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REVIEW

The influence of geometry and other fundamental challenges for bio-sensing with field effect transistors

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Abstract

We present a review of field effect transistors (FET) from the point of view of their applications to label-free sensing in the era of genomics and proteomics. Here, rather than a collection of Bio-FET achievements, we propose an analysis of the different issues hampering the use of these devices into clinical applications. We make a particular emphasis on the influence of the sensor geometry in the phenomena of mass transport of analytes, which is a topic that has been traditionally overlooked in the analysis and design of biosensors, but that plays a central role in the achievement of low limits of detection. Other issues like the screening of charges by the ions in liquids with physiological ionic strength and the non-specific binding are also reviewed. In conclusion, we give an overview of different solutions that have been proposed to address all these challenges, demonstrating the potential of field effect transistors owing to their ease of integration with other semiconductor components for developing cost-effective, highly multiplexed sensors for next-generation medicines.

Keywords Field effect transistors · Bio-sensing · Diffusion

Introduction

Progress in genomics (Lockhart and Winzeler 2000) and proteomics (Chandramouli and Qian 2009) is undergoing a revolution from the perspective of the next-generation health system, with the eruption of personalized medicines that promise a better classification of diseases with more effective diagnosis and therapies with less side effects. For the effective implementation of these developments in biology, there is a need, within the medical technology sector, for fast and accurate label-free sensors able to detect deoxyribonucleic and ribonucleic acid (DNA and RNA, respectively) and their proteomic expression at the ultralow concentrations in which they are found in biological fluids. This new class of biosensors would make possible the progress in the applications of precision medicines such as the diagnosis of diseases like cancer (Stern et al. 2010; Ladd et al. 2009; Zheng et al. 2005), drug discovery (Xi et al. 2008), and the development of therapies with the best outcomes considering the intrinsic differences among individuals (Whirl-Carrillo et al. 2012). New kinds of biosensors for the recently validated bio-recognition molecules have been proposed differing in the way the bio-conjugation event is transduced (Mehrotra 2016). Among these, bio-field effect transistors (Bio-FETs) are a category where the transducing element is provided by the capacitance effect of a dielectric material in contact with an electrolyte (Matsumoto and Miyahara 2013). Its main working principle is the same of the metal oxide field effect transistor (MOSFET), where the metal gate is replaced by the electrolyte connected to the circuit by a reference electrode. An example of one of the typical FET configurations is depicted in Fig. 1. Basically, the field effect transduction is based on the displacement of the charge of the conduction channel of the transistors by the charge of the analytes binding to its surface in contact with the electrolyte (Bergveld 1970). The FET high sensitivity is supported by the fact that it is possible to tune both the carrier concentration of the semiconductor channel (by doping or electrical gating) and the channel dimensions, so as to be close to the charge and size of the analyte to detect, improving the efficiency of the sensing process (Matsumoto and Miyahara 2013; Tabata et al. 2016). Using the right molecules as bio-recognition elements, Bio-

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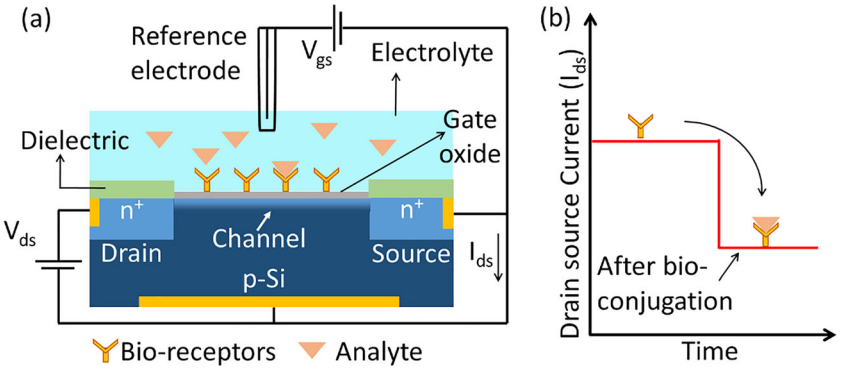

