157: H7 (102~107CFU/mL).

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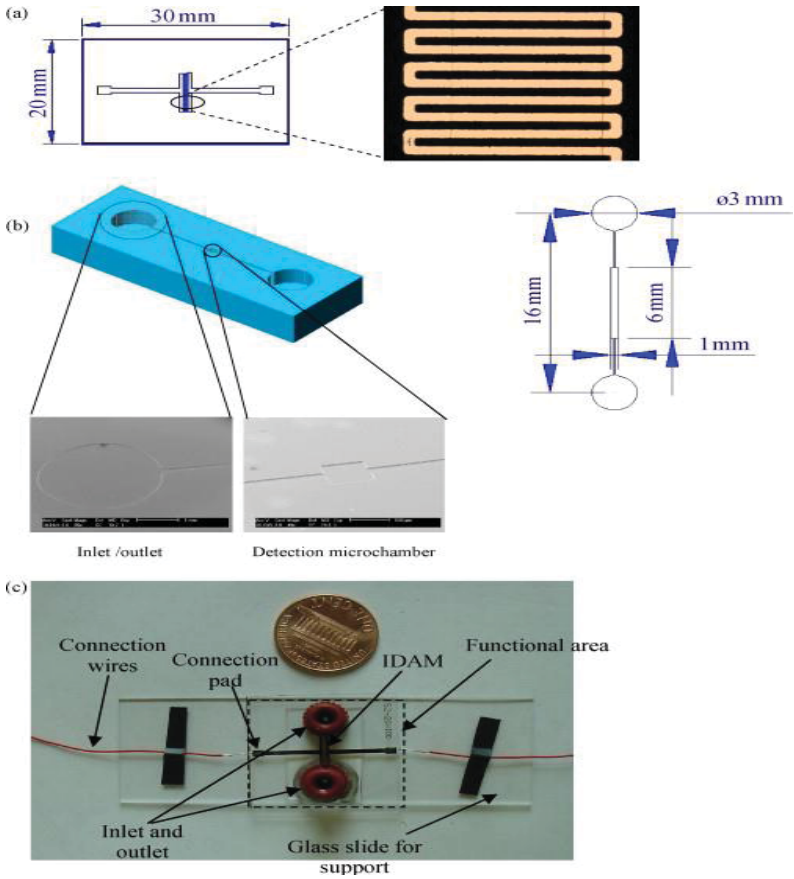

Figure 3: Schematic diagram of microfluidic chip based on golden IDAM [29].
(a) IDAM chips with gold microelectrodes on glass chips;(b) Microchannels with detection microchambers, as well as entry and exit channels;(c) Assembly microfluidic flow pools with embedded IDAM and connection lines.

Although IDAM research has broad prospects, IDAM still has some shortcomings. Due to the less repeatable detection of the IDAM chip, the detection cost is increased. In addition, the effective integration of IDAM on microfluidic chips also faces challenges. It is urgent to use more advanced processing technology and advanced materials to further develop the production of IDAM microfluidic impedance biosensors.

Dielectrophoresis

DEP is the electrokinetic movement of the dielectric material in a non-uniform electric field. The dielectrophoresis used for impedance measurement is called DEPIM, the dielectrophoretic impedance technique. It is one of the effective techniques for microfluidic impedance detection of pathogens because of its ability to highly enrich target cells while achieving low detection limits and high-throughput detection [39,40]. Gomez, et al. [31] developed a microfluidic impedance sensing device based on DEP technology. The design concept is to use DEP to transfer bacterial cells from the main channel to a small channel, allowing the cells to enter a measurement chamber with a volume of 400 µL (Figure 4). The impedance growth curves of Listeria cells using DEP technology and not using DEP were compared. Impedance metabolic signals grow exponentially at approximately 1 hour during DEP action, while samples containing similar concentrations of DEP-free cells require approximately 7.5 hours to produce a detectable impedance signal. The detection time has been significantly reduced, and 8.0×104 CFU/mL Listeria can be detected within 2 hours.

