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ISFET SENSORS FOR BIOMEDICAL APPLICATIONS

The importance of biosensors developing and manufacturing for biochemical applications was considered. The main achievements concerning the use of field transistors as biosensors for the detection of various biomolecular compounds were presented. The main advantages of using such sensors in recent years, prospects of their use were summarized. Examples of the use of ISFET for reliable and sensitive analysis of various biomolecules such as DNA, proteins, enzymes, and cells were presented, and a new application of the ISFET-sensor of C-reactive protein was proposed.

Key words: antigen; antibody; biosensor; biomolecules; C-reactive protein; DNA, ion-selective field-effect transistor; enzyme.

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СЕНСОРИ НА ОСНОВІ ІОНОСЕЛЕКТИВНИХ ПОЛЬОВИХ ТРАНЗИСТОРІВ ДЛЯ БІОХІМІЧНОГО ЗАСТОСУВАННЯ

Розглянуто важливість розроблення та виготовлення біосенсорів для біохімічного застосування. Наведено основні досягнення щодо використання польових транзисторів як біосенсорів для детектування різних біомолекулярних сполук. Узагальнено основні переваги використання таких сенсорів останніми роками, перспективи їх використання. Наведено приклади застосування ІСПТ кількісного аналізу різних біомолекул, таких як ДНК, білки, ферменти та клітини, та запропоновано нове застосування ІСПТ-сенсора для С-реактивного білка.

Ключові слова: антиген; антитіло; біосенсор; біомолекули; ДНК; іоноселективний польовий транзистор; С-реактивний білок, фермент.

Introduction

Until recently, medical diagnostics used highly skilled and experienced staff and a large number of laboratory instruments and devices for laboratory research. These laboratory diagnostic methods give precise results, but also require a lot of time, money, and sometimes the use of bulky devices. Fast, cheap and easy-to-use portable systems for work in real time and in the places where the patient is located, without the need for additional transportation of samples to the laboratories, can significantly improve the quality of medical services. A quick analysis without the use of additional labels to recognize biological processes provides a good prospect of use. Operational analysis of various analyzes is a necessary task in many areas, including chemical analysis, clinical monitoring, development of new types of drugs, food quality testing, and more.

We know different ways of implementing sensors, but in recent years the number of articles and scientific materials that describe the advantages and disadvantages of sensors based on field transistors have been increased. Scientific developments that describe the new biosensors for detecting analyte in clinical diagnosis have been increasing each year. The use of such biosensors is particularly important in places with limited access to laboratories. It is impossible to do without the use of the possibilities of

nanotechnologies that allow to increase the productivity of biosensors, using electrochemical, optical, mechanical and physical transmission principles, as well as to build biosensors for simultaneous measurement of several parameters.

The biosensors described in this work are preferably used to detect cancer markers, cardiovascular and infectious diseases, DNA/RNA, etc.

The functional interface, in conjunction with field-based devices, allows to get a portable biosensor without special extra tags, making the analysis process easier, cheaper and more convenient. Several of these methods, including surface plasmon resonance (SPR), quartz crystal microbalance and electrochemical methods.

With the rapid development of technology in medicine and biology, the number and types of molecules, as well as the ways of their registration, are also increasing. In order to facilitate the processes of information processing, miniaturization of devices and understanding of the mechanism of interaction of molecules in biology use the possibilities of micro-and nanotechnologies. Solid-state biosensors, in which the semiconductor is used as a transmitter, is a typical example of combining biotechnology and microelectronics. Biochemical field effect transistors have several advantages, namely: small size, low cost and the ability to integrate with other sensors and signal processing schemes on the one chip. The type of molecules that can be detected and the sensitivity is determined by the bound molecules and the material covered with the surface in the gate area. In order to ensure the greater importance of biosensors in everyday life, it is necessary to significantly improve their sensitivity, specificity and the ability to simultaneously measure several parameters. It is the thin layer of molecular thickness (membrane) on a solid surface that is important for the use in the biosensor.

The design and manufacture of a functional interface in the field of the transistor gate is a key for achieving effective recognition of molecules and transforming it into an electrical signal in a solid-state structure.

The Bio-FET sensors have some advantages over ordinary sensors in terms of miniaturization and integration, using the capabilities of already known semiconductor technologies. The main task for Bio-FET sensors is to develop sensitive surfaces that can capture a wide range of particles from the real liquid, natural environment. Therefore, it is important to create methods for designing such a functional interface.

