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ABSTRACT
Hafnium(IV) oxide is a material with properties that can increase the sensitivity, durability, and reliability of biosensors made from silicon dioxide and other semiconductor materials due to its high dielectric constant, thermodynamic stability, and the simplicity with which it can be deposited. This work describes the use of this material in biosensors based on field-effect transistors to detect ions and DNA, in immunosensors to detect an antigen-antibody complex, its use as a contrast material in computed tomography scans and the possibility of using it in optic biosensors in the infrared region. Its low cost and versatility in the field of biosensors is underscored.

KEYWORDS
Biosensor; immunosensor; hafnium(IV) oxide; field-effect transistor; DNA sensor

Introduction

Hafnium(IV) oxide (HfO_2) or hafnia has been studied extensively because its properties make it suitable for a variety of applications. In the form of thin films this material has a relatively high refraction index (1.89), a density of 9.7 g/cm^3, and a high mechanical thermal (fusion point = 3031.15 K) and chemical stability. This stability is partially due the relatively high transition temperatures between its three crystalline phases, monoclinic, tetragonal, and cubic. It also has the advantage of being able to be deposited with different growth methods such as ultrasonic spray pyrolysis[1], sol-gel[2], sputtering[3], atomic layer deposition[4], and electron beam evaporation.[5]

This material has the potential to be used as an electrical insulator in electronic and opto-electronic devices, due to its high dielectric constant, $\varepsilon = 25$, which is four to six times greater than the dielectric constant of silicon dioxide[6]; as well as having a higher band gap (5.3–5.9 eV), which makes it transparent to visible light. Therefore, this oxide is substituting silicon dioxide as insulator for the dielectric gates of metal-oxide-

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semiconductor field-effect transistors (MOSFET), which are widely used in microelectronics.[7] Since a material with a higher dielectric constant increases the capacitance of the gate, the current leak is reduced, and the dielectric reliability is increased. HfO_2 films have also been used as gas detection thin films[8] and as optical anti-reflective layers due to its high optic transmission (80–87%) in the visible and near-infrared regions.[9] Recently it has been used in biosensor fabrication because of its biocompatibility, it also has a high permittivity, and it can passivate other surfaces against electrolytic solutions.[10]

The term biosensor was introduced by Cammann[11], but its origin goes back to the work by Clark and Lyons with their enzyme electrode.[12] The definitions of the different types of biosensors and their classification were reported by the IUPAC in 1999.[13] A biosensor is defined as a device with an interphase between an electrical instrument and a biological system. The device serves the purpose of detecting and measuring quantitatively a physiological property of the biological system.[14] The Figure 1 shows the basic elements of a biosensor. The sample analyte that include a biological agent. The transducer that receives and respond to a signal of the physical system and consists of a biorecognition element that recognize and interact with the

