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Review

Smart sensors/actuators for biomedical applications: Review

J. Ponmozhi [a,*], Clara Frias [a,b,*], Torres Marques [b], O. Frazão [c]

[a] Instituto de Engenharia Mecânica e Gestão Industrial (INEGI), Universidade do Porto, Rua Dr. Roberto Frias, 4200-465 Porto, Portugal
[b] Faculdade de Engenharia da Universidade do Porto (FEUP), Universidade do Porto, Rua Dr. Roberto Frias, 4200-465 Porto, Portugal
[c] INESC Porto, Unidade de Optoelectrónica e Sistemas Electrónicos, Rua do Campo Alegre, 687, 4169-007 Porto, Portugal

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ABSTRACT

This paper reflects on review of smart sensor activities for biomedical applications. The rise of biotechnology has provided innovative development of new therapies and detection methods for life threatening diseases. As a worldwide research focus, there is especially a strong interest in the use of microsystems in health care, particularly as smart implantable devices. Recent years have seen an increasing activity of hip and knee replacement and other type of implants, which are some of the most frequently performed surgical procedures in the world. Loosening of hip prosthesis is the dominant issue for many patients who undergo a hip arthroplasty. Artificial joints are subject to chronic infections associated with bacterial biofilms, which only can be eradicated by the traumatic removal of the implant followed by sustained intravenous antibiotic therapy. This review focuses on the clinical experience using all kinds of smart implants like orthopedic implants instrumented with strain gauges, retina implant system using image sensors. Technical design improvements will enhance function, quality of life, and longevity of total knee arthroplasty and all other kind of implants. Application of biocompatible nanomaterials in implantable biosensors for continuous monitoring of metabolites is an area of sustained scientific and technological interests.

Contents

* Corresponding authors. Address: Instituto de Engenharia Mecânica e Gestão Industrial (INEGI), Universidade do Porto, Rua Dr. Roberto Frias, 4200-465 Porto, Portugal (J. Ponmozhi, C. Frias).

E-mail addresses: jponmozhi@inegi.up.pt, jponmozhi@gmail.com (J. Ponmozhi), cfrias@inegi.up.pt (C. Frias), marques@fe.up.pt (T. Marques), ofrazao@inescporto.pt (O. Frazão).

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1. Introduction

A biosensor is defined as a specific type of chemical sensor comprising a biological recognition element and a physic-chemical transducer. Work in biosensors and actuators are usually based around the bio-Micro Electro Mechanical Systems (MEMS) concept. So MEMS is reviewed when it is integrated in the implants, for the development of novel, microtechnology assisted modalities for the delivery of pharmaceuticals, in the case of identifying and treating metastatic solid tumors, controlling glucose levels, release of therapeutic agents in response to biomolecular or physical trigger is on the go for minimizing the intervention of healthcare professionals and hospital stay. Thus a multidisciplinary biomedical-engineering approach to develop a self-diagnosing, self-treating, self-monitoring smart implant is needed to combat the devastating problem of post-implantation bacterial biofilm infections that form on the artificial joint prostheses. Actually, there does not exist in the market, the medical devices which are capable of delivering in-loco the right drugs to reduce or eradicate the colonies of bacteria that form in the orthopedic implant surface and most of the time result in aseptic loosening. The solution to this problem lies in the advancement of biotechnology with base in the nanotechnology.

In this review work, we are discussing about the possibility to develop a flow biosensor with the biosensor technologies based on the properties of the carbon nanotubes (CNTs) and at the end approach will be made as how to apply this development and knowledge to standard orthopedic implants.

2. Biosensors

2.1. Surface plasmon resonance (SPR) biosensor

A surface plasmon wave (SPW) is a collective oscillation of free electrons propagating at the interface of a metal layer and a dielectric layer. When the wave vectors for the incident photon and plasmon are equal in magnitude and direction at the same frequency, the energy of an incident photon is transferred to an electron and it is called surface plasmon resonance (SPR). The SPR biosensor will become an indispensable tool in drug discovery for the reason that it measures the quantity of a complex formed between two molecules in real-time and without the need for fluorescent or radioisotopic labels and lack of labeling leads to characterization of unmodified biopharmaceuticals, studying the interaction of drug candidates with macromolecular targets and identifying binding partners during ligand fishing experiments [77]. The most popular commercial instruments for SPR biosensing are those with trademark BIACORE®, [89,90], the SPR-based sensors have been intensively developed. Like BIACORE® AB [8] in Sweden and some companies have been successful in commercializing SPR-based biosensor systems.

To illustrate a typical SPR biosensor assay, the format used to characterize an antibody–antigen interaction is presented in the context of the BIACORE® system. The antibody is covalently immobilized on the biosensor surface and is referred to as the ligand (see Fig. 1). SPR detectors monitor the change in the refractive index of the solvent layer near the surface induced by association and dissociation of the analyte–ligand complex formation. Fägerstam et al. [34], has given the detailed description of how does SPR biosensor work.

The most widely used configurations of SPR sensors (a) prism coupler based SPR system (attenuated total reflection method – ATR), (b) grating coupler based SPR system, (c) optical waveguide based SPR system. The momentum of the incident optical wave has to be enhanced to match that of the SPW. This momentum change is commonly achieved using ATR in prism couplers, optical waveguides and diffraction at the surface of diffraction gratings (see Fig. 2).

The commonly used detection approaches in SPR sensors are measurement of the resonant momentum of the optical wave including angular and wavelength interrogation of SPR and also the measurement of intensity of the optical wave near the resonance. Nylander et al. [79], have done a theoretical and experimental investigation of the possibilities of using SPR for gas detection, which was sensitive to variations in the optical properties of the film upon gas exposure down to the ppm range. Application of an intermediate layer with high permittivity can be useful in suppressing background responses [59]. Yeatman [127], has been concerned with the interrogation of planar surfaces by surface plasmons, and in analysing the attainable sensitivity and lateral resolution for such measurements and the relationship between them, had compared with the more general technique of optical guided wave sensing. Homola [46], found that to attain higher sensitivity of a spectral SPR sensor, it should be designed to operate at longer wavelengths and to use a surface plasmon active metal layer with a higher modulus of the real part of the dielectric constant. The noise in SPR-sensing devices has been systematically studied including an analysis of the influence of temperature, the light source, and photodetector noise on SPR sensor resolution [58].

Compared with many other interaction technologies, SPR biosensors exhibit several distinct advantages for characterizing molecular interactions [88]. Prism-based SPR sensors using angular interrogation have been extensively

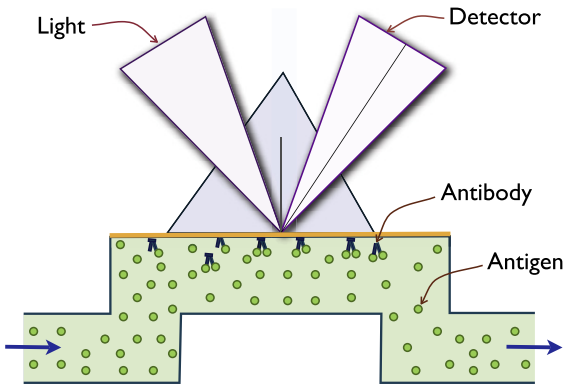

Fig. 1. Typical biosensor assay. (the antigen referred to as the analyte passes over the surface through a microfluidic flow cell.)

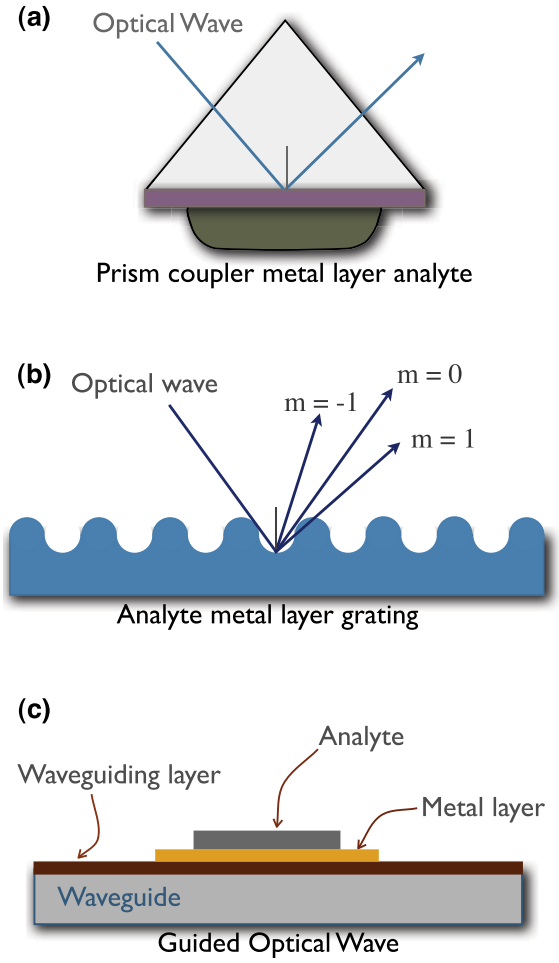

Fig. 2. Typical configurations of SPR sensors.

studied as angular shifts calculated as a function of the amount of organic material in the matrix [64]. A compact and reliable SPR sensor is described by Manuel et al. [68] which used the ATR method in a special design sensing element. Table 1 describes the typical SPR sensing technology developed over years.

A rigorous coupled-wave analysis for metallic surface-relief allows an arbitrary complex permittivity to be used for the material and thus avoids the infinite conductivity (a perfect conductor) approximation [37], [18]. Therefore modeling of the response of grating-based SPR sensor structures and analysis of sensor data is more difficult [52]. The prototype gas sensor measures maximum resonance on a background of weak signal, senses remotely the condensation of ≈0.9 nm of isopropyl alcohol onto a silver-coated grating surface with a sensitivity of 1000 nm RIU^{-1} in wavelength interrogation mode and 100 deg RIU^{-1} in angular interrogation mode [32]. Gold based SPR grating sensors have been used for monitoring biomolecular interactions in aqueous environments with estimated refractive index sensitivity of 30 deg RIU^{-1} and 900% RIU^{-1} in the angular interrogation and intensity measurement modes, respectively [31].

