# Biosensor Systems in Standard CMOS Processes: Fact or Fiction?

Byungchul Jang and Arjang Hassibi
Electrical and Computer Engineering Department, the University of Texas at Austin, Texas, USA

***Abstract*–In this paper, we discuss the advantages and limitations of using standard CMOS fabrication processes for the design of integrated affinity-based biosensor systems. In particular, we examine the compatibility of CMOS with various assaying techniques and the possibility of fabricating their transducer structures.**

## I. Introduction

Affinity-based detection is a fundamental method to identify and measure the abundance of biological and biochemical analytes and it is one of the most important analytical methods in biotechnology. Affinity-based detectors (or so-called biosensors [1] in case of detecting biological analytes) take advantage of the selective interaction and binding (affinity) of the target analyte with immobilized capturing probes to specifically capture the target analyte onto a solid surface (see Fig.1). The essential goal of a detection platform is to facilitate specific capturing and ultimately to produce detectable signal based on the captured analytes. The generated signals correlate with the presence of the target analytes in the sample (e.g., toxins, polymers, hormones, DNA strands, proteins, bacteria, and etc.), and hence are used to estimate their abundance.

To create target-specific signals in biosensors the target analytes in the sample volume first need to collide with the capturing layer, interact and bind to the probes, and ultimately take part in a transduction process, i.e., a physiochemical process which produces certain measurable electrical, mechanical, or optical parameter produced solely by the captured entities. The analyte motion in typical biosensor settings (e.g., aqueous biological mediums) is dominated by diffusion spreading, which from a microscopic point of view is a probabilistic mass-transfer process (i.e., random walk events for a single analyte molecule [2]). Accordingly, the analyte collisions with the probes become probabilistic processes. Moreover, because of the quantum-mechanical nature of chemical bond formation [3-4], interactions between probes and analytes molecules, are also probabilistic, adding more uncertainty to the capturing procedure. On top of these two processes which can be considered the biochemical noise of the system, we also have the detector and the readout circuitry (e.g. optical scanners for fluorescent-based transducers), which likely add additional noise to the already noisy signal.

Besides the inevitable uncertainty associated with the target analyte capturing and detection, in all practical biosensors, binding of other species to the probes (non-specific binding) is also possible. Non-specific binding (e.g., cross-hybridization in DNA microarrays [5-6]) is generally less probable than the specific binding when target analytes and the interfering species have the same abundance. Nonetheless, when the concentration of the non-specific species becomes much higher than the target analyte, non-specific bindings (or essentially interference) may dominate the measured signal and hence limit the minimum-detectable-level (MDL) [7]. It is imperative to understand that in almost all biosensors the MDL is either biochemical noise- or interference-limited, while the highest detection level (HDL), is solely a function of capturing probe density and its saturation level [8].

Due to such impediments, as of today, the accuracy of biosensors systems does not satisfy the stringent requirements of many high-performance biotechnology applications in molecular diagnostics and forensics. In addition, biosensors systems have not successfully made the transition to portable and compact point-of-care devices because their detection platforms still consists of fluidic systems and bulky detectors.

One proposed solution to address the challenges of biosensor systems is to use semiconductor fabrication technologies to build compact, high-performance, and cost-efficient biosensor systems. It is envisioned that such systems, i.e., lab-on-a-chip platforms, include not only the fluidic (macro or micro) systems and sample preparation processes, but also the integrated transducers [9].

The challenge of designing sample preparation modules in biosensors, to some extents, has to been addressed in recent years, particularly in the form of micro-fluidic and automated the liquid handling systems; however the integration of the detector and readout circuitry have not. There are numerous reasons for this, but there are two prominent limitations. One is the technical challenges of manufacturing transducers using custom surface and bulk MEMS procedures [10], and the other is performance and cost justification of monolithic integration of all components.

