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A review on ion-sensitive field effect transistor (ISFET) based biosensors

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Abstract

The invention of sensors that can identify and measure biomolecules is a crucial advancement for biology. Sensors have become widely used in several industries during the last few decades, most notably in the area of medical diagnosis. Biosensors constitute a bio-detecting system by integrating signal conversion and biological recognition components. They have been developed for a wide range of bio-detecting applications. A class of biosensors known as electrochemical biosensors uses electroanalytical equipment and has the advantages of higher sensitivity, simplicity, speed, and biomolecule recognition selectivity. One of the most popular electrochemical biosensors nowadays is the ISFET sensor, which performs biochemical measuring and biomolecule recognition. ISFETs, which were first suggested a little over fifty years ago, now the most promising devices for care diagnostics and lab on a chip are made with ISFETs. In this review paper, the history, working principles, fabrication processes, and modeling and simulation techniques of ISFET are presented. Additionally, some physical aspects and simulation methodologies are explained. Finally, we discuss their applications in sensitively and reliably analyzing diverse biomolecules, including DNA, enzymes, and cells.

Keywords: Biosensors, ISFET, CMOS, pH sensor

1. Introduction

Sensors detect or directly measure a test compound in a sample and record, indicate, or otherwise respond to it [1,2]. A critical type of sensor is used to measure biological or chemical reactions that combine a biological component with a physicochemical detector. These sensors are called biosensors [3,4].

Biosensors are used in various applications such as disease monitoring, the food industry to measure carbohydrates, alcohols, and acids, and Processing and monitoring for Industry and military purposes [3, 5, 6]. Silicon-based biosensors have received much interest in bio – analytical applications for several decades because of their advantages, such as high sensitivity, low cost, high speed, and miniaturization feasibility. Many types of biosensors can be classified according to their biological element or their transduction element, as shown in Fig. 1.

The biological element detects the target analyte's presence and concentration. The biological factors are such as (Antibody, DNA, and enzyme). The antibody is a protein that the body's immune system produces when it discovers dangerous compounds. Antibody-based biosensors have been in use for many years due to their broad applications and potent antigen-antibody interactions.

In smart grids, the networked sensor topologies give the ability to merge these sensors and come up with new data based on these sensor complementarities [9-13]. Data from any sensor can be predicted based on other sensors, which may be in different places, in case the

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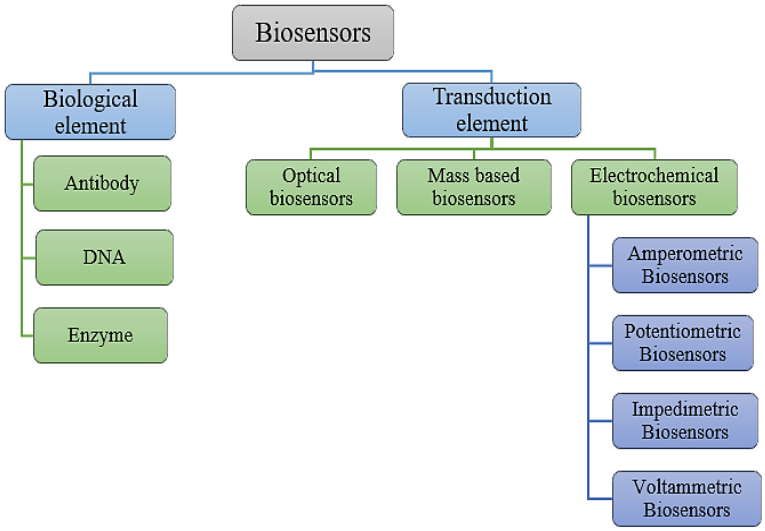

Fig. 1 Types of Biosensors.

required sensor readings are missed. The correlation between data obtained from these sensors depends on historical observation [13]. interactions.

Biosensors that rely on the interaction between an antibody and an antigen or incorporate antibodies such as ligands are known as Immunosensors [7]. DNA is the molecule that has the genetic information of an organism that is important for its functionality and development. DNA biosensors are used to identify proteins and non-macromolecular substances that interact with specific DNA segments and are called DNA probes or DNA primers. Nucleic acids serve as the biological receptors for DNA biosensors. DNA biosensors have a high selectivity for their target analytes [8]. Enzymes are common biocatalysts that are effective at speeding up biological reaction rates. The enzyme-based biosensor's operation is based on the ability to detect the target analyte through binding and catalytic reactions, and enzymes must be stable for normal operating conditions [9]. For biosensing, the transducer is used to convert the bio-recognition event into a measurable signal. According to their transduction element, biosensors can be classified into three types: optical, mass-based, and electrochemical.

Optical biosensors are small analytical instruments with a transducer system and a built-in biorecognition component. They use the principles of optical measurement such as absorbance, fluorescence, chemiluminescence, etc. They contain a light source and numerous optical elements to generate a light beam with specific characteristics directly proportional to the analyte concentration [10]. Optical biosensors use different spectroscopies by recording other spectrochemical properties such as absorption, fluorescence, surface electron resonance, refraction, diffusion, etc [11]. Mass-based biosensors Measuring the small change in the mass is based on piezoelectric crystals; when the mass changes due to a chemical bond, the resonance frequency of the piezoelectric crystals changes that can be translated into an electrical signal proportional to the difference [12,13].

Electrochemical biosensors are biosensors that convert biological information (biochemical receptors) into electrical signals (current or voltage) [14]. Electrochemical biosensors are classified into four types. The first type is amperometric biosensors. They are based on a link between the intensity of the current and a biochemical reaction in these biosensors for a constant voltage passes between the electrodes. Then, in an enzymatic reaction, the substrate can transfer an electron (electric current) at the electrode surface to be oxidized or reduced, and the amount of the current is proportional to the substrate concentration. It's used for the determination of glucose-by-glucose oxidase [15].

The second type is potentiometric biosensors. They are based on measuring the potential difference between the potentiometric electrode and the reference electrode, which is proportional to the concentration of the sample. It gives information about both the ion concentration and the sample construction. For a potentiometric biosensor, the most important electrodes are pH, ammonia-selective, and CO_2-selective electrodes [1,16].

