Published in final edited form as:

J Biomed Nanotechnol. 2013 January ; 9(1): 1–25.

Biomedical Detection via Macro- and Nano-Sensors Fabricated with Metallic and Semiconducting Oxides

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Abstract

Originally developed as gas sensors, the benefits of metallic and semiconducting oxide materials are now being realized in other areas of sensing, such as chemical, environmental, and biomedical monitoring and detection. Metallic and semiconducting oxides have continuously expanded their roles to date, and have also established their significance in biosensing by utilizing a variety of modes for signal generation and detection mechanism. These sensors are typically based either on their optical, electrochemical, electrical, gravimetric, acoustic, and magnetic properties for signal transduction. This article reviews such biosensors that employ metallic and semiconducting oxides as active sensing elements to detect nucleic acids, proteins, cells, and a variety of important biomarkers, both in thin film and one-dimensional forms. Specific oxide materials (M_xO_y) examined comprehensively in this article include $M = \text{Fe, Cu, Si, Zn, Sn, In}$. The derivatives of these oxide materials resulting from incorporation of dopants are examined as well. The crystalline structures and unique properties that may be exploited for various biosensing applications are discussed, and recent efforts investigating the feasibility of using these oxide materials in biosensor technology are described. Key biosensor characteristics resulting from reduced dimensionality are overviewed under the motif of planar and one-dimensional sensors. This article also provides insight into current challenges facing biosensor applications for metallic and semiconducting oxides. In addition, future outlook in this particular field as well as different impacts on biology and medicine are addressed.

Keywords

Semiconducting Oxides; Metallic Oxides; Biosensors; Solid-State Biodetection; Nanobiosensors; Nanomaterials; Biomedical Detection

1. INTRODUCTION

Metallic and semiconducting oxides (M_xO_y) initially drew considerable attention from the research community as potential as gas sensors due to their unsurpassed capability for operating at high-temperatures with high sensitivity.^{1–4} When compared to sensor devices fabricated from organic and polymeric materials, sensors constructed from these materials permit stable detection under harsh environments due to their mechanical and thermal robustness. While this original interest for metallic and semiconducting oxides in gas sensing application still continues, the use of M_xO_y has been extended further to other areas of detection including chemical, biological, and environmental agents. The development of new metallic and semiconducting oxide materials and their unique properties has diversified not only the applicable sensing fields but also significantly improved the performance capacities of these materials as biomedical sensors. The latest progress in nanotechnology related to the development of nanoscale metallic and semiconducting oxides has led to the discovery of novel exquisite properties that result from their reduced dimension. In turn, such progress has fueled growing research interest in these sensor materials. In particular,

their recent applications as biosensors are noteworthy since the use of various metallic and semiconducting oxides as sensing materials has greatly improved the detection limit and facilitated the measurement of important biomolecules such as DNA, proteins, and cells. Therefore, various research efforts pertinent to biosensing applications of metallic and semiconducting oxides are specifically reviewed in this article. Firstly, M_xO_y materials used frequently for detecting important bioconstituents and biocomplexes are introduced. Different modes of biological detection performed on those materials are discussed, while focusing on their desired material properties and detection mechanisms. Both macroscopic and nanoscale sensors are reviewed to identify their advantages and disadvantages in biodetection. Reflecting on the fact that the optical detection route is the most dominantly applied mechanism in biology, recent research endeavors for employing nanoscale metallic and semiconducting oxides in optical detection are highlighted. Current challenges and areas for improvement in the bioapplications of various materials are discussed from the two crucial standpoints of material development and biosensor performance. Future outlook in this field and areas of immediate impact on biology and medicine are then addressed.

2. MATERIALS: METALLIC AND SEMICONDUCTING OXIDES USED IN BIOSENSING

The family of metallic and semiconducting oxides encompasses a large number of compounds such as iron oxide, tantalum oxide, copper oxide, vanadium oxide, tungsten oxide, gadolinium oxide, gallium oxide, rhenium oxide, silicon oxide, titanium oxide, tin oxide, and zinc oxide. Therefore, rather than providing an exhaustive background for this long list of oxides, the scope of this section is narrowed down to only those oxide materials whose biosensor applications have been previously demonstrated.

2.1. Metal Oxides

2.1.1. Iron Oxide—A class of paramagnetic materials such as gadolinium-based complexes has traditionally been used as magnetic resonance imaging (MRI) contrast agents and for image-guided therapy.^{5–7} A new class of materials is being developed in the search for alternative materials that provide a higher magnetic moment (and magnetic susceptibility), increased relaxivity, and reduced toxicity. Ferromagnetic and ferrimagnetic materials exhibit aligned dipoles parallel to an external magnetic field that remain magnetic after the removal of the field. Critical to this process is the domain size and structure of the material: when the particle size becomes smaller than the domain size, the ambient thermal energy becomes sufficient to allow spontaneous disorganization of the magnetization direction. This super-paramagnetic behavior of single domain-sized particles of iron oxide (compounds such as maghemite ($\gamma\text{Fe}_2\text{O}_3$) and magnetite (Fe_3O_4)) has been employed for *in vivo* biomedical imaging.^{8–12} In particular, magnetite has drawn considerable attention from biosensor research fields due to its biocompatibility in conjunction with its superparamagnetic characteristics. Magnetite possesses a cubic inverse spinel structure in which the smaller iron cations occupy interstitial tetrahedral and octahedral sites and the larger oxygen atoms are in a close-packed, cubic arrangement,¹³ Table I. Since electrons can move between Fe^{2+} and Fe^{3+} ions, magnetite falls in the class of half-metallic materials. Nanosized magnetite crystals have been demonstrated for use as cell labeling/targeting, cancer therapy, as well as MRI contrast agents.^{8,9,14} Figure 1 shows transmission electron microscope images of magnetite nanocrystals and confocal microscopy z-stack images of dendrimer-functionalized magnetite nanoparticles used in cell imaging. More recently, magnetic particle contrast agents have been transformed into sensing elements. Biomolecular interactions in biological media can be detected by grafting probe moieties on the surface of the superparamagnetic particles. Interactions can also be detected through the aggregation or dispersion of the nanoparticles in the presence of biological targets. This

process, in turn, results in cooperative assembly or disassembly, leading to changes in the spin–spin relaxation time of water molecules. This signal is further detected by magnetic relaxation measurements without the need for protein purification or signal amplification.¹⁵

2.1.2. Copper Oxide—Copper metal can oxidize substances easily without surface poisoning. This catalytic effect is known to be mediated by multielectron contributions from the surface oxide layers of the material.¹⁶ Unlike its metal counterpart, copper oxide has the advantage of relatively high stability in air and solution, high natural abundance, and low production cost.^{17–19} These beneficial properties of copper oxide (cupric oxide (CuO) and cuprous oxide (Cu₂O)) have been exploited in glucose sensing, in which the high electron transfer rate of copper oxide enables enzyme-free detection of glucose.^{20,21} The working principles of glucose oxidation/reduction are discussed in detail in Section 4. Although not discussed at length in this article, other oxides that are typically incorporated into electrochemical glucose sensors for their ability to increase the signal response include Mn, Ce, Zr, Ti, and Zn.^{20–22}

2.2. Semiconductor Oxides

2.2.1. Tin Oxide—SnO₂ exhibit many technologically important properties such as low electrical resistance and high optical transparency in the visible range of the electromagnetic spectrum. In the infrared range, SnO₂ exhibits high reflectance, which makes it suitable for applications related to energy conservation.²³ For applications requiring higher electrical conductivity than the inherent conductance of SnO₂, dopants such as Sb and F are incorporated into the crystal structures of the material.²⁴ Although the electrical conductivity of doped SnO₂ does not generally reach that of indium tin oxide or zinc oxide, the material shows high surface sensitivity. Therefore, SnO₂ has been extensively used in solid-phase gas sensing, where the surface sensitivity is exploited in generating a detectable electrical response upon surface adsorption of gas molecules.²³ In addition to gas sensing, SnO₂ has been used in developing transparent conducting oxides and heterogeneous catalysts.^{25–28}

