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Silicon carbide: a versatile material for biosensor applications

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Abstract Silicon carbide (SiC) has been around for more than 100 years as an industrial material and has found wide and varied applications because of its unique electrical and thermal properties. In recent years there has been increased attention to SiC as a viable material for biomedical applications. Of particular interest in this review is its potential for application as a biotransducer in biosensors. Among these applications are those where SiC is used as a substrate material, taking advantage of its surface chemical, tribological and electrical properties. In addition, its potential for integration as system on a chip and those applications where SiC is used as an active material make it a suitable substrate for micro-device fabrication. This review highlights the critical properties of SiC for application as a biosensor and reviews recent work reported on using SiC as an active or passive material in biotransducers and biosensors.

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1 Introduction

The realization of bioelectronic devices based on wide bandgap (WBG) compound semiconductors has shown an increased interest in the recent years. The application of such materials for the realization of field effect transistors (FETs) (Lloyd Spetz et al. 2006; Yakimova et al. 2007) are just some examples of the multifunctional properties that make them promising materials in the fabrication of high performance microelectronic devices to interface with biological systems. One of the main concerns in materials research for biomedical applications is the search for materials that produce low or no adverse reaction when implanted in the body and that can be implanted for long term. In the field of semiconductors, silicon (Si) has always been the preferred substrate material for micro-devices due to its low cost and ready availability. However, it presents several drawbacks that limit its use in biomedical applications. Several researchers maintain that its cytotoxicity is cell dependent, and even Kubo et al. demonstrated the formation of nodules on periodontal fibroblasts as a release from the Si-bearing bioglass studied (Kubo et al. 1997). Moreover, the crystal orientation and bond strength of Si makes it relatively brittle (Chong et al. 2004) and hence prone to breakage upon insertion into living tissues, thus posing problems of retrieval and/or requiring complex packaging techniques, which limit both its appeal and applicability for microprobe fabrication (Gabriel et al. 2007). Si has been used in Ion Sensitive Field Effect Transistors (ISFETs) for interfacing with neuronal networks or living tissue (Bergveld 2003; Fromhertz 2005). Nevertheless, the implantation of a Si Utah probe in a cat's brain has resulted in a chronic astroglial response that limits the time of functionality of the device (Rousche and Normann 1998). The fact that Si is also opaque

to visible wavelengths, limits its applicability in certain fields (e.g. retinal implants) and may be undesired in others, where optical inspection/sensing might be also convenient (e.g. labeled biomarker detection). In general, the properties of WBG materials are superior to those of Si for biological applications, and can yield long term stability under chemically harsh environments and physiological conditions (Yakimova et al. 2007). A few examples of the extensive use of some WBG materials in the biomedical field include: GaN and AlGaN which have proven to be chemically stable and naturally biocompatible (Steinhoff et al. 2003). Particularly, the AlGaN/GaN heterostructures that give rise to the spontaneous formation of a two-dimensional electron gas at the heterointerface and which can be used for the efficient transduction of the surface adsorption of ions into a change of electronic conductivity. This technique has already been used for the sensitive recording of cell action potentials (Steinhoff et al. 2005) and is also a promising approach for protein-based biosensors. Likewise, AlGaN, AlN and ZnO present piezoelectric properties ideal to build resonator devices for high mass sensitive sensor devices and for biosensor applications (Otoole et al. 1992; Deger et al. 1998). AlN based light emitter devices (LEDs) are expected to emit in the deep UV (~210 nm) which makes it appealing for the detection of small toxic and cancer causing particles (Kawakami et al. 2007). Silicon carbide (SiC), possesses good biocompatibility (Kotzar et al. 2002; Coletti et al. 2007b; Frewin et al. 2009; Saddow et al. 2011) in addition to high chemical inertness and can be used to make different types of electronic devices with similar processes used in Si processing. For example, gas sensors (Fawcett et al. 2006; Lloyd Spetz et al. 2006) have been built, strong needles for organ transplantation monitoring (Gabriel et al. 2007) and Schottky devices for high power applications, which are commercially available (Infenion-Technologies 2012) among others.

In this paper we present a survey of the progress in SiC biosensor related research. We cover several aspects of this promising material in the biomedical area including the synthesis and preparation of SiC, its unique properties in biomedical and biosensing applications, the bio-functionalization of SiC and the ongoing research toward biosensor configurations that employ SiC both as a supporting substrate and as an active material, from neural prosthetics, microelectronic probes to its use as a BioMEMs substrate.

2 SiC polytypes, synthesis and preparation

SiC is a material that consists of the covalent bonding of Si and C atoms, in a tetrahedron form in which Si (or C) is the central atom. The high mechanical and chemical stability of the material are determined by the very short bond length, shown in Fig. 1, and hence, a very high bond strength

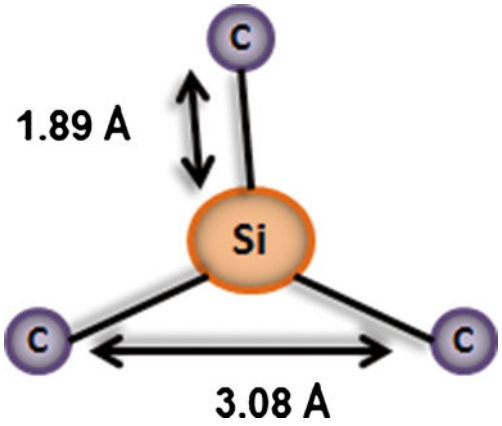

Fig. 1 All SiC crystals are formed via bi-layers of C and Si, covalently bonded to form a tetrahedron that forms the basic building block of SiC, adapted from (Saddow and Agrawal 2004)

present in the SiC structure (Mehregany et al. 1998; Deva Reddy et al. 2008). It belongs to the class of wide band gap (WBG) semiconductors with band gap energy that varies from 2.4 to 3.2 eV depending on the polytype.

SiC can be formed in amorphous, polycrystalline and monocrystalline solid forms. SiC has more than 200 polymorphic forms, called polytypes, but 3C-SiC, 4H-SiC and 6H-SiC are the most readily grown and can be purchased on the market and hence these are the polytypes for which most biomedically-oriented scientific work has been done. The stacking order of the double layers of Si and C atoms defines the different polytypes of SiC. In Fig. 2, the three different positions that the stacking sequence assumes in the lattice are reported as A, B and C, where k and h denote crystal symmetry points that are cubic and hexagonal, respectively. For example, 3C-SiC (or β-SiC), is the cubic form where the 3 delineates that 3 bi-layers of Si-C are needed to form the basic structure and C indicates that the crystal form is cubic. This polytype presents an ABC… sequence (Fig. 2 far right). 4H-SiC and 6H-SiC (α-SiC)

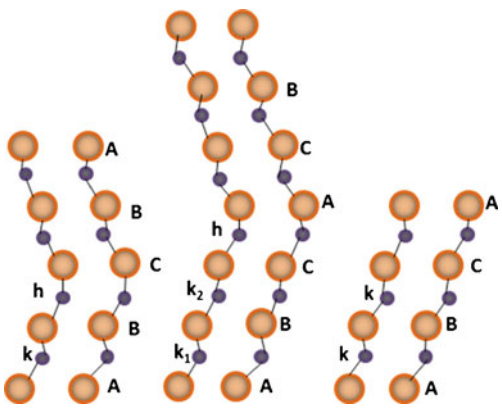

Fig. 2 Atomic stacking sequence of the relevant SiC polytypes viewed in the (Ellison et al.) plane. From left to right, 4H-SiC, 6H-SiC, and 3C-SiC, adapted from (Saddow and Agrawal 2004)

are the hexagonal forms, where the 4 and 6 delineate that 4 and 6 bi-layers are needed while the H indicates that the crystal form is hexagonal. They have stacking sequences that are ABCB (Fig. 2 far left) and ABCACB (Fig. 2 middle) for 4H-SiC and 6H-SiC, respectively.

