Review Article

Prospects of Nanobiomaterials for Biosensing

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Progress and development in biosensor development will inevitably focus upon the technology of the nanomaterials that offer promise to solve the biocompatibility and biofouling problems. The biosensors using smart nanomaterials have applications for rapid, specific, sensitive, inexpensive, in-field, on-line and/or real-time detection of pesticides, antibiotics, pathogens, toxins, proteins, microbes, plants, animals, foods, soil, air, and water. Thus, biosensors are excellent analytical tools for pollution monitoring, by which implementation of legislative provisions to safeguard our biosphere could be made effectively plausible. The current trends and challenges with nanomaterials for various applications will have focus biosensor development and miniaturization. All these growing areas will have a remarkable influence on the development of new ultrasensitive biosensing devices to resolve the severe pollution problems in the future that not only challenges the human health but also affects adversely other various comforts to living entities. This review paper summarizes recent progress in the development of biosensors by integrating functional biomolecules with different types of nanomaterials, including metallic nanoparticles, semiconductor nanoparticles, magnetic nanoparticles, inorganic/organic hybrid, dendrimers, and carbon nanotubes/graphene.

1. Introduction

Nanomaterial utilizes nanoscale engineering and system integration of existing materials to develop better materials and products. Applications of nanomaterials have made their presence strongly felt in various areas like healthcare, implants, and prostheses; smart textiles, energy generation and conservation with energy generating materials and highly efficient batteries, defence, security, terrorism, and surveillance [1]. Bionanomaterial's research has emerged as a new exciting field, recognized as a new interdisciplinary frontier in the field of life science and material science. Great advances in nanobiochip materials, nanoscale biomimetic materials, nanomotors, nanocomposite materials, interface biomaterials, nanobiosensors, and nano-drug-delivery systems have the enormous prospect in industrial, defense, and clinical medicine applications. Biomolecules assume the very important role in nanoscience and nanotechnology, for example, peptide nucleic acids (PNAs) replace DNA, act as a biomolecular tool/probe in the molecular genetics, diagnostics, cytogenetics, and have enormous potentials in pharmaceuticals for the development of biosensors. Biosensor consists of a biosensing material and a transducer that can be

used for detection of biological and chemical agents. Biosensing materials, like enzymes, antibodies, nucleic acid probes, cells, tissues, and organelles, selectively recognize the target analytes, whereas transducers like electrochemical, optical, piezoelectric, thermal, and magnetic devices can quantitatively monitor the biochemical reactions shown in Figure 1.

Singh et al. reported a disposable biosensor for rapid determination of not only H_2O_2 but also of azide in biological samples using CAT/PANi/ITO electrode as a bioelectrode. This film is very efficient for retaining the enzyme activity and preventing its leakage out of the film. It suggests that this efficient film can be used for the immobilization of not only catalase but also other enzymes and bioactive molecules that is, a promising platform for the development of biosensors [2] as shown in Figure 2.

Biosensors have become an emerging area of interdisciplinary research. Various types of biosensors are used with inherent advantages and limitations in conjunction with different transducers forming the biosensing devices for the detection of various kinds of targeted biomolecules. Nucleic acid elements, including aptamers, DNAzymes, aptazymes, and PNA, are widely used in nanobiotechnology (lab-on-a-chip, nanobiosensors array) [3–5]. In addition,

FIGURE 1: it shows the basic concept of biosensor.

FIGURE 2: It shows schematic representation of bioelectrode in the development of biosensor for the H_2O_2 determination under optimal conditions.

the nanobiosensor can be easily integrated into disposable polymer lab-on-a-chip for numerous applications in biochemical analysis and clinical diagnostics. The recent developments in nanobiosensors and their applications in biology, especially in medical diagnostics, encompass the concepts of coordinated nanobiosensors integrating the desirable properties of the individual components: protein machinery for sensitivity and specificity of binding, peptide or nucleic acid chemistry for aligning the various electron transducing units, and the nanoelectrodes for enhancing sensitivity in electronic detection. Results from these systems focus on the potential advantages of use of nanoscale biosensor diligence, which will revolutionize biomedical diagnostics and treatments drastically. Thus the development

and application of nanodevices in biology and medicine will have enormous implications for the benefit of society and human health. The biosensors integrated with the new technologies in molecular biology, microfluidics, and nanomaterials have applications in agricultural production, food processing, clinical care, and environment for rapid, specific, sensitive, inexpensive, in-field, online, and/or real-time detection as well as monitoring of pesticides, antibiotics, pathogens, toxins, proteins, microbes, plants, animals, foods, soil, air, and water. Thus, ultrasensitive biosensors offer to be an excellent analytical tool for pollution monitoring enabling the surveillance of biosphere possible. The future emerging trends toward biosensor development, in the context of bioelectronics, nanotechnology, and biotechnology, seem to be all growing areas that will have a remarkable influence on the development of new biosensing platform to resolve our future clinical diagnostics and address the challenges relating to severe pollution problems concerning not only human health but also all living entities [6–8]. To understand biological processes at a single molecule level and to implement them for the possible future applications in nanobiotechnology are of current interest. Studies relating to single molecule enabled probe have opened exciting avenues of research, especially in nanoscience and nanotechnology for the development of versatile biomolecule detection technology [9].

Nanomaterials have enabled the development of ultrasensitive biosensors, because of their high surface area, electronic properties, and electrocatalytic activity as well as good biocompatibility. They have been used to achieve direct wiring of enzymes to the electrode surface, to promote

FIGURE 3: It shows representative nanobioelectrode fabrication for ultra biosensing detection.

electrochemical reaction, and to amplify a signal of biorecognition events. The nanomaterials, including nanoparticles, nanowire, nanoneedle, nanosheet, nanotube, nanorod, nanobelt, for biosensing have been reported in several research articles [10, 11] as shown in the representative Figure 3. Few important examples are low-potential detection of NADH using carbon nanotube (CNT) modified electrodes, gold nanoparticles for electrochemical immunosensors, carbon nanotube-based sensors [12–21], nanoparticles-based biosensing [22–25], and nanowire as sensing materials [26].

Nanowires belong to a growing family of nanoobjects, which also includes nanotubes, nanoparticles, nanorods, and many more. Nanowires can serve as the electrode or interconnects between micro- and nanoelectronic devices. Their dimensions are sometimes at the same scale as biomolecules, which enables exciting possibilities for their interaction with biological species, such as cells, antibodies, DNA, and other proteins. Chen et al. reported positively charged Ni-Al layered double hydroxide nanosheets (Ni-Al LDHNS) for the first time as matrices for immobilization of horseradish peroxidase (HRP) in order to fabricate enzyme electrodes for the purpose of studying direct electron transfer between the redox centers of proteins and underlying electrodes. The immobilized HRP in Ni-Al LDHNS on the surface of a glassy carbon electrode (GCE) exhibited good direct electrochemical and electrocatalytic responses to the reduction of hydrogen peroxide and trichloroacetic acid (TCA). The linear detection results showed that Ni-Al LDHNS provides

a novel and efficient platform for the immobilization of enzymes and the fabrication of third-generation biosensors [27]. Several investigators have reported ZnO nanosheet and other metal oxides as sensing materials in electrochemical biosensors [28–31].

An ideal biosensing platform is pre-requisite and it requires miniaturization, cost effectiveness, and simultaneous detection of multiple analytes. The biorecognition arrays (microarrays) have posed new technical challenges for the probes, transducers, and their detection apparatus. Microarrays can analyze large numbers of biological molecules using small amounts of material that has separated on a substrate (e.g., plastic, glass, and semiconductor). The biological materials deposited or synthesized on the chip surface include nucleic acids, proteins, peptides, antibody, and carbohydrates. The methods used for placing materials onto the chip surface rely on physical spotting, piezoelectric deposition, and *in situ* synthesis. Developments of DNA biosensors and DNA microarrays have progressed tremendously as reported by the several investigators [32]. DNA microarrays (gene chips, DNA chips, or biochips) utilize the preferential binding of complementary single-stranded nucleic acid sequences. Unlike DNA biosensors, DNA microarrays are made onto the glass, plastic, or silicon supports consisting of tens to thousands of 10–100 μm reaction sites onto which individual oligonucleotide sequences have been immobilized [33]. The immobilization of a DNA probe in DNA biosensors was achieved directly onto a transducer surface. The exact number of DNA probes

varies in accordance with the application. Contrary to DNA biosensors that allow single shot measurements, DNA microarrays allow multiple parallel detection and analysis of the patterns of expression of thousands of genes in a single experiment. The most common method for analyzing hybridization events on DNA microarrays is fluorescence. Additional methods have developed, including surface plasmon resonance, atomic force microscopy, quartz crystal microbalance, and cantilevers. However, electrochemical detection offers several advantages over conventional fluorescence, such as portability, higher performance with lower background, fewer expensive components, and measurements even in turbid samples. Electrochemical transducers have used for detecting DNA hybridization because of their high sensitivity, small dimensions, low cost, and compatibility with micro manufacturing technology. There are numerous labeled electrochemical DNA biosensors where the tag can be an enzyme, ferrocene, an interactive electroactive substance (a groove binder, such as Hoechst 33258, or an intercalator) or nanomaterials and label-free electrochemical DNA biosensors [34]. Kumar and Dill have reported applications of microarray in the development of electrochemical DNA microarray biosensors. Microelectrode arrays are composites of microelectrodes, where single microelectrodes wired in parallel with each one, acting diffusionally independent; generating a signal, which is thousands times larger [35]. One of the microelectrode arrays was RAM electrode, where thousands of carbon wires sealed into epoxy resin producing random assemblies of microdisks [36]. Microfluidic environments add value to biosensing tasks because they consume lower amounts of probe molecules and target analyte [37]. A microelectrode array consisting of boron-doped diamond (BDD) microelectrode disks, a versatile electrode device with the advantages of both microelectrode arrays and of boron-doped diamond as an electrode, was also developed. The BDD-microelectrode arrays are excellent substrates for the deposition copper, silver, and gold allowing a single electrode array to act as a template for a microelectrode array of many different electrode materials for a variety of analytical tasks, all of which can be carried out with a single BDD array after a suitable electrodeposition [38, 39].

Microfluidic technology consisting of microfluidic mixer, valves, pumps, channels, chambers in a single-chip device has been established for detecting infectious particles (viruses and bacteria) in complex biological samples. These sensors are miniaturized arrays of individually addressable microelectrodes controlled by active complementary metal oxide semiconductor (CMOS) circuitry. The devices with capabilities of on-chip sample processing and detection provide a cost effective solution to direct sample-to-answer biological analysis for point-of-care genetic analysis, disease diagnosis, and in-field biothreat detection [40, 41]. Hassibi and Lee [42] reported an integrated CMOS electrochemical sensor array capable of performing impedance, potentiometry, voltammetry, and ion-sensitive detection. The complete system is fabricated within a single chip and built in a standard digital $0.18\ \mu\text{m}$ CMOS processor with no 8 post processing requirements.

2. Nanoparticles in Biosensing

The sensitivity and performance of devices are being improved using nanomaterials. Nanomaterials with at least one of their dimensions ranging in scale from 1 to 100 nm display unique and remarkably different property as compared to its bulk because their nanometer size gives rise to high reactivity and other enhanced beneficial physical properties (electrical, electrochemical, optical, and magnetic) owing to nonlinearity after crossing the performance barrier threshold. Their applications can potentially translate into new assays that improve upon the existing methods of biomolecular detection. Nanoparticles have been widely used in biosensors for detection of nucleic acids, peptide nucleic acid, and proteins [43–45]. The enhancement in redox properties of gold nanoparticles coupled with silver has led to their widespread application as electrochemical labels in biosensor development with remarkable sensitivity [46, 47]. The gold nanoparticles coated with ferrocenyl hexanethiol and streptavidin were used to monitor the DNA hybridization. Nanoparticles have also coupled with magnetic particles to capture target DNA, which then hybridizes with a secondary probe DNA tagged to metal nanoparticle and detected by anodic stripping voltammetry [48, 49]. A common problem with silver enhancement is a high background signal resulting from nonspecific precipitation of silver onto the substrate electrode and to overcome the setback, various electrode surface treatments and electrochemically or enzymatically controlled deposition methods of silver have reported. For reducing the silver related background signal and increasing the sensitivity, a new system of electrochemical detection of DNA hybridization based on stripping voltammetry of enzymatically deposited silver has developed. The target DNA and a biotinylated DNA immobilized probe hybridize to a capture DNA probe tethered onto a gold electrode. NeutrAvidin- (NA-) conjugated alkaline phosphatase binds to the biotin of the detection probe on the electrode surface converting the nonelectroactive substrate to a reducing agent. The latter reduces the metal ions in solutions leading to the deposition of metal onto the electrode surface and DNA backbone [50, 51].

