Biosensors a promising future in measurements

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Abstract. A biosensor is an analytical device which can be used to convert the existence of a molecule or compound into a measurable and useful signal. Biosensors use stimulus to translate changes to recognisable signals and have great importance to society. Applications include diagnosis tools for diseases, security appliances, and other biomedical equipments. Biosensors can also be used in the detection of pathogens and other microbes in foodstuffs, drugs and processing industries. Enormous progress and advancement has been witnessed in this area. Research and development in micro level systems serves to interface biology with novel materials such as nanomaterial. Development of high speed and accurate electronic devices for use in medicine and energy storage (such as biofuel cells) is one of the target areas. This paper discusses the importance, use and current and future trend in the application of biosensors.

1. Introduction
Humans have sensors to sense and recognize the environment around us. In order to delegate some of responsibilities to equipments/instruments in sensing humans developed sensor. Sensors are the devices which can reacts to a perceptible action, such as heat, light, or pressure [1]. Sensor then responds to that action by generating a signal that can be deduced. In the instrumentation industry biosensors are among the fascinating areas of research. Biosensor generally, determines the concentration of various constituents and other parameters of biological interest and contributing in a broad spectrum of applications. Application of biosensors dated back to 1962 when Clark and Lyons developed a fast and more precise biosensor for glucose measurement. Biological sensors are analytical devices that detect biochemical and physiological changes. Transducers are essential to convert the particular biological and chemical change into electrical data which can identify different biochemical components of a complex compound to isolate the desired biochemical compounds [2].

At the moment biosensors have expansive application in medicine, agriculture, environmental monitoring and the bioprocessing areas [3, 4]. During last two decades great advances in the design of sensor architectures, the integration of biological systems with monolithic silicon and optical technologies has been observed. The development of effective electron-transfer systems and the configuration of direct immunosensors recently got prominent appraisal from the users. Recent progress in these areas has already led to the introduction of new-generation biosensors into the competitive diagnostics market place [5].

Engineering advances during last decade made possible the advances in of electro-chemical DNA biosensors which have molecular investigative competences [6]. These sensors based on electro-chemical DNA provides numerous advantages over molecular detection methods. This includes the capability to examine the multifaceted body fluids, better sensitivity, suitability with micro-fabrication technology, having lower energy requirement, compact and compatible handy devices [5, 7].
It is reported that, electrochemical sensors based on continuous potentiometric or amperometric detection of enzyme reaction products demonstrated excellent results in the development of biosensors. This makes the electrochemical transducers economical, rapid to use and portable [8].

Advances in nanomaterial provoked the development of more sophisticated sensors in the field of measurement. Biosensors developed from nanomaterial generally utilize restrained bio receptor probe which is selective for the analyte molecules under investigation. Nanomaterial developed is more responsive to analytes and provides sensitive biological and chemical sensors which exhibit distinctive properties [9].

Among the recently developed biosensors is one which is being used for sensing cytosolic concentration of the analyte cAMP (cyclic adenosine monophosphate) on the cell membrane [10]. A comparable system is developed to investigate cellular responses to instinctive. These assays are being frequently used in the pharmaceutical and biotechnology research [11]. During last decade application of biosensors were at peak demand in various fields of animal science, animal husbandry, food industry and ecological control and monitoring [6].

The future of biosensor is promising in broad area of applications. One may see the diversity of biosensors which has been developed based on artificial recognition component this innovation allows the applicability of biosensors in a wider range of analytes and means of transduction this has encompassed the lower limits of selectivity and sensitivity [12]. Miniaturization in field instrumentation also permits biosensors to be constructed as arrays. In the recent future biosensors will offer a powerful tool which will be drastically mutable method to analytical approaches. Medical and pharmaceutical industries motivated the development of swift and reliable analysis of laboratory samples. Recently in the area of environmental monitoring, optimization of response duration, selectivity, permanence and economy are the prime targets of research priorities [13].

Diverse range of biosensors has been developed and other is under investigation. These sensors are based on antibodies, enzymes, artificial membranes, cells, and even entire animal tissues. These biosensors can be used in environmental assessment and monitoring which may lead to efficient and reliable measuring systems in the future [14].