Table 1
SPR sensors with limit of detection (LOD).

Type of SPR Sensor	Principle	Analyte	Limit of detection (LOD)	Referenced by
Integrated optical ways guide sensors	Optical principles underlying chemo-optical wave guiding sensors	Methylene iodide	Using electro optic effect refractive indices can be changed by about 0.1% and by using thermo-optic effects about a 1% change is feasible	Paul [84]
Optical fiber	–	Analyte with a resonant wavelength resolution of 0.5 nm	5×10^{-5} (RIU)	Jorgenson and Yee [51]
Fiber optic SPR sensor	Planar waveguide approach and the transfer matrix method (Theoretical Analysis)	Any sensed medium	2×10^{-5} (RIU)	Homola and Slavik [44]
Spectral SPR sensor	Theoretical Analysis	Any bulk medium	–	Homola and Yee [45]
SPR probe sensing	Retro-reflection method	Sucrose and water sample	3.36×10^{-5} (RIU)	Cahill et al. [15]
Optical chemical sensor	Light-excited surface plasmon measurement	Ethanol concentration in water	10^{-4} (RIU)	Matsubara et al. [70]
SPR multisensing on immunosystems	Immunologic specificity for all antibody-antigen combinations	Multianalyte (Human chorionic gonadotrophin (hCG), luteinizing hormone (LH))	Refractive index bSA, 1.45^{13} (RIU)	Berger et al. [6]
Dual colour optical fiber	Differential reflectance method	Ethanol	5.2×10^{-4} (RIU)	Suzuki et al. [105]

Note: Refractive index unit (RIU).

Optical fiber SPR probes present the highest level of miniaturization of SPR devices, allowing for chemical and biological sensing in inaccessible locations make the use of optical fibers very attractive. The use of optical fibers for SPR sensing was first proposed by [51]. A sensing device based on the monitoring of immunobinding reactions using WaveSPR was developed by Mouvet et al. [75] for the determination of simazine in water samples. Likewise the following authors have developed SPR sensors based on integrated optical waveguides [123,63]. A highly sensitive SPW sensor was designed by [103] for detecting changes of the order of 10^{-5} in the refractive index of a layer adsorbed on the surface and showed that the inclusion of a dielectric layer of high refractive index between the metal and the buffer layer allows spectral tuning of the SPR to any convenient wavelength. A theoretical model was developed for measuring atmospheric humidity by [121] using nafion fluorpolymer as a transducing layer on SPW. A compact, simple optical fiber SPW chemical sensor was designed by [111] that showed good sensitivity to refractive index of 5×10^{-4} being detectable. Reduction of the sensing area in SPR sensor based single mode optical fiber has been proposed by [44]. The Major areas of applications of SPR sensors are for the measurement of physical quantities, chemical sensing and biosensing. The Swedish BIACORE® AB systematically developed the SPR biosensor technology and commercialized it in 1990. Many other firms like Texas Instruments (USA), Quantech (USA), BioTul Bio Instruments (Germany), Xantech Analysensysteme GbR (Germany) followed Biacore. SPR biosensors are exemplified by the novel technologies like optoelectronics, integrated optic, fast replication technology, microfluidics and nanofabrication technology. In the future there will be nanostructured surfaces and materials for SPR biosensors and new modeling will lead to more sensitive sensors.

2.2. Smart implantable biosensor

A major obstacle to the widespread application of implantable biosensors is that they progressively lose function with time. Problems with biocompatibility have proved to be the barriers to the development of reliable implantable devices. Most glucose biosensors lack the biocompatibility necessary for a prolonged and reliable operation in whole blood [117], that led to the development of subcutaneously implantable needle-type electrodes [9]. Success in this direction has reached the level of short-term implantation. Miniaturized, implantable biosensors form an important class of biosensors in view of their ability to provide metabolite(s) level(s) continuously without the need for patient intervention and regardless of the patient's physiological state (rest, sleep, exercise, etc.) [114].

Cygnus Inc. has developed an attractive wearable glucose monitor, based on the coupling of reverse iontophoretic collection of glucose and biosensor functions, the biosensor is capable of measuring electroosmotically extracted glucose with clinically acceptable level of accuracy [109]. The Glucowatch biographer is a wearable device containing both iontophoretic and biosensor functions which provides up to three glucose readings per hour for up to 12 h. The electronic control module has been miniaturized using a custom ASIC chip with a separate microprocessor and memory chip for data reduction and storage.

The implant sensors should be extremely small so that it can be easily implanted and explanted with less damage to the tissues nearby. There can be potential risk of bacterial contamination during the production process of sensors that does not only focus on the presence of pathogens, but also on the content of bacterial lipopolysaccharide/endotoxin from gram-negative bacteria. Endotoxin is a pyrogen that induces fever and shock and can initiate inflammation through production of cytokines [10]. In vivo biocompatibility was investigated through histological examination of implanted sensor membranes in pigs. The healing of subcutis was assessed histologically from 3 to 14 days after removal of sensors [62]. To sense the analyte, the sensing electrode should be of micro or nanosize and to establish this concept the SWCNT (single walled CNT) and MWCNT (multi walled CNT) with all its remarkable properties like high strength, large flexibility, excellent chemical stability and high surface area made them use as electrodes in biosensors, since the first demonstrations of SWNT – field effect transistors (FETs) shown in Fig. 3 by Martel et al. [69].

Tans et al. [107], said that a number of configurations have emerged for efficient detection of variety of biomolecules, with detection limits down to picomolar (pM) range. In reality, the SWNTs in their FET configuration act as "channel modulation label" to sense changes in their immediate environment, as a result of specific interactions between proteins and DNA [21].

Lin et al. [65] have developed a sensitive glucose biosensors based on CNT–nanoelectrode ensembles (CNT–NEEs) for the selective detection of glucose. Limit of detection (LOD), based on a signal-to-noise ratio (S/N) of 3, was 0.08 mM. CNT–NEE is thus suitable for the highly selective detection of glucose in a variety of biological fluids (e.g., saliva, sweat, urine, and serum). The size reduction of each individual electrode and the increased total number of electrodes result in improvements in both the (S/N) and LOD [72,120,113]. Having concerns on miniaturization has opened lots of opportunities in the field of bionanotechnology. The biocompatibility of these nanomaterials will be the first and foremost concern in

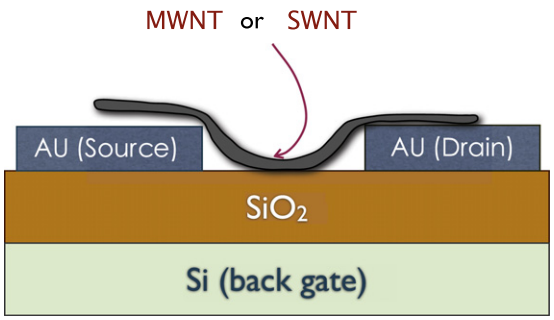

Fig. 3. Schematic cross section of the FET device. (A single NT of either MW or SW type bridges the two gold electrodes. The silicon substrate is used as the back gate.)

this field. There was collaboration between toxicologists and materials scientists in the joint development [49] of 'green' nanomaterial formulations – those co-optimized for function and minimal health impact. The future of nano-biosensor depends on the further studies in toxicity and biocompatibility in view of the fact that nanoparticles used in implantable devices can eventually enter the human body if required care is not exerted to inhibit such action. Implant microfabrication uses a broad range of techniques including photolithography and micromachining to create devices with features ranging from 0.1 to hundreds of microns with high aspect ratios and precise features. With the increasing development of micro-structured glass surfaces, as well as the proven biocompatibility of surfaces, the application of these surfaces for implanted devices is inevitable [2,3]. Brauker et al. [12] made a comparison on vascularization of the membrane–tissue interface of 5-μm-pore-size polytetrafluoroethylene (PTFE) membranes to 0.02-μm-pore-size PTFE membranes, it was found that the larger pore membranes had 80–100-fold more vascular structures. The increased vascularization was observed even though the larger pore membrane was laminated to a smaller pore inner membrane to prevent cell entry into the prototype immunoisolation device. In vivo sensing of blood gases and electrolytes remains a difficult challenge owing to biocompatibility issues that occur when chemical sensors are implanted into the blood stream, that can also cause a significant change in the local oxygen concentration [125] use of a biocompatible outer coating that mimics the body tissue has been shown to minimize these negative responses while maintaining sensor functionality. This can be achieved through the use of a hydrogel coating. Anti-inflammatory agents released at the local site have been the most successful in preventing inflammation and fibrosis. A hydrogel coating has been developed that provides a slow release of anti-inflammatory drugs and other agents while allowing rapid diffusion of analytes through the hydrogel for sensing [83,7]. It is anticipated that these efforts to develop biocompatible materials for glucose biosensors will assist in the realization of totally implantable long-term biosensors in the near future [81].

The other types of implantable devices that are intensively researched are developing implantable optical biosensor [132] where the ability to synthesize or separate nanotubes by their (n, m) chirality has the potential to aid the development of an implantable multi-analyte biosensor. Sensors for monitoring fluctuations of extracellular lactate levels in brain [47] Using MEMs technology for drug delivery [91] local delivery of basic fibroblast growth factor (BFGF) over a specific dose and time course is critical for mesenchymal tissue regeneration. The release of BFGF was regulated at 40 ng/day for four weeks; bioactivity was assessed by monitoring the growth of 3T3 fibroblasts. Sacristán-Riquelme and Osés [92] have reported the design, fabrication and test of a high performance prototype for neural stimulation and recording to be used for the control of artificial limb prosthesis. Finally the combination of biocompatible and biodegradable materials within the same implantable device is not trivial but not impossible considering the tremendous growth of nanotechnology in the years to come [114].

