

Biosensors: A New Era in Disease Diagnosis and Industrial Biotechnology

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ABSTRACT

Biosensor concept and its widespread applications have drawn global research attention. They have been successfully utilized in many ways for the betterment of quality life. Their applications have been spreading in each field starting from simple glucose test to nuclear tests. Here in this present study few applications of biosensors in the field of Disease Diagnosis & Industrial biotechnology have been reviewed. The future of these biosensors is also mentioned at the end considering the recent trends and the literature available on publication web.

INTRODUCTION

Biosensor

Primarily, a sensor can be defined as a device which is capable to detect or measures a physical property. It may also records or indicates and may respond to it otherwise. Microphone for sound, Thermometer, thermocouple and pyrometer for temperature, Hydrometer for density, Barometer for pressure, Breath analyser for chemical, and anemometer for wind speed are few popular sensors to exemplify. The sensor which uses a biological component to detect the analyte to detection of various compounds with more specificity and sensitivity will now be called as a biosensor [1-3]. They contribute to the advancement of number of fields including biotechnology, disease diagnosis, and health care to improve quality of life [4], industrial applications [5], environment and food industry. They are being used as pivotal elements in forensic science [6]. They are popularly being used in 1) Industry for process monitoring and control, particularly food and drink; 2) Medicine for diagnostics, metabolites, hormones; 3) Military for battlefield monitoring of poison gases, nerve agents & people; 4) Domestic for home monitoring of non-acute conditions [7].

Biosensor is an emerging tool which combines both the principles of biology and electronics. In other words, this is to combine the advantages of sensor technology [8] and the life sciences. The success of developing biosensors may depend of efficient assembly, devices, and architectures. It also requires ones understanding towards Biology, Chemistry, Material Science, Electronics and Physics [6].

Biosensors comprise of a bio component that traces out molecules (analyte), a transducer and an electronic processor [9]. The reaction between the bio component and the analyte leads to a physicochemical change, which then converts to electrical signal by transducer. Biological component might be any tissue, microorganisms, organelles, cell receptors, chemicals, antibodies, nucleic acids, and so forth. A biologically derived material or biomimetic part that associates (ties or perceives) the analyte under study [9]. Their capacity is to distinguish the sign from environment through some biochemical reactions. Whereas transducer converts the bio chemical signal to electric signal and then is processed by electronic processor. Conventional methods do suit for the analysis

however they lack sensitivity and specificity [10]. Biosensors overcome these limitations [11] and could provide reliable data with more specificity and even at low sensitivities.

APPLICATIONS OF BIOSENSORS

Disease Diagnosis

Cancer diagnosis

Cancer is the alarming cause for the medical deaths around the globe. Early diagnosis is crucial for the successful treatment and for the better chances [12,13]. Tumour development is linked with gene and protein changes generally come about because of the mutations and these changes can be used as biomarkers for the diagnosis. Cancer biomarkers are possibly a standout amongst the most significant tools for early cancer detection. Biosensors have been developed with an end goal to enhance the analysis and treatment of different cancers. Aptamers, ssDNA, dsDNA, antibodies and particular antigens (p53 antigen) can be utilized as the bio-component in these biosensors. Aptamer based biosensors combined with gold nanoparticles has been developed. The principle of detection is based on absorption changes. Nanoparticles are met up on the tumor cell when particular aptamer is bound to its target cell; upon which colour and absorption will change for the sample which in turn enables us to detect cancers.

This procedure can also be utilized for the finding of non-small cell lung disease (NSCLC). In another study, Kwon et al. joined the aptamers with directing polymer tubes in a biosensor for the identification of a specialist in charge of angiogenesis amid disease named as Vascular Epidermal Growth Factor (VEGF) furthermore uncovered that tubes with smaller size demonstrates the high level of sensitivity during detection [14,15].

Alzheimer disease

Biosensors have additionally spread their way into the recognition of neurodegenerative issue [16,17].

Diabetes mellitus

Diabetes mellitus is caused due to abnormal levels of blood glucose [18]. Amperometric enzyme electrode, based on glucose oxidase (GOx), is used in developing easy-to-use glucose testing. It can be used for monitoring glucose level on continuous mode. Since Clark and Lyons proposed in 1962 the underlying idea of glucose chemical terminals [7,9,19], we have seen colossal exertion coordinated toward the improvement of solid gadgets for diabetes control. Distinctive methodologies have been investigated in the operation of glucose enzyme electrodes [20-25].

