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Biomolecular Piezoelectric Materials for Biosensors

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Abstract
Piezoelectric biosensors are a type of analytical equipment that works based on recording affinity interactions. A piezoelectric platform, also known as a piezoelectric crystal, is a sensor component that works on the premise of oscillations changing according to the presence of a mass on the piezoelectric crystal surface. Owing to their high piezoelectricity, biocompatibility, as well as different electrical properties, biomolecular piezoelectric materials are thought to be promising candidates for future piezoelectric biosensors. When biological components in the human body are stressed, they are estimated to produce electric fields that promote cell growth and repair. As a by-product, piezoelectricity research in biological tissues and their elements has drawn much attention recently. This article specifies the principle of the advancement in piezoelectricity research of representative biomolecular materials, which are nucleic acids such as amino acids (DNA, RNA), peptides, proteins, and viruses. We also explored the origins and processes of piezoelectricity in biomolecular materials for biosensor application. Various advantages of using piezoelectric biomolecular materials for biosensor applications are elaborated. Lastly, a comprehensive idea of future challenges and discussion are provided.

Keywords- Biomolecular; Piezoelectric; Biosensor; Biomaterials.

1. Introduction

In the field of medicine, environment, food, and pharmaceuticals, biosensors have been intensely explored and developed (Babacan et al., 2000; Pohanka, 2018b; Wei et al., 2013a). Biosensors are devices that use bio-functionalities like recognition and catalysis to sense any type of disease, foreign factors, contaminants, pollutants, etc (Lowe, 1984; Kissinger, 2005). Biosensors are built from a combination of biological components and transducers (Castillo et al., 2004; Mehrvar & Abdi, 2004). Many biosensors are designed to provide a digital electrical signal proportional to the concentration of a given biochemical or a collection of biochemicals in the presence of a variety of interfering species (Turner, 2000; Wang & Katz, 2010). Many research trials have studied a few innovative biosensors (Wadhera et al., 2019) such as piezoelectric biosensors (Pohanka, 2018a), in recent years with high affectability (Wei et al., 2013b). These biosensors have some fundamental advantages, including functional simplicity (Ziegler & Göpel, 1998), high affectability (Skládal, 2016), and low-cost instrumentation (Perumal & Hashim, 2014), robotization capabilities, and innate scaling down (Janshoff et al., 2000). The great development of novel biosensors is taking place due to the wide availability of cutting-edge microfabrication techniques (Vo-Dinh & Cullum, 2000), cost-effective signal processing setups, and developments in the design of organic sensors (Mohankumar et al., 2021; Rivet et al., 2011). One of the newer possibilities is in the field of healthcare, more specifically in the development of solitary medications. A notable example is a rise in the popularity of personal monitoring devices like newly designed HIV sensors (Farzin et al., 2020) or glucose sensors for diabetics (Haleem et al., 2021; Wang & Lee, 2015).

Biosensors can also bring clinical care closer to the patient's home and tailor it to specific needs. The most promising biosensor improvements at the present are electrochemical (Zhang et al., 2000) and piezoelectric

biosensors (Tombelli et al., 2005). Biosensor development has depended heavily on technologies that were originally developed for other medical uses. Significant study in the field of piezoelectric biosensors has led to the development of extensive conceptual and test data in the last decade (Xu et al., 2021). In experiments conducted in research institutions, piezoelectric sensors were demonstrated to successfully identify the majority of signals crucial to the pharmaceutical industry (Oh et al., 2021). Piezoelectric biosensors are appealing due to their multi-space detecting capabilities, repetition as a sensor signal yield, and tolerable temperature stability (Zu et al., 2016). Additionally, they refer to particular project concepts associated with the notion of a piezoelectric transducer-natural interface. The mechanical nature of piezoelectric detecting devices, for example, could cause issues in detecting the mechanical movement of a biosensor to test-taking care of microfluidics, and this reality can affect faulty sensor execution (Karthik et al., 2022).

