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Microelectronic Biosensors: Materials and Devices

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1. Introduction

The advent of novel materials for electronics, optoelectronics and nanoelectronics holds the promise for new microelectronic device designs and applications across all fields of science and technology. Furthermore, the increasing sophistication of fabrication processes and techniques used in the semiconductor industry has resulted in the ability to produce circuits of greater complexity at remarkably reduced costs, a trend which has been continuing over the past half-century. Application of progress made in the microelectronics industry to the biomedical and biotechnology fields is a research area rich in possibilities, given the rapid parallel growth in both microelectronics and biotechnology.

It is an unfortunate fact that new advances in biotechnology and biomedical engineering have historically tended to increase the costs of medicine and healthcare (Patel & Rushefsky, 2006). For example, a computed tomography (CT) scan is typically more expensive than traditional digital or "plain film" x-ray imaging, and a magnetic resonance (MR) scan is typically more expensive than a CT scan. Incorporation of the principles and techniques used in the microelectronics field has the potential for reversing this trend. Based on a batch-fabrication approach, mature processing techniques used in the semiconductor industry have the potential for dramatically reducing the cost of manufacture for diagnostic devices used for the detection, treatment and management of disease.

It is thus of critical importance to develop a knowledge base which spans the interdisciplinary boundary between microelectronics and biotechnology. In this chapter we will review the materials and devices which can serve to bridge the interdisciplinary boundary between microelectronics and biomedicine, and we will discuss some of the resulting novel biosensor designs which have been proposed for biomedical applications. The material will focus on so-called *in vitro* biosensors which are used to detect or sense the presence of specific biomolecule—such as proteins, peptides, nucleic acids (DNA or RNA), oligonucleotides, or peptide nucleic acids (PNAs)—in an analyte sample. We will not consider *in vivo* techniques which seek to diagnose disease within the body, typically using imaging modalities. Successful development of low-cost biosensors can facilitate screening programs for early diagnosis and treatment of disease, reducing the resulting morbidity and mortality and lowering the overall cost of healthcare.

2. Materials

This section provides a brief summary of various materials and material systems which have received significant attention for their potential for biological application, in specific, for sensing applications in molecular diagnostics. The list is by no means exhaustive, but is intended to focus on a relevant subset of materials of interest. Table 1 summarizes a number of advantages and disadvantages of the major material systems to be discussed in the sections below.

Material system	Advantages	Disadvantages
Silicon	Low cost Mature processing techniques	Limits in operating frequency range
Compound semiconductors	High carrier mobility, high frequency operation Suitability for optoelectronics Capability for bandgap engineering and epitaxially-grown layers	Cost
Organic semiconductors	Ease of application (inkjet, spin casting) Suitability for flexible substrates Suitability for optoelectronics	Low carrier mobility Not amenable to standard process flows
Nanomaterials	Novel physicochemical and electronic properties	Not amenable to standard process flows Unproven safety profile

Table 1. Advantages and disadvantages associated with various relevant material systems.

2.1 Silicon

As a member of column IV of the periodic table of the elements, silicon manifests a unique set of properties which has resulted in profound technological advances over the last half-century. Silicon exhibits a crystal structure in which each silicon atom bonds covalently with four neighboring atoms in a tetrahedral arrangement, forming a so-called diamond lattice (Sze & Ng, 2006). At a temperature of absolute zero, all outer shell electrons are confined to covalent bonds, leaving no free electrons for conduction. As temperatures rise above absolute zero, thermal energy can result in the liberation of electrons available for conduction. Thus, silicon behaves neither as a perfect insulator nor a perfect conductor, but instead a 'semiconductor' whose electrical properties can be readily altered through the addition of a very small number of impurity atoms ('doping'). Doping of selected regions of a silicon substrate allows for the spatial definition of electronically-active devices which can then be interconnected to perform complex circuit functions.

Crystalline silicon also possesses properties which allow for the coupling of mechanical and electrical effects, as effectively illustrated by the development of devices for MicroElectroMechanical Systems (MEMS). An early example is given by silicon pressure sensors, in which a thin diaphragm etched into silicon is used to transduce applied mechanical stresses into resistance (and voltage) variations (Kim & Wise, 1983). Likewise, the resonance frequency of appropriately-designed thin silicon cantilever structures is sensitive to small changes in mass loading; this effect has been used in the detection of biomolecular binding events, discussed later in this chapter.