The current commercially available wafers are 100 mm (4 in.) in diameter and are available in both n-, p- and intrinsic form (Müller et al. 2000). SiC bulk wafers are grown in a high temperature (>2,000 °C) furnace that is either gas-fed (Si and C containing precursors transported in a carrier gas) or solid-fed with SiC powder that is sublimated and condenses on a single-crystal SiC seed. Typical resistivities range from $1x10^5$ to $1x10^7$ Ω-cm for semi-insulating crystals (Aloysius et al. 2010).

The preferred method for single crystalline SiC films grown epitaxially is chemical vapor deposition (CVD) (Ellison et al. 1999), but liquid phase epitaxy (LPE) (Syvajarvi et al. 1999) and molecular beam epitaxy (MBE) (Chen et al. 1998) have also been used. As it is the case for SiC bulk growth, the growth of SiC thin films via homo-epitaxy also involves the use of a Si (e.g. silane (SiH_4), trichlorosilane (TCS) and dichlorosilane) and a C (e.g. propane (C_3H_8), methane (CH_4), and acetylene (C_2H_2)) containing precursor transported to the growth surface via carrier gas, which are typically hydrogen or helium (Larkin et al. 1994), for more details the reader is referred to (Saddow and Agrawal 2004). The growth of 3C-SiC on Si (hetero-epitaxy) typically involves three steps: first hydrogen surface etching to remove any native oxide that may be present, then a buffer layer is formed with the so-called carbonization step, which seeks to bond C to Si dangling bonds to create a first SiC layer, and finally the growth step which involves Si and C atoms delivered in the same way as described above for homoepitaxy (Nishino et al. 1983). Recently this process was adapted by several groups to allow for use of the hot-wall CVD reactor (Kordina et al. 1997) and it was discovered that the removal of the hydrogen etching step and the inclusion of a small amount of silane between the carbonization and growth steps resulted in very high quality films (Reyes et al. 2006, 2007). A more extensive description of the growth of homo-epitaxial films of 4H-SiC can be found in (Myers et al. 2005; Locke et al. 2012a).

Amorphous silicon carbide, denoted typically as *a*-SiC, is inherently insulating, it has high-K dielectric properties, high wear resistance, and works well as a durable coating, which is the product of the amorphous microstructure and low deposition temperatures used. The lower deposition temperature prevents any dopants that may be present during the deposition process from being electrically activated (Locke et al. 2012b). *a*-SiC is now being used as an inert encapsulating coating for *in vivo* prosthetics and it has been approved for commercial use as a coating for heart stents (Dzyadevych et al. 2006; Hehrlein 2009b). The deposition of *a*-SiC can be performed in a number of ways. including sputtering, CVD or PECVD, and pulsed laser deposition (PLD) (Locke et al. 2012b)

Polycrystalline materials consist of several small crystalline regions, called grains or crystallites, bonded together by crystallographically defective regions called grain boundaries. Grain formation in polycrystalline films grown using CVD processes is sensitive to several parameters such as temperature, deposition rate, dopant concentration, pressure, and impurity concentration. Unlike single-crystal SiC, polysilicon carbide, or poly-SiC, can be grown on a wide variety of substrates, at lower temperatures (500–1,200 °C), and a wider set of processes exist compared to monocrystalline epitaxial film growth. Poly-SiC growth has been demonstrated on widely used surface micromachining substrates such as Si, Si_3N_4, and SiO_2 (Beheim and Evans 2006). Likewise, the deposition of a poly-Si seed-layer on oxide to realize MEMS structures such as cantilevers and membranes can be easily released leaving behind high-quality 3C-SiC structures (Locke et al. 2010). For the crystalline form of SiC the dominant application is power electronic devices, where the crystal of choice is 4H-SiC due to it having the highest band gap (3.2 eV) while 6H-SiC is ideally suited for solid-state lighting (LEDs) as its lattice constant is close to that of the GaN family of alloys used in advanced LEDs (Saddow and Agrawal 2004).

On the other hand, the production of SiC nanoparticles can be done by different means. Yang et al., performed laser ablation of Si in ethanol, using a Ti/sapphire laser with a 1 mJ/pulse energy (1KHz repetition rate) at 800 nm wavelength to produce 3C-SiC nanoparticles in a water suspension (Yang et al. 2011b). Electrochemical methods, that involve etching of polycrystalline 3C-SiC followed by ultrasonication has been proposed by Wu et al. This method results in 3C-SiC particles with average size of 3.9 nm (Wu et al. 2005). A similar process has also been used by other authors to produce 6H-SiC nanoparticles (Rossi et al. 2008). A combination of UV radiation assisted electrochemical anodization etching and mechanical grinding of nanoporous 6H-SiC also yielded 6H-SiC nanocrystals as demonstrated by Botsoa et al. (Botsoa et al. 2007). Other methods include the production of SiC nanoparticles via a low pressure microwave plasma (Lin et al. 2008), and Leconte et al. showed the controlled synthesis of β-SiC nanopowders using an inductively coupled plasma (Leconte et al. 2008). These two methods give rise to amorphous and non-perfectly stoichimetric nanoparticle, whereas the synthesis of α-SiC nanocrystals by carbothermic reduction produces defective nanoparticles (Zhokhov et al. 2009). Laser pyrolisis of silane and acetylene have been used to produce nanoparticles with 10–25 nm size (Kamlag et al. 2001; Kassiba et al. 2002; Bouclé et al. 2005) and

some present a 2.5 nm diameter crystalline core and an amorphous shell that gives them a red luminescence. For more details and complete reviews in the topic, the reader is referred to (Andrievski 2006; Andrievski 2009).

3 SiC a unique material for biosensing

SiC's electrical, mechanical and thermal properties determine its suitability as a biomaterial and biosensing substrate. It possesses high thermal conductivity, on par with copper at room temperature (Wright and Horsfall 2007), its Young's modulus is higher than that of Si, and its high breakdown field~2 $MVcm^{-1}$ (Harris 1995), is double than that of Si.

SiC has been recognized as a viable material for applications involving high temperatures or hostile environments (Wright and Horsfall 2007). The chemical inertness of SiC suggests a high resistance to corrosion in harsh environments such as body fluids. In addition, its high elastic modulus, and low friction coefficient (Goldberg et al. 2001), make SiC an ideal material for smart-implants and *in-vivo* biosensors (Li et al. 2004).

Compared to other semiconductors, SiC's wide band-gap increases its sensing capabilities. For instance, 4H-SiC presents a bandgap of 3.23 eV thus greatly reducing the number of electron–hole pairs formed from the thermal activation across the band-gap, which allows high temperature operation of SiC sensors (indeed the intrinsic carrier concentration of SiC is ~10^{16}–10^{18} cm^{-3} while for Si is ~10^{10} cm^{-3}, more than 6 orders of magnitude lower than SiC (Sproul and Green 1991; Goldberg et al. 2001). In addition to the fact that its refractive index is greater than that of other materials, such as diamond, its transparency to visible light and UV wavelength absorption, make it an ideal material for optical based biosensing devices (Godignon 2005). Moreover, SiC nano-particles have the ability to exhibit photoluminescence (PL) at shorter wavelengths compared to Si nanoparticles, hence they are considered a promising material for optoelectronic devices (Boucle et al. 2002). The optical properties of SiC quantum dots and the luminescence behavior of *a*-SiC films may be found in the literature (Reboredo et al. 2004).

