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CMOS Imaging for Biomedical Applications

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Dear Dr. Todi:

Please find attached the article titled "CMOS Imaging for Biomedical Applications" by N. Faramarzpour, M. M. El-Desouki, M.J. Deen, Q. Fang, S. Shirani and L.W.C. Liu for consideration for publication in IEEE Potentials.

We look forward to hearing from you in due course on the status of this manuscript.

Finally, if you require any further information, please contact me immediately. Kind regards.

Sincerely

Jamal Deen

Jamal Deen

CMOS Imaging for Biomedical Applications

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Abstract

Miniaturization of biomedical test and measurement equipment using commercial micro- and nanofabrication technologies offers many advantages such as low-cost, small size and hence portability and incorporation of "intelligence" in photodetector image sensing elements. However, for biomedical applications such as disease screening or detection, these image sensing systems must be capable of detecting very low-levels of emitted light from the biological samples. Currently, either chargecoupled devices (CCDs) or photomultiplier tubes (PMTs) that are expensive, consume high power or are bulky, are used. In the recent past, CMOS photodetectors and imaging systems have shown that they possess adequate performance characteristics to replace the CCDs or PMTs, thereby providing low power, portable and cheap integrated bioimaging systems. This replacement has only recently become possible by the improvements in the dynamic range and sensitivity of modern CMOS photodetectors. This work addresses some of these advanced solutions, likenovel active pixel sensors that detect ultra-low light levels, and avalanche photodiodes that are integrated in CMOS and perform single photon detection.

Index terms: Active pixel sensor, avalanche photodiode, biomedical imaging, CMOS, photodetectors.

30 October 2007

I. Introduction

Optical molecular imaging systems are used to measure and characterize chemical or biological processes on the cellular and molecular level. Such applications have a revolutionary impact on medicine, agriculture, biodefense and environmental testing through techniques such as DNA sequencing, protein detection, gene expression, cell migration and evaluation of animal models of human cancer. These techniques are even more attractive when developed in hand-held, portable devices that can be used for forensics and biohazard studies on-site. Compared with established diagnosis techniques such as x-ray, computed tomography (CT), magnetic-resonance imaging (MRI) and the gamma-camera in the case of nuclear medicine, non-invasive fluorescence imaging systems for the detection of cancers has been considered to have many advantages, such as patient safety, high spatial resolution, small size and low equipment cost.

The basis of non-invasive optical molecular detection is the imaging device. The most sensitive detection system that is currently used, employs photomultiplier tubes (PMTs), which can generate up to one billion electrons for every incident photon. However, PMTs are expensive and require high operating voltages within the range of 1000V to 2000V, thus making themunsuitable for hand -held systems. Also, PMT systems have a limited photon detection efficiency of below 4% and their bulky large size makes multiplexed imaging infeasible and hence, they are not suitable for dense arrays.

A silicon imager consists of a one- or two- dimensional array of pixels, with each pixel containing a photodetector to convert incident light into photocurrent. The array also includes decoders and multiplexers to access it, and readout circuits to convert the photocurrent into electric charge or voltage and read it out of the array.

The fraction of the area occupied by the photodetector (the photosensitive area) in a pixel, compared to the total area of the pixel, is known as the fill-factor (FF), see Fig. 1. Array sizes vary from a few tens of pixels for low-resolution sensor applications to megapixels for commercial cameras, while individual pixel sizes can be as small as $2 \ \mu m \ x \ 2 \ \mu m$. The color detection in an imager is usually done using filters that are typically deposited on top of the pixel array. Microlenses are also fabricated over the array to increase the amount of light incident on the photosensitive area of each pixel. The photodetector converts incident photon flux to photocurrent, which is then converted to an output voltage. The photocurrent is not readout directly since the current levels produced are very low, in the femto- to nano-amperes range; rather, it is integrated in a capacitance and read out as charge or voltage at the end of the integration time. The size of the integration capacitor, which is usually the

parasitic capacitance of the photodetector, determines the well capacity, which is the maximum amount of charge that can be stored, and also sets the charge-to-voltage conversion gain, which is measured in microvolts per electron.