2.2 Compound semiconductors

Elements from column III and column V of the periodic table can be combined in a 1:1 stoichiometric ratio and used to form crystalline materials. Substrates from these III-V materials also exhibit semiconducting properties in a manner similar to the column IV semiconductors such as silicon and germanium (Williams, 1990). Numerous semiconductor materials are based on III-V compounds, most notably gallium arsenide (GaAs) and, more recently, gallium nitride (GaN). Compound semiconductor materials tend to be more expensive than their silicon counterparts, primarily due to the difficulties associated with the growth of high-purity crystals for large-diameter (150mm and higher) wafer substrates. Notwithstanding, these materials have the advantage of higher electron mobility and suitability for use at high frequencies. These materials also exhibit higher resistivity than silicon, allowing for their use in applications which demand very low leakage currents and high sensitivities; for this reason, some III-V materials have been termed “semi-insulators.” In addition, III-V materials have unique optoelectronic properties which render them useful for photonic (and biophotonic) applications, such as fluorescence detection. The fact that III-V materials can be grown, layer-by-layer, into complex epitaxial structures has allowed for the development of novel “bandgap-engineered” devices such as high-electron-mobility transistors (HEMTs), heterojunction bipolar transistors (HBTs) and complex optoelectronic devices such as quantum well lasers (Golio, 1991). Although these materials have traditionally been used less frequently in biosensing applications, their high-frequency and optoelectronic capabilities make them good candidates for future innovations in microwave and optoelectronic device applications in biosensing.

2.3 Organic semiconductors

Intense research activity in semiconducting materials has recently focused on so-called organic semiconductors, typically based on carbon-containing compounds and polymers. The electron distribution in organic molecules composed of π-conjugated systems (i.e., carbon-containing molecules composed of repeating double-bond/single-bond units) is delocalized, allowing for relative ease of electron (current) flow in these materials. In addition, proper selection of the conjugation length allows for interesting optoelectronic activity, hence these materials have found great use as organic light-emitting diodes (OLEDs) and as photovoltaic materials (Shinar, 2003; Brabec et al., 2008). Figure 1 illustrates a monomer of one such material used in organic semiconducting applications, 2-methoxy-5-(3′,7′-dimethyloctyloxy)-1,4-phenylenevinylene, or MDMO-PPV (Sigma-Aldrich Corp, Milwaukee, WI, U.S.A.); the conjugated nature of the molecule is evident.

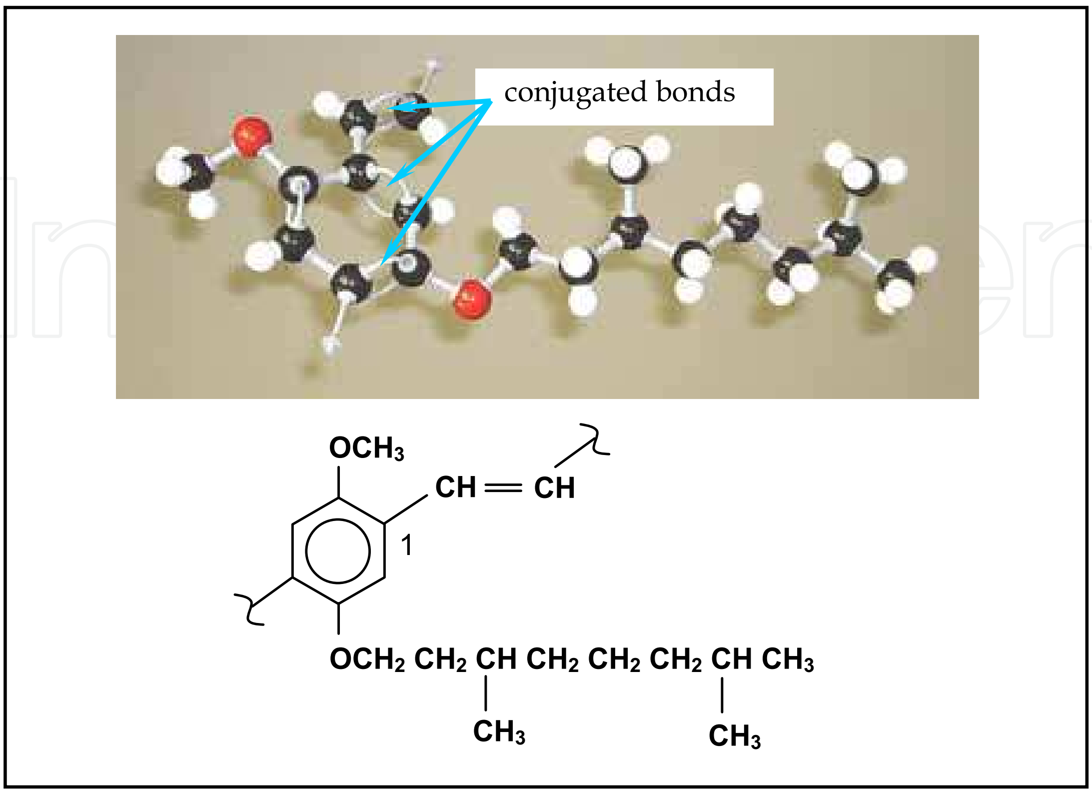

Fig. 1. The organic semiconducting monomer MDMO-PPV.