There are several biomedical applications that have been reported in the literature that employ SiC as a substrate. For instance, SiC has been used as substrate material for the construction of myocardial biosensors (Godignon 2005) and the amorphous form has been employed for coatings of neural probes (Hsu et al. 2007). Nevertheless, one of the main applications of SiC has been as a hard coating for non-fouling coronary heart stents (Rzany et al. 2000; Kalnins et al. 2002; Dzyadevych et al. 2006; Hehrlein 2009a). *In-vitro* and *in-vivo* tests done by Amon et al. showed that *a*-SiC on stainless steel stents had no cytotoxic reaction to L929 mice fibroblasts, and showed no thrombus formation on stented vessels after blood perfusion for 3 days (Amon et al. 1996). Moreover, they found that fibrin formation is significantly reduced at the *a*-SiC surface as compared with 316 L stainless steel heart stents. Rzany et al., exposed both 316 L stainless steel uncoated and coated with *a*-SiC to circulating human blood for 15 min, and observed a dense fibrin network with incorporated blood cells on the metallic surface whereas only single thrombi and erythrocytes were observed on the *a*-SiC-coated surface (Rzany et al. 2000).

A 2-year clinical study was conducted on 300 patients using the BIOTRONIK (Germany) Tenax stent covered with *a*-SiC. Only 1 % of the patients with the *a*-SiC coated stent presented an early coronary event due to subacute stent thrombosis compared to 2 % of patients with stainless steel stents and 3 % of those that had coronary angioplasty only. The authors concluded that *a*-SiC stents significantly reduced early and late coronary events, possibly due to the attenuation of progressive endothelial cell growth at the site of intervention (Kalnins et al. 2002). Several studies found similar results when implanting *a*-SiC stents with low rates of death, emergency revascularization, stent-related myocardial infarction and stent thrombosis (Ozbek et al. 1997; Carrié et al. 2001; Fournier et al. 2001). For a complete review in the topic see (Hehrlein 2009a).

SiC is also considered a popular material to be used as a passivation layer for prosthetic bone and hip implants. Biomorphic SiC ceramics are very promising as load bearing and base material for dental and orthopedic implants, mainly due to its excellent mechanical properties. Will et al. (Will et al. 2010) used biomorphous SiC that was processed from sipo wood by heating in an inert atmosphere and infiltrating the resulting carbon replica with a liquid silicon melt at 1,450 °C. After treatment with HF/HNO_3 the biomorphous preform consisted of β-SiC. An additional chemical treatment with HF/HNO_3 oxidized the surface producing negatively charged carboxylic ($-COO^-$) groups that effectively adsorbed Ca^{2+} ions on the surface of the porous biomorphous SiC. After performing in-vitro experiments using simulated body fluid, the authors observed a formation of a bone-like apatite reaction layer on the biomorphic SiC surface (Hehrlein 2009a). On the other hand, Santavirta et al. (Santavirta et al. 1998) investigated the cytotoxicity of Ti based pins for hip replacement implants compared to coated SiC-Ti pins. By using a colony outgrowth inhibition test of JCRB0603 cells, they found that SiC-Ti particles did not inhibit colony outgrowth (Santavirta et al. 1998). In their work, Saki et al. (Saki et al. 2009) investigated the viability and cell attachment of osteoblast like cell (Saos-2) on a ceramic bio-scaffold of hydroxyapatite-alumina and SiC (HA-Al_2 SiC). Cell growth and viability studies, using trypan blue, showed that the scaffold is able to support osteoblast attachment and growth, with 89 % of the cells harvested alive on the scaffolds compared to 97.5 % of

the cells harvested from tissue culture polystyrene flasks after 1 week. However, the authors concluded that the scaffold fabrication method needed to be optimized in order to improve the morphology of the cells that adhered to the surfaces (Saki et al. 2009).

It has been reported in the literature that some SiC-based whiskers and powders show a certain degree of toxicity (Svensson et al. 1997). For this reason, it is necessary to understand what form of SiC is needed for a particular application because SiC shows different biocompatibility trends according to the SiC type and the organism that it is brought in contact with (Saddow et al. 2011). Svensson et al. have studied the toxicity of asbestos and compared the hazardous crocidolite to SiC whiskers by studying the cloning efficiency of V79 cells (Svensson et al. 1997). These authors concluded that if the materials are not handled or processed properly they can exhibit high cytotoxiciy levels, dependent also on the concentration of the material. Nevertheless, Rödelsperger and Brückel demonstrated that carcinogenicity of SiC based particles is related to the shape and size of the fragments; whiskers being carcinogenic while granular SiC has a lower carcinogenic potency (Rodelsperger and Bruckel 2006). Bluet et al., reported on a selective cytotoxicity of 3C-SiC QDs *in-vitro* to epithelial and cancer cells. They investigated AT-84 cells, derived from oral squamous carcinoma as well as HSC-2 cells and S-G cells which are immortalized gingival epithelioid cells. The authors observed that significant changes of the AT-84 cells occurred after incubation with the SiC-QDs with indented borders and irregular shapes. Using MTTs assays they were able to show that treatment of the cells with 10 μg/ml and 50 μg/ml of NPs did not affect their viability after 72 h, however this was not so for the immortalized epithelioid cell line, which suggests the potential of SiC QDs as antitumoral agents (Bluet et al. 2012).

The porous form of SiC has also proven to be biocompatible and useful as a protein filter. The filters consist of suspended membranes fabricated from n-type and p-type 6H-SiC substrates. Rosenbloom et al. were able to pass proteins of up to 29000 Da and to exclude proteins in excess of 45000 Da which such membranes. The porous SiC membranes also exhibited low protein adsorption compared to commercially available polymer-based membranes indicating the potential of SiC membranes for bio-filtration (Rosenbloom et al. 2004)

The use of SiC in tissue engineering has also been investigated with particular interest in hernia repair and breast reconstruction. The work reported by Deeken et al. (Deeken et al. 2011) is one of the first to implement amine-functionalized SiC nanowires (SiCNWs) cross-linked to the extracellular matrix of a porcine tendon and compared to Au nanoparticles (AuNPs). In this case, SiC was chosen with the purpose to optimize the mechanical strength, resistance to degradation, and overall biocompatibility of the porcine tendon. They analyzed the viability of L929 murine fibroblast cells after 3 days of contact with uncrosslinked porcine tissue and used flow cytometry to demonstrate a viability of 72±4 % of cells on the uncrosslinked tissue compared to the viability of the cells on SiCNW-crosslinked tissues of 78±2 %, indicating that tissues crosslinked with SiCNWs are biocompatible, which was closer to the values obtained to crosslinked tissues with AuNPs (83± 3 %). The inclusion of SiCNWs or AuNPs did not alter the tensile strength of the tendons but they showed an improvement in their resistance to degradation by the collagenase enzyme with respect to the uncrosslinked tissue. This indicates the possibility to prevent early recurrence of hernias and provided more strength to the repair site during the remodeling process (Deeken et al. 2011).