K'Owino et al. the first time reported the underpotential deposition of Ag monolayer for the enhancing electrochemical sensitivity of biomolecular reaction. The metal-enhanced electrochemical sensing, using immobilized metal layer, as continuous film, particle, colloids, or monolayer for the detection of parts per trillion (ppt) levels of anticancer drug cisplatin, and PCBs, has been reported [52]. A modified metal-enhanced electrochemical detection (MED) concept was developed for the detection of two base pair mismatches using *Microcystis* as a model for monitoring DNA-cisplatin interactions [53, 54]. The detection has also used to monitor other biomolecular reactions, including DNA hybridization, mismatch detection, DNA-protein, antigenantibody, and DNA-RNA reactions [55]. Aptamer is the artificial nucleic acid ligand consisting of single-stranded DNA and/or RNA sequences, which are typically synthesized *in vitro* using systematic evolution of ligands by exponential enrichment

(SELEX). It has been utilized as a recognition element for biosensing applications for the detection of various analytes of interest [56–59] to enhance high sensitivity and selectivity using nanoparticles and quantum dot labels [60–63].

Semiconductor or conducting polymer nanowires (NWs) are extremely attractive for designing high density protein arrays, because of their high surface-to-volume ratio and electron transport properties as the electronic conductance is strongly influenced by minor surface perturbations (e.g., binding on biomolecules). Hahm and Lieber have reported the potential of functionalized NW for the highly sensitive real-time biodetection for monitoring DNA hybridization [64]. Patolsky et al. have reported single viruses in connection with p-type silicon NW (SiNW) functionalized with PNA probes or antibodies for influenza [65]. Zheng et al. have demonstrated the use of an antibody functionalized silicon nanowire sensor array for the multiplexed label-free real-time monitoring of cancer markers in undiluted serum samples [66]. The biosensing utility of conducting polymer NW or carbon nanotubes has also been reported [67, 68]. Tang et al. have reported a simple and sensitive label-free electrochemical immunoassay electrode (poly-OAP/CEAAb-AuNP/Au electrode) for detection of carcinoembryonic antigen (CEA) [69]. The microfabricated interdigitated array microelectrodes (IDAMs) have received great attention and reported one or multiple electrode pairs in an IDA in the range from micron to nanometer. Impedance biosensor for the bacteria detection based on impedance analysis due to electrical properties of bacterial cells, when they are attached to or associated with the electrodes [70]. The advances in microfabrication technologies have enabled the use of micro-fabricated microarray electrodes in impedance detection and the miniaturization of impedance microbiology into a chip format, which has shown great promise for rapid detection of bacterial growth. Yang and Bashir have reviewed the electrical/electrochemical impedance for the rapid detection of food-borne pathogenic bacteria, including microchip micro-fabricated microelectrodes-based (interdigitated array microelectrodes) and microfluidic-based Faradic electrochemical impedance biosensors (microchips), non-Faradic impedance biosensors, and the integration of impedance biosensors with other techniques such as dielectrophoresis and electroporability. Magnetic particles are useful in separating target cells from a mixture of bacteria and food matrices and help to concentrate separated cells into a very small volume with the help of a magnetic field and improve the sensitivity [71]. A microfluidic flow cell (embedded gold interdigitated array microelectrode) based impedance biosensor detected pathogenic bacteria in the ground beef samples containing *E. coli* O157:H7 [72–78]. Cretich et al. have reported a new, rapid, and robust method for PDMS functionalization, based on chemisorptions of copolymer (DMA-NAS-MAPS), which provides an effective way to immobilize DNA fragments for the bacterial genotyping and food pathogen identification. Actually, PDMS-bound surface of biomolecules can be applied to DNA, protein and peptide microarrays, biosensors, and cell culturing. Furthermore, PDMS, with its attractive physicochemical properties and the ease of patterning, is the material of

choice for the development of lab-on-chip devices. Liao et al. have reported the first species-specific detection of bacterial pathogens in human clinical fluid samples, using a micro-fabricated electrochemical sensor array. Each of the 16 sensors in the array consisted of three single-layer gold electrodes: working, reference, and auxiliary [79]. Karasinski et al. [80] have described the integration of a fully autonomous electrochemical biosensor (96-well-type electrodes array, DOX-dissolved oxygen sensor) with pattern recognition techniques for the detection and classification of the bacteria kingdom at subspecies and strain levels. The operational principle of 96-electrode DOX sensor was based on the measurements of the difference in the oxygen consumed by different bacteria classes and strains over a period of time and monitoring the oxygen reduction current at a fixed potential (-700 mV versus gold), suggested the highest sensitivity and additional selectivity, which allows better differentiation and classification of bacteria.

Clark and Lyons [81] had proposed for the first time in 1962 the initial concept of glucose enzyme electrodes. Now, tremendous efforts directed towards the development of reliable devices for diabetes control have developed like electrochemical glucose biosensors [82, 83]. Varieties of nanomaterials, including gold nanoparticles or carbon nanotubes, have used as electrical connectors between the electrode and the redox center of glucose oxidase. Carbon nanotubes can be coupled to enzymes to provide a favorable surface orientation and thus can act as an electrical connector between their redox center and the electrode surface as molecular wires (nanoconnectors) between the underlying electrode and a redox enzyme [84]. Patolsky et al. demonstrated that the edge of single-walled carbon nanotubes (SWCNT) can be linked to an electrode surface. Such enzyme reconstitution on the end of CNT represents an extremely efficient approach for plugging an electrode into glucose oxidase. Electrons were transported along distances higher than 150 nm with the length of the SWCNT controlling the rate of electron transport. An interfacial electron-transfer rate constant of 42 s^{-1} was estimated for 50 nm long SWCNT [85]. Gooding and coworkers have reported an efficient direct electrical connection to GOx using aligned SWCNT arrays [86] by improving the contact between the nanomaterial and the electrode. Subsequently, nanowires as sensing materials were used for hydrogen peroxide and glucose sensors to overcome the overvoltage in the detection of H_2O_2 [87]. Gold nanowires were prepared by an electrodeposition strategy using nanopore polycarbonate (PC) membrane, with the average diameter of the nanowires of about 250 nm and length of about 10 nm. The nanowires were prepared and dispersed into chitosan (CHIT) solution and stably immobilized onto the glassy carbon electrode surface. The modified electrode allows low-potential detection of hydrogen peroxide with a high sensitivity and fast response time. Glucose oxidase was adsorbed onto the nanowire surface to fabricate glucose biosensor as an application [88, 89]. Similarly, platinum nanowires (PtNWs) prepared with the help of porous anodic aluminum oxide (AAO) templates have been solubilized in chitosan together with carbon nanotubes (CNTs) to form a PtNW/CNT/CHIT

organic-inorganic system. The PtNW-CNT-CHIT film-modified electrode offers a significant decrease in the overvoltage for the hydrogen peroxide, and it was shown to be excellent amperometric sensors for hydrogen peroxide at -0.1 V over a wide range of concentrations with the sensitivity recorded being $260 \mu\text{A} \text{mM}^{-1} \text{cm}^{-2}$. By linking glucose oxidase, an amplified biosensor toward glucose was prepared, which exhibits selective determination of glucose at -0.1 V. The application of polypyrrole-coated glucose oxidase nanoparticles (GOx/Ppy) in electrochemical biosensor design was described, and the increase of K_m by over 10 times was determined for polypyrrole-coated GOx, compared with native GOx [90]. Li et al. [91] developed a conductivity-based glucose nanobiosensor-based on conducting-polymer-based nanogap. Such nano-junction-based sensor was formed by using polyaniline/glucose oxidase for bridging a pair of nanoelectrodes separated with a small gap (20–60 nm) [92]. Ultimately, one would like to eliminate the mediator and develop a glucose biosensor with a low operating potential, close to that of the redox potential of the enzyme. The absence of mediators is the main advantage of such third-generation biosensors, leading to a very high selectivity (owing to the very low operating potential). Jing and Yang have reported oxidized boron-doped diamond electrodes suggesting some promise for mediator-free glucose detection based on direct electron transfer [93]. An ideal sensor would be one that provides a reliable real-time continuous monitoring of all blood glucose variations throughout the day with high selectivity and speed over extended periods under harsh conditions. Wilson has reported continuous glucose monitoring, which addresses the deficiencies of the test strip-based meters and provides the opportunity of making fast and optimal therapeutic interventions [94], and further Wilson and Gifford have reported a needle type of multielectrode array for the hypodermic continuous glucose-monitoring sensor using MEMS technology. The developed multielectrode sensor had four electrodes of two working (Pt) electrodes, one counter (Pt) electrode, and one reference (Ag/AgCl) electrode [95]. Jung et al. have reported two working electrodes for the enzyme and nonenzyme electrodes, which measure glucose concentration and the background current. This would minimize short-term crises and long-term complications of diabetes leading to improved quality and length of life for diabetic people [96]. Heller has reported glucose biosensors based on closed loop glycemic control systems for regulating a person's blood glucose. The concept of closed loop (sense/release) systems is expected to have a major impact upon the treatment and management of other diseases, revolutionizing the patient monitoring [97]. However, the challenges for meeting these demands include rejection of the sensor by the body, miniaturization, long-term stability of the enzyme, *in vivo* calibration, short stabilization times, baseline drift, safety, and convenience. The sensor must be of a very tiny size and of proper shape to allow for easy implantation resulting in minimal discomfort. Alternative sensing sites, particularly the subcutaneous tissue, have thus received growing attention. The subcutaneous tissue is minimally invasive, and its glucose level reflects the blood

glucose concentration. However, such subcutaneous implantation generates a wound site that experiences an intense local inflammatory reaction. This inflammatory response associated with the wound formation is characterized with the problems such as scar tissue formation accompanied by adhesion of bacteria and macrophage leading to distortion of the glucose concentration in the immediate vicinity of the sensor. Recent approaches for designing more biocompatible *in vivo* glucose sensors focused on preparing interfaces that resist biofouling [98–100]. Nitric oxide is an effective inhibitor of platelet and bacterial adhesion. Gifford et al. reported nitric oxide release glucose sensors fabricated by doping the outer polymeric membrane coating of needle-type electrochemical sensors with suitable lipophilic diazeniumdiolate species or diazeniumdiolate-modified sol-gel particles. The utility and application of nanomaterials are targeted for the improved electrical contact between the redox center of GOx and electrode supports using genetically engineered GOx [101]. Recently, Andreescu and Luck reported genetically engineered periplasmic glucose receptors as a biomolecular recognition element on gold nanoparticles (AuNPs) that holds promise for sensitive and electrochemical glucose biosensor.

The receptors were immobilized on AuNPs by a direct sulfur-gold bond through a cysteine residue that was engineered in position 1 on the protein sequence. This finding will result in the advances in new painless *in vitro* testing, artificial (biomimetic) receptors for glucose, advanced biocompatible membrane materials, invasive monitoring with a compact insulin delivery system, new innovative approaches for noninvasive monitoring, and miniaturized long-term implants [102].

