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REVIEW ARTICLE

Diagnosis, Bacterial Density, Food, and Agricultural Applications of Magnetoelastic Biosensors: Theory, Instrumentation, and Progress

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Abstract

Magnetoelastic biosensors have emerged as a promising technology for the sensitive and label-free detection of a wide range of biological analytes. These biosensors use the magnetoelastic effect, which describes how the mechanical properties of magnetostrictive materials change in response to a magnetic field. This effect is utilized to detect biological analytes by immobilizing specific recognition elements, such as antibodies or nucleic acids, on the magnetoelastic material's surface. The binding of target analytes to the recognition elements induces a mass change, leading to a shift in the resonance frequency of the magnetoelastic material. Magnetoelastic biosensors find applications across various fields, including medical diagnostics, environmental monitoring, and food safety. In medical diagnostics, they offer rapid and sensitive capabilities for detecting pathogens, biomarkers, and toxins. For environmental monitoring, they demonstrate the ability to detect pollutants and heavy metals. Furthermore, in ensuring food safety and quality, magnetoelastic biosensors detect allergens, pathogens, and contaminants effectively. Ongoing research and technological advancements suggest that these biosensors hold great potential for revolutionizing various fields, including healthcare, environmental monitoring, and food safety, contributing to improved disease diagnosis, environmental protection, and public health. This review article provides an overview of the principles, fabrication methods, diagnosis, bacterial density, food, and agricultural applications of magnetoelastic biosensors.

Keywords Magnetoelastic biosensor · Magnetic field · Food safety · Medical diagnosis · Pathogen detection

1 Introduction

A biosensor is a device designed to detect and measure biological or biochemical substances or processes [1]. Typically, it comprises a biological sensing element—such as an enzyme, antibody, or nucleic acid—that specifically interacts with a target analyte, and a transducer that converts this biological interaction into an electrical or optical signal [1–4]. The transducer can be made of different materials, including metals, semiconductors, or polymers, and its design depends on the type of biosensor being used. Among these materials, polymers or their composites hold the most important place, especially in biological applications.

Statement of Significance This review thoroughly analyzes the progress and uses of magnetoelastic biosensors in various fields like disease diagnosis, environmental monitoring, and ensuring food safety. These sensors use the magnetostrictive phenomenon for the label-free and sensitive identification of biological analytes, offering a new approach to detection and monitoring techniques. The review aims to explain how magnetoelastic biosensors work, particularly their ability to detect without labels by noticing shifts in resonance frequency due to mass changes on their surface. It evaluates their use in medical diagnostics for the quick and precise identification of pathogens, biomarkers, and toxins, which aids in better disease management. It also looks into their role in environmental monitoring by detecting pollutants and heavy metals, thus protecting environmental health and public safety. Furthermore, the study explores their effectiveness in food safety by identifying contaminants, pathogens, and allergens in food. It discusses the challenges and future possibilities in enhancing the sensitivity, specificity, and usability of magnetoelastic biosensors for wider application across different areas.

The methodology of this review includes a detailed literature search and analysis. It involves systematically collecting relevant publications using specific keywords; screening these publications based on set criteria; extracting important data on sensor design, operational principles and application areas; and then analyzing this data to identify developments, gaps, and innovations. This review aims to offer a detailed perspective on the current state and future prospects of magnetoelastic biosensors, highlighting their importance in improving public health, environmental protection, and food safety.

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Polymer-based sensors have become invaluable in modern sensor technology due to the crucial role they play. These sensors are distinguished by their diversity, low cost, easy processability, and functionalization capabilities. Polymers, divided into two main categories—natural and synthetic—offer unique properties and application areas. Natural polymers are known for being environmentally friendly and biocompatible, while synthetic polymers stand out with their customizable structures and wide application ranges. Among natural polymers, cellulose, chitin, and chitosan are commonly used in sensor applications due to their water absorption and biological compatibility properties. These polymers play a significant role in developing biosensors for environmental monitoring, food safety, and health tracking. Synthetic polymers, on the other hand, have a broad range of uses due to their ability to be tailored for specific features like biocompatibility, thermal, and chemical resistance. Polymers such as polyacrylonitrile and polyvinyl chloride actively participate in sensors designed to detect and analyze specific molecules. The diversity of polymers in sensors makes them ideal for detecting various analytes. They can be customized to selectively recognize and bind ions, molecules, or cells. Moreover, polymers facilitate the development of sensors that offer high selectivity and sensitivity towards specific target molecules through techniques such as molecular imprinting. This feature enables polymers to serve as synthetic receptors, substituting for biomolecules like natural receptors. For instance, the integration of polymers such as poly(o-phenylenediamine) and its nanocomposites in electrochemical sensors through solid-state oxidative polymerization method has been instrumental in enhancing electrocatalytic activities for applications including hydrazine and hydrogen peroxide detection in trace level gases [5]. Similarly, the use of polyaniline composites for non-enzymatic glucose sensing shows the potential of conducting polymer composites in biosensor applications, where the synergy between conducting polymers and metal oxides improves electrical conductivity, catalytic properties, and chemical stability [6]. Moreover, the role of polymers extends to the development of breath analyzers for non-invasive disease diagnosis, highlighting the capacity of nanomaterial-polymer composites to detect metabolic process-related gases, thereby offering a promising route towards revolutionizing personalized medicine and home care diagnostics through non-invasive means [7]. Consequently, these advancements highlight the major role of polymers and their composites in biosensors, demonstrating their essential contribution to the development of innovative sensing technologies. Polymer-based sensors emerge as revolutionary, cost-effective, and versatile solutions for analyte detection and analysis across various biomedical, food, and environmental applications, positioning them at the forefront of future sensor technology advancements [8].

Biosensors exhibit a broad range of applications across various fields including medical diagnosis, environmental monitoring, and food safety assessment [3, 9]. These devices are capable of identifying specific biomarkers present in bodily fluids, detecting hazardous substances in food products or aquatic systems, and continuously observing environmental pollutants. Their functionality and adaptability make them invaluable tools in advancing public health, safety, and environmental protection efforts [1–4, 9, 10].

There are several types of biosensors, each with its own sensing mechanism and application. Here are some common types of biosensors:

- Optical biosensors: These biosensors rely on the detection of light, such as fluorescence or surface plasmon resonance, to detect the interaction between the biological molecule and the sensing surface [11, 12].
- Electrochemical biosensors: These biosensors use an electrochemical signal, such as current, voltage, or impedance, to detect the binding of the biological molecule to the sensing surface [13, 14].
- Piezoelectric biosensors: These biosensors use a piezoelectric material, such as quartz crystal microbalance, to measure the mass change of the sensing surface due to the binding of the biological molecule [15, 16].
- Thermal biosensors: These biosensors measure the temperature change caused by the binding of the biological molecule to the sensing surface [17].
- Magnetic biosensors: These biosensors use the magnetic properties of a material, such as a magnetoelastic sensor (MES), to detect the binding of the biological molecule to the sensing surface [18–20].
- Mass spectrometry–based biosensors: These biosensors use mass spectrometry to detect and identify the biological molecule in the sample [21].

Each biosensor category exhibits specific advantages and constraints, and the selection of a suitable biosensor is predicated on the application's unique requirements and the properties of the biological molecule.

Among these, magnetoelastic sensors (MESs) have been widely utilized across physical, chemical, biological, and medical platforms, highlighting their role as an interdisciplinary subject of study [22–26]. When comparing different biosensor methods to MESs, each technology has its unique strengths and challenges. PCR is highly sensitive, ideal for detecting low concentrations of DNA, surpassing MES in specialized applications. However, its operational complexity and need for sophisticated instruments may

favor the simplicity and portability of MES. Quartz crystal microbalance (QCM) offers excellent sensitivity and online tracking but struggles with nonspecific bias and complex data processing. MES might offer a more straightforward approach to sensing with simpler signal processing. Optical biosensors are rapid, sensitive, and specific, competitive with MES in critical applications. Still, their operational complexity and reliance on advanced instruments could make MES more accessible and user-friendly. Electrochemical sensors are noted for their rapid, sensitive detection and label-free operation. Despite this, their challenges with repeatability and stability might make MES a more reliable choice in some applications, thanks to its robustness and simplicity. Overall, while each biosensor method has distinct advantages, MES's versatility and potential for integration and simplification might provide broader applications, addressing some of the limitations inherent in PCR, QCM, optical, and electrochemical techniques [27].

This review is dedicated to enhancing awareness about MESs, which are increasingly being incorporated into biosensor applications. MESs are a type of physical sensor that measures changes in the magnetic properties of a material as a result of mechanical stress or applied magnetic field. The principle of operation of these sensors is based on the magnetostriction effect, which refers to the phenomenon of a magnetic material changing its dimensions when subjected to an external magnetic field [22, 23]. MESs typically consist of a thin strip or wire made of magnetostrictive material, such as nickel or iron that is excited with a magnetic field. When a magnetic field is applied to the sensor, or when there is a mass change due to the binding of different materials, the magnetic properties of the sensor material change, causing a change in the amplitude and frequency of the magnetic response. These changes can be detected and measured using a pickup coil or other magnetic sensing element [26, 28–30]. MESs have been used in a variety of applications, including pressure [31–33], humidity [33–35], temperature [36, 37], liquid viscosity-density [38–41], chemical gases [42–44], and pH [45–47]. They present numerous advantages over other types of sensors. Overall, MESs offer a simple, disposable, cost-effective, and highly sensitive approach to measuring mechanical stress, magnetic field and the mass change of the sensing surface due to the binding of the biological molecule [22–26]. They are also highly reliable, as they do not have any moving parts and are not subject to wear and tear. Additionally, MESs are relatively inexpensive and can be easily mass-produced. Given their wide range of applications, they are likely to continue to play an important role in a variety of fields. Furthermore, they require neither complex electronics nor power sources for operation, allowing for easy integration into diverse systems [26, 28–30].

2 Working Principles of MESs

To monitor the resonance spectra of a MES, various techniques are utilized, including optical, acoustic, and magnetic methods. However, this article will primarily concentrate on the magnetic technique. By focusing on this approach, we aim to offer a detailed insight into its utility for monitoring resonance characteristics. The longitudinal vibrations of the sensor can provide information on its resonance frequency and vibration amplitude.