2.2.2. Zinc Oxide—Useful properties of ZnO include a wide, direct band gap of 3.37 eV and a large exciton binding energy of 60 meV at room temperature.²⁹ The wide band gap of ZnO may permit higher blocking voltages, switching frequencies, stability, efficiency, and reliability of devices.^{29–34} The direct bandgap of ZnO enables very efficient absorption and emission of light. Unlike most other semiconductor materials, the large exciton binding energy of ZnO permits lower temperature operation of devices. ZnO has higher chemical and thermal resistance, higher electromechanical coupling efficiency, and lower growth temperature, when compared to other wide band gap materials such as SiC, GaN, and diamond.²⁹ For these reasons, ZnO thin films and micro/nano structures have been previously demonstrated as candidate materials for use in a broad range of optical and optoelectric applications including short-wavelength light-emitters,^{31,35,36} field-emitters,^{30,37} UV lasers,³⁸ and highly efficient solar cells.^{39–44}

2.2.3. Indium Oxide—In₂O₃ displays good electrical conductance, high optical transparency in the UV and visible region, and good chemical stability.²⁸ In₂O₃ has direct and indirect bandgaps of approximately 3.6 eV and 2.5 eV, respectively. The exact electrical and optical properties of In₂O₃ (or better known as indium tin oxide, ITO, for tin doped indium oxide) are governed by the atomic ratio between In, O, and dopants. In addition to Sn, elements such as Zr, Mo, and Ti have been used as dopants for In₂O₃ in the past.^{45,46} Similar to other wide band gap materials described above, their properties make them suitable for use as gas sensors, transparent conducting oxides, display coatings, photovoltaic materials, and solar cells.^{3,4,28,47–49}

2.2.4. Silicon Oxide—Silicon has been used for applications in electronics, optoelectronics, energy storage, chemical sensors, and biosensors.^{50–54} Electrical, optical, and chemical properties of Si are extensively studied as Si remains one of the most important elements in the semiconductor industry. Important areas such as crystal growth methods, incorporation of dopants, device fabrication processes, and surface modification techniques have been comprehensively examined in the past. For sensor applications, these materials are often synthesized with *p*- or *n*-type dopants such as boron and phosphorous to control their electrical behavior. In typical atmospheric sensing environments, silicon is coated with a layer of very thin oxide (typical several nm in thickness). The surface hydroxyl group in this thin layer of silicon oxide is often used to couple functional chemical groups or biological constituents to increase detection selectivity. Recently, fused silica (synthetic amorphous SiO₂) has been applied to the transducing layer of a surface acoustic wave (SAW) biosensor to increase the detection signal by maximizing the difference in wave's shear velocity between the surface (SiO₂) and the bulk (ST-cut quartz) layers of the sensor.⁵⁵ Quartz (piezoelectric crystalline SiO₂) is also commonly used in quartz crystal microbalance (QCM) biosensors.⁵⁶ Regardless of the material selected for the piezoelectric layer in various QCM and SAW sensors, such as lithium tantalite (LiTaO₃), lithium niobate (LiNbO₃), zinc oxide (ZnO) and aluminium nitride (AlN), many of these sensors rely on silicon oxide as the sensor surface layer due to the extensive current understanding of Si-based crystal preparation and device fabrication.^{56–59}

3. DETECTION MECHANISMS: VARIOUS PROPERTIES OF METALLIC AND SEMICONDUCTING OXIDES USED FOR BIOLOGICAL DETECTION

3.1. Physical and Thermal Property

Metallic and semiconducting oxides discussed above have the common physical properties of good mechanical durability and thermal stability in common biodetection environments, making them suitable for use as biosensor materials. Tables I and II list melting point and hardness of the metallic and semiconducting oxides discussed in this article. Physical and thermal properties also affect the degree of difficulty in synthesizing or fabricating given metallic and semiconducting oxides into sensors, and this manufacturing consideration is important for selecting appropriate biosensor materials. In addition to these properties, the size scale (dimensionality) of biosensors can have a significant influence on the sensitivity and throughput of biodetection, even though their chemical compositions are identical. These dimensional contributions to crucial sensor properties will be discussed in Section 5.

3.2. Optical Properties

Many optical measurement settings that require clear platforms for excitation and emission light pathways take advantage of the optical transparency exhibited by various forms of SiO₂. They are often used as assay platforms in instruments such as bright/dark field optical microscopy, UV-vis absorption and emission spectroscopy, fluorescence spectroscopy, and attenuated total reflection devices. In solid-phase ligand binding assays of biomolecules, fluorescence-based biosensors often employ glass or quartz, since well-established surface modification techniques of silicon oxide can be readily applied to the covalent coupling of bioconstituents onto the material.^{60,61} In addition, SiO₂ has been extensively utilized in fiber optic-based biosensors operating in diverse optical transduction modes such as absorption, reflectance, fluorescence, evanescent wave, and surface plasmon resonance.^{62–67} Figure 2 displays the core and cladding sections of single- and multi-mode optical fibers as well as the instrumental setup for their application in DNA hybridization and protein detection. In typical fiber optic applications, the higher refractive index of the core compared to the cladding material confines and guides the light through total internal reflection at the interface between the core and cladding. When used as biosensors, the cladding layer is

removed and further covalently modified with chemical or biological moieties in order to increase the selectivity and sensitivity of biodetection. In biosensor applications, the incident light is reflected at the interface between the core and a biological medium during detection. The intensity of the reflected light does not abruptly become zero at the interface. A small portion of light penetrates into the reflecting medium and propagates away from the interface in the form of an evanescent wave which can excite nearby fluorescence molecules in biosamples. The evanescent wave decays exponentially, and can reach into the medium approximately 100 nm away from the reflecting interface. This technique provides high surface sensitivity upon binding of bioanalytes.^{64,66} The exact field strength of the evanescent wave is determined by a number of factors such as extinction coefficient, concentration, surface area of interaction of the bioanalyte, wavelength and refractive index of the waveguide, and the surrounding medium. In the most common mode of evanescent wave detection, the light dependence on these parameters is measured by coupling evanescence with fluorescence of binding analytes. More recently, the possibility of employing absorption and reflectance modes of fiber optic biosensors is being explored due to their advantage of label-free detection involving nonfluorescent biomolecules.⁶⁶

The light guiding capability of other semiconductor oxides, such as thin films and nanomaterials of ZnO, SnO₂, and In₂O₃, has been also utilized in sensors whose detection mechanism is based on changes in planar optical waveguides.^{68–71} Optical waveguides are the basic element of a photonic integrated circuit where a planar waveguide consists of a high refractive index guiding layer that is sandwiched between two lower index guiding layers. The optical signal travels in the guiding layer and is confined in the transverse directions as a result of total internal reflection at the interfaces. Similar to fiber optic sensors, three different types of waveguide sensors are commonly found; absorption, refractive, and fluorescence/chemiluminescence sensors. In absorption sensors, a direct change in the intensity of the transmitted light through the waveguide due to the presence of an absorbing medium is monitored. For refractive index sensors, the change in refractive index resulting from the alteration of the propagation coefficient of the waveguide mode is recorded. In fluorescence/chemiluminescence sensors, light emission from the sources in the evanescent region is triggered due to fluorescence/chemiluminescence which is subsequently collected by the waveguide. In other cases, the use of nanoscale semiconductor oxide materials such as ZnO and SnO₂ nanobelts, enables enhanced optical detection of various biomolecules with increased sensitivity. These research aspects will be discussed in more detail in Sections 5 and 6.