Most noticeably, many human organs are made up of biomolecules, such as bone, skin, and hair, which are all made up of amino acids such as deoxyribonucleic acid (DNA) and ribonucleic acid (RNA), proteins, and peptides, which are both known as piezoelectric materials, have been observed to have piezoelectricity (Kim et al., 2020; Purohit et al., 2020). In this paper, I describe the piezoelectric properties of various biomolecules and their applications in the field of biosensors in detail. This summary primarily focuses on the most recent advancements and varieties of biosensors based on bio-piezo materials, including DNA-based, enzyme-based, amino acid-based, and virus-based biosensors. The advantages of piezoelectric biosensors are also discussed in this paper. Following a discussion of the opportunities and potential challenges, a conclusion is provided. Figure 1 shows the structure and components of the typical biosensor.

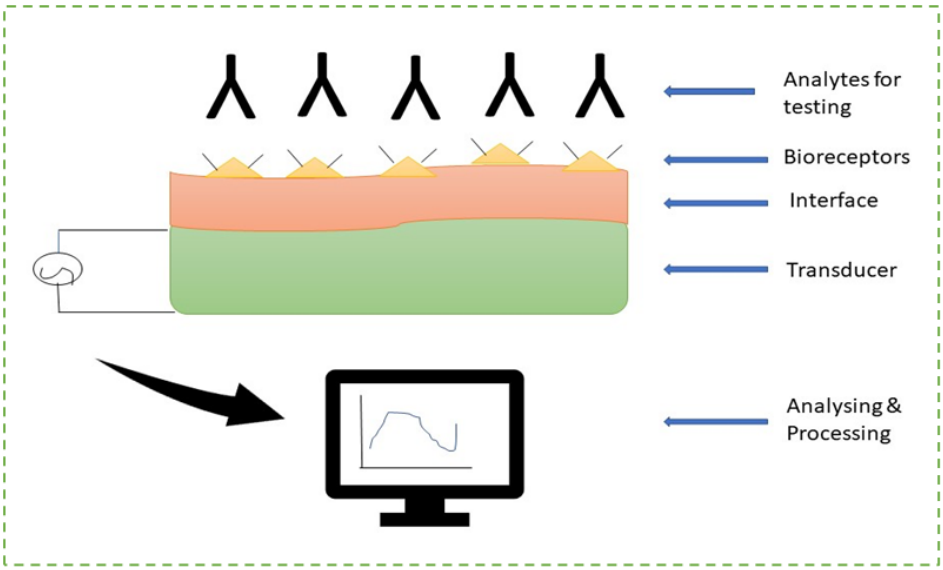

Figure 1. Structure and components of biosensors.

2. Piezoelectricity

Piezoelectricity is caused by crystal deformation, the coupling of electrical and mechanical states of a material. Under mechanical strain and deformation, the positive and negative charge centers in piezoelectric materials migrate, resulting in an external electrical field and current flow (Katzir, 2003, 2007; Panda et al.,

2022; Preetam & Panda, 2021). The inverse is also feasible. Piezoelectric materials are stretched or compressed when an electrical field is applied (Peláiz-Barranco & González-Abreu, 2013; Lang, 1976). Pierre Curie, Marie Curie, and Paul-Jacques Curie first scientifically described the direct piezoelectric action in 1880 (McGahey, 2009; Ito & Uchino, 2005; Rao & Sunar, 1994). They used their expertise in pyroelectricity with their comprehension of crystal forms and behavior to demonstrate the first piezoelectric effect using quartz crystals and Rochelle salt. Since then, a large number of researchers have recognized and reported the piezoelectric properties of organic, inorganic, and biomaterials (Bassett, 1967). These piezoelectric characteristics are the result of the crystal structure's deformation and the charge rearrangement within the material. In the equilibrium situation, the distribution of charges inside the material lattice is neutral. Under mechanical stress, the unit cell will nevertheless undergo a redistribution of charges that generates net charges on its faces and results in a net dipole moment. These total dipole moments from all the unit cells in piezoelectric materials result in charge separation and electrical polarization (Anton & Sodano, 2007; Maeder et al., 2004). The main prerequisite for this combination is that none of the materials contain a center of symmetry because if they did, their net dipole moments would sum to zero (Dineva et al., 2014; Uchino, 2017).