Table 1: Examples of microfluidic impedance sensors with different IDAM materials.

Electrode material	Assistive technology/ material	Pathogen	LOD (CFU/ mL)	Reference
Pt	DEP	Listeria	8×10^4	[31]
Au	-	Salmonella	3×10^3	[18]
Au	Nano magnetic beads	Listeria	1.6×10^3	[32]
Au	-	E.coli	10^3	[33]
Au	DEP	E.coli O157H7	3×10^2	[34]
Au	DEP	E.coli	3×10^2	[35]
Pt	Nanomagnetic beads	E.coli O157:H7	1.6×10^2	[26]
ITO	Nanomagnetic beads	Listeria	1.6×10^2	[36]
C	Nanomagnetic beads	S. Typhimurium	7.7	[37]
Au	Nanomagnetic beads	E.coli O157:H7	1.2	[38]

Dastider, et al. [33] used two sets of IDA. The agminated E.coli is concentrated by pDEP to the center of the microchannel towards the detection zone, the volume of the detection zone being significantly smaller than the volume of the flow channel, and wherein the polyclonal anti-E. coli antibody is not specifically immobilized on the sensing electrode array. The impedance results showed that the detection limit of

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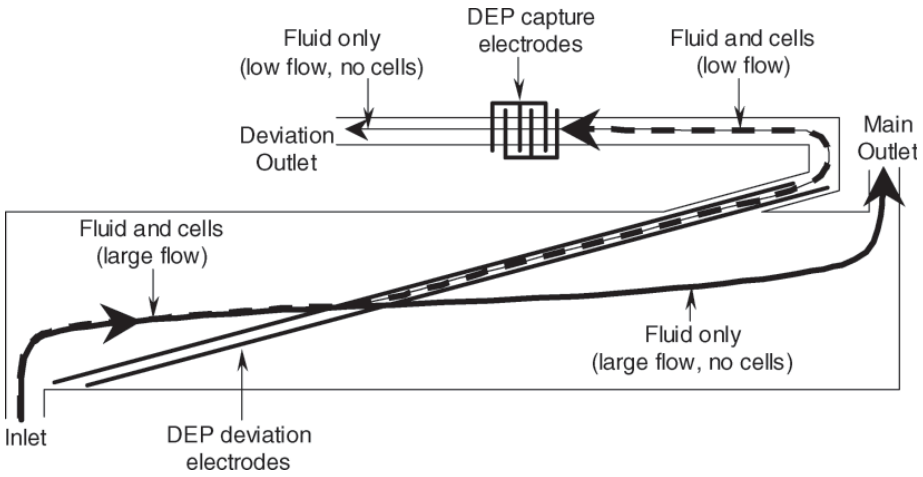

Figure 4: Schematic diagram of mesopores technology to capture bacteria [31].

E.coli O157:H7 bacterial cells was 3×102 CFU/mL. Kim [34] used high pDEP force to aggregate E.coli and pass the sensing electrode. The trapped bacteria form a bridge on the electrode gap, thereby reducing the impedance of the sensing electrode. After detection, E.coli cells were released by shutting off the DEP force. The efficacy of the system was confirmed using four different concentrations of E.coli with a detection limit of 300 CFU/mL.

Páezavilés, et al. [41] reported a number of studies on the detection of pathogenic bacteria in combination with dielectrophoresis on microfluidic chips and impedance methods. In addition, there are also studies on the separation and concentration of bacteria by dielectrophoresis under the action of a magnetic field and sound waves [42-44]. DEP technology can effectively separate pathogens from microfluidics, but high DEP collection efficiency can only be obtained at low sample flow rates. So there is still a need for pre-sorting steps using filtration or immunomagnetic separation methods to increase sample throughput.