The design and fabrication of devices based on organic semiconductors varies significantly from traditional solid-state devices based on silicon or compound semiconductors, at once both an advantage and a disadvantage. Organic semiconducting materials may be deposited onto rigid or flexible substrates using low-cost inkjet printing or spin-casting techniques, but these materials are relatively less amenable to traditional photolithographic techniques for patterning and device definition. Although this may be advantageous for simple devices, it can complicate the processing for more complex devices or integrated circuits.

2.4 Nanomaterials

The term 'nanomaterials' has been applied to materials that incorporate structures having dimensions in the range 1-100 nm, and whose electrical and/or chemical properties are also influenced by their small dimensional scale. These materials have a wide variety of morphologies, including nanotubes, nanowires, nanoparticles (also termed quantum dots), and sheet-like two-dimensional structures (Vollath, 2008). The unique optical, electrical, mechanical and chemical properties of nanomaterials have attracted considerable interest—these properties are influenced by quantum mechanical effects, and may vary from those of the individual constituent atoms or molecules, as well as those of the corresponding bulk material. As the prototypical example, carbon nanotubes have been the subject of great research focus, given their great strength, high thermal and electrical conductivity, and chemical stability. The number of new nanomaterial systems is growing rapidly, from carbon-based structures (nanotubes and fullerines) to those based on compound semiconductors (CdSe, CdTe quantum dots and ZnO nanowires) and metallic nanoparticles such as colloidal gold.

Material systems based on combinations of nanomaterials (so-called hybrid nanomaterials) have also received a great deal of attention in the research community based on the proposed synergistic effects of nanomaterials of different compositions and morphologies in close proximity. Hybrid nanomaterial systems may exhibit great sensitivity to variations in the local electrochemical milieu, and this has led to the design of novel sensing devices for biological and chemical applications.

The quantum effects associated with the small dimensional scale of nanostructures result in unique physicochemical properties which may be used to advantage in biosensing systems. Quantum dot nanoparticles, for example, produce a fluorescence emission which can be tuned by adjusting the particle diameter during synthesis (Rogach, 2008). The Stokes shift—the difference between the fluorescence emission wavelength and the excitation wavelength—can be much larger than for the organic fluorophores which have traditionally been widely used in fluorescence labeling, imaging and biomolecular sensing.

2.5 Photonic and optoelectronic materials

In addition to their useful electronic properties, many of the semiconducting materials and nanomaterial structures mentioned in the previous sections also have interesting optoelectronic properties which can be exploited in biophotonic applications. Light-emitting semiconductor diodes and diode lasers based on III-V compound semiconductors are ubiquitous (Chuang, 1995), although research continues into optoelectronic devices based on other compound semiconducting materials (e.g., II-VI materials such as ZnSe) and silicon-based optoelectronic devices. Likewise, a large percentage of the commercial organic semiconductor market is devoted to organic light-emitting diodes (OLEDs). Finally, as mentioned in the previous section, quantum dot nanomaterials fabricated from cadmium- and indium-based compounds also have interesting optical fluorescence properties which have been proposed for biophotonic applications.

The use of optoelectronic materials in biomedicine represents a very large and significant research field. Research and development in biophotonics is such a large and important area that it would require a chapter specifically devoted to the topic. Accordingly, the discussion of biophotonic devices in the remainder of this chapter will be limited, with primary focus on devices which are microelectronic, rather than optoelectronic, in nature.

3. Biosensor technologies

In the most common biosensor implementation, a probe molecule is affixed to a sensing platform and used to recognize or detect a target molecule which is complementary to the probe—it is this feature of biosensors which provides high specificity and a low false-positive rate in qualitative sensing applications (Prasad, 2003). As an example, a protein antibody may serve as the probe, used to detect a specific protein antigen, or a single stranded oligonucleotide may be used as a biorecognition probe for the complementary segment of single-stranded DNA. There are numerous candidates for biorecognition probes, including antigen and antibody molecules, protein lectins (which bind to specific carbohydrate or glycoprotein molecules), protein receptor molecules (which bind to a specific ligand), and nucleic acid (oligonucleotide) probes.