Over the last few decades, biosensors based on silicon for bioanalytical applications, due to their high sensitivity, speed, reliability, compactness and cheapness, are of great importance [1]. Since 1971, silicon field-effect sensors have been used as chemo-sensors for the study of pH in electrolytes [2]. Due to the properties of semiconductors, devices based on FET can convert biochemical processes of binding in a liquid or changing the ionic concentration on the transistor surface in measuring electrical signals that are associated with the properties of the gate surface [3]. Among them, ISFET, is one of the most popular electrical biosensors and is the first compact chemical silicon-based sensor.

The ISFET pH-sensitive is used as a transducer in combination with enzymes that generate or absorb hydrogen ion in enzymatic reactions. As a result, the pH changes around the enzyme membrane deposited and these changes are recorded using the ISFET.

ISFET, conventionally referred as a pH sensor, is used to measure the concentration of ions (H + or OH-) in a solution that causes a certain surface potential at the gate.

After investigated ISFET biosensors in 1970 [4] by Bergveld, a large number of biosensors were created on its basis. There are numerous scientific papers, including reviews of the detailed principle of his work [5]. Various sensors based on the ISFET are related to the inorganic nature of the gate, by modifying the material for the gate, or by applying a sensitive membrane or biodegradable element to the gate. Such sensors are called chemical sensors based on field effect transistors. Initially, ion-sensitive sensors based on field effect transistors used as membrane silver halides and membranes based on polyvinyl chloride [6]. And later, various derivatives of polymers began to be used for this purpose.

Principle of work of ISPT-biosensors

Much attention has been paid to Bio-FET sensors for bioanalytical applications. Bio-FETs sensors can detect a variety of biological processes, such as nucleic acid hybridization, protein-protein interaction and the result of enzyme reaction to the surface.

Generally, biosensors consist of a transducer and a membrane to which the substrate is immobilized. In the transducer, physical and chemical changes in the membrane resulting from biochemical reactions are converted into electrical signals. This device can register electrical, thermal or optical output signals as a result of biological reactions on a sensitive surface.

The principle of the FET is as follows. In the normal mode, the channel between source and drain starts to conduct current only when the gate voltage reaches a certain threshold (V_T). It depends on the material of the gate, the dielectric, the channel, and the physical properties of the transistor. The most common type of sensors based on FET are ISFET sensors, whose work additionally depends on the change in charge between the interstitial dielectric and the analyte, where the binding itself occurs. Changing the value of the V_T parameter can be used to determine the sensitivity of the sensor. However, in the ISFET, instead of the gate electrode, reference electrode is used, immersed in the analyte (Fig. 1). ISFET sensors are used not only as pH meters but also for determining the sequencing of the genome, for the detection of various substances, ions, molecules and as bimolecular sensors in different configurations. In general, bioanalysis requires the use of special fluorescent labels or radioactive substances. In contrast, ISFET's sensors do not need special labels which makes it simpler, cheaper, portable and convenient.

A large number of applications of FET's are known as sensors: enzyme-FET sensors (for the detection of glucose, urease) [7–9] for pH [10], for the study of DNA hybridization [11], and cell-based on FET's for cell analysis, namely, metabolism or measurement of extracellular pressure [12]. Particular interest about applications those sensors are biochemical, biomedical [13] and environmental monitoring. The article has summarized the recent advances applications of ISFET's biosensors.

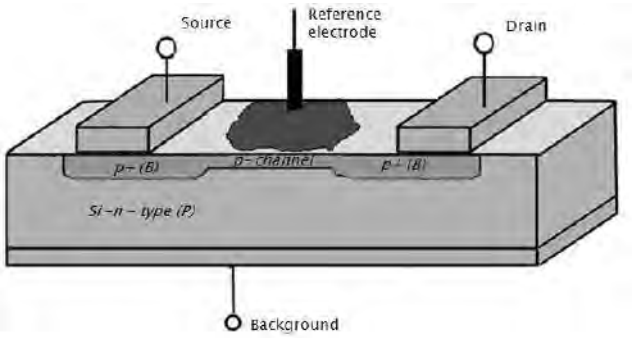

Fig. 1. ISFET structure

For classical ISFET's, SiO_2, Al_2O_3, Si_3N_4, Ta_2O_5 and others are used as a sensitive insulator. In the case of ISFET, the magnitude of the current strength is determined not only by the charge of the interaction of the biomolecules, but also by the sensitivity to change in pH, concentration of various ions, products of enzymatic reactions and others. A good feature of such bio-FET sensors is the ability to detect the interaction of biomolecules without the use of special labels, and through direct registration of changes in conductivity or other electrical properties. However, apart from the advantages of ISFET's, some disadvantages significantly limit their service life and scope. An important feature of the ISFET's is to provide reliable all-electric contacts to prevent the electrolyte leakage and form a high-quality dielectric layer to avoid the instability of the threshold voltage and prevent the existence of leakage currents.