3.3. Electronic Structure

The electronic structure of a material, especially at conduction and valence band edges, determine important properties such as electrical and optical behavior of materials. Therefore, it is important to determine key characteristics of the band structure such as the position, dispersion, and character of the lowest conduction band that are responsible for electro-optical properties of useful semiconductor oxide materials. Adding dopants into intrinsic semiconductor oxides particularly affects the electronic structures of pure materials, yielding significant changes in their electric, optical, and magnetic properties. For example, when compared to those measured from native ZnO, Al-doped ZnO exhibits decreased electrical resistance and increased carrier concentration. In addition, a larger optical bandgap is observed due to a shift in Fermi-level to a higher energy, as the Burstein-Moss effect dominates over the band gap renormalization in Al-doped ZnO,⁷² see Figure 3. For these reasons, electronic structures of many semiconductor oxides have been investigated for intrinsic and doped states both experimentally and theoretically.^{73–75} Figure 4 shows the crystal structures and energy band diagrams of undoped SnO₂ (rutile), ZnO (wurtzite), and In₂O₃ (cubic *C*-type).^{73–75}

3.4. Electrical Properties

Electrical properties of semiconductor oxides such as ZnO, SnO₂, In₂O₃, and Si/SiO₂ are tuned during their synthesis in order to produce either *n*- or *p*-type electrical devices for biomolecular sensing. For example, *N* and *P* may be used in *p*-doping ZnO, whereas Al and Ga can serve as *n*-doping elements of ZnO. Table II lists some common types of dopants used to modify electrical properties of such semiconducting oxides. Intrinsic ZnO, SnO₂, and In₂O₃ typically exhibit *n*-type electrical conductivity. The presence of atomic defects in their crystal structures such as oxygen vacancies (and hydrogen atom in these vacancies) is often attributed to the *n*-type conductivity observed from as-grown or annealed ZnO, SnO₂, and In₂O₃ materials.^{76–78} Reproducibly synthesizing *p*-type analogues for these semiconducting oxides still remains challenging.

During electrical detection, charges carried by bio-molecules can effectively serve as gating components when they are covalently or physically bound to the surface of the semiconductor oxides. Detection is carried out by recording a signal change in conductance or current through the semiconductor oxide sensors. In particular, the direct band gap semiconductor oxides of ZnO, SnO₂, and In₂O₃ show notably high surface sensitivity (as supposed to bulk sensitivity). Therefore, even a small change in charge carrier concentration and the associated band-bending can yield a strong alteration in electrical signal of the material upon surface binding of the bioanalytes. This strong signal change is promoted by the dispersing conduction band with its minimum at the Γ -point and the high mobility of the charge carriers, see Figure 4. Figure 5 displays some examples of such semiconducting oxide-based electrical sensors used in biodetection.^{79,80}

3.5. Mass-Sensitive Property

With the recent advancement of microfabrication techniques in micro electro mechanical system (MEMS) fields, detection devices that rely largely on microfabricated fabrication process such as various modes of acoustic wave biosensors and microcantilever sensors are being actively developed. Acoustic wave sensors detect mass changes on sensor surfaces by using mechanical acoustic waves as their transduction mechanism. Acoustic sensors are categorized as bulk acoustic wave (BAW), surface acoustic wave (SAW), and acoustic plate mode (APM). Unguided acoustic wave travels through the bulk substrate material in BAW; this is in contrast to SAW, where a guided or unguided wave propagates through a single substrate surface. In APM, waves are guided through reflection from multiple surfaces instead. In particular, SAW sensors are extensively used in cell and microorganism detection due to their sensitivity to surface bound biomolecules.^{55,57–59} Example modes of acoustic wave devices include shear horizontal surface acoustic wave (SH-SAW), surface transverse wave (STW), love wave (LW), flexural plate wave (FPW), shear horizontal acoustic plate mode (SH-APM), and layered guided acoustic plate mode (LG-APM).^{55,57}

QCM is a well-known example of a BAW device that has demonstrated its effectiveness in gravimetric biosensing. It monitors a signal difference (in this case, resonance frequency shift) resulting from a change in mass of the sensing resonator due to the coupling of bioanalytes on the sensor layer.^{56,81–83} In addition to resonance frequency, other parameters such as electrical impedance and resonance dissipation of the sensor are also used in its detection scheme to examine binding events and the kinetics of bioanalytes on the sensor surface. QCM with dissipation monitoring capability (QCM-D) is often used for biological monitoring due to its ability to measure mass and viscoelastic property changes simultaneously.^{82,84} Figure 6 displays a QCM-D sensor employed to study adsorption kinetics of a mussel adhesive protein to a nonpolar Au surface. Microcantilever resonator-based devices also make use of mass-induced frequency and beam deflection changes as the signal transduction mechanism for biodetection.^{85–87} The resonance frequency and surface

stress of a cantilever are exquisitely sensitive to biomolecular adsorption. The resulting change in cantilever deflection and resonance frequency can be precisely measured to monitor biological samples *in situ*. Microcantilever sensors can be easily produced using standard micromachining techniques, and have a high potential to be integrated into on-chip detection circuitry for high throughput measurements.

3.6. Magnetic Properties

Paramagnetism and superparamagnetism in metallic oxides such as gadolinium complexes (spin-lattice relaxation T_1 agents) and iron oxides (spin-spin relaxation T_2 agents) have been successfully exploited in nuclear imaging and superconducting quantum imaging device (SQUID)-based techniques.^{88–90} When they are placed in an external magnetic field, their magnetic moment will induce alignment along the field which results in an increase in magnetic flux. This change of the local magnetic field, induced from the large magnetic moments of the magnetic particles, leads to dephasing of nearby proton spins. The dephasing process occurs through energy transfer between the atomic nuclei and, consequently, longitudinal (T_1) and transverse (T_2) relaxation of the nuclei. This process generates a detectable signal in magnetic resonance measurements. When compared to Gd-based compounds, iron oxide particles exhibit a higher magnetic susceptibility and significantly reduced spin-spin relaxation (T_2) time.^{91,92} The use of iron oxides in bioimaging requires the addition of a coating layer such as dextran and silane to provide colloidal stability and biocompatibility.¹¹ Surface coating and complexation agents can help cellular uptake of iron oxide particles and reduce their cytotoxicity as well.^{93,94} Polymers such as polymethylmethacrylate, polyethylene glycol, and polyvinylalcohol are also used as an additional coating layer.¹¹ Paramagnetic Gd(III)-chelate possesses a longitudinal relaxivity (r_1) of water protons of 3–5/(s · mM), and prevails in clinical use due to their versatility in being able to be used in various organs. Dextran-coated superparamagnetic iron oxide nanoparticles possess a transverse relaxivity (r_2) of water protons of 100–200/(s · mM), and they are liver-specific due to larger particle size. Substantial research efforts are currently being made to develop alternative materials with similar or better magnetic and biocompatible properties in order to expand the choice of approved nanomaterials for *in vivo* imaging agents permitted for use in human patients.

4. DETECTION TARGETS: BIOLOGICAL SYSTEMS EXAMINED BY METALLIC AND SEMICONDUCTING OXIDE SENSORS

This section describes various biomolecular systems investigated by different detection techniques involving metallic and semiconducting oxide sensors. The types of bioconstituents and the associated detection techniques exploited for the measurement of specific bioanalytes are discussed.

4.1. Biomarkers: Nucleic Acids and Proteins

A variety of sensors has been developed and assessed to detect nucleic acids and proteins due to their paramount importance and ubiquity in basic research as well as in clinical diagnosis. Such sensors include optical, electrochemical, electrical, gravimetric, acoustic, and magnetic types. As these research efforts are numerous and an exhaustive list of these methods is too lengthy to be covered here, the discussion in this section will focus on several recent approaches for detecting nucleic acids and proteins with high detection sensitivity.

