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REVIEW ARTICLE

State-of-the-Art on Functional Titanium Dioxide-Integrated Nano-Hybrids in Electrical Biosensors

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ABSTRACT

Biosensors operating based on electrical methods are being accelerated toward rapid and efficient detection that improve the performance of the device. Continuous study in nano- and material-sciences has led to the inflection with properties of nanomaterials that fit the trend parallel to the biosensor evolution. Advancements in technology that focuses on nano-hybrid are being used to develop biosensors with better detection strategies. In this sense, titanium dioxide (TiO_2) nanomaterials have attracted extensive interest in the construction of electrical biosensors. The formation of TiO_2 nano-hybrid as an electrical transducing material has revealed good results with high performance. The modification of the sensing portion with a combination (nano-hybrid form) of nanomaterials has produced excellent sensors in terms of stability, reproducibility, and enhanced sensitivity. This review highlights recent research advancements with functional TiO_2 nano-hybrid materials, and their victorious story in the construction of electrical biosensors are discussed. Future research directions with commercialization of these devices and their extensive utilizations are also discussed.

KEYWORDS

Electrochemical biosensor; electronic transducer; nanocomposite; organic–inorganic materials; quantitative biosensor

Introduction

Biosensor was initially introduced in 1962 by Leland Clark, a well-known scientist called the "Father of Biosensor".[1] It is an analytical device used for the detection of biomolecular interactions due to the existence of a biorecognition element and a transducer. Generally, the biorecognition element is immobilized onto the device surface and produces a signal when an analyte (such as enzyme substrate, complementary DNA, and antigen) is detected.[2,3] Biosensors can be categorized into three parts which are: i) the sensing element (derived material: TiO_2 nano-hybrid); ii) the transducer (transforms the detected signal into a readable output); and iii) the signal processor (transforms the signal into a quantified graphical form). A transducer is used to transfigure the bio-chemical signal into an electronic one (Figure 1). In this case, the biochemical signal is caused by the interaction of the analyte with the bioreceptor (biorecognition element), and the intensity of the generated signal is purely dependant on the concentration of the analyte that binds on the biorecognition element.

Practically, biosensors are classified based on their type of platforms and biorecognition elements. Biosensors can be divided into three general classes: biocatalytic, bioaffinity and electrocatalytic sensors. A biocatalytic sensor uses enzyme as the platform to detect the interaction of immobilized enzymes, known as enzymatic reactions. On the other hand, an affinity device includes several platforms based on antibody, receptor, or a single oligonucleotide strand for the interaction.[4] The third biosensor type is the electrocatalytic biosensor, where the electrodes or the sensing materials act as electrocatalysts.[5] This type is depending on the physico-chemical properties of a transducer.[6] For example, glucose in enzymeless sensor will directly attach on the sensing material, and a redox reaction occurs between them. As a result, there is electron transfer to the contact, known as output current.[7] Figure 2 displays the differences between the two major classes of biosensors.

However, the determination of target biomolecules using conventional methods is challenging as they require the use of a number of equipment that need a certain level of skill to operate. Moreover, the conventional methods are time-consuming, require special pretreatments prior to each use, and lack long-term stability. Due to these limitations, biosensors have been improved with the introduction of electrical biosensors.

Electrical biosensor

Generally, an electrical biosensor reports the trapping of an analyte by a biorecognition-element-modified electrode

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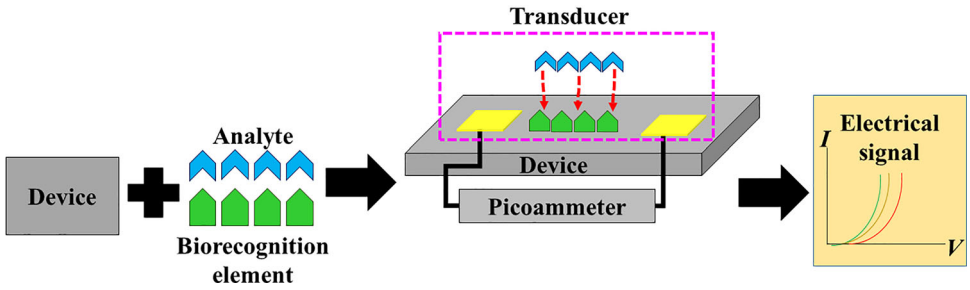

Figure 1. Structure of electrical biosensor. It has basic elements, namely receptor and detection molecules, transducer and signal output unit.