Literature available revealed that innovative discoveries originating from microelectronics, bioelectronics and nanotechnologies are now altering the meaning of environmental samples analysis. These consist of chemical and biochemical analytics which will provide clinicians new theranostic tools in the coming era [15].

Present study discusses a brief review of the biological sensors, their application and recent improvements in addition to their present and future uses. Furthermore, the technical importance, techniques, performance, benefits, and limitations of different types of biosensors are potted to present the current and future applications of electrochemical and other biosensors especially in the field of environmental assessment and monitoring.

2. Biosensor and Measurements
The need for rapid, efficient and reliable instruments to monitor the environment has motivated the instrumentation industry to develop state of the art expertisewith better methodologies which may have the capability to investigate the conventional and emerging analytes rapidly, reliably and economically. Biosensors proved to be the most attractive analytical tools for better monitoring and to implement environmental legislations in these areas [16].

2.1. Biosensors Developments for Environmental Monitoring
Conventional methods which are being used present day in environmental applications having high precision and accuracy with lowestpossible detection limits, however these sensors are more costly, time consuming, and sometimes entail skilled personnel to operate [3]. In order to fulfill the requirement of environmental monitoring biosensors found to be more efficient and dependable...
analytical tools to provide rapid, reliable, and sensitive measurements with relatively more economical way; many of them aimed for in situ analysis. Biosensors can be utilized by industries as well as by regulatory authorities which may provide flexibility and broad usage of instrument for testing and screening of variety of environmental samples [17].

Generally, biosensors are divided into two broad classes i) based on the signal transduction and ii) based on the bio recognition method. In the transducing element class biosensors can be characterized as electro-chemical, bioluminescence, optical, piezoelectric, and thermal sensors [18].

Electrochemical biosensors are more pliable to create compact instruments with compatible instrumental sensitivity. These biosensors having ability to even operate in turbid media [19]. Electrochemical biosensors emerge as the most commonly used biosensors in monitoring and diagnosis tests in environmental and clinical analysis. Electrochemical biosensors can be classifyas conductometric, potentiometric, and amperometric biosensors [18].

Bioluminescence or bioanalytical biosensors are designed on the basis of utilizing certain enzymes to radiate photons as a by-product of these reactions. Bioluminescent biosensors is mainly used for toxicity and water quality monitoring [20]. Optical biosensors are more suitable for direct monitoring systems. Optical biosensors are designed to detect and emit the light as a result of a biological and/or chemical reaction [20].

Piezoelectric biosensors developed by coating the surface of the biosensor with a selectively binding biologically active substance [18,21]. Piezoelectric biosensors are favorite because they provide real-time output, simplicity of use, broader pH range, and lower cost [22].

Calorimetric biosensors detect various material of concern due to heat evolved from biochemical reactions when the analyte reacts with appropriate biologically active material such as an enzyme [23].

A variety of components in the environment needs monitoring and detection. In the area of environmental quality monitoring biosensors are the successful technology which can provide swifter and cost competitive results.

2.2. Toxicity Genotoxicity and Mutagenicity

The determination of toxicity is very important in environmental monitoring because it can provide the actual picture of the extent of environmental pollution originated from aqueous, gaseous effluent and sediment [20]. It is implicit that physical and chemical analysis alone cannot give information to evaluate the environmental risk associated with the contaminant [24]. However, the impact of such pollutants can be evaluated, through the use of some biological gears [4].

Due to the increase in variety of pollutants and their persistence researchers searched for rapid and reliable sensors which can detect at lower limit. At present among popular sensors enzymatic sensors getting more interest of many researchers. These sensors working on the principle of inhibiting an specific enzyme of interest. At present most entertained biosensors which are used for the determination of various environmental compounds are enzymatic biosensors. In general, majority of environmental biosensors have focused on variety of bacteria and their morphology while eukaryotic biosensors are sporadic; specially the use of mammalian cells. These cells are extramultifaceted system than bacterial cells and can give a more subtle response than a bacterial cell. Mammalian cells can also retort to the estrogenic effects of various chemicals [25].