2.3. Textile sensors

Highly durable, flexible, and even washable multilayer electronic circuitry can be constructed on textile substrates, using conductive yarns and suitably packaged components. The growing demand for economic, low power, conformal and durable wireless nodes with sensing capabilities is driven by applications such as: item-level tracking of temperature and humidity, pharmaceutical logistics, transport and storage of medical products and bio-sensing. The major challenge in this type of applications is the need for low-cost eco-friendly wireless sensor nodes that can be easily implemented out in different environments.

Radio-Frequency IDentification (RFID) is a low-cost compact wireless technology, wearable RFID-enabled sensor is such a branch attracting strong interest and will soon become another fast growing field in application-oriented research [126]. Design and fabrication of textile based computing makes them as wearable intelligent textiles for monitoring the patient in the medical field [85]. The wearable RFID-enabled sensor nodes can find broad usage in real-time monitoring and medical monitoring applications. The capabilities of inkjet-printing technology ensure the low-cost fabrication by reel-to-reel mass process of textile. Key steps leading to a successful function module, such as dielectric characterization, RFID antenna design and integration of sensor were introduced in this paper [126]. The textile sensors were designed and integrated in biotelemetry applications by Cerny et al. [17].

A system was designed by Jourand et al. [54] on flexible substrates to measure two of the most important physiological parameters in human life: breathing rhythm and ECG, the accelerometers quantify the breathing cycle. The realized designs were placed on a T-shirt and tested on adults and infants. Data is sent to a computer wirelessly for analysis. As an alternative to conventional ECG gel electrodes, both woven and knitted stainless steel electrodes called textrodes were developed by Coosemans et al. [29]. Wireless bi-directional data communication is provided through the same inductive link as the power transfer. The data transmission to the implant is used to adapt the measuring algorithm to the patient's specific needs and is done by on/off keying of the driver. This passive telemetry is implemented based on the proven techniques in [28]. One key parameter in the clinical monitoring of patients is the number of breaths per minute, known as the respiratory rate. Many heart and lung diseases, particularly pneumonia, affect respiratory rate [5], therefore, monitoring of the respiratory rate is an important diagnostic method in planning of medical care. Respiratory rate measurements using a sensor belt with a high-resolution accelerometer (capacitive MEMS) and an Electromechanical film (EMFit) pressure sensor. Results obtained showed that the reliability of the MEMS was 90%, while that of the EMFit was 90–100% [87]. A common method for respiratory rate measurements is based on analyzing heart rate

variability from ECG signals [128]. Another method was wearing mechanically stretching belt on the chest of the patient equipped with a piezoelectric or a strain gauge to measure chest movements during breathing. A third method applies a temperature sensor or a facemask to record breathing airflow. Further, Torres et al. [110] said that respiratory rates are calculated using accelerometers to detect movements of the diaphragm. Finally, a high-sensitive sensor, referred to as EMFit film, has also been applied to various high-resolution measurements for recording vital signs in humans [57].

Yarn-based sensors of single and double wrapping methods were utilized to fabricate the yarn. Three different kinds of fibers which include piezoresistive fibers, elastic fibers, and polyester were used to form the yarn. The piezoresistive fiber was chosen as the carbon-coated fiber (CCF) (resistivity $3 \times 105\ \Omega$/cm, RESISTAT F901). The sensitivity of the double wrapping yarn is lower than CCFs and conducted the experiments on respiratory monitoring systems with these fabricated yarns [25].

In the sport field, monitoring sweat can lead to tailored rehydratation strategies improving the health and the performance of the athlete. For example, a disposable sweat collector developed consisted of capsule, created inside a flexible adhesive membrane pasted onto the skin [13]. These collected samples are then stored at low temperatures for later analysis in a laboratory. The design of a textile based fluid handling system and pH sensor based on paired emitter-detector LEDs has been outlined. The ability of the fluid handling system to collect sweat from the skin and transport it in a controlled way down the channel and into the absorbent has been demonstrated during invitro and invivo trials and also demonstrated that by placing sensors along the channel, a biochemical analysis of that sweat can be obtained [73].

Wearable Health Systems (WHSs) are a specific category of Personal Health Systems [67]. They are integrated systems on body-worn platforms like wrist-worn devices or "biomedical clothes", offering pervasive solutions for continuous health status monitoring though non-invasive biomedical, biochemical and physical measurements. It is expected that the increasingly positive attitude of users towards the application of Information and Communication Technologies (ICTs) in healthcare and the WHS field is attracting increased interest from various technological disciplines. In particular, the convergence of ICT, biotechnologies and micro-nanotechnologies opens opportunities for new generation of disruptive systems and solutions for healthcare.

2.4. CNT based biosensor

There has been great progress in the field of nanomaterials given their great potential in biomedical applications. CNTs have unique physical and chemical properties such as high aspect ratio, ultralight-weight, high mechanical strength, high electrical conductivity, and high thermal conductivity, these characteristics makes CNT a unique nanomaterial with the potential for diverse applications, especially in biomedical field [100]. CNTs can be used as a cathode material for generating free flowing electrons [129,23,11,116]. Yue et al. [129], has generated X-rays making use of CNT as cathode which can be used in producing miniaturized X-ray devices that can be inserted into the body by endoscopy to deliver precise X-ray doses directly at a target area without damaging the surrounding healthy tissues, as malignant tumors are highly localized during the early stage of their development. It is reported by most of the authors that CNTs have high electrocatalytic effect and fast electron transfer rate [118,119]. Cao et al. [16], have investigated the temperature dependence of piezoresistive effect on MWCNT films and suggested that the performance of CNT based sensors may be significantly superior to that of polycrystalline silicon. The transporting capabilities of CNT combined with appropriate surface modifications and their unique physicochemical properties can lead to a new kind of nanomaterials for cancer therapy [99]. The Fig. 4 shows the latest advances in cancer therapy.

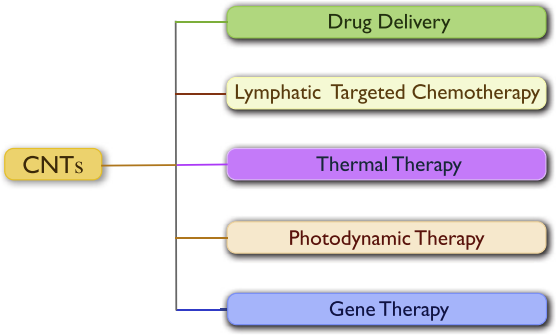

Fig. 4. Multifunctional carbon nanotubes in cancer therapy [99].

A glucose biosensors based on CNT–NEEs was developed by Lin et al. [65]. Similarly another enzymatic biosensor was developed with CNT paste. The bamboo-structured CNT shows superior electrocatalytic activity toward hydrogen peroxide. Kurusu et al. [61] have incorporated glucose oxidase into the bamboo structured CNT paste electrode and this has allowed selective detection of glucose in the presence of common interferents without using any permselective membranes. A list of all biosensors based on CNTs in given in Table 2. Kum et al. [60] developed a CNT biosensor for the detection of hydrogenperoxide.

When speaking about all the advantages of CNTs in nanobiotechnology, toxicity becomes its disadvantage. So there are plenty of papers saying about the adverse effects. Smart et al. [101] have reviewed the performance of existing carbon biomaterials and gave an outline of the emerging field of nanotoxicology and have discussed on toxicity of carbon nanotubes on lung, skin irritation and cytotoxicity of CNTs. Table 3 provides more cytotoxicity test carried by different authors. More study is needed on the toxicity of nanotubes as to proceed further and reaching horizons in biomedical field.

Previous studies have concluded that it may be necessary to increase the concentration of CNTs in a CNT bucky paper to increase the electromechanical response [71]. They have termed the third generation biosensors as mediated – free biosensors as its design is simple without chemical mediators. A sensitive electrochemical DNA

Table 2
Biosensors based on CNTs.

Type	To detect	Experiment carried on	Methodology	Referenced by
CNT powder microelectrodes electrodes	Hydrogen peroxide (H_2O_2)	Hemoglobin (Hb)	The adsorbing Hb can transfer electron directly at CNT interface with an electron transfer rate of Hb 0.062 s^{-1}	Zhao et al. [131]
CNT nanoelectrode ensembles [NEEs]	Blood glucose monitoring	Amperometric responses were obtained by a batch addition of interfering species (0.5 mM ascorbic acid, 0.5 mM uric acid and 0.5 mM acetaminophenm after the 5 mM glucose addition at two different potentials [+0.40(A) and −0.2(B)V]	A solution of glucose was injected into the electrolytic cell, and its response was measured	Lin et al. [65]
CNTs	V-type nerve agents, VX (O-ethyl-S-2-diisopropylaminoethyl methylphosphonothioate] and R-VX (O-isobutyl-S-2-diethylaminoethylmethylphosphonothioate]	Demeton-S was used as a nerve agent mimic	Amperometric detection of the thiol-containing hydrolysis products at carbon nanotube-modified screen-printed electrodes	Joshi et al. [53]
Carbon nanotubes paste electrode (CNTPE)	Glucose	None	Detection of glucose due to the combination of the electroactivity of CNTs with the electrocatalytic properties of metal microparticles towards the hydrogen peroxide enzymatically generated	Luque et al. [66]
MWCNTs	Phenolic compound; (catecholic compounds, such as dopamine, norepinefrine and epinephrine]	None	Co-immobilization of Methylene Blue and HRP on MWCNTs	Santos et al. [95]
SWNTs	Malignant tumour	Human hepatocellular cell line (Hep3B and HepG2 and Pancreatic cancer cell line [Panc-1] invitro	Injecting SWNTs treated with Radio-frequency(RF)-induced thermoablation	Gannon et al. [36]
MWCNT and gold colloidal nanoparticles	Hydrogen peroxide[H_2O_2]	Hb was used as a model protein	Based on the direct electron transfer between redox proteins and electrode	Chen et al. [22]

Table 3
Cytotoxicity test for CNTs.

