

Recent Advances on Bioreceptors and Metal Nanomaterials-based Electrochemical Impedance Spectroscopy Biosensors

Zibo Chen¹, Huihui Jin², Daping He^{1,2*}, Zhugen Yang³

¹ School of Materials and Science Engineering, Wuhan University of Technology,
430070, Wuhan, China

² Hubei Engineering Research Center of RF-Microwave Technology and Application,
School of Science, Wuhan University of Technology, Wuhan 430070, China

³ School of Water Science Institute, Cranfield University, Cranfield, MK43 0AL, UK

* *Corresponding author*

E-mail: hedaping@whut.edu.cn

Abstract

Metal-based nanomaterials have a wide range of applications in energy conversion, catalysis, bioimaging, and sensors. In our review, we mainly introduce metal nanomaterials-based electrochemical impedance spectroscopy (EIS) biosensors in medical healthcare, environmental monitoring, and food safety instructively, with collecting and analyzing the current achievement of predecessors. In general, metal nanomaterials-based EIS biosensors can be divided into four components, in which bioreceptors and metal nanomaterials transducers are vital for designs. Bioreceptors and metal nanomaterials determine the feasibility, specificity, sensitivity and simplicity of manufacture and operations. With the demonstration and discussion of bioreceptors and metal nanomaterials of biosensors in different fields, our review aims to assist brief acknowledge of current achievement and inspire tremendous innovation in the future.

Keywords: Metal Nanomaterials; Electrochemical Impedance Spectroscopy; Biosensors; Bioreceptors

Highlights:

1. Key analysis and comparison of different biological receptors.
2. Systematical summary for the characteristics of metal nanomaterials-based EIS biosensors and their respective advantages and disadvantages.

1.Introduction

Nature is the mother of curiosity and inspiration, for which has tested and evolved its recognition among specific substance over the past billions of years, especially for modern sensor researchers. Among all the recognition, the identification between target molecules and biomolecules has a promotion for sensor designing with its diversity [1], accuracy [2], and programmability [3]. Therefore, a variety of biosensors have been synthesized to detect the presence of target molecules and cellular structures or changes of related parameters in health care monitoring [4], food safety sensing [5] and environmental protection detection [6]. However, biosensors demand new concepts to achieve low cost due to the difficulty in forming required biomolecules, low durability of the biomolecules, and time-consuming way for sensing through heavy facilities. Herein, new materials and sensing methods are introduced into biosensors for solving the mentioned challenges. For new materials, such as metal materials [7], carbon materials [8] and non-metallic/carbon materials [9] have assisted biosensors, among which metal materials have been maturely and widely used. For new sensing methods, it mainly includes electrochemical [10], photoelectric [11], field-effect transistor [12], fluorescence [13], etc., in which electrochemical biosensors is one of the most popular type.

Among all candidate materials that can be applied to biosensors, metal nanomaterials stand out and play a significant role. Generally, the metal nanomaterials exhibit diverse properties, such as variety of nanostructures [14], high conductivity [15], abundant chemical active sites [16], and high surface to volume ratio [17], which are

curtail factors for optimizing biosensors performance. Metal nanomaterials typically contain three classes of metal simple substance nanomaterials, metal compound nanomaterials, and alloy nanomaterials, which differ in properties from each other, but the alternativity of properties offer great potential for adapting to different sensing requirement. However, most of the chosen metal nanomaterials are based on precious metal, which is the barrier to outpatient and commercialization. Thus, the upcoming discussions include various biosensors based on non-precious metal nanomaterials.

There are numerous electrochemical sensing methods, among which electrochemical impedance spectroscopy (EIS) is indispensable for evaluation, because it is a sensitive approach to detect the occurrence and change of electrochemical events that appear on the electrode/electrolyte interfaces. Therefore, it has shown great usability in multiple biosensors [18–20]. Nearly 120 years have passed since Oliver Heaviside first described EIS in the late 19th century [21]. In EIS theory, electrochemical events cause current to flow at the electrode-electrolyte interfaces and change the electrical characteristics of the interfaces. The current transmitted to the external circuit through the interface contains a Faradaic component and a non-Faradaic component. The Faradaic component results from the directional movement of redox electrons. While the electrons in charging and discharging double-layer capacitors results in the inevitable non-Faradaic component [22]. These two types of components response to corresponding signals of current (voltage) under stimulations of small amplitudes, different frequency, AC sinusoidal voltage (current) signals. Furthermore, these corresponding signals can be transformed to impedance or admittance in the

equivalent circuits to help us analyze electrochemical events caused by the above identifications. Herein, it is crucial and instructive to collect and analyze the current achievement of predecessors. In general, metal nanomaterials-based EIS biosensors can be categorized into 4 components, as shown in **Figure 1**, which are targets, bioreceptors, metal nanomaterials transducers and outputs. It is a top-down linear logic chain from the target to the output where the bioreceptors and metal nanomaterials transducers are vital for designs. Although targets limit the selection of bioreceptor, the adaptation between bioreceptors and metal nanomaterials transducers determines the feasibility, specificity and sensitivity for metal nanomaterials-based EIS biosensors. Moreover, some metal nanomaterials transducers can also function as bioreceptors because of their potential catalytic ability to switch on the recognition under a set environment. With the demonstration and discussion of bioreceptors and metal nanomaterials of biosensors in different fields, our review aims to assist brief acknowledge of current achievement and to inspire tremendous innovation in the future.

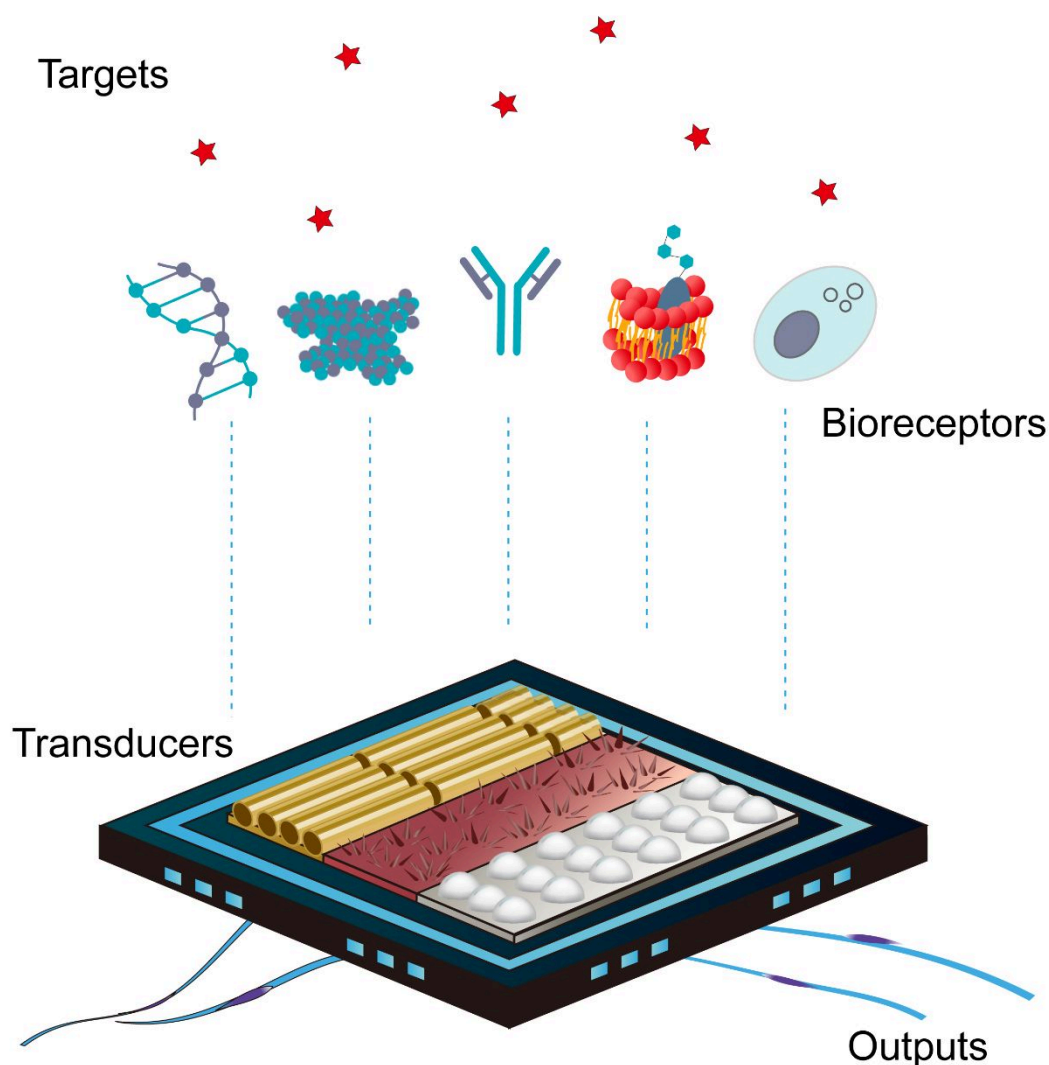


Figure 1 Structure of metal nanomaterials-based EIS biosensors

2. Different bioreceptors

2.1 Nucleotide bioreceptors

2.1.1 Nucleic acids

Nucleic acids are indispensable materials for all known creatures. Due to their different composition, they can be divided into deoxyribonucleic acid (DNA) and ribonucleic acid (RNA). DNAs and RNAs are the fundamental materials for heredity, variation, transferring and expression of bioactivities for organism. The linear

arrangement of deoxyribonucleotides and ribonucleotides leads to their abundance and encodability, as shown in **Figure 2a** [23]. In the meantime, the covalent bond between them and the simple linear structure bring DNAs and RNAs much higher stability than common proteins. Moreover, every deoxyribonucleotides and ribonucleotides has a nitrogen-containing base that can be paired with each other particularly, which cause their unique specific recognition. And with the emergence of mature technologies such as PCR, its production and separation are facilitated. Xu et al. developed a DNA biosensor for the sensing of E. coil O157:H7 with a broader range (1.0×10^{-14} - 1.0×10^{-8} M) and a more sensitive limitation (3.584×10^{-15} M) [24]. Cai et al. proclaimed biosensors for Hg^{2+} detecting based on DNA hydrogel, showing the limitation down to 0.042 pM, with sensitivity and selectivity between 0.1 pM to 10 nM [25]. Chen et al. introduced a DNA biosensor for the detection of hepatitis B virus DNA with R^2 values of 0.801 in the linear ranger of 10^2 - 10^3 and R^2 values of 0.996 in the linear ranger of 10^3 - $10^{5.1}$, respectively [26].

2.1.2 Aptamers

Aptamers, on the contrary, are single-stranded nucleic acids which are obtained by SELEX mostly. Due to their bare nitrogen-containing bases and the linear arrangement of nucleic acid, aptamers show the availability of modification, the abundance of functionalization and the controllability of secondary structures [27]. With these properties, aptamers are compatible for specific biorecognitions, which is similar to the selective biorecognitions of proteins, relying on the unique 3D structures matching variety of targets, such as nucleic acids and proteins (**Figure 2b**) [28]. Besides,

aptamers can be designed as non-fixed bioreceptors for the targets, which upgrades the biorecognitions from a surface to the whole solution, thus greatly increasing the probability of occurrence of biorecognitions and making the biosensor have a lower limitation of detection. Tan et al. invented an aptamer biosensor for the detecting of Hg^{2+} in water environment with a sensitivity down to 0.5 nM [29]. Ensafi et al. claimed a biosensor based on Aptamer-Au modified graphite for the existence of insulin, which shows the linear range of 1.0-1000.0 nmol L⁻¹ and a limit of 0.27 nmol L⁻¹ [30]. Istamboulié et al. reported an aptasensor for the existence of aflatoxin M1 in dairy products after 0.2 µm PTFE filtration, whose concentrations vary from 20 to 1000 ng kg⁻¹ [31].

2.1.3 Molecular beacons

Molecular beacons (MBs) are single-chain nucleic acids designed as a shape of hairpins, which are first reported in 1996 [32]. Similar to aptamers, their distinctive structures show tremendous possibilities of biosensing detection. The nitrogen-containing bases from the single chains help researchers to shape them into potential variable structures. When the target molecules, including DNAs and RNAs, are combined with MBs, the hairpin-shape MBs will forcibly expand to form a linear structure due to the complementary base pairing, as shown in **Figure 2c** [33]. In contrast, some other molecules, such as proteins and peptides, show the ability of folding MBs into hairpin-like shape. Through the above-mentioned biomolecular transformation, electrochemical event labels (EELs) will lengthen or shorten the distance to the electrode surface, functionalize at the 3'-end and 5'-end of MBs, change the distance of

electron tunneling and further affect the electrical signal further. In electrochemical biosensing, methylene blue (MTB) [34] and ferrocene (Fc) [35] are widely used as EELs, but metal particles [36] and metal organic framework (MOF) [37] are tagged more these days because of the difficulty of preparation of MTB or Fc based EELs. Li et al. invented a biosensor with molecular beacon combining with nafion-graphene composite film modified screen-printed carbon electrodes (nafion-graphene/SPCE) for the sensitive existence of HIV-1 in homogeneous solutions, which showed a linear range from 40 nM to 2.56 μ M and a determination limit of 5 nM (S/N=3). [38] He et al. reported a biosensor for nicotinamide adenine dinucleotide (NAD⁺) detecting with the help of molecular beacon (MB)-like DNA and E. coil DNA ligase, which has a linear response from 3 nM to 5 μ M and a determination limit of 1.8 nM [39]. Xiong et al. announced a reusable molecular beacon biosensor with accessibility for the sensitive sensing of mercury ions (Hg²⁺) with a liner range from 0.5 nM to 5000 nM and a determination limit of 0.08 nM [40].