Cardiovascular maladies

Cardiovascular infection is another generally happening sickness with developing frequencies and consequently identification of the cardiovascular biomarkers is essential in clinical viewpoints [26-32]. Research has found on the schemes required to develop an RNA based aptasensor. The principle is the charge dissemination marvel displayed by an aptamer-CRP complex on the GID capacitor under electric field. It can recognize C-reactive protein (CRP), the most widely recognized biomarker for CVD with a location farthest point of 100–500 pg/ml. Recently, little and effectively compact aptamer based electrochemical biosensor was produced for the identification of vasopressin, a biomarker for traumatic wounds [33-35].

Systemic lupus erythematosus

SLE is an auto-immune confusion which affects diverse parts of human body. The patients experiencing SLE build up a wide assortment of serologic signs. SPR based biosensor chip was created to recognize pathogenic dsDNA in the event of immune system issue SLE.

Tuberculosis

Tuberculosis, one of the world's dangerous illness and is brought on by pathogenic bacterium *M. tuberculosis*. Early diagnosis of the disease may be profited in clinical point of view. Numerous assortments of Biosensors (DNA/RNA/PNA) were created for Tuberculosis detection utilizing the outfits of Optical, Piezoelectric, electro-chemical principles.

Hepatitis

Hepatitis is an infectious disease caused by different strains of hepatitis virus (HAV- HGV). Gold nanoparticle based DNA biosensor has also been executed to screen hepatitis B virus DNA with a detection cut-off of 15 pmol/L. In another study, non-auxiliary viral protein 3 (NS3) has been recognized by biotinylated RNA test based biosensor with an identification limit of 500 pg/ml [36-38].

Diarrhoea

Caused by pathogenic microbes such as *E. coli* O157:H7, *S. typhimurium* etc. Aptamer based biosensor was developed for the detection of these microscopic organisms utilizing unmodified gold nanoparticles by colorimetric examine [39].

Cholera

Caused by *Vibrio cholerae*. A DNA biosensor was created for the discovery of PCR amplicons of *Vibrio cholera* [40].

Salmonellosis

It is a globally spread disease caused by *Salmonella* sp. Determination of the *invA* gene of *Salmonella* is crucial and is done by SPR detection method [41,42]. DNA biosensors have found its application in the diagnosis.

Dengue

Dengue fever is an infectious disease and is vector-borne. It is mainly caused by Dengue viruses. Nucleic acid based biosensors and now being used to detect this fever because of the benefits of high surface area [42]. Studies reveal that there has been a non-porous alumina layered electrochemical DNA biosensor is developed for the detections of cDNA arrangement. Recently, identification of 31-mer oligonucleotide grouping of Dengue infection has been identified by the use of DNA sensing technology [43,44].

BIOSENSORS: INDUSTRIAL BIOTECHNOLOGY**Biosensors and Foodborne Bacteria Monitoring**

Microbiological safety is the primary concern of most food manufacturing units and has to be monitored on regular basis. Biosensors would be preferred in such cases to avoid any safety inspection lag. These biosensors would detect the specific molecules connected with bacterial action [45,46].

Milk Purification

Lead (Pb II) has drawn the attention of the world health researchers because of its expanding pollution level and the adorable consequences. Hence continuous monitoring is required in all the means in which the possibility of lead to enter in human body prevails [47]. Various methodologies have been utilized by researchers to create biosensor for lead detection in the milk. Durrieu and Tran-Minh reported restraint of soluble phosphatase within the sight of lead as a bioassay standard for the advancement of an optical algal biosensor [48-54]. Kuswandi [54] utilized fiber optic innovation, to build up an optical Pb (II) biosensor. Urease movement based optical biosensor was produced by Tsai [55,56]. Later a multi examination 50 spot cluster based optical biosensor was produced by Tsai and Doong [56], the sensor depended on fundamental rule of hindrance of urease and acetylcholinesterase by overwhelming metals. Both the chemicals were co - immobilized with FITC dextran in sol - gel grid for multianalyte discovery. The biosensor showed identification range from 10 nM to 100 nM for Cd (II), Hg (II) and Cu (II), yet no reaction was seen against Pb (II). Haron and Ray built up a biosensor taking into account hindrance of urease and acetyl cholinesterase by Pb (II) and a recognition point of confinement of 4.83 nM was accomplished utilizing cyclotetrachromotropyrene (CTCT) as a marker [57-67].