Other authors have found that the effect of single crystalline SiC on cells or tissues proved to be non-invariant. The fact that SiC can be formed in different polytypes, as explained before, could be one of the reasons for this behavior. For instance, Colleti et al. tested the biocompatibility of crystalline SiC using *in-vitro* techniques with B16-F10 mouse melanoma, BJ human fibroblast, and human keratinocyte (HaCaT) cell lines, and found that there was qualitatively no difference between 3C, 4H- and 6H-SiC in terms of cell viability and proliferation (Coletti et al. 2007b). An *in-vitro* study performed by Frewin et al. on 3C-SiC and nanocrystalline diamond with PC12 (rat pheochromocytoma) and H4 (human neuroglioma) cell lines showed superior lamellipodia permissiveness on 3C-SiC compared to Si. But the cells on the other polytypes, 6H- and 4H-SiC, showed reduced cell viabilities and substrate permissiveness (Frewin 2009; Frewin et al. 2009). The same group also investigated biocompatibility of 3C-SiC *in-vivo* using C56BL/6 mice. They compared the response of 3C-SiC against Si at 5, 10, and 35 days after implanting the materials in the mouse's brain. Using CD45 dye to observe the activation of microglia and macrophages, the authors showed that the 3C-SiC surfaces revealed limited immunoresponse and significantly reduced microglia compared to the Si substrate (Frewin et al. 2011).

It has also been determined that less biofouling and platelet aggregation occurred on 3C-SiC when exposed to blood, which can be an advantage for bioelectronic device fabrication. Schettini et al., concluded that 3C-SiC is a hemacompatible material compared to 4H- and 6H-SiC which did not show the same behavior. In fact 4H- and 6H-SiC were similar to Si, a known non-hemacompatible material (Schettini et al. 2012). The different responses of the skin, brain and blood cells to the three popular SiC polytypes may be attributed to the surface charge, roughness and the chemical properties of the surface. Clearly it is very important to know which form of SiC is being exposed to biological matter as it may indeed affect the response.

Finally, implantable biosensors formed from 3C-SiC, while bio-benign, must also adopt approaches to address the challenges of chronic indwelling biocompatibility. Among these are; design approaches that eliminate sharp edges that will otherwise be a source of tissue irritation that provoke the inflammatory response (Anderson 1993), surface modification with biomimetic chemistries such as polyethylene glycol (PEG) and methacryloyloxyethyl phosphorylcholine (MPC) that have been shown to resist extracellular matrix protein adsorption/denaturation (Abraham et al. 2005; Nederberg et al. 2006), the use of bioresponsive hydrogels (Wilson and Guiseppi-Elie 2012) in support of the chronic release of anti-inflammatory and immunosuppressant drugs such as dexamethasone (Barnes 1995; Goodman et al. 2011) and the release of factors such as vascular endothelial growth factor (VEGF) that promotes vascularization (Ward et al. 2003) and basic fibroblastic growth factor (bFGF) that promotes angiogenesis (Takagi et al. 2011). These approaches are among those actively under investigation as a means to limit fibrotic encapsulation (Ratner 2004) of implantable biosensors (Kotanen et al. 2012).

The major advantages of 3C-SiC in biosensor application are its chemical inertness and thus likely robustness to wear and oxidative degradation following implantation. The ease and reproducibility of quantitative surface modification and functionalization also supports quantitative immobilization of biomolecules leading to high reproducibility and a likely low coefficient of variation in bioanalytical applications. The likely disadvantages are its lack of compliance with tissue and the challenge of its functional integration with more complex systems, including forming ohmic contacts.

3.1 Chemical modification of SiC

Most biomolecule recognition-based systems require immobilization of specific molecules with controlled structural order and composition. A viable immobilization approach is covalent attachment (Brahim et al. 2003) Surface functionalization provides many advantages in the development of semiconductor based biosensors, including the control of the interfacial properties of the substrate material itself. In addition, surface functionalization is one of the main tools used for covalent biomolecule immobilization. It may be used for imparting molecular functionality to the substrate, thus enabling sensitivity towards chemical stimuli (Stutzmann et al. 2006). The surface functionalization of silicon dioxide (SiO_2) has been widely studied (Bierbaum et al. 1995), however, it is an unsuitable material as a gate-dielectric for biochemical field-effect transducers (ISFETs) because it can be unstable in electrolytic solutions (Matsuo et al. 1979). Likewise, high noise levels in Si-based electrolyte SiO_2 FETs have been documented because of trapping and de-trapping carriers at the SiO_2-Si gate interface (Jakobson et al. 1998).

SiC is a very promising and interesting material for surface functionalization because the formation of a very thin native oxide on its surface facilitates the successful surface termination that is the prerequisite in the realization of devices (e.g. MOSFETs). In general, hydrogen- (−H) or hydroxide- (−OH) terminated surfaces provide the reactive sites necessary to obtain high quality monolayers and both have been extensively studied and provide evidence for the passivation of the SiC surface (Tsuchida et al. 1999; Seyller 2004; Coletti et al. 2007a; Dhar et al. 2009).

Both theoretical and practical studies have been performed to gain insight into the bio-functionalized SiC. Cicero and Catellani employed first principle predictions of the chemical processes that lead to the adsorption of organic molecules on the Si face of the 3C-SiC (001) surface. They focused their work on acetic acid (CH_3–COOH), methanol (CH_3–OH), methanethiol (CH_3–SH) and methylamine (CH_3–NH_2). Their results suggest a larger stability of the functionalization for the studied groups on SiC compared to those on Si (Cicero and Catellani 2005; Catellani and Cicero 2007). Other theoretical studies have shown that biotin chemisorption, a link to specific proteins such as streptavidin and avidin, occurs on hydroxylated SiC (001) surfaces retaining its electronic properties responsible for its strong affinity to proteins (Kanai et al. 2005). Preuss et al. combined *ab initio* calculations of structure, energetics and surface core-level shifts with LEED (electron diffraction) and XPS (X-ray photoelectron spectroscopy) experimental data to study pyrrole-functionalized Si- and C-terminated SiC surfaces (Preuss et al. 2006). The comparison with theoretical calculations led to the conclusion that the molecules adsorbed on the surface via N-H dissociation and the formation of covalent N–Si bonding. However, the adsorption on the C face was unstable and the authors postulated that this may be due to the negative adsorption energy. Baffou et al. combined scanning tunneling microscopy (STM) and density-functional theory (DFT) studies to understand the interaction of phthalocyanine molecules (H_2Pc) with the 6H-SiC (0001) surface. H_2Pc molecules were found to chemisorb through a cycloaddition reaction of two conjugated imide groups with two Si adatoms (Baffou et al. 2007; Baffou et al. 2009). In the work performed by Boudrioua et al. the authors presented a similar study but also studied the chemisorption of the N,N'-bis(1-hexylheptyl)perylene-3,4:9,10-bis(dicarboximide) (DHH-PTCDI) and phthalocyanine (H_2Pc) on the 6H-SiC (0001) surface. They showed that larger molecules like PTCDI were able to adsorb on the hexagonal SiC crystal surface and that the adatom-adatom distance on SiC may allow direct adsorption of larger molecules via cycloaddition, as was the case for the H_2Pc molecules. In fact, they observed the formation of two Si-N bonds in the H_2Pc/SiC system and two Si-O bonds in the PTCDI/SiC system. They considered the first molecule

as a good candidate for organic functionalization, and the second for use in the field of nanomachines (Boudrioua et al. 2012).