Type	Affected area	Refered by
SWNT, MWNT and Fullerene (C_{60})	Observed a profound cytotoxicity a level alveolar	Jia et al. [50]
Macrophages exposed to SWNTs or MWNT	Necrosis and degeneration and signs of apoptotic cell death	Wick et al. [122]
SWCNT on human HEK293 cells	Stoped the normal cycle and induce the HEK293 cells apoptotic death	Cui et al. [30]
SWCNTs on cultured human dermal fibroblast (HDF)	Cell death	Sayes et al. [96]
Carbon nanofibers and nanotubes in vitro	Nanotubes in lung, liver and spleen have ability to stimulate the release of the pro-inflammatory cytokine TNF-α and reactive oxygen species (ROS) from monocytic cells, and these cells show "frustrated phagocytosis"	Brown et al. [14]

biosensor was developed by Chang et al. [19] using palladium nanoparticles, in combination with MWCNTs. Regarding immunosensors, a nanotube array immunosensor for direct electrochemical detection of antigen was reported by Yun et al. [130]. Another immunosensor for detecting cholera toxin was developed using liposomes and poly(3,4-ethylenedioxythiophene) coated on nafion supported MWCNTs [115]. There are many label free immunosensors developed using CNTs, a few are developed by Okuno et al. [80], Ou et al. [82] and Munge et al. [76]. A SWNT forest and 5 nm glutathione protected gold nanoparticles were used for developing an electrochemical immunosensors for the measurement of human cancer biomarker interleukin-6 [76].

The electrocatalytic ability of CNTs modified electrodes, anti-fouling capability of the modified surface, enhanced active surface area makes a new field of research on novel nanostructured biosensors. As CNTs have unique properties, high performance, cost effective nanotube based sensors can be produced in huge amounts after proper engineering research is conducted in vitro. So far the research is carried out in models alone.

2.5. Enzyme-based biosensors

Potentiometry is the measurement of an electrical potential difference between two electrodes when the cell current is zero. The two electrodes are known as the indicator and reference electrodes. The Ion Selective Electrode (ISE) for the measurement of electrolytes works on the potentiometric technique. A large variety of potentiometric biosensors is developed using biocatalytic and bioaffinity-based biosensing schemes. However, only few of them could be applied for the biomedical analysis. The most promising are those for the detection of main products of protein metabolism, namely urea and creatinine. Urea is the main end-product of protein metabolism and can be easily detected using potentiometric enzyme-based biosensors. Creatinine is one of the most significant analytes in the modern clinical analysis. Determination of this metabolite in various physiological fluids is useful for the evaluation of renal, muscular and thyroid dysfunctions. Such analyses are helpful for the biomedical diagnosis of acute myocardial infarction as well as for the quantitative description of hemodialysis treatment.

The developed bioelectronic tongue [42] provides an extraordinarily simple procedure, with direct measurement, to determine the concentration of urea in real samples without the necessity of eliminating the alkaline interferences or compensating endogenous ammonia. The models based on artificial neural network (ANN) and partial least squares (PLS1) were built, tested and compared for the simultaneous determination of urea, ammonium, potassium and sodium. The modeling capacity of the ANN was examined in terms of the root mean squared error (Eq. (1)).

$$RMSE = \sqrt{\sum_{i,j} \frac{(x_{i,j} - \hat{x}_{i,j})^2}{4n - 1}} \quad (1)$$

where n is the number of samples ($4n$, as many as four species were determined) and $x_{i,j}$ and $x_{i,j}$ are the expected concentration value and that provided by the ANN, respectively, for each compound, with i denoting samples and j species.

Applications of conductometric biosensors are limited due to the variable ionic background of clinical samples and the requirement to measure small conductivity changes in media of high ionic strength. One commercial system for the measurement of urea in serum, plasma and urine is a BUN analyzer (Beckman–Coulter).

Amperometry is the electrochemical technique usually applied in the commercial biosensors. They generally have response times, dynamic ranges and sensitivities similar to the potentiometric biosensors.

Amperometric biosensors for flavo-oxidase enzymes illustrating the three generations in the development of a biosensor is shown below (Fig. 5). [20] All electrode potentials (E_0) are relative to the Cl^-/AgCl, Ag^0 electrode. The following reaction occurs at the enzyme in all three biosensors:

$$\text{Substrate}(2H) + \text{FAD-oxidase Product} + FADH_2\text{-oxidase}$$

This is followed by the processes:

(a) biocatalyst

$$FADH_2\text{-oxidase} + O_2 \rightarrow \text{FAD-oxidase} + H_2O_2$$

electrode

$$H_2O_2 \rightarrow O_2 + 2H^+ + 2e^-$$

(b) biocatalyst

$$FADH_2\text{-oxidase} + 2\text{Ferricinium}^+ \rightarrow \text{FAD-oxidase} + 2\text{Ferrocene} + 2H^+$$

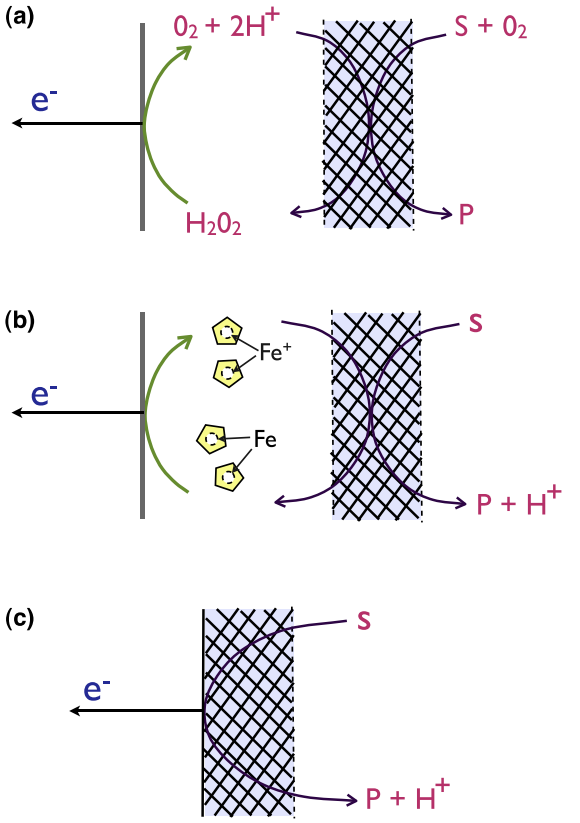

Fig. 5. Illustration of amperometric biosensors for flavo-oxidase: (a) biocatalyst, (b) biocatalyst and (c) biocatalyst/electrode. The biocatalyst is shown schematically by the cross-hatching: (a) First generation electrode utilizing the H_2O_2 produced by the reaction ($E_0 = +0.68$ V); (b) second generation electrode utilizing a mediator (ferrocene) to transfer the electrons, produced by the reaction, to the electrode ($E_0 = +0.19$ V); (c) third generation electrode directly utilizing the electrons produced by the reaction ($E_0 = +0.10$ V).

electrode

$$2\text{Ferrocene} \rightarrow 2\text{Ferricinium}^+ + 2e^-$$

(c) biocatalyst/electrode

$$\text{FADH}_2\text{-oxidase} \rightarrow \text{FAD-oxidase} + 2H^+ + 2e^-$$

The current (i) produced by such amperometric biosensors are related to the rate of reaction (v_A) by the expression:

$$i = nFAv_A$$

where n represents the number of electrons transferred, A is the electrode area, and F is the Faraday.

A typical application for this simple type of biosensor is the determination of glucose concentrations by the use of an immobilised glucose oxidase membrane which was the first amperometric biosensor found in the literature by Clark and Lyons [26]. The oxidation of glucose, catalyzed by glucose oxidase, was the principle of measurement.

$$\text{Glucose} + O_2 \xrightarrow{\text{glucose oxidase}} \text{gluconic acid} + H_2O_2$$

Substitution of other oxidases for glucose oxidase in the above equation allows amperometric biosensors in a similar manner for the analysis of their substrates. Screen printed and disposable amperometric cholesterol biosensor by Gilmartin and Hart [40] operates effectively at low cholesterol levels (10^{-6} mol/dm^3), which is imperative for the diagnosis of syndromes linked to abnormalities in lipid metabolism. Different types of enzyme based biosensors are provided in Table 4. Determination of creatinine and creatine in biological fluids is of significant value for diagnosis of renal, muscular and thyroid function.

2.6. Integrated sensors

The lithographically based technology developed for integrated circuits extended to realize a wide variety of sensors and actuators. MEMS is now being joined with wireless transceivers and embedded signal processing to form wireless integrated microsystems. It has taken four decades to move integrated sensors from the component level to full microsystems [124]. The addition of advanced, one-chip microcomputers to both control the sequencing of the gas chromatography (GC) operation and analyze the detector output. This miniature analysis system found wide application in a number of fields including implanted biological monitors, portable air contaminant analyzers and unmanned planetary probes. A thermal conductivity detector is separately batch fabricated using integrated circuit processing techniques, and is integrally mounted on the substrate wafer [108]. A wireless, fully-implantable neural recording system is being developed to facilitate neuroscience research and neuroprosthetic applications (Fig. 6).