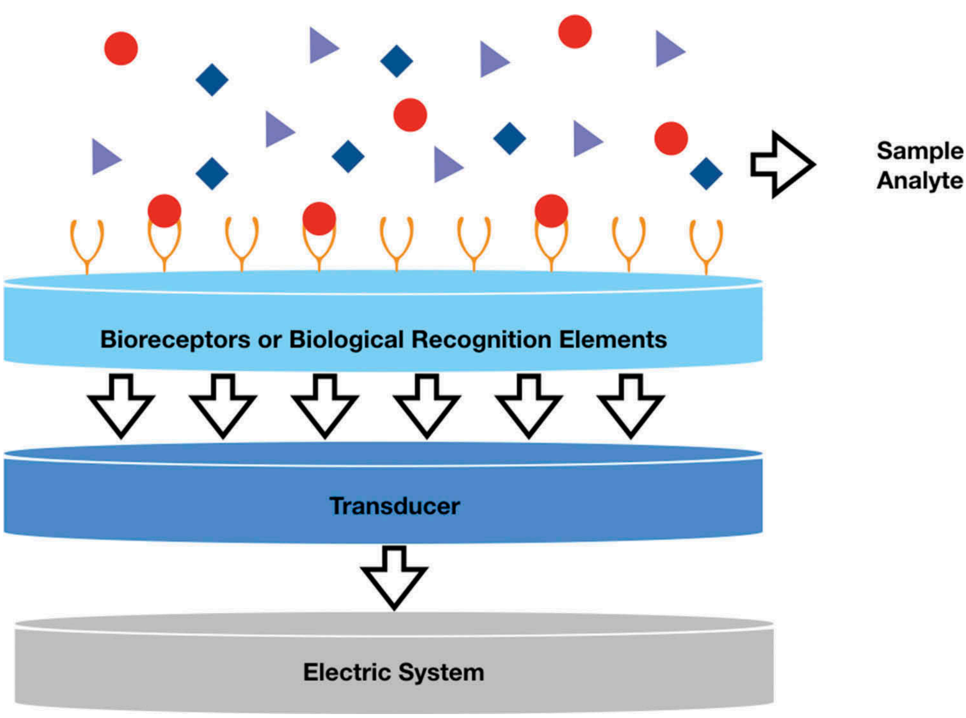

Figure 1. Basic elements of a biosensor. The sample analyte must include a biological element. The transducer recognizes and interacts with the biological element. The electronic system amplifies, process, and display the signals.

sample analyte, and an array of electrodes, nanowires, or nanoparticles. Finally, the electronic system amplifies, process, and display the obtained signals. Ideally the biosensor must be reusable, highly specific for the biological property analyzed and not affected by physical parameters such as pH, temperature, and humidity.

The materials used in the fabrication of biosensors can be classified into three groups based on the functional mechanism: biocatalytic materials, which use enzymes; materials based on microorganisms, and biocompatible materials that use antibodies and nucleic acids. Hafnium(IV) oxide is a biocompatible material that has mainly been used in immunosensors and for detection of DNA in biosensors based on field-effect transistors (FETs), as will be described in further sections.

Biosensors that use enzymes require methods to immobilize them through van der Waals forces, cross-linking, entrapment or ionic and covalent links. The most common enzymes used for these sensors are oxidoreductases, polyphenol oxidases, peroxidases, and amino-oxidases.[15] Biosensors based on microorganisms require animal or vegetable tissue because they use cellular membranes, chloroplasts, microsomes, or mitochondria. The studied metabolite can be an inhibitor or a substrate from a process. The disadvantages are long detection time and low specificity. DNA biosensors are based on the property that one molecule of nucleic acid of one strand can recognize and intervene with a complementary strand. The interaction is produced with the formation of stable hydrogen bonds between two strands of nucleic acids.[16] Portable DNA biosensors have the potential to significantly improve diagnosis of diseases, forensic field analysis, monitoring food security, and even detecting biological weapons. Immunosensors are based on the high affinity that an antibody has for its respective antigen. This type of biosensors could substitute diagnostic methods that are expensive and no versatile, such as ELISA. In DNA biosensors and immunosensors it is necessary to immobilize biomolecules in solid substrates either by a DNA probe on an electrode or an antibody over a transducer.[17]

The motivation behind the publication of this review is to present the state of the art of the use of hafnium(IV) oxide in biosensors since our group is currently developing hafnium(IV) oxide immunosensors and we intend to fabricate biosensors based on FETs.

Hafnium(IV) oxide biosensors based on field-effect transistors

The FET is a device in which current is controlled with electric tension, when used as amplifiers those return an exit current that is proportional to the applied electric potential at the entrance. The FET is also known as unipolar transistor due to the fact that it only involves single-carrier-type operation, electrons or holes. The device consists of an active channel through which charge carriers flow of the drainage source.

The three FET terminals are: source, through which carriers enter the channel; drainage, whence carriers exit the channel; and gates, which modulate the conductivity of the channel.[18] Source and drain terminal conductors are connected to the semiconductor with ohmic contacts. The conductivity of the channel is a function of the applied potential through the terminals of the gate and the source. In the past, silicon dioxide was the semiconductor material used for the gate in biosensors, but hafnium(IV) oxide gates have a superior sensitivity due to its greater dielectric constant and not require a superficial activation for biosensing applications.