The third type is impedimetric biosensors. An impedimetric biosensor is a sensor that discovers the analytes or biological entities by measuring the

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variation in electrical conductance/impedance. Electrochemical impedance spectroscopy uses this technique to indicate a broad range of physical and chemical properties [16,17].

The last type is voltammetric biosensors. Voltammetric is a type of electro-analytical method in which information of an analyte is determined by varying potential and then measuring the resulting current. There are many types of voltammetric biosensors, such as polarography (DC Voltage), linear sweep voltammetry (LSV), square wave voltammetry (SWV), regular pulse, reverse pulse, differential pulse voltammetry (DPV), and more [15,18]. The voltammetric technique helps sense platforms because of their high sensitivity, selectivity, and low cost [19].

Electrochemical biosensors have many advantages, such as high sensitivity, detection of a broad range of targets, simplicity, rapid response times, and selectivity [20]. Electrochemical biosensors are also suitable for detecting a high range of analytes and, thus, can be used as powerful, portable, low cost, and minimized for many applications [21]. Electrochemical biosensors also suffer from disadvantages such as short lifetime, low levels of stability, and high cost [22]. These days, numerous industries, including the food safety business, wastewater treatment, air pollution monitoring, and human health care, use electrochemical reaction monitoring.

ISFET is a potentiometric biosensor type whose working principle is similar to conventional MOSFET (Metal Oxide Semiconductor Field-Effect Transistor). ISFETs have a structure very similar to MOSFETs with the metal gate replaced by reference electrode and electrolyte gate. Since its introduction in 1970, the ISFET has received a lot of attention [23], As it has various benefits in electrochemical reactions monitoring. ISFET may be utilized at high temperatures and has a small size and relatively high sensitivity. Furthermore, it can be manufactured using a traditional CMOS process and is suitable for continuous monitoring. It also has the potential for large-scale integration. On the other hand, ISFET fabrication is simple and follows a similar procedure to that of MOSFET production. ISFET theory of operation is explained by the site-bending hypothesis, which Yates et al. put forth in 1974 [24]. It describes how ion pairs form at the oxide/aqueous ISFET's well-known electrolyte interface approach for defining ion-sensing applications. Since an ISFET's sensitivity plays a key role in deciding how well it performs, numerous attempts to model it have been documented [25,26].

The structure of the paper will be as follows: we will review the history of the ISFET in section 2. In Section 3, the ISFET device's working principle is explained. In Section 4 the modeling technique will be discussed. Section 5 presents the fabrication process of ISFET. Finally, Section 6 discusses various applications of ISFET followed by the conclusion in Section 7.

1. History of ISFET

ISFET is a field effect transistor (FET) that is convenient for use with micro/nano-systems that are used for measuring ion concentrations in electrolyte solution. In 1970 ISFET was the first proposed as the first biosensor FET(BioFET)when Na+ was detected by drain-source current (IDS) output [23]. The ISFET with a gate produced by noble metal was successfully constructed in 1975 for the first time to detect gas [27]. Following that, Steve Caras and Jiri Janata announced for the first time in 1980 that ISFET can identify penicillin biomolecules by enzymatic reactions [28]. After that, a lot of ISFET-based biosensors have been developed. Since 1983, for instance, various functions, including acetyl cellulose, polyvinyl alcohol, and albumin immobilized on the ISFET gate, have been used to detect urea [23]. In 1984, using the enzymatic functions on the ISFET gate, Jun-ichi Anzai et al. created a tiny urea sensor [29]. In order to detect urea and glucose simultaneously with less interference, Yuji Miyahara et al. developed the anti-interface performance of the sensor in 1985 [30]. Clinical applications concentrating on the detection of glucose, DNA, antibodies, and cells served as the foundation for the ISFET sensor's later development.
For instance, in 1996, Vjacheslav et al. increased the dynamic range of detection of glucose by modifying the ISFET gate enzymatically. In 2002, Maya Zayats et al. created a brand-new immunosensor as a result of an antigen-antibody complex they had formed on an ISFET device [31]. In 2006, Sunil Purushothaman et al. published a new technique for locating nucleotide polymorphisms using an ISFET sensor [32] In 2008, Goncalves et al. developed an amorphous silicon-based ISFET for label-free DNA hybridization detection [33].

Today, with clinical detection potential established, the focus of research has switched to a method to boost ISFET biosensors performance. The material, design, and operation of the gate of the ISFET are the key topics of related studies [34]. ISFETs have rapidly

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advanced over the past 30 years and are now among the most widely used biochemical sensors, with hundreds of high-caliber studies published each year [35].

2. Working principle of ISFET sensor

ISFETs have a structure that is comparable to MOSFETs, and a reference electrode and electrolyte gate replace the metal gate; consequently, the signal transfer mechanism is comparable. Figs. (2a) and (2b) show the structures of MOSFET and ISFET, respectively. The sensitive film is applied to the oxide layer to detect other types of ions and molecules. The solution is connected directly with the oxide and achieves linear detection of ions.

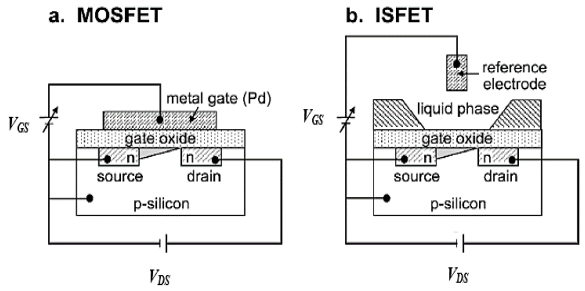

Fig. 2 (a) the structure of the MOSFET (b) the structure of the ISFET [36].