The system is based on the Utah Microelectrode Array (UEA), a 10 × 10 array of platinum-tipped silicon extracellular electrodes [78]. Harrison et al. [43] described the development of a mixed-signal integrated circuit that will be flip chip bonded to the back of the UEA using Au/Sn reflow soldering. This chip will directly connect to all 100 electrodes, amplify the neural signals from each electrode, digitize this data, and transmit it over an RFl.

Integrated GC based microsystems is used in the MEMS technology promises smaller size, lower power consumption, increased portability, and improved functionality as sensors, heaters, valves, pumps. A high speed temperature programmed microfabricated GC column capable of analyzing eleven component gas samples in a few seconds was reported by [1]. This high speed gas analysis can be applied in defence and security systems.

It is widely agreed that blood flow is one of the most important physiological parameters, and also one of the most difficult to measure accurately. The incidence of cardiovascular disease alone necessitated to research further. Two custom integrated circuits were developed for an implantable pulsed Doppler ultrasonic blood flowmeter with the input of 2.7 mW power for the chip [39]. The implantable miniature ultrasonic sensors were attached to the surface of the blood vessel and carried out invivo studies to evaluate the accuracy and performance of the system. Studies are done on fish with a fully implantable radio-based blood flow biotelemetry system which allows

Table 4
Different types of enzyme based biosensors.

Enzyme based biosensor	Technology	Determination of species	Operation & lifetime	Referenced by
Creatinine biosensor	Two types of enzyme electrodes were developed, combining CA/CI/SO or the CI/SO membranes and a polarographic electrode for sensing hydrogen peroxide	Creatine and creatinine in serum	9 months	Suchida and Yoda [104]
Model for conductimetric area biosensor	The biosensor is formed by urease enzyme immobilization onto a planar surface interdigitated electrode array	Urea (the model shown to be in agreement with the experimental data over the entire range of concentrations)	No specified	Sheppard and Mears [97]
Amperometric biosensor	The principle is based on the electrochemical oxidation of the hexacyanoferrate(II) ion	L-analine and pyruvate (blood, fermentation media)	1 month	Gilis et al. [38]
Amperometric and Potentiometric biosensor	Three-enzyme method for amperometric biosensor	Creatinine	3 months	Killard and Smyth [56]
Amperometric creatinine biosensor	Creatinine microsensor with a three-layer configuration with interference-removing	Creatinine	35 days	Shin et al. [98]
Biosensor array	The electrochemical measuring setup has a printed circuit board as the microsystem flow device	Simultaneous measurement of glucose, lactate, glutamate, glutamine	42 days and less	Moser et al. [74]
Disposable Potentiometric sensor	The electrodes are fabricated entirely with screen-printing technology	No specified	9 months	Tymecki et al. [112]
Creatinine sensitive biosensor (ISFETs)	Biosensor based on ion sensitive field-effect transistors (ISFETs) with immobilised creatinine deiminase was developed	Creatinine and well suitable for hemodialysis	6 months and more	Soldatkin et al. [102]
Disposable creatinine sensitive biosensor	ChemFET microsensors developed by using polyvinyl alcohol enzymatic layers deposited and patterned either by dip-coating, or spin-coating and photolithographic techniques	Creatinine, blood analysis and more precisely for hemodialysis	7 days	Sant et al. [94]
Potentiometric creatinine biosensor	Creatinine biosensor based on ammonium ion selective electrode	Creatinine in urine, serum and posthemodialysate	None	Radomska et al. [86] and Rasmussen et al. [4]
Potentiometric bioetectronic tongue	Covalently immobilized on ro ammonium and hydrogen ion-selective electrodes were included in arrays together with ammonium, potassium, sodium, hydrogen and generic response to alkaline sensors	Urea, ammonium, potassium and sodium	Direct determination of urea in the real samples without the necessity of eliminating the alkaline interferences	Gutierrez et al. [42]

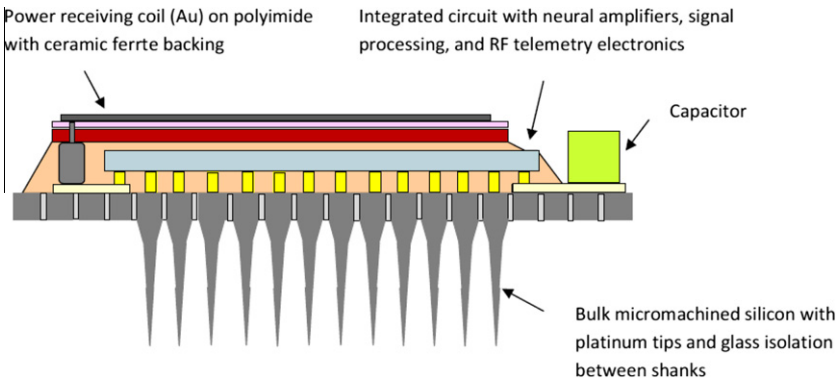

Fig. 6. Complete integrated neural interface assembly. (The entire assembly is coated in parylene and silicon carbide.)

simultaneously measurement of blood flow on two channels and temperature on one channel which minimizes the risk of infection/expulsion and maximizes the likelihood that the studied fish will behave naturally and be treated normally by surrounding fish [41].

There are mainly two types of micropressure sensors, namely, the piezoresistive (PRP) and capacitive pressure (CP) sensors. The PRP sensor has high linearity but it is very sensitive to temperature change and temperature compensation circuits have to be employed and would fit for smaller pressure ranges of 500 mmHg. On the other hand, the CP sensors have better sensitivity and higher rejection to environmental temperature variations and would fit the biomedical applications. Huang and Wise [48] have developed a single chip sensor which is capable of simultaneously measuring pH and pressure on a multisite catheter for use in diagnosis of abnormalities in esophageal motor function and gastroesophageal reflux. The chip consists of a CP transducer and an ion-sensitive field effect transistor [27].

An implantable micropressure sensor for measuring the interface pressure between nerve trunk and cuff electrode is designed and fabricated successfully by Chia-Chu et al. [24]. The micro-CP sensor was first fabricated by using the micromachining technology [93]. A monolithic CP sensor has the advantages of small size, due to fabrication by integrated-circuit techniques, and high sensitivity through the use of capacitance change as a transduction mechanism. Telemedicine is the use of electronic information and communications technologies to provide and support health care when distance separates the participants [35]. There are various micromachined pressure sensors for use in blood pressure measurement, for sensing intraocular pressure, intracranial and spinal pressure, orthopedic stresses but none have been tested successfully invivo. Tan et al. [106], have constructed a fully implantable wireless invivo pressure sensor for use in short term urological studies and patient monitoring. The sensor is fully implantable and transmits pressure data once every second, was the first step in developing a ubiquitous sensing platform for telemedicine and remote patient monitoring. A miniature battery powered internal bladder pressure monitoring system implantable through minimal invasive catheterization was developed and tested for off-line monitoring of behavior and evolution of bladder pressure by Jourand and Puers [55]. A fully integrated battery-free sensing system that uses a two-site wireless pressure measurement for the detection of arterial stenosis was characterized by DeHennis and Kensall [33].

3. Conclusion

Clark is considered the "Father of Biosensors", and the modern-day glucose sensor used daily by millions of diabetics is based on his research. Since then Clark type biosensor technology have seen growth in terms of device complexity, usability and has entered in the commercial market. Biosensors promise low-cost, rapid, and simple-to-operate analytical tools for applications in numerous fields such as medical diagnosis, environmental monitoring, and food industries. There are various glucose monitoring kit commercially available in the market is the best example of the enzymatic biosensor. There are different biosensors capable of measuring whole group of analytes, namely cholesterol, triglycerides and phospholipids by using enzyme electrodes.

So far there were many related articles regarding biosensors in the biomedical field. With these successfully developed biosensor the next criteria in the biomedical field would be of making the sensors as chimeric protein switch, for detecting the unusual activity thereby activating the enzymatic function, to detect the pre development of any antigen or antibody invitro. By fabricating bio MEMS and NEMS biosensors, the implants will undergo miniaturization with the help of nanotechnology. With the indigenous capability of biocompatible nanotubes, there are positive emergence of niche applications in bioactuators and smart biosensors in the near future with potentials in the fabrication of artificial muscles with bioactuators, heart attack temperature sensors, bone implants on stimulated growth, pointed drug delivery system. One such real time implication of making the chimeric switch into reality is by sensing the viscosity change in the bacteria infected area of the prosthesis by the development of the flow biosensor which can sense the development of bacteria with the SWNT biosensor and produce voltage that could be utilized to give displacement to SWNT bioactuator, which can be infused in the prosthesis (hip or knee) to release the medicine stored in the reservoir. Our future research is pointed to this application. The development for smart implants like hip and knee arthroplasty is going to revolutionize the medical field with less work for the doctors and less worry for the patients.

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References

[1] M. Agah, G.R. Lambertus, R.D. Sacks, K.D. Wise, High-speed MEMS-based gas chromatography, in: Proceedings of the IEEE International Electron Devices Meeting. Washington, DC, 2004, pp. 27–30.
[2] K.M. Ainslie, T.A. Desai, Microfabricated implants for applications in therapeutic delivery, tissue engineering, and biosensing, Lab Chip 8 (2008) 1864–1878.
[3] K.M. Ainslie, S.L. Tao, K.C. Popat, T.A. Desai, In vitro immunogenicity of silicon-based micro- and nanostructured surfaces, ACS Nano 2 (2008) 1076–1084.
[4] C.D. Rasmussen, J.E.T. Andersen, B. Zachau-Christiansen, Improved performance of the potentiometric biosensor for the determination of creatinine, Anal. Lett. 52 (2007) 39–52.
[5] D. Aujesky, T.E. Auble, D.M. Yealy, R.A. Stone, D.S. Obrosky, T.P. Meehan, L.G. Graff, J.M. Fine, M.J. Fine, Prospective comparison of three validated prediction rules for prognosis in community-acquired pneumonia, Am. J. Med. 118 (2005) 384–392.
[6] C.E.H. Berger, T.A.M. Beumer, R.P.H. Kooyman, J. Greve, Surface plasmon resonance multisensing, Anal. Chem. 70 (1998) 703–706.
[7] U. Bhardwaj, R. Sura, F. Papadimitrakopoulos, D.J. Burgess, Controlling acute inflammation with fast releasing dexamethasone-PLGA microsphere/PVA hydrogel composites for implantable devices, J. Diabetes Sci. Technol. 1 (2007) 8–17.
[8] Biacore. <http://www.biacore.com> (acedido 15.06.10).