Sometimes complete microorganisms also used to determine the potential toxicity inwater or other environmental sample. Cell-sense is one of the amperometric sensors which uses E.Coli cells for quick check of toxicity in the environment. It was suggested as one of the fast and more accurate toxicity evaluation methods in the toxicity assessment demonstration program operated by the United Kingdom Environmental Agency [26].

Sensors are developed for various areas of environmental toxicology, such as geno-toxicity and mutagenicity; they are reported as “biosensors for environmental stresses”. These sensors are generally operates by interacting with the concerned toxicant with genetically engineered
microorganisms or there nucleic acids and they are premeditated to react to applied toxicity [4]. Genotoxicity is mainly concomitant in various environmental materials, such as aromatic hydrocarbon, chlorophenols, PCBs and PAHs, and many other components identified as potential cancer-causing pollutants [20]. Use of green fluorescent having base of protein used to device biosensor for detecting activity of various genotoxicant [28].

2.3. Endocrine-effect biosensors
It is reported by many researchers that many contaminants in an environment can produce adverse health effects by interfering with endogenous hormone systems of a living body known as EDCs. These EDCs are a group of substances which cannot be demarcated by their chemical nature, they can be due to their biological influence. As the binding ability of the chemicals toward the natural estrogen receptors (ER) can be measured biosensors are developed. Utilizing natural estrogen receptor of humans, the SPR biosensor used to determine the estrogens and xenoestrogens in addition to investigate the binding capabilities of concerned components [9, 18]. Furthermore, other than piezoelectric and electrochemical biosensors [35], optical biosensors also developed [29] which are based on estrogen receptors.

2.4. Organic compounds
Organic pollutants in the environments mainly consist of proteins, carbohydrates, fats and nucleic acids in an assortment of combinations. Following are the major areas of application of biosensors:

2.4.1. PCBs. Even though the production was restricted and even banned in some countries since long, it is still an environmental contaminant of the concern. A variety of biosensors have been designed with diverse configurations to monitor the PCBs in the environment [20, 30].

2.4.2. Petroleum products and polycyclic aromatic hydrocarbons (PAHs). These compounds are globally suspected as carcinogen and are of great concern for public health and safety. These compounds are principally formed during pyrolysis or incomplete combustion of organic materials. These contaminants generally of great concern due to their known and suspected carcinogenic effect along with their persistent in the environment. Lee and co-workers in the year 2005 described an integrated mini biosensor system which was based on green fluorescent protein-based Pseudomonas which can be utilized for continuous water toxicity monitoring [20]. The biosensor was developed for its ability to determine phenol, benzene, ethylbenzene, toluene, and various other compounds in aqueous phase solutions. Researchers designed the biosensors working on the basis of the capacity of a plasmid which can carry the toluene-benzene transcriptional activator [20]. Biosensors also developed to determine the naphthalene in environmental samples. These Amperometric biosensors were fabricated by utilizing Sphingomonas yanoikuyae B1 [31]. In order to monitor benzo(a)pyrene (BaP) in environmental samples, fluoroimmunosensor made up of fiberoptic was developed in recent past. These sensors are extremely sensitive because they are based on laser excitation along with the optical detection system [29].

2.4.3. Dioxins. One of the potential contaminant of environmental pollution is Dioxins. They are polychlorinated compounds and released in the environment as a by-product during various chemical processes utilizing chlorine. EPA has a great concern on Dioxins because of its known carcinogenic effects on human health [30], therefore they are in the list of potential Endocrine Disrupting Compounds (EDCs) [31]. The SPR biosensor which was developed to monitor the PCBs in the environment also utilized for the monitoring of the dioxin 2,3,7,8- TCDD successfully [32]. During recent past, the DRESSA biosensor are preprepared in hepatome cells whose working principle is binding the dioxins to an aryl hydrocarbon receptor [33].
2.4.4. Phenols. Major contributor of phenolic compounds are pulp and paper industry however, during manufacturing of medicines, colours, and antioxidants these compounds may be formed. Among the various phenolic compounds, chlorophenols are significant contributors of environmental contaminants because these compounds having greater toxicity and bioaccumulation tendency in the ecological system [20]. Parellada and colleagues in 1998 developed an amperometric biosensor, with tyrosinase bound in a higrogel on a graphite electrode was [34]. This biosensor was reasonably associated with other available techniques being utilized to measure the phenolic compounds in various samples. An optical fibre sensor having reflectance for p-aminophenol was developed which is based on immobilized bis-8-hydroxyquinoline [35].

