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Review Article

Biosensors from the First Generation to Nano-biosensors

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ABSTRACT

All living creatures tend to sense the changes in their habitat and have to comply with them to survive. At first, the basics of the biosensor theory began with *in vitro* studies based on sensing ability of living beings. Then, scientists have started to use this ability in some devices. Lately, these devices have been smaller and smaller. They are in used for medical, chemical, food and some other sciences to make easier, cheaper, accurate and rapid detection of specific reactions, compounds, enzymes, cells according to their electrical, thermal or optical signals. Lastly, the 4th generation of biosensor technology, as lived now, has started with the developments of Micro, Nano or BioNano Electro-Mechanical Systems (MEMS/NEMS/BioNEMS), nanotechnology and biotechnology that are expected to have lots of features. Furthermore molecular recognition elements like aptamers which are synthetic oligonucleotide ligands against various target molecules ranging from small ions to large proteins, toxins and other analytes as receptors. The studies on using aptamers conjugated with nanomaterials to fabricate and design novel biosensors appear to continue due to various advantages such as frequency of usage, practical use and time-saving.

1. Introduction

All living creatures tend to sense the changes in their habitat and comply with them to survive. These creatures have the ability of sensing over the imagination of all scientists. The dogs' smelling ability, the eels' sensing ability of a little difference in tons of water, the butterflies' having a sense on their partners' secretion, the algae' sensing of toxins are some examples in nature [1].

The basics of the biosensor theory have commenced with *in vitro* studies based on mimicking of living creatures' sensing ability. Biosensor technology has come up with this idea and developed so fast. Later on, International Union of Pure and Applied Chemistry (IUPAC) have established a commission to classify and name the biosensors in 1996 and defined the biosensor as: "A device that uses specific biochemical reactions mediated by isolated enzymes, immune systems, tissues, organelles or whole cells to detect chemical compounds usually by electrical, thermal or optical signals" [2]

Furthermore, this definition has been improved due to the recent developments of bio-microchips in science and technology. Smaller, cheaper and more accurate devices than microelectronics could be produced as the basics of biosensor systems which have the sensing mechanisms such as to see, to hear, to smell, to taste and to touch [3].

By the developments of nanotechnology which provides to be able to study, to manipulate, to create and to utilize of materials in miniature scale, biosensors could be reduced to nano size [4]. Nano-biosensors are the revolution in sensor technologies due to enabling rapid analyzes of multiple samples at desired time and place [5, 6]. Showing high performance in selectivity, biocompatibility, non-toxicity, reversibility, rapid response and the sensitivity of determination by utilizing nanomaterials to introduce lots of brand new signal transduction technologies have been in used recently (Table 1). Morphologies of nanotubes, nanowires, nanofibers, nanorods have also been effective on transduction of analytes [7]. Along with all these, biological material usage like aptamers as alternative molecules to sensing materials give its benefits to this area [8].

There have also been portable instruments which are

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able to analyze multiple components at one time [9]. These technologies provide us to work in enormous application areas which involve medicine, food, agricultural, bioprocess and/or national defense due to the bio-molecular interactions, by combining the biological and physicochemical or mechanical features of transducers, which give much better and more accurate datum than traditional methods such as nucleic acid microarrays [10].

Table 1. The Properties of the Biosensors' Parts [11][53]

Analyte	**Bio-component**	**Transducer based on**
Hormones	Enzymes	Electrochemical
Enzymes	Antibody	Semiconductors
Coenzymes	Cell	Optics
Substrate	Tissue	Photometric
Activator	Receptors	Fluorometric
Inhibitor	Microorganisms	Fluorometric
Antibody-Antigen	Nucleic Acid	Piezoelectric
Nucleic Acid	Lipids	Quartz Crystal Microbalance (QCM)
Microorganisms	Organelles	Micro cantilever
Vitamin B_{12}	Aptamer	Aptasensors

2. The history of biosensors

The first biosensor was designed by Clark and Lyons (1962) [12] using an enzyme electrode. In this system, glucose is the target substance and its oxidation reaction was triggered by glucose oxidase.