[9] D.S. Bindra, Y. Zhang, G.S. Wilson, R. Sternberg, D.R. Thévenot, D. Moatti, G. Reach, Design and in vitro studies of a needle-type glucose sensor for subcutaneous monitoring, Anal. Chem. 63 (1991) 1692–1696.
[10] T.S. Blackwell, J.W. Christman, Sepsis and cytokines: current status, Br. J. Anasthesia 77 (1996) 110–117.
[11] J.M. Bonard, T. Stöckli, F. Maier, W.A. de-Heer, A. Châtelain, Field-emission-induced luminescence from carbon nanotubes, Phys. Rev. Lett. 81 (1998).
[12] J.H. Brauker, V.E. Carr-Brendel, L.A. Martinson, J. Crudele, W.D. Johnston, R.C. Johnson, Neovascularization of synthetic membranes directed by membrane microarchitecture, J. Biomed. Mater. Res. 29 (2004) 1517–1524.
[13] G.R. Brisson, P. Boisvert, F. Peronnet, H. Perrault, D. Boisvert, J.S. Lafond, A simple and disposable sweat collector, Eur. J. Appl. Physiol. 63 (1991) 269–272.
[14] D.M. Brown, I.A. Kinloch, U. Bangert, A.H. Windle, D.M. Walter, G.S. Walker, C.A. Scotchford, K. Donaldson, V. Stone, An in vitro study of the potential of carbon nanotubes and nanofibres to induce inflammatory mediators and frustrated phagocytosis, Carbon 45 (2007) 1743–1756.
[15] C.P. Cahill, K.S. Johnston, S.S. Yee, A surface plasmon resonance sensor probe based on retro-reflection, Sens. Actuators, B 45 (1997) 161–166.
[16] C.L. Cao, C.G. Hu, Y.F. Xiong, X.Y. Han, Y. Xi, J. Miao, Temperature dependent piezoresistive effect of multi-walled carbon nanotube films, Diam. Relat. Mater. 16 (2007) 388–392.
[17] M. Cerny, L. Martinak, M. Penhaker, M. Rosulek, Design and implementation of textile sensors for biotelemetry applications, in: 14th Nordic-Baltic Conference on Biomedical Engineering and Medical Physics, Riga, Latvia, 2008, p. 194–197.
[18] J. Chandezon, M.T. Dupuis, G. Cornet, D. Maystre, Multicoated gratings: a differential formalism applicable in the entire optical region, J. Opt. Soc. Am. 72 (1982) 839–846.
[19] Z. Chang, H. Fan, K. Zhao, M. Chen, P. He, Y. Fang, Electrochemical DNA biosensors based on palladium nanoparticles combined with carbon nanotubes, Electroanalysis 20 (2008) 131–136.
[20] Martin Chaplin, Amperometric Biosensors, 20th December 2004. <http://www1.lsbu.ac.uk/biology/enztech/amperometric.html> (acedido 01.06.10).
[21] R.J. Chen, S. Bangsaruntip, K.A. Drouvalakis, N.W.S. Kam, M. Shim, Y. Li, W. Kim, P.J. Utz, H. Dai, Noncovalent functionalization of carbon nanotubes for highly specific electronic biosensors, Proc. Natl. Acad. Sci. 100 (2003) 4984–4989.
[22] S. Chen, R. Yuan, Y. Chai, L. Zhang, N. Wang, X. Li, Amperometric third-generation hydrogen peroxide biosensor based on the immobilization of hemoglobin on multiwall carbon nanotubes and gold colloidal nanoparticles, Biosens. Bioelectron. 22 (2007) 1268–1274.
[23] Y. Cheng, J. Zhang, Y.Z. Lee, B. Gao, S. Dike, W. Lin, J.P. Lu, O. Zhou, Dynamic radiography using a carbon-nanotube-based field-emission X-ray source, Rev. Sci. Instrum. 75 (2004) 3264–3267.
[24] C. Chiang, C. Klin, M. Ju, An implantable capacitive pressure sensor for biomedical applications, Sens. Actuators, A 134 (2007) 382–388.
[25] H. Ching-Tang, S. Chien-Lung, T. Chien-Fa, C. Shuo-Hung, A wearable yarn-based piezo-resistive sensor, Sens. Actuators, A 141 (2008) 396–403.
[26] L.C. Clark Jr., C. Lyons, Electrode systems for continuous monitoring in cardiovascular surgery, Ann. N. Y. Acad. Sci. 102 (1962) 29–45.
[27] S.K. Clark, K.D. Wise, Pressure sensitivity in anisotropically etched thin-diaphragm pressure-sensors, IEEE Trans. Electron Devices 26 (1979) 1887–1896.
[28] J. Coosemans, R. Puers, An autonomous bladder pressure monitoring system, Sens. Actuators, A (2005) 155–161 (Rome).
[29] J. Coosemans, B. Hermans, R. Puers, Integrating wireless ECG monitoring in textiles, in: The 13th International Conference on Solid-State Sensors, Actuators and Microsystems, Sens. Actuators, A, Seoul, Korea, 2006, pp. 48–53.
[30] D. Cui, F. Tian, C.S. Ozkan, M. Wang, H. Gao, Effect of single wall carbon nanotubes on human HEK293 cells, Toxicol. Lett. 155 (2005) 73–85.
[31] D.C. Cullen, R.G.W. Brown, C.R. Lowe, Detection of immuno-complex formation via surface plasmon resonance on gold-coated diffraction gratings, Biosensors 3 (1987) 211–225.
[32] D.C. Cullen, C.R. Lowe, A direct surface plasmon—polariton immunosensor: preliminary investigation of the non-specific adsorption of serum components to the sensor interface, Sens. Actuators, B 1 (1990) 576–579.
[33] A.D. DeHennis, D.W. Kensall, A fully integrated multisite pressure sensor for wireless arterial flow characterization, J. Microelectromech. Syst. 15 (2006) 678–685.
[34] L.G. Fägerstam, A.F. Karlsson, R. Karlsson, B. Persson, I. Rönnberg, Biospecific interaction analysis using surface plasmon resonance detection applied to kinetic, binding site and concentration analysis, J. Chromatogr. A 597 (1992) 397–410.
[35] M.J. Field, J. Grigsby, Telemedicine and remote patient monitoring, J. Am. Med. Assoc. 288 (2002) 423–425.
[36] C.J. Gannon, P. Cherukuri, B.I. Yakobson, L. Cognet, J.S. Kanzius, C. Kittrell, R.B. Weisman, M. Pasquali, H.K. Schmidt, R.E. Smalley, S.A. Curley, Carbon nanotube-enhanced thermal destruction of cancer cells in a noninvasive radiofrequency field, Am. Cancer Soc. 110 (2007) 2654–2665.
[37] M.G. Gaylord, T.K. Moharam, Rigorous coupled-wave analysis of metallic surface-relief gratings, J. Opt. Soc. Am. A 3 (1986) 1780–1787.
[38] M. Gilis, H. Durliat, M. Comtat, Amperometric biosensors for L-analine and pyruvate assays in biological fluids, Anal. Chim. Acta 355 (1997) 235–240.
[39] R.W. Gill, J.D. Meindl, Low power integrated circuits for an implantable pulsed doppler ultrasonic blood flowmeter, IEEE J. Solid-State Circ. 10 (1975) 464–471.
[40] M.A.T. Gilmartin, J.P. Hart, Fabrication and characterization of a screen-printed disposable amperometric cholesterol biosensor, The Analyst 119 (1994) 2331–2336.
[41] A. Grans, M. Axelsson, K. Pitsillides, C. Olsson, J. Hojesjo, R.C. Kaufman, J.J. Cech Jr., A fully implantable multi-channel biotelemetry system for measurement of blood flow and temperature: a first evaluation in the green sturgeon, Hydrobiologia 619 (2009) 11–25.
[42] M. Gutierrez, S. Alegret, M. del Valle, Potenciometric bioelectronic tongue for the analysis of urea and alkaline ions in clinical samples, Biosens. Bioelectron. 22 (2007) 2171–2178.
[43] R. Harrison, P. Watkins, R. Kier, R. Lovejoy, D. Black, R. Normann, F. Solzbacher, A low-power integrated circuit for a wireless 100-electrode neural recording system, in: IEEE International Solid-State Circuits Conference, 2006, pp. 554–555.
[44] J. Homola, R. Slavik, Fibre-optic sensor based on surface plasmon resonance, Electron. Lett. 32 (1996) 480–482.
[45] J. Homola, S.S. Yee, Surface plasmon resonance sensor based on planar light pipe: theoretical optimization analysis, Sens. Actuators, B 37 (1996) 145–150.
[46] J. Homola, On the sensitivity of surface plasmon resonance sensors with spectral interrogation, Sens. Actuators, B 41 (1997) 207–211.
[47] Y. Hu, G.S. Wilson, A temporary local energy pool coupled to neuronal activity: fluctuations of extracellular lactate levels in rat brain monitored with rapid-response enzyme-based sensor, J. Neurochem. 69 (1997) 1484–1490.
[48] J.C.M. Huang, K.D. Wise, A monolithic pressure-pH sensor for esophageal studies, IEEE, 1982, pp. 316–319.
[49] R.H. Hurt, M. Monthioux, A. Kane, Toxicology of carbon nanomaterials: status, trends, and perspectives on the special issue, Carbon 44 (2006) 1028–1033.
[50] G. Jia, H. Wang, L. Yan, X. Wang, R. Pei, T. Yan, Y. Zhao, X. Guo, Cytotoxicity of carbon nanomaterials: single-wall nanotube, multi-wall nanotube, and fullerene, Environ. Sci. Technol. 39 (2005) 1378–1383.
[51] R.C. Jorgenson, S.S. Yee, A fiber-optic chemical sensor based on surface plasmon resonance, Sens. Actuators, B 12 (1993) 213–220.
[52] M.J. Jory, P.S. Vukusic, J.R. Sambles, Development of a prototype gas sensor using surface plasmon resonance on gratings, Sens. Actuators, B 17 (1994) 203–209.
[53] K.A. Joshi, M. Prouza, M. Kum, J. Wang, J. Tang, R. Haddon, W. Chen, A. Mulchandani, V-type nerve agent detection using a carbon nanotube-based amperometric enzyme electrode, Anal. Chem. 78 (2006) 331–336.
[54] P. Jourand, H. De Clercq, R. Corthout, R. Puers, Textile integrated breathing and ECG monitoring system, in: Eurosensors XXIII Conference, 2009, pp. 722–725.
[55] P. Jourand, R. Puers, An autonomous, capacitive sensor based and battery powered internal bladder pressure monitoring system, in: Eurosensors XXIII Conference, Procedia Chemistry, 2009, pp. 1263–1266.
[56] A.J. Killard, M.R. Smyth, Creatinine biosensors: principles and designs, TIBTECH 18 (2000) 433–437.
[57] T. Koivistoinen, S. Junnila, A. Värri, T. Kööbi, A new method for measuring the ballistocardiogram using EMFi sensors in a normal chair, in: Proceedings of 26th Conference, IEEE EMBS, 2004, pp. 2069–2029.