Various physicochemical properties of sensing structures have been used to detect the presence of a target molecule in analyte solution. Binding of a target with an immobilized probe molecule may result in changes which can be detected using electromagnetic energy across the spectrum—from low frequencies used in impedimetric sensors to very high frequencies involved in the detection of radiolabeled target molecules. As another example, changes in optical properties at the sensor surface may be used in various detection schemes—for example, a fluorescence emission or a change in optical reflectance at a sensor surface may be used to indicate the presence of a target molecule (Liedberg et al., 1995).

Other parameters, such as the acoustic properties of surface-acoustic wave devices or the mass of a resonant structure may be altered by probe-target binding, and these parameters may also serve to transduce a binding event into a detectable signal. This signal can then be further processed to provide a qualitative or quantitative metric of the presence of the target biomolecule. In the following sections, specific biosensor implementations are discussed, based on the material systems discussed in Section 2.

3.1 Quartz crystal (piezoelectric) microbalances

The piezoelectric properties of various materials have been exploited in electronic circuits and systems for decades. Perhaps the largest and best-known application of piezoelectric devices is their use in precision timing and frequency reference applications, from wristwatches to computer clock-generation circuits. The resonant frequency of a crystal piezoelectric resonator will vary inversely with mass, a fact which is routinely used to advantage in crystal thickness monitors used to indicate thicknesses in vacuum thin-film deposition systems. Figure 2 illustrates a small circular quartz disc with metalized gold electrodes deposited on opposite faces. The piezoelectric properties of the quartz material confer a resonance behavior which can be modeled by the equivalent circuit shown; embedding this crystal in an oscillator circuit allows variations in mass to be transduced into a change in oscillator frequency.

When used to sense very small changes in mass based on variations in resonance frequency, quartz crystal resonators have been termed 'quartz crystal microbalances,' and these devices have been used in the detection of biological molecules to complete unicellular organisms (Zeng et al., 2006). In practice, the piezoelectric disc would be coated with a probe biomolecule which is immobilized onto the surface, and the disc (placed in a suitable electrical mount) would be located in an analyte flow cell. Applications of these devices as molecular biosensors range across all specialties of medicine, including infectious disease, oncology, rheumatology, neurology and others.

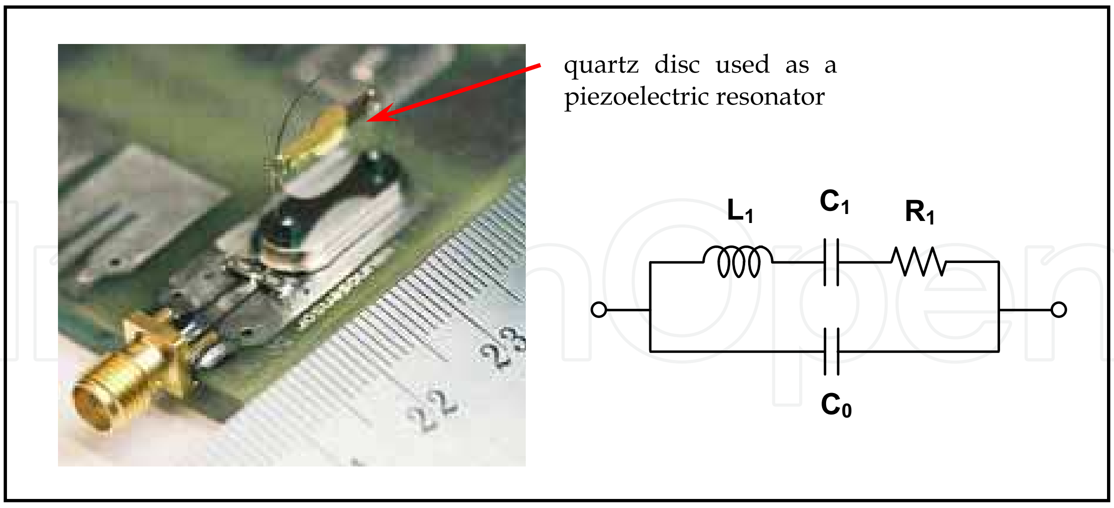

Fig. 2. A quartz disc with gold electrodes in a circuit mount. This device exhibits electrical resonance behaviour, modelled by the equivalent circuit shown. (Scale for size reference; small divisions represent 1mm.)