Magnetoelastic materials in free state begin to vibrate (shorten and elongate) when exposed to a time-varying (AC) magnetic field. The vibration frequency of these samples varies based on their geometry, elastic modulus, and either density or mass. Amorphous ferromagnetic ribbons or sensors generate longitudinal vibrations and elastic waves when they are exposed to a time-varying magnetic field [26]. Elastic waves generated within magnetoelastic materials induce a magnetic flux that is detectable from a certain distance away. A sensing coil can capture this flux, providing valuable insights into the sensor's vibration patterns as illustrated in Fig. 1. The longitudinal vibrations of the ribbon-like thick film sensor are primarily influenced by its length (L), elasticity (E), and density (ρ). By analyzing the frequency and amplitude of these vibrations, we can assess the sensor's performance and identify any changes or anomalies. Therefore, understanding the factors that affect the longitudinal vibrations is crucial for effective sensor monitoring and fundamental resonance frequency of the thin strip material:

$$f = \sqrt{\frac{E}{\rho\left(1-\sigma^2\right)}}\frac{\pi}{L} \tag{1}$$

where σ is Poisson's ratio, ρ is the density of the sensor material. In its fundamental resonant mode, the resonator exhibits the greatest dimensional change, resulting in the emission of the highest magnetic flux compared to all other resonant modes. As a result, the fundamental resonant frequency is typically utilized as the output signal for actuation and measurement in practical applications. When a small mass is loaded on the sensor surface, it causes a change in the density of the sensor and hence the resonance frequency according to Eq. (1). A magnetoelastic sensor initially resonating at frequency f_o with mass m_o experiences a decrease in resonance frequency Δf when subjected to a mass loading of Δm, as described in [26, 28–30]. The magnetoelastic sensor system is therefore also referred to as a microbalance.

$$\Delta f = -f_0\frac{\Delta m}{2m_0} \tag{2}$$

Further, when immersed in a viscous liquid, the magnetoelastic sensor surface experiences a dissipative shear force,

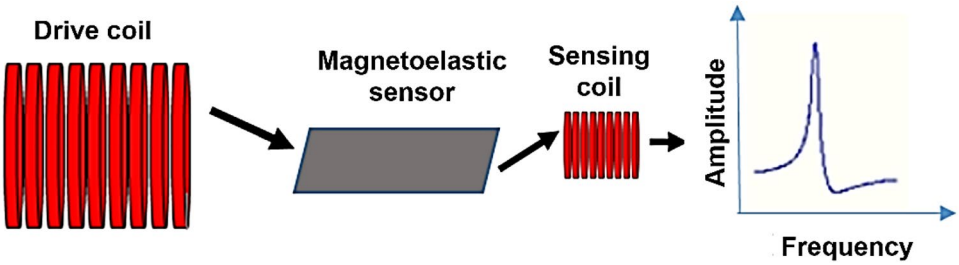

Fig. 1 Symbolic representation of the basic operating principle of the magnetoelastic sensor

which reduces the frequency and amplitude of vibrations [26, 28–30]. This damping effect can be significant and is important to consider when designing and operating sensors. The shift in resonance frequency Δf is related to the viscosity η and density ρ_l of the surrounding medium as follows:

$$\Delta f = \frac{\sqrt{\pi f_0}}{2\pi\rho d}\sqrt{\eta\rho_l} \tag{3}$$

Here, d is the thickness of the magnetoelastic sensor. Magnetoelastic materials demonstrate magnetostrictive behavior, meaning they exhibit expansion or contraction on the order of 10^{-5}–10^{-6} in size when exposed to an external magnetic field. Magnetoleastic sensors typically use magnetic materials with high magnetostriction values. Amorphous ferromagnetic materials, commonly found in wire or strip form, are the most commonly used materials for these sensors. In particular, 2826 MB ($Fe_{40}Ni_{38}Mo_4B_{18}$) amorphous ferromagnetic strips are commonly utilized as MESs, owing to their high magnetomechanical coupling factor, k, and low magnetic damping. This combination of properties makes them ideal for use in sensors that require high sensitivity and low noise. The typical parameters for a 2826 MB ribbon are shown in Table 1.

3 Magnetoelastic Measurement Systems

This section introduces two distinct systems we have employed for resonance measurement. The initial approach utilizes an impedance analyzer, illustrated schematically in Fig. 2. In this system, the vibration frequency of the sample is measured by the impedance analyzer. The sample is placed in a sensing coil, and the two ends of the coil are connected to the analyzer, which measures the impedance value of the coil. The resonance frequency of the magnetoelastic sensor is identified by the peak value of the impedance. Typically, we use small-length strips of samples ranging in size from 0.1 to 10 mm. The system scans the desired frequency range with a specific frequency step and measures the impedance value of the coil at each frequency value, using the software we developed. Additionally, the system is capable of measuring resonance frequencies under varying magnetic field strengths by applying an external DC magnetic field to the sensor using Helmholtz coils and a power supply. In certain applications, however, a DC bias field is generated through the use of a magnet rather than a Helmholtz coil. The measurement time takes approximately 2 s. However, when the impedance analyzer parameters (such as sweep time, number of data, and averaging) are changed to obtain more precise measurements, the time is increased up to 5 s. The Hewlett-Packard HP4294 and its connected HP4294A probe are used as the impedance analyzer. The main problem of the measurements made using the impedance analyzer was observed as a long loop time. It is also possible that a network analyzer can be utilized as an alternative to the impedance analyzer in Fig. 2. We use different sizes of detection coils based on the size of the magnetoelastic sensor, for example, a detection coil with a length of 10 mm, a diameter of 5 mm, and a number of turns of 100 are used for the 6 × 1 mm sample. The second method employs a lock-in amplifier or a nano voltmeter and will be explained in the following section.

Figure 3A_1, A_2, and A_3 provides both a graphical representation and an image of the 2nd magnetoelastic resonance measurement system. Figure 3B shows how the sample is placed on the sensing coil. In general, the system is more convenient for longer samples. The sensor can vibrate freely without the use of any holders. A 10A/m AC magnetic field, applied longitudinally along the strip by the driver coil, induces longitudinal vibrations and generates small voltages in the pickup coil. A Stanford 345

Table 1 Magnetic properties of Metglas 2826 MB strips [48]

Saturation magnetization	**0.88 T**
Susceptibility max	800,000
Saturation magnetostriction	12 ppm
Magnetostriction	12 ppm
Elastic modulus	100*110 GPa
Magnetomechanical coupling coefficients	0.98
Electrical resistance	138 μΩ.cm
Curie temperature	353 °C
Crystallization temperature	410 °C
Continuous maximum operating temperature	125 °C

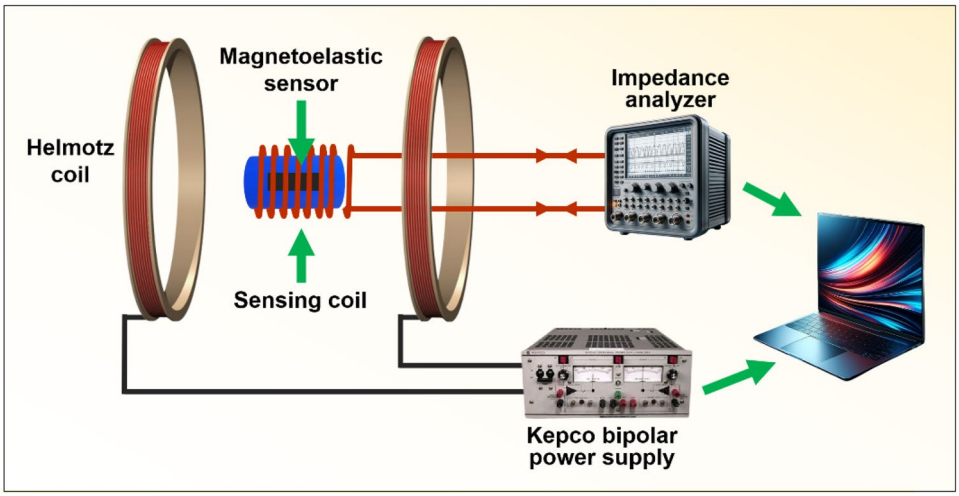

Fig. 2 Magnetoelastic resonance measurement system using an impedance analyzer

AC function generator is used to generate the AC magnetic field, from which the signal is amplified using an Accel TS200 amplifier. The sensing (or collector) coil is placed perpendicular to the direction of the AC magnetic field. Furthermore, the signal generated in the coil in the absence of the sensor is recorded by software, and during measurements with the sample, this background signal is subtracted by the software, ensuring that the resulting data represented only the signal from the sample. To avoid interference, it is ensured that the natural resonance frequency of the coil and the sample's vibrational resonance frequencies are significantly different. For instance, for a sample measuring 40×5 mm with a resonance frequency range of 50–60 kHz, the coil's resonance frequency is chosen to be above 120–150 kHz. The entire system is computer-controlled. External AC and DC magnetic fields are generated using Helmholtz coils. The software systematically scanned the frequency of the signal generator, and at each frequency value, the amplitude of the induced signal was measured using a nano voltmeter connected to the sensing coil. Here, a lock-in amplifier could be used in place of the nano voltmeter. The resonance frequency of the sensor is determined by identifying the frequency at which the amplitude of vibration reaches its maximum for each magnetic field value. As illustrated in the measurement system screenshot (Fig. 3B), the resonance curve appears in the light blue section. In the lower right graphs, one graph records the resonance frequency as a function of the magnetic field, while the other captures the signal amplitude in the resonance value as a function of the magnetic field. Furthermore, the program allows for adjustments to the frequency scanning range, frequency scanning step size, and the intensity of the applied AC magnetic field. A key feature of this system is its capability for rapid data acquisition, enabled by operating the nano voltmeter in its fast mode.

In long-term measurements under a constant magnetic field, it is observed that the resonance frequency remains constant and the system is stable. However, the frequency step size is identified as a critical factor; lower frequency steps resulted in reduced interference. For example, if the scanning frequency is 30 Hz, the system measures the resonance frequency with an error of ± 30 Hz, or if the scanning frequency step is 0.1 Hz, the system measures the resonance frequency with an error of ± 0.1 Hz. Naturally, while a smaller step size reduces measurement error, it also prolongs the measurement duration.

Some systems measure the MES resonance value in different approaches, for example, Zeng et al. [47] developed a microcontroller-based system to achieve a functional and practical magnetoelastic sensor that meets the requirements of compact design, portability, ease of operation, and high signal-to-noise ratio. In addition to these, some studies design the coil system differently for practical applications [51].

Figure 3C illustrates the resonance curves of an MES with dimensions of 7 mm in width and 30 mm in length for different magnetic field values. The resonance frequency measurements are conducted at four magnetic field values, covering the entire range of magnetic field change. The first and second curves represent low magnetic field values of $H = 200$ A/m and 550 A/m, respectively, and a maximum amplitude change is observed at 550 A/m. The third and fourth curves are taken at high magnetic field values of $H = 750$ A/m and 1000 A/m, respectively. The influence of the magnetic field on the resonance frequency value and shape of the resonance curve is quite significant. Figure 3D displays the resonance frequency and vibration amplitude variation as a function of the magnetic field.

Generally, amorphous strips are shaped into the desired dimensions using either laser cutting or a micro dicing-saw system. However, mechanical dicing-saw cutting can