Nanotechnology

The function of nanomaterials serves two purposes: to improve the response characteristics of the transducer and the immobilization matrix of the bioreceptor [45]. Nanomaterials have been used to improve pathogen enrichment capture efficiency and amplified the detection signal to achieve lower detection limits and high sensitivity due to their high specific surface area, good electronic properties and electrocatalytic activity, and good biocompatibility and adsorption due to nanometer size and specific physicochemical properties [46-48]. Nanomaterials currently used in microfluidic impedance sensors include nanoparticles, nanotubes, nanoporous membranes, and nanometer two-dimensional materials.

Nanotechnology

Nanoparticles are used to enhance electron transfer and capture more surface loading due to superior conductivity and ultra-high surface area to improve bio-impedance signal conversion levels. Typical are gold nanoparticles AuNPs. For example, Kang, et al. [49] used a double-layered gold nanoparticle and chitosan to prepare a microfluidic impedance sensor for the detection of Bacillus cereus. The use of double-layer gold nanoparticles increased the amount of antibody immobilized and retained the antibody activity. The detection sensitivity of the device is 5.0×101~5.0×104 CFU/mL, the detection limit is 10.0 CFU/mL, and the stable impedance response is maintained for a certain period of time. Michael, et al. [50] developed an impedance immunosensor based on a porous volume microfluidic detection element and a silver-enhanced gold nanoparticle probe. The porous method is used to increase the rate of pathogen capture, and the silver particles are used to enhance the impedance response. The device has a detection limit of 10 CFU/mL.

In addition to being used as a marker and improving the impedance signal level, the magnetic nanoparticles can form an immunomagnetic bead IMB with the target antibody, and the IMB binds to the target bacteria to form a beaded bacterial complex. The composite is oriented and moved under the action of an external magnetic field and is finally absorbed and retained in the magnetic field so that the target bacteria can be easily separated from the food substrate and the sample background. This method is called immunomagnetic separation technology (IMS). The immunomagnetic separation technology can effectively eliminate the background interference in the sample, and achieve the purification and enrichment of the sample, so as to shorten the detection time and improve the sensitivity [51]. Damira, et al. [52] used magnetic nanoparticles with a diameter of 30 nm in combination with functionalized Listeria monocytogenes antibodies to form immunomagnetic nanoparticles (MNPs). Impedance measurements indicate that 104 and 105 CFU/mL of Listeria monocytogenes were detected in samples of lettuce, milk, and ground beef. Recently, drawing on the experience of Chen [30] and Wang [53] using nanoparticle immunomagnetic separation technology and urease to amplification signal, Yao, et al. [38] skillfully combined magnetic nanoparticles (MNPs) for bacterial separation, urease for biosignal amplification, and microfluidic chips for impedance measurement for rapid, sensitive, and continuous flow detection of E.coli O157:

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H7.As shown in Figure 5, after streptavidin-modified MNPs bind to biotinylated polyclonal antibodies (PAbs) to form immune MNPs, the target bacteria are first isolated from the background by MNPs to form MNP-bacteria complexes. Then, MNP-bacteria was conjugated with E.coli O157:H7 modified with urease and gold nanoparticles (GNPs) to form an MNP-bacteria-GNP-urease complex. Finally, the complex is used to catalyze the hydrolysis of urea to ammonium carbonate, resulting in a decrease in impedance. the concentration of E.coli O157:H7 was determined by measuring impedance online and using impedance normalization analysis. A good linear relationship between relative impedance change and bacterial concentration was obtained at a low detection limit of 12 CFU/mL.

The application of nano-magnetic beads in the field of microbial detection has been relatively mature. The efficiency of nano-magnetic beads in capturing pathogenic bacteria can reach 60%~100%, and the interference of non-specific adsorption can be reduced. Especially under the combined action of nanomagnetic beads, bioligands and functional modifiers, the detection limit of microfluidic impedance can be lower, but it is necessary to pay attention to the interference of excess magnetic beads or dense magnetic beads for impedance response.