Applications of quartz crystal microbalances and related piezoelectric devices for biosensing are wide-ranging, and include the detection of *Mycobacterium tuberculosis* (He & Zhang, 2002), *Francisella tularensis* (Pohanka et al., 2007), *Escherichia coli* (Sung et al., 2006), as well as such tumor biomarkers as carcinoembryonic antigen (Shen et al., 2005) and alpha-fetoprotein (Ding et al., 2007).

3.2 Solid state biosensors

Most complex biomolecules (such as proteins and nucleic acids) have internal distributions of positive and negative charge; indeed, these charge distributions may determine the three-dimensional structure of the molecule. The distribution of this charge may influence current flow in solid state devices such as field-effect transistors, serving as a mechanism for direct transduction of binding events into an electrical signal. So-called ion-sensitive field effect transistors (ISFETs) have been designed and implemented based on this phenomenon. A typical ISFET device incorporates conductive (n-type) drain and source islands, and the flow of electrons between the drain and source is modulated by binding events between target and probe biomolecule. An external counterelectrode is used to establish a reference gating potential which biases the transistor device (Offenhäusser & Rinaldi, 2009).

Figure 3 illustrates the cross-sectional structure of an ISFET device; a protein antibody immobilized onto the surface region between the drain and source serves as the biorecognition molecule. An analyte solution which may contain target antigen is presented to the device via a microfluidic flow cell. Binding of the target antigen with immobilized antibody (shown for two of the molecules in Figure 3) modulates current flow from drain to source in a suitably-biased ISFET device.

ISFET sensors fabricated on silicon have been used to implement these types of biosensing devices, and arrays of ISFET sensors can be fabricated using standard silicon processing techniques. A major advantage of designing ISFET sensors in arrays is the ability to perform sensing of multiple different target biomolecules, using appropriately-immobilized probes. So-called multiplexed arrays are useful for rapid diagnosis involving multiple biomarkers, with applications in infectious disease diagnosis, genetic screening, and assays for drug development.

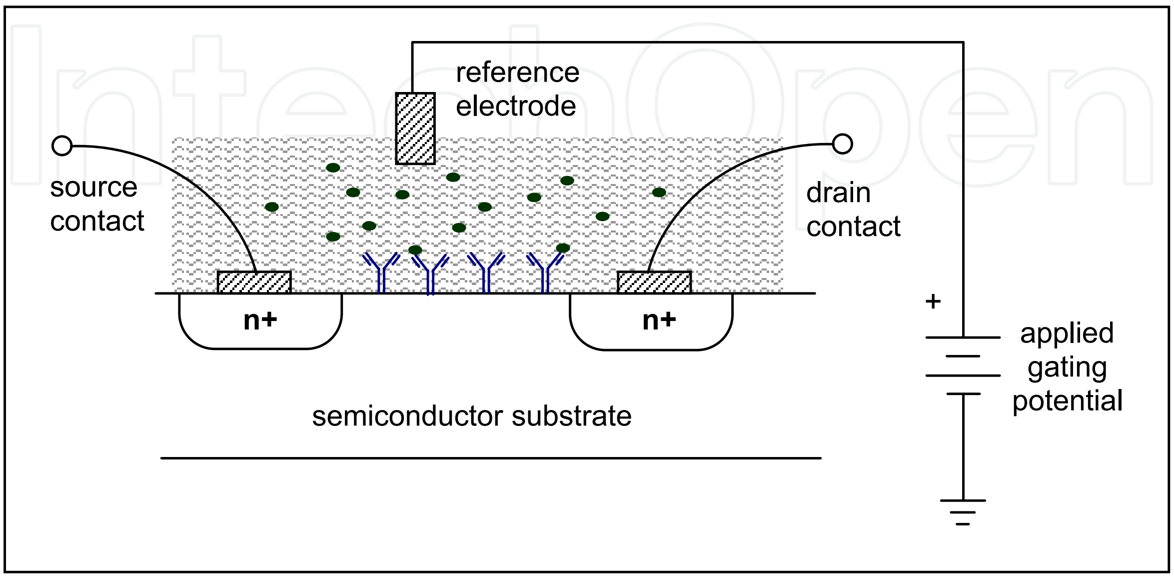

Fig. 3. A schematic illustration of the cross-section of the ISFET device. An immobilized biomolecule in the gate region between drain and source is used to recognize target molecules.

Arrays of solid-state field-effect devices have been fabricated using the same standard transistor fabrication techniques used to make complementary metal-oxide-semiconductor (CMOS) integrated circuits, and used for multiplexed DNA biosensing applications (Levine et al., 2009) as well as for biochemical detection (Chang et al., 2008).