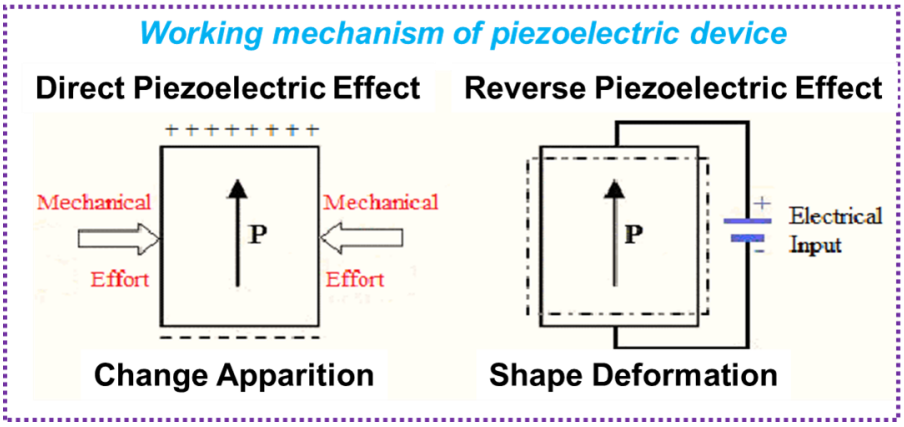

Figure 2. Working mechanism of piezoelectricity.

3. Piezoelectric Biomolecules

Amino acids are the fundamental site of protein synthesis, composed of nucleic acids, and peptides, and they have piezoelectric properties that seem to be structure-dependent (Lemanov, 2000; Vasilescu et al., 1970;). A group of organic molecules is composed of a basic amino group (NH_2), an acidic carboxyl group (COOH), and a specific organic R group for each amino acid. Amino acids can create three-dimensional crystal structures which can display piezoelectric characteristics like other crystals. The transition region and decrease of the elastic vibration in the crystal lead to a change in piezoelectric characteristics of amino acids with a change in temperature, which is similar to standard piezoelectric crystals. A peptide is an amino acid-based compound with structure-dependent piezoelectric characteristics (Lemanov, 2012). Proteins are complicated macromolecules that exhibit piezoelectricity and are composed of peptide bonds involving amino acids. Numerous investigations of piezoelectric proteins collagen, keratin, and lysozyme, for example, are done. Collagen is found in cellular organelles and connective tissue including bones, tendons, epidermis, and also joints, and organ membranes, and is the most abundant structural protein in the body (Anderson & Eriksson, 1970; Lemanov et al., 2011; Rossi et al., 1986). Keratin, a right-handed -helical

fibril-organized protein enriched with alanine, leucine, arginine, and cysteine abundant in skin, hair, and nails, has a similar piezoelectric potential (Guerin et al., 2019; Maeda, 1989). The abundance of piezoelectric properties which are present in bone, cartilage, tendon, and ligaments (Williams & Breger, 1975). The origin of piezoelectricity in bone has been demonstrated to be piezoelectric collagen the generated electricity is in charge of the bone replacement. The piezoelectric effect is hither in tendons compared to bones because the collagen is positioned in a right position along the longitudinal plane of the ligament. Piezoelectric constants of collagens vary dramatically with hydration (Fukada & Yasuda, 1964; Fukada et al., 1976; Silva et al., 2001). Table 1 shows the comparison of the bio-piezoelectric materials and their piezoelectric coefficient.

Table 1. Types of piezoelectric biomolecular materials and piezoelectric coefficients.