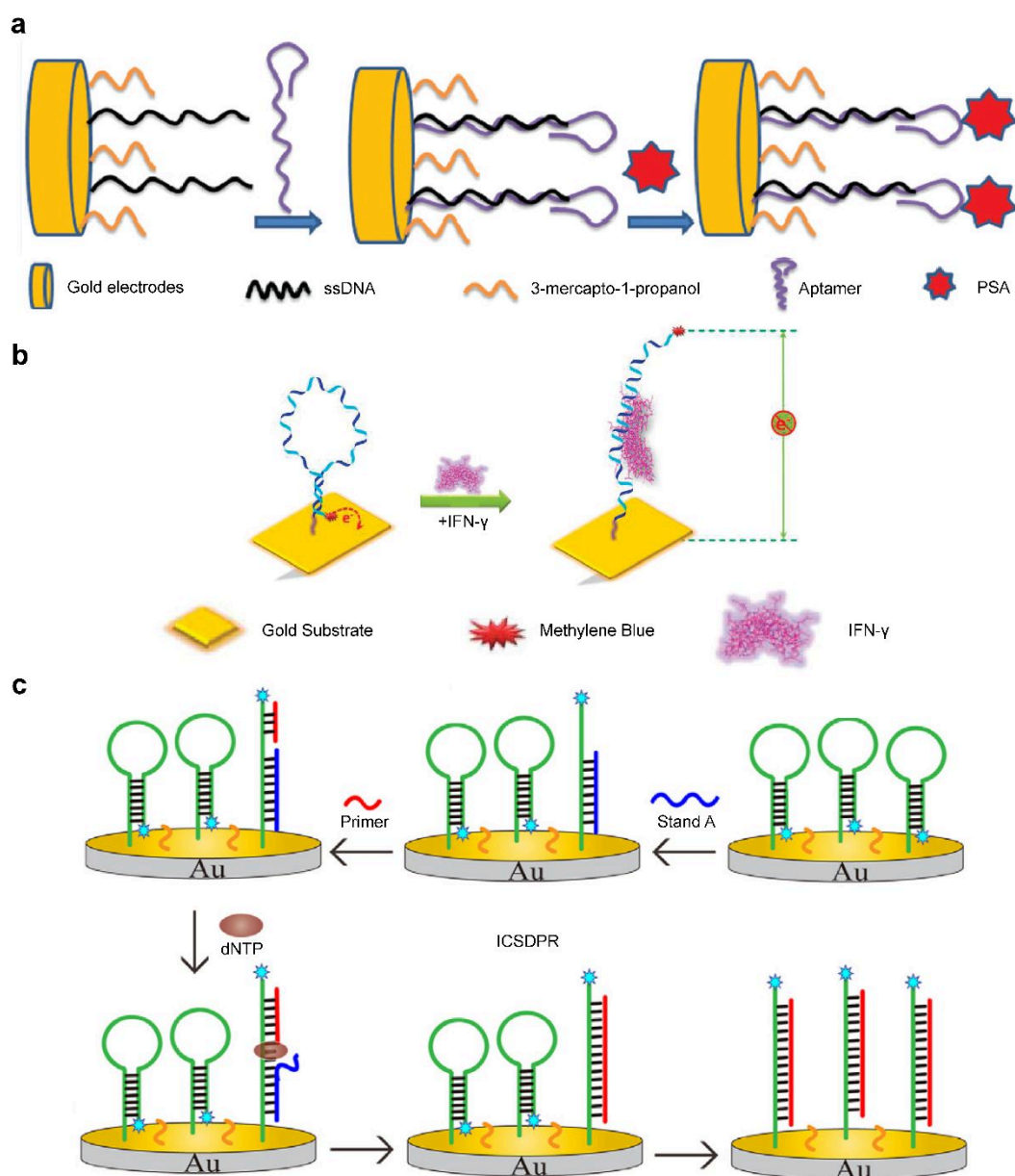


Figure 2 Structure of Nucleotide Bioreceptors. (a) Linear Arrangement of Nucleic Acids [23]: Reprinted (adapted) with permission from {Royal Society of Chemistry}. Copyright 2015, Royal Society of Chemistry; (b) Hair-pin Structure Change of Aptamers [28]: Reprinted (adapted) with permission from {American Chemical Society}. Copyright 2010, American Chemical Society; (c) Structure Change of MBs [33]: Reprinted (adapted) with permission from {Elsevier B.V.}. 2021 Elsevier B.V. All rights reserved.

2.2 Protein bioreceptors

2.2.1 Enzymes

Enzymes are protein molecules that reduce the activation energy of biological reactions to increase the rates of reactions. Through their unique 3D structures and abundant secondary frameworks, the enzymes provide specific binding sites for substrates of biological reactions (**Figure 3a**) [41]. When enzymes accelerate biological reaction, electrochemical events occur at the interface, which generate redox electron movement and change the interface electrical characteristics. Therefore, researchers have invented variety of enzyme receptor biosensors by direct enzymatic methods and enzyme-linked methods to detect enzyme targets around the electrode/electrolyte interfaces. Naima et al. reported a bovine liver catalase biosensor to detect catalase reaction with cyanide as ligand and inhibitor [42]. Carmen et al. announced a real-time biosensor relied on glucose oxidase that responds linearly to glucose consistences from 0 mM to 20 mM [43]. Mohanarangan et al. invented a urease biosensor whose maximum velocity (V_{max}) is 5000 ohms/min [44]. Even though enzymes can achieve precise identification, their vulnerability and high production costs still restrict their wide applications.

2.2.2 Receptors

Receptors, different from enzymes, are protein molecules which recognize signal ligand molecules from inside or outside of cells to adjust cell functions, showing in **Figure 3b** [45]. They are highly evolved to detect their target signal molecules with outstanding specificity and sensitivity. Receptors can be divided into three types based

on their different functions: relay, amplify, or integrate a signal [46]. These three functions lead receptors compatible for more electrochemical events in biorecognition. In addition, these functions have great prospects in programming logic circuits to form biochips. Roshan et al. reported a fruit fly receptor biosensor to detect odorant molecules down to femtomolar concentrations [47]. Maarten et al. invented a mGlu₂ receptor biosensor to research its pharmacology, as the mGlu₂ receptor is a medicine target for many psychiatric disease treatments [48]. Mayall et al. announced a lipopolysaccharide biosensor using TLR-4 protein dimers to detect Gram-negative bacteria with a high sensitivity and insensitive to both Gram-positive bacteria and virus [49]. However, due to the hydrophilic and hydrophobic properties of the cell membrane phospholipid bilayer, there are certain obstacles to the purification and expression of the receptor protein [50].

2.2.3 Immunoreceptors

Immune systems are the fundamental systems for animals to protect them from various microbial infections or cellular carcinogenesis. Immune systems can be divided into two categories, nonspecific immune and specific immune. Among them, specific immunity has huge biosensor potential due to its unique antigen-antibody response. Antigens are the specific molecules that are different from autologous tissue cells and mostly greater than 10,000 in relative molecular mass. Antigens trigger the generation of antibodies in specific immune response, which is humoral immunity produced by immune B cells. Antibodies produced in this way have specific recognition functions for various antigens. The specific bonding between antigens and antibodies, as shown

in **Figure 3c** [51], leads many inventions of biosensors with antibodies receptors. Tubía et al. reported an antibody-based interdigitated biosensor to monitor *Brettanomyces* in wine and cider spoilage filed, which showed approximately 55% higher sensitivity values in low frequency area than its competitors [52]. Dawid et al. announced an antibody biosensor with boron-doped diamond electrodes, which reached a limitation of 1 fg mL^{-1} in saliva buffer for the M1 protein of influenza virus [53]. Jacobs et al. invented an antibody nanochannel biosensor to detect the erythromycin in different water environment and achieved a sensitivity of 0.001 parts per trillion [54]. Besides, different specific antibody components still show non-negligible potential for biosensors, such as antibody fragments [55], single-chain variable fragments [56] and monobodies [57].

2.2.4 Peptides

Peptides, similar to the relationship between nucleic acids and aptamers/molecular beacons, are the precursor molecules of tremendous number of proteins, which are designed in linear or cyclic chain shapes, as shown in **Figure 3d** [58]. Differing from the frangibility and costliness of proteins, peptides can be acquired easily by chemical synthesis methods in laboratories or in factories while most proteins require participation of eukaryotic cell engineering. Analogous to the editable sequence of nucleic acids, peptides perform an exceeding variability due to their twenty-two kinds of amino acid base elements while nucleic acids are base from eight kinds of riboses with smaller numbers of nucleic acid analogues used widely including peptide nucleic acid (PNA), morpholino (MNA) and threose nucleic acid (TNA). Accordingly,

peptides reveal tremendous potential of combining positions with diverse bonding methods without complex secondary structures. Cho et al. proclaimed a novel affinity peptide-incorporated biosensor for the detection of neutrophil gelatinase-associated lipocalin (NGAL) under acute kidney injury and diabetes with a more sensitive limit of detection (LOD) was 1.74 ng mL^{-1} comparing to a SWV's LOD of 3.93 ng mL^{-1} . Furthermore, the peptide they introduced was designed with the information of the M13 phage display library, which shows an alternative way for peptide biosensors [59]. Malvano et al. obtained a nisin-based EIS biosensor using its antimicrobial properties and responding the distinct impedimetric behaviors captured after the exposure to pathogenic and non-pathogenic *Salmonella* strains separately, with a limit of $1.5 \times 10^1 \text{ CFU mL}^{-1}$ [60]. Shi et al. develop a label-free biosensor with affinity peptides selected from phage-displayed peptide library and modified later, which is equipped with a low sensing limit of 20 CFU mL^{-1} and a linear scope from 2×10^2 to $2 \times 10^6 \text{ CFU mL}^{-1}$ [61].

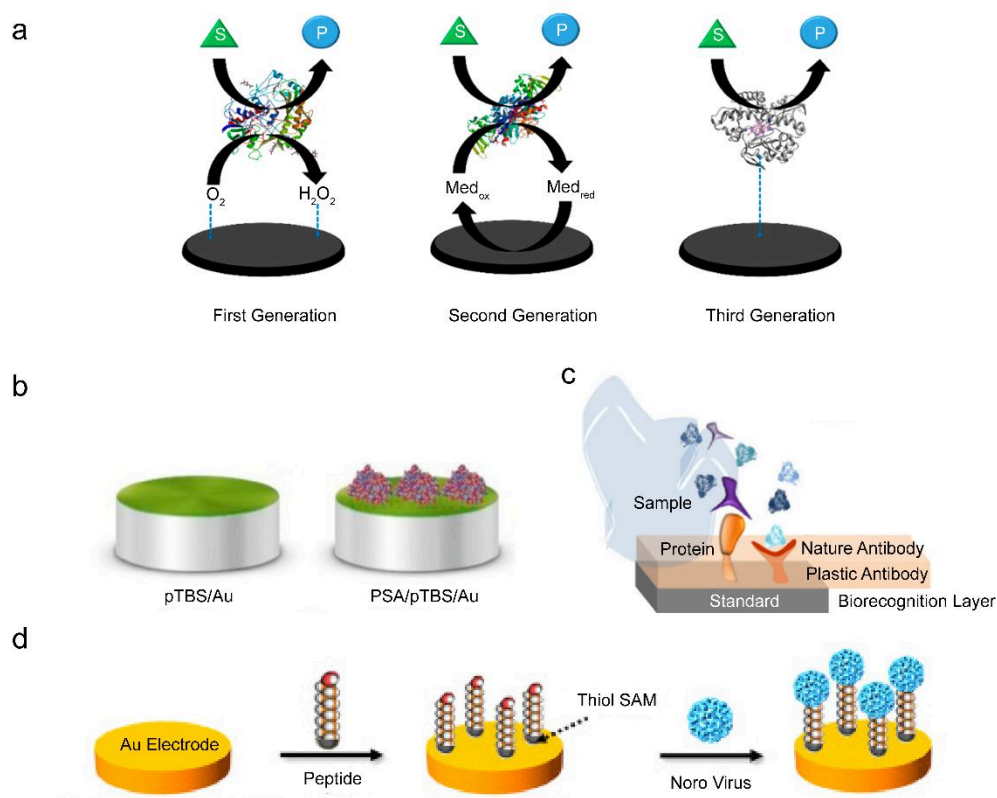


Figure 3 Protein bioreceptors. (a) 3D Structures and Abundant Secondary Frameworks of Enzymes [41]: Open Access from {MDPI}. Copyright 2019, MDPI; (b) Demonstration of Receptor-based Biosensors [45]: Reprinted (adapted) with permission from {Elsevier B.V.}. 2020 Elsevier B.V. All rights reserved; (c) An Example of Receptor-based Biosensors [51]: Reprinted (adapted) with permission from {Elsevier B.V.}. 2018 Elsevier B.V. All rights reserved; (d) Structures of a Peptide-based Biosensor [58]: Reprinted (adapted) with permission from {Elsevier B.V.}. 2018 Elsevier B.V. All rights reserved.