3. Biomaterials

The biomaterial is natural or man made that comprise whole or part of a living structure or biomedical device, which performs or replaces a natural function. They are used every day in dental applications, surgery, and drug delivery. A biomaterial may also be an autograft, allograft, or xenograft used as a transplant material. Natural biomaterials are silicates in algae and diatoms, carbonates in invertebrates, calcium phosphates, and carbonates in vertebrates [103–108]. Molecular crystals, liquid crystals, colloids, micelles, emulsions, phase separated polymers, thin films, and self-assembled monolayers, all represent examples of highly ordered structures [109, 110]. In the biomedical field, artificial materials have been used in the human body to measure, restore, improve physiologic function, and enhance survival and quality of life. Typically, inorganic (metals, ceramics, and glasses) and polymeric (synthetic and natural) materials have been used for such items as artificial heart valves, (polymeric or carbon based), synthetic blood vessels, artificial hips (metallic or ceramic), medical adhesives, sutures, dental composites, and polymers for controlled slow drug delivery. The biocompatible materials are integrated into the biological environment as well as other tailored properties depending on the specific *in vivo* application [111]. The biomimetics may be described as the abstraction

of good design from nature or the stealing of ideas from nature. The aim is to make materials for nonbiological uses under an inspiration from the natural world by combining them with man-made, nonbiological devices or processes. The aim of the controlled release devices is to maintain the drug in the desired therapeutic range with just a single dose, the need for follow-up care, medications that have rapidly destroyed by the body, and patient comfort and/or compliance [112]. Biodegradability can therefore be engineered into polymers by the addition of chemical linkages such as anhydride, ester, or amide bonds, among others. The mechanism for degradation is by hydrolysis or enzymatic cleavage resulting in a scission of the polymer backbone [113]. Biodegradable polymers with hydrolysable chemical bonds have used extensively for biomedical, pharmaceutical, agricultural, and packaging applications. In order to use in medical devices and controlled drug release applications, the biodegradable polymer must be biocompatible and should meet other criteria to be qualified as biomaterial processable, sterilizable, and capable of controlled stability or degradation in response to biological conditions [114]. Chitosan is an environmentally biodegradable polymer that possesses a wide range of useful properties. It is a biocompatible, antibacterial and has a variety of applications, including water treatment, chromatography, additives for cosmetics, textile treatment for antimicrobial activity, novel fibers for textiles, photographic papers, biodegradable films, biomedical devices, and microcapsule implants for controlled release in drug delivery [115]. Poly(ethylene oxide) (PEO) is a polymer which shows biocompatibility, hydrophilicity, and versatility. The simple water-soluble linear polymer can be modified by chemical interaction to form water insoluble but water swellable hydrogels retaining the desirable properties associated with the ethylene oxide part of the structure. Poly(ethylene glycol) (PEG) has been used increasingly for a variety of pharmaceutical applications. Multiblock copolymers of poly(ethylene oxide) (PEO) and poly(butylene terephthalate) (PBT) are under development process for the prosthetic devices and artificial skin. Ethylene-vinyl acetate copolymer is a widely used nondegradable polymer and displays excellent biocompatibility, physical stability, biological inertness, and processability [116].

New bio-nanocomposites are influencing diverse areas, in particular, biomedical science. Generally, polymer nanocomposites are the results of the combination of polymers and inorganic/organic fillers at the nanometer scale. The extraordinary versatility of these new materials may spring from the large selection of biopolymers and fillers available to researchers. Few existing biopolymers, including (but not limited to) polysaccharides, aliphatic polyesters, polypeptides, proteins, and polynucleic acids, are predominantly reported in the literature along with fillers like clays, hydroxyapatite, and metal nanoparticles [117]. The interaction between filler components of nanocomposites at the nanometer scale enables them to act as molecular bridges in the polymer matrix. This is the basis for enhanced mechanical properties of the nanocomposites as compared to conventional microcomposites [118]. Bio-nanocomposites add a new dimension to these enhanced properties in

that they are biocompatible and/or biodegradable materials. The biodegradable materials can be described as materials degraded and gradually absorbed and/or eliminated by the body, whether degradation is caused mainly by hydrolysis or mediated by metabolic processes [119]. Therefore, these nanocomposites are of immense interest to biomedical technologies such as tissue engineering, bone replacement/repair, dental application, and controlled drug delivery. Current opportunities for polymer nanocomposites in the biomedical arena arise from the multitude of applications and the vastly different functional requirements for each of these applications. For example, the screws and rods that are used for internal bone fixation bring the bone surfaces in close proximity to promote healing. This stabilization must persist for weeks to months without loosening or breaking. The modulus of the implant must be close to that of the bone for efficient load transfer [120]. The screws and rods must be noncorrosive, nontoxic, and easy to remove if necessary. Thus, a polymer nanocomposite implanted must meet certain design and functional criteria, including biocompatibility, biodegradability, mechanical properties, and, in some cases, aesthetic demands [121, 122]. Yamaguchi et al. have synthesized and studied flexible chitosan-HAP nanocomposites [123]. The matrix used for this study was chitosan (a cationic, biodegradable polysaccharide), which is flexible and has a high resistance against heating because of intramolecular hydrogen bonds formed between the hydroxyl and amino groups [124, 125]. The resulting nanocomposites, prepared by the coprecipitation method are mechanically flexible and can be formed into any desired shape. Nanocomposites formed from gelatin and HAP nanocrystals are conducive to the attachment, growth, and proliferation of human osteoblast cells [126]. Collagen-based polypeptidic gelatin has a high number of functional groups and is currently being used in wound dressings and pharmaceutical adhesives in clinics [127, 128]. The flexibility and cost-effectiveness of gelatin can be combined with the bioactivity and osteoconductivity of HAP to generate potential engineering biomaterials. The traditional problem of HAP aggregation was overcome by precipitation of the apatite crystals within a polymer solution [129, 130]. The porous scaffold generated by this method exhibited well-developed structural features and pore configuration to induce blood circulation and cell in growth. Such nanocomposites have the high potential for their use as hard tissue scaffolds. Three-dimensional porous scaffolds from biomimetic HAP/chitosan-gelatin network composites with micro scale porosity have shown adhesion, proliferation, and expression of osteoblasts [131, 132]. Porosity is critical for tissue engineering applications because it enables the diffusion of cellular nutrients and waste and provides support for cell movement [133, 134]. Polysaccharides, such as alginate, provide a natural polymeric sponge structure that has been used in tissue engineering scaffold design. The weak, soft alginate scaffolds can be strengthened with HAP and have widespread applications [135, 136]. Composite membranes from HAP nanoparticles and chitosan/collagen sols have also been synthesized to study connective tissue reactions [137, 138]. Studies that target the nucleation of

calcium phosphates and bone cell signaling within the matrix have used acidic macromolecules as the nanocomposite matrix [139]. Specifically, amino acids like aspartic acid and glutamic acid have been used as the matrix protein. Both amino acids have known to play an important role in intercellular communication and osteoblast differentiation that increases extracellular mineralization. Related studies have also highlighted the significance of aspartic acid in the treatment of osteoporosis and other bone dysfunctions [140].

Aliphatic polyester nanocomposites have been used for the predominant choice for materials in degradable drug delivery systems [141, 142]. Of the polyesters that show promise in biomedical fields, poly(L-lactic acid) (PLLA) is the most prevalent. It has widespread applications in sutures, drug delivery devices, prosthetics, scaffolds, vascular grafts, bone screws, pins, and plates for temporary internal fixation [143, 144]. Good mechanical properties and degradation into nontoxic products are the main reasons for such an array of applications [145, 146]. Poly(glycolic acid) (PGA) is aliphatic polyester with applicability for biomedical use. However, unlike PLLA, PGA is readily soluble in water. Mechanical properties of self-reinforced PGA have investigated and found to worsen on exposure to distilled water. Thus, water solubility and its high melting point limit the use of PGA in bio-nanocomposites. Poly(ϵ -caprolactone) (PCL) is also a promising candidate for controlled release and soft tissue engineering. The range of properties can be furthered by copolymerization with other lactones such as glycolide, lactide, and poly(ethylene oxide) (PEO) or by nanofiller incorporation. Nanocomposite polymer clay hydrogels have also been studied extensively by microscopy and scattering techniques [147, 148]. Recently, electrospinning has been used as an alternative scaffold fabrication technique in soft tissue transplantation and hard tissue regeneration. This method provides woven mats with individual fiber diameters ranging from 50 nm to a few microns. The interconnected, porous network so formed is desirable for drug delivery as well as biomedical substrates for tissue regeneration, wound dressing, artificial blood vessels, and other uses. Electrospinning helps tailor the mechanical, biological, and kinetic properties of the scaffolds by varying parameters such as polymer solution properties and processing conditions (e.g., electrical force, the distance between the electrospinning needle and the oppositely charged surface acting as ground, spinneret geometry, and solution flow rate). However, some of the restrictions of this method, like controlling the pore size and softness of the electrospun mat, currently prevent it from being used for hard tissue applications. Polypeptides as matrices provide an additional array of opportunities in materials design and application in terms of a unique ability to adopt specific secondary, tertiary, and quaternary structures, a feature not available with synthetic polymers. Functionality can also be incorporated using natural and nonnatural amino acids with desired activity at specific sites along the polypeptide backbone. Materials like this, in addition to proteins, introduce the possibility of fibril incorporation into nanocomposites as re-enforcement with biodegradable matrices. Such unique nanocomposites

combine the degradability and strength of the gel matrix with control over functionality and morphology of the fibrillar fillers. Potential applications of a nanomaterial include drug delivery matrices, tissue engineering scaffolds, and bioengineering materials. Nanocomposites from bioactive molecules and clays have been reported. One such example is smectite nanocomposites that use the ability of smectites to induce specific cointercalation of purines and pyrimidines [149, 150]. Several bioactive compounds like DNA and pharmaceuticals have been incorporated within layered double hydroxides LDH hosts [151, 152]. Poly(urethane urea) (PUU) segmented block copolymers are common in ventricular assisted devices and total artificial hearts as blood sacs. One of the main disadvantages of PUUs in these devices is their relatively high permeability to air and water vapor, a result of the diffusion through the poly(tetramethylene oxide) soft segments that are present as the majority component of the copolymer. The use of organically modified layered silicates seems particularly attractive for the variety of approaches taken to reduce permeability while maintaining desired biocompatibility and mechanical properties. Nanocomposites used for various biomedical applications have different requirements, for example, nanocomposites used for dental applications have unique necessities. To exemplify it further, thermoset methacrylate-based composites are commonly used as dental restorative materials, because of relatively high cure efficiency by free radical polymerization and excellent aesthetic qualities. However, the demands of the oral environment and the masticatory loads encountered by dental restoratives require further property improvements in these materials. Specifically, nanocomposites with improved modulus, better efficiency of the free radical polymerization, low water sorption, improved processability, and low shrinkage needed. Selective functionalization of the filler can lead to better interactions at the filler matrix interphase. A few practical advantages of the dual silanization are improved workability of the composite paste, higher filler loadings leading to better modulus values, and nanocomposites with lower polymer shrinkage [153, 154]. The design of cardiovascular interfaces necessitates a combination of amphiphilicity and antithrombogenicity. Amphiphilicity ensures an optimal endothelial cell response at the vascular interface. Thrombogenicity refers to blood clot formation and can lead to early graft occlusion. Using reports of polyhedral oligomeric silsesquioxanes (POSSs) acting as an amphiphile at the water air interface, researchers have explored the possibility of using POSS at the vascular interface. The strong intermolecular forces between constituent molecules and neighbors and the robust framework of shorter bond lengths make POSS nanocomposites more resistant to degradation. Initial work has shown that POSS nanocomposites are cytocompatible, making them potentially suitable for tissue engineering. Future efforts in this field have directed to assessing the thrombogenic potential of these nanocomposites, which would be critical in their application as cardiovascular interfaces [155, 156]. Devices that have used within the body must be able to withstand corrosion in a biological environment and endure use for years without undue wear (and without causing damage

to surrounding tissues). The biomaterials discipline itself evolves the startling advances in genomics and proteomics in the last few years, in various high-throughput cells processing techniques, in supramolecular and permutational chemistry, and in information technology and bioinformatics promise to support the quest for new materials with powerful analytic tools and insights of boundless energy and sophistication [157].

4. Carbon Nanotubes/Fullerenes/Graphene for Biosensing

The discovery of fullerenes in 1985 by Curl, Kroto, and Smalley, culminated in their Nobel Prize in 1996. Fullerenes, or Buckminsterfullerenes, have named after Buckminster Fuller the architect and designer of the geodesic dome and sometimes called buckyballs. The names derived from the basic shape that defines fullerenes, an elongated sphere of carbon atoms formed by interconnecting six member rings and twelve isolated five-member rings forming hexagonal and pentagonal faces. The first isolated and characterized fullerene, C_{60} , contains 20 hexagonal faces and 12 pentagonal faces just like a soccer ball and possess perfect icosahedral symmetry [158]. Magnetic nanoparticles (nanomagnetic materials) show great potential for high-density magnetic storage media. Recent work has shown that C_{60} dispersed into ferromagnetic materials such as iron, cobalt, or cobalt iron alloy can form thin films with promising magnetic properties. A number of organometallic fullerene compounds have been synthesized, for example, a ferrocene-like C_{60} derivative and pair of fullerenes bridged by a rhodium cluster. Carbon nanotubes (CNTs) are hollow cylinders of carbon atoms. Their appearance is that of rolled tubes of graphite such that their walls are hexagonal carbon rings and often formed in large bundles. The ends of CNTs are domed structures of six-membered rings capped by a five-membered ring. Generally speaking, there are two types of CNTs: single-walled carbon nanotubes (SWNTs) and multiwalled carbon nanotubes (MWNTs). As their names imply, SWNTs consist of a single, cylindrical graphene layer, whereas MWNTs consist of multiple graphene layers telescoped about one another [159–164].

