Nano-optical CMOS Systems for Bio-molecular Sensing: In-vitro and In-vivo

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Abstract: In this paper, I will highlight approaches towards enabling CMOS-based integrated nano-optical sensing systems that are wireless connected, of millimeter-scale and capable of allowing multiplexed bio-molecular sensing platforms in in-vitro and in-vivo settings.

OCIS codes: 170.0170, 130.0130,250.0250, 280.0280

1. Introduction

CMOS-based integrated systems have revolutionized computing and communication due to its ability to integrate complex systems at scale, high yield, low-cost and low power [1]- [5]. Translating some of these properties into health diagnostics can transform personalized medicine, but interfacing with biology needs a co-design approach that cuts across the entire stack from sample preparation, handling, bio-chemistry to interface and sensor design, circuits and architecture, signal processing and algorithms. In this paper, we demonstrate such a path towards enabling a network of massively multiplexed CMOS-based biosensing platforms that are of millimeter-scale and can enable sub-pM sensitivity while consuming mW levels of power for both in-vitro and in-vivo sensing.

We will particularly focus on fluorescence-based bio-molecular sensing since it is the most widely used labeling method for a wide range of bio-molecular assays including nucleic acids, immunoassays, and small molecules. The paper will demonstrate that integrated nano-optical structures in CMOS that are co-designed with the detection electronics and signal processing can completely eliminate classical bulky, optical based elements that dominate such fluorescence sensing systems, thereby miniaturizing them to millimeter-scale sensors [6, 7]. We will illustrate techniques to integrate multi-functional nanoplasmonic elements in an industry standard CMOS process that allows scattering and angle-independent filtering of fluorescence-tagged bio-molecules on the surface of the chip. With integrated 96-sensors in the chip, we show for the first time fully external optics-free CMOS-based fluorescence sensing chips in 65 nm CMOS process with 100fM sensitivity for DNAs and pM levels of sensitivity for proteins, comparable to if not better than commercial reader and ELISA systems [8]- [10].

Taking this forward, we integrate a low power integrated RF transceiver for bidirectional communicating inside the chip and package the system in a pill for quasi-real time in-vivo sensing [11]. This co-design of electronics and photonics in a silicon IC platform with integrated sensing, wireless and signal processing (and potentially AI) hardware can have transformative impact on future optical sensing and imaging systems.

2. In-vitro Sensing: Millimeter-scale and Multiplexed Optics-free CMOS Fluorescence Sensors with Integrated Nano-optical Processing

The multiplexed biosensor encompasses 96-sensors (including photodetection, low-noise analog read-out circuitry, and digital serial readouts) and integrated nano-waveguide based filters that operate in the visible and near-IR realized with the embedded copper-based metal interconnect layers in the chip (Fig. 1a). A disposable glass interfaces with the sensor. The interface can be printed with capture probes for sandwich assays for proteins and DNAs. We incorporate a packaged LED that excites the assay, where both the incident field (405 nm) and the fluorescence field (780 nm) (from the quantum-dot based fluorescence labeled biomolecules on the chip surface) interact with the copper-based 100 nm wide and 1.4 m tall nano-waveguide array. The filtering exploits coupled surface-plasmon polariton mode (first time demonstrated in CMOS) to allow angle and scattering insensitive filtering by more than 50 dB. This allows the entire system ($\sim$ 0.1 cc) to achieve sensitivity levels of 100 fM for DNAs and 5 pM for proteins [8, 9].

3. In-vivo Sensing: Bio-molecular Sensor Pills with Wireless Connectivity

With the system small enough to fit inside a pill, we integrate a low-power radio-frequency transceiver into the chip to allow for ingestible pill based diagnostics that can relay quasi- real time information to an external base station. As shown in Fig. 2, we demonstrated a fully packaged biosensor system ($\sim$ 1.2 cm $\times$ 2.5 cm) with antennas, CMOS IC that consumes only 196 μW of DC power and reception energy efficiency of 28 pJ/bit at 7

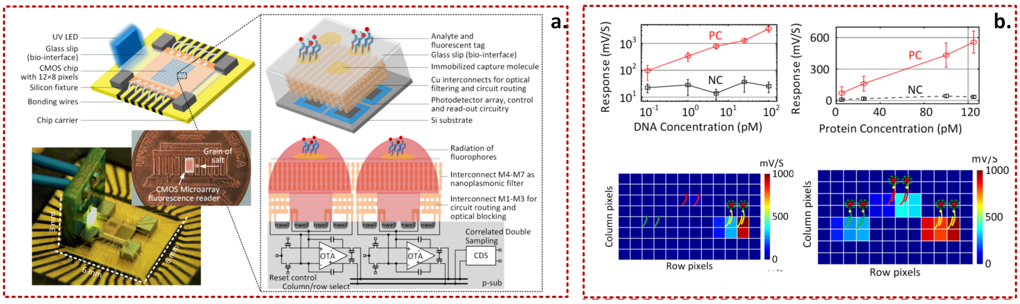

Fig. 1. In-vitro sensing: CMOS-based 96-sensor, optics-free biosensor platform **a.** CMOS chip with a disposable bio-interface. **b.** Measured DNA and protein sensitivity [8, 9].

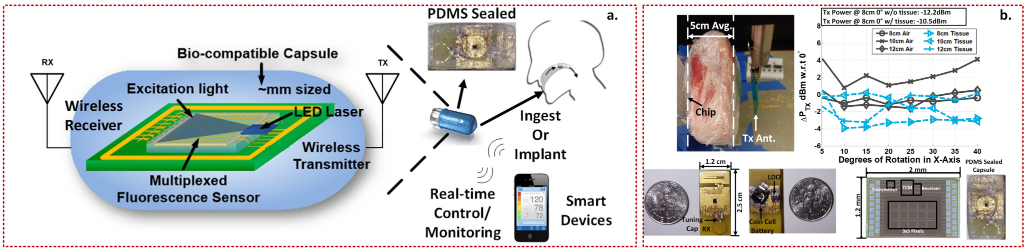

Fig. 2. In-vivo sensing. **a.** Ingestible 15-pixel sensor with integrated wireless connectivity. **b.** Measured transmission through tissue for bidirectional communication in an in-vivo setting [11].

Mbps at 430 MHz. We demonstrate transmission capabilities through inches of tissue showing the path towards enabling in-vivo sensing for a wide range of applications such as for intestinal monitoring, gut microbiome etc. Such a bio-to-optics-to-electronics co-design methodology can create a new class of connected bio-sensors for future personalized and preventive healthcare.

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