For MOSFET, the most crucial parameter is the threshold voltage (V_{th}); V_{th} can be defined as the minimum gate voltage (V_G) value required to produce surface inversion and is provided by [37].

$$V_{th(MOS)} = \varphi_{ms} - \frac{Q_{ox} + Q_{ss} + Q_B}{C_{ox}} + 2\varphi_f \qquad (1)$$

where, φ_{ms} is the difference between the metal and the semiconductor work function, φ_f is the potential difference between the intrinsic fermi level and fermi level, Q_{ox} is the fixed oxide charge per unit area, Q_{ss} is the surface- state charge per unit area at the interface of the insulator and the semiconductor, Q_B is the depletion charge per unit area, C_{ox} is the oxide capacitance per unit area. Fig. 3 shows the energy band diagram of *P*-type MOSFET. The ISFET uses the same construction process, which produces a constant physical component of the threshold voltage. In more detail, as the ISFET works for ion detection, the gate (VG) voltage is applied by the reference electrode to the electrolyte. For *n* - type ISFET, the holes on the substrate are pushed

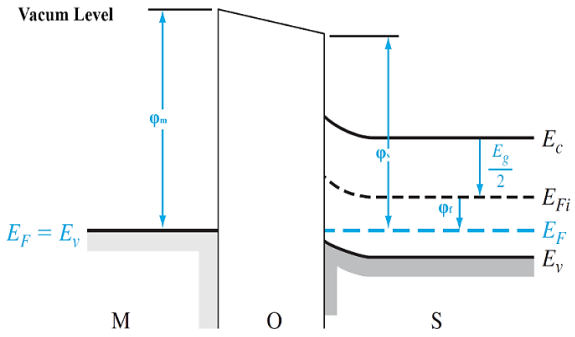

Fig. 3 The energy band diagram of P-type MOSFET [38].

down when VGS is raised, and the accumulated electrons start forming the channel that connects the source's electrodes and drain. When V_{GS} reaches the value of V_{th} the channel becomes conductive there are a current I_{DS} and voltage V_{DS} created between the drain and the source. Two more potentials are produced due to the electrolyte between the insulator and reference electrode: E_{ref}, the potential of the reference electrode, and the interfacial potential at the interface of the solution and the oxide $\psi_0+\chi^{sol}$, where χ^{sol} is the potential of the surface dipole of the solvent (constant value), and ψ_0 is the surface potential and is a function of the pH of the solution.

$$V_{th(ISFFET)} = E_{ref} - \psi_0 + \chi^{sol} - \varphi_s - \frac{Q_{ox} + Q_{ss} + Q_B}{C_{ox}} + 2\varphi_f (2)$$

Where φ_s is the work function of the semiconductor. For ISFET V_{th} can control the on/off current and determine the ion concentration. The expression of current at saturation mode for ISFET is:

$$I_{DS} = \mu C_{ox} \frac{W}{L}\left((V_{GS} - V_{th(ISFET)})V_{DS} - 0.5 * V_{DS}^2\right) \qquad (3)$$

Where μ is the electron mobility, W is the channel width, L is the channel length, V_{GS} is the Gate to Source voltage, V_{DS} is the Drain to Source voltage.

For MOSFET V_{DS} is maintained constant by the used electrical circuit. Therefore, the only possible input parameter is V_{GS}. For conventional MOSFET the curves of I_{DS} / V_{DS} are drawn as a function of V_{GS}. For ISFET V_{th} can thus be indirectly output by other parameters such as I_{DS}, V_{GS}, and V_{DS}, and the corresponding sensor can be specified as amperometric or potentiometric sensors by choosing some of the parameters of Equation (5) as fixed values. For the principle of potentiometric sensor, V_{th} change caused by ion concentration change will result in V_{GS} comparable

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change that when the values of I_{DS} and V_{DS} are fixed. For instance, an ISFET-based microsensor that monitors V_{GS} when V_{DS} and I_{DS} are fixed was constructed using the principle of potentiometric [39]. For a principle of amperometric, the change of V_{th} can be reflected by the change of I_{DS} when V_{DS} and VGS are held constant. Compared to the method of changing IDS, the method of changing V_{GS} is the most frequently employed method. For ISFET, as V_{GS} is maintained constant, V_{th} can be modified through the surface potential, ψ_0. The surface potential is a function of the pH of the solution. Curves of I_{DS} / V_{DS} are consequently recorded in ISFET as a function of solution pH, as illustrated in Fig. 4.

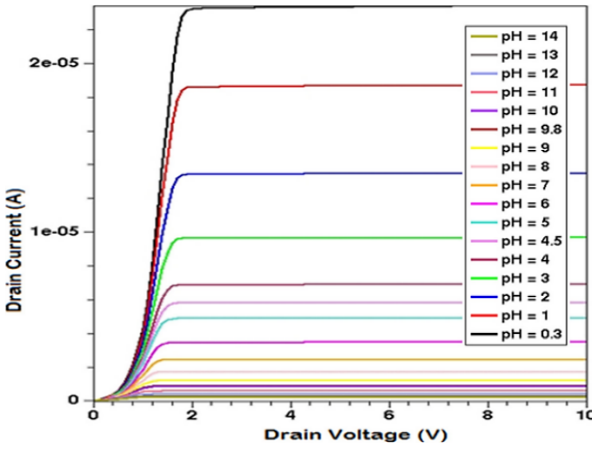

Fig. 4 I_{DS} as a function of V_{DS} at different pH concentration at E_{ref}=0 [40].

