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A CMOS active pixel sensor based DNA micro-array with nano-metallic particles detection protocol

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Abstract

A DNA micro-array (DMA) for DNA detection is reported. The DMA combines a standard CMOS active pixel image sensor with a DNA detection protocol utilizing the binding of DNA targets and probes functionalized with gold nano-particles that can modify the opaqueness at the detection site. The DMA has been fabricated using a 0.5 μm CMOS process together with on-chip timing control and correlated double sampling. Experimental results show that the system can detect DNA samples with extremely low concentration down to 10 pM using ordinary light source.

Keywords: CMOS compatible; Adjustable dynamic range; High sensitivity

1. Introduction

Biochip fabricated with micro-electronic technology has become a new powerful tool in molecular biology. In particular, high-density deoxyribonucleic acid (DNA) micro-array can significantly reduce cost and time to perform complicated clinical diagnosis like DNA mutations responsible for some genetic diseases (such as cancers) and DNA sequence analysis for virus detection [1–5]. Currently, the most well developed DNA detection methodology is based on the modification of DNA sample with fluorescent labels so that DNA matched with a particular probe immobilized at a specific location of a solid support (e.g., glass slides) can be identified by the optical emission from the fluorescence label [6,7]. This method requires some expensive optical instruments to excite the fluorescent labels (such as laser or UV light sources) and to capture the output of the fluorescence (such as fluorescent microscope or array scanner with CCD camera). In addition, the signal intensity of the fluorescence quenches with time, which makes the experimental result depend on the transient response of the label [8]. Some efforts to combine fluorescence-based DNA detection with CCD camera have been reported [9], but the need of specialized excitation UV light source and color filter results in complication of the surface chemistry between the DNA material and the array.

Besides fluorescent label, nano-metallic particle can also be used as labels. Compared with the fluorescence-based detection method, nano-particle based DNA detection method has the advantages of: (1) physical property (such as conductivity and opacity) is easier to be electronically detected; (2) signal is stable with time; (3) no external excitation needed. These three advantages lead to more consistent experimental results. Previous work using the conducting property of the metal particle has been proposed but it requires modifications to the CMOS process

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to include inert metal (such as gold or platinum) and different surface passivation techniques, making it more difficult to be fabricated in ordinary IC foundries [10].

In this work, we have developed a DNA micro-array based on CMOS active pixel sensor (APS) together with the nano-metallic particle detection protocol. The DMA is fully compatible with the standard CMOS process and has been fabricated using a standard 0.5 μm CMOS technology. The experimental result is reported in this paper.

2. Chip design and fabrication

The fabricated DMA is composed of active pixel sensors (APS). Each pixel consists of a photodiode for sensing and active pixel sensor for readout. Its schematic together with a cross-section of a detection cell is shown in Fig. 1. The active pixel sensor is in a traditional 3-transistor structure. The DNA probes are attached on the surface of the detection cell. The photodiode is formed with an n+ diffusion and p− structure. A metal layer is used to create an optical window and guard ring to prevent any crosstalk from the neighboring pixels. The cell size is $15 \times 20\ \mu m^2$ with a fill factor of 50%. Furthermore, due to the elimination of direct contact of the metal layer to the biomaterial, we do not need to introduce the inert metal material as in our previous work [10]. This makes the DMA fully CMOS compatible and can be fabricated in any CMOS foundry. Unlike fluorescent detection, the nano-particle detection protocol does not require exciting light filtering and thus no on-chip filter is required. It allows the use of the chip surface as a direct solid support for the DNA hybridization.

3. Experimental procedures

The post-fabrication experiment composed of two parts: (1) surface treatment of the chip to attach DNA probes for detection; and (2) applying the sample DNA for detection. It is illustrated in Fig. 2 and described below in detail.

3.1. Surface treatment for DNA detection

The top SiO_2 passivation layer of the chip is modified by mercaptopropyltrimethoxysilane (MPTS) to form covalent bonding with the DNA probes [11]. The MPTS serves as a molecular bridge layer to chemically connect DNA to silicon dioxide layer.

The methoxyl groups on one end of the MPTS molecule can react with SiOH groups on the SiO_2 surface. On the other end, the thiol group could react with another thiol group, which was chemically labeled on the five-terminal of DNA probes. Different kinds of DNA probes with known sequences and 16mer selected thiol-modified oligonucleotides are attached to the chip surface by a pin spotter machine, micro-printing system (MicroSysTM 5100). Each spot size has a diameter of 100 μm and covers around 20 pixels to provide redundancy and reduce error reading. Some dummy rows/columns are left uncovered for background subtraction and dynamic range adjustment. Fig. 2(b) illustrates the condition of the chip after immobilizing the DNA probes. The chips are ready to be used for DNA detection.

3.2. DNA detection process

The application of sample to the DMA is done by two hybridizations and one silver enhancement steps as shown in Fig. 2(c–e). In the first hybridization step, target DNA with special added tails is applied to the DMA in solution form by pipetting. The sample DNA that matches one of the immobilized probes is captured, while those mismatched DNA targets will be washed away. In the second hybridization step, the DMA is treated with a solution of

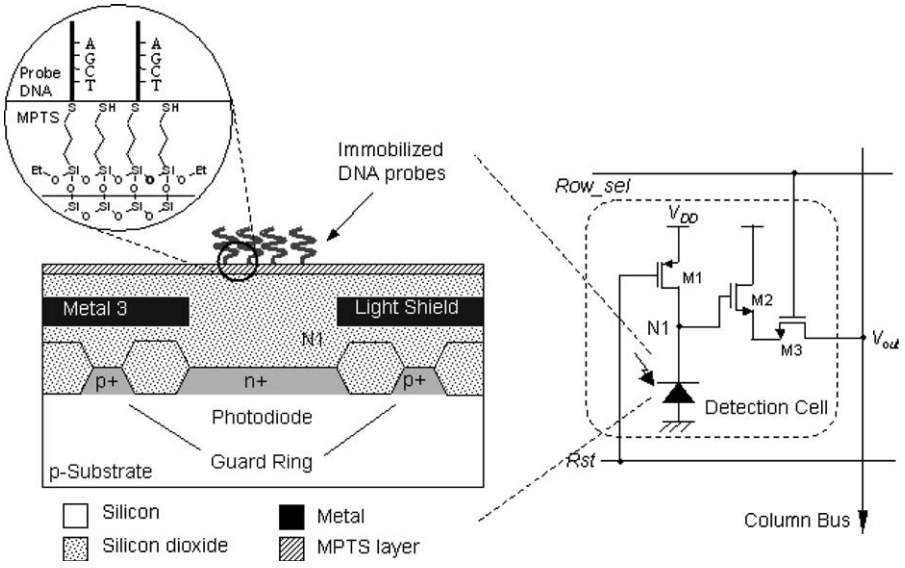

Fig. 1. The APS structure used for DNA detection.