The living period of bacterial spores rotates around two stages i.e. torpid state and metabolically dynamic vegetative state. This change starting with one stage then onto the next stage is finished only when favourable conditions prevails in its near environment and presence or absence microbial or non-microbial contaminants. So this trait can be focused to sense the presence of contaminants in milk and henceforth create spore based biosensor frameworks. Various spore based detecting framework have been created to identify aflatoxin, anti-toxins and microbial pathogens in milk. These biosensing frameworks are better over existing strategies as far as better sensitivity, ease and help in fast examination of milk and milk products. The spore based biosensor is a novel system to guarantee safe and healthy milk to each consumer.

OTHER APPLICATIONS

1) Environmental and military; 2) Dip stick test; 3) Agri and Aquaculture; 4) Biosensors has found their way even in detection of viral, fungal and bacterial diseases of plants. Freshness of the food items can also be found.

RECENT TRENDS IN BIOSENSOR APPLICATIONS

The usage of biosensors in the field of environmental monitoring is rapidly increasing in recent times. After the establishment of Kyoto Protocol, nations started focusing on measuring the pollution control that may start diminishing environmental damage. Biosensors then gained huge popularity as a device to perform such detections. A standout amongst the most investigated strategy for measuring contamination is the Biochemical Oxygen Demand (BOD5) technique, which measures the organic oxygen interest of wastewaters amid 5 days at

20°C. An expansion in these type of biosensors is increasing in recent times because of their capacity to enhance identification quantification of chemical and biological agents [68-71]. Recently the focus has been shifted in developing genetically encoded FRET Biosensors as they are capable to analyse the signalling pathways both in living cells and organisms [72-76].

Carbon nanotube based biosensors are now been able to recognize various foodborne pathogens such as *E. coli* and *S. aureus* with an examine time of 1 min. *S. aureus* and *S. typhimurium* are additionally recognized from food tests by a double excitation detecting strategy [16,77]. Biosensors assumed an essential part in diagnosing UTIs and identifying the related uropathogen, which helped in endorsing a suitable antibiotic treatment [16,78].

Graphene (GE) is a new and evolving approach of carbon material as a biosensor as it is advantageous in quick electron transportation and in low crude material costs [79-83]. It is primarily is with single layer of carbon particles in a two-dimensional grid, the combination of GE with Nobel metal nanoparticles had demonstrated the promising applications in electrochemical biosensors. Looking at the advantageous trend Zhang et al. [79] have developed a cholesterol biosensor by the fusion of Chox with the aid of chitosan (CS). They have also determined the free cholesterol in human serum successfully [84,85].

BIOSENSORS: THE FUTURE

Smart-farming with Biosensor Equipped Stock

Smart farming enables farmers' to access the full information and about their stock in time to time. Real-time physiological and behavioural traits from animals will give markers that empower quick administration activities that avoid stock and subsequently profit losses [86]. Utilizing Biosensors to enhance decision supportive networks avoids stock losses and can help the general sustainability and productivity [87,88].

E-health

Research on cell phone based nanobiosensor models, for example, Lateral flow assays (LFA), flow cytometry, and optical recognition has been of global research interest. Case of few marketed cell phone based models are iHealth, AliveCor, GENTAG, Mobile Assay, and CellScope and so on [89-92].

Lab-on-a-chip (LOAC)

The idea was started from microfluidics related thoughts. Recent trend confirm us that it can be fall into nanofluidic field now in light of reducing the size of devices and response volume of fluidics. Fundamentally, LOAC is a flow channels either in glass or silicon substrates and will be incorporated with stream infusion/pumping framework considering liquid transport inside the chip and sample handling for detection. In the view of biosensor innovation, LOAC is the finished framework which can do a complete bio-sample handling and investigation framework on a chip scale [93-100]. A bio-sample with a little measure of liquid is acquainted with the chip, then blended with reagents and supports, responded to frame items took after by assembly of it to a division unit for investigation, coordinated on the same wafer. LOAC will significantly affect the diagnostics business, both regarding concentrated lab examination and the point of care testing [16].