The two most commonly used silicon image sensors are charge-coupled devices (CCDs) and CMOS imagers. CCDs, which store electric charges on a matrix of capacitors that can be serially readout from one pixel to the other through charge-transfer, are usually cooled below room temperature in order to increase their sensitivity for low-level light biomedical applications. CMOS image sensors can offer low-power and high-speed operation while offering a much higher level of integration. The advances in deep submicron CMOS technologies and integrated microlens has made CMOS image sensors a practical alternative to the long dominating charge-coupled device (CCD) imaging technology. Perhaps the main advantage of CMOS image sensors is that they are fabricated in standard CMOS technologies, which allows for full integration of the image sensor along with the analog and digital processing and control circuits on the same chip. This camera-on-chip system leads to reduction in power consumption, cost and sensor size and it also allows for integration of new sensor functionalities.

The advantages of CMOS image sensors over CCDs include lower power consumption, lower system cost, on-chip functionality leading to camera-on-chip solutions, smaller overall system size, random access of image data, selective readout (Fig. 2), higher speed imaging, and finally the capability to avoid blooming and smearing. Some of the disadvantages of CMOS image sensors compared to CCDs are lower sensitivity, lower fill-factor, lower quantum efficiency, lower dynamic-range (DR), all of which translate into the CMOS imager's lower overall image quality. Typical CMOS active-pixel-sensors (APS) have a FF of around 30% and the FF is typically limited by the interconnection metals and silicides that shadow the photosensitive area and recombination of the photo-generated carriers with majority carriers.

II. Applications

One of the most common optical imaging techniques used for scientific and medical characterization is fluorescence imaging. The word fluorescence comes from the mineral fluorite, which is composed of calcium fluoride and often exhibits this luminescence or light emission phenomenon. Fluorescence is the property of certain atoms and molecules absorbing light at a particular wavelength (ultraviolet (UV) or visible range) and emitting light at a longer wavelength (Fig. 3a), over a short interval of time known as the fluorescence lifetime. The shift in wavelength between the absorbed and the emitted waveforms is known as the Stokes shift. Immediately following

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excitation, the fluorescence intensity decays exponentially, usually over a few nanoseconds for most biological fluorophores (a fluorophore is the component of a molecule that fluoresces).

There are many applications of fluorescence in biomedicine. For example, DNA microarrays are used for studying levels of gene expression in living cells. In a micorarray experiment, the DNA fragments are tagged with fluorescent dies before being introduced to the microarray. The fragments that find their match on the surface of the microarray, get attached to the corresponding spot in a process called hybridizatin. The DNA microarray is then exposed to light, and the level of fluorescent emission from each spot determines the level of expression of the corresponding gene in the sample. Some of the spots can have extremely low levels of fluorescence emission, which need to be detected by ultra-sensitive imaging devices.

When testing molecules that have overlapping spectra, such as cancerous and non-cancerous cells, one valuable method is time-resolved measurements such as fluorescence lifetime imaging. In such measurements, time resolved techniques are used to determine the relaxation times of fluorescence signals, which is the time it takesfor the electronically excited fluorophores to relax back to their ground state. Since the signal has an exponential decay over time, integrating approaches that have integration times much longer than the average fluorescent lifetime can not be used. Rather, averaging a number of repeated measurements in narrow sampling windows or gates (Fig. 3b) have been shown to be more effective. The background can also be removed by averaging the samples of a number of measurements without excitation. Such high-frame-rate applications require a fast and sensitive CMOS imager. CMOS imagers that can achieve timing resolutions between 150-800 ps from 64×64 pixel imagers with two point per transient waveform sampling and 150 frames/s, have been reported in the literature.

III. Different pixel structures

Different pixel structures have been reported for CMOS imagers. Each pixel structure has its advantages and can be suitable for different applications. Here we will present some of the widely used CMOS pixel structures, and discuss their applicability to low-light-level applications.