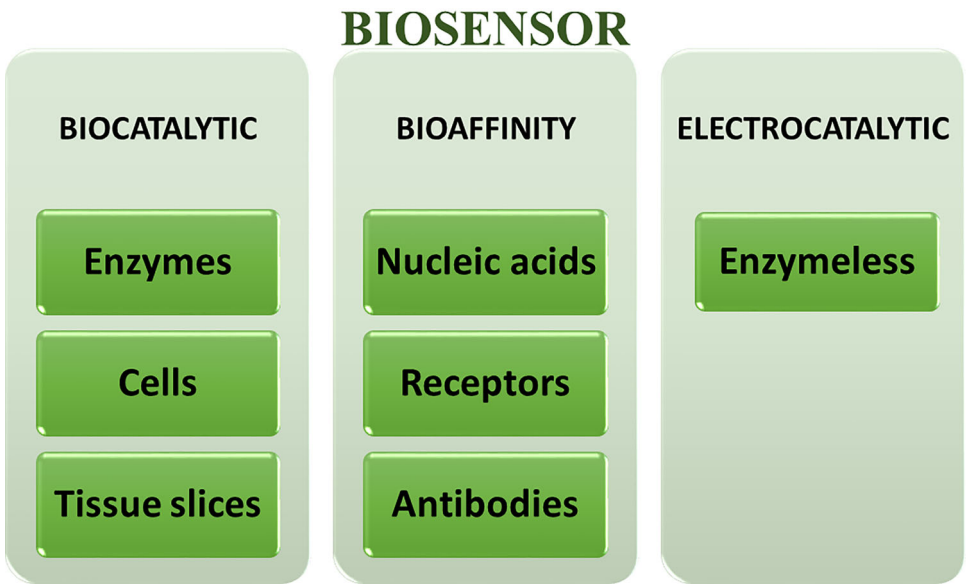

Figure 2. Classification of biosensors based on bioreceptor and physico-chemical properties. These are widely used with different receptor molecules involvement.

interface, generates an electrical signal and displays the bio-interactions. There are a few electrical units that have been reported to have generated signals, such as output current, electrical impedance, potential or charge accumulation, and conductance. Basically, the output units of the electrical signals depend on the design of the biosensor devices, as shown in Table 1.

Electrical biosensors can be classified into electrochemical or electronic sensors. The history of electronic biosensor began in 1962 when Clark and Lyons introduced the development of an enzyme-electrode biochemical-based transducer.[8] Following this work, a variety of biosensors with sensing mechanisms have been reported and continuously improving until today. Generally, electrochemical biosensors transfigure the production of ions or electrons by the chemical reactions among immobilized biorecognition element and target analyte to graphical.[9] However, this approach involves complex preparation and uses a lot of reagents which contribute to high costs. In addition, it is also time-consuming to complete an assay. Hence, people started to explore an electronic approach for biosensing applications.

Table 1. The electrical output reading of different device designs.

Biosensor	Output measurement
Amperometric/Voltammetric	Current
Potentiometric	Potential/charge accumulation
Conductometric	Modulation of medium conductance
Impedance	Electrical impedance
Transistor	Current
Capacitive	Capacitance/Impedance
Resistive	Resistivity/Current/Impedance

Electronic biosensor

Electronic biosensors are a subclass of biological sensors, exploited by modern electronic devices designed to measure or detect a chemical substance by the combination of a biological component with a physicochemical detector.[10] The device is designed as an electronic component like a capacitor or transistor, but focuses on micro-to-nano dimensions.[11] The output data is created mechanically or electrically, and transmits the detection information into an electrical signal. In these bio-sensing mechanisms, one of the prominent sensing devices is the field effect transistor (FET)-based biosensor (Bio-FET). It became widely explored as an emerging field due to the rapid evolution in solid-state technologies. Hence, it was embellished for applications that require ultra-sensitivity and fast response time. This is based on the fundamental concept of biosensors, where most biomolecules have electrostatic charges and bioactivities involve charge mobility that contributes to electrical potential changes. Besides that, modern manufacturing techniques of complementary metal-oxide semiconductors (CMOS) are able to miniaturize the electronic components, perform parallel detection, and be integrated as a complete electronic

circuits and systems. These are the major advantages for bio-CMOS to stand higher than the other bio-sensing mechanisms in the future.

Electrochemical biosensor

Another subclass of biological sensor is electrochemical biosensor. An electrochemical biosensor is made up of a biological sensing element and an electrochemical transducer. The recognition element reacts selectively with the target.[12–14] Compared to the electronic biosensor, this sensor reads the reduction-and-oxidation (redox) reaction during an electrolysis process. As a result of the redox reactions of the recognition element with the target, an electrical signal is produced, and the plotted graph is used to interpret the reaction. It possesses an innate ability to sensitively track the changes of charges on the transducer interface and is reported in the form of output electrical signal. Among the traditional techniques of electrochemical biosensors such as potentiometry, amperometry, and conductometry, the Electrochemical Impedance Spectroscopy (EIS) promises a nondestructive sensing mechanism and enables *in-situ* measurements.[15] EIS can be divided into Faradaic and non-Faradaic,[16] depending on the presence of a redox charge transfer over the interface of electrode interface during the measurement. In a Faradaic EIS, the redox process happens when there are occurrences of oxidation and reduction of an added solution on the modified and appropriately biased surface. Hence, it measures the charge transfer. In contrast, for a non-Faradaic EIS, there is no redox process as no addition is made up and it measures the stored charge.[17] This is simpler and potentially more compliant for practical or point-of-care applications.

This overview is aimed on the usage of TiO_2 nano-hybrid as the active area for sensing target biomolecules. Therefore, the history until the most recent advances of TiO_2 nano-hybrid-based biosensor was compiled. Various organic and inorganic materials that have been used to work with TiO_2 nanostructure in order to obtain a surface that is able to attract target analytes are discussed. Additionally, some advanced strategies on reducing preparation or fabrication steps on the biosensor by improving the sensing material are discussed. The most suitable organic material with TiO_2 is suggested, and these sources hold a notable prospect of producing alternative efficient TiO_2 that could enhance the sensing performance as compared to the single TiO_2 material. Finally, this review concludes a general view on the future trends, challenges in real life, and the potential point of view on this interesting and promising research subject.