There are four main ways of developing a potential on the interface solids/electrolyte, which underlie on the working principal of the ISFET's:

1) the transfer of charge through the interface solids/electrolyte;

2) the difference in the specific adsorption of the ions with opposite sign on a solid surface;

3) adsorption or orientation of molecules having their own dipole moment;

4) the polarization of atoms and molecules in a non-uniform force field near the interface.

The potential established as a result of the chemical interaction operates consistently with any external displacement applied to the gate and therefore is recorded in the same way as the gate voltage changes in the typical FET's. There are various solid materials, LaF_3, AgCl, Si_3N_4, Pt and others that are selective to fluorine, silver, and hydrogen ions are used as reference electrodes.

Many materials that are sensitive to H^+ simultaneously serve as an effective barrier to prevent the diffusion of ions and water. Therefore, they are often used as the upper dielectric layer of the ISFET, as well as the encapsulating material made by PCVD or oxidation together with lithography. To produce ISFET's to detect other chemicals, usually use special ion-selective membranes or biomaterials, which are cowered the dielectric surface and deposited on it by physical and chemical adhesion. These additional membranes are selectivity to the required substance and made a signal that is then recorded.

Application of biosensors based on ISFET

The main advantage of ISFET, compared with optical systems, is the possibility of their use in miniature measuring systems, and the simplicity of mounting in electronic devices [14]. Because of this, the lightweight and small ISFET's sensors can be used in portable monitoring systems, for example, portable control systems for drug levels in the body.

Many developments in the field of electronic analysis of biomolecules are carried out by controlling the change in the density of charge using the ISFET's [15]. To date, different types of biological materials for biological analysis, such as DNA, proteins, enzymes and cells, are used in the ISFET's due to its unique electrical and biological properties, increasing the sensitivity and specificity of the detection of the component under study. A large number of scientific papers on ISFET's sensors that contain various biocomponents for biological analysis, such as ISFET like enzyme sensors, immune-ISFET's sensors and DNA-ISFET's sensors containing layers of immobilized enzymes, antibodies and DNA regions, are well known [16].

The process of biosensor manufacturing combines a solution of some issues:

- to choose the converter and the specific reaction that can be used to identify the test substance;
- integration the biological material and the converter surface, while maintaining it's activity;
- to choose of optimal conditions for the measurement and the investigation of the influence of various factors on the output signal;
- to determine stability, accuracy of the sensor and the conditions to storage it between measurements.

DNA sensors based on ISFET

Using ISFET for DNA test, a single-stranded DNA region is immobilized onto the dielectric surface due to electrostatic or covalent interactions. Due to the special treatment of the oxide layer of the FET-transistor, DNA samples are immobilized on an oxide surface in a definite order. According to the well-known methods for DNA detection, the most common methods are the definition with enzymatic, fluorescent or radiochemical labels. Despite that ISFET sensors have high sensitivity and low threshold detection, they still need to be improved.

Many studies about DNA biosensors are conducted in conjunction ISFET with electron-based aptamer [22]. Aptamers are nucleic acids (DNA or RNA) or peptides that selectively bind to their specific target molecules, such as small molecules, nucleic acids, proteins or even cells.

Fig. 2 shows a schematic model of aptasensor based on ISFET for adenosine. This sensor has a detection limit approximately 5×10^{-5}M, and a high specificity because it does not respond to any other nucleotides.