III. 1: Pixels with photocurrent integration: PPS, APS and DPS

Passive pixel sensor (PPS) is the earliest and most simple CMOS pixel structure. In this structure, each pixel consists of a photodiode and a row-select transistor. Fig. 4a shows the PPS structure. During integration, the internal capacitance of the photodiode integrates the generated photocurrent. At the end of integration, rows are selected one at a time, and conneced to the column read buses.

The pixel charges are read in parallel for pixels in each row. Then, photodiodes are reset and ready for next integration cycle. PPS has only one transistor per pixel, and thus has the highest FF. However, column readout of the rather small integrated charge of the photodiodes, significantlyreduces the performance of this approach.

Active pixel sensor (APS) is the most popular CMOS pixel structure. The three transistor APS circuit is shown in Fig. 4b. In this structure the reset is done internally. The sense node is also isolated from the readout column by using a source follower. Compared to PPS, this structure has better SNR. Individual circuitry in each pixel however, increases the non-uniformity of the pixels outputs under same illumination levels (known as fixed pattern noise, FPN). A large part of FPN is due to the variation of the sense node voltage after reset, which is known as reset noise. Correlated double sampling (CDS) can be used, to remove this noise. CDS reads every pixel output twice. Once just after reset, and once just before readout. The output is then considered to be the difference between the two levels. In most of the CMOS imagers, the output data is in digital format. Analog to digital conversion is usually done in parallel for each row of data. Fig. 5 shows an example of a CMOS imager in a standard CMOS 0.18 μ m technology. The array is based on 256 APS pixels of 20 μ m × 30 μ m size with a FF of 60 %.

The most recent CMOS pixel structure is DPS, as shown in Fig. 4c. In this pixel structure, the A/D conversion of the signal is done partially inside the pixel, so that the output of the pixel is digital. DPS is a great solution for integrated and high speed digital imaging. It however has lower fill-factor, and it suffers from the inherent quantization noise due to the A/D conversion, which limits its applicability to ultra sensitive measurements.

III. 2: DC level mode APS

Active pixel sensors, in general, have an output with low signal to noise ratio for low levels of light. One way to increase the sensitivity of APS is to increase its photodiode size. This solution however, will decrease the resolution of the imager. Another solution is to lengthen the integration time of the APS. The pixel is capable of detecting lower levels of light with longer integration times. However, the rate of spatial variation of the sample can limit the applicability of this solution. Also, at high integration times, the internal dark current of the pixel may saturate it.

Fig. 6a shows the simulated sense node voltage of the APS circuit, shown in Fig. 4b. Fig. 6a shows several reset and integration cycles of the sense node voltage, simulated for different levels of photocurrent. The voltage drop during integration, which is shown in Fig. 6a as swing output, is

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proportional to the power of incident light. This is expected, as for higher levels of light, the photocurrent is higher and discharge of the capacitance of the photodiode happens faster. Interestingly, Fig. 6a also shows that the DC level of the sense node voltage varies with light. This is mainly due to the incomplete reset of the photodiode, during the short integration time. Fig. 6b compares the DC level and swing outputs, and suggests that DC level can have much more significant variation than the swing for similar levels of incident light. Our measurements approve this fact, and show that DC level can in fact detect two orders of magnitude lower levels of light than swing, for the same pixel.

III. 3: Pixels with avalanche photodiode

All of the above pixel structures operate by integrating the photocurrent. In applications where the signal is changing very fast, short integration times are necessary to obtain the desired temporal resolution. However, detection of lower levels of light requires the small photocurrent to be integrated during longer integration times. These approaches can not serve the applications that require sensitivity and fast response at the same time.