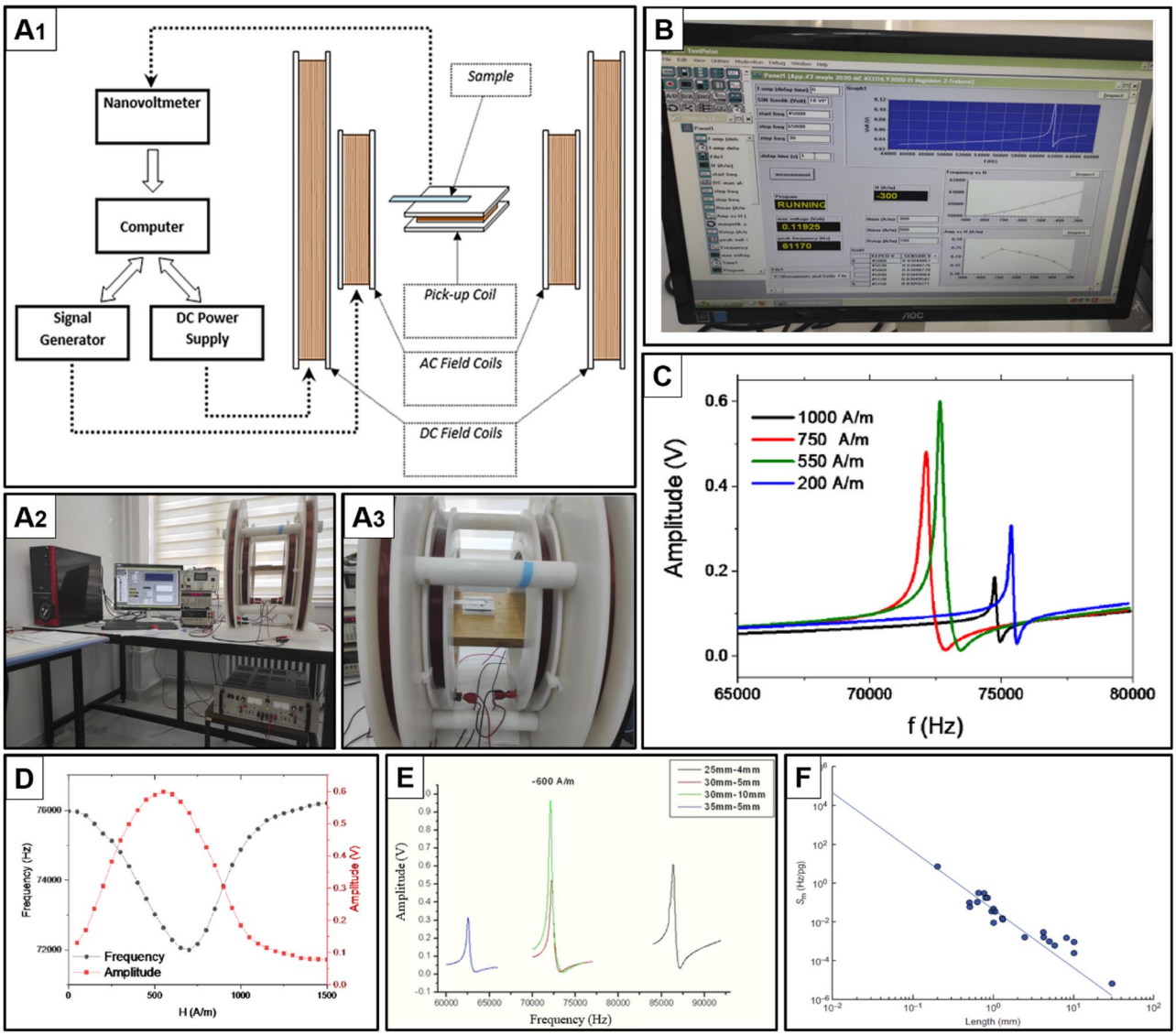

Fig. 3 **A** Graphical representation (A_1) and image (A_2 and A_3) of magnetoelastic resonance measurement system using nano voltmeter. **B** Display of the output of the magnetoelastic measurement system on the computer screen. **C** Magnetoelastic resonance curve of 2826 MB ribbon (reproduced from [49]). **D** Variation of magnetoelastic resonance frequency values and resonance amplitude with applied DC magnetic field (reproduced from [49]). **E** Magnetoelastic resonance curves of 2826 MB ribbon with different lengths. **F**Mass sensitivity of the Fe-B alloy ME film sensor in air (reproduced from[50].)

introduce dimensional inaccuracies and edge defects; it is only possible to prepare MESs up to a certain size. Therefore, the photolithography method is used to produce an MES with a length of around 100 μm. Moreover, the production cost for a single micro-ME resonator is remarkably low, costing less than one-thousandth of a cent [50].

As seen in Eq. (1), the resonant frequency of the sample depends on the length of the sample. Figure 3E presents resonance curves for 2826 MB samples cut into various sizes using a dicing saw. It is observed that a decrease in sample length results in an increase in resonant frequency, with these measurements taken under a 600 A/m DC bias magnetic field. For samples of identical length but differing widths, the resonant frequency remains approximately the same, although the resonant frequency increases for the sample with greater thickness.

The length of the sensor sample is a critical parameter in the design of MESs. For example, the resonance frequency of a 50-mm-long amorphous ferromagnetic ribbon is about 50 kHz, but reducing its length to 5 mm increases the resonance frequency to nearly 1 MHz. This indicates that the measurement accuracy of Δm is increased by approximately 20 times, according to Eq. (2). Moreover, the mass of an amorphous ribbon measuring 50 mm in length, 5 mm

in width, and 25 μm in thickness is approximately 0.04 g. Reducing the dimensions to 5 mm by 200 μm by 5 μm lowers its mass to about 9×10^{-5} g. Thus, by decreasing the sample dimensions, we can obtain a measurement accuracy of Δm that is increased by approximately 440 times. In short, by reducing the sample dimensions, we can achieve the opportunity to measure the accumulated mass on the sensor (the amount of matter to be detected) approximately 8800 times more accurately. In research by Li et al. on a Fe-B alloy film magnetoelastic sensor, it was found that a 5-mm-long sensor was about 100 times more sensitive than one measuring 0.5 mm in length, across different sensor sizes [50]. In Fig. 3F, the mass sensitivity obtained by depositing controlled amounts of gold on the MES surface and measuring the resonance frequency is shown. The length of the MES ranges from 200 μm to 30 mm. Notably, the 200 μm MES exhibited a sensitivity of around 7 Hz/pg, proving its efficacy in detecting mass changes in the picogram range [50].

4 Detection Process of ME Biosensors

The essential process for creating MESs from a roll of amorphous ferromagnetic ribbon is depicted in Fig. 4. Initially, as mentioned earlier, to fabricate the rectangular MES, a precision, computer-controlled micro dicing-saw system is employed to cut them from the ribbon. After being cut, the sensors undergo ultrasonic cleaning in acetone and alcohol for 10 to 20 min to remove any residual dirt or grease. Subsequently, a chromium layer is applied to all sides of the resonators through sputtering, followed by a layer of gold. The chromium layer serves to enhance the adhesion of the gold film to the substrate, while the gold layer enhances the sensor's corrosion resistance and creates a suitable surface for creates a suitable surface for receptor elements. Generally, antibodies or phage elements serve as receptors. After the appropriate receptor, or in other words, a biomolecular recognition element is fixed onto the surface of the MES, species can sent to the environment to be detected. As a result, the receptor can attach to the targeted species. This leads to a change in the sensor mass and consequently a decrease in the resonance frequency of MES.

Two methods are commonly used to introduce targeted species into the sensor environment for detection. The first and most prevalent method involves two main steps. Initially, the MES is enclosed within a closed container, and following this, a pump is used to introduce the targeted species in solution to the sensor's environment. Subsequently, any change in the sensor's resonance frequency is measured. The second method involves using a micropipette to directly drop the targeted species in solution onto the MES, and then measuring the change in resonance frequency. Regardless of the method used, a reference measurement is typically necessary, which involves measuring and comparing the

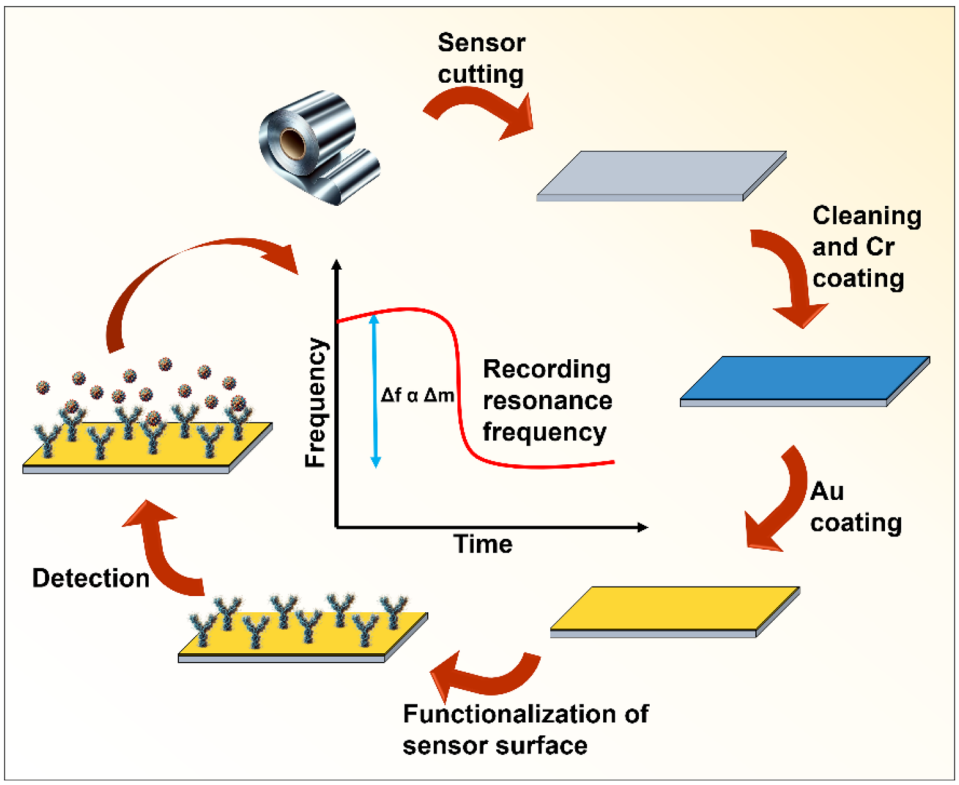

Fig. 4 Steps in the manufacturing and detection process of the magnetoelastic sensor

response of the MES with and without the targeted species present in the solution.

5 Applications of Magnetoelastic Sensors

MESs are increasingly gaining attention for their versatile applications across various fields, as illustrated in Fig. 5. In the medical field, they play an important role in the early diagnosis of various diseases, determination of hospital infections, and tissue healing applications [52, 53]. They are also used in the food and agriculture industry to monitor environmental conditions and measure bacterial density to ensure food safety [50]. Owing to their wireless, battery-free design and the capability for specialized coatings to enhance sensing, MESs are emerging as a versatile and transformative technology in diagnostics, monitoring, and beyond.

5.1 Measuring Bacterial Density

The need for fast and accurate ways to measure bacteria is increasing, especially in the fields of health and food safety. MESs are attracting more and more attention day by day, thanks to the fact that they do not need batteries, are wireless and are very sensitive. This section will discuss how MES is used to quantify bacteria in environments ranging from hospitals to food production lines.

Maintaining human health and quality of life requires healthy eating habits and the safety of the foods we consume. However, despite growing public awareness of healthy eating habits, the incidence of foodborne diseases is rising with increased consumption of fresh fruits and vegetables. The infectious bacteria that cause *Escherichia coli O157:H7*, *Campylobacter jejuni*, *Listeria monocytogenes*, *Shigella* spp., *Bacillus anthracis*, *Tuberculosis*, *Staphylococcus aureus*, and *Salmonella spp*. infection cases are the most significant threats originating from fresh vegetables and fruits. Like many of these infectious agents, it is known that *Salmonella*, among others, can be transmitted to humans through fresh products such as tomatoes, seed sprouts, cantaloupe, apple juice, eggs, orange juice, and spinach. Given that contamination can occur at any stage—production, packaging, transportation, or storage—developing fast, accurate, specific, and inexpensive detection technologies to identify contaminated products is crucial [54–59]. Accordingly, ME biosensors are among the most widely used methods, offering a real-time, label-free, and sensitive approach. Bacterial detection studies are based on the measurement of ME biosensors by providing surface modification with various phages, proteins, enzymes, and antibodies. It is estimated that the weight of a bacterial cell is approximately 2 pg. As indicated in Table 2, an ME biosensor shorter than 50 μm could, in theory, detect the mass of a single bacterial cell [50].

For magnetoelastic biosensors used to measure bacterial density, the detection methodology for a specific pathogen involves a biomolecular recognition element layer immobilized on the sensor platform. Upon contact with the target pathogen, the biomolecular recognition elements initiate a binding process that increases the magnetoelastic biosensor's mass and subsequently decreases its resonance frequency, as shown in Fig. 6. There are many studies on this subject in the literature.

