

## ULTRAFAST SINGLE-PHOTON IMAGE DIAGNOSTICS SENSORS WITH APD ARRAYS FOR INDUSTRIAL AND BIO APPLICATIONS

EDOARDO CHARBON<sup>1,2</sup> AND SILVANO DONATI<sup>3</sup>

<sup>1</sup> *Quantum Architecture Group (AQUA), EPFL, 1015 Lausanne, Switzerland*

[edoardo.charbon@epfl.ch](mailto:edoardo.charbon@epfl.ch)

<sup>2</sup> *Circuits and Systems Group, TU Delft, 2600 AA Delft, The Netherlands*

<sup>3</sup> *Dipartimento di Elettronica, Università di Pavia, 27100 Pavia, Italy*

[silvano.donati@unipv.it](mailto:silvano.donati@unipv.it)

We review recent advances in the field of ultrafast imagers with single-photon detection capability. These sensors in general are capable of photon counting and time-of-arrival analysis, thus enabling an increasingly broad range of diagnostics techniques. The current trend is to migrate the designs to increasingly smaller feature sizes and to push integration to new highs, so as to enable placing more functionality and more processing at the pixel level. Examples of these new trends are given in the context of industrial and bio applications.

### 1. INTRODUCTION

In recent years, there has been increasing activity in the acceleration of acquisition and readout speed in imaging technology [1]. Among the reasons for this trend, there has been the creation of new biomedical and/or improved diagnostics techniques based on optical imaging. The emergence of more powerful and faster light sources has only accelerated this trend and placed an increasing burden on conventional image sensors.

Image sensors capable of one million frames-per-second (fps) in bursts of over 100 subsequent frames have been proposed for charge-coupled devices (CCDs) [2],[3]. CMOS active pixel sensor (APS) chips have achieved over 10,000fps in continuous mode in sub-megapixel format and more recently up to 100Mfps but only on small line sensors [4].

Time-correlated imaging has become one of the most influential techniques currently available to scientists and doctors for research and diagnostics purposes. In order to take advantage of the potential of this technique at its best, it is necessary to detect photons in small quantities and at high time correlations, typically of the order of tens or hundreds of picoseconds. Thus, image sensors for time-resolved applications should in principle exceed 10Gfps. To our knowledge, imagers with this speed, especially in continuous mode, do not exist and are not likely to be developed in the next few years.

As an alternative, scientists have developed sensors capable of detecting the arrival of single or multiple photons with picosecond resolution within a longer frame of perhaps a few tens of microseconds. There exist many non-solid-state implementations of such sensors, most notably photomultiplier tubes (PMTs) and microchannel or multichannel plates (MCPs).

The operating principle of a PMT is well known [5]. Photoelectrons emitted by the input sensitive surface – the photocathode – are accelerated to a first dynode where they are multiplied by secondary emission. Secondary electrons become the primary of next stage and multiplication through a number of stages of the dynode chain allows the gain go up to  $10^8$ , so that single detected photon gives a sizeable current spike at the anode, easily counted.

The main limitation of PMTs is their size and the high voltage required - up to a few thousand volts. In addition, they are basic single-point detector not easily partitioned to multi-point operation.

A solution to this problem is the use of a MCP, a device in which photoelectron multiplication is achieved inside a micro-channel [5], much more compact than a dynode chain and already sectioned in a large number of individual pixels. Photoelectrons emitted by the photocathode are multiplied by the MCP and then readout by a CCD used in place of a normal anode.

Unfortunately, MCPs are still not solid-state devices and require deep vacuum as well as high bias voltages. In addition, though the sensitivity to single-photons may be achieved, the speed of detection is limited by the reaction time of the phosphor screen and of the CCD. Nonetheless over the years, PMTs and MCPs have become the sensors of choice in many biomedical applications [6].

Solid-state alternatives to these sensors have been known for some time. For instance, silicon avalanche photodiodes (SiAPDs) have been studied since the 1960s [7] and have recently become a serious competitor to MCPs and PMTs. In SiAPDs, carriers generated by the absorption of a photon in the p-n junction, are multiplied by impact ionization in the lattice thus producing an avalanche. The resulting optical gain is usually in the hundreds. The main drawback of these devices however, is a relatively complex amplification scheme and/or complex ancillary electronics. In addition, specific technologies are often required. Nevertheless, these devices offer flexible, versatile, and relatively low-cost solutions to imaging where sensitivity, low noise, and high time resolution are needed.