Nanoporous membrane

The nanoporous alumina membrane is simple and inexpensive to manufacture, and its application in the microfluidic impedance sensor is because it allows a large number of target molecules to be adsorbed on the nanopore wall by covalent bonding, which can significantly improve the detection sensitivity. Jiang [54] used the sensor system of the smartphone as a platform to realize high sensitivity and rapid on-site detection of E.coli in water based on microfluidic bacteria preconcentration and electrical impedance spectroscopy. The device filtered out macromolecular particles through a large number of nano-aluminum pore membranes with a diameter of 16 micrometers, and the detected bacteria were left in the microfluidic detection chamber through the filtration membrane. The process that detected bacteria passed through the pore membranes corresponded to the preconcentration of the bacteria. Subsequently, the pre-concentrated bacterial cells distributed around the interdigitated electrodes are subjected to impedance sensing. The smartphone sensing platform obtained the impedance spectrum through the scanning frequency of 2 kHz to 100 kHz. The E.coli concentration can be obtained by fitting the measurement result to the calibration curve and the corresponding formula by the mobile phone program. The detection limit of bacterial detection of this device is 10 CFU/mL, and the detection concentration range is 10 CFU/mL~103 CFU/mL.

Tan, et al. [55] efficiently detected S.aureus and E.coli O157:H7 using an antibody-immobilized nanoporous alumina membrane integrated into the device. The antibody was covalently immobilized on a nanoporous alumina membrane by trimethoxysilane (GPTMS) (Figure 6a). The film has a diameter of 13 mm and a thickness of 60 μm, the film was integrated between two PDMS layers treated by oxygen plasma, and the platinum wire electrode was used for impedance sensing (Figure 6b). The sample containing the bacteria was loaded into the upper compartment, and the antibody bound on the nanoporous alumina membrane was