The voltage between electrodes was enough for reduction of O_2 and electric current was measured by the rate of the concentration of O_2. The reduction of electric current was directly proportional to glucose concentration.

Another important innovation in developing biosensors is the potentiometric urea electrode designed [13]. These type electrodes were classified as the first generation biosensors.

As the second generation biosensors, auxiliary enzymes and/or co-reactants are co-immobilized with the analyte converting enzyme in order to improve the analytical quality and to simplify the performance [14] as shown in Figure 1.

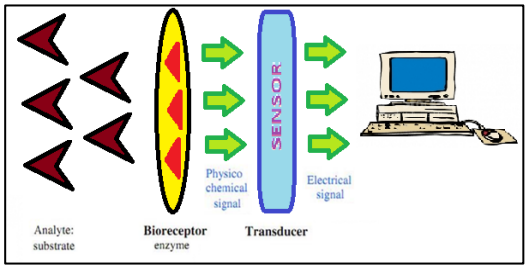

Figure 1. Schematic illustration of a biosensor

Typically, a transducer surface next to a biosensing material's attachments is modified by chemicals. ELISA (enzyme-linked immunosorbent assay) electrodes were included in this group.

In the third generation biosensors, biomolecules get involved to biosensing material such as SPR (Surface Plasmon Resonance) biosensors.

Lastly, for the 4th generation, with the developments in MEMS/NEMS/BioNEMS (Micro, Nano or BioNano Electro-Mechanical Systems), nanotechnology and biotechnology, are expected to have lots of features [15]. With the contributions of engineers and the scientists from different fields, biosensor production has many recent, creative and versatile opportunities to be developed. These biosensors are also used for the determination of biological and chemical effective substances in agricultural production, food analyzes and environmental monitoring in addition to mining, bioprocess, bio war and homeland security [8].

3. Applications of biosensors in agricultural and food industries

Biosensors have a transducer, a detector and a biological element (like enzyme, organelle or antibody) interacting with the analyte to give a meaningful response to read from the detector [11, 16]. They should have characteristics like the linearity of a calibration curve, the sensitivity of least amounts of concentration, the selectivity/specificity of getting true outcome and response time of at least %95 [17].

In the antibody-antigen interactions; an immunosensor is used for binding of an antibody to an antigen. There is a lock-key confirmation in this binding that results in physicochemical changes which constitute electrical signals. These interactions are irreversible and also depended on some conditions such as pH and temperature [18].

In the enzymatic interactions; analyte recognition is used for some mechanisms: a) enzyme converts the analyte into a product which can be detectable; b) enzyme interaction detection by the analyte; c) monitoring final properties of the enzyme. However, using this interaction limits the sensor's life based on the stability of the enzyme [19]. Enzyme-based biosensors and their use in industries were defined in the literature [20-23].

The use of nucleic acid as sensors' analyte is named as genosensors because of their recognition process, which is based on base pairing, cytosine: guanine and/or adenine: thymine in DNA. Based on known sequence, integral sequences can be synthesized, lined and immobilized. Then, the base pair is created and generate an optical signal [18].

The use of cells as sensors' analyte is based on their sensitivity to the environment, the responsibility of all kinds of stimulants and the reproducibility to be reusable. Cells are global bioreceptors to detect stress conditions, toxicity, organic derivates, effect of drugs, herbicides and the microbial corrosion [24, 25].

The use of organelles as sensors' analyte is based on their cellular functions through metabolic ways and enzymes'

effects. Mitochondria, for instance, give response to high calcium concentrations and high toxicity of detergent compounds [26].

