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# Applications of Field-Effect Transistor (FET)-Type Biosensors

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A field-effect transistor (FET) is one of the most commonly used semiconductor devices. Recently, increasing interest has been given to FET-based biosensors owing totheir outstanding benefits, which are likely to include a greater signal-to-noise ratio (SNR), fast measurement capabilities, and compact or portable instrumentation. Thus far, a number of FET-based biosensors have been developed to study biomolecular interactions, which are the key drivers of biological responses in *in vitro* or *in vivo* systems. In this review, the detection principles and characteristics of FET devices are described. In addition, biological applications of FET-type biosensors and the Debye length limitation are discussed.

Keywords : Field-effect transistor, Biosensor, MOSFET, ISFET, Nanowire FET

## I. Introduction

Biosensor technology has great potential to detect disease markers and micro-organisms in clinics. Biosensor systems can also be used as an effective analytical tool for detecting biomolecular interactions such as DNA hybridization, antibody-antigen interactions, protein-protein interactions, receptor-ligand binding, DNA-protein binding, andother types of interaction [1-5]. Since the introduction of the biosensor in 1962, as reported first by Clark and Lyon [6], biosensors have been employed in a wide range of applications in the biomedical, environmental, industrial, and agricultural fields. According to the transduction process, biosensors are generally classified as optical, electrochemical/electrical, piezoelectric, or thermal systems [7-10]. Among the many different biosensing systems available at present, the FET-type biosensor is one of the most attractive electrical biosensors given its advantages of sensitive measurements, portable instrumentation, easy operation with a small amount of sample, low cost with mass production, and high speeds.

The principle of an ion-sensitive FET biosensor based on a traditional metal-oxide semiconductor FET (MOSFET) structure was initially reported in 1970 as a short communication by Bergveld [11], and was again discussed in 1976 as a proof-of-concept study of enzyme FETs by Janata and Moss [12]. Caras and Janata described the first practical use of a FET-type biosensor for an assay of penicillin in 1980 in their study involving a pH-based enzyme FET [13]. Starting with this proof-of-principle experiment, several examples of FET-based detection have been

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conducted [14-16]. With their outstanding electrical characteristics and dimensions, thus far FET-type biosensors have been considered to be useful in the areas of clinical diagnosis and point-of-care or on-site detections. The metal gate of a FET-type biosensor is generally replaced by a biofilm layer material such as a receptor, enzyme, antibody, DNA or other type of capturing molecule biologically specific for the target analyte. In response to target molecules in the solution, the bio-modified gate (G) surface modulates the channel conductivity of the FET, leading to a change in the drain current. Although there are numerous advantages of using a FET biosensor in biological sensing, FET technology remains associated with a critical problem related to the Debye screening length. The limitation of the Debye screening length is sometimes considered to be fundamental for FET devices. During the past three decades, considerable efforts have been made to develop a better FET architecture with improved performance and to overcome the physical limitations of FET technology.

## II. FET Basics

All field-effect transistors (FETs) have three semiconductor devices, called the source (S), the drain (D), and the gate (G). There is no physical contact between source and drain, but a current path, which is called a conduction channel, forms between the source and the drain. The gate-to-source voltage (Vgs) will turn on (or off) the device, as a FET-type device can function as an on/off switch. The electric field strength, which serves as a control mechanism, is associated with the voltage applied to the gate. The current flow is determined by the actual motion of the carriers to be more exact, of the electrons for the n-type channel or the holes for the p-type channel [17,18]. For an n-type FET, the applied gate voltage will cause electrons to pass through the channel from the source to the drain. If positive voltage is applied to the gate of an n-type FET, a channel is created and the charge effect on the conductance across the channel increases accordingly [19]. In contrast, if negative gate voltage is applied, the n-type channel will pinch off. For a p-type FET, the opposite occurs, as positive (negative) gate voltage will turn off (on) the transistor device.