Avalanche photodiodes (APDs) operated in Geiger mode, are the semiconductor equivalent of PMTs. Geiger mode APDs are capable of detecting single photons. A sample circuit structure of an APD with its peripheral circuitry is shown in Fig. 7a. Our fabricated layout of the APD circuit is shown in Fig. 7b. The octagonal shape APD can bee seen at the top of Fig. 7b, with a 10µm diameter. The mechanism of single photon detection is illustrated in Fig. 8. When no current flows in the APD, its reverse bias $(V_{DD} + V_{OP})$ is above the APD breakdown voltage. An electron-hole pair can be generated in the depletion region of the APD, either by an incident photon (step 0 in Fig. 8) or thermal generation. The electron and hole will then accelerate in the high electric field. They will collide with the lattice atoms at high speeds and ionize them, thereby releasing other carriers to start the avalanche process. This avalanche current builds up very fast. The current will flow in the quench resistor, and cause the voltage at the sense node to drop (step 1). This drop will be sensed by the quenching loop, and an output pulse will be generated by the peripheral circuit. The quench transistor will then bring the sense node voltage down to zero (step 2). This will, in turn, bring the reverse bias of the APD below breakdown, and the avalanche current will quickly dissipate. The quench transistor is then turned off and the reset transistor is turned on. The reset transistor will then bring the sense node voltage back up (step 3), for the pixel to be ready for detection of next photon (step 4). The time from the arrival of the photon, until being ready for detection of the next photon, is called the dead-time. It can be seen in Fig. 8 that our fabricated APD system has a dead time of about 40ns.

III. Comparison and conclusion

Table I shows a general comparison of different CMOS photodetector solutions. It can be assumed that all the solutions offer the requirements of low cost, low power and the possibility of integration with other circuitry. Compared to passive pixel sensors that are rarely used in modern applications, APS can still be applicable due to its simplicity and moderate sensitivity. The DC level APS is an excellent choice for low-light-level applications. It uses the same pixel structure as APS. The speed of APS-based structures are however limited, due to the fact that they integrate the photocurrent. Even digital pixel sensors cannot offer high speeds required for fluorescence lifetime measurements, for example. For applications that require both sensitivity and fast response, active pixel sensors should be selected. Passive APD circuits consist of only an APD and a resistor. Passive APD is simple and sensitive, however it is relatively slow. APDs with active peripheral circuitry offer the highest speed at the cost of larger pixel sizes. However, by incorporating the advantage of small transistor sizes of modern CMOS technologies, APDs with peripheral circuitry are an excellent choice for achieving both high speed and high sensitivity performance.

Acknowledgements

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Read more about it:

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Tables and figures:

	PPS	APS	DC level APS	DPS	Passive APD	Active APD
Complexity	Low	Low	Low	High	Low	High
Fill-factor	Very high	High	High	Moderate	Moderate	Low
Sensitivity	Low	Moderate	High	Moderate	High	High
Speed	Low	Moderate	Low	Moderate	High	Very high

Table I: Comparison of the CMOS pixel structures



Figure 1: The fill-factor in a pixel is the ratio of the photosensitive area to the total pixel area.





Figure 2: Different readout architecture in CMOS and CCD systems. (a) In CCDs, pixel data is transferred serially out of the array. (b) In CMOS imagers, pixels in the array are randomly addressable.



Figure 3: (a) Fluorescence spectral response showing the excitation pulse and the emission pulse. (b) Time-resolved and fluorescence lifetime measurements.



Figure 4: (a) Passive pixel sensor, (b) three transistor active pixel sensor and (c) digital pixel sensor, with internal analog to digital conversion.





Figure 5: An example of a 16×16 CMOS imager block diagram and equivalent layout in a CMOS 0.18 µm technology.



Figure 6: (a) Simulated sense node voltage of an APS as a function of time. It can be seen that the DC level, at which the sense node voltage oscillates, varies with the level of light. (b) Variation of the DC level, compared to the swing of the sense node voltage. At lower light levels, DC level generates higher output value than swing.



Figure 7: A Geiger mode APD can be implemented in CMOS to detect single photons. (a) Schematic and (b) layout of our APD with peripheral circuitry fabricated in 0.18µm CMOS technology.



Figure 8: Output signal of the Geiger mode APD with active quench and active reset. Different cycles of operation of the APD circuit are shown.