Solid-state devices based on compound semiconductors are also receiving notable attention. ISFET devices have been made using a III-V (AlGaN/GaN) system and are being proposed for biosensing applications (Steinhoff et al., 2003). Solid-state diode and transistor structures have been fabricated on GaN and proposed for use as chemical and biological sensors (Pearton et al., 2004). Other investigations include the study of functionalization of GaAs surfaces with self-assembled monolayers of organic molecules (Voznyy & Dubowski, 2008).

3.3 MEMS devices

As discussed in Section 2.1, semiconductor devices having unique three-dimensional structures may be fabricated using standard processing techniques developed for the semiconductor and integrated circuit industry. MicroElectroMechanical Systems (MEMS) may be fabricated with structures having interesting electronic and mechanical properties; one such standard structure is a simple microcantilever which can be etched into silicon. Like piezoelectric sensors, such cantilevers have a resonance frequency which is mass-dependent; accordingly, they can also be used as sensitive detectors of biomolecular binding events. Figure 4 schematically illustrates a MEMS cantilever to which an antibody biorecognition element is attached. Binding of the corresponding antigen results in a mass change which can be detected as a change in frequency of a resonant circuit fabricated as part of the cantilever structure (Marie et al., 2002).

Other applications of MEMS devices as biosensors are based on other physicochemical properties of MEMS structures. These include thermally-sensitive MEMS devices for metabolic monitoring (Wang et al., 2008), MEMS devices for diagnosis of neoplastic disease (Ortiz et al., 2008), and a high-sensitivity acoustic-wave biosensor fabricated using MEMS technology (Valentine et al., 2007).

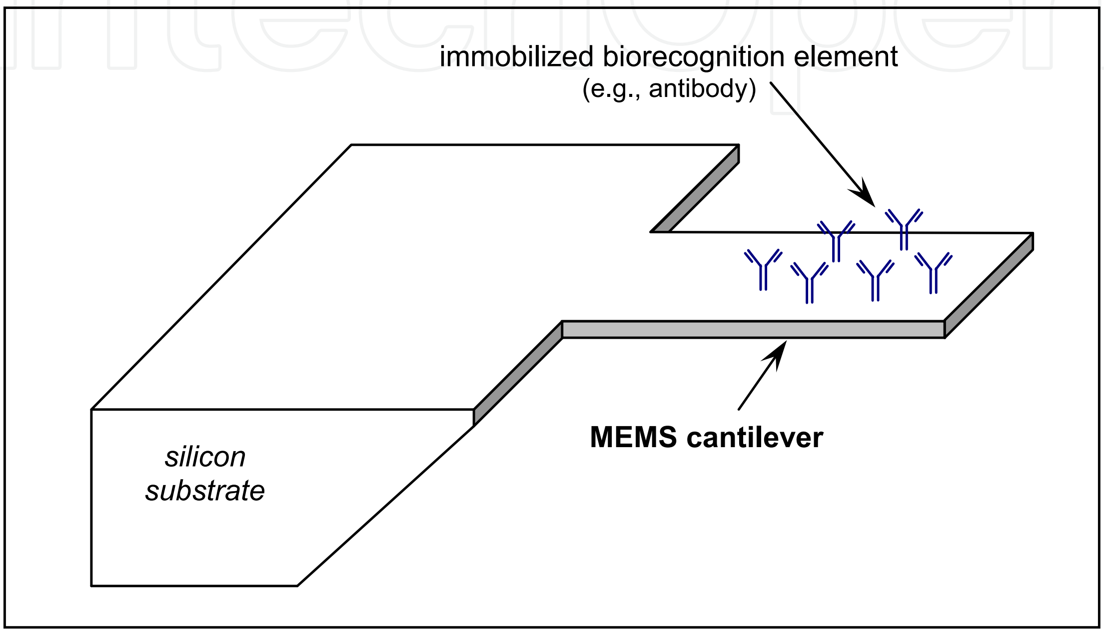

Fig. 4. A MEMS cantilever biosensor, based on mass changes which occur during binding.

3.4 Nanomaterial-based sensors

A wide variety of biosensing devices that are based on nanomaterials have been investigated, ranging from amperometric devices for quantification of glucose, to quantum dots as fluorescent probes. Colloidal gold nanoparticles have been used for several decades and can be readily conjugated to antibodies for use in immunolabeling and immunosensing; in addition, these nanoparticles also find application as a contrast agent for electron microscopy. Gold nanoparticles have also been used as probes for optoelectronic detection of nucleic acid sequences (Martins et al., 2007). Magnetic nanoparticles (based, for example, on iron) may also be used in immunolabeling applications as well as for cell separation under the influence of a magnetic field. Like gold nanoparticles, iron-based nanoparticles may also be used an a imaging contrast agent—specifically, for magnetic resonance imaging.