2.4.5. Surfactants. Surfactants are the key ingredient of detergents among which anionic surfactants are the prevalent in the environment. Utilizing Pseudomonas rathonis T microorganism an amperometric biosensor was developed which can detect the anionic surfactants. In an study researchers claimed to achieved detection limit for sodium dodecyl sulfate (SDS) below 0.75 mg/L [14]. Researchers also investigated the sensitivity and selectivity of biosensors developed on bacterial strains who are capable of degrading the anionic surfactants. Researchers reported that by measuring the dissolved oxygen uptake which can change the current in the oxygen electrode a biosensor can measure the surfactants up to the concentration of 0.25 μg/L [18].

2.4.6. Biocides/pesticides. Many researchers worked on the detection of bioxides and pesticides by utilizing inhibition property of acetyl cholinesterase (AChE) and colin oxidase. Such type of biosensors utilized to detect organo-phosphorous and carbamate pesticides [18, 24]. A fiber-optic biosensor for the detection of pesticides carbaryl and dichlorvos has also been developed. A three-layer structure in which enzyme cholinesterase was immobilized on the outer layer developed which was in attached to an intermediate sol–gel layer which incorporated bromoresol purple, accumulated on an inner glass plate. The detection limit is reported as low as 5.2 μg/l [31].

2.4.7. Hormones. The extensive use of hormones in the environment with the evidence of impact in aquatic animals at concentrations below picogram per liter, have warned the environmentalist to act accordingly. The potential hazardous impact of hormones is generally in the aquatic life. This is at present a promising area of interest for ecological research [18, 36]. Servos and colleagues in 2005 detected female hormones such as 17beta-estradiol and estrone, in various municipal wastewater treatment plants in Canada during their study in significant concentrations [36].

Rodriguez-Mozaz and coworkers in 2005 developed biosensor to determine hormones. Estrone, and some other organic pollutants, was investigated with the help of optical immune-sensor in various water bodies in concentrations having range of ng/l. In recent past researchers were working on the development and improvement of sensors for the swift detection of metabolites and testosterone [18, 37].

2.4.8. Antibiotics. At present the extensive production and use of antibiotics initiated the issue of antibiotic resistance which in fact can be transferred to humans and release to the environment through excreta. These antibiotics may also reach the meat and milk products if used on animals as well and may disrupt the food chain [14]. Scientist developed a biosensor known as BIACORE 3000 to study interactions sulfamethazine and furosemide [38, 39].

2.4.9. Toxins. Presence of toxins in the environment is of great concern for health and safety point of view. In order to assess and monitor bacterial toxins variety of sensors are prepared in the past for foodstuff and ecological control [30]. A fibre optic biosensor and impedance-based immunosensor was developed to investigate staphylococcal enterotoxin B in various samples [18]. A fibre optic based biosensor which uses evanescent wave of a conical optical fibre for signal perception was prepared to
measure the Clostridium botulinum toxin. The biosensor is rapid and enables to detect the toxin up to 5 ng/mL within 1 min [41].

2.5. Microorganisms
Conventional practices to control diseases caused by pathogens are to control the suspected pathogenic microorganisms in food industry and environmental assessment. However, in addition to various other disadvantages lengthy and cumbersome detection methods made them unpopular in the medical and environmental monitoring area. Detection of disease causing viruses, bacteria, protozoa, and helminthes are generally less reliable, time-consuming, and uneconomical.

Researchers involved in health and environmental areas are interested in rapid and more accurate biosensors development. Salmonella enteriditis and Listeria monocytogenes are detected by utilizing SPR immobilizing on the gold cladded sensor. The detection limit was as low as concentrations below to 106 cell/ml [18]. Researchers reported the detection of Salmonella typhimurium in water in less than 2 minutes by using an immunosensor working on the basis of acoustic wave principle [29].