In recent years the idea of employing Complementary Metal Oxide Semiconductor (CMOS) fabrication processes, which are the most robust and widely used fabrication processes in the semiconductor industry, for biosensors has emerged. The rationale behind this, as opposed to using MEMS or other custom processes, is the unmatched yield, cost-efficiency, and the integration capabilities of CMOS processes. While CMOS processes, from the electronic design point of view, offer huge

978-1-4244-1666-0/08/$25.00 ©2008 IEEE 

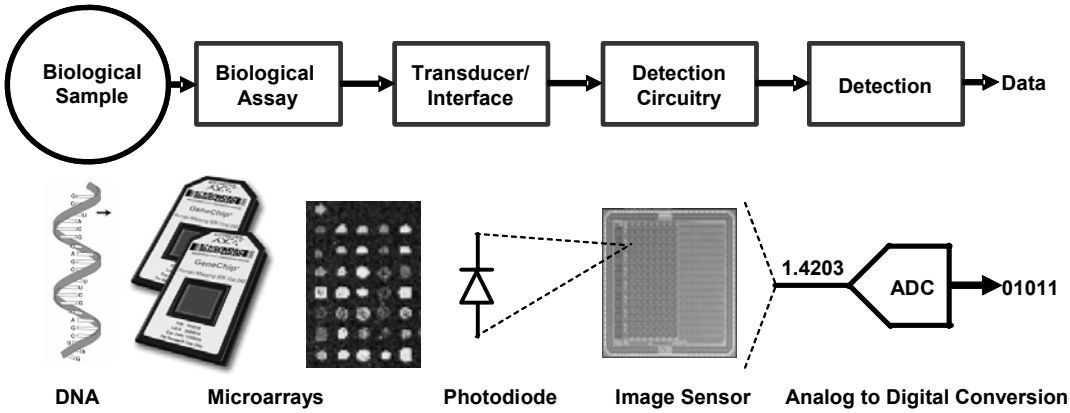


Fig. 1. A typical biosensor system which includes the biological sample, biological assay, transducer, detection circuitry, and the data converter.

degree of design flexibility, they are not very flexible in terms of form factor and transducer design.

In this paper, our goal is to examine all the aforementioned topics in the context of biosensor system-level design. We will examine if CMOS is a good candidate for becoming the "backbone" of integrated biosensor systems. Initially in Section II, we look at the biosensor assay and the requirements it creates for the transducer and the detection circuitry. Subsequently in Section III, we examine CMOS processes and discuss what they can offer to the biosensor systems. Finally at Section IV, we discuss the practical issues and limitations of merging these two to create integrated CMOS biosensor systems.

## II. Biosensor Systems

In order to create and measure analyte-specific signals in biosensors, different functional blocks are typically implemented and put together. Biosensors are detection platforms which comprise of not only biological samples and biochemical systems, but also electronic components (an example is illustrated in Fig.1). While biosensors have different blocks, the assay and the transducer are considered to be the fundamental components, since they are necessary for the functionality of the systems. In this section we will discuss some of the important characteristics of the blocks relevant to integrated biosensors.

### *A. Assay*

The essential role of the assay in all affinity-based biosensors (e.g., microarrays assays [5-6], or immunoassays [11]) is to facilitate the binding of the probe-target complexes to produce a detectable signal, which correlates with the presence of the target and conceivably its abundance. The minimum components required for affinity-based detection include a molecular recognition layer (capturing probe), immobilized on a solid surface and a transducer.

Generally biosensors are assayed in an aqueous solution comprised of the target analytes in addition to different ions, molecules and other particles The assaying procedure in biosensors beside the incubation step (see Fig. 2) may include processes (biochemical or biophysical) of attaching distinctive labels to the analytes such as florescent labels or metallic nano-particles. The goal of such labels is to create analyte-specific signals while distinguishing from the interferers (e.g., background molecules) in the detection.

Independent of using the intrinsic characteristics of analytes or labels to detect analytes, all measurements in biosensors systems are essentially counting processes. It has been previously shown and widely recognized that the performance-

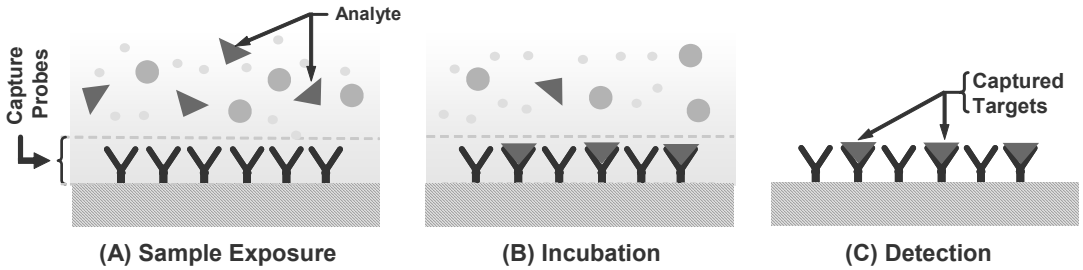


Fig. 2. Affinity-based detection uses the selective binding of the analytes with the capturing probes to capture and detect analytes.