S. No.	Biomolecular Piezoelectric Type	Piezoelectric Coefficient	Reference
1	Glycine (Amino acid)	d_{16} = 178 pC N^{-1}	Kim et al. (2020)
2	Collagen (Peptide)	d_{14} = 12 pC N^{-1}	
3	Cornew (Tissue)	d_{33} = 2250 pC N^{-1}	
4	Cysteine (Amino acid)	d_{22} = 11.4 pC N^{-1}	
5	Bone (Tissue)	d_{14} = 0.2 pC N^{-1}	
6	Epidermis (Tissue)	d_{14} = 0.03 pC N^{-1}	

4. Types of Bio-Piezo Materials for Biosensors

Recently, there has been a rise in demand for biosensors for quick and simple methods of hybridization detection (Justino et al., 2017). To build such devices, single-stranded oligonucleotides (probes) are immobilized on the transducing element's surface, and fluctuations in the transducer signal are brought on by the hybridization of the probe with the complementary strand in solution are then recorded (target) (Wang et al., 2009). Piezoelectric biosensors have been proposed as replacements for gel electrophoresis and other conventional techniques where labeled probes are frequently required since they allow for the real-time monitoring of the hybridization reaction without the use of any labels (Chadha et al., 2022; Ye et al., 2019).

4.1 DNA-Based Piezoelectric Biosensors

In recent years, a variety of nucleic acid-based biosensors have been invented (Abi et al., 2018; Hahn et al., 2005). Higher selectivity and dependability are provided by DNA sensors. Similarly, no labels are required for the identification of DNA by immunosensors. However, more unexpected immobilization methods provide a hurdle to the advancement of DNA sensors (Lucarelli et al., 2008). In most DNA biosensors, the integral strand in a sample is hybridized with an immobilized single-stranded DNA molecule (Teles & Fonseca, 2008). DNA Biosensors reports on successful research into DNA denaturation, DNA polymorphism identification, and continuous monitoring of enzymatic nucleic acid cleavage. Unlike traditional DNA testing methods, acoustic sensors can detect nucleic corrosive hybridization quickly and without leaving a trace. The diagnosis of diseases with a genetic basis is ideally suited for the use of DNA biosensors. The beta thalassemia gene's codon DC17 was studied by Pang et al. The hybridization of gold nanoparticles with DNA probes and sample DNA provided the basis for the detection. For the studied oligonucleotides, the assay had a limit of detection of 2.6 nmol/L, and the hybridization apparatus was installed on a QCM sensor as shown in figure 3 (Pang et al., 2006). To identify Staphylococcus aureus, Lian and colleagues developed a DNA detecting biosensor using an aptamer crosslinked by 4-mercaptobenzene-diazonium tetrafluoroborate on graphene interdigitated gold electrode on a crystal (Lian et al., 2015). DNA sensors should find a wide range of uses in the clinical setting for quick and low-cost

disease screening, in the pharmaceutical business during drug development, and in environmental monitoring.