The change in the electric field that is directed vertically downwards depends on the applied gate voltage [17]. When the applied gate voltage reaches the threshold voltage (Vth), the drain current starts to flow from the source to the drain. The threshold voltage is defined as the value of Vgs at which a sufficient density of mobile electrons or holes in the channel gathers to give rise to a conducting channel. When Vgs is close to Vth or greater (that is, when $Vgs > Vth$), the n-type FET starts to turn on the device. In contrast, for a p-type FET, Vgs should be lower than Vth (that is, $Vgs < Vth$) to produce a p-type channel underneath the gate oxide layer. The equation below is commonly used as the theoretical principle of FET operation in order to elucidate the cause of any change in the electric field upon saturation or in an active regime in which the channel displays pinch-off behavior near the drain. Here, the following are assumed for the FET: electron mobility, μn gate capacitance, C gate length, L gate width, W threshold voltage, Vth and an applied gate bias of Vg.

$$Id = 1/2\mu_n C(W/L)(Vgs-Vth)^2$$

(in an active or saturated regime)

The surface charge density of the analyte affects the applied gate bias of Vgs. In order to detect biological molecules using a FET, the probe molecules should bind to the active sensing layer. In this case, equation (1) above can be modified as follows:

$Id=1/2\mu_nC(W/L)(Vgs-Vth+Vbio)^2$
(in an active or saturated regime)

An additional factor, the biomolecular potential (Vbio), is highly associated with the drain current (Id). In accordance with the FET principle mentioned above, the drain current decreases (or increases) when negatively (or positively) charged biomolecules bind to the surface of an n-type FET (or a p-type FET) [19]. The electric field caused by changes in the surface charge density of an analyte near the gate is equivalent to the gate voltage (Vg) [2,20]. Based on the FET principle, receptor molecules or ion-sensing membranes are prepared for binding to the analyte of interest as a bio-recognition layer.

## III. Applications of FET-type Biosensors

### 1. MOSFET

Of all types of FETs currently available, the metal-oxide semiconductor FET (MOSFET) is one of the most widely used FET devices. As the name MOSFET implies, this type has a metal-insulator-semiconductor structure with a metal gate electrode placed on top of an insulating layer of oxide. It is not necessarily true that the top gate electrode is metal and the insulator is an oxide in the MOS structure. Nevertheless, the term MOSFET is still used, and the MOS structure is often called a metal insulator semiconductor (MIS). The operation of a MOSFET utilizes an electric field which is modulated by the size and shape of the source-drain channel in what is referred to as channel length modulation and channel shape modulation, respectively. In response to a target analyte, a gate electrode controls the flow of the carrier (electrons or holes) through the channel formed between the source and the drain, thereby leading to a change in the drain current (Id). Han et al. reported the MOSFET-based detection of DNA-protein interactions [21]. In their research, the DNA-binding abilities of a p53 tumor suppressor and the mutant p53, which is found in more than 50% of all human tumors, were monitored using an n-type MOSFET device. Wild p53 binds to DNA, and mutant p53 is a DNA-binding-defective molecule. The surface charge density of the biomolecules (Vbio) directly affects the drain current (Id), which reduces (increases) in response to negatively (or positively) charged molecules on the gate electrode in the case of an n-type MOSFET (Fig. 1). After the immobilization of the p53