2.3 Glycan and lipid bioreceptors

Glycans, also called as polysaccharide, mix monosaccharide with proteins and lipids, which are one of the main biomolecules. They play a crucial role in the biorecognition between cell-cell, pheromones and immune molecules, obtaining far more information and ultra-higher structural variability compared to nucleic acids,

proteins or peptides [62]. Recently, glycemics has been developed rapidly and brought a new and tremendous motivation for biosensors.

2.3.1 glycoproteins and glycolipids

According to the current study, glycans are capable to be distinguished as glycoproteins and glycolipids. Specifically, O-glycans combined through -OH of Ser or Thr and N-glycans through -NH₂ of a peptide sequence -Asn-X-Ser/Thr constitute glycoproteins, which is shown in **Figure 4a** [63]. Besides, glycolipids content rhamnolipids, trehalolipids, mannosylerythritol-lipids, cellbiolipids and sophorolipids, 5 derivatives in total, as shown in **Figure 4b** [64]. Notably, lectin has been selected by researchers as a natural library for biosensor designing and assembling, and their interaction is concluded in **Figure 4c** [65]. Klukova et al. first announced a label-free lectin/GO biosensor without any synergy of polymer for the detection of 1 aM glycoproteins, which also reveal that GO benefits the sensitivity [66]. Simão et al. achieved a biosensor which is based on cysteine (Cys), zinc oxide nanoparticles (ZnONp), and Concanavalin A (ConA) lectin aiming to differentiate arboviruses infections, including Dengue type 2 (DENV2), Zika (ZIKV), Chikungunya (CHIKV), and Yellow fever (YFV), showing significant distinct in impedance responses [67]. Rangel et al. proclaimed a biosensors using the lectin from *Arachis hypogaea* (peanut agglutinin, PNA), which showed a 7.2% increase in impedance at 100 ng of target, with very high stability under interfering proteins [68]. Ramkumar et al. introduced a biosensor for detection of dopamine by gold electrodes with thiourea linked glycolipid to synthesize polyaniline (PANI) spheres, which performed a linear scope of ~ 1 to 640

μM , a sensitivity range of $370 \mu\text{A cm}^{-2} \mu\text{M}^{-1}$, a limit of 10 nM , a response time of $\sim 5 \text{ s}$ and a selectivity for real sample analysis [69].

2.3.2 liposomes and lipid bilayers

Recently, liposomes and lipid bilayers biosensors have attracted quite a few attentions. Lipids, due to their structure in one end is hydrophilic and the other end is hydrophobic, perform excellent capability for diversity of biorecognitions. General speaking, liposomes are typically 20nm - $10\mu\text{m}$ in size, while the lipid bilayers are $4\text{-}5 \text{ nm}$ thick. This structure characteristics brings them a relatively big surface and abundant combining position, which can also designed as arrays, thus offering significant potential for use in biosensors, showing in **Figure 4d** [70]. Khadka et al. announced that OrX/Orco liposomes bind NHS/EDC-activated SAMs of 6-MHA and were immobilized on gold surfaces for receptor function with the integrity of membrane, enabling of their target ligands down to sub-femtomolar levels via EIS with sensitive and selective detection [71]. Divya et al. announced a biosensor based on the vesicle structure formed by binary liposome mixture of cationic liposome N-[1-(2,3-Dioleoyloxy) propyl]-N,N,N-trimethylammonium propane (DOTAP) and the zwitterionic liposome 1,2-Dioleoyl-sn-Glycero-3-Phosphoethanolamine (DOPE) for detection of label free DNA and streptavidin, which access the limit of $1 \times 10^{-14} \text{ M}$, 1 ng ml^{-1} and linearity range of 1×10^{-13} to $1 \times 10^{-13} \text{ M}$, 100 ng to $1 \mu\text{g}$, respectively [72]. Gomes et al. constructed a biosensor relied on nitric oxide reductase co-structed with phospholipid bilayer and carbon nanotubes, which exhibited a sensitive Michaelis-Menten constant ($4.3 \mu\text{M}$), broad linear range ($0.44\text{-}9.09 \mu\text{M}$), precise limit ($0.13 \mu\text{M}$),

promising repeatability (4.1% RSD), reproducibility (7.0% RSD), and stability (ca. 5 weeks) [73].

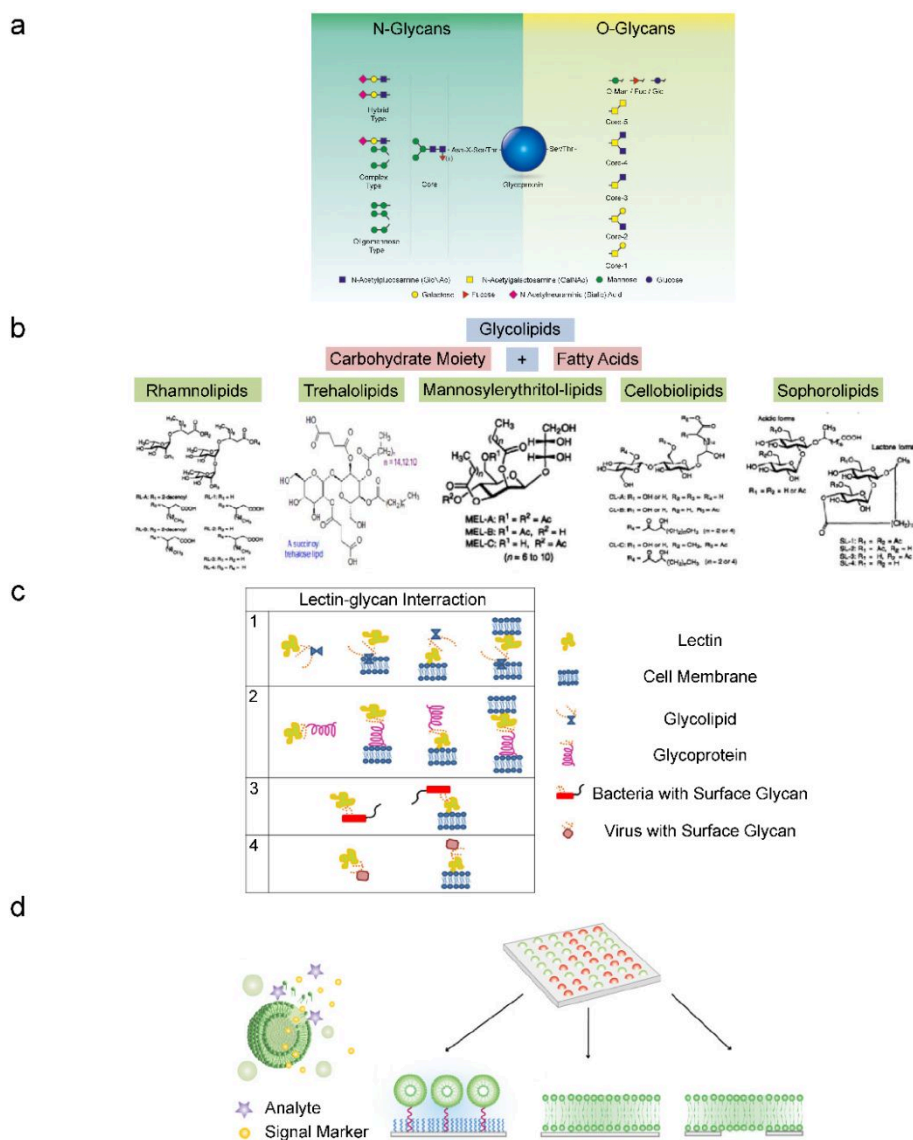


Figure 4 Glycan and lipid bioreceptors. (a) Glycoproteins and Glycolipids [63]: Reprinted (adapted) with permission from {Portland Press LTD}. Copyright 2016, Portland Press LTD; (b) Different Types and Their Structures of Glycolipids [64]: Reprinted (adapted) with permission from {Springer Science Business Media, LLC}. Copyright 2017, Springer Science Business Media, LLC; (c) Lectin-carbohydrate Interactions [65]: Reprinted (adapted) with permission from {Elsevier Inc}. Copyright 2019 Elsevier Inc. All rights reserved.; (d) Liposomes and lipid bilayers in biosensors

[70] Reprinted (adapted) with permission from {Elsevier B.V.}. Copyright 2017 Elsevier B.V. All rights reserved.:

2.4 Cell bioreceptors

Cells, standing on a more integral and macroscopic level than molecules mentioned above, are the fundamental elements for nearly all kinds of bioreactions. Cells provide a natural and complete environment for multiple kinds of bioreactions, and accordingly show a better accuracy and more possibilities for potential subsequent bioreactions of biosensors targets. Under different target stimulants, cells preform quantizable changes, such as metabolic custom change, fluorescence, electron transmission, acquisition or release of chemicals, lysis or remodeling of biofilm and cell apoptosis, some of which can be transformed into electrochemical signals and measured [74]. Besides, cell biosensors are capable for multitargets and those bioreactions whose mechanism have not been well studied. In general, cell-based biosensors can be divided into two categories, one is fixed cell array biosensors, and the other are floated cell biosensors (**Figure 5**) [74]. Fixed cell array biosensors are designed with a certain cell subsequence to detect the bio-electrochemical transforming of cells induced by targets. Floated cell biosensors are based on the ‘fishing net effect’ to capture cell before and after irritations. Either of these two species of cell biosensors are constructed from the multimolecular biorecognitions between cell membranes and functionalized materials, which thanks to the achievements of material science and molecular biology.

With the intriguing future of cell-based biosensors, massive efforts have been

contributed into this field. Classified by the type of cell used in cell sensors, they can be distinguished into prokaryote and eukaryotes biosensor. Prokaryotes are widely used in environmental monitoring and food-toxin detections for their low cultivation cost under massive usages and robust durability under external environment change. In addition, the primitive restriction of their genetic materials brings promising prospective for researchers to design and express requirements. However, because of their primitivity, biomolecules on cell membranes are relatively simple, thus limiting the diversity of biometric recognitions between nanomaterials and cells. Being distinct from prokaryotes, eukaryotes are used as bioreceptors for drug screening and disease surveillance for their larger number and better-evolved biomolecules on the membranes. Ye et al. introduced a method to appraise the antioxidant effect of Ph through 3D cell modification upon a glassy carbon electrode (GCE), who has a determination limit (LOD) of $1.96 \mu\text{mol L}^{-1}$ and an obvious correlation between reactive oxygen species (ROS) and R_{et} , while the value of Ph is varying [75]. Xia et al. invented a cell biosensor for assessing the individual and mixed toxicity of deoxynivalenol (DON), zearalenone (ZEN), and Aflatoxin B1 (AFB1) on Hep G2 cells, which achieved 48.5, 59.0, and $3.10 \mu\text{g mL}^{-1}$ of IC_{50} , respectively [76]. Ge et al. proclaimed a cell-based biosensor used to accomplish the antioxidant capacity of cell-free extracts from *Lactobacillus plantarum* strains isolated from Chinese dry-cured ham, which relies on the existence of cellular reactive oxygen species (ROS) (the flux of H_2O_2 released from RAW 264.7 macrophage cells) to indirectly detect changes in intracellular oxidative stress influenced by *L. plantarum* strains, with the limitation of $0.02 \mu\text{M}$ and a linear

response from 0.05 μM to 0.85 μM [77].

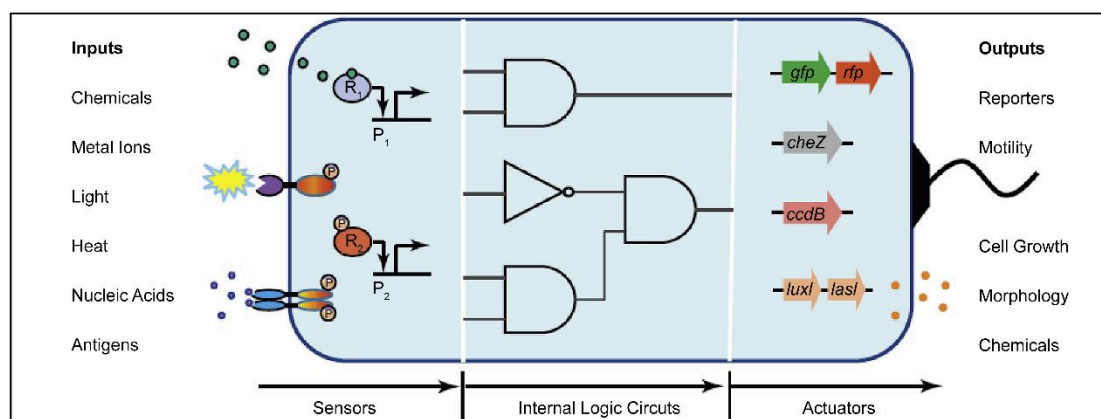


Figure 5 General design of cell-based biosensors [70]: Reprinted (adapted) with permission from {Elsevier B.V.}. Copyright 2019 Elsevier B.V. All rights reserved.