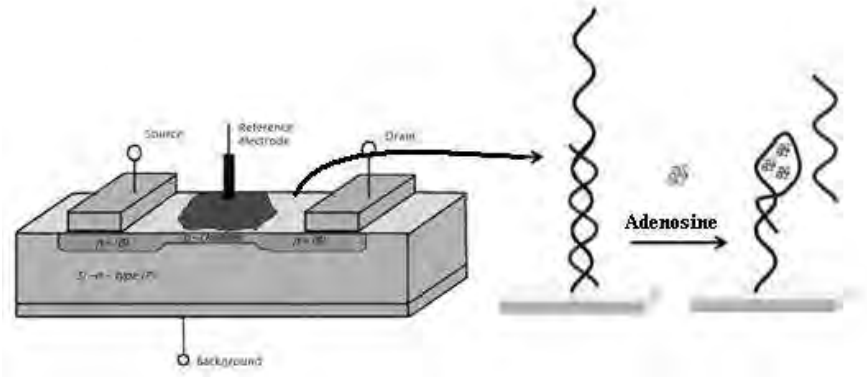

Fig. 2. Adenosine sensor based on aptamer markers using ISFET

Main problems and solutions in the production of sensors

Problem	Sensors type	Solution
Speed, low cost, and ease of implementation	DNA sensor	Platform developed on the basis of amorphous silicon (a-Si: H) [17]
The impossibility of detecting the charge of DNA through a relatively thick layer of oxide, which adversely affects the movement of charged DNA from the electrolyte to the sensitive layer of the solution	DNA sensor	FET's with diamond substrate [18]
The reaction of DNA hybridization takes place at a distance greater than the length of the Debye	DNA sensor	More complicated registration methods [19].
The effect off light onto the sensor shift response	Enzyme-ISFET with Ta2O5	To use different manufacturing methods for ISFET and post annealing in different gases [20]
The impossibility to analyze complex samples based on arginase/urease system	ISFET to determine L-arginine	Conductometric sensor production [21]

In addition to use ISFET like DNA sensors, there is a growing interest to investigate the restriction of DNA hybridization charges based on FET's biosensors. However, in this case, there may be some problems in the implementation of the sensor (Table). The proposed sensor can quickly detect trimer mismatches of DNA, and can be used to monitor single-stranded DNA discrepancies without changing sensitivity [25]. In addition, when hybridizing DNA at a distance greater than the length of Debye from a sensitive layer, MDN sensors are unable to detect DNA (Fig. 3).

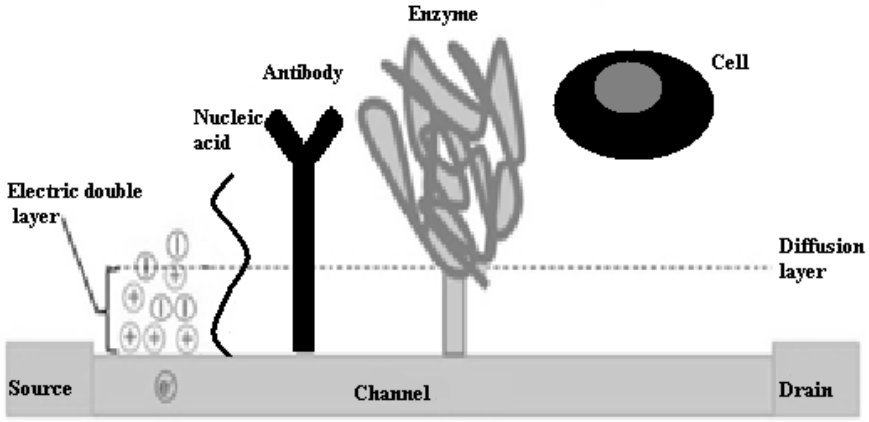

Fig. 3. Schematic image of the sensitive area of the ISFET and assays with different sizes in relation to the thickness of the electric double layer

Use of ISFET for immunological testing

ISFET's which are sensitive to pH change – the most popular devices as an immunosensor using different dielectrics (SiO_2, Si_3N_4, Al_2O_3 and Ta_2O_5) [23]. As for the biodegradation elements, antibodies are often used to capture antigens that allow the identification and quantification of individual analysts due to the specific interaction of the antigen-antibody, Fig.4. Immunological ISFET consists of a specific gate covered by special antibody that recognizes the antigen and can be used for clinical diagnosis [18]. As for the medical application of immuno-ISFET-biosensors, "Debye length" should be taken into account. As it is known, the electric field disappears beyond its limits, that is, at the distance where moving electric charge carriers shield the external electric field. That why this is one of the main disadvantages during measuring bimolecular recognition using biosensors based on FET. In order to use FET's for these the reactions should occur within the limits of the Debye length (λ_D). Should be noted that the application of

immuno-ISFET for diagnostic monitoring may be limited only because bimolecular interaction usually that are occurred at a distance of 10 nm from the gate surface due to the additional height of the antibody.