limiting step in this process is the uncertainty of the binding and the non-idealities of the capturing process [8]. The detection limitation when the concentration of analyte is low, i.e., MDL, is generally limited the shot-noise of the binding and the interference of the background molecules. On the other hand, when the concentration of the analyte is high, i.e., HDL, the detection is limited by the saturation level of the probes [7-8].

### *B. Transducer*

To count the number of captured analytes different transducers can be used in biosensors. A transducer is a device, usually electrical, electronic, electro-mechanical, electromagnetic, photonic, or photovoltaic that converts from one type of energy to another for various purposes. In the case of affinity-based biosensors, the signal is created by the captured target analytes.

The main transducers in biosensors are electrochemical [11-12], mechanical (mass-based) [13], and optical [14]. This categorization is based on the kind of signal or parameter the biosensor system creates or alters. Mechanical transducers in biosensors are systems which the electromechanical parameter of a system (e.g., cantilever) is changed by the additional of mass of the captured analytes. Electrochemical transducers exploit analyte capturing to change the electrochemical characteristics of electrode-electrolyte systems. Optical transducers in biosensors either create or selectively absorb certain wavelength of light based on the captured analytes.

In the next sections, we explore the feasibility of implementing the aforementioned types of transducers in CMOS and what kind of limitations or advantages they introduce.

## III. CMOS Fabrication Process

### *A. Anatomy of the CMOS Integrated Systems.*

Complimentary metal-oxide-semiconductor (CMOS) is a semiconductor fabrication technology used predominantly in microprocessors, microcontrollers, static RAM, and other digital logic circuits. CMOS technology is also used for a wide variety of analog circuits such as image sensors, data converters, and highly integrated transceivers for many types of communication systems [15-16].

The important characteristics of CMOS processes, which distinguish them from other integrated circuit (IC) fabrication processes such as Bipolar or BiCMOS is the structure of their active devices (i.e., transistors). The available active devices in CMOS are p-type and n-type metal oxide semiconductor field effect transistors (MOSFET). These devices are fabricated on the surface a planar of a crystalline semiconductor (typically silicon) substrate.

The phrase "metal–oxide–semiconductor" describes the physical structure of the transistors. The MOSFET transistors have a gate electrode (hence the term “metal”) placed on top of an oxide insulator, which is positioned on top of a

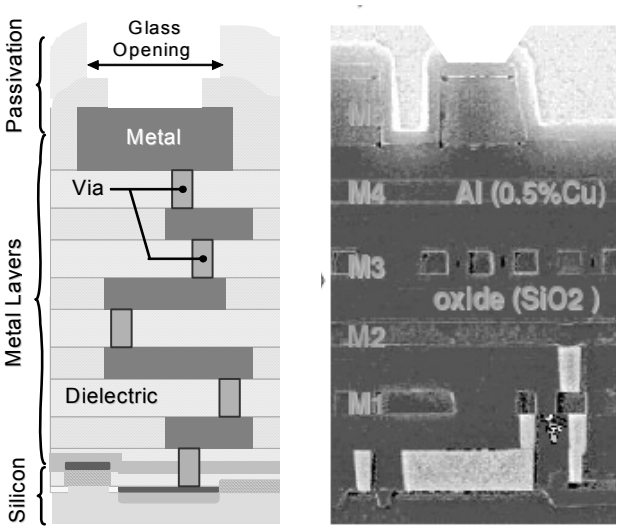


Fig. 3 The cross-section of a CMOS process, where the active MOSFET transistors are built on the surface of the crystalline semiconductor substrate, and the planar metal interconnect layers are fabricated on top of the active layers.

semiconductor material. The state-of-the-art MOSFET transistors today can have extremely small dimensions and commercially available processes have gate dimensions of as small as 45nm. In Fig. 3, we have illustrated the cross-section of a typical CMOS process. In order to electrically access the transistors and create a certain circuit topology, multiple interconnect metal layers are also fabricated in this process. These planar metal layers can be connected together and to the transistors. The external access to these devices is also allowed using the top metal layer via openings in the covering passivation layer.