Fig. 1. **a** Schematic representation of a p-type planar Bio-FET where Source and Drain (both n-type Si, and isolated with from the electrolyte, typically with a dielectric) are connected by a p-type Si body in contact with the electrolyte through a dielectric gate (e.g., SiO2). Using a potential Vgs between the Si p-type region and the electrolyte applied through a reference electrode, it is possible to modulate the charge carriers, opening a conduction channel upon an applied voltage Vds, thereby allowing the current (Ids) to flow between source and drain electrodes. **b** On binding of analytes to bio-receptors functionalized to the gate oxide surface, there is a change in the surface potential that can be measured directly as a change in Ids as a function of time at a fixed Vds and Vgs. The case shown illustrates the detection of a charge similar to the one in the conductive channel (negative in the example illustrated here)

FETs are able to detect biomarkers of interest at the low concentrations (Hahm and Lieber 2004; Kim et al. 2009). Bio-FETs are able to cater to requirements for small size, large multiplexing capabilities, label-free sensing, real-time detection, and selectivity, with the potential to reduce the costs of fabrication owing to the well-established fabrication techniques from the electronic industry.

Figure 2 shows the time evolution of representative Bio-FETs discussed in this review. The first Bio-FETs developed were planar ion-sensitive FETs (ISFETs) that were introduced as miniaturized silicon-based electrochemical sensors to detect the proton concentration (Bergveld 2003). Over time, variations of planar ISFET configurations have been developed to allow the detection of different analytes, including nucleic acids and proteins. In the field of genetic analysis, ISFETs are the building blocks of one of the most successful techniques of DNA sequencing. Confining the same single strands of DNA into isolated wells, and using polymerase-assisted nucleotide additions that produce an increase of acidity proportional to the number of nucleotides added, DNA can be sequenced in high parallel chips (Rothberg et al. 2011). This method offers the advantages of high throughput and cost-effective solutions in respect to other available techniques. While the detection of ions, mainly pH, has been implemented successfully for its commercial use (including DNA sequencing), the implementation of Bio-FETs for label-free sensing of DNA and other complex molecules in clinical applications still holds several challenges regarding the reliability of the high figures of merit that they have shown in research. One of these new possible applications is label-free DNA sensing, which is propposed for detecting DNA or related molecules (in particular RNA) as the concentration of nucleotides can also be quantified using the capacitance detecting their charge (in contrast with the polymerase enzymatic effect used for DNA sequencing, which detects protons). When the DNA or RNA strands bind to the complementary ones, which are functionalized at the dielectric surface, changes in the sensing gate surface potential occur due to the negative charge of nucleotides, thereby allowing label-free detection. The demonstrated limits of detection for these kinds of modified planar FETs are in the concentration range of a few tenths of a micromolar (Mahdavi et al. 2014; Uno et al. 2007). Immuno and enzyme FETs (immuno-FETs and ENFETs, respectively) are used for the detection of proteins. An immuno-FET is made with an antibody or an analogue molecule with similar selectivity (aptamers, peptides, truncated antibodies, etc.) coated onto the gate material recognizing its antigen (Schenck 1980). ENFETs are based on a similar principle to the one used for next-generation sequencing where the pH-sensitive ISFETs detect concentration of hydrogen ions produced during an enzymatic reaction that is proportional to the analyte concentration. To the present day, detection of different species has been reported in literature, which included glucose (Park et al. 2002), penicillin (Poghossian et al. 2001; Caras and Janata 1980), and urea (Soldatkin et al. 2003).

