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Review

Capacitive microsystems for biological sensing

V. Tsouti[a,*], C. Boutopoulos[b], I. Zergioti[b], S. Chatzandroulis[a]

[a] Institute of Microelectronics, NCSR Demokritos, Terma Patriarchou Grigoriou, Agia Paraskevi 15310, Greece
[b] Department of Applied Sciences, National Technical University of Athens, Zografou 15780, Greece

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ABSTRACT

The growing interest in personalized medicine leads to the need for fast, cheap and portable devices that reveal the genetic profile easily and accurately. To this direction, several ideas to avoid the classical methods of diagnosis and treatment through miniaturized and label-free systems have emerged. Capacitive biosensors address these requirements and thus have the perspective to be used in advanced diagnostic devices that promise early detection of potential fatal conditions. The operation principles, as well as the design and fabrication of several capacitive microsystems for the detection of biomolecular interactions are presented in this review. These systems are micro-membranes based on surface stress changes, interdigitated micro-electrodes and electrode–solution interfaces. Their applications extend to DNA hybridization, protein–ligand binding, antigen–antibody binding, etc. Finally, the limitations and prospects of capacitive microsystems in biological applications are discussed.

Contents

1. Introduction

Microsystems literally are “very small systems” or “systems made of very small components” and emerged in the early 1960s while attempting to form integrated sensors. The motivation for their development is related to cost reduction and the possibility to put the sensors on the same chip with the associated circuit. Thus, the term microsystems became common in referring to the integration of sensors, actuators and signal-processing electronics on a common substrate (Senturia, 2001). The development of microelectronics and micromachining lead to a worldwide interest in microsystems, now widely called MEMS (Microelectromechanical Systems), and their application to several aspects of everyday life. Sensors constitute about 40% of the market of MEMS and their advantages extend to economical and technological sections (Bryzek et al., 2006).

A sensor is a device that detects a signal and converts it into a measurable quantity. A chemical sensor is a device that transforms chemical information into an analytically useful signal. Chemical sensors usually contain two basic components connected in series: a chemical (molecular) recognition system (receptor) and a physicochemical transducer. Biosensors are defined as chemical sensors in which the recognition system utilizes a biochemical mechanism. The biosensors that can be repeatedly calibrated and are suitable for monitoring both the increase and decrease of the analyte concentrations in batch reactors or flow-through cells can be called multiple-use biosensors contrary to the single-use biosensors, which are disposable and non-regenerative devices (Thévenot et al., 1999). In this review we will mainly refer to affinity biosensors, in which a specific binding between the receptor molecules on the biosensor surface (probes) and the analyte molecules under detection (targets) occurs. These are typically

* Corresponding author.
E-mail address: vasso@imel.demokritos.gr (V. Tsouti).

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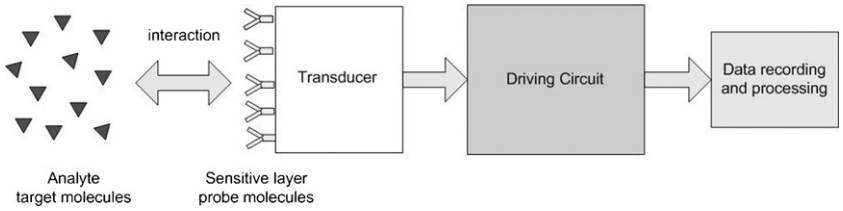

Fig. 1. Schematic diagram of an affinity biosensor.

single-use biosensors. However, following an appropriate cleaning procedure, the devices can be regenerated and reused up to several times reducing the analysis cost (Numnuam et al., 2009).

The receptor component of the biosensor, which is, in most cases, immobilized probe molecules, is selective to a particular analyte or target molecule. The physicochemical transducer, which is the most important part of the biosensor, converts the signal caused by the interaction between probe and target molecules into a macroscopic measurable signal. This signal is finally converted to a more stable and amplified electrical signal through the driving circuit, which is the third component of a biosensor (Fig. 1). The capacitive microsystems that are described next represent the transducer of a biosensor device and are able to convert the signal of the biological interactions into variations of a capacitance value.