[58] A.A. Kolomenskii, P.D. Gershon, H.A. Schuessler, Sensitivity and detection limit of concentration and adsorption measurements by laser-induced surface-plasmon resonance, Appl. Opt. 36 (1997) 6539–6547.
[59] R.P.H. Kooyman, H. Kolkman, J.V. Gent, J. Greve, Surface plasmon resonance immunosensors: sensitivity considerations, Anal. Chim. Acta 213 (1988) 35–45.
[60] M.C. Kum, K.A. Joshi, W. Chen, N.V. Myung, A. Mulchandani, Biomolecules-carbon nanotubes doped conducting polymer nanocomposites and their sensor application, Talanta 74 (2007) 370–375.
[61] F. Kurusu, S. Koide, I. Karube, M. Gotoh, Electrocatalytic activity of bamboo-structured carbon nanotubes paste electrode toward hydrogen peroxide, Anal. Lett. 39 (2006) 903–911.
[62] P.H. Kvist, T. Iburg, B. Aalbaek, M. Gerstenberg, C. Schoier, P. Kaastrup, T. Buch-Rasmussen, E. Hasselager, H.E. Jensen, Biocompatibility of an enzyme-based, electrochemical glucose sensor for short-term implantation in the subcutis, Diabetes Technol. Therapeutics 8 (2006) 546–560.
[63] C.R. Lavers, J.S. Wilkinson, A waveguide-coupled surface-plasmon sensor for an aqueous environment, Sens. Actuators, B 22 (1994) 75–81.
[64] B. Liedberg, I. Lundström, E. Stenberg, Principles of biosensing with an extended coupling matrix and surface plasmon resonance, Sens. Actuators, B 11 (1993) 63–72.
[65] Y. Lin, F. Lu, Y. Tu, Z. Ren, Glucose biosensors based on carbon nanotube nanoelectrode ensembles, Nano Lett. 4 (2004) 191–195.
[66] G.L. Luque, N.F. Ferreyra, G.A. Rivas, Glucose biosensor based on the use of a carbon nanotube paste electrode modified with metallic particles, Microchim. Acta 152 (2006) 277–283.
[67] A. Lymberis, L. Gatzoulis, Wearable health systems: from smart technologies to real applications, in: Engineering in Medicine and Biology Society, 28th Annual International Conference of the IEEE EMBS, NY, 2006, pp. 6789–6792.
[68] M. Manuel, B. Vidal, R. López, S. Alegret, J. Alonso-Chamarro, I. Garces, J. Mateo, Determination of probable alcohol yield in musts by means of an SPR optical sensor, Sens. Actuators, B 11 (1993) 455–459.
[69] R. Martel, T. Schmidt, H.R. Shea, T. Hertel, Ph. Avouris, Single- and multi-wall carbon nanotube field-effect transistors, Appl. Phys. Lett. 73 (1998) 2447–2449.
[70] K. Matsubara, S. Kawata, S. Minami, Optical chemical sensor based on surface plasmon measurement, Appl. Opt. 27 (1988) 1160–1163.
[71] A. Mazzoldi, M. Tesconi, A. Tognetti, W. Rocchia, G. Vozzi, G. Pioggia, A. Ahluwalia, D. De Rossi, Electroactive carbon nanotube actuators: soft-lithographic fabrication and electro-chemical modelling, Mater. Sci. Eng. C 28 (2008) 1057–1064.
[72] V.P. Menon, C.R. Martin, Fabrication and evaluation of nanoelectrode ensembles, Anal. Chem. 67 (1995) 1920–1928.
[73] D. Morris, S. Coyle, Y. Wua, K.T. Lau, G. Wallace, D. Diamond, Bio-sensing textile based patch with integrated optical detection system for sweat monitoring, Sens. Actuators, B 139 (2009) 231–236.
[74] I. Moser, G. Jobst, G.A. Urban, Biosensor arrays for simultaneous measurement of glucose, lactate, glutamate, and glutamine, Biosens. Bioelectron. 17 (2002) 297–302.
[75] C. Mouvet, R.D. Harris, C. Maciag, B.J. Luff, J.S. Wilkinson, J. Piehler, A. Brecht, G. Gauglitz, R. Abuknesha, G. Ismail, Determination of simazine in water samples by waveguide surface plasmon resonance, Anal. Chim. Acta. 338 (1997) 109–117.
[76] B.S. Munge, C.E. Krause, R. Malhotra, V. Patel, J.S. Gutkind, J.F. Rusling, Electrochemical immunosensors for interleukin-6. Comparison of carbon nanotube forest and gold nanoparticle platforms, Electrochem. Commun. 11 (2009) 1009–1012.
[77] D.G. Myszka, R.L. Rich, Implementing surface plasmon resonance biosensors in drug discovery, Pharm. Sci. Technol. Today 3 (2000) 310–317.
[78] C.T. Nordhausen, E.M. Maynard, R.A. Normann, Single unit recording capabilities of a 100 microelectrode array, Brain Res. 726 (1996) 129–140.
[79] C. Nylander, B. Liedberg, T. Lind, Gas detection by means of surface plasmon resonance, Sens. Actuators, A 3 (1982) 79–88.
[80] J. Okuno, K. Maehashi, K. Kerman, Y. Takamur, K. Matsumoto, E. Tamiya, Label-free immunosensor for prostate-specific antigen based on single-walled carbon nanotube array-modified microelectrodes, Biosens. Bioelectron. 22 (2007) 2377–2381.
[81] Y. Onuki, U. Bhardwaj, F. Papadimitrakopoulos, D.J. Burgess, A review of the biocompatibility of implantable devices: current challenges to overcome foreign body response, J. Diabetes Sci. Technol. 2 (2008) 1003–1015.
[82] C. Ou, R. Yuan, Y. Chai, M. Tang, R. Chai, X. He, A novel immunosensor based on layer-by-layer assembly of gold nanoparticles-multi-walled carbon nanotubes-thionine multilayer films on polyelectrolyte surface, Anal. Chim. Acta 603 (2007) 205–213.
[83] S.D. Patil, F. Papadimitrakopoulos, D.J. Burgess, Dexamethasone-loaded poly(lactic-co-glycolic) acid microspheres/poly(vinyl alcohol) hydrogel composite coatings for inflammation control, Diabetes Technol. Therapeutics 6 (2004) 887–987.
[84] V.L. Paul, Integrated opto-chemical sensors, Sens. Actuators, B 8 (1992) 103–116.
[85] E.R. Post, M. Orth, P.R. Gershenfeld, N. Russo, E-broidery—design and fabrication of textile-based computing, IBM Syst. J. 39 (2000) 840–860.
[86] A. Radomska, E. Bodenszac, S. Głab, R. Koncki, Creatinine biosensor based on ammonium ion selective electrode and its application in flow-injection analysis, Talanta 64 (2004) 603–608.
[87] T. Reinvuo, M. Hannula, H. Sorvoja, E. Alasaarela, R. Myllylä, Measurement of respiratory rate with high-resolution accelerometer and EMFit pressure sensor, in: Proceedings of the IEEE Sens. J., 2006, pp. 192–195.
[88] R.L. Rich, D.G. Myszka, Advances in surface plasmon resonance biosensor analysis, Curr. Opin. Biotechnol. 11 (2000) 54–61.
[89] R.L. Rich, D.G. Myszka, Survey of the year 2000 commercial optical biosensor literature, J. Mol. Recognit. 14 (2001) 273–294.
[90] R.L. Rich, D.G. Myszka, Survey of the year 2001 commercial optical biosensor literature, J. Mol. Recognit. 15 (2002) 352–376.
[91] W.H. Ryu, Z. Huang, F.B. Prinz, S.B. Goodman, R. Fasching, Biodegradable micro-osmotic pump for long-term and controlled release of basic fibroblast growth factor, J. Controlled Release 124 (2007) 98–105.
[92] J. Sacristán-Riquelme, M.T. Osés, Implantable stimulator and recording device for artificial prosthesis control, Microelectron. J. 38 (2007) 1135–1149.
[93] C.S. Sander, J.W. Knutti, J.D. Meindl, A monolithic capacitive pressure sensor with pulse-period output, IEEE Trans. Electron Devices 27 (1980) 927–930.
[94] W. Sant, M.L. Pourciel-Gouzy, J. Launay, T. Do Conto, R. Colin, A. Martinez, P. Temple-Boyer, Development of a creatinine-sensitive sensor for medical analysis, Sens. Actuators, B 103 (2004) 260–264.
[95] A.S. Santos, A.C. Pereira, M.D.P.T. Sotomayor, C.R.T. Tarley, N. Durán, L.T. Kubota, Determination of phenolic compounds based on co-immobilization of methylene blue and HRP on multi-wall carbon nanotubes, Electroanalysis 19 (2007) 549–554.
[96] C.M. Sayes, F. Liang, J.L. Hudson, J. Mendez, W. Guob, J.M. Beach, V.C. Moore, C.D. Doyle, J.L. West, W.E. Billups, K.D. Ausman, V.L. Colvin, Functionalization density dependence of single-walled carbon nanotubes cytotoxicity in vitro, Toxicol. Lett. 161 (2006) 135–142.
[97] N.F. Sheppard Jr., D.J. Mears, Model of an immobilized enzyme conductimetric urea biosensor, Biosens. Bioelectron. 11 (1996) 967–979.
[98] J.H. Shin, Y.S. Choi, H.J. Lee, S.H. Choi, J. Ha, I.J. Yoon, H. Nam, G.S. Cha, A planar amperometric creatinine biosensor employing an insoluble oxidizing agent for removing redox-active interferences, Anal. Chem. 73 (2001) 5965–5971.
[99] Shun-rong Ji, Chen Liu, Bo Zhang, Feng Yang, Jin Xu, Jiang Long, Chen Jin, De-liang Fu, Quan-xing Ni, Xian-jun Yu, Carbon nanotubes in cancer diagnosis and therapy, BBA 1806 (2010) 29–35.
[100] N. Sinha, J.T.W. Yeow, Carbon nanotubes for biomedical applications, IEEE Trans. Nanobiosci. 4 (2005) 180–195.
[101] S.K. Smart, A.I. Cassady, G.Q. Lu, D.J. Martin, The biocompatibility of carbon nanotubes, Carbon 44 (2006) 1034–1047.
[102] A.P. Soldatkin, J. Montoriol, W. Sant, C. Martelet, N. Jaffrezic-Renault, Creatinine sensitive biosensor based on ISFETs and creatinine deiminase immobilised in BSA membrane, Talanta 58 (2002) 351–357.
[103] R. Srivastava, M.N. Weiss, H. Groger, P. Lo, S.F. Luo, A theoretical investigation of environmental monitoring using surface plasmon resonance waveguide sensors, Sens. Actuators, A 51 (1995) 211–217.
[104] T. Suchida, K. Yoda, Multi-enzyme membrane electrodes for determination of creatinine and creatine in serum, Clin. Chem. 29 (1983) 51–55.
[105] H. Suzuki, M. Sugimoto, Y. Matsui, J. Kondoh, Development of a dual-color optical fiber SPR sensor, IEEE Xplore (2005) 865–868.