Fahrenkopf et al.[19] demonstrated that the 5′-terminal phosphate group in DNA can be used directly in a HfO_2 surface. They proved that there is no need to add a silane group or another molecule to immobilize DNA in HfO_2 and once immobilized it can be hybridized with complementary DNA. This constitutes a DNA biosensor that can be used in FET based biosensors and in high-electron-mobility transistors (HEMT). In a later work,[20] they confirmed the phosphate-dependent immobilization of DNA in a wide variety of surfaces of HfO_2 and observed an unfavorable interaction between DNA and monocyclic HfO_2. They proposed, based on experimental studies and modeling of the density functional theory, that this interaction is between the exposed bases of single-stranded DNA and the surface, given that the spaces between monocyclic hafnium dioxide cells coincide with the spacing between DNA bases, which cause an unspecific surface interactions. They proved that, although monocyclic hafnium(IV) oxide has many nanoelectronic advantages, in biosensing applications the phosphate dependent immobilization should preferably be carried out in amorphous or polycrystalline hafnium (IV) dioxide.

The functionalization with DNA has also been used to detect small particles of biological interest. Wang et al.[21] developed a nanosensor using a graphene field-effect transistor (GFET) with an amplified sensitivity, through a new geometry that uses hafnium(IV) dioxide at the gate. To eliminate the inefficient conventional external cable electrode that is used in the liquid gate GFET devices, which limits its portability to make on-site measurements a gate was used in the same plane that supplies electric field through a HfO_2 dielectric layer of 30 nm. The Figure 2 shows this GFET device. It employs a planar metal electrode covered by the dielectric to supply the gate voltage V_g. A graphene sheet extended over the drain/source electrodes serve as the conducting channel and is gated by the gate electrode under it. The device conductivity can be measured by monitoring the drain current I_d driven by a fixed drain voltage V_d. The conductivity depends on the graphene surface charge. The source electrode is connected to the ground together with the device substrate to provide a reference potential. The

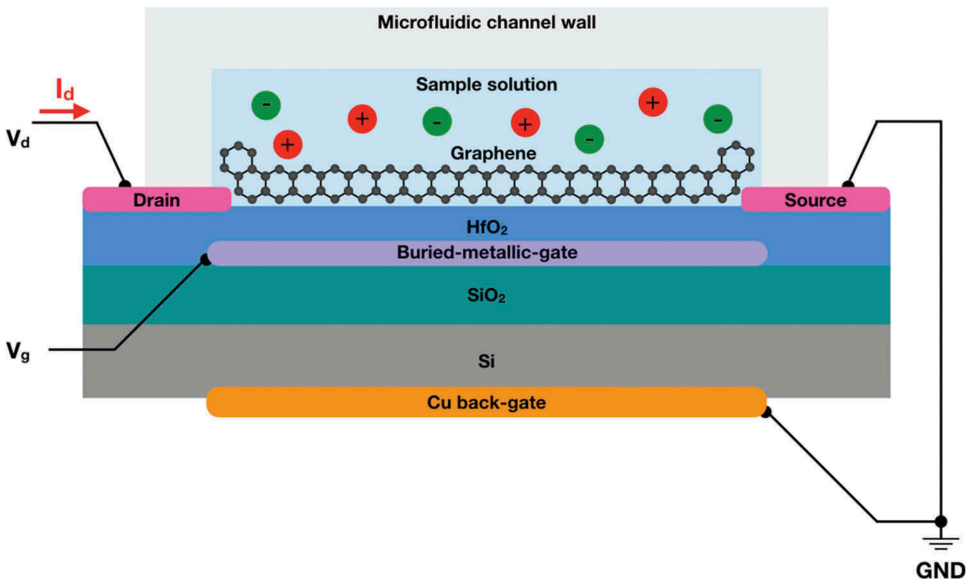

Figure 2. Schematic and electrical circuitry of the GFET device reported by C. Wang.[21] An electrode covered with the HfO_2 supplies the gate voltage V_g. A graphene sheet extended over the drain/source electrodes serve as the conducting channel, gated by the electrode under it. The conductivity can be measured by monitoring the drain current I_d, driven by a fixed drain voltage V_d. The source electrode is connected to the ground (GND) to provide a reference potential.