3. Metal nanomaterial-based biosensors

In the previous section we focused on the different bioreceptors. In fact, in order to improve the accuracy and selectivity of the biosensor, the material and structural design of the receptor is particularly important. Numerous materials have been demonstrated their promisingly biosensing capabilities, including metal nanoparticles [78], and metal compounds [79], and a variety of nanocarbon materials (co-structed quantum dots [80], carbon nanotubes [81], graphene, [82] and metal organic frameworks [83]), etc. In particular, the wide application of metal nanomaterials in the field of electrochemistry has greatly stimulated innovations in EIS biosensing, where they are used as biological receptors and transducers. In this section, we present various biosensors based on metal nanomaterials (Table 1), which can not only combine with biological receptors to form more sensitive transducer, but their own selectivity and notable catalytic capabilities are beneficial to inspire the development of unique biosensors.

Table 1 Summary of Metal Nanomaterials-based Biosensors

Target	Sensor composition	detection limit	Ref.
E. coli O157:H7	gold electrodes/1,6-hexadithiol /AuNPs	48 cfu/mL	98
glycerol	gold electrode/molecular imprinted polymer/acrylamide/bisacrylamide /AuNPs	0.001 µg/mL	99
DNA	Pt electrodes/polyaniline nanowires/AgNPs	2.80×10^{-15} M	101
H ₂ O ₂	screen-printed carbon electrode/PtNPs	24.9 nM	103
glucose	Cu electrode/monolayer and bilayer graphene/CuNPs	1.39 µM	105
acetylcholine	Glass carbon electrode/Acetylcholinesterase/ Fe ₂ O ₃ nanoparticles/poly (neutral red) film	1.04 µM	114
H ₂ O ₂	glass carbon electrode/MnO ₂ /graphene nanosheets	0.19 µM	118
3-phenoxybenzoic acid	glass carbon electrode/Cu-doped MoS ₂ thin films	3.8×10^{-6} M	55
Aeromonas hydrophila	glass carbon electrode/ZnS ₂ nanospheres	1×10^{-13} mol/L	121

bisphenol A	carbon paste electrode/TiN/reduced graphene oxide	0.19 nmol/L	126
4-nitroquinoline N-oxide	screen-printed carbon electrode/Fe ₂ N NPs/reduced graphene oxide	9.24 nM	29
glucose	screen-printed carbon electrode/hierarchical Au-Ni alloy/conductive polymer	0.29 μM	134
organophosphate	glass carbon electrode/Pd-Ni	0.05 pM	136
pesticides	nanowires/monolayer MoS ₂ nanosheet		

3.1 Metal simple substance nanomaterials

Gold (Au), as a typical precious metal, has been widely assembled in EIS biosensing over the past several decades. Venditti et al. published a comprehensive review and distinguished Au simple substance nanomaterials into six categories, namely spheres, rods, stars, cubes, hollow particles and capsules/cages, as shown in **Figure 6** [84]. Among all these shape types of Au simple substance nanomaterials, spherical particles are most frequently used in EIS biosensing. Au spherical particles as a potential material for transducer, several properties lead to its selection: 1) high specific surface area, 2) high conductivity, 3) non-toxicity and 4) abundant bonding forms. As well known, nanoparticles have high specific surface area. More importantly, gold has high conductivity, with a theoretical conductivity of $4.25 \times 10^7 \text{ S m}^{-1}$, quite close to $6.30 \times 10^7 \text{ S m}^{-1}$ for silver and $5.96 \times 10^7 \text{ S m}^{-1}$ for copper, which enhances the sensitivity and intensity of the electric signals coming from biorecognitions. Regarding

the toxicity of Au nanoparticles, there is no uniformity, because their toxicity is caused by different sizes and surface chemical states. Several reports revealed an interesting fact that particles around 4-5 nm are usually not toxic under acute exposure [85] [86] [87]. On the contrary, nanoparticles larger than 5nm perform totally the opposite under the same situation resulting from high density and specific cell bioreactions [88] [89] [90] [91]. As for the bonding forms, they can be differed into two factors: a) covalent bonding and b) non-covalent bonding. In general, Au-S-R and Au-NH₂-R bonds are two common covalent bonds because of the convenient functionalization with sulfhydryl groups (-SH) and amino groups (-NH₂) and the robust stabilities of these two types of bonds [92]. This effect of functionalization results from three factors: 1) the dosage of functionalized molecules, 2) the size of Au nanoparticles (AuNPs) and 3) the steric hindrance of functionalized molecules [93]. Besides, this binding occurs not only between AuNPs and biomolecules, but also between AuNPs and electrodes. Non-covalent bonds, more often designed to be emerged between AuNPs and electrodes, can be concluded as follows: direct mixing [94], electrodeposition [95] and electrostatic attraction [96]. Direct mixing contains spin coating, drip coating and stirring, using the Van der Waals forces and high surface to volume ratio for the assembly. Electrodeposition relies on the interface redox reaction between HAuCl₄ and the electrode, or the self-charging properties of AuNPs by external voltage/current method to produce electric field force deposition. Notably, AuNPs always carry a negative charge, so they can achieve self-assembly by electrostatic attraction.

With all the peripeties mentioned above, tremendous number of EIS biosensors

based on Au simple substance nanomaterial have been invented and development these years. Khater et al. announced a biosensor for the DNA detection of citrus tristeza virus, where they electrodeposited AuNPs on the electrode through the reduction of HAuCl_4 and attached AuNPs to hybridized target DNAs for detection with sulfate-functionalized probe DNA, using impedance as a means of evaluation, whose impedance has a linear range for consistence from 0.1 to 10 μM of synthetic DNA [97]. Lin et al. used 1,6-hexadithiol as a bridging molecule connecting gold electrodes and AuNPs to obtain an EIS biosensor for sensing *E. coli* O157:H7, with a limit of 48 colony-forming units (cfu mL^{-1}), three times lower than panel biosensors, and a broader dynamic range (up to 10^7 cfu mL^{-1}) [98]. Motia et al. invented a molecular imprinted polymer (MIP)/acrylamide/bisacrylamide (AAM/NNMBA) and AuNPs biosensor formed on screen-printed gold electrode (Au-SPE) for the sensing of glycerol in cosmetics, whose linear range is 20.00-227.81 $\mu\text{g mL}^{-1}$ and a determination limit of 0.001 $\mu\text{g mL}^{-1}$ (signal-to-noise ratio $S/N = 3$) [99]. The reason for the unique deposition of MIP to create cavities over a large area is not mentioned in their report, it may be owing to the electron withdrawal conjugation between carbon-carbon double bonds and carbonyl groups, resulting in the deposition and attachment of MIPs to AuNPs.

Since Au attracts plenty of attention in this field, silver (Ag), as a family member of Au, also plays an essential role as transducers. Douaki et al. reported a biosensor based on the Ag-S binding between 1,8-octanedithio and silver nanoparticles (AgNPs), showing that the covalent linkage of sulfhydryl groups is also applicable to AgNPs. And the sensor showed a relatively wide linear range of 1 fM-35 μM , when used for

the detection of furfural in the food industry [100]. Tran et al. prepared a biosensor formed by polyaniline nanowires and AgNPs, showing not only the potential for adhesion to the electrode surface, but also a new electrodeposition and electropolymerization, which was used to detect target DNA with a limit of 2.80×10^{-15} M [101]. Liu et al. invented a AgNPs EIS biosensor for the determination of IgE (Immunoglobulin E) in asthma, with a limitation of 1 pg mL^{-1} and its linear range from 10 pg mL^{-1} to $1 \mu\text{g mL}^{-1}$ [102], which proved that the heavy metal toxicity of silver ions is invalid for certain proteins.

Above we presented metallic singlet nanomaterials attached to enzymes or DNA as sensors, but in fact the catalytic effect of these metallic singlet nanomaterials in an electrochemical environment can also make them a biosensor with a non-enzymatic strategy. Currently, more non-enzymatic sensors based on catalyzed effect that have been studied include noble metal-catalyzed H_2O_2 to monitor H_2O_2 content, and non-precious metal-catalyzed glucose to detect glucose content. Jiménez-Pérez et al. modified a screen-printed carbon electrode with platinum nanoparticles to obtain a biosensor for monitoring H_2O_2 monitoring in living cells with a limit of 24.9 nM and a real-time tracking durability for more than 12 h [103]. Gholami et al. introduced a biosensor based on silver nanoparticles coated with carbon microfibers for the super selective detection of H_2O_2 , obtaining two linear ranges of 2.0-10 mM and 10.0-100 mM with the limitation of 0.48 μM [104]. Wang et al. announced a biosensor for glucose sensing with monolayer and bilayer graphene doped with copper nanoparticles produced by CVD, which has a linear range of 0.02-2.3 mM, a determination limit of

1.39 μM , $\text{S/N} = 3$ and high sensitivity with relatively fast response time [105]. Palve invented a glucose biosensor with copper nanowire–carbon nanotube bilayer, who had a linear range of 10 μM –2000 μM , a limit value of 0.33 nM and a quick response time within 1 s [106]. Wang reported a biosensor formed with Cu nanoparticles deposited on carbon nanotubes and ferrocene-branched chitosan for the determination of glucose, which performed a broad linear range of 0.2 mM to 22 mM, a limit of 13.52 μM and a sensitive limitation of 1.256 $\mu\text{A mM}^{-1} \text{cm}^{-1}$ [107].



Figure 6 Schematic representation of the main morphologies of gold-based nanomaterials [84]:

Open Access from {MDPI}. Copyright 2019, MDPI.

3.2 Metal compound nanomaterials

Metal compound nanomaterials, due to their unique chemistry and physics properties notably, have drew researchers' interests to extend their own crucial share in EIS biosensing. Among all the diversity of metal compound nanomaterials, metal oxides, metal sulfides and metal nitrides are the most eye-catching topics [108] [109] [110]. Different from metal simple substance nanomaterials, these three kinds of metal compound nanomaterials show totally opposite peripeties, which are: a) relative low conductivity; b) abundant nanostructures; c) the diversity of bonding forms and sites; d) relative high catalysis ability; e) durability for extreme environment; f) considerable compatibility with biomolecules [111] [112] [113]. However, because of the disappearance bonding between metal atoms, changes in their crystal structure and the alteration of metal atoms' electrons resulting from the introduction of non-metallic atoms, these three types of metal compounds acquire wide band gaps and become semiconductors or even insulators, and accordingly result in poor ion transport kinetics and unexpected volume change under charging and discharging [112]. Therefore, metal compound nanomaterials are usually compounded with carbon materials, other metal nanomaterials and polymers to obtain synergy for a broad range of applications, as shown in **Figure 7** [108] .

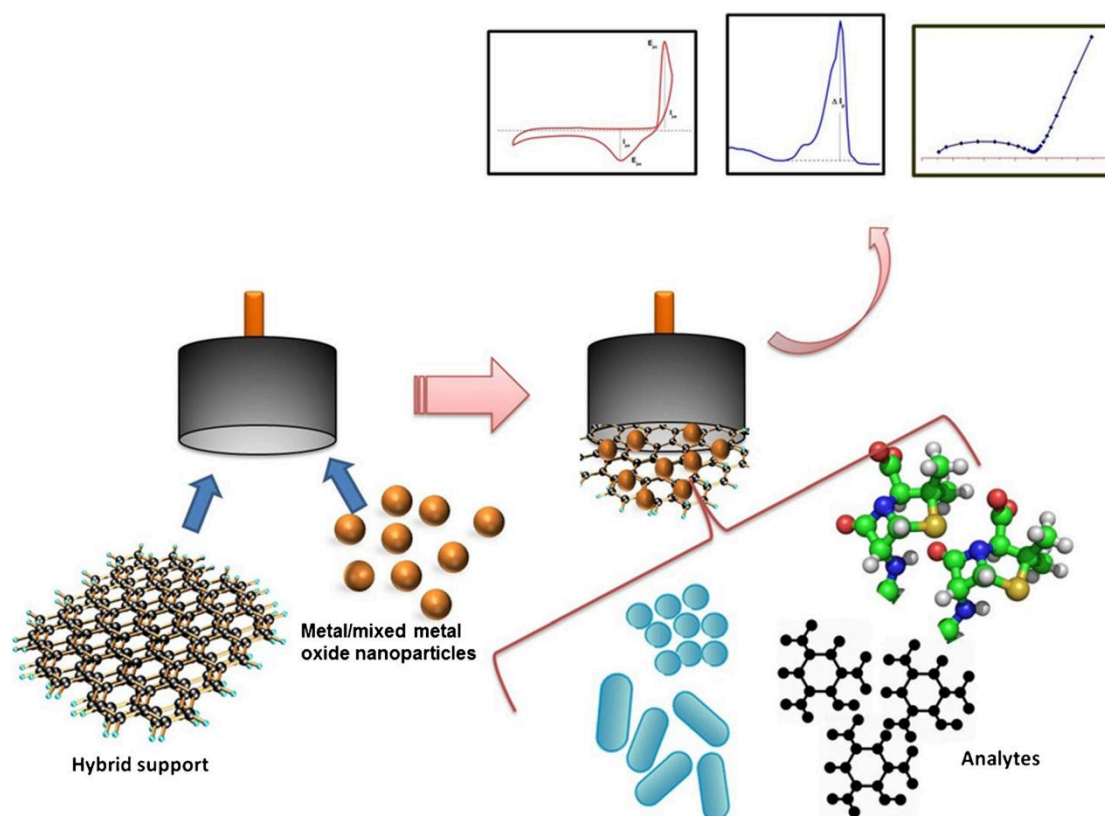


Figure 7 Schematic representation of metal oxide nanoparticle in electrochemical sensing

[108]: Reprinted (adapted) with permission from {Springer-Verlag GmbH Austria, part of Springer Nature}. Copyright 2018, Springer-Verlag GmbH Austria, part of Springer Nature.