Carbon nanotubes (CNTs) were first isolated and characterized by Iijima in 1991 [165]. The unique physical and chemical properties of CNTs, such as structural rigidity, flexibility, and strongness (about 100 times stronger, i.e., stress resistant than steel at an one-sixth the weight). CNTs as conductors or semiconductors depending on their chirality, possess an intrinsic superconductivity, are ideal thermal conductors, and can behave as field emitters [166–169]. Carbon nanotubes (CNTs) are exceptionally multifaceted nanomaterials with a wide range of applications such as electrodes, power cables, fibers, composites, actuators, sensors, biosensors, in the field emission-based flat panel displays, novel semiconducting devices, molecular electronics or computers, and many other devices. CNTs can have metallic or variable semiconducting properties with energy gaps ranging from a few meV to a few tenths of an eV. Conductivity of single nanotubes has rectification effects for

some nanotubes and ohmic conductance for others [170]. The individual CNT bundles within the brush-like end act as multi-nanoelectrodes that facilitate the efficient capture and promotion of electron transfer increase the electroactive surface area for enzyme immobilization [171]. Owing to its small size, high electrochemical activity, excellent physical properties, low density, and biocompatibility, the CNT fiber has a huge potential for implantable applications for continuous monitoring of clinically relevant analytes, including glucose (to aid the control of diabetes), lactate, antibodies, and antigens. Other areas of interest include the analysis of analytes in bioreactors, veterinary and clinical chemistry, the food industry, and environmental science [172].

Still, the carbon-based nanomaterials are currently one of the most attractive nanomaterials with their different forms, such as fullerenes, single- and multiple-walled carbon nanotubes, carbon nanoparticles, and nanofibers. Although carbon nanotubes are less toxic than carbon fibers and nanoparticles, but the toxicity of carbon nanotubes increases significantly when a carbonyl ($C=O$), carboxyl ($COOH$), and/or hydroxyl (OH) groups are present on their surface [173]. The carbon-based nanomaterials used into living systems have opened the way for the investigation of their potential applications in an emerging field of nanomedicine. A wide variety of different nanomaterials based on allotropic forms of carbon to be explored towards different biomedical applications. The characteristics, the advantages, the drawbacks, the benefits, and the risks associated with these novel biocompatible forms of carbon are very crucial. Especially, carbon-based nanomaterials (CBNs) are currently considered to be one of the key elements in nanotechnology. Thus, it is primordial to know the health hazards related to their exposure. Carbon-based nanomaterials, due to their numerous and wide range applications and increasing real-life usage, get nanotoxicological attention. Toxicity of carbon-based nanomaterials (nanotubes, nanofibers, and nanowires) as a function of their aspect ratio and surface chemistry indicates that these materials are toxic while the hazardous effect [174]. Li et al. have fabricated a biosensor based on chitosan doped with carbon nanotube (CNT) to detect salmon sperm DNA using methylene blue (MB) as a DNA indicator. They found a low detection limit of 0.252 nM fish sperm DNA, and no interference was found in the presence of 5 microg/mL human serum albumin. The differential pulse voltammetry signal of MB was linear over the fish sperm DNA concentration (0.5–20 nM) [175]. So et al. have reported the real-time detection of protein using SWNT-FET-based biosensors comprising DNA aptamers as molecular recognition elements. Antithrombin aptamers that are highly specific to serine protein thrombin were immobilized on the sidewall of an SWNT-FET using CDI-Tween linking molecules. The binding of thrombin aptamers to SWNT-FETs causes a rightward shift of the threshold gate voltages, presumably due to the negatively charged backbone of the DNA aptamers, while the addition of thrombin solution causes an abrupt decrease in the conductance of the thrombin aptamer immobilized SWNT-FET [176]. Wang has reported the unique properties of nanoscale materials for the interfacing biological recognition events

with electronic signal transduction, and designing a new generation of bioelectronic devices [177]. Carbon nanotubes (CNTs) constitute a class of nanomaterials for a variety of possible applications due to their biocompatibility with aqueous environments and chemical functionalization of their surface. Singh et al. reported the functionalized CNTs (f-CNTs) which are highly utilized in advanced biotechnological applications ranging from molecular biosensors to cellular growth substrates [178]. Kerman et al. have fabricated an electrochemical hybridization biosensor based on the intrinsic oxidation signals of nucleic acids and proteins that makes use of the unique binding event between *Escherichia coli* single-strand binding protein (SSB) and single-stranded DNA (ssDNA). The voltammetric signal from guanine oxidation significantly decreased upon binding of SSB to single-stranded oligonucleotides (probe), anchored on a single-walled carbon nanotube- (SWCNT-) modified screen-printed carbon electrode (SPE). Simultaneously, oxidation of the tyrosine (Tyr) and tryptophan (Trp) residues of the SSB protein increased upon binding of the SSB protein to ssDNA and ss-oligonucleotides. After the hybridization, SSB did not bind to the double helix form, and the guanine signal could be observed along with the disappearance of the oxidation signal of the protein. The amplification of intrinsic guanine and protein oxidation signals by SWCNT, and a washing step with sodium dodecylsulfate, enabled the specific detection of a point mutation. Monitoring the changes in the guanine and protein signals upon hybridization greatly simplified the detection procedure. The detection limit of 0.15 microg/mL target DNA can be applied to genetic assays [179]. Wang et al. have proposed DNA biosensors based on self-assembled multi-walled carbon nanotubes (MWNTs), in which the probe DNA oligonucleotides were immobilized by forming covalent amide bonds between carboxyl groups at the nanotubes and amino groups at the ends of the DNA oligonucleotides. Hybridization between the probe and target DNA oligonucleotides was confirmed by the changes in the voltammetric peak of the indicator of methylene blue [180]. Wang et al. have developed carbon-nanotube-modified glassy carbon (CNT/GC) transducers for enhancing the sensitivity and stability of enzyme-based electrochemical bioassays of DNA hybridization. The amplified signal reflects the interfacial accumulation of phenolic products of the alkaline-phosphatase tracer onto the CNT layer [181]. Katz and Willner have revealed carbon nanotubes (CNTs) metallic or semiconductive properties depending on the folding modes of the nanotube walls represent a novel class of nanowires. Tailoring hybrid systems consisting of CNTs and biomolecules (proteins and DNA) has rapidly expanded and attracted substantial research effort. The integration of biomaterials with CNTs enables the use of the hybrid systems as active field-effect transistors or biosensor devices (enzyme electrodes, immunosensors, or DNA sensors). The rapid progresses in the interdisciplinary field of CNT-based nanobioelectronics and nanobiotechnology have reviewed by summarizing the present scientific accomplishments and addressing the future goals and perspectives of the area [182]. Jung et al. have demonstrated for the first time DNA oligonucleotides can be covalently attached to immobilized

SWNT multilayer films. The anchored DNA oligonucleotides were shown to exhibit excellent specificity, realizing their potential in future biosensor applications [183]. Cai et al. have proposed a novel and sensitive electrochemical DNA biosensor based on multi-walled carbon nanotubes functionalized with a carboxylic acid group (MWNTs-COOH) for covalent DNA immobilization, and enhanced hybridization detection was monitored by differential pulse voltammetry (DPV) analysis using an electroactive intercalator daunomycin as an indicator [184]. Gao et al. have fabricated a new amperometric immunosensor for the determination of carcinoembryonic antigen (CEA) via layer-by-layer (LBL) assembly of positively charged carbon nanotubes wrapped by poly(diallyldimethylammonium chloride) and negatively charged poly(sodium-p-styrenesulfonate), which could provide a high accessible surface area and a biocompatible microenvironment [185]. Meng et al. have developed a novel electrochemical immunosensor for tumor biomarker detection based on three-dimensional, magnetic, and electroactive nanoprobe. The negatively charged iron oxide nanoparticles ($\text{Fe}_3\text{O}_4\text{NPs}$) and gold nanoparticles (AuNPs) were first loaded on the surface of multiple-wall carbon nanotubes (MCNTs) which were functionalized with redox-active hemin and cationic polyelectrolyte poly(dimethyldiallylammonium chloride) (PDDA). The nanoprobe-based electrochemical immunosensor was sensitive to AFP detection; it also demonstrated good selectivity against other interferential substances [186]. Cao et al. have proposed a novel electrochemical immunosensor for the determination of casein based on gold nanoparticles and poly(L-Arginine)/multi-walled carbon nanotubes (P-L-Arg/MWCNTs) composite film. The P-L-Arg/MWCNTs composite film was used to modify glassy carbon electrode (GCE) to fabricate P-L-Arg/MWCNTs/GCE through electropolymerization of L-Arginine on MWCNTs/GCE. Gold nanoparticles were adsorbed on the modified electrode to immobilize the casein antibody and to construct the immunosensor for the determination of casein in cheese samples [187]. Piao et al. have demonstrated a highly sensitive electrochemical immunosensor based on the combined use of substrate recycling and carbon nanotubes (CNTs) coated with tyrosinase (TYR) and magnetic nanoparticles (MNP). Both TYR and MNP were immobilized on the surface of CNTs by covalent attachment, followed by additional cross-linking via glutaraldehyde treatment to construct multi-layered cross-linked TYR-MNP aggregates (M-EC-CNT). Magnetically capturable, highly active, and stable M-EC-CNTs were further conjugated with primary antibody against a target analyte of hIgG and used for a sandwich-type immunoassay with a secondary antibody conjugated with alkaline phosphatase (ALP). In the presence of a target analyte, a sensing assembly of M-EC-CNT and ALP-conjugated antibody was attracted onto a gold electrode using a magnet. On an electrode, ALP-catalyzed hydrolysis of phenyl phosphate generated phenol, and successive TYR-catalyzed oxidation of phenol produced electrochemically measurable o-quinone that was converted to catechol in substrate recycling. The present immunosensing system also displayed a long-term stability by showing a negligible loss

of electrochemical detection signal even after reagents were stored in an aqueous buffer at 4°C for more than 6 months [188]. Zhuo et al. have reported a novel electrochemical immunosensor for sensitive detection of cardiac biomarker N-terminal pro-B-type natriuretic peptide (NT-proBNP) based on the nanostructural gold and carbon nanotubes composite as desirable platform for the capture antibodies immobilization and gold nanochains (AuNCs) and horseradish peroxidase (HRP) complex labeled secondary antibodies (AuNCs-HRP-Ab(2)) for signal amplification. The gold nanochains were prepared by the employment of L-ascorbic acid (AA) as a mediator and template. With the surface area enhancement by nanostructural gold functionalized carbon nanotubes composite, the amount of immobilized primary antibodies (Ab(1)) can be enhanced. More importantly, enhanced sensitivity can be achieved by introducing the multibioconjugates of AuNCs-HRP-Ab(2) onto the electrode surface through “sandwich” immunoreactions [189]. Zhuo et al. have proposed a new strategy for amplifying the response of the antigen-antibody sensing processes by functionalizing SiO₂ nanoparticles labeled secondary antibodies based on a sandwich immunoassay. At first, the multi-walled carbon nanotubes (CNTs) were individually dispersed in the aqueous bovine serum albumin (BSA) to obtain BSA molecules coated CNTs (BSA-CNTs). Then the amide and disulfide groups of BSA absorbed the gold colloids (nano-Au) on the BSA-CNTs surface. Later, a functionalized gold/carbon nanotube composite nanohybrid (DpAu/nano-Au/BSA-CNTs) modified electrode was developed by electrochemical deposition of Au³⁺ onto nano-Au/BSA-MWNTs surface. Thus, immunosensor for carbohydrate antigen 19-9 (CA19-9) has been constructed by further employment of Nafion-coated SiO₂ nanoparticles labeled secondary antibody (SiO₂-Ab₂ for the signal amplification). More importantly, the loading of SiO₂-Ab₂ can not only cause the construction of the dielectric antigen-antibody immunocomplex layer but also introduce the insulated Nafion-coated SiO₂ nanoparticles which demonstrate the relatively high resistance, resulting in a strong detection signal. Moreover, the extremely high stability of the functionalized gold/carbon nanotube composite nanohybrid monolayer allows the designed biosensing interface to obtain a good stability and long-term life [190]. Tang et al. have reported a new electrochemical immunoassay protocol for sensitive detection of alpha-fetoprotein (AFP, as a model) using carbon nanoparticles- (CNPs-) functionalized biomimetic interface as immunosensing probe and irregular-shaped gold nanoparticles (ISNGs) labeled horseradish peroxidase-anti-AFP conjugates (HRP-anti-AFP-ISNG) as trace label [191]. Li et al. have reported a novel strategy for the construction of reagentless and mediatorless immunosensors based on the direct electrochemistry of glucose oxidase (GOD). A composite material containing carbon nanotubes (CNTs) and core-shell organosilica-chitosan nanospheres was prepared onto the glassy carbon electrode surface, and then, Pt nanoclusters (Pt NCs) as an electron relay were deposited on it to form the interface of biocompatibility and huge surface, free energy for the adsorption of the first GOD layer. Subsequently, the second Pt NCs layer was deposited