CMOS Imaging for Biomedical Applications

N. Faramarzpour¹, M. M. El-Desouki¹, M. J. Deen¹, Q. Fang² S. Shirani¹ and L. W. C. Liu³.

Abstract—Miniaturization of biomedical test and measurement equipment using commercial micro- and nano-fabrication technologies offers many advantages such as low-cost, small size and hence portability and incorporation of "intelligence" in photodetector image sensing elements. However, for biomedical applications such as disease screening or detection, these image sensing systems must be capable of detecting very lowlevels of emitted light from the biological samples. Currently, either charge-coupled devices (CCDs) or photomultiplier tubes (PMTs) that are expensive, consume high power or are bulky, are used. In the recent past, CMOS photodetectors and imaging systems have shown that they possess adequate performance characteristics to replace the CCDs or PMTs, thereby providing low power, portable and cheap integrated bioimaging systems. This replacement has only recently become possible by the improvements in the dynamic range and sensitivity of modern CMOS photodetectors. This work addresses some of these advanced solutions, like novel active pixel sensors that detect ultra-low light levels, and avalanche photodiodes that are integrated in CMOS and perform single photon detection.

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Q. Fang is with the Department of Engineering Physics, McMaster University, Hamilton, ON, Canada L8S 4K1.

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I. INTRODUCTION

PTICAL molecular imaging systems are used to measure and characterize chemical or biological processes on the cellular and molecular level. Such applications have a medicine, revolutionary impact on agriculture. biodefense and through environmental testing techniques such as DNA sequencing, protein detection, gene expression, cell migration and evaluation of animal models of human cancer. These techniques are even more attractive when developed in hand-held, portable devices that can be used for forensics and biohazard studies on-site. Compared with established diagnosis techniques such as x-ray, computed tomography (CT), magnetic-resonance imaging (MRI) and the gamma-camera in the case of nuclear medicine, non-invasive fluorescence imaging systems for the detection of cancers has been considered to have many advantages, such as patient safety, high spatial resolution, small size and low equipment cost.

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Fig. 1. The fill-factor in a pixel is the ratio of the photosensitive area to the total pixel area.

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III. DIFFERENT PIXEL STRUCTURES

Different pixel structures have been reported for CMOS imagers. Each pixel structure has its advantages and can be suitable for different applications. Here we will present some of the widely used CMOS pixel structures, and discuss their applicability to low-light-level applications.

A. Pixels with Photocurrent Integration: PPS, APS and DPS

Passive pixel sensor (PPS) is the earliest and most simple CMOS pixel structure. In this structure, each pixel consists of a photodiode and a rowselect transistor. Fig. 4a shows the PPS During integration, structure. the internal capacitance of the photodiode integrates the generated photocurrent. At the end of integration, rows are selected one at a time, and connected to the column read buses. The pixel charges are read in parallel for pixels in each row. Then, photodiodes are reset and ready for next integration cycle. PPS has only one transistor per pixel. and thus has the highest FF. However, column readout of the rather small integrated charge of the photodiodes, significantly reduces the performance of



Fig. 4. (a) Passive pixel sensor, (b) three transistor active pixel sensor and (c) digital pixel sensor, with internal analog to digital conversion.

this approach.

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Stokes shift

Time emission

Detection gate 2

Detection gate 1

fluorescence

Emission

Spectral

overlap

700

Detection

gate N

lifetime

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Active pixel sensors, in general, have an output with low signal to noise ratio for low levels of light. One way to increase the sensitivity of APS is to increase its photodiode size. This solution however, will decrease the resolution of the imager. Another solution is to lengthen the integration time of the APS. The pixel is capable of detecting lower levels of light with longer integration times. However, the rate of spatial variation of the sample can limit the applicability of this solution. Also, at high integration times, the internal dark current of the pixel may saturate it.

Fig. 6a shows the simulated sense node voltage of the APS circuit, shown in Fig. 4b. Fig. 6a shows several reset and integration cycles of the sense node voltage, simulated for different levels of photocurrent. The voltage drop during integration, which is shown in Fig. 6a as swing output, is proportional to the power of incident light. This is expected, as for higher levels of light, the photocurrent is higher and discharge of the capacitance of the photodiode happens faster. Interestingly, Fig. 6a also shows that the DC level of the sense node voltage varies with light. This is mainly due to the incomplete reset of the photodiode, during the short integration time. Fig. 6b compares the DC level and swing outputs, and suggests that DC level can have much more significant variation than the swing for similar levels of incident light. Our measurements approve this fact, and show that DC level can in fact detect two orders of magnitude lower





Fig. 6. (a) Simulated sense node voltage of an APS as a function of time. It can be seen that the DC level, at which the sense node voltage oscillates, varies with the level of light. (b) Variation of the DC level, compared to the swing of the sense node voltage. At lower light levels, DC level generates higher output value than swing.