CONCLUSION

Biosensors have grabbed in the business sector through different applications, for example, In vivo observing, blood checking, disease diagnosis, water quality and so on. Biosensor comprises of bio-material that is delicate and sensitive. The factors like durability and solidity can grow the business sector and can make significant additions in the exploration and creation of bio sensors. The future is very promising for the development of biosensors and their applications.

REFERENCES

1. Kaur H and Sharma A. Biosensors: Recent Advancements in Tissue Engineering and Cancer Diagnosis. *Biosens J.* 2015;4:131.
2. Clark L C and Lyons C. Electrode systems for continuous monitoring cardiovascular surgery. *Ann NY Acad Sci.* 1962;102: 29-45.
3. Vijaya Krishna V. Biosensors. *J Bioeng Biomed Sci.* 2011;1:e101.
4. Bosticardo G, et al. Biosensor Implementation in Haemodialysis Monitors to Improve Treatment Quality. *J Biosens Bioelectron.* 2012;3:e108.
5. Müller G. Glycosylphosphatidylinositol-Based Protein Chips and Biosensors for Biopharmaceutical Process Analytics. *J Bioprocess Biotechniq.* 2012;2:115.
6. Choi D. Biosensors and Bioelectronics. *Sensor Netw Data Commun.* 2016;S1:e002.
7. Brian B. Introduction to Biosensors. LIRANS University of Luton UK.

8. Halamek J. Biosensors Technology. *J Biochips Tiss Chips*. 2012;2:e112.
9. Girousi ST. Electrochemical Biosensors; A Promising Tool in Pharmaceutical Analysis. *Pharm Anal Chem Open Acces*. 2016;2:e104.
10. Patel PN, et al. Optical Biosensors: Fundamentals & Trends. *J Engineer Res Stud*. 2010;1:15-34.
11. Achyuthan K. Whither Commercial Nanobiosensors? *J Biosens Bioelectron*. 2011;2:102e.
12. Bohunicky B and Mousa SA. Biosensors: the new wave in cancer diagnosis. *Nanotechnol Sci Appl*. 2011;4:1-10.
13. Zhang Y, et al. Early Lung Cancer Diagnosis by Biosensors. *Int J Mol Sci*. 2013;14:15479-15509.
14. Medley CD, et al. Gold nanoparticle-based colorimetric assay for the direct detection of cancerous cells. *Anal Chem*. 2008;80:1067-1072.
15. Kwon OS, et al. A high-performance VEGF aptamer functionalized polypyrrole nanotube biosensor. *Biomaterials*. 2010;31:4740-4747.
16. Das AP. Biosensors: The Future of Diagnostics. *Sensor Netw Data Commun*. 2016;S1:e107.
17. Poncin-Epaillard F. Biosensors Applied to the Detection of Neurodegenerative Diseases, A Multidisciplinary Domain? *J Biosens Bioelectron*, 2012;3:e103.
18. Saleh AJ. Hydrogen Peroxide Biosensors Based on Horseradish Peroxidase and Hemoglobin. *J Biosens Bioelectron*, 2013;S9:001.
19. Pisoschi AM. Glucose Determination by Biosensors. *Biochem Anal Biochem*, 2012;1:e119.