sample solution is handled by a microfluidic channel and flows over the graphene surface creating the sensitive interface. In addition to the portability and the integration level of the device, another advantage is an increase in the transconductance, around 50%, in comparison to other liquid gate GFET devices in a liquid medium. This increases the performance of sensitivity in sensors and biosensors. Kanamycin A was used to evaluate the detection capacity of biological substances with this device. This is a small molecule antibiotic detected by the principle of competitive affinity of aptamers. Competitive affinity of Kanamycin A and the mechanism of electrical response follow these steps: first the graphene surface is functionalized with aptamers by a complementary reversible hybridization, and in the detection phase the specific affinity towards Kanamycin A releases competitively the aptamers from the graphene surface. When the biological molecules are observed as punctual charges, competitive affinity is understood as the electrostatic inductive charge and the charge redistribution at the graphene-solution interface. Negatively charged molecules released from the graphene surface can be surrounded within the Debye length by buffer ions and lose their charging capacity. This shows that the chemical potential and the density of spaces in the graphene sheet are reduced and based on the energy band diagram of a GFET device, the decrease in the density of spaces in the conductor graphene channel has the effect of doping it with n-type dopants. It was experimentally demonstrated that the specific quantification, without markers for Kanamycin A, with a concentration resolution of 11.5×10^{-9}M is achieved by simple observation of a 200s bioassay without any type of noise or interference. These results showed the utility and practicality of these devices in biosensing without markers and are a new analytical tool that promises important biomedical applications.

HfO_2 has also been used to detect biologically relevant ions since their concentration is an indicator of the electrolytic equilibrium of a patient. Particularly, sodium (Na^+) and potassium ions (K^+) are interesting in biomedical research because changes in the concentration of K^+ in human serum increase the risk of suffering acute cardiac arrhythmias, and changes in the concentration of Na^+ can lead to renal failure.[22,23] An ion sensitive field-effect transistor (ISFET) is an electrochemical sensor based on a MOSFET that reacts to changes in the activity of a given ion. If the change in activity is in the hydrogen ion (H^+), then it is a pH sensitive ISFET. When the ionic concentration changes, the quantity of ions that pass through the membrane and arrive at the gate of the transistor also changes; meaning that the electric current that flows through the transistor can also be altered. This happens when the transistor is in contact with the analyzed substance and this principle applies for other ions. Lu[24] developed an ISFET with a hafnium(IV) oxide gate and compare it to the same gate treated with CF_4 plasma; the treatment increase five times the sensitivity, with lower selectivity coefficients for K^+ and Na^+ ions against H^+, as well as increasing durability. This treatment is compatible with technology for CMOS transistor manufacturing and can be used for biosensors. The Figure 3 shows the schematic diagram of the cross-section of this fluorinated-HfO_2 gate ISFET.

Recently, transistors that use HfO_2, together with other materials, have been developed to increase the sensitivity of detection when compared to a MOSFET. Singh et al.[25] introduced for the first time the concept of "charge-plasma" to implement a dielectric-modulated junctionless tunnel field-effect transistor (DM-JLTFET) that does not use markers, has a lower cost and is easier to produce. In this case the formation of the source region p^+ and drainage region n^+ is created by depositing platinum (work function = 5.93 eV) and hafnium(IV) oxide (work function = 3.9 eV), respectively, on the silicon dioxide surface. Also, a nanogap cavity forms in the dielectric gate milling a portion in the direction of the terminal source in order to detect biomolecules. When researching the sensing capacity in terms of the dielectric constant, charge density, length, and thickness of the cavity in different voltage conditions and currents, the results were very superior compared to a biosensor based on MOSFET technology.

Another example of the use of HfO_2 with other materials are the silicon dioxide nanowires (SiNW) made by Bae.[26] This pH sensor uses a SiNW chip with thin films of $SiO_2/HfO_2/Al_2O_3$ (OHA). When these materials are