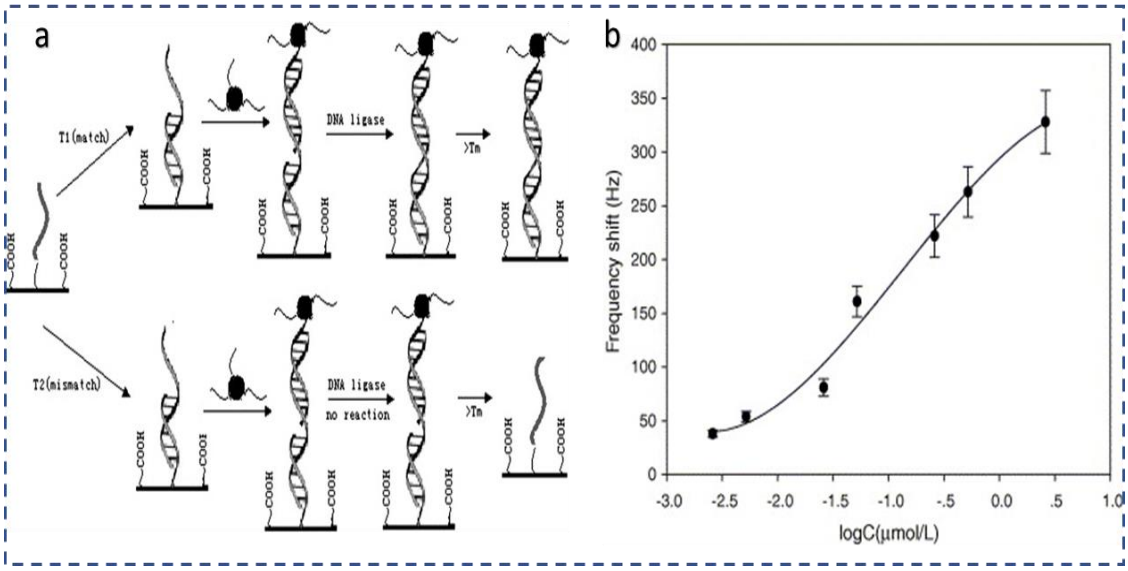

Figure 3. (a) Sketch diagram for the experimental process of DNA point mutation detection based on DNA ligase reaction and nano-Au amplification; (b) Frequency responses of the biosensor to different concentrations of the perfect match target. Reprinted with permission from (Pang et al., 2006).

4.2 Enzyme-Based Biosensors

Another key interface for achieving extremely precise reactions with a range of biological components is enzymes (Ispas et al., 2012). Enzymes, on the other hand, are biocatalysts that play a role in natural transduction and have been employed to improve biosensors in the past. Biosensors based on enzymes are more focused than those based on cells. Enzymes catalyze bioreactions quickly, have well-defined activity characteristics while being easily immobilized, are helpful in a wide range of applications, and are affordable. Several glucose sensors based on immobilized hexokinase and glucose oxidase have been investigated. By estimating gluconic corrosive, a consequence of glucose oxidase in glucose fluid solutions, a piezoelectric screen glucose catalyst sensor was developed. The impedance of several typical species found in human blood was discovered to be unimportant. Piezoelectric glucose meters have the potential to be a viable alternative to popular electrochemical glucometers.

4.3 Amino Acid-Based Piezoelectric Sensor

Protein, Amino acids, and peptides, in particular, are plentiful & affordable piezoelectric biomolecules (Er et al., 2021). Those proteins are biodegradable piezoelectric materials with significant potential for biomedical applications in the future. Furthermore, several biological piezoelectric sensors have been reported to have significant piezoelectricity equivalent to that of standard piezoelectric materials. Another benefit of adopting biomolecular piezoelectric materials for biosensor applications is that they have a lesser electrical conductivity than standard piezoelectric materials. In various structures, piezoelectric biomolecules have been reported to have a significant connection to human health Collagen's piezoelectric characteristics, for example, have been shown to influence the bone formation, healing, and remodeling.

Moreover, many live cells, such as ligaments, tendons, skin, cartilage & hair have been made up of numerous piezoelectric proteins which are amino acids, and the piezoelectricity of these living tissues is assumed to be intimately connected to the healthy life of humans (Pundir et al., 2018). The prospective use of peptide-based antifouling biosensors for long-term assaying of patient cases was severely hampered by peptides' sensitivity to proteolytic degradation in human serum. As a result, Zhao et al. designed a reliable antifouling biosensor with improved stability based on D-peptides, which exhibit strong proteolytic resistance. A common antibody specific for immunoglobulin M (IgM) was immobilized after the electrode was electropolymerized with poly(3,4-ethylene dioxythiophene) and electrodeposited using Au nanoparticles (AuNPs). Figure 4 illustrates this process.

