Rev. Adv. Mater. Sci. 36 (2014) 62-69

RECENT TRENDS IN NANOBIOSENSORS AND THEIR APPLICATIONS - A REVIEW

Suresh Sagadevan[1] and Mathan Periasamy[2]

[1]Department of Physics, Sree Sastha Institute of Engineering and Technology, Chembarambakkam, Chennai-600 123, India
[2]Department of Biotechnology, Sree Sastha Institute of Engineering and Technology, Chembarambakkam, Chennai-600 123, India

Received: May 30, 2013

Abstract. Nanotechnology plays an important role in the development of biosensors. The sensitivity and performance of biosensors are improved by using nanomaterials through new signal transduction technologies. The development of tools and processes used to fabricate, measure and image nanoscale objects, has led to the development of sensors that interact with extremely small molecules that need to be analyzed. These advances are particularly exciting in the context of biosensing, where the demands are for low concentration detection and high specificity. The use of biomolecule-functionalized surfaces can drastically boost the specificity of the detection system, but may also pose reproducibility problems and increased complexity. Several nanobiosensor architecture-based mechanical devices, optical resonators, functionalized nanoparticles, nanowires, nanotubes, and nanofibers have been in use. As nanobiosensor technology becomes more refined and reliable, it will eventually make lab-on-a-chip devices for rapid screening of a wide variety of analyses at low cost. In particular, nanomaterials such as gold nanoparticles, carbon nanotubes, magnetic nanoparticles and quantum dots have been actively investigated for their applications in biosensors, which have become a new interdisciplinary frontier between biological detection and material science. This paper reviews the status of the various nanostructure-based biosensors and their applications.

1. INTRODUCTION

A biosensor is a device that combines a biological recognition element with a physical or chemical transducer to detect a biological product. More technically, biosensor is a probe that integrates a biological one with an electronic component to yield a measurable signal. These biosensors consist of three components: the biological recognition element, the transducer and the signal processing electronics. Researchers from various fields such as; physics, chemistry, biology, engineering and medicine are interested in developing, constructing and manufacturing new sensing devices to get more efficient and reliable information (illustrated in Fig. 1) [1]. Several biosensors are being developed for different applications, including environmental and bioprocess control, quality control of food, agriculture, military and more significantly the medical and pharmaceutical fields [2].

A typical biosensor functions at five different levels as shown in Fig. 2 [3] (i) bioreceptors that bind the specific form to the sample ; (ii) an electrochemical interface where specific biological processes occur giving rise to a signal (iii) a transducer that converts the specific biochemical reaction in an electrical signal (iv) a signal processor for converting the electronic signal into a meaningful physical parameter, and finally (v) a proper interface to display the results to the operator. Currently, biosensors are applied to a large variety of samples including

Corresponding author: Suresh Sagadevan, e-mail: sureshsagadevan@yahoo.co.in

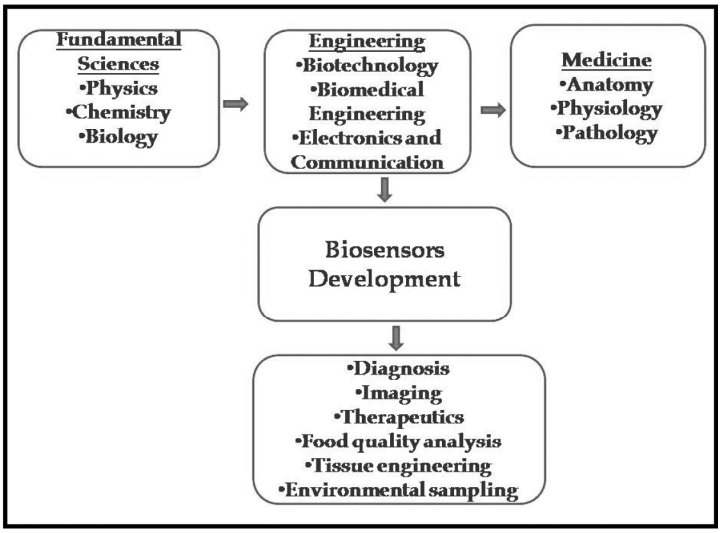

Fig. 1. Biosensors; an excellent example of multi and interdisciplinary research area.