TiO_2: a potential material for biosensor development

TiO_2 belongs to the family of transition metal oxides and three phases structure have been reported, commonly known as anatase (tetragonal), brookite (orthorhombic), and rutile (tetragonal). The bandgaps are 3.2, 3.02, and 2.96 eV, respectively.[18] Among these structures, the anatase and rutile phases have been widely used because they are more stable than the brookite phase. In fact, rutile has higher chemical stability and is the most stable structure at high temperature and pressure. These properties are beneficial in the development of reusable biosensors by contributing a stable sensing area.

Naturally, synthesized TiO_2 is in the brookite phase and heat treatment is the key to transform the brookite phase to anatase or rutile phases. Researchers reported that by increasing the calcination temperature to 300–500 °C, the amorphous structure can be transformed into anatase, and when the temperature rises to 600–700 °C, anatase can be further transformed into rutile. In addition, through improved synthesis technique, researchers were able to obtain the rutile structure below 400 °C.[19–21] After improvements in calcination temperature, another innovation was performed to obtain stable electrical properties of TiO_2. Researchers focused on the use of chemical stabilizers that vary in acidity and basicity. The results showed that TiO_2 synthesized by an acidic solution has excellent electrical properties in terms of stability. TiO_2 has been widely used since 1956, starting with photocatalyst applications.[22] Simple preparation techniques, high availability, high electrical stability, and cost-effective synthesis processes, make it an interesting material to be used in biosensors. Most importantly, TiO_2 materials are environmentally friendly and biocompatible.

Fabricated TiO_2 types (N and P types)

Generally, TiO_2 can be either N or P type semiconductor, but is intrinsically an N-type. However, it can be a P-type semiconductor and made to conduct through holes by a doping process. Naturally, TiO_2 is an N-type semiconductor due to higher number of oxygen vacancies in oxides. In other words, TiO_2 is rich in electrons at this state. The vacancies are generated when the number of oxygen in a particular compound is incomplete as in a perfect crystal lattice. In a P-type TiO_2, oxygen is removed from the compound by annealing in a reducing atmosphere, called electron doping (addition of two electrons due to the removal of one oxygen atom from the parent atom). On the other hand, N-type TiO_2 is obtained by annealing in an oxidizing atmosphere (O_2). It involves a process of removing two electrons, as there is an addition of an oxygen atom from the parent atom. Among them, most sensors use N-type TiO_2 as the sensing material,[23,24] while P-type has been extensively used in emerging transparent electronics such as in gas and ultra-violet light-based solar cells.[25,26]

Role of TiO_2 nanomaterials in biosensor

Fundamentally, biosensors are developed based on the recombination or introduction of chemical linkers. The linker is used to conjugate (in surface modification step) the biorecognition element and immobilize it. However, these techniques have essential limitations which are: i) linker-biorecognition element instability and ii) weak produced signal

response. As a solution, researchers began to functionalize nanomaterials by synthesizing nano-hybrid materials; hence, the linker-technique can be waved off.[27] This new approach provides high impact in developing biosensors, including enhanced output signals, retention of biomolecular activity for a long-term, and extension of investigation tools using plasmonic and optical properties. Up till now, researchers have been extensively synthesizing and reporting on various nanomaterials. They widely use gold nanoparticles-to-novel-nanomaterials. The nanomaterials can either be carbon-based or any transition-metal dichalcogenide (TMD)-based.[27] Researchers have proved the ability of TiO_2 material in biosensor applications.[28,29] In fact, the performance of a biosensor was enhanced by using TiO_2 at nanoscale to implement a sensing mechanism. It is well known that the ability of nanoscale materials is to amplify the electrical response due to smooth electrons transfer rate in the nanostructure medium. In addition, it works based on its large surface area and provides ease of surface modification and high possibility of biomolecular immobilization on the transducer surface, which is a key point to improve the sensitivity of the sensors. Electrically, TiO_2 nanostructures have shown potential in improving electron mobility and electric current stability which lead toward the development of efficient electrical sensors.

Au[30–32] and TiO_2[24,33,34] have been widely applied as transducers in biosensors. This is due to their high stability, biocompatibility, high surface-to-volume ratio, and strong amplification effect on signals. However, TiO_2 nanomaterials have attracted much attention for electrical biosensors thanks to their great biocompatibility, wettability, low-cost, and facile synthesis. Besides that, TiO_2 has the potential to bind perfectly with various bio-recognition-elements. For example, enzymes can be directly immobilized onto the surface of TiO_2 material due to the bond formation with amine and carboxyl groups of the enzyme. TiO_2 holds great promise for the immobilization of biological components due to its structural properties, valance band location, and hole generation and availability at the surface of the material to be harvested by outer free electrons. The interaction between the biorecognition element and analyte generate electrons. Those electrons are then collected by TiO_2, due to its electron accepting character.[35] Studies have shown that TiO_2 photocatalyst could kill the bacterial cells in water due to the generation of reactive oxygen species.[36] Cai et al. reported the ability of TiO_2 NP to induce cytotoxicity against HeLa cancer cells.[37] In addition, some researchers reported the treatment of human colon carcinoma cells by the photoexcited TiO_2.[38]

Integration of TiO_2 for nano-hybrid biosensors

The continuous development of nanotechnology offers new horizons for electrical biosensor applications. For biomolecular interaction applications, several nanomaterials are already being used to fabricate sensing materials, such as nanocomposites,[39] quantum dots,[40] metal nanoparticles,[41] and conducting polymers,[42] to amplify the detection signal. In the quest for superior performance, most researchers have focused on developing a better nanostructured matrix to entrap more analytes in a single step with high specificity. Unfortunately, this approach seems to have reached saturation. Therefore, an innovation that focuses on nano-hybrids was introduced. It is an improved technology to strengthen the binding of nanomaterials with the bio-recognition element.