Variety of metal oxide nanomaterials have shown their splendid potential to the application of biosensors, including iron oxide, manganese oxide, titanium dioxide, copper oxide, zinc oxide, zirconia, cobalt oxide, nickel oxide, tungsten oxide, vanadium oxide, silver oxide, etc. Some of them have only shown one of the two functions while others have contributed into both two fields, which we will discuss below selectively. As the role of transducer function, Silva et al. proposed a electrochemical biosensor based on acetylcholinesterase grafted Fe_2O_3 nanoparticles/poly(neutral red) modified electrodes, which acquired a dtermination limit of $1.04 \mu\text{M}$ for acetylcholine [114]. Xue et al. presented an impedance biosensor rooted in manganese dioxide nanoflowers

modified with capture antibodies for *Salmonella typhimurium*, capable of isolating approximately ~60% of *Salmonella* from 10 mL samples with its linear range from 3.0×10^1 to 3.0×10^6 CFU mL⁻¹ in 1.5 h and reaching a determination limit of 19 CFU mL⁻¹ [115]. Yu et al. achieved a p-nonylphenol biosensor formed by TiO₂ and polypyrrole, and the linear concentration range of this sensor was from 1.0×10^{-8} to 8.0×10^{-5} with a detection limit of 3.91×10^{-9} [116]. As the role of transducer-catalysis function, Li et al. invented a biosensor using α -Fe₂O₃ nanoparticles to catalyze the electrooxidation of dopamine, which showed linearity over the dopamine concentration range of 2 μ M–80 μ M and a detecting limit (3 σ /s) and sensitivity of 1.15 nM and 95.57 μ A μ M⁻¹ cm⁻¹ [117]. Guan et al. proclaimed a non-enzyme H₂O₂ biosensor with manganese dioxide-graphene nanosheets, which reported with a linear range of 0.5–350 μ M, a determination limit of 0.19 μ M (S/N = 3) and a sensitivity of 422.10 μ A mM⁻¹ cm⁻¹ [118]. Chen et al. obtained a theophylline electrocatalytic detection biosensor based on rutile-type titanium dioxide microspheres and its decorated graphene oxide, whose linear range accessed from 0.02 to 209.6 μ M, its limit reached 13.26 nM and sensitivity achieved 1.183 μ A μ M⁻¹ cm⁻² [119].

Metal sulfide nanomaterials, as one of the representatives of metal compounds, their diversity demonstrate their potential in biosensors. Binary sulfides, ternary sulfides and quaternary sulfides also have performed both transducer function and catalysis function. For the transducer function, Li et al. announced a biosensor based on multiwalled carbon nanotubes and cobalt(II) sulfide nanoparticles immobilized with glucose oxidase for glucose detection, which had a linear range of 8 μ M to 1.5 mM and

a high sensitivity of $15 \text{ mA M}^{-1} \text{ cm}^{-2}$ [120]. Giang et al. introduced an EIS biosensor based on PSA antibodies fragments and Cu doped CoS_2 /3-phenoxybenzoic acid thin films, which reached a sensitivity of $5.9 \times 10^8 \Omega \text{ cm}^2 \text{ M}^{-1}$ and a detection limit of $3.8 \times 10^{-6} \text{ M}$ [55]. Negahdary et al. claimed a DNA sensor for the detection of *Aeromonas hydrophila* with ZnS_2 nanospheres, which obtained a range of 1.0×10^{-4} to $1.0 \times 10^{-9} \text{ mol L}^{-1}$ with a detection limit of $1 \times 10^{-13} \text{ mol L}^{-1}$ [121]. For the transducer-catalysis function, Govindasamy et al. invented a biosensor with reduced graphene oxide decorated on Cu_2S nanospheres, which was used for the non-enzymes detection of chloramphenicol with a LOD for CAP of 15.3 nM , linear range of 60 nM to $1954.5 \mu\text{M}$ and sensitivity of $12.538 \mu\text{A } \mu\text{M}^{-1} \text{ cm}^{-1}$ [122]. Guo et al. proclaimed a nonenzymatic glucose sensor consisting of NiCo_2S_4 nanowire arrays and electrospun graphitic nanofiber films, which achieved a splendid linear range of $0.0005\text{--}3.571 \text{ mM}$ with $R^2 = 0.995$ and detection limit of $0.167 \mu\text{M}$ with $S/N = 3$ [123]. Zhou et al. reported a $\text{Cu}_2\text{ZnSnS}_4$ quantum dot for the non-enzymatic detection of glucose, which is claimed to be the first electrochemical quantum dots on tin oxide glass, and significantly enhanced its remarkable sensitivity from 1561 to $2503 \mu\text{A mM}^{-1} \text{ cm}^{-2}$ [124].

Metal nitride nanomaterials are also considered as unrivaled candidates for electrochemical impedance biosensors. Among all the nanomaterials we have discussed, nitride nanomaterials are divided into two categories. One is the field-effect transistor biosensors, which are based on the variation of two-dimensional electron gas resulting from the surface environment transforming caused by capture biomolecules, and change their conductance accordingly [125], of which the Group III nitride

nanomaterials are the one of the most mentioned and have been extensively reviewed by Li et al. [110]. Although field-effect transistor biosensors can be regarded as electrochemical biosensors broadly, metal nitride nanomaterials are more representative for their wide application as working electrodes in electrochemical sensing. Regarded as transducer, Xu et al. proposed a titanium nitride-reduced graphene oxide composite incorporating molecular imprinting for the sensing of bisphenol A (BSA), reaching a linear dependence from 0.5 to 100 nmol L⁻¹ and observing a limitation of 0.19 nmol L⁻¹ [126]. Liu et al. demonstrated a biosensor utilizing the integration of polydopamine (PDA) on the surface of GaN nanowire modified with AuNPs to monitor alpha-fetoprotein (AFP), whose linear range between 0.01 and 100 ng mL⁻¹. and its limitation touched downward 0.003 ng mL⁻¹ [127]. Regarded as transducer-catalysis function, Chen et al. announced a non-enzyme glucose sensor with nickel nitride decorated nitrogen doped carbon spheres through one-pot fabrication, which performed two broad linear ranges from 1 μM to 3000 μM and 3000 μM to 7000 μM, while its high sensitivity was 2024.18 μA mM⁻¹ cm⁻² and 1256.98 μA mM⁻¹ cm², respectively [128]. Rajaji et al. designed a biosensor towards 4-nitroquinoline N-oxide (4-NQO) using reduced graphene oxide (rGOS) functionalized with iron nitride nanoparticles (Fe₂N NPs), which obtained a broad linear window between 0.05-574.2 μM and a limitation of 9.24 nM down to nanomolar level [129].

3.3 Alloy nanomaterials

Monolithic metals may have shortcomings in sensor applications, so alloyed materials have entered the vision of researchers with their more competitive properties

for biosensing. Scientists briefly identified several types of nanoalloys such as: a) mutual regulation in crystallization [130]; b) template effect in nano construction [131]; c) distortion of electron cloud caused by heteroatoms [132] and d) facultative usage of properties from original component atoms [133]. Therefore, it can be concluded that the interactions between alloy atoms would contribute to enhance the overall effect of the alloy materials to further promote their wide application in the field of biosensors.

Fertilized as transducer function, Lee et al. announced a glucose biosensor consisting of hierarchical Au-Ni alloy and conductive polymer, which attained a linear range from 1.0 μM to 30.0 mM and a determination limit of 0.29 μM . Additionally, they compared the coefficient of variation of enzymatic and non-enzymatic strategies, which obtained 1.82%, $n = 5$ of enzymatic sensors and 2.93% for non-enzymatic sensors [134]. Yadav et al. invented a Pb^{2+} ions detection biosensor based on the Ag-Au alloy nanoparticles conjugated with aptamer, which led to a linear slope of 0.01-10 $\mu\text{g L}^{-1}$ and minimum detectable Pb^{2+} concentration of 0.8 μM [135]. Song et al. designed several three-dimensional porous bimetallic alloy nanowires compounded and monolayer MoS_2 nanosheet (m- MoS_2) as biosensor for the determination of organophosphate pesticides via acetylcholinesterase inhibition pathway. Among all the candidates, Pd-Ni NWs/m- MoS_2 showed the most stunning outcome, which achieved a linear range from 10^{-13} M to 10^{-7} M with a sensitive limitation of 0.05 pM under a signal-to-noise ratio of 3 [136].

Fertilized as transducer-catalysis function, Gao et al. claimed a non-enzyme glucose biosensor with in situ assemble of $\text{Ni}(\text{OH})_2/\text{TiO}_2$ film on NiTi alloy, which

reached a sensitivity of $192 \mu\text{A mM}^{-1} \text{cm}^{-2}$, a determination limit of $8 \mu\text{M}$ and a response time of within 1 s [137]. Shim et al. demonstrated a core-shell structured Au@Pt alloy with particle sizes ranging from 35 nm to 60 nm, which was further used as a non-enzymatic glucose biosensor to determine glucose in two dynamic ranges of 0.5-10.0 μM and 0.01-10.0 mM with 0.99 as its correlation coefficient and a limit of 445.7 (± 10.3) nM [138]. Li et al. illustrated an amaranth biosensor based on molecularly imprinted Pd-Cu bimetallic alloy modified graphene, which performed a linear relationship with amaranth concentration of 0.006-10 μM and its limit reached downward 2 nM with considerable selectivity [139].

4. Conclusions and perspectives

In conclusion, metal nanomaterials-based EIS biosensors are widely used in medical healthcare, environmental monitoring, and food safety instructively. Bioreceptors and metal nanomaterials are the topic of our demonstration and discussion, which shows multiple strategies to accomplish the feasibility, specificity, sensitivity and simplicity of manufacture and operations for metal nanomaterials-based EIS biosensors. Their respective properties and combined features are exhibited and compared for researchers to form a vivid method library. Our review aims to assist brief acknowledge of current achievement and inspire tremendous innovation in the future.

Although this review summarizes many achievements of metal nanomaterials in the field of electrochemical sensing, the development of electrochemical sensing is still limited, mainly by the current lack of development of metal nanomaterials, including structural limitations and cost constraints. Therefore, we are eager to discuss and

witness more breathtaking improvements in the following prospects. 1, Designing new metallic nanomaterials with secondary structures that may lead to a future of nanomaterials with biometric and specificity in terms of structural matching. 2, Reducing the amount of precious metals to decrease costs, such as the application of single atoms, carbonization of metal-organic framework, and metal-black phosphorus composites. 3, Exploring more non-precious metals to replace the existing precious metals is also an avenue for biosensor development, such as manganese, cadmium, nickel, etc.

Conflicts of interest

There are no conflicts to declare.

Acknowledgments

This work was financially sponsored by the National Natural Science Foundation of China (51672204, 22102128).