20. Kumar N, et al. Bacterial Spore Based Biosensor for Detection of Contaminants in Milk. *J Food Process Technol*, 2013;4:277.
21. Prandini A, et al. On the occurrence of aflatoxin M1 in milk and dairy products. *Food Chem Toxicol*, 2009;47:984-991.
22. Shundo L, et al. Estimate of aflatoxin M1 exposure in milk and occurrence in Brazil. *Food Control*, 2009;20:655-657.
23. Hudson KD, et al. Localization of GerAA and GerAC germination proteins in the *Bacillus subtilis* spore. *J Bacteriol*, 2001;183:4317-4322.
24. Paidhungat M, et al. Genetic requirements for induction of germination of spores of *Bacillus subtilis* by Ca(2+)-dipicolinate. *J Bacteriol*, 2001;183:4886-4893.
25. Saleem W and Broderick PA. Biomarkers for Brain Disorders Electrochemically Detected By BRODERICK PROBE® Microelectrodes/Biosensors. *J Biosens Bioelectron*, 2013;S12:003.
26. Wolgamott GD and Durham NN. Initiation of spore germination in *Bacillus cereus*: a proposed allosteric receptor. *Can J Microbiol*, 1971;17:1043-1048.
27. Chen D, et al. Real-time detection of kinetic germination and heterogeneity of single *Bacillus* spores by laser tweezers Raman spectroscopy. *Anal Chem*, 2006;78:6936-6941.
28. Hashimoto T, et al. Germination of single bacterial spores. *J Bacteriol*, 1969;98:1011-1020.
29. Popham DL, et al. Muramic lactam in peptidoglycan of *Bacillus subtilis* spores is required for spore outgrowth but not for spore dehydration or heat resistance. *Proc Natl Acad Sci USA*, 1996;93:15405-15410.
30. Cowan AE, et al. A soluble protein is immobile in dormant spores of *Bacillus subtilis* but is mobile in germinated spores: implications for spore dormancy. *Proc Natl Acad Sci USA*, 2003;100:4209-4214.
31. Sangal A. Stability of Spore-Based Sensing Systems. Unpublished M.Sc., University of Kentucky, Kentucky, 2010.
32. Date A, et al. Construction of spores for portable bacterial whole-cell biosensing systems. *Anal Chem*, 2007;79:9391-9397.
33. Bora U, et al. Nucleic Acid Based Biosensors for Clinical Applications. *Biosens J*, 2013;2:104.
34. He P, et al. Label-free electrochemical monitoring of vasopressin in aptamer-based microfluidic biosensors. *Anal Chim Acta*, 2013;759:74-80.
35. Buhl A, et al. Novel Biosensor based analytic device for the detection of anti-double-stranded DNA antibodies. *Clin Chem*, 2007;53:334-41.
36. Lu X, et al. A gold nanorods-based fluorescent biosensor for the detection of hepatitis B virus DNA based on fluorescence resonance energy transfer. *Analyst*, 2013;138:642-650.
37. Roh C, et al. A Simple and Rapid Detection of Viral Protein Using RNA Oligonucleotide in a Biosensor. *Journal of Analytical Chemistry*, 2012;67:925-929.