Detection platforms for DNA and proteins include both homogeneous and heterogeneous assays.⁹⁵ The former is carried out by solution-based detection and the latter utilizes surface-bound, array-based probes. Fluorescence-based sensors exhibit very high sensitivity when compared to other techniques, and are widely considered the sensors of choice, both in

homogeneous and heterogeneous DNA and protein measurements.^{96–104} In addition, recent applications of fiber optics and Forster resonance energy transfer (or fluorescence resonance energy transfer, FRET) sensors have shown high sensitivity, detecting nucleic acid and protein binding events even in the single molecule regime.^{105,106} For label-free, high sensitivity detection, surface plasmon resonance (SPR) sensors have demonstrated their capability for DNA and protein detection. Biodetection frequently involves measuring very small analyte quantities, and this dearth of analytes can often be below the sensitivity limit for conventional sensors to discern without any amplification processes. One such example pertains to low levels of proteins in single cells that play an important role in the functioning of cells through processes such as cell signaling and regulation of gene expression. In these cases, microfluidic devices are developed to manipulate, lyse, label, separate, and quantify the protein content using single-molecule fluorescence counting.^{107–115}

In FRET, the energy of an excited donor fluorophore is transferred to an adjacent ground state acceptor fluorophore using an induced-dipole, induced-dipole interaction. This nonradiative energy transfer process results in the return of the donor to the ground state while exciting the acceptor. The efficiency (E) in FRET measurements is defined as the loss of donor fluorescence intensity in the presence of an acceptor fluorophore, $E = [1 + (R/R_0)^6]^{-1}$, where R is the distance between the donor and the acceptor, and R_0 is the distance at which 50% of the energy is transferred. R_0 is a function of the spectral overlap of the donor emission, acceptor absorption, the refractive index of the medium, quantum yield of the donor, and a factor called κ^2 . κ^2 depends on the relative orientation in space between the transition dipoles for the donor and the acceptor. E can be measured by determining the lifetime or fluorescence intensity of the donor in the presence and absence of the acceptor that is incorporated into nucleic acid and protein assays.^{95–104} FRET energy depends largely on the proximity of the donor–acceptor molecules in a range comparable to the biomolecular dynamic distance (30–80 Å). Therefore, single molecule measurements by FRET detection have been developed in recent years and enabled the investigation of DNA and protein dynamics at a single molecule level.^{98,99}

Fiber optic sensors have been also used for nucleic acid and protein detection with high sensitivity. Fiber optic sensors measure the intensity of fluorescence from the intercalated dye in a total internal reflection geometry, and this signal is proportional to the amount of hybridized DNA or protein. Operating principles of fiber optic sensors were previously discussed in Section 3.2. For example, such DNA sensors are fabricated by first activating the surface of quartz optical fibers with a long-chain aliphatic spacer arm and covalently attaching single stranded DNA to the fiber. Detection of duplex DNA formation at the fiber surface is then achieved by a fluorescent intercalating dye.^{62–64,116–119} Figure 7 displays such a sensor where multiple fibers in a fiber bundle are used for an array-type detection of DNA hybridization. A fiber optic DNA sensor array is fabricated via a covalent coupling of DNA to the fiber optic surface.¹¹⁷ The distal tip of the fiber shown in the AFM image in Figure 7 is used for sensing and the subsequent data are acquired using a charge coupled device (CCD). Images in Figure 7 are the results from a small section of a fiber-optic array containing 25 different probe-functionalized microspheres among which a random selection of 12 images is obtained after hybridization to one labeled target. A similar approach is applied for detecting a variety of protein systems in which sensor design involves optimal linking strategies for coupling probe biomolecules to fiber optic surfaces and incorporating fluorophores in protein assay schemes for signal detection.^{65–67,119–122}

SPR-based devices have shown promise as effective nucleic acid and protein sensors without the need for employing fluorophores or radioactive tags.^{123–130} During measurement, the incident light generates an electric field whose intensity decays rapidly with distance from a thin sensor layer as an evanescent wave. The sensor layer is

conventionally made of Au, but a class of conducting metal oxides such as ITO that are plasmonic can also serve as the SPR sensing layer.^{131–133} The evanescent wave interacts with the charge density, originating from collectively oscillating electrons, in the sensing layer material and generates surface plasmons. This process leads to a reduction in the intensity of the reflected light. SPR is a function of the effective refractive index integrated along an electromagnetic field. Small changes in reflectivity due to a binding occurrence of nucleic acids or proteins on sensor surfaces can be quantitatively detected in real time.^{134–138} Therefore, SPR permits direct inference of kinetic and equilibrium parameters of biomolecular interactions. In normal operations, the SPR sensor surface is modified with a thin hydrogel matrix containing covalently immobilized receptor molecules for capturing specific analytes such as single stranded DNA and antibodies. The apparent refractive index is determined by the dielectric properties and adsorbed amount of the bioanalytes, where the magnitude and distribution of polarity of the adsorbed molecules play important roles.

4.2. Other Biomarkers

Biomarkers are becoming increasingly important since they provide early warnings of disease and are active monitors that translate patient responses to treatments. Various biological constituents including genetic fragments, proteins/enzymes, and metabolites can serve as biomarkers. New biomarkers are constantly being developed and tested in order to identify more reliable, quantifiable, and easily measured bioindicators that can correlate well with biochemical measures of disease progression.

Glucose is one example of such a biomarker that is important for the diagnosis and treatment of diabetes. Glucose sensors are generally categorized into two groups; enzymatic and non-enzymatic sensors. The biosensor industry is dominated by enzymatic glucose sensors with self-testing and continuous blood glucose monitoring systems. In many cases, enzymatic glucose sensors monitor oxygen consumption based on the catalytic oxidation of glucose carried out by glucose 1-oxidase (GO_x) in the presence of oxygen.^{139,140} The key component of this large protein molecule is its redox center, flavin adenine dinucleotide (FAD). This reaction center is embedded deep in the protein, protected by a thick protein layer. The electron transfer process from the inner active center of an enzyme to an electrode in such case can be explained by Marcus theory which predicts exponential decrease in the electron transfer mechanism.^{141,142} Therefore, the electron transfer process into this active center is a major limiting step of the reaction, $GO_x(FAD) + \text{glucose} \rightarrow GO_x(FADH_2) + \text{glucolactone}$. Another important aspect of these biosensors is the effective catalytic regeneration of the reduced $FADH_2$ center via the reaction, $GO_x(FADH_2) + O_2 \rightarrow GO_x(FAD) + H_2O_2$. As such, enzymatic glucose sensors are often classified depending on the following three regeneration mechanisms: reduction with naturally present oxygen, reaction with another chemical mediator, and direct oxidation by the electrode. Instead of relying on the enzyme with the above-mentioned limitations, non-enzymatic glucose sensors directly oxidize glucose in the sample.¹⁴³ Practical application of these sensors is currently undermined by the lack of selectivity and sensitivity. Although sensitivity varies with the electrode geometry and treatment, detection limits of typical glucose sensors are generally within the range of blood glucose levels of 2–10 mM. Since glucose oxidation at most untreated electrodes is kinetically slow and fouling of the electrode can often occur by background sample constituents, only a limited number of electrode systems can be applicable to operation at physiological pH. Metal oxide systems used for glucose sensing include CuO and RuO_2 .^{144–147}

Similar electrochemical detection methods are applied for measuring other biomarker systems. For example, enzyme-modified semiconductor oxide electrodes are utilized to detect urea.^{148,149} During urea detection, urease catalyzes hydrolysis of urea to NH_4^+ and

HCO_3^- and the subsequent biochemical reaction $(\text{NH}_2)_2\text{CO} + 2\text{H}_2\text{O} + \text{H}^+ \rightarrow 2\text{NH}_4^+ + \text{HCO}_3^-$ ensues in the presence of urease. Glutamate dehydrogenase (GLDH) has been used as an alternative indicator for urea detection, since it catalyzes the reaction between α -ketoglutarate (α -KG) and nicotinamide adenine dinucleotide (NADH) to produce L-glutamate with simultaneous oxidation of NADH to NAD^+ . This reaction occurring in the presence of GLDH is $2\text{NH}_4^+ + 2\alpha\text{-KG} + 2\text{NADH} \rightarrow 2\text{L-glutamate} + 2\text{NAD}^+ + 2\text{H}_2\text{O}$. Electrons generated during this biochemical reaction are transferred to the electrode and the current is measured as a function of urea concentration. Metal oxide sensors that are used for such electrochemical detection include SnO_2/ITO and ZnO .^{148,149}