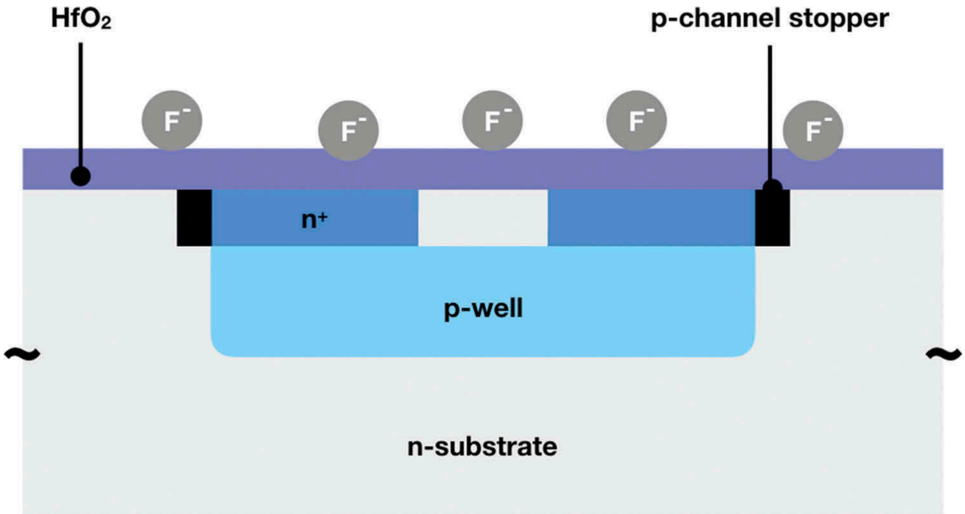

Figure 3. Schematic diagram of the cross-section of the fluorinated-HfO_2 gate ISFET reported by Lu.[24] The gate modulates the channel conductivity.

piled in that order, there is a lower density of states at the interphase, a higher capacitance and stronger chemical immunity. Altogether, this allows a two times increase in the sensitivity, lower hysteresis voltage, less drift rate, and a higher exit current compared to a conventional SiNW sensor that only has a thin layer of SiO_2. According to these results, the SiNW sensors with thin sensing layers of OHA are sensing structures with the potential to detect biological and chemical species with ultra-high sensitivity, without markers, with real time detection, and compatible with CMOS.

Use of hafnium(IV) dioxide in infrared biosensors and as a contrast medium

The polar crystal structure and the optical phonon energies of the HfO_2 result in a negative permittivity in the mid-infrared, allowing the polarization of surface phonons so it can be used in optical sensors.[27,28] McGinnity[29] studied the interaction of HfO_2 nanoparticles with X-rays and radiation in mid-infrared to evaluate its potential as a multifunctional tool in diagnostics by computerized tomography and biosensors in mid-infrared. They prepared nanoparticles of HfO_2 with a sol-gel process and stabilized the surface with polyvinylpirrolidone, resulting in relatively spherical monodisperse nanoparticles with an adjustable diameter in the range of 7–31 nm. The attenuation of HfO_2 nanoparticles in X-rays was measured in concentrations of 0.5–50 mM and compared to attenuation with iodine and gold nanoparticles, which are the most common X-ray contrast agents used in research and clinical diagnostics. When using the same potentials as used in X-ray computerized tomography (> 80 kVp) the nanoparticles of HfO_2 showed the same or higher contrast compared to gold nanoparticles and both types of nanoparticles showed a greater contrast to X-rays than iodine. This is due to the favorable localization of the absorption limit of the k-shell of hafnium and gold. The nanoparticles also showed a high absorption in mid-infrared in the Reststrahlen band of 250–800 cm^{-1} and a negative permittivity under 695 cm^{-1}, which will allow the development of optic biosensors in mid-infrared, and contrast agents that take advantage of polarized phonon absorption in the surface and/or the amplified absorption of the surface in the mid-infrared.

Hafnium(IV) oxide immunosensors

The cells and molecules that are responsible for immunity constitute the immune system and the global coordinated reaction to foreign substances in the body constitutes the immune response. Antigens are substances that induce an immune response. This response can be an antibody, which is a protein that specifically attaches to a certain antigen. One of the first demonstrations of specific immunity was the induction of humoral immunity against microbial toxins. Now it is known that the protective effects of humoral immunity are mediated by a family of glycoproteins that are structurally related called antibodies.[30] One of the most characteristic properties of antibodies is their capacity to react only to the antigens that triggered their production. The antigen-antibody reaction occurs in two stages. In the first, there is a physical and chemical reaction between the molecules of the antigen and antibody; and in the second, this interaction becomes an antigen-antibody complex because of the formation of electrostatic bonds. The antigen-antibody complex is a precipitate when the antigen is soluble or when it is agglutinated.[31]