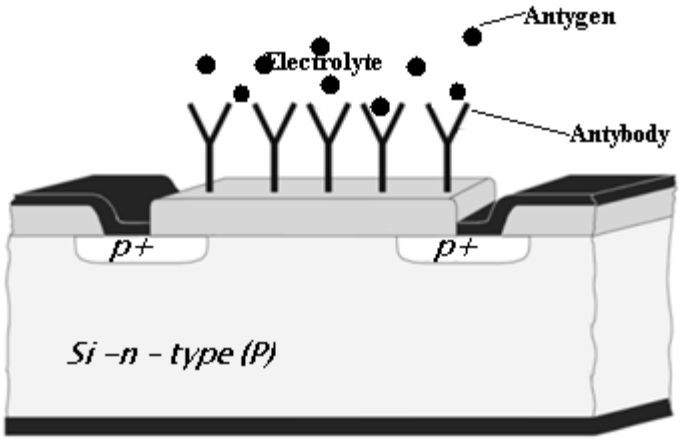

Fig. 4. Schematic structure of immune-ISFET with antibodies

In [24], a new alternative potentiometric method for defining the protein at the ISFET gate was considered. The surface of the ISFET is coated with a monolayer ligand-bound amino particles (diameter of 0.9 μm), which provide specific binding properties. This approach provided a general method for the coverage of ISFET for immunochemical solid phase reactions. Typically, potentiometric immunosensors require the immobilization of immunoactive biomolecules, such as antibodies. As an alternative method to modify the surface of the ISFET's, conductive polymers were used because of their high chemical resistance, biocompatibility, and their ability to doping. In the paper [25] a micro-potentiometric Hb/HbA1c ISFET-immunosensor was developed for detecting hemoglobin (Hb) and hemoglobin-A1c (HbA1c) in blood with higher sensitivity and immobilizing antibodies onto the gold electrode.

Application of ISFET's sensors for enzyme detections

Over the past few years, a lot of work has been done to solve several issues related to the operation of enzyme FET transistors, such as the stability, reproducibility and compatibility of FET systems.

Although the possibility of ISFET as an enzyme sensor was first proposed in 1976, and the practical use of ISFET as a penicillin-responsive device was first proposed just after 4 years, in 1980. For the detection of penicillin, an enzyme ISFET-biosensor is based on two pH-sensitive ISFETs, one has a cross-linked albumin-penicillinase membrane, and another only an albumin membrane. Investigating them it was proved that the tested on the enzyme ISFET-biosensor can be used to detect faster a small amount of analyte with high sensitivity. In addition, through the automated penicillin measurement system, such sensors can significantly reduce the time for analysis and can be applied to analyze complex samples. Another approach to using ISFET for monitoring certain proteins is the use of proton or hydroxyl ion obtained as a result of protein hydrolysis in response to trypsin. For example, in [26], an ISFET trypsin biosensor for substrate analysis (α-benzoyl-L-arginineethyl ester hydrochloride) was proposed, thus demonstrating the feasibility of using ISFET's to monitor small pentapeptides that consist of five amino acids. The authors suggested using this biosensor to control the quality of cosmetic products, since this peptide is their ingredient. However, the use of pH-sensitive electrodes makes it possible to investigate the concentration of protein in the products of proteins decomposition.

A new potentiometric biosensor, which allows for the quantitative analysis of proteinases through the activity of esterase, is shown in [27]. The device is based on pH-ISFET and immobilized α_2-macroglobulin-trypsin complex. This pH-sensitive ISFET biosensor showed linear correlation with esterase activity in the range of 0.1 to 30 V/ml, and also demonstrated good stability and reproducibility. The authors suggested that such sensors could also be used to simultaneously detect other trypsin-like proteinases.

As for application ISFET-sensors for monitoring toxicity, potentiometric and conductometric biosensors in combination with cholinesterases for the detection of toxic substances in ecological monitoring have been developed. The basis working principals of these sensors areenzymes inhibition mechanism, which makes it possible to use them for systems for the early detection of hazardous chemicals.