References

1. Hao N, Lu J, Zhou Z, Hua R, Wang K. A pH-Resolved Colorimetric Biosensor for Simultaneous Multiple Target Detection. *ACS Sensors*. 2018;3(10):2159-2165. doi:10.1021/acssensors.8b00717
2. Cennamo N, Zeni L, Tortora P, et al. A High Sensitivity Biosensor to detect the presence of perfluorinated compounds in environment. *Talanta*. 2018;178:955-961. doi:10.1016/j.talanta.2017.10.034
3. Xiang W, Lv Q, Shi H, Xie B, Gao L. Aptamer-based biosensor for detecting carcinoembryonic antigen. *Talanta*. 2020;214:120716. doi:10.1016/j.talanta.2020.120716
4. Mao K, Zhang H, Yang Z. An integrated biosensor system with mobile health and wastewater-based epidemiology (iBMW) for COVID-19 pandemic. *Biosens Bioelectron*. 2020;169:112617. doi:10.1016/j.bios.2020.112617
5. da Silva MKL, Vanzela HC, Defavari LM, Cesarino I. Determination of carbamate pesticide in food using a biosensor based on reduced graphene oxide and acetylcholinesterase enzyme. *Sensors Actuators, B Chem*. 2018;277:555-561. doi:10.1016/j.snb.2018.09.051
6. Uniyal S, Sharma RK. Technological advancement in electrochemical biosensor based detection of Organophosphate pesticide chlorpyrifos in the environment: A review of status and prospects. *Biosens Bioelectron*. 2018;116:37-50. doi:10.1016/j.bios.2018.05.039
7. Zheng L, Cai G, Wang S, Liao M, Li Y, Lin J. A microfluidic colorimetric

- biosensor for rapid detection of Escherichia coli O157:H7 using gold nanoparticle aggregation and smart phone imaging. *Biosens Bioelectron.* 2019;124-125:143-149. doi:10.1016/j.bios.2018.10.006
8. Peña-Bahamonde J, Nguyen HN, Fanourakis SK, Rodrigues DF. Recent advances in graphene-based biosensor technology with applications in life sciences. *J Nanobiotechnology.* 2018;16(1):1-17. doi:10.1186/s12951-018-0400-z
9. Su L, Zou L, Fong CC, et al. Detection of cancer biomarkers by piezoelectric biosensor using PZT ceramic resonator as the transducer. *Biosens Bioelectron.* 2013;46:155-161. doi:10.1016/j.bios.2013.01.074
10. Maduraiveeran G, Sasidharan M, Ganesan V. Electrochemical sensor and biosensor platforms based on advanced nanomaterials for biological and biomedical applications. *Biosens Bioelectron.* 2018;103:113-129. doi:10.1016/j.bios.2017.12.031
11. Huang L, Yang L, Zhu CC, Deng H, Liu G, Yuan Y. Methylene blue sensitized photoelectrochemical biosensor with 3,4,9,10-Perylene tetracarboxylic acid film as photoelectric material for highly sensitive Pb²⁺ detection. *Sensors Actuators, B Chem.* 2018;274:458-463. doi:10.1016/j.snb.2018.07.135
12. Seo G, Lee G, Kim MJ, et al. Rapid Detection of COVID-19 Causative Virus (SARS-CoV-2) in Human Nasopharyngeal Swab Specimens Using Field-Effect Transistor-Based Biosensor. *ACS Nano.* 2020;14(4):5135-5142. doi:10.1021/acsnano.0c02823

13. Han Y, Chen J, Li Z, Chen H, Qiu H. Recent progress and prospects of alkaline phosphatase biosensor based on fluorescence strategy. *Biosens Bioelectron.* 2020;148:111811. doi:10.1016/j.bios.2019.111811
14. Negahdary M, Heli H. An electrochemical peptide-based biosensor for the Alzheimer biomarker amyloid- β (1–42) using a microporous gold nanostructure. *Microchim Acta.* 2019;186(12):1-8. doi:10.1007/s00604-019-3903-x
15. Xuan X, Kim JY, Hui X, Das PS, Yoon HS, Park JY. A highly stretchable and conductive 3D porous graphene metal nanocomposite based electrochemical-physiological hybrid biosensor. *Biosens Bioelectron.* 2018;120:160-167. doi:10.1016/j.bios.2018.07.071
16. Xu W, Kang Y, Jiao L, et al. Tuning Atomically Dispersed Fe Sites in Metal–Organic Frameworks Boosts Peroxidase-Like Activity for Sensitive Biosensing. *Nano-Micro Lett.* 2020;12(1):1-12. doi:10.1007/s40820-020-00520-3
17. Cui S, Gu S, Ding Y, Zhang J, Zhang Z, Hu Z. Hollow mesoporous CuCo₂O₄ microspheres derived from metal organic framework: A novel functional materials for simultaneous H₂O₂ biosensing and glucose biofuel cell. *Talanta.* 2018;178:788-795. doi:10.1016/j.talanta.2017.09.074
18. Zhang D, Lu Y, Zhang Q, et al. Protein detecting with smartphone-controlled electrochemical impedance spectroscopy for point-of-care applications. *Sensors Actuators, B Chem.* 2016;222:994-1002.

- doi:10.1016/j.snb.2015.09.041
19. Bahner N, Reich P, Frense D, Menger M, Schieke K, Beckmann D. An aptamer-based biosensor for detection of doxorubicin by electrochemical impedance spectroscopy. *Anal Bioanal Chem.* 2018;410(5):1453-1462. doi:10.1007/s00216-017-0786-8
 20. Yu L, Zhang Y, Hu C, et al. Highly sensitive electrochemical impedance spectroscopy immunosensor for the detection of AFB1 in olive oil. *Food Chem.* 2015;176:22-26. doi:10.1016/j.foodchem.2014.12.030
 21. Randviir EP, Banks CE. Electrochemical impedance spectroscopy: An overview of bioanalytical applications. *Anal Methods.* 2013;5(5):1098-1115. doi:10.1039/c3ay26476a
 22. Chang BY, Park SM. Electrochemical impedance spectroscopy. *Annu Rev Anal Chem.* 2010;3(1):207-229. doi:10.1146/annurev.anchem.012809.102211
 23. Yang Z, Kasprzyk-Hordern B, Goggins S, Frost CG, Estrela P. A novel immobilization strategy for electrochemical detection of cancer biomarkers: DNA-directed immobilization of aptamer sensors for sensitive detection of prostate specific antigens. *Analyst.* 2015;140(8):2628-2633. doi:10.1039/c4an02277g
 24. Xu S, Zhang Y, Dong K, Wen J, Zheng C, Zhao S. Electrochemical DNA biosensor based on graphene oxide-chitosan hybrid nanocomposites for detection of *Escherichia coli* O157:H7. *Int J Electrochem Sci.* 2017;12(4):3443-3458. doi:10.20964/2017.04.16

25. Cai W, Xie S, Zhang J, Tang D, Tang Y. An electrochemical impedance biosensor for Hg²⁺ detection based on DNA hydrogel by coupling with DNAzyme-assisted target recycling and hybridization chain reaction. *Biosens Bioelectron.* 2017;98:466-472. doi:10.1016/j.bios.2017.07.025
26. Chen CC, Lai ZL, Wang GJ, Wu CY. Polymerase chain reaction-free detection of hepatitis B virus DNA using a nanostructured impedance biosensor. *Biosens Bioelectron.* 2016;77:603-608. doi:10.1016/j.bios.2015.10.028
27. Zhou W, Jimmy Huang PJ, Ding J, Liu J. Aptamer-based biosensors for biomedical diagnostics. *Analyst.* 2014;139(11):2627-2640. doi:10.1039/c4an00132j
28. Liu Y, Tuleouva N, Ramanculov E, Revzin A. Aptamer-based electrochemical biosensor for interferon gamma detection. *Anal Chem.* 2010;82(19):8131-8136. doi:10.1021/ac101409t
29. Tan F, Cong L, Saucedo NM, Gao J, Li X, Mulchandani A. An electrochemically reduced graphene oxide chemiresistive sensor for sensitive detection of Hg²⁺ ion in water samples. *J Hazard Mater.* 2016;320:226-233. doi:10.1016/j.jhazmat.2016.08.029
30. Ensafi AA, Khoddami E, Rezaei B. Aptamer@Au-o-phenylenediamine modified pencil graphite electrode: A new selective electrochemical impedance biosensor for the determination of insulin. *Colloids Surfaces B Biointerfaces.* 2017;159:47-53. doi:10.1016/j.colsurfb.2017.07.076
31. Istamboulié G, Paniel N, Zara L, Granados LR, Barthelmebs L, Noguer T.

- Development of an impedimetric aptasensor for the determination of aflatoxin M1 in milk. *Talanta*. 2016;146:464-469. doi:10.1016/j.talanta.2015.09.012
32. Tyagi S, Kramer FR. Molecular Beacons: Probes that Fluoresce Upon Hybridization. *Nat Biotechnol*. 1996;14(3):303-308. doi:10.1038/nbt0396-303
33. Zhang Z, Zhang L, Wang Y, et al. Ultrasensitive electrochemical biosensor for attomolar level detection of let 7a based on toehold mediated strand displacement reaction circuits and molecular beacon mediated circular strand displacement polymerization. *Anal Chim Acta*. 2021;1147:108-115. doi:10.1016/j.aca.2020.12.057
34. Tortolini C, Bollella P, Antonelli ML, Antiochia R, Mazzei F, Favero G. DNA-based biosensors for Hg²⁺ determination by polythymine-methylene blue modified electrodes. *Biosens Bioelectron*. 2015;67:524-531. doi:10.1016/j.bios.2014.09.031
35. Wang X, Dong P, Yun W, Xu Y, He P, Fang Y. A solid-state electrochemiluminescence biosensing switch for detection of thrombin based on ferrocene-labeled molecular beacon aptamer. *Biosens Bioelectron*. 2009;24(11):3288-3292. doi:10.1016/j.bios.2009.04.019
36. Fang X, Jiang W, Han X, Zhang Y. Molecular beacon based biosensor for the sequence-specific detection of DNA using DNA-capped gold nanoparticles-streptavidin conjugates for signal amplification. *Microchim Acta*. 2013;180(13-14):1271-1277. doi:10.1007/s00604-013-1044-1
37. Zhan F, Liao X, Gao F, Qiu W, Wang Q. Electroactive crown ester-Cu²⁺

- complex with in-situ modification at molecular beacon probe serving as a facile electrochemical DNA biosensor for the detection of CaMV 35s. *Biosens Bioelectron.* 2017;92(August 2016):589-595. doi:10.1016/j.bios.2016.10.055
38. Li B, Li Z, Situ B, et al. Sensitive HIV-1 detection in a homogeneous solution based on an electrochemical molecular beacon coupled with a nafion-graphene composite film modified screen-printed carbon electrode. *Biosens Bioelectron.* 2014;52:330-336. doi:10.1016/j.bios.2013.09.016
39. He X, Ni X, Wang Y, Wang K, Jian L. Electrochemical detection of nicotinamide adenine dinucleotide based on molecular beacon-like DNA and *E. coli* DNA ligase. *Talanta.* 2011;83(3):937-942. doi:10.1016/j.talanta.2010.10.051
40. Xiong E, Wu L, Zhou J, Yu P, Zhang X, Chen J. A ratiometric electrochemical biosensor for sensitive detection of Hg^{2+} based on thymine- Hg^{2+} -thymine structure. *Anal Chim Acta.* 2015;853(1):242-248. doi:10.1016/j.aca.2014.10.015
41. Nguyen HH, Lee SH, Lee UJ, Fermin CD, Kim M. Immobilized enzymes in biosensor applications. *Materials (Basel).* 2019;12(1):121. doi:10.3390/ma12010121
42. Bouyahia N, Hamlaoui ML, Hnaïen M, Lagarde F, Jaffrezic-Renault N. Impedance spectroscopy and conductometric biosensing for probing catalase reaction with cyanide as ligand and inhibitor. *Bioelectrochemistry.* 2011;80(2):155-161. doi:10.1016/j.bioelechem.2010.07.006

43. Mayorga Martinez CC, Treo EF, Madrid RE, Felice CC. Real-time measurement of glucose using chrono-impedance technique on a second generation biosensor. *Biosens Bioelectron.* 2011;29(1):200-203. doi:10.1016/j.bios.2011.08.018
44. Sundararam M, Janakiraman K, Kumar AS, Lakshminarayanan V, Sankaran K. AC impedance measurement for the enzyme kinetics of urea–urease system: a model for impedimetric biosensor. *Bull Mater Sci.* 2020;43(1):77. doi:10.1007/s12034-020-2055-2
45. Abbasy L, Mohammadzadeh A, Hasanzadeh M, Razmi N. Development of a reliable bioanalytical method based on prostate specific antigen trapping on the cavity of molecular imprinted polymer towards sensing of PSA using binding affinity of PSA-MIP receptor: A novel biosensor. *J Pharm Biomed Anal.* 2020;188:113447. doi:10.1016/j.jpba.2020.113447
46. Furst AL, Francis MB. Impedance-Based Detection of Bacteria. *Chem Rev.* 2019;119(1):700-726. doi:10.1021/acs.chemrev.8b00381
47. Khadka R, Aydemir N, Carraher C, et al. An ultrasensitive electrochemical impedance-based biosensor using insect odorant receptors to detect odorants. *Biosens Bioelectron.* 2019;126:207-213. doi:10.1016/j.bios.2018.10.043
48. Doornbos MLJ, Van der Linden I, Vereyken L, et al. Constitutive activity of the metabotropic glutamate receptor 2 explored with a whole-cell label-free biosensor. *Biochem Pharmacol.* 2018;152:201-210. doi:10.1016/j.bcp.2018.03.026

49. Mayall RM, Renaud-Young M, Chan NWC, Birss VI. An electrochemical lipopolysaccharide sensor based on an immobilized Toll-Like Receptor-4. *Biosens Bioelectron.* 2017;87:794-801. doi:10.1016/j.bios.2016.09.009
50. Chambers JP, Arulanandam BP, Matta LL, Weis A, Valdes JJ. *Biosensor Recognition Elements*. Vol 10.; 2008. doi:10.21775/cimb.010.001
51. Cabral-Miranda G, Cardoso AR, Ferreira LCS, Sales MGF, Bachmann MF. Biosensor-based selective detection of Zika virus specific antibodies in infected individuals. *Biosens Bioelectron.* 2018;113:101-107. doi:10.1016/j.bios.2018.04.058
52. Tubía I, Paredes J, Pérez-Lorenzo E, Arana S. Antibody biosensors for spoilage yeast detection based on impedance spectroscopy. *Biosens Bioelectron.* 2018;102:432-438. doi:10.1016/j.bios.2017.11.057
53. Nidzworski D, Siuzdak K, Niedziałkowski P, et al. A rapid-response ultrasensitive biosensor for influenza virus detection using antibody modified boron-doped diamond. *Sci Rep.* 2017;7(1):1-10. doi:10.1038/s41598-017-15806-7
54. Jacobs M, Nagaraj VJ, Mertz T, Selvam AP, Ngo T, Prasad S. An electrochemical sensor for the detection of antibiotic contaminants in water. *Anal Methods.* 2013;5(17):4325-4329. doi:10.1039/c3ay40994e
55. Giang H, Pali M, Fan L, Suni II. Impedance Biosensing atop MoS₂ Thin Films with Mo–S Bond Formation to Antibody Fragments Created by Disulphide Bond Reduction. *Electroanalysis.* 2019;31(5):957-965.