38. Broderick PA. Biosensors and Biochips Sense Central and Peripheral Disease. *J Biochips Tiss Chips*,2013;3:e122.
39. Wu WH, et al. (2012) Aptasensors for rapid detection of *Escherichia coli* O157:H7 and *Salmonella typhimurium*. *Nanoscale Res Lett*, 2012;7:658.
40. Chua A, et al. A rapid DNA biosensor for the molecular diagnosis of infectious disease. *Biosens Bioelectronics*, 2011;26:3825-3831.
41. Zhang D, et al. Label-free and high-sensitive detection of *Salmonella* using a surface plasmon resonance DNA-based biosensor. *Journal of Biotechnology*, 2012;160:123-128.
42. Rai V, et al. Ultrasensitive cDNA Detection of Dengue Virus RNA Using Electrochemical Nanoporous Membrane-Based Biosensor. *PLoS ONE*, 2012;7:e42346.
43. Deng J and Toh CS. Impedimetric DNA Biosensor Based on a Nanoporous Alumina Membrane for the Detection of the Specific Oligonucleotide Sequence of Dengue Virus. *Sensors*, 2013;13:7774-7785.
44. Teles FRR and Fonseca LP. Trends in DNA biosensors. *Talanta*, 2008;77:606-623.
45. Vanegas DC, et al. Biosensors for Indirect Monitoring of Foodborne Bacteria. *Biosens J*, 2016;5:137.
46. Fernández H. Mycotoxins Quantification in the Food System: Is there Any Contribution from Electrochemical Biosensors? *J Biosens Bioelectron*, 2013;4:e121.
47. Hardeep K and Verma N. High Throughput Optical Biosensor for Monitoring Pb (II) Ions in Milk through Fluorescence based Microarray Approach. *J Biosens Bioelectron*, 2015;6:166.
48. Patra RC, et al. Milk trace elements in lactating cows environmentally exposed to higher level of lead and cadmium around different industrial units. *Sci Total Environ*, 2008;404:6-43.
49. Sahayaraj PA and Ayyadirai K. Bioaccumulation of Lead in milk of buffaloes from Cooum river belt in Chennai. *J Environ Biol*, 2009;5:651-654.
50. Ogabiela EE, et al. (2011) Assessment of metal levels in fresh milk from cows grazed around Challawa industrial estate of Kano, Nigeria. *J Basic ApplSci Res*, 2011;7:533-538.
51. www.codexalimentarius.net/input/download/.../17/CXS_193e.pdf
52. Swarup D, et al. Blood lead levels in lactating cows reared around polluted localities; transfer of lead into milk. *Sci Total Environ*, 2005;349:67-71.
53. Durrieu C and Tran-Minh C. Optical Algal Biosensor using Alkaline Phosphatase for determination of Heavy metals. *Ecotox& Environ safe*, 2002;51:206-209.
54. Kuswandi B. Simple optical fiber biosensor based on immobilized enzyme for monitoring of trace heavy metal ions. *Anal BioanalChem*, 2003;376:1104-1110.
55. Tsai HC, et al. Sol-gel derived urease based optical biosensor for the rapid determination of heavy metals. *LaxalActa*, 2003;481:75-84.
56. Tsai HC and Doong R. Simultaneous detection of pH, urea, acetylcholine and heavy metals using array based enzymatic optical biosensor. *Biosens Bioelectron*, 2005;9:1796-1804
57. Haron S and Ray AK. Optical Biodetection of cadmium and lead ions in water. *Med Eng Phys*, 2006;28:978-981.
58. Verma N, et al. Fiber Optic Biosensor for the Detection of Cd in Milk. *J Biosens Bioelectron*, 2010;1:102.
59. Wu CM and Lin LY. Immobilization of metallothionein as a sensitive biosensor chip for the detection of metal ion by surface Plasmon response. *Biosens Bioelectron*, 2004;20:864-871.
60. Ogonnczyk D, et al. Screenprinted disposable urease based biosensors for inhibitive detection of heavy metal ions. *Sens Actuators B Chem*, 2005;106:450-454.
61. Chouteau C, et al. A bienzymatic whole cell conductometric biosensor for heavy metal ion and pesticide in water samples. *Biosens Bioelectron*, 2005;21: 273-281.
62. Liao VH, et al. Assessment of heavy metal bioavailability in contaminated sediments and soils using green fluorescent protein based bacterial biosensors. *Environ Pollut*, 2006;142:17-23.
63. Haron S and Ray AK (2006) Optical biodetection of cadmium and lead ions in water. *Med Eng Phys*, 2006;28:978-981.
64. Chong KF, et al. Whole cell environmental biosensor on diamond. *Analyst*, 2008;133:739-743.
65. Lin TJ and Chung MF. Detection of cadmium by a fiber-optic biosensor based on localized surface plasmon resonance. *Biosens Bioelectron*, 2009;24:1213-1218.
66. Cha T, et al. Enzymatic activity on a chip: The critical role of protein orientation. *Proteomics*, 2005;5:416-419.