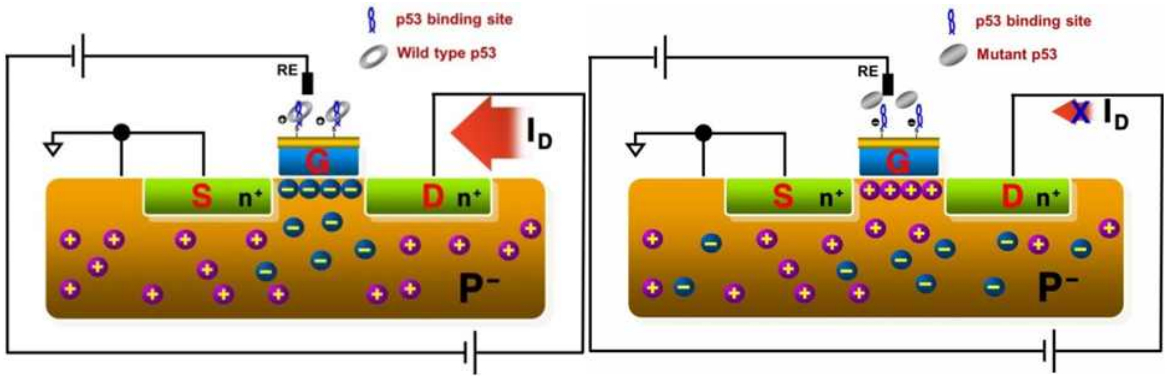


Figure 1. Schematic diagram of the MOSFET-based detection of p53 binding to cognate DNA [21]. Upon the binding of wild type p53 to a DNA-modified MOSFET surface, the resultant current increased. No change in the drain current was observed in response to the mutant p53.

DNA-binding consensus sequence onto the metal gate electrode, the drain current (Id) down-shifts owing to the negative value of Vbio. Upon the binding of wild p53 (the positively charged DNA-binding domain) to the negatively charged DNA, a significant up-shift in the drain current was observed as a consequence of the positive charge placed on the gate. The MOSFET-based biosensor may be useful for detecting the DNA-binding activity of DNA-binding proteins in a sequence-specific manner.

FET measurements depend on the charge density of the biomolecules on the gate surface. FET-type biosensors can detect changes in the surface charge density after the hybridization of double-stranded DNA (dsDNA), as Souteyrand et al. reported in the first experimental results of DNA hybridization based on field-effect measurements [22]. Using a MOSFET device, single-stranded DNA (ssDNA) as a capture agent can be directly immobilized onto the metal gate surface without any surface modification. In this case, gold (Au) is used as a gate metal in order to immobilize thiol-modified ssDNA, as gold (Au) has good chemical affinity with thiol (-SH). As shown in Fig. 2, the thiol-modified DNA molecules were immobilized onto the gold (Au) gate surface of an n-type MOSFET in a good orientation [21].

Kim et al. also reported the MOSFET-based detection of DNA hybridization based on variations in the charge density caused by the electrical charge of DNA molecules near the gate surface [23]. In their study, a p-type MOSFET was used and the drain current was significantly up-shifted when the solution was treated with thiol-modified DNA and the target DNA. The DNA sequence can be detected by measuring the variation of the drain current according to the variation of the DNA charge.

## 2. ISFET

The use of an ISFET as a transducer represents a promising tool for biological applications. The ISFET and MOSFET share a good degree of structural similarity. In general, an ISFET device has no metal gate electrode due to the replacement of the metal gate material with an ion-selective electrode, an electrolyte solution and a reference electrode [24]. The current magnitude of an ISFET device depends on the charge density of the analyte molecules on the gate surface [24]. Park et al. was the first to describe the application of an ISFET-based biosensor to

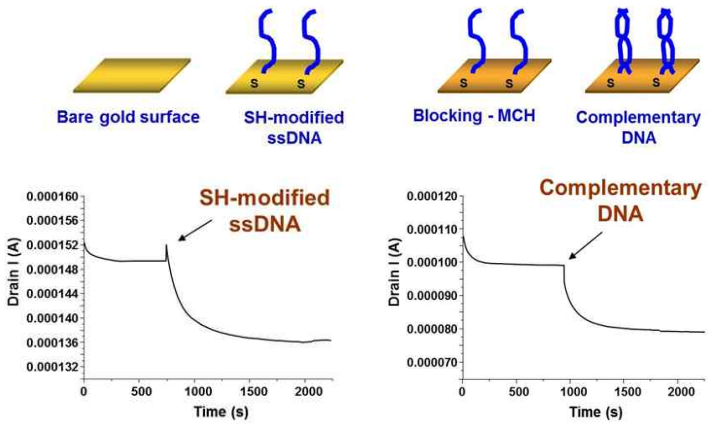


Figure 2. DNA hybridization detection using a MOSFET-based biosensor [21]. When thiol-labelled negatively charged DNA was immobilized onto the gold surface and complementary DNA was subsequently hybridized, a drop in the drain current was induced.