FIGURE 4: shows the zero-dimensional (0D) fullerene, 1D carbon nanotubes, and 2D graphene.

on the surface of GOD to capture CA15-3 antibodies (anti-CA15-3). Finally, GOD, as a blocking reagent instead of bovine serum albumin, was employed to block the possible remaining active sites of the Pt NCs and avoid the nonspecific adsorption. Such a detection of immunointeraction proposed a new promising platform for clinical immunoassay [192]. Sánchez et al. have reported a facile and capable method of preparation of sensitive carbon nanotube (CNT)/polysulfone/RIG immunosensor. The immunosensor is based on the modification of disposable screen-printed electrodes by phase inversion method. CNT/polysulfone membrane acts as the reservoir of immunomolecules as well as a transducer. This configuration offers large surface area, elevated porosity, and mechanical flexibility. The comparison with graphite/polysulfone/RIG immunosensors shows a significantly improved sensitivity for those prepared with CNTs coupled with polysulfone (PSf) and found sensitivity six times higher for MWCNT-based than for graphite-based electrodes [193]. Munge et al. have reported a novel electrochemical immunosensor for the detection of matrix metalloproteinase-3 (MMP-3), a cancer biomarker protein, based on vertically aligned single-wall carbon nanotube (SWCNT) arrays. This immunosensor based on SWCNT arrays offers great promise for a rapid, simple, cost-effective method for clinical screening of cancer biomarkers for point-of-care diagnosis [194].

The nanocarbon in its sp³ and sp² forms is an inert material when interacting with living organisms, but metallic impurities having heavy metals, such as Fe, Ni, Co, Cu, and Mo, are toxic to living organisms. The impurities strongly influence the redox behavior of important biomarkers. Graphene is an allotrope of carbon; its structure is one-atom-thick planar sheets of sp²-bonded carbon atoms. In another way, graphene is single sheets of graphite or a flat monolayer of carbon atoms that are tightly packed into a 2D honeycomb lattice, that is, one atom thick with some amazing properties, the thinnest possible material that is feasible, and about stronger than steel, which conducts electricity better than any material known at room temperature. Graphene is the

basic structural element of some carbon allotropes, including graphite, charcoal, carbon nanotubes, and fullerenes. Sp^2 -carbon nanomaterials typically include zero-dimensional (0D) fullerene, 1D carbon nanotubes, and 2D graphene [195, 196] as shown in Figure 4. Graphene's Konstantin Novoselov and Andre Geim won the 2010 Nobel Prize in physics, for groundbreaking experiments regarding the two-dimensional material graphene, now star in the material science. They managed to extract single-atom-thick crystallites (graphene) from bulk graphite in 2004. Graphene has interesting electrical, optical, mechanical, and chemical properties with potential applications in a wide range. Graphene is used for making lighter aircraft and satellites, transistors, embedded in plastics to conduct electricity, sensors, electric batteries, optoelectronics, leak-tight, transparent conductive coatings for solar cells, wind turbines, medical implants, sports equipment, supercapacitors, high frequency electronic devices, artificial cell membranes, touchscreens, LCDs, OLEDs, and so forth. Graphene nanoribbons for ballistic transistors, nanogaps in graphene sheets for rapid DNA sequencing, functionalized nanosized graphene as a drug carrier for *in vitro* intracellular delivery of anticancer chemotherapy drugs, nanographene with a biocompatible polyethylene glycol (PEG) coating for passive *in vivo* tumor uptake in a mouse model, graphene-based biosensors to detect various biomolecules, and graphene-based nanomedicine are very emerging applications. It appears to be encouraging and may bring novel opportunities for future disease diagnosis and treatment. Thus, graphene and its derived structures, that is, graphene oxide, graphene platelets, and graphene nanoflakes, are becoming popular materials [197]. Zhao et al. have reported for the first time a graphene oxide-DNAzyme-based biosensor for amplified fluorescence "turn-on" detection of Pb^{2+} in river water samples with satisfying results [198]. Tang et al. have reported for the first time the use of DNA hybridization for the controllable assembly of a graphene nanosheet. The DNA-graphene-dispersed sheets have an ultrasensitive detection of oligonucleotides with high sensitivity and excellent selectivity. This research of graphene-based biofunctional materials will have specific applications in bionanotechnology, nanoelectronics, and bionanotechnology [199]. He et al. have reported the electronic sensors based on graphene which show high potential in detection of both chemical and biological species like fibronectin and avidin with high sensitivity. They have reported the fabrication of all-reduced graphene oxide (rGO) thin film transistors by a combination of solution-processed rGO electrodes with micropatterned rGO channel devices, which are cost-effective, highly reproducible, and reliable [200]. Liu et al. have established a facile, rapid, stable, and sensitive approach for fluorescent detection of single-nucleotide polymorphism (SNP) based on DNA ligase reaction and π -stacking between the graphene and the nucleotide bases. Unique surface property of graphene and the high discriminability of DNA ligase, the proposed protocol exhibits good performance in SNP genotyping [201]. Xu et al. have reported a cathodic electrogenerated chemiluminescence (ECL) of luminol at a positive potential (ca. 0.05 V versus Ag/AgCl) with a strong light

emission on the graphene-modified glass carbon electrode and an excellent platform for high-performance biosensing applications. They have developed an ECL sandwich immunosensor for sensitive detection of cancer biomarkers at low potential with a multiple signal amplification strategy from functionalized graphene and gold nanorods multilabeled with glucose oxidase (GOx) and secondary antibody (Ab(2)). The graphene-based ECL immunosensor accurately detected PSA concentration in 10 human serum samples from patients demonstrated by excellent correlations with standard chemiluminescence immunoassay. The results suggest that the as-proposed graphene ECL immunosensor will be promising in the point-of-care diagnostics application of clinical screening of cancer biomarkers [202]. Li et al. have reported the first graphene oxide- (GO-) based platform to detect protease activity in a homogeneous real-time format. In this fabrication of GO-peptide-QDs nanoprobe, a protease substrate peptide as the linker between the energy transfer donor (QDs), and the energy transfer acceptor (GO) reported. The GO-based platform has been applied in the sensitive detection of matrix metalloproteinase (MMP) and thrombin activity. The proposed GO-based platform is anticipated to find applications in the diagnosis of protease-related diseases and screening of potential drugs with high sensitivity in a high-throughput way [203]. Liu et al. have reported a novel, enzyme-free amperometric immunoassay of biomarkers with sensitive enhancement by using gold nanoflower-labeled detection antibodies toward the catalytic reduction of p-nitrophenol and redox cycling of p-aminophenol on a graphene-based Au (111) platform [204]. Xu et al. have fabricated an amperometric biosensor of hydrogen peroxide by immobilization of hemoglobin (Hb) on a pluronic P123-nanographene platelet (NGP) composite. The resulting biosensor showed fast amperometric response, with very high sensitivity, reliability, and effectiveness [205]. Lu et al. have developed a nonenzymatic electrochemical biosensor for the detection of glucose based on an electrode modified with palladium nanoparticles- (PdNPs-) functionalized graphene (nafion-graphene). Such a PdNPs-graphene nanohybrids-based electrode shows a very high electrochemical activity for electrocatalytic oxidation of glucose in alkaline medium. The experiment results also showed that the sensor exhibits good reproducibility and long-term stability, as well as high selectivity with no interference from other potential competing species [206]. Zhang et al. have a novel graphene-based biosensing platform using peptides as probe biomolecules and demonstrated its feasibility in the application of real-time monitoring of protease activity based on FRET between GO and dye-labeled peptides [207]. Choi et al. have demonstrated the SPR imaging biosensors with a graphene-on-silver substrate used to achieve the dramatically high sensitivity as well as to prevent silver oxidation. A silver substrate with a few graphene layers can significantly increase the imaging sensitivity, compared to the conventional gold-film-based SPR imaging biosensor. Therefore, the proposed SPR substrate could potentially open a new possibility of SPR imaging detection for sensitive and high-throughput assessment of multiple biomolecular interactions [208]. Feng et al. have

reported an electrochemical sensor that can realize label-free cancer cell detection using the first clinical trial II used aptamer AS1411 and functionalized graphene. AS1411 has high binding affinity and specificity to the overexpressed nucleolin on the cancer cell surface, which gives a good example for label-free cancer cell detection based on aptamer and graphene-modified electrode [209]. Zhang et al. have designed a versatile molecular beacon- (MB-) like probe for the multiplex sensing of targets such as sequence-specific DNA, protein, metal ions, and small molecule compounds based on the self-assembled ssDNA-graphene oxide (ssDNA-GO) architecture, which gives superior sensitivity and rapid response. The ssDNA-GO architecture probe has been successfully applied in the multiplex detection of sequence-specific DNA, thrombin, Ag^+ , Hg^{2+} , and cysteine, and the limit of detection was 1 nM, 5 nM, 20 nM, 5.7 nM, and 60 nM, respectively [210]. Song et al. have reported a highly efficient enzyme-based screen-printed electrode (SPE) by using covalent attachment between 1-pyrenebutanoic acid, succinimidyl ester (PASE) adsorbing on the graphene oxide (GO) sheets, and amines of tyrosinase-protected gold nanoparticles (Tyr-Au). The fabricated disposable biosensor (Tyr-Au/PASE-GO/SPE) has exhibited a rapid amperometric response (less than 6 s) with a high sensitivity and good storage stability for monitoring catechol. This disposable tyrosinase biosensor could offer a great potential for rapid, cost-effective and on-field analysis of phenolic compounds [211]. Lu et al. have reported on a back-gated field-effect transistor platform with chemically reduced graphene oxide (R-GO) as the conducting channel, and they suggested that the work on sensor signal processing method and the inherent simplicity of device fabrication is a significant step toward the real-world application of graphene-based chemical sensors [212]. Wan et al. have functionalized graphene oxide (GO) sheets coupled with a signal amplification method based on the nanomaterial-promoted reduction of silver ions for the sensitive and selective detection of bacteria. The GO sheet-mediated silver enhancement holds great potential for the rapid analysis of protein, DNA, and pathogens [213]. Zhang et al. have reported a novel polymeric ionic liquid functionalized graphene. Poly(1-vinyl-3-butylimidazolium bromide)-graphene, a strong positive charge, due to this nature, the negatively charged glucose oxidase (GOD) immobilized onto the poly (ViBuIm⁺Br⁻)-G to form a GOD/poly (ViBuIm⁺Br⁻)-G/glassy carbon (GC) electrode under mild conditions. This bioelectrode displayed an excellent sensitivity, together with a wide linear range and excellent stability for the detection of glucose [214]. Ohno et al. have reported a label-free immunosensor based on an aptamer-modified graphene field-effect transistor (G-FET). The aptamer-modified G-FET showed selective electrical detection of IgE protein. From the dependence of the drain current variation on the IgE concentration, the dissociation constant was estimated to be 47 nM, indicating good affinity and the potential for G-FETs to be used in biological sensors [215]. Hu et al. have reported negative-charge change and conformation transition upon DNA immobilization and hybridization on functionalized graphene sheets by the EIS technique and adopted as the signal for label-free electro-