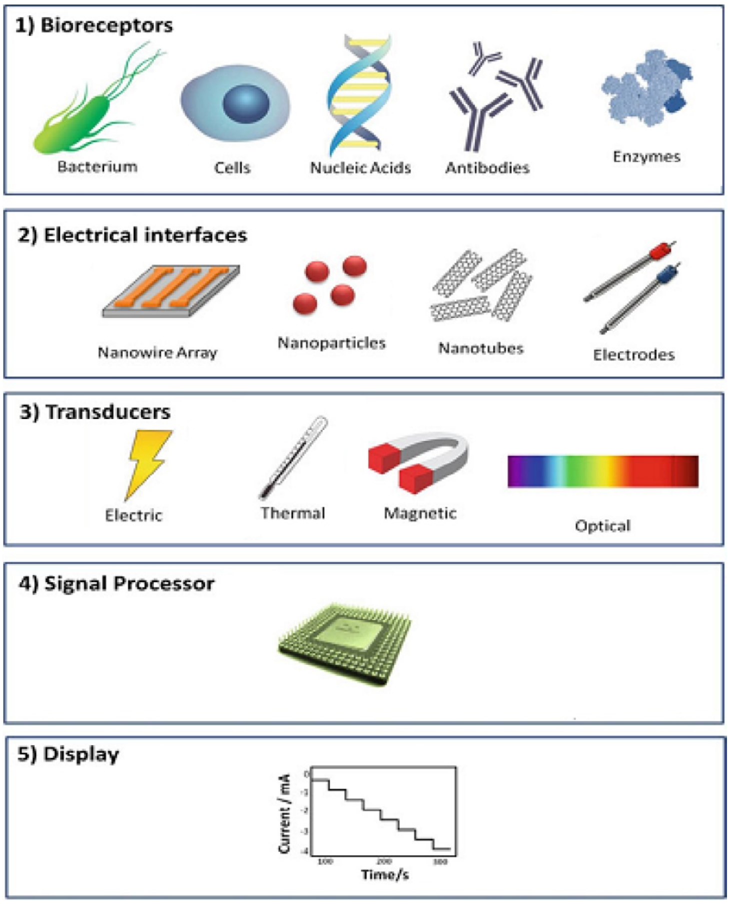

Fig. 2. Components of a typical biosensor.

body fluids, and food and environmental samples [4]. Researchers tend to integrate nanoparticles into the materials used for biosensor construction, in order to improve the performance of the system in both the existing and potential sensing applications. This paper reviews the major aspects of the nanotechnology-based biosensors, their applications in various fields and addresses the need for fundamental and continued research for further development.

2. NANOBIOSENSORS

Nanotechnology is a new branch of science that deals with the generation and alteration of materials to nanosize (10^{-9} m). Various nanomaterials have