In addition, biosensors with photopolymers and other polymers for enzymatic biosensors are known [28]. Recently, scientists [29] have developed an enzyme biosensor based on ISFET for measuring urea, also named as an ISFET-sensor of urea. In this paper, a simple and fast way the enzyme immobilization on the ISFET gate is based on a liquid photopolymerized composite where the polymer is formed under the UV action. The developed ISFET-urea sensor showed a significant improvement in sensitivity and time response, a linear response in the range of 0.05-20 mM, and time response of 5-10 minutes. These properties of ISFET-urea sensor make it possible to assert that it can be used for clinical analysis in blood samples.

In order to stable enzymes immobilization to the surface into the ISFET sensitive region, various methods have been developed, including the use of magnetic nanoparticles [30], where the lipase is immobilized on magnetic nickel-ferrite nanoparticles, and then the enzyme-modified nanoparticles can be stored on the surface of the working region for a long time (Fig. 5). The proposed method is based to improve mass transfer, as well as the possibility to use it in the multidetection system based on FET's and to increase the amount of bound enzyme to the surface.

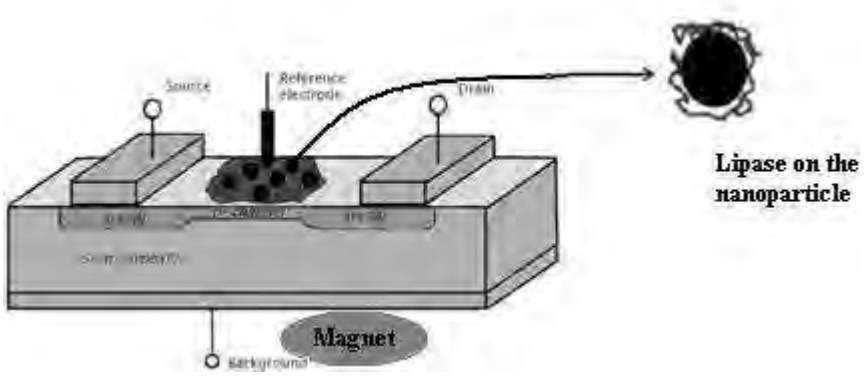

Fig. 5. Schematic representation of the ISFET with nanoparticles and a magnet [30]

In recent years, attention has been increasing to detect the adenosine triphosphate (ATP), using ISFET's sensors [31]. Apart from ATP is known as the main substance responsible for the level of energy in all living systems, it is still used as a label to research micro-fungal contamination in the food industry and in other industries which are required to control purity level.

In addition to ATP control, it is also important for medicine to determine and control the level of L-carnitine. Since it plays a major role in the transport of fatty acids in the mitochondria, where, in fact, their oxidation are occurs with the formation of ATP, contributing to the decomposition of fats. L-carnitine ISFET-sensor with a pH-sensitive membrane has patented [32]. L-carnitine also provides better tissue regeneration and improves appetite and is involved in a lot of vital body functions.

Despite the fact that ISFET-based sensors have good activity and reliability, in some cases they may have some restrictions associated with buffer characteristics, such as pH or buffer capacity, because the working principal is the measurement of pH changes caused by the enzyme-catalytic reaction on dielectric, which is very influenced by buffer conditions. In [33] proposed to solve this problem using several principles, namely, the use of additional charged polymeric membranes and low-capacity buffer solutions. Another example of an enzyme FET sensor is an extended gate sensor, which allows to measure changes in the oxidation-reduction potential in enzyme-catalytic reactions. Although the sensitivity of an ISFET based enzyme sensor is highly influenced by buffer conditions, the proposed sensor is not exposed to pH or buffer capacity. From the results it is likely that the enzyme-catalytic reaction due to the chemical reaction is responsible for the change in the potential, and not for pH changing in the extended gate field effect transistor. More recently, in order to increase the effectiveness of the ISFET, [34] proposed another type of

ISFET, the so-called local ISFET. This type of ISFET has an extraordinary peculiarity, the productivity depends on the force of the electric field formed as a result of the ionic reaction occurring in the local region around the electrode. The authors suggested that this type of sensor have a perspective to be used as a nanobiosensor, since it allows detecting simple enzymes, using a small amount of liquid.

ISFET for monitoring living cell responses

Cell-based biosensors give various information about the analyte, allow controlling cytotoxic effects in response to hazardous substances, as well as physiological cell responses to multiple irritants. Thus, living cells are used as biocontent and this allows to control the living cells activity electrochemically. Due to these advantages, cellular sensors are promising devices for use in biomedicine and pharmacology. In particular, more and more attention is paid to the integration of living cells with silicon FET devices. First of all, cell-based biosensors based on ISFET have a great interest for use in neural networks.