chemical DNA hybridization detection [216]. Li et al. have presented a novel strategy to carry out direct and sensitive determination of antitumor herbal drug aloe emodin in complex matrices based on the graphene-Nafion-modified glassy carbon (GN/GC) electrode. The GN/GC electrode may hold great promise for fast, simple, and sensitive detection and biomedical analysis of AE in complex matrices [217]. Ang et al. have reported the electronic properties of graphene modulated by charged lipid bilayer adsorbing on the surface. Biorecognition events, which lead to changes in membrane integrity, can be monitored electrically using an electrolyte-gated biomimetic membrane-graphene transistor. They have demonstrated the bactericidal activity of antimicrobial peptides, which senses electrically by graphene based on a complex interplay of biomolecular doping and ionic screening effect [218]. Huang et al. have developed a nano-material carboxylic acid functionalized graphene (graphene-COOH) used to construct a novel biosensor for the simultaneous detection of adenine and guanine by cyclic voltammetry and differential pulse voltammetry. Both adenine and guanine showed the increase of the oxidation peak currents with the negative shift of the oxidation peak potentials in contrast to that on the bare glassy carbon electrode [219]. Goh and Pumera reported the detection of explosives in seawater and compared response of single-, few-, and multilayer graphene nanoribbons and graphite microparticle-based electrodes toward the electrochemical reduction of 2,4,6-trinitrotoluene (TNT) and established the limit of detection of TNT in untreated seawater at 1 $\mu\text{g/mL}$ [220]. Husale et al. have reported the interaction of polyelectrolytes such as ssDNA and dsDNA molecules with graphene as a substrate using AFM technique. They quantify the π - π stacking interaction by correlating the amount of deposited DNA with the graphene layer thickness and suggested the suitability of using a graphene as a substrate for DNA origami-based nanostructures [221]. Wang et al. have reported a graphene based composite with enzyme, which provides a potent strategy to enhance biosensor performance due to their unique physicochemical properties. They have reported the utilization of graphene-CdS (G-CdS) nanocomposite as a novel immobilization matrix for the enzymes, which glucose oxidase (GOD) was chosen as model enzyme. This immobilization matrix is not used only for immobilizing GOD, but also for extending to other enzymes and bioactive molecules, thus providing a promising platform for the development of biosensors [222]. Wan et al. have reported a facile, sensitive, and reliable impedimetric immunosensor doped with reduced graphene sheets (RGSs) and combined with a controllable electrodeposition technique for the selective detection of marine pathogenic sulphate-reducing bacteria (SRB). It showed a high selectivity for the detection of the pathogen. Based on a combination of the biocompatibility of CS and good electrical conductivity of RGSs, a nanocomposite film with novel architecture was used to immobilize biological and chemical targets and to develop a new type of biosensor [223]. Li et al. have reported a new electrocatalyst, MnO_2 /graphene oxide hybrid nanostructure for the nonenzymatic detection of H_2O_2 in alkaline medium. The nonenzymatic biosensors displayed

good performance along with low working potential, high sensitivity, low detection limit, and long-term stability, which could be attributed to the high surface area of graphene oxide providing for the deposition of MnO_2 nanoparticles. These results demonstrate that this new nanocomposite with the high surface area and electrocatalytic activity offers great promise for new class of nanostructured electrode for nonenzymatic biosensor and energy conversion applications [224]. Liu et al. have designed a promising one-step homogeneous fluoroimmunoassay based on nanoscale graphene sheets as powerful fluorescence acceptors and CdTe quantum dots as vigorous donors to detect trace biomarker protein with distance-independent quenching efficiency, which significantly broke the distance limit (100 Å) in traditional fluorescent biosensors [225]. Wang et al. have developed for the first time a novel amperometric biosensor for nitromethane based on immobilization of graphene (GR), chitosan (CS), hemoglobin (Hb), and room temperature ionic liquid (IL) on a glassy carbon electrode (GCE). The presence of both GR and IL not only dramatically facilitated the electron transfer of Hb, but also greatly enhanced electrocatalytic activity towards nitromethane [226]. Huang et al. have demonstrated the use of large-sized CVD grown graphene films configured as field-effect transistors for real-time biomolecular sensing. Glucose or glutamate molecules were detected by the conductance change of the graphene transistor as the molecules are oxidized by the specific redox enzyme (glucose oxidase or glutamic dehydrogenase) functionalized onto the graphene film. This study indicates that graphene is a promising candidate for the development of real-time nanoelectronic biosensors [227]. Lu et al. have developed a novel electrochemical sensing system for direct electrochemistry-based hydrogen peroxide biosensor that relied on the virtues of excellent biocompatibility, conductivity, and high sensitivity to the local perturbations of single-layer graphene nanoplatelet (SLGnP). The SLGnP/TPA-(tetrasodium 1,3,6,8-pyrenetetrasulfonic acid-) HRP composite film demonstrated excellent electrochemical responses for the electrocatalytic reduction of hydrogen peroxide, thus suggesting its great potential applications in direct electrochemistry-based biosensors [228]. Zeng et al. have developed an unconventional method for the layer-by-layer (LbL) assembly of graphene multilayer films. Graphene sheets were modified by pyrene-grafted poly(acrylic acid) (PAA) in aqueous solution, and then the modified graphene sheets were used for layer-by-layer alternating deposition with poly(ethyleneimine) (PEI). The graphene-multilayer-film-modified electrode shows enhanced electron transfer for the redox reactions of $\text{Fe}(\text{CN})_6^{3-}$ and excellent electrocatalytic activity of H_2O_2 . Based on this property, they have fabricated a bienzyme biosensing system for the detection of maltose by successive LbL assembly of graphene, glucose oxidase (GOx), and glucoamylase (GA). LbL assembly of graphene combines the excellent electrochemical properties of graphene and the versatility of LbL assembly, showing great promise in highly efficient sensors and advanced biosensing systems [229]. Zhang et al. have designed a novel electrocatalytic biosensing platform by the functionalization of reduced graphene oxide sheets (rGO) with conducting

polypyrrole graft copolymer, poly(styrenesulfonic acid-g-pyrrole) (PSSA-g-PPY), via π - π noncovalent interaction. Based on the advantageous functions of PSSA-g-PPY and RGO, the functional nanocomposite-modified platinum electrode has showed high electrocatalytic activity toward the oxidation of hydrogen peroxide and uric acid in neutral media. Further, they have constructed a hypoxanthine biosensor by combining the modified electrode with the enzymatic reaction of xanthine oxidase. The water-soluble conducting copolymer could serve as an efficient species for functionalization and solubilization of graphene sheets in biosensing and biocatalytic applications [230]. Chen et al. have reviewed on single-layer graphene devices in solution and their properties including their charge transport, controlled by electrochemical gates, interfacial and quantum capacitance, charged impurities, and surface potential distribution. The sensitive dependence of graphene charge transport on the surrounding environment points to their potential applications as ultrasensitive chemical sensors and biosensors. The interfacial and quantum capacitance studies are directly relevant to the ongoing effort of creating graphene-based ultracapacitors for energy storage [231]. Yang et al. have developed an ultrasensitive electrochemical immunosensor for the detection of cancer biomarker based on graphene sheet (GS). GS was used to immobilize mediator thionine (TH), horseradish peroxidase (HRP), and secondary anti-prostate-specific antigen (PSA) antibody (Ab2), and the resulting nanostructure (GS-TH-HRP-Ab2) was used as the immunosensor. Thus, graphene-based labels may provide many potential applications for the detection of different cancer biomarkers [232].

Norethisterone is widely used anabolic steroid to promote livestock growth and sometime illegally used for livestock breeding. The residues of norethisterone in animal food harm people's health. Wei et al. have developed a sandwich-type protocol to prepare the immunosensor with the primary antibody (Ab1) immobilized onto thionine (TH) and graphene sheet- (GS-) modified glassy carbon electrode surface. The proposed immunosensor shows good reproducibility, selectivity, and acceptable stability. This new type of labels for immunosensors may provide many potential applications for the detection of growth hormone in animal-derived food [233]. Li et al. have designed a novel graphene-based molecular beacon (MB) that could sensitively and selectively detect specific DNA sequences. The ability of water-soluble graphene oxide (GO) to hairpin and dsDNA offered a new approach to detect DNA. They found that the background fluorescence of MB was significantly suppressed in the presence of GO, which increased the signal-to-background ratio, hence the sensitivity. Moreover, the single-mismatch differentiation ability of hairpin DNA was maintained, leading to high selectivity of this new method [234]. Wu et al. have developed a surface plasmon resonance (SPR-) based graphene biosensor. The biosensor uses attenuated total reflection (ATR) method to detect the refractive index change near the sensor surface, which is due to the adsorption of biomolecules. The improved sensitivity is due to increased adsorption of biomolecules and the optical property of graphene [235]. Yang and Gong have developed a

simple and sensitive immunosensor for the detection of cancer biomarker prostate-specific antigen (PSA). Around the percolation threshold of the graphene film, the conductivity of the graphene film varies significantly with the surface adsorption of molecules, which can be used for the detection of proteins based on antibody-antigen binding [236]. Zhang et al. have designed a novel electrochemical platform by combining the biocompatibility of single-stranded DNA (ss-DNA) and the excellent conductivity of graphene (GP). This nanocomposite (denoted as ss-DNA/GP) was first used as an electrode material for the immobilization and biosensing of redox enzymes. The HRP/ss-DNA/GP/GC electrode demonstrates direct electron transfer between the immobilized HRP and the electrode for hydrogen peroxide detection. The ss-DNA/GP nanocomposite provides a novel and efficient platform for the immobilized redox enzyme to realize direct electrochemistry and has a promising application in the fabrication of third-generation electrochemical biosensors [237]. Dong et al. have designed a novel platform for effective sensing of biomolecules by fluorescence resonance energy transfer (FRET) from quantum dots (QDs) to graphene oxide (GO). The QDs were first modified with a molecular beacon (MB) as a probe to recognize the target analyte. The strong interaction between MB and GO led to the fluorescent quenching of QDs. Upon the recognition of the target, the distance between the QDs and GO increased, and the interaction between target-bound MB and GO became weaker, which significantly hindered the FRET and, thus, increased the fluorescence of QDs. The change in fluorescent intensity produced a novel method for detection of the target. The GO-quenching approach could be used for detection of DNA sequences, with advantages such as less labor for synthesis of the MB-based fluorescent probe, high quenching efficiency and sensitivity, and good specificity. By substituting the MB with aptamer, this strategy extended for detection of other biomolecules, which demonstrated by the interaction between aptamer and protein. To the best of our knowledge, this is the first application of the FRET between QDs and GO and opens new opportunities for sensitive detection of biorecognition events [238]. He et al. have reported the fabrication of centimeter-long, ultrathin (1–3 nm), and electrically continuous micropatterns of highly uniform parallel arrays of reduced graphene oxide (rGO) films on various substrates including the flexible polyethylene terephthalate (PET) films by using the micromolding in capillary method. They have demonstrated that the nanoelectronic FETs-based rGO patterns are able to freely label detection of the hormonal catecholamine molecules and their dynamic secretion from living cells [239]. Wu et al. have developed a novel electrochemical approach for detection of the extracellular oxygen released from human erythrocytes. The sensing is based on the bioelectrocatalytic system of graphene integrated with laccase (Lac) and 2,2-azino-bis(3-ethylbenzothiazoline-6-sulfonic acid) (ABTS) toward the reduction of oxygen. ABTS and laccase are assembled on the surface of graphene, which is synthesized by a chemistry route, utilizing the pi-pi and electrostatic interactions of these components [240]. Cheng et al. have reported enhanced performance of suspended