Over the last few decades, the miniaturization of transistors has led to nano Bio-FETs with different proposed geometries including nanowires (NWs), nanoribbons, and nanoplates (Cui et al. 2001; Lee et al. 2012; Li et al. 2004) and even some transduction configurations beyond the capacitive effect (Gao et al. 2016). These devices share with their planar precursor characteristics such as the compatibility with complementary metal oxide semiconductor (CMOS) circuits, fabrication processes based on semiconductor industry, improvements in multiplexing, differential readout possibilities, and the same surface functionalization chemistries. The research interest in nano Bio-FETs has been mainly driven by the improved current sensitivity $\Delta I/I$ (change in current divided by the original current) upon analyte adsorption compared to planar FETs, often attributed to the large surface area-to-volume ratio. This

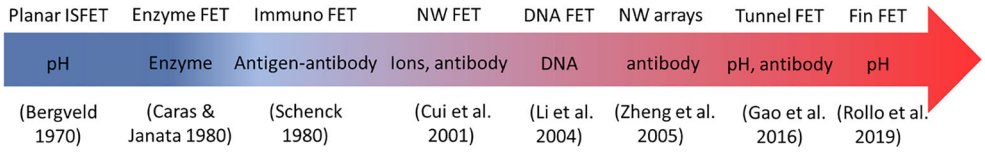

Fig. 2 Time evolution of some representative Bio-FET devices discussed in this review

miniaturization has allowed decreasing the limits of detection from few tens of micromolars to femtomolar (Gao et al. 2011; Tian et al. 2011). However, when measuring low concentrations of samples, the characteristic that determined the smallest resolvable ΔI, and thus the sensitivity, is the current noise of the sensor (Bedner et al. 2014; Deen et al. 2006; Rajan et al. 2010). This represents an issue in the development of nanosensors related to their reliability arising from the difficulties in control of the fabrication parameters and surface functionalization (Balasubramanian 2010).

The role of geometry in Bio-FETs

While from a device perspective the transduction limit is determined by the device noise, the concentration limits of detection of an assay depend also on the rate of the diffusion of the analyte to the surface of the sensor (Nair and Alam 2006; Nair and Alam 2007). In laboratory conditions, the sample concentration can be maintained constant using a microfluidic flux that replaces the analytes, but at static conditions more similar to clinical applications where the sample volumes are reduced, nano Bio-FETs offer advantages compared to the planar ones for detecting lower concentrations, down to femtomolar, as demonstrated for detection of DNA hybridization and antibody-antigen binding in low ionic strength buffers (Gao et al. 2011; Li et al. 2013; Luo et al. 2011; Tian et al. 2011). This higher sensitivity of nano Bio-FETs in particular in static conditions is due to 2D diffusion of the analyte towards the sensor surface, which allows the sensor to collect measurable amount of molecules in a relatively short time.

The phenomenon can be described as follows, when the analyte is adsorbed by the surface, a concentration gradient forms into the solution and the analytes further from the sensor must travel through it to reach the binding sites on the sensor surface. The steady-state signal is provided after the equilibrium is reached, and the time needed to reach this depends on sensor geometry (Nair and Alam 2006; Rajan et al. 2014). Nanowires provide faster response since they can sense molecules coming from the two dimensions perpendicular to the sensor surface, while planar FET can only collect molecules diffusing in one direction as an effect of the reduced dimensionality in the diffusion. Figure 3 shows gradients of analytes created by different geometries. In planar ISFETs and NWs (Fig. 3a, b, respectively), the represented iso-concentration lines indicate diffusion in one and two dimensions, respectively. For the NW arrays (Fig. 3c), at high concentrations, the analytes interact with the sensor in a similar way as a single NW FET. As the concentration decreases, the molecules from further regions reach the sensor surface from fronts parallel to the sensor array and their behavior becomes similar to the planar sensors decreasing the overall efficiency. Recently, we proposed a new design (Fig. 3d) of a large height-to-width aspect ratio of the semiconductor layer called as FinFET structure (Rollo et al. 2019) (height ~ few μm, width < 200 nm). At high concentrations, analytes close to the surface reach the sensor in a similar way to a planar device but due to the double side of the semiconductor layer exposed to the electrolyte, the gating effect is double. Moreover, at lower concentrations, associated with long incubation times, analytes reach the sensor from further regions and the diffusion process becomes more similar to the 2D case. Contrary to the NW arrays and planar FETs, where at low concentrations the diffusion of the molecules is determined by 1D diffusion, the FinFET architecture allows the diffusion process to be in 2D regime, increasing the number of analytes reaching the surface and thus the sensitivity. In addition, the FinFET configuration has the potential to decrease the impact of parameters such as surface inhomogeneities, lithography tolerances, or surface functionalisation, since the planar-like semiconductor channel improves the transport characteristics in comparison to the NWs. The large surface area along the sidewalls will result in more homogeneous receptor immobilization. Also the planar facets of the FinFET account for a more linear response, which can be improved in symbiosis with improved chemical interfaces. This can be achieved with high K dielectrics which also improve the capacitance effect in the transduction (Rollo et al. n.d.)