[106] R. Tan, T. McClure, C.K. Lin, D. Jea, F. Dabiri, T. Massey, M. Sarrafzadeh, M. Srivastava, C.D. Montemagno, P. Schulam, J. Schmidt, Development of a fully implantable wireless pressure monitoring system, Biomed. Microdevices 11 (2009) 259–264.
[107] S.J. Tans, M.H. Devoret, R.J.A. Groeneveld, C. Dekker, Electron–electron correlations in carbon nanotubes, Nature 394 (1998) 761–764.
[108] S.C. Terry, J.H. Jerman, J.B. Angell, A gas chromatographic air analyzer fabricated on a silicon wafer, Electron Devices, IEEE Trans. (1979) 1880–1886.
[109] M.J. Tierney, H.L. Kim, M.D. Burns, J.A. Tamada, R.O. Potts, Electroanalysis of glucose in transcutaneously extracted samples, Electroanalysis 12 (2000) 666–671.
[110] A. Torres, B. Fiz, J.A. Galdiz, J. Gea, J. Morera, R. Jané, Assessment of respiratory muscle effort studying diaphragm movement registered with surface sensors, in: Animal Model (dogs) Conference of the IEEE EMBS, USA, 2004, pp. 3917–3920.
[111] A.J.C. Tubb, F.P. Payne, R.B. Millington, C.R. Lowe, Single-mode optical fibre surface plasma wave chemical sensor, Sens. Actuators, B 41 (1997) 71–79.
[112] L. Tymecki, E. Zwierkowska, R. Koncki, Screen-printed reference electrodes for potentiometric measurements, Anal. Chim. Acta 526 (2004) 3–11.
[113] P. Ugo, L.M. Moretto, F. Vezzà, Ionomer-coated electrodes and nanoelectrode ensembles as electrochemical environmental sensors: recent advances and prospects, ChemPhysChem 3 (2002) 917–925.
[114] S. Vaddiraju, I. Tomazo, D.J. Burgess, F.C. Jain, F. Papadimitrakopoulos, Emerging synergy between nanotechnology and implantable biosensors: a review, Biosens. Bioelectron. 25 (2010) 1553–1565.
[115] S. Viswanathan, Wu Li-chen, Ming-Ray Huang, Ja-an Annie Ho, Electrochemical immunosensor for cholera toxin using liposomes and poly(3,4-ethylenedioxythiophene)-coated carbon nanotubes, Anal. Chem. 78 (2006) 1115–1121.
[116] A.De. Vita, J.C. Charlier, X. Blase, R. Car, Electronic structure at carbon nanotube tips, Appl. Phys. A: Mater. Sci. Process. 68 (1999) 283–286.
[117] J. Wang, Glucose biosensors: 40 years of advances and challenges, Electroanalysis 13 (2001) 983–988.
[118] J. Wang, M. Li, Z. Shi, N. Li, Z. Gu, Direct electrochemistry of cytochrome c at a glassy carbon electrode modified with single-wall carbon nanotubes, Anal. Chem. 74 (2002) 1993–1997.
[119] J. Wang, M. Musameh, Y. Lin, Solubilization of carbon nanotubes by nafion toward the preparation of amperometric biosensors, J. Am. Chem. Soc. 125 (2003) 2408–2409.
[120] S.G. Weber, Signal-to-noise ratio in microelectrode-array-based electrochemical detectors, Anal. Chem. 61 (1989) 295–302.
[121] M.N. Weiss, R. Srivastava, H. Groger, Experimental investigation of a surface plasmon-based integrated-optic humidity sensor, Electron. Lett. 32 (1996) 842–843.
[122] P. Wick, P. Manser, L.K. Limbach, U. Dettlaff-Weglikowska, F. Krumeich, S. Roth, W.J. Stark, A. Bruinink, The degree and kind of agglomeration affect carbon nanotube cytotoxicity, Toxicol. Lett. 168 (2007) 121–131.
[123] R.D. Wilkinson, J.S. Harris, Waveguide surface plasmon resonance sensors, Sens. Actuators, B 29 (1995) 261–267.
[124] K.D. Wise, Integrated sensors, MEMS, and microsystems: reflections on a fantastic voyage, Sens. Actuators, A 136 (2007) 39–50.
[125] Y. Wu, A.P. Rojas, G.W. Griffith, A.M. Skrzypchak, N. Lafayette, R.H. Bartlett, M.E. Meyerhoff, Improving blood compatibility of intravascular oxygen sensors via catalytic decomposition of S-nitrosothiols to generate nitric oxide in situ, Sens. Actuators, B 121 (2007) 36–46.
[126] L. Yang, R. Vyas, A. Rida, J. Pan, M.M. Tentzeris, Wearable RFID-enabled sensor nodes for biomedical applications, in: Electronic Components and Technology Conferenc, IEEE, 2008, pp. 2156–2159.
[127] E.M. Yeatman, Resolution and sensitivity in surface plasmon microscopy and sensing, Biosens. Bioelectron. 11 (1996) 635–649.
[128] T. Yoshimura, Y. Yonezawa, H. Maki, H. Ogawa, I. Ninomiya, W.M. Caldwell, An ECG electrode-mounted heart rate, respiratory rhythm, posture and behavior recording system, in: International Conference of the IEEE EMBS, San Francisco, USA, 2004, pp. 2373–2374.
[129] G.Z. Yue, Q. Qiu, B. Gao, Y. Cheng, J. Zhang, H. Shimoda, S. Chang, J.P. Lu, O. Zhou, Generation of continuous and pulsed diagnostic imaging X-ray radiation using a carbon-nanotube-based field-emission cathode, Appl. Phys. Lett. 81 (2002) 355–357.
[130] Y.H. Yun, A. Bange, W.R. Heineman, H.B. Halsall, V.N. Shanov, Z. Dong, S. Pixley, M. Behbehani, A. Jazieh, Y. Tu, D.K.Y. Wong, A. Bhattacharya, M.J. Schulz, A nanotube array immunosensor for direct electrochemical detection of antigen–antibody binding, Sens. Actuators, B 123 (2007) 177–182.
[131] Yuan-Di Zhao, Yan-Hua Bi, Wei-De Zhang, Qing-Ming Luo, The interface behavior of hemoglobin at carbon nanotube and the detection for H_2O_2, Talanta 65 (2005) 489–494.
[132] K.J. Ziegler, Developing implantable optical biosensors, Trends Biotechnol. 23 (2005) 440–444.