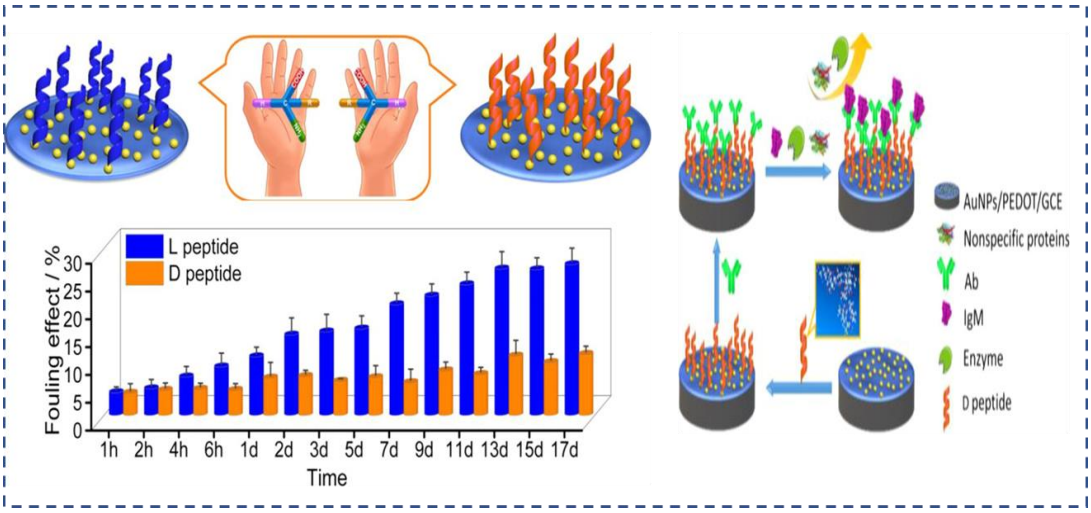

Figure 4. D-Amino Acid-Based Antifouling Peptides for the Construction of Electrochemical Biosensors Capable of Assaying Proteins in Serum with Enhanced Stability. Reprinted with permission from (Zhao et al. 2022).

4.4 Virus-Based Piezoelectric Sensor

Virus-based sensor systems based on M13 bacteriophage infrastructure have recently gained a lot of attention (Mao et al., 2009). The ssDNA and capsid proteins that make up M13 phages are each divided into three areas: a positively charged area, a neutral charged area, and a negatively charged area. As a result, each capsid protein possesses a dipole moment (Janczuk-Richter et al., 2019). Due to the pentagonal shape of these main coat proteins, M13 phages have no inversion center, two-fold screw symmetry, and five rotational symmetry folds. M13 phages may therefore have piezoelectric characteristics (Moon et al., 2019). Surprisingly, the M13 phages' intricate structural characteristics enable them o make use of a variety of piezoelectric behaviors. Net dipole moments and electrical polarization are produced when tension is applied along the phage-long axis. On the other hand, when the stress is applied along the body, net dipole moments and electrical polarization are generated in two different directions. Because of its mobility and intuitiveness, a biosensor based on M13 bacteriophages has sparked considerable interest. Using silver nanowires and genetically modified M13 bacteriophages that express the tryptophan-histidine-tryptophan peptide sequence, Koh et al. (2018) designed a surface-enhanced Raman scattering (SERS) sensor that has dramatically improved capture capabilities for pesticide detection (Figure 5a) (Koh et al., 2018). For cysteine and Salmonella spp. detection, M13 bacteriophage was used as an electrode support material.

Based on the M13 bacteriophage, Niyomdecha et al. identified Salmonella species in a capacitive flow injection system. Using glutaraldehyde as a crosslinker, salmonella-specific M13 bacteriophage was mounted on a polyytyramine/gold surface as shown in Figure 5b (Niyomdecha et al., 2018). M13 bacteriophages that have been functionalized can successfully identify a variety of cancer cells. Colour sensors have also been tested as a technique for applying M13 bacteriophages to sensor systems.