In materials science, hybrid stands with the mixing of two different elements, forming a new material, known as "mongrel".[43] As a hybrid material, they are attached through chemical bonding. The organic/inorganic nano-hybrid materials can be covalently bonded or noncovalently bonded together, which is known as hydrogen bond, van der Waals force, and electro static force.[44] It is possible to expect very interesting characteristics that are not found in the single material independently. Through studies, this binding has enhanced various characteristics including conductivity properties, membrane permeability, and stability. Moreover, the binding is cheaper, has optimum water retention and mechanical properties. The unique properties of advanced nano-hybrid nanomaterials create huge advantageous in many fields, such as optical,[45] electronic materials,[46] biomaterials,[47] catalysis,[48] sensing,[49] coating,[50] and energy storage.[51] In fact, the unlimited possible combinations of the distinct properties of inorganic, organic, or even bioactive components in a single material, either in molecular or nanoscale dimensions, have attracted considerable attention. In the scope of TiO_2, its hybrid material can be categorized into two types: inorganic-organic and inorganic-inorganic. The performances of these two types in biosensing applications have been widely reported.

TiO_2/organic nano-hybrid

Organic/inorganic nano-hybrids form a new class of hybrid nanomaterials that demonstrates improved optical, thermal, electrical, and mechanical properties. This is due to the cooperation of the physical or chemical interactions that occur in conjunction of the inorganic and organic elements. They combine advantages of organic polymers (flexibility, lightweight, good processability, and good impact resistance) and inorganic materials (high brittleness, high thermal stability, and good chemical resistance).[52–54] In modern chemistry, organic materials are defined as carbon-based compounds, where the carbon is bonded to the hydrogen (C-H).[55] On the other hand, an inorganic material has chemical compounds that lack carbon-hydrogen bonds. Generally, organic-inorganic nanohybrid could be prepared using the covalent linkages approach.

TiO_2 nanohybrids have been explored for the past 10 years and recently, tremendous research on nanohybrid TiO_2 with organic materials has highly impacted the nanomedicine and engineering fields. Examples of organic materials are poly [3-aminophenylboronic acid, poly (3-hexylthiophene), and Polypyrrole–chitosan. These organic materials work uniquely with TiO_2 for the effective diagnosis of biosensors. Table 2

Table 2. Summary of organic materials hybridized with TiO_2 for biosensor applications.

Hybrid material	Detection method	Analyte	LOD	Ref.
Poly[3-aminophenylboronic acid] (PAPBA)	Electrochemical & photoelectrochemical	• Glucose • Glycated hemoglobin (HbA1c)	0.11 mM	[64]
Poly (3-hexylthiophene) (PHT)	Electrochemical	• Glucose	0.62 ± 0.02 mg dL^{-1}	[67]
Cellulose	Electrochemical	• Glucose	1 nM	[66]
Graphene	Electrochemical	• Glucose	0 – 8 mM	[77]
MWCNT	Photoelectrochemical	• Methyl orange	Not mentioned	[85]
Graphene	Electrochemical	• Organophosphate compounds	0.3 ng mL^{-1}	[75]
CNT/Co_3O_4	Photoelectrochemical	• Glucose	0.16 μM	[86]
Reduced graphene	Electrochemical	• Breast cancer cell (MCF-7)	40 cells.ml^{-1}	[78]
Graphene	Electrochemical	• Human lung fibroblasts • Human skin cells	56.89 μM	[76]
APTES	Electrochemical	• Recovering of nucleic acid	Not mentioned	[59]
Dacarbazine (DITC)	Electrochemical	• DNA	80 μM / each base	[87]
ENR-50	Optical	• Visible light	Not mentioned	[52]
Chitosan	Optical	• *E. coli*	100% growth reduction	[69]

lists out the organic materials that have been used in TiO_2 hybrids.

TiO_2/polymer nanohybrid

Most of the used organic materials are polymer-based. Conductive polymers and metal oxide nanohybrids are of special interest for improving the properties of sensors.[56–58] In fact, studies on TiO_2/polymer nanohybrid for biosensor applications are still lacking. Kim et al[59] reported the hybridization of (3-Aminopropyl)triethoxysilane (APTES) with titanate for nucleic acid recovery. Titanate is naturally an inorganic anion and to make it work on the hybridization of another anion like DNA, the titanate needs to be modified to become a cation. To overcome this limitation, APTES was attached onto the surface of titanate and was ready to stably hold the biorecognition element (DNA probe).[18] As a result, there was an electrostatic interaction between the cationic APTES-anchored titanate nanosheets and anionic DNA. Hence, an immediate formation of DNA–layered titanate nanohybrid was developed.