Affinity biosensors can be label-free or labelled sensors. Labels are often used as an easy way to confirm the interaction between the probe and target molecules. The target molecules are usually labelled with fluorescent markers, active enzymes, magnetic beads, radioactive species or quantum dots (Waggoner and Craighead, 2007; Daniels and Pourmand, 2007). Labelling occurs either directly on the target molecules prior to the interaction or in a step after binding of the target molecules on the sensing sites. In a typical analysis using microarrays, probe molecules are immobilized on different sites of the same piece of glass and the labelled target molecules indicate the occurrence of an interaction depending on the site where the label signal is observed. These arrays are suitable for fast and easy genome analysis with a potential to accommodate a million sensing sites on a square centimetre (Kennedy et al., 2003).

However, label based techniques are characterized by several disadvantages. For example, it is known that labelling is a time and cost consuming process and may affect the interaction between the probe and target molecules, especially in the case of proteins. In addition, in most label based techniques, the interaction cannot be monitored in real time but only after the molecule binding. Real time measurements allow for studying the kinetics of the observed interactions and consequently understanding the prevailing physical processes. Most of the biosensors that are presented here allow for continuous real time measurements. The need for costly and bulky systems to measure fluorescence, or in general the label signal, is another drawback of labelled techniques as it hinders the miniaturization of the systems.

Miniaturized biosensors are necessary for many applications that need portable integrated systems. The need for miniaturization arises from the need to increase throughput and automation and reduce the cost of the diagnostic assays, which consume hundreds of microliters of expensive reagents. Miniaturized systems, on the contrary, reduce reagent consumption by a factor of 10^3–10^4, providing dramatic savings for the repetitive assays often performed in diagnostic laboratories (Figeys and Pinto, 2000). Through miniaturized systems the diagnostic laboratories can be obviated allowing detection at point-of-care, e.g. in a clinic or a doctor's office, at home or at remote places.

The applications of miniaturized biosensors involve environmental monitoring such as water and air pollution or food contamination and point-of-care (PoC) diagnostics that can be realized analysing just drops of e.g. blood or saliva. PoC systems allow early disease or infection diagnosis and thus can speed intervention, which is of crucial importance in the case of viruses and epidemics. In addition, early treatment is more efficient and usually less expensive compared to treatment at later stages of a disease. For instance, biomarkers that may be presymptomatic indicators of diseases such as cancer or cardiovascular disease could be detected in a quick and easy way by a PoC system. The option of PoC systems capable to detect several biomarkers in parallel, namely biosensor arrays, holds enormous potential for directing personalized therapy and treatment monitoring of these diseases (Rusling et al., 2010). Similarly to disease diagnosis, in environmental monitoring, the timely detection of pathogens is an issue that is not addressed by conventional methods. Portable biosensors appear as promising candidates for rapid detection, although their performance is still not adequate (Laczka et al., 2007). Another potential use of micro array chips is finding and characterizing life at remote places on earth and other planets (http://www.spaceref.com/news/viewpr.html?pid=14312).

In order to address the need for fast, cheap and portable devices, miniaturized and label-free systems, including electrical biosensors and some surface stress based biosensors, have been developed. The electrical biosensors can be amperometric, voltametric, impedance or capacitive sensors (Daniels and Pourmand, 2007; Berggren et al., 2001). Surface stress based biosensors are usually bimorph microcantilevers with optical or piezoresistive readout or alternatively the capacitive membranes, which will be extensively described in this paper.

The main advantages of electrical sensing, and in particular capacitive readout, are the ease of detection, low power consumption and flexibility in the sensor size and sensitivity parameters. In many cases, capacitive sensors can also be fabricated very easily and have the ability of integration of the readout setup in the sensor. In addition, these devices have the merits of label-free sensors, although the use of signal amplification schemes has also been reported in order to increase the sensitivity. Label-free biosensors cannot reach at the moment such high densities of sensing sites as those of typical microarrays and their sensitivity is still under investigation. Nevertheless their advantages over labelled techniques, such as real time measurements, simplicity as well as cost and volume reduction of the devices are sufficient reasons for continuing research on this field.

The term "capacitive biosensors" is usually referred to a subcategory of impedance biosensors, in which the changes in capacitance value are measured indirectly. In particular, impedance biosensors are divided into nonfaradaic and faradaic sensors. A faradaic process refers to charge transfer across an interface, namely the metal–biological material interface, whereas a nonfaradaic process does not involve charge transfer and may refer to transient currents charging a capacitor. Thus, the signal of nonfaradaic impedance biosensors is mainly due to capacitance changes resulting in the use of the term capacitive biosensor (Levine et al., 2009).

The reviews concerning capacitive biosensors mainly focus on electrodes with impedimetric readout (Berggren et al., 2001). In the following, we overview the operation principle and applications of