Applications of biosensors especially in agricultural and food industries have focused on two folds: the first is to detect (and/or measure the amounts) of carbohydrates, alcohols, acids, amino acids, vitamins, amines, amides, phenol etc. in beverages; the second is to detect of microorganisms and components/toxins occurring by their affects [27].

Pathogen detection in foods and beverages has been one of the major challenges in biosensor technologies due to results in foodborne diseases in recent years. Ali et al [28] designed a biosensor to detect *E.coli* O157:H7 in food sample. While traditional methods took a few days to detection, they managed to detect *E.coli* O157:H7 in a few minutes by using AuNPs. Xiang et al [29] developed an electrochemical immunosensor to detect *Salmonella* based on gold nanoparticles (GNPs) dispersion in chitosan hydrogel and modified glassy carbon electrode (GCE). The demonstrated immunosensor was revealed as having good selectivity and reproducibility properties with a low sensitivity of 5 CFU/mL.

Biosensors specific to agricultural and food industries due to their analytes were given in Table 2.

Table 2. Some specific biosensors for various analytes in agricultural and food industries [16, 30, 31]

Biosensors	Analytes
Enzyme sensors	organic and inorganic substances (drugs, foods, vitamins, antibiotics)
Enzyme sensors	ingredients such as carbohydrates, alcohols and/or acids in quality control processes in the fermented food industry especially in wine, beer and yogurt production
Enzyme sensors (cholinesterase)	organophosphates and carbamates in pesticides
Microbial sensors	organic and inorganic substances (drugs, foods, vitamins, antibiotics) + dissolved oxygen needed by organisms
Microbial sensors	ammonia and methane
DNA sensors	viruses, pathogens, microorganisms
Immunosensor	viruses, pathogens, microorganisms and xenobiotics
Immunosensor	small amounts of molecules and pathogens which present in different kind of meat products
Aptasensors	various target molecules ranging from small ions to large proteins

4. Nano-biosensors in industry

These sensors work in the size of a few nanometers that they can detect the presence of nanomaterials or molecules in that size and even smaller. The application of nano-scale biosensors can differ from the transducer, the perception ligand, the label and the running instruments. Due to working advantages in miniaturization, nano-scale biosensors may be able to increase the sensitivity of the devices [4].

The nanomaterial should be selected for nanofabrication of the nano-sensor. In the process of nanofabricating, four methods are mostly in used: photolithography, thin film etching/growth, surface etching and chemical bonding. These kinds of patterning methods are needed for fabrication of the nano-structures easily and efficiently. Due to lithography (electron beam, X-ray and extreme UV) techniques, nano-scale electrode production could be managed and resulted in high accuracy of biosensing with a greater surface area to be accomplished in high precision [32, 33].

Variety of nanomaterials, such as metallic nanoparticles (i.e. GNPs which give different color in different nano size), carbon nanotubes (CNTs), magnetic nanoparticles (NPs) and quantum dots, which are nanoscale semiconductor devices, are used to design novel biosensors because of their high sensitivity and specificity of detection on materials' physical, chemical, physicochemical, mechanical, optics and magnetic features [34]. In producing of glucose biosensors, the enzyme of glucose oxidase is used. Furthermore, with a use of platinum nanoparticles over the sheets of carbon nanotubes helped to increase of immobilization of glucose oxidase to determine the analyte [35].

The glucose sensors have been widely utilized in medicine. GNPs, CNTs, magnetic NPs, platinum nanoparticles (Pt-NPs) and Quantum dots show excellent contribution in glucose sensors [36, 37]. Pt-NPs especially can be electrodeposited on multi-wall nanotubes (MWNTs) matrix in a simple and strong way. The immobilization of the enzyme (glucose oxidase) on the surface of Pt-MWNTs' electrode could be applied by chitosan-SiO_2 gel matrix. Thus, glucose levels of blood samples could be measured with high sensitivity [38].