The experimental studies of SiC functionalization has been based mainly in SAMs (self-assembled monolayers). Rosso et al. demonstrated successful alkyl monolayers covalently bound on HF-treated silicon carbide surfaces (SiC), including 6H-SiC (0001) and 6H-SiC $(000\bar{1})$ and polycrystalline 3C-SiC, through thermal reaction (Rosso et al. 2008) and UV irradiation (Rosso et al. 2009) with 1-alkenes. They concluded that the attachment of alkyl chains on the SiC surfaces seemed to occur via the formation of an ether bond between a thin oxycarbide layer and the second carbon of the double bond. Their results included very hydrophobic methyl-terminated surfaces on flat SiC, which they showed to be stable under harsh acidic conditions (e.g., no change in water contact angle after 4 h in 2 M HCl at 90 °C), while their stability in alkaline conditions (pH11 at 60 °C) also superseded that of analogous monolayers such as those on Au, Si, and SiO_2. Similarly, Schoell et al. demonstrated the covalent functionalization of aminopropyldiethoxymethylsilane (APDEMS) and octadecyltrimethoxysilane (ODTMS) on n-type 6H-SiC (0001) (i.e., Si-face) surfaces via wet chemical processing techniques (Schoell et al. 2008). Desorption temperatures in the range of 830 K proved the covalent bonding of the organic molecules to the SiC surface. They also immobilized fluorescence-labeled proteins on patterned APDEMS monolayers to prove the functionality of the surface and the wettability contrast obtained on a micropatterned ODTMS-modified 3C-SiC surface (Schoell et al. 2008). This group also developed a plasma-based method to passivate n-type 6H-SiC with chlorine and obtained almost flat band conditions on the 6H-SiC (0001) surface. Hence, they were able to perform successful ultraviolet light-induced grafting of trifluoroacetamid (TFAAD-protected long-chain ω-unsaturated amine (10-aminodec-1-ene)) and thermally induced alkylation with 1-octadecene on both 6H-SiC (0001) and 6H-SiC $(000\bar{1})$ (Schoell et al. 2011). Later, Howgate et al. focused on the impact of UV photocatalytic cleavage on n- and p-type GaN and SiC with covalently bound self-assembled monolayers (SAMs) formed from ODTMS. They found that significant and rapid photocatalytic degradation of the organic layer occurred on n-type GaN. Their results proved that the charge-transfer processes between semiconductors and organic systems depends on the positions of the conduction and valence band edges and can be tailored by appropriate choice of the semiconductor Fermi level (Howgate et al. 2010).

Aghdassi et al., investigated the suitability of octadecylsiloxane (ODS) on 6H-SiC (0001) as an insulating dielectric for electronic passivation of the surface. They used XPS, ultraviolet photoemission spectroscopy (UPS) and inverse photoemission (IPE) experiments and concluded that a large HOMO–LUMO energy gap of about 9 eV is present in the ODS-SiC system. Barrier heights of 3.3 eV and 2.7 eV were observed for electron and hole transport from the substrate into the adlayer and contributed to demonstrate their hypothesis and presented an extensive description of the electronic and structural properties of the silane-SiC interface (Aghdassi et al. 2012).

Williams et al. also looked into the immobilization of proteins onto functionalized SiC. They demonstrated selective immobilization of streptavidin via biotinylation of 4H-SiC (0001) functionalized with APTES. The biotin-streptavidin is a strong bond (K_d, on the order of 4×10^{-14} M; ca. 425 pN) (Wong et al. 1999) that is routinely used as a model substrate for biomolecule detection. In their work, the authors found, using different characterization techniques that included XPS, ellipsometry, contact angle and fluorescence microscopy, that an optimization of the APTES layer was critical to the successful streptavidin immobilization, in addition to a biotinylation step prior to the streptavidin attachment to prevent non-specific binding of this protein with the 4H-SiC|APTES surfaces (Williams et al. 2012). What is interesting in their work is that they present an alternative hydroxylation to the diluted HF dip step used by other authors, and employed instead a treatment with oxygen plasma (20 % O_2/80 % Ar) to grow a thin oxide followed by exposure to air for 2–3 h to allow for chemisorption of water molecules that facilitates the silanization process (Williams et al. 2012).

Petoral et al. reported on the surface functionalization with mercaptopropyltrimethoxysilane (MPTMS) of wide band gap semiconductors including SiC, ZnO, and GaN. They used n-type 4H-SiC (both 4H-SiC (0001) and 4H-SiC $(000\bar{1})$), and the MPTMS monolayers were prepared by evaporation of a pure solution in a sealed vacuum chamber for 1 h. Using XPS and water contact angle measurements they observed the formation of a monomolecular layer of MPTMS on the SiC surfaces (Petoral et al. 2007). In addition, they immobilized an amino acid derivative pTyr-PT but only on MPTMS-functionalized ZnO and GaN surfaces. Yakimova et al. used a similar process to functionalize SiC and, in addition to MPTMS, also studied APTES films on 4H-SiC. They also evaluated the electrical contribution from the organic layers and their behavior as a possible insulator on SiC, similar to SiO_2. They used silver epoxy as a back contact and a thick probe as the gate contact. What they found was that the device exhibited a Schottky diode like I-V characteristic similar to a refer a reference sample with no isolation layer and one sample with a 1 nm SiO_2 (Yakimova et al. 2007).

Bhowmick et al. demonstrated the successful covalent functionalization of quartz and n-type 6H-SiC with APTES and benzo(ghi)perylene-1,2-dicarboxylic dye. The authors used XPS to show the presence of the APTES layer

but concluded that not all amino groups of the APTES-functionalized surfaces reacted to bind the dye molecules (Bhowmick et al. 2012). They also found that the dye functionalization was not uniform throughout the surface, showing different island sizes of the dye and including different chemical environments on SiC. Nevertheless, their fluorescence lifetime measurements indicate the presence of more than one local environment for surface-bound benzo (ghi)perylene-1,2-dicarboxylic anhydride independent of the substrates and that the single-crystal SiC surface provided a more homogeneous environment than the quartz surface (Bhowmick et al. 2012). Protein resistant SiC surfaces, to prevent device failure due to fibrous encapsulation, were investigated by Qin et al. The authors prepared films terminated with oligo(ethylene glycol) (OEG) via photochemical grafting onto 3C-SiC. By immersing the OEG coated samples in a 0.1 % fibrinogen solution in PBS for 1 h they determined, using the N1s signal from XPS, that the OEG coating reduced the non-specific adsorption of fibrinogen on the substrates by 99.5 % and remained resistant after storage in PBS for 4 weeks at 37.1 °C (Qin et al. 2010).

In a previous study, we have also implemented the surface functionalization of 6H-SiC (0001) to increase its *in-vitro* biocompatibility to H4 and PC12 cells. We performed silanization with APDEMS and APTES to realize hydrophilic surfaces and alkylation with 1-octadecene to produce hydrophobic surfaces. In all cases, the cell proliferation was observed to improve with respect to untreated, 6H-SiC surfaces, with up to a 2 times increase in viability on 1-octadecene modified surfaces, up to 6 times increase with APDEMS modified surfaces, and up to 8 times increase with APTES modified surfaces (Oliveros et al. 2012).

Recently, the preparation of polymer brushes on SiC substrates has been demonstrated by Steenackers et al. as a strategy to obtain biosensors with higher loading capacities and enhanced sensitivities. It is also assumed these would create systems that more closely resemble real biological environments (Steenackers et al. 2010). They implemented a self-initiated photografting process and photopolymerization (SIPGP) of styrene and N,N-dimethylaminoethyl methacrylate (MAEMA) onto C-OH terminated 6H-SiC $(000\overline{1})$ surfaces in a single step reaction. The same process was achieved on the Si-OH terminated 6H-SiC (0001) surfaces using a carbon templating (CT) technique. They found that the CT technique could allow for the control of the 2D location of the polymer brushes and the grafting density of functional groups that could lead to patterned protein functionalized SiC surfaces (Steenackers et al. 2010).

4 Biosensor configurations employing SiC

From the device design perspective, SiC has mainly been considered an ideal material for power devices and systems. However, as we have described in the previous sections, its properties also make it suitable for biomedical applications. For the construction of biological MEMs devices, 3C-SiC is the material of choice because it is less expensive, less polar than other SiC polytypes and is grown on Si which permits the implementation of the processing techniques used for that material (Zorman 2009; Godignon et al. 2010). Depending on the device to be built, the different forms/polytypes of SiC provide specific advantages. For instance, for biomedical devices that requires low leakage and/or biochemical inertness whereas the films needed for construction of MEMs devices demand certain mechanical properties. In Table 1 a list of typical applications with potential for success and the material type recommended, based in the work of (Godignon 2005).