measure conformational changes in proteins [25]. A receptor-modified FET was developed to investigate the surface charge variations caused by structurally changed maltose binding protein (MBP) in response to maltose (Fig. 3). For the maltose-bound MBP, the N-terminus and C-terminus of the MBP come closer together, leading to a change in its conformation [26]. Subsequently, the electrical properties of an ISFET change according to the maltose-mediated three-dimensional alteration in the MBP. Maltose-free MBP immobilized onto the oxide layer displayed a down-shift in the value of the drain current (Id). When treated with maltose, MBP undergoes a structural change, which causes the drain current to decrease by 1.175 μA. Possible interpretations of how this type of maltose binding can serve to decrease the drain current include a geometric effect and a charge effect. The capacitance (C), area (A), and distance (d) are the geometric factors contributing to the electric field of an ISFET biosensor. With regard to the charge effect, the positively charged moiety of MBP moves away from the oxide layer of an ISFET device, which may be partly responsible for the reduced field effect.

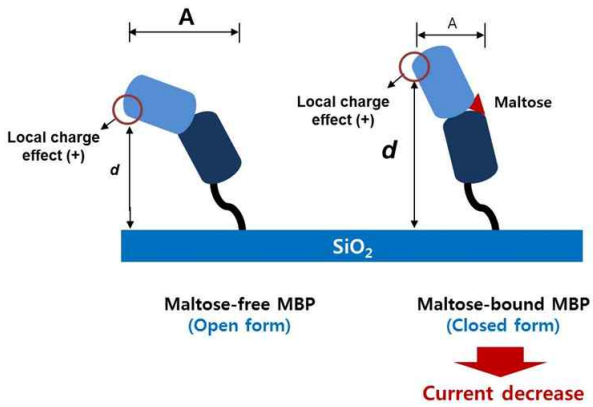


Figure 3. Research design for monitoring the conformational change in MPB by an ISFET-based biosensor [25]. When treated with maltose, MBP undergoes a conformational change from open configuration to a closed configuration, which concomitantly leads to a current decrease in the ISFET device.

For bio-recognition elements (or receptors), antibodies are one of the most commonly used capture agents for identifying, isolating, and quantifying analytes of interest due to their specificity for binding antigen. When antigen-antibody binding occurs, a substantial change in the gate potential caused by altered the value of the surface charge takes place. The magnitude of the charge density on the surface appears to be an important determinant when measuring the interaction patterns of biomolecules using FET-based biosensors. Note that the isoelectric point (IEP), which is the pH value of the solution at which the surfaces carries no net charge, is affected by the surface charge density. If the pH value of the buffer solution is below (or above) the IEP value of the analyte, the analyte will carry a net positive (or negative) charge. The resultant carriers flow through the channel from the source to the drain according to the variations in the surface charge density of the target analyte. Park et al. reported the ISFET-based detection of a CRP (C-reactive protein) antigen whose concentration is useful indicator of inflammation in the early stages of an infection [27]. In that study, the CRP antigen was recognized by its specific antibody immobilized onto the oxide layer, as governed by the pH dependence of the surface charge density of the target antigen (Fig. 4). Upon the binding of CRP to an anti-CRP antibody on the ISFET surface, a measurable decrease in the drain current was observed, as CRP (pI 5.45) has a net negative charge at the given buffer at pH 7.4. (Note that an analyte has a net negative charge when its pH exceeds the pI value.)

The concept of an enzyme FET was initially proposed by Janata and Moss in 1976 [12]. In 1980, Caras and Janata showed the practical applicability of an ISFET as a pH-based enzyme FET for the measurement of penicillin [13]. Subsequently, many designs were suggested for enzyme-FET biosensors [28-31]. The enzyme FET originates from a pH-sensitive detector in which the concentration of protons derived