3. ISFET modelling

Site-bending theory, which was proposed by Yates et al. in 1974, is employed to explain ISFET operation, [24] which determines how ion pairs develop at the oxide/aqueous interface of ISFET's. According to the Site-bending theory, depending on the concentration of the hydrogen ions in the electrolyte, hydroxyl groups (OH) on the insulating surface can be either protonated (by acquiring H^+) or deprotonated (by losing H^+) [41]. As a result, the surface charge density on the insulating surface depends on the solution's pH. Assuming that the insulating layer is SiO_2, reactions that occurred at the interface of ISFET (pH sensor) will be as follows:

$$SiOH \leftrightarrow SiO^- + H^+ \quad (4)$$

$$SiOH + H^+ \leftrightarrow SiOH_2^+ \quad (5)$$

With H^+ standing in for the protons close to the surface. It follows that releasing or absorbing protons to or from the electrolyte solution can turn the initially neutral surface into a negative or positive site, respectively. The neutral oxide surface that initially had just neutral sites is changed into a charged surface with negative and positive charges. The excess of one sort of charged site over another determines the surface charge that results, which is dependent on the pH of the solution. Gouy-Chapman-Stern theory is an excellent way to explain how ions are distributed in the electrolyte solution [37]. From the Gouy-Chapman-Stern theory, two layers are formed in the solution. An inner layer and a diffuse layer make up a double layer. The inner layer consists of two regions:

1. The first is from the Insulator-Electrolyte interface to the Inner Helmholtz Plane (IHP).
2. The second from the (IHP) to the Outer Helmholtz Plane (OHP) is shown in Fig. 5.

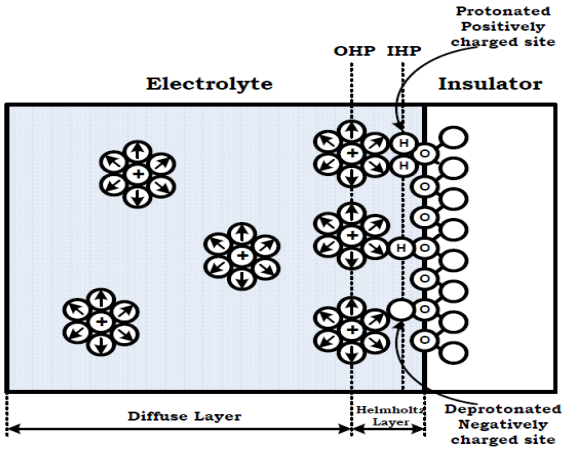

Fig. 5 electric double layer and site bending of the electrolyte [41].

IHP is the location of the centers of specially adsorbed ions. The OHP is where the solvated ion centers that are closest to the surface are located. Finally, the diffuse layer extends from (OHP) to the bulk [42].

ISFET device combines two parts: the electronic part, which is made up of a MOSFET, and the electrochemical part, which contains the interface of the electrolyte and the insulator. There are three sections of the charge distribution in the direction perpendicular to the interface, as in Fig. 6a:

1. σ_S is the inversion charge in the semiconductor channel.

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2. σ_i is the surface charge on the interface of the insulator and electrolyte.
3. σ_{diff} is the diffuse layer's continuous charge distribution.

The corresponding distribution of the potential is shown in (Fig. 6b), E_{ref} is the electric potential at the reference gate electrode, ψ_{diff} is the electric potential at the edge of (OHP), ψ_i is the electric potential at the interface of the electrolyte, and insulator, and ψ_s is the electric potential at the interface of the semiconductor and insulator [43]. From the Gauss law [44]:

$$\sigma_{diff} + \sigma_i + \sigma_s = 0 \quad (6)$$

From the electric double layer theory [45], [46]:

$$\sigma_{diff} = \sqrt{8\varepsilon_0\varepsilon_w c_0 K_B T} * \sinh\left(\frac{e\left(E_{ref} - \psi_{diff}\right)}{2K_B T}\right) \quad (7)$$

Where ε_0 is the permittivity of the vacuum, ε_w is the dielectric permittivity of the water, c_0 is the ion concentration of the solution, K_B is the Boltzmann constant, T is the temperature in kelvin, and e is the electric charge. From the Helmholtz layer we can write:

$$\sigma_{diff} = C_{helm}\left(\psi_{diff} - \psi_i\right) \quad (8)$$

Where C_{helm} is the Helmholtz layer's capacitance. The surface charge density on the interface of the insulator and the electrolyte is:

$$\sigma_i = eN_{sil}\left(\frac{[H^+]_s^2 - K_a K_b}{[H^+]_s^2 + K_a[H^+]_s + K_a K_b}\right) \quad (9)$$

where Nsil is the surface density of silanol site, K_a and K_b are the dissociation constants for protonation and deprotonation, respectively; $[H^+]_s$ is the proton's concentration near the interface of the electrolyte and the insulator. We can relate $[H^+]_s$ to the bulk concentration of the proton $[H^+]_b$

$$[H^+]_s = [H^+]_b \exp\left(\frac{e\left(E_{ref} - \psi_i\right)}{K_B T}\right) \quad (10)$$

Where pH(solution) = - log($[H^+]_b$). From gauss law we can get σ_s.

$$\sigma_s = C_i(\psi_s - \psi_i) \quad (11)$$

Where C_i is the insulator's capacitance.

On the other hand, the surface charge is related to the surface potential through:

$$\sigma_s = \pm\sqrt{2\varepsilon_{si}\varepsilon_0 K_B T p_0}\ [(\frac{e\psi_s}{K_B T} - 1 + \exp\left(\frac{-e\psi_s}{K_B T}\right)) + \frac{n_0}{p_0}(\frac{-e\psi_s}{K_B T} - 1 + \exp\left(\frac{e\psi_s}{K_B T}\right))]^{0.5} \quad (12)$$

where $\varepsilon_{si}$is dielectric constant of silicon, p_0 and n_0 are the hole and electron concentrations at equilibrium

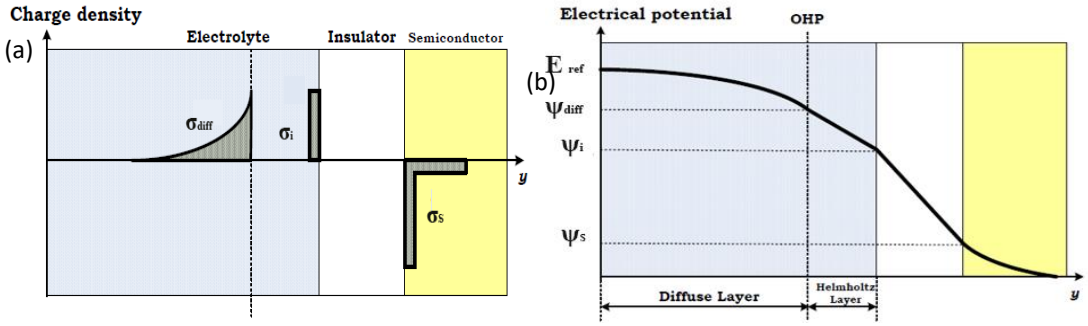

Fig. 6 (a), (b) shows the y-directional distribution of charges and the associated potential distribution respectively. σMOS is the inversion charge in the semiconductor channel, σ_o is the surface charge on the interface of the insulator and electrolyte, σ_d is the diffuse layer's continuous charge distribution, V_{ref} is the electric potential at the reference gate electrode, ψ_d is the electric potential at the edge of (OHP), ψ_o is the electric potential at the interface of the electrolyte and insulator, and ψ_s is the electric potential at the interface of the semiconductor and insulator [41].