Table 1 shows a collection of representative data from literature to provide an overview of different label-free Bio-FET configurations for DNA and protein sensing, using the limits of detection and time to results as the relevant parameters for the performance of the devices. To compare the influence of geometry, Fig. 4 plots the data extracted from the literature reported in Table 1 for sensing of DNA molecules having similar diffusion constants. The graph shows the correlation between concentration of limits of detection versus the time employed in each assay for planar (black squares) and NW (red dots) FETs. Planar FETs take a longer time for the detection of DNA at any concentration (region shadowed in green), which is attributed to the reduced dimensionality of the diffusion process (1D diffusion towards the sensor). Noteworthy, NWs provide faster response times, also attributed to the increased dimensionality of the diffusion process (in the yellow shadowed region). The

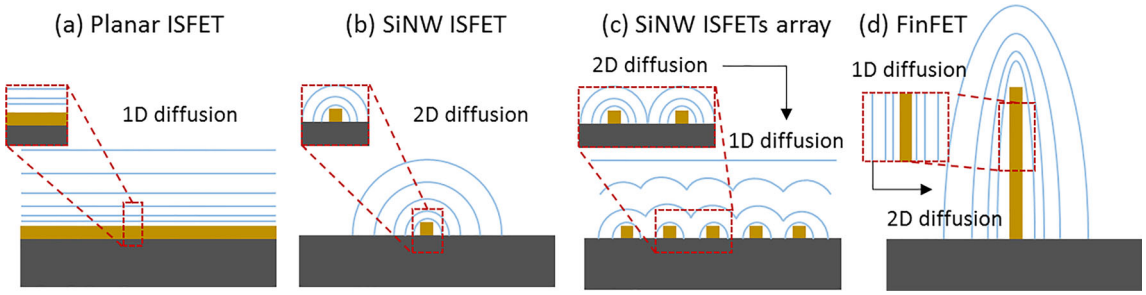

Fig. 3 **a**–**d** Schematics of the iso-concentration diffusion lines (in blue) in close proximity and further from the sensor surface on planar, silicon nanowire, nanowires array, and high aspect ratio Fin FET, respectively. The FET channel is represented in yellow. (Figure adapted from Rollo et al. 2019)

theoretical model of the concentration limits of detection and its evolution with time based on the diffusion supports these assumptions (Nair and Alam 2006; Nair and Alam 2007).

On comparing the protein detection by planar, single NW, and NW array FETs shown in Table 1, it is observed that for the same assay times, NW FETs perform better than their planar counterparts in terms of limits of detection. NW array FETs perform the best detecting the lowest concentrations in a comparable time with respect to the other two configurations, also due to a better compromise between the noise characteristics and the diffusion (Accastelli et al. 2016).

Limitations of bio-sensing using FETs

Probably, the most restrictive limitation of Bio-FET sensors is represented by the Debye screening, which refers to the effect of screening of the charged analyte by the ions dissolved in the solution. Figure 5 a shows a schematic representation of the formation of the electrical double layer at the dielectric-electrolyte solid-liquid interface and the Debye length using a Gouy Chapman Stern model in the case of proton sensing when the receptors are just oxide groups in the surface of the gate (Van Hal et al. 1996). In this case, as the dielectric in the sensing gate surface has a certain total charge due to the capture of ions here represented by the protonation and deprotonation of a reactive surface site, it will attract ions of opposite charge from the solution. The layer of ions closest to the surface forms the Stern layer that compensates the charge of the analytes. Ions further from the surface form a diffuse layer neutralizing the charge at the dielectric surface by forming a double-layer capacitor. Figure 5 b shows the potential distribution from the dielectric surface to the bulk of the electrolyte. The biggest drop of potential happens in the stern layer. Further, the potential decreases exponentially until zero in the bulk.