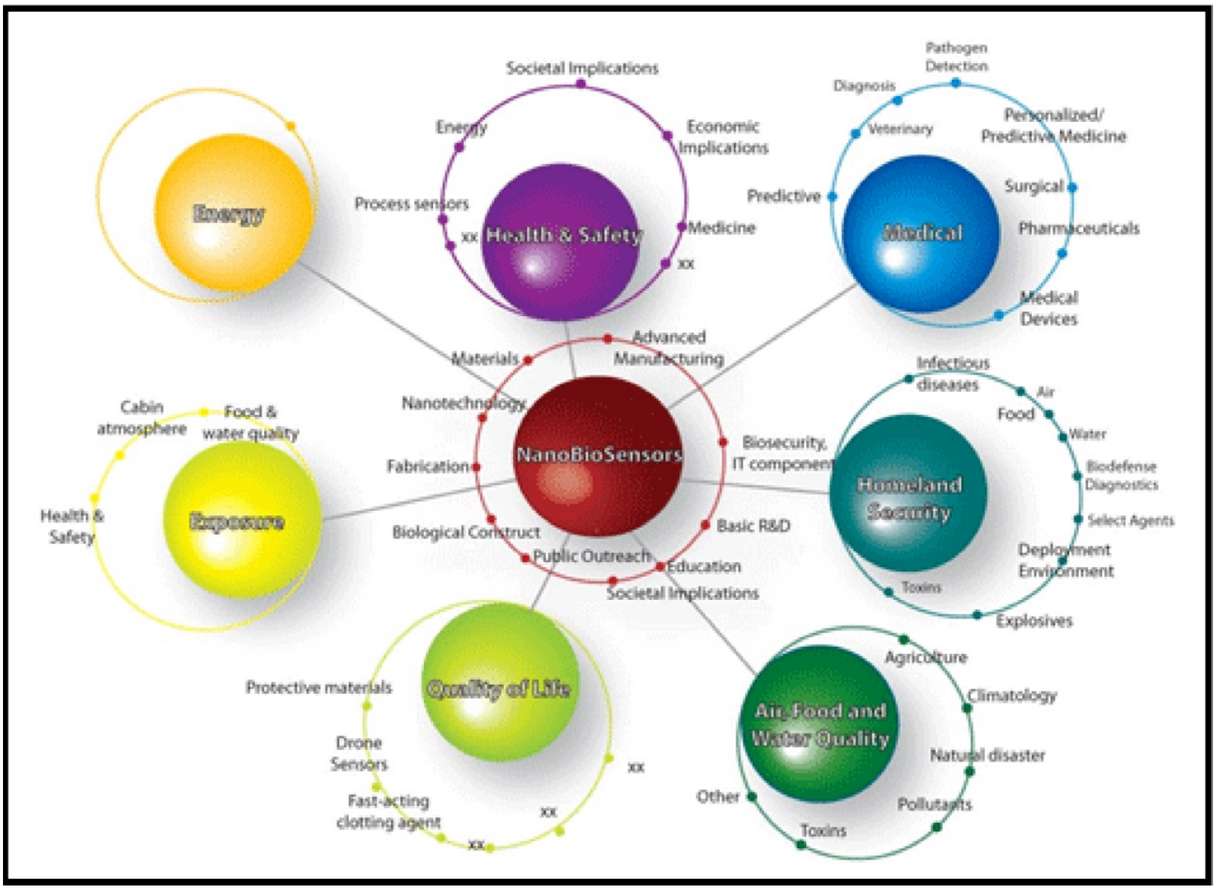

Fig. 3. Different field applications of nanobiosensors.

been discussed to analyze their properties and recent applications in biosensors [5]. The research in biosensor technology shows a constant increase in relation to the various nanomaterials with the interest to be implemented either into transducers or receptors operation parts, so as to enhance their multidetection capability and sensitivity. These nanomaterials are nanoparticles, nanotubes, quantum dots or other biological nanomaterials. These nanomaterials can contribute to either the bio-recognition element or the transducer or both, of a biosensor. Because of their submicron size, nanosensors, nanoprobes and other nanosystems have revolutionized in the fields of chemical and biological analysis, to enable the rapid analysis of multiple substances *in vivo*. In recent years, a wide variety of nanoparticles with different properties, such as small size, high speeds, smaller distances for electrons to travel, lower power, and lower voltages, have found broad application in biosensors [6]. Important advances in the field of nanotechnology have led to the utilization of nanomaterials such as metal nanoparticles [7], oxide nanoparticles [8], magnetic nanomaterials [9], carbon materials [10,11], Quantum Dots [12] and metallophthalocyanines [13] to improve the electrochemical signals of biocatalytic events that occur at the electrode/electrolyte interface. Functional nanoparticles that bound to biological molecules (e.g. peptides, proteins, nucleic acids) have been developed for use in biosensors to detect and amplify various signals [14].

3. NANOSTRUCTURED MATERIALS FOR BIOSENSING DEVICES

Nanostructured materials are interesting tools with specific physical and chemical properties because of their quantum-size effects when compared to bulk materials [3]. The exploration of these different characteristics provides the possibility to improve the sensitivity of biosensors. Interesting approaches have been reported on the increase in electronic properties with metallic nanostructures as components [15]. These include the utilization of nanostructured materials with specific forms like quantum dots and nanoparticles (0D), Nanowires and carbon nanotubes (1D), and metallic platelets or graphene sheets (2D) orientations that reflect their properties. These devices offer improved sensitivities, due to their large surface-to-volume ratios, which enable the bound analyse molecules to more