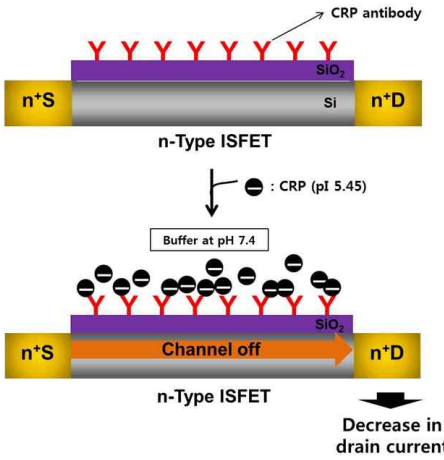


Figure 4. Real-time detection of CRP using an immunologically modified n-type ISFET [27]. When CRP (pI=5.45) binds to the antibody-immobilized ISFET surface, a measurable change in the conductance of the device is observed due to the net negative surface charge of the target analyte in the given buffer solution (pH=7.4).

from the enzyme-catalyzed reaction is directly proportional to that of the substrate. Essentially, an enzyme FET is operated by enzyme-substrate reaction in which the enzyme can distinguishits substrate, subsequently converting the substrate to the product. The FET can be used to investigate these enzyme-catalyzed reactions quantitatively and qualitatively. These enzymatic reactions allow the accumulation of charge carriers at the gate surface in proportion to the analyte concentration. The concentration of the charge carriers accumulated onto the gate electrode increases in accordance with the enzyme-substrate reaction until the substrate molecules are depleted. This enzymatic reaction can cause a measurable change in the electrical signal between the source (S) and the drain (D).

A common example of an enzyme FET may be the glucose-sensitive FET sensor, which has a glucose oxidase membrane-modified gate surface. The enzyme FET used to determine the level of blood glucose serves as a glucose oxidase-based enzyme electrode. Caras et al. reported a glucose oxidase-based enzyme

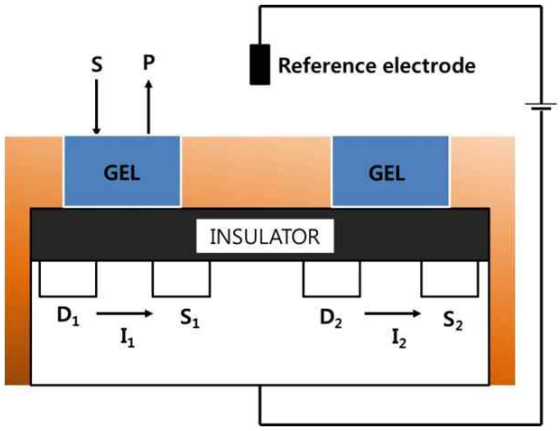


Figure 5. Cross-sectional diagram of a glucose oxidase-based enzyme ISFET [5]. The enzyme glucose oxidase was covalently cross-linked to the polyacrylamide gel as a matrix for enzyme immobilization. S and P indicate the substrate and the product.

ISFET as a glucose sensor [5], where the enzyme was immobilized in a polyacrylamide gel matrix which is chemically inactive and electrically neutral (Fig. 5). The covalent immobilization of the enzyme in the uncharged polyacrylamide gel allows for well-controlled enzyme loading, and the alterationin the matrix structure associated with swelling or shrinking caused by the altered ionic concentration inside the gel can be minimized. In that study, to avoid nonspecific variations which may be affected by factors such as the temperature or pH, the value from a reference electrode was subtracted from the measurement obtained from the ISFET sensor during the enzyme-substrate reaction. The result showed that changes of the pH value induced by the variation of the glucose concentration can be measured effectively using the enzyme ISFET sensor, as the pH value decreases in accordance with the higher rates of proton production caused by the increase in the glucose concentration.