graphene field effect transistors (Gra-FETs) as sensors in aqueous solutions using etching of the silicon oxide (SiO_2) substrate underneath graphene. They have demonstrated the suspended nanodevices, which represent attractive platforms for chemical and biological sensors [241]. Liu et al. have demonstrated a novel, highly efficient enzyme electrode using covalent attachment between carboxyl acid groups of graphene oxide sheets and amines of glucose oxidase. The resulting biosensor has potential advantages with respect to cell attachment and proliferation, leading to opportunities for using graphene-based biosensors for the clinical diagnosis [242]. Du et al. have described a novel electrochemical immunosensor for sensitive detection of cancer biomarker alpha-fetoprotein (AFP) using a graphene sheet sensor platform and functionalized carbon nanospheres (CNSs) labeled with horseradish peroxidase-secondary antibodies (HRP-Ab2) which is a promising platform for clinical screening of cancer biomarkers and point-of-care diagnostics [243]. Xu et al. have developed a novel, biocompatible sensing strategy based on graphene and chitosan composite film for immobilizing the hemoglobin protein. The appearance of graphene in the composite film could facilitate the electron transfer between matrix and the electroactive center of hemoglobin and would be a promising platform for protein immobilization and biosensor preparation [244]. Chang et al. have combining nanomaterials and biomolecule recognition units in novel clinic diagnostic and protein analysis techniques. They have developed a highly sensitive and specific fluorescence resonance energy transfer (FRET) aptasensor for thrombin detection based on the dye-labeled aptamer-assembled graphene [245]. Lightcap et al. have reduced graphene oxide (RGO) as a two-dimensional support and succeeded in selective anchoring of semiconductor and metal nanoparticles at separate sites. The findings pave the way for the development of next-generation catalyst systems using in graphene-based composites for chemical and biological sensors [246]. Pisana et al. have demonstrated graphene-based extraordinary magnetoresistance devices that combine the Hall effect and enhanced geometric magnetoresistance, yielding sensitivities rivaling those of state-of-the-art sensors but do so with subnanometer sense layer thickness at the sensor surface [247]. Shan et al. have reported low-potential NADH detection and biosensing for ethanol at an ionic liquid-functionalized graphene- (IL-graphene-) modified electrode. The ability of IL-graphene to promote the electron transfer between NADH and the electrode exhibited a novel and promising biocompatible platform for development of dehydrogenase-based amperometric biosensors. They have also constructed ADH/IL-graphene/chitosan-modified electrode through a simple casting method for ethanol detection [248]. Further, Shan et al. have developed a novel glucose biosensor based on immobilization of glucose oxidase in thin films of chitosan containing nanocomposites of graphene and gold nanoparticles (AuNPs) at a gold electrode. The graphene/AuNPs/GOD/chitosan composite-modified electrode shows prominent electrochemical response to glucose, which makes a promising application for electrochemical detection of glucose [249]. Wu et al. have developed the bio-nanocomposite

film consisting of glucose oxidase/Pt/functional graphene sheets/chitosan (GOD/Pt/FGS/chitosan) for glucose sensing. The large surface area and good electrical conductivity of graphene suggest that graphene is a potential candidate as a sensor material. The hybrid nanocomposite glucose sensor provides new opportunity for clinical diagnosis and point-of-care applications [250]. Shan et al. have described graphene sheets functionalized covalently with biocompatible poly-L-lysine (PLL) in an alkaline solution. PLL-functionalized graphene is water soluble and biocompatible, which makes it a novel material promising for biological applications. Graphene sheets played an important role as connectors to assemble these active amino groups of poly-L-lysine, which provided a very biocompatible environment for further functionalization, such as attaching bioactive molecules [251]. Zhou et al. have proposed a chemically reduced graphene-oxide-modified glassy carbon (CR-GO/GC) electrode, for the electrochemical sensing and biosensing platform of different kinds of free bases of DNA (guanine (G), adenine (A), thymine (T), and cytosine (C)), hydrogen peroxide, dopamine (DA), ascorbic acid (AA), uric acid (UA), and acetaminophen (APAP). They reveal that CR-GO with the nature of a single sheet showing favorable electrochemical activity should be a kind of more robust and advanced carbon electrode material which may hold great promise for electrochemical sensors and biosensors design [252]. Mohanty and Berry established large-contact-area interfaces of sensitive nanostructures with microbes and mammalian cells, which will lead to the development of valuable tools and devices for biondiagnostics and biomedicine. Chemically modified graphene (CMG) nanostructures with their microscale area, sensitive electrical properties, and modifiable chemical functionality are excellent candidates for such biodevices at both biocellular and biomolecular scale. They have reported the fabrication and functioning of a novel CMG-based on (i) single-bacterium biodevice, (ii) label-free DNA sensor, and (iii) bacterial DNA/protein and polyelectrolyte chemical transistor [253]. Shan et al. have reported the polyvinylpyrrolidone-protected graphene, dispersed well in water, and had good electrochemical reduction toward O_2 and H_2O_2 . They have constructed polyvinylpyrrolidone-protected graphene/polyethylenimine-functionalized ionic liquid/GOD electrochemical biosensor, which achieved the direct electron transfer of GOD, maintained its bioactivity, and showed potential application for the fabrication of novel glucose biosensors with linear glucose response up to 14 mM [254]. Lu et al. have reported the novel fabrication of a highly sensitive, selective, fast responding, and affordable amperometric glucose biosensor using exfoliated graphite nanoplatelets (xGnPs) decorated with Pt and Pd nanoparticles, using nafion to solubilize metal-decorated graphite nanoplatelets [255].

5. Inorganic-Organic Hybrid Nanoparticles for Biosensing

Hybrid inorganic-organic composites are an emerging class of new materials that hold significant promise. Materials are

being designed with the good physical properties of ceramics and the excellent choice of functional group chemical reactivity associated with organic chemistry. New silicon containing organic polymers, in general, and polysilsesquioxanes, in particular, generated a great deal of interest because of their potential replacement for and compatibility with currently employed, silicon-based inorganics in the electronics, photonics, and other materials technologies. Hydrolytic condensation of trifunctional silanes yields network polymers or polyhedral clusters having the generic formula $(RSiO_{1.5})_n$. Hence, they are known by the not quite on the tip of the tongue name silsesquioxanes. Each silicon atom is bound to an average of one and a half (sesqui) oxygen atoms and to one hydrocarbon group (ane). Typical functional groups that may be hydrolyzed or condensed include alkoxy or chlorosilanes, silanols, and silanates [256–259]. Synthetic methodologies that combine pH control of hydrolysis/condensation kinetics, surfactant mediated polymer growth, and molecular templating mechanisms have been employed to control molecular scale regularity as well as external morphology in the resulting inorganic/organic hybrids from transparent nanocomposites, to mesoporous networks, to highly porous and periodic organosilica crystallites, all of which have the silsesquioxane (or $RSiO_{1.5}$) stoichiometry. These inorganic-organic hybrids offer a unique set of physical, chemical, and size-dependent properties that could not be realized from just ceramics or organic polymers alone. Many of these silsesquioxane hybrid materials also exhibit an enhancement in properties such as solubility, thermal and thermo mechanical stability, toughness, optical transparency, gas permeability, dielectric constant, and fire retardancy, for example, beryllium silsesquioxane, poly(hydridosilsesquioxane), and polyhedral oligomeric silsesquioxane, and so forth [260].

Nanostructured films, dispersions, large surface area materials, and supramolecular assemblies are the high utility intermediates to many products with improved properties such as solar cells and batteries, sensors, catalysts, coatings, and drug delivery systems using various techniques. Nanoparticles are obvious building blocks of nanosystems but require special techniques such as the self-assembly to properly align the nanoparticles. Recent developments have led to air resistant, room temperature systems for nanotemplates with features as small as 67 nm. More traditionally, electron beam systems are used to fabricate devices down to 40 nm [261]. Liu et al. have synthesized nanocomposite of poly-p-phenyleneethynylene gold nanoparticles (PPE-Au) via directly grafting maleimide functionalized gold nanoparticles (MA-Au) onto PPE chains by a mild Diels-Alder reaction and established self-assembly of the MA-Au as well as enhanced electronic communication between the copolymers and inorganic particles. The as-prepared hybrid nanoassemblies show homogeneous status, and well-defined interfaces, which facilitate the electronic interaction between conjugated polymers and gold nanoparticles [262]. Sperling and Parak have highlighted inorganic colloidal nanoparticles, dispersed in a solvent, possess different properties, such as high electron density, strong optical absorption, photoluminescence in the form of fluorescence (CdSe or CdTe) or phosphorescence (doped oxide materials), or magnetic moment

(e.g., iron oxide or cobalt nanoparticles) [263]. Barbadillo et al. have designed and characterized a new organic-inorganic hybrid composite material for glucose electrochemical sensing. The entrapment of both gold nanoparticles (AuNPs) and glucose oxidase, as a model, into a sol-gel matrix including graphite to the system, which confers conductivity, leads to the development of a material particularly attractive for electrochemical biosensor fabrication [264]. Puranik et al. have developed an efficient and facile procedure for concurrent *in situ* synthesis and ordered assembly of metal nanoparticles on a periodic two-dimensional protein array. The S-layer protein of *Bacillus subtilis* exhibiting uniform pore size is used as template. Synthesis of gold and silver nanoparticles anchoring on the pores of S-layer has achieved by chemical reduction of respective metal salt laden protein template, used for biosensing [265]. Guan et al. have established the Au nanoparticles functionalized by poly-L-histidine (PLH), a simple polypeptide with a pKa value (approximately 6.2) around the physiological pH, sensitive to pH and temperature simultaneously, and can be well recognized by the color change of the Au nanoparticles by naked eyes [266]. Basel et al. have reported the octameric porin MspA from *Mycobacterium smegmatis*, stable to form a nonmembrane-supported stand-alone porin on mica surfaces and demonstrated that the gold nanoparticles can be positioned at different, well-defined distances from the underlying surface using the MspA pore as a template and used for electrically insulating stable proteins in combination with metal nanoparticles in nanodevices [267]. Shen and Shi have reported recent advances on the synthesis, self-assembly, and biofunctionalization of various dendrimer based organic/inorganic hybrid nanoparticles (NPs) for various biomedical applications, including protein immobilization, gene delivery, molecular diagnosis, and targeted molecular imaging of cancer [268]. Reynolds et al. have reported calcium ion-mediated carbohydrate-carbohydrate interactions and synthesized four lactose derivatives for assembly on gold nanoparticles. They have shown that the self-assembled deposition of lactose derivatives on gold nanoparticles provides multivalent carbohydrate surfaces that can be used as mimics for the measurement of biologically relevant carbohydrate-carbohydrate interactions [269]. Kerman et al. have demonstrated the application of Au nanoparticles in the electrochemical detection of protein phosphorylation based on the labeling of a specific phosphorylation event with Au nanoparticles. The performance of the biosensor was optimized, including the kinase reaction, incubation with streptavidin-coated Au nanoparticles, and the small molecule inhibitors. Kinase peptide-modified electrochemical biosensors are promising candidates for cost-effective kinase activity and inhibitor screening assays [270]. Chen et al. have reported gold nanoparticles with controlled size, shape, and passivating agents, along with a new process of guided self-assembly to create two-dimensional nanostructures from such nanoparticles for the applications in biochemical sensing and biological imaging [271]. Zhou et al. have reported the high sensitive immunoassay of protein cancer biomarkers by using of peroxidase-mimicking DNAzyme heavily functionalized gold nanoparticles as