Wang et al. [60] designed a phage-based ME biosensor functionalized with the E2 phage which exhibits a high binding affinity to *Salmonella* and used to detect the presence of *Salmonella* spp. on contaminated spinach leaves. The ME biosensor surface was also modified to minimize nonspecific binding, such as with bovine serum albumin, casein, and superblock, and to reduce interference effects. Before measurement, the ME biosensors were treated with spinach homogenate for 30 min to allow interaction between the sensor surface and the bacteria in the environment. Measurements were then taken, and the presence of bacteria was detected by changes in resonance frequency. In another study, Hiremath et al. [61] designed a liquid phage-functionalized ME biosensor that allows for the specific measurement of a single bacterium in a mixture of different bacteria. The study investigated the interaction of a specific binding of ME biosensor with *Escherichia coli* O157:H7 (EO), *Listeria monocytogenes* (LM), *Salmonella typhimurium* (ST), *Vibrio parahaemolyticus*, *Yersinia enterocolitica*, and methicillin-resistant *Staphylococcus aureus* (MRSA). The results showed that MRSA could be detected at much lower concentrations compared to the other bacteria. The resonance frequency shift varied depending on the MRSA concentration. The study showed that lytic phages could bind specifically and selectively to MRSA, even in the presence of other competing bacteria. Chin et al. [62] aimed to attach ST to the surface of a wireless ME biosensor. The phage-coated ME biosensors were treated with low-concentration ST suspension to capture approximately 300 cells on the sensor surface.

Liu et al. [63] developed an ME biosensor coated with E2 phage and applied it on polyethylene cutting boards at low and high concentrations of ST (1.5×10^6 CFU/mm^3–1.5×10^6 CFU/mm^2) using a high-sensitivity surface scanning system. They detected the presence of bacteria through the change in resonance frequency in their measurements. Li et al. [64] conducted a study where they detected a decrease in resonance frequency in ME biosensor measurements due to the increase in mass caused by contact with pathogenic bacteria, and they recorded a detection limit of 10^2 CFU/cm^2. Liu et al. [65] observed resonance frequency shifts of approximately 9 kHz and 6 kHz using the

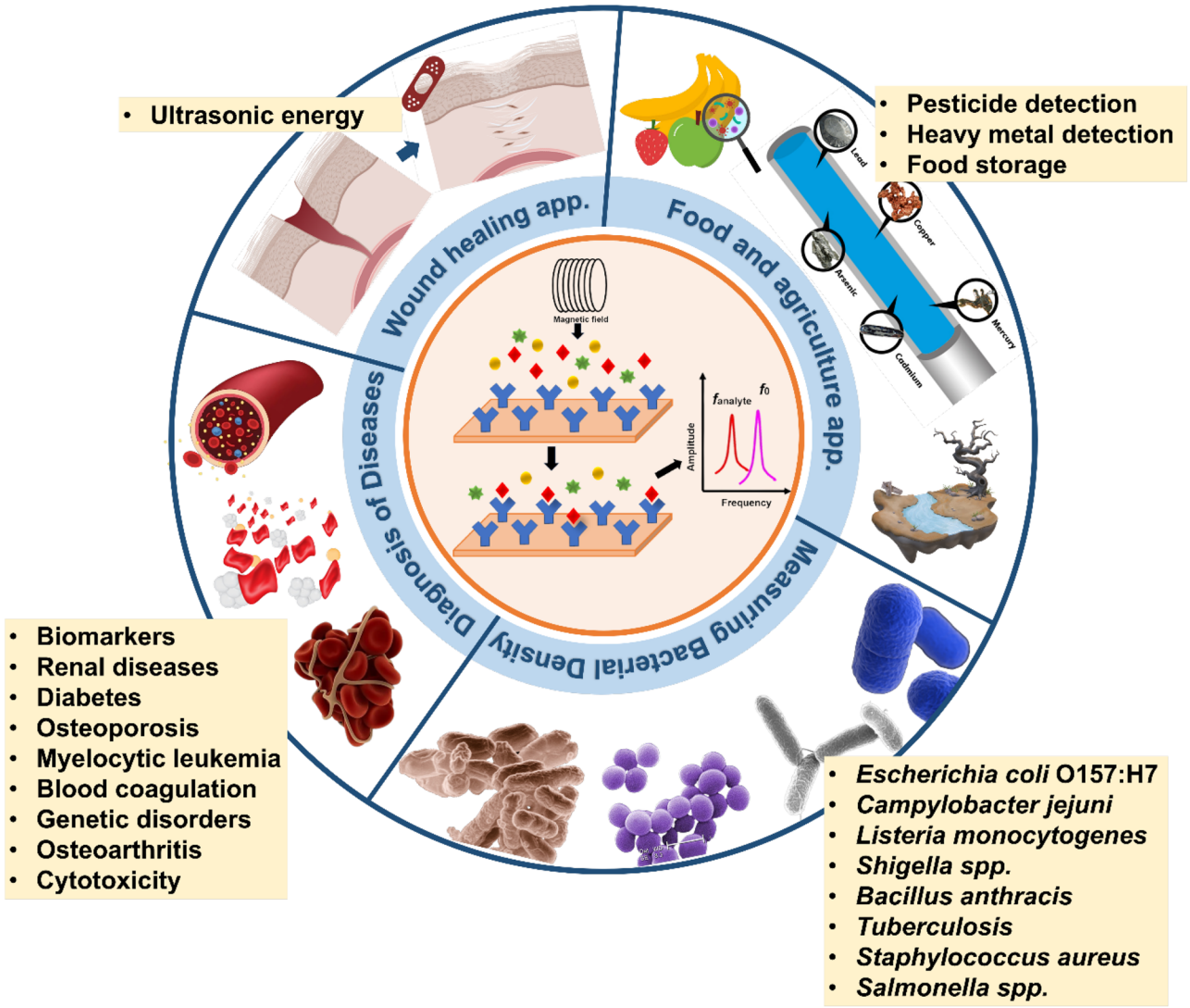

Fig. 5 Biomedical, agricultural, and food applications of MESs

E2 phage-modified ME biosensor on plastic food plates for ST detection. This demonstrates that ME biosensors enable high-sensitivity measurements at low concentrations. Chai et al. [66] recorded a detection limit (LOD) of statistically less than 1.5×10^3 CFU/mm^2 in measurements made with the ME biosensor they developed for on-site detection of ST on food surfaces. Park et al. [67] inoculated ST on tomato surfaces suitable for environmental conditions for ST detection. After 24 h of incubation at 37 °C and 100% relative humidity, bacterial populations increased from 3.0 and 5.0 log CFU/cm^2 to 6.1 and 7.8 log CFU/cm^2, respectively. After these growths, they placed measurement sensors with and without immobilized E2 phages on the bacteria-inoculated tomato surfaces to measure frequency changes. SEM images confirmed that these changes in sensor resonance frequency were due to the binding of ST to the E2 phage. Park et al. [68] investigated the effect of different surface morphologies based on E2 phages for ST detection with an ME biosensor. A vaccination system was used to observe the surface morphologies of tomatoes and spinach and for bacterial

Table 2 ME biosensor measurement accuracy in different sizes [50]

Sensor dimensions	Frequency shift (Δf) (Hz)	Number of cells
2.0×0.4×0.015 mm	117	10,000
1.0×0.2×0.015 mm	94	1000
500×100×4 μm	1279	500
200×40×4 μm	4260	100
100×20×4 μm	3363	10
50×10×4 μm	2727	1

cells to adhere to the surfaces. As the concentration of ST on these surfaces increased, the detection limit of the ME biosensor was determined to be 1.87 log CFU/cm^2 for tomatoes, 1.72 log CFU/cm^2 for spinach, and 2.16 log CFU/cm^2 for the outer surface of spinach [68]. In their study, Park and colleagues [69] measured resonance frequency shifts on the surface of tomatoes for 15 and 30 min and determined it to be 3439 ± 185 and 5312 ± 248 Hz, respectively. In another study on tomato surfaces, Park and colleagues [70] recorded the detection limit as 1.78 ± 0.17 log CFU/cm^2 and 922.7 Hz. In their work on E2 phage-based ME biosensors, Park and colleagues [71] investigated the impact of temperature on resonance frequency by conducting experiments at various temperatures, including 20, 25, 30, 35, 40, 45, and 50 °C. The largest resonance frequency shift was observed at 35 °C, with a value of 5663 ± 554 Hz, and the smallest was at 20 °C, with a value of 1811 ± 432 Hz. Chai and colleagues [72] developed an E2 phage-based ME biosensor to detect of ST in eggshells. In multiple measurements, the concentration range of ST was determined to be 5×10^6–5×10^8 CFU/ml. The frequency shift on the ME biosensor surface was recorded as 820 Hz for control sensors and 5900 Hz for measurement sensors [72]. Horikawa and colleagues [73] developed an ME biosensor coated with filamentous fd-tet phage specifically for *Salmonella* detection. The study screened for *Salmonella* concentrations ranging from 0 to 5×10^8 cells/ml on spinach leaves, and a decrease in resonance frequency was observed based on the mass increase. Shen et al. [74] worked with ME biosensors developed for *Salmonella* analysis in fresh foods, operating within a concentration range of 5×10^2–5×10^8 CFU/ml, with a recorded shift in resonance frequency of approximately 3000 Hz. Li et al. [75], in their study, recorded resonance frequency shifts of 275 Hz at 5×10^8 CFU/ml, 3.075 kHz at 5×10^6 CFU/ml, and 6.325 kHz at 5×10^8 CFU/ml in measurements taken within a concentration range of 5×101–5×10^8 CFU/ml using control sensors. Shen et al. [76] developed a pulsed biosensor capable of simultaneous detection in a magnetic field. In the study, a *Salmonella* concentration of 5×10^5 CFU/ml was determined, and resonance frequency shifts were recorded in measurements taken on three different sensor surfaces, with recorded shifts of 2.353 kHz, 0.753 kHz, and 0.942 kHz, respectively, confirming the presence of bacteria [76]. Lia et al. [77] produced micron-sized ME biosensors and used them for ST detection. The sensor dimensions used in the study were determined to be $500 \times 100 \times 4$ µm, and measurements were taken after coating the sensors with E2 phage. As a result of the measurements taken, a shift in resonance frequency due to an increase in mass was recorded as 150 kHz [77].