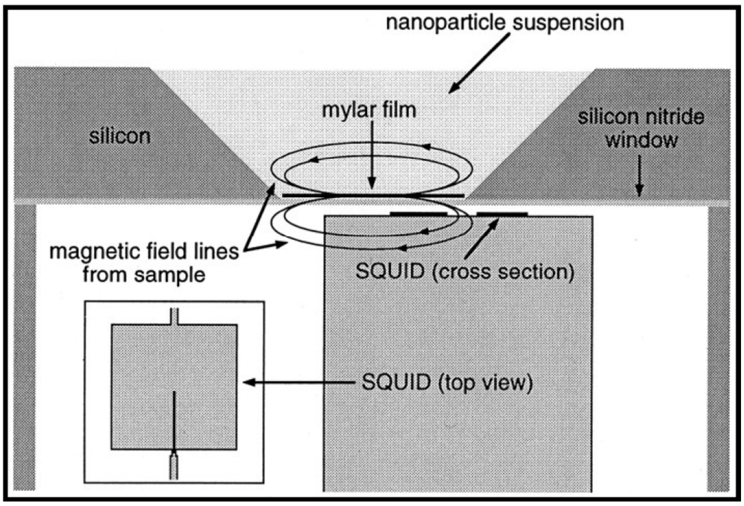

Fig. 4. Magnetic nanoparticle based biosensor.

significantly affect the bulk electrical properties of the structure. Due to their small size, nanomaterials may be taken up by cells [16-18], and thus are promising candidates for *in vivo* sensing applications. In some cases, the inherent electrical properties of the device, such as carbon nanotubes, are particularly extraordinary and lend themselves to improved sensor sensitivity. Several sensing platforms have been developed with nanomaterials that exploit a change in output signal [19]. Nanobiosensors are categorized based on these nanomaterials, and play a vital role in different fields, as shown in Fig. 3.

4. NANOPARTICLES-BASED BIOSENSORS

Metallic nanoparticles are very interesting materials with unique electronic and electrocatalytic properties depending on their size and morphology [20,21]. Nanoparticle-based biosensors are particularly attractive because they can be easily synthesized in bulk using standard chemical techniques, and do not require advanced fabrication approaches. They also offer particularly high surface areas due to their extremely small size and are typically used as suspensions in solutions (during the time when they interact with the analyse). Most biological molecules can be labelled with metal nanoparticles without compromising their biological activities [22]. In particular, gold nanoparticles are much explored materials as components for biosensors, due to their capability to increase an electronic signal when a biological component is maintained in contact with its nanostructured surface [23]. The exploration of gold nanostructured materials has provided new paths for enzymatic biosensor development. Gold nanoparticles also greatly improve the electron transfer across the monolayer molecules self-assembled on the surfaces of electrodes [24]. This observation is especially useful in the development of electroluminescence-based biosensors [25]. Apart from gold, silver, platinum, palladium, copper, cobalt and other nanoparticles are also extensively explored in the development of biosensors [22, 27-29].

Gold nanoparticle modified DNA has been used to develop a microcantilever-based DNA biosensor [30] (Su *et al.*) to detect DNA even at very lower concentration through a hybridization reaction. This reaction leads to the attachment of gold nanoparticles, and acts as a nucleating agent for the growth of silver particles when exposed to a photographic developing solution. The growth of silver particles increased the effective mass of the microcantilever and led to an enhanced frequency shift. This method could detect the target DNA at a concentration of 0.05 nM or lower. Microcavity resonators made of porous silicon have been used in biosensors. These resonators possess the unique characteristics of line narrowing and luminescence enhancement. Porous silicon has been used as an optical interferometric transducer for detecting small organic molecules, such as biotin and digoxigenin, 16-nucleotide DNA oligomers, and proteins (streptavidin and antibodies) at pico- and femtomolar level concentrations [31].

Magnetic nanoparticles are always powerful and versatile diagnostic tools in biology and medicine. A new technique has been introduced for the rapid detection of biological targets by using super paramagnetic nanoparticles based on a high-transition temperature DC Superconducting Quantum Interference Device (SQUID) [32]. In this technique, a Mylar film with a bound target is placed

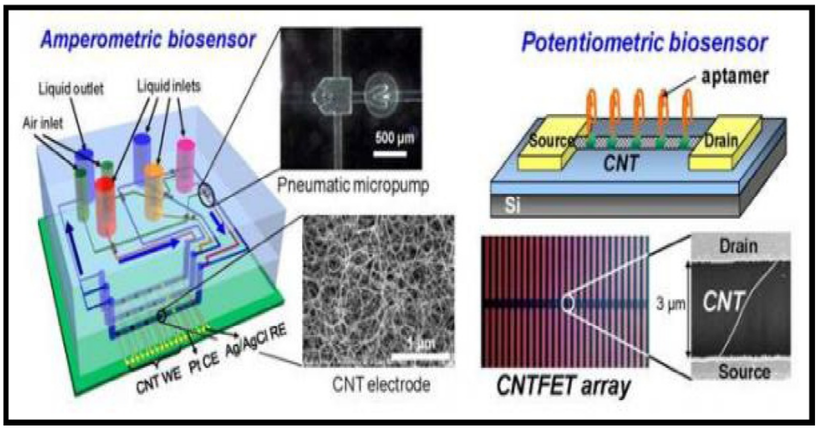

Fig. 5. Carbon nanotubes based biosensor.