for silicon respectively. Now we have seven unknowns and seven equations: σ_{diff}, σ_i , σ_s, ψ_{diff}, ψ_i, ψ_s, and $[H^+]_s$, We can solve the equations and get all the unknown potentials. We can express the sensitivity of ISFET in two ways: the first way S_1 is the absolute value of the ratio of the change in I_{DS} to the change in pH when E_{ref} is fixed.

$$S_1 = \left|\frac{I_{DS}}{pH}\right|_{E_{ref}} \quad (15)$$

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The second way S_2 is the absolute value of the ratio of the change in Eref to the change in pH when I_{DS} is fixed.

$$S_2 = \left|\frac{E_{ref}}{pH}\right|_{I_{Ds}} \quad (16)$$

4. ISFET fabrication

ISFET fabrication is simple to do with the current CMOS (complementary metal-oxide-semiconductor) semiconductors is based on silicon and germanium, which have used specific procedure to create smooth, thin layers while also taking into account the manufacturing costs. It is important to choose the material of the ISFET's gate carefully, as it has a significant impact on the device's selectivity and sensitivity. It must be able to avoid hydration and stop ion migration to the surface of the semiconductor in addition to serving as an ISFET passivation layer [48]. Additionally, two important factors need to be considered: the electrical conductivity and crystal

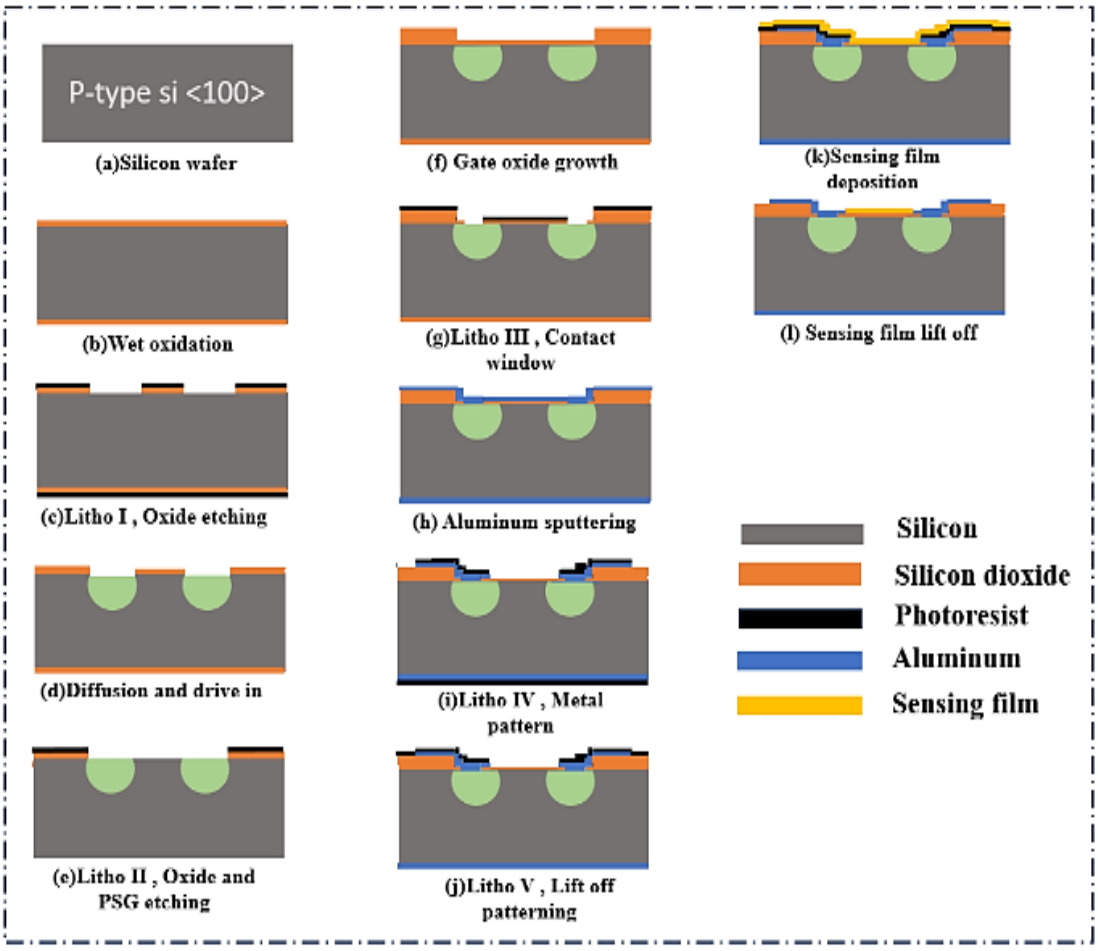

Fig. 7 ISFET pH sensor fabrication process.

fabrication and follows a similar procedure to that of MOSFET production. Because the gate region must be exposed to electrolyte, ISFET packaging is different from MOSFET packaging. For fabrication choosing the substrate material comes first. Elemental semiconductors, like silicon and germanium or compound semiconductors, like gallium arsenide, are the two main types of substrate materials that are most frequently utilized [47]. The earliest research of orientation [49]. For these two important factors, we usually choose silicon with a *p*-type substrate and 100-crystal, which leads to highly effective mobility of charge carriers, high drain current, and high electrical output, resulting in improved performance of ISFET [50].