More recently, new CMOS compatible APDs have emerged, with lower operating voltages and a high potential of integration. CMOS APDs can operate in linear or proportional mode as well as in Geiger mode. In the latter mode of operation they are known as single-photon avalanche diodes (SPADs). In a SPAD the optical gain is virtually infinite, thus it enables the detection of single photons. The time resolution is generally in excess of 100ps while the detection cycle, dominated by the dead time of the

device, is generally of the order of 10 to 100ns. Thanks to the high level of integration possible in these devices, large arrays of single-photon detectors may be built while unprecedented levels of parallelism may be achieved.

In this paper, we focus on these devices and we review some of the latest results achieved using SPADs and SPAD arrays.

## 2. SINGLE-PHOTON DETECTION IN CMOS

If biased above breakdown, a p-n junction can operate in so-called Geiger mode. In Geiger mode of operation, SPADs exhibit a virtually infinite optical gain, however a mechanism must be provided to quench the avalanche. There exist several techniques to accomplish quenching, classified in active and passive quenching. The simplest approach is the use of a ballast resistance. The avalanche current causes the diode reverse bias voltage to drop below breakdown, thus pushing the junction to linear avalanching and even pure accumulation mode. After quenching, the device requires a certain recovery time, to return to the initial state. The quenching and recovery times are collectively known as *dead time*.

SPADs have been integrated in CMOS achieving large arrays of pixels that operate independently with noise and timing resolutions comparable to those of PMTs and MCPs [8]. Current developments in more advanced CMOS technologies have demonstrated full scalability of SPAD devices, a 25 $\mu$ m pitch, and dead time as low as 32ns [9],[10],[11],[12]. The sensitivity, characterized in SPADs as photon detection probability (PDP), can exceed 25-50%. The noise, measured in SPADs as dark count rate (DCR), can be as low as a few Hertz [9]. Thanks to these properties, CMOS SPAD arrays have been proposed for imaging where speed and/or event timing accuracy are critical. Such applications range from fluorescence-based imaging, such as Förster Resonance Energy Transfer (FRET), fluorescence lifetime imaging microscopy (FLIM) [13], and fluorescence correlation spectroscopy (FCS) [14], to voltage sensitive dye (VSD) based imaging [15],[16], particle image velocimetry (PIV) [17], instantaneous gas imaging, [18],[19], etc.

Recently, the first fully integrated single-photon sensor with on-chip deep sub-nanosecond time-discriminators has appeared [20]. This sensor enabled to determine photon time-of-arrival upon detection at the chip level for the first time. The EC project MEGAFRAME has gone even further, creating a new family of SPADs implemented in 130nm CMOS technology [21]. These new devices, coupled with deep sub-nanosecond time-to-amplitude (TAC) and time-to-digital (TDC) converters, have yielded a new generation of ultrafast imagers capable of sustained speeds of 1Mfps [22],[23],[24]. These speeds could be achieved thanks to the implementation of pixel-level time discrimination and ultrafast readout schemes, capable of sustained of over 10Gb/s.

The development of architectures that support time-correlated modes with some degree of resource sharing is currently underway in many research groups. The main trade-off is at the architectural level, due to the nature of the signal

generated by SPADs. Application-specific optimal architectures are possible, provided a model of the application is built to characterize the performance of the sensor *a priori*. The sharing of resources may involve a number of pixels, say 4 or 16, or on-demand sharing based upon the reaction of SPADs may be used. Other trade-offs may include the complexity of the time discriminator itself.

## 3. APPLICATIONS

### *Fluorescence Correlation Spectroscopy*

FCS is often used to measure transitional diffusion coefficients of macromolecules, to count fluorescent transient molecules, or to determine the molecular composition of a fluid being forced through a bottleneck or a gap. In FCS a femtoliter volume, is exposed to a highly focused laser beam that causes the molecules in it to emit light in a well-defined spectrum and with a time-response that depends on the modality of the movement of the molecules to and from the detection volume. The photon time-dependent response is quantified by means of the autocorrelation function  $G(\tau)$

$$G(\tau) = \frac{\langle I(t+\tau)I(t) \rangle}{\langle I(t) \rangle^2},$$

where  $I(t)$  represents the intensity of fluorescence emission and  $\langle \rangle$  denotes time average. To be give useful results  $G(\tau)$  is generally evaluated for a total range of several microseconds [25].

The average molecular concentration  $C$  and radial diffusion time  $\tau_D$  through the illumination region may be derived from  $G(\tau)$  by fitting standard analytical models of the molecular processes involved in a given experimental setup. Such models are generally single or multi-exponential, as well as rational functions of  $C$ ,  $\tau_D$ , and of the geometry of the gap [26]. Thus, for normal gap sizes, and most molecules, sub-nanosecond time resolutions are necessary. In addition, the availability of multi-pixel sensors with simultaneous, parallel operation allows one to better characterize the diffusion processes underlying the experimental setup.