Some organophosphorus pesticides (which are about 10^{-10} M concentration) could be monitored by liposome-based nano-biosensors at low amounts. Acetylcholine-esterase enzyme is used as fluorescent biosensor in this process [39]. In *E. coli* detection by flow injection analysis, a method was developed by using bismuth nanofilm modified GCE [34]. A biochip sensor system was designed with titanium pads and 150 nanometers Ti-well on a LiNbO3 substrate. If the bacteria were uninfected, a small value of voltage was carried out in the nanowell [40].

Another important phenomenon in biosensor technology is surface plasmon resonance (SPR). Its effects are based on the refractive index and the flow of light through a medium. Nanoparticles are also in used to maximize the ultimate scale optical response of the sensing materials with an incident light. Due to this light's effect, particles get excited from the surface as ionic species and resulted in fluids of their charged states. In this way, nanoparticles get photonic properties and they can be used as fluorophores

[41].

Along with all these, on the one hand, NEMS and MEMS technologies which are the combinations of biological materials and electromechanical systems, provide us to use of complex electrical, mechanical, fluidic, thermal, optical and magnetic properties of the materials at nano-scale.

MEMS and NEMS technologies have been combined with biological systems and molecules to have the best modeling of biochemical interactions to have good biosensing ability. MEMS and NEMS as biological sensing mechanisms are designed to measure of cellular structure surfaces using cantilevers as electrodes. The principle of the sensing is based on the thermal conductivity between the cantilever and the substrate changes according to the spacing between them [15].

On the other hand, molecular recognition elements like aptamers, which are single-stranded oligonucleotide sequences that are randomly chosen from sequencing pools as biosensing materials, are used in biosensors. In terms of the development of biosensors, aptamers are recognized as alternative molecular materials to antibody or other biomimetic sensing materials [8, 31]. Aptamers have the ability to bind the non-nucleic acid targets such as small molecules and proteins [42].

Aptamer probes are combined with electrochemical, optic, piezoelectric and magnetic transducers. Aptamers are able to be barcoded by radiation to detection of proteins qualitatively and quantitatively at the same time in a complex biologic matrix [43]. Li et al. [44] developed an electrochemical aptasensor to detect the adenosine simply and conveniently by measuring of impedance spectroscopy. Moreover compared to conventional sensing systems, this aptasensor system was mentioned as not only provided high sensitivity of detection, it also provided easily reusable sensing equipment. Besides reusability brought the cost-effectiveness together.

Medley et al. [45] revealed that previous methods were time-consuming, expensive and need complicated instrumentation and developed a new aptamer-based nanosensor. They thought that the selectivity and affinity of aptamers can be modified with nanomaterials to provide high sensitivity and accurate detection. The researchers developed a colorimetric test for the detection of diseased cells by using aptamer-conjugated GNPs (ACGNPs) to benefit of the selectivity and the affinity of aptamers and the spectroscopic advantages of GNPs. While previous methods needed much time, complex instruments and higher cost to develop, using ACGNPs required simple instrumentation and much lower cost.

Wang et al. [46] demostrated an aptamer-based silver (Ag) nanosensor to detect multiple proteins (Thrombin and Immunoglobulin E). According to the study, after target proteins and aptamer were introduced, aptamer-protein complexes have formed like key-locked or antigen-antibody models. Then by the removal of the aptamer part, fluorescent signals of the complex decreased. The researchers stated that this nanosensor provides high sensitivity, rapidity, high throughput, and miniaturization advantages. Moreover, revealing a comparison with the conventional systems, their sensor provided the detection of lower amounts due to being smaller and the process was very simple and low-cost.

Datta et al. [47] designed a sensor complex consisted of deoxyribonucleic acid (DNA) aptamer, GNPs and semiconductor quantum dot (QD), attached to a graphene oxide (GO) particle for detection of potassium at a very low concentration with high sensitivity in the field of medical detection applications.