Fig. 7 illustrates the fabrication steps of an ISFET. (Fig. 7a) shows a *p*-type < 100 > silicon wafer, the first to be started with. At first, a 2µm-thick oxide layer is

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created on both sides of the wafer by a wet oxidation process using the thermal oxidation approach at 1100 °C with a 20 to 120 min (Fig. 7b). Then, the front side oxide is photolithographed to delineate the source and drain zones (Fig. 7d). Third, following second-level lithography, we use a buffered oxide etch (BOE), also known as buffered HF(hydrofluoric acid) or BHF, to etch the oxide in the gate region on the backside (Fig. 7e). Fourth, a SiO2 layer is created by using dry oxidation; the layer is approximately 60 nm thick in order to develop gate oxide (Fig. 7f). Additionally, the third-level lithography forms the contact windows, and BHF solution is used to etch the oxide (Fig. 7g). Aluminum is also deposited on the two sides of the wafer to create electrical connections using the DC sputtering technique (Fig. 7h).

To pattern the aluminum, we use the fourth-level lithography, and the metal is removed by aluminum etchant before sintering to create gas (Fig. 7i). The lift-off pattern of the sensing layer is then created using the last level of lithography (Fig. 7j). The optimized process recipe deposits an Al2O3 sensing layer (Fig. 7k). We use the lift-off procedure to pattern the sensing layer (Fig. 7l). The wafer was finally diced and packaged as individual devices, and the sensor was employed for pH-detecting applications.

The Dam-and-Fill method is used for the encapsulation [48,49]. This method uses a dam surrounding the device to stop the epoxy from flowing into the area next to it. A low-viscosity compound surrounds the high-viscosity potting compound that forms the dam. Thick-film alumina technology is employed in the device packaging process.

5. Applications of ISFET

Due to the characteristics of the gate material of ISFET, there is a strong direct interaction between the gate and the ions in the solution, which impacts the electrical output of the ISFET. Numerous concepts of biosensors, including enzyme FETs, DNA FETs, and immunological FETs, which comprise layers of enzymes, DNA, and antibodies, respectively, have been published in the ISFET system based on various bio-contents for biological analysis [50].

ISFET effectively detect ions and biomolecules such as cell-related chemicals, antibodies, enzyme, and DNA molecules [53]. The following sections provide a more thorough presentation of their most recent advancements.

5.1. Ion detection

Nowadays, successful and reliable ion detection using ISFET is a very essential topic since it serves as the basis for the detection of other biomolecules. Ion concentration in the solution is measured by the changes in the current, as the change in the concentration of the ion can cause instability in the current flowing from the source to the drain. It is undeniable that ion detection can be influenced by both the material of the gate and the technique. As an example, by using precise controlling to investigate the gate thickness to achieve an excellent sensitivity of 425.89 mV/pH, it is found that a thicker gate performs better [54]. Moreover, the variable design of gate architecture significantly affects the performance. For instance, Jin-Hyeok Jeon and Won-Ju Cho studied an Extended Gate ISFET (EG ISFET) to achieve improved ionic sensing capability beyond the limit of 59 mV/pH to 379.2 mV/pH. Consequently, an in-plane control gate that achieves a pH sensitivity of 2364 mV/pH was also proposed [55].

Today, ISFET ionic sensors that are flexible, wearable, and practical can finally be created [56]. Also, nanosized ISFETs may be produced effectively using nanowires, and numerous nano-ISFETs were integrated onto a single chip to achieve cheap cost, low power, low noise, and increased sensitivity [57]. Furthermore, ISFET-sensing arrays can be created, and numerous ion types can be detected simultaneously with high resolution. This is highly encouraging for clinical applications of the human body since different ion kinds are constantly usually present together [58].

5.2. DNA detection

The accuracy in DNA detection is crucial in several areas, including diagnosing genetic illnesses, developing new drugs, and screening cancer [59]. ISFET is an outstanding candidate for DNA detection due to its straightforward measurement circuit, compact size of the sensing system, easy fabrication process, and manageable sensing processes. Combining DNA with ISFET exhibits additional benefits, including low detection limits, high sensitivity, strong specificity, easy production, and low cost.

Due to the negative charge of DNA, changes in surface potential happen when DNA strands bond to the gate surface of ISFETs, making good DNA sensing performance possible. DNA Probe can be immobilized onto the oxide surface of the ISFET in an orientation-controlled manner by applying specific treatments to the oxide layer. When a DNA probe molecule binds to its complementary DNA, the electric double layer's

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electric potential changes, which causes a difference in the C-V or I-V properties.

ISFET's DNA sensor primarily uses two sensing methods at the moment. One is using enzymes based on DNA polymerase to produce H+ ions that modify the ISFET gate's surface charge distribution and cause a change in the gate surface potential that is output as an electrical signal to detect DNA. Similarly, the other one is based on DNA strand hybridization, which produces negative charges, affects the surface charge distribution of the ISFET gate, and ultimately leads to a change in the electrical output of the ISFET [50].

Goncalves et al. developed a detection based on ISFET of an amorphous silicon to detect label free of the DNA covalent immobilization and simultaneous hybridization of its supplementary DNA [33]. In this study, an ISFET biosensor was used to track the behavior of DNA binding, which was seen as variations in the threshold voltage (Vth). Using a DNA-ISFET device, the study's results showed that the gate potential changed with the decreasing DNA surface density ranging from 30 mV to 100 mV. In general, the model of transfer doping can be used to explain variations in the conductivity of the surface because it predicts that as hole density increases, the pH value of the surface conductive layer of the diamond will drop. For the electrical detection of label-free DNA hybridization, Estrela et al. used a MOS capacitor that was made of Au/SiO2/Si and Poly-Si TFTs with a golden metal gate as ISFET biosensors [60]. Numerous investigations on ISFET paired with electronic aptamer sensors have been reported in relation to DNA biosensors [61]. Aptamers are nucleic acids that attach to their particular target molecules, such as tiny molecules, proteins, nucleic acids, and even cells, precisely and preferentially [62]. Zayatset et al. recently published a report on adenosine monitoring, as a target molecule in this context [61]. An ISFET was used to track changes in the electrical signal following the adenosine binding to the homologous aptamer. ISFET for adenosine that is based on an aptamer sensor is shown in Fig. 8.