Several studies on glucose sensors have been made using organic materials. They were built to be used as flexible and wearable sensors to detect glucose levels in blood. Looking on the bright side, researchers are aware of the potential to further develop glucose sensors until the point-of-care testing (POCT) level.[60–62] After that, a lot of optical sensors have been developed due to the qualitative detection-concept which is easily to observe. Unfortunately, it has poor sensitivity for quantitative measurements. There have been remarkable developments in electrical glucose sensors. However, the limitations on the fabrication of the consistent glucose analysis are still unsolved. Researchers have different perspectives on whether to design an enzymatic or non-enzymatic glucose biosensor. Glucose oxidase (GOx)-based enzymatic biosensors have been used for the detection of blood glucose since 1962.[63] However, thermal and chemical deformations can occur during fabrication and storage. Besides that, the introduction of enzyme into a biosensor involves a complex immobilization process and requires being stored in low temperature instead of at ambient temperature. Until now, the stability of sensors at sensor operating temperature is still questionable, and the laboratory setup for low temperature equipment is expensive. In 2017, Nallal and team[64] demonstrated the application of TiO_2-poly(3-aminophenylboronic acid) for non-enzymatic glucose and glycated hemoglobin (HbA1c) detections, independently. Fundamentally, boronic acid is one of the best candidates as glucose biorecognition element, as boronic acid is able to tie up with the 1,2-diols of glucose.[65]

In contrast, Maniruzzaman et al.[66] used TiO_2-cellulose hybrid nanocomposite for enzymatic glucose sensor. The enzyme (GOx) was successfully immobilized on the TiO_2/cellulose hybrid by physical adsorption. Then, the immobilization of GOx onto the TiO_2/cellulose hybrid was based on the covalent bonding between GOx and TiO_2. The response of this glucose sensor was 1 mM detection limit. Further study on enzymatic glucose sensor was done by Kadian and team[67] and the sensor was developed using poly (3-hexylthio- phene) (PHT)/TiO_2 nanohybrid. The conducting polymer of PHT not only had good field effect mobility but was also a suitable candidate for element grafting (biorecognition element) with several biomolecules. In addition, the combination of TiO_2/conducting polymer nano-hybrid is able to promise efficient electrical biosensor performance, as both materials are good conductors.[68] The nanohybrid of PHT/TiO_2 was based on covalent bonding, while amide bonds I and II were formed when the nanocomposite was immobilized with GOx. They have tested for human saliva as a real sample analysis without involving any treatment steps. The result was obtained in less than 10 s with 0.62 ± 0.02 mg/dL of LOD. In the another research, Haldorai and Shim[69] explored on photocatalytic activity using TiO_2/Chitosan dye removal. The fabrication purposely met the need of high-adsorption, self-regeneration, easy separation, and cost-effective with enhanced antimicrobial properties. The Ti^{4+} ions immediately formed co-ordination bonds with –OH and $–NH_2$ groups of chitosan chains and formed CS-Ti^{4+} ions. After the addition of NaOH and heat treatment, it formed TiO_2/Chitosan. As a result, 90% of methylene blue was degraded, and within 24 h, it exhibited superior antibacterial activity with 100% growth reduction of *Escherichia coli*.

The latest report on organic hybrid biosensor is TiO_2/Epoxidized Natural Rubber (ENR-50) nanohybrid by Dahham and Noriman.[52] For this project, TiO_2 played

pivotal roles in preparing a strong bonding of Ti-O-C in the nanohybrid material. The formation of covalent bonds between inorganic and organic materials can prevent phase separation.[70] The study was used to improve the optical properties, focusing on visible light sensing. Indirectly, it has the potential to be used as a flexible biosensor (due to polymer-based material) that functions well under visible light (power saving).

TiO_2/graphene nanohybrid

Graphene hybrids have been widely explored in terms of design, preparation methods, and application in electrical biosensors. However, graphene-hybrids with metal oxides have gained great attention in recent years due to significant physicochemical properties by effective adjustment or interaction of graphene sheets and incorporated materials.[71,72] Besides reducing toxicity of graphene toward cells, TiO_2 also acts as a stabilizer for graphene layers (sheets) to resist strong accumulation between the layers which is naturally generated by strong Van der Waals interactions between them.[73,74] Wang and team[75] synthesized TiO_2-graphene nanohybrids for organophosphate compounds (OPs) detection. OPs are most commonly applied as pesticides in agriculture. The nanohybrid was produced directly from graphene oxide (GO) in a facile one-step reaction, where the reduction of GO and the deposition of TiO_2 on graphene occurred simultaneously. Due to the development of this hybrid, the immobilized Acetylcholinesterase (AChE) showed greater affinity to its substrate and excellent catalytic effect. The enzyme activity was employed as an indicator for the quantitative measurement of insecticides. The material showed a detection limit of 0.3 ng mL^{-1}, which was better than their previous study of TiO_2-hybrid CdS.