- doi:10.1002/elan.201800845
56. Li J, Wang J, Grewal YS, et al. Multiplexed SERS Detection of Soluble Cancer Protein Biomarkers with Gold-Silver Alloy Nanoboxes and Nanoyeast Single-Chain Variable Fragments. *Anal Chem*. 2018;90(17):10377-10384. doi:10.1021/acs.analchem.8b02216
57. Furst AL, Hoepker AC, Francis MB. Quantifying Hormone Disruptors with an Engineered Bacterial Biosensor. *ACS Cent Sci*. 2017;3(2):110-116. doi:10.1021/acscentsci.6b00322
58. Baek SH, Kim MW, Park CY, et al. Development of a rapid and sensitive electrochemical biosensor for detection of human norovirus via novel specific binding peptides. *Biosens Bioelectron*. 2019;123:223-229. doi:10.1016/j.bios.2018.08.064
59. Cho CH, Kim JH, Song DK, Park TJ, Park JP. An affinity peptide-incorporated electrochemical biosensor for the detection of neutrophil gelatinase-associated lipocalin. *Biosens Bioelectron*. 2019;142:111482. doi:10.1016/j.bios.2019.111482
60. Malvano F, Pilloton R, Albanese D. A novel impedimetric biosensor based on the antimicrobial activity of the peptide nisin for the detection of *Salmonella* spp. *Food Chem*. 2020;325:126868. doi:10.1016/j.foodchem.2020.126868
61. Shi F, Gan L, Wang Y, Wang P. Impedimetric biosensor fabricated with affinity peptides for sensitive detection of *Escherichia coli* O157:H7. *Biotechnol Lett*. 2020;42(5):825-832. doi:10.1007/s10529-020-02817-0

62. Paleček E, Tkáč J, Bartošík M, Bertók T, Ostatná V, Paleček J. Electrochemistry of nonconjugated proteins and glycoproteins. Toward sensors for biomedicine and glycomics. *Chem Rev.* 2015;115(5):2045-2108. doi:10.1021/cr500279h
63. Belický Š, Katrlík J, Tkáč J. Glycan and lectin biosensors. *Essays Biochem.* 2016;60(1):37-47. doi:10.1042/EBC20150005
64. Mnif I, Ellouz-Chaabouni S, Ghribi D. Glycolipid Biosurfactants, Main Classes, Functional Properties and Related Potential Applications in Environmental Biotechnology. *J Polym Environ.* 2018;26(5):2192-2206. doi:10.1007/s10924-017-1076-4
65. Silva MLS. *Lectin Biosensors in Cancer Glycan Biomarker Detection*. Vol 93. 1st ed. Elsevier Inc.; 2019. doi:10.1016/bs.acc.2019.07.001
66. Klukova L, Filip J, Belicky S, Vikartovska A, Tkac J. Graphene oxide-based electrochemical label-free detection of glycoproteins down to aM level using a lectin biosensor. *Analyst.* 2016;141(14):4278-4282. doi:10.1039/c6an00793g
67. Simão EP, Silva DBS, Cordeiro MT, Gil LHV, Andrade CAS, Oliveira MDL. Nanostructured impedimetric lectin-based biosensor for arboviruses detection. *Talanta.* 2020;208:120338. doi:10.1016/j.talanta.2019.120338
68. Rangel MGH, Silva MLS. Detection of the cancer-associated T antigen using an *Arachis hypogaea* agglutinin biosensor. *Biosens Bioelectron.* 2019;141:111401. doi:10.1016/j.bios.2019.111401
69. Ramkumar R, Mathiselvam M, Sangaranarayanan M V. Thiourea linked

- glycolipid-assisted synthesis of sub-micrometer sized polyaniline spheres for enzyme less sensing of dopamine. *J Appl Electrochem.* 2020;50(4):439-449. doi:10.1007/s10800-020-01402-7
70. Mazur F, Bally M, Städler B, Chandrawati R. Liposomes and lipid bilayers in biosensors. *Adv Colloid Interface Sci.* 2017;249(May):88-99. doi:10.1016/j.cis.2017.05.020
71. Khadka R, Carraher C, Hamiaux C, Travas-Sejdic J, Kralicek A. Synergistic improvement in the performance of insect odorant receptor based biosensors in the presence of Orco. *Biosens Bioelectron.* 2020;153:112040. doi:10.1016/j.bios.2020.112040
72. Karutha Pandian D, Dharuman V. Supported binary liposome vesicle-gold nanoparticle for enhanced label free DNA and protein sensing. *Biosens Bioelectron.* 2017;95:168-173. doi:10.1016/j.bios.2017.04.022
73. Gomes FO, Maia LB, Loureiro JA, et al. Biosensor for direct bioelectrocatalysis detection of nitric oxide using nitric oxide reductase incorporated in carboxylated single-walled carbon nanotubes/lipidic 3 bilayer nanocomposite. *Bioelectrochemistry.* 2019;127:76-86. doi:10.1016/j.bioelechem.2019.01.010
74. Gupta N, Renugopalakrishnan V, Liepmann D, Paulmurugan R, Malhotra BD. Cell-based biosensors: Recent trends, challenges and future perspectives. *Biosens Bioelectron.* 2019;141:111435. doi:10.1016/j.bios.2019.111435
75. Ye Y, Ji J, Pi F, et al. A novel electrochemical biosensor for antioxidant

- evaluation of phloretin based on cell-alginate/L-cysteine/gold nanoparticle-modified glassy carbon electrode. *Biosens Bioelectron.* 2018;119:119-125. doi:10.1016/j.bios.2018.07.051
76. Xia S, Zhu P, Pi F, et al. Development of a simple and convenient cell-based electrochemical biosensor for evaluating the individual and combined toxicity of DON, ZEN, and AFB1. *Biosens Bioelectron.* 2017;97:345-351. doi:10.1016/j.bios.2017.06.002
77. Ge Q, Ge P, Jiang D, et al. A novel and simple cell-based electrochemical biosensor for evaluating the antioxidant capacity of *Lactobacillus plantarum* strains isolated from Chinese dry-cured ham. *Biosens Bioelectron.* 2018;99:555-563. doi:10.1016/j.bios.2017.08.037
78. Bagheri H, Hajian A, Rezaei M, Shirzadmehr A. Composite of Cu metal nanoparticles-multiwall carbon nanotubes-reduced graphene oxide as a novel and high performance platform of the electrochemical sensor for simultaneous determination of nitrite and nitrate. *J Hazard Mater.* 2017;324:762-772. doi:10.1016/j.jhazmat.2016.11.055
79. Meng F, Shi W, Sun Y, et al. Nonenzymatic biosensor based on Cu_2O nanoparticles deposited on polypyrrole nanowires for improving detection range. *Biosens Bioelectron.* 2013;42(1):141-147. doi:10.1016/j.bios.2012.10.051
80. Li Y, Jiang Y, Mo T, Zhou H, Li Y, Li S. Highly selective dopamine sensor based on graphene quantum dots self-assembled monolayers modified

- electrode. *J Electroanal Chem.* 2016;767:84-90.
doi:10.1016/j.jelechem.2016.02.016
81. Song Y, Lu X, Li Y, et al. Nitrogen-Doped Carbon Nanotubes Supported by Macroporous Carbon as an Efficient Enzymatic Biosensing Platform for Glucose. *Anal Chem.* 2016;88(2):1371-1377.
doi:10.1021/acs.analchem.5b03938
82. Cai ZX, Song XH, Chen YY, Wang YR, Chen X. 3D nitrogen-doped graphene aerogel: A low-cost, facile prepared direct electrode for H₂O₂ sensing. *Sensors Actuators, B Chem.* 2016;222:567-573. doi:10.1016/j.snb.2015.08.094
83. Wang MQ, Zhang Y, Bao SJ, Yu YN, Ye C. Ni(II)-Based Metal-Organic Framework Anchored on Carbon Nanotubes for Highly Sensitive Non-Enzymatic Hydrogen Peroxide Sensing. *Electrochim Acta.* 2016;190:365-370.
doi:10.1016/j.electacta.2015.12.199
84. Venditti I. Engineered gold-based nanomaterials: Morphologies and functionalities in biomedical applications. a mini review. *Bioengineering.* 2019;6(2):53. doi:10.3390/bioengineering6020053
85. Falagan-Lotsch P, Grzincic EM, Murphy CJ. One low-dose exposure of gold nanoparticles induces long-term changes in human cells. *Proc Natl Acad Sci U S A.* 2016;113(47):13318-13323. doi:10.1073/pnas.1616400113
86. Rossi A, Donati S, Fontana L, et al. Negatively charged gold nanoparticles as a dexamethasone carrier: Stability in biological media and bioactivity assessment: In vitro. *RSC Adv.* 2016;6(101):99016-99022.

- doi:10.1039/c6ra19561j
87. Soenen SJ, Rivera-Gil P, Montenegro JM, Parak WJ, De Smedt SC, Braeckmans K. Cellular toxicity of inorganic nanoparticles: Common aspects and guidelines for improved nanotoxicity evaluation. *Nano Today*. 2011;6(5):446-465. doi:10.1016/j.nantod.2011.08.001
88. Alkilany AM, Murphy CJ. Toxicity and cellular uptake of gold nanoparticles: What we have learned so far? *J Nanoparticle Res*. 2010;12(7):2313-2333. doi:10.1007/s11051-010-9911-8
89. Fratoddi I, Venditti I, Cametti C, Russo MV. The puzzle of toxicity of gold nanoparticles. The case-study of HeLa cells. *Toxicol Res (Camb)*. 2015;4(4):796-800. doi:10.1039/c4tx00168k
90. Khlebtsov N, Dykmana L. Biodistribution and toxicity of engineered gold nanoparticles: A review of in vitro and in vivo studies. *Chem Soc Rev*. 2011;40(3):1647-1671. doi:10.1039/c0cs00018c
91. Mironava T, Hadjiargyrou M, Simon M, Jurukovski V, Rafailovich MH. Gold nanoparticles cellular toxicity and recovery: Effect of size, concentration and exposure time. *Nanotoxicology*. 2010;4(1):120-137. doi:10.3109/17435390903471463
92. Pingarrón JM, Yáñez-Sedeño P, González-Cortés A. Gold nanoparticle-based electrochemical biosensors. *Electrochim Acta*. 2008;53(19):5848-5866. doi:10.1016/j.electacta.2008.03.005
93. Wang F, Wang YC, Dou S, Xiong MH, Sun TM, Wang J. Doxorubicin-

- tethered responsive gold nanoparticles facilitate intracellular drug delivery for overcoming multidrug resistance in cancer cells. *ACS Nano*. 2011;5(5):3679-3692. doi:10.1021/nn200007z
94. Wang Y, Sun S, Luo J, et al. Low sample volume origami-paper-based graphene-modified aptasensors for label-free electrochemical detection of cancer biomarker-EGFR. *Microsystems Nanoeng*. 2020;6(1). doi:10.1038/s41378-020-0146-2
95. Shariati M, Ghorbani M, Sasanpour P, Karimizefreh A. An ultrasensitive label free human papilloma virus DNA biosensor using gold nanotubes based on nanoporous polycarbonate in electrical alignment. *Anal Chim Acta*. 2019;1048:31-41. doi:10.1016/j.aca.2018.09.062
96. Zhuo Y, Yuan R, Chai Y, et al. An amperometric immunosensor based on immobilization of hepatitis B surface antibody on gold electrode modified gold nanoparticles and horseradish peroxidase. *Anal Chim Acta*. 2005;548(1-2):205-210. doi:10.1016/j.aca.2005.05.058
97. Khater M, de la Escosura-Muñiz A, Quesada-González D, Merkoçi A. Electrochemical detection of plant virus using gold nanoparticle-modified electrodes. *Anal Chim Acta*. 2019;1046:123-131. doi:10.1016/j.aca.2018.09.031
98. Lin D, Pillai RG, Lee WE, Jemere AB. An impedimetric biosensor for *E. coli* O157:H7 based on the use of self-assembled gold nanoparticles and protein G. *Microchim Acta*. 2019;186(3):1-9. doi:10.1007/s00604-019-3282-3