Silicon MOSFET transistors do not have the best noise and speed performances compared to active devices built in alternative processes. However, they have extremely low static power consumption and their fabrication process is the most cost-efficient with the highest level of integration. Accordingly, CMOS process is the ideal fabrication process for low-cost, low-power, and highly integrated electronic systems.

### *B. Transducers in CMOS*

To implement biosensor systems in CMOS, we need to first identify which components of a typical biosensor system can be fabricated using the process. Clearly, the interface circuitry, data converters and all DSP blocks are all electronic circuits that can be integrated in CMOS. Building transducers in CMOS processes, on the other hand, does not have the same degree of flexibility as electronic circuits do. The main reason is that CMOS is primarily optimized to be used for digital circuits and not necessarily sensors. Nonetheless, we can build transducers in CMOS and use them to design high-performance sensors. In the following sub-section, we will discuss a number

of the transducer structures which might be relevant in biosensor systems.

*Electrochemical or electro-analytical transducers* [12] are perhaps the most compatible transducer structure with CMOS processes. Electrochemical transducers consist of electrodes where electrons are charge carriers and electrolyte where ions are charge carriers. Electrochemical transducers essentially extract information from the electrical characteristics of the electrode-electrolyte systems. Some of these characteristics are potential, current, impedance, and I-V curves. The detection of low-level current, impedance, and voltage used in electrochemical transducers in CMOS is a very well-understood area in analog circuit design. The primary challenge to create such systems is to connect the electrode to the chip, inevitably through pads and top of the CMOS process.

The major challenge for creating electrochemical biosensors is the lack of a proper electrode in CMOS processes. The only metal available in CMOS, which can be exposed to potential electrolytes, as shown in Fig.3, is the top metal layer [17-18]. The top metal layer in CMOS ICs is made of Aluminum which includes certain impurities. Aluminum can in fact be used as an electrode, however it is not as widely used and robust as gold, platinum, titanium, or Ag/AgCl. This is the main limitation of CMOS for electrochemical analysis. One of the solutions that have been proposed and implemented is to use post-fabrication processes to create an more robust and versatile electrode on top of the top layer metal, or use electrode structure which do not use direct exposure of electrolyte to the electrode.

The other limitation that CMOS introduces in electro-analytical systems is the voltage limitation of CMOS ICs. Although many electro-analytical systems (e.g., electrophoresis) require 100s to 1000s of volts for proper operation, CMOS processes can generate only at maximum tens of volts.

*Optical transducers* in CMOS are limited by silicon substrate in which devices are fabricated. Silicon is suitable for high-performance visible-range (i.e., 400-800nm wavelength range) detectors. Silicon photodiodes and photogates used in CMOS and CCD image sensors respectively are examples of the silicon-based topical transducers [15, 19]. Photons in the IR and UV range cannot be effectively detected using CMOS ICs since silicon is transparent in IR wavelengths while having a very small penetration depth in the UV range. Consequently, CMOS is most applicable in biosensors which create visible range photons.

Many of the biosensors systems utilize fluorescent reporters which have emission spectra in the visible range but also require optical excitation [14]. Unfortunately, silicon is an indirect bandgap semiconductor and hence it is a very inefficient light source. It is not practical to use CMOS to build an entire fluorescence-based biosensor because the impracticality of integrating the excitation source in CMOS. Moreover, CMOS transducers do not have the wavelength selectivity required for fluorescence spectroscopy, in particular the stringent requirement the excitation blocking filter.

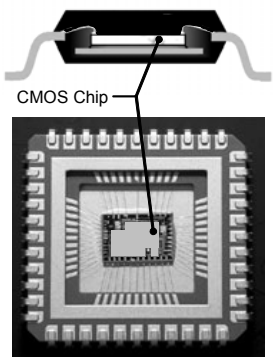


Fig. 4. Typical CMOS IC packaging method where the chip is electrically connected to the package pins using bond wires.