Another study on hybrid graphene was performed by Siew and team.[76] They reported the synthesis of TiO_2/graphene for hydrogen peroxide (H_2O_2) detection, a by-product of most enzymatic processes, as the analyte of interest. The limit of detection (LOD) was 56.89 μM. Jang and team[77] reported on the development of glucose sensor using TiO_2/GO nanohybrid. The material was prepared by the self-assembly of GO and TiO_2, followed by the reduction of GO. As a result, it provided the highest electrical current flow as compared to the separate application of graphene and TiO_2. However, it was suggested to have lower graphene ratio on TiO_2 in order to have better and steady current flows. The sensitivity of this sensor was ~6.2 μA/mM cm^2 with glucose ranging from 0 to 8 mM. The team identified that the response current with the glucose biosensor based on TiO_2/graphene was larger than those of the biosensors based on TiO_2 or graphene.

Recently, a breast cancer cell (MCF-7) sensor was developed by Safavipour and team[78] using TiO_2 nanotube-reduced graphene oxide (rGO) hybrid. The material was synthesized by UV-assisted reduction of GO and subsequent TiO_2 nanotubes attachment on rGO sheets. MCF-7 cells are the most common breast cancer cells that show the over expression of human mucin-1 (MUC1) on their surface. The aptasensor successfully detected breast cancer cells with a detection limit of 40 cells.ml^{-1} within the detection range of 10^3–10^7 cells.ml^{-1}. Hence, this technology has been recommended for clinical tests of MUC1 marker analysis on real samples.

TiO_2/CNTs nanohybrid

The discovery of carbon nanotubes (CNTs) in the early 1990s revolutionized the research in many fields,[79] such as nanoelectronics, biosensors, removable energy, solar system, and medicine. The latest application of CNTs was developed by Zettl and Cohen's laboratory, to detect coronavirus antigens within 15 mins at the early stages of infection.[80] CNTs and TiO_2 themselves have shown to have astonishing characteristics, hence, combining both materials allow the enhanced performance. CNTs ratio is the critical parameter for synthesizing TiO_2/CNT nanohybrid. Many researchers have reported on the synthesis of TiO_2/CNT nanocomposites for biosensor applications.[81–84] Unfortunately, it requires complicated techniques compared to the nanohybrid.

Nanohybrid TiO_2/CNTs was synthesized by Abega[85] to detect contaminants in the water system. Three steps were involved in the synthesization process, which begun with the functionalization of CNTs with negatively charge functionalities (-COOH or –OH) via acid treatment. Then, titanium ion (positive charge) produced at low pH was electrostatically attracted to the CNTs. Finally, TiO_2 nanoparticles were formed *in situ* on the outer surface of CNTs, where lone pairs of electrons from the oxygen atom on CNTs interacted with TiO^{3+} ion and formed C-O-Ti bonds. Methyl orange was used as an indicator for the photocatalytic application. The binding of C–O–Ti, N–Ti–O, and Ti–C bonding between CNT and TiO_2 in the nanohybrid material showed better photocatalytic activity as compared with TiO_2 alone.

In 2018, a self-powered enzymatic glucose sensor was introduced using a hybrid material of TiO_2/CNTs-Co_3O_4.[86] It provided an efficient photocurrent generation that was sensitive toward visible light. They reported that the optimum volume ratio of Co_3O_4: CNTs was found to be 1:1 instead of 1:3. This material was ready to be immobilized with glucose oxidase (GOx) without any surface modification. The performance of this sensor was more efficient compared to using TiO_2 or TiO_2/Co_3O_4 alone. Besides that, the sensitivity of this sensor was 44.88 $\mu AmM^{-1}cm^{-2}$, noted as one time larger than the sensor without light illuminator and the LOD was 0.20 μM.

TiO_2/other-organic nanohybrid

Song and team reported on the ability of TiO_2 NP/dacarbazine [5-(3,3-dimethyl-1-triazenyl) imidazole-4-carboxamide; DTIC) directly bonded with DNA.[87] DTIC is one of the antitumor drugs used to bind DNA. However, the performance was quite weak. Hence, TiO_2 was introduced to hybridize with DTIC to enhance the binding behavior of DTIC to DNA/DNA bases. They were electrostatically bonded when the negative charge of TiO_2 was diluted in water with DTIC. In water, the amide bond of DTIC was positively charged once oxidized. Hence, DTIC can be self-assembled onto the surface of TiO_2. This

happened in a buffer solution of pH 7.2. The research found that TiO_2 NP showed unique oxidizing properties based on nanosized interface, and the presence increased the binding affinity of DTIC to DNA.

Inorganic/TiO_2 nano-hybrid

High demand for efficient biosensors has motivated researchers to explore the performance of inorganic/inorganic nanohybrid materials. Zhang et al.[88] fabricated a TiO_2/graphite nanohybrid-based glucose sensor using *in situ* technology nanorods on the surface of graphite microfiber. However, this material needed chitosan to act as the connection molecule between TiO_2 with GOx. They clearly reported the formation of TiO_2 nanorods on the surface of graphite. Furthermore, complete immobilization of GOx on TiO_2 was observed by Fourier-transform Infrared spectroscopy peak shift from Ti-O-Ti bonds to Ti-O-C. The sensitivity can be considered as the best performance among other obtained sensitivities, with a LOD of 2.2 µM. In another research, TiO_2/Au nanohybrid for DNA sequence detection has been explored by Liu and team.[89] Au nanoparticles and TiO_2 film were chemically bound and the hairpin DNA was tightly attached to the surface. It showed promising performances in terms of stability and reproducibility with ultralow LOD of 3 fM. Table 3 exhibits the inorganic materials that have been used in TiO2 hybrids.