Huang et al. [78] developed ME biosensors coated with E2 phage for *Salmonella* detection and JRB7 phage for *B.*

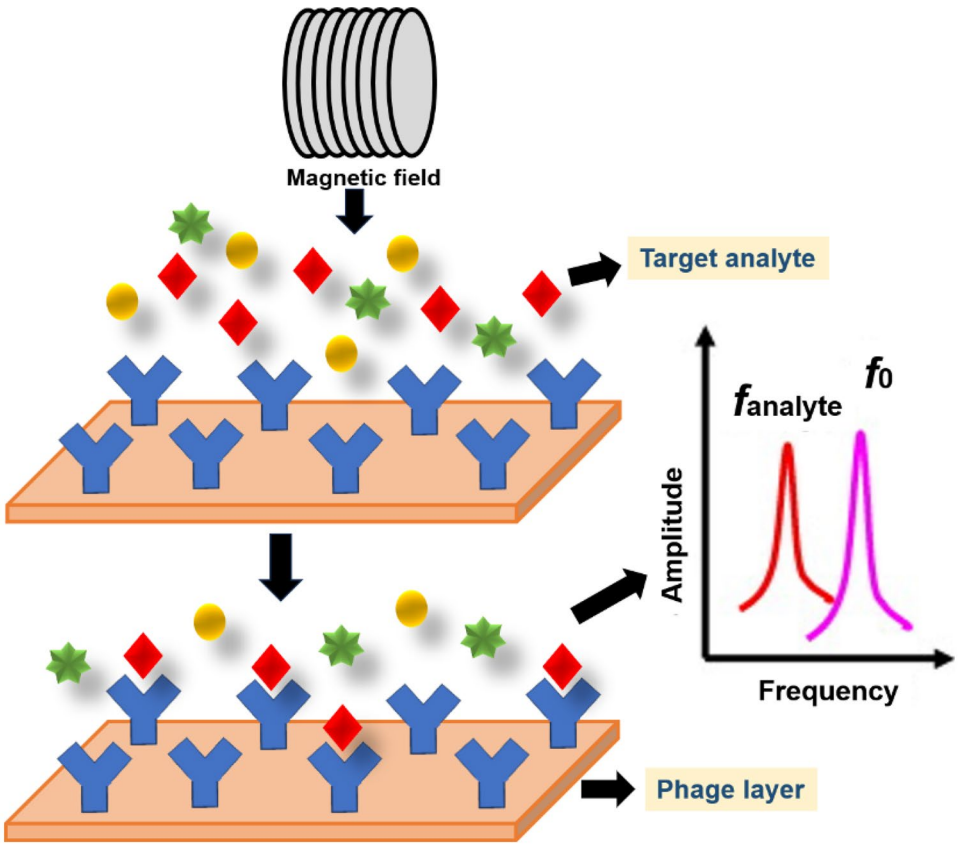

Fig. 6 Mechanism of measuring bacterial density

anthracis spores, enabling simultaneous detection of both bacteria. Bacterial concentrations were identified in the range of 5×10^{1} to 5×10^{8} CFU/ml. Resonance frequency shifts of 1250 Hz for E2 phage and 1123 Hz for JRB7 phage indicated the presence of the bacteria [78]. Lakshmanan et al. [79] performed measurements on ST bacteria in the concentration range of 5×10^{1} to 5×10^{8} CFU/ml. They used ME biosensors with lengths of 2 mm and 1 mm. The 2-mm sensors showed a sensitivity of 159 Hz/decade, which increased approximately fivefold to 770 Hz/decade in the 1-mm sensors [79]. When they performed the same study for Salmonella detection in skim milk samples, they recorded measurement sensitivities in the range of 159–188 Hz/decade [80]. Guntupalli et al. [81] detected ST sensitively by working with different concentrations of the bacterium (5×10^{1}–5×10^{8} CFU/ml) in a mixed microbial population (*E.coli* and *Listeria monocytogenes*). They used Langmuir–Blodgett (LB) monolayer technique and rectangular strip (2 mm × 0.4 mm × 0.015 μm) ME biosensor in this study. Consequently, the detection limit was found to be 5×10^{3} CFU/ml, with a measurement sensitivity of 139 Hz/decade [81].

In their study, Xie et al. [82] developed a micrometer-scale ME biosensor using a pulsed wave stimulation technique to detect *Bacillus Anthracis Sterne* strain spores. The ME biosensor surface was coated with JRB7 phage. Upon contact with the measurement area, an increase in sensor mass and corresponding resonance frequency shifts were observed. Significant differences were observed in concentrations of 5×10^{2} spores/ml and above. In another study, Shen et al. [83] developed a micro-scale ME biosensor coated with JRB7 phage for on-site detection of *Bacillus Anthracis* spores. The spores were used at different concentrations (5×10^{1}–5×10^{8} spores/ml) with a sensor size of 1000 μm × 200 μm × 15 μm and a flow rate of 40 μl/min. A total frequency change of 1.83 kHz was recorded. Huang et al. [84] used multiple phage systems for the detection of various biological pathogens. E2 and JRB7 phages were used for detecting ST and *B. Anthracis* spores, respectively. To prevent nonspecific bindings, the sensor surface was coated with 1 mg/ml BSA (blocking agent). As the cells/spores were bound to the phage-coated sensor surface, the mass increased and the resonance frequency decreased. Consequently, the frequency shift for E2 phage-coated sensor was found to be 1280 Hz, and for JRB7 phage, it was 1120 Hz.

Johnson et al. [85] developed a micro-scale biosensor for detecting *B. anthracis* using magnetic iron-boron alloy particles. They created the biosensor by immobilizing bacteriophage onto a gold-coated surface. The frequency shift was recorded to be 200 kHz. Chen et al. [86] developed an ME biosensor for detecting *B. anthracis* spores by combining a phage imaging technique with a remote detection platform. The sensitivity of the sensor was tested with a detection limit of 10^{3} spores/ml and a frequency shift of 130 Hz per order of magnitude of spore concentration. The frequency shift was recorded to be 426.2 kHz for measurements in air and 423.9 kHz for measurements in a spore solution. Compared to an antibody-based biosensor, the phage-based biosensor exhibited a longer lifespan. Huang et al. [87] developed a phage-based ME biosensor for detecting *Bacillus anthracis* and investigated the effect of salt and phage concentrations on binding sensitivity. They reported that employing a higher concentration of phages did not enhance the binding sensitivity of the sensor. This was attributed to the ME biosensor's performance being directly dependent on phage-antigen interactions. As various studies have demonstrated, phages are prone to self-assemble into bundles, a phenomenon driven by electrostatic interactions. Such bundling leads to a decrease in the availability of protein binding sites, consequently lowering the overall binding affinity on the surface of the biosensor. To prevent this, they checked whether they could change the immobilization level by changing the salt concentration in the phage solution. Using the JRB7 phage, specific to *B. anthracis*, various salt/phage concentration ratios (140, 420, and 840 mM and 10^{10}, 10^{11}, and 10^{2} Vir/ml) were tested. Frequency responses were measured to determine the effect of salt concentration on sensor performance. The optimal distribution of immobilized phages on the sensor surface was achieved with 420 mM salt and a phage concentration of 1×10^{11} Vir/ml. The total frequency shift for measuring *B. anthracis* concentration was recorded to be 1420 Hz. Huang et al. [88] developed an ME biosensor to detect *E. coli* O157:H7 concentrations. The study observed that during the growth and reproduction of *E. coli*, the nutrients in the solution were consumed, which reduced the solution viscosity and changed the resonance frequency of the ME sensor in the environment. Here, the concentrations of *E. coli* were determined to be 2×10^{2}–3×10^{6} cells/ml, and it was observed that gentamicin sulfate injection inhibited the growth of bacteria. Lu et al. [89] developed an ME biosensor for detecting *E. coli* by modifying it with a 1-μm-thick layer of Bayhydrol 110 (a type of aliphatic polyester urethane resin) and a layer of mannose. The results showed that the resonance frequency shift of the sensor with mannose applied in the *E. coli* solution was 240 Hz, while the frequency shift of the sensor without mannose was 80 Hz.

Rahman et al. [90] developed an aptamer-based ME biosensor for the detection of *Staphylococcus aureus*. Here, the sensor surface was modified with an aptamer specific to *S. aureus* to ensure specific and selective binding of bacteria. To form colonies on the sensor surface, *S. aureus* at a concentration of 1×10^{1}–1×10^{11} CFU/ml was treated per milliliter, and the resonance frequency shifts obtained from the measurements showed that pathogenic species could be

specifically detected with high sensitivity. Hinemath et al. [91] developed a liquid phage-modified ME biosensor for the detection of *S. aureus*. The research utilized a range of phage concentrations (from 10^8 to 10^{12} pfu/ml) and different immobilization times (10, 30, 90, 270, 810, and 2430 min) to functionalize the surface of the ME biosensor using liquid phage. BSA was used to prevent gaps between phages. The optimal phage concentration and immobilization time for sensor surface binding were identified as 10^{11} pfu/ml and 30 min, respectively. Concurrently, it was observed that the quantity of *S. aureus* adhered to the sensor surface was recorded to be 1 mg/ml. The detection of *S. aureus* was achieved with high sensitivity, reaching a detection limit of 3.0 log CFU/ml. This sensitivity is approximately 2 log units lower than that of the surface plasmon resonance method.

In their study, Hu et al. [92] developed an ME technology-based biosensor for detecting bacterial contamination in boxed milk. The study focused on the *S. aureus* bacterium and observed that the growth of *S. aureus* spores in milk significantly changed the milk's viscosity. ME biosensor measurements were taken, and the mass of the sensor increased depending on the viscosity of the milk. The shift in resonance frequency was recorded, and the presence of bacteria was detected with high sensitivity. In another study, Pang et al. [93] designed a polyurethane protective film-coated ME biosensor for detecting *Mycobacterium tuberculosis* (M.TB). M.TB was found to consume nutrients in the environment during growth and reproduction, changing the physical properties of the environment (such as viscosity). The biosensor was tested with different concentrations of bacteria, and the measurements showed an increase in sensor mass and a shift in resonance frequency. The resonance frequency shift was detected at 100 Hz for 1×10^4 CFU/ml, 300 Hz for 1×10^6 CFU/ml, and 500 Hz for 1×10^9 CFU/ml. The results showed that the polyurethane film-coated ME biosensors could detect the presence of bacteria at different concentrations with high sensitivity.

Pang et al. [94] developed a polyurethane protective film-coated ME biosensor for the detection of *Pseudomonas aeruginosa* (P. aeru) bacteria. The study observed that the shift in resonance frequency values was dependent on the changes in the liquid culture medium, the consumption of nutrients during bacterial growth and reproduction, and the binding of bacteria to the sensor surface. The measurements were made directly in the concentration range of 10^3–10^8 cells/ml P. aeru, with a noise level of 20 Hz and a detection limit of 10^3 cells/ml. It was noted that the complete coverage of a single cell produced an approximately 300 Hz resonance frequency shift based on a film density of 1 g/ml.

In summary, the exploration of MESs as a method for quantifying bacterial density has shown great promise. Owing to their sensitivity to surface mass changes, these sensors enable real-time, in situ bacterial detection, providing a highly accurate alternative to traditional microbiological assays. Through immobilizing bacteriophages or antibodies on the sensor surface, an interaction occurs with the targeted bacteria, resulting in a detectable frequency shift. This response is measurable and provides quantitative data about the bacterial density. The adaptability of MESs in different environments and the ability to tailor them for a broad range of bacterial species further emphasize their potential for advancing current capabilities in bacterial detection and monitoring. However, it is crucial to optimize sensor coating procedures and the binding conditions to ensure the accuracy and efficiency of bacterial detection. Future research attempts to explore these features promise to enhance the utility and reliability of MESs, establishing them as an invaluable tool in microbiological studies and public health surveillance.

5.2 Diagnosis of Diseases

Accurate and timely diagnosis is critical in many diseases [60, 64, 95]. ME sensors, with their exceptional sensitivity, specificity, and real-time monitoring capabilities, have many advantages over traditional methods such as ELISA, PCR, and fluorescence-based assays in disease diagnosis. By delivering real-time data, ME sensors facilitate the immediate diagnosis or treatment of diseases, including diabetes and certain cancers. Their simplicity, speed, and cost-effectiveness make them an attractive alternative to complex, expensive diagnostic devices. The fact that ME sensors are wireless and portable, their non-invasive or minimally invasive nature, improves and simplifies patient comfort and testing methods. This title will investigate the studies conducted employing ME sensors to analyze biological fluids, examining the sensors' performance, the insights gleaned from these studies, and the prospective applications they may offer [22].

One of the main benefits of ME sensors in disease diagnosis is their ability to be designed to detect a wide variety of biological analytes. Through tailored surface chemistry, these sensors can be customized to detect specific biomarkers associated with certain diseases. Furthermore, the sensitivity of ME sensors often exceeds traditional diagnostic methods such as ELISA. For instance, Huang et al. [96] developed an ME immunosensor to detect the lysozyme enzyme in human urine, which is an indicator of renal tubular and glomerular diseases. The sensor design involves the specific binding of a magnetoelastic chip coated with a lysozyme-specific antibody with lysozyme (LYZ), and through this binding, the increased mass results in a change in the resonance frequency of the magnetoelastic sensor due to the magnetostrictive effect (Fig. 7). The limit of detection of the sensor was found to be 1.26 ng/ml, which is lower than that of conventional methods.