For biochemical sensing, zinc oxide nanostructures have been proposed for use as a cholesterol biosensor (Umar et al., 2009) and carbon nanotubes have been investigated as biosensors for glucose (Chen et al., 2008) and insulin quantification (Qu et al., 2006). In addition, hybrid nanomaterial systems consisting of two or more types of nanostructures are also receiving considerable attention for sensing (Figure 5).

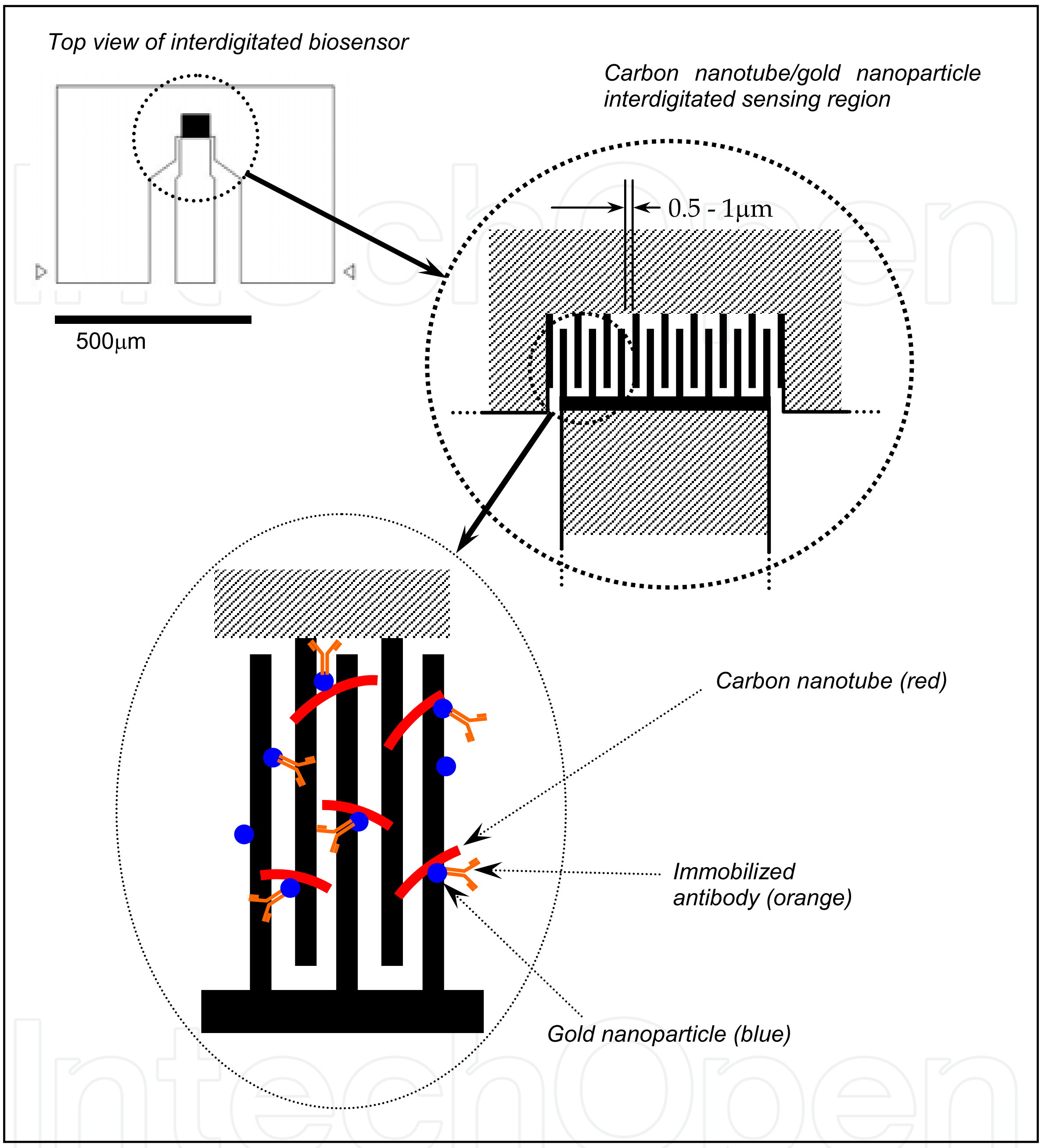

Fig. 5. A proposed carbon nanotube/gold-labeled antibody biosensor.