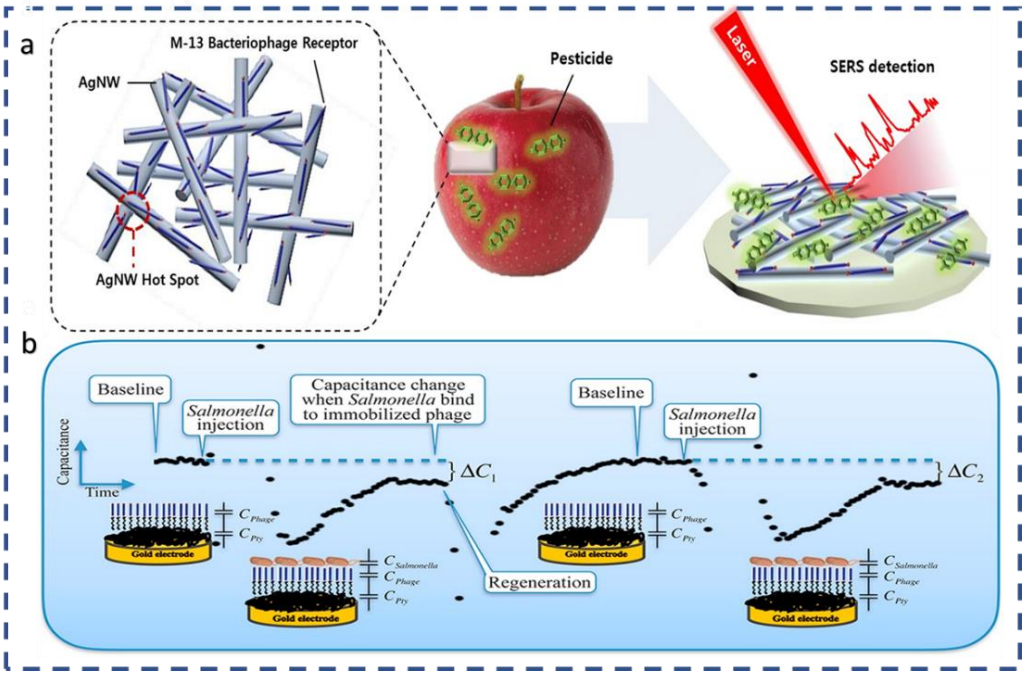

Figure 5. (a) M13 bacteriophage/silver nanowire surface-enhanced Raman scattering sensor for sensitive and selective pesticide detection. Reprinted with permission from (Koh et al., 2018), (b) Phage-based capacitive biosensor for Salmonella detection. Reprinted with permission from (Niyomdecha et al., 2018).

5. Advantages of Piezoelectric Biosensors

Piezoelectric properties can be located in a range of biological components, including the skeleton, ligament, collagen, joint, hairline, and epidermis. Since biological tissues are composed of piezo biomolecules, the electrical effects that occur in the human body's live tissues are well understood (Ngeh-Ngwainbi et al., 1990). Alive cells are capable of displaying piezoelectricity if they do not frame correct frames. Proteins, amino acids, and peptides are examples of biomolecules that are both inexpensive and readily available as piezoelectric biomolecules (Chorsi et al., 2019), which are biodegradable piezoelectric materials with a lot of potential for future biological applications (Marco & Barceló, 1996; Marrazza, 2014), as shown in Figure 5. Aside from this, it has been discovered that certain biological piezoelectric materials possess significant piezoelectric properties that are equivalent to those of conventional piezoelectric materials. Additional advantages of piezoelectric biomaterials would be their lower dielectric constant compared to the typical piezoelectric crystals, which makes piezo-biomaterials to be more suitable for low-frequency applications (Fu et al., 2017; Narita et al., 2021).