4.1 Electrically-based SiC biosensors

The electronic properties of SiC have made it a suitable material for biomedical devices, especially those that are based on a surface impedance change or are electrochemistry related. For these particular applications, the dopants, doping level, surface termination and choice of SiC polytype play an important role, since the background current

Table 1 Main sensors application and SiC polytype and requirements, adapted from (Godignon 2005)

Device application	SiC polytype/form	Material criteria for application
Biomedical sensors	Semi-insulating hexagonal polytype (4H-SiC/6H-SiC)	• Transparency • Low leakage (at room temperature)
	Porous hexagonal polytype (6H-SiC)	• Thick free standing layers
	SiC (amorphous) coating	• Biochemical inertness
Hall and temperature sensors	Semi-insulating 4H-SiC with epilayer	• Low leakage (at high temperature)
MEMs-NEMs resonators	Heteroepitaxial (3C-SiC)	• Low gradient and in-plane stress
Pressure sensors, accelerometer, HT gas sensors	Heteroepitaxial (3C-SiC)	• Low gradient and in-plane stress • Appropriate electrical characteristics

and voltammetric reactivity of SiC electrodes would be affected. When SiC is appropriately doped, the conductivity of this material dramatically increases and exhibits electrical characteristics similar to carbon materials (Chu et al. 1995). But in contrast to carbon, the close-packed hexagonal or cubic-SiC structure should afford a well-defined surface for electron transfer (Pierson 1999). Thus, the use of doped SiC as an electrode material has not been widely researched for electrochemistry based applications. In the work performed by Hume and Kolthoff, a SiC electrode was used as an oxidation-reduction indicator electrode in potentiometric titrations of potassium iodide with permanganate and with ceric sulfate of ferrous iron with permanganate, of titanous chloride with ferric chloride, and of hydrochloric acid with sodium hydroxide (Hume and Kolthoff 1941). The electrodes were made with single crystal SiC and their behavior was studied by measuring their potential against a calomel electrode. The authors concluded that the SiC electrode behaved similarly to an oxidation-reduction indicator material such as Au and Pt. Meier et al. implemented a chemical vapor deposition method using tetramethylsilicon and a resistively heated carbon fiber to produce a concentric SiC conductor that proved to be suitable for voltammetric measurements (Meier et al. 1996). They found that the SiC electrode in 0.1 M H_2SO_4 showed a wide potential window, free from interference from +1.4 V to −1.2 V vs Ag/AgCl electrode. These findings led to the construction of different SiC electrode applications. For instance, Singh and Buchanan built a SiC-C fiber electrode for detection of electroactive neurotransmitters, namely dopamine and vitamin C (Singh and Buchanan 2007). The fabrication of this electrode was based on an electrolytic etching technique developed by the authors. The SiC provided insulation near the carbon tip and highly localized charge transfer, stiffness and protection by inhibition of O_2, H_2O and ionic diffusion. The sensing of dopamine hydrochloride and vitamin C was done by voltammetric and impedance spectroscopy techniques, monitoring oxidation currents that varied linearly with their concentration. They also recorded *in-vivo* action potentials from anesthetized rat brains with very high signal to noise ratio. Wu et al. also worked on the detection of ascorbic acid (AA) and dopamine (DA) (Wu et al. 2011). In their study they were able to resolve the overlapping voltammetric responses of AA, DA and uric acid (UA) on a SiC-coated glassy carbon (GC) electrode, and the selective determination of DA in the presence of AA and UA with a sensitivity of 16.9 A $M^{-1}cm^{-2}$ and a detection limit of 0.05 μM. Their sensor exhibited excellent selective electrocatalytic behavior for the electro-oxidation of AA, DA, and UA for simultaneous determination of AA, DA, and UA (Wu et al. 2011). Salimi et al. used SiC nanoparticles to modify a GC electrode to detect insulin concentrations via electrocatalytic oxidation (Salimi et al. 2009). Using cyclic voltammetry, differential pulse voltammetry (DPV) and flow injection analysis (FIA), the authors found a dynamic linear range of detection up to 600 pM, sensitivity of 710 $pApM^{-1}cm^{-1}$ and detection limit of 3.3 pM. Their electrode demonstrated high sensitivity, excellent catalytic activity, short response time, and long term stability. They also showed a simple sensor preparation method without using any specific electron transfer mediator or specific reagent (Salimi et al. 2009). A superoxide dismutase (SOD) biosensor based on SiC nanoparticles has been reported by Rafee-Pour et al. The characterization and analytical performance of the biosensor was based on direct voltammetry and amperometry of immobilized SOD onto the surface of a GC electrode modified with silicon carbide nanoparticles. They found that the response of the sensor was stable after 24 h. of storage in a pH7 solution, perhaps due to the chemical stability of the SiC film. And the sensor response showed 95 % of the initial response after 10 days and 90 % after 15 days, which could be due to the time when the enzyme activity starts decreasing. In addition, they demonstrated that the sensor presented a sensitivity of 1.46 $nA*\mu M^{-1}$ and 1.375 $nA*\mu M^{-1}$ with a detection limit of 1.66 μM and 1.4 μM for cathodic or anodic detection of superoxide respectively (Rafiee-Pour et al. 2010) . In the recent years, research has been focused on the detection of DNA bases via electrochemical methods on SiC modified sensors. Ghavami et al. implemented a glassy carbon (GC) electrode modified with SiC nanoparticles for simultaneous determination of DNA bases using differential pulse voltammetry (DPV) (Ghavami et al. 2011). They found that no specific electron transfer mediator or reagent was necessary to build the biosensor. The detection limit of the GC/SiC electrodes toward guanine (G), adenine (A), thymine (T) and cytosine (C) determinations were 0.015, 0.015, 0.14, and 0.14 μM, respectively and the sensitivities were 0.3877 0.3289 0.0175 and 0.0499 μA/μM, respectively. The sensor exhibited good stability, reproducibility and long lifetime. They also studied the effect of interferences of bovine serum albumin (BSA), L-cysteine, ascorbic acid, uric acid and lactic acid in 0.1 M PBS (pH7.4) on differential current response of the DNA bases and found that the interference effects of the above analytes toward electrode response of DNA bases were negligible when the concentration ratio of interferences to DNA base was more than 20 times (Ghavami et al. 2011). Yang et al. presented the surface modification of nanocrystalline SiC with diazonium salts via electrochemical methods for later DNA bonding with a nitrophenyl film to the modified electrodes (Yang et al. 2011a). They showed that the modified electrode presented a wider potential window and lower background current than GC electrodes. The authors also demonstrated successful DNA immobilization on the modified SiC surfaces using Cy5 labeled cDNA with increased red fluorescence on the

nitrophenyl|SiC surfaces compared to the bare SiC. Likewise, the voltammogram of hybridized DNA indicated the presence of target DNA (Yang et al. 2011a).