Although the availability of ISFET sensors for DNA detection, there are limitations to the detection of DNA hybridization charge by ISFET biosensors. An example of these limitations is that the FET device cannot detect DNA when the DNA hybridization reaction occurs farther away from the sensing layer than the Debye length. Therefore, the Debye length of the supplied solution must contain an electric field created by redistributed charged molecules for the measurement of DNA hybridization to be successful.

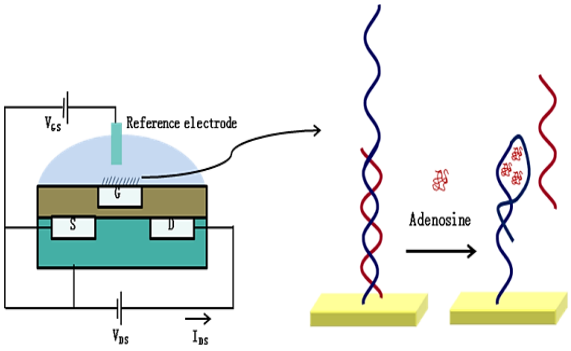

Fig. 8 ISFET-based label-free, reagent-free aptamer sensor for adenosine [50].

5.3. Cell-related detection

Cell related biosensors provide various Biologically active information for analytes, which enable the monitoring of the effects of cytotoxic in response to harmful compounds as well as the physiological response of cells to various stimuli. As a result, living cells are used as their bio-contents, and a cell-related biosensor system allows for the electrochemical monitoring of the residing cells activity. These advantages have led to the perception of cell-related sensor systems as a potential technology for biomedical and pharmaceutical uses [63].

The ISFET sensor can monitor the activities of living cells by detecting the secretions produced by cell metabolism processes, such as OH, H^+, and K^+. ISFET sensing systems have been used to realize numerous cell-related sensor applications, as it is low in cost, simple to use, highly biocompatible, and very sensitive when compared to the most popular methods, such as microscopic examination and fluorescent staining [64].

ISFET-based intercellular ion screening was utilized by Kenneth B. Walsh et al. to track human physiological processes such as the contraction of muscle and transmission of neurotransmitters. In detail, we can accurately measure K+ produced by cell metabolism by inserting the ISFET sensor into glioma or epithelial cells so K^+ efflux can be obtained quickly and noninvasively (Fig. 9a) [65]. Daniel Schaffhauser et al. created a new ISFET pH sensor that can successfully sense rapid pH changes near the cell membrane (Fig. 9b), making a substantial contribution to tissue pH adjustment and cell volume management [66]. Toshiya Sakata and colleagues cultivated cells on the ISFET Ta_2O_5 gate surface. For this device, the pH values of the two extracellular microenvironments can be appropriately separated by comparing healthy cells and cancer cells [67]. Furthermore, this sensing device

has high stability, as after a week of immersion in cell culture media, the pH sensitivity remains nearly unaltered at 58 mV/pH.

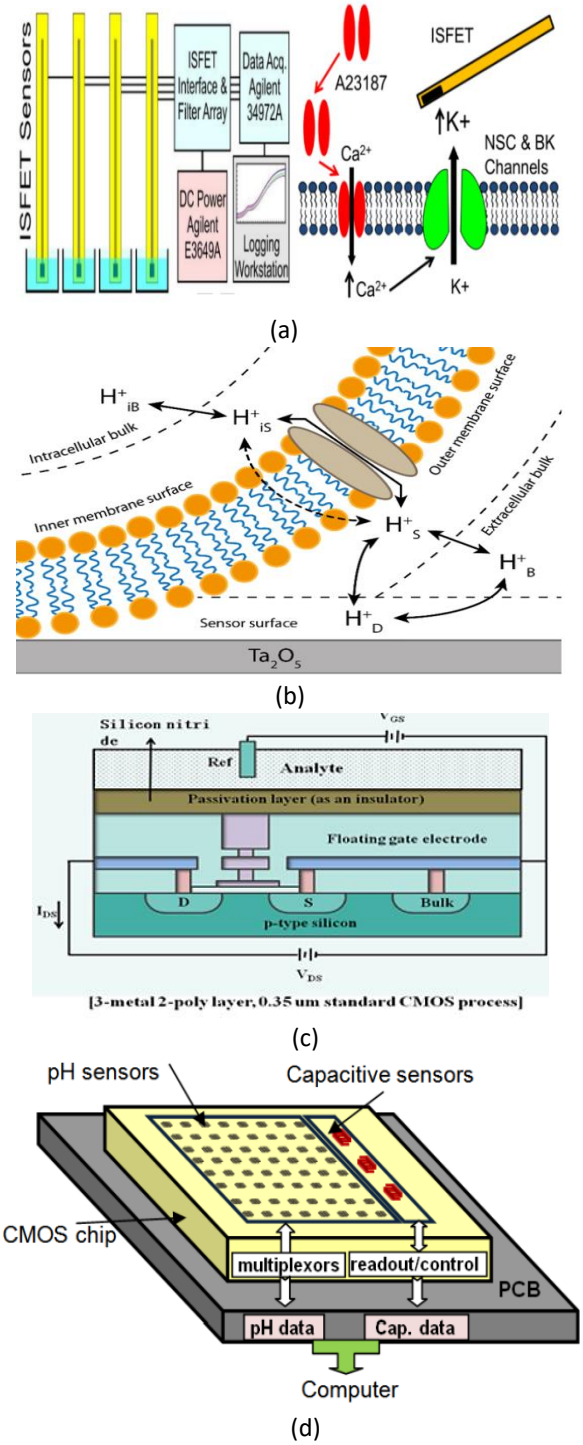

Fig. 9 a) Creation of ISFET sensor for intercellular ion screening to track physiological activity in people [71], b) Ta_2O_5 gated ISFET sensor that gauge pH variations close to the cell membrane [66]. c) ISFET cross-section diagram made with a standard CMOS process.[50], d) The illustration of the 64-pixel ISFET sensor arrays that simultaneously measure extracellular pH [71].