2.6. Biochemical oxygen demand
The conventional BOD test such as wrinkle method has been used in environmental monitoring since many decades. This method has many attractions to use such as it is being used all over the world as a universal standard technique, it has low analysis cost due to the use of simple and inexpensive equipments. However, this method has some limitation such as it consume at least 5 days to complete the and required skilled person. Furthermore, method is not appropriate for online monitoring. Rapid measurement of BOD is possible if one may use modern biosensor-based procedures. Several biosensors have been developed to measure BOD specially for higher strength waste effluents. In recent past, Chee et al. demonstrated an optical fibre biosensor to determine low concentration BOD such as for surface water samples. Instrument required only 15 minutes determining the BOD present in the sample [18]. Some biosensors based on the photocatalysis are also introduced recently [17]. These BOD biosensors are based on a novel microbial membrane [14].

2.7. Inorganic compounds
High toxicity of various inorganic pollutants makes their determination important for the environmental protection. Following are applications of biosensors for some important inorganic pollutants:

2.7.1. Metals. One of the frequent contaminants in the environment is metals which actually forced the researchers to obtain sensors which are rapid, reliable and having very low detection limit. Recent development has been made in the improvement of sensors exploiting intact microbial cells to determine heavy metals of concern. Whole-cell biosensors are more advantageous due to their capability to interact only with the available fraction of metal ions. At the other hand, common methods are not having the ability to distinguish between fractions of metals that are available or not available to the biological systems [42]. Heavy metals are common cause of inhibiting the activity of enzymes, and utilization of this phenomenon for the determination of hazardous toxic elements provides many advantages, such as method is simple and having better detection sensitivity [18]. Biosensors for the determination of other heavy metals ions which based on urease inhibition are generally applied for the measurement of mercury [14, 20].

2.7.2. Inorganic phosphate. Presence of inorganic phosphate in surface waters may cause the eutrophication and environmental degradation. Determination of inorganic phosphate in various water bodies is important to monitor the extent of eutrophication [43]. Variety of enzymatic biosensors have been developed in past to determine phosphate level in the environment [18]. Parellada and coworkers in 1998 developed biosensor which works on the principle of sequential action of three enzymes that
opens up a way to construct reagent less sensor [44]. Conrath and co-workers developed an enzyme sensor to measure inorganic phosphate sensor exploiting the maltose phosphorylase, acid phosphatase, glucose oxidase and mutarotase to determine the concentration of phosphate. Researchers demonstrated that the sensor output is well linear in the range 0.1 to 1 μM, and sensor is now being used in environmental monitoring [45].

2.7.3. Nitrate/nitrite: Nitrate and nitrite are the important environmental contaminants causing environmental pollution. Various environmental agencies including US-EPA and EU authorities promulgated standards for drinking water. Biosensors found to be promising tool to detect and monitor level of nitrate and nitrite. A biosensor was developed by exploiting immobilized denitrifying bacteria for the determination of NO\textsubscript{3} in water samples. In a reaction chamber bacterial mediated reduction of NO\textsubscript{3} form N\textsubscript{2}O occurs and it is measured by a specific nitrous oxide micro-electrode, which is the main sensing part of the sensor [14]. New improvement in nitrate biosensor utilizes a whole-cell fluorescence system which is based on recombinant E. Coli bacteria without the interference of phosphate, chloride and nitrite [18]. Nitrate biosensor based on electro-chemical technique also developed and provides more reliable and rapid detection of nitrate [46].

3. Conclusions
Application of biosensors is enormously increasing in many areas of environmental monitoring and assessment. However, some limitations such as selectivity, sensitivity, response time and usable lifetime is of great concern and vital study area for researchers. There is a need to improve the present biosensors and make them desirable analytical tool in all aspects. The most probable areas of improvements that are expected to have a significant change and enhance the application of biosensor technology are: immobilization systems, nanotechnology, compactness, and multisensory array fortitudes for multiple contaminants determination [45]. Furthermore, there is a need to develop advanced biosensors based on modified base component and sensing elements which should be reliable, simple in manufacturing and having the competence to widen the spectra of selectivity.