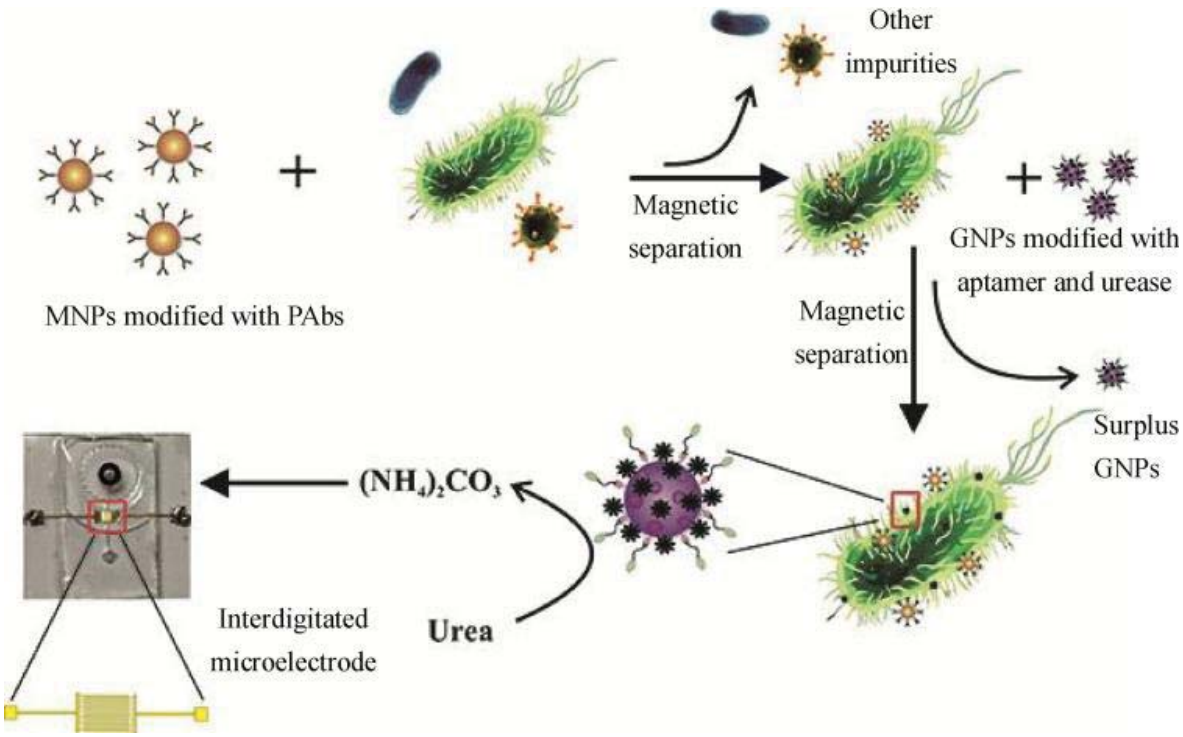

Figure 5: Schematic diagram of microfluidic impedance sensor based on immune magnetic bead separation and urease catalysis [38].

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able to capture the pathogen, causing electrolyte current to clog through the membrane and thus causing an increase in impedance (Figure 6c). The microfluidic immunosensor device quickly detected bacteria within 2 hours with a detection limit of 102 CFU/mL, which shows better sensitivity than conventional microelectrode-based impedance sensors. Tian, et al. [56,57] slightly improved the above device and installed two nanoporous membranes to simultaneously detect E.coli O157:H7 and Staphylococcus aureus at a concentration of 102 CFU/mL.

Immobilization of antibodies on nanoporous alumina membrane. The membranes were first treated with 10% hydrogen peroxide (H2O2) to remove any contaminants and generate a reactive hydroxyl group on the surface. After drying, toluene solution with 1% GPMS was applied overnight to functionalize the surface with epoxide groups. Next, the antibody was immobilized on the surface through the reaction of the amine groups on the antibody with the epoxy groups on the surface of the membrane. (b) Schematic illustration of the PDMS microfluidic device integrated with nanoporous alumina membrane and SEM image of the porous membrane. (c) The mechanism of impedance sensing via antibody immobilized on nanoporous alumina membrane. The pathogen will anchor to complimentary antibodies on the modified nanoporous alumina membrane, once the sample with target bacteria loads into the upper compartment. When bacteria are captured on the membrane, the nanopores will be blocked, and subsequently, the electrolyte current through the membrane will decrease and can be observed in the impedance spectrum. (d) Fluorescence image of S. aureus captured on the antibody-modified membrane with a concentration of 1 × 105 CFU/ml.

The application of nanoporous membranes has the advantages of high sensitivity and fast on-site detection, but the disadvantages of nanoporous membranes are that their own preparation process is complex, and the success rate of generating nanoporous layers is low, affecting the stability of the sensor. In general, membrane-assisted sample enrichment in microfluidic systems is still in an early stage, so additional efforts are needed to investigate new concepts that can be practically applied to design such miniaturized sensing devices.

Nano two-dimensional material

Graphene and molybdenum disulfide (MoS2) are novel nano-two-dimensional materials that have generated significant interest in designing electrochemical devices for biosensing applications. Nano-two-dimensional materials, whether as electrode materials or chemical modification, bring higher sensitivity to microfluidic impedance sensors. For graphene, since all the carbon atoms in the graphene layer are located on the surface, intermolecular interactions and electron transfer are very advantageous. These properties make graphene material with high electrical conductivity, good