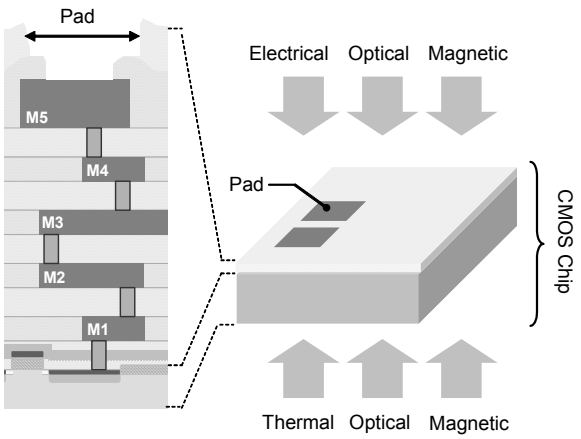


Fig. 5. CMOS transducers can sense different signals applied from top and bottom of the chip.

*Magnetic transducers* are not widely used in detection, but they are used extensively in biosensor sample preparation processes. Generally speaking, magnetic sensors and actuators can be built in CMOS processes using different devices. The Hall effect sensors in silicon substrates of CMOS can be used to detect both DC and time-varying magnetic fields [20]. In addition, integrated spiral indictors can be fabricated in standard CMOS to both create detect time-varying magnetic fields.

*Thermal transducers* or temperature sensors are also available in CMOS processes. Most of these active and passive devices have temperature-dependency characteristics which can be exploited to measure temperature [21].

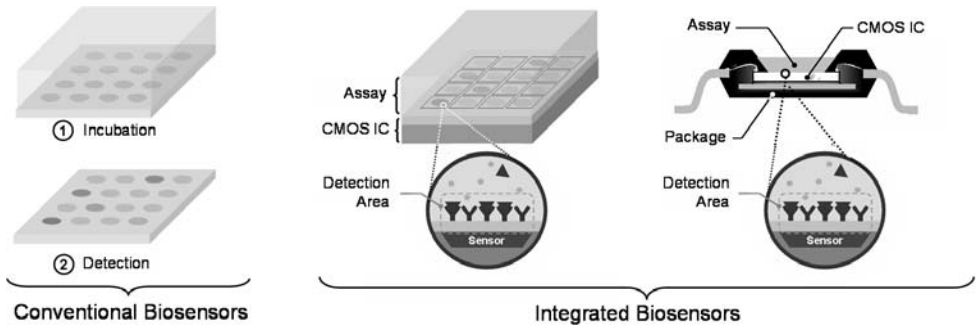


Fig. 6. Conventional biosensor vs. integrated biosensor.

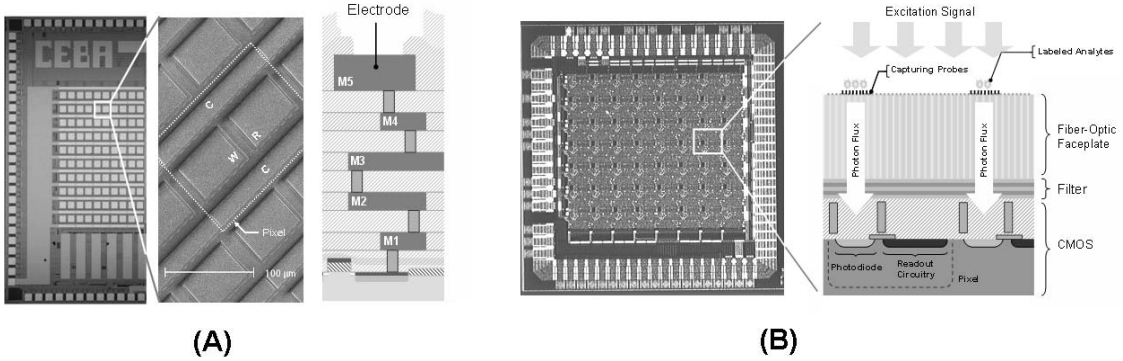


Fig. 7. (A) Electrochemical integrated biosensor array and (B) fluorescence-based biosensor array.

*Mechanical transducers* although popular can not be fabricated using standard CMOS processes. CMOS processes, unlike many MEMS processes, offer no component or device which can move or respond to mechanical motion.