4.3. Cells and Microorganisms

Due to the physical characteristics of cells and microorganisms, mass-sensitive devices such as QCM, SAW, and microcantilever sensors are often used to detect these relatively large bioanalytes. For example, a disposable QCM sensor is used for detecting lipopolysaccharide (LPS) moieties on pathogen surfaces.^{150,151} LPS (carbohydrates covalently bound to a lipid component, lipid A moiety) are found on the outer cell surface of many pathogens and play an important role in assessing the resistance of Gram-negative bacteria toward toxins.¹⁵² Therefore, detecting LPS offers an indirect means to screen for carbohydrate-based pathogens. QCM is also used to detect bacterial toxins and whole cells such as cholera toxin (CT) and human endothelial cells. In this case, the QCM sensor surface is modified with a biomimetic film containing glycolipids or a self assembled monolayer of the ganglioside GM1 which is the cell surface ligand of CT.^{153,154} QCM is frequently employed to study adsorption characteristics of cells on a particular surface in order to gain insight into cellular adhesion mechanisms. One example is the QCM-D measurement of fibronectin adsorption and the subsequent adhesion study of human umbilical vein endothelial cells.¹⁵⁵ Another example is the real-time QCM-D investigation of living cells of *Streptococcus mutans* and their biofilm formation.¹⁵⁶

In addition, SAW devices are applied to the investigation of cell adhesion and growth mechanisms. Examples of cell types probed by SAW sensors are *Escherichia coli* (*E. coli*), *Legionella*, *Bacillus thuringiensis* (B8) and M13 bacteriophage.^{57,157,158} Most of these devices are SAW immunosensors where the SiO_2 wave-guiding layer is modified either with antibodies against specific cells or with a double layered binding structure to increase sensitivity. In the latter case, cells are first adsorbed onto the sensor surface. Subsequent antibody reactions are carried out in order to couple cell-antibody layers on the sensing surface, and detection is accomplished by probing the formation cell-antibody-cell complexes.¹⁵⁷

More conventional routes of optical, electrochemical, and magnetic detection may also be employed for detecting cells and microorganisms. These techniques include fluorescence cellular imaging, amperometric cell detection, and magnetic resonance imaging. For example, fluorescence *in situ* hybridization (FISH) is a powerful technique for detecting chromosomal changes in tumor cells and often used for studying structural cytology of the cell nucleus.^{159,160} Cells are also detected via magnetic resonance imaging and other related techniques both *in vivo* and *in vitro*.^{11,88,89,161–165}

5. SENSOR DIMENSIONS: MACROSCOPIC AND NANOSCALE SENSORS

When compared to conventional macroscopic scale sensors comprised of three- or two-dimensional (3D or 2D) materials, sensors fabricated with one-dimensional (1D) materials such as nanowires, nanotubes, and nanorods have demonstrated their ability for more efficient electron transport and optical excitation. The higher surface-to-volume ratio of

materials with reduced dimensionality often contributes to the increased detection sensitivity of biosensors observed from detection systems fabricated using nanomaterials, Figure 8. For example, the electrical property of 1D materials is strongly influenced and easily altered by small variations in the sensing environment. Changes in binding or unbinding events of bioanalytes on sensor surfaces (i.e., the accumulation and depletion of charge carriers) directly affect the entirety of the 1D materials.^{166,167} Conversely, this effect will be localized only to the surface area of 2D or 3D structures. The size scales of many biologically important molecules are in the nanometer range, and match well with those of 1D materials. In addition, materials with reduced dimensionality offer an excellent opportunity to integrate a large number of sensors into extremely high density arrays and lab-on-a-chip platforms for point-of-care devices, which can increase the throughput of desired biodetection. They can also permit fabrication of highly miniaturized devices with low cost, good portability, and minimum invasiveness for detection.

5.1. Two Dimensional (2D) Sensors

2D detection platforms, known as solid-state biosensors, are developed and used extensively in many applications ranging from basic research to clinical diagnostic operations. Such 2D sensing platforms enable reduced volume detection both in the amount of biochemical reagents and the size of each sensor, when compared to the traditional solution-based detection techniques performed in macroscopic scale reaction vessels. Furthermore, many lab-on-a-chip devices are nowadays fabricated from 2D sensors and allow integrating a large number of sensors onto a single chip. The employment of such solid state ligand binding assays, for example, has led to very sensitive optical detection of DNA duplexes and protein complexes with reduced cost and detection time. These optical platforms are commercially available in the form of DNA chips and protein arrays.^{168–172} Figure 9 displays an overall schematic for fabricating a solid-state optical array to detect DNA.¹⁶⁹ Electrochemical and electrical solid-state biosensors are also commonly employed in the detection of various biological systems as discussed in Section 4.

5.2. One Dimensional (1D) Sensors

The advantages of higher detection sensitivity and integration potential are even greater in various recently developed sensors employing 1D semiconductor oxides. Biosensing applications of 1D semiconducting materials have led to dramatically improved detection sensitivity in miniaturized devices. These recent research efforts are discussed in this section.

Doped silicon nanowires (SiNWs) have demonstrated their versatile biosensing capability in the form of 1D field effect transistors (FETs). Selectivity of such sensing applications is achieved through the native oxide layer on SiNWs, in which the silicon oxide layer is modified both chemically and biologically to couple capture probes to the sensor surface. These FET sensors have been applied for DNA hybridization reactions, protein–protein interactions, single cell detection, and different biomarker assays.^{54,80,167,173–176} In these FET devices, the signal is mainly generated by a doping effect which can be explained by either charge transfer or electrostatic interaction mechanisms.^{177,178} The charge transfer mechanism is determined by the degree of alignment between the chemical potential of the sensor and that of the bioanalyte, as well as the resistance to charge transfer.^{179,180} In contrast to relying on the direct transfer of charge carriers through the interface, the electrostatic interaction mechanism is largely dependent on a characteristic Debye screening length (λ_D), and this length is associated with the dielectric properties of the biodetection environment where the electrostatic interaction occurs.^{181,182}

Although other semiconducting oxides have not been used as extensively as SiNW FET sensors for electrical biodetection, several 1D FET biosensing applications of materials such as nanoscale ZnO, SnO₂, and In₂O₃ have been attempted.^{183–188} ZnO NWs have been fabricated into a biotin-modified FET device to detect fluorescein isothiocyanate-conjugated streptavidin with the detection level of 2.5 nM.¹⁸⁴ Glucose oxidase-modified ZnO NWs have been employed as extended gates in a standard low-threshold metal oxide semiconductor FETs (MOSFET) for glucose sensing, though the lowest detection limit of this approach was not evaluated in this study.¹⁸⁵ Additionally,

n-type In₂O₃ NWs have demonstrated their potential as electrical sensors of low-density lipoprotein (LDL) cholesterol. Positive charges from amino groups carried by the ApoB-100 protein in LDL molecules lead to an increase in both charge carrier concentration as well as conductance upon their adsorption to the sensor surface (Fig. 10).¹⁸⁶ In addition to electrical biosensors, semiconductor oxide nanowires are utilized in electrochemical biosensing purposes. Sb-doped SnO₂ NWs modified with horseradish peroxidase (HRP) are used as electrochemical H₂O₂ sensors.¹⁸⁷ In this setup, electrochemical properties of HRP are monitored through a direct electron transfer process from HRP to a glassy carbon electrode that is pretreated with Sb-doped SnO₂ NWs. New biolinking strategies are also explored to increase detection selectivity of semiconducting oxides. An electrochemical cell containing a mat of In₂O₃ NWs on the sensor electrode may be coupled with single stranded DNA after electrochemical activation of the sensor surface in order to expand the existing surface modification strategies of metal oxides for electrochemical biosensing.¹⁸⁸