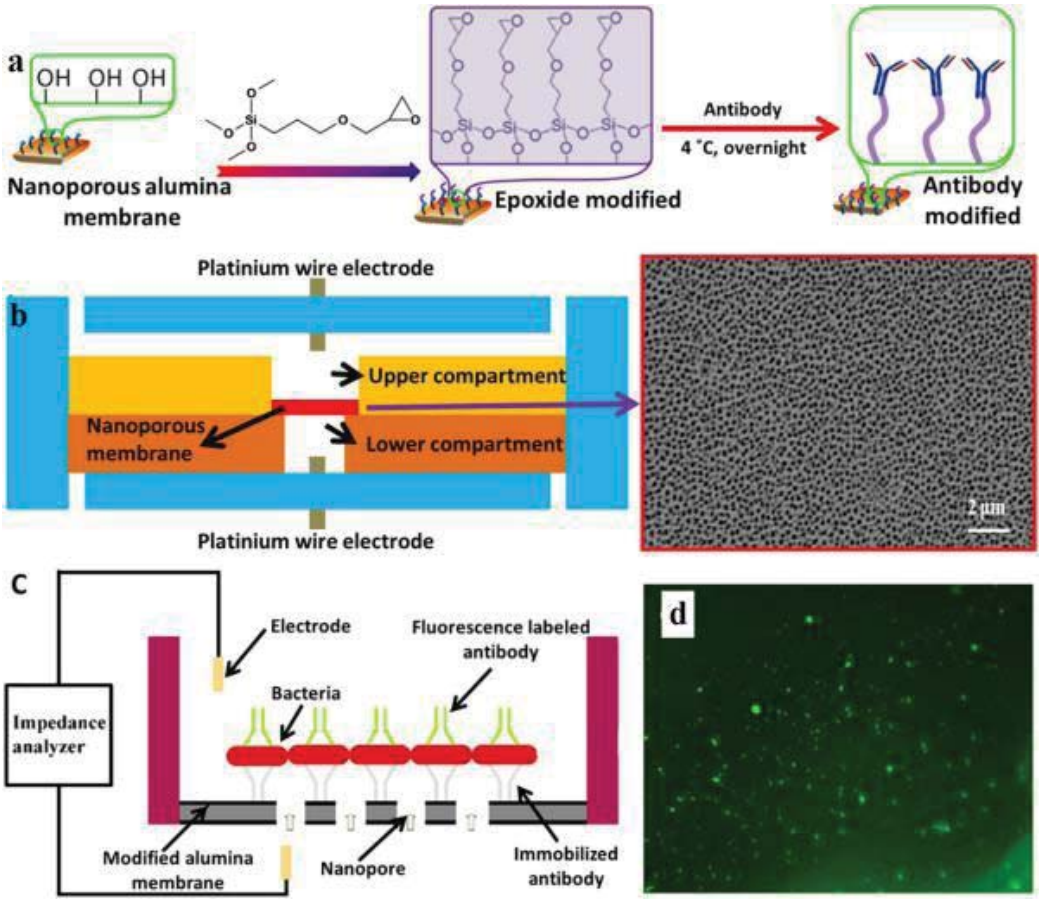

Figure 6: Schematic diagram of nanometer porous alumina membrane for bacteria detection [55].

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catalytic activity of electrochemical reaction, and high specific surface area [58]. For example, Pandey, et al. [59] utilized graphene for excellent electron transfer and bacterial capture to specifically detect E.coli. The graphene nanostructures directly bind to the interdigitated microelectrodes to capture bacteria and amplify the impedance signal, resulting in a detection limit of 10 CFU/mL. Chandra, et al. [60] based on graphene-coated copper oxide-cysteine for detection of Escherichia coli. After 40 days, the impedance response of the sensor remained at 90.2% of the initial value, indicating the electrocatalytic activity and stability of the graphene material.

