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Molecular recognition by synthetic receptors: Application in field-effect transistor based chemosensing☆

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ABSTRACT

Molecular recognition, i.e., ability of one molecule to recognize another through weak bonding interactions, is one of the bases of life. It is often implemented to sensing systems of high merits. Preferential recognition of the analyte (guest) by the receptor (host) induces changes in physicochemical properties of the sensing system. These changes are measured by using suitable signal transducers. Because of possibility of miniaturization, fast response, and high sensitivity, field-effect transistors (FETs) are more frequently being used for that purpose. A FET combined with a biological material offers the potential to overcome many challenges approached in sensing. However, low stability of biological materials under measurement conditions is a serious problem. To circumvent this problem, synthetic receptors were integrated with the gate surface of FETs to provide robust performance. In the present critical review, the approach utilized to devise chemosensors integrating synthetic receptors and FET transduction is discussed in detail. The progress in this field was summarized and important outcome was provided.

1. Introduction

Preparation of novel man-made materials capable to mimic functioning of biorecognition systems, such as enzymes, nucleic acids, or antibodies, signifies the most challenging task that has recently gained large scientific interest (Mahon and Fulton, 2014). The activity of bio-receptors is governed by selective analyte molecular recognition through weak reversible binding. Generally, biosensor activity engages the receptor recognition sites and the analyte binding sites in a particular shape and size configuration that is only one of its kind. The preparation and fabrication of tailor-made biorelevant receptor compounds featuring desired recognition properties require perception and understanding of functioning of the biological systems, in which they operate. Several bio-receptors exhibit specific recognition of organic molecules. This recognition can be explained via the mechanism of “lock and key” (Jones et al., 1995; Liao et al., 2013) and “induced fit model” (Boehr et al., 2009; Sawada et al., 2014). This awareness leads to designing and fabricating novel nature-inspired synthetic receptors in molecular recognition.

Molecular imprinting is a rapidly developing technique used to fabricate synthetic receptors with a great potential in many applications, particularly in the health and life sciences (Figueiredo et al., 2016; Iskierko et al., 2016a; Ndunda and Mizaikoff, 2016; Schirhagl, 2014; Tang, 2018). With this technique, new artificial recognition systems, capable of mimicking features of the corresponding biological recognition systems, are being devised (Chen et al., 2016b; Yoshikawa et al., 2016). The imprinting offers appreciable affinity, selectivity, and robustness at a relatively low cost (Whitcombe et al., 2011). In imprinting, a target analyte is first used as a template. For that, it is complexed by functional monomers in solution of a porogenic solvent. Then, this complex is co-polymerized with an excess of a cross-linking monomer in order to wrap it up in a permeable molecularly imprinted polymer (MIP) shell. The subsequent template removal results in the formation of the nanometer and sub-nanometer-size molecular cavities in the polymer. These cavities are complementary in size, shape, and orientation of their recognizing functionalities and, therefore, capable

List of abbreviations: ACh^+, Acetylcholine; AOCB[6], $(Allyloxy)_{12}$ cucurbit[6]uril; AFM, Atomic force microscopy; cAMP, 3’,5’-Cyclic monophosphate; ChemFET, Chemical field-effect transistor; CB[6], Cucurbit[6]uril; DDFTTF, 5,5′-Bis-(7-dodecyl-9*H*fluoren-2-yl)-2,2′-bithiophene; ENFET, Enzyme field-effect transistor; EG-FET, Extended-gate field-effect transistor; FET, Field-effect transistor; HEMT, High-electron-mobility transistor; HSA, Human serum albumin; ISFET, Ion selective field-effect transistor; LOD, Limit of detection; MIP, Molecularly imprinted polymer; MOSFET, Metal oxide field-effect transistor; MOF, Metal-organic framework; NGAL, Neutrophil gelatinase-associated lipocalin (or Human lipocalin-2); NW, Nanowire; OFET, Organic field-effect transistor; PVC, Poly(vinyl chloride); POC, Point-of-care; PPi, Inorganic pyrophosphate; SAM, Self-assembled monolayer; TESBA, triethoxysilybutyraldehyde; TOF-SIMS, Time-of-flight secondary ion mass spectrometry

☆ Dedicated to Prof. Wlodzimierz Kutner, on his 70th birthday, for his contribution in the field of electroanalytical chemistry and molecular imprinting.

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of selective binding of the molecules of the target analyte. The selectivity, owing to the three-dimensional structure of the cavities, is due to multiple supramolecular bindings, such as the ion-ion, ion-dipole, and hydrogen bonding, as well as hydrophobic and van der Waals interactions. Although, separately, each interaction is weak, collectively they afford a relatively strong selective capture of the analyte. Due to these advanced features, the MIPs have become promising materials as recognition units for fabrication of chemical sensors for both low- and high-molecular-weight compounds (Chen et al., 2016b). In contrast, organic macrocyclic receptors, synthesized by common synthetic approaches, are excellent hosts for recognition of a range of low-molecular-weight small guest biocompounds and inorganic ions (Beer and Schmitt, 1997; Chinai et al., 2011; Dun et al., 2017; Klärner et al., 1999; Mahon and Fulton, 2014).