## 3. Nanowire FET

Nanowires are widely used as excellent building

blocks for nanoscale devices. It is assumed that one of the most fascinating sensing platforms can be a FET sensor system based on nanostructures, including semiconductor nanowires and carbon nanotubes. Even if the operating principle of a nanowire FET is similar to that of a typical FET-type device, a nanowire FET shows advanced sensitivity due to the nanoscale channel confinement effect [32]. Nanowire-type FET sensors are considered as sensitive devices because the surface-to-volume (S/V) ratio drastically increases when the diameter of the wire decreases on the nanometer scale, as a high S/V ratio is responsible for the sensitivity of the device. Fig. 6 depicts the concept of a conduction channel along nanowires which is affected by surface interactions [33]. The overall entire conduction of the wires can be influenced by both the surface conduction and the internal conduction. Nanowires with larger diameters show a low surface-to-volume (S/V) ratio. In this case, even if target analytes bind to the surface area of the nanowires, the surface interactions make only a minor contribution to the overall conduction of the wires, as the internal region of the wire is greater than the surface area. Based on this concept, Elfstrom et al. reported the size-dependent surface charge sensitivity of silicon nanowires [34], suggesting that silicon nanowires with different widths display different electrical performance levels of their device sensitivity during biological responses.

Cui et al. developed a FET biosensor using silicon nanowires [20]. In these devices, boron-doped silicon nanowires were used as a bridge between the source and the drain of the silicon nanowire FET (SiNW FET). This FET device was fabricated out of high-quality silicon nanowire functionalized with amine and oxide materials for highly sensitive, real-time detection (Fig. 7). The silicon nanowire FET showed a substantial change in the channel conductance, which depends on the external pH condition in a wide dynamic range. Variation in the surface charge density during the protonation and deprotonation of biological and chemical species resulted in a change in the conductance of the device. In order to detect streptavidin, the surface of the silicon nanowire FET was modified with biotin and streptavidin-biotin binding was detected using the nanowire FET in the picomolar range. The biotinylated p-type nanowire FET exhibited a significant up-shift in its con-

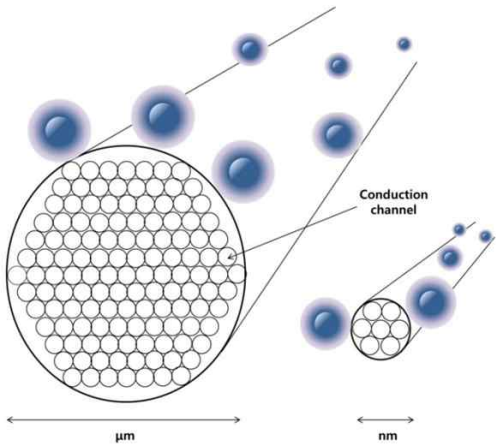


Figure 6. Schematic representation to explain the relationship between surface interactions and conduction within a nanowire [34]. An increased surface-to-volume (S/V) ratio leads to a substantial increase in the detection sensitivity.

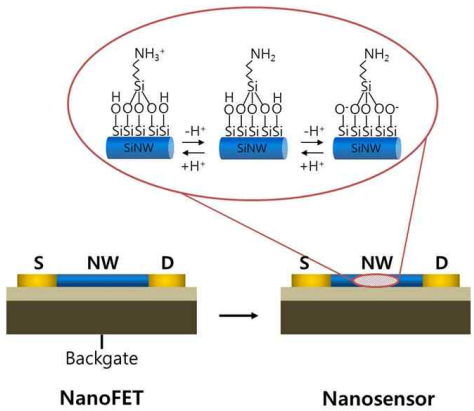


Figure 7. Schematic representation of a pH-dependent silicon nanowire FET (SiNW FET) functionalized with amine and oxide materials [20]. The silicon nanowire FET can be used for sensitive pH sensing.

ductance in response to streptavidin, which is a negatively charged biomolecule (pI=around 5.6).

Patolsky et al. electrically detected the influenza (type A) virus using a p-type silicon nanowire FET in an array [1]. Fig. 8 shows a schematic illustration of the antibody-modified silicon nanowire FET used for detecting the influenza virus. In that study, the effect of the pH value on the conductance caused by the surface charge density of the virus particles was tested at a constant ionic strength. In their results, the pH variation was found to be primarily responsible for the change in the conductance associated with the binding (or unbinding) of the virus particles. The conductance decreased (increased) below (above) a pH of approximately 6.8, which indicates that the value of the isoelectric point (IEP) of the target virus is between pH 6.5 and 7.0. The results and estimated IEP values were in good agreement with the result obtained from electrophoretic mobility measurements, suggesting that the nanowire FET is also a useful tool for the determination of isoelectric points.