Analysis of complex real samples is possible with the development of advanced receptors which will support the in situ measurements eliminating the responses from nonspecific background effects. Present study revealed that the future of biosensors is promising however it depends on the proper implementation of evolving erudite micro and nanotechnologies, chemistry, biochemistry, doping physics, and applied electronics. Biosensors development is a continuous process and there is always room for improvement in the design and components of emerging biosensors. With the addition of more environmental contaminants which may be threat for humans and the overall ecosystem, the need for faster and more accurate biosensors will always at high-rise. Biosensors at present required to get the trust of potential consumers, keeping in mind that the acceptance of new manoeuvres is the best indicator of the success and achievement for an emerging technology [14].

References
[1] Piliarik, M., Šipová, H., Kvasnička, P., Galler, N., Krenn, J. R., & Homola, J. (2012). High-resolution biosensor based on localized surface plasmons. Optics Express, 20(1), 672-680.
[2] Xiao, Y., Lubin, A. A., Heeger, A. J., & Plaxco, K. W. (2005). Label-free electronic detection of thrombin in blood serum by using an aptamer-based sensor. Angewandte Chemie, 117(34), 5592-5595.
[3] Krishnamurthy V, Monfared S, Cornell B (2010). "Ion Channel Biosensors Part I Construction Operation and Clinical Studies". IEEE Transactions on Nanotechnology 9 (3): 313–322.
[4] Anthony P. F. Turner (2013). Biosensors: sense and sensibility Chem. Soc. Rev., 42(1): 3184-3196.
[5] Palecek, E., and F. Jelen. (2002). Electrochemistry of nucleic acids and development of DNA sensors. Crit. Rev. Anal. Chem. 3:261-270.
[6] Phoenix, P., Keane, A., Patel, A., Bergeron, H., Ghoshal, S., & Lau, P. C. K. (2003).
Characterization of a new solvent-responsive gene locus in Pseudomonas putida F1 and its functionalization as a versatile biosensor. *Environmental microbiology*, 5(12), 1309-1327.

[7] Drummond, T. G., Hill, M. G., & Barton, J. K. (2003). Electrochemical DNA sensors. *Nature biotechnology*, 21(10), 1192-1199.

[8] Albers, J., T. Grunwald, E. Nebling, G. Piechotta, and R. Hintsche. 2003. Electrical biochip technology—a tool for microarrays and continuous monitoring. *Analytical and bioanalytical chemistry*, 377(3), 521-527.

[9] Albers, J., Grunwald, T., Nebling, E., Piechotta, G., & Hintsche, R. (2003). Electrical biochip technology—a tool for microarrays and continuous monitoring. *Analytical and bioanalytical chemistry*, 377(3), 521-527.

[10] Hung, Y. P., Albeck, J. G., Tantama, M., & Yellen, G. (2011). Imaging Cytosolic NADH-NAD<sup>+</sup> Redox State with a Genetically Encoded Fluorescent Biosensor. *Cell metabolism*, 14(4), 545-554.

[11] Cavalcanti, A., Shirinzadeh, B., Zhang, M., & Kretly, L. C. (2008). Nanorobot hardware architecture for medical defense. *Sensors*, 8(5), 2932-2958

[12] Turner, A. P. F., & Piletsky, S. (2005). Biosensors and Biomimetic Sensors for the Detection of Drugs, Toxins and Biological Agents. In *Defense against Bioterror* (pp. 261-272). Springer Netherlands.

[13] Gooding, J. J. (2002). Electrochemical DNA hybridization biosensors. *Electroanalysis*, 14(17), 1149-1156.

[14] Rodriguez-Mozaz, S., De Alda, M. L., Barceló, D., & Marco, M. P. (2004). Biosensors for environmental applications: future development trends. *Pure and Applied Chemistry*, 76(4), 723-752.

[15] Urban, G. A. (2009). Micro-and nanobiosensors—state of the art and trends. *Measurement Science and Technology*, 20(1), 012001.