### *Lifetime imaging*

Among time-correlated imaging methods, time-correlated single photon counting (TCSPC) is perhaps one of the most used in bioimaging. Multiple exposures are employed to reconstruct the statistical response of matter to sharp and powerful light pulses. The study of calcium at the cellular level has made intensive use of fluorescent  $Ca^{2+}$  indicator dyes. Examples of heavily used dyes or fluorophores are Oregon Green Bapta-1 (OGB-1), Green Fluorescent Protein (GFP) and many others. Calcium concentration can be determined precisely by measuring the lifetime of the response of the corresponding fluorophore, when excited at a given wavelength. Lifetime is generally characterized using FLIM. There exist several flavors of FLIM based on how lifetime is characterized or based on the excitation mode.

In [27] a two-photon FLIM setup was employed based on a SPAD array capable of a time resolution of 79ps at a system level. The sensor made it possible to fit the lifetime

dependency of OGB-1 on  $\text{Ca}^{2+}$  using a triple exponential fit. Unlike previous approaches that exploit detector with lower resolutions [13], our model required no calibration factors, nor corrections of any kind, thus proving the robustness of the measurement system.

$$I_k = \frac{1}{2} \left[ \frac{1 + e^{-T/\tau_k}}{1 - e^{-T/\tau_k}} - \text{erf} \left( \frac{\sigma_{IRF}}{\sqrt{2}\tau_k} - \frac{t}{\sqrt{2}\sigma_{IRF}} \right) \right] \times \exp \left( -\frac{t}{\tau_k} + \frac{\sigma_{IRF}^2}{2\tau_k^2} \right), k = \{f, i, s\}.$$

$I_k$  represents the intensity of fluorescence emission, where  $k$  denotes the fast ‘f’, intermediate ‘i’ and slow ‘s’ components

of it. Terms  $\sigma_{IRF}^2$  and  $\tau_k$  denote the variance of the instrument response function (IRF) and the corresponding lifetime time constants, respectively.

#### Time-of-flight Imaging

Time-of-flight (TOF) is the time a light ray takes to propagate between two points in the three-dimensional space. There exist several applications requiring a precise measurement of TOF to image particular properties of targets and environments. In TOF based 3D imaging, for example, pulsed or continuously modulated light is used to determine the distance between the sensor and a reflecting target (Fig.1).

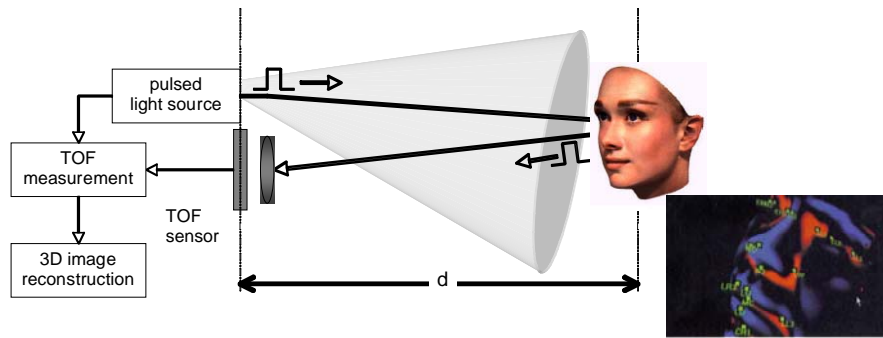


Fig. 1. Time-of-flight based imaging setup (left); resulting 3D image (right). The distance is computed in every pixel using the relation  $d = c/2 \text{ TOF}$ , where  $c$  is the speed of light. Again, for a resolution of 1mm, time resolutions of at least 6.6ps are necessary, whereas statistical methods may be used to relax the resolution of a single measurement.

In positron emission tomography, the exact location of positron emission is found by monitoring all gamma radiation reaching a pair of detectors on an axis at exactly the same time and then cross-correlate all estimated arrival times. The emission loci may be derived by measuring the TOF of the particle with respect to a reference point of known coordinates.

#### 4. CONCLUSIONS

With the introduction of CMOS single-photon avalanche diodes, it is possible today to achieve great levels of miniaturization without compromising time resolution and overall speed. Not only large arrays of photon counters are

now possible, but also very high dynamic range and timing accuracy have become feasible. Thanks to these advances, applications requiring time-resolved single photon detection are now possible using low-cost CMOS detectors. We have outlined some of these applications and we have discussed system issues related to these and novel applications in the field of bio- and medical imaging.

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