An immunosensor is a solid-state apparatus capable of detecting antigen-antibody binding based on changes in mass, changes in optical properties, electrochemical changes or, as in the case of immunosensors of HfO_2, changes in electrical properties. In this type of sensor, the biological component is immunoreactive, usually antibodies, and it is necessary to carry out a surface modification to immobilize this component in the sensing surface. Immobilization methods can be by physisorption or chemisorption. One method for immobilizing antibodies on solid substrates is to functionalize the surface with a molecule that has functional groups such as amino or carboxyl to form covalent bonds with the antibody. L. C. Ortiz-Dosal[32] described a method to immobilize antibodies on HfO_2 surfaces by forming self-assembled monolayers of (3-aminopropyl)triethoxysilane (3-APTES). First, the surface is oxidized to generate the anchor groups of the monolayer, then functionalizes the surface with 3-APTES and adds glutaraldehyde as

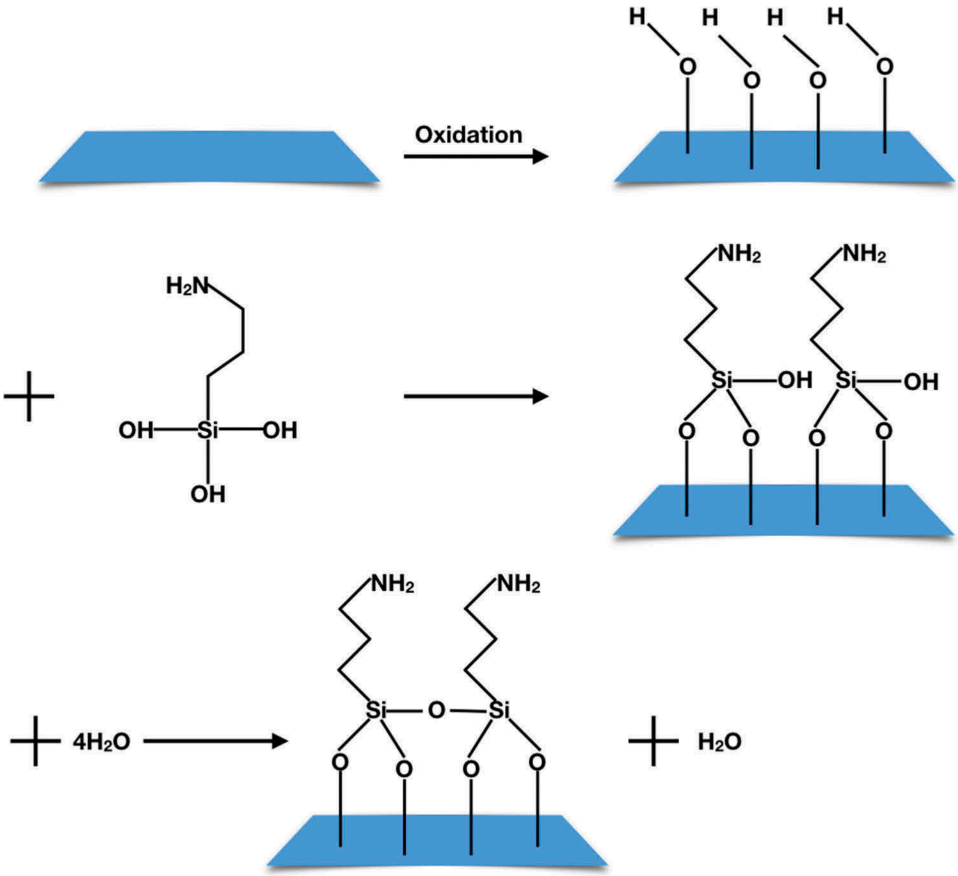

Figure 4. Reaction mechanism of the functionalization of the oxidized surface with the hydrolyzed molecules of 3-APTES. The surface is oxidized in a first step to generate hydroxy groups. Then the hydrolyzed 3-APTES molecules condensate over this anchor groups and a self-assembled monolayer is formed. The amino group of the molecule is responsible for the immobilization of the antibodies.