67. Grieshaber D, et al. Electrochemical Biosensors - Sensor Principles and Architecture. *Sensors*, 2008;8:1400-1458.
68. Lopez-Barbosa N and Osma JF. Biosensors: Migrating from Clinical to Environmental Industries. *Biosens J*, 2016;5:e106.
69. Bahadur E and Sezgin M. Applications of commercial biosensors in clinical, food, environmental, and biothreat/biowarfare analyses. *Anal Biochem*, 2015;478:107-120.
70. Chee GJ. Development and characterization of microbial biosensors for evaluating low biochemical oxygen demand in rivers. *Talanta*, 2013;117:366-370.
71. Tamee K, et al. Multicolor Solitons for Biosensors. *J Biosens Bioelectron*, 2013;4:e122.
72. Vandame P, et al. Dissecting Signaling Pathways by the Use of Genetically-Encoded Biosensors: Dynamic Matters. *Biosens J*, 2016;5:1000138.
73. Kamioka Y. Live imaging of protein kinase activities in transgenic mice expressing FRET biosensors. *Cell Struct Funct*, 2012;37:65-73.
74. Mohanty SP and Kougiannos E. Biosensors: A tutorial review. *IEEE Potentials* March-April, 2006;35-40.
75. Castillo J, et al. Biosensors for life quality Design, development and applications. *Sensors and Actuators B*, 2004;102:179-194.
76. Vo-Dinh T and Cullum B. Biosensors and biochips: advances in biological and medical diagnostics. *Fresenius J Anal Chem*, 2000;366:540-551.
77. Gu L. Simulation and Optimization of Microcantilever Biosensors. *J Biosens Bioelectron*, 2012;3:e113.
78. Bai S, et al. A Rapid Approach for Detecting Seven Genetically Modified Canola Events using Optical Thin-Film Biosensor Chips. *J Biochip Tissue chip*, 2012;2:101.
79. Zhang H, et al. One-Step Electrodeposition of Gold-Graphene Nanocomposite for Construction of Cholesterol Biosensor. *Biosens J*, 2015;4:128.
80. Cao S, et al. Electrochemistry of cholesterol biosensor based on a novel Pt-Pd bimetallic nanoparticle decorated graphene catalyst. *Talanta*, 2013;109:167-172.
81. Cao S, et al. An integrated sensing system for detection of cholesterol based on TiO₂-graphene-Pt-Pd hybrid nanocomposites. *Biosens Bioelectron*, 2013;42:532-538.
82. Aravind SSJ, et al. A cholesterol biosensor based on gold nanoparticles decorated functionalized graphene nanoplatelets. *Thin Solid Films*, 2011;519:5667-5672.
83. Hussain M, et al. Blood Coagulation Thromboplastin Time Measurements on a Nanoparticle Coated Quartz Crystal Microbalance Biosensor in Excellent Agreement with Standard Clinical Methods. *J Biosens Bioelectron*, 2013;4:139.
84. Sanghavi BJ, et al. Real-time electrochemical monitoring of adenosine triphosphate in the picomolar to micromolar range using graphene-modified electrodes. *Anal Chem*, 2013;85:8158-8165.
85. Sanghavi BJ, et al. Electrokinetic preconcentration and detection of neuropeptides at patterned graphene-modified electrodes in a nanochannel. *Anal Chem*, 2014;86:4120-4125.
86. Andrewartha SJ, et al. Aquaculture Sentinels: Smart-farming with Biosensor Equipped Stock. *J Aquac Res Development*, 2016;7:393.
87. Bhatia P and Chugh A. Synthetic Biology Based Biosensors and the Emerging Governance Issues. *Curr Synthetic Sys Biol*, 2013;1:108.
88. Fang Y. Biosensors: From Biomolecular Interaction Analysis to Cell Phenotypic Screening and From Bench to Bedside. *J Biochips Tiss Chips*, 2012;2:e113.
89. Mahato K, et al. Nanobiosensors: Next Generation Point-of-Care Biomedical Devices for Personalized Diagnosis. *J Anal Bioanal Tech*, 2016;7:e125.
90. Roda A, et al. Smartphone-based biosensors: A critical review and perspectives. *TrAC Trends in Analytical Chemistry*, 2015.
91. Sirivisoot S and Webster TJ. Biosensors as Implantable Medical Devices for Personalized Medicine. *J Biosens Bioelectron*, 2012;3:e104.
92. Chien-Chong H. Microfluidic Biochips and Plastic-Antibody Biosensors for Point-of-Care Diagnostics. *J Biochip Tissue chip*, 2011;1:e104.
93. Xuan J, et al. Gold nanoparticle assembled capsules and their application as hydrogen peroxide biosensor based on hemoglobin. *Bioelectrochemistry*, 2011.
94. Joshi R and Joshi RM. *Biosensors*. Gyan Publishing House, 2006.

95. Wu G, et al. Bioassay of prostate-specific antigen (PSA) using microcantilevers. *Nat Biotechnol*, 2001;19:856-860.
96. Lee CY and Lee GB. Micromachine-based humidity sensors with integrated temperature sensors for signal drift compensation. *J Micromech Microeng*, 2003;13:620.
97. Raiteri R, et al. Sensing of Biological Substances Based on the Bending of Microfabricated Cantilevers. *Sens Actuators B Chem*, 1999;61:213-217.
98. Cherian S, et al. Detection of heavy metal ions using protein-functionalized microcantilever sensors. *Biosens Bioelectron*, 2003;19:411-416.
99. Barnes JR, et al. Photothermal spectroscopy with femtojoule sensitivity using a micromechanical device. *Nature*, 1994;372:79-81.
100. Hwang KS, et al. Micro-and nanocantilever devices and systems for biomolecule detection. *Annu Rev Anal Chem (Palo Alto Calif)*, 2009;2:77-98.