In this implementation, carbon nanotubes are coupled with gold nanoparticles attached to antibodies which serve as biorecognition molecules. The schematic illustration in Figure 5 (not drawn to scale) indicates this impedimetric biosensing approach, in which an interdigitated electrode is used to make electrical contact to the nanomaterial system consisting of carbon nanotubes with attached gold-conjugated antibody. Other hybrid systems employing carbon nanotubes and platimum nanowire structures, for example, have been investigated for glucose quantification (Qu et al., 2007) as well as for immunosensing.

In other "hybrid-material-system" approaches, nanomaterials have also been investigated for their ability to enhance sensitivity in a material system which includes an organic semiconductor component. In addition, systems which incorporate carbon nanostructures into MEMS systems ("C-MEMS devices") have also been proposed for arrays for detection of DNA (Wang & Madou, 2005).

3.5 Organic semiconductor-based sensors

Organic semiconductors find their greatest application in photonics, as a result of extensive development of organic light-emitting diodes (OLEDs) and photovoltaic devices. There has been relatively little investigation into the potential use of organic semiconductors as biosensing devices. This, despite the fact that it has been suggested (Cooreman et al., 2005) that the organic nature of conjugated polymer semiconductors may provide an ideal platform for the development of sensors suitable for biomolecular detection. Impedimetric biosensors based on organic semiconducting polymers have been investigated, including sensors which incorporate a hybrid organic semiconductor/gold nanoparticle sensing platform, shown in Figure 6 (Omari et al., 2007).

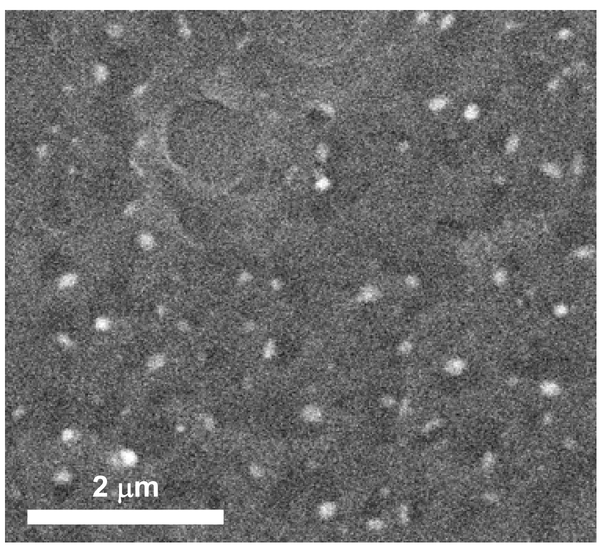

Fig. 6. Illustration of a hybrid material system consisting of gold nanoparticles applied to an organic semiconducting polymer layer, viewed by scanning electron microscopy.

This organic semiconductor/gold nanoparticle sensing platform has also been investigated as a platform for immunoassays (Li et al., 2008). The development of biosensors based on this material system is facilitated by the fact that the conjugation of gold nanoparticles to antibodies is a mature technology, with a large variety of gold-labeled antibodies commercially available.

4. Conclusion

Numerous material systems exist which can support the design and development of novel biosensing approaches for *in vitro* biomolecular diagnostic applications, ranging from traditional materials such as silicon and GaAs to novel materials such as conjugated organic polymer semiconductors. In addition, newly discovered nanomaterials offer the potential for increased sensitivity and lower cost, and the hope of reversing an unfortunate historic trend towards increased costs associated with new, more sophisticated advances in healthcare technology. Although microelectronic biosensors have great potential for facilitating the development of inexpensive devices for molecular diagnostics, this research requires a knowledge of materials science, electrical engineering, semiconductor device design and fabrication, chemistry and biochemistry, nanotechnology, biology and medicine. Developing an intellectual base which will aid this research requires an interdisciplinary teamwork approach. The fertile boundary at the intersection of these disparate fields of knowledge holds the potential for novel, interesting and useful developments in biomicroelectronics.

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Biomedical Engineering can be seen as a mix of Medicine, Engineering and Science. In fact, this is a natural connection, as the most complicated engineering masterpiece is the human body. And it is exactly to help our “body machine” that Biomedical Engineering has its niche. This book brings the state-of-the-art of some of the most important current research related to Biomedical Engineering. I am very honored to be editing such a valuable book, which has contributions of a selected group of researchers describing the best of their work. Through its 36 chapters, the reader will have access to works related to ECG, image processing, sensors, artificial intelligence, and several other exciting fields.