[16] Scognamiglio, V., Pezzotti, G., Pezzotti, I., Cano, J., Buonasera, K., Giannini, D., & Giardi, M. T. (2010). Biosensors for effective environmental and agrifood protection and commercialization: from research to market. *Microchimica Acta*, 170(3-4), 215-225.

[17] Wang, J., Rivas, G., Cai, X., Palecek, E., Nielsen, P., Shiraishi, H., ... & Flair, M. N. (1997). DNA electrochemical biosensors for environmental monitoring. A review. *Analytica Chimica Acta*, 347(1), 1-8.

[18] Rodriguez-Mozaz, S., de Alda, M. J. L., & Barceló, D. (2006). Biosensors as useful tools for environmental analysis and monitoring. *Analytical and bioanalytical chemistry*, 386(4), 1025-1041.

[19] Kostrzynska, M., Leung, K. T., Lee, H., & Trevors, J. T. (2002). Green fluorescent protein-based biosensor for detecting SOS-inducing activity of genotoxic compounds. *Journal of microbiological methods*, 48(1), 43-51.

[20] Lee, J. H., & Gu, M. B. (2005). An integrated mini biosensor system for continuous water toxicity monitoring. *Biosensors and Bioelectronics*, 20(9), 1744-1749.

[21] Ouyang, H., Striemer, C. C., & Fauchet, P. M. (2006). Quantitative analysis of the sensitivity of porous silicon optical biosensors. *Applied Physics Letters*, 88(16), 163108-163108.

[22] Tombelli, S., Minunni, M., & Mascini, M. (2005). Piezoelectric biosensors: Strategies for coupling nucleic acids to piezoelectric devices. *Methods*, 37(1), 48-56.

[23] Zhang, Y., & Tadigadapa, S. (2004). Calorimetric biosensors with integrated microfluidic channels. *Biosensors and Bioelectronics*, 19(12), 1733-1743.

[24] Brack, W., Ulrich, N., & Bataineh, M. (2011). Separation Techniques in Effect-Directed Analysis. In *Effect-Directed Analysis of Complex Environmental Contamination* (pp. 83-118). Springer Berlin Heidelberg.

[25] Yamaguchi, A., Ishibashi, H., Kohra, S., Arizono, K., & Tominaga, N. (2005). Short-term effects of endocrine-disrupting chemicals on the expression of estrogen-responsive genes in male medaka (<i>Oryzias latipes</i>). *Aquatic toxicology*, 72(3), 239-249.
[26] Philp, J. C., Balmhand, S., Hajto, E., Bailey, M. J., Wiles, S., Whiteley, A. S., ... & Dunbar, S. A. (2003). Whole cell immobilised biosensors for toxicity assessment of a wastewater treatment plant treating phenolics-containing waste. Analytica Chimica Acta, 487(1), 61-74.

[27] McKnight, T. E., Melechko, A. V., Griffith, G. D., Guillorn, M. A., Merkulov, V. I., Serna, F., ... & Simpson, M. L. (2003). Intracellular integration of synthetic nanostructures with viable cells for controlled biochemical manipulation. Nanotechnology, 14(5), 551.

[28] Ptitsyn, L. R., Horneck, G., Komova, O., Kozubek, S., Krasavin, E. A., Bonev, M., & Rettberg, P. (1997). A biosensor for environmental genotoxin screening based on an SOS lux assay in recombinant Escherichia coli cells. Applied and environmental microbiology, 63(11), 4377-4384.

[29] Rodríguez-Mozaz, S., Marco, M. P., de Alda, M. J. L., & Barceló, D. (2004). Biosensors for environmental monitoring of endocrine disruptors: a review article. Analytical and bioanalytical chemistry, 378(3), 588-598.

[30] Rier, S., & Foster, W. G. (2003). Environmental dioxins and endometriosis. In Seminars in reproductive medicine (Vol. 21, No. 02, pp. 145-154). Copyright© 2003 by Thieme Medical Publishers, Inc., 333 Seventh Avenue, New York, NY 10001, USA. Tel:+ 1 (212) 584-4662.