### C. *Interface and Packaging*

Designing CMOS ICs as biosensors (or part of it) has to be carried out in view of the IC packaging. In particular, we need to examine the means by which we can interface the signal from the biosensor assay to the integrated transducers. In Fig. 4, we have illustrated a standard IC package where the CMOS IC chip is electrically connected to the pins of the package. Although CMOS ICs are built to interface electrically, it is still possible to interface them to certain non-electrical signals. This alternative "coupling" approaches can be used in biosensors where non-electrical signals need to be detected.

Generally speaking, signals can be coupled into the CMOS ICs either from the top of the chip where the passivation layer, glass opening and pads exist, or from bottom and through the substrate. Fig. 5 illustrates a CMOS chip and the directions that the signals can reach the integrated transducers. Electrical signals can only couple from the top and through pads, while optical signals (in the visible range) can reach the transducers from both sides. It is imperative to understand that although silicon oxide and the passivation layers are transparent in the visible range, silicon is not. Accordingly, when light is coupled from bottom, we need to ensure that the silicon substrate thickness is reduced enough using post-fabrication processes such that light reaches the integrated photodiode or photogate structures efficiently. Thermal signals or temperature gradients couple faster and more efficiently from the bottom to the CMOS temperature sensors. This is because of the high thermal conductivity of silicon (bottom) compared to silicon oxide and other dielectric materials (top) used in metal layers. Magnetic fields can be applied from top or bottom.

## IV. INTEGRATED BIOSENSORS

Integrated biosensors in CMOS are sensors which use CMOS fabrication processes to detect analytes using affinity-based techniques. In contrast to conventional biosensor systems where incubation and detection are carried out separately, integrated biosensors detect binding in real-time. One popular design for integrated biosensors is illustrated in Fig. 6 where the surface of the CMOS chip is used as the solid substrate required for affinity-based detection. In this architecture, the detectors are integrated using CMOS and each capturing spot can have its own dedicated transducer and read out circuitry. The aqueous biological sample is also isolated from the I/O pads located at the periphery of the CMOS IC chip. In such a system, depending on the sensor size, available silicon area and CMOS process used, the data converters and signal processing blocks can also be integrated. The choice of integration ultimately is a function of system cost and performance requirements.

Recently different CMOS integrated biosensors system using similar architecture has been reported using various transducers

TABLE I
CHALLENGES FOR CMOS BIOSENSORS

| Transduction | Detection Method | Integrated Transducers | Sensor Challenge | Limitations in CMOS |
|---|---|---|---|---|
| Electrochemical | Amperometry | Electrode/Electrolyte | LF* pA-nA range current measurement | Proper electrode fabrication<br>Capturing probe immobilization |
| | Potentiometry | Electrode/Electrolyte | LF 1-100μV range voltage measurement | Proper electrode fabrication<br>Capturing probe immobilization |
| | Cyclic Voltammetry | Electrode/Electrolyte | LF I-V curve measurement | Proper electrode fabrication<br>Capturing probe immobilization |
| | Impedance Spectroscopy | Electrode/Electrolyte | LF impedance measurements | Proper electrode fabrication<br>Capturing probe immobilization |
| Optical | Bioluminescence | Photodiode | LF 1fA-10pA range photocurrent measurement | None |
| | Fluorescence Spectroscopy | Photodiode | LF 1fA-10pA photocurrent measurement in presence of 100pA range background | Excitation source<br>Emission filter |
| | Infra-Red Spectroscopy | NA | LF 1fA-10pA current measurement in presence of 100pA range background | Transducer |
| Magnetic | Magnetic Particle Labels | Spiral Inductors<br>Hall- Effect Devices | 10nA-10μA current measurement<br>1-100pH range inductance measurement | None |

*LF: Low frequency

[16,18-20]. In Fig. 7, we show two CMOS integrated biosensors as examples. In Fig. 7a, electrochemical transducers are implemented for microarray applications using the available top metal layer of the CMOS process. In Fig. 7b, an integrated fluorescent biosensor is shown where the photodetectors are fabricated using standard CMOS, while the excitation blocking filter and fiber optical faceplate (FOF) are added to the system using post fabrication processes.

Independent of the transduction method used in integrated biosensors, one challenge is always to properly immobilize capturing probes on the surface to create the capturing spots. This step might become extremely challenging and show a huge degree of variability when using non-conventional substrates such as Al, Si3N4, or poly-silicon.