Godignon's group has focused their efforts on developing temperature and impedance based sensors on SiC. Mainly needles for open heart surgery monitoring or graft monitoring of organs during transplantation and transportation. They concluded that the control of the surface properties of the material is a challenge when building biomedical devices (Godignon 2005). Their impedance microsystem consisted of four Pt electrodes on an isolated semi-insulating SiC substrate. A Pt serpentine conductor served as the temperature sensor with the aim of distinguishing impedance changes due to either tissue or thermal effects. In their work, the authors also identified the advantages and potential of using SiC for DNA polymerase chain reaction (PCR) electrophoresis chips because of the high electric field strength and resistivity of semi-insulating SiC, in addition to its high thermal conductivity (Godignon 2005). The same group expanded the description of myocardial ischemia monitoring probes and transplantation organ/tissue ischemia monitoring with SiC impedance based needles in the articles by Pascual et al. (Pascual et al. 2004), Gabriel et al. (Gabriel et al. 2007) and Gomez et al. (Gomez et al. 2006). The article by Pascual et al. focuses on the fabrication, packaging and mechanical properties of the devices for such application, whereas the last two also consider the electrical characterization of the probes.

In their study, Pascual et al. described the fabrication of the needles on both 6H-SiC and 4H-SiC wafers with four Pt electrodes insulated from the substrate and passivated with SiO_2 and Si_3N_4 layers including the temperature sensor structure described above. The mechanical tests they performed included simulations with ANSYS 5.6 and an INSTRON 4464 system to test compression and bending of the needles. The authors also determined the forces needed to penetrate heart tissue. The values obtained were 1.32 N, which was lower than 1.35 N for Si. Likewise, the maximum bending force that could be applied to the needle tip without breakage of the same was 17.4 N compared to 16.4 N for Si. The fact that the needles fulfill the mechanical requirements for this application are an indication of the possibility of using these types of probes to reduce organ bleeding upon needle insertion (Pascual et al. 2004).

In terms of the benefits of using SiC as ischemia monitoring probes, both Gomez et al. (Gomez et al. 2006) and Gabriel et al. (Gabriel et al. 2007) concluded that there is less leakage current in a SiC impedance sensor compared to Si-based devices that present current leakage paths across the substrate at high frequencies (i.e. above 5 kHz), which generates a false impedance change (Gomez et al. 2006). In fact, Gomez et al. compared *in-vitro* experiments of four electrode measurements in 0.09 % or 0.9 % NaCl from 10 Hz to 1 MHz with a modified *in-vivo* system where the probes where placed close to the cortico-medullar junction of male Wistar rats (*Ifa Credo*) and measured the impedance in the 100 Hz to 100 kHz range. They demonstrated that the operating range of SiC-based impedance probes can be extended up to the 100 kHz range with the possibility of performing multi-frequency analysis and the creation of more accurate frequency-dependent analytical models of impedance (Gomez et al. 2006). Gabriel et al., besides performing *in-vitro* characterization of the device, present in their article an extensive mechanical analysis of the Si and SiC wafers used to build their probes (Gabriel et al. 2007). They confirmed the values for hardness, elastic modulus and fracture toughness of the SiC and Si substrates but also the modulus of rupture for the fabricated probes. They emulated real-life conditions in a deflection test whereby they anchored the needle at one end and applied force from the nanoindenter on the other. The critical load at which the SiC needles fractured was 2.5 times higher than for Si needles (1053±200 mN *vs.* 452±37 mN). In addition, they found a modulus of rupture 4 times higher for SiC needles than that of Si needles (774 MPa *vs.* 188 MPa), which demonstrated the superior mechanical and electrical properties of SiC for impedance based needle probes (Gabriel et al. 2007)

Multi-electrode arrays (MEAs) with semi-insulating 6H-SiC have also been demonstrated by Godignon et al. In their article, the authors describe the construction of a 16 electrode MEA with locally grown carbon nanotubes (CNTs) on Pt electrodes to improve the electrode to medium impedance and growth of neurons on the MEAs. A reduction in the electrode impedance was obtained with CNTs grown on the Pt electrodes compared to bare Pt electrodes. In addition a uniform CNT growth on SiC based MEAs was achieved because of the better temperature uniformity on the material. In the same work the authors describe the material considerations to build a micro-fluidic chamber with 3C-SiC on silicon-on-insulator (SOI) wafers, for magnetic resonance imaging (MRI) equipment (Godignon et al. 2010).

The area of Field Effect Transistors (FETs) on SiC has not been significantly exploited for biological applications. FETs made of SiC can function at high temperatures, in particular FET-based gas sensors that operate around 1,000 °C have made used of this property (Lloyd Spetz et al. 2004). Also, prototypes and commercially available devices can be found that operate at very high frequency, high power and in harsh environments, such as Schottky devices from Infineon Technologies (Germany) (Infenion-Technologies 2012), UV flame detectors from General Electric (U.S.A.) (Brown et al. 2002) and gas sensors developed by SensicAB (Sweeden) (SenSiCAB 2012) . The possibility to integrate SiC and grow other materials on its surface, for example AlN that enables a wider bandgap~6 eV (depending on the polytype), allows the

integration with resonators on the same chip (Lloyd Spetz et al. 2006). Lloyd Spetz et al. reported the measurement of NO, an interesting gas to measure due to its participation in the metabolism in an individual's breath (Lloyd Spetz et al. 2009). They proposed a multifunctional sensor device with an integrated transistor, resonator and resistivity change measurements. A heterostructure that may be realized, for example SiC|ZnO, as in Fig. 3, can provide biosensing based on the current change between the source and drain as a function of the gate voltage after immobilization of biomolecules in the gate area. A FET biosensor of this type, responsive to E_H changes in the environment modulated by a biological reaction, is known as an ion specific FET (ISFET) device. An ISFET is in essence a transistor without a gate electrode that requires an external reference electrode for operation. For this reason, the authors investigated a preliminary device using a MOS (metal on semiconductor) structure using Ti/Au, Al_2O_3 and a Si substrate (Lloyd Spetz et al. 2009).

4.2 Optically-based SiC biosensors

As was mentioned in Section 3, SiC also presents appropriate optical properties to develop biocompatible optical based detection sensors. In particular, quantum dots (QDs) have proven to be a growing research field for SiC. QDs are interesting tools for cell tagging because of their properties including: their size and tunable emission spanning from the ultraviolet to the near infrared, the high extinction coefficient combined with a comparable quantum yield to fluorescent dyes, and resistance to photo-oxidation (i.e. photobleaching) (Botsoa et al. 2008). Botsoa et al. bioimaged living cells with SiC QDs. They fabricated 3C-SiC nanoparticles by means of electrochemical anodization of a low resistivity 3C-SiC polycrystalline wafer and subsequent grinding and centrifugation to collect particles less than 10 nm in size. Different concentrations (0.1 to 2 g/l) of the SiC QD suspension was added to 3 T3-L1 fibroblasts and incubated for 15 h. and then analyzed with fluorescent microscopy, using UV/violet excitation. The authors found that the QDs are strongly localized inside the cells, mainly at the nucleus and noticed a heterogenous distribution of the fluorescent intensity. The cells were also incubated for 1 week with QDs and were found to be alive, which evidenced the non-toxic effect of the 3C-SiC particles to the cells (Botsoa et al. 2008) . Another material that is showing good promise as an optical biosensor substrate is amorphous SiC, or a-SiC. Caputo et al. have reported on a two-color a-Si/a-SiC photosensor for DNA detection. The sensor is based in the detection of DNA strands labeled with two fluorochromes (Alexa Fluor 350 and Cy5) using a p-i-n-i-p a-Si/a-SiC stacked structure that basically detects different spectral regions depending on the voltage applied to the diode structure (Caputo et al. 2008). They used a UV radiation source that excited the biomolecule markers inducing fluorescence; the re-emitted light passed through a glass/TCO layer and was absorbed by the a-Si/a-SiC photosensor producing a photocurrent that was proportional to the quantity of fluorochromes present. In this work, the authors reported detection limits of 10 nmol/l and 400 nmol/l for Alexa Fluor 350 and Cy5 labeled DNA strands, respectively (Caputo et al. 2008). But SiC can also be used for biological imaging in fluidic environments. Taubner et al. reported the successful development of a 3C-SiC based superlens for near-field scanning optical microscopy (NSOM) (Taubner et al. 2006). A free standing 440 nm thick 3C-SiC film grown on a (100) Si substrate is the core of the superlens with a 220 nm thick SiO_2 film that allows the thin film superlens to be displaced at the required distance (~880 nm) from the specimen when applying the NSOM technique. The use of a SiC superlens structure allowed them to enhance the spatial resolution of the subsurface features by a factor of 4 compared with near-field imaging without superlensing of the SiC slab. The possibility of incorporating a 3C-SiC superlens to a microfluidic device could enable in-situ NSOM imaging of biological samples. An evanescent waveguide structure microfabricated in SiC on Si substrates was recently reported by Pandraud et al. Interestingly, the relatively large index of refraction of a-SiC, compared to similarly-deposited Si_3N_4 and SiO_2, enhances the ability of the waveguide structure to sense chemicals. The authors concluded that surface roughness of the a-SiC is such that the propagation loss was reduced to 1–5 dB/cm (Pandraud et al. 2008).