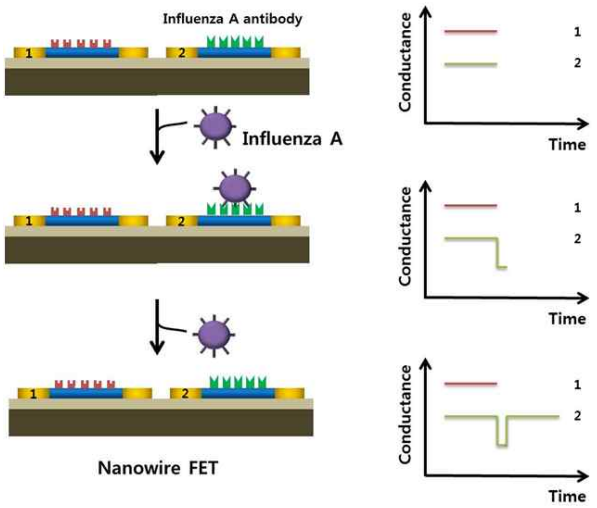


Figure 8. Schematic illustration of a virus-specific antibody-modified nanowire FET for detecting the influenza virus [1]. Nanowires 1 and 2 are modified with a specific antibody and a non-specific antibody, respectively. When the virus moves away from the surface, the conductance goes back to the baseline.

Stern et al. developed a nanowire FET biosensor capable of detecting antigen-specific T-cell responses [4]. Monitoring of the immune response of antigen-specific T-cells has been considered to be crucial before therapeutic strategies for many immune-related diseases can be established. In their study, a nanowire FET device was used to detect proton secretion caused by extracellular acidification. To turn on the T-cell signaling mechanism, splenocytes isolated from B6 mice were treated with the anti-CD3 antibody and the extracellular acidification rate was investigated. In addition, the antigen-specific T-cell response was observed 40 seconds after the addition of peptide/MHC (major histocompatibility complexes) agonists, as T-cell activation is triggered by the association between the T-cell receptor (TCR) and the peptide/MHC (peptide-loaded major histocompatibility complexes). Fig. 9 represents the nanowire FET-based sensing strategy used for measuring the antigen-specific T-cell response. For pre-T-cell activation, most of the silanol groups are fully deprotonated at the nanowire FET surface. Following T-cell activation, numerous protonated silanol groups are observed at the nanowire surface due to extracellular acidification, which subsequently leads to a down-shift in the drain current.

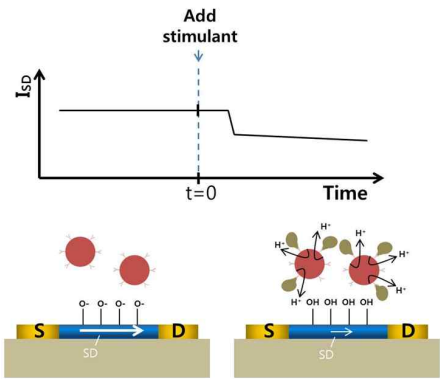


Figure 9. Nanowire FET-based measurement strategy for monitoring the antigen-specific T-cell response [4]. Bottom left: pre-T-cell stimulation (or activation) bottom right: post-T-cell stimulation (or activation).

## IV. Debye Screening

The electric field affected by the surface charge density of biomolecules near the gate layer vanishes beyond the Debye screening length, which is the distance over which the electric field is screened out by mobile charge carriers such as electrons or ions in the solution. The limit of detection (LOD) in FET-type biosensors is strongly associated with the Debye screening length between the gate surface and the analyte solution. Therefore, the accuracy of FET measurements may be negatively affected by the Debye length limitation. Therefore, the Debye length limitation is considered to be one of the most critical problems arising measuring biomolecular responses using FET-type biosensors. In particular, the Debye shielding effect is closely related to the ionic strength of the buffer solution. The surface charges of biomolecules in a buffer solution are shielded by oppositely charged buffer ions. On a certain length scale, the number of net negative (positive) charges approaches the number of positive (negative) charges on the molecules. The electrostatic potential that results from the variation in the surface charge density of the analyte molecules exponentially declines towards zero due to the screening effect. This critical length scale is called the "Debye screening length" ($\lambda_D$). For an electrolyte buffer solution, this length is expressed by thefollowing equation:

$$\lambda_D = \sqrt{\frac{\varepsilon_0 \varepsilon_r k_B T}{\sum \rho_i z_i^2}}$$