The Debye screening length depends on the ionic strength of the electrolyte varying from less than 1 to 10 nm. When using longer receptor molecules, like antibodies, different interaction events of interest can occur beyond the few nanometer range from the sensing gate surface (the length of the attached probe), and this effect represents a serious drawback for sensing (Chu et al. 2017; Elnathan et al. 2012). As represented in Fig. 5c, d, the analytes captured beyond the Debye length do not influence the

Table 1 Overview of sensing response of NW and planar FETs for DNA and proteins

Sensor type		Analyte type				References
		DNA		Protein		
		Limit of detection (M)	Response time (s)	Limit of detection (M)	Response Time (s)	
NW FETs	Single	1E−6 to 1E−15	50 to 600	1E−12	500 to 2000	Adam and Hashim (2015); Duan et al. (2012); Gao et al. (2012); Hahm and Lieber 2004; Li et al. (2004); Lin et al. (2009); Zheng et al. (2010)
	NW arrays			1E−13 to 1E−16	50 to 3600	Lu et al. (2014); Zhang et al. (2015)
Planar FETs		1E−4 to 1E−7	300 to 54,000	1E−5 to 1E−7	300 to 1200	Braeken et al. (2008); Freeman et al. (2007); Sakata et al. (2005); Shin et al. 2004); Uno et al. (2007); Xu et al. (2016); Zafar et al. (2018); Zayats et al. (2006)

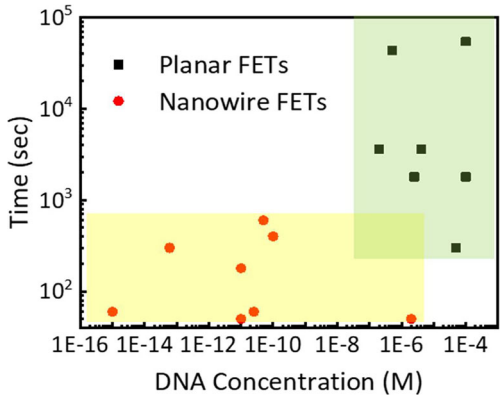

Fig. 4 Data from literature of DNA sensing using planar FETs and SiNWs FETs. The time needed for detection is reported versus the DNA concentration

static charge of the sensor, and thus are not recognized using a static (DC) gate bias. The solution normally implemented is the use of lower ionic strength buffers at the measuring time, after different washing steps, but this procedure may affect the stability and activity of biological species, in particular changes in the conformation of the receptor/target molecules and the affinity of the interaction. Over the last years, different strategies have been implemented to overcome the Debye limit. One approach has been the use of nanostructures with higher polarizability than the medium to capture the charges and transfer the capacitance effect (Abouzar et al. 2012; Abouzar et al. 2011). A second possibility has been the use of AC signal that decreases the effect of the double-layer capacitance created by the screening ions (Kulkarni and Zhong 2012; Laborde et al. 2015). A third method proposed to overcome the Debye screening actually uses the electric double-layer capacitance created by the screening ions as the dielectric replacing the traditional oxide (Chu et al. 2017).

Other limitations influencing the sensitivity of Bio-FETs are the gate oxide stability, their sensitivity to temperature, the influence of pH in the gate oxide, and the ionic strength variability during measurement, which may result in false positive/negative measurements. Finally, a common issue to most biosensors regards the non-specific binding. Fewer studies aim to detect the biomarkers directly into blood or serum because of the complexity of these media. In order to overcome the abovementioned issues of Bio-FETs, the passivation of the sensor surface (Chang et al. 2011), integration with microfluidic separation components (Stern et al. 2010), and differential readout methods have been proposed.