[31] Götz, R., Sokollek, V., & Weber, R. (2012). The dioxin/POPs legacy of pesticide production in Hamburg: part 2—waste deposits and remediation of Georgswerder landfill. Environmental Science and Pollution Research, 1-12.

[32] Chen, H., & Zhuang, H. (2012). Determination of 3, 4-dichlorinated biphenyl in soil samples by real-time immuno-PCR assay. Journal of Environmental Sciences, 24(12), 2191-2197.

[33] Kasai, A., Hiramatsu, N., Meng, Y., Yao, J., Maeda, S., & Kitamura, M. (2005). Fast-track DRESSA: a bioassay for fast, sensitive, and selective detection of halogenated and polycyclic aromatic hydrocarbons. Analytical biochemistry, 337(1), 84-88.

[34] Parellada, J., Narvaez, A., Lopez, M. A., Dominguez, E., Fernandez, J. J., Pavlov, V., & Katakis, I. (1998). Amperometric immunosensors and enzyme electrodes for environmental applications. Analytica chimica acta, 362(1), 47-57.

[35] Filik, H., Hayvalı, M., Kılıç, E., Apak, R., Aksu, D., Yanaz, Z., & Çengel, T. (2008). Development of an optical fibre reflectance sensor for <i>p</i>-aminophenol detection based on immobilised bis-8-hydroxyquinoline. Talanta, 77(1), 103-109.

[36] Servos, M. R., Bennie, D. T., Burnison, B. K., Jurkovic, A., McInnis, R., Neheli, T., ... & Ternes, T. A. (2005). Distribution of estrogens, 17β-estradiol and estrone, in Canadian municipal wastewater treatment plants. Science of the total environment, 336(1), 155-170.

[37] Rodríguez-Mozaz, S., Marco, M-P., de Alda, M. J. and Barceló, D. (2005). A global perspective: Biosensors for environmental monitoring, Talanta. 65(1), 291-297.

[38] Rodríguez-Mozaz, S., Marco, M. P., de Alda, M. J., & Barceló, D. (2004). Biosensors for environmental applications: Future development trends. Pure and applied chemistry, 76(4), 723-752.

[39] Hansen, L. H., & Sørensen, S. J. (2000). Detection and quantification of tetracyclines by whole cell biosensors. FEMS microbiology letters, 190(2), 273-278.

[40] Arora, P., Sindhu, A., Kaur, H., Dilbaghi, N., & Chaudhury, A. (2013). An overview of transducers as platform for the rapid detection of foodborne pathogens. Applied microbiology and biotechnology, 97(5), 1829-1840.

[41] Ibarra-Escutia, P., Gómez, J. J., Calas-Blanchard, C., Marty, J. L., & Ramírez-Silva, M. T. (2010). Amperometric biosensor based on a high resolution photopolymer deposited onto a screen-printed electrode for phenolic compounds monitoring in tea infusions. Talanta, 81(4), 1636-1642.

[42] Chouteau, C., Dzyadevych, S., Durrieu, C., & Chovelon, J. M. (2005). A bi-enzymatic whole cell conductometric biosensor for heavy metal ions and pesticides detection in water samples. Biosensors and Bioelectronics, 21(2), 273-281.

[43] Ongaro, M., & Ugo, P. (2012). Bioelectroanalysis with nanoelectrode ensembles and arrays.
Analytical and bioanalytical chemistry, 1-15.

[44] Parellada, J., Narvaez, A., Lopez, M. A., Dominguez, E., Fernandez, J. J., Pavlov, V., & Katakis, I. (1998). Amperometric immunosensors and enzyme electrodes for environmental applications. Analytica chimica acta, 362(1), 47-57

[45] Conrath, N., Gründig, B., Hüwel, S., & Cammann, K. (1995). A novel enzyme sensor for the determination of inorganic phosphate. Analytica chimica acta, 309(1), 47-52.

[46] Cosnier, S., Da Silva, S., Shan, D., & Gorgy, K. (2008). Electrochemical nitrate biosensor based on poly (pyrrole–viologen) film–nitrate reductase–clay composite. Bioelectrochemistry, 74(1), 47-51.