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Integrated CMOS optical sensor for cell detection and analysis

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ABSTRACT

To circumvent the complexity of the detection systems of microfluidic devices, Hartley et al. recently reported on a CMOS optical active pixel sensor (APS) for near-field detection and counting of microscopic particles. To further enhance the digital cytometric capabilities of the original sensor, we modified and utilized a dual APS-array scheme to facilitate the determination of the velocity and size of particles flowing in microfluidic channels. Our findings indicate that the prototype dual-APS sensor is capable of detecting particle velocities up to ~500 μm/s and particles with diameter in the range of 5–15 μm. The dual APS CMOS sensor, as a result of the hybrid integration with a microfluidic, provides a low cost and practical means of noninvasively monitoring the contents of microfluidic and lab-on-a-chip devices.

1. Introduction

Flow cytometers are routinely utilized for analyzing the physical and chemical properties of biological cells or particles of interest and furthermore capable of separating/sorting cells of interest, carrying a desired phenotype from a heterogeneous population of cell. To facilitate selective detection, biological cells are tagged with fluorescent labels and transported in fluidic channel under conditions of laminar flow where the cell sample stream is focused and supported by a sheath flow. The hydrodynamic focusing aligns the single stream of cells to the center of a laser beam illumination and both the scattered and fluorescence light emitted by the tagged cells is collected by an optical detection system through a series of optical filters, and subsequently analyzed to characterize the cell population.

Conventional flow cytometers require a high amount of reagent for analysis and furthermore are both bulky and expensive and require trained personnel for operation and maintenance. Therefore, there is a significant demand for developing miniaturized flow cytometers, which also offer high throughput performance in sorting cells and especially to support the development and application of lab-on-a-chip technologies for bioanalysis.

Recent advancement in microfluidic has partially solved this problem by enabling new alternative to the conventional procedure of performing cytometry. Microfabricated flow cytometers fabricated in silicon (and polymer) [1–7] or glass [8–15] substrates only require a few micro liters of reagent for sorting and analysis. Hence, replacing large flow chamber of conventional flow cytometers has enabled the development of lower cost and miniaturized cytometers.

Utilizing microfluidics, the fluidic systems in these micro flow cytometers have been miniaturized, however, many of the optical components, such as laser source, photomultiplier (PMT) detector and optical filters and electronics required for light scattering/fluorescence detection and data analysis reside off-chip as in conventional bench-top systems.

Continuous research effort and progress has been made in recent years to circumvent the complexity of the detection systems of microfluidic devices. In some cases, optical fibers or waveguides have been incorporated inside the microfluidic chip to transmit optical signal from the light source to the microfluidic channel or from the microfluidic channel to the photo detector [3–4,7–10,16]. The utilization of waveguides has minimized the complexity of the detection system by circumventing the need of optical lenses and filters required to confine or collect the light beam. Miniaturized light sources such as LEDs, laser diodes, or dye lasers can also be fabricated within the microfluidic chip [3,10–12,17]. In addition a few research groups have demonstrated the fabrication or integration of miniaturized photo detectors such as PIN photodiodes or CMOS sensors within the microfluidic chip [2,3,10,11,13–15]. The aim of all these research efforts has been to maximize the mobility and minimize the complexity and cost of the overall system. Furthermore, along with the miniaturization of the detection system, the capabilities of the cytometer have been enhanced further by real-time analysis of the detection signal [3,8,14,15].

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In this regard, Hartley et al. [15] have developed a CMOS optical active pixel sensor (APS) with a glass microfluidic chip capable of detecting and counting microscopic particles. This miniaturized sensor was directly coupled to the microfluidic chip utilizing a flip-chip bonding technique, which enabled the near-field detection of microscopic particles and consequently eliminated the need of optical filters and waveguides. The CMOS optical sensor benefits from a linear array of sixteen active pixel sensors (APSs) and as the particles pass over it, the detected signal from the output of the sensor is analyzed in real-time by an embedded control system enabling the count of particles.

This paper demonstrates the redesign of the CMOS sensor to further enhance the cytometric application of the sensor by replacing the original single-APS-array with a dual-APS-array scheme. This dual-APS-array arrangement facilitates quantification of the velocity and size measurement of particles in addition to digital counting capabilities of the original sensor. Furthermore, this paper outlines the fabrication process of the microfluidic chip and the methodology adopted to integrate the CMOS sensor to the microfluidic chip. Finally, the capabilities of this device are demonstrated by detecting and categorizing microscopic sized polystyrene polyspheres based on their size.