6. FOCUS ON RECENT OPTICAL BIODETECTION USING 1D METALLIC AND SEMICONDUCTING OXIDES

Although conventional biodetection carried out for basic biology research and medical applications typically rely heavily on optical mechanisms, the development of 1D metallic and semiconducting oxides has largely been in the areas of electrochemical, electrical, gravimetric, and magnetic detection. Recently, several types of semiconducting oxide nanostructures were successfully employed in optical biodetection. Therefore, this section focuses on reviewing these efforts for their potential impact related to the use of nanoscale semiconducting oxides in the most dominant field of optical biodetection. Semiconducting oxides of ZnO and tin-doped In₂O₃ NRs have been recently utilized in the optical detection of simple and complex biological systems.^{189–194} Specifically, ZnO NR platforms are developed for enhanced fluorescence detection of relatively simple assays such as DNA hybridization and protein–protein interactions, as well as more complex biomedical reactions, such as cytokine and telomerase measurements. Figure 11 displays several examples of such fluorescence measurements, in which both the fluorescence panels obtained from various biosystems on ZnO NR platforms and their concentration-dependent detection curves are shown. When a covalent linking method is used to couple oligonucleotides to the ZnO NR surface, formation of fully complementary duplex can be monitored down to a few fM concentration level.¹⁹⁰ The fluorescence detection sensitivity on ZnO NRs is higher approximately by a factor of five when compared to the detection sensitivity using ZnO thin films, and a few orders of magnitude higher when compared to other common biosupports such as glass, silica, quartz, polymer, and silicon.¹⁸⁹ Therefore, one of the main advantages of ZnO NRs is their capability for enabling efficient monitoring of low fluorescence signals in common detection settings, especially those that involve low-abundance biosamples and target biomolecules of ultratrace-level concentrations.

This enhanced fluorescence detection capability is employed to analyze more complex and multistep biological reactions such as cytokine sandwich assays and telomerase repeat elongation assays. Levels of two important cytokines, interleukin-18 (IL-18) and tumor

necrosis factor alpha (TNF α), in biologically relevant fluids have been determined and compared to the detection limit of commercially available detection platforms based on enzyme-linked immunosorbent assays (ELISA). The detection sensitivity of ZnO NR platforms for those cytokines is in the femtogram per milliliter regime without any chemical or biological signal amplification, whereas the commercial ELISA-based platforms permit detection at levels around tens of picograms per milliliter.¹⁹³

1D materials inherently show an increased surface-to-volume ratio compared to their higher dimension counterparts and can provide a larger number of biomolecular adsorption sites than 2D and 3D systems. However, such enhancement in fluorescence detection is not observed from all nanoscale materials under study. For example, no similar effect in fluorescence has been observed from biosamples assayed on SiNWs or on carbon nanotubes (CNTs). Variability in the degree of biomolecular adsorption can exist between various support materials due to differences in their surface properties and the resulting variations in the interactions between biomolecules and given surfaces. However, a control experiment has demonstrated that fluorescence signal intensity does not necessarily correspond to the amount of adsorbed proteins.¹⁹³ In this control study, fluorescence signal from proteins on polymeric supports is much lower in intensity when compared to the signal obtained from those on ZnO NR platforms, even though the polymeric surfaces contain more adsorbed protein molecules per unit area. The exact fluorescence enhancement mechanisms are still under investigation. It is probable that both the unique optical property and its reduced dimensionality of ZnO NRs attribute to the fluorescence enhancement effect. The degree of fluorescence enhancement observed in ZnO NRs combined with the aforementioned potential benefits in biosensing justifies careful assessment of the exquisite optical properties of nanoscale ZnO and other similar materials in future biodetection systems.

Wide band gap semiconductor nanomaterials such as GaN, SnO₂ and ZnO nanowires show near-cylindrical geometry and high dielectric constants. Such nanomaterials are known to exhibit two-dimensional confinement of ultraviolet and visible light. Highly crystalline 1D materials with diameters ranging from 100~500 nm can predominantly support axial Fabry-Perot waveguide modes that are separated by $\Delta\lambda = \lambda^2/(2Ln(\lambda))$ where L is the cavity length and $n(\lambda)$ is the dispersion-corrected index of refraction. Light in the transverse trajectories along the short axis of a one-dimensional nanomaterial is largely lost due to diffraction in these materials. Therefore, diffraction limits photoluminescence or lasing from nanomaterials with very small diameters. For example, greater than 90% of the field intensity is retained within the wire for the lowest-order guided-mode travelling through ZnO nanowires with a radius (r) larger than 100 nm, whereas less than 25% of the intensity is present in the wire for ZnO with $r = 50$ nm.³³ Based on these observations, subwavelength wave guiding properties of similar nano-structures of SnO₂ and ZnO nanoribbons whose diameters are below the wavelength of light are examined.^{33,195,196} They serve as excellent waveguides of their own photoluminescence and nonresonant UV/visible light emitted from adjacent nanowires. In assessing their potential advantages in sensor applications through emission or absorption mechanism, approximately 15% of the electric field intensity is found to exist outside of the nanomaterial when the wavelength of light is 442 nm. The radial field intensity decays to 10% of its maximum value by about 135 nm into the surrounding medium.¹⁹⁶ When compared to conventional optical fibers, these subwavelength fibers carry a larger fraction of their modal power outside the core. Consequently, they enhance the intensity of the evanescent wave field and increase the penetration depth into the probing region. Figure 12 displays the images of photoluminescence and guided nonresonant excitation light through a SnO₂ nanoribbon. It also shows fluorescence and absorbance images of a fluorophore with a SnO₂ ribbon cavity and the guided photoluminescence spectra.

7. CURRENT CHALLENGES AND AREAS OF IMPROVEMENTS

Numerous research efforts have been made for synthesizing oxide materials that might be useful for various applications in sensing. Typical methods employed for producing the metallic and semiconducting oxide materials discussed above are gas-phase synthesis, vacuum deposition, and solution chemical reaction.^{18,19,29,197–221} The most commonly used gas-phase synthesis and vacuum deposition approaches include physical vapor deposition, pulsed laser deposition, chemical vapor deposition, metal-organic chemical vapor deposition, vapor–liquid–solid epitaxial mechanisms, and epitaxial electrodeposition. In solution-based synthetic approaches, methods such as hydrothermal decomposition and homogeneous precipitation in aqueous solutions are being pursued.

For those metallic and semiconducting oxides with already proven biosensor capability, further development of reproducible synthetic methods is currently warranted in order to minimize any variation of material's sensing properties between different batches. For reproducible and quantitative sensor performance, the development of precisely controlled synthetic methods that yield uniformity in crystallinity, extent of atomic defect, size, orientation, and spatial density is crucial. This aspect becomes especially important when dopants are introduced to the materials and when device characteristics are needed to be compared between sensors comprising of different materials. It also becomes crucial for *in vivo* biomedical applications in which the size, charge, and surface chemistry of materials strongly affect blood circulation times, as well as the bioavailability of nanoscale objects within the body. For example, exact magnetic properties and internalization tendency of nanoparticles heavily depend on the particle size. Large particles with diameters greater than 200 nm are typically sequestered through mechanical filtration by the spleen and are eventually removed by the cells of the phagocyte system, effectively decreasing blood circulation time. Smaller particles with diameters less than 10 nm are quickly removed through extravasation and renal clearance. Particles of intermediate size (diameters ranging between 10–100 nm) are considered to be optimal for subcutaneous injection to promote prolonged blood circulation time.