Typically, for a chemo- or biosensor, the recognition element, containing artificial or natural receptor cavities, respectively, is assembled in an intimate contact with the transducer surface to generate an output detection signal (Nakamura and Karube, 2003). Preferential binding of the analyte by the receptor sites induces changes in the physicochemical properties of the sensing system. Those changes are detected using proper signal transducers. Usually, the target analyte binding by selective recognition unit is transduced to generate an electrochemical (Holthoff and Bright, 2007; Kumar et al., 2008), optical (Chen et al., 2015; Henry et al., 2005), piezoelectric (Liu et al., 2003b; Lu et al., 2012), and electric using field-effect transistor (FET) signals (Iskierko et al., 2016b, 2015). Among these transducers, FET is an attractive platform for the rapid and accurate determination of various analytes (Nehra and Singh, 2015). The real time results are monitored with low cost meters (Chen et al., 2017). Moreover, the FET-based transducers are easy to miniaturize and capable to produce low-cost diagnostic tools for health care (Gao et al., 2016).

The FET transducer is built to meet microelectronic fabrication principle and operates on the basis of an electrostatic field induced modulation of carrier mobility across a biased semiconductor. When a gate surface of the FET is coated with a film of a synthetic receptor, then this receptor provides selectivity to the resulting sensing system. In the present review, the approach, utilized to devise chemosensors integrating FET transducers with synthetic receptors, including macrocyclic and MIP receptors, is discussed in detail. Moreover, these approaches aiming at selective chemosensor development are herein summarized and critically evaluated.

2. Fundamentals of FET operation in chemical sensing

The standard FET can be either of the *n*- or *p*-type (Scheme 1). The *n*-type FET is prepared by forming a channel of an *n*-type material in a *p*-type semiconducting substrate and, vice versa, *p*-type FET is prepared by forming a channel of a *p*-type material in an *n*-type semiconducting substrate. One end of this channel is connected to the source electrode and the other to the drain electrode. In the *n*-channel FET, electrons are majority charge carriers while holes are charge carriers in the *p*-channel FET. An additional metal-over-dielectric gate electrode, deposited on the semiconducting channel, controls effective electrical diameter of the channel (Liu and Guo, 2012). A small variation in gate voltage is responsible for the observed change in the current flowing from the source to the drain.

This conducting gate region can be coated with a membrane or another sensing element to provide selectivity, which is a much desired property for sensing. Bergveld et. al fabricated the first ion-sensitive field effect transistor (ISFET) (Bergveld, 1970). Several pH-sensitive ion-selective membranes, including SiO_2 (Berg et al., 1985), Al_2O_3 (Chen et al., 2011b), Si_3N_4 (Liu et al., 1989), Ta_2O_5 (Branquinho et al., 2011), and SnO_2 (Cheng et al., 2008) were devised and used afterwards.

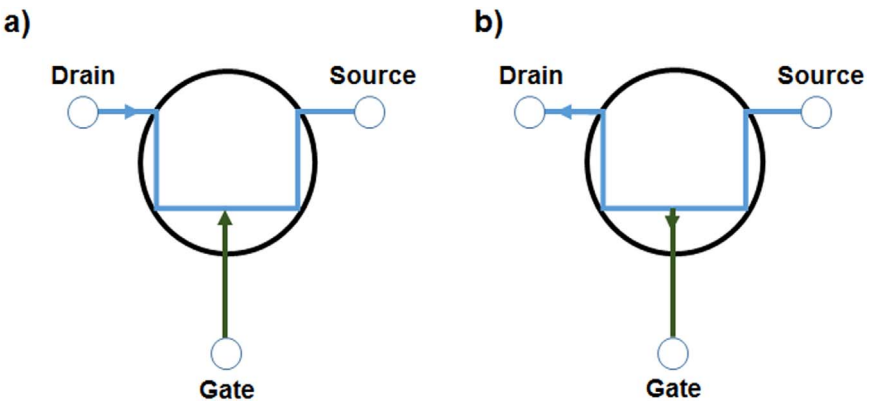
Depending on the type of modification of the gate surface, FET devices are known as ChemFETs if the charge on the gate electrode is generated by a chemical process (Bergveld, 2003), ENFETs if these devices use enzymes for specific recognition of bio-molecular compounds (Belkhamssa et al., 2016; Dzyadevych et al., 2003; Melzer et al., 2016), or OFETs if a channel of the transistor consists of an organic semiconductor (Liu et al., 2015a). In order to isolate the FET from the chemical environment, an extended-gate field-effect transistor (EGFET) was also devised (Chen et al., 2011a; Sakata et al., 2005; Yin et al., 2000). For a similar purpose, a high-electron mobility transistor (HEMT) has been used for sensor development (Schalwiga et al., 2002).

When a sufficiently high gate voltage (V_G) is applied, the FET device is turned to the “on” state. Then, the gate voltage generates an electric field across gate and channel. This field controls the source-drain current flow (Banica, 2012), which is characterized as the transfer curve. The saturation region current measured during transistor characteristic can be expressed as

$$I_{d,max} = \frac{\mu_o C_{ox}}{2} \times \frac{W}{L} \times (V_{ref} - V_T)^2(1 + \lambda V_{ds}) \quad (1)$$

where μ_o is the electron mobility in the channel, λ is the channel length modulation factor, C_{ox} is the dielectric oxide layer capacity per unit area, W/L is the channel width-to-length ratio, V_T, $V_{ref,}$ and V_{ds} is the threshold voltage, applied reference electrode voltage and the drain-source voltage, respectively.

The FET can be operated in either a constant-current or constant-voltage mode. For the former, the change in the gate-source voltage must be exactly equal to the change in the threshold voltage. When molecules of the target analyte are bound by a synthetic receptor, the surface potential changes and, therefore, the channel conductance is changed. These conductance changes can be recorded and further processed by an electric measurement system. In the simplest case, when the negatively charged analyte molecules are captured by the receptor immobilized on an *n*-type semiconductor channel, the number of electron carriers decreases and, hence, electrical conductance is



Scheme 1. Illustration of (a) *n*-channel and (b) *p*-channel FET.