Moreover, as ISFET sensing technology advances, ISFET arrays can be produced using a complementary metal-oxide-semiconductor approach for improved sensitivity and sensing efficiency in cell-based detection. For instance, Hongmei Li et al. created graphene related ISFET arrays with 25 devices that are more sensitive to K^+ than single devices [68]. Milgrewa et al. announced the creation of a sensor array chip for direct extracellular imaging based on pH-sensitive ISFETs [69], which is constructed of a 16 * 16 array of ISFETs with circuits of biopotential readout for signal acquisition systems. Each pixel array, as shown in (Fig. 9c), features a floating rate structure passivated by a sensitive membrane for pH. Ghazal Nabovati et al. suggested a multiplexed biosensor of an 8*8 array of ISFET for monitoring simultaneously cell growth rate and extracellular pH on a single chip [70], resulting in highly efficient detection (Fig. 9d). As a result, a cell-related ISFET has a high-accuracy system for monitoring the pharmacodynamic consequences of the cell's behavior in response to a range of chemical stimuli in real-time.

5.4. Enzymatic detection

Enzyme FETs are often based on the pH-sensitive ISFET principle, where the enzymatic reactions take place at the interface of the gate or the electrolyte, changing the distribution of the charge on the gate surface, which can be observed through changes in electrical output. Several enzyme FETs have been created to date for detecting various biological analytes such as glucose, urea, penicillin, phenolic chemicals, dopamine, creatinine, and others [56,68–71]. Intensive efforts have been made in recent years to develop enzyme FETs to address numerous concerns, such as FET system stability, compatibility, and reproducibility. Although Janata and Moss proposed using ISFETs as enzyme sensors in 1976 [76], in 1980 the enzymatic ISFET was developed in both theory and practice as a penicillin-responsive device [28].

Numerous researchers have created a variety of material biosensors for enzyme biosensors using photopolymers and other polymers [77]. Rebriievet al. recently developed an ISFET-based enzyme biosensor for measuring urea, also known as an ISFET urea sensor [78]. In that study, a liquid photopolymerizable composition, in which the resulting polymer could be produced under UV, was the foundation for an easy and quick enzyme immobilization approach on the ISFET gate surface. The developed urea sensor of ISFET showed a significant improvement in detection limit,

sensitivity, and reaction time, indicating that it may have practical applicability for monitoring urea in the blood samples.

Enzymatic ISFET still has issues that prevent it from developing further. First, Enzymatic ISFET's sensitivity needs to be increased. Continuous advancements in the gate immobilization approach may be researched as a solution. For instance, high-density nanoporous (porous solids with nano-sized pores) Al_2O_3 was immobilized on the gate of an ISFET as produced by Alexandre Kisner et al. Higher dopamine sensitivity was achieved as the nanoporous surface area was completed because it allows more immobilization of tyrosinase to oxidize dopamine [79]. Further research on the shapes of the employed nanostructures confirmed that those with curved surfaces can hold more enzymes per unit area to improve the performance of enzymatic ISFETs. For instance, immobilizing enzymes with spherical biomolecules is very well suited to the curved surface carbon nanotube (CNT) [80]. Additionally, it has been demonstrated that adding materials rich in electrons to the gate can enhance the efficiency of an enzymatic ISFET. For instance, to create an enzymatic ISFET sensor with exceptional sensing sensitivity, Gaurav Keshwani and Jiten Chandra Dutta produced a gate doped by polyethyleneimine with amines inside that is rich in a high electron density [81]. The Kalium-doped metal boosts the enzymatic ISFET sensor's sensitivity by introducing more internal free-charge carriers [82].

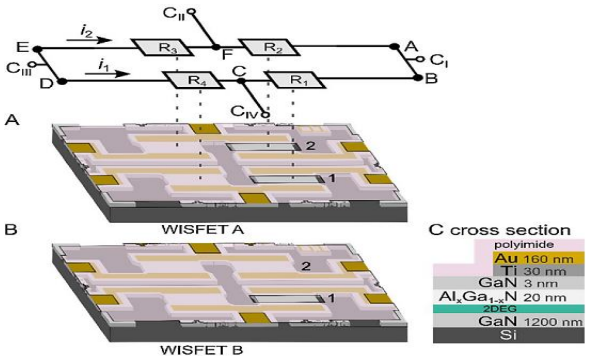

Fig.10 a schematic illustration of an ISFET with a Wheatstone design and an incredibly thin Al_2O_3 gate [71].

The stability of enzymatic ISFET is impacted by environmental changes like pH and temperature, a second drawback that can't be ignored. Various efforts have been undertaken by scientific organizations to solve this. As an illustration, a Wheatstone arrangement can be employed to reduce the drift of the temperature of the enzymatic ISFET sensor, and an ultrathin Al_2O_3 gate can be used to produce intensive and uniform penicillinase immobilization for higher stability (Fig. 10) [83].

6. Conclusions

In this work, we discussed the history of ISFET since it was first proposed in 1970. We discussed the working principle of the ISFET, which could be a guideline for building the ISFET-sensing platform. We revised the ISFET operation, which is explained by the site-bending theory and determines how ion pairs develop at the oxide/aqueous ISFET. And we discussed the Gouy-Chapman-Stern theory to explain the distribution of ions in the electrolyte solution. We also explained how to model the ISFET and the fabrication process of an Al_2O_3-gate ISFET pH sensor. Finally, we discussed some of the applications of the ISFET, concluding that ISFET provides the advantages of improved speed, sensitivity, simplicity of use, and low cost, and thus, it has been developed for a wide range of bio detecting applications like (ion detection, DNA detection, Enzymatic detection, and cell-related detection).

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