catalytic probe [272]. Liang et al. have developed a simple and sensitive conductometric immunoassay for IL6 in human serum by using an organic/inorganic hybrid membrane-functionalized interface. The organic/inorganic hybrid membrane offers a good microenvironment for the immobilization of biomolecules, enhanced the surface coverage of protein and improved the sensitivity of the immunosensor. In addition, the detection methodology offers a promising approach for other proteins or biosecurity [273]. Baptista et al. have reported the thiol linking of DNA and chemical functionalization of gold nanoparticles for specific protein/antibody binding for the detection of specific desired DNA sequences to clinical diagnosis [274]. Castellana and Russell have reported gold nanoparticles capped with 4-aminothiophenol for laser desorption ionization mass spectrometry of biomolecules and demonstrated that the capped nanoparticles increase ion yields, decrease ion fragmentation, and increase the useful analyte mass range when compared to other nanoparticle systems, which offers desired biomarker screening [275]. Han et al. have reported the sandwich architectures based on a layer-by-layer (LbL) technique, prepared by the self-assembling of gold nanoparticles on a poly(diallyldimethylammonium chloride) (PDDA-) coated glass slide followed by silver layer by the interactions between proteins. They have obtained highly reproducible surface-enhanced resonance Raman scattering (SERRS) and SERS spectra, which offer highly sensitive and reproducible protein detections [276]. Li et al. have fabricated a mediator-free hydrogen peroxide biosensor based on immobilization of horseradish peroxidase (HRP) on layered calcium carbonate-gold nanoparticles (CaCO_3 -AuNPs) inorganic hybrid composite. This facile, inexpensive, and reliable sensing platform based on layered CaCO_3 -AuNPs inorganic hybrid composite offers a huge potential for the fabrication of more other biosensors [277]. Jiménez et al. have reported a simple, powerful technique based on the laser ablation of a target immersed in a water solution of a metal salt, which processed nanoparticles of different metals and alloys very fast. The advantage of the simultaneous production of silica during laser ablation is not only the stabilization of the metal nanoparticle colloid but also the possibility to reduce the toxicity of these nanoparticles [278]. Choi et al. have reported the sensitivity enhancement in chemical sensors by coupling Au nanoparticles that have the specific size and surface density on sensor chips which were conjugated by amine groups of cystamines [279]. Mukherjee and Nandi have developed an interesting interfacial redox method for the preparation of Au nanoparticles of various shapes in organic medium using Au seeds in aqueous medium without using phase-transfer reagent, which offers for biosensing [280]. Wang et al. have reported SERS aptasensors for protein recognition based on Au nanoparticles labeled with aptamers and Raman reporters, which opens a new way for protein recognition of high sensitivity and selectivity [281]. Pradhan et al. have developed CdSe semiconductor films on glass substrates, coated with Au nanoparticles (10 nm) by the pulsed-laser deposition technique. They have demonstrated a large enhancement of Raman intensity and photoluminescence of CdSe semiconductor via excitation

of surface plasmon resonances in proximate gold metal nanoparticles deposited on the surface of CdSe film, which offer a variety of approaches for improving the performance of various devices, including biosensors [282]. Plasmonic metal nanoparticles have great potential for chemical and biological sensor applications, due to their sensitive spectral response to the local environment of the nanoparticle surface and ease of monitoring the light signal due to their strong scattering or absorption. Lee and El-Sayed investigated the dependence of the sensitivity of the surface plasmon resonance (frequency and bandwidth) response to changes in their surrounding environment and the relative contribution of optical scattering to the total extinction, on the size and shape of nanorods. The nanorods with higher Ag concentration show a great enhancement in magnitude and sharpness of the plasmon resonance band, which gives better sensing resolution [283]. Refera et al. have electrodeposited gold nanoparticles using KAuCl_4 solution under potentiostatic conditions on glassy carbon substrates with multiple deposition steps followed by self-assembled monolayers (SAMs) of decanethiol or mercaptoethanol. The charge flow of the electroactive SAM is used for surface measurement of the gold surface area. A sixfold increase in the redox signal in comparison to a bulk gold surface is observed. The enhancement in signal of the nanoparticle-modified surface in comparison to bulk gold is due to an increase in surface area [284]. Fahnestock et al. have reported a selective removal of hexavalent chromium ions from aqueous solutions using a chitosan/gold nanoparticles composite film using localized surface plasmon resonance (LSPR), to measure the interface stability and detect the incorporation of chromium ions over time [285]. Lee et al. have reported immunoassay based on surface plasmon resonance (SPR) system; the signal enhancement was done by means of the conjugate of gold (Au) nanoparticle-antibody fragment [286]. Zheng et al. have reported newly designed porter proteins, which catch gold nanoparticles and deliver the nanoparticles selectively to a silicon dioxide (SiO_2) surface under the specific conditions. Recombinant apoferritin subunits, each of which has gold-binding peptide and titanium-binding peptide at the C- and N-terminus, respectively, can efficiently encapsulate a gold nanoparticle. The bioconjugate, nanogold, and surrounding mutant protein subunits had a property, which can deliver itself to the SiO_2 surface through the interaction. The genetically manipulated apoferritin subunits can encapsulate gold nanoparticles of various sizes, which is a promising property for applications involving surface plasmon resonance [287]. Berti and Burley have reported a practical method for DNA metallization, using nucleic acids as template for the synthesis of inorganic nanoparticles (NPs) [288].

6. Dendrimers: High-Performance Nanostructures for Biosensing

Dendrimers are like organic nanoparticles, that is, a new structural class of organic polymer macromolecules, nanometer-sized, hyperbranched materials having compact hydrodynamic volumes in solution and high, surface, functional group content. They may be water soluble, but due

to their compact dimensions, they do not show usual rheological thickening properties like many polymers in solution [289]. Dendrimers are defined by their three components: a central core, an interior dendritic structure (the branches), and an exterior surface (the end groups). The characteristic features of dendrimers are nearly spherical structures, nanometer sizes, large numbers of reactive end group functionalities, shielded interior voids, and low systemic toxicity. These unique combinations of properties have made them ideal candidates for potential nanotechnology applications in both biological and material sciences including a broad range of the fields, like materials engineering, industrial, pharmaceutical, biomedical, nanoscale catalysts, novel lithographic materials, rheology modifiers, targeted drug delivery systems, MRI contrast agents, and bioadhesives [290–292]. Dendrimers' architectural component manifests a specific function and property, as they are grown generation by generation. The core may be thought of as the molecular information center from which size, shape, directionality, and multiplicity are expressed via the covalent connectivity to the outer shells. Branch cell multiplicity (N_b) determines the density and degree of amplification as an exponential function of generation (G). The interior composition and volume of solvent filled void space determine the extent and nature of guest host (endoreceptor) properties that are possible within a particular dendrimer family and generation. Finally, the surface consists of reactive or passive terminal groups that may perform several functions. With appropriate functionalization, they serve as a template polymerization region, as each generation amplified and covalently attached to the precursor generation. The surface groups may also function as passive or reactive gates controlling entry or departure of guest molecules from the dendrimer interior. These three architectural components (core, interior, and periphery) essentially determine the physical and chemical properties, as well as the overall size, shape, and flexibility of a dendrimer. The dendrimer diameters increase linearly as a function of shells or generations added, whereas the terminal functional groups increase exponentially as a function of generation. The lower generations are generally open, floppy structures, whereas higher generations become robust, less deformable spheroids, ellipsoids, or cylinders depending on the shape and directionality of the core [293–295]. The future use of dendrimers as fundamental, reactive building blocks expected to provide the enabling platform required for the routine synthesis of broad classes of well-defined synthetic organic, inorganic, and hybridized biomolecular nanostructures. Dendrimers are spheroid or globular nanostructures, precisely engineered to carry molecules encapsulated in their interior void spaces or attached to the surface. Generation (shells) and chemical composition of the core, interior branching, and surface functionalities determine size, shape, and reactivity. Dendrimers have constructed through a set of repeating chemical synthesis procedures that build up from the molecular level to the nanoscale region. The dendrimer diameter increases linearly whereas the number of surface groups increases geometrically. Dendrimers are uniform with extremely low polydispersities and are commonly created with dimensions incrementally

grown in approximately nanometer steps from 1 to over 10 nm. The control over size, shape, and surface functionality makes dendrimers one of the smartest or customizable nanotechnologies commercially available. Dendrimers provide polyvalent interactions between surfaces and bulk materials for applications such as adhesives, surface coatings, or polymer cross-linking [296–301].

Dendrimers resemble covalent micelles characterized by well-defined cavities responsible for their particular endoreceptor properties and terminal groups that define the solubility, the reactivity, and the exoreceptor characteristics of the molecule. Due to their intrinsic and exciting properties, dendrimers have studied as an important new class of potential drug delivery system, protein models, molecular antennas, and catalytic materials. The dendrimers have used to modify an electrode surface due to their good biocompatibility and adequate functional groups for chemical fixation. It was reported that these materials are capable of increasing the concentration of hydrophobic molecules at the electrode solution interface, improving the sensitivity as well as the selectivity of certain specific electrochemical reactions [302–306]. Tsukruk et al. have systematically studied assembled films of dendrimers in monolayers or multilayers on a solid surface [307–309]. Recently, Hierlemann et al. have published a short communication reporting individual G4 and G8 PAMAM dendrimers adsorbed on the Au (111) substrate visualized by AFM [310]. Li et al. have obtained AFM images of PAMAM dendrimers ranging from G5 to G10 ethylenediamine (EDA). The fourth-generation polyamidoamine (PAMAM) polymers have a particular interest because of nanoscopic spherical structure and good biocompatibility. PAMAM dendrimer possesses 64 primary amine groups on the surface and has a globular shape with a diameter of about 4.5 nm. The mixture of proteins and PAMAM was cast on the electrode surface, forming protein-PAMAM films, and the direct electrochemistry of proteins was realized in the PAMAM films environment [311–313]. A new class of macromolecules, known as dendrimers, have been synthesized and deposited onto several electrode surfaces by forming layers that exhibit high mechanical stability and can be functionalised without loss of material from the electrode surface. Dendritic macromolecules containing a controlled number of redox-active organometallic units at the core, within the branches or at the periphery of the dendritic structure, have been investigated [6, 314–322]. Armada et al. have reported the preparation, electrochemical, and enzymatic characterization of amperometric enzyme electrodes based on glucose oxidase immobilized on Pt electrodes modified with octamethylferrocenyl dendrimers and their use for the determination of glucose under aerobic conditions [323].

Yoon and Kim have developed a glucose biosensor by alternate depositions of periodate-oxidized glucose oxidase (GOX) and PAMAM or ferrocenyl-tethered PAMAM. They also constructed a biosensor in which PAMAMs functionalized with ferrocenyl and biotin analogues were assembled layer by layer on the gold electrode. There were also some works reporting that PAMAM dendrimers form self-assembled monolayers (SAMs) on a gold support for

development biosensors [324]. Hianik has reported the suitability of the polyamidoamine (PAMAM) dendrimer G1 for the development of the glucose biosensor. Also, he has reported biosensor based on acetylcholinesterase (AChE) and choline oxidase (ChO), using poly(amidoamine) (PAMAM) dendrimers of the fourth generation (G4) mixed with 1-hexadecanethiol (HDT) [325, 326]. Immobilization of polyamidoamine (PAMAM) dendrimers (star-like structures) onto solid surface was reported in a variety of applied and basic sciences [327]. Several immobilization strategies have reported for the modification of solid surface with dendrimers, including chemical and physical methods, such as covalent binding and layer-by-layer (LbL) assembly techniques [328, 329]. Recently, Crook's group reported a direct immobilization of hydroxyl terminated PAMAM dendrimers on glassy carbon electrodes (GCEs). They utilized multiple hydroxyl terminals of the PAMAM dendrimers for oxidative coupling of the dendrimers on GCEs via ether bond [330–332].

7. Conclusions

Nanoscience and nanotechnology is actually a field of applied science and technology whose main theme is the control of matter on the molecular level in scales smaller than 1 micrometer (i.e., 1 to 100 nm) and the fabrication of devices within that size range. The nanosized systems perform specific electrical, mechanical, biological, chemical, or computing tasks based on the fact that nanostructures, nanodevices, and nanosystems exhibit novel properties and functions as a result of their small size, that means it is a highly multidisciplinary field, including subjects such as applied physics, materials science, colloidal science, device physics, supramolecular chemistry, and mechanical and electrical engineering.

The current trends and challenges for nanomaterials for the various applications are the focus of this paper, including importance in areas of cancer diagnostics, detection of pathogenic organisms, food safety, environmental measurements, and clinical applications. Aptamer-based microarrays for the quantitation of multiple protein analytes as well as a metal-enhanced electrochemical detection concept had been demonstrated for the sensitive detection of Ab-Ag, DNA-DNA, DNA-drug, and DNA-toxin interactions. The key issues to be addressed in the future are the increasing demand for higher sensitivity and selectivity that will allow molecules to be monitored in real time at minimal cost in the analysis of complex clinical and environmental samples. In addition, this paper, comprehensively surveys the past, present, and future of fast expanding and burgeoning research activities, the impact of nanotechnology on biosensors. It is backed up with the rapid strides of nanotechnology; these pieces of research are making a progress in multidisciplinary research, which are beginning to make their way to the market place. Focusing on the salient developments with the viewpoints of novel smart materials, device structures, and functionalities introduced, the paper highlights the significant milestones achieved and elucidates further the emerging future prospects in this area.

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