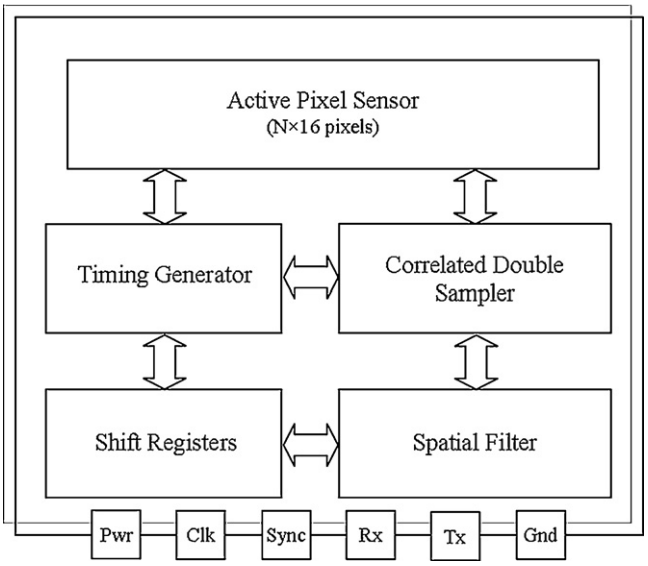

Fig. 1. Schematic block diagram of CMOS APS sensor.

2. The CMOS optical active pixel sensor

The principle electro-optical components of the mixed-signal, 0.18 μm CMOS optical sensor are shown in Fig. 1. The optically sensitive front end of the CMOS sensor consists of a matrix of $N \times 16$ APS. As shown in the design diagram, the number of arrays (N) can be optimally chosen and depends on different cytometric applications, which will be further discussed later in this section.

The APS operates at a reset-integrate-sample mode. Each mode begins with insertion of associated signal which is generated by the Timing Generator unit. During the integration period, the optical illumination is detected by the photodiode pixels of the APSs.

The circuit schematic diagram of the active pixel sensor, implemented in this design is shown in Fig. 2(a). At the beginning of each sensor integration period, the photodiode pixel is reversed biased through the pMOS transistor (*Mrst*). During the integration period, the light falling on photodiode pixels discharges and proportionally changes the voltage of photodiode pixels.

The CDS block, as shown in Fig. 2(b), is designed to minimize the noise and eliminate DC offset of the downstream signals of the APS block. At the beginning of the integration period, *srst* signal is asserted and the output voltage (*Vrst*) of APS is transferred and stored on the capacitor *Crst*. At the end of the integration period, *ssig* signal is asserted and the output (*Vsig*) of APS is similarly stored on the capacitor *Csig*. Finally, when *en* signal is asserted, *Vsig* is subtracted from *Vrst*, and the result of this operation is transferred to the input of a unity gain buffer.

The Spatial Filter (SF), shown in Fig. 3, processes the output of the each-pixel's CDS circuit and determines the binary comparison of each-pixel's value against the average of all sixteen pixels'

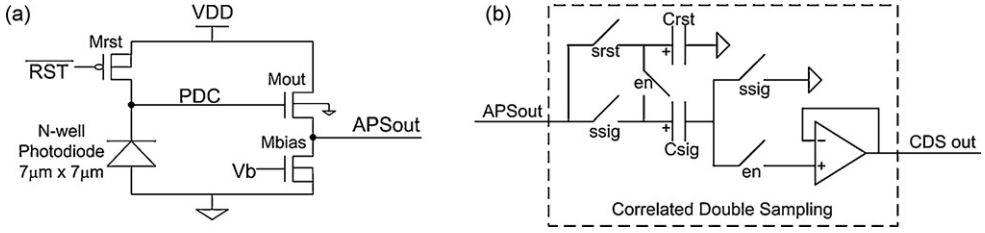

Fig. 2. (a) Circuit schematic of active pixel sensor topology and (b) correlated double sampling circuit. Reproduced from Hartley et al. [15] (Copyright 2007 IEEE).

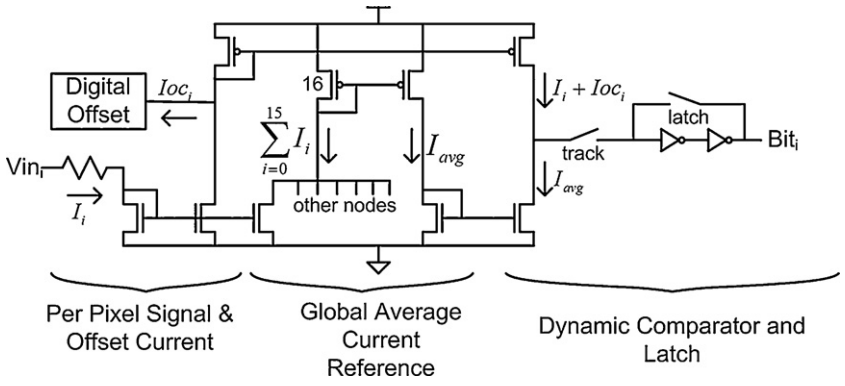

Fig. 3. Schematic diagram of SF and digital block performing serialization of the SF's outputs. Reproduced from Hartley et al. [15] (Copyright 2007 IEEE).