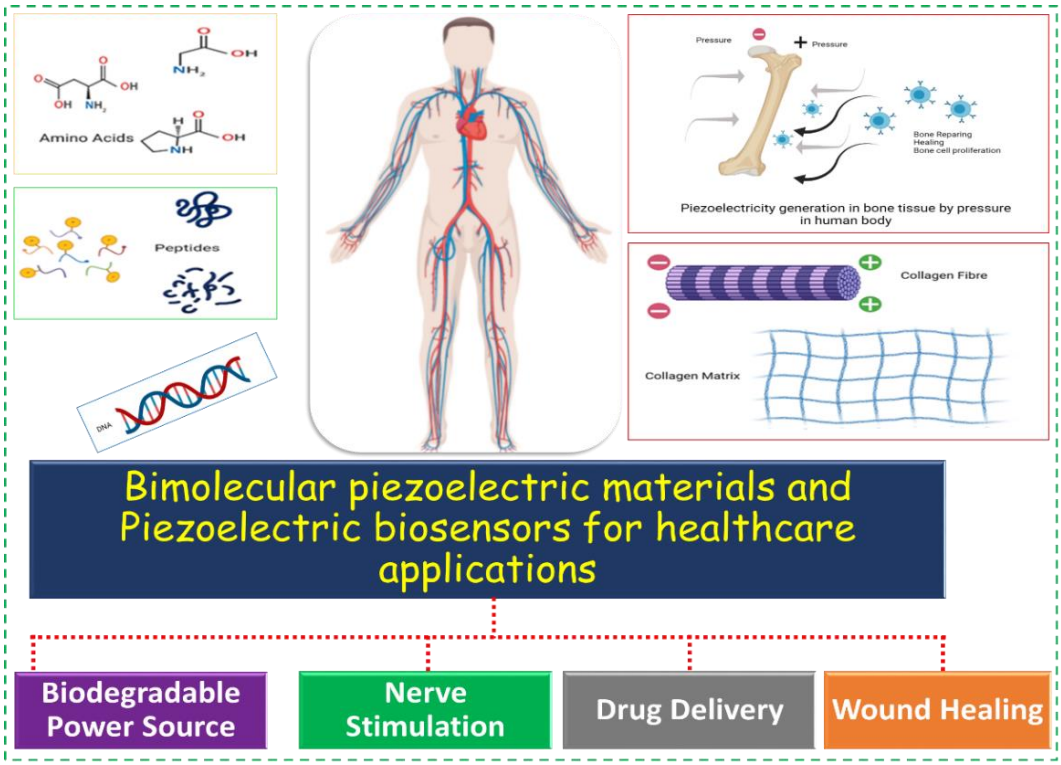

Figure 6. Piezoelectricity on the bone for the tissue formation, Theoretical framework of piezoelectric bone made up of piezoelectric collagen, Peptide, and amino acids applications towards the piezoelectric biosensors. Created with Bio Render.

6. Future Challenges and Discussions

Even though bio-piezoelectric compounds have such promising piezoelectric properties, extensive studies on the mechanical features of biomolecules are required to fully understand the piezoelectric mechanism. In the development of feasible bio-piezoelectric materials and the implementation of applications such as biosensors, electric motors, and energy harvesters at present, the most significant challenges are constrained patterning, orientation control, and polarization directions. To meet these obstacles, researchers have lately attempted bio-piezoelectric components identity, screen printing, cloud computing, and an electromagnetic field-induced configuration technique. Piezoelectric biomolecules have indeed been discovered in a variety of aspects of the human body and have also been connected to improved human health outcomes. Bone development, healing, and remodeling have all been proven to be influenced by the piezoelectric characteristics of collagen, for example. With the presence of various piezoelectric proteins in a variety of living tissues such as the ligament, joint, bone, keratin, and epidermis & the dielectric constants of these living tissues are well recognized as being significantly associated with human health. Piezoelectricity in natural materials such as biomolecules can be improved by making composites, blending organic and inorganic materials, or making multilayer piezoelectric devices. Biodegradable piezoelectric materials can be handled under various conditions (for example, different temperatures, stretching ratios, or poling electrical fields) to tailor their breakdown rate, which will allow the development of novel biodevices.

4. Conclusions

Biosensor research is becoming more important as a result of innovative knowledge that enables novel biosensing methodologies. Piezoelectric biosensors are a type of analytical device that can be used to determine an analyte without the use of a label. Such biosensors have been proven to be reliable in the lab, as well as several modifications have been discovered. Although piezoelectric biosensors have not yet been commercialized, the observational results are encouraging, and this state is predicted to change soon. The development of technologies for the mass manufacture of specific materials like inexpensive piezoelectric materials shows the strength of this sector. Of course, the excellent analytical performance of the disclosed piezoelectric biosensors is required for this concept to be implemented. Functional simplicity, remarkable conveyance, limited monitoring, robotization abilities, and inherent scaling down are all advantages of biomolecular biosensors. I have summarized the impact of several biological piezoelectric materials, such as proteins, peptides, amino acids, and living tissues, and their respective electrical properties. I expect that this review will contribute to an improved understanding of piezoelectric materials as well as potential applicability in physiological biosensors development.

Conflicts of Interest

The author confirms that there is no conflict of interest to declare for this publication.

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