Furthermore, ME sensors provide real-time and continuous monitoring, a significant advantage in managing diseases that require close monitoring of specific parameters. For instance, glucose monitoring in diabetes management can be aided by an ME sensor, ensuring accurate glucose readings and patient safety. Cai et al. [97] designed an ME glucose biosensor coated with a pH-sensitive polymer and glucose oxidase (GOx) layer. The oxidation of glucose by GOx resulted in the production of gluconic acid, which causes the pH-responsive polymer to shrink and decrease in mass. The sensor's response was linear and reversible for glucose concentrations between 1 and 10 mmol/L. The wireless nature of this sensor makes it a potential tool for in vivo and in situ glucose measurements.

Additionally, ME sensors are low-cost, durable, and have potential for miniaturization, making them an attractive option for point-of-care diagnostics. Their robustness also allows them to withstand varying conditions, providing reliable readings irrespective of the environment. Guo et al. [98] developed an ME sensor to detect Alpha2-Macroglobulin (α2-M), a critical factor in diagnosing diabetic nephropathy (DN). They used $MnFe_2O_4$@chitosan/MWCNTs/PDMS composite film for the sensor and facilitated specific antigen–antibody binding by immobilizing α2-M antibodies to the surface through chitosan-coated $MnFe_2O_4$ particles. They found that the limit of detection (LOD) was 10 ng. ml^{-1}, significantly lower than the limit of health diagnostics.

Gaseous biomarkers, molecules in human breath linked to abnormal biological activities or external influences, are valuable for early disease diagnosis and monitoring. Factors like smoking, medication, age, diet, and body mass index can influence these biomarkers. Ammonia and acetone are key biomarkers associated with conditions like type 2 diabetes, bacterial infections, kidney dysfunction, and asthma. Their detection offers a non-invasive alternative to traditional blood glucose meters. Benzene, a biomarker from external sources like smoking or air pollution, can interfere with gas sensors targeting different biomarkers. Humidity sensors, which detect water vapor naturally produced by the human body, can identify irregular breathing patterns indicative of conditions such as sleep apnea, asthma, or cardiac arrest [99]. In this context, Pena et al. [99] introduced a proof of concept for a real-time resonant frequency characterizing magnetoelastic transducer. The transducer, functionalized with sensitive polyvinylpyrrolidone (PVP) nanofibers, was engineered into a sensor that can differentiate between regular air and exhaled breath. Additionally, it can detect relative humidity, acetone, and ammonia in gaseous environments without direct contact. The sensor's selectivity capacity was also tested using benzene. According to the results, the device demonstrated the ability to monitor relative humidity (RH) quickly and reproducibly, with a sensitivity linear up to 73% and a low limit of detection (5% RH). Furthermore, it successfully identified concentrations as low as 40 ppm of acetone or ammonia within a 2-min exposure period, demonstrating outstanding recovery and reproducibility.

The unusually high level of acid phosphatase (ACP) activity in biological fluids is consistently associated with a variety of diseases, including osteoporosis, myelocytic leukemia, hematological disorders, human prostatic diseases, and prostate cancer. Consequently, measuring ACP activity holds significant clinical value. Wu et al. [52] developed an ME biosensor for the detection of ACP. In the study, the enzymatic hydrolysis of 5-bromo-4-chloro-3-indolyl phosphate (BCIP) causes a frequency shift, providing a linear response to ACP concentrations from 1.5 to 15 U/1. The sensitivity was comparable to spectrometry and surface acoustic wave sensors.

Sang et al. [100] developed an ME biosensor for measuring the level of warfarin, an anticoagulant commonly used in the treatment of thrombotic disorders. Since small changes in warfarin concentration in the body can significantly affect

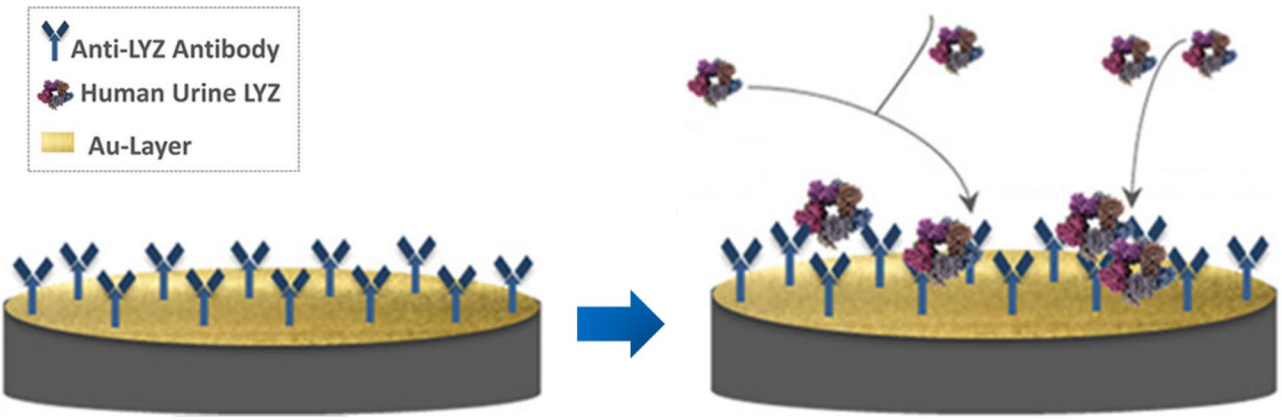

Fig. 7 Schematic diagram of the ME immunosensor sensing mechanism for the LYZ detection. Adapted with permission from ref [96]. Copyright (2021) American Chemical Society

the treatment process, warfarin levels in patients should be measured in real-time, accurately, and precisely during treatment. A biosensor was designed using Metglas alloy 2826 to detect the VKORC1 genotype, one of the most important genetic determinants of warfarin dose. The sensor surface was functionalized for DNA binding and arranged as a biotin-avidin interaction system. The signal obtained from the measurements was then calculated for resonance frequency shift, and the detection limit (LOD) was confirmed to be 0.00389 fM (S/N = 3), and the sensitivity was 45.7 Hz/pMol. This study demonstrates the high application potential of ME biosensors in the biomedical diagnosis of nucleic acids and proteins, as well as their easy application and low-cost measurement system [100].

The ME biosensor and DNA composition provide unique advantages for remote diagnosis of the globin gene, which causes serious complications in blood disorders such as β-thalassemia. Guo et al. [101] designed an ME biosensor with a functionalized surface of gold nanoparticles that yielded significant results in diagnosing β-thalassemia. In the study, a thiolated capture probe (CP) was used to modify the surface of the gold-coated (Au) ME biosensor, which was then hybridized with tDNA. A signal probe (sDNA-AuNP) was modified with thiol and served as a signal amplifier that enabled direct detection of the signal. The specific binding of the sDNA-AuNP to tDNA caused an increase in mass, resulting in a decrease in the resonance frequency of the DNA nanobiosensor. The frequency shift was found to be 72.7 Hz/nM, with a sensitivity detection limit (LOD) in the range of 1.0×10^{-8} M to 1×10^{-12} M. The ME-DNA nanobiosensor was able to detect high-sensitivity mutations in DNA that cause β-thalassemia. Based on the results obtained, the study is very promising for the diagnosis and treatment of hereditary diseases caused by DNA mutations, such as β-thalassemia. In another study, Wang et al. [102] developed an ME sensor for the detection of carcinoembryonic antigen (CEA) and coated it with Au. Then, the single-stranded HS-DNA, which includes a sequence half-complementary to the CEA aptamer, was modified to the surface by Au–S binding. In the sensor, DNA-templated silver nanoclusters (DNA-AgNCs), which contain a sequence half-complementary to the aptamer, were used to magnify the signals approximately 2.1 times more than when only the aptamer was used. CEA aptamers were used as a bio-recognition element to connect HS-DNA and DNA-AgNCs via DNA hybridization. They reported that the CEA aptamer showed a preference to bind with CEA over hybridizing with DNA.

Protein concentrations in biological fluids, like urine and blood serum, are crucial for the pre-clinical diagnosis of various diseases, including cancer, liver diseases, infections, diabetic nephropathy, and autoimmune diseases [27, 103]. Sang et al. [104] designed an ME biosensor based on magnetostrictive effects that can monitor the molecular state of human serum albumin (HSA) to detect its levels in small microliter samples. Anti-HSA immunoglobulin G (IgG) was modified on the ME sensor surface for the selective detection of HSA. During measurement, the antibody and antigen conjugations changed the normal state of the sensor surface, resulting in time-dependent resonance frequency shifts (RFS) for the analysis of HSA. The RFS yielded an accuracy rate of up to 0.998, a sensitivity of 8.70 Hz/μg.ml^{-1}, and a detection limit of 0.038 μg/ml. The results suggest that portable ME biosensor systems could provide a new direction for monitoring and researching human health and detecting harmful agents threatening health, such as carcinogens. Guo et al. [105] developed a NiFe2O4/paper-based ME biosensor for HSA detection, aimed at diagnosing microalbuminuria and neuropathy. By immobilizing anti-HSA antibodies on the biosensor surface, a specific binding with HSA was achieved. This interaction improves the compressive stress on the biosensor surface, leading to a reduction in static magnetic permeability. They found the biosensor detection limit as 0.43 μg.ml^{-1} and reported that this value met the diagnostic criteria.

Osteoarthritis (OA) is a prevalent joint disorder impacting human health significantly. Early diagnosis of OA is crucial for treating the disease effectively. Techniques for highly sensitive detection of trace OA indicators are increasingly in demand. Guo et al. [106] developed a magnetoelastic (ME) biosensor, based on Metglas alloy 2826 MB, for the detection matrix metalloproteinase-3 (MMP-3), an osteoarthritis (OA) biomarker. The biosensor, ultra-sensitive to mass changes, uses a frequency shift from mass changes caused by antibody-antigen-specific binding to measure MMP-3 levels. The study, which has been successfully used to detect MMP-3 in actual joint fluid samples of OA patients, could identify MMP-3 concentrations from 30.7 to 2000 ng·ml^{-1}.

Xiao et al. [107] developed an ME biosensor for in situ monitoring of breast cancer cells (MCF-7) and detecting the cytotoxicity of anti-cancer drugs, including fluorouracil and cisplatin. The ME sensor material was coated with a biocompatible polyurethane-based polymer to protect it from oxidation, and the sensors were modified with drug solutions of different concentrations and brought into contact with cancer cells. The resulting mass increase due to the cells adhering to the sensor surface was measured by examining the shift in resonant frequency. The detection limit for cell concentrations was determined to be 1.2×10^4 cells/ml at concentrations ranging from 5×10^4 to 1×10^6 cells/ml. After 20 h of incubation with the drugs, the lethal concentration (LC50) was 19.9 μM for fluorouracil and 13.1 μM for cisplatin.

Gao et al. [108] developed an ME biosensor to investigate the interaction between tannin and BSA. Since the

interaction of tannin, a polyphenolic compound, and proteins is closely related to leather making, the physiological activity of herbal medicines, the taste of food and beverages, and the nutritional value of feed, easy, and fast measurement are crucial. The biosensor was fabricated by coating a magnetoelastic strip with a polyurethane layer, followed by the addition of a BSA layer. The insoluble tannin-BSA complex binds tightly to the sensor surface and causes a change in resonant frequency. The reaction rate constant was recorded as 0.119 min^{-1} by examining the changes in the curves. The ME biosensor showed a linear shift in resonant frequency with varying tannin concentrations (0.60–1.08 mM), and it was observed that as the tannin concentration on the biosensor surface increased, the frequency shift decreased. The frequency shifts were recorded as -303.5 Hz/mM at 0.60 mM, 391.0 Hz/mM at 0.72 mM, and 458.9 Hz/mM at 0.84 mM.