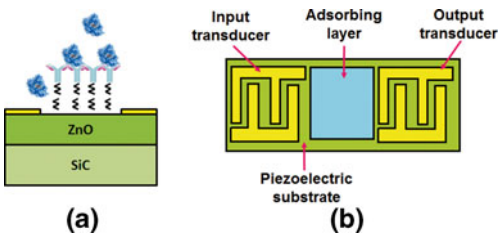

Fig. 3 Scheme of a sensor device that includes a transistor, a resonator and resistive measurements between the finger electrodes. **a** Side view and **b** Top view of the device proposed by (Lloyd Spetz et al. 2009)

4.3 SiC BioMEMs

The mechanical, chemical and electrical properties of SiC that were described in the previous sections also make SiC an attractive structural material for MEMS and NEMS applications. SiC MEMs have been typically used in applications that include harsh chemical, high radiation or high temperature environments; for which Si is not suitable. The evaluation of MEMs materials performed by Kotzar et al., demonstrated the biocompatibility of seven MEMs materials

including single crystal 3C-SiC (Kotzar et al. 2002). The materials were evaluated using a baseline of ISO10993 for physicochemical and biocompatibility tests. The main focus of the article was to understand the effect of sterilization on the material surface and its cytotoxic effect by culturing L-929 mouse fibroblast cells on the surfaces for 48 h. The authors showed that neither Si_3N_4 nor SiC elicited significant non-biocompatible responses which renders them suitable for future BioMEMs applications (Kotzar et al. 2002).

The high Young's modulus of SiC enables the fabrication of wide frequency resonators. Until now, this has been the main structure developed and studied on 3C-SiC, with cantilevers or bridge structures that could be very useful for mass detection, gas sensing or biomolecule identification (Godignon 2005). SiC membranes vary in thickness and typically a 2 μm-thick membrane is able to withstand pressures of over 100 PSI without breaking. For practical, long-term micromachined bioMEMS pressure sensors, one would need to incorporate biocompatible and antifouling characteristics (Zorman 2009). *a*-SiC is also an attractive material for MEMS and NEMS applications because it retains the mechanical and chemical durability of its crystalline counterparts (Zorman and Parro 2008), while being electrically insulating and being processed at much lower substrate temperatures. Its electrically insulating properties enable its use for dielectric isolation instead of SiO_2 and Si_3N_4. Typically *a*-SiC is used as an etch mask for bulk micromachining as in the work by Iliescu et al. (Iliescu et al. 2007) where *a*-SiC is implemented as a protecting mask to increase the etching resistance towards SiO_2 with the aim to fabricate microfluidic channels. In some cases, *a*-SiC is used as a planarizing membrane to cover the microchannel. Later, Iliescu et al. studied the use of 2.5 μm low stress *a*-SiC membranes for cell culture, potentially valuable for bioMEMs applications. They pre-treated micromachined *a*-SiC membranes with 40 % NH_4F and incubated NIH3T3 fibroblasts for 24 and 48 h on the membranes. Using microscopy they found that the cells proliferated more on the *a*-SiC membrane than on monocrystalline SiC (Iliescu et al. 2008).

5 Conclusions

In this paper, we reviewed the major types and potential applications of SiC for biomedical sensors. There are many opportunities for SiC as a substrate and active material to be incorporated in such devices that require certain chemical, mechanical and electrical properties when implanted in the harsh environment of the human body. The possibility of the integration of other materials and systems on SiC increases the possibilities to create complex devices that can perform multiple biomolecule detection and analysis on a single platform. At first glance, some of the proposed devices built on SiC could be considered costly because of the costs associated with material fabrication. In addition, the fact that 3C-SiC is not commercially available as bulk material but only as a thin film grown on Si can be an advantage for MEMs fabrication but also a disadvantage for devices where Si is not desired. In this case an additional etching step is required to remove the backside material. At the same time, since SiC is a potential material for long term device implantation, other costs associated with patient treatment and multiple surgeries for implant replacement can be reduced thus rendering SiC-based biosensors more than cost effective, not to mention the obvious improvement in the quality of life for patients who can avoid repetitive surgical procedures.

We also discussed several SiC material properties that put it in the advantage with respect to other materials. Besides the remarkable chemical and mechanical properties, the fact that SiC can be produced into different forms (e.g. BioSiC made from wood, *a*-SiC, nanoporous SiC, etc.) and polytypes (i.e. cubic, tetrahedral and hexagonal) make it suitable for a wide variety of applications. For instance, Bio-SiC has proven to provide good osteo-integration, nanoporous SiC is an ideal candidate for protein filtration, *a*-SiC improves the mechanical properties of hip implants and heart stents that are in the clinical trial phase and will soon be implanted in patients with certain coronary diseases. SiC nanowires (NWs) can not only be used as a tissue engineering scaffold to strengthen tendons but there is considerable potential to integrate them into electronic devices, e.g. FETs and SiC quantum dots that can be used for cell labeling. Moreover, researchers still need to look for more explanations regarding the effect of surface charge, morphology, and chemical termination in cell attachment and proliferation as well as toxic and pharmacokinetic effects of SiC *in-vivo*. This presents a challenge, for example, in order to address hemocompatibility *in vivo*, hemocompatibility must be first studied under blood flow conditions and target the expression of specific proteins such as P-selectin and fibrinogen (Corash 1990; Lazarus et al. 1995; Schettini et al. 2012)

Both the mono-crystalline and poly-crystalline forms have their field of application as well depending on the doping levels to be used in impedance or electrochemically active platforms and in MEMs structures, respectively. However, care should be taken in the characterization of the SiC material to used, given the inherent presence of defects (e.g. stacking faults, voids etc.) that could affect the response of especially those electrically based biosensors.

Surface functionalization with organic molecules is recognized as a crucial step in biological sensor development, and it has been demonstrated on all relevant forms of SiC. Despite the demonstrated progress via silanization, alkoxylation and self-initiated photografting and photopolymerization (SIPGP)

a more extensive toolkit for grafting different proteins simultaneously and in an oriented matter would provide the development of multifunctional SiC biomedical devices.

The implementation of the techniques presented in this review, in addition to the other properties of SiC, could challenge Si technology in the realization of biological devices. As is the case for power devices where SiC is recognized as the soon to be preferred material (Ozpineci and Tolbert 2011), we should not discount that even though SiC biotechnology is still in its early stages of development, and more research still needs to be done, in a few years the biomedical field will likely adopt SiC due to its superior biological performance and sensing potentiality.

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