Here, $\varepsilon_0$ and $\varepsilon$ are the dielectric constant of the free space and the relative dielectric constant, respectively; $k_B$ and T are the Boltzmann's constant and the temperature, respectively; and $\rho_i$ and $z_i$ are correspondingly the density and the valence of ions of species i. This value determines the total thickness of the electrical double layer. For a symmetrical ($+z_i$:$-z_i$) electrolyte with a concentration ci at room temperature (25°C), the value of the Debye length can be described as shown below [35],

$$\lambda_D = \frac{2.15 \times 10^{-10}}{\sqrt{I_s}},$$

where the ionic strength Is is expressed as follows:

$$I_s = \frac{1}{2}\sum c_i z_i^2$$

Stern et al. demonstrated the effect of molecular charge shielding with a dissolved solution with oppositely charged ions on the p-type nanowire FET sensor response using a biotin-streptavidin system [32]. The Debye screening effect is a critical point to consider when developing optimal protocols for FET-based biosensors. It has been shown that an increase in the ionic strength of the solution buffer contributes to the sensitivity of the FET-based detection process. Negatively charged streptavidin, whose pI value is approximately 5.6, and the biotinylated FET surface are conjugated through the affinity between streptavidin and biotin. Upon the binding of streptavidin and biotin, a significant up-shift in the drain current of the p-type FET was observed. As shown in Fig. 10, in the ionic strength of a 0.01 X PBS buffer, where the value of $\lambda_D$ is nearly 7.3 nm, most of the charge of streptavidin was unshielded to a large extent near the FET surface, thereby influencing the carrier density. The use of the ionic strength of a 0.1 X PBS buffer, with a $\lambda_D$ value of approximately 2.3 nm, showed a partial screening effect of the charge of streptavidin. Meanwhile, using the ionic strength of a 1 X PBS buffer ($\lambda_D$=around 0.7 nm), the majority of the charge of the protein was properly screened. These results strongly indicate that ionic concentrations play a

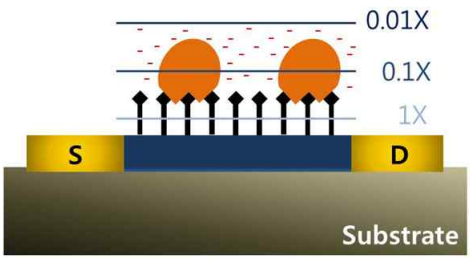


Figure 10. Schematic representation of the Debye screening length ($\lambda_D$) from the FET surface [32]. The navy-blue bar indicates the gate (G), and the yellow bars are the source (S) and drain (D). The black diamonds represent biotin and the orange objects are streptavidin.

major role in the detection sensitivity of devices.

## V. Summary

Thus far, FET-based devices have shown numerous biological applications involving the recognition of various biological elements (i.e., small molecules, DNA, peptides, proteins, and cells). Studies have demonstrated that FET biosensors can potentially provide a versatile tool for clinical diagnosis and for point-of-care detection because FET-based detection is label-free, portable, sensitive, specific, speedy, and affordable. In spite of these advantages of FET-type biosensors, FET devices still need to be improved for better performance with regard to real sample detection and multiple-sample detection. Moreover, the issue of the Debye length should be carefully considered before applications of FET-based biosensors can be realized, as biological events such as antigen-antibody binding, protein-protein interaction, receptor-ligand binding, DNA hybridization and DNA-protein binding must occur within the Debye length. Regarding this point, it is assumed that conformationally changed proteins in a single polypeptide can be good model bio-contents, as any variation in the structural configuration is more likely to take place close to the gate surface compared to complex biomolecules.

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