99. Motia S, Bouchikhi B, Llobet E, El Bari N. Synthesis and characterization of a highly sensitive and selective electrochemical sensor based on molecularly imprinted polymer with gold nanoparticles modified screen-printed electrode for glycerol determination in wastewater. *Talanta*. 2020;216:120953. doi:10.1016/j.talanta.2020.120953
100. Douaki A, Abera BD, Cantarella G, et al. Flexible screen printed aptasensor for rapid detection of furaneol: A comparison of CNTs and AgNPs effect on aptasensor performance. *Nanomaterials*. 2020;10(6):1-18. doi:10.3390/nano10061167
101. Tran LT, Tran HV, Thi Minh Dang H, Huynh CD, Mai TA. Silver Nanoparticles Decorated Polyaniline Nanowires-Based Electrochemical DNA Sensor: Two-step Electrochemical Synthesis. *J Electrochem Soc*. 2020;167(8):087508. doi:10.1149/1945-7111/ab8fdb
102. Liu YF, Tsai JJ, Chin YT, Liao EC, Wu CC, Wang GJ. Detection of allergies using a silver nanoparticle modified nanostructured biosensor. *Sensors Actuators, B Chem*. 2012;171-172:1095-1100. doi:10.1016/j.snb.2012.06.039
103. Jiménez-Pérez R, Almagro L, González-Sánchez MI, Pedreño MÁ, Valero E. Non-enzymatic screen-printed sensor based on PtNPs@polyazure A for the real-time tracking of the H₂O₂ secreted from living plant cells. *Bioelectrochemistry*. 2020;134:107526. doi:10.1016/j.bioelechem.2020.107526
104. Gholami M, Koivisto B. A flexible and highly selective non-enzymatic H₂O₂ sensor based on silver nanoparticles embedded into Nafion. *Appl Surf Sci*.

- 2019;467-468:112-118. doi:10.1016/j.apsusc.2018.10.113
105. Wang S, Zhao L, Xu R, Ma Y, Ma L. Facile fabrication of biosensors based on Cu nanoparticles modified as-grown CVD graphene for non-enzymatic glucose sensing. *J Electroanal Chem.* 2019;853:113527. doi:10.1016/j.jelechem.2019.113527
106. Palve YP, Jha N. A novel bilayer of copper nanowire and carbon nanotube electrode for highly sensitive enzyme free glucose detection. *Mater Chem Phys.* 2020;240:122086. doi:10.1016/j.matchemphys.2019.122086
107. Wang F, Hu S, Shi F, Huang K, Li J. A non-enzymatic sensor based on fc-chit/cnt@cu nanohybrids for electrochemical detection of glucose. *Polymers (Basel).* 2020;12(10):1-12. doi:10.3390/polym12102419
108. George JM, Antony A, Mathew B. Metal oxide nanoparticles in electrochemical sensing and biosensing: a review. *Microchim Acta.* 2018;185(7). doi:10.1007/s00604-018-2894-3
109. Li C, Wang Y, Jiang H, Wang X. Biosensors based on advanced sulfur-containing nanomaterials. *Sensors (Switzerland).* 2020;20(12):1-27. doi:10.3390/s20123488
110. Li X, Liu X. Group III nitride nanomaterials for biosensing. *Nanoscale.* 2017;9(22):7320-7341. doi:10.1039/c7nr01577a
111. Katz E, Willner I, Wang J. Electroanalytical and Bioelectroanalytical Systems Based on Metal and Semiconductor Nanoparticles. *Electroanalysis.* 2004;16(1-2):19-44. doi:10.1002/elan.200302930

112. Argueta-Figueroa L, Martínez-Alvarez O, Santos-Cruz J, et al. Nanomaterials made of non-toxic metallic sulfides: A systematic review of their potential biomedical applications. *Mater Sci Eng C*. 2017;76:1305-1315.
doi:10.1016/j.msec.2017.02.120
113. Kirste R, Rohrbaugh N, Bryan I, Bryan Z, Collazo R, Ivanisevic A. Electronic Biosensors Based on III-Nitride Semiconductors. *Annu Rev Anal Chem*. 2015;8(1):149-169. doi:10.1146/annurev-anchem-071114-040247
114. da Silva W, Brett CMA. Novel biosensor for acetylcholine based on acetylcholinesterase/poly(neutral red) – Deep eutectic solvent/Fe₂O₃ nanoparticle modified electrode. *J Electroanal Chem*. 2020;872:114050.
doi:10.1016/j.jelechem.2020.114050
115. Xue L, Guo R, Huang F, et al. An impedance biosensor based on magnetic nanobead net and MnO₂ nanoflowers for rapid and sensitive detection of foodborne bacteria. *Biosens Bioelectron*. 2021;173:112800.
doi:10.1016/j.bios.2020.112800
116. Yu M, Wu L, Miao J, Wei W, Liu A, Liu S. Titanium dioxide and polypyrrole molecularly imprinted polymer nanocomposites based electrochemical sensor for highly selective detection of p-nonylphenol. *Anal Chim Acta*. 2019;1080:84-94. doi:10.1016/j.aca.2019.06.053
117. Li G, Zhong P, Ye Y, et al. A Highly Sensitive and Stable Dopamine Sensor Using Shuttle-Like α -Fe₂O₃ Nanoparticles/Electro-Reduced Graphene Oxide Composites. *J Electrochem Soc*. 2019;166(15):B1552-B1561.

- doi:10.1149/2.1071915jes
118. Guan JF, Huang ZN, Zou J, Jiang XY, Peng DM, Yu JG. A sensitive non-enzymatic electrochemical sensor based on acicular manganese dioxide modified graphene nanosheets composite for hydrogen peroxide detection. *Ecotoxicol Environ Saf.* 2020;190:110123. doi:10.1016/j.ecoenv.2019.110123
119. Chen TW, Chinnapaiyan S, Chen SM, et al. Facile sonochemical synthesis of rutile-type titanium dioxide microspheres decorated graphene oxide composite for efficient electrochemical sensor. *Ultrason Sonochem.* 2020;62:104872. doi:10.1016/j.ultsonch.2019.104872
120. Li J, Liu Y, Tang X, et al. Multiwalled carbon nanotubes coated with cobalt(II) sulfide nanoparticles for electrochemical sensing of glucose via direct electron transfer to glucose oxidase. *Microchim Acta.* 2020;187(1):1-9. doi:10.1007/s00604-019-4047-8
121. Negahdary M, Jafarzadeh M, Rahimzadeh R, Rahimi G, Dehghani H. A DNA biosensor for molecular diagnosis of *Aeromonas hydrophila* using zinc sulfide nanospheres. *J Sensors Sens Syst.* 2017;6(2):259-267. doi:10.5194/jsss-6-259-2017
122. Govindasamy M, Wang SF, Kumaravel S, Ramalingam RJ, Al-lohedan HA. Facile synthesis of copper sulfide decorated reduced graphene oxide nanocomposite for high sensitive detection of toxic antibiotic in milk. *Ultrason Sonochem.* 2019;52:382-390. doi:10.1016/j.ultsonch.2018.12.015
123. Guo Q, Wu T, Liu L, He Y, Liu D, You T. Hierarchically porous NiCo₂S₄

- nanowires anchored on flexible electrospun graphitic nanofiber for high-performance glucose biosensing. *J Alloys Compd.* 2020;819:153376. doi:10.1016/j.jallcom.2019.153376
124. Zhou X, Gu X, Chen Z, Wu Y, Xu W, Bao J. A novel and sensitive Cu₂ZnSnS₄ quantum dot-based non-enzymatic glucose sensor. *Sensors Actuators, B Chem.* 2021;329:129117. doi:10.1016/j.snb.2020.129117
125. Poghosian A, Schöning MJ. Capacitive field-effect eis chemical sensors and biosensors: A status report. *Sensors (Switzerland).* 2020;20(19):1-32. doi:10.3390/s20195639
126. Xu W, Zhang Y, Yin X, et al. Highly sensitive electrochemical BPA sensor based on titanium nitride-reduced graphene oxide composite and core-shell molecular imprinting particles. *Anal Bioanal Chem.* 2021;413(4):1081-1090. doi:10.1007/s00216-020-03069-7
127. Liu Q, Yang T, Ye Y, et al. A highly sensitive label-free electrochemical immunosensor based on an aligned GaN nanowires array/polydopamine heterointerface modified with Au nanoparticles. *J Mater Chem B.* 2019;7(9):1442-1449. doi:10.1039/c8tb03233e
128. Chen J, Yin H, Zhou J, et al. Non-enzymatic glucose sensor based on nickel nitride decorated nitrogen doped carbon spheres (Ni₃N/NCS) via facile one pot nitridation process. *J Alloys Compd.* 2019;797:922-930. doi:10.1016/j.jallcom.2019.05.234
129. Rajaji U, Muthumariyappan A, Chen SM, Chen TW, Ramalingam RJ. A novel

- electrochemical sensor for the detection of oxidative stress and cancer biomarker (4-nitroquinoline N-oxide) based on iron nitride nanoparticles with multilayer reduced graphene nanosheets modified electrode. *Sensors Actuators, B Chem.* 2019;291:120-129. doi:10.1016/j.snb.2019.04.041
130. Sun X, Jiang K, Zhang N, Guo S, Huang X. Crystalline Control of {111} Bounded Pt₃Cu Nanocrystals: Multiply-Twinned Pt₃Cu Icosahedra with Enhanced Electrocatalytic Properties. *ACS Nano.* 2015;9(7):7634-7640. doi:10.1021/acsnano.5b02986
131. Malgras V, Ataee-Esfahani H, Wang H, et al. Nanoarchitectures for Mesoporous Metals. *Adv Mater.* 2016;28(6):993-1010. doi:10.1002/adma.201502593
132. Jiao Y, Zheng Y, Jaroniec M, Qiao SZ. Design of electrocatalysts for oxygen- and hydrogen-involving energy conversion reactions. *Chem Soc Rev.* 2015;44(8):2060-2086. doi:10.1039/c4cs00470a
133. Cai H, Zhu N, Jiang Y, He P, Fang Y. Cu@Au alloy nanoparticle as oligonucleotides labels for electrochemical stripping detection of DNA hybridization. *Biosens Bioelectron.* 2003;18(11):1311-1319. doi:10.1016/S0956-5663(03)00084-8
134. Lee WC, Kim KB, Gurudatt NG, et al. Comparison of enzymatic and non-enzymatic glucose sensors based on hierarchical Au-Ni alloy with conductive polymer. *Biosens Bioelectron.* 2019;130:48-54. doi:10.1016/j.bios.2019.01.028
135. Yadav R, Berlina AN, Zherdev A V., Gaur MS, Dzantiev BB. Rapid and

- selective electrochemical detection of Pb^{2+} ions using aptamer-conjugated alloy nanoparticles. *SN Appl Sci.* 2020;2(12):1-11. doi:10.1007/s42452-020-03840-6
136. Song D, Li Q, Lu X, et al. Ultra-thin bimetallic alloy nanowires with porous architecture/monolayer MoS_2 nanosheet as a highly sensitive platform for the electrochemical assay of hazardous omethoate pollutant. *J Hazard Mater.* 2018;357:466-474. doi:10.1016/j.jhazmat.2018.06.021
137. Gao A, Zhang X, Peng X, et al. In situ synthesis of $Ni(OH)_2/TiO_2$ composite film on NiTi alloy for non-enzymatic glucose sensing. *Sensors Actuators, B Chem.* 2016;232:150-157. doi:10.1016/j.snb.2016.03.122
138. Shim K, Lee WC, Park MS, et al. Au decorated core-shell structured $Au@Pt$ for the glucose oxidation reaction. *Sensors Actuators, B Chem.* 2019;278:88-96. doi:10.1016/j.snb.2018.09.048
139. Li L, Zheng H, Guo L, Qu L, Yu L. A sensitive and selective molecularly imprinted electrochemical sensor based on Pd-Cu bimetallic alloy functionalized graphene for detection of amaranth in soft drink. *Talanta.* 2019;197:68-76. doi:10.1016/j.talanta.2019.01.009



DSPACE

<https://dspace.org/>

Recent advances on bioreceptors and metal nanomaterials-based electrochemical impedance spectroscopy biosensors

Chen, Zibo; Jin, Hui-Hui; Yang, Zhugen; He, Daping

2023-04-01

Springer

<https://doi.org/10.1007/s12598-022-02129-4>

Chen Z, Jin H, Yang Z, He D. (2022) Recent advances on bioreceptors and metal nanomaterials-based electrochemical impedance spectroscopy biosensors. Rare Metals, Volume 42, Issue 4, April 2023, pp. 1098-1117