Wikle et al. [109] have developed an ME biosensor to study an autonomous pathogen system that mimics a biological defense mechanism. The autonomous system is known to have the ability to detect and capture pathogens in liquid environments. In this measurement, contact with the target pathogen caused a change in the resonant frequency of the protective element due to the binding of the bio-recognition element on the protective element to the target cell and immediate detection of the target pathogen. Additionally, autonomous protectors in white blood cells move during the analysis after the addition of liquid analyte, capturing and neutralizing target pathogens. The results demonstrate the concept of autonomous protectors.

Classical swine fever (CSF), triggered by the classical swine fever virus (CSFV), is a devastating and highly infectious disease that severely affects the worldwide swine industry economically. CSFV, a member of the Flaviviridae family within the Pestivirus genus, is characterized by its positive-stranded, enveloped RNA structure, spanning a genome size of approximately 12.3 kb. The identification of the CSFV E2 antibody is critical for diagnosing CSF and plays a vital role in the surveillance of vaccination programs aimed at eradicating the disease. Therefore, the sensitive detection of the CSFV E2 antibody is essential for the effective management and containment of CSF. In their research, Guo et al. [110] employed a MES that was functionalized with E2 glycoprotein for the detection of CSFV E2 antibody. The study introduced a CSFV E2-rabbit anti-CSFV E2 antibody-alkaline phosphatase (AP) conjugated goat anti-rabbit IgG to form a sandwich complex. This complex facilitated a bio-catalytic deposition, amplifying the mass change resulting from the antigen–antibody specific binding reaction, which in turn, significantly altered the resonance frequency of the biosensor. The biosensor demonstrated a linear response to varying concentrations of CSFV E2 antibody, ranging from 5 ng/ml to 10 µg/ml, achieving a detection limit (LOD) of 2.466 ng/ml and a sensitivity of 56.2 Hz/µg·ml^{-1}. This study developed a low-cost and highly sensitive new system for the selective detection of CSFV E2 antibody. Guo et al. [111] developed an ME sensor system for detecting the swine flu virus (CSFV). The ME biosensor surface was modified with anti-CSVF-IgG absorption. It was determined that the shift in the resonant frequency of the ME biosensor was due to an increase in the concentration of CSVF bound to the sensor surface. The observed shift in resonant frequency was found to be proportional to concentrations spanning from 0 to 25 µg/ml. The MES achieved a detection limit of 0.6 µg/ml for detecting CSFV and demonstrated a sensitivity of approximately 95 Hz/µg/ml.

Existing anticoagulants and antifibrinolytic agents are known to potentially cause life-threatening side effects. Therefore, blood coagulation is a very important subject, and a search for novel agents of natural origin is still in demand nowadays. The typical methods for the measurements of blood coagulation need dedicated personnel and involve blood sampling process. For ME sensors, during blood coagulation, the viscosity changes due to fibrin clot formation, shifting the sensor's resonance frequency and enabling real-time monitoring. The low cost and minimal blood volume requirement make these sensors ideal for disposable use in at-home and point-of-care testing devices [112].

In conclusion, the field of magnetoelastic (ME) sensor applications in the analysis of biological fluids has demonstrated remarkable potential for revolutionizing diagnostic and therapeutic strategies in healthcare. The body of research conducted thus far showcases the ability of ME sensors to accurately and sensitively detect minute changes in various biological fluids, thereby enabling early disease detection and progression monitoring. However, despite these promising findings, there are several challenges related to sensor stability, biofouling, and non-specific binding that must be overcome to fully realize the clinical potential of this technology. The true potential of these sensors will be unlocked through continued research and development efforts focused on addressing existing challenges and broadening their range of applications.

5.3 Wound Healing Applications

The long-term success of biomedical implants such as bone-anchored prostheses and percutaneous catheters depends on the ability to effectively monitor and control the wound healing process, also known as the host response. Uncontrolled wound healing often leads to fibrosis, a condition characterized by excessive tissue growth at the interface between the implant and the surrounding soft tissue. This fibrosis can result in some complications such as the formation of irregular skin folds, implant instability, susceptibility to infections, and eventual implant failure.

Current methods for managing fibrosis around biomedical implants involve anti-fibrotic drugs and surface modifications. While anti-fibrotic drugs can temporarily modulate factors like inflammation, they are not ideal for long-term use. Surface modifications aim to reduce fibrosis by altering the implant's physical and chemical properties, but they have not been able to fully eliminate the risk of fibrotic encapsulation.

Magnetoelastic (ME) materials offer a potential solution for real-time monitoring and control of wound healing, without the thermal side effects associated with other treatments like ultrasonic energy. These materials produce localized, controlled submicron vibrations (100–200 nm) that have been shown to inhibit cell adhesion and influence the nature of cell attachment, without causing cell death.

Despite limited research on the tissue healing effects of MESs, Vlaisavljevich et al. demonstrated that ME coatings could act as real-time monitoring tools for observing post-implantation host responses and the therapeutic effects of vibrations on cell adhesion [53]. The system uses the amplitude of vibrations, which is inversely proportional to the mass charge on the pavement, to remotely measure the magnetic field created by a particular vibration profile. The study shows that this ME system can monitor small mass changes on the ME surface through the secondary magnetic field generated during vibrations. It also shows that changes in local matrix stiffness can be monitored in real-time. Furthermore, the study reveals that real-time monitoring is associated with changes in cell adhesion observed in vitro due to therapeutic vibrations. It also demonstrates that in vivo surface adhesion behavior can be monitored and correlated with measures of staging of the host response at the implant surface. In summary, the study suggests that ME materials offer a promising, real-time, and potentially self-aware method for monitoring and controlling wound healing, thus serving as an effective adjuvant therapeutic tool for managing fibrosis and prolonging the life of biomedical implants.

5.4 Food and Agriculture Applications

The use of ME bisensors in food and agriculture spans from detecting contaminants in food products to monitoring soil moisture levels for optimal crop growth. They can be used to ensure food safety by detecting pathogens and toxins, thereby preventing foodborne illnesses. In agriculture, these sensors can aid in precision farming by providing real-time data about soil conditions, helping farmers make informed decisions about irrigation and fertilization. In this title, the various applications of ME sensors in food and agriculture, highlighting their potential in improving food safety and agricultural productivity are provided.

Due to the developments in technology and industry, heavy metals released into the environment pose a significant threat to human health. There is an increasing need to detect and monitor heavy metal ions in food, medicine, and the environment. Guo et al. [113] developed a modified ME biosensor with bovine serum albumin (BSA) for the detection of heavy metal ions. The ME biosensor surface was first coated with gold and then modified with BSA. The mass increase resulting from the interaction between heavy metal ions and BSA was recorded, and a decrease in resonance frequency was observed depending on the mass increase. Some metal ions such as Pb^{2+}, Cd^{2+}, and Cu^{2+} were studied in this research. The produced ME biosensor was found to be more sensitive to heavy metals with a larger molecular weight. The sensitivity for Pb^{2+}, Cd^{2+}, and Cu^{2+} ions was measured to be approximately 9.4×10^{7} Hz, 7.1×10^{7} Hz, and 4.7×10^{7} mol per liter, respectively. The detection limit was recorded as 3.3×10^{-7} mol/L and 2.4×10^{-7} mol/L for Pb^{2+} and Cd^{2+} ions, respectively. These detection limits were below the standard limit (GB 8978–1996). While similar studies in the literature often do not achieve such low detection limits for heavy metal ions, this study offers a highly sensitive measurement capability for detecting heavy metals at minimal concentrations.

As foodborne illnesses caused by pathogens continue to increase, new research areas are emerging, and studies are being conducted from different perspectives. Detection of pathogenic bacteria on solid surfaces is a challenging process. In this sense, the detection and precise measurement of pathogenic bacteria on solid surfaces constitutes an important field of study to prevent the spread of diseases caused by these bacteria. Park et al. [114] developed a novel phage-based ME biosensor specifically designed to detect *Salmonella enterica* serovar Typhimurium in soil samples. The soil samples were prepared for ME biosensor measurements through filtration and cation exchange treatments. The ME biosensor surface was modified with BSA, polyethylene glycol (PEG), and casein powder, and the measurements of the relevant bacteria were taken based on resonance frequency. Following the application of the cation exchange resin method, the count of ST in soil significantly dropped from 7.10 log CFU/soil to a range between 4.45 and 4.72 log CFU/soil. The resonance frequency shift of the PEG-blocked measurement sensor was measured as 3.219 ± 755 Hz, which was significantly larger than that of the BSA and casein-blocked ME sensors. Finally, the modified MES technique was employed for the dose–response detection of ST in soil. Despite the fact that these alterations to the ME biosensor methodology entail compromises in terms of cost, time efficiency, and ease of use, this research presents a novel strategy for identifying ST in soil through the MES approach. Horikawa et al. [115] designed an ME biosensor for the direct detection of pathogens on solid surfaces. Pathogen measurements in fresh foods are also among the highly

studied topics. In general, in the studies conducted, materials (phages, antibodies, and proteins) that will ensure the specific recognition of the pathogen to be detected on the ME material surface are coated, and biosensors are measured individually. Chai et al. [116] designed multiple ME biosensors that can be measured simultaneously for different pathogens. E2 and JRB7 phages were coated on the ME biosensor surface as specific recognition agents, and *Salmonella typhimurium* and *B. anthracis* bacteria were analyzed. The multiple measurements of ME biosensors were carried out by incorporating a spiral planar coil detector into the system. The biggest advantage of the study is the possibility of multiple measurements, enabling a large number of screenings in a short time.

Pesticide residues in food and agricultural products pose significant health risks to consumers and the environment, and therefore their fast and practical measurement is significant. Sang et al. [117] designed an AuNP-coated ME biosensor for the detection of atrazine, an herbicide. Firstly, the ME material was coated with AuNPs. Then, to improve the performance of the biosensor, the atrazine antibody was immobilized on the sensor surface via protein-A. In addition, atrazine-albumin conjugate (Atr-BSA) was induced on the sensor surface to enhance sensitivity and signal response. The sensitivity limit of 3.43 Hz/μgml^{-1} and 1 ng/ml was recorded in the measurements. Zhao et al. [118] designed an ME biosensor for the detection of uranium in water by coating a starch gel layer on an ME material and measuring the effect of uranium cation on α-amylase. The ME biosensor caused a shift in the resonance frequency due to the change in the sensor mass as a result of starch hydrolysis in α-amylase. The detection limit and linear range values were observed as 3.6 mg/L and 9.2–103.5 mg/L, respectively, according to the results. In a previous study, we engineered an MES specifically for detecting the organophosphate pesticide diazinon [119]. To enhance the sensitivity of the sensor, the surface area of the sensor was enlarged by coating it with chitosan/polycaprolacton nanofibers. Figure 8B shows the SEM images of the fibers coated on the MB ribbon surface. The average fiber diameter in the study was measured to be approximately 314 nm ± 68 nm. The nanofibers were then functionalized with acetylcholinesterase (AChE) enzyme for the detection of diazinon since it is an irreversible inhibitor for AChE. Figure 8A shows the binding mechanism of OP to the AChE enzyme. The study revealed that a significant change in resonance frequency occurs when OPs bind to the AChE on the functionalized surface of the amorphous ribbon (Fig. 8C). The results of the study showed that the functionalized MES exhibited a linear change based on the quantity of OP detected in the solution, with a range of 0–140 nL or 0–150 ppm (Fig. 8D). Additionally, our study investigated other commonly used insecticides in recent years, such as malathion, parathion, chlorpyrifos, and dichlorvos, known for their toxic effects. We employed the same method for these substances and obtained similar values.