cross-linking agent, finally, the bovine serum albumin is immobilized using the amino group of the 3-APTES molecule for the passivation of the grafting layer, to prevent non-specific adsorption of the antigen. The Figure 4 shows the reaction mechanism of the functionalization of the oxidized surface with the hydrolyzed molecules of 3-APTES. The evaluation of this method for its use as immunosensor has been demonstrated by G. Gonzalez.[33] Interdigitated capacitors (IDC's) are the most used transductors in chemical and biological sensors were a change in capacitance or impedance is measured as a response to the interaction between the analyte and the sensitive surface.[34] They are also used to evaluate electrical properties close to the surface such as conductivity, permeability, and permittivity.[35,36] Gonzalez[33] used the previously described method to functionalize IDC's of nickel covered with a 60 nm layer of HfO_2 and carried out measurements of current vs voltage showing that the IDC increases the electrical response of the capacitance and they test the IDC sensor with bovine serum albumin and anti-bovine serum albumin as a proof-of-concept that the IDC can be used as an immunosensor.

3-APTES has also been used for the functionalization of HfO_2 nanoparticles. Kumar[37] developed a non-invasive label free immunosensor using nanoparticles of hafnium(IV) oxide ($nHfO_2$) deposited on an indium-tin-oxide coated glass to detect the oral cancer biomarker CYFRA-21–1 in human saliva. They synthesized the nanoparticles with a hydrothermal one step process and modified the surface with 3-APTES for the covalent immobilization of monoclonal antibodies anti-CYFRA-21–1 and used bovine serum albumin to block non-specific sites in the surface of the anti-CYFRA-21–1/APTES/$nHfO_2$/ITO electrode. Composition and structural studies confirm the type of electrode that was fabricated. The results of the evaluations performed on this immunoelectrode, such as analysis of real samples, electrochemical response studies and cyclic voltammetry studies revealed a high sensitivity, high linear detection range, and short response time, in addition to being validated by enzyme-linked immunosorbent assay (ELISA).

The surface of HfO_2 can also be functionalized with other molecules different from APTES such as 11-(triethoxysilyl)undecanal as in the work of[38]. They developed an immunosensor that can detect cardiac failure by detecting a cytokine. Cardiovascular diseases are a predominant cause of death in developed countries. Death after an open-heart surgery can be due to an increase in the levels of various cytokines and immune cells. This fatal acute rejection can be determined by measuring specific biomarkers that indicate inflammation in biochemical and cellular events. Inflammatory cytokine interleukin-10 (IL-10) contributes to this process when patients suffer a cytokine storm. To achieve this, they deposited monolayers of 11-(triethoxysilyl)undecanal over a capacitive substrate of HfO_2 to directly immobilize the monoclonal antibody anti-human IL-10. They characterized the antigen-antibody interaction with fluorescence patterns and electrochemical impedance spectroscopy. These results demonstrated bio-recognition of the recombined protein and the Nyquist graphs showed variations at extremely low concentrations, which make it useful to prevent cardiac failure.

Limitations

Even though there are many advantages as previously described, it should be considered that there is a need for an extra process to cover a surface with HfO_2, so the cost will be greater when compared to sensors that only uses SiO_2. It should also be considered that organofunctional silanes, that are frequently used to form self-assembled monolayers on the surface of an immunosensor and immobilize proteins, are highly toxic so they must be handled with extreme caution during the fabrication process.

Conclusions

Biosensors based on HfO_2 show superior capacities to currently used silicon dioxide-based biosensors. These can be used in medical diagnosis, process control, environmental surveillance, and in food analysis. The use of HfO_2 allows a high sensitivity in electric sensors and its chemical and thermodynamic stability make it a very resistant and long-lasting material. It is also easier to fabricate and has a lower cost than other materials with a high dielectric constant such as barium strontium titanate (BST). Even though it has many advantages, the development of biosensors based on HfO_2 is recent and new biosensors must be developed to allow the detection of a wider range of substances and specific biomarkers to certain diseases.

Although hafnium(IV) oxide has recently been used for the development of different types of biosensors, there is still a lot of work to be done. Biosensing applications for other important analytes should be promoted; the detection ranges should be established based on tests that let know the sensitivity and selectivity of the biosensor to the analyte in question. The costs of growing thin films of hafnium[IV) oxide must also be reduced so that it can replace silicon dioxide as a semiconductor in the biosensing applications discussed in this review, among others.

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