In addition to improving current materials, growth and assessment of novel materials for their biosensing capability is equally important in order to expand the choice of materials with much improved sensitivity and selectivity than what the existing metallic and semiconducting oxides can offer. In developing new materials for novel biosensors, several essential factors should be considered. Their surface chemistry should be amenable to immobilization strategies for hosting suitable bioreceptors or chemical recognition molecules. A defined transducing mechanism should be present for translating a biological binding event to a measurable signal. Fabrication methods should be also available for packaging of sensors into a device.

When these requirements are met, key performance criteria related to biosensor characteristics are needed to be considered. The key factors for biosensor evaluation include sensitivity (the response of a sensor per unit change in bioanalyte concentration, the slope of the calibration curve), selectivity (the ability for a sensor to discriminate between different bioanalytes), dynamic range (i.e., linearity, concentration range over which the measured signal does not deviate from the ideal curve), response time (the time required for a sensor to indicate a defined percentage which is typically set to 90% of its final response), reproducibility (identical results of the sensor output for the same methodology), detection limit (lowest concentration of bioanalyte with a measurable signal response), lifetime (the time period over which a sensor can be used without significant deterioration in performance characteristics), and stability (the change in its baseline or sensitivity over a fixed period of time). Although numerous research efforts are made for developing biosensors from metallic

and semiconducting oxides, the scope of these efforts is often limited to addressing a subset of these key biosensor characteristics at a time. Sensitivity and detection limit are the two major parameters under consideration in many efforts. For these sensors to be more useful and widely applicable to a variety of biodetection motifs, new research endeavors encompassing a complete evaluation of all key characteristics are warranted. The aforementioned metallic and semiconducting biosensors should be investigated beyond the simple biodetection environments involving only a few purified bioconstituents at a time to more complex and multilayered reactions involving physiologically relevant conditions. Another important factor of biosensors is to be able to compare quantitatively multiple data sets obtained from different sensors within the same device in lab-on-a-chip applications. It is also important to minimize device-to-device variation for those large library assays requiring more than one device for complete data acquisition. For example, it is very difficult to conduct a meaningful comparison between different values of detection limits currently reported in literature, even though those values are obtained from the assays measuring the same bioanalytes and using the same type of sensor materials. Developing standardized assays involving metallic and semiconducting oxide biosensors will be highly beneficial for quantitative data analysis and, thus for more biologically meaningful and straightforward data interpretation.

8. CONCLUDING REMARKS AND OUTLOOK

This article reviews metallic and semiconducting oxides that are playing increasingly important roles in many modes of biosensors. Metallic and semiconducting oxide sensors based either on their optical, electrochemical, electrical, gravimetric, acoustic, and magnetic properties for signal transduction are discussed. The crystalline structures and unique properties of metallic and semiconducting oxides are addressed to provide insight into their specific roles in different biosensing schemes. Various types of biosensors employing metallic and semiconducting oxides as active sensing elements are discussed for the detection of nucleic acids, proteins, cells, and biomarkers. Key biosensor characteristics resulting from the contributions of reduced dimensionality are overviewed while focusing on the 1D and 2D sensors. In the hope of guiding the field to better impact biology and medicine, current challenges facing biosensor applications of metallic and semiconducting oxides are identified from an interdisciplinary research point of view, while focusing on material development and sensor performance.

Acknowledgments

The author acknowledges support on this work by the National Institutes of Health, National Research Service Award (1R01DK088016-01) from the National Institute of Diabetes and Digestive and Kidney Diseases. The author also thanks D. Y. Joh and N. Aras for their careful reading of the manuscript.

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Biography

Hahm has received her Ph.D. in Physical Chemistry at the University of Chicago. After her postdoctoral appointment in the Department of Chemistry at Harvard University, she served as an Assistant Professor in the Department of Chemical Engineering at Pennsylvania State University in University Park, PA. Currently, she is an Assistant Professor in the Department of Chemistry at Georgetown University in Washington DC, USA. She is a recent recipient of Dreyfus Lectureship Award and WISE Lectureship Award from American Chemical Society. She is an Executive Editor of *J. Bioanal. Anal. Tech*. Professor Hahm's research program is highly interdisciplinary, and utilizes both biotechnology and the fundamental properties of polymeric, metallic, and semi-conducting nanomaterials (including 1D nanostructures such as nanotubes, nanowires, and nanorods). She studies the fundamental properties of metallic, semiconducting, and polymeric nanomaterials in order to identify their unique physical, chemical, optical, or electrical properties for advancing biotechnology and medicine. Examples of her research in biotechnology and medicine include highly advanced detection of DNA sequences as well as telomerase and cytokine assays through nanostructure array-based platforms.

Fig. 1.

Examples of superparamagnetic iron oxide nanoparticles used in biodetection. (a) Transmission electron microscope images of iron oxide nanoparticles and (b) confocal microscope images of 50 nm iron oxide nanoparticles used in internalization into cells. Adapted with permission from [10], K. J. Landmark et al., Synthesis, characterization, and *in vitro* testing of superparamagnetic iron oxide nanoparticles targeted using folic acid-conjugated dendrimers. *ACS Nano* 2, 773 (2008). © 2008, American Chemical Society; from [12], J. Park et al., Ultra-large-scale syntheses of monodisperse nanocrystals. *Nat. Mater.* 3, 891 (2004). © 2004, Nature Publishing Group.

Fig. 2.

Fiber optic biosensors. (a) and (b) Cartoon showing light propagation through (a) a step-index single mode fiber with the typical core and overall diameter of 8–12 μm and 125 μm , respectively, and (b) a step-index multimode fiber with the typical core and overall diameter of 50–200 μm and 125–400 μm , respectively. (c) Schematic diagram of a fiber optic biosensor setup for hybridization assay. (d) Antibody-immobilized optical fiber nanobiosensor for the detection of cytochrome c in a single cell. Reprinted with permission from [63], S. Pilevar et al., Tapered optical fiber sensor using near-infrared fluorophores to assay hybridization. *Anal. Chem.* 70, 2031 (1998). © 1998, American Chemical Society; from [65], J. M. Song et al., Detection of cytochrome c in a single cell using an optical nanobiosensor. *Anal. Chem.* 76, 2591 (2004). © 2004, American Chemical Society; from [66], A. Leung et al., A review of fiber-optic biosensors. *Sens. Actuators, B: Chemical* 125, 688 (2007). © 2007, Elsevier.

Fig. 3.

Optical band gap and band diagram of as-grown versus Al-doped ZnO prepared by various methods. Reprinted with permission from [72], Y. Kim et al., Optical and electronic properties of post-annealed ZnO:Al thin films. *Appl. Phys. Lett.* 96, 171902 (2010). © 2010, American Institute of Physics.

Fig. 4. Crystal structures and energy band diagrams of (a) rutile SnO₂, (b) wurtzite ZnO, and (c) cubic C-type In₂O₃. Adapted with permission from [73], O. N. Mryasov and A. J. Freeman, Electronic band structure of indium tin oxide and criteria for transparent conducting behavior. *Phys. Rev. B* 64, 233111 (2001). © 2001, American Physical Society; from [74], K. C. Mishra et al., Electronic structure of antimony-doped tin oxide. *Phys. Rev. B* 51, 13972 (1995). © 1995, American Physical Society; from [75], W. Korner and C. Elsasser, First-principles density functional study of dopant elements at grain boundaries in ZnO. *Phys. Rev. B* 81, 085324 (2010). © 2010, American Physical Society.

(a) Silicon Nanowire:FET PSA Sensor **(b) ZnO: Electrochemical Glucose Sensor** **Fig. 5.**

Examples of semiconducting oxide-based biosensors exploiting the electrical properties of the materials. (a) SiNW FET sensors are used to detect prostate specific antigen (PSA) and (b) ZnO nanocomb materials are incorporated to the sensing electrode of an electrochemical cell designed to detect glucose. Reprinted with permission from [79], J. X. Wang et al., Zinc oxide nanocomb biosensor for glucose detection. *Appl. Phys. Lett.* 88, 233106 (2006). © 2006, American Institute of Physics; from [80], G. Zheng et al., Multiplexed electrical detection of cancer markers with nanowire sensor arrays. *Nat. Biotech.* 23, 1294 (2005). © 2005, Nature Publishing Group.