When it comes to the usage of the ISFET at the cellular level, it is possible to simultaneously control both cellular respiration and acidification. In [9], the dependence of pH on the change of extracellular acidification and respiratory rate using the same cellular fluid is presented. It is known to manufacture a touch-sensitive chip based on a pH-sensitive ISFET for direct extracellular visualization, which consists of an array of 16×16 pixels of ISFET that have a readout circuit for signal acquisition.

Meanwhile, the development of cell-based ISFET biosensors was used to record extracellular signals, which are often used in pharmacology. Also, cell-based sensors are used to control the extracellular concentration of ions depending on the potential of the membrane in response to various chemical irritants. For example, there is a non-invasive monitoring system for studying the modulation of ion channels, which is very important for therapy. This ISFET sensor makes it possible to detect concentrations of extracellular ions such as Na^+, K^+ and Ca^{2+}, indicating that these biosensors are worked in real-time and long-term analysis of cellular compounds. To use cells in biosensors, it is important to place cells into the sensor active area, which can be done using dielectrophoresis (DEF) [35].

To use such an ISFET sensor with DEF electrode as a tool for characterizing the localization of bacteria also can detect the bacteria metabolism in a few hours after adding glucose by monitoring the pH changing. After adding glucose, it is absorbed by bacterial cells.

After the first publication on the application of semiconductor nanotechnologies, interest is rising due to their high sensitivity, the possibility of real time research with biomolecules and, most importantly, label-free detection. Therefore, it provided a new direction to use it for diagnostic diseases that have other sensitivity mechanisms compared with conventional analyzes. For example, silicon nanowires can be easily done and they show promising results in the application to detect the specific markers [35], DNA and viruses. FET's with silicon nanowires consist of source, drain and nanowires that act as an electric resistance. The sensitivity mechanism depends on the change of electric charge, which is the main advantage of silicon nanowires compared with other nanotechnological sensing mechanisms. Since it provides a simple detection label-free mechanism and have ultra-sensitive detection level of biomolecules. Silicon nanowires are used for the quantitative analysis of C-reactive protein (CRP). A nanowires array, which are shown better sensitivity and less contacts resistance and provide the signal stability. In addition, the passivation of the electrodes provided a high sensitivity in comparison with the previous measurements.

CRP is a well-known protein marker that is used as a precursor to recognize a symptom of cardiovascular disease. Its elevated blood levels are risk factor because it is a possible indicator of inflammation, as well as rapid angiogenesis, for example, tumors. Therefore, the rapid detection of elevated blood levels is important for biotechnology. Sensors based on silicon nanowires have shown excellent biocompatibility with CRP molecules and can be used to manufacture multisensors to simultaneously detect markers of various diseases.

However, in addition application FET with nanowires, the ISFET application to detect CRS is still unknown. A well-known method for detecting this protein is an enzyme-linked immunoassay, but it is expensive and requires special additional laboratory capabilities [36].

It is precisely the use of the ISFET that meets the requirements mention above. Thus, the task is to select and apply a special sensitive layer on the surface of the ISFET for the possible detection of CRP.

To detect CRP, SiNWs [37] sensors demonstrate a linear response, and their respective signal changes were recorded, and these results are similar to those clinically obtained. But this sensors can't use several time, since the nanowires are deleted after clining.

Therefore, there is still a need to develop a portable, high-sensitivity and reliable sensor that does not require long-term treating and additional specialist skills in the implementation of CRS analysis.

Conclusions

The article presents the main application of the ISFET biosensors. The most common use is for the detection of glucose, urea, pH, DNA hybridization, cell-based ISFET sensors, and cell analysis, namely metabolism or extracellular pressure measurements. For each application a special sensitive membrane was applied to the appropriate component.

However, to detect the level of CRP, elevated levels of which indicate the presence of inflammatory processes in the body, and for some values, even the possibility of cardiovascular disease is still used by immuno-enzymatic methods that require pre-sampling and additional materials for analysis. Therefore, the purpose of the further research was chosen, the development of a portable, highly sensitive and recoverable sensor for the diagnosis of CRF. The solution to this problem might be the development of an ISFET sensor.

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