Field-effect transistor

A field-effect transistor (FET) is designed with a semiconductor channel and three electrodes namely: i) source, ii) drain, and iii) gate. Figure 3 shows the ideal design of a FET. In a typical Bio-FET system, the sensing elements are immobilized on the sensing channels between the source and drain electrodes. Then, a bias potential is applied to the gate electrode for electric conduction and the electrical measurement is recorded to be plotted by a system. The charge carriers (electrons or holes) flow from the source to the drain. However, as a Bio-FET, the gate does this by changes in the surface potential induced by the binding of the molecules. When charged molecules, such as biomolecules, bind to the FET gate, which is usually a dielectric material, they can change the charge distribution of the underlying semiconductor material, resulting in a change in conductance of the FET channel. The versatility of the FET device for electronic biosensor has been well-recognized through a vast development of electronic products with diverse functionalities and portability.[90–92] FET plays a pivotal role in instant translation of the interaction from probe analyte on the FET surface into a readable signal. Recent developments on Bio-FET have shown promising results with excellent specificity, sensitivity, and possess the ability to detect ultra-low concentrations of the target biomolecule. This development is still under study to fulfill the requirement of point-of-care testing.

Table 3. Summary of inorganic materials hybridized with TiO_2 for biosensor applications.

Hybrid material	Detection method	Detection	LOD	Ref.
Graphite microfiber	Electrochemical	Glucose	2.2 µM	[88]
Au	Photoelectrochemical	DNA	3 fM	[89]

Interdigitated electrode (IDE)

IDE-shaped electrode is designed with two separated metal plates, each having a number of individual digits (fingers) and overlap with the digits from the other section (Figure 4), essentially creating the structure as a microfabricated sensor. Basically, the sensitivity of an IDE depends on the digit-width and digit-spacing. Dimensions in the range of several micrometers have been shown to be effective for biosensor applications.[93,94] However, nanometer-scale of digits is still being studied to achieve workability under ambient condition. An electric field between the fingers is produced when a direct current (DC) or alternating current (AC) is applied on the pads. The existence of biomolecules on the fingers causes the changes in the electric field reading. The

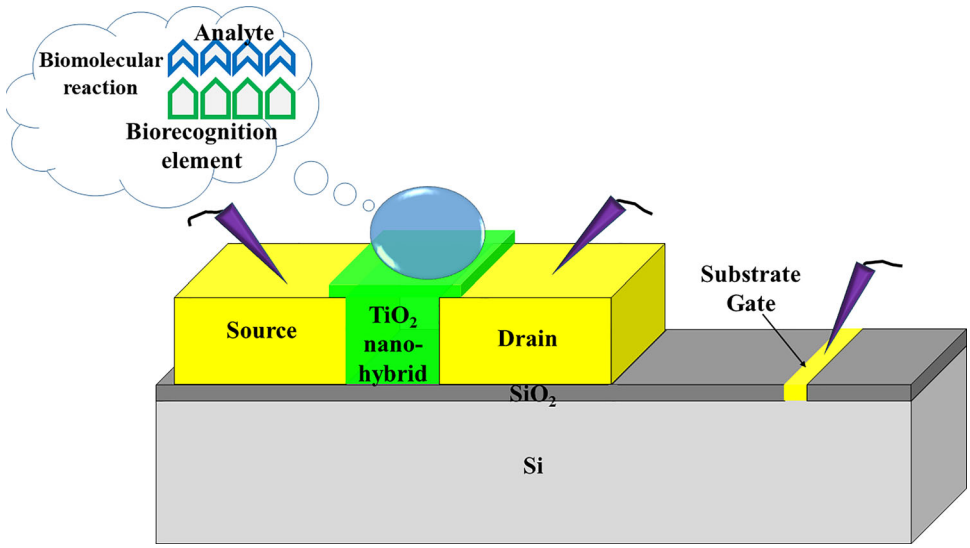

Figure 3. Cross-sectional view of an ideal FET. The biomolecular interactions occur between source and drain are shown in the figure.