In Table I, we have summarized the design of biosensors in CMOS processes based on their transduction method. We also have included their limitation and detection challenges.

## V. CONCLUSION

CMOS processes are the most widely used semiconductor fabrication process which offers the highest degree of integration and cost-efficiency. Recently, there has been a trend implementing CMOS as the "backbone" fabrication method for integrated biomedical systems, particularly biosensors. Although CMOS is optimized for digital electronics, it still can be used to realize transducers, readout circuitry, and signal processing blocks required for biosensor systems. The challenges are essentially the interface design which couples the assay to the IC chip which may require additional post-fabrication processes.

## REFERENCES


[1] E.A.H. Hall, *Biosensors*, Prentice-Hall, Englewood Cliffs, NJ, 1991.

[2] H.C. Berg, *Random Walks in Biology*, Princeton University Press, New Jersey, 1993.

[3] N. Levine, *Quantum Chemistry*, 5th ed. Prentice-Hall, New York, 1999.

[4] N.G. Van Kampen, *Stochastic Processes in Physics and Chemistry*, North-Holland, Amsterdam, 1981.

[5] M. Schena, *Microarray Analysis*, Wiley, New York, 2003.

[6] M. Schena, *Protein Microarrays*, Johns and Bartlett, Sudbury, MA, 2003.

[7] A. Hassibi, S. Zahedi, R. Navid, R.W. Dutton, and T.H. Lee, "Biological Shot-Noise and Quantum-Limited Signal-to-Noise Ratio in Affinity-Based Biosensors", *J. Appl. Phys*. 97, 084701, 2005.

[8] A. Hassibi, H. Vikalo, and A. Hajimiri, "On Noise Processes and Limits of Performances of Biosensors," *J. Appl. Phys*. 102, 014909, 2007.

[9] O. Geschke, H. Klank, and P. Telleman, eds.: *Microsystem Engineering of Lab-on-a-chip Devices*, 1st ed., Wiley, New York, 2004.

[10] G.T.A. Kovacs, *Micromachined Transducers*, McGraw-Hill, New York, 1998.

[11] A.J. Bard and L.R. Faulkner, *Electrochemical Methods: Fundamentals and Applications*, 2nd ed., Wiley, New York, 2001.

[12] J. Wang, Analytical Electrochemistry, 2nd ed., Wiley, New York, 2000.

[13] C.A. Savran, S.M. Knudson, A.D. Ellington, and S.R. Manalis, "Micromechanical Detection of Proteins Using Aptamer-Based Receptor Molecules," *Anal. Chem*., 76(11), 3194-3198, 2004.

[14] R. Lacowicz, *Principles of Fluorescence Spectroscopy*, 2nd ed. Plenum, New York, 1999.

[15] J.D. Plummer, M.D. Deal, and P.B. Griffin, *Silicon VLSI Technology: Fundamentals, Practice, and Modeling*, Prentice-Hall, Englewood Cliffs, NJ, 2000.

[16] A. El Gamal and H. Eltoukhy, "CMOS Image Sensors" *IEEE Circuits and Devices Magazine*, 21(3), 2005.

[17] M. Schienle, *et al*., "A Fully Electronic DNA Sensor with 128 Positions and in-Pixel A/D Conversion," *J. Solid-State Circuits*, 39(12), 2004.

[18] A. Hassibi, and T.H. Lee, "A Programmable 0.18μm CMOS Electrochemical Sensor Microarray for Biomolecular Detection", *IEEE Sensors Journal*, 6(6), 2006.

[19] H. Eltoukhy, K. Salama and A. El Gamal, "A 0.18um CMOS $10^{-6}$lux Bioluminescence Detection System-on-Chip," *J. Solid State Circuits*, 41(3), 2006.

[20] T.S. Aytur *et al*., "An Immunoassay Platform Based on CMOS Hall Sensors", *Digest Solid-State Sensors and Actuators Workshop*, 2001.

[21] M. Pertijis K. Makinwa and J. Huijsing, "A CMOS Temperature Sensor with a 3σ Inaccuracy of ±0.1°C from –55°C to 125°C," *Digest ISSCC*, 2005.