Fig. 5. An example of a 16×16 CMOS imager block diagram and equivalent layout in a CMOS 0.18 μm technology.

levels of light than swing, for the same pixel.

C. Pixels with Avalanche Photodiode

All of the above pixel structures operate by integrating the photocurrent. In applications where the signal is changing very fast, short integration times are necessary to obtain the desired temporal resolution. However, detection of lower levels of light requires the small photocurrent to be integrated during longer integration times. These can approaches not serve the applications that require sensitivity and fast response at the same time.

Avalanche photodiodes (APDs) operated in Geiger mode, are the semiconductor equivalent of PMTs. Geiger mode APDs are capable of detecting single photons. A sample circuit structure of an APD with its peripheral circuitry is shown in Fig. 7a. Our fabricated layout of the APD circuit is shown in Fig. 7b. The octagonal shape APD can bee seen at the top of Fig. 7b, with a 10µm diameter. The mechanism of single photon detection is illustrated in Fig. 8. When no current

flows in the APD, its reverse bias (VDD + VOP) is above the APD breakdown voltage. An electron-hole pair can be generated in the depletion region of the APD, either by an incident photon (step 0 in Fig. 8) or thermal generation. The electron and hole will then accelerate in the high electric field. They will collide with the lattice atoms at high speeds and ionize them, thereby releasing other carriers to start the avalanche process. This avalanche current builds up very fast. The current will flow in the quench resistor, and cause the voltage at the sense node to drop (step 1). This drop will be sensed by the quenching loop, and an output pulse will be generated by the peripheral circuit. The quench transistor will then bring the sense node voltage down to zero (step 2). This will, in turn, bring the reverse bias of the APD below breakdown, and the avalanche current will quickly dissipate. The quench transistor is then turned off and the reset transistor is turned on. The reset transistor will then bring the sense node voltage back up (step 3), for the pixel to be ready for detection of next photon (step 4). The time from the

arrival of the photon, until being ready for detection of the next photon, is called the dead-time. It can be seen in Fig. 8 that our fabricated APD system has a dead time of about 40ns.

IV. COMPARISON AND CONCLUSION

Table I shows a general comparison of different CMOS photodetector solutions. It can be assumed that all the solutions offer the requirements of low cost, low power and the possibility of integration with other circuitry. Compared to passive pixel sensors that are rarely used in modern applications, APS can still be applicable due to its simplicity and moderate sensitivity. The DC level APS is an excellent choice for low-light-level applications. It uses the same pixel structure as APS. The speed of APS-based structures are however limited, due to the fact that they integrate the photocurrent. Even digital pixel sensors cannot offer high speeds required for fluorescence lifetime for measurements, example. For applications that require both sensitivity and fast response, active pixel sensors

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TABLE I COMPARISON OF THE CMOS PIXEL STRUCTURES

	PPS	APS	DC level APS	DPS	Passive APD	Active APD
Complexity	Low	Low	Low	High	Low	High
Fill-factor	Very high	High	High	Moderate	Moderate	Low
Sensitivity	Low	Moderate	High	Moderate	High	High
Speed	Low	Moderate	Low	Moderate	High	Very high





should be selected. Passive APD circuits consist of only an APD and a resistor. Passive APD is simple and sensitive, however it is relatively slow. APDs with active peripheral circuitry offer the highest speed at the cost of larger pixel sizes. However, by incorporating the advantage of small transistor sizes of modern CMOS technologies, APDs with peripheral circuitry are an excellent choice for achieving both high speed and high sensitivity performance.



Fig. 8. Output signal of the Geiger mode APD with active quench and active reset. Different cycles of operation of the APD circuit are shown.

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