Aptamers or single-stranded DNA-CNTs' (ssDNA-CNTs') probes could also be used for *in situ* sensing of the DNA hybridization events and detection of specific kinds of DNA oligonucleotides as optical nano-biosensors [48]. For the detection of deep DNA damages, a nano-bio-composite layer of MWNTs in chitosan was engineered [49]. Then, GNPs with alkane ethiol-capped DNA chimeras in a tail to tail hybridization mode of this DNA-CNTs show notable distinction between the integral part and base mismatch and fulfill perfectly [50]. In another example, a nano-SiO_2/*p*-aminothiophenol film which was self-assembled and electrodeposited was carried out to detect of *p*-aminothiophenol gene sequences by a label free electrochemical impedance spectroscopy (EIS) method [51].

Wang et al. [52] fabricated a single gold nanowire electrodes (Au-NWEs) by laser-assisted pulling/hydrofluoric acid (HF) etching technique, to develop an electrochemical aptamer-based nanosensors (E-AB nanosensor) to use for ATP determination even in a complex system like cerebrospinal fluid of rat brain. The researchers stated this E-AB nanosensor provides the unique properties of good stability, larger surface area and smaller overall dimensions in living bio-system.

In general, compared to the conventional methods, aptamer based nano-biosensors provide more benefits such as frequency of usage, practical use and time-saving, lower-cost, greater durability, reusability, simple instrumentation [44-46, 53-77].

As seen in the Table 3, same analytes can be detected by using different probes or transducers, providing different sensitivity and response time values. On the one hand, Apt-Au NPs as probe was used for adenosine detection based on colorimetric, SPR or electrochemical type transducers, which give responses between 20 seconds to 30 minutes with sensitivities from about 0.18nM to 2mM [53, 54, 78-80]. On the other hand, Apt-Au NPs or Apt-QD was used as probe for cocaine detection based on colorimetric or fluorometric transducer that give response between 20 seconds to 5 minutes with sensitivities of 2 μM to 2 mM [53, 55, 78, 81].

For Hg^{2+} detection using the same probe (Apt-Au NPs) and the same type of transducer (colorimetric) was achieved with sensitivities of 10nM to about 3 μM [58-61, 82]. While, for Pb^{2+} detection using the same probe (Apt-Au NPs & DNAzyme) for colorimetric type transducer gave almost similar sensitivity values [64, 65, 83]. In another study, the sensitivity could be down to 3nM [84]. On the other hand, using a different probe (Guanine - Quadruplex DNA aptamer, China) and fluorometric transducer resulted in

high sensitivity (0.4nM)[66].

Using three different probes based on three different types of transducers gave results from 10fM to 2nM in terms of sensitivity [75-77] for Bisphenol A detection. Moreover, with the highest sensitivity value (10fM) in Table 3 was also achieved in a very short time (10min) for Bisphenol A detection [75].

Some other aptamer-based nano-biosensor studies with sensitivity and response time values were exemplified in Table 3.

5. Conclusions

In this review, some improvements of biosensors and the contribution of nanotechnology to biosensors were discussed. Nanotechnology doped biosensors, which have just started to be used in the 90s, are still in their infancy and are precursors of the future technologies. With the effect of nanotechnology, the 4th generation of biosensors is called nano-biosensors. They are in use in industrial areas such as medicine, drug, food, agricultural, environmental etc. Due to nano-biosensors provide some advances such as frequency of usage, practical use and time-saving, high sensitivity, high selectivity, lower-cost, greater durability, reusability, simple instrumentation in the near future; there is no doubt that these technologies are going to continue to find their places with an increasing rate. On the other hand, aptamers provide specific contributions to detection of biologic components. Besides, using aptamers conjugated with nanomaterials is pretty new technology that should be developed and study on. Furthermore, when the studies on biosensors go down to pico, femto or maybe lower sizes. There will be techno-revolutions in those mentioned areas with the developments of science and technology.