on the microscope. A suspension of magnetic nanoparticles carrying antibodies is added to the mixture in a well, and 1-s pulses of magnetic field are applied parallel to the SQUID. In the presence of this aligning field, the nanoparticles develop a net magnetization, which relaxes when the field is turned off. Unbound nanoparticles relax rapidly by Brownian rotation, and contribute no measurable signal. Nanoparticles bound to the target are captured and undergo Neel relaxation, producing a slowly decaying magnetic flux, which is detected by the SQUID. The working mechanism of the SQUID is diagrammatically represented in Fig. 4.

Nanowire biosensors can be decorated with virtually any potential chemical or biological molecular recognition unit, through convenient surface properties. The nanomaterials transduce the chemical binding event on their surface into a change in the conductance of the nanowire in an extremely sensitive, real time and quantitative fashion. Boron-doped silicon nanowires (SiNWs) have been used to create highly sensitive, real-time electricity based sensors for biological and chemical species. Biotin-modified SiNWs were used to detect streptavidin down to at least a picomolar concentration range. The small size and capability of these semiconductor nanowires for sensitive, label-free, real-time detection of a wide range of chemical and biological species could be exploited in array-based screening and *in vivo* diagnostics.

5. CARBON NANOTUBE-BASED BIOSENSORS

Carbon materials have received great attention in the last two decades with the emergence of nanoscience [33]. These include the modification of electrodes with different nanocarbons, such as carbon powder, carbon nanotubes, graphene sheets and carbon capsules [34-36]. The investigation of the electronic properties of carbon nanotubes by Iijima and co-workers [38] is one of the most reported approaches to explain their detection capability. Carbon nanotubes (CNT) are formed by a hollow cylinder of a unique carbon sheet with a single walled carbon nanotube (SWCNT) or concentric carbon sheets of different diameters forming multiwalled carbon nanotubes (MWCNT) with sp2 bonding [33]. The particular cylindrical form of CNT is the principal aspect that provides the quantum confinement effect in the oriented 1D nanostructured materials [38]. These characteristics provide the possibility to increase the chemical reactivity and electronic properties of this particular carbon material, which becomes a crucial point for biosensing devices [35].

Recent studies have established the fact that CNT can enhance the electrochemical reactivity of important biomolecules [39,40], and can promote the electron-transfer reactions of proteins [41,42]. In addition to enhanced electrochemical reactivity, CNT-modified electrodes have been shown to be useful in accumulating important biomolecules (e.g., nucleic acids) [43], and alleviating surface fouling effects [40]. The remarkable sensitivity of CNT conductivity to the surface adsorbates permits the use of CNT as highly sensitive nanoscale sensors. These properties make CNT extremely attractive for a wide range of electrochemical biosensors ranging from amperometric enzyme electrodes to DNA hybridization biosensors. To take advantage of the remarkable properties of these unique nanomaterials in such electrochemical sensing applications, the CNTs need to be properly functionalized and immobilized. Among the many potential applications, carbon nanotubes have recently become promising functional materials for the development of advanced biosensors, such as amperometric and potentiometric biosensors, that are represented in Fig. 5.

6. BIOLOGICAL NANOMATERIALS-BASED BIOSENSORS

In a biosensor, the bioreceptor is combined with a suitable transducer which produces a signal after interaction with the target molecule of interest. The presence of the biological element makes the biosensor systems extremely specific and highly sensitive, giving an upper edge over the conventional methods. Over the years, a number of different natural and artificial biological elements have been used in biosensors; the most important ones are enzymes, dendrimers, thin films etc. In enzyme-based biosensors, the biological element is the enzyme which reacts selectively with its substrate [44]. Enzymes are the most used biocatalytic elements, enabling the detection of analyses in various ways. Since enzymatic reactions are followed by the consumption or production of various species, transducers can easily detect as well as correlate these consumed or produced species to the substrates.