Recently, synergistic effects based on graphene and other nanomaterials have been extensively studied, and it has been found that the combination of graphene and other nanostructured materials further enhances electron transfer and bacterial capture efficiency. Ma, et al. [61] proposed a glassy carbon electrode modified with graphene oxide and gold nanoparticles as an impedance biosensor for Salmonella detection, whose limitation of detection reached 3 CFU/mL and the bacterial recovery rate was close to 100% in 10~1000 CFU/mL pork samples. In addition, Romano, et al. [62] reported that graphene oxide-carbon nanotube (GO-CNTs) nanocomposites have a maximum electroactive surface area that can control porosity and provide a larger surface for immobilized biomolecules. Carbon nanotubes themselves have a high surface area and strong electrical conductivity for the development of electrochemical immunosensors for the detection of pathogens, achieving an excellent detection sensitivity of 13 CFU/mL [63]. Recently, Chandan, et al. [64] used graphene oxide (GO) nanosheets encapsulating multi-walled carbon nanotubes (cMWCNTs) to modify ITO microelectrodes to detect Salmonella typhimurium without labeling. The measured impedance signal is much higher compared to microfluidic chips based solely on cMWCNT/ITO or GO/ITO modifications. In summary, the application of two-dimensional graphene-based nanomaterials in microfluidic impedance devices has made great progress, greatly improving the sensitivity of pathogen detection. In particular, the synergistic effect of graphene and its nanomaterials makes nanotechnology more advantageous in efficiently capturing pathogens and amplifying impedance signals, but the latest technology in the field cannot be used in the field or point-of-use applications.

MoS2 has a higher surface area than graphene, and the presence of the MoS2 band gap can increase the detection sensitivity by a factor of two. Chandan, et al. [64] described an effective microfluidic chip for the detection of Salmonella typhimurium with a detection limit of 1.56 CFU/mL and a detection range of 10-107 CFU/mL. They used MoS2 nanosheets functionalized by stripped CTAB as transducer materials. The positively charged CTAB-MoS2-NS formed a film on the surface of the ITO electrode by electrostatic interaction, capturing the target bacteria and changing the impedance signal.

In general, the traditional advantages of impedance biosensors, such as rapidity, ease of manufacture, and field suitability, can be further enhanced with the help of two-dimensional nanomaterials. In addition, nanomaterials and microfluidic chips are both micro-technologies, minimizing the sensitivity and specificity of devices for electrochemical biosensors, and giving them great potential for assessing food safety on site. However, the mass production technology of nano two-dimensional materials is immature and the cost is high, which is a problem that needs to be solved in the application of microfluidic impedance sensors.

Microfluidic impedance detection technology and principle

Microfluidic impedance biosensors concentrate the entire process of pathogenic bacteria samples on the microfluidic chip from injecting, mixing, and detecting to measuring, reducing detection time, saving detection costs, and improving analysis efficiency. Detection technology based on IDAM can take advantage of the high sensitivity of IDAM and fast impedance measurement, but it needs to solve the problem of less repeatable detection. DEP technology can achieve efficient isolation and capture pathogenic bacteria at low throughput so which improves detection sensitivity, but the capture rate of pathogenic bacteria needs to be improved at high throughput. Nanotechnology and the union of multiple nanotechnologies can reduce the detection limit of foodborne bacterial to single digits, but there are still some defects: if the nanoparticles are too dense the results will be affected, and the success rate of nanoporous membrane production is not high and the mass production technology of two-dimensional nanomaterials is immature. These defects have limited the field application of microfluidic impedance sensors [65-72].

At present, the construction of microfluidic impedance biosensors is still in the stage of continuous exploration. In future research, we need to continuously learn from optical and other electrochemical-based methods and technologies, and we need to rely on the development of the latest nanomaterials and technologies suitable for impedance detection. So that it can be used to quickly detect foodborne pathogens in the field in real-time. In addition, in order to meet the low price requirements of microfluidic devices for pathogen detection, future research can shift from highly complex manufacturing technologies to polymers or paper devices that can meet the needs of end users. Such as polymers and paper-based chips replacing silicon and glass, and screen-printed electrodes or semiconductor nanomaterials replacing metal electrodes.

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Availability of data and material

The datasets used or analyzed during the current study are available from the corresponding author upon reasonable request.

Authors' contributions

All authors contributed to the study's conception and design. Material preparation, data collection, and analysis were performed by Mu Yuan, Chen Li, and Qingdao Xu. The first draft of the manuscript was written by Mu Yuan and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript

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