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Table 3. Aptamer-based nano-biosensors studies

Analyte	Probe	Transducer type	Sensitivity	Response Time	Reference
Adenosine and Cocaine	Apt-Au NPs	colorimetric	from 0.3 to 2 mM	1 minute	[78]
Cocaine	Apt-Au NPs	colorimetric	about 20 µM	20 seconds	[53]
Adenosine	Apt-Au NPs	colorimetric	about 10µM	1 minute	[79]
Adenosine	Apt-Au NPs	SPR	from 1nM to 1 µM	30 minutes	[80]
Adenosine	Apt-Au NPs	electrochemical	0.18 nM	-	[54]
Cocaine	Apt-Au NPs	colorimetric	2µM	5 minutes	[81]
Cocaine	Apt-QD	fluorometric	50µM	1 minute	[55]
ATP	Apt-Au NPs	colorimetric	0.6 µM	-	[56]
ATP	Apt-Au NPs	colorimetric	10.0 nM	30 minutes	[57]
Cysteine	Apt-Au NPs & DNA-Au NP-Hg^{2+} aggregates	colorimetric	from 50 nM to 10 µM	-	[85]
Hg^{2+}	Apt-Au NPs	colorimetric	100 nM	-	[82]
Hg^{2+}	Apt-Au NPs	colorimetric	10 nM	-	[58]
Hg^{2+}	Apt-Au NPs	colorimetric	25 nM	-	[59]
Hg^{2+}	Apt-Au NPs	colorimetric	about 3 µM	5 minutes	[60]
Hg^{2+}	Apt-Au NPs	colorimetric	250 nM	-	[61]
K^{+}	Apt-Au NPs	colorimetric	about 20-2000 µM	1 minute	[62]
K^{+}	Apt-Au NPs	colorimetric	about 1 mM	4 minutes	[63]
Pb^{2+}	Apt-Au NPs & DNAzyme	colorimetric	from 0.1 to 4 µM	-	[64]
Pb^{2+}	Apt-Au NPs & DNAzyme	colorimetric	from 0.4 to 2 µM	-	[65]
Pb^{2+}	Apt-Au NPs & DNAzyme	colorimetric	from 0.1 to 2 µM	5 minutes	[83]
Pb^{2+}	Apt-Au NPs & DNAzyme	colorimetric	3 nM	5 minutes	[84]
Pb^{2+}	Guanine - Quadruplex DNA aptamer	fluorometric	0.4 nM	-	[66]
As(III)	Apt-Au NPs	colorimetric	40 ppb	-	[86]
As(III)	Apt-Au NPs	resonance scattering	0.6 ppb	-	[86]
Ethanolamine (EA)	Guanine-rich apt. DNA	electrochemical	0.08 nM	-	[67]
K^{+}	Guanine-rich apt. DNA	electrochemical	0.1 nM	-	[68]
Organophosphorus Pesticides	Apt-Au NPs	colorimetric	0.143-2.696 ppm	-	[69]
Malathion	Apt-Au NPs	colorimetric	0.06 pM	-	[70]
Acetamiprid	The ABA (acetamiprid binding aptamer)-stabilized Au NPs	resonance scattering	1.2 nM	10 minutes	[71]
Oxytetracycline	DNA aptamer-templated silver nanoclusters (AgNCs)	fluorometric	0.1 nM	180 minutes	[72]
Fluoroquinolone antibiotics	DNA Aptamers	fluorometric	0.1–56.9 nM	-	[73]
Progesterone	DNA Aptamers	electrochemical	0.90 ng/mL	-	[74]
Bisphenol A (BPA)	ds DNA-embedded Au/Ag core–shell NPs	surface-enhanced raman scattering	10fM	10 minutes	[75]
Bisphenol A (BPA)	Au NPs activated ZnO nanopencils	photoelectrochemical(PEC)	0.5 nM	-	[76]
Bisphenol A (BPA)	anti-BPA apt. and molybdenum carbide nanotubes	fluorometric	2 nM	-	[77]