Dendrimers are known as organic macromolecules with tridimensional and highly defined structure functionality [45]. The capability of these dendrimeric structures to stabilize and maintain the integrity of metallic nanoparticles was reported by Crooks [46]. The development of microelectrodes for the measurement of oxygen and hydrogen peroxide concentration is based on silicon substrate utilization through microfabrication technology. Enzymes or microorganisms are fixed on these oxygen-sensing chips by the use of photoresists. Thin nanostructured films have opened the possibility, to fabricate biosensors with a high power of detection, with intrinsic properties associated with their dimensions at the nanoscale level [47]. These interesting properties can be explained at the organizational level, when a molecular arrangement is obtained at a solid conductor substrate. Moreover, the possibility to improve the detection limit in biosensing devices can also be explained, by using compatible materials such as natural polymers.

7. CURRENT TRENDS IN NANOBIOSENSORS

There is a big demand for fast, reliable and low-cost systems for the detection, monitoring and diagnosis of biological molecules and diseases in medicine [48,49,1]. Of course, this demand is not restricted only to the field of medicine; it exists in the areas of environmental pollutant monitoring, detection of food borne pathogens, and the potential danger of bioterrorism. The development of ultra-sensitive biological and chemical sensors is one of the grand scientific, engineering, and educational challenges of the 21st century. The next generation biosensor platforms require significant improvements in sensitivity and specificity, in order to meet the needs in a variety of fields including in vitro medical diagnostics, pharmaceutical discovery and pathogen detection. Advances in diagnostic technology have been essential to the progress of medicine. The ability to identify diseases and pathogens by detecting associated proteins, nucleic acid sequences, organelles, cell receptors, enzymes, and other markers, can provide biomedical researchers and healthcare professionals with a detailed knowledge of disease pathways and patients conditions. However, many of the conventional tests currently available are slow, and require large amounts of sample materials, and may lead to false positive or negative results. Thus, there is a need for rapid, trustworthy, low-cost, multiplexed screening to detect a wide range of biomaterials. The current state-of-the art diagnostic biosensors are based on several technologies, often including either the enzyme-linked immunosorbent assay (ELISA), or amplification of a sample by polymerase chain reaction (PCR), using appropriate primers and detection methods. The research on nanobioelectronics & biosensors aims at the integration of nanoelectronics, tools and materials into low cost, user friendly and efficient sensors and biosensors, with interest in several fields such as diagnostics, food analysis, environment monitoring and other industries.

8. CONCLUSION

Nanotechnology is revolutionizing the development of biosensors in recent years. **Nanobiosensor research** focuses on developing innovative technologies that have the ability to make significant contributions in the areas of human and animal disease marker detection, promising therapeutic compound identification and analysis, nano-and biomaterials characterization, and biocatalyst development. These technologies take the form of nanometrically engineered, biologically active surfaces, or liquid-solid interfaces, and the tools necessary to characterize them. The emergence of nanotechnology has opened up new horizons for the development of nanosensors and nanoprobes with submicron-sized dimensions, that are suitable for intracellular measurements.The attention is being focussed on the study of various nanoeffects, such as the quantum size effect, mini size effect, surface effect, and the macro-quantum tunnel effect, that is unique to nanomaterials, and is actually their most attractive aspect. New nanomaterials and nanostructures need to be explored for use in biosensors. Preferably, nanotechnology-based biosensors should be integrated within tiny biochips with on-board electronics, sample handling and analysis. This will greatly enhance their functionality, by providing devices that are small, portable, easy to use, low cost, disposable, and highly versatile diagnostic instruments. Laser nanosensors can be used for the *in vivo* analysis of proteins and biomarkers in individual living cells.

Even though a wide range of nanobiosensors have been developed in the past two decades, the futuristic goal of low-cost, high throughput, multiplexed clinical diagnostic lab-on-a-chip devices is yet to be truly realized. It is still unclear which nanobiosensor architectures are best matched to which diagnostic tasks. Moreover, nanobiosensors that are functional in the lab may not be of use in the field or clinic for several reasons. Well-structured interdisciplinary research programs that involve, life science researchers, engineers and physicians have to be conducted, to reveal more refined and affordable biosensors.

ACKNOWLEDGEMENTS

The authors thank the Management, Principal and Faculty members of Sree Sastha Institute of Engineering and Technology, Chembarambakkam, Chennai-600123, for their constant encouragement and support throughout this work.

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