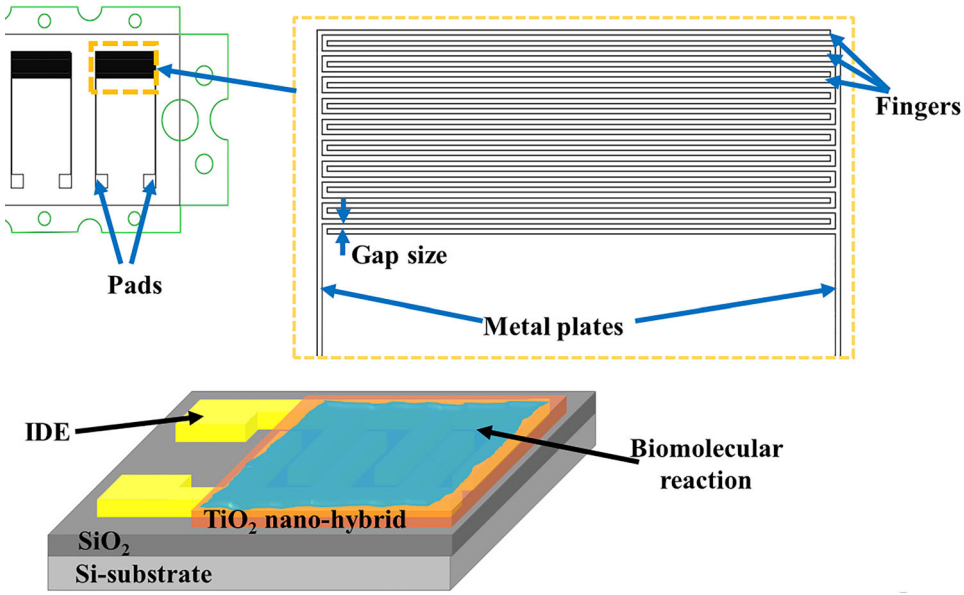

Figure 4. IDE structure. The yellow box shows the individual digits (fingers) of each metal plate. The biomolecular interactions occur on TiO_2/nanohybrid are shown in the figure.

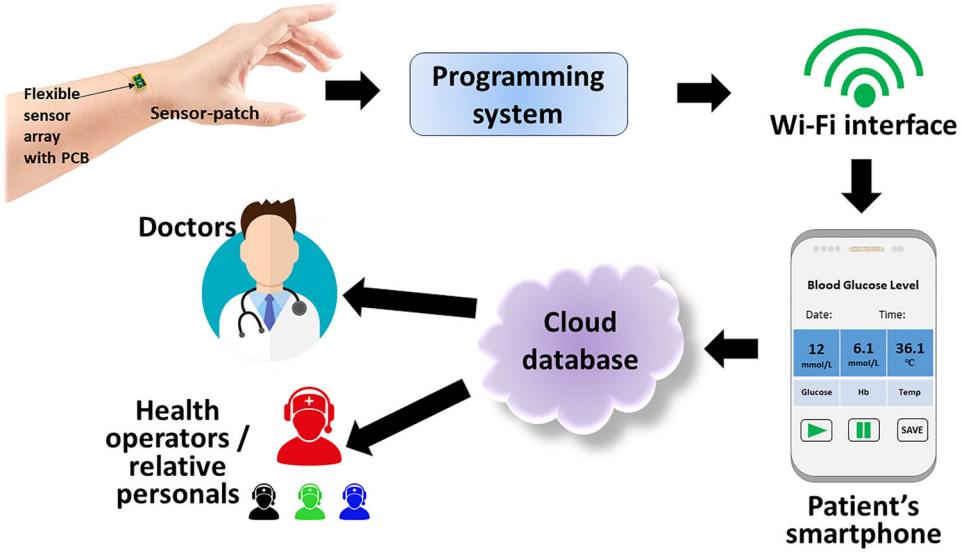

Figure 5. Overview of designed architecture system: Connectivity between noninvasive wearable sensors, programming system, Wi-Fi module, smartphone and data transmission network.

changes-measured to be the correlation of electrical charges between the biomolecules and fingers' surface.

Future perspectives of TiO_2 nano-hybrid electronic biosensor

For commercialization and world-wide usage, it is crucial to develop a biosensor with low-cost, high sensitivity, and high selectivity. Among the steps required for biomolecular detection, the use of TiO_2 nano-hybrid materials allows the elimination of surface modification. Hence, it reduces the production time and cost. Besides, electrical biosensors are highly responsible for showing the results in a user-friendly manner (digitalized). Therefore, this eliminates the necessity of experts to interpret the results and directly lowers the cost. Indirectly, this transducer is a step forward toward in-house detection using high-technology remote digital monitoring system. Several advantages are engaged with the remote digital monitoring, like early detection and avoiding potential complications. It proves that it is possible to have highly efficient care at a fraction of the cost with traditional remote patient monitoring. As the world is attacked by the Corona virus that prohibits patients to closely interact with their doctors, remote digital monitoring system technology provides opportunities for doctors to watch patients in need of frequent monitoring at home. This new norm may reduce emergency visits, shorten hospital stays, and create efficient treatment for health systems. Figure 5 shows the idea on how remote digital monitoring system works. The system consists of the connection between a wearable sensor and Wi-Fi module to a smart phone. An electronic interface

connects the electrical circuits to the smartphone application to monitor, analyze, process, and transmit the data.

Conclusions

TiO_2 nano-hybrids have increased the number of scientific researches in biosensors with improved analytical features and merits. The integration of TiO_2 nano-hybrid in biosensor has been receiving much interest in developing an ideal biosensor due to the reflection of unique features for an outstanding detection. The function of different TiO_2 nano-hybrid biosensors were clearly presented based on the current researches. The impact of different hybrids with organic and inorganic materials toward bio-detection was discussed. TiO_2/organic nano-hybrid sensor is more flexible, which has huge potential to be further utilized as a wearable sensor. Then, the production of TiO_2 nano-hybrids, followed by the configuration of TiO_2 nano-hybrids for electrical biosensor development was evidently narrated. The exploration of a remote monitoring system in the healthcare industry is indicated as a huge turning point for medical professionals. Besides that, the future innovation in remote digital monitoring system to improve the currently available direction of TiO_2 nano-hybrid biosensors was reviewed.

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