Perspectives

Field effect transistor biosensors have been suggested with different materials that are still under intensive research so as to improve their transduction capabilities. For example, III-V semiconductor devices can offer higher mobility and polarizability than silicon, while reducing the intrinsic depletion region at the interface between the semiconductor channel and the dielectric and providing better optical response to combine electrochemical and optical sensing (Chu et al. 2017; Janissen et al. 2017). To improve the capacitance effect, high K dielectrics that have better chemical properties and stability with respect to SiO_2 (initially the first dielectric employed) have also been proposed (Dorvel et al. 2012; Rollo et al. 2019 submitted). Novel systems based on 2D materials like graphene (Cai et al. 2014) or MoS_2 (Sarkar et al. 2014) and 1D materials like carbon nanotubes (Allen et al. 2007) are also under investigation. However, all these devices will continue

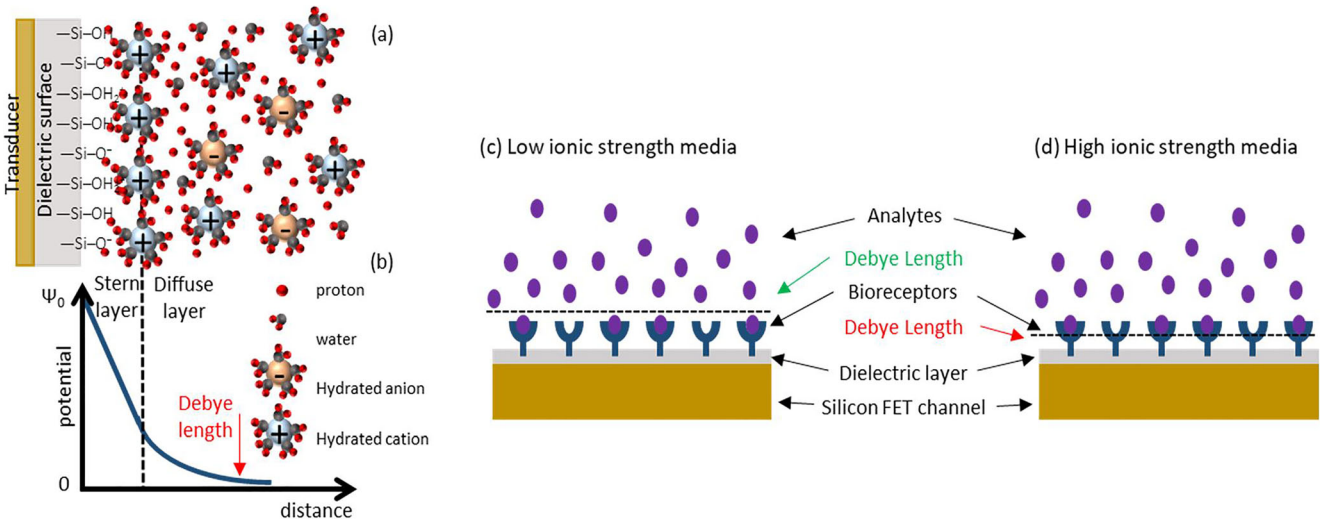

Fig. 5 **a** Schematic of the formation of the Debye length using a Guy Chapman Stern model. **b** Potential distribution from the dielectric surface to the bulk of the electrolyte. **c**, **d** Schematic representation of the formation of Debye length at different ionic strengths and the subsequent effect in the bio-recognition events, analytes captured beyond the Debye length are not sensed by the FET. The bio-receptors functionalized on the surface are represented in blue. The analyte molecules are represented in purple

to face the fundamental challenges of analyte mass transport, charge screening of free ions, and non-specific binding issues. While the ability to work with all these materials improves, the silicon technology offers a great control in the mass fabrication possibilities (Rani et al. 2018) (Zafar et al. 2018). The combination of different approaches shown in this review may, in the near future, provide valid solutions for the clinical demand of a fast, sensitive, selective, and cost-effective biosensor able to detect multiple biomarkers.

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