Staphylococcal enterotoxin B (SEB) is a heat-stable toxin produced by *Staphylococcus aureus*, causing symptoms like nausea, vomiting, and diarrhea if ingested, or fever and cough if inhaled. Although rarely lethal, as little as 100 ng can cause illness. In the food industry, detection methods need to identify SEB concentrations at the ng/g level for solid food and ng/ml for liquid samples. Ruan et al. [120] have developed a rabbit anti-SEB antibody-modified ME immunosensor for the detection of Staphylococcal enterotoxin B. To enhance the binding of the antibody to the ME biosensor surface, biotin-avidin and biocatalytic deposition reactions were used. The alkaline phosphatase substrate, 5-bromo-4-chloro-3-indolyl phosphate (BCIP), was tightly bound to the sensor surface and caused a shift in the resonant frequency of the sensor. In these measurements, a detection limit of 0.5 ng/μL and a linear shift in resonant frequency between SEB concentrations of 0.5 and 5 ng/μL were obtained. The sensor mass in the measurement was approximately 3 mg, and the theoretical sensitivity of $\Delta f/\Delta m$ was recorded as 62 Hz/mg.

6 Discussion

ME sensors are revolutionizing bacterial detection in health and food safety due to their high sensitivity and ability to operate wirelessly. These sensors are particularly effective against foodborne pathogens like *Escherichia coli* O157:H7 and *Salmonella* spp., using surface modifications with phages and antibodies for specific pathogen identification. Key studies demonstrate the sensors' capacity for specific, real-time detection of bacteria, including in mixed bacterial populations. ME sensors have proven their utility across various food products, highlighting their role in enhancing food safety through rapid and accurate pathogen monitoring.

ME sensors represent a significant advancement in medical diagnostics, offering distinct advantages over traditional diagnostic methods such as ELISA, PCR, and fluorescence-based assays. These sensors excel in sensitivity and specificity, often exceeding the capabilities of traditional methods. For instance, an ME immunosensor developed by Huang et al. demonstrated a detection limit of 1.26 ng/ml for the lysozyme enzyme, surpassing conventional methods [96]. This high sensitivity is crucial for early disease detection and accurate monitoring. The real-time and continuous monitoring capability of ME sensors is another notable advantage, particularly for diseases requiring close parameter monitoring, such as diabetes. This feature ensures timely interventions, enhancing patient safety and treatment efficacy. In

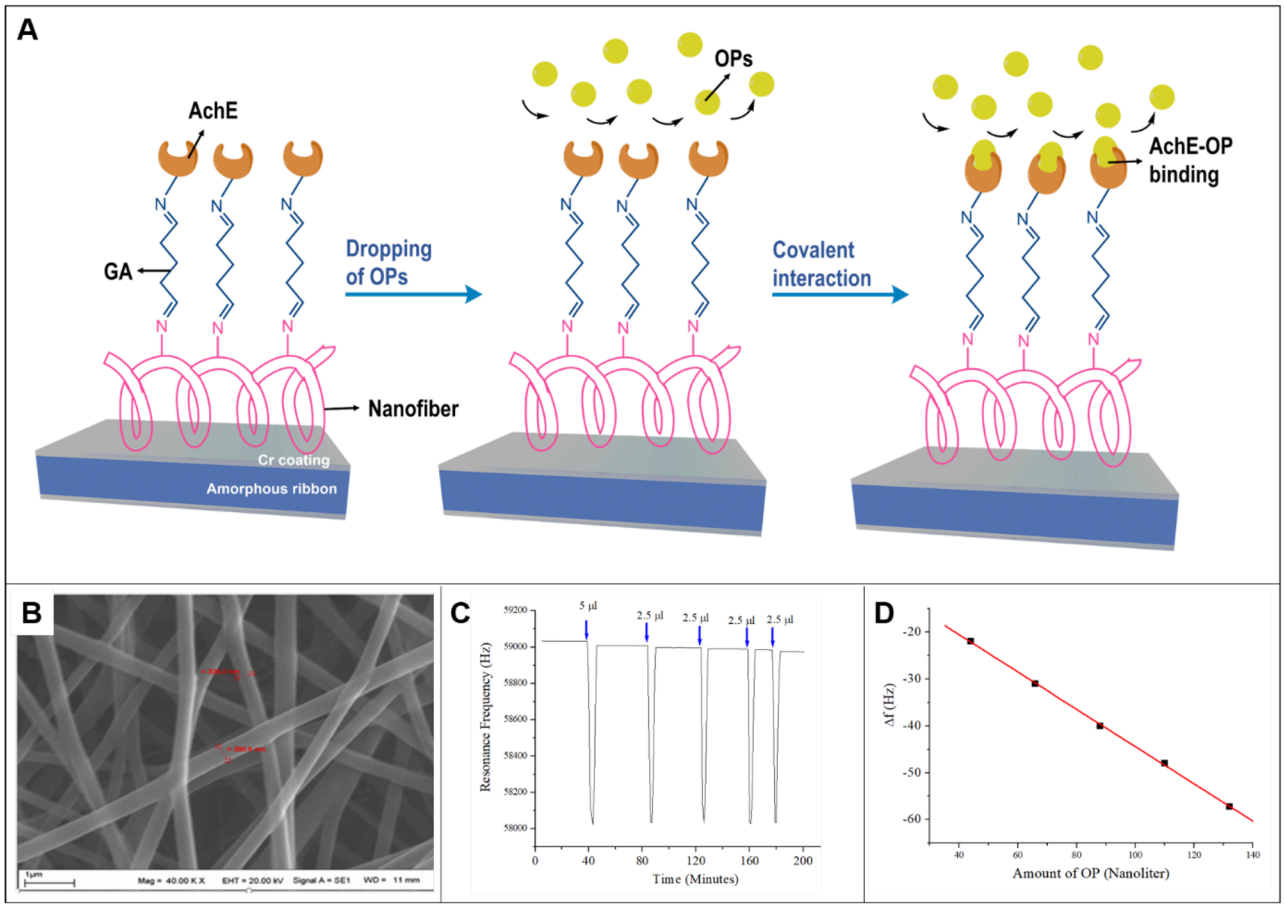

Fig. 8 **A** Detection process of OPs using nanofiber-coated magnetoelastic biosensor. **B** SEM picture of nanofiber coated 2826 MB amorphous ribbon. **C** Effect of OP solution dropping with a micropipette on the resonance frequency of magnetoelastic biosensor. **D** The change in resonance frequency of magnetoelastic biosensor with the amount of OP solution dropped

contrast, traditional methods often require batch processing and cannot provide immediate feedback. Cost-effectiveness and simplicity are where ME sensors notably outshine their counterparts. The development of ME sensors for various applications, including glucose monitoring and detection of specific biomarkers, illustrates their potential for widespread clinical use without the need for expensive, complex equipment. This makes ME sensors particularly appealing for point-of-care diagnostics and in resource-limited settings. Furthermore, the wireless and portable nature of ME sensors, combined with their non-invasive or minimally invasive capabilities, enhances patient comfort and facilitates easy integration into daily life. This contrasts with many traditional methods that are invasive, require complex sample preparation, or are limited by the need for stationary equipment. Customizability is a critical feature of ME sensors, allowing for the tailored detection of a wide array of biological analytes through specific surface chemistry. This adaptability extends their applicability across various diseases and conditions, outpacing many traditional diagnostic methods that are often designed for a narrower range of targets. Despite these advantages, challenges such as sensor stability, biofouling, and non-specific binding exist and must be addressed to fully realize the clinical potential of ME sensors. Continued research and development efforts are vital for overcoming these hurdles and expanding the applications of ME sensors in healthcare. Comparatively, while traditional methods have established a solid foundation for disease diagnosis, ME sensors offer a promising direction for advancement with their enhanced sensitivity, real-time monitoring capabilities, cost-effectiveness, and patient-friendly features. This comparative analysis highlights the significant potential of ME sensors to revolutionize diagnostics, offering insights into their unique benefits and the challenges that lie ahead.

The long-term success of biomedical implants is significantly influenced by the management of the wound healing process to prevent fibrosis, which can lead to complications like implant failure. Traditional methods, such as antifibrotic drugs and surface modifications, have limitations in

effectively managing fibrosis over time. ME materials emerge as a novel solution, enabling real-time monitoring and control of the wound healing process through localized, controlled vibrations that prevent cell adhesion without causing cell death. This approach is distinct from conventional methods, as it not only offers a non-invasive means to monitor implant-tissue interactions but also provides a therapeutic mechanism to influence cell behavior and reduce fibrosis. This dual diagnostic and therapeutic capability of ME materials represents a significant advancement, offering a more adaptive and responsive strategy to prolong the life and effectiveness of biomedical implants by mitigating the risk of fibrosis.

The application of ME biosensors in food safety and agriculture is a prime example of how advanced technology can transform traditional practices. ME biosensors offer a comprehensive approach to detecting contaminants, monitoring soil moisture levels, and ensuring the overall safety of food products. Their significance is particularly evident when compared with traditional methods such as microbiological cultures for pathogen detection and chemical assays for contaminant identification. Traditional methods, while effective, often involve time-consuming processes and require specialized laboratory equipment and conditions. For instance, the detection of heavy metals in food and environmental samples typically relies on techniques like AAS or ICP-MS, which, despite their accuracy, are not only costly but also require extensive sample preparation and analysis time. In contrast, ME biosensors offer a rapid, sensitive, and less time-consuming alternative. In pathogen detection, ME biosensors provide superior performance compared to conventional methods by eliminating the need for sterile conditions and lengthy culture incubations. Summarily, these biosensors elevate agricultural productivity and food safety by quickly and accurately detecting a wide range of analytes without complex preparation or specialized equipment, showcasing their transformative impact on traditional agricultural practices.

7 Future Perspectives and Challenges

ME biosensors have emerged as a versatile and promising technology for sensitive and label-free detection of biological analytes. The integration of magnetostrictive materials with specific recognition elements has enabled the development of biosensors capable of detecting a wide range of targets, including pathogens, biomarkers, toxins, pollutants, and contaminants. The applications of magnetoelastic biosensors span across diverse fields, including medical diagnostics, environmental monitoring, and food safety. In medical diagnostics, they offer rapid and sensitive detection capabilities, facilitating early disease diagnosis and personalized medicine. In environmental monitoring, these biosensors provide valuable insights into pollutant levels and heavy metal contamination, contributing to environmental protection. Furthermore, their implementation in food safety ensures the detection of allergens, pathogens, and contaminants, safeguarding public health.

However, challenges in selectivity and sensitivity remain significant hurdles, necessitating the development of new surface functionalization strategies and molecular recognition elements to enhance biosensor specificity. Moreover, ensuring long-term stability and reproducibility under varied conditions is essential for reliable performance, calling for innovative solutions in biofunctionalization and protective coatings. The integration of ME biosensors into portable, user-friendly devices presents its own set of challenges, particularly in power consumption, wireless communication, and device ergonomics. The exploration of self-powered biosensors, utilizing energy-harvesting technologies, could eliminate some of these obstacles, facilitating the widespread adoption of ME biosensors across various fields.

Overall, magnetoelastic biosensors have the potential to revolutionize various fields, offering sensitive, selective, and label-free detection of biological analytes. Overcoming the existing challenges through focused interdisciplinary research and collaboration will be key to unlocking this potential. The development of sustainable, intelligent, and user-friendly ME biosensor platforms remains a priority, promising to meet the diverse demands of the twenty-first century.

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