Fig. 6. QCM-D sensor used for the kinetic detection of mussel adhesive protein adsorbing on a methyl-terminated Au surface. Reprinted with permission from [84], F. Hook et al., Variations in coupled water, viscoelastic properties, and film thickness of a Mefp-1 protein film during adsorption and cross-linking: A quartz crystal microbalance with dissipation monitoring, ellipsometry, and surface plasmon resonance study. *Anal. Chem.* 73, 5796 (2001). © 2011, American Chemical Society.

Fig. 7.

An overview of a fiber optic DNA sensor array with a covalent coupling strategy to immobilize DNA. The inserted AFM image shows microspheres to which the distal tip of the fiber is placed for sensing. Charge coupled device (CCD) images for a small section of a fiber-optic array containing 25 different probe-functionalized microspheres are also displayed. A random selection of 12 images is obtained after hybridization to one labeled target. Adapted with permission from [117], J. A. Ferguson et al., High-density fiber-optic DNA random microsphere array. *Anal. Chem.* 72, 5618 (2000). © 2000, American Chemical Society.

Fig. 8. Examples of highly sensitive, one-dimensional biosensors. (A) Detection of a single influenza A virus via monitoring conductance and (B) real-time QCM and electrical sensing of model proteins. Adapted with permission from [166], R. J. Chen et al., Noncovalent functionalization of carbon nanotubes for highly specific electronic biosensors. *PNAS* 100, 4984 (2003). © 2003, National Academy of Sciences; from [167], F. Patolsky et al., Electrical detection of single viruses. *PNAS* 101, 14017 (2004). © 2004, National Academy of Sciences.

Fig. 9.

An overall scheme to fabricate an optical DNA array sensor. Reprinted with permission from [169], A. Sassolas et al., DNA biosensors and microarrays. *Chem. Rev.* 108, 109 (2008). © 2008, American Chemical Society.

Fig. 10.

In₂O₃ nanowire biosensor for the detection of LDL cholesterol. (a) Time domain measurement using the device after exposure to LDL, (b) current versus voltage, I - V , measurements before and after exposure to LDL in ethanol, (c) and (d) I - V curves before and after exposure to LDL in ethanol while sweeping the gate voltage, V_g . Reprinted with permission from [186], C. Li et al., Chemical gating of In₂O₃ nanowires by organic and biomolecules. *Appl. Phys. Lett.* 83, 4014 (2003). © 2003, American Institute of Physics.

Fig. 11.

Enhanced fluorescence detection carried out on various biological systems coupled to ZnO nanorod platforms. (A) Scanning electron microscopy (panel 1) and fluorescence (panels 2 through 5) images of biotinylated bovine serum albumin (*b*BSA) and fluorescein derivative-conjugated streptavidin (DTAF-strept) on ZnO nanorods. (B) Fluorescence obtained from 5 μm -period, square-array ZnO NR platforms after carrying out IL-18 assays in urine. Panels (1) $140 \times 140 \mu\text{m}$, (2) $60 \times 60 \mu\text{m}$, and (3) $30 \times 30 \mu\text{m}$ display fluorescence images obtained from a sandwich assay involving 20 fg/ml of IL-18 in urine. (4) Fluorescence signal obtained from performing IL-18 assays on ZnO NR platforms and (5) ELISA assay of urine containing the indicated amounts of IL-18 using a commercially available kit. Reprinted with permission from [191], A. Dorfman et al., Nanoscale ZnO-enhanced fluorescence detection of protein interactions. *Adv. Mater.* 18, 2685 (2006). © 2006, WILEY-VCH Verlag GmbH & Co. KGaA, Weinheim; from [193], V. Adalsteins-son et al., Ultrasensitive detection of cytokines enabled by nanoscale ZnO arrays. *Anal. Chem.* 80, 6594 (2008). © 2008, American Chemical Society.

Fig. 12.

Examples of 1D nanomaterials for subwavelength waveguides. (A) through (F) images of photoluminescence and guided nonresonant excitation light through a $275 \text{ nm} \times 520 \text{ nm} \times 425 \text{ }\mu\text{m}$ SnO_2 nanoribbon and (G) fluorescence and absorbance images of a fluorophore (Rhodamine 6G) with a $240 \text{ nm} \times 260 \text{ nm} \times 540 \text{ }\mu\text{m}$ SnO_2 ribbon cavity as well as the guided photoluminescence spectra of dry SnO_2 , Rhodamine 6G, and 1,5-pentanediol solvent. Reprinted with permission from [195], M. Law et al., Nanoribbon waveguides for subwavelength photonics integration. *Science* 305, 1269 (2004). © 2004, The American Association for the Advancement of Science; from [196], D. J. Sirbulu et al., Optical routing and sensing with nanowire assemblies. *PNAS* 102, 7800 (2005). © 2005, National Academy of Sciences.

Table I

Various properties of metal oxides used in biosensors.

Property	$\gamma\text{-Fe}_2\text{O}_3$	Fe_3O_4	CuO	Cu_2O
Crystal structure				
Crystal structure	Cubic	Inverse spinel	Monoclinic	Cubic
Lattice constant (Å)	$a = 8.35$	$a = 8.391$	$a = 4.684, b = 3.423, c = 5.129$	$a = 4.269$
Density (g/cm^3)	5.23	5.15	6.31	6
Net magnetic moment ($\mu_B/\text{formula unit}$)	2.5	4	–	–
Magnetization, M_s (A/m)	4.5×10^5	4.8×10^5	–	–
Curie temperature ($^\circ\text{C}$)	675	578	–	–
Melting temperature ($^\circ\text{C}$)	1565	1538	1201	1235
Hardness (Mohs scale)	5–6	5–6	3.5–4	3.5–4

Table II

Various properties of semiconducting oxides used in biosensors.

Property	SnO ₂	ZnO	In ₂ O ₃	Si
Abundance (amount of metal in ppm in the earth's crust)	40	132	0.1	2.58×10^5
Crystal structure	Tetragonal, rutiles	Hexagonal, wurtzite	Cubic, bixbyite	Cubic, diamond
Lattice parameters (nm)	a : 0.474, c : 0.319	a : 0.325, c : 0.5207	a : 1.012	a : 0.5431
Density (g/cm ³)	6.99	5.67	7.12	2.33
Bandgap at 300 K (eV)	3.6 (direct)	3.4 (direct)	2.7 (indirect) 3.75 (direct)	1.12 (indirect) 4.18 (direct)
Static dielectric constant	$\parallel c$: 9.6 $\perp c$: 13.5	$\parallel c$: 8.75 $\perp c$: 7.8	~9	11.9
Effective density of states in conduction band at 300 K (cm ⁻³)	3.7×10^{18}	3.7×10^{18}	4.1×10^{18}	4.9×10^{18}
Common extrinsic dopants	Sb, As, P, F, Cl	B, Al, Ga, In, Si, Ge, Sn, Y, Sc, Ti, Zr, Hf, F, Cl	Sn, Ti, Zr, F, Cl, Sb, Ge, Zn, Pb, Si	B, Al, Ga, In, P, As, Sb
Thermal expansion at 300 K 10 ⁻⁶ /K	$\parallel c$: 3.7 $\perp c$: 4.0	$\parallel c$: 2.92 $\perp c$: 4.75	6.7	2.59
Melting point (°C)	–	2240	2190	> 1600 (for SiO ₂)
Metal melting point (°C)	232	420	157	1415
Heat of formation (eV)	6.0	3.6	9.7	–

Source: Adapted with permission from [32], K. Ellmer, Resistivity of polycrystalline zinc oxide films: Current status and physical limit. *J. Phys. D: